



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Lymphoblastic Leukemia

Version 2.2021 — July 19, 2021

NCCN.org

NCCN Guidelines for Patients® available at: www.nccn.org/patients

Continue



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

***Patrick A. Brown, MD/Chair €**
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

***Bijal Shah, MD/Vice-Chair †**
Moffitt Cancer Center

Anjali Advani, MD † ‡
Case Comprehensive Cancer Center/University
Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

Patricia Aoun, MD, MPH ≠
City of Hope National Medical Center

Michael W. Boyer, MD ‡ § €
Huntsman Cancer Institute
at the University of Utah

Patrick W. Burke, MD † ‡
University of Michigan Rogel Cancer Center

Daniel J. DeAngelo, MD, PhD † ‡
Dana-Farber/Brigham and Women's
Cancer Center

Shira Dinner, MD † ‡
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Amir T. Fathi, MD † ‡ †
Massachusetts General Hospital
Cancer Center

Jordan Gauthier, MD, MSc ‡
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Nitin Jain, MD † ‡
The University of Texas
MD Anderson Cancer Center

Suzanne Kirby, MD ‡
Duke Cancer Institute

Michaela Liedtke, MD ‡
Stanford Cancer Institute

Mark Litzow, MD ‡
Mayo Clinic Cancer Center

Aaron Logan, MD, PhD ‡
UCSF Helen Diller Family
Comprehensive Cancer Center

Selina Luger, MD †
Abramson Cancer Center
at the University of Pennsylvania

Lori J Maness, MD ‡
Fred & Pamela Buffett Cancer Center

Stephanie Massaro, MD, MPH € ‡
Yale Cancer Center/Smilow Cancer Hospital

Ryan J. Mattison, MD † ‡ †
University of Wisconsin Carbone Cancer Center

William May, MD €
UCLA Jonsson Comprehensive Cancer Center

Olalekan Oluwale, MD ‡
Vanderbilt-Ingram Cancer Center

Jae Park, MD †
Memorial Sloan Kettering Cancer Center

Amanda Przespolewski, DO ‡
Roswell Park Comprehensive Cancer Center

Sravanti Rangaraju, MD † ‡
O'Neal Comprehensive Cancer Center at UAB

Jeffrey E. Rubnitz, MD, PhD €
St. Jude Children's Research Hospital/The
University of Tennessee Health Science Center

Geoffrey L. Uy, MD ‡ † §
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Madhuri Vusirikala, MD § ‡
UT Southwestern Simmons
Comprehensive Cancer Center

Matthew Wieduwilt, MD, PhD ‡ §
UC San Diego Moores Cancer Center

NCCN
Beth Lynn, RN, BS
Deborah Freedman-Cass, PhD
Mallory Campbell, PhD
Ryan Berardi, MSc

[NCCN Guidelines Panel Disclosures](#)

Continue

§ Bone marrow transplantation	≠ Pathology
‡ Hematology/Hematology oncology	€ Pediatric oncology
† Internal medicine	§ Radiotherapy/Radiation oncology
† Medical oncology	* Discussion Section Writing Committee



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

[NCCN Acute Lymphoblastic Leukemia Panel Members](#)

[Summary of the Guidelines Updates](#)

[Diagnosis \(ALL-1\)](#)

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

[Ph+ ALL \(AYA/Adult\) Treatment Induction and Consolidation Therapy \(ALL-3\)](#)

[Ph- ALL \(AYA\) Treatment Induction and Consolidation Therapy \(ALL-4\)](#)

[Ph- ALL \(Adult\) Treatment Induction and Consolidation Therapy \(ALL-5\)](#)

[Surveillance \(ALL-6\)](#)

[Relapsed/Refractory Disease, Treatment \(ALL-7\)](#)

[Cytogenetic Risk Groups for B-ALL \(ALL-A\)](#)

[Evaluation and Treatment of Extramedullary Involvement \(ALL-B\)](#)

[Supportive Care \(ALL-C\)](#)

[Principles of Systemic Therapy \(ALL-D\)](#)

[Response Assessment \(ALL-E\)](#)

[Minimal/Measurable Residual Disease Assessment \(ALL-F\)](#)

Clinical Trials: NCCN believes that the best management for any patient with cancer 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/member_institutions.aspx](#).

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

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

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. 2021.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Updates in Version 2.2021 of the NCCN Guidelines for Acute Lymphoblastic Leukemia from Version 1.2021 include:

[ALL-C 3 of 4](#)

- **Asparaginase Toxicity Management**

- ▶ Second bullet revised: There are ~~three~~ **four** formulations of asparaginase in clinical use: 1) pegaspargase (PEG), 2) calaspargase pegol-mknl (Cal-PEG) (in patients ≤21 years), 3) asparaginase *Erwinia chrysanthemi* (**Erwinia**ERW),^a and 4) *asparaginase Erwinia chrysanthemi* (recombinant)-rywn (ERW-rywn).^a

- **Hypersensitivity, Allergy, and Anaphylaxis**

- ▶ Second bullet revised: ~~Erwinia ERW, or ERW-rywn may be is commonly~~ used as a second-line agent in patients who have developed a systemic allergic reaction or anaphylaxis due to PEG hypersensitivity.

- **Footnote a added: ERW and ERW-rywn are for patients who had an allergic reaction to E. coli-derived asparaginase.**

[ALL-D 1 of 10](#)

- **Footnote f added: For patients who develop hypersensitivity to E. coli-derived asparaginase, ERW or ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course. (Also pages ALL-D 2 of 10, and ALL-D 9 of 10).**

[MS-1](#)

- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2021 of the NCCN Guidelines for Acute Lymphoblastic Leukemia from Version 2.2020 include:

[ALL-1](#)

- **Molecular Characterization**

- ▶ Third bullet revised: **Comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended** ~~encouraged for gene fusions and pathogenic mutations~~, particularly if known to be BCR-ABL1/*Ph*-negative or *Ph*-like.

- ▶ Additional optional tests include, first bullet revised: **Assessment (array cGH) with chromosomal microarray (CMA)/array cGH** in cases of aneuploidy or failed karyotype.

- **Classification**

- ▶ Sentence was revised: Together, these studies allow determination of the World Health Organization (WHO) ALL subtypes and cytogenetic and *clinical* risk groups.

[ALL-1A](#)

- **Footnote g revised to include: In cases of hypodiploid ALL where germline *TP53* mutations are common, testing should be considered.**

- **Footnote i added: High WBC count (≥30 x 10⁹/L for B lineage or ≥100 x 10⁹/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population and likely superseded by MRD quantification after treatment. (Also pages ALL-2, ALL-3A, ALL-4A, and ALL-5)**

- **Footnote j added: ALL arising from prior chemotherapy or underlying hematologic malignancy may be associated with adverse outcomes. Saygin C, et al. Blood Adv 2019;3:4228-4237.**

[ALL-2](#)

- **Workup**

- ▶ Urinalysis removed.

- ▶ Last bullet revised: **Strongly consider human leukocyte antigen (HLA) typing and early evaluation and search for family or an alternative donor early transplant evaluation and donor search.**

- **Risk Stratification, top pathway, added: and Adult.**

[Continued](#)



Updates in Version 1.2021 of the NCCN Guidelines for Acute Lymphoblastic Leukemia from Version 2.2020 include:

[ALL-3](#)

- **Ph+ AYA pathway** was combined with the Ph+ Adult pathway.
- **Risk Stratification**
 - **Top pathway**, added: AYA and adult.
 - **Bottom pathway**, added: Adult.
- **Consolidation Therapy** was extensively revised. The following: “Allogeneic hematopoietic cell transplantation (HCT), in appropriate candidates followed by the option to consider post-HCT TKI or Continue multiagent chemotherapy + TKI followed by the option maintenance therapy + TKI” was replaced with:
 - **Persistent/Rising MRD**
 - ◊ Blinatumomab ± TKI (B-ALL) or Continue multiagent chemotherapy/corticosteroid + TKI or Allogeneic HCT in appropriate candidates.
 - **MRD**
 - ◊ Continue multiagent chemotherapy/corticosteroid + TKI or Allogenic HCT in appropriate candidates.

[ALL-3A](#)

• Footnotes

- **Added:**
 - ◊ Footnote h: See Cytogenetic Risk Groups for B-ALL (ALL-A). (Also page ALL-4A)
 - ◊ Footnote cc: Consider dose modifications appropriate for patient age and performance status. See Principles of Systemic Therapy - Treatment of Older Adults (≥65 years) or Adults with Substantial Comorbidities (ALL-D 9 of 10).
 - ◊ Footnote dd: The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible (See Discussion). (Also pages ALL-4A and ALL-5)
 - ◊ Footnote ee: Consider using an alternative and more broadly acting TKI. See Principles of Systemic Therapy - Regimens for Ph-Positive B-ALL (ALL-D 3 of 10).
 - ◊ Footnote ff: TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Dasatinib and imatinib are the preferred TKIs for induction therapy; ponatinib is also preferred for the hyper-CVAD regimen. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, BCR-ABL1 mutations, and disease-related features. For contraindicated mutations, see ALL-D 3 of 10.
 - ◊ Footnote gg: See Supportive Care: Toxicity Management (ALL-C 2 of 4). (Also page ALL-4A)
 - ◊ Footnote hh: Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. (Also page ALL-4A)

[Continued](#)



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Updates in Version 1.2021 of the NCCN Guidelines for Acute Lymphoblastic Leukemia from Version 2.2020 include:

► **Revised:**

- ◊ Footnote r: All ALL treatment regimens include CNS prophylaxis. See *Evaluation and Treatment of Extramedullary Involvement (ALL-B)*. (Also pages ALL-4A and ALL-5)
- ◊ Footnote v: Optimal timing of HCT is not clear. For fit patients, additional therapy *is recommended* to eliminate MRD prior to transplant. *Proceeding to allogeneic HCT with MRD is not optimal*. (Also pages ALL-4A and ALL-5)
- ◊ Footnote w: Data suggest that for younger patients (aged ≤21 y), *particularly for those who achieve MRD negativity*, allogeneic HCT may not offer an advantage over chemotherapy + TKI...

[ALL-4A](#)

- Footnote ii added: Consider retesting for MRD at first available opportunity. (Also page ALL-5)

[ALL-6](#)

- Surveillance, Other General Measures, first bullet revised: Bone marrow aspirate *can be considered* as clinically indicated **every** at a frequency of up to 3–6 months for at least 5 years.

[ALL-7](#)

• Relapsed/Refractory Disease

- "B" added to Ph+ and Ph- ALL.
- T-ALL pathway added.

• Treatment

- Following *ABL1* Kinase domain mutation testing, options revised: ... Blinatumomab ± TKI (TKI intolerant/refractory B-ALL) or Inotuzumab ozogamicin ± *bosutinib* (TKI intolerant/ refractory, B-ALL)...

[Cytogenetic Risk Groups for B-ALL \(ALL-A\)](#)

• Poor risk

- Removed: Ph-like ALL.
- Added:
 - ◊ *BCR-ABL 1*-like (Ph-like) ALL.
 - ◊ JAK-STAT (*CRLF2r*, *EPORr*, *JAK1/2/3r*, *TYK2r*, mutations of *SH2B3*, *IL7R*, *JAK1/2/3*)
 - ◊ ABL class (rearrangements of *ABL1*, *ABL2*, *PDGFRA*, *PDGFRB*, *FGFR*)
 - ◊ Other (*NTRKr*, *FLT3r*, *LYNr*, *PTL2Br*)
 - ◊ t(17;19): *TCF3-HLF* fusion
 - ◊ Alterations of *IKZF1*

• Footnotes added:

- Footnote c: Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone. Hypodiploid ALL is also often associated with *TP53* loss of function mutations and Li-Fraumeni syndrome.
- Footnote d: Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood* 2017;129:572-581; Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activation lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med*

[Continued](#)

UPDATES



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Updates in Version 1.2021 of the NCCN Guidelines for Acute Lymphoblastic Leukemia from Version 2.2020 include:

2014;371:1005-1015.

- ▶ Footnote e: Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med* 2009;360:470-480; Stanulla M, Dagdan E, Zaliouva M, et al. IKZF1plus defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. *J Clin Oncol* 2018;36:1240-1249.
- ▶ Footnote f: Emerging evidence suggests *DUX4r* ALL is favorable. Additionally in cases of *DUX4r*, *IKZF1* alterations do not confer poor prognosis.

[ALL-B](#)

- Evaluation and Treatment of Extramedullary Involvement, third bullet, third sub-bullet revised: The panel recommends that LP be done concurrently with initial IT therapy. *IT therapy be administered with initial LP.*

[ALL-C \(2 of 4\)](#)

- Supportive Care: Toxicity Management Inotuzumab, Blinatumomab, and Tisagenlecleucel
 - ▶ Blinatumomab, second bullet, last sentence revised: Consider tocilizumab for patients with refractory severe CRS.

[ALL-C \(3 of 4\)](#)

- Supportive Care: Asparaginase Toxicity Management
 - ▶ Second bullet, added: (in patients ≤21 years).
 - ▶ Third bullet added: The panel recommends that the dose of PEG or Cal-PEG should be capped at 1 vial (3,750 IU).
 - ▶ Hypersensitivity, Allergy, and Anaphylaxis:
 - ◊ Fourth bullet revised: For Grade 1 reactions and Grade 2 reactions (rash, flushing, urticaria, and drug fever ≥38°C) without bronchospasm, hypotension, edema, or need for parenteral intervention, the asparaginase that caused the reaction may be continued, with consideration for anti-allergy premedication (such as hydrocortisone, *famotidine* or *ranitidine*, diphenhydramine, and acetaminophen).
 - ◊ Fifth bullet added: Measures that can be considered for preventing or limiting severity of infusion reactions or hypersensitivity reactions include slowing the infusion to ≥2 hours, infusing normal saline concurrently, and use of premedications provided above.
 - ◊ Sixth bullet, sub-bullets added:
 - TDM for asparaginase therapy using the serum asparaginase activity (SAA) is available as a CLIA-certified test with a turnaround time of less than one week, allowing real-time decision-making and therapeutic adjustments. Generally accepted SAA assay targets include a minimum trough of ≥0.1 IU/mL. However, data indicate that when SAA levels fall below 0.4 IU/mL, asparagine is no longer completely depleted, and begins to rebound, suggesting an optimal trough of ≥0.4 IU/mL.
 - Routine premedication has generally been avoided in the past for fear of “masking” hypersensitivity reactions. However, given the difficulty in distinguishing hypersensitivity and non-allergic infusion reactions and the availability of TDM, universal premedication and TDM can be considered, which can reduce the incidence and severity of adverse events and the need for substitution of pegaspargase with Erwinia.

[Continued](#)

UPDATES



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Updates in Version 1.2021 of the NCCN Guidelines for Acute Lymphoblastic Leukemia from Version 2.2020 include:

[ALL-C \(4 of 4\)](#)

- **Supportive Care: Asparaginase Toxicity Management (continued); Hepatotoxicity; first bullet revised:** For direct bilirubin >5.0, either discontinue asparaginase or hold asparaginase until <2.0 mg/dL, then resume with *very consideration for dose reduction and close monitoring*.

[Principles of Systemic Therapy \(ALL-D\)](#)

[ALL-D \(1 of 10\)](#)

- **Heading revised: Induction Regimens for Ph-Positive B-ALL.**
 - ▶ **Protocols for AYA Patients, option added:** Blinatumomab ± TKI.
 - ▶ **Adult Patients (<65 y) added:** and without substantial comorbidities. (Also page ALL-D 2 of 10)
 - ◊ Option added: Blinatumomab ± TKI.
 - ▶ **Statement following table revised:** For treatment of older adult patients ≥65 y with ALL *or adult patients with substantial comorbidities*, see ALL-D 9 of 10. (Also page ALL-D 2 of 10)

[ALL-D1A](#)

- **Footnotes revised:**
 - ▶ **Footnote c:** *There are data to support the benefit* ~~The use of rituximab should be considered~~ in addition to chemotherapy for CD20-positive patients (especially in patients <60 years). (Also page ALL-D 2A)
 - ▶ **Footnote e:** ~~These regimens are used for~~ *The specific drugs listed are primarily used in induction. therapy and additional therapy is needed* *For post-induction components, see listed references.* (Also page ALL-D 2A)
 - ▶ **Footnote g:** last sentence added: For contraindicated mutations, see ALL-D 3 of 10. (Also page ALL-D 9 of 10).
 - ▶ **Footnote i:** For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. *Testing for both TPMT and NUDT15 variant status should be considered, especially for patients of East Asian origin. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.* (Also page ALL-D 2A)
- **Footnotes added:**
 - ▶ **Footnote d:** An FDA-approved biosimilar is an appropriate substitute for rituximab. (Also pages ALL-D 2A and ALL-D 4 of 10)
 - ▶ **Footnote h:** For consolidation.
- **Footnote removed:** These regimens are used for induction therapy and additional therapy is needed.

[ALL-D \(2 of 10\)](#)

• AYA Patients

- ▶ **Preferred regimens, first and last options, removed:** (ongoing study in patients aged <40 years).
 - ◊ Third option, removed: added to consolidation regimen.
- ▶ **Other Recommended Regimens**
 - ◊ **Third option revised:** Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; *with rituximab for CD20-positive disease*.
 - ◊ **Fourth option revised:** USC/MSKCC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged 18–60 years).

[Continued](#)

UPDATES



Updates in Version 1.2021 of the NCCN Guidelines for Acute Lymphoblastic Leukemia from Version 2.2020 include:

- ◊ Fifth option revised: Linker 4-drug regimen: daunorubicin, vincristine, pegaspargase, and prednisone; *with rituximab for CD20-positive disease*.
- Adult Patients (<65 y and without substantial comorbidities)
 - ▶ Other Recommended Regimens
 - ◊ Third option revised: Hyper-CVAD \pm rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; *with rituximab for CD20-positive disease*.
 - ◊ Fourth option added: USC/MSKCC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged <60 years).
 - ◊ Fifth option revised: Linker 4-drug regimen \pm rituximab: daunorubicin, vincristine, prednisone, and pegaspargase; *with rituximab for CD20-positive disease* (patients aged <60 years).
- Statement after table revised: For treatment of older adult patients ≥ 65 y with ALL *or adult patients with substantial comorbidities* see ALL 9 of 10.

[ALL-D \(3 of 10\)](#)

- Heading revised: Regimens for Relapsed or Refractory Ph-Positive B-ALL.
 - ▶ Other Recommended Regimens
 - ◊ Options revised:
 - Blinatumomab \pm TKI (for B-ALL) (TKI intolerant/refractory).
 - Inotuzumab ozogamicin \pm bosutinib (for B-ALL) (TKI intolerant/refractory).
 - The regimens listed on ALL-D 4 of 10 for Ph-negative B-ALL may be considered for Ph-positive B-ALL refractory to TKIs.
 - ◊ Option removed: MOPAD regimen (category 2B): methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20 positive disease and TKI.

[ALL-D \(4 of 10\)](#)

- Heading revised: Regimens for Relapsed or Refractory Ph-Negative B-ALL.
 - ▶ Other Recommended Regimens
 - ◊ Option removed: Nelarabine alone or in combination (eg, nelarabine, etoposide, cyclophosphamide) for T-ALL.
 - ◊ Option revised: MOPAD regimen (*for R/R Ph-negative ALL only*): methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease.

[ALL-D \(5 of 10\)](#)

- New section added: Principles of Systemic Therapy: Regimens for Relapsed or Refractory Ph-Negative T-ALL.

[ALL-D \(6 of 10\)](#) and [ALL-D \(7 of 10\)](#) and [ALL-D \(8 of 10\)](#)

- References updated.

[ALL-D \(9 of 10\)](#)

- Header revised: Treatment of Older Adults (≥ 65 years) *or Adults with ALL Substantial Comorbidities*. (Also page ALL-D 10 of 10)
 - ▶ Induction Regimens for Ph-negative ALL header, removed: Adults Aged ≥ 65 y
 - ▶ Induction Regimens for Ph-positive B-ALL header, removed: Adults Aged ≥ 65 y
- Footnote f revised: TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Dasatinib and imatinib are the preferred TKIs for induction therapy; ponatinib is also preferred for the hyper-CVAD regimen. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance and disease-related features. *For contraindicated mutations, see ALL-D 3 of 10.*

[ALL-F](#)

Minimal/Measurable Residual Disease Assessment

- ▶ First bullet revised: The *preferred* sample for MRD assessment is the first *small volume (of up to 3 mL)* pull of the bone marrow aspirate, *if*



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

DIAGNOSIS

Acute
lymphoblastic
leukemia
(ALL)^{a,b,c}

Patients should undergo evaluation and treatment at specialized centers

The diagnosis of ALL generally requires demonstration of $\geq 20\%$ bone marrow lymphoblasts^{d,e} 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^f
- Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal/measurable residual disease (MRD) analysis ([see ALL-F](#))
- Karyotyping of G-banded metaphase chromosomes

MOLECULAR CHARACTERIZATION

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

- Interphase fluorescence in situ hybridization (FISH) testing, including probes capable of detecting the major recurrent genetic abnormalities^a
- Reverse transcriptase-polymerase chain reaction (RT-PCR) testing *BCR-ABL1* in B-ALL (quantitative or qualitative) including determination of transcript size (ie, p190 vs. p210)
- Comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended, particularly if known to be *BCR-ABL1*/Ph-negative or Ph-like.⁹

Additional optional tests include:

- Assessment with chromosomal microarray (CMA)/array cGH in cases of aneuploidy or failed karyotype.

CLASSIFICATION

Together, these studies allow determination of the World Health Organization (WHO) ALL subtypes and cytogenetic and clinical risk groups.^{h,i,j}

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

[See footnotes on ALL-1A](#)

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

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



FOOTNOTES

- ^a Subtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities includes hyperdiploidy, hypodiploidy, and commonly occurring translocations: t(9;22)(q34.1;q11.2)[*BCR-ABL1*]; t(v;11q23.3)[*KMT2A* rearranged]; t(12;21)(p13.2;q22.1)[*ETV6-RUNX1*]; t(1;19)(q23;p13.3)[*TCF3-PBX1*]; t(5;14)(q31.1;q32.3)[*IL3-IGH*]; Ph-like; B-lymphoblastic leukemia/lymphoma with iAMP21; early T-cell precursor lymphoblastic leukemia.
- ^b Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2016 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis.
- ^c Burkitt leukemia/lymphoma, see the [NCCN Guidelines for B-Cell Lymphomas](#).
- ^d While these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (LL) (B- or T-cell) also benefit from ALL-like regimens versus traditional lymphoma therapy. Such patients should be treated in a center that has experience with LL. See [Discussion](#).
- ^e If there are sufficient numbers of circulating lymphoblasts (at least 1,000 per microliter as a general guideline) and clinical situation precludes bone marrow aspirate and biopsy, then peripheral blood can be substituted for bone marrow.
- ^f The following immunophenotypic findings are particularly notable: CD10 negativity correlates with *KMT2A* rearrangement; ETP T-ALL (typically lacking expression of CD5, CD8, and CD1a and expression of one or more myeloid/stem cell markers); CD20 positivity: definition not clear, most studies have used >20% of blasts expressing CD20. See [Discussion](#).
- ^g The Ph-like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, or *PDGFRB* and mutations involving *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. The safety and efficacy of targeted agents in this population is an area of active research. For more information regarding Ph-like ALL, please see the [Discussion](#). In cases of hypodiploid ALL where germline *TP53* mutations are common, testing should be considered.
- ^h See [Cytogenetic Risk Groups for B-ALL \(ALL-A\)](#).
- ⁱ High WBC count ($\geq 30 \times 10^9/L$ for B lineage or $\geq 100 \times 10^9/L$ for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population and likely superseded by MRD quantification after treatment.
- ^j ALL arising from prior chemotherapy or underlying hematologic malignancy may be associated with adverse outcomes. Saygin C, et al. Blood Adv 2019;3:4228-4237.

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

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



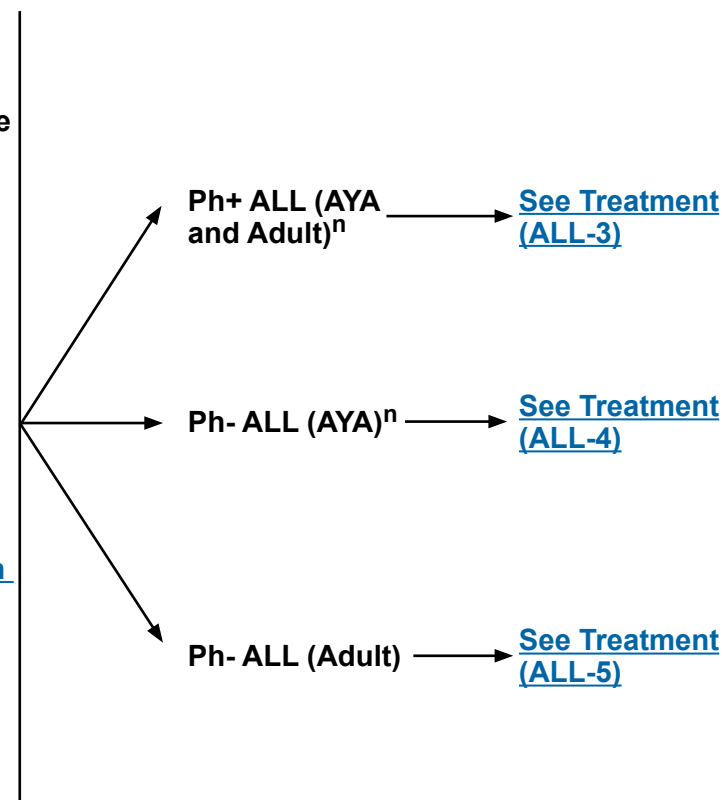
NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

WORKUP^k

- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, chemistry profile, liver function tests (LFTs)
- Disseminated intravascular coagulation (DIC) panel: d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Tumor lysis syndrome (TLS) panel: Lactate dehydrogenase (LDH), uric acid, potassium, calcium, phosphorus (See Tumor Lysis Syndrome in the [NCCN Guidelines for B-Cell Lymphomas](#))
- Hepatitis B/C, HIV, CMV Ab testing
- Pregnancy testing, fertility counseling, and preservation
- CT/MRI of head with contrast, if neurologic symptoms^k
- Lumbar puncture (LP)^{l,m} with intrathecal (IT) chemotherapy
 - ▶ [See Evaluation and Treatment of Extramedullary Involvement \(ALL-B\)](#)
- CT of neck/chest/abdomen/pelvis with IV contrast, as indicated for symptoms
 - ▶ Consider PET/CT if lymphomatous involvement is suspected
- Testicular exam, including scrotal ultrasound as indicated
- Infection evaluation:
 - ▶ Screen for opportunistic infections, as appropriate ([See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#))
- Echocardiogram or cardiac nuclear medicine 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 or clinical symptoms suggestive of cardiac dysfunction.
- Central venous access device of choice
- Strongly consider early transplant evaluation and donor search.

RISK STRATIFICATIONⁱ



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

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

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

^m The panel recommends first LP be performed at time of initial scheduled IT therapy unless directed by symptoms to perform earlier.

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

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

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



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021

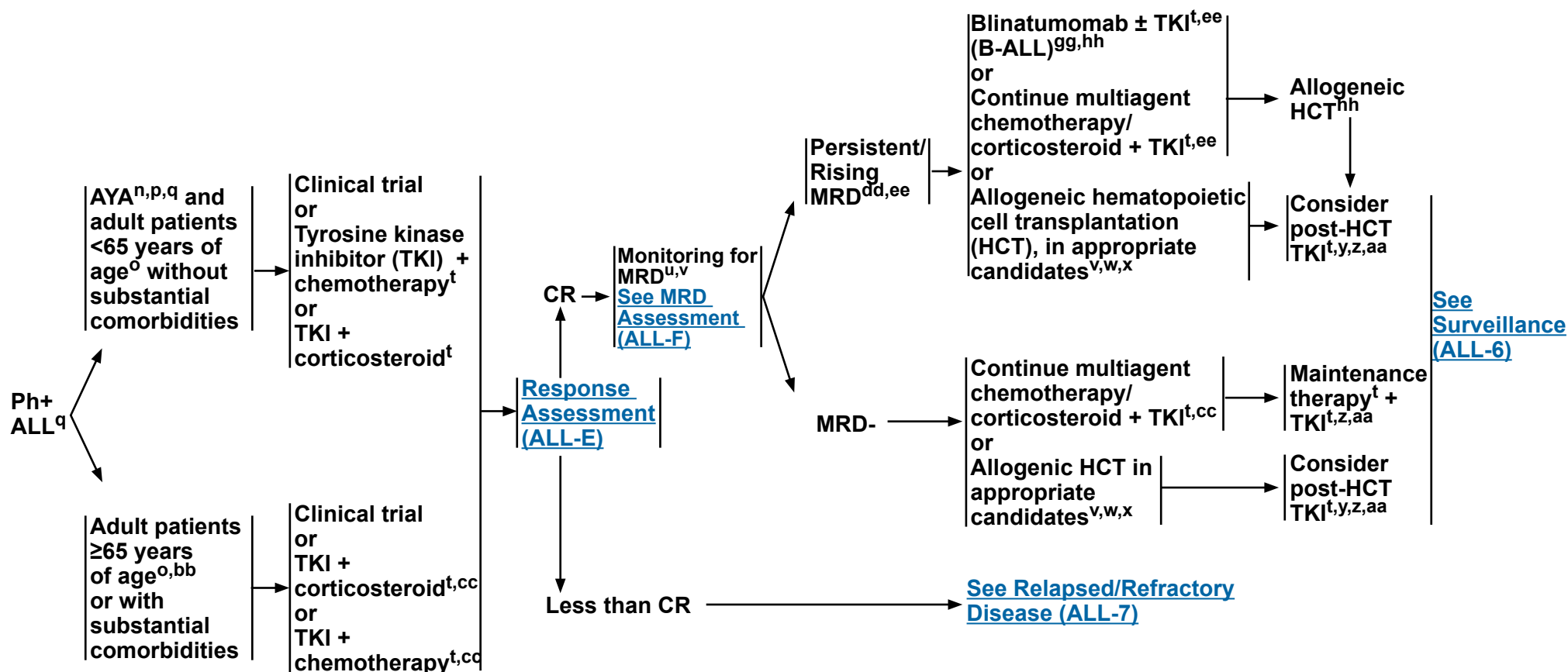
Acute Lymphoblastic Leukemia

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

RISK STRATIFICATION^{h,i}

TREATMENT INDUCTION^{ff,r,s}

CONSOLIDATION THERAPY^{ff,r,s}



[See footnotes on ALL-3A](#)

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

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

**FOOTNOTES**

^h [See Cytogenetic Risk Groups for B-ALL \(ALL-A\).](#)

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

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

^o 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.

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

^q It is reasonable to approach the initial treatment of blast phase CML with similar strategies to Ph+ ALL, with a goal of proceeding to HCT.

^r All ALL treatment regimens include CNS prophylaxis. This may be particularly important when using agents without known CNS penetrance including blinatumomab and certain TKIs. [See Evaluation and Treatment of Extramedullary Involvement \(ALL-B\).](#)

^s [See Principles of Supportive Care \(ALL-C\).](#)

^t [See Principles of Systemic Therapy \(ALL-D\).](#)

^u [See Minimal/Measurable Residual Disease Assessment \(ALL-F\).](#)

^v Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal.

^w Data suggest that for younger patients (aged ≤ 21 y), particularly for those who achieve MRD negativity, allogeneic HCT may not offer an advantage over chemotherapy + TKI. Schultz KR, et al. J Clin Oncol 2009;27:5175-5181; Schultz KR, et al. Leukemia 2014;28:1467-1471.

^x Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.

^y See [Discussion](#) for use of different TKIs in this setting.

^z The recommended duration of TKI after HCT is at least one year. The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy. The optimal duration of TKI is unknown in both settings.

^{aa} Consider periodic MRD monitoring (no more than every 3 months) for patients with complete molecular remission (undetectable levels). Increased frequency may be indicated for detectable levels.

^{bb} For additional considerations in the management of older adult patients with ALL, see the [NCCN Guidelines for Older Adult Oncology](#).

^{cc} Consider dose modifications appropriate for patient age and performance status. [See Principles of Systemic Therapy - Treatment of Older Adults \(\$\geq 65\$ years\) or Adults with Substantial Comorbidities \(ALL-D 9 of 10\).](#)

^{dd} The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible ([See Discussion](#)).

^{ee} Consider using an alternative and more broadly acting TKI. [See Principles of Systemic Therapy - Regimens for Ph-Positive B-ALL \(ALL-D 3 of 10\).](#)

^{ff} TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Dasatinib and imatinib are the preferred TKIs for induction therapy; ponatinib is also preferred for the hyper-CVAD regimen. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, *BCR-ABL1* mutations, and disease-related features. For contraindicated mutations, [see ALL-D 3 of 10](#).

^{gg} [See Supportive Care: Toxicity Management \(ALL-C 2 of 4\).](#)

^{hh} Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.

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

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



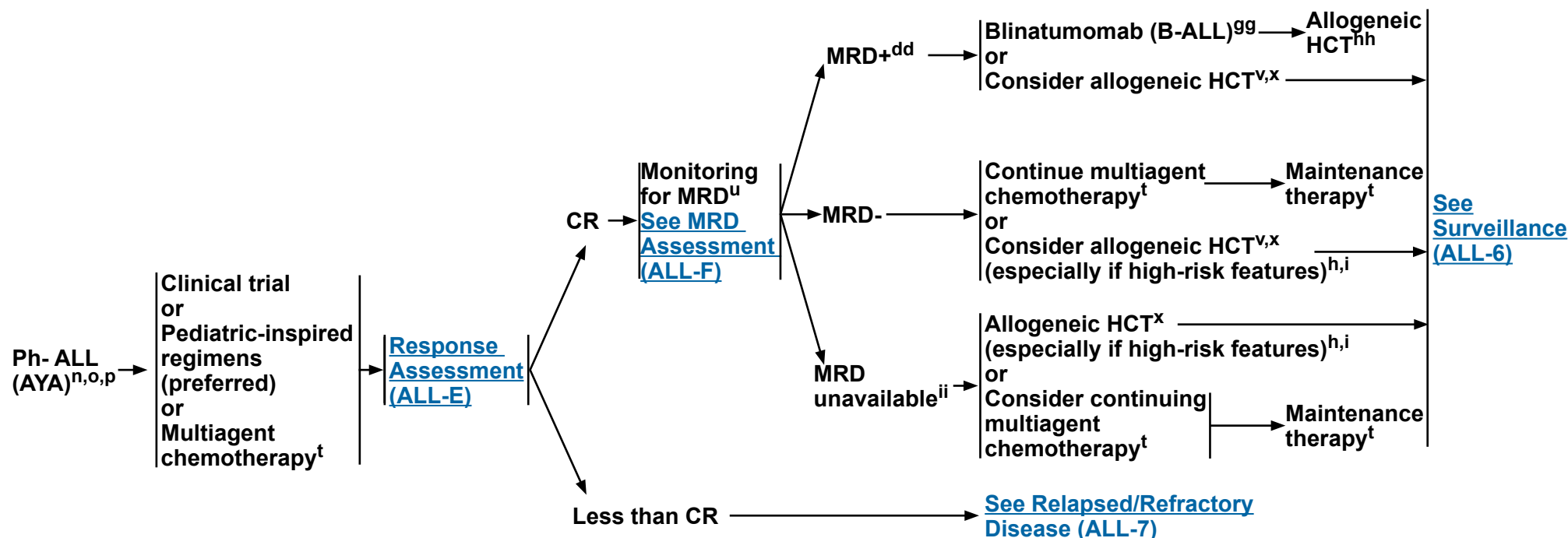
NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

RISK STRATIFICATION^{h,i}

TREATMENT INDUCTION^{r,s}

CONSOLIDATION THERAPY^{r,s}


[See footnotes on ALL-4A](#)

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

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



FOOTNOTES

^h [See Cytogenetic Risk Groups for B-ALL \(ALL-A\).](#)

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

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

^o 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.

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

^r All ALL treatment regimens include CNS prophylaxis. [See Evaluation and Treatment of Extramedullary Involvement \(ALL-B\).](#)

^s [See Principles of Supportive Care \(ALL-C\).](#)

^t [See Principles of Systemic Therapy \(ALL-D\).](#)

^u [See Minimal/Measurable Residual Disease Assessment \(ALL-F\).](#)

^v Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal.

^x Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.

^{dd} The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible ([See Discussion](#)).

^{gg} [See Supportive Care: Toxicity Management \(ALL-C 2 of 4\).](#)

^{hh} Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.

ⁱⁱ Consider retesting for MRD at first available opportunity.

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

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

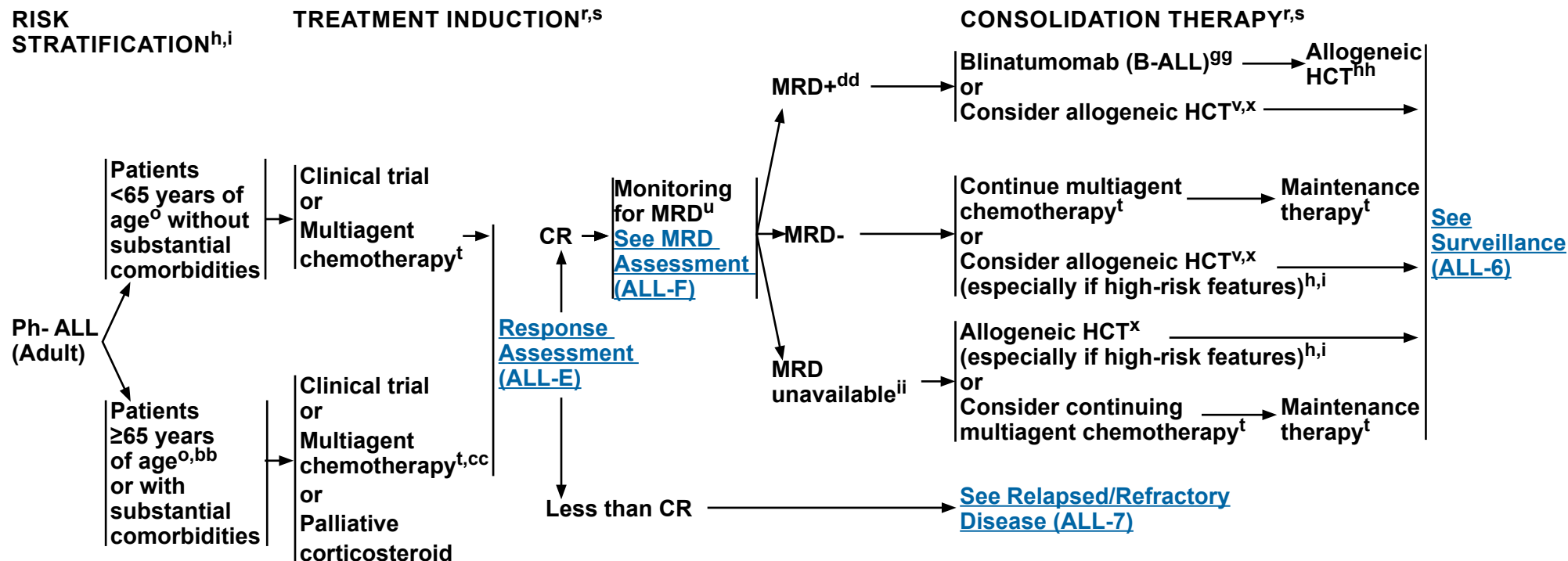


National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)



^h [See Cytogenetic Risk Groups for B-ALL \(ALL-A\)](#).

ⁱ High WBC count (≥30 x 10⁹/L for B lineage or ≥100 x 10⁹/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population and likely superseded by MRD quantification after treatment.

^o 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.

^r All ALL treatment regimens include CNS prophylaxis. [See Evaluation and Treatment of Extramedullary Involvement \(ALL-B\)](#).

^s [See Principles of Supportive Care \(ALL-C\)](#).

^t [See Principles of Systemic Therapy \(ALL-D\)](#).

^u [See Minimal/Measurable Residual Disease Assessment \(ALL-F\)](#).

^v Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal.

^x Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.

^{bb} For additional considerations in the management of older adult patients with ALL, see the [NCCN Guidelines for Older Adult Oncology](#).

^{cc} Consider dose modifications appropriate for patient age and performance status. [See Principles of Systemic Therapy - Treatment of Older Adults \(≥65 years\) or Adults with Substantial Comorbidities \(ALL-D 9 of 10\)](#).

^{dd} The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible ([See Discussion](#)).

^{gg} [See Supportive Care: Toxicity Management \(ALL-C 2 of 4\)](#).

^{hh} Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.

ⁱⁱ Consider retesting for MRD at first available opportunity.

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

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



SURVEILLANCE^{jj}

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

Other General Measures

- Bone marrow aspirate can be considered as clinically indicated at a frequency of up to 3–6 months for at least 5 years^{kk}
 - If bone marrow aspirate is done: Flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular testing, and MRD assessment
- Periodic *BCR-ABL1* transcript-specific quantification (Ph+ ALL)
- Refer to Survivorship recommendations in the [NCCN Guidelines for Survivorship](#)
- Refer to the ALL Long-term Follow-up Guidelines from the Children's Oncology Group (COG): <http://www.survivorshipguidelines.org/>

[See Relapsed/Refractory Disease \(ALL-7\)](#)

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

^{kk} While there is insufficient evidence to guide MRD monitoring for Ph-negative patients following completion of maintenance therapy, the approval of blinatumomab, and potentially future therapies for the MRD-positive relapse, may warrant testing in this regard. Alternatively, for patients showing evidence of symptomatic relapse, the diagnostic workup should be repeated as per [ALL-1](#).

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

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

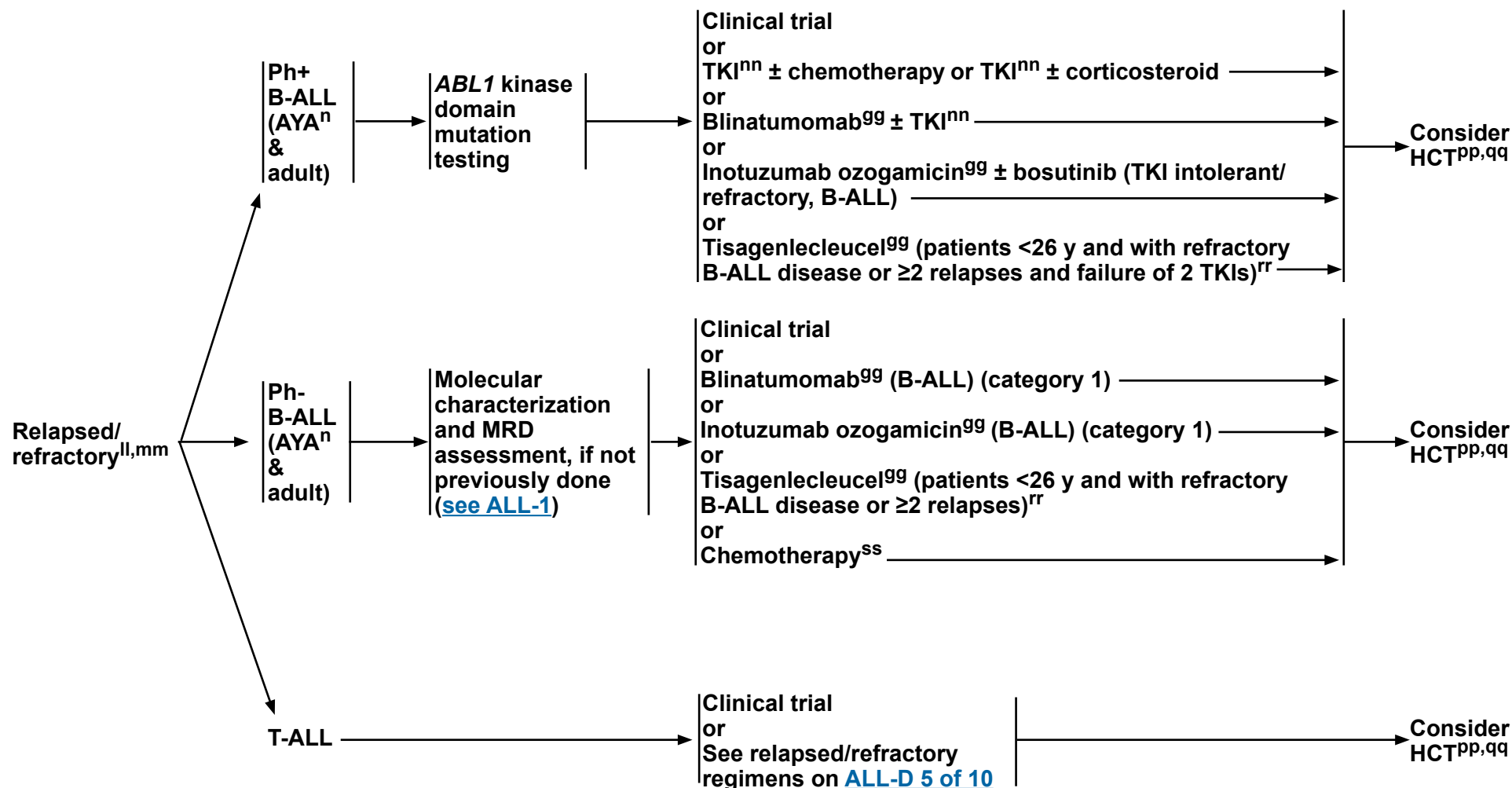


NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

RELAPSED/REFRACTORY DISEASE

TREATMENT^{oo}



[See footnotes on ALL-7A](#)

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

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



FOOTNOTES

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

^{gg} [See Supportive Care: Toxicity Management \(ALL-C 2 of 4\)](#).

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

^{mm} [See NCCN Guidelines for Palliative Care](#).

ⁿⁿ [See Treatment Options Based on BCR-ABL 1 Mutation Profile \(ALL-D 3 of 10\)](#).

^{oo} See Principles of Systemic Therapy ([ALL-D 3 of 10](#), [ALL-D 4 of 10](#), and [ALL-D 5 of 10](#)).

^{pp} If second remission is achieved prior to transplant and patient has not had a prior HCT, consolidative HCT is recommended.

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

^{rr} The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent HCT. In the global registration trial, relapse-free survival was 59% at 12 months, with only 9% of patients proceeding to HCT.

^{ss} For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See [ALL-D 2 of 10](#)).

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

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

CYTOGENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	CYTOGENETICS
Good risk	<ul style="list-style-type: none"> Hyperdiploidy (51–65 chromosomes) <ul style="list-style-type: none"> Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome t(12;21)(p13;q22): <i>ETV6-RUNX1</i>^a
Poor risk	<ul style="list-style-type: none"> Hypodiploidy^{b,c} (<44 chromosomes) <i>KMT2A</i> rearranged (t[4;11] or others) t(v;14q32)/IgH t(9;22)(q34;q11.2): <i>BCR-ABL1</i> (defined as high risk in the pre-TKI era) Complex karyotype (5 or more chromosomal abnormalities) <i>BCR-ABL1</i>-like (Ph-like) ALL <ul style="list-style-type: none"> JAK-STAT (<i>CRLF2r</i>,^{d,c} <i>EPORr</i>, <i>JAK1/2/3r</i>, <i>TYK2r</i>, mutations of <i>SH2B3</i>, <i>IL7R</i>, <i>JAK1/2/3</i>) ABL class (rearrangements of <i>ABL1</i>, <i>ABL2</i>, <i>PDGFRA</i>, <i>PDGFRB</i>, <i>FGFR</i>) Other (<i>NTRKr</i>, <i>FLT3r</i>, <i>LYNr</i>, <i>PTL2Br</i>) Intrachromosomal amplification of chromosome 21 (iAMP21) t(17;19): <i>TCF3-HLF</i> fusion Alterations of <i>IKZF1</i>^{e,f}

^a The translocation t(12;21)(p13;q22) is typically cryptic by karyotyping and requires FISH or PCR to identify.

^b There are other results that are not less than 44 chromosomes that may be equivalent to hypodiploidy and have the same implications. It is important to distinguish true hypodiploidy from masked hypodiploidy, which results from the doubling of hypodiploid clones. Carroll AJ, Shago M, Mikhail FM, et al. Masked hypodiploidy: Hypodiploid acute lymphoblastic leukemia (ALL) mimicking hyperdiploid ALL in children: A report from the Children's Oncology Group. *Cancer Genet* 2019;238:62-68.

^c Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone. Hypodiploid ALL is also often associated with *TP53* loss of function mutations and Li-Fraumeni syndrome.

^d Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood* 2017;129:572-581; Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activation lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014;371:1005-1015.

^e Mullighan CG, Su X, Zhang J, et al. Deletion of *IKZF1* and prognosis in acute lymphoblastic leukemia. *N Engl J Med* 2009;360:470-480; Stanulla M, Dagdan E, Zaliouva M, et al. *IKZF1*plus defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. *J Clin Oncol* 2018;36:1240-1249.

^f Emerging evidence suggests *DUX4r* ALL is favorable. Additionally in cases of *DUX4r*, *IKZF1* alterations do not confer poor prognosis.

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

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



EVALUATION AND TREATMENT OF EXTRAMEDULLARY INVOLVEMENT

- 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 white blood cell (WBC) counts, and elevated serum LDH levels.¹
- 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 IT therapy be administered with initial LP.
- Classification of CNS status:
 - ▶ CNS-1: No lymphoblasts in cerebrospinal fluid (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/red blood cell (RBC) ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.
- All patients with ALL should receive CNS prophylaxis. Although the presence of CNS involvement at the time of diagnosis is uncommon (about 3%–7%), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.
- CNS-directed therapy may include cranial irradiation, IT chemotherapy (eg, methotrexate, cytarabine, corticosteroid), and/or systemic chemotherapy (eg, high-dose methotrexate, intermediate or high-dose cytarabine, pegaspargase). Generally, IT therapy should start during the induction phase.
- CNS leukemia (CNS-3 and/or cranial nerve involvement) at diagnosis, or persisting after induction, may warrant treatment with cranial irradiation of 18 Gy in 1.8 to 2.0 Gy/fraction. The recommended dose of radiation, where given, is highly dependent on the intensity of systemic chemotherapy; thus, it is critical to adhere to a given treatment protocol in its entirety. The entire brain and posterior half of the globe should be included. The inferior border should include C2.
- Note that areas of the brain targeted by the radiation field in the management of ALL are different from areas targeted for brain metastases of solid tumors.
- With the incorporation of adequate systemic chemotherapy (eg, high-dose methotrexate, intermediate or high-dose 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 prophylactic cranial irradiation except in cases of overt CNS leukemia at diagnosis, and to reserve the use of irradiation for relapsed/refractory therapy settings.
- Adequate systemic therapy should be given in the management of isolated CNS relapse.
- Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of the induction therapy should be considered for radiation to the testes in the scrotal sac, which is typically done concurrently with the first cycle of maintenance chemotherapy. Testicular total dose should be 24 Gy in 2.0 Gy/fraction.

¹ 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.

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

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

SUPPORTIVE CARE

Best Supportive Care

- Infection control ([See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#))
 - ▶ For infection risk, monitoring, and prophylaxis recommendations for immune-targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#)
- Acute TLS (See Tumor Lysis Syndrome on NHODG-B in the [NCCN Guidelines for B-Cell Lymphomas](#))
- Toxicity Management for Inotuzumab ozogamicin, Blinatumomab, and Tisagenlecleucel ([ALL-C 2 of 4](#))
- Pegaspargase Toxicity Management ([ALL-C 3 of 4](#) and [ALL-C 4 of 4](#))
- Methotrexate and Glucarpidase
 - ▶ Trimethoprim/Sulfamethoxazole may be held when high-dose methotrexate is administered and re-started when methotrexate clearance is achieved per protocol or institutional guidelines.
 - ▶ Consider use of glucarpidase in patients with significant renal dysfunction and toxic plasma methotrexate concentrations with delayed methotrexate clearance (plasma methotrexate concentrations >2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered). 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.
- Consider defibrotide for patients who develop veno-occlusive disease (VOD) related to inotuzumab ozogamicin toxicity.
- Steroid management
 - ▶ Acute side effects
 - ◊ Steroid-induced diabetes mellitus
 - Tight glucose control using insulin to decrease infection complications
 - ◊ Steroid-induced psychosis and mood alteration
 - Consider anti-psychotics. If no response, consider dose reduction.

- Use of a histamine-2 antagonist or proton pump inhibitor (PPI) should be considered during steroid therapy.
- There may be important drug interactions between PPIs and methotrexate that need to be considered prior to initiation of methotrexate-based therapy.
- There are significant interactions between PPIs and TKIs regarding the bioavailability of certain *BCR-ABL1* TKIs with gastric acid suppression that should be considered.
- ▶ Long-term side effects of corticosteroids
 - ◊ Osteonecrosis/avascular necrosis (also [see Discussion](#))
 - Obtain vitamin D and calcium status and replete as needed.
 - Consider radiographic evaluation with plain films or MRI or bone density study.
 - Consider withholding steroid in patients with severe avascular necrosis.
- Transfusions
 - ▶ Products should be leukoreduced/irradiated.
- Use of granulocyte colony-stimulating factor (G-CSF)
 - ▶ Recommended for myelosuppressive blocks of therapy or as directed by treatment protocol
- Hyperleukocytosis
 - ▶ Although uncommon in patients with ALL, symptomatic hyperleukocytosis may require emergent treatment (See Symptomatic Leukocytosis in the [NCCN Guidelines for Acute Myeloid Leukemia](#)).
- 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 if receiving vincristine.
- Nutritional support
 - ▶ Consider enteral or parenteral support for >10% weight loss.
- Palliative treatment for pain ([See NCCN Guidelines for Adult Cancer Pain](#))

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

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

[Continued](#)



SUPPORTIVE CARE

Toxicity Management for Inotuzumab, Blinatumomab, and Tisagenlecleucel

Inotuzumab Ozogamicin:

- Cytoreduction should be considered for those with WBC >10,000 cells per microliter. On clinical trial, hydroxyurea or a combination of steroids and vincristine was used.
- Myelosuppression is common, and prophylactic antimicrobial strategies in accordance with institutional practice should be employed.
- Liver enzymes, and particularly bilirubin, should be closely monitored, as sinusoidal obstruction syndrome (SOS) (or VOD) may occur, particularly among patients at higher risk (including those who are status-post allogeneic HCT, those whose treatment extends beyond two cycles, and/or those who previously received or will receive double alkylator conditioning prior to allogeneic HCT. For those patients receiving inotuzumab as a bridge to allogeneic transplant, double alkylator conditioning is strongly discouraged. Ursodiol may be considered for VOD prophylaxis.

Blinatumomab:

- Cytoreduction should be considered for those with WBC >15,000 cells per microliter, as high tumor burden may increase the risks of toxicity. On clinical trial, steroids were most commonly used.
- Patients should be monitored for cytokine release syndrome (CRS), a systemic inflammatory condition characterized by fever or hypothermia, that may progress to hypotension, hypoxia, and/or end organ damage. Infusion should be held with consideration for steroids and/or vasopressors for those with severe symptoms in accordance with manufacturer guidelines and prescriber information. Consider tocilizumab for patients with severe CRS.
- Because concurrent severe infection may mimic CRS, an evaluation for underlying infection and consideration of empiric antimicrobial therapy in accordance with institutional practice should be performed.
- Patients should be monitored for neurologic toxicity, which may include confusion, word-finding difficulty, somnolence, ataxia, tremor, seizure, or syncope. Infusion should be held with consideration of steroids for those with severe symptoms in accordance with manufacturer guidelines and prescribing information, and re-started (once symptoms have sufficiently improved) with dosing adjustments as per manufacturer guidelines and prescribing information.

Tisagenlecleucel:

- Severe CRS and/or neurologic toxicity may accompany therapy, and should be managed in accordance with the manufacturer Risk Evaluation and Mitigation Strategies (REMS) program, to include tocilizumab (preferred for CRS) and steroids (preferred for tocilizumab-refractory CRS and/or neurologic toxicity).
- Prophylaxis with anti-seizure medication may be considered during the first month after tisagenlecleucel infusion.
- Severe neutropenia, T-cell depletion, and B-cell aplasia can occur, for which growth factor, prophylactic antimicrobial therapy, and intravenous immunoglobulin administration should be considered, in accordance with institutional practice.
- See [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

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

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

[Continued](#)

ALL-C
2 OF 4



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

SUPPORTIVE CARE

Asparaginase Toxicity Management

- Asparaginase should only be used in specialized centers and patients should be closely monitored in the period during and after infusion for allergic response.
- There are four formulations of asparaginase in clinical use: 1) pegaspargase (PEG), 2) calaspargase pegol-mknl (Cal-PEG) (in patients ≤21 years), 3) asparaginase Erwinia chrysanthemi (ERW),^a and 4) asparaginase Erwinia chrysanthemi (recombinant)-rywn (ERW-rywn).^a PEG is a common component of therapy for children, adolescents, and young adults with ALL. The preferred route for administration for both PEG and Cal-PEG is intravenous (IV). The toxicity profile of these asparaginase products presents significant challenges in clinical management. The following guidelines are intended to help providers address these challenges.
- The panel recommends that the dose of PEG or Cal-PEG should be capped at 1 vial (3,750 IU).
- For more detailed information, refer to Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegaspargase-associated toxicities in adults and older adolescents: recommendations of an expert panel. *Leuk Lymphoma* 2011;52:2237-2253. All toxicity grades refer to CTCAE v4.03. National Cancer Institute; National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 2010. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Hypersensitivity, Allergy, and Anaphylaxis

- There is a significant incidence of hypersensitivity reactions with asparaginase products in some regimens. Of particular concern are **Grade 2 or higher** systemic allergic reactions, urticaria, or anaphylaxis, because these episodes can be (but are not necessarily) associated with neutralizing antibodies and lack of efficacy.
- ERW, or ERW-rywn may be used as a second-line agent in patients who have developed a systemic allergic reaction or anaphylaxis due to PEG hypersensitivity.
- Anaphylaxis or other allergic reactions of Grade 3–4 severity (CTCAE 4.0) merit permanent discontinuation of the type of asparaginase that caused the reaction.
- For Grade 1 reactions and Grade 2 reactions (rash, flushing, urticaria, and drug fever ≥38°C) without bronchospasm, hypotension, edema, or need for parenteral intervention, the asparaginase that caused the reaction may be continued, with consideration for anti-allergy premedication (such as hydrocortisone, famotidine or ranitidine, diphenhydramine, and acetaminophen).
- Measures that can be considered for preventing or limiting severity of infusion reactions or hypersensitivity reactions include slowing the infusion to ≥2 hours, infusing normal saline concurrently, and use of premedications provided above.
- If anti-allergy premedication is used prior to PEG or Erwinia administration, consideration should be given to therapeutic drug monitoring (TDM) using commercially available asparaginase activity assays, since premedication may “mask” the systemic allergic reactions that can indicate the development of neutralizing antibodies.
 - ▶ TDM for asparaginase therapy using the serum asparaginase activity (SAA) is available as a CLIA-certified test with a turnaround time of less than one week, allowing real-time decision-making and therapeutic adjustments. Generally accepted SAA assay targets include a minimum trough of ≥0.1 IU/mL. However, data indicate that when SAA levels fall below 0.4 IU/mL, asparagine is no longer completely depleted, and begins to rebound, suggesting an optimal trough of ≥0.4 IU/mL.
 - ▶ Routine premedication has generally been avoided in the past for fear of “masking” hypersensitivity reactions. However, given the difficulty in distinguishing hypersensitivity and non-allergic infusion reactions and the availability of TDM, universal premedication and TDM can be considered, which can reduce the incidence and severity of adverse events and the need for substitution of pegaspargase with Erwinia.

^a ERW and ERW-rywn are for patients who had an allergic reaction to E. coli-derived asparaginase

¹ Bleyer A, Asselin BL, Koontz SE, Hunger S. Clinical application of asparaginase activity levels following treatment with pegaspargase. *Pediatr Blood Cancer* 2015;62:1102-1105.

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

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

[Continued](#)

ALL-C
3 OF 4



SUPPORTIVE CARE

Asparaginase Toxicity Management (continued)

Pancreatitis

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

Non-CNS Hemorrhage

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

Non-CNS Thromboembolism

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

Intracranial Hemorrhage

- Discontinue asparaginase. Consider coagulation factor replacement. For Grade 3 or less, if symptoms/signs fully resolve, consider resuming asparaginase at lower doses and/or longer intervals between doses. For Grade 4, permanently discontinue asparaginase.
- Magnetic resonance angiography (MRA)/magnetic resonance venography (MRV) to rule out bleeding associated with sinus venous thrombosis.

Cerebral Thrombosis, Ischemia, or Stroke

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

Hyperglycemia

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

Hypertriglyceridemia

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

Hepatotoxicity (elevation in bilirubin, AST, ALT)

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

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

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PRINCIPLES OF SYSTEMIC THERAPY^a REGIMENS FOR Ph-POSITIVE B-ALL^{b,c,d,e,f}

Protocols for AYA Patients^g:

Other Recommended Regimens

- EsPhALL regimen: TKI^h + backbone of the Berlin-Frankfurt-Münster regimen (cyclophosphamide, vincristine, daunorubicin, dexamethasone, cytarabine, methotrexate, pegaspargase, and prednisone)¹⁻³
- TKI^h + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine⁴⁻⁸
- TKI^h + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)⁹⁻¹³
- TKI^{h,14,15} + corticosteroid
- TKI^h + vincristine + dexamethasone¹⁶
- CALGB 10701 regimen: TKI^h + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)¹⁷
- Blinatumomab ± TKI^{i,18}

Adult Patients (<65 y and without substantial comorbidities):

Other Recommended Regimens

- TKI^h + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine⁴⁻⁸
- TKI^h + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)⁹⁻¹³
- TKI^{h,14,15} + corticosteroid
- TKI^h + vincristine + dexamethasone^{16,19}
- CALGB 10701 regimen: TKI^h + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)¹⁷
- Blinatumomab ± TKI^{i,18}

For treatment of older adult patients ≥65 y with ALL or adult patients with substantial comorbidities, see [ALL-D 9 of 10](#).

Maintenance Regimens:

- Add TKI^h to maintenance regimen; optimal duration is unknown.
- Monthly vincristine/prednisone pulses (for 2–3 years). May include weekly methotrexate + daily 6-mercaptopurine (6-MP) as tolerated.^{j,k}

[Induction Regimens for Ph-Negative ALL](#)

[See footnotes on ALL-D1A](#)

[References](#)

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

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



FOOTNOTES

- ^a For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).
- ^b All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
- ^c There are data to support the benefit of rituximab in addition to chemotherapy for CD20-positive patients (especially in patients <60 years).
- ^d An FDA-approved biosimilar is an appropriate substitute for rituximab.
- ^e The specific drugs listed are primarily used in induction. For post-induction components, see listed references.
- ^f For patients who develop hypersensitivity to E. coli-derived asparaginase, ERW or ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.
- ^g The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.
- ^h TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Dasatinib and imatinib are the preferred TKIs for induction therapy; ponatinib is also preferred for the hyper-CVAD regimen. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance and disease-related features. For contraindicated mutations, [see ALL-D 3 of 10](#).
- ⁱ For consolidation.
- ^j For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both *TPMT* and *NUDT15* variant status should be considered, especially for patients of East Asian origin. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.
- ^k 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.

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

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PRINCIPLES OF SYSTEMIC THERAPY^a REGIMENS FOR Ph-NEGATIVE ALL^{b,c,d,e,f}

AYA Patients^g:

Preferred Regimens
<ul style="list-style-type: none"> • CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase.^{20,m,n} • COG AALL0232 regimen: daunorubicin, vincristine, prednisone, and pegaspargase^l (patients aged ≤21 years).^{21,n} • COG AALL0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, pegaspargase;^l and nelarabine.^{22,n} • DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase.^{23,m,n}
Other Recommended Regimens
<ul style="list-style-type: none"> • GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase,^m and cyclophosphamide (patients aged <60 years), with rituximab for CD20-positive disease.^{24,n} • PETHMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase,^m and cyclophosphamide (patients aged <30 years).^{25,n} • Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with rituximab for CD20-positive disease.²⁶ • USC/MSKCC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase^m (patients aged 18–60 years).^{27,28,n} • Linker 4-drug regimen: daunorubicin, vincristine, pegaspargase,^m and prednisone;²⁹ with rituximab for CD20-positive disease.

Adult Patients (<65 y and without substantial comorbidities):

Other Recommended Regimens
<ul style="list-style-type: none"> • CALGB 8811 Larson regimen: daunorubicin, vincristine, prednisone, pegaspargase,^m and cyclophosphamide; for patients aged ≥60 years, reduced doses for cyclophosphamide, daunorubicin, and prednisone.^{30,31} • GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase,^m and cyclophosphamide (patients aged <60 years) with rituximab for CD20-positive disease.²⁴ • Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with rituximab for CD20-positive disease.^{26,32} • USC/MSKCC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase^l (patients aged <60 years).^{27,28,n} • Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase;^m with rituximab for CD20-positive disease (patients aged <60 years).^{29,33} • MRC UKALLXII/ECOG2993 regimen: daunorubicin, vincristine, prednisone, and pegaspargase^l (induction phase I); and cyclophosphamide, cytarabine, and 6-MP^g (induction phase II).³⁴

For treatment of older adult patients ≥65 y with ALL or adult patients with substantial comorbidities, see [ALL 9 of 10](#).

Maintenance Regimen:

- Weekly methotrexate + daily 6-MP^{k,l} + monthly vincristine/prednisone pulses (duration based on regimen)

[Induction Regimens for Ph-Positive ALL](#)

[See footnotes on ALL-D2A](#)

[References](#)

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

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



FOOTNOTES

- ^aFor infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).
- ^bAll regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
- ^cThere are data to support the benefit of rituximab in addition to chemotherapy for CD20-positive patients (especially in patients <60 years).
- ^dAn FDA-approved biosimilar is an appropriate substitute for rituximab.
- ^eThe specific drugs listed are primarily used in induction. For post-induction components, see listed references.
- ^fFor patients who develop hypersensitivity to E. coli-derived asparaginase, ERW or ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.
- ^gThe ALL Panel considers AYA to be within the age range of 15–39 years. However, this age is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.
- ⁱFor patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both *TPMT* and *NUDT15* variant status should be considered, especially for patients of East Asian origin. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.
- ^jDose 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.
- ^kPegaspargase may be substituted with calaspargase pegol-mknl, an asparagine-specific enzyme, in patients ≤21 years for more sustained asparaginase activity. Silverman LB, et al. Blood 2016;128:175; Angiolillo AL, et al. J Clin Oncol 2014;32:3874-3882.
- ^lPediatric-inspired regimen.

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

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PRINCIPLES OF SYSTEMIC THERAPY^a

REGIMENS FOR RELAPSED OR REFRACTORY Ph-POSITIVE B-ALL^{b,m}

Other Recommended Regimens

- TKI (dasatinib,^{35,36} imatinib,³⁷ ponatinib,³⁸ nilotinib,³⁹ or bosutinib⁴⁰)
 - ▶ The TKIs noted above may also be used in combination with any of the induction regimens noted on [ALL-D 1 of 10](#) that were not previously given.
- Blinatumomab ± TKI (for B-ALL)^{18,41,o}
- Inotuzumab ozogamicin ± bosutinib (for B-ALL) (TKI intolerant/refractory)^{42,o}
- Tisagenlecleucel (for B-ALL) (patients <26 y and with refractory disease or ≥2 relapses and failure of 2 TKIs)^{43,o}
- The regimens listed on [ALL-D 4 of 10](#) for Ph-negative B-ALL may be considered for Ph-positive B-ALL refractory to TKIs.

TREATMENT OPTIONS BASED ON *BCR-ABL1* MUTATION PROFILE

Therapy	Contraindicated Mutations ^p
Bosutinib	<i>T315I</i> , <i>V299L</i> , <i>G250E</i> , or <i>F317L</i> ^q
Dasatinib	<i>T315I/A</i> , <i>F317L/V/I/C</i> , or <i>V299L</i>
Nilotinib	<i>T315I</i> , <i>Y253H</i> , <i>E255K/V</i> , or <i>F359V/C/I</i> or <i>G250E</i>
Ponatinib ^r	None ^m

Regimens for Relapsed/Refractory Ph-Negative B-ALL

^a For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).

^b All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

^m The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established. Please see [ALL-D 9 of 10](#) for additional information.

ⁿ Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). The FDA indications are for the treatment of adult patients with *T315I*-positive, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of adult patients with Ph+ ALL for whom no other TKI therapy is indicated. For details, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203469s034lbl.pdf.

^o See Supportive Care: Toxicity Management (ALL-C 2 of 4).

^p Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

^q Bosutinib has minimal activity against *F317L* mutation. Nilotinib may be preferred over bosutinib in patients with *F317L* mutation.

^r Ponatinib is a treatment option for patients with a *T315I* mutation and/or for patients for whom no other TKI is indicated.

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

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

References



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PRINCIPLES OF SYSTEMIC THERAPY^a

REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE B-ALL^{b,m,s}

Preferred Regimens
<ul style="list-style-type: none"> • Blinatumomab (for B-ALL) (category 1)^{44,o} • Inotuzumab ozogamicin (for B-ALL) (category 1)^{42,o} • Tisagenlecleucel (for B-ALL) (patients <26 y and with refractory disease or ≥2 relapses)^{43,o}
Other Recommended Regimens
<ul style="list-style-type: none"> • Inotuzumab ozogamicin^o + mini-hyperCVD for B-ALL (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine)⁴⁵ • Augmented hyper-CVAD: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase; alternating with high-dose methotrexate and cytarabine⁴⁶ • Vincristine sulfate liposome injection (VSLI)^{47,48} • Clofarabine alone⁴⁹⁻⁵² or in combination (eg, clofarabine, cyclophosphamide, etoposide^{50,53,54}) • MOpAD regimen (for R/R Ph-negative ALL only): methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab^d for CD20-positive disease⁵⁵ • Fludarabine-based regimens <ul style="list-style-type: none"> ▶ FLAG-IDA: fludarabine, cytarabine, granulocyte colony-stimulating factor, ± idarubicin⁵⁶ ▶ FLAM: fludarabine, cytarabine, and mitoxantrone⁵⁷ • Cytarabine-containing regimens: eg, high-dose cytarabine, idarubicin, IT methotrexate⁵⁸ • Alkylator combination regimens: eg, etoposide, ifosfamide, mitoxantrone⁵⁹

[Regimens for Relapsed/Refractory Ph-Positive B-ALL](#)

^a For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).

^b All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

^d An FDA-approved biosimilar is an appropriate substitute for rituximab.

^m The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established. Please see [ALL-D 9 of 10](#) for additional information.

^o See [Supportive Care: Toxicity Management \(ALL-C 2 of 4\)](#).

^s For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See [ALL-D 2 of 10](#)).

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

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

[References](#)



PRINCIPLES OF SYSTEMIC THERAPY^a

REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE T-ALL^{b,m,s}

Preferred Regimens
• Nelarabine ⁶⁰⁻⁶³ ± etoposide and cyclophosphamide ⁶⁴⁻⁶⁶
Other Recommended Regimens
<ul style="list-style-type: none"> • Bortezomib⁶⁷ + chemotherapy • Daratumumab (Category 2B)⁶⁸⁻⁷² • HiDAC: high-dose cytarabine • Mitoxantrone, etoposide, and cytarabine⁷³ • Venetoclax + chemotherapy (eg decitabine, hyper-CVAD, nelarabine, mini-hyper-CVD) (Category 2B)⁷⁴⁻⁷⁷ • The regimens listed on ALL-D 4 of 10 for relapsed/refractory Ph-negative B-ALL may be appropriate/considered for R/R T-ALL.

^a For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).

^b All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

^m The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established. Please see [ALL-D 9 of 10](#) for additional information.

^s For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See [ALL-D 2 of 10](#)).

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

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

References



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PRINCIPLES OF SYSTEMIC THERAPY - REFERENCES

- ¹ 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.
- ² Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol* 2012;13:936-945.
- ³ Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: Results of Children's Oncology Group Trial AALL0622. *J Clin Oncol* 2018;36:2306-2314.
- ⁴ Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood* 2010;116:2070-2077.
- ⁵ Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood* 2004;103:4396-4407.
- ⁶ Thomas DA, Kantarjian HM, Cortes J, et al. Outcome after frontline therapy with the hyper-CVAD and imatinib mesylate regimen for adults with de novo or minimally treated Philadelphia chromosome (Ph) positive acute lymphoblastic leukemia (ALL) [abstract]. *Blood* 2008;112(Supple 11):Abstract 2931.
- ⁷ Thomas DA, O'Brien SM, Faderl S, et al. Long-term outcome after hyper-CVAD and imatinib (IM) for de novo or minimally treated Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-ALL) [abstract]. *J Clin Oncol* 2010;28:Abstract 6506.
- ⁸ Jabbour EJ, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol* 2015;16(15):1547-1555.
- ⁹ Mizuta S, Matsuo K, Yagasaki F, et al. Pre-transplant imatinib-based therapy improves the outcome of allogeneic hematopoietic stem cell transplantation for BCR-ABL-positive acute lymphoblastic leukemia. *Leukemia* 2011;25:41-47.
- ¹⁰ Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol* 2006;24:460-466.
- ¹¹ Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Blood* 2015;126:746-756.
- ¹² Slayton W, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: results of Children's Oncology Group Trial AALL0622. *J Clin Oncol* 2018;36:2306-2314.
- ¹³ Yoon JH, Yhim HY, Kwak JY, et al. Minimal residual disease-based effect and long-term outcome of first-line dasatinib combined with chemotherapy for adult Philadelphia chromosome-positive acute lymphoblastic leukemia. *Ann Oncol* 2016;27:1081-1088.
- ¹⁴ Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. *Blood* 2007;109:3676-3678.
- ¹⁵ Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2011;118:6521-6528.
- ¹⁶ Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood* 2015;125:3711-3719.
- ¹⁷ Wieduwilt MJ, Yin J, Wetzler M, et al. A phase II study of dasatinib and dexamethasone as primary therapy followed by transplantation for adults with newly diagnosed Ph/BCR-ABL1-positive acute lymphoblastic leukemia (Ph+ ALL): Final results of Alliance/CALGB Study 10701. *Blood* 2018;132:309.
- ¹⁸ Foa R, Bassan R, Vitale A, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. *N Engl J Med* 2020;383:1613-1623.
- ¹⁹ Rousselot P, Coude MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. *Blood* 2016;128:774-782.
- ²⁰ Stock W, Luger SM, Advani AS, et al. Favorable outcomes for older adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL): Early results of U.S. Intergroup Trial C10403. 2014 ASH Annual Meeting. Abstract 796. Presented December 9, 2014.
- ²¹ Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* 2015;126:964-971.
- ²² Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434.
- ²³ DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia* 2015;29:526-534.
- ²⁴ Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med* 2016;375:1044-1053.
- ²⁵ Ribera JM, Oriol A, Sanz MA, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Espanol de Tratamiento en Hematologia pediatric-based protocol ALL-96. *J Clin Oncol* 2008;26:1843-1849.
- ²⁶ Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol* 2010;28:3880-3889.
- ²⁷ Douer D, Aldoss I, Lunning MA, et al. Pharmacokinetics-based integration of multiple doses of intravenous pegaspargase in a pediatric regimen for adults with newly diagnosed acute lymphoblastic leukemia. *J Clin Oncol* 2014;32:905-911.
- ²⁸ Geyer MB, Ritchie EK, Rao AV, et al. Pediatric-inspired chemotherapy incorporating pegaspargase is safe and results in high rates of minimal residual disease negativity in adults up to age 60 with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Haematologica* 2020; Online ahead of print.
- ²⁹ Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. *J Clin Oncol* 2002;20:2464-2471.
- ³⁰ Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood* 1995;85:2025-2037.
- ³¹ Stock W, Johnson JL, Stone RM, et al. Dose intensification of daunorubicin and cytarabine during treatment of adult acute lymphoblastic leukemia: results of Cancer and Leukemia Group B Study 19802. *Cancer* 2013;119:90-98.

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PRINCIPLES OF SYSTEMIC THERAPY - REFERENCES

- 32 Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer* 2004;101:2788-2801.
- 33 Wieduwilt MJ, Jones BA, Schiller GJ, et al. A phase II study of pegylated asparaginase, cyclophosphamide, rituximab, and dasatinib added to the UCSF 8707 (Linker 4-drug) regimen with liposomal cytarabine CNS prophylaxis for adults with newly diagnosed acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL): University of California Hematologic Malignancies Consortium Study (UCHMC) 1401. *Blood* 2018;132:4018.
- 34 Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood* 2005;106:3760-3767.
- 35 Lilly MB, Ottmann OG, Shah NP, et al. Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. *Am J Hematol* 2010;85:164-170.
- 36 Ottmann O, Dombret H, Martinelli G, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* 2007;110:2309-2315.
- 37 Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood* 2002;100:1965-71.
- 38 Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013;369:1783-1796.
- 39 Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006;354:2542-2551.
- 40 Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. *Am J Hematol* 2015;90:755-768.
- 41 Martinelli G, Boissel N, Chevallerier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia Chromosome-positive B-Precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. *J Clin Oncol* 2017;35:1795-1802.
- 42 Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016;375:740-753.
- 43 Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* 2018;378:439-448.
- 44 Kantarjian H, Stein A, Gökbüget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017;376: 836-847.
- 45 Jabbour E, Ravandi F, Kebriaei P, et al. Salvage chemoinmunotherapy with inotuzumab ozogamicin combined with mini-Hyper-CVD for patients with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia: A phase 2 clinical trial. *JAMA Oncol* 2018;4:230-234.
- 46 Faderl S, Thomas DA, O'Brien S, et al. Augmented hyper-CVAD based on dose-intensified vincristine, dexamethasone, and asparaginase in adult acute lymphoblastic leukemia salvage therapy. *Clin Lymphoma Myeloma Leuk* 2011;11:54-59.
- 47 Deitcher OR, O'Brien S, Deitcher SR, et al. Single-agent vincristine sulfate liposomes injection compared to historical single-agent therapy for adults with advanced, relapsed and/or refractory Philadelphia chromosome negative acute lymphoblastic leukemia [abstract]. *Blood* 2011;118:Abstract 2592.
- 48 O'Brien S, Schiller G, Lister J, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. *J Clin Oncol* 2012;31:676-683.
- 49 Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J Clin Oncol* 2006;24:1917-1923.
- 50 Alkhateeb HB, Damlaj M, Lin T, et al. Clofarabine based chemotherapy in adult relapsed/refractory acute leukemia/lymphoma: a single institution. *Blood* 2015;126:4910.
- 51 Kantarjian H, Gandhi V, Cortes J, et al. Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. *Blood* 2003;102:2379-2386.
- 52 Kantarjian HM, Gandhi V, Kozuch P, et al. Phase I clinical and pharmacology study of clofarabine in patients with solid and hematologic cancers. *J Clin Oncol* 2003;21:1167-1173.
- 53 Miano M, Pistorio A, Putti MC, et al. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. *Leuk Lymphoma* 2012;53:1693-1698.
- 54 Hijiya N, Thomson B, Isakoff MS, et al. Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *Blood* 2011;118:6043-6049.
- 55 Kadia TM, Kantarjian HM, Thomas DA, et al. Phase II study of methotrexate, vincristine, pegylated-asparaginase, and dexamethasone (MOPAD) in patients with relapsed/refractory acute lymphoblastic leukemia. *Am J Hematol* 2015;90:120-124.
- 56 Specchia G, Pastore D, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. *Ann Hematol* 2005;84:792-795.
- 57 Giebel S, Krawczyk-Kulis M, Adamczyk-Cioch M, et al. Fludarabine, cytarabine, and mitoxantrone (FLAM) for the treatment of relapsed and refractory adult acute lymphoblastic leukemia. A phase study by the Polish Adult Leukemia Group (PALG). *Ann Hematol* 2006;85:717-722.
- 58 Weiss MA, Aliff TB, Tallman MS, et al. A single, high dose of idarubicin combined with cytarabine as induction therapy for adult patients with recurrent or refractory acute lymphoblastic leukemia. *Cancer* 2002;95:581-587.
- 59 Schiller G, Lee M, Territo M, Gajewski J, Nimer S. Phase II study of etoposide, ifosfamide, and mitoxantrone for the treatment of resistant adult acute lymphoblastic leukemia. *Am J Hematol* 1993;43:195-199.
- 60 DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood* 2007;109:5136-5142.
- 61 Zwaan CM, Kowalczyk J, Schmitt C, et al. Safety and efficacy of nelarabine in children and young adults with relapsed/refractory T-lineage acute lymphoblastic leukaemia or T-lineage lymphoblastic lymphoma: results of phase 4 study. *Br J Haematol* 2017;179:284-293.
- 62 Gökbüget N, Basara N, Baumann H, et al. High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. *Blood* 2011;118:3504-3511.

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

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

**PRINCIPLES OF SYSTEMIC THERAPY - REFERENCES**

- ⁶³ Candoni A, Lazzarotto D, Ferrara F, et al. Nelarabine as salvage therapy and bridge to allogeneic stem cell transplant in 118 adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoma. A CAMPUS ALL study. *Am J Hematol* 2020;95:1466-1472.
- ⁶⁴ Lusk MR, Ganetsky A, Landsburg DJ, et al. Nelarabine, cyclophosphamide and etoposide for adults with relapsed T-cell acute lymphoblastic leukemia and lymphoma. *BR J Haematol* 2016;174:332-334.
- ⁶⁵ Commander LA, Seif AE, Insogna IG, Rheingold SR. Salvage therapy with nelarabine, etoposide, and cyclophosphamide in relapsed/refractory paediatric T-cell lymphoblastic leukaemia and lymphoma. *Br J Haematol* 2010;150:345-351.
- ⁶⁶ Whitlock J, dalla Pozza L, Goldberg JM, et al. Nelarabine in combination with etoposide and cyclophosphamide is active in first relapse of childhood T-acute lymphocytic leukemia (T-ALL) and T-lymphoblastic lymphoma (T-LL). *Blood* 2014;124:795.
- ⁶⁷ Horton TM, Whitlock JA, Lu X, et al. Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group. *Br J Haematol* 2019;186:274-285.
- ⁶⁸ Ofra Y, Ringerstein-Harlev S, Sloukey I, et al. Daratumumab for eradication of minimal residual disease in high-risk advanced relapse of T-cell/CD19/CD22-negative acute lymphoblastic leukemia. *Leukemia* 2020;34:293-295.
- ⁶⁹ Ruhayel SD, Valvi S. Daratumumab in T-cell acute lymphoblastic leukemia: A case report and review of the literature. *Pediatr Blood Cancer* 2020;e28829.
- ⁷⁰ Cerrano M, Castella B, Lia G, et al. Immunomodulatory and clinical effects of daratumumab in T-cell acute lymphoblastic leukemia. *Br J Haematol* 2020;191:e28-e32.
- ⁷¹ Mirgh S, Ahmed R, Agrawal N, et al. Will daratumumab be the next game changer in early thymic precursor-acute lymphoblastic leukemia? *Br J Haematol* 2019;187:e33-e35.
- ⁷² Bonda A, Punatar S, Gokarn A, et al. Daratumumab at the frontiers of post-transplant refractory T-acute lymphoblastic leukemia-a worthwhile strategy? *Bone Marrow Transplant* 2018;53:1487-1489.
- ⁷³ Liedtke M, Dunn T, Dinner S, et al. Salvage therapy with mitoxantrone, etoposide and cytarabine in relapsed or refractory acute lymphoblastic leukemia. *Leuk Res* 2014;38:1441-1445.
- ⁷⁴ Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-Cell acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2020;20:212-218.
- ⁷⁵ Parovichnikova E, Gavrulina O, Troitskaya V, et al. Veneotoclax plus decitabine in the treatment of MRD-persistent and relapsed/refractory T-cell acute lymphoblastic leukemia. *European Hematology Association Congress* 2020;EP427.
- ⁷⁶ Rubnitz J, Alexander TB, Laetsch TW, et al. Venetoclax and navitoclax in pediatric patients with acute lymphoblastic leukemia and lymphoblastic lymphoma. *ASH Annual Meeting Abstracts* 2020;Abstract #466.
- ⁷⁷ Jain N, Stevenson KE, Winer ES, et al. A multicenter phase I study combining venetoclax with mini-hyper-CVD in older adults with untreated and relapsed/refractory acute lymphoblastic leukemia. *Blood* 2019;134:3867.

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PRINCIPLES OF SYSTEMIC THERAPY^a

Treatment of Older Adults (≥65 years) or Adults with Substantial Comorbidities

- Older adults (defined as those aged 65 years and older) benefit from therapy, in spite of higher treatment-related morbidity and mortality.
- Careful assessment of comorbid conditions, performance status, and ability to attend to activities of daily living (ADLs) and instrumental ADLs (IADLs) is important when deciding treatment intensity.
 - ▶ For tools to aid optimal assessment and management of older adults with cancer, see the [NCCN Guidelines for Older Adult Oncology](#).
- Dose reduction of pegylated asparaginase (1000 IU/m²), anthracycline (50% dose), and/or other myelosuppressive agents may be warranted.
- The categorization of regimens as low, moderate, or high intensity is based on two factors: 1) the presence or absence of myelosuppressive cytotoxic agents; and 2) the relative dose intensity of the included agents.
- All regimens should include CNS prophylaxis, antimicrobial prophylaxis, and growth factor support.
- For appropriate fit individuals achieving remission, consideration of autologous or reduced-intensity allogeneic SCT may be appropriate.

INDUCTION REGIMENS for Ph-negative ALL^f

- Low intensity
 - ▶ Vincristine + prednisone¹
 - ▶ Prednisone, vincristine, methotrexate, and 6-mercaptopurine (POMP)²
- Moderate intensity
 - ▶ GMALL: idarubicin + dexamethasone + vincristine + cyclophosphamide + cytarabine ± rituximab³
 - ▶ PETHEMA-based regimen⁴
 - ◊ ALLOLD07 regimen: vincristine, dexamethasone, idarubicin, cyclophosphamide, cytarabine, methotrexate, and L-asparaginase
 - ▶ GRAALL: doxorubicin + vincristine + dexamethasone + cytarabine + cyclophosphamide⁵
 - ▶ Modified DFCI 91-01 protocol: dexamethasone, doxorubicin, vincristine, methotrexate, cytarabine, L-asparaginase, and IT chemotherapy⁶
 - ▶ Inotuzumab ozogamicin + mini-hyperCVD for B-ALL (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine)⁷
- High intensity
 - ▶ Hyper-CVAD⁸ with dose-reduced cytarabine to 1 g/m²
 - ▶ CALGB 9111⁹ (cyclophosphamide, daunorubicin, vincristine, prednisone, and pegaspargase)

INDUCTION REGIMENS for Ph-positive B-ALL^f

- Low intensity
 - ▶ TKI^h ± corticosteroid^{10-13,14}
 - ▶ TKI^h + vincristine + dexamethasone¹⁵⁻¹⁷
- Moderate intensity
 - ▶ EWALL: TKI^h with multiagent chemotherapy (vincristine, dexamethasone, methotrexate, cytarabine, asparaginase)¹⁸
 - ▶ CALGB 10701: TKI^h + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, cytarabine)¹⁹
- High intensity^{20,21}
 - ▶ TKI^h + HyperCVAD with dose-reduced cytarabine to 1 g/m²

^a For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).

^h TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Dasatinib and imatinib are the preferred TKIs for induction therapy; ponatinib is also preferred for the hyper-CVAD regimen. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance and disease-related features. For contraindicated mutations, [see ALL-D 3 of 10](#).

^f For patients who develop hypersensitivity to E. coli-derived asparaginase, ERW or ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.

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

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

References

ALL-D
9 OF 10



PRINCIPLES OF SYSTEMIC THERAPY - Treatment of Older Adults (≥65 years) or Adults with Substantial Comorbidities

References

- ¹ Hardisty RM, McElwain TJ, and Darby CW. Vincristine and prednisone for the induction of remissions in acute childhood leukaemia. *Br Med J* 1969;2:662-665.
- ² Berry DH, Pullen J, George S, et al. Comparison of prednisolone, vincristine, mehtotrexate, and 6-mercaptopurine vs. vincristine and prednisone induction therapy in childhood acute leukemia. *Cancer* 1975;36:98-102.
- ³ Gokbuget N, Beck J, Bruggemann M et al. Moderate intensive chemotherapy including CNS prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): results of a prospective trial from the German multicenter study group for adult ALL (GMALL). *Blood* 2012;120:1493.
- ⁴ Ribera JM, Garcia O, Oriol A et al. PETHEMA group: Feasibility and results of subtype-oriented protocols in older adults and fit patients with acute lymphoblastic leukemia: results of three prospective parallel trials from the PETHEMA group. *Leuk Res* 2016;41:12-20.
- ⁵ Hunault-Berger M, Leguay T, Thomas X, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. *Haematologica* 2011;96(2):245-252.
- ⁶ Martell MP, Atenafu EG, Minden MD, et al. Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. *Br J Haematol* 2013;163:458-464.
- ⁷ Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2018;19:240-248.
- ⁸ O'Brien S, Thomas DA, Ravand F et al. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone in elderly patients with acute lymphocytic leukemia. *Cancer* 2008;113:2097-2101.
- ⁹ Larson RA, Dodge RK, Linker CA et al. A randomized control trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB 9111. *Blood* 1998;92:1556-1564.
- ¹⁰ Ottmann OG, Wassmann B, Pfeiffer H et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Ph-chromosome positive acute lymphoblastic leukemia. *Cancer* 2007;109:2068-2076.
- ¹¹ Foa R, Vitale A, Vignetti M, et al Dasatinib as first-line treatment for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Blood* 2011;118:6521-6528.
- ¹² Vignetti M, Fazi P, Cimino G et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell Adulto (GIMEMA) LAL0201-B protocol. *Blood* 2007;109:3676-3678.
- ¹³ Papayannidis C, Fazi P, Piciocchi A, et al. Treating Ph+ acute lymphoblastic leukemia (ALL) in the elderly: the sequence of two tyrosine kinase inhibitors (TKI) (nilotinib and imatinib) does not prevent mutations and relapse. *Blood* 2012;120:Abstract 2601.
- ¹⁴ Martinelli G, Piciocchi A, Papayannidis C, et al. First report of the GIMEMA LAL 1811 prospective study of the combination of steroids with ponatinib as frontline therapy of elderly or unfit patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2017;139:99.
- ¹⁵ Rousselot P, Coude MM, Gokbuget N et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. *Blood* 2016;128:774-82.
- ¹⁶ Rousselot P, Coude MM, Hugué F, et al. Dasatinib and low intensity chemotherapy for first-line treatment in patients with de novo Philadelphia Positive ALL aged 55 and over: final results of the EWALL-Ph-01 study [abstract]. *Blood* 2012;120:Abstract 666.
- ¹⁷ Rea D, Legros L, Raffoux E, et al. High-dose imatinib mesylate combined with vincristine and dexamethasone (DIV regimen) as induction therapy in patients with resistant Philadelphia-positive acute lymphoblastic leukemia and lymphoid blast crisis of chronic myeloid leukemia. *Leukemia* 2006;20:400-403.
- ¹⁸ Ottmann OG, Pfeifer H, Cayuela JM, et al. Nilotinib (Tasigna®) and low intensity chemotherapy for first-line treatment of elderly patients with BCR-ABL1-positive acute lymphoblastic leukemia: Final results of a prospective multicenter trial (EWALL-PH02). *Blood* 2018;132:Abstract 31.
- ¹⁹ Wieduwilt MJ, Jones BA, Schiller GJ, et al. A phase II study of pegylated asparaginase, cyclophosphamide, rituximab, and dasatinib added to the UCSF 8707 (linker 4-drug) regimen with liposomal cytarabine CNS prophylaxis for adults with newly diagnosed acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL): University of California Hematologic Malignancies Consortium Study (UCHMC) 1401. *Blood* 2018;132:4018.
- ²⁰ Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood* 2010;116:2070-2077.
- ²¹ Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol* 2015;16:1547-1555.

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

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



RESPONSE ASSESSMENT

Response Criteria for Blood and Bone Marrow:

- **CR**
 - ▶ No circulating lymphoblasts 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)**
 - ▶ Meets all criteria for CR except platelet count or ANC
- **Overall response rate (ORR = CR + CRi)**
- **NOTE:** MRD assessment is not included in morphologic assessment and should be obtained ([see ALL-F](#))
- **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-B](#)) 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 without another explanation.

Response Criteria for Lymphomatous Extramedullary Disease:

- **CT of neck/chest/abdomen/pelvis with IV contrast and PET/CT** should be performed to assess response for extramedullary disease.
- **CR:** Complete resolution of lymphomatous enlargement by CT. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
- **PR:** >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.
- **PD:** >25% increase in the SPD of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.
- **No Response (NR):** Failure to qualify for PR or PD.
- **Relapse:** Recurrence of mediastinal enlargement after achieving CR. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

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

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

**MINIMAL/MEASURABLE RESIDUAL DISEASE ASSESSMENT**

- The preferred sample for MRD assessment is the first small volume (of up to 3 mL) pull of the bone marrow aspirate, if feasible.
- 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 validated MRD assessment technology with appropriate sensitivity (at least 10^{-4}) is not available locally, there are commercially available tests.
- 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.¹
- The most frequently employed methods for MRD assessment include at least 6-color flow cytometry assays^{2,3} specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (eg, *BCR-ABL1*), and NGS-based assays, to detect clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes.
- Current 6-color flow cytometry can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ ($<0.01\%$) bone marrow mononuclear cells (MNCs).^{2,3} PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-6}$ ($<0.0001\%$) bone MNCs.^{4,5} The concordance rate for detecting MRD between these methods is generally high. Methods not achieving these sensitivity levels are not suitable.
 - ▶ For flow cytometric analysis of MRD, notify lab performing the MRD assessment if immunotherapy (such as rituximab, blinatumomab, inotuzumab ozogamicin, or tisagenlecleucel) has been used.
 - ▶ Timing of MRD assessment:
 - ◊ Upon completion of initial induction.
 - ◊ Additional time points should be guided by the regimen used.
 - ◊ Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.
 - ◊ For some techniques, a baseline sample may be needed or helpful for the MRD assessment to be valid.

¹ Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult lymphoblastic leukemia. *JAMA Oncol* 2017;3:e170580.

² Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. *Haematologica* 2012;97(10):1582-1593.

³ Denys B, van der Sluijs-Gelling AJ, Homburg C, et al. Improved flow cytometric detection of minimal residual disease in childhood acute lymphoblastic leukemia. *Leukemia* 2013;27:635-641.

⁴ 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.

⁵ 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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 indicated.

NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Discussion

This discussion corresponds to the NCCN Guidelines for Acute Lymphoblastic Leukemia. Last updated: 07/19/2021.

Table of Contents

Overview	MS-2
Literature Search Criteria and Guidelines Update Methodology	MS-2
Diagnosis	MS-3
Clinical Presentation and Diagnosis	MS-3
Immunophenotyping	MS-4
Cytogenetic and Molecular Subtypes	MS-5
Table 1: Common Chromosomal and Molecular Abnormalities in ALL	MS-6
Workup	MS-7
Prognostic Factors and Risk Stratification	MS-8
Prognostic Factors in AYA Patients with ALL	MS-8
Prognostic Factors in Adults with ALL	MS-9
NCCN Recommendations for Risk Assessment in ALL	MS-11
Overview of Treatment Phases in ALL Management	MS-11
Induction	MS-12
CNS Prophylaxis and Treatment	MS-12
Consolidation	MS-13
Hematopoietic Stem Cell Transplantation	MS-13
Maintenance	MS-13
Targeted Agents	MS-14
Management of Ph-Positive ALL	MS-14
Initial Treatment in AYA Patients with Ph-Positive ALL	MS-14

Initial Treatment in Adults with Ph-Positive ALL	MS-18
Treatment of Relapsed Ph-Positive ALL	MS-22
NCCN Recommendations for Ph-Positive ALL	MS-25
Management of Ph-Negative ALL	MS-27
Initial Treatment in AYA Patients with Ph-Negative ALL	MS-27
Initial Treatment in Adults with Ph-Negative ALL	MS-34
Treatment of Relapsed Ph-Negative ALL	MS-37
NCCN Recommendations for Ph-Negative ALL	MS-43
Management of Lymphoblastic Lymphoma	MS-45
Evaluation and Treatment of Extramedullary Disease	MS-46
CNS Involvement in ALL	MS-46
NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement	MS-47
Response Assessment and Surveillance	MS-48
Response Criteria	MS-48
Surveillance	MS-48
Role of MRD Evaluation	MS-49
MRD Assessment in Childhood ALL	MS-49
MRD Assessment in Adult ALL	MS-52
NCCN Recommendations for MRD Assessment	MS-54
Supportive Care for Patients with ALL	MS-55
NCCN Recommendations for Supportive Care	MS-55
References	MS-60



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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 focus on the classification of ALL subtypes based on immunophenotype and cytogenetic/molecular markers; risk assessment and stratification for risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)–positive and Ph-negative ALL for both adolescent and young adult (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 heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.¹ The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year,² with approximately 5,690 new cases and 1,580 deaths estimated in 2021.³ The median age at diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years of age.² In contrast, 29.6% of cases are diagnosed at 45 years or older and only approximately 13.7% of patients are diagnosed at 65 years or older.² 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.^{1,4}

Risk factors for developing ALL include older age (>70 years), exposure to chemotherapy or radiation therapy, and genetic disorders, particularly Down syndrome.^{5,6} Although rare, other genetic conditions have been categorized as a risk factor for ALL and include Li–Fraumeni syndrome,⁷

neurofibromatosis,⁸ Klinefelter syndrome,⁹⁻¹¹ Fanconi anemia,^{12,13} Shwachman-Diamond syndrome,^{14,15} Bloom syndrome,¹⁶ and ataxia telangiectasia.¹⁷

The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children.¹⁸ Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of minimal residual disease (MRD) testing, the refinement of risk-adapted treatment algorithms, the advent of new targeted agents, and the use of allogeneic hematopoietic stem cell transplantation (HCT).

Analyses from the SEER database have shown improvements in survival for children and AYA patients with 5-year overall survival (OS) rates of 89% and 61%, respectively.^{18,19} However, survival rates for adult patients remain low at approximately 20% to 40%.²⁰⁻²² Survival rates are especially poor in older adult patients at approximately 20%.^{21,23,24} Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA, and adult patients, the trend is nonetheless clear that OS decreases substantially with increased age.²¹ The exception is infants younger than age 1, which is an age group that has not seen any improvement in survival over the last 30 years. The 5-year OS in this population is 55.8%¹⁸ (see *Cytogenetic and Molecular Subtypes*). Cure rates for AYAs with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the adoption of pediatric treatment regimens.²⁵ AYA patients represent a unique population, because they may receive treatment based on either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. Favorable cytogenetic subtypes, such as *ETV6-RUNX1* ALL and hyperdiploidy, occur less frequently among AYA patients compared with children, whereas the



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

incidence of ALL in high-risk subgroups such as *BCR-ABL* (Ph-positive ALL) or with Ph-like ALL²⁶ is higher in AYA patients.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Acute Lymphoblastic Leukemia, an electronic search of the PubMed database was performed to obtain key literature published in the field since the previous Guidelines update, using the following search terms: acute lymphoblastic leukemia, B-cell acute lymphoblastic anemia, and T-cell acute lymphoblastic anemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.²⁷

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, II; Clinical Trial, III; Clinical Trial, IV; Guideline; Meta-Analysis; Multicenter Study; Randomized Controlled Trial; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis

Clinical Presentation and Diagnosis

The clinical presentation of ALL is typically nonspecific, and may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or

bleeding.^{1,28} Among children, pain in the extremities or joints may be the only presenting symptom.¹ 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 (B-ALL).^{1,28}

The diagnosis of ALL generally requires demonstration of 20% or greater bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. Peripheral blood may be substituted for bone marrow provided there is a significant amount of circulating disease,^{29,30} with the NCCN ALL Panel suggesting a general guide of greater than or equal to 1,000 circulating lymphoblasts per microliter. The 2008 WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease.^{31,32} 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.^{31,32} Lymphoblastic lymphoma was previously categorized with non-Hodgkin lymphoma and is associated with exposure to radiation or pesticide and congenital or acquired immunosuppression. However, based on morphologic, genetic, and immunophenotypic features, lymphoblastic lymphoma is indistinguishable from ALL. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens versus traditional lymphoma therapy and should be treated in a center that has experience with lymphoblastic lymphoma (see *Management of Lymphoblastic Lymphoma*).

Hematopathology evaluations should include morphologic examination of malignant lymphocytes using Wright-Giemsa–stained slides and hematoxylin and eosin–stained core biopsy and clot sections;



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

comprehensive immunophenotyping with flow cytometry (see *Immunophenotyping*); and baseline flow cytometric and/or molecular characterization of leukemic clone(s) to facilitate subsequent analysis of MRD.

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-ALL with recurrent genetic abnormalities include the following: hyperdiploidy (51–65 chromosomes); hypodiploidy (<44 chromosomes); t(9;22)(q34;q11.2), *BCR-ABL1*; t(4;11) and other *KMT2A rearranged*, t(v;11q23); t(12;21)(p13;q22), *ETV6-RUNX1*; t(1;19)(q23;p13.3), *TCF3-PBX1*; and t(5;14)(q31;q32), *IL3-IGH*.³³ During the 2016 WHO classification update, two new provisional entities were added to the B-ALL classification: B-lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases or cytokine receptors (*BCR-ABL1*-like ALL or Ph-like ALL)^{34,36} and B-lymphoblastic leukemia/lymphoma with *intrachromosomal amplification of chromosome 21 (iAMP21)*.^{34,37} Two new provisional entities were also added to T-cell ALL (T-ALL): early T-cell precursor (ETP) lymphoblastic leukemia and natural killer (NK) cell lymphoblastic leukemia/lymphoma.³⁴ The Ph-like ALL, B-ALL with *iAMP21* and ETP T-ALL subtypes are no longer considered provisional entities.

Presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics), and interphase fluorescence in situ hybridization (FISH) assays that include probes capable of detecting the genetic abnormalities and/or reverse transcriptase-polymerase chain reaction (RT-PCR) testing, using qualitative or quantitative methods, to measure transcript sizes (ie, p190 vs. p210) of *BCR-ABL1* in B-ALL. If samples are *BCR-ABL1/Ph*-negative or Ph-like, comprehensive testing by next-generation sequencing (NGS) for other gene fusions and pathogenic mutations associated with

Ph-like ALL is recommended. In cases of aneuploidy or failed karyotype, additional assessment may include chromosomal microarray (CMA)/array comparative genomic hybridization (aCGH). The translocation t(12;21)(p13;q22) is typically cryptic by karyotyping and requires FISH or PCR to be identified.

Immunophenotyping

Immunophenotypic classification of ALL involves flow cytometry to determine the presence of cell surface antigens on lymphocytes. ALL can be broadly classified into three groups based on immunophenotype, which include precursor B-ALL, mature B-ALL, and T-ALL.^{1,38} Among children, B-cell lineage ALL constitutes approximately 88% of cases;³⁹ in adult patients, subtypes of B-cell lineage ALL represent approximately 75% of cases (including mature B-ALL that constitutes 5% of adult ALL), whereas the remaining 25% comprise T-cell lineage ALL.^{39,40} Within the B-cell lineage, the profile of cell surface markers differs according to the stage of B-cell maturation, which includes early precursor B-cell (early pre-B-cell), pre-B-cell, and mature B-ALL. Early pre-B-ALL is characterized by the presence of terminal deoxynucleotidyl transferase (TdT), the expression of CD19/CD22/CD79a, and the absence of CD10 (formerly termed *common ALL antigen*) or surface immunoglobulins. CD10 negativity correlates with *KMT2A* rearrangement and poor prognosis.^{41,42} Pre-B-ALL is characterized by the presence of cytoplasmic immunoglobulins and CD10/CD19/CD22/CD79a expression^{1,28,31,40} and was previously termed common B-ALL due to the expression of CD10 at diagnosis. Mature B-ALL shows positivity for surface immunoglobulins and clonal lambda or kappa light chains, and is negative for TdT.¹ The definition of CD20 positivity is unclear, though most studies use 20% or greater of blasts expressing CD20.⁴³ 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-ALL.^{43,44}



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

T-cell lineage ALL is typically associated with the presence of cytoplasmic CD3 (T-cell lineage blasts) or cell surface CD3 (mature T cells) in addition to variable expression of CD1a/CD2/CD5/CD7 and expression of TdT.^{1,28,32} CD52 may be expressed in 30% to 50% of T-cell lineage ALL in adults.¹ Combined data from the German Multicenter Study Group for Adult ALL (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-ALL.³⁸ The latter is further divided between ETP ALL and early immature T-ALL. Early immature T-ALL includes both pro-T-ALL and pre-T-ALL immunophenotypes.

ETP ALL represents a distinct biologic subtype of T-cell lineage ALL that accounts for 12% of pediatric T-ALLs (and about 2% of ALL), and is associated with poor clinical outcomes even with contemporary treatment regimens. This subtype is characterized by the absence of CD1a/CD8, weak expression of CD5 (<75% positive lymphoblasts), and the presence of 1 or more myeloid or stem cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65) on at least 25% of lymphoblasts.⁴⁵ In a study of 239 patients with T-ALL, gene expression profiling, flow cytometry, and single nucleotide polymorphism array analysis were employed to identify patients with ETP-ALL.⁴⁵ ETP-ALL was associated with a 10-year OS of 19% (95% CI, 0%–92%) compared with 84% (95% CI, 72%–96%) in the non-ETP-ALL patients. The 10-year event-free survival (EFS) was similarly poor in patients with ETP-ALL (22%; 95% CI, 5%–49%) compared with non-ETP-ALL patients (69%; 95% CI, 53%–84%). Remission failure and hematologic relapse were significantly higher for patients with ETP-ALL ($P < .0001$).⁴⁵

A pivotal study from Zhang et al⁴⁶ 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 other subtypes of ALL, suggesting that myeloid-derived therapies and targeted therapy may be better treatment options for select ALL subtypes. The data indicate a need for alternative treatments to standard intensive chemotherapy in this subpopulation. Due to the nature of ETP-ALL, myeloablative therapy followed by HCT in first remission may be an alternative. This regimen had previously demonstrated superior results for patients with T-ALL and poor early responses.⁴⁷

Hematologic malignancies related to ALL include acute leukemias with ambiguous lineage, such as the mixed phenotype acute leukemias (MPALs). MPALs include bi-lineage leukemias, in which two distinct populations of lymphoblasts are identified, with one meeting the criteria for acute myeloid leukemia. Bi-phenotypic MPAL is defined as a single population of lymphoblasts that expresses markers consistent with B-cell or T-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, nor is it associated with adverse prognosis.^{31,32} The identification of mixed lineage leukemias should follow the criteria presented in the 2008 WHO classification of neoplasms, which did not change with the 2016 update.³⁴ The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype that may include expression of non-lineage 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 differs between adult and



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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.^{39,48} The *ETV6-RUNX1* subtype (also within the B-cell lineage) resulting from chromosomal translocation t(12;21) is among the most commonly occurring subtypes in childhood ALL (22%) compared to adults (2%).³⁹ Both hyperdiploidy and *ETV6-RUNX1* subtypes are associated

Table 1: Common Chromosomal and Molecular Abnormalities in ALL

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>ETV6-RUNX1</i> (<i>TEL-AML1</i>)	2%	22%
t(v;11q23) [eg, t(4;11) and others], t(11;19)	<i>KMT2A</i> rearranged	10%	8%
t(1;19)(q23;p13)	<i>TCF3-PBX1</i> (<i>E2A-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</i> ^a	12%	7%
t(10;14)(q24;q11)	<i>HOX11</i> (<i>TLX1</i>) ^a	8%	1%
t(5;14)(q35;q32)	<i>HOX11L2</i> ^a	1%	3%
t(11;14)(q11) [eg, (p13;q11), (p15;q11)]	<i>TCRα</i> and <i>TCRδ</i>	20%–25%	10%–20%
<i>BCR-ABL1</i> –like/Ph–like	various ^b	10%–30%	15%

B-ALL with <i>iAMP21</i>	<i>RUNX1</i>	--	2%
ETP	various ^b	2%	2%
Ikaros	<i>IKZF1</i>	25%–35%	12%–17%

^aAbnormalities observed exclusively in T-cell lineage ALL; all others occur exclusively or predominantly in B-cell lineage ALL. ^bSee text for more details.

with favorable outcomes in ALL.^{48–50} Ph-positive ALL, which has been historically associated with poor prognosis, is relatively uncommon among childhood ALL (3%), whereas this abnormality is the most common subtype among older adults (25%).³⁹ The frequency of Ph-positive ALL increases with age (10%, patients 15–39 years; 25%, patients 40–49 years; 20%–40%, patients >50 years).^{49,51–53} Moreover, younger children (1–9 years) with Ph-positive ALL have a better prognosis than adolescents with this subtype.⁵⁴

BCR-ABL1–like or Ph–like ALL is a subgroup of B-cell lineage ALL associated with unfavorable prognosis.^{35,36} A study using gene expression signatures to classify pediatric patients with ALL into subtypes estimated the 5-year disease-free survival (DFS) in the *BCR-ABL1*–like ALL group to be 60%.³⁵ In adult patients with *BCR-ABL1*–like ALL, the 5-year EFS is significantly lower (22.5%; 95% CI, 14.9%–29.3%) compared to patients with non-*BCR-ABL1*–like ALL (49.3%; 95% CI, 42.8%–56.2%).³⁶ 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.⁵⁵ Genomically, this subtype is typically associated with gene fusions and mutations that activate tyrosine kinase pathways as the common mechanism of transformation. These gene fusions and mutations include *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK1*, *JAK2*, *JAK3*, *TYK2*, *PDGFRβ*, *PDGFRα*, *FGFR*, *EBF1*, *FLT3*, *IL7R*, *NTRK3*, *PTL2B*, and *SH2B3* genes.^{35,55–59} A genomic profiling study found kinase-activating alternations in 91% of Ph-like ALL cases,⁵⁶ suggesting potential for



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

ABL-class tyrosine kinase inhibitors (TKIs) or other targeted therapies to significantly improve patient outcomes in this subgroup.⁶⁰

B-ALL with *iAMP21* is characterized by amplification of a portion of chromosome 21, detected by FISH with a probe for the *RUNX1* gene.^{61,62} Occurring in approximately 2% of children with ALL, B-ALL with *iAMP21* is associated with adverse prognosis.^{61,62} Children with *iAMP21* are typically older, with a median age of 9 years, and have low platelet counts and low white blood cell (WBC) counts.⁶³

Other cytogenetic and molecular subtypes are associated with ALL and prognosis. Although not as common, translocations in the *KMT2A* gene [in particular, cases with t(4;11) translocation] are known to have poor prognosis.^{25,44} Hypodiploidy, alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone, is associated with poor prognosis and is observed in 1% to 2% of patients.^{25,64} Low hypodiploidy (30–39 chromosomes)/near triploidy (60–68 chromosomes) and complex karyotype (≥5 chromosome abnormalities) are also associated with poor prognosis, and occur more frequently with increasing age (1%–3%, patients 15–29 years; 3%–6%, patients 30–59 years; 5%–11%, patients >60 years).⁴⁹ Of note, low hypodiploidy is associated with a high frequency of *TP53* alterations.^{65,66} In addition, masked hypodiploidy, which results from a doubling of hypodiploid clones, needs to be distinguished from true hyperdiploidy to allow appropriate treatment selection.⁶⁷

In B-ALL, mutations in the Ikaros gene (*IKZF1*) are associated with a poor prognosis and a greater incidence of relapse.⁶⁸ *IKZF1* mutations are seen in approximately 15% to 20% of pediatric B-ALL^{69,70} and at a higher frequency of greater than 75% in patients who are also *BCR-ABL* positive.^{55,70,71} Incidence in adults is about 25% to 35% in B-ALL⁷²⁻⁷⁵ and about 65% in patients who are *BCR-ABL* positive.^{76,77} A study evaluating

the relationship between *BCR-ABL1*-like and *IKZF1* in children with B-cell precursor ALL showed that 40% of cases had co-occurrence of these mutations.⁷⁸ The presence of either mutation was indicative of poor prognosis and was independent of conventional risk factors.⁷⁹ Both mutations are considered strong independent risk factors for B-ALL and are applicable across a broad range of stratified ALL including patients with intermediate MRD.

Workup

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

All patients should be evaluated for opportunistic infections as appropriate (see [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#)). In addition, an echocardiogram or multigated acquisition (MUGA) scan should be obtained for all patients due to the use of



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

anthracyclines as the backbone of nearly all treatment regimens.

Assessment of cardiac function is particularly important for patients with prior cardiac history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction, and for elderly patients. An early transplant evaluation and donor search should be strongly considered.

Appropriate imaging studies (eg, CT/MRI scan of the head with contrast) should be performed to detect meningeal disease, 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; the NCCN ALL Panel recommends that the first lumbar puncture be performed at the time of initial scheduled intrathecal therapy unless directed by symptoms to perform earlier (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 on clinical symptoms. Procurement of cells should be considered for purposes of future research (in accordance with institutional practices or policies).

Prognostic Factors and Risk Stratification

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

Prognostic Factors in AYA Patients with ALL

In 1993, a common set of risk criteria was established by the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) at an international conference hosted by the NCI.⁸⁰ In this system, two risk groups were designated: standard risk and high risk. Standard risk was assigned to patients age 1 to younger than 10 years of age and with a WBC count less than 50×10^9 cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk.⁶⁴ It should be noted that despite exclusion from this report, patients younger than age 1 should also be considered very high risk.^{81,82} The POG and CCG have since merged to form the Children's Oncology Group (COG) and subsequent risk assessment has produced additional risk factors, particularly in precursor B-ALL, to further refine therapy. Specifically, in B-ALL, a group identified as very high risk was defined as patients with any of the following characteristics: t(9;22) chromosomal translocation (ie, Ph-positive ALL) and/or presence of *BCR-ABL1* fusion protein; hypodiploidy (<44 chromosomes);⁸³ *BCR-ABL1*-like or Ph-like ALL;⁸⁴ *iAMP21*;⁸² or failure to achieve remission with induction therapy.^{25,64} *KMT2A* rearrangements and a poor response to induction chemotherapy also re-categorized patients into this group.⁸⁵⁻⁸⁷ Conversely, criteria were refined for lower risk and included patients with hyperploidy, the t(12;21) chromosomal translocation (*ETV6-RUNX1* subtype),⁸⁸ or simultaneous trisomies of chromosomes 4, 10, and 17.^{64,89} Presence of extramedullary disease and the early response to treatment also modified risk. Early marrow response to therapy was a strong positive prognostic factor while the presence of extramedullary disease at diagnosis was correlated with a poorer prognosis. Using the refined risk assessment, four risk categories for B-ALL, designated as low risk, standard risk, high risk, and very high risk, were identified encompassing 27%, 32%, 27%, and 4% of cases, respectively.⁶⁴



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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

Historically, the AYA population has been treated on either a pediatric or an adult ALL regimen, depending on referral patterns and the institution. In recent years, several retrospective studies from both the United States and Europe have shown that AYA patients (15–21 years of age) treated on a pediatric protocol have substantially improved EFS compared to same-aged patients treated on adult ALL regimens.^{25,50} Comparison of adult and pediatric protocols has shown that adults received lower doses of nonmyelosuppressive chemotherapy and less intense intrathecal chemotherapy regimens.^{90,91} Adult protocols also are more likely to include allogeneic HCT compared to pediatric protocols, but the benefits of HCT in the AYA population have not been sufficiently studied, and the available data include conflicting findings.⁹²⁻⁹⁶ There is clearly a significant difference between the way adults and pediatric patients are treated and this may be a variable in the treatment of AYA patients. Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.

Despite improved outcomes for AYA patients treated on pediatric-inspired regimens versus adult ALL regimens, studies have shown poorer outcomes among patients in the AYA group compared with children younger than 10 years.⁹⁷ 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 *ETV6-RUNX1*,⁹⁸ and a greater incidence of poor-risk cytogenetics

including Ph-positive ALL, Ph-like ALL, hypodiploidy, and complex karyotype,⁹⁹ and a higher incidence of ETP-ALL.^{45,100} Furthermore, the positive prognostic values of the *ETV6-RUNX1* mutation and hyperdiploidy are greater in the patients less than 10 years of age, suggesting that the benefits decline with age.⁹⁹ The effects of 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 older than 10 years are more resistant to chemotherapy compared to the cells from children younger than 10 years.¹⁰¹ The COG AALL0232 study reported an initial delay in response to induction therapy in older AYA patients (aged 16–30 years) compared to younger patients (aged 1–15 years).¹⁰² There was a statistically significant reduction in the number of patients in the older cohort who had negative end-induction MRD compared to the younger cohort (59% vs. 74%; $P < .0001$) with fewer patients achieving M1 marrow on day 15 of induction (67% vs. 80%, respectively; $P = .0015$). 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;¹⁰³ however, only 2% of AYA patients enroll in clinical trials compared to the 60% enrollment of pediatric patients.¹⁰⁴ Pediatric patients have been shown to be more compliant with treatment protocols compared to AYA patients,¹⁰⁵ which may be due to greater parental supervision of the treatment and better insurance.¹⁰⁶

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.^{38,44} Early prospective multicenter studies defined values for older age (>35 years) and higher initial WBC count ($>30 \times 10^9/\text{L}$ for B-cell lineage; $>100 \times 10^9/\text{L}$ for T-cell lineage) that were predictive of significantly decreased remission duration.^{107,108} Subsequent studies have confirmed the prognostic importance of these clinical parameters, although the cutoff values differed between studies.^{38,44}



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

In one of the largest studies to date ($n = 1521$) conducted by the Medical Research Council (MRC) UKALL/ Eastern Cooperative Oncology Group (ECOG), both age (>35 years) and WBC count ($>30 \times 10^9/L$ for B-cell lineage; $>100 \times 10^9/L$ for T-cell lineage) were found to be significant independent prognostic factors for decreased DFS and OS among patients with Ph-negative ALL; the independent prognostic value remained significant when these factors were evaluated as continuous variables in multivariate analysis.¹⁰⁹ All patients, regardless of Ph status, had received induction therapy followed by intensification (for patients with a complete response [CR] postinduction) with contemporary chemotherapy combination regimens. Patients with a CR after induction received allogeneic HCT (for patients <50 years of age and with HLA-compatible siblings), autologous HCT, or consolidation/maintenance treatment. Because Ph-positive ALL is associated with a very poor prognosis, patients with this subtype were assigned to undergo allogeneic HCT (including matched, unrelated donor [URD] HCT) when possible. The 5-year OS rate among patients with Ph-positive and Ph-negative disease was 25% and 41%, respectively.¹⁰⁹ Among 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.¹⁰⁹ 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.¹⁰⁹

In a subsequent analysis from this MRC UKALL XII/ECOG E2993 study, cytogenetic data were evaluated in approximately 1000 patients.¹¹⁰ 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%; $P < .001$, adjusted for age, gender, and WBC count). Among patients with Ph-negative disease, the following cytogenetic subgroups had significantly decreased 5-year EFS (13%–24%) and OS rates (13%–28%) based on univariate analysis: $t(4;11)$ *KMT2A* translocation, $t(8;14)$, complex karyotype (≥ 5 chromosomal abnormalities), and low hypodiploidy (30–39 chromosomes)/near triploidy (60–78 chromosomes).¹¹⁰ 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%).¹¹⁰ 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.¹¹¹ Based on multivariate Cox regression analysis reported in the MRC UKALL XII/ECOG E2993 study, $t(8;14)$, low hypodiploidy/near triploidy, and complex karyotype remained significant independent predictors for risk of relapse or death; the prognostic impact of these cytogenetic markers was independent of factors such as age, WBC count, or T-cell immunophenotype, and their significance was retained even after excluding patients who had undergone postinduction HCT.¹¹⁰

The importance of cytogenetics as a prognostic factor for survival outcomes was shown in other studies, including the Southwest Oncology Group (SWOG) study conducted with 200 adult patients with ALL.¹¹² 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,



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

cytogenetics remained a significant independent predictor of outcomes, whereas factors such as age and WBC count lost prognostic significance.¹¹² 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) *KMT2A* (*MLL*) translocation; t(8;14); complex karyotype; or low hypodiploidy] had substantially decreased 5-year RFS and OS rates (22%, for both endpoints). Analysis by ploidy status was not possible because only two 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.¹¹²

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.

The NCI defines the age range for AYA patients as 15 to 39 years. For Ph-positive ALL, the AYA patient population is grouped with fit, adult patients aged less than 65 years. However, additional considerations for the management of ALL in AYA can be found in the [NCCN Guidelines for Adolescent and Young Adult \(AYA\) Oncology](#). For Ph-negative ALL, the AYA patient population is considered separately from the adult population (defined as age ≥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. 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. In the NCCN Guidelines for ALL, specific age references are not included for AYA and adult categories, considering that age is not a firm reference point and some of the recommended regimens have not been comprehensively tested across all ages.

AYA patients and adult patients younger than 65 years of age (or for those with no substantial comorbidities) with Ph-negative ALL can be further categorized as having high-risk disease, which may be particularly helpful when consolidation with allogeneic HCT is being considered. Patients may be considered high risk if they have positive MRD, an elevated WBC count ($\geq 30 \times 10^9/L$ for B-cell lineage; $\geq 100 \times 10^9/L$ for T-cell lineage), or presence of poor-risk cytogenetics as previously defined. The absence of all poor-risk factors is considered standard risk. Evaluation of WBC count and age for determination of prognosis should ideally be made in the context of treatment protocol-based risk stratification. 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, studies in adult patients have demonstrated that WBC counts may lose independent prognostic significance when cytogenetic factors and MRD assessments 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 and likely superseded by MRD quantification after treatment. 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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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 (BFM) group 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 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.^{1,25,38,44,50}

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.¹¹³⁻¹¹⁷ Some studies from the CALGB group have utilized a 5-drug regimen, which adds cyclophosphamide to the above 4-drug combination.¹¹⁸ 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.^{119,120} The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of dexamethasone into the CNS.¹²¹ In a meta-analysis comparing outcomes with dexamethasone versus prednisone in induction regimens for childhood ALL, dexamethasone was associated with a significantly

reduced event rate (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).¹²² 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.¹²² Although dexamethasone was reported to reduce the 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 the CALGB regimen, and comprises eight alternating treatment cycles with the “A” regimen (hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and the “B” regimen (high-dose methotrexate and cytarabine).^{20,123,124} CNS prophylaxis and/or CNS-directed treatment (which may include intrathecal chemotherapy, cranial irradiation, and/or systemic therapy for patients with CNS leukemia at diagnosis) and maintenance treatment are also used with the hyper-CVAD regimen (see *CNS Prophylaxis and Treatment and Maintenance*).

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 systemic chemotherapy (eg, high-dose methotrexate, intermediate-/high-dose cytarabine, L-asparaginase).^{1,50,121} CNS



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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. Methotrexate, cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, vincristine, corticosteroids, and L-asparaginase are frequently incorporated into consolidation/intensification regimens.^{28,38,44,50,116,117}

Hematopoietic Stem Cell Transplantation

As part of postremission consolidative therapy, the decision to proceed with allogeneic/autologous HCT or prolonged maintenance are mutually exclusive approaches in ALL therapy. Each case will need to be individualized based on disease setting and features. Allogeneic HCT is more likely to be a primary part of post-consolidative therapy in AYA and adult patients with evidence of high-risk features (including Ph-positivity, Ph-like disease, or persistent MRD). Notably, while younger patients may experience lower transplant-related mortality, older age is by itself not a contraindication. For this reason, HLA typing and bone marrow transplant referral should be considered for all newly diagnosed and relapsed transplant-naïve patients to facilitate timely donor identification, and ultimately allogeneic transplant if warranted.

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 to 3 years.^{25,38,44,50} Maintenance therapy is omitted for patients with mature B-ALL (see the [NCCN Guidelines for B-Cell Lymphomas](#): Burkitt Lymphoma), given that long-term remissions are seen early with short courses of intensive therapy in these patients, with relapses rarely occurring beyond 12 months.^{38,125}

Factors that affect the bioavailability of 6-MP can significantly impact patient care. Oral 6-MP can have highly variable drug and metabolite concentrations among patients.^{126,127} Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.¹²⁸⁻¹³⁰ The concomitant use of other chemotherapeutic agents such as methotrexate can alter toxicity.¹³¹ The efficacy of maintenance therapy is determined by the metabolism of 6-MP to the antimetabolite chemotherapeutic agent 6-thioguanine nucleotide (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-guanine phosphoribosyltransferase (HPRT), and thiopurine methyltransferase (TPMT). Because 6-MP is administered orally, it can be converted to an inactive metabolite in the intestinal mucosa and liver.^{132,133} Diet has been shown to affect absorption of 6-MP.^{134,135} 6-MP can undergo thiol methylation by TPMT. 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.¹³⁶ Compared to the wild-type TPMT phenotype, patients who are homozygous TPMT-deficient require a 10- to 15-fold reduction in 6-MP to alleviate hematopoietic toxicity.^{137,138} Heterozygosity at the *TPMT* gene locus occurs in 5% to 10% of the population and has been shown to have intermediate enzyme



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

activity.^{136,139,140} Therefore, a 10% to 15% reduction in 6-MP dose is necessary in these patients to prevent toxicity.^{141,142} Determination of patient TPMT genotype using genomic DNA is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses.¹⁴³⁻¹⁴⁵

Dose reductions may be necessary if patients have genetic polymorphisms and/or hepatotoxicity, whereas dose escalation may be necessary in patients who fail to demonstrate myelosuppression. This should be performed in accordance with the protocol being used. In general, 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. In 2014, the FDA approved an oral suspension of 6-MP, which may be more amenable to dose adjustments than the tablet form.¹⁴⁶ This may be especially beneficial for dose adjustment in pediatric patients.¹⁴⁷ Outcomes are better in patients who achieve myelosuppression during maintenance compared with patients who have higher neutrophil counts,^{105,148} emphasizing the need for optimal dosing of 6-MP.

Noncompliance also results in undertreatment, particularly in the AYA population. Compliance issues should be addressed for patients without cytopenia. If increasing doses of 6-MP are given during maintenance but no drop in the counts is observed, this may be indicative of noncompliance.¹³¹ Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to non-compliance or hypermetabolism.

Targeted Agents

The emergence of targeted therapies for hematologic malignancies, including the treatment of Ph-positive disorders with TKIs, including imatinib, dasatinib, nilotinib, ponatinib, and bosutinib represents an important advancement in ALL therapy.¹⁴⁹⁻¹⁵⁷ Incorporation of TKIs into

treatment regimens should include evaluation of clinical pharmacokinetics.¹⁵⁸ Clinicians should be aware of variation among the TKIs relating to absorption from the gastrointestinal tract. Additionally, histamine-2 antagonist or proton pump inhibitors can affect the bioavailability of some TKIs.

Other targeted agents include an anti-CD20 monoclonal antibody (eg, rituximab) for CD20-expressing B-cell lineage ALL (especially for mature B-ALL).^{159,160} In addition, the purine nucleoside analog nelarabine has been approved for the treatment of relapsed/refractory (R/R) T-cell lineage ALL or lymphoblastic lymphoma.¹⁶¹⁻¹⁶³ These agents may be incorporated as part of frontline induction, consolidation, and/or maintenance regimens during the course of initial ALL therapy, and in the relapsed or refractory disease settings.

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.³⁹ The frequency of Ph-positive ALL among AYA patients ranges from 5% to 25% and increases with age,^{110,117} although this subtype is still uncommon relative to the incidence in older adults. Historically, children and adolescents with Ph-positive disease had a poorer prognosis compared with patients with Ph-negative B-ALL. However, recent improvements in the treatment options are closing this gap.

Hematopoietic Cell Transplant

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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

This study showed that allogeneic HCT from a matched related donor offered improvements in outcomes over chemotherapy alone.

In a subsequent analysis of outcomes in children with Ph-positive ALL treated between 1995 and 2005 but also without targeted TKIs, the 7-year EFS and OS rates were 32% and 45%, respectively.¹⁶⁴ Outcomes with allogeneic HCT from either matched related donors or URDs appeared similar, and HCT improved disease control over intensive chemotherapy alone.¹⁶⁴ Although this analysis showed an improved 7-year EFS rate, outcomes remained suboptimal in patients with Ph-positive ALL.

Allogeneic HCT has been considered the standard of care for AYA patients with Ph-positive ALL; however, its role has become less clear with the advent of *BCR-ABL*-targeted TKIs. Several studies evaluated the role of allogeneic HCT in the era of imatinib and whether imatinib-based therapies provided an additional benefit to HCT.

COG AALL-0031 Regimen

In a multicenter COG study (AALL-0031) of children and adolescents with high-risk ALL, the group of patients with Ph-positive ALL ($n = 92$; aged 1–21 years) was treated with an intensive chemotherapy regimen combined with imatinib (340 mg/m²/day; given during postremission induction therapy and maintenance).¹⁶⁵ 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% ($P < .0001$).¹⁶⁵ Moreover, the 3-year EFS rates were similar among the groups of patients who received chemotherapy combined with continuous imatinib (88%; $n = 25$) or allogeneic HCT from a related donor (57%; $n = 21$) or URD (72%; $n = 11$). No major toxicities were found to be associated with the addition of imatinib to the intensive chemotherapy regimen.¹⁶⁵ Subsequent follow-up

after 5 years confirmed these outcomes.¹⁶⁶ In a phase II single-arm COG trial (AALL-0622) of children and young adults with Ph-positive ALL ($n = 60$; aged 1–30 years), imatinib was replaced with dasatinib on induction day 15 and combined with the same chemotherapy used in AALL-0031.¹⁶⁷ The 5-year overall OS and EFS rates (\pm standard deviation [SD]) were $86\% \pm 5\%$ and $60\% \pm 7\%$, respectively, and outcomes were similar to those observed in AALL-0031.¹⁶⁷

EsPhALL

The European intergroup study of post-induction treatment of Ph-chromosome positive ALL (EsPhALL) reported results of the randomized open-label trial designed to evaluate the safety and long-term efficacy of discontinuous postinduction imatinib plus chemotherapy with the BFM backbone intensive treatment versus chemotherapy alone.¹⁶⁸ The study enrolled 108 good-risk and 70 poor-risk patients aged 1 year to 18 years. Good-risk patients were randomized 1:1 and poor-risk patients were all assigned to receive chemotherapy plus imatinib. There was a trend towards improved 4-year DFS for good-risk patients who received imatinib plus chemotherapy versus those who received chemotherapy alone (72.9% vs. 61.7%; $P = .24$). In the as-treated analysis, good-risk patients who received imatinib with chemotherapy had a 4-year EFS of 75.2% versus 55.9% in patients who did not receive imatinib ($P = .06$). The incidence of serious adverse events was not statically different between the two groups ($P = .64$).¹⁶⁸ Enrollment in this trial was stopped in 2009 following results of the COG AALL0031 study that demonstrated a benefit of continuous imatinib. The EsPhALL study was amended into a single-arm study to add continuous imatinib on induction day 15, with 97% of patients achieving first CR.¹⁶⁹ However, the 5-year EFS and OS rates (57% and 71.8%, respectively) were similar in cohorts that received discontinuous postinduction imatinib and continuous imatinib plus chemotherapy with the BFM backbone intensive treatment.^{168,169} Additionally, a phase II trial evaluated the safety and efficacy of adding



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

continuous dasatinib at day 15 to the intensive BFM regimen in pediatric patients with newly diagnosed Ph-positive ALL (n = 109 enrolled; age range, 1–17 years).¹⁷⁰ The efficacy analysis included 104 patients, who all achieved CR; 15 of the patients received allogeneic HCT at first CR (CR1). An interim analysis showed a 3-year EFS of 66.0% (95% CI, 54.8%–75.0%) and a 3-year OS of 92.3% (95% CI, 85.2%–96.1%).¹⁷⁰

Blinatumomab

Treatment of newly diagnosed Ph-positive ALL adults was evaluated in a phase 2 single-group trial using dasatinib chemotherapy-free induction followed by first-line consolidation therapy blinatumomab.¹⁷¹ Sixty-three patients, aged 24 to 84, were enrolled. At the end of induction, 29% patients had a molecular response, which increased to 60% after two cycles of blinatumomab. *ABL1* mutations occurred in 6 patients who had an increase in MRD, however were cleared upon treatment with blinatumomab. Few toxic effects of grade 3 or higher were observed, with CMV reactivation or infection occurring in six patients. As a result of high molecular response, OS and DFS at a median follow-up of 18 months was achieved in 95% and 88% (95% CI, 90–100; 80–97) of patients, respectively.¹⁷¹ DFS was lower in patients with *IKZF1* deletions.

The safety and efficacy of blinatumomab in combination with TKIs has recently been evaluated in the treatment of Ph-positive ALL.¹⁷²⁻¹⁷⁴ In a small retrospective study, adults with R/R Ph+ ALL (n = 9) and chronic myeloid leukemia (CML) (n = 3) who had previously failed one line of chemotherapy and one class of TKIs were treated with the combination blinatumomab and a TKI (ponatinib, dasatinib, or bosutinib). Of the 12 total patients, 75% (9/12) achieved complete molecular responses with no cardiovascular adverse events.¹⁷²

A recent single-arm phase II study exploring the chemotherapy-free combination of blinatumomab plus ponatinib in 28 newly diagnosed or R/R Ph-positive ALL showed an overall 95% response rate combined.¹⁷⁵ In the

newly diagnosed cohort, a 1-year EFS and OS of 100% was reported, with no patients undergoing transplant. The 1-year EFS was 55% in the R/R cohort, with 88% OS reported.¹⁷⁵ Four patients (44%) with R/R disease underwent HSCT.

TKIs Combined with Hyper-CVAD

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 HCT.¹⁵⁶ The 3-year OS rate for this regimen was 54%. Among the patients aged 40 years or younger (n = 16), a strong trend was observed for OS benefit with allogeneic HCT (3-year OS rate, 90% vs. 33%; *P* = .05).¹⁵⁶ Among patients aged 60 years or younger, no statistically significant difference was observed in the 3-year OS rate between patients who received HCT and those who did not (77% vs. 57%).

Studies have shown the promising activity of other TKIs, including dasatinib and ponatinib when incorporated into frontline regimens for patients with ALL. In a phase II study from MDACC, dasatinib was combined with hyper-CVAD and subsequent maintenance therapy in patients with previously untreated Ph-positive ALL (n = 35; median age, 53 years; range, 21–79 years; 31% were >60 years); four of the patients received allogeneic HCT in CR1.¹⁷⁶ The 2-year OS and EFS rates were 64% and 57%, respectively. The efficacy and safety of ponatinib combined with hyper-CVAD was examined in patients with Ph-positive ALL (n = 37; aged ≥18 years; median age, 51 years; 12 patients were ≥60 years) in a phase II prospective trial.¹⁵⁰ Of the 32 patients with Ph-positive metaphases at the start of therapy, an overall complete cytogenetic response was observed in 32 patients (100%). By multiparametric flow cytometry, 35 of 37 patients (95%) had no MRD after a median of 3 weeks of therapy.¹⁵⁰ However, it is worth noting that only half of the patients



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

greater than or equal to 60 years were able to complete therapy with this regimen, and were switched to alternate TKIs. The 2-year OS and EFS rates were 80% and 81%, respectively. A follow-up study (n = 76; age ≥18 years; median age, 47 years) demonstrated long-term efficacy for ponatinib and hyper-CVAD with a 3-year EFS rate of 70%.¹⁷⁷

TKIs Combined with Multiagent Chemotherapy

In the phase II study from the Group for Research on Adult ALL (GRAALL; GRAAPH-2003), patients with previously untreated Ph-positive ALL (n = 45; median age, 45 years; range, 16–59 years) received imatinib in combination with chemotherapy during either induction or consolidation therapy.^{178,179} Patients in complete remission with a donor received allogeneic HCT (n = 24), whereas those in complete remission with good molecular response but without a donor were eligible for autologous HCT (n = 10). Nine patients did not receive HCT and were treated with imatinib-based maintenance therapy. The 4-year OS rate did not differ significantly for patients with a sibling donor compared to patients undergoing autologous HCT (76% vs. 80%). The 4-year OS for patients who received only maintenance imatinib was 33%.¹⁷⁹ These data suggest that improved survival with imatinib-based therapy can be further enhanced by the addition of HCT.

In the subgroup of patients with Ph-positive ALL (n = 94; median age, 47 years; range, 19–66 years) from the Northern Italy Leukemia Group study (NILG-09/00), outcomes were compared among patients who received chemotherapy with imatinib (n = 59) or without imatinib (n = 35), with or without subsequent HCT (allogeneic or autologous).¹⁸⁰ The patients who received imatinib (63% of eligible patients underwent allogeneic HCT) had significantly higher 5-year OS (38% vs. 23%; $P = .009$) and DFS rates (39% vs. 25%; $P = .044$) compared with those who did not receive imatinib (39% of eligible patients underwent allogeneic HCT).¹⁸⁰ The 5-year OS rates by treatment type were 47% for allogeneic HCT (n = 45), 67% for

autologous HCT (n = 9), 30% for imatinib without HCT (n = 15), and 7% for no imatinib and no HCT (n = 13); the corresponding treatment-related mortality rates were 17%, 0%, 36%, and 23%, respectively. The 5-year relapse rates were 43%, 33%, 87%, and 100%, respectively.¹⁸⁰

The Japan Adult Leukemia Study Group (ALL-202) treated patients with Ph-positive ALL (n = 100) with chemotherapy combined with imatinib administered during induction, consolidation, and maintenance phases.^{181,182} An early analysis (n = 80; median age, 48 years; range, 15–63 years) reported a 1-year OS rate of 73% among patients who underwent allogeneic HCT, compared with 85% for those who did not.¹⁸² A subsequent analysis compared outcomes for the subgroup of patients who received allogeneic HCT at first CR in this study (n = 51; median age, 38 years; range, 15–64 years) versus those for a historical cohort of patients who received allogeneic HCT without prior imatinib (n = 122).¹⁸¹ 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 non-relapse mortality rate was similar between cohorts (21% vs. 28%, respectively).¹⁸¹

A multicenter phase II study from the Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology investigated the effects of multiagent chemotherapy combined with nilotinib in patients with newly diagnosed Ph-positive ALL (n = 90; median age, 47 years; range, 17–71 years).¹⁸³ Chemotherapy combined with nilotinib was administered during induction, consolidation, and maintenance phases. Of 90 evaluable patients, 82 (91%) experienced complete hematologic remission with a median time of 27 days (range, 13–72). The 2-year hematologic RFS and OS rates were both 72%.¹⁸³

In a phase II multicenter trial (CALGB 10701), patients with newly diagnosed Ph-positive ALL (n = 64; median age, 60 years; range, 22–87 years) were treated with multiagent chemotherapy combined with



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

dasatinib, and the efficacy of different post-remission strategies were evaluated including allogeneic HCT, autologous HCT, and chemotherapy alone, followed by maintenance with dasatinib.¹⁸⁴ The CR rate was 97% with no induction deaths. With a median follow-up of 48 months for survivors, 3-year OS and DFS were 55% and 43%, respectively.¹⁸⁴ For patients who underwent consolidation with allogeneic HCT, autologous HCT, or chemotherapy, 3-year OS was 75%, 71%, and 55%, respectively, with median OS not reached (NR) for all groups. The 3-year DFS was 55%, 43%, and 46%, respectively.¹⁸⁴

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 rates with chemotherapy regimens were generally less than 20%.¹⁸⁵

Hematopoietic Cell Transplant

Allogeneic HCT, in the pre-imatinib era, resulted in some improvements over chemotherapy alone, with 2-year OS rates of 40% to 50%^{186,187} and 3-year OS rates of 36% to 44%.^{93,181} In the large, international, collaborative MRC UKALL XII/ECOG E2993 trial conducted in patients with previously untreated ALL, the subgroup with Ph-positive disease (n = 267; median age, 40 years; range, 15–60 years) was eligible for allogeneic HCT if its patients were younger than 50 (in the ECOG E2993 trial) or 55 (in the MRC UKALL XII trial) years of age and had a matched sibling or matched URD.¹⁸⁸ Among the Ph-positive patient cohort, postremission treatment included matched sibling allogeneic HCT (n = 45), matched URD allogeneic HCT (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.¹⁸⁸ Both the OS and EFS outcomes for patients who underwent allogeneic HCT (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 HCT and 39% with matched URD HCT. An intent-to-treat analysis of patients with a matched sibling donor versus those without a matched sibling donor showed no statistically significant difference in 5-year OS rates (34% vs. 25%, respectively).¹⁸⁸ The incorporation of imatinib in the treatment regimen for Ph-positive ALL has led to improvements in outcomes over chemotherapy alone.^{156,182,185}

Some retrospective studies suggest similar outcomes between myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) followed by allogeneic HCT in adult patients with Ph-positive ALL.¹⁸⁹⁻¹⁹¹

The Center for International Blood and Marrow Transplant Research (CIBMTR) group conducted a multicenter retrospective analysis examining the efficacy RIC and MAC allogeneic HCT in adult patients with Ph-positive ALL (n = 197).¹⁸⁹ At a median follow-up of 4.5 years, the 1-year transplant-related mortality was significantly lower in the RIC versus MAC group (13% vs. 36%; $P = .001$), and 3-year OS rates were similar (39% vs. 35%, respectively).¹⁸⁹

TKIs Combined with Hyper-CVAD

Studies evaluating TKIs plus hyper-CVAD have included both AYA and adult patients.^{150,156,176} For discussion of these studies, refer to the previous section (see *Initial Treatment in AYA Patients with Ph-Positive ALL*).

TKIs Combined with Multiagent Chemotherapy

Studies evaluating TKIs plus multiagent chemotherapy have been discussed in the previous section^{178-181,183,184,192} (see *Initial Treatment in AYA Patients with Ph-Positive ALL*). Several studies evaluating the efficacy of TKIs combined with multiagent chemotherapy in patients with previously untreated ALL have shown improved outcomes, particularly when treatment was followed by allogeneic HCT.^{153,180-182,184} A multicenter trial from the European Working Group for Adult ALL (EWALL;



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

EWALL-PH02) evaluated the efficacy and safety of nilotinib with multiagent chemotherapy in older patients with Ph-positive ALL (n = 79 [72 evaluable]; age range, 55–85 years).¹⁵³ The CR rate was 94.4% and the MRD response (*BCR-ABL/ABL* ratio $\leq 0.1\%$) increased from 41% after induction to 86% after consolidation II. At 4 years, the EFS and OS rates were 42% and 47%, respectively. By landmark analyses using median time to transplant as a cutoff, the 4-year OS rate was 61% in patients who underwent allogeneic HCT.

TKIs Combined with Corticosteroids

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.¹⁹³ 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.¹⁹⁴ The median OS was numerically higher (but not statistically significant) among patients who received imatinib induction compared with those randomized to receive 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.¹⁹⁴

In a study by 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.¹⁴⁹ Twelve patients were

older than 60 years. Postinduction therapy included no further therapy (n = 2), TKI only (n = 19), TKI combined with chemotherapy (n = 10) with or without autologous HCT (n = 4), or allogeneic HCT (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.¹⁴⁹ T315I mutation was detected in 12 of 17 patients with relapsed disease (71%).

In a small phase II study from GRAALL (AFR-09 study), older patients (aged ≥ 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.¹⁹⁵ The 1-year OS rate in this study was significantly higher compared with 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 the 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%; $P < .001$).¹⁹⁵ 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).¹⁹⁶ 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.¹⁹⁶ In a separate study from GIMEMA (LAL-1205), patients with Ph-positive ALL (n = 53 evaluable; age range, 24–76.5 years) received induction therapy with dasatinib and prednisone.¹⁴⁹ Postinduction therapy included no further therapy (n = 2), TKI only (n = 19), TKI combined with chemotherapy (n = 10) with or without autologous HCT (n = 4), or allogeneic HCT (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.¹⁴⁹



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

A phase II study from GIMEMA (LAL1811) also evaluated the efficacy and safety of ponatinib and prednisone in older adult patients with untreated Ph-positive ALL (n = 42 evaluable; median age, 68 years; range, 27–85 years).¹⁹⁷ Dose reduction of ponatinib was allowed for adverse events. At week 24, the primary endpoint of the study, complete hematologic response, was prematurely reached in 75% of patients. During the study, 75 adverse events were reported; 36 were related to ponatinib.¹⁹⁷

TKIs Combined with Vincristine and Dexamethasone

The phase II GRAALL study (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.^{198,199} Eligible patients proceeded to HCT (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 PCR) after induction/consolidation. In an early report from this study (n = 118; n = 83 evaluable; median age 42 years), 52 patients proceeded to HCT (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).¹⁹⁸ 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 4.8 years (n = 268; median age, 47 years), the CR rate was higher in arm A compared to arm B (98% vs. 91%; *P* = .006), but MRD response rates after two cycles of therapy were similar between arm A and arm B (66.1% vs. 64.5%).²⁰⁰ The estimated 5-year EFS and OS rates were 37.1% and 45.6%, respectively, and no significant differences were

observed between arm A and arm B.²⁰⁰ Among patients who proceeded to allogeneic HCT or autologous HCT after MRD response, the outcomes were similar in terms of the 5-year post-transplant RFS (48.3 % vs. 46.1 %) and OS (56.7% vs. 55.1%) rates. This study suggests that outcomes with less intensive chemotherapy regimens (using high-dose imatinib) may offer similar benefits to more intensive imatinib-containing chemotherapy regimens.²⁰⁰

In the EWALL-Ph-01 study, induction therapy with dasatinib combined with low-intensity chemotherapy (vincristine and dexamethasone) was evaluated in older patients (aged ≥55 years) with Ph-positive ALL (n = 71; median age, 69 years; range, 58–83 years). The CR rate after induction was 96% and MRD response (*BCR-ABL*/*ABL* ratio ≤0.1%) occurred in 65% of patients.²⁰¹ At 3 years, the RFS, EFS, and OS were 33% (95% CI, 22%–44%), 31% (95% CI, 21%–42%), and 41% (95% CI, 29%–52%), respectively.²⁰¹ At 5 years, the cumulative incidence of relapse was 54% (95% CI, 42%–66%). 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.

TKIs in Maintenance Therapy

Collectively, the incorporation of TKIs into the therapeutic regimen has demonstrated improved outcomes for adult patients with Ph-positive ALL, particularly when administered before allogeneic HCT. Given that patients can experience relapse following allogeneic HCT, strategies are needed to prevent disease recurrence. One strategy involves the incorporation of post-HCT 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 HCT (n = 15 with ALL; median age, 37 years; range, 4–49 years), imatinib was administered from the time of



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

engraftment until 1 year after HCT.²⁰² The median time after HCT 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 HCT and 80% (12 of 15) after HCT. Two patients died after hematologic relapse and one patient died due to acute respiratory distress syndrome approximately 1 year post-HCT. At a median follow-up of 1.3 years, 12 patients (80%) were alive without detectable disease.²⁰² This was one of the first prospective studies to show the feasibility of administering imatinib maintenance early in the post-HCT period (<90 days) when the leukemic tumor burden tends to be low.

Maintenance therapy with imatinib was also evaluated in a prospective study in patients who underwent allogeneic HCT (n = 82; median age, 28.5 years; range, 3–51 years).²⁰³ 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 HCT 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.²⁰³ 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, graft-versus-host disease [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.²⁰³

The previous study was not designed as a randomized controlled trial, and the number of patients in the non-imatinib group was small. A 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 HCT with a planned duration of imatinib therapy for 1 year.²⁰⁴ MRD was defined by the 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 HCT. In the MRD-triggered arm, imatinib was started in 14 patients (48%) at a median time of 70 days (range, 39–567 days) after HCT. 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.²⁰⁴ Ongoing CR was observed in 81% of patients in the prophylaxis arm (median follow-up, 30 months) and in 78% of patients 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%).²⁰⁴ 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 HCT) was associated with significantly decreased EFS compared with late MRD detection (median, 39 months vs. NR; 4-year EFS, 39% vs. 65%; $P = .037$).²⁰⁴ This trial suggested that imatinib given post-allogeneic HCT (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 HCT. Although no randomized controlled trials have yet been conducted to establish the efficacy of TKIs (compared with observation only or other interventions) following allogeneic HCT, the collective results from these studies suggest that TKI maintenance may have a potential role in reducing the relapse risk in this setting.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Treatment of Relapsed Ph-Positive ALL

The treatment of patients who experience relapse after initial therapy for ALL remains a challenge, because these patients have a very poor prognosis. Several large studies using conventional chemotherapy for relapsed adult patients have reported a median OS of 4.5 to 6 months, and a 5-year OS rate of 3% to 10%.²⁰⁵⁻²⁰⁸ One major factor associated with poorer survival outcomes after subsequent therapy for relapsed ALL is the duration of response to frontline treatment. In an analysis of data from the PETHEMA (Programa Español de Tratamientos en Hematología) trials, patients with disease that relapsed more than 2 years after frontline therapy had significantly higher 5-year OS rates than the groups of patients who relapsed within 1 to 2 years or within 1 year of frontline therapy (31% vs. 15% vs. 2%; $P < .001$).²⁰⁶ Similarly, in the MRC UKALL XII/ECOG E2993 trial, patients with disease that relapsed more than 2 years after initial diagnosis and frontline therapy had a significantly higher 5-year OS rate than those who relapsed within 2 years (11% vs. 5%; $P < .001$).²⁰⁵ In the pre-imatinib era, patients with Ph-positive ALL who relapsed after frontline therapy had dismal outcomes; subgroup data from the large, prospective trials LALA-94 and MRC UK XII/ECOG E2993 showed a median OS of 5 months and a 5-year OS rate of 3% to 6% among patients subsequently treated for relapsed Ph-positive ALL.^{205,207}

Hematopoietic Cell Transplant

Treatment options are extremely limited for patients with Ph-positive ALL who experience relapse after receiving consolidation with allogeneic HCT. Some investigators have reported on the feasibility of inducing a second molecular CR with dasatinib in those who have experienced an early relapse after first allogeneic HCT, which allowed for a second allogeneic HCT.^{209,210} Studies that include donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in those who relapse after allogeneic HCT have reported little to no benefit, though it has been suggested that this is due to excessively high leukemic burden.^{211,212} Indeed, published

case reports have suggested that the use of DLI for residual disease or molecular relapse (as noted by levels of *BCR-ABL* fusion mRNA measured with PCR) after allogeneic HCT may eliminate residual leukemic clones and thereby prevent overt hematologic relapse.²¹³⁻²¹⁵

Moreover, case reports have described using newer TKIs, such as dasatinib and nilotinib, along with DLI to manage relapse after allogeneic HCT.^{216,217} Although these approaches are promising, only limited data are available. Evidence from prospective studies is needed to establish the role of DLI, with or without TKIs, in the treatment of relapsed disease.

Tyrosine Kinase Inhibitors

The emergence of resistance poses a challenge for patients relapsing after initial treatment with TKI-containing regimens. Point mutations within the *ABL* kinase domain and alternative signaling pathways mediated by the SRC family kinase have been implicated as mechanisms of resistance.²¹⁸⁻²²⁰ The former has been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy.^{221,222} Moreover, *ABL* kinase domain mutations may be present in a small group of imatinib-naïve patients even before initiation of any TKI therapy.^{223,224}

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.²²⁵⁻²²⁸ 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.^{226,228} 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.²²⁷ Patients with imatinib-resistant disease who developed CNS disease rapidly died from progressive disease (PD); conversely, patients with



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

imatinib-sensitive disease who developed isolated CNS relapse could be successfully treated with intrathecal therapy with or without cranial irradiation.^{225,227}

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.^{154,229-231} In addition, dasatinib has better CNS penetration than imatinib, and therefore may have advantages in preventing CNS relapse. Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL that is resistant to imatinib treatment.²³²⁻²³⁴ 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;²³³ the once-daily dosing resulted in a higher response rate (major cytogenetic response) than the twice-daily dosing (70% vs. 52%). Although the median OS was shorter with the once-daily dosing (6.5 vs. 9 months), the median progression-free survival (PFS) was longer (4 vs. 3 months).²³³ These differences in outcomes between the dosing arms were not statistically significant.

Dasatinib in combination with the hyper-CVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was investigated in a phase II trial that included patients with Ph-positive relapsed ALL (n = 19) and lymphoid blast phase (BP) CML (n = 15).²³⁵ An overall response rate (ORR) of 91% was obtained with 26 patients (84%) achieving complete cytogenetic remission, 13 patients (42%) having complete molecular response, and 11 patients (35%) having a major molecular response. There were nine patients who went on to receive allogeneic HCT, including two patients with ALL. In the patients with relapsed ALL, 30% remained in complete remission at 3

years with a 3-year OS of 26%. At the median follow-up of 52 months (range, 45–59 months), two patients (11%) with ALL were still alive.

Bosutinib, a second-generation TKI that acts as a dual inhibitor of *BCR-ABL* and SRC family kinases,^{236,237} was approved in September 2012 by the FDA for the treatment of chronic, accelerated phase (AP), or BP Ph-positive CML in adult patients with resistance to prior TKI treatment based on an open-label, multicenter phase I/II trial.²³⁷ Efficacy and safety analyses of bosutinib monotherapy included patients with advanced leukemia [AP CML (n = 79), BP CML (n = 64), or ALL (n = 24)] who were previously treated with at least one TKI.^{238,239} Of the 22 evaluable patients with ALL, two patients (9%) attained or maintained a confirmed overall hematologic response by 4 years.²³⁸ Common overall treatment-related adverse events reported in patients with advanced leukemia included diarrhea (74%), nausea (48%), and vomiting (44%).^{238,239}

Ponatinib is a third-generation TKI that was initially approved by the FDA in December 2012 for the treatment of adult patients with chronic, AP, or BP Ph-positive CML or Ph-positive ALL, with resistance to prior therapy, and was added as a treatment option for R/R Ph-positive ALL in 2013. Though temporarily removed from the market in November 2013, ponatinib distribution resumed in December 2013 following revision to both the prescribing information and risk evaluation and mitigation strategies program to address the risk for serious cardiovascular adverse events. This TKI has been shown to inhibit both native and mutant forms of *BCR-ABL* (including those resulting from T315I mutation) in preclinical studies.²⁴⁰ In a multicenter, open-label, phase II study (PACE trial; n = 449), ponatinib showed substantial activity in patients with Ph-positive leukemias resistant or intolerant to second-generation TKIs.²⁴¹ Major hematologic response was observed in 41% of the subgroup with Ph-positive ALL (n = 32). In the subset of patients with Ph-positive ALL with *ABL* T315I mutation (n = 22), major hematologic response was



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

observed in 36%.²⁴¹ Common overall treatment-related adverse events in the PACE trial included thrombocytopenia (37%), rash (34%), and dry skin (32%). Additionally, arterial thrombotic events were observed and 7.1% of patients experienced cardiovascular events,²⁴¹ though dose reduction may impart a lower risk.

Not all imatinib-resistant *ABL* mutations are susceptible to the newer TKIs. For instance, dasatinib is not as active against cells harboring the *ABL* mutations T315I, V299L, and F317L.^{220,230,242,243} Thus, for patients with disease resistant to TKI therapy, it becomes important to identify potential *ABL* mutations that may underlie the observed resistance to treatment. A panel of experts from the European LeukemiaNet published recommendations for the analysis of *ABL* kinase domain mutations in patients with CML, and treatment options according to the presence of different *ABL* mutations.²⁴⁴ (See *Principles of Systemic Therapy* in the algorithm for TKI treatment options for *Treatment Options Based on BCR-ABL1 Mutation Profile*).

Blinatumomab

In December 2014, the FDA approved blinatumomab for the treatment of relapsed or refractory Ph-negative precursor B-ALL (see *Treatment of Relapsed Ph-Negative ALL* for a detailed discussion of blinatumomab). In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-ALL (Ph-negative and Ph-positive). A follow-up, open-label, single-arm, multicenter, phase II study evaluated the efficacy and safety of blinatumomab in patients with R/R Ph-positive ALL who had progressed after imatinib and at least one second- or third-generation TKI (n = 45).²⁴⁵ During the first two cycles of blinatumomab, 36% achieved complete remission or complete remission with partial hematologic recovery, and 88% of these responders achieved a complete MRD response.²⁴⁵ Notably, responses were independent of T315I mutation status (see *Initial Treatment in AYA Patients with*

Ph-Negative ALL for a discussion of studies related to blinatumomab and chemotherapy-resistant MRD).

Inotuzumab ozogamicin

Inotuzumab ozogamicin (InO) is a calicheamicin-based antibody-drug conjugate targeting CD22. Following the generation of encouraging single-agent phase II data,²⁴⁶ a randomized study was conducted comparing InO with standard intensive chemotherapy regimens in Ph-negative or Ph-positive ALL in first or second relapse, defined as greater than 5% marrow blasts (n = 326). Compared to standard therapy, InO produced a significantly higher CR/CRi rate (80.7% vs. 29.4%; $P < .001$) and higher MRD-negative rates (78.4% vs. 28.1%; $P < .001$).²⁴⁷ Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with Ph-positive leukemia. The overall incidence of severe adverse events were similar across treatment arms, with a higher incidence of hepatic veno-occlusive disease observed in the inotuzumab group, related in part to dual alkylator-based transplant conditioning administered in remission. These data translated into a significant benefit in the median duration of remission (4.6 vs. 3.1 months; $P = .03$), median PFS (5 vs. 1.8 months; $P < .001$), and mean OS (13.9 vs. 9.9 months; $P = .005$).²⁴⁷ In August 2017, InO received full approval from the FDA for the treatment of R/R precursor B-ALL.

CAR T Cells

Currently, bone marrow transplant is the only cure for R/R ALL, but many patients are not eligible for transplant based on age or progression of the disease. The generation of chimeric antigen receptor (CAR) T cells to treat ALL represents a significant advance in the field and has shown significantly greater OS than current regimens.²⁴⁸ The pre-treatment of patients with CAR T cells has served as a bridge for transplant, and patients who were formerly unable to be transplanted due to poor



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

remission status achieve a CR and ultimately proceed to transplantation. CAR T-cell therapy relies on the genetic manipulation of a patients' T cells to engender a response against a leukemic cell-surface antigen, most commonly CD19²⁴⁹ (see *Treatment of Relapsed Ph-Negative ALL* for a detailed discussion of CAR T cells). CAR T-cell therapy/tisagenlecleucel was recommended for accelerated approval by the FDA Oncologic Drug Advisory Committee in July 2017 and fully approved by the FDA in August 2017 for the treatment of patients up to age 25 years (aged <26 years) with R/R precursor B-ALL.

NCCN Recommendations for Ph-Positive ALL

AYA and Adult Patients with Ph-Positive ALL

The panel recommends that Ph-positive ALL AYA and adult patients less than 65 years of age and no substantial comorbidities be treated in a clinical trial, when possible. In the absence of an appropriate clinical trial, the recommended induction therapy would comprise multiagent chemotherapy or corticosteroids combined with a TKI. However, the panel notes that not all TKIs have been studied within the context of each regimen, and there are limited data for bosutinib in Ph-positive ALL. Use of a specific TKI should account for anticipated or prior TKI intolerance and disease-related features. Treatment regimens should include adequate CNS prophylaxis for all patients, which may be particularly important when using agents without known CNS penetrance, such as imatinib. 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 and adult (aged <65) patients experiencing a CR after initial induction therapy, an MRD assessment should be performed prior to consolidation with allogeneic HCT in appropriate candidates. Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.²⁵⁰ The

optimal time for a patient to receive allogeneic HCT is unclear; however, proceeding to allogeneic HCT with MRD is not optimal and additional therapy is recommended to eliminate MRD before transplant. In cases of persistent or rising MRD, consolidation therapy options may include blinatumomab (B-ALL) with or without TKI,¹⁷¹ or continuation of multiagent chemotherapy or corticosteroid combined with a TKI. Although long-term remission after blinatumomab treatment is possible, HCT in appropriate candidates should also be evaluated following MRD positivity at the end of induction. In younger AYA patients (aged ≤21 years), emerging data suggest that allogeneic HCT may not confer an advantage over chemotherapy combined with TKIs.¹⁶⁵ Maintenance therapy with a TKI, with or without monthly pulses of vincristine/prednisone (for 2–3 years), is recommended. Although the optimal duration of post-transplant or maintenance TKI is unknown, the minimum suggested duration is 1 year. Periodic MRD assessments should be considered (no more than every 3 months) for patients with complete molecular remission (undetectable levels). The frequency may be increased if MRD levels are detectable. For patients with CD20-positive disease, consider adding rituximab to chemotherapy.

For patients who achieve MRD negativity, consolidation therapy after a CR should comprise a continuation of multiagent chemotherapy or corticosteroid combined with a TKI, considering dose modifications for appropriate for patient age and performance status. These patients should continue to receive post-consolidation maintenance therapy with a regimen that includes a TKI. Allogeneic HCT may be useful in appropriate candidates with MRD negativity, while considering post-HCT TKI following consolidation therapy. 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. Individuals who inherit a nonfunctional variant allele of the *TPMT* gene are known to be at high risk



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

of developing hematopoietic toxicity (in particular, severe neutropenia) after treatment with 6-MP.¹⁴² Testing for the *TPMT* gene polymorphism should be considered in patients receiving 6-MP as part of maintenance therapy, particularly those who experience severe bone marrow toxicities (see *Role of MRD Evaluation*).

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

Adult Patients Aged ≥65 with Ph-Positive ALL

For Ph-positive ALL adult patients ≥65 years of age or with substantial comorbidities, the panel recommends treatment in 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 age, performance status, end-organ function, and end-organ reserve. Dose modifications for patients age and performance status should also be considered.

For adult patients who are less fit (aged ≥65 years or with substantial comorbidities), consolidation therapy is recommended to follow the same treatment preferences and considerations noted for AYA and adult patients (see NCCN Recommendations for Ph-Positive ALL; *AYA and Adult Patients with Ph-Positive ALL*).

Patients with Relapsed/Refractory Ph-Positive B-ALL

Mutation testing for the *ABL1* kinase domain is recommended in patients with Ph+ B-ALL that have relapsed after or are refractory to initial TKI-containing therapy. The panel has largely adopted the recommendations for treatment options based on *ABL* mutation status for CML, as published by the European LeukemiaNet.²⁴⁴ If not administered during initial induction, TKIs (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) are recommended options for patients with R/R Ph+ ALL. For second- and third-generation TKIs, relevant *BCR-ABL1* mutations should be considered as outlined in the algorithm table titled, *Treatment Options Based on BCR-ABL1 Mutation Profile*.

For all patients with R/R Ph-positive B-ALL, participation in a clinical trial is preferred. In the absence of an appropriate trial, patients may be considered for second-line therapy with an alternative TKI (ie, different from the TKI used as part of induction therapy) alone, TKI combined with multiagent chemotherapy, or TKI combined with corticosteroids (especially for elderly patients who may not tolerate multiagent combination therapy). Blinatumomab with or without TKI may also be considered. For patients that are refractory or intolerant to TKIs, InO with or without bosutinib is recommended. Compared to standard care, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease, and increased risk of post-HCT non-relapse mortality.²⁵¹ Tisagenlecleucel is also an option for patients up to age 25 years (aged <26 years) and with refractory disease or greater than or equal to 2 relapses and failure of 2 TKIs.

If transplant-naïve patients experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCT following treatment with tisagenlecleucel is unclear. While



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT, further study will be required before conclusive recommendations can be made.²⁵² In the absence of an appropriate clinical trial, patients with T-ALL that is refractory to TKIs, regimens for R/R Ph-negative ALL can be considered. (See *Treatment of Relapsed Ph-Negative ALL*).

Management of Ph-Negative ALL

Initial Treatment in AYA Patients with Ph-Negative ALL

The AYA population with ALL can pose a unique challenge given that patients may be treated with either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. Retrospective analyses based on cooperative group studies from both the United States and Europe have consistently shown the superior outcomes for AYA patients (aged 15–21 years) treated on pediatric versus adult ALL regimens. In the AYA population, 5-year EFS rates ranged from 63% to 74% for patients treated on a pediatric study protocol versus 34% to 49% for those receiving the adult protocol.^{90,91,117,253,254} In a retrospective comparative study that analyzed outcomes of AYA patients (aged 16–20 years) treated on a pediatric CCG study protocol (n = 197; median age, 16 years) versus an adult CALGB study protocol (n = 124; median age, 19 years), patients treated on the pediatric regimen compared with those on the adult regimen had significantly improved 7-year EFS (63% vs. 34%, respectively; $P < .001$) and OS (67% vs. 46%, respectively; $P < .001$) rates.¹¹⁷ 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 largely attributed to the use of greater cumulative doses of drugs, such as corticosteroids (prednisone and/or dexamethasone), vincristine, and L-asparaginase, and to earlier,

more frequent, and/or more intensive CNS-directed therapy compared with adult regimens.¹¹⁷ Given the success seen with multiagent intensive chemotherapy regimens for pediatric patients with ALL, several clinical trials have evaluated pediatric-inspired regimens for the AYA patient population.

Hematopoietic Cell Transplant

For AYA patients with Ph-negative ALL in first CR, allogeneic HCT may be considered for high-risk cases—particularly for patients with disease that is MRD positive any time after induction; or patients with elevated WBC counts; or patients with B-ALL and poor-risk cytogenetics [eg, hypodiploidy, *KTM2A* (*MLL*) rearrangement] at diagnosis. A large multicenter trial (LALA-94 study) evaluated the role of postinduction HCT as one of the study objectives in adolescent and adult ALL patients receiving therapy for previously untreated ALL (n = 922; median age, 33 years; range, 15–55 years).⁹³ Patients were stratified into four 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 $<30 \times 10^9/L$]; 2) Ph-negative high-risk ALL (defined as patients with non-standard-risk disease and without CNS involvement); 3) Ph-positive ALL; and 4) evidence of CNS disease. After induction therapy, patients with Ph-negative high-risk ALL were eligible to undergo allogeneic HCT if a matched sibling donor was available; those without a sibling donor were randomized to undergo autologous HCT or chemotherapy alone.⁹³ Among the subgroup of patients with Ph-negative high-risk ALL (n = 211), the 5-year DFS and OS rates were 30% (median, 16 months) and 38% (median, 29 months), respectively. Based on intent-to-treat analysis, outcomes in patients with Ph-negative high-risk ALL were similar for autologous HCT (n = 70) and chemotherapy alone (n = 59) in terms of median DFS (15 vs. 11 months), median OS (28 vs. 26 months), and 5-year OS rate (32% vs. 21%).⁹³ Outcomes were improved in patients with



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Ph-negative high-risk ALL and those with CNS involvement allocated to allogeneic HCT. The median DFS was 21 months for these patients, and the median OS has not yet been reached; the 5-year OS rate was 51%.⁹³ Thus, it appears that in patients with Ph-negative high-risk disease, allogeneic HCT in first CR improved DFS outcomes, whereas autologous HCT did not result in significant benefit compared with chemotherapy alone.

In the PETHEMA ALL-93 trial, adult patients with high-risk ALL [defined as having at least one of the following criteria: 30–50 years of age; WBC count $\geq 25 \times 10^9/L$; presence of t(9;22), t(4;11), or other 11q rearrangements; and t(1;19)] received postremission induction therapy (n = 222 eligible; median age, 27 years; range, 15–50 years) with allogeneic HCT (n = 84; if matched related donor available), autologous HCT (n = 50), or chemotherapy alone (n = 48).²⁵⁵ Based on intent-to-treat analysis of data from patients with Ph-negative high-risk disease, no significant advantage was observed in a donor versus no-donor comparison of median DFS (21 months vs. 38 months), median OS (32 months 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 HCT; 55% for autologous HCT; and 54% for chemotherapy alone).²⁵⁵

The role of allogeneic HCT in adults with ALL was also evaluated in the large multicenter MRC UKALL XII/ECOG E2993 study (n = 1913; aged 15–59 years).⁹⁴ 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-ALL; $>100 \times 10^9/L$ for T-ALL); or the presence of Ph chromosome. All other patients were considered to be standard risk. Patients experiencing a remission with induction therapy were eligible to undergo allogeneic HCT if a matched sibling donor was available or, in the

absence of a sibling donor, were randomized to undergo autologous HCT or chemotherapy. The 5-year OS rate was higher for patients randomized to chemotherapy alone compared with autologous HCT (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 in the no-donor group (53% vs. 45%; $P = .01$). This advantage in OS outcomes for the donor group was observed for patients with standard risk (62% vs. 52%; $P = .02$) but not for those with Ph-negative high-risk disease (41% vs. 35%).⁹⁴ This was partly because of the high rate of non-relapse 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 non-relapse mortality rate at 2 years was 19.5% for the donor group and 7% for the no-donor group. Relapse rate was significantly lower in the donor group than in the no-donor group for both patients with standard risk (24% vs. 49%; $P < .001$) and those with high risk (37% vs. 63%; $P < .001$).⁹⁴ Nevertheless, the high non-relapse mortality rate in the donor group among patients with high-risk disease seemed to diminish the advantage of reduced risk for relapse in this group. This study suggested that allogeneic HCT in first CR was beneficial in patients with standard-risk ALL.

The benefit of matched sibling allogeneic HCT in adult patients with standard-risk ALL was also reported by the HOVON cooperative group. In a donor versus no-donor analysis of patients with standard-risk ALL undergoing postremission therapy with matched sibling allogeneic HCT or autologous HCT, the donor arm was associated with a significantly reduced 5-year relapse rate (24% vs. 55%; $P < .001$) and a higher 5-year DFS rate (60% vs. 42%; $P = .01$) compared with the no-donor arm.²⁵⁶ In the donor group, the non-relapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.²⁵⁶



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

As evidenced by the previously described studies, matched sibling HCT has been established as a valuable treatment strategy for patients with both standard and high-risk Ph-negative ALL, but subsequent studies have examined the role of URD transplants in high-risk Ph-negative ALL. In a retrospective analysis of 169 patients who underwent URD HCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57%) had multiple risk factors. The 5-year survival rate was 39%, which is higher than survival rates reported in studies of high-risk patients receiving chemotherapy alone.²⁵⁷ The most significant percentage of treatment-related mortality occurred in patients who were given mismatched donors compared to partially or well-matched donors. There was no significant difference in outcome between older and younger patients, suggesting that URD transplants may be an option for older patients. In a follow-up retrospective study by the same group, RIC was evaluated to lower treatment-related mortality.²⁵⁸ RIC conditioning most commonly comprised busulfan (9 mg/kg or less), melphalan (150 mg/m²), low-dose total body irradiation (TBI) (<500 cGy single dose or less than 800 cGy fractionated), or fludarabine plus TBI of 200 cGy. RIC is more prominent in the treatment of older patients; therefore, the median age for patients receiving full-intensity (FI) conditioning was 28 years (range, 16–62 years), and for patients receiving RIC, the median age was 45 years (range, 17–66 years). Despite the variation in age, results from the study have shown no difference in relapse (35% vs. 26%, $P = .08$) or in treatment-related mortality (FI, 33%; 95% CI, 31%–36% vs. RIC, 32%; 95% CI, 23%–43%; $P = .86$) at 3 years.²⁵⁸ The 3-year survival for HCT was similar following first CR (FI, 51%; 95% CI, 48%–55% vs. RIC, 45%; 95% CI, 31–59%) and second CR (FI, 33%; 95% CI, 30%–37% vs. RIC, 28%; 95% CI, 14%–44%). The DFS was similar in both groups following first CR (FI, 49%; 95% CI, 45%–53% vs. RIC, 36%; 95% CI, 23%–51%) and in second CR (FI, 32%; 95% CI, 29%–36% vs. RIC, 27%; 95% CI, 14%–43%).²⁵⁸

A systematic review and meta-analysis of published randomized trials on post-remission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HCT in first CR (RR, 0.88; 95% CI, 0.80–0.97) compared with autologous HCT or chemotherapy.²⁵⁹ A subgroup analysis showed a significant survival advantage with allogeneic HCT in standard-risk ALL, whereas a nonsignificant advantage was seen in high-risk ALL.²⁵⁹ Autologous HCT in first remission was not shown to be beneficial relative to chemotherapy in several large studies and meta-analyses.^{93,94,259,260}

CCG-1961

The CCG-1961 trial was a seminal study that allowed comparison of adult versus pediatric regimens in AYA patients. In an analysis of outcomes in children and AYA patients treated in the Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocols (1991–2000), the 5-year EFS rate among younger AYA patients (age 15–18 years; $n = 51$) was 78%, which was not significantly different from the EFS rates observed for children aged 10 to 15 years (77%; $n = 108$) or those aged 1 to 10 years (85%; $n = 685$).²⁶¹ 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.¹¹⁶ 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.¹¹⁶ In the subgroup of AYA patients (aged 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.²⁶² Among the AYA patients who were considered



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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%.²⁶²

COG AALL0232

The AALL0232 trial enrolled 2154 patients between the ages of 1 and 30 years who were diagnosed with high-risk B-ALL.²⁶³ In this study patients were randomly assigned to receive dexamethasone versus prednisone during induction and high-dose methotrexate versus Capizzi escalating-dose methotrexate plus pegaspargase (PEG) during interim maintenance. High-dose methotrexate showed improved 5-year EFS (80% vs. 75%; $P = .008$) and OS (88.9% \pm 1.2% vs. 86.1% \pm 1.4%; $P = 0.25$) rates compared to Capizzi escalating-dose methotrexate. No statistically significant difference was reported in the occurrence of mucositis, neurotoxicity, osteonecrosis, or other toxicities. The ALL0232 trial compared dexamethasone 10 mg/m²/day for 14 days to 60 mg/m²/day of prednisone for 28 days. Dexamethasone showed improved outcomes during induction in patients younger than 10 years of age; however, it was associated with a higher risk of osteonecrosis in patients aged 10 years or older. These data suggest that age may be an important factor for the selection of a corticosteroid.²⁶³

PETHEMA ALL-96 Regimen

In the PETHEMA ALL-96 trial, adolescent (n = 35; aged 15–18 years) and young adult (n = 46; aged 19–30 years) patients with standard-risk Ph-negative ALL [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.²⁶⁴ The 6-year EFS and OS rates for the entire patient cohort were 61% and 69%, respectively. No difference in EFS rate was observed between adolescents (60%; 95% CI, 43%–77%) and young adults (63%; 95% CI, 48%–78%); similarly, no significant difference was observed in OS for adolescents (77%; 95% CI, 63%–91%) versus young adults (63%; 95% CI, 46%–80%).²⁶⁴ 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).²⁶⁴

DFCI ALL Regimen Based on DFCI Protocol 00-01

A multicenter phase II trial evaluated the pediatric-inspired regimen based on the DFCI Childhood ALL Consortium Protocol 00-01 in AYA and adult patients (aged 18–50 years) with previously untreated ALL; 20% of the patients in this study had Ph-positive disease.²⁶⁵ 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.²⁶⁵ 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%).²⁶⁵ After a median follow-up of 4.5 years, the 4-year DFS rate for patients with Ph-negative ALL (n = 64) and those who achieved CR was 71% (95% CI, 58%–81%), and the 4-year OS rate for all patients with Ph-negative ALL was 70% (95% CI, 58%–79%).²⁶⁶ A phase II successor trial was initiated to determine whether pegylated-asparaginase could be substituted for L-asparaginase in this regimen.²⁶⁷ A high frequency of asparaginase toxicities precipitated reverting to



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

L-asparaginase during induction and a dose-reduction of pegylated-asparaginase during consolidation. After 4 weeks, the CR rate was 89%, and with a median follow-up of 39 months, the estimated 3-year DFS and OS rates were 73% and 75%, respectively.²⁶⁷ These data suggest that intensive pediatric regimens are feasible, with potential modifications, in young adults with previously untreated ALL; however, further follow-up data are needed to evaluate long-term survival outcomes.

GRAALL-2005 Regimen

The prospective phase II GRAALL-2003 study evaluated a pediatric-inspired regimen using intensified doses of vincristine, prednisone, and asparaginase for adolescents and adults with Ph-negative ALL (n = 225; median age, 31 years; range, 15–60 years).²⁶⁸ The induction regimen comprised vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide. Patients with high-risk disease and donor availability were allowed to proceed to allogeneic HCT. The EFS and OS rates at 42 months were 55% and 60%, respectively. When data from patients who underwent transplantation at first CR were censored, the DFS rates at 42 months were 52% for patients with high-risk disease and 68% for patients with standard-risk disease (risk assignment based on GRAALL protocol); these DFS outcomes by risk groups were similar to outcomes using the MRC UKALL/ECOG definition for risk classification.²⁶⁸ Advanced age was predictive of poorer survival outcomes on this study; the OS rate at 42 months was 41% for patients older than 45 years compared with 66% for those aged 45 years or younger. Moreover, compared to the younger cohort, patients older than 45 years had a higher cumulative incidence of therapy-related deaths (23% vs. 5%) and deaths in first CR (22% vs. 5%).²⁶⁸ Thus, it seems that the benefit of this pediatric-inspired regimen outweighed the risks for therapy-related deaths only for those patients up to 45 years of age with Ph-negative ALL. The design of the GRAALL-2005 study was similar to the GRAALL-2003 trial, with the addition of randomized evaluation of hyperfractionated

cyclophosphamide during induction and late intensification, as well as randomized evaluation of rituximab in patients with CD20-positive Ph-negative ALL (n = 209; median age, approximately 40 years; range, 18–59 years).²⁶⁹ The estimated 2-year EFS rate in the rituximab group was 65% (95% CI, 56%–75%) compared to the control group at 52% (95% CI, 43%–63%). After a median follow-up of 30 months, EFS was longer in the rituximab group than in the control group (HR, 0.66; 95% CI, 0.45–0.98; *P* = .04).²⁶⁹

USC/MSKCC ALL Regimen Based on CCG-1882 Regimen

The USC ALL trial based on the pediatric CCG-1882 regimen has studied the regimen of daunorubicin, vincristine, prednisone, and methotrexate with augmented PEG in patients between the ages of 18 years and 60 years of age with newly diagnosed ALL (n = 51).^{270,271} The augmented arm included one long-lasting PEG dose in each cycle of the 6 total scheduled doses. Each dose of PEG (2000 IU/m² IV) was preceded with hydrocortisone for hypersensitivity prophylaxis followed by 1 to 2 weeks of oral steroids. Patients on this trial received a mean of 3.8 doses per patient with 45% of patients receiving all 6 doses, while 20% of patients discontinued treatment based on toxicity. The 7-year OS was 51% (58% of these patients were Ph-negative) and the 7-year DFS was 58%. The dose of PEG was lower than the FDA-approved dose of 2500 IU/m² and adjustments to the dosing interval were made to be greater than or equal to 4 weeks. This deviated from the pediatric protocol to account for the difference in drug enzymatic activity in adults. Study data suggest that adaptation of the pediatric regimen to the adult population may be feasible with modifications to reduce toxicity.

CALGB 10403 Regimen

A multicenter phase II Intergroup study (CALGB 10403) was conducted to evaluate a pediatric-inspired regimen in the treatment of AYA patients with Ph-negative ALL. One of the study objectives was to compare the



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

outcomes of patients treated in this trial with those of a similar group of patients (in regard to age and disease characteristics) treated by pediatric oncologists in the COG trial (AALL-0232). The treatment protocol included a 4-drug induction regimen with intrathecal cytarabine and intrathecal methotrexate, consolidation, interim maintenance, delayed intensification, maintenance (for 2–3 years), and radiotherapy (for patients with testicular or CNS disease or those with T-ALL). Results from 295 evaluable patients (median age, 24 years; range 17–39 years) reported 2 post-remission deaths and 3% overall treatment-related mortality.²⁷² The median EFS was 78.1 months (95% CI, 41.8 months to NR) and the 3-year EFS rate was 59% (95% CI, 54%–65%). The estimated 3-year OS rate was 73% (95% CI, 68%–78%).²⁷² It was also noted that post-induction MRD positivity, Ph-like gene expression signatures, and obesity were associated with worse treatment outcomes.²⁷²

COG AALL0434 Regimen

Nelarabine is a nucleoside metabolic inhibitor and a prodrug of ara-G, approved for the treatment of patients with T-ALL with disease that has not responded to or that has relapsed after at least 2 chemotherapy regimens. The randomized phase III COG study (AALL0434) evaluated the safety of nelarabine as part of frontline therapy, using the augmented BFM chemotherapy regimen, with or without nelarabine, and showed that the toxicity profiles were similar between patients with high-risk T-ALL who received nelarabine (n = 47) and those who did not (n = 47).²⁷³ No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral neuropathy, or CNS neurotoxicity. The incidence of adverse events such as febrile neutropenia and elevation of liver enzymes was also similar between treatment groups. These initial safety data suggest that nelarabine may be better tolerated in frontline regimens than in the R/R setting.²⁷³

Results from the efficacy phase of this study evaluated data from 1,895 patients with newly diagnosed T-ALL and T-LL.²⁷⁴ Patients were randomized to receive escalating dose methotrexate without leucovorin rescue and PEG or high-dose methotrexate with leucovorin rescue. Intermediate and high-risk patients with T-ALL and T-LL all received prophylactic or therapeutic cranial irradiation and were randomized into arms with or without nelarabine (650 mg/m²/day). The 4-year DFS rate for T-ALL patients in the nelarabine arm (n = 323) versus those who did not receive nelarabine (n = 336) was 88.9% ± 2.2% and 83.3% ± 2.5%, respectively (P = .0332).²⁷⁴ Compared to the high-dose methotrexate and nelarabine arm, use of escalating-dose methotrexate and nelarabine appeared to enhance the 4-year DFS rates.²⁷⁴ Another report from the COG AALL0434 study determined that compared to high-dose methotrexate, escalating-dose methotrexate combined with augmented BFM chemotherapy improves DFS and OS outcomes in patients with T-ALL.²⁷⁵

A single-arm phase II study from the MDACC evaluated the efficacy of hyper-CVAD plus nelarabine as frontline therapy in adult patients with T-ALL (n = 23).²⁷⁶ With a median follow-up of 30.4 months (range, 2.4–69.2 months), the CR rate for patients with T-ALL was 89%; however, a trend for inferior DFS and OS was observed for patients with ETP ALL.²⁷⁶ After a median follow-up of 42.5 months, the 3-year complete remission duration and OS rates were 66% (95% CI, 52%–77%) and 65% (95% CI, 51%–76%), respectively.²⁷⁷ These studies suggest that for patients with T-ALL, the addition of nelarabine to frontline therapy may be a promising approach.

Hyper-CVAD With or Without Rituximab

The hyper-CVAD regimen constitutes another commonly used ALL treatment regimen for adult patients. A phase II study from MDACC evaluated hyper-CVAD in adolescents and adults with previously



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

untreated ALL (n = 288; median age, 40 years; range, 15–92 years; Ph-positive in 17%).²⁰ The median OS for all patients was 32 months and the 5-year OS rate was 38%, with a median follow-up of 63 months. Among the patients with Ph-negative ALL (n = 234), the 5-year OS rate was 42%.²⁰ Among patients who experienced a CR (92% of all patients), the 5-year CR duration rate was 38%.²⁰ Death during induction therapy occurred in 5% of patients, and was more frequent among patients aged 60 years or older. The 5-year OS in patients aged 60 or older was 17%.²⁰ A subsequent retrospective review from the same institution suggested that this may be related to higher rates of death in remission (34%) relative to younger patients (7%).²⁷⁸

Based on retrospective analyses of data from adults with B-ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on >20% of blasts) was found to be associated with adverse outcomes measured by a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.^{43,279} 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).¹⁶⁰ Among the subgroup of patients with CD20-positive ALL who were treated with hyper-CVAD combined with rituximab, the 3-year CR duration and OS rates were 67% and 61%, respectively. In addition, among the younger patients (age <60 years) with CD20-positive disease, modified hyper-CVAD plus rituximab resulted in a significantly improved CR duration (70% vs. 38%; $P < .001$) and OS rate (75% vs. 47%; $P = .003$) compared with the standard hyper-CVAD regimen without rituximab.¹⁶⁰ No significant differences in outcomes with the addition of rituximab were noted for the subgroup of patients with CD20-negative disease. Notably, older patients (aged ≥60 years) with CD20-positive disease demonstrated higher rates of MRD

negativity with the inclusion of rituximab; however, this did not translate into a survival benefit, again largely due to increased mortality in CR. It is worth noting that this high rate of death in CR for older patients may relate to anthracycline intensification as opposed to rituximab.²⁸⁰

Linker 4-Drug Regimen

Linker et al²⁸¹ evaluated an intensified chemotherapy regimen that incorporated a 4-drug induction regimen (comprising vincristine, daunorubicin, prednisone, and asparaginase) with or without rituximab for CD-20 positive disease in adolescent and adult patients with ALL (n = 84; Ph-positive in 16%; median age, 27 years; range, 16–59 years). The 5-year EFS and OS rates for all patients were 48% and 47%, respectively. Among the patients who experienced a CR (93% of all patients), the 5-year EFS rate was 52%. The 5-year EFS rate was 60% for the subgroup of patients without high-risk features (n = 53).²⁸¹

Blinatumomab

Blinatumomab has shown promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multicenter, single-arm, phase II study, Topp et al²⁸² evaluated the efficacy of blinatumomab in MRD-positive patients with Ph-negative B-ALL (n = 21; age range, 20–77 years). Patients were considered MRD-positive if they had never achieved MRD negativity before blinatumomab, or had experienced a hematologic CR with MRD greater than or equal to 10^{-4} . After blinatumomab treatment, 16 of 20 evaluable patients were determined to be MRD-negative at a detection threshold of 10^{-4} .²⁸² After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.²⁸³ Gökbüget et al²⁸⁴ examined the efficacy of blinatumomab in an expanded cohort (n = 116) using a higher threshold for MRD positivity (hematologic CR with MRD $\geq 10^{-3}$). After one 28-day cycle of blinatumomab, 88 of 113 evaluable patients achieved a complete MRD response, and the RFS rate at 18 months was 54%.²⁸⁴ In both of



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HCT, establishing blinatumomab as an effective “bridge to transplant” in MRD-positive patients. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in patients with R/R B-precursor ALL.²⁸⁵⁻²⁸⁷ In March 2018, the FDA approved blinatumomab use for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR with MRD defined as disease $\geq 0.1\%$ (see *Treatment of Relapsed Ph-Negative ALL* for discussion of studies related to blinatumomab use in R/R B-ALL).

Initial Treatment in Adults with Ph-Negative ALL

Hematopoietic Cell Transplant

Studies evaluating HCT in first CR for AYA patients with Ph-negative ALL have generally been inclusive of adult patients and therefore have been discussed previously (see *Initial Treatment in AYA Patients with Ph-Negative ALL*). More aggressive therapies are being considered for older or less fit patients. A retrospective study of 576 adults, 45 years of age or older, compared RIC or MAC allogeneic HCT from HLA-matched siblings.¹⁹¹ Patients who received RIC (n = 127) versus MAC (n = 449) did not show any statistically significant difference in leukemia-free survival ($P = .23$; HR, 0.84), thereby supporting the incorporation of more aggressive treatments for this population.¹⁹¹

CALGB 8811 Larson Regimen

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).¹¹⁸ Patients aged greater than or equal to 60 years received

a dose-adjusted regimen with a prednisone pulse for only 7 days and a 33% reduction of daunorubicin and cyclophosphamide doses. 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 or patients 60 years and older (69% vs. 39% vs. 17%; $P < .001$). This was largely due to high induction-related mortality (50%) in patients aged greater than or equal to 60 years, contributing to a median OS of 1 month in this population.¹¹⁸ Among the subgroup of patients negative for the Philadelphia chromosome by both cytogenetics and molecular testing (n = 29), median OS was 39 months and the 3-year OS rate was 62%.¹¹⁸

The CALGB 9111 study evaluated the impact of adding granulocyte colony-stimulating factor (G-CSF) after intensive therapy (CALGB 8811 Larson regimen) on neutrophil recovery in adult patients with ALL (n = 198; median age, 35 years; range, 16–83 years).²⁸⁸ Patients were randomized to receive either placebo or G-CSF beginning 4 days after induction, and the G-CSF group continued G-CSF treatment during consolidation. Although the addition of G-CSF did not result in a significant impact in OS or DFS, patients in the G-CSF group had significantly shorter durations of neutropenia and thrombocytopenia, a higher CR rate, and lower induction mortality ($P = .04$) compared to patients in the placebo group.²⁸⁸ Among the 41 patients aged greater than or equal to 60 years randomized to G-CSF (n = 21) or placebo (n = 20), G-CSF use was associated with lower induction mortality (10% vs. 25%); however, this failed to meet statistical significance. The reduction observed with induction mortality was accompanied by a similarly non-significant increase in CR rate for those receiving G-CSF (81% vs. 55%; $P = 0.1$). For the entire elderly group, median OS was improved to 12 months, but 3-year OS remained poor at 17%.²⁸⁸



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

GRAALL-2005 Regimen

Studies evaluating the GRAALL-2003 regimen and GRAALL-2005 regimen with the addition of rituximab for CD20-positive disease included both AYA and adult patients.^{268,269} For discussion of these studies, refer to the previous section (see *Initial Treatment in AYA Patients with Ph-Negative ALL*). The role of standard-dose versus hyperfractionated cyclophosphamide during first induction and late intensification in adults with newly diagnosed Ph-negative ALL was evaluated in a subsequent report from the GRAALL-2005 trial.²⁸⁹ After a median follow-up of 5.2 years, randomization to the hyperfractionated cyclophosphamide arm did not increase the CR rate or prolong EFS or OS rates, and tolerability to this regimen was poor in patients aged greater than or equal to 55 years.²⁸⁹

USC/MSKCC ALL Regimen Based on CCG-1882 Regimen

Studies evaluating USC/MSKCC ALL regimen have included both AYA and adult patients.^{270,271} For discussion of these studies, refer to the previous section (see *Initial Treatment in AYA Patients with Ph-Negative ALL*).

Linker 4-Drug Regimen

The referenced study evaluating the Linker 4-drug regimen included both AYA and adult patients.²⁸¹ For a summary of this study, refer to the previous section (see *Initial Treatment in AYA Patients with Ph-Negative ALL*). In a phase II study, Wieduwilt et al investigated whether the Linker 4-drug regimen could be safely intensified with the addition of pegylated asparaginase, cyclophosphamide, rituximab, dasatinib, and intrathecal liposomal cytarabine in adult patients with ALL or lymphoblastic lymphoma (n = 29; median age, 28 years; range, 20–54 years).²⁹⁰ The CR rate for ALL was 88%. For Ph-negative B-ALL (n = 16), the CR rate was 86%, and for Ph-positive B-ALL (n = 7), the CR rate was 88%.²⁹⁰ With a median follow-up of 32 months, the 2- and 3-year EFS were 59%, and EFS was

similar for B-ALL, T-ALL, lymphoblastic lymphoma, Ph-negative B-ALL, and Ph-positive B-ALL.²⁹⁰

MRC UKALL XII/ECOG E2993

In one of the largest multicenter prospective trials conducted to date (MRC UKALL XII/ECOG E2993 study), previously untreated adolescent and adult patients (n = 1521; aged 15–59 years) received induction therapy consisting of 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).¹⁰⁹ After completion of induction therapy, patients who experienced a CR received intensification therapy with three 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 HCT; all others were randomized to receive autologous HCT or consolidation/maintenance treatment.¹⁰⁹ For Ph-negative disease, high risk was defined as having any of the following factors: aged 35 years or older; time to CR greater than 4 weeks; or elevated WBC count ($>30 \times 10^9/\text{L}$ for B-cell lineage; $>100 \times 10^9/\text{L}$ 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 rates for the subgroups with standard risk (n = 533) and high risk (n = 590) were 54% and 29%, respectively.¹⁰⁹ In the subgroup of patients with T-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 a lower incidence of cumulative relapse.²⁹¹ Among the patients with T-ALL, those with complex cytogenetic abnormalities had a poor 5-year OS outcome (19%).

Hyper-CVAD With or Without Rituximab

Studies evaluating hyper-CVAD with or without rituximab have included both AYA and adult patients.^{20,160} For discussion of these studies, refer to



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

the previous section (see *Initial Treatment in AYA Patients with Ph-Negative ALL*).

Inotuzumab Ozogamicin with Mini-Hyper-CVD

In a phase II study, the efficacy and safety of InO combined with low-intensity chemotherapy (mini-hyper-CVD) was evaluated in older adults with newly diagnosed Ph-negative ALL and an ECOG performance status less than or equal to 3 (n = 52; median age, 68 years; interquartile range, 64–72 years).²⁹² Compared to hyper-CVAD, mini-hyper-CVD has no anthracycline and is composed of reduced doses of dexamethasone (50% reduction), methotrexate (75% reduction), and cytarabine (given every 12 hours at 0.5 g/m² on days 2 and 3). In this study, InO was given on day 3 of the first 4 courses at 1.3–1.8 mg/m² for cycle 1, followed by 1.0–1.3 mg/m² for subsequent cycles.²⁹² In addition, maintenance therapy with dose-reduced POMP (6-MP, vincristine sulfate, methotrexate, and prednisone) was given for 3 years. With a median follow-up of 29 months, the 2-year PFS was 59% (95% CI, 43–72%).²⁹² Some of the most frequent grade 3 and 4 adverse events were prolonged thrombocytopenia (81%), infections during induction and consolidation (52% and 69%, respectively), and hyperglycemia (54%).²⁹² In this study, veno-occlusive disease occurred in 4 patients (8%).

GRAALL-SA1 Regimen

In an effort to decrease toxicity, the GRAALL-SA1 study compared the efficacy and toxicity of pegylated liposomal doxorubicin (Peg-Dox) to continuous infusion doxorubicin (CI-Dox) in elderly patients (≥55 years) with ALL.²⁹³ In this moderate-intensity regimen containing vincristine, dexamethasone, and cyclophosphamide, patients were randomized to receive either CI-Dox (n = 31; 12 mg/m²/day) or Peg-Dox (n = 29; 40 mg/m²).²⁹³ Compared to the CI-Dox arm, the Peg-Dox arm was significantly associated with reduced toxicity and fewer infections, but there was no survival benefit: the induction mortality rate was 8%

(CI-Dox arm, 7% vs. Peg-Dox arm, 10%), the frequency of refractory disease after induction was 10% (CI-Dox arm, 17% vs. Peg-Dox arm, 3%; *P* = .1), and the CR rate was 82% (CI-Dox arm, 90% vs. Peg-Dox arm, 72%; *P* = .1).²⁹³ At 2 years, the estimated death in CR was 26.5% (CI-Dox arm, 37% vs. Peg-Dox arm, 19%), and the OS and EFS rates were statistically similar at 35% and 24% in the CI-Dox and Peg-Dox arms, respectively.²⁹³

GMALL Regimen

In a prospective trial, the GMALL group evaluated the efficacy of a moderate-intensity regimen in older adult patients with Ph-negative ALL (n = 268; age range, 55–85 years).²⁹⁴ The induction therapy consisted of induction I (dexamethasone, vincristine, idarubicin) and induction II (cyclophosphamide, cytarabine), with rituximab added for patients with CD20-positive disease. The original treatment protocol (group 1) was modified to evaluate CNS prophylaxis with liposomal cytarabine and alternative consolidation with asparaginase (group 2); and after induction, one cycle with 500 U/m² pegylated asparaginase was scheduled to evaluate feasibility (group 3). The reported overall CR rate was 76% (n = 203), and the CR rates in groups 1, 2, and 3 were 72%, 86%, and 82%, respectively.²⁹⁴ The 5-year OS rate was 23%, and the 2-year OS rates observed in groups 1 and 2 were 33% and 52%, respectively.²⁹⁴ A major finding from this study included the importance of the ECOG performance status *before* the onset of ALL (ECOGb) at predicting induction mortality. Patients with an ECOGb score greater than or equal to 2 correlated with higher induction mortality rates compared to those with an ECOGb score of 0 to 1 (53% vs. 7%, respectively; *P* < .0001).²⁹⁴ In addition, the study showed that consolidation with native *Escherichia coli* (*E. coli*) asparaginase and pegylated asparaginase was feasible and well tolerated, and was associated with improvements in CR rates and 2-year OS in this older patient subset.²⁹⁴



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

PETHEMA-Based Regimen

The Spanish PETHEMA group conducted phase II prospective studies in older patients with Ph-negative ALL (ALLOLD07; n = 56; age range, 56–79 years).^{295,296} The ALLOLD07 protocol was based on a protocol from EWALL, and treatment comprised a 4-week induction with dexamethasone, vincristine, idarubicin, cyclophosphamide, and cytarabine, followed by consolidation with intermediate-dose methotrexate and native *E. coli* asparaginase. The CR rate was 74% with an early death rate of 13%. The median DFS was 8 months with a median OS of 12 months. This trial included other adapted regimens for Ph-positive ALL and mature B-ALL groups, but the outcomes were poorest in the Ph-negative ALL group.²⁹⁶

Modified DFCI 91-01 Protocol

A retrospective analysis examined the efficacy of a modified version of a DFCI pediatric protocol, DFCI 91-01,^{261,297} in adult patients with newly diagnosed ALL (n = 51; age range, 60–79 years).²⁹⁸ Induction consisted of dexamethasone (in place of prednisone), doxorubicin, cytarabine, and reduced doses of methotrexate, vincristine, and native asparaginase. For patients who achieved CR, the median time to recurrence was 30 months (range, 1–94 months).²⁹⁸ In patients with Ph-negative disease (n = 35), the CR rate was 71%, with induction mortality and primary refractory rates of 20% and 9%, respectively.²⁹⁸ The DFS rate amongst those achieving CR was 57.4% (95% CI, 32.8–75.8%), while the overall estimated 5-year OS was 40.5% (95% CI, 20–60.2%).²⁹⁸

Low-Intensity Chemotherapy and Corticosteroids

For older adult patients with ALL who may also have multiple comorbidities, the utility of traditional chemotherapy backbones based on vincristine, corticosteroids, and an anthracycline is limited largely due to treatment-related toxicities.²⁹⁹ Attempts to identify optimal therapy in this population have included adaptations of palliative regimens including vincristine and corticosteroids, and POMP.³⁰⁰⁻³⁰³ While these regimens are

unlikely to generate cure, they can palliate the disease and extend survival, with clinical outcomes similar to those achieved with more intensive protocols. It is important to note that older adult patients with ALL and multiple comorbidities have not typically qualified for clinical trials. To improve clinical outcomes, trials designed specifically for this population are needed. These should include novel, personalized approaches based on immunophenotype and/or genetic mutation status.

Blinatumomab

The referenced studies evaluating the efficacy of blinatumomab at eradicating MRD during or after multiagent chemotherapy included both AYA and adult patients.²⁸²⁻²⁸⁴ For a discussion of these studies, refer to the previous section (see *Initial Treatment in AYA Patients 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.³⁰⁴⁻³⁰⁶ Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.^{161,307,308} 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%.³⁰⁴ For cases of isolated bone marrow relapse, the 5-year survival estimates among early (n = 412), intermediate (n = 324), and late (n = 387) relapsing disease were 11.5%, 18.0%, and 43.5%, respectively ($P < .0001$). Intermediate relapse was defined as relapse occurring between 18 and 36 months from time of diagnosis; late cases were defined as relapse occurring 36 months or more from time of diagnosis. For cases of isolated CNS relapse, the 5-year survival estimates among early (n = 175), intermediate (n = 180), and late (n = 54) relapsing disease were 43.5%,



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

68.0%, and 78.0%, respectively ($P < .0001$).³⁰⁴ 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.³⁰⁴ In a separate analysis of data from one of the above COG studies (CCG-1952), the timing and site of first relapse were significantly predictive of EFS and OS outcomes, even among the patients with standard-risk ALL ($n = 347$; based on NCI criteria: aged 1 to <10 years and WBC count $<50 \times 10^9/L$).³⁰⁹ Early bone marrow relapse (duration of first CR <36 months) was associated with significantly shorter estimated 3-year EFS (30% vs. 44.5%; $P = .002$) and OS (35% vs. 58%; $P = .001$) rates compared with late bone marrow relapse.³⁰⁹ Similarly, early isolated extramedullary relapse (duration of first CR <18 months) was associated with significantly shorter estimated 3-year EFS (37% vs. 71%; $P = .01$) and OS (55% vs. 81.5%; $P = .039$) rates compared with late extramedullary relapse. In a multivariate regression analysis, early bone marrow and extramedullary relapse were independent predictors of poorer EFS outcomes.³⁰⁹

Data from patients with disease relapse after frontline therapy in the MRC UKALL XII/ECOG E2993 study and PETHEMA studies showed that the median OS after relapse was only 4.5 to 6 months; the 5-year OS rate was 7% to 10%.^{205,206} Approximately 20% to 30% of patients experience a second CR with second-line therapies.^{206,208} Factors predictive of more favorable outcomes after subsequent therapies included younger age and a first CR duration of more than 2 years.^{188,206} Among younger patients (aged <30 years) whose disease relapsed after experiencing a first CR duration longer than 2 years with frontline treatment in PETHEMA trials, the 5-year OS rate from the time of first relapse was 38%.²⁰⁶

Hematopoietic Cell Transplant

HCT is the only potentially curative modality for R/R ALL. Based on findings from evidence-based review of the published literature, the American Society for Blood and Marrow Transplantation guidelines recommend HCT over chemotherapy alone for adult patients with ALL experiencing a second CR.³¹⁰ Several studies have shown that for AYA patients in second CR, allogeneic HCT may improve outcomes, particularly for patients who have early bone marrow relapse or have other high-risk factors.^{307,308,311} Seemingly contradictory data were reported in the COG CCG-1952 study that showed prognosis after early bone marrow relapse in patients with standard-risk ALL (aged 1 to <10 years and WBC count $<50 \times 10^9/L$) remained poor with no apparent advantage of HCT, regardless of timing (ie, early or late) of bone marrow relapse.³⁰⁹ However, data were not available on the conditioning regimen used for HCT in this study for comparison with other trials. The UKALLXII/ECOG2993 trial ($n = 609$; age range, 15–60 years) examined the efficacy of transplantation after relapse in a subgroup of patients with relapsed ALL who had not received prior transplant.²⁰⁵ Patients treated with HCT demonstrated a superior OS at 5 years compared to those treated with chemotherapy alone.²⁰⁵ The CIBMTR group conducted an analysis of outcomes of patients with ALL ($n = 582$; median age, 29 years; range, <1 –60 years) who underwent transplant during relapse.³¹² At 3 years, OS rates were 16% (95% CI, 13%–20%).³¹² Response to salvage therapy prior to HCT may also predict outcome. One retrospective study has shown 3-year OS and EFS estimates of 69% and 62% (respectively) for patients in second or later MRD-negative remission at the time of HCT, similar to the outcomes of those who underwent HCT in MRD-negative first remission at the same center.¹⁹⁰

Blinatumomab

A component of the growing arsenal of immunotherapies for cancer treatment, blinatumomab is a bispecific anti-CD3/CD19 monoclonal



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

antibody that showed high CR rates (69%; including rapid MRD-negative responses) in patients with R/R B-precursor ALL (n = 25).^{287,313}

Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 patients with R/R Ph-negative B-ALL that demonstrated a CR or CR with incomplete platelet recovery (CRp) in 43% of patients within the first two cycles of treatment.^{286,314} In a follow-up prospective, multicenter, randomized, phase III trial, patients with R/R B-cell precursor ALL (n = 405) were assigned to receive either blinatumomab (n = 271) or standard chemotherapy (n = 134).²⁸⁵ The OS was longer in the blinatumomab group, with median OS at 7.7 months, compared to the standard chemotherapy group, with median OS at 4.0 months (95% CI, 0.55–0.93, $P = .01$).²⁸⁵ Remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the standard chemotherapy group with respect to both CR with full hematologic recovery (CR, 34% vs. 16%; $P < .001$) and CR with full, partial, or incomplete hematologic recovery (CR, CRh, or CRi, 44% vs. 25%; $P < .001$).²⁸⁵ Of note, prespecified subgroup analyses of patients with high bone marrow count ($\geq 50\%$) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.²⁸⁵

There are significant and unique side effects to blinatumomab treatment compared to the current standard-of-care regimens. The most significant toxicities noted in clinical studies are CNS events and cytokine release syndrome (CRS). Neurologic toxicities have been reported in 50% of patients (median onset, 7 days) and grade 3 or higher neurologic toxicities, including encephalopathy, convulsions, and disorientation, have occurred in 15% of patients.³¹⁵ CRS typically occurs within the first 2 days following initiation of blinatumomab infusion.³¹⁵ Symptoms of CRS include pyrexia, headache, nausea, asthenia, hypotension, increased transaminases, and increased total bilirubin. The incidence of adverse events can be reduced with monitoring for early intervention at onset of symptoms. However, the serious nature of these events underscores the

importance of receiving treatment in a specialized cancer center that has experience with blinatumomab.

Inotuzumab Ozogamicin

Clinical studies described earlier include patients with relapsed or refractory Ph-positive and Ph-negative ALL.^{246,247} For discussion of these studies, see *Treatment of Relapsed Ph-Positive ALL*.

In a phase II study, the efficacy and safety of InO combined with low-intensity chemotherapy (mini-hyper-CVD) was evaluated in adults with R/R B-ALL (n = 59; median age, 35 years; range, 18–87 years).³¹⁶ The response rate was 78%, with 35 of these patients achieving CR (59%).³¹⁶ The overall MRD negativity rate among responders was 82%. With a median follow-up of 24 months, the median RFS and OS were 8 and 11 months, respectively. The 1-year RFS and OS rates were 40% and 46%, respectively. When using this regimen, the risk of veno-occlusive disease should be considered in patients with previous liver damage and among transplant candidates. In this study, veno-occlusive disease occurred in 9 patients (15%).³¹⁶

In a subsequent report, to reduce the risk of veno-occlusive disease and improve outcomes, the investigators amended the protocol by lowering the weekly InO doses and including 4 cycles of blinatumomab in the consolidation phase.³¹⁷ In a cohort of adult patients with Ph-negative B-ALL treated in first relapse (n = 48; median age, 39 years; range, 18–87 years), the rates of veno-occlusive disease prior to the protocol amendment and after the protocol amendment were 13% (n = 5 of 38) and 0% (n = 0 of 10), respectively.³¹⁷ In addition, based on propensity score matching, the combination of InO with mini-hyper-CVD with or without blinatumomab resulted in better outcomes than inotuzumab alone or intensive salvage chemotherapy.³¹⁷



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

CAR T Cells

One of the early treatments for patients with advanced ALL included adoptive cell therapy to induce a graft-versus-leukemia effect through allogeneic HCT or DLI. However, this method resulted in a significant risk of GVHD. To circumvent this issue, current advances are focused on the use of the patient's own T cells to target the tumor. The generation of CAR T cells to treat ALL is a significant advancement in the field.^{248,318,319} CAR T-cell therapy relies on the genetic manipulation of a patient's T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.²⁴⁹ Briefly, T cells from the patient are harvested and engineered with a receptor that targets a cell surface tumor-specific antigen (eg, CD19 antigen on the surface of leukemic cells). The ability of CAR T cells to be reprogrammed to target any cell-surface antigen on leukemic cells is advantageous and avoids the issue of tumor evasion of the immune system via receptor down regulation.²⁴⁹ The manufacture of CAR T cells requires *ex vivo* viral transduction, activation, and expansion over several days to produce a sufficient cell number to engender disease response.³²⁰ Following infusion, debulking of tumors occurs in less than a week and these cells may remain in the body for extended periods of time to provide immunosurveillance against relapse.

There are several clinical trials using CAR T cells that differ in the receptor construct for patients with relapsed or refractory ALL. One of the first CAR constructs to be investigated, termed 19-28z—which links the CD19 binding receptor to the costimulatory protein CD28—demonstrated an overall CR in 14 out of 16 patients with relapsed or refractory B-ALL following infusion with CAR T cells.³²¹ This average remission rate is significantly improved compared to the average remission rate for patients receiving standard-of-care chemotherapy following relapse (88% vs. approximately 30%).^{205,321-323} Furthermore, 7 out of 16 patients were able to receive an allogeneic HCT, suggesting that CAR T cells may provide a bridge to transplant.³²¹ No relapse has been seen in patients who had

allogeneic HCT (follow-up, 2–24 months); however, 2 deaths occurred from transplant complications. Follow-up data of adult patients enrolled on this trial (n = 53) showed an 83% CR rate after the infusion and 32 patients achieved an MRD-negative CR.³²⁴ At a median follow-up of 29 months (range, 1–65), the median OS was 12.9 months (95% CI, 8.7–23.4 months) and subsequent allogeneic HCT did not appear to improve survival.³²⁴ In contrast, data in children and young adults treated on another clinical trial at the National Institutes of Health/National Cancer Institute with a similar CAR construct suggested consolidative allogeneic HCT post-CAR T-cell therapy might be associated with superior outcomes (2-year cumulative incidence of relapse post-transplant, 9.5%; 5-year EFS post-transplant, 62%).³²⁵ The ZUMA-3 clinical trial phase II results using the CAR T-cell product KTE-X19 (brexucabtagene autoleucel) also showed promising efficacy in adults with R/R ALL, by demonstrating MRD-negative CR in 76% of patients, with a median duration of remission of 12.8 months, a median RFS of 11.6 months, and a median OS of 18.2 months.³²⁶ KTE-X19 is currently being evaluated in children and young adults with R/R ALL.

Other CD19-targeted constructs have been investigated—some comprising an alternative costimulatory protein, 4-1BB—have shown similar results to the 19-28z CAR T cells in terms of overall CR.³²⁷ Relevant in this context are data from the ELIANA trial of CTL019 (tisagenlecleucel) in 75 children and young adults with R/R B-ALL, which demonstrated an overall remission rate of 81% within 3 months of infusion, all of which were notably MRD negative.²⁵² These results led to the approval of CTL019 by the FDA in August 2017 for the treatment of patients up to age 25 years (aged <26 years) with R/R precursor B-ALL. The efficacy of CTL019 in children and young adults with R/R B-ALL in the non-trial setting was recently confirmed using registry data from the CIBMTR. This retrospective analysis showed morphologic CR in 85% of patients.³²⁸ MRD negativity was reported in 99% of CR patients with



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

available data. A comparable proportion of patients experienced durable responses at 12 months in the CIBMTR cohort compared to patients treated on the ELIANA clinical trial (61% and 67%, respectively). At the last update of the ELIANA data at the 2019 American Society of Transplantation and Cellular Therapy (ASTCT) Annual Meeting (median follow-up, 24 months), the median duration of remission and OS was NR and the 24-month RFS probability in responders was 62%. Survival probability curves plateaued after 1 year. Consolidation with allo-HCT after CTL019 was reported in only 9% of CR patients. These updated results suggest treatment with CTL019 in children and young adults with R/R B-ALL could be curative in a subset of patients in the absence of consolidative allo-HCT.³²⁹

As with blinatumomab, T-cell and CAR T-cell activation can be accompanied by severe CRS and neurologic toxicity (immune effector cell-associated neurotoxicity syndrome or ICANS), as well as infectious risks—though treatment-related mortality remains low.²⁵² While side effects from CAR T cells can be severe, they are reversible in most cases. CRS is clinically characterized by high fever, hypotension, tachycardia, and hypoxia; ICANS includes delirium, aphasia, headaches, tremor, focal deficits, and cerebral edema. Higher CRS and ICANS severity have been reported in B-ALL patients compared to non-Hodgkin lymphoma patients after CD19 CAR T-cell therapy.³³⁰ It is recommended to evaluate CRS and ICANS severity using the ASTCT consensus criteria.³³¹ Tocilizumab (interleukin-6 receptor antagonist) and corticosteroids are the cornerstone of CRS and ICANS management. Expert consensus clinical guidelines were recently published by the Society of Immunotherapy of Cancer to guide toxicity management.³³²

Nelarabine

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-ALL who have unresponsive or relapsed disease after at least two chemotherapy regimens. A phase II study of nelarabine monotherapy in children and adolescents with R/R T-ALL or T-cell non-Hodgkin lymphoma (n = 121) showed a 55% response rate among the subgroup with T-ALL with first bone marrow relapse (n = 34) and a 27% response rate in the subgroup with a second or greater bone marrow relapse (n = 36).¹⁶¹ Major toxicities included grade 3 or higher neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single-agent therapy was also evaluated in adults with R/R T-ALL or T-cell lymphoblastic leukemia in a phase II study (n = 39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, n = 26).¹⁶³ The CR rate (including CRi) was 31%; an additional 10% of patients experienced a partial remission. The median DFS and OS were both 20 weeks and the 1-year OS rate was 28%. Grade 3 or 4 myelosuppression was common, but only one case of grade 4 CNS toxicity (reversible) was observed.¹⁶³

There are limited studies of nelarabine combination regimens in adults with R/R T-ALL. In a study by Commander et al, pediatric patients with R/R T-ALL (n = 7; range, 1–19 years) were treated with nelarabine, etoposide, and cyclophosphamide.³³³ In addition, all patients received intrathecal prophylaxis with methotrexate or triple intrathecal therapy with methotrexate, cytarabine, and hydrocortisone. All patients experienced a CR after 1 or 2 courses of therapy. The most common adverse events attributed to nelarabine were grade 2 and 3 sensory and motor neuropathy and musculoskeletal pain.³³³ In phase I of the NECTAR trial, pediatric patients with R/R T-ALL and T-LL (range, 1–21 years) were also treated with nelarabine, etoposide, and cyclophosphamide.³³⁴ Of nine evaluable T-ALL patients, there were two CRs, one partial CR, and one CR in the bone marrow/PR in an extramedullary site for a response rate of 44%.³³⁴



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Augmented Hyper-CVAD

A phase II study from the MDACC evaluated an augmented hyper-CVAD regimen (that incorporated asparaginase, intensified vincristine, and intensified dexamethasone) as therapy in adults with R/R ALL (n = 90; median age, 34 years; range, 14–70 years; median 1 prior regimen).³³⁵ Among evaluable patients (n = 88), the CR rate was 47%; an additional 13% experienced a CRp and 5% experienced a partial remission. The 30-day mortality rate was 9% and median remission duration was 5 months. The median OS for all evaluable patients was 6.3 months; median OS was 10.2 months for patients who experienced a CR. In this study, 32% of patients were able to proceed to HCT.³³⁵

Vincristine Sulfate Liposomal Injection

Vincristine sulfate liposome injection (VSLI) is a novel nanoparticle formulation of vincristine encapsulated in sphingomyelin and cholesterol liposomes; the liposome encapsulation prolongs the exposure of active drug in the circulation and may allow for delivery of increased doses of vincristine without increasing toxicities.^{336,337} VSLI was evaluated in an open-label, multicenter, phase II study in adult patients with Ph-negative ALL (n = 65; median age, 31 years; range, 19–83 years) in second or greater relapse, or with disease that progressed after 2 or more prior lines of therapy (RALLY study).³²³ The CR (CR + CRi) rate with single-agent VSLI was 20%. The median duration of CR was 23 weeks (range, 5–66 weeks) and the median OS for all patients was 20 weeks (range, 2–94 weeks); median OS for patients achieving a CR was 7.7 months.³²³ The incidence of early induction death (30-day mortality rate) was 12%.³²³ These outcomes appeared favorable compared with published single-center historical data in patients with Ph-negative ALL treated with other agents at second relapse (n = 56; CR rate, 4%; median OS, 7.5 weeks; early induction death, 30%).^{323,338} The most common grade 3 or greater treatment-related toxicities with VSLI included neuropathy (23%), neutropenia (15%), and thrombocytopenia (6%).³²³ Based on phase II data

from the RALLY study, VSLI was given accelerated FDA approval in September 2012 for the treatment of adult patients with Ph-negative B-ALL in second or greater relapse. Confirmation of benefit from phase III studies is pending.

Clofarabine

Clofarabine is a nucleoside analog approved for the treatment of pediatric patients (aged 1–21 years) with ALL that is relapsed or refractory after at least two prior regimens. In a phase II study of single-agent clofarabine in heavily pretreated pediatric patients with R/R ALL (n = 61; median age, 12 years; range, 1–20 years), the response rate (CR + CRp) was 20%.³³⁹ Single-agent clofarabine in this setting was associated with severe liver toxicities (generally reversible) and frequent febrile episodes including grade 3 or 4 infections and febrile neutropenia.³³⁹ Phase II studies evaluating the combination of clofarabine with cyclophosphamide and etoposide in pediatric patients with R/R ALL have resulted in response rates ranging from 44% to 52%.^{340,341} This combination has been associated with prolonged and severe myelosuppression, febrile episodes, severe infections (including sepsis or septic shock), mucositis, and liver toxicities including fatal veno-occlusive disease (the latter occurring in the post-allogeneic HCT setting).³⁴⁰

There are limited studies of clofarabine combination regimens in adults with R/R disease. In a study by Miano et al,³⁴² pediatric patients with R/R ALL (n = 24; median age, 7.6 years; range, 1–20 years) were treated with clofarabine, etoposide, and cyclophosphamide, and 42% (10 of 24) of patients responded to treatment, with a 24-month OS rate of 25%.³⁴² In a study from GRAALL, adult patients with R/R ALL (n = 55) were treated with clofarabine in combination with conventional chemotherapy (cyclophosphamide [ENDEVOL cohort; median age, 53 years; range, 18–78 years], or a more intensive regimen with dexamethasone, mitoxantrone, etoposide, and PEG-asparaginase [VANDEVOL cohort;



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

median age, 34 years; range, 19–67 years]). Patients in the ENDEVOL cohort achieved a CR of 50% (9 of 18) and patients in the VANDEVOL cohort yielded a CR rate of 41% (15 of 37); the median OS was 6.5 months after a median follow-up of 6 months.³⁴³ The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%), with an early death rate of 11%.³⁴³ Because the use of clofarabine-containing regimens require close monitoring and intensive supportive care measures, patients should only be treated in centers with expertise in the management of ALL, preferably in the context of a clinical trial.

MOpAD Regimen

A single-arm trial evaluating the efficacy of the MOAD regimen (methotrexate, vincristine, L-asparaginase, and dexamethasone) in newly diagnosed adults with ALL (n = 55) demonstrated a CR rate of 76% with a median CR duration of over 12 months.³⁴⁴ A phase II trial incorporated a new PEGylated formulation of L-asparaginase due to improved tolerability,³⁴⁵ and examined the safety and efficacy of the MOpAD regimen (methotrexate, vincristine, PEG-L-asparaginase, and dexamethasone) in adults with relapsed or refractory ALL (n = 37).³⁴⁶ For patients with Ph-positive ALL, TKIs (ie, imatinib, dasatinib, nilotinib) were added to the regimen and if patients had CD20-positive B-ALL, rituximab was added to the regimen. The CR and ORR rates were 28% and 39%, respectively, with a median duration of response of 4.3 months.³⁴⁶ Patients with Ph-positive ALL had CR and ORR rates of 50% and 67%, respectively.³⁴⁶ This regimen may be considered in patients who have received a maximal dose of anthracycline and have cardiac dysfunction and limited performance status.

TKIs

Studies evaluating other novel TKIs in targeting specific genetic subtypes have been evaluated for the treatment of R/R T-ALL disease. While daratumumab has efficacy in its application for MRD, it has been

reported to have potential preclinical benefit in T-ALL with positive CD38 expression.³⁴⁷ The use of selective BCL2 inhibitor, venetoclax, has been retrospectively analyzed in the treatment of R/R T-ALL. In this analysis, 60% of patients receiving venetoclax plus various chemotherapeutic agents such as hyper-CVAD, nelarabine, or decitabine, achieved remission in marrow blasts, with the median OS of 7.7 months.³⁴⁸ Proteasome inhibition with the use of bortezomib in combination with chemotherapeutic agents has been suggested to improved relapse response rates in T-ALL patients. In a phase II COG study, patients with ALL were treated with reinduction chemotherapy plus bortezomib.³⁴⁹ Relapsed T-ALL patients showed a CR rate of 68%, with end of induction MRD significantly predicting survival.³⁴⁹

NCCN Recommendations for Ph-Negative ALL

AYA Patients with Ph-Negative ALL

The panel recommends that AYA patients with Ph-negative ALL (regardless of risk group) be treated in 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 and data from multi-institutional studies, such as the COG AALL0232, PETHEMA ALL-96, GRAALL-2005 (with rituximab for CD20-positive disease), COG AALL0434 (for T-ALL), DFCI-00-01, or the ongoing CALGB 10403 regimens. Multiagent chemotherapy protocols based on data from single-institution studies, including CCG-1882, the Linker regimen, and hyper-CVAD (with or without rituximab), are also recommended.¹⁶⁰ Treatment regimens should include adequate CNS prophylaxis for all patients. It is 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.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

For patients experiencing a CR following initial induction therapy, monitoring for MRD should be initiated (see *NCCN Recommendations for MRD Assessment*). If the resulting MRD status is negative, continuation of the multiagent chemotherapy protocol for consolidation and maintenance would be appropriate. Consolidation with allogeneic HCT may also be considered, especially if the patient has high-risk features. If the MRD status is positive, blinatumomab (for B-ALL) is recommended or allogeneic HCT may be considered. Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. If the MRD status is unknown, allogeneic HCT is recommended, especially if the patient has high-risk features, although MRD retesting should be considered at first available opportunity. A continuation of multiagent chemotherapy may also be considered, and MRD assessments should be performed at the earliest subsequent opportunity. In all cases, the optimal timing of HCT is unclear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. 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 R/R ALL (see *Patients with Relapsed/Refractory Ph-Negative B-ALL*).

Adult Patients with Ph-Negative ALL

For adult patients with Ph-negative ALL, the panel recommends treatment in 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 (aged <65 years without 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, GRAALL-2005 (with rituximab for CD20-positive disease), hyper-CVAD (with or without rituximab), USC/MSKCC ALL regimen (CCG-1882 regimen), or the MRC UKALL XII/ECOG E2993 regimen. For patients experiencing a CR after initial induction therapy, monitoring for MRD should be initiated (see *NCCN Recommendations for MRD Assessment*). If the resulting MRD status is negative, continuation of the multiagent chemotherapy protocol for consolidation and maintenance is recommended. Consolidation with allogeneic HCT may also be considered, especially if the patient has high-risk features. The effect of WBC counts on prognosis in adult patients with ALL is less firmly established than in pediatric populations. If the MRD status is positive, blinatumomab (for B-ALL) is recommended or allogeneic HCT may be considered. After blinatumomab treatment, consolidative therapy with allogeneic HCT should be considered. If the MRD status is unknown, allogeneic HCT is recommended, especially if the patient has high-risk features. A continuation of multiagent chemotherapy may also be considered. In all cases, the optimal timing of HCT is unclear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplant.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

For adult patients experiencing less than a CR after initial induction therapy, the treatment approach would be similar to that for patients with R/R ALL (see *Patients with Relapsed/Refractory Ph-Negative B-ALL*).

For patients who are less fit (aged ≥ 65 years or patients with substantial comorbidities), the recommended induction therapy includes multiagent chemotherapy regimens or palliative corticosteroids. Dose modifications may be required for chemotherapy agents, as needed. Patients with a CR to induction should be monitored for MRD to identify potential candidates for blinatumomab. If the resulting MRD status is positive, blinatumomab (for B-ALL) is recommended. If the MRD status is negative or unknown, continuation of consolidation with chemotherapy regimens and 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 options are similar to those outlined for patients with R/R ALL (see *Patients with Relapsed/Refractory Ph-Negative B-ALL*).

For recommendations on the treatment of adult patients with mature B-ALL, refer to the [NCCN Guidelines for B-Cell Lymphomas](#).

Patients with Relapsed/Refractory Ph-Negative B-ALL

For patients with R/R Ph-negative B-ALL, the approach to second-line treatment may depend on the duration of the initial response. For late relapses (ie, relapses occurring ≥ 36 months from initial diagnosis), re-treatment with the same induction regimen is a reasonable option. For other patients, participation in a clinical trial is preferred, when possible. In the absence of an appropriate trial, for patients with R/R Ph-negative precursor B-ALL, recommended category 1 options include blinatumomab or InO. As previously mentioned, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease, and increased risk of post-HSCT non-relapse mortality.²⁵¹

Tisagenlecleucel is also an option for patients up to age 25 years/less than 26 years and with refractory disease or greater than or equal to 2 relapses. Other options that may be considered include subsequent chemotherapy, with regimens containing clofarabine, VSLI, augmented hyper-CVAD, MOpAD regimen [for R/R Ph-negative ALL], or other fludarabine-, cytarabine-, or alkylator-containing regimens.³⁵⁰⁻³⁵³ If transplant-naïve patients experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCT following treatment with tisagenlecleucel is unclear. While persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT, further study will be required before conclusive recommendations can be made.²⁵²

The regimens listed for R/R Ph-negative B-ALL may be appropriate for R/R T-ALL; however, nelarabine^{163,354,355} in combination with etoposide and cyclophosphamide is the preferred treatment approach for Ph-negative T-ALL.^{333,334} Other recommended regimens that may be considered include HiDAC, daratumumab,³⁵⁶⁻³⁵⁸ mitoxantrone-, etoposide-, cytarabine,³⁵⁹ chemotherapy containing venetoclax,^{348,360} and bortezomib³⁴⁹ with chemotherapy.

Management of Lymphoblastic Lymphoma

As previously discussed, patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens and should be treated in a center that has experience with lymphoblastic lymphoma. Chemotherapy should be initiated as soon as possible; combination chemotherapy has shown improved response though relapse is common.³⁶¹ In patients with lymphoblastic lymphoma, a 5-year DFS rate between 60% and 80% in children and between 55% and 95% in adults was seen following a



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other CHOP-like regimens.^{362,363} Hyper-CVAD (cycles of fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine) is also a common regimen used for lymphoblastic lymphoma. A response rate of 100% was seen in a singular study, with 91% of patients achieving a CR and a 3-year PFS of 66%.¹⁵⁵ However, it should be noted that 40% to 60% of adults relapse, suggesting that other treatments including HCT may be warranted.

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.^{1,50} CNS leukemia is defined by a WBC count of 5 leukocytes/mcL or greater in the CSF with the presence of lymphoblasts.^{1,50} In children with ALL, CNS leukemia at diagnosis was associated with significantly decreased EFS rates.^{115,364,365} Factors associated with an increased risk for CNS relapse 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.¹²¹ 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.^{366,367} CNS leukemia at diagnosis was associated with a significantly decreased 5-year OS rate in one trial (29% vs. 38%; $P = .03$)³⁶⁶ but not in another trial (35% vs. 31%).³⁶⁷ Factors associated with an increased risk for CNS leukemia in adults include mature B-cell immunophenotype, T-cell immunophenotype, high WBC counts at presentation, and elevated serum LDH levels.^{44,366} 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).^{1,50,121}

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.^{1,121} 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.^{113,365}

Data from the Total Therapy (XV) study by the St. Jude Children's Research Hospital 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 MRD evaluation during induction (day 19) to determine the need for additional doses of asparaginase.^{365,368} The 5-year EFS rate for the AYA population (aged 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).^{365,368} 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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

cumulative incidence of isolated CNS relapse and any CNS relapse was 3% and 4%, respectively, for the entire study population (n = 498).³⁶⁵ Moreover, all 11 patients with isolated CNS relapse were children younger than 12 years of age. 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 HCT.^{365,368}

In adult patients with ALL who received intrathecal chemotherapy and intensive systemic chemotherapy for CNS prophylaxis, the overall CNS relapse rate was 2% to 6%.^{20,123,369,370} 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

CNS involvement should be evaluated with lumbar puncture at timing in accordance with the specific treatment protocol used for each patient. Pediatric-inspired treatment regimens typically include lumbar puncture at diagnostic workup. The panel recommends that intrathecal therapy be administered with initial lumbar puncture. 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 ≥ 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) or with CNS disease that fails to clear after induction intrathecal chemotherapy should receive 18 Gy (in 1.8–2 Gy/fraction) of cranial irradiation. The entire brain and posterior half of the globe should be included. The inferior border should include C2. 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 as well as intrathecal therapy containing methotrexate throughout the treatment course. Adequate systemic therapy should also be given in the management of patients with isolated CNS relapse.

A testicular examination should be performed for all male patients at diagnostic workup; testicular involvement is especially common among patients with T-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 both testes in the scrotal sac. Radiation therapy is typically performed concurrently with the first cycle of maintenance chemotherapy. Testicular total dose should be 24 Gy (in 2.0 Gy/fraction).



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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, CNS involvement, other sites of disease). 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 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. PD 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 or CNS-3 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) without an alternative explanation.

Response in Lymphomatous Extramedullary Disease

To assess treatment response, a CT of the neck/chest/abdomen/pelvis with IV contrast and PET/CT imaging should be performed. A CR in this

context is defined as complete resolution of lymphomatous enlargement by CT scan. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR if it is PET negative. A partial response (PR) is defined as a greater than 50% decrease in the sum product of the greatest perpendicular diameters (SPD) of mediastinal enlargement. PD 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 PD (as defined earlier). For patients with a previous positive PET scan, the post-treatment PET must be positive in at least one previously involved site.

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 (including a testicular examination) and blood tests (CBC with differential). Liver function tests should be performed until normal values are achieved. An assessment of bone marrow aspirate can be considered as clinically indicated at a frequency of 3 to 6 months for the first 5 years; if a bone marrow aspirate is performed, flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests, and MRD assessments should be carried out. If relapse is suspected, a full workup should be considered. For Ph-positive ALL, periodic quantification of the *BCR-ABL1* transcript should be determined. During the second year after completion of therapy, a physical examination (including a testicular examination) and blood tests (CBC with differential) should be performed every 3 to 6 months. During the third year (and beyond) after completion of therapy, physical examination (including a testicular examination) and blood tests (CBC with differential) can be performed every 6 to 12 months or as clinically indicated. Recommendations for survivorship are available



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

in the [NCCN Guidelines for Adolescent and Young Adult \(AYA\) Oncology](#) and [NCCN Guidelines for Survivorship](#).

The COG has published guidelines on long-term survivorship issues for survivors of childhood cancers.³⁷¹ These guidelines serve as a resource for clinicians and family members/caretakers, and have the goal of providing screening and management recommendations for late effects (those that may impact growth, cognitive function, emotional concerns, reproductive health, risks for secondary malignancies, and other important health issues) that may arise during the lifetime of an AYA cancer survivor as a result of the therapeutic agents used during the course of antitumor treatment.

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.^{38,372}

The most frequently used methods for MRD quantification include multiparameter flow cytometry (eg, 6-color or higher) to detect leukemia-associated immunophenotypes, PCR assays to detect fusion genes (eg, *BCR-ABL1*), and NGS-based assays to detect clonal rearrangements in immunoglobulin and/or T-cell receptor genes.³⁷³⁻³⁸⁰ Assays to detect alternative leukemia-specific fusion genes specifically using NGS (as opposed to PCR) are also in development, but are not recommended for MRD quantification outside the context of a clinical trial. The NCCN Panel acknowledges FDA approval of an NGS-based MRD test based on quantification of immunoreceptor genes in patients with ALL, but panel members agreed that both multiparameter flow cytometry or this

FDA-approved NGS approach are suitable methods for MRD quantification.

Current multi-parameter flow cytometry methods can detect leukemic cells at a sensitivity threshold of fewer than 10^{-4} ($<0.01\%$) bone marrow mononuclear cells (MNCs), and PCR/NGS methods can detect leukemic cells at a sensitivity threshold of fewer than 10^{-6} ($<0.0001\%$) bone marrow MNCs.^{374,376,379,380} The concordance rate for quantifying MRD between these methods is generally high at disease burdens 10^{-4} ($>0.01\%$), but NGS is able to detect MRD at lower thresholds.^{375,377,380-384} 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%.³⁸² In another study, both flow cytometry and high-throughput sequencing techniques were used to analyze MRD at a threshold of 0.01% in samples from 619 patients with pediatric B-ALL.³⁸⁰ At the 0.01% threshold, the concordance between both methods was high, but high-throughput sequencing was able to detect MRD at lower thresholds.³⁸⁰ The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.^{376,382,385} However, this practice could lead to an increase in cost without a clear directive in terms of modification of treatment. 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. New multiplexed PCR and NGS for MRD are emerging methodologies.

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 MNCs).^{386,387} An early study in



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

children with ALL (n = 178) showed that patients with detectable MRD after initial induction therapy (42% of patients) had significantly shorter time to relapse than patients with MRD-negative status ($P < .001$), defined by a PCR sensitivity level of less than 1.5×10^{-4} .³⁸⁸ Patients with MRD after induction had a 10-fold increase in risk of death compared with those without detectable MRD. Moreover, the level of detectable MRD was found to correlate with relapse; patients with MRD of 1×10^{-2} or greater had a 16-fold higher risk of relapse compared with those who had MRD levels less than 1×10^{-3} .³⁸⁸ In another study in children with ALL (n = 158), patients with detectable MRD (flow cytometry sensitivity level $< 1 \times 10^{-4}$) at the end of induction therapy had a significantly higher 3-year cumulative incidence of relapse than those who were MRD negative (33% vs. 7.5%; $P < .001$).³⁸⁹ Subsequent studies have confirmed these findings. In a study of 165 patients, the 5-year relapse rate was significantly higher among patients with MRD (flow cytometry sensitivity $< 1 \times 10^{-4}$) versus those without detectable disease (43% vs. 10%; $P < .001$).³⁸⁷ Persistence of MRD during the course of therapy was associated with risk of relapse; the cumulative rate of relapse was significantly higher among patients with MRD persisting through week 14 of continued treatment compared with patients who became MRD-negative by 14 weeks (68% vs. 7%; $P = .035$).³⁸⁷ MRD evaluation was shown to be a significant independent predictor of outcome.

MRD assessments at an earlier time point in the course of treatment (eg, during induction therapy) have been shown to be highly predictive of outcomes in children with ALL. In one study, nearly 50% of patients had MRD clearance (MRD $< 1 \times 10^{-4}$ by flow cytometry) before day 19 of induction therapy (about 2–3 weeks from initiation of induction); the 5-year cumulative incidence of relapse was significantly higher among patients with MRD at day 19 of treatment than those without detectable MRD (33% vs. 6%; $P < .001$).³⁸⁶ 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.³⁷⁹ 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%; $P < .001$).³⁷⁹ Furthermore, the 5-year cumulative incidence of relapse was higher among the subgroup of patients with MRD less than 0.01% (but $\geq 0.001\%$) versus those with MRD less than 0.001% or undetectable disease (13% vs. 5%; $P < .05$). MRD status at the end of induction therapy strongly correlated with MRD levels (flow cytometry sensitivity level $< 0.01\%$) at day 19 during induction; all patients who had MRD of 0.01% or greater at the end of induction had MRD of 0.01% or greater at day 19. Although this study showed that a higher risk of relapse was seen among patients with MRD below the generally accepted threshold level ($< 0.01\%$ but $\geq 0.001\%$) compared with those with very low MRD ($< 0.001\%$) or no detectable disease, further studies are warranted to determine whether this MRD threshold at day 19 should be used to risk stratify patients or guide decisions surrounding treatment intensification.³⁷⁹

In one of the largest collaborative studies conducted in Europe (the AIEOP-BFM ALL 2000 study), children with Ph-negative B-cell lineage ALL (n = 3184 evaluable) were risk stratified according to MRD status (PCR sensitivity level $\leq 0.01\%$) at two time points (days 33 and 78), which were used to guide postinduction treatment.³⁹⁰ 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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

the *ETV6-RUNX1* subtype or hyperdiploidy were either standard risk or intermediate risk based on MRD evaluation.³⁹⁰ The 5-year EFS rate was 92% for patients categorized as standard risk ($n = 1348$), 78% for intermediate risk ($n = 1647$), and 50% for high risk ($n = 189$), resulting in a statistically significant difference among the groups ($P < .001$); the 5-year OS rates were 98%, 93%, and 60%, respectively. MRD-based risk stratification significantly differentiated risks for relapse (between standard- and intermediate-risk subgroups) even among patient populations with *ETV6-RUNX1* or hyperdiploidy. Importantly, in this large-scale study, MRD remained a significant and powerful independent prognostic factor for relapse in the overall population.³⁹⁰

A randomized controlled trial in children and young adults with low-risk ALL according to MRD compared treatment reduction to standard induction ($n = 521$).³⁹¹ Patients were randomized to receive either one or two delayed intensification courses consisting of PEG on day 4; vincristine, dexamethasone (alternate weeks), and doxorubicin for 3 weeks; and 4 weeks of cyclophosphamide and cytarabine. The 5-year EFS between the two cohorts was not statistically significant (94.4% vs. 95.5%; OR, 1; 95% CI, 0.43–2.31; two-sided $P = .99$). No statistical difference was seen regarding relapse or serious adverse events; however, there was a singular treatment-related death in the second delayed intensification cohort and 74 episodes of grade 3 or 4 toxic events. The results suggest that treatment reduction is reasonable for children and young adults with ALL who have a low risk of relapse based on MRD at the end of induction.

A randomized study investigated whether improved outcome could be seen with augmented post-remission therapy for children and young adults stratified by MRD.³⁹² In this trial, 533 patients with a high risk of MRD (defined as clinical standard-risk and intermediate-risk patients with MRD of 0.01% or higher at day 29 of induction) were randomized to receive

standard therapy or augmented post-remission therapy. The augmented treatment regimen included 8 doses of PEG, 18 doses of vincristine, and escalated dosing of intravenous methotrexate without folinic acid rescue during the interim maintenance courses. The 5-year EFS was higher in patients receiving the augmented regimen versus the standard treatment group (89.6% vs. 82.8%; OR, 0.61; 95% CI, 0.39–0.98; $P = .04$). However, it should be noted that more adverse events were seen with the augmented regimen, and no statistically significant benefit was seen in OS at 5 years (92.9% vs. 88.9%; OR, 0.67; 95% CI, 0.38–1.17; $P = .16$).

Stratification based on MRD may also indicate which patients should undergo allogeneic HCT versus continued chemotherapy. Children with an intermediate risk of relapse based on MRD were stratified based on a cutoff MRD level of 10^{-3} .³⁹³ Patients with greater than or equal to MRD of 10^{-3} were allocated to receive HCT ($n = 99$). In this group, 83% had donors and underwent HCT versus 17% who had no suitable donor and therefore continued chemotherapy. The EFS was higher for patients receiving HCT ($64\% \pm 5\%$) versus patients remaining on chemotherapy ($24\% \pm 10\%$). Patients who had a low level of MRD (less than 10^{-3}) were directed to receive continued chemotherapy ($n = 109$). Within this cohort, 83 patients received either chemotherapy or radiotherapy alone and 22 patients received an allogeneic HCT. There was no significant difference in EFS between these two groups ($66\% \pm 6\%$ vs. $80\% \pm 9\%$; $P = .45$). Results indicate that MRD can be useful to further risk stratify patients with intermediate risk of relapse to the appropriate treatment regimen. However, the study acknowledges that MRD cutoff values are regimen dependent as indicated by the divergence from the earlier ALL R3 trial. While the earlier trial advocated for the use of MRD to stratify patients for HCT, a higher threshold for MRD level was used (10^{-4}), a difference that may reflect the more intensive induction regimen.³⁹⁴ Therefore, MRD levels may influence treatment decisions, but the application of this



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

prognostic factor must be carefully evaluated on a regimen-by-regimen basis.

Approximately 20% of children treated with intensive therapies for ALL will ultimately experience disease relapse.³⁹⁵ MRD assessment may play a prognostic role in the management of patients in the relapsed setting.^{396,397} 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% ($P = .008$).³⁹⁶ In addition, in the subgroup of patients who experienced first relapse after cessation of treatment, the 2-year cumulative incidence of second relapse was 49% in patients 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.³⁹⁶ In another study, MRD (PCR sensitivity level $<0.01\%$) was evaluated in high-risk children with ALL ($n = 60$) who experienced first relapse within 30 months from the time of diagnosis.³⁹⁷ Categories based on MRD evaluation after the first chemotherapy cycle (3–5 weeks after initiation of reinduction treatment) included MRD negative (undetectable MRD), MRD positive but unquantifiable (levels $<0.01\%$), and MRD of 0.01% or greater. The 3-year EFS rates based on these MRD categories were 73%, 45%, and 19%, respectively ($P < .05$).³⁹⁷ 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.

Several studies suggest early assessment of MRD during induction treatment (eg, day 15 from initiation of treatment) may be highly predictive

of subsequent relapse in children with ALL.^{398,399} This raises the possibility of identifying patients with high-risk disease who may potentially benefit from earlier intensification or tailoring of treatment regimens, or for potentially allowing less-intensive treatments to be administered in patients at low risk for relapse based on early MRD measurements. Large trials are warranted to address these possibilities, although serial MRD measurements may likely be needed to monitor leukemic cell kinetics during the long course of treatment.

MRD Assessment in Adult ALL

Studies in adults with ALL have shown the strong correlation between MRD and risk for relapse, and the prognostic significance of MRD measurements during and after initial induction therapy.^{372,400-403} In an analysis of postinduction MRD (flow cytometry sensitivity level $<0.05\%$) in adult patients with ALL ($n = 87$), median RFS was significantly longer among patients with MRD less than 0.05% at day 35 compared with those with MRD of 0.05% or greater (42 vs. 16 months; $P = .001$).⁴⁰³ A similar pattern emerged when only the subgroup of patients with morphologic CR at day 35 was included in the MRD evaluation. Although patient numbers were limited, 90% of patients with MRD less than 0.03% at an earlier time point (day 14 during induction therapy) remained relapse-free at 5 years.⁴⁰³ MRD after induction therapy was a significant predictor of relapse in a subgroup analysis from the MRC UKALL/ECOG study of patients with Ph-negative B-cell lineage ALL ($n = 161$).⁴⁰² 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%; $P = .0002$).⁴⁰²

Postinduction MRD can serve as an independent predictor of relapse even among adult patients considered to be standard risk based on traditional prognostic factors. In a study of adult patients with Ph-negative ALL ($n = 116$), MRD status after induction therapy (flow cytometry sensitivity level $<0.1\%$) was significantly predictive of relapse regardless of whether the



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

patient was standard risk or high risk at initial evaluation.⁴⁰¹ Among patients who were initially classified as standard risk, those with MRD of less than 0.1% after induction had a significantly lower risk of relapse at 3 years compared with patients who had higher levels of MRD (9% vs. 71%; $P = .001$). Interestingly, MRD measured during post-consolidation within this protocol was not significantly predictive of outcomes.⁴⁰¹ In the GMALL 06/99 study, patients with standard-risk disease ($n = 148$ evaluable) were monitored for MRD (PCR sensitivity level $<0.01\%$) at various time points during the first year of treatment.⁴⁰⁰ 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 (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%.⁴⁰⁰ 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% on days 11 and 24 (during and after initial induction), and had 3-year DFS and OS rates of 100% (for both endpoints). Patients in the high-risk group (23%) had MRD of 0.01% or greater persisting through week 16, and 3-year DFS and OS rates of 6% and 45%, respectively. All other patients (67%) categorized as intermediate risk had 3-year DFS and OS rates of 53% and 70%, respectively.⁴⁰⁰ Importantly, MRD was the only independently significant predictor of outcome in a multivariate Cox regression analysis that included gender, age, WBC count, B- or T-cell lineage, and MRD. In a prospective study from the MDACC, adult patients with B-ALL ($n = 340$; median age, 52 years; range, 15–84 years) were monitored for MRD by multi-parameter flow cytometry (sensitivity level = 0.01%) at CR and at approximately 3-month intervals after CR.⁴⁰⁴ MRD negative status at CR

significantly correlated with improved DFS and OS, and was an independent predictor of DFS ($P < .05$).⁴⁰⁴

A prospective study (Japan ALL MRD2002) evaluated outcomes by MRD status in adult patients with Ph-negative ALL.⁴⁰⁵ Among the patients who achieved a CR after induction/consolidation ($n = 39$), those who were MRD negative ($<0.1\%$) after induction had a significantly higher 3-year DFS (69% vs. 31%; $P = .004$) compared with patients who were MRD positive; 3-year OS was higher among patients with MRD-negative status after induction, although the difference was not statistically significant (85% vs. 59%). Based on multivariate Cox regression analysis, older age (>35 years) and MRD positivity after induction were significant independent factors predictive of decreased DFS. WBC counts and MRD status after consolidation were not significant predictors of DFS outcomes.⁴⁰⁵

MRD assessment after consolidation therapy has been shown to have prognostic significance, offering the possibility to adjust post-consolidation treatment approaches. In a study that evaluated MRD (PCR sensitivity level $<0.01\%$) after consolidation therapy (weeks 16–22 from initiation of induction) in adult patients with ALL ($n = 142$), patients with MRD of less than 0.01% ($n = 58$) were primarily allotted to receive maintenance chemotherapy for 2 years, whereas those with MRD of 0.01% or greater ($n = 54$) were eligible to undergo allogeneic HCT after high-dose therapy.⁴⁰⁶ 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 post-consolidation (75% vs. 33%; $P = .001$).⁴⁰⁶ In a follow-up to the GMALL 06/99 study mentioned earlier, patients with standard-risk ALL (as defined by Bruggemann et al⁴⁰⁰) who experienced MRD negativity (PCR sensitivity $<0.01\%$ leukemic cells) during the first year of treatment underwent sequential MRD monitoring during



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

maintenance therapy and follow-up.⁴⁰⁷ 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.⁴⁰⁷ 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 non-quantifiable cases) to clinical relapse was 9.5 months; the median time from quantitative MRD detection to clinical relapse was only 4 months.⁴⁰⁷ Detection of post-consolidation MRD was highly predictive of subsequent hematologic relapse and introduced the concept of molecular relapse in ALL.

GMALL investigators evaluated the potential advantage of intensifying or modifying treatment regimens (eg, incorporation of allogeneic HCT) based on post-consolidation 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 $\geq 0.01\%$).⁴⁰⁸ Based on multivariate analysis, molecular response status was a significant independent predictor of both 5-year continuous CR and OS outcomes. Among the patients with disease that did not result in a molecular CR, the subgroup who underwent allogeneic HCT in clinical CR ($n = 57$) showed a significantly higher 5-year continuous CR (66% vs. 12%; $P < .0001$) and a trend for higher OS (54% vs. 33%; $P = .06$) compared with the subgroup without HCT ($n = 63$).⁴⁰⁸ In this latter subgroup of patients with disease that did not result in a molecular CR and who did not undergo HCT, the median time from MRD detection to clinical relapse was approximately 8 months.⁴⁰⁸ 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 HCT.

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 at the end of induction therapy (typically 5–6 weeks after initiation of induction).^{379,386-389,409} In one study, nearly 50% of children had MRD clearance ($<0.01\%$ by flow cytometry) at day 19 of induction therapy.³⁸⁶ 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.^{400,403} Approximately 50% of cases remained MRD positive at 2 months after initiation of induction, with further reductions in the proportion of MRD-positive cases occurring beyond 3 to 5 months.^{372,400} Possible determinants for differences in the kinetics of leukemic cell reduction in the bone marrow may be attributed to the therapeutic regimens, variations in the distribution of immunophenotypic or cytogenetic/molecular features, and other host factors.

NCCN Recommendations for MRD Assessment

Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies. The preferred sample for MRD assessment is the first small-volume (up to 3 mL) pull or early pull of the bone marrow aspirate, if feasible. If the patient is not treated at an academic medical center, there are commercially available tests that should be used for MRD assessment. Six-color flow cytometry can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-4} ($<0.01\%$) bone marrow MNCs, and PCR or NGS methods can detect leukemic cells



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

at a sensitivity threshold of fewer than 1×10^{-6} (<0.0001%) bone marrow MNCs.^{374,376,410,411} The concordance rate for detecting MRD between these methods is generally high. Methods not achieving these sensitivity levels are not suitable. For flow cytometric analysis of MRD, if immunotherapy has been used (eg, rituximab, blinatumomab, InO, or tisagenlecleucel), the lab performing the MRD assessment should be notified.

The timing of MRD assessment varies depending on the ALL treatment protocol used, and may occur during or after completion of initial induction therapy. Therefore, it is recommended that the initial measurement be performed on completion of induction therapy; additional time points for MRD evaluation should be guided by the treatment protocol or regimen used.^{410,411} Importantly, both immunophenotype (B- vs. T-lineage) and genotype may impact the prognostic significance of various levels of MRD at different time points, reflecting the influence of these variables on the kinetics of response to therapy.^{408,412-414} This further highlights the importance of referring to the protocol or regimen being used when interpreting MRD results.

An increase in the frequency of serial monitoring of MRD may be useful in patients with molecular relapse and low-level disease.⁴¹⁵ In general, MRD positivity at the end of induction predicts high relapse rates and should prompt an evaluation for allogeneic HCT. When possible, therapy aimed at eliminating MRD prior to allogeneic HCT is preferred.

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 avascular necrosis with long-term use) and asparaginase (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](#). 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 if receiving vincristine. 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



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

individual patients (see [NCCN Guidelines for Hematopoietic Growth Factors](#)).

Patients with ALL undergoing intensive chemotherapy or allogeneic HCT 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*, CMV 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. For recommendations for the prevention and management of infections in patients with cancer, see the [NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections](#).

High doses of methotrexate can result in toxic plasma methotrexate concentrations in patients with significant renal dysfunction, large effusions/ascites, and delayed methotrexate clearance (plasma methotrexate concentrations >2 SDs of the mean methotrexate excretion curve specific for the dose of methotrexate administered). Toxic plasma methotrexate concentrations in patients may also be observed due to other interacting medications. 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* in the algorithm). Drug interactions with trimethoprim-sulfamethoxazole (TMP/SMX) and methotrexate can worsen methotrexate toxicity,⁴¹⁶ so the panel recommends holding TMP/SMX when high-dose methotrexate is administered, and re-starting when methotrexate clearance is achieved per treatment protocol or institutional guidelines.

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 B-Cell Lymphomas](#). 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](#). Leukostasis is characterized by highly elevated WBC count (usually >100 × 10⁹/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, immunotherapies, 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 every ALL induction regimen, and are 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 to minimize the risk of developing



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

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 should be considered during steroid therapy to reduce these risks. There may also be important drug interactions between PPIs and methotrexate that need to be considered prior to initiation of methotrexate-based therapy. Although uncommon, the use of high-dose corticosteroids can be associated with mood alterations, psychosis, and other neuropsychiatric complications in patients with malignancies;⁴¹⁷⁻⁴²⁰ in this context, consider anti-psychotics. If no response, dose reductions may be required in these situations. A potential long-term side effect associated with steroid therapy includes osteonecrosis/avascular necrosis.^{421,422} 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.^{421,423-427} In children and adolescents (aged 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, to 10% to 13.5% in patients between the ages of 10 and 15 years, to 18% to 20% in patients aged 16 years and older.^{423,424} 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.⁴²¹ Older children (aged >10 years) had a significantly higher cumulative incidence of osteonecrosis (45% vs. 10%; $P < .001$) compared with younger children (aged ≤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.⁴²¹

In a 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.⁴²⁷ 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).⁴²⁴ 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 CCG-1961 trial randomized patients ($n = 2056$; aged 1–21 years) to postinduction intensification treatment with intermittent dose scheduling of dexamethasone (10 mg/m² daily on days 0–6 and days 14–20) versus continuous doses of dexamethasone (10 mg/m² daily on days 0–20).⁴²³ Among older children and adolescents (aged ≥10 years) who had rapid response to induction, use of intermittent dexamethasone during the 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.⁴²³ 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. In severe avascular necrosis cases, consider withholding steroids from therapy.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

When patients are treated with InO, liver enzymes— especially bilirubin— should be closely monitored because veno-occlusive disease or sinusoidal obstruction syndrome may occur.⁴²⁸ Ursodiol may be considered for veno-occlusive disease prophylaxis.^{429,430} Defibrotide may be considered for patients who develop veno-occlusive disease related to InO toxicity.⁴³¹ If InO is being given as a bridge to allogeneic HCT, double alkylator conditioning is strongly discouraged.^{429,430} Patients treated with blinatumomab and tisagenlecleucel should be monitored for CRS and neurologic toxicity. For CRS (including refractory CRS), tocilizumab should be considered.⁴³² Upon development of CRS, the panel recommends holding blinatumomab infusions with consideration for steroids and/or vasopressors for patients with severe symptoms according to manufacturer guidelines and prescribing information. During the first month after tisagenlecleucel infusion, prophylaxis with anti-seizure medication may be considered.^{433,434} For additional information regarding guidelines for immunotherapy-related toxicities, see [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

Asparaginase is also a core component of ALL regimens, most often given during induction and consolidation for Ph-negative disease and should only be used in specialized centers. In this context, patients should also be closely monitored in the period during and after infusion for allergic response. Four different formulations of the enzyme have been approved by the FDA: 1) asparaginase derived from *E. coli* that has been modified with a covalent linkage to PEG; 2) calaspargase pegol-mknl (Cal-PEG) (in patients ≤21 years); 3) asparaginase derived from a different Gram-negative bacteria *Erwinia chrysanthemi* (*Erwinia* asparaginase); and 4) asparaginase *Erwinia chrysanthemi* (recombinant). These formulations differ in their pharmacologic properties, and may also differ in terms of immunogenicity.⁴³⁵⁻⁴³⁸ In some regimens, asparaginase is significantly associated with potentially severe hypersensitivity reactions (including anaphylaxis) due to anti-asparaginase antibodies and lack of efficacy in

some cases. PEG seems to be associated with a lower incidence of neutralizing antibodies compared with native asparaginase.⁴³⁹ However, cross-reactivity between neutralizing antibodies against native *E. coli* asparaginase and pegaspargase has been reported.^{440,441} Moreover, a high anti-asparaginase antibody level after initial therapy with native *E. coli* asparaginase was associated with decreased asparaginase activity during subsequent therapy with pegaspargase.⁴⁴² In contrast, no cross-reactivity between antibodies against native *E. coli* asparaginase and *Erwinia* asparaginase was reported,^{440,441} and enzyme activity of *Erwinia* asparaginase was not affected by the presence of anti-*E. coli* asparaginase antibodies.⁴⁴² 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.⁴⁴³

Similar to PEG, calaspargase pegol is a newer asparaginase enzyme formulation with a different linker molecule that enhances its hydrolytic stability.⁴³⁵ A multicenter, open-label, randomized study determined the pharmacokinetic and pharmacodynamic profiles of PEG and calaspargase pegol to be similar in patients with high-risk ALL (n = 165; age range, 1–30.99 years), with the latter exhibiting a longer half-life.⁴³⁵ The DFCI ALL Consortium also evaluated whether calaspargase pegol could be administered less frequently than PEG with similar toxicity profiles and serum asparaginase activity (SAA).⁴⁴⁴ In this study, patients with newly diagnosed ALL (n = 230; age range, 1–21 years) were randomized to receive an intravenous dose (2500 IU/m²) of either PEG or calaspargase pegol. The SAA was similar for both enzymes at 4, 11, and 18 days after the induction dose, but the SAA was higher for calaspargase pegol 25 days after induction, suggesting the potential for this enzyme to be given less frequently than PEG.⁴⁴⁴ However, longer follow-up is needed to



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

determine the survival outcomes associated with this finding. The FDA approved calaspargase pegol in December 2018 for use as part of multiagent chemotherapy in pediatric and AYA patients (aged ≤21 years) with ALL.

Native *E. coli* asparaginase is no longer available; therefore, the NCCN Panel recommends the use of PEG in the treatment of patients with ALL. For patients who develop severe hypersensitivity reactions during treatment with PEG, *Erwinia* asparaginase or recombinant *Erwinia* asparaginase may be substituted (see *Supportive Care: Asparaginase Toxicity Management* in the algorithm). *Erwinia* asparaginase and recombinant *Erwinia* asparaginase are currently approved by the FDA for patients with ALL who have developed hypersensitivity to *E. coli*-derived asparaginase. If the patient experiences grade 1 or grade 2 reactions including rash, flushing, urticaria, and drug fever greater than or equal to 38°C without bronchospasm, hypotension, edema, or need for parenteral intervention, the asparaginase that caused the reaction may be continued with consideration for anti-allergy premedication (such as hydrocortisone, famotidine or ranitidine, diphenhydramine, and acetaminophen). Measures can be considered for preventing or limiting severity of infusion reactions or hypersensitivity including slowing infusion to greater than or equal to 2 hours, infusing normal saline concurrently, and use of premedications. If anti-allergy medication is used prior to PEG or *Erwinia* asparaginase administration, consideration should be given to therapeutic drug monitoring using commercially available asparaginase activity assays, since premedication may mask the systemic allergic reactions that can indicate the development of neutralizing antibodies.⁴⁴⁵ However, if the patient experiences anaphylaxis or other allergic reactions of grade 3 or 4 severity (CTCAE 4.03), permanent discontinuation of the causative asparaginase is warranted.

Asparaginase can be associated with various toxicities, including pancreatitis (ranging from asymptomatic cases with amylase or lipase elevation, to symptomatic cases with vomiting or severe abdominal pain), hepatotoxicity (eg, increased alanine or glutamine aminotransferase), and coagulopathy (eg, thrombosis, hemorrhage). Detailed recommendations for the management of asparaginase toxicity in AYA and adult patients were published,⁴³⁸ and have been incorporated into the NCCN Guidelines for ALL (see *Supportive Care: Asparaginase Toxicity Management* in the algorithm).

Pain management should be employed for patients with cancer, regardless of disease stage. For discussion of the central principles of pain assessment and management, see the [NCCN Guidelines for Adult Cancer Pain](#).



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

References

1. Jabbour EJ, Faderl S, Kantarjian HM. Adult acute lymphoblastic leukemia. Mayo Clin Proc 2005;80:1517-1527. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16295033>.
2. Howlader N NA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review 1975-2018. National Cancer Institute 2021. Available at: https://seer.cancer.gov/csr/1975_2018/.
3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33. Available at: <https://pubmed.ncbi.nlm.nih.gov/33433946/>.
4. Esparza SD, Sakamoto KM. Topics in pediatric leukemia--acute lymphoblastic leukemia. MedGenMed 2005;7:23. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16369328>.
5. Hasle H. Pattern of malignant disorders in individuals with Down's syndrome. Lancet Oncol 2001;2:429-436. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11905737>.
6. Whitlock JA. Down syndrome and acute lymphoblastic leukaemia. Br J Haematol 2006;135:595-602. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17054672>.
7. Swaminathan M, Bannan SA, Routbort M, et al. Hematologic malignancies and Li-Fraumeni syndrome. Cold Spring Harb Mol Case Stud 2019;5. Available at: <https://pubmed.ncbi.nlm.nih.gov/30709875/>.
8. Stiller CA, Chessells JM, Fitchett M. Neurofibromatosis and childhood leukaemia/lymphoma: a population-based UKCCSG study. Br J Cancer 1994;70:969-972. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7947106>.
9. Shaw MP, Eden OB, Grace E, Ellis PM. Acute lymphoblastic leukemia and Klinefelter's syndrome. Pediatr Hematol Oncol 1992;9:81-85. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1558779>.
10. Gurgey A, Kara A, Tuncer M, et al. Acute lymphoblastic leukemia associated with Klinefelter syndrome. Pediatr Hematol Oncol 1994;11:227-229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8204450>.
11. Machatschek JN, Schrauder A, Helm F, et al. Acute lymphoblastic leukemia and Klinefelter syndrome in children: two cases and review of the literature. Pediatr Hematol Oncol 2004;21:621-626. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15626018>.
12. Flatt T, Neville K, Lewing K, Dalal J. Successful treatment of fanconi anemia and T-cell acute lymphoblastic leukemia. Case Rep Hematol 2012;2012:396395. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22937327>.
13. Yetgin S, Tuncer M, Guler E, et al. Acute lymphoblastic leukemia in Fanconi's anemia. Am J Hematol 1994;45:94. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8250016>.
14. Strevens MJ, Lilleyman JS, Williams RB. Shwachman's syndrome and acute lymphoblastic leukaemia. Br Med J 1978;2:18. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/277273>.
15. Woods WG, Roloff JS, Lukens JN, Krivit W. The occurrence of leukemia in patients with the Shwachman syndrome. J Pediatr 1981;99:425-428. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7264801>.
16. Passarge E. Bloom's syndrome: the German experience. Ann Genet 1991;34:179-197. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1809225>.
17. Taylor AM, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. Blood 1996;87:423-438. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8555463>.
18. Ma H, Sun H, Sun X. Survival improvement by decade of patients aged 0-14 years with acute lymphoblastic leukemia: a SEER analysis. Sci



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Rep 2014;4:4227. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24572378>.

19. Pulte D, Gondos A, Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. *Blood* 2009;113:1408-1411. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18974371>.

20. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer* 2004;101:2788-2801. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15481055>.

21. Pulte D, Jansen L, Gondos A, et al. Survival of adults with acute lymphoblastic leukemia in Germany and the United States. *PLoS One* 2014;9:e85554. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24475044>.

22. Sive JI, Buck G, Fielding A, et al. Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. *Br J Haematol* 2012;157:463-471. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22409379>.

23. Geyer MB, Hsu M, Devlin SM, et al. Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. *Blood* 2017;129:1878-1881. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28122741>.

24. Wermann WK, Viardot A, Kayser S, et al. Comorbidities are frequent in older patients with de novo acute lymphoblastic leukemia (ALL) and correlate with induction mortality: Analysis of more than 1200 patients from GMALL data bases. *Blood* 2018;132:660. Available at:

http://www.bloodjournal.org/content/132/Suppl_1/660.

25. Stock W. Adolescents and young adults with acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program* 2010;2010:21-29.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21239766>.

26. Tasian SK, Loh ML, Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. *Blood* 2017;130:2064-2072. Available at:

<https://pubmed.ncbi.nlm.nih.gov/28972016/>.

27. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed February 1, 2019.

28. Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. *Cancer* 2010;116:1165-1176. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20101737>.

29. Amin HM, Yang Y, Shen Y, et al. Having a higher blast percentage in circulation than bone marrow: clinical implications in myelodysplastic syndrome and acute lymphoid and myeloid leukemias. *Leukemia* 2005;19:1567-1572. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16049515>.

30. Weinkauff R, Estey EH, Starostik P, et al. Use of peripheral blood blasts vs bone marrow blasts for diagnosis of acute leukemia. *Am J Clin Pathol* 1999;111:733-740. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10361507>.

31. Borowitz MJ, Chan JKC. B lymphoblastic leukaemia/lymphoma, not otherwise specified In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* (ed 4th). Lyon: IARC; 2008:168-170.

32. Borowitz MJ, Chan JKC. 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 176-178.

33. Borowitz MJ, Chan JKC. B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities. In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* (ed 4th). Lyon: IARC; 2008:171-175.

34. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

leukemia. Blood 2016;127:2391-2405. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/27069254>.

35. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009;10:125-134. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19138562>.

36. Roberts KG, Gu Z, Payne-Turner D, et al. High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. J Clin Oncol 2017;35:394-401. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27870571>.

37. Harrison CJ, Moorman AV, Schwab C, et al. An international study of intrachromosomal amplification of chromosome 21 (iAMP21): cytogenetic characterization and outcome. Leukemia 2014;28:1015-1021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24166298>.

38. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol 2011;29:532-543. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21220592>.

39. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med 2004;350:1535-1548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15071128>.

40. Bassan R, Gatta G, Tondini C, Willemze R. Adult acute lymphoblastic leukaemia. Crit Rev Oncol Hematol 2004;50:223-261. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15182827>.

41. Burmeister T, Meyer C, Schwartz S, et al. The MLL recombinome of adult CD10-negative B-cell precursor acute lymphoblastic leukemia: results from the GMALL study group. Blood 2009;113:4011-4015. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19144982>.

42. Gleissner B, Goekbuget N, Rieder H, et al. CD10- pre-B acute lymphoblastic leukemia (ALL) is a distinct high-risk subgroup of adult ALL associated with a high frequency of MLL aberrations: results of the German Multicenter Trials for Adult ALL (GMALL). Blood

2005;106:4054-4056. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16123216>.

43. Thomas DA, O'Brien S, Jorgensen JL, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. Blood 2009;113:6330-6337. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18703706>.

44. Gokbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2006:133-141. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17124052>.

45. Coustan-Smith E, Mullighan CG, Onciu M, et al. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol 2009;10:147-156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19147408>.

46. Zhang J, Ding L, Holmfeldt L, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 2012;481:157-163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22237106>.

47. Schrauder A, Reiter A, Gadner H, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results from ALL-BFM 90 and 95. J Clin Oncol 2006;24:5742-5749. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17179108>.

48. Armstrong SA, Look AT. Molecular genetics of acute lymphoblastic leukemia. J Clin Oncol 2005;23:6306-6315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16155013>.

49. Moorman AV, Chilton L, Wilkinson J, et al. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Blood 2010;115:206-214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19897583>.

50. Seibel NL. Treatment of acute lymphoblastic leukemia in children and adolescents: peaks and pitfalls. Hematology Am Soc Hematol Educ



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Program 2008:374-380. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19074113>.

51. Burmeister T, Schwartz S, Bartram CR, et al. Patients' age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group. *Blood* 2008;112:918-919. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18650471>.

52. Gleissner B, Gokbuget N, Bartram CR, et al. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. *Blood* 2002;99:1536-1543. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11861265>.

53. Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006;354:166-178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16407512>.

54. Arico M, Valsecchi MG, Camitta B, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med* 2000;342:998-1006. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10749961>.

55. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med* 2009;360:470-480. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19129520>.

56. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014;371:1005-1015. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25207766>.

57. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. *Cancer Cell* 2012;22:153-166. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22897847>.

58. Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood* 2017;129:572-581. Available at: <https://pubmed.ncbi.nlm.nih.gov/27919910/>.

59. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014;371:1005-1015. Available at: <https://pubmed.ncbi.nlm.nih.gov/25207766/>.

60. Roberts KG, Yang YL, Payne-Turner D, et al. Oncogenic role and therapeutic targeting of ABL-class and JAK-STAT activating kinase alterations in Ph-like ALL. *Blood Adv* 2017;1:1657-1671. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29296813>.

61. Heerema NA, Carroll AJ, Devidas M, et al. Intrachromosomal amplification of chromosome 21 is associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary standard-risk children's oncology group studies: a report from the children's oncology group. *J Clin Oncol* 2013;31:3397-3402. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23940221>.

62. Moorman AV, Robinson H, Schwab C, et al. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. *J Clin Oncol* 2013;31:3389-3396. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23940220>.

63. Moorman AV, Richards SM, Robinson HM, et al. Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). *Blood* 2007;109:2327-2330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17095619>.

64. Schultz KR, Pullen DJ, Sather HN, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). *Blood* 2007;109:926-935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17003380>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

65. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet* 2013;45:242-252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23334668>.

66. Muhlbacher V, Zenger M, Schnittger S, et al. Acute lymphoblastic leukemia with low hypodiploid/near triploid karyotype is a specific clinical entity and exhibits a very high TP53 mutation frequency of 93%. *Genes Chromosomes Cancer* 2014;53:524-536. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24619868>.

67. Carroll AJ, Shago M, Mikhail FM, et al. Masked hypodiploidy: Hypodiploid acute lymphoblastic leukemia (ALL) mimicking hyperdiploid ALL in children: A report from the Children's Oncology Group. *Cancer Genet* 2019;238:62-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31425927>.

68. Boer JM, van der Veer A, Rizopoulos D, et al. Prognostic value of rare IKZF1 deletion in childhood B-cell precursor acute lymphoblastic leukemia: an international collaborative study. *Leukemia* 2016;30:32-38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26202931>.

69. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature* 2008;453:110-114. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18408710>.

70. Caye A, Beldjord K, Mass-Malo K, et al. Breakpoint-specific multiplex polymerase chain reaction allows the detection of IKZF1 intragenic deletions and minimal residual disease monitoring in B-cell precursor acute lymphoblastic leukemia. *Haematologica* 2013;98:597-601. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23065506>.

71. Stanulla M, Dagdan E, Zaliouva M, et al. IKZF1(plus) Defines a New Minimal Residual Disease-Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia. *J Clin Oncol* 2018;36:1240-1249. Available at: <https://pubmed.ncbi.nlm.nih.gov/29498923/>.

72. Beldjord K, Chevret S, Asnafi V, et al. Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia. *Blood* 2014;123:3739-3749. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24740809>.

73. Dupuis A, Gaub MP, Legrain M, et al. Biclinal and biallelic deletions occur in 20% of B-ALL cases with IKZF1 mutations. *Leukemia* 2013;27:503-507. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22868967>.

74. Mi JQ, Wang X, Yao Y, et al. Newly diagnosed acute lymphoblastic leukemia in China (II): prognosis related to genetic abnormalities in a series of 1091 cases. *Leukemia* 2012;26:1507-1516. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22297722>.

75. Ribera J, Morgades M, Zamora L, et al. Prognostic significance of copy number alterations in adolescent and adult patients with precursor B acute lymphoblastic leukemia enrolled in PETHEMA protocols. *Cancer* 2015;121:3809-3817. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26194343>.

76. Martinelli G, Iacobucci I, Storlazzi CT, et al. IKZF1 (Ikaros) deletions in BCR-ABL1-positive acute lymphoblastic leukemia are associated with short disease-free survival and high rate of cumulative incidence of relapse: a GIMEMA AL WP report. *J Clin Oncol* 2009;27:5202-5207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19770381>.

77. Iacobucci I, Storlazzi CT, Cilloni D, et al. Identification and molecular characterization of recurrent genomic deletions on 7p12 in the IKZF1 gene in a large cohort of BCR-ABL1-positive acute lymphoblastic leukemia patients: on behalf of Gruppo Italiano Malattie Ematologiche dell'Adulto Acute Leukemia Working Party (GIMEMA AL WP). *Blood* 2009;114:2159-2167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19589926>.

78. van der Veer A, Waanders E, Pieters R, et al. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. *Blood*



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

2013;122:2622-2629. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23974192>.

79. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med* 2009;360:470-480. Available at: <https://pubmed.ncbi.nlm.nih.gov/19129520/>.

80. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol* 1996;14:18-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8558195>.

81. Brown P, Pieters R, Biondi A. How I treat infant leukemia. *Blood* 2019;133:205-214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30459160>.

82. Hunger SP, Loh ML, Whitlock JA, et al. Children's Oncology Group's 2013 blueprint for research: acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2013;60:957-963. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23255467>.

83. Gadner H, Masera G, Schrappe M, et al. The Eighth International Childhood Acute Lymphoblastic Leukemia Workshop ('Ponte di legno meeting') report: Vienna, Austria, April 27-28, 2005. *Leukemia* 2006;20:9-17. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16281070>.

84. Reshmi SC, Harvey RC, Roberts KG, et al. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. *Blood* 2017;129:3352-3361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28408464>.

85. Behm FG, Raimondi SC, Frestedt JL, et al. Rearrangement of the MLL gene confers a poor prognosis in childhood acute lymphoblastic leukemia, regardless of presenting age. *Blood* 1996;87:2870-2877. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8639906>.

86. Pui CH, Chessells JM, Camitta B, et al. Clinical heterogeneity in childhood acute lymphoblastic leukemia with 11q23 rearrangements.

Leukemia 2003;17:700-706. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12682627>.

87. Donadieu J, Auclerc MF, Baruchel A, et al. Prognostic study of continuous variables (white blood cell count, peripheral blast cell count, haemoglobin level, platelet count and age) in childhood acute lymphoblastic leukaemia. Analysis Of a population of 1545 children treated by the French Acute Lymphoblastic Leukaemia Group (FRALLE). *Br J Cancer* 2000;83:1617-1622. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11104555>.

88. Romana SP, Mauchauffe M, Le Coniat M, et al. The t(12;21) of acute lymphoblastic leukemia results in a tel-AML1 gene fusion. *Blood* 1995;85:3662-3670. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7780150>.

89. Sutcliffe MJ, Shuster JJ, Sather HN, et al. High concordance from independent studies by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favorable prognosis with combined trisomies 4, 10, and 17 in children with NCI Standard-Risk B-precursor Acute Lymphoblastic Leukemia: a Children's Oncology Group (COG) initiative. *Leukemia* 2005;19:734-740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15789069>.

90. Boissel N, Auclerc M-F, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *J Clin Oncol* 2003;21:774-780. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12610173>.

91. Ramanujachar R, Richards S, Hann I, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. *Pediatr Blood Cancer* 2007;48:254-261. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16421910>.

92. Zhang MJ, Hoelzer D, Horowitz MM, et al. Long-term follow-up of adults with acute lymphoblastic leukemia in first remission treated with chemotherapy or bone marrow transplantation. *The Acute Lymphoblastic*



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Leukemia Working Committee. Ann Intern Med 1995;123:428-431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7639442>.

93. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol 2004;22:4075-4086. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15353542>.

94. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2008;111:1827-1833. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18048644>.

95. Vey N, Thomas X, Picard C, et al. Allogeneic stem cell transplantation improves the outcome of adults with t(1;19)/E2A-PBX1 and t(4;11)/MLL-AF4 positive B-cell acute lymphoblastic leukemia: results of the prospective multicenter LALA-94 study. Leukemia 2006;20:2155-2161. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17039234>.

96. Thiebaut A, Vernant JP, Degos L, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation. A follow-up report of the French protocol LALA 87. Hematol Oncol Clin North Am 2000;14:1353-1366, x. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11147227>.

97. Nachman J. Clinical characteristics, biologic features and outcome for young adult patients with acute lymphoblastic leukaemia. Br J Haematol 2005;130:166-173. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16029445>.

98. Aguiar RC, Sohal J, van Rhee F, et al. TEL-AML1 fusion in acute lymphoblastic leukaemia of adults. M.R.C. Adult Leukaemia Working Party. Br J Haematol 1996;95:673-677. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8982044>.

99. Secker-Walker LM, Craig JM, Hawkins JM, Hoffbrand AV. Philadelphia positive acute lymphoblastic leukemia in adults: age distribution, BCR breakpoint and prognostic significance. Leukemia 1991;5:196-199. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2013979>.

100. Neumann M, Heesch S, Gokbuget N, et al. Clinical and molecular characterization of early T-cell precursor leukemia: a high-risk subgroup in adult T-ALL with a high frequency of FLT3 mutations. Blood Cancer J 2012;2:e55. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22829239>.

101. Pieters R, Kaspers GJ, Klumper E, Veerman AJ. Clinical relevance of in vitro drug resistance testing in childhood acute lymphoblastic leukemia: the state of the art. Med Pediatr Oncol 1994;22:299-308. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8127253>.

102. Raetz EA, Devidas M, Carroll AJ, et al. Cytogenetic and early-response characteristics of adolescents and young adults with acute lymphoblastic leukemia (ALL): A Children's Oncology Group (COG) study [abstract]. J Clin Oncol 2010;28:Abstract 9509. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.9509.

103. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. Cancer 2006;107:1645-1655. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16906507>.

104. Fern LA, Whelan JS. Recruitment of adolescents and young adults to cancer clinical trials--international comparisons, barriers, and implications. Semin Oncol 2010;37:e1-8. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20494693>.

105. Schmiegelow K, Heyman M, Gustafsson G, et al. The degree of myelosuppression during maintenance therapy of adolescents with B-lineage intermediate risk acute lymphoblastic leukemia predicts risk of relapse. Leukemia 2010;24:715-720. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20130603>.

106. Martin S, Ulrich C, Munsell M, et al. Delays in cancer diagnosis in underinsured young adults and older adolescents. Oncologist



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

2007;12:816-824. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17673613>.

107. Hoelzer D, Thiel E, Loffler H, et al. Intensified therapy in acute lymphoblastic and acute undifferentiated leukemia in adults. *Blood* 1984;64:38-47. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/6375764>.

108. Hoelzer D, Thiel E, Loffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood* 1988;71:123-131. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/3422030>.

109. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood* 2005;106:3760-3767. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16105981>.

110. Moorman AV, Harrison CJ, Buck GAN, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood* 2007;109:3189-3197. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17170120>.

111. Charrin C, Thomas X, Ffrench M, et al. A report from the LALA-94 and LALA-SA groups on hypodiploidy with 30 to 39 chromosomes and near-triploidy: 2 possible expressions of a sole entity conferring poor prognosis in adult acute lymphoblastic leukemia (ALL). *Blood* 2004;104:2444-2451. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15039281>.

112. Pullarkat V, Slovak ML, Kopecky KJ, et al. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. *Blood* 2008;111:2563-2572. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18156492>.

113. Kamps WA, Bokkerink JP, Hakvoort-Cammel FG, et al. BFM-oriented treatment for children with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk patients: results of DCLSG protocol ALL-8 (1991-1996). *Leukemia* 2002;16:1099-1111.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12040440>.

114. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 2008;111:4477-4489.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18285545>.

115. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. *Blood* 2000;95:3310-3322. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10828010>.

116. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood* 2008;111:2548-2555. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18039957>.

117. Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. *Blood* 2008;112:1646-1654. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18502832>.

118. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood* 1995;85:2025-2037. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/7718875>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

119. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood* 2003;101:3809-3817. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12531809>.

120. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol* 2005;129:734-745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15952999>.

121. Pui CH. Central nervous system disease in acute lymphoblastic leukemia: prophylaxis and treatment. *Hematology Am Soc Hematol Educ Program* 2006:142-146. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17124053>.

122. Teuffel O, Kuster SP, Hunger SP, et al. Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. *Leukemia* 2011;25:1232-1238. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21527934>.

123. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol* 2000;18:547-561. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10653870>.

124. Koller CA, Kantarjian HM, Thomas D, et al. The hyper-CVAD regimen improves outcome in relapsed acute lymphoblastic leukemia. *Leukemia* 1997;11:2039-2044. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9447817>.

125. Hoelzer D, Ludwig WD, Thiel E, et al. Improved outcome in adult B-cell acute lymphoblastic leukemia. *Blood* 1996;87:495-508. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8555471>.

126. Chrzanowska M, Kolecki P, Duczmal-Cichocka B, Fiet J. Metabolites of mercaptopurine in red blood cells: a relationship between 6-thioguanine

nucleotides and 6-methylmercaptopurine metabolite concentrations in children with lymphoblastic leukemia. *Eur J Pharm Sci* 1999;8:329-334. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10425383>.

127. Lennard L, Lilleyman JS. Variable mercaptopurine metabolism and treatment outcome in childhood lymphoblastic leukemia. *J Clin Oncol* 1989;7:1816-1823. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2585022>.

128. McLeod HL, Relling MV, Crom WR, et al. Disposition of antineoplastic agents in the very young child. *Br J Cancer Suppl* 1992;18:S23-29. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1503923>.

129. Hawwa AF, Collier PS, Millership JS, et al. Population pharmacokinetic and pharmacogenetic analysis of 6-mercaptopurine in paediatric patients with acute lymphoblastic leukaemia. *Br J Clin Pharmacol* 2008;66:826-837. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18823306>.

130. McLeod HL, Coulthard S, Thomas AE, et al. Analysis of thiopurine methyltransferase variant alleles in childhood acute lymphoblastic leukaemia. *Br J Haematol* 1999;105:696-700. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10354134>.

131. Bhatia S, Landier W, Shangguan M, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. *J Clin Oncol* 2012;30:2094-2101. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22564992>.

132. Grant DM, Tang BK, Kalow W. Variability in caffeine metabolism. *Clin Pharmacol Ther* 1983;33:591-602. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6687705>.

133. Grant DM, Tang BK, Campbell ME, Kalow W. Effect of allopurinol on caffeine disposition in man. *Br J Clin Pharmacol* 1986;21:454-458. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3754760>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

134. Burton NK, Barnett MJ, Aherne GW, et al. The effect of food on the oral administration of 6-mercaptopurine. *Cancer Chemother Pharmacol* 1986;18:90-91. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/3757164>.

135. Riccardi R, Balis FM, Ferrara P, et al. Influence of food intake on bioavailability of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 1986;3:319-324. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3153245>.

136. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am J Hum Genet* 1980;32:651-662. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/7191632>.

137. Evans WE, Horner M, Chu YQ, et al. Altered mercaptopurine metabolism, toxic effects, and dosage requirement in a thiopurine methyltransferase-deficient child with acute lymphocytic leukemia. *J Pediatr* 1991;119:985-989. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/1960624>.

138. Lennard L, Gibson BE, Nicole T, Lilleyman JS. Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993;69:577-579. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8257179>.

139. McLeod HL, Lin JS, Scott EP, et al. Thiopurine methyltransferase activity in American white subjects and black subjects. *Clin Pharmacol Ther* 1994;55:15-20. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8299312>.

140. Collie-Duguid ES, Pritchard SC, Powrie RH, et al. The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. *Pharmacogenetics* 1999;9:37-42. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10208641>.

141. Lennard L, Lilleyman JS. Individualizing therapy with 6-mercaptopurine and 6-thioguanine related to the thiopurine

methyltransferase genetic polymorphism. *Ther Drug Monit* 1996;18:328-334. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8857546>.

142. Relling MV, Hancock ML, Rivera GK, et al. Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. *J Natl Cancer Inst* 1999;91:2001-2008. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10580024>.

143. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. *Clin Pharmacol Ther* 2013;93:324-325. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23422873>.

144. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther* 2011;89:387-391. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21270794>.

145. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. *Clin Pharmacol Ther* 2019;105:1095-1105. Available at:

<https://pubmed.ncbi.nlm.nih.gov/30447069/>.

146. U.S. Food and Drug Administration. Prescribing information. PURIXAN (mercaptopurine) oral suspension. 2014. Available at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205919s000lbl.pdf. Accessed September 29, 2016.

147. Hanff LM, Mathot RA, Smeets O, et al. A novel 6-mercaptopurine oral liquid formulation for pediatric acute lymphoblastic leukemia patients - results of a randomized clinical trial. *Int J Clin Pharmacol Ther* 2014;52:653-662. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24800919>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

148. Chessells JM, Harrison G, Lilleyman JS, et al. Continuing (maintenance) therapy in lymphoblastic leukaemia: lessons from MRC UKALL X. Medical Research Council Working Party in Childhood Leukaemia. *Br J Haematol* 1997;98:945-951. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9326194>.

149. Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2011;118:6521-6528. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21931113>.

150. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol* 2015;16:1547-1555. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26432046>.

151. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood* 2002;100:1965-1971. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12200353>.

152. Ottmann OG, Larson RA, Kantarjian HM, et al. Nilotinib in patients (pts) with relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to imatinib [abstract]. *Blood* 2007;110:Abstract 2815. Available at: <http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;110/11/2815>.

153. Ottmann OG, Pfeifer H, Cayuela JM, et al. Nilotinib (Tasigna®) and low intensity chemotherapy for first-line treatment of elderly patients with BCR-ABL1- positive acute lymphoblastic leukemia: Final results of a prospective multicenter trial (EWALL-PH02). *Blood* 2018;132:31. Available at: http://www.bloodjournal.org/content/132/Suppl_1/31.

154. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med*

2006;354:2531-2541. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16775234>.

155. Thomas DA, O'Brien S, Cortes J, et al. Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma. *Blood* 2004;104:1624-1630. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15178574>.

156. Thomas DA, O'Brien SM, Faderl S, et al. Long-term outcome after hyper-CVAD and imatinib (IM) for de novo or minimally treated Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-ALL). *J Clin Oncol* 2010;28:6506. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.6506.

157. Wassmann B, Gokbuget N, Scheuring UJ, et al. A randomized multicenter open label phase II study to determine the safety and efficacy of induction therapy with imatinib (Glivec, formerly STI571) in comparison with standard induction chemotherapy in elderly (>55 years) patients with Philadelphia chromosome-positive (Ph+/BCR-ABL+) acute lymphoblastic leukemia (ALL) (CSTI571ADE 10). *Ann Hematol* 2003;82:716-720. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14648032>.

158. Di Gion P, Kanefendt F, Lindauer A, et al. Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on pyrimidines, pyridines and pyrroles. *Clin Pharmacokinet* 2011;50:551-603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21827214>.

159. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer* 2006;106:1569-1580. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16502413>.

160. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol* 2010;28:3880-3889. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20660823>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

161. Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol* 2005;23:3376-3382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15908649>.

162. Cohen MH, Johnson JR, Justice R, Pazdur R. FDA drug approval summary: nelarabine (Arranon) for the treatment of T-cell lymphoblastic leukemia/lymphoma. *Oncologist* 2008;13:709-714. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18586926>.

163. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood* 2007;109:5136-5142. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17344466>.

164. Arico M, Schrappe M, Hunger SP, et al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. *J Clin Oncol* 2010;28:4755-4761. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20876426>.

165. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19805687>.

166. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia* 2014;28:1467-1471. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24441288>.

167. Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: Results of Children's

Oncology Group Trial AALL0622. *J Clin Oncol* 2018;36:2306-2314. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29812996>.

168. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol* 2012;13:936-945. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22898679>.

169. Biondi A, Gandemer V, De Lorenzo P, et al. Imatinib treatment of paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (EsPhALL2010): a prospective, intergroup, open-label, single-arm clinical trial. *Lancet Haematol* 2018;5:e641-e652. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30501871>.

170. Hunger SP, Saha V, Devidas M, et al. CA180-372: An international collaborative phase 2 trial of dasatinib and chemotherapy in pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). *Blood* 2017;130:98. Available at: http://www.bloodjournal.org/content/130/Suppl_1/98.

171. Foà R, Bassan R, Vitale A, et al. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. *N Engl J Med* 2020;383:1613-1623. Available at: <https://pubmed.ncbi.nlm.nih.gov/33085860/>.

172. Assi R, Kantarjian H, Short NJ, et al. Safety and Efficacy of Blinatumomab in Combination With a Tyrosine Kinase Inhibitor for the Treatment of Relapsed Philadelphia Chromosome-positive Leukemia. *Clin Lymphoma Myeloma Leuk* 2017;17:897-901. Available at: <https://pubmed.ncbi.nlm.nih.gov/28927784/>.

173. Couturier MA, Thomas X, Raffoux E, et al. Blinatumomab + ponatinib for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia in adults. *Leuk Lymphoma* 2021;62:620-629. Available at: <https://pubmed.ncbi.nlm.nih.gov/33153370/>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

174. King AC, Pappacena JJ, Tallman MS, et al. Blinatumomab administered concurrently with oral tyrosine kinase inhibitor therapy is a well-tolerated consolidation strategy and eradicates measurable residual disease in adults with Philadelphia chromosome positive acute lymphoblastic leukemia. *Leuk Res* 2019;79:27-33. Available at: <https://pubmed.ncbi.nlm.nih.gov/30831480/>.

175. Short N, Kantarjian HM, Konopleva M, et al. Combination of ponatinib and blinatumomab in Philadelphia chromosome-positive acute lymphoblastic leukemia: Early results from a phase II study [Abstract]. ASCO Meeting Abstracts 2021. Available at: <https://meetinglibrary.asco.org/record/195835/abstract>.

176. Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood* 2010;116:2070-2077. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20466853>.

177. Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol* 2018;5:e618-e627. Available at: <https://pubmed.ncbi.nlm.nih.gov/30501869/>.

178. de Labarthe A, Rousselot P, Huguet-Rigal F, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. *Blood* 2007;109:1408-1413. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17062730>.

179. Tanguy-Schmidt A, Rousselot P, Chalandon Y, et al. Long-term follow-up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: a GRAALL study. *Biol Blood Marrow Transplant* 2013;19:150-155. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22960387>.

180. Bassan R, Rossi G, Pogliani EM, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. *J Clin Oncol* 2010;28:3644-3652. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20606084>.

181. Mizuta S, Matsuo K, Yagasaki F, et al. Pre-transplant imatinib-based therapy improves the outcome of allogeneic hematopoietic stem cell transplantation for BCR-ABL-positive acute lymphoblastic leukemia. *Leukemia* 2011;25:41-47. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20944676>.

182. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol* 2006;24:460-466. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16344315>.

183. Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Blood* 2015;126:746-756. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26065651>.

184. Wieduwilt MJ, Yin J, Wetzler M, et al. A phase II study of dasatinib and dexamethasone as primary therapy followed by transplantation for adults with newly diagnosed Ph/BCR-ABL1-positive acute lymphoblastic leukemia (Ph+ ALL): Final results of Alliance/CALGB Study 10701. *Blood* 2018;132:309. Available at: <https://doi.org/10.1182/blood-2018-99-120029>.

185. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood* 2004;103:4396-4407. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14551133>.

186. Cornelissen JJ, Carston M, Kollman C, et al. Unrelated marrow transplantation for adult patients with poor-risk acute lymphoblastic leukemia: strong graft-versus-leukemia effect and risk factors determining



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

outcome. Blood 2001;97:1572-1577. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/11238093>.

187. Esperou H, Boiron JM, Cayuela JM, et al. A potential graft-versus-leukemia effect after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: results from the French Bone Marrow Transplantation Society. Bone Marrow Transplant 2003;31:909-918. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12748668>.

188. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood 2009;113:4489-4496. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/19244158>.

189. Bachanova V, Marks DI, Zhang MJ, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. Leukemia 2014;28:658-665. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23989431>.

190. Cassaday RD, Alan Potts D, Jr., Stevenson PA, et al. Evaluation of allogeneic transplantation in first or later minimal residual disease - negative remission following adult-inspired therapy for acute lymphoblastic leukemia. Leuk Lymphoma 2016;57:2109-2118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27002921>.

191. Mohty M, Labopin M, Volin L, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood 2010;116:4439-4443. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/20716774>.

192. Ribera JM, Oriol A, Gonzalez M, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in

newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. Haematologica 2010;95:87-95. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/19797728>.

193. Larson RA. Management of acute lymphoblastic leukemia in older patients. Semin Hematol 2006;43:126-133. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/16616046>.

194. Ottmann OG, Wassmann B, Pfeifer H, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer 2007;109:2068-2076. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17429836>.

195. Delannoy A, Delabesse E, Lheritier V, et al. Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRAALL AFR09 study. Leukemia 2006;20:1526-1532. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16838024>.

196. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676-3678. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/17213285>.

197. Martinelli G, Piciocchi A, Papayannidis C, et al. First report of the Gimema LAL1811 phase II prospective study of the combination of steroids with ponatinib as frontline therapy of elderly or unfit patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2017;130:99. Available at:
https://doi.org/10.1182/blood.V130.Suppl_1.99.99.

198. Chalandon Y, Thomas X, Hayette S, et al. First results of the GRAAPH-2005 study in younger adult patients with de novo Philadelphia



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

positive acute lymphoblastic leukemia [abstract]. Blood 2008;112:Abstract 12. Available at: <http://www.bloodjournal.org/content/112/11/12>.

199. Chalandon Y, Thomas X, Hayette S, et al. Is less chemotherapy detrimental in adults with Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) treated with high-dose imatinib? Results of the prospective randomized GRAAPH-2005 study [abstract]. Blood 2012;120:Abstract 138. Available at: <http://www.bloodjournal.org/content/120/21/138>.

200. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood 2015;125:3711-3719. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25878120>.

201. Rousselot P, Coude MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood 2016;128:774-782. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27121472>.

202. Carpenter PA, Snyder DS, Flowers ME, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. Blood 2007;109:2791-2793. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17119111>.

203. Chen H, Liu KY, Xu LP, et al. Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. J Hematol Oncol 2012;5:29. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22682059>.

204. Pfeifer H, Wassmann B, Bethge W, et al. Randomized comparison of prophylactic and minimal residual disease-triggered imatinib after allogeneic stem cell transplantation for BCR-ABL1-positive acute lymphoblastic leukemia. Leukemia 2013;27:1254-1262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23212150>.

205. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood 2007;109:944-950. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17032921>.

206. Oriol A, Vives S, Hernandez-Rivas JM, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica 2010;95:589-596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20145276>.

207. Tavernier E, Boiron JM, Huguet F, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia 2007;21:1907-1914. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17611565>.

208. Thomas DA, Kantarjian H, Smith TL, et al. Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. Cancer 1999;86:1216-1230. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10506707>.

209. Ishida Y, Terasako K, Oshima K, et al. Dasatinib followed by second allogeneic hematopoietic stem cell transplantation for relapse of Philadelphia chromosome-positive acute lymphoblastic leukemia after the first transplantation. Int J Hematol 2010;92:542-546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20824399>.

210. Millot F, Cividin M, Brizard F, et al. Successful second allogeneic stem cell transplantation in second remission induced by dasatinib in a child with Philadelphia chromosome positive acute lymphoblastic leukemia. Pediatr Blood Cancer 2009;52:891-892. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19202569>.

211. Collins RH, Jr., Goldstein S, Giral S, et al. Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant 2000;26:511-516. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11019840>.

212. Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

1995;86:2041-2050. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/7655033>.

213. Keil F, Kalhs P, Haas OA, et al. Relapse of Philadelphia chromosome positive acute lymphoblastic leukaemia after marrow transplantation: sustained molecular remission after early and dose-escalating infusion of donor leucocytes. *Br J Haematol* 1997;97:161-164. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9136959>.

214. Matsue K, Tabayashi T, Yamada K, Takeuchi M. Eradication of residual bcr-abl-positive clones by inducing graft-versus-host disease after allogeneic stem cell transplantation in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Bone Marrow Transplant* 2002;29:63-66. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11840146>.

215. Yazaki M, Andoh M, Ito T, et al. Successful prevention of hematological relapse for a patient with Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic bone marrow transplantation by donor leukocyte infusion. *Bone Marrow Transplant* 1997;19:393-394. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9051252>.

216. Tiribelli M, Sperotto A, Candoni A, et al. Nilotinib and donor lymphocyte infusion in the treatment of Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) relapsing after allogeneic stem cell transplantation and resistant to imatinib. *Leuk Res* 2009;33:174-177.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18471874>.

217. Yoshimitsu M, Fujiwara H, Ozaki A, et al. Case of a patient with Philadelphia-chromosome-positive acute lymphoblastic leukemia relapsed after myeloablative allogeneic hematopoietic stem cell transplantation treated successfully with imatinib and sequential donor lymphocyte infusions. *Int J Hematol* 2008;88:331-335. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18696183>.

218. Branford S, Rudzki Z, Walsh S, et al. High frequency of point mutations clustered within the adenosine triphosphate-binding region of BCR/ABL in patients with chronic myeloid leukemia or Ph-positive acute

lymphoblastic leukemia who develop imatinib (STI571) resistance. *Blood* 2002;99:3472-3475. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11964322>.

219. Hu Y, Liu Y, Pelletier S, et al. Requirement of Src kinases Lyn, Hck and Fgr for BCR-ABL1-induced B-lymphoblastic leukemia but not chronic myeloid leukemia. *Nat Genet* 2004;36:453-461. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15098032>.

220. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. *Clin Cancer Res* 2006;12:7374-7379. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17189410>.

221. Hofmann WK, Jones LC, Lemp NA, et al. Ph(+) acute lymphoblastic leukemia resistant to the tyrosine kinase inhibitor STI571 has a unique BCR-ABL gene mutation. *Blood* 2002;99:1860-1862. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11861307>.

222. Jones D, Thomas D, Yin CC, et al. Kinase domain point mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia emerge after therapy with BCR-ABL kinase inhibitors. *Cancer* 2008;113:985-994.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18615627>.

223. Hofmann WK, Komor M, Wassmann B, et al. Presence of the BCR-ABL mutation Glu255Lys prior to STI571 (imatinib) treatment in patients with Ph+ acute lymphoblastic leukemia. *Blood* 2003;102:659-661.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12663457>.

224. Pfeifer H, Wassmann B, Pavlova A, et al. Kinase domain mutations of BCR-ABL frequently precede imatinib-based therapy and give rise to relapse in patients with de novo Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood* 2007;110:727-734. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17405907>.

225. Bujassoum S, Rifkind J, Lipton JH. Isolated central nervous system relapse in lymphoid blast crisis chronic myeloid leukemia and acute lymphoblastic leukemia in patients on imatinib therapy. *Leuk Lymphoma*



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

2004;45:401-403. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15101732>.

226. Leis JF, Stepan DE, Curtin PT, et al. Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and Philadelphia chromosome positive acute lymphoblastic leukemia treated with imatinib (STI-571). *Leuk Lymphoma* 2004;45:695-698. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15160941>.

227. Pfeifer H, Wassmann B, Hofmann WK, et al. Risk and prognosis of central nervous system leukemia in patients with Philadelphia chromosome-positive acute leukemias treated with imatinib mesylate. *Clin Cancer Res* 2003;9:4674-4681. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14581336>.

228. Takayama N, Sato N, O'Brien SG, et al. Imatinib mesylate has limited activity against the central nervous system involvement of Philadelphia chromosome-positive acute lymphoblastic leukaemia due to poor penetration into cerebrospinal fluid. *Br J Haematol* 2002;119:106-108. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12358909>.

229. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. *J Clin Oncol* 2009;27:469-471. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19075254>.

230. Shah NP, Tran C, Lee FY, et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 2004;305:399-401. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15256671>.

231. Verstovsek S, Golemiovic M, Kantarjian H, et al. AMN107, a novel aminopyrimidine inhibitor of p190 Bcr-Abl activation and of in vitro proliferation of Philadelphia-positive acute lymphoblastic leukemia cells. *Cancer* 2005;104:1230-1236. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16078266>.

232. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med*

2006;354:2542-2551. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16775235>.

233. Lilly MB, Ottmann OG, Shah NP, et al. Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. *Am J Hematol* 2010;85:164-170. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20131302>.

234. Ottmann OG, Larson RA, Kantarjian HM, et al. Phase II study of nilotinib in patients with relapsed or refractory Philadelphia chromosome--positive acute lymphoblastic leukemia. *Leukemia* 2013;27:1411-1413. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23138184>.

235. Benjamini O, Dumlao TL, Kantarjian H, et al. Phase II trial of hyper CVAD and dasatinib in patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia. *Am J Hematol* 2014;89:282-287. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24779033>.

236. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood* 2011;118:4567-4576. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21865346>.

237. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood* 2012;119:3403-3412. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22371878>.

238. Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. *Am J Hematol* 2015;90:755-768. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26040495>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

239. Kantarjian HM, Cortes JE, Kim DW, et al. Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. *Blood* 2014;123:1309-1318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24345751>.

240. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med* 2012;367:2075-2088. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23190221>.

241. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013;369:1783-1796. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24180494>.

242. Soverini S, Colarossi S, Gnani A, et al. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. *Haematologica* 2007;92:401-404. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17339191>.

243. Soverini S, Martinelli G, Colarossi S, et al. Presence or the emergence of a F317L BCR-ABL mutation may be associated with resistance to dasatinib in Philadelphia chromosome-positive leukemia. *J Clin Oncol* 2006;24:e51-52. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17114651>.

244. Soverini S, Hochhaus A, Nicolini FE, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. *Blood* 2011;118:1208-1215. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21562040>.

245. Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: Results from a phase II, single-arm,

multicenter study. *J Clin Oncol* 2017;35:1795-1802. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28355115>.

246. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol* 2012;13:403-411. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22357140>.

247. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016;375:740-753. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27292104>.

248. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* 2013;368:1509-1518. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23527958>.

249. Sadelain M, Riviere I, Brentjens R. Targeting tumours with genetically enhanced T lymphocytes. *Nat Rev Cancer* 2003;3:35-45. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12509765>.

250. Deeg HJ, Sandmaier BM. Who is fit for allogeneic transplantation? *Blood* 2010;116:4762-4770. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20702782>.

251. Kantarjian HM, DeAngelo DJ, Advani AS, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. *Lancet Haematol* 2017;4:e387-e398. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28687420>.

252. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med* 2018;378:439-448. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29385370>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

253. de Bont JM, Holt B, Dekker AW, et al. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. *Leukemia* 2004;18:2032-2035. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15483674>.

254. Hallbook H, Gustafsson G, Smedmyr B, et al. Treatment outcome in young adults and children >10 years of age with acute lymphoblastic leukemia in Sweden: a comparison between a pediatric protocol and an adult protocol. *Cancer* 2006;107:1551-1561. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16955505>.

255. Ribera JM, Oriol A, Bethencourt C, et al. Comparison of intensive chemotherapy, allogeneic or autologous stem cell transplantation as post-remission treatment for adult patients with high-risk acute lymphoblastic leukemia. Results of the PETHEMA ALL-93 trial. *Haematologica* 2005;90:1346-1356. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16219571>.

256. Cornelissen JJ, van der Holt B, Verhoef GE, et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. *Blood* 2009;113:1375-1382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18988865>.

257. Marks DI, Perez WS, He W, et al. Unrelated donor transplants in adults with Philadelphia-negative acute lymphoblastic leukemia in first complete remission. *Blood* 2008;112:426-434. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18398065>.

258. Marks DI, Wang T, Perez WS, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. *Blood* 2010;116:366-374. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20404137>.

259. Ram R, Gafter-Gvili A, Vidal L, et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission: systematic

review and meta-analysis. *Cancer* 2010;116:3447-3457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20564092>.

260. Yanada M, Matsuo K, Suzuki T, Naoe T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. *Cancer* 2006;106:2657-2663. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16703597>.

261. Barry E, DeAngelo DJ, Neuberg D, et al. Favorable outcome for adolescents with acute lymphoblastic leukemia treated on Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium Protocols. *J Clin Oncol* 2007;25:813-819. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17327603>.

262. Nachman JB, La MK, Hunger SP, et al. Young adults with acute lymphoblastic leukemia have an excellent outcome with chemotherapy alone and benefit from intensive postinduction treatment: a report from the children's oncology group. *J Clin Oncol* 2009;27:5189-5194. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19805689>.

263. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: A report from Children's Oncology Group Study AALL0232. *J Clin Oncol* 2016;34:2380-2388. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27114587>.

264. Ribera JM, Oriol A, Sanz MA, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Espanol de Tratamiento en Hematologia pediatric-based protocol ALL-96. *J Clin Oncol* 2008;26:1843-1849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18398150>.

265. DeAngelo DJ, Dahlberg S, Silverman LB, et al. A multicenter phase II study using a dose intensified pediatric regimen in adults with untreated acute lymphoblastic leukemia [abstract]. *Blood* 2007;110:Abstract 587. Available at: <http://www.bloodjournal.org/content/110/11/587?sso-checked=true>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

266. DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia* 2015;29:526-534. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25079173>.

267. DeAngelo DJ, Stevenson K, Neuberg DS, et al. A multicenter phase II study using a dose intensified pegylated-asparaginase pediatric regimen in adults with untreated acute lymphoblastic leukemia: A DFCI ALL Consortium Trial. *Blood* 2015;126:80-80. Available at: <http://www.bloodjournal.org/content/126/23/80>.

268. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol* 2009;27:911-918. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19124805>.

269. Maury S, Chevret S, Thomas X, et al. Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia. *N Engl J Med* 2016;375:1044-1053. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27626518>.

270. Douer D, Aldoss I, Lunning MA, et al. Pharmacokinetics-based integration of multiple doses of intravenous pegaspargase in a pediatric regimen for adults with newly diagnosed acute lymphoblastic leukemia. *J Clin Oncol* 2014;32:905-911. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24516026>.

271. Geyer MB, Ritchie EK, Rao AV, et al. Pediatric-inspired chemotherapy incorporating pegaspargase is safe and results in high rates of minimal residual disease negativity in adults up to age 60 with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Haematologica* 2020;Online ahead of print. Available at: <https://pubmed.ncbi.nlm.nih.gov/33054114/>.

272. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30658992>.

273. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. *Pediatr Blood Cancer* 2015;62:1176-1183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25755211>.

274. Dunsmore KP, Winter S, Devidas M, et al. COG AALL0434: A randomized trial testing nelarabine in newly diagnosed t-cell malignancy. *J Clin Oncol* 2018;36:10500-10500. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.10500.

275. Winter SS, Dunsmore KP, Devidas M, et al. Improved survival for children and young adults with T-lineage acute lymphoblastic leukemia: Results from the Children's Oncology Group AALL0434 Methotrexate Randomization. *J Clin Oncol* 2018;36:2926-2934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30138085>.

276. Jain P, Kantarjian H, Ravandi F, et al. The combination of hyper-CVAD plus nelarabine as frontline therapy in adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma: MD Anderson Cancer Center experience. *Leukemia* 2014;28:973-975. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24157581>.

277. Abaza Y, H MK, Faderl S, et al. Hyper-CVAD plus nelarabine in newly diagnosed adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma. *Am J Hematol* 2018;93:91-99. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29047158>.

278. O'Brien S, Thomas DA, Ravandi F, et al. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. *Cancer* 2008;113:2097-2101. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18720356>.

279. Maury S, Huguet F, Leguay T, et al. Adverse prognostic significance of CD20 expression in adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. *Haematologica* 2010;95:324-328. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19773266>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

280. Thomas D, O'Brien S, Faderl S, et al. Anthracycline dose intensification in adult acute lymphoblastic leukemia: lack of benefit in the context of the fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen. *Cancer* 2010;116:4580-4589. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20572037>.

281. Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. *J Clin Oncol* 2002;20:2464-2471. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12011123>.

282. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol* 2011;29:2493-2498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21576633>.

283. Topp MS, Gokbuget N, Zugmaier G, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. *Blood* 2012;120:5185-5187. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23024237>.

284. Gokbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood* 2018;131:1522-1531. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29358182>.

285. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017;376:836-847. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28249141>.

286. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2015;16:57-66. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25524800>.

287. Topp MS, Gokbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol* 2014;32:4134-4140. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25385737>.

288. Larson RA, Dodge RK, Linker CA, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. *Blood* 1998;92:1556-1564. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9716583>.

289. Huguet F, Chevret S, Leguay T, et al. Intensified therapy of acute lymphoblastic leukemia in adults: Report of the randomized GRAALL-2005 clinical trial. *J Clin Oncol* 2018;36:2514-2523. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29863974>.

290. Wieduwilt MJ, Jonas BA, Schiller GJ, et al. A phase II study of pegylated asparaginase, cyclophosphamide, rituximab, and dasatinib added to the UCSF 8707 (Linker 4-drug) regimen with liposomal cytarabine CNS prophylaxis for adults with newly diagnosed acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL): University of California Hematologic Malignancies Consortium Study (UCHMC) 1401. *Blood* 2018;132:4018-4018. Available at: http://www.bloodjournal.org/content/132/Suppl_1/4018.

291. Marks DI, Paietta EM, Moorman AV, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). *Blood* 2009;114:5136-5145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19828704>.

292. Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2018;19:240-248. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29352703>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

293. Hunault-Berger M, Leguay T, Thomas X, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. *Haematologica* 2011;96:245-252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20971822>.

294. Goekbuget N, Beck J, Brueggemann M, et al. Moderate intensive chemotherapy including CNS-prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): Results of a prospective trial from the German Multicenter Study Group for Adult ALL (GMALL). *Blood* 2012;120:1493. Available at: <http://www.bloodjournal.org/content/120/21/1493>.

295. Ribera JM, Garcia O, Fernandez-Abellan P, et al. Lack of negative impact of Philadelphia chromosome in older patients with acute lymphoblastic leukaemia in the tyrosine kinase inhibitor era: comparison of two prospective parallel protocols. *Br J Haematol* 2012;159:485-488. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22966847>.

296. Ribera JM, Garcia O, Oriol A, et al. Feasibility and results of subtype-oriented protocols in older adults and fit elderly patients with acute lymphoblastic leukemia: Results of three prospective parallel trials from the PETHEMA group. *Leuk Res* 2016;41:12-20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26686475>.

297. Storrington JM, Minden MD, Kao S, et al. Treatment of adults with BCR-ABL negative acute lymphoblastic leukaemia with a modified paediatric regimen. *Br J Haematol* 2009;146:76-85. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19438471>.

298. Martell MP, Atenafu EG, Minden MD, et al. Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. *Br J Haematol* 2013;163:458-464. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24033272>.

299. Kozlowski P, Lennmyr E, Ahlberg L, et al. Age but not Philadelphia positivity impairs outcome in older/elderly patients with acute

lymphoblastic leukemia in Sweden. *Eur J Haematol* 2017;99:141-149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28419558>.

300. Berry DH, Pullen J, George S, et al. Comparison of prednisolone, vincristine, methotrexate, and 6-mercaptopurine vs. vincristine and prednisone induction therapy in childhood acute leukemia. *Cancer* 1975;36:98-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1203854>.

301. Hardisty RM, McElwain TJ, Darby CW. Vincristine and prednisone for the induction of remissions in acute childhood leukaemia. *Br Med J* 1969;2:662-665. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/5254045>.

302. Hess CE, Zirkle JW. Results of induction therapy with vincristine and prednisone alone in adult acute lymphoblastic leukemia: report of 43 patients and review of the literature. *Am J Hematol* 1982;13:63-71. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6958203>.

303. Rodriguez V, Hart JS, Freireich EJ, et al. Pomp combination chemotherapy of adult acute leukemia. *Cancer* 1973;32:69-75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4515259>.

304. Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia* 2008;22:2142-2150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18818707>.

305. Pui CH, Evans WE. Acute lymphoblastic leukemia. *N Engl J Med* 1998;339:605-615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9718381>.

306. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia* 2010;24:371-382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20010620>.

307. Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy:



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Munster Group 87. *J Clin Oncol* 2005;23:7942-7950. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16258094>.

308. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. *J Clin Oncol* 2010;28:2339-2347. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20385996>.

309. Malempati S, Gaynon PS, Sather H, et al. Outcome after relapse among children with standard-risk acute lymphoblastic leukemia: Children's Oncology Group study CCG-1952. *J Clin Oncol* 2007;25:5800-5807. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18089878>.

310. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant* 2006;12:1-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16399566>.

311. Eapen M, Raetz E, Zhang MJ, et al. Outcomes after HLA-matched sibling transplantation or chemotherapy in children with B-precursor acute lymphoblastic leukemia in a second remission: a collaborative study of the Children's Oncology Group and the Center for International Blood and Marrow Transplant Research. *Blood* 2006;107:4961-4967. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16493003>.

312. Duval M, Klein JP, He W, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. *J Clin Oncol* 2010;28:3730-3738. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20625136>.

313. Topp MS, Goekbuget N, Zugmaier G, et al. Anti-CD19 BiTE blinatumomab induces high complete remission rate in adult patients with relapsed B-precursor ALL: Updated results of an ongoing phase II trial [abstract]. *Blood* 2011;118:Abstract 252. Available at: <http://www.bloodjournal.org/content/118/21/252>.

314. Topp MS, Goekbuget N, Stein AS, et al. Confirmatory open-label, single-arm, multicenter phase 2 study of the BiTE antibody blinatumomab in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) [abstract]. *J Clin Oncol* 2014;32:Abstract 7005. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2014.32.15_suppl.7005.

315. U.S. Food and Drug Administration. Prescribing information. Blincyto® (blinatumomab) injection. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125557lbl.pdf. Accessed September 29, 2016.

316. Jabbour E, Ravandi F, Kebriaei P, et al. Salvage chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD for patients with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia: A phase 2 clinical trial. *JAMA Oncol* 2018;4:230-234. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28859185>.

317. Jabbour E, Sasaki K, Ravandi F, et al. Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. *Cancer* 2018;124:4044-4055. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30307611>.

318. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med* 2013;5:177ra138. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23515080>.

319. Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. *Blood* 2012;119:2709-2720. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22160384>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

320. Hollyman D, Stefanski J, Przybylowski M, et al. Manufacturing validation of biologically functional T cells targeted to CD19 antigen for autologous adoptive cell therapy. *J Immunother* 2009;32:169-180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19238016>.

321. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med* 2014;6:224ra225. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24553386>.

322. Gokbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood* 2012;120:2032-2041. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22493293>.

323. O'Brien S, Schiller G, Lister J, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. *J Clin Oncol* 2013;31:676-683. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23169518>.

324. Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med* 2018;378:449-459. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29385376>.

325. Shah NN, Lee DW, Yates B, et al. Long-Term Follow-Up of CD19-CAR T-Cell Therapy in Children and Young Adults With B-ALL. *J Clin Oncol* 2021;39:1650-1659. Available at: <https://pubmed.ncbi.nlm.nih.gov/33764809/>.

326. Shah BD, Ghobadi A, Oluwale OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet* 2021. Available at: <https://pubmed.ncbi.nlm.nih.gov/34097852/>.

327. Grupp SA, Frey NV, Aplenc R, et al. T Cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) produce significant in vivo proliferation, complete responses and long-term

persistence without GVHD in children and adults with relapsed, refractory ALL [abstract]. *Blood* 2013;122:Abstract 67. Available at: <http://bloodjournal.hematologylibrary.org/content/122/21/67.short#aff-1>.

328. Pasquini MC, Hu ZH, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood Adv* 2020;4:5414-5424. Available at: <https://pubmed.ncbi.nlm.nih.gov/33147337/>.

329. Stephan A. Grupp SLM, Susana Rives, Andre Baruchel, Michael Boyer, Henrique Bittencourt, Peter Bader, Jochen Buchner, Theodore W Laetsch, Heather Stefanski, Gary Douglas Myers, Muna Qayed, Michael A. Pulsipher, Barbara De Moerloose, Gregory A. Yanik, Kara L Davis, Paul L. Martin, Eneida R. Nemecek, Christina Peters, Joerg Krueger, Adriana Balduzzi, Nicolas Boissel, Francoise Mechinaud, Mimi Leung, Lamis Eldjerou, Eric Bleickardt, Karen Thudium Mueller, Hidefumi Hiramatsu. Tisagenlecleucel for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia: Updated Analysis of the ELIANA Clinical Trial. *Biology of Blood and Marrow Transplantation* 2019;25:S126-S127. Available at: <https://www.sciencedirect.com/science/article/pii/S1083879118312321>.

330. Sheth VS, Gauthier J. Taming the beast: CRS and ICANS after CAR T-cell therapy for ALL. *Bone Marrow Transplant* 2021;56:552-566. Available at: <https://pubmed.ncbi.nlm.nih.gov/33230186/>.

331. Lee DW, Santomaso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019;25:625-638. Available at: <https://pubmed.ncbi.nlm.nih.gov/30592986/>.

332. Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. *J Immunother Cancer* 2020;8. Available at: <https://pubmed.ncbi.nlm.nih.gov/33335028/>.

333. Commander LA, Seif AE, Insogna IG, Rheingold SR. Salvage therapy with nelarabine, etoposide, and cyclophosphamide in



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

relapsed/refractory paediatric T-cell lymphoblastic leukaemia and lymphoma. *Br J Haematol* 2010;150:345-351. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20528871>.

334. Whitlock J, dalla Pozza L, Goldberg JM, et al. Nelarabine in combination with etoposide and cyclophosphamide is active in first relapse of childhood T-acute lymphocytic leukemia (T-ALL) and T-lymphoblastic lymphoma (T-LL). *Blood* 2014;124:795. Available at: <http://www.bloodjournal.org/content/124/21/795>.

335. Faderl S, Thomas DA, O'Brien S, et al. Augmented hyper-CVAD based on dose-intensified vincristine, dexamethasone, and asparaginase in adult acute lymphoblastic leukemia salvage therapy. *Clin Lymphoma Myeloma Leuk* 2011;11:54-59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21454191>.

336. Thomas DA, Kantarjian HM, Stock W, et al. Phase 1 multicenter study of vincristine sulfate liposomes injection and dexamethasone in adults with relapsed or refractory acute lymphoblastic leukemia. *Cancer* 2009;115:5490-5498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19708032>.

337. Silverman JA, Reynolds L, Deitcher SR. Pharmacokinetics and pharmacodynamics of vincristine sulfate liposome injection (VSLI) in adults with acute lymphoblastic leukemia. *J Clin Pharmacol* 2013;53:1139-1145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23907766>.

338. O'Brien S, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. *Cancer* 2008;113:3186-3191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18846563>.

339. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J Clin Oncol* 2006;24:1917-1923. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16622268>.

340. Hijiya N, Thomson B, Isakoff MS, et al. Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *Blood* 2011;118:6043-6049. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21967976>.

341. Locatelli F, Testi AM, Bernardo ME, et al. Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. *Br J Haematol* 2009;147:371-378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19747360>.

342. Miano M, Pistorio A, Putti MC, et al. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. *Leuk Lymphoma* 2012;53:1693-1698. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22303898>.

343. Pigneux A, Sauvezie M, Vey N, et al. Clofarabine combinations in adults with refractory/relapsed acute lymphoblastic leukemia (ALL): A GRAALL Report. *Blood* 2011;118:2586-2586. Available at: <http://www.bloodjournal.org/content/118/21/2586?sso-checked=true>.

344. Wiernik PH, Dutcher JP, Paietta E, et al. Long-term follow-up of treatment and potential cure of adult acute lymphocytic leukemia with MOAD: a non-anthracycline containing regimen. *Leukemia* 1993;7:1236-1241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8350624>.

345. Wetzler M, Sanford BL, Kurtzberg J, et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. *Blood* 2007;109:4164-4167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17264295>.

346. Kadia TM, Kantarjian HM, Thomas DA, et al. Phase II study of methotrexate, vincristine, pegylated-asparaginase, and dexamethasone (MOPAD) in patients with relapsed/refractory acute lymphoblastic leukemia. *Am J Hematol* 2015;90:120-124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25368968>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

347. Bride KL, Vincent TL, Im SY, et al. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. *Blood* 2018;131:995-999. Available at: <https://pubmed.ncbi.nlm.nih.gov/29305553/>.

348. Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical Experience With Venetoclax Combined With Chemotherapy for Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia. *Clin Lymphoma Myeloma Leuk* 2020;20:212-218. Available at: <https://pubmed.ncbi.nlm.nih.gov/32035785/>.

349. Horton TM, Whitlock JA, Lu X, et al. Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group. *Br J Haematol* 2019;186:274-285. Available at: <https://pubmed.ncbi.nlm.nih.gov/30957229/>.

350. Giebel S, Krawczyk-Kulis M, Adamczyk-Cioch M, et al. Fludarabine, cytarabine, and mitoxantrone (FLAM) for the treatment of relapsed and refractory adult acute lymphoblastic leukemia. A phase study by the Polish Adult Leukemia Group (PALG). *Ann Hematol* 2006;85:717-722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16832677>.

351. Schiller G, Lee M, Territo M, et al. Phase II study of etoposide, ifosfamide, and mitoxantrone for the treatment of resistant adult acute lymphoblastic leukemia. *Am J Hematol* 1993;43:195-199. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8352235>.

352. Specchia G, Pastore D, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. *Ann Hematol* 2005;84:792-795. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16047203>.

353. Weiss MA, Aliff TB, Tallman MS, et al. A single, high dose of idarubicin combined with cytarabine as induction therapy for adult patients with recurrent or refractory acute lymphoblastic leukemia. *Cancer* 2002;95:581-587. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12209751>.

354. Gokbuget N, Basara N, Baurmann H, et al. High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. *Blood* 2011;118:3504-3511. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21715318>.

355. Candoni A, Lazzarotto D, Ferrara F, et al. Nelarabine as salvage therapy and bridge to allogeneic stem cell transplant in 118 adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoma. A CAMPUS ALL study. *Am J Hematol* 2020;95:1466-1472. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32777149>.

356. Bonda A, Punatar S, Gokarn A, et al. Daratumumab at the frontiers of post-transplant refractory T-acute lymphoblastic leukemia-a worthwhile strategy? *Bone Marrow Transplant* 2018;53:1487-1489. Available at: <https://pubmed.ncbi.nlm.nih.gov/29884853/>.

357. Mirgh S, Ahmed R, Agrawal N, et al. Will Daratumumab be the next game changer in early thymic precursor-acute lymphoblastic leukaemia? *Br J Haematol* 2019;187:e33-e35. Available at: <https://pubmed.ncbi.nlm.nih.gov/31452197/>.

358. Ofra Y, Ringelstein-Harlev S, Sloukkey I, et al. Daratumumab for eradication of minimal residual disease in high-risk advanced relapse of T-cell/CD19/CD22-negative acute lymphoblastic leukemia. *Leukemia* 2020;34:293-295. Available at: <https://pubmed.ncbi.nlm.nih.gov/31435023/>.

359. Liedtke M, Dunn T, Dinner S, et al. Salvage therapy with mitoxantrone, etoposide and cytarabine in relapsed or refractory acute lymphoblastic leukemia. *Leuk Res* 2014;38:1441-1445. Available at: <https://pubmed.ncbi.nlm.nih.gov/25449689/>.

360. Jain N, Stevenson KE, Winer ES, et al. A Multicenter Phase I Study Combining Venetoclax with Mini-Hyper-CVD in Older Adults with Untreated and Relapsed/Refractory Acute Lymphoblastic Leukemia. *Blood* 2019;134:3867-3867. Available at: <https://doi.org/10.1182/blood-2019-129988>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

361. Bailey LC, Lange BJ, Rheingold SR, Bunin NJ. Bone-marrow relapse in paediatric acute lymphoblastic leukaemia. *Lancet Oncol* 2008;9:873-883. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18760243>.

362. Hoelzer D, Gokbuget N, Digel W, et al. Outcome of adult patients with T-lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. *Blood* 2002;99:4379-4385. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12036865>.

363. Morel P, Lepage E, Brice P, et al. Prognosis and treatment of lymphoblastic lymphoma in adults: a report on 80 patients. *J Clin Oncol* 1992;10:1078-1085. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1607914>.

364. Burger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. *J Clin Oncol* 2003;21:184-188. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12525508>.

365. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med* 2009;360:2730-2741. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19553647>.

366. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16556888>.

367. Reman O, Pigneux A, Huguet F, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis and/or at first relapse: results from the GET-LALA group. *Leuk Res* 2008;32:1741-1750. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18508120>.

368. Pui CH, Pei D, Campana D, et al. Improved prognosis for older adolescents with acute lymphoblastic leukemia. *J Clin Oncol* 2011;29:386-391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21172890>.

369. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. *Blood* 2002;99:863-871. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11806988>.

370. Sancho JM, Ribera JM, Oriol A, et al. Central nervous system recurrence in adult patients with acute lymphoblastic leukemia: frequency and prognosis in 467 patients without cranial irradiation for prophylaxis. *Cancer* 2006;106:2540-2546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16700036>.

371. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. 2018. Available at: http://survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf. Accessed January 31, 2019.

372. Mortuza FY, Papaioannou M, Moreira IM, et al. Minimal residual disease tests provide an independent predictor of clinical outcome in adult acute lymphoblastic leukemia. *J Clin Oncol* 2002;20:1094-1104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11844835>.

373. Carlson CS, Emerson RO, Sherwood AM, et al. Using synthetic templates to design an unbiased multiplex PCR assay. *Nat Commun* 2013;4:2680. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24157944>.

374. Denys B, van der Sluijs-Gelling AJ, Homburg C, et al. Improved flow cytometric detection of minimal residual disease in childhood acute lymphoblastic leukemia. *Leukemia* 2013;27:635-641. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22945774>.

375. Faham M, Zheng J, Moorhead M, et al. Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Blood 2012;120:5173-5180. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23074282>.

376. Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. *Haematologica* 2012;97:1582-1593. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22581001>.

377. Ladetto M, Bruggemann M, Monitillo L, et al. Next-generation sequencing and real-time quantitative PCR for minimal residual disease detection in B-cell disorders. *Leukemia* 2014;28:1299-1307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24342950>.

378. Short NJ, Jabbour E, Albitar M, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts. *Am J Hematol* 2019;94:257-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30394566>.

379. Stow P, Key L, Chen X, et al. Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia. *Blood* 2010;115:4657-4663. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20304809>.

380. Wood B, Wu D, Crossley B, et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. *Blood* 2018;131:1350-1359. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29284596>.

381. Logan AC, Zhang B, Narasimhan B, et al. Minimal residual disease quantification using consensus primers and high-throughput IGH sequencing predicts post-transplant relapse in chronic lymphocytic leukemia. *Leukemia* 2013;27:1659-1665. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23419792>.

382. Neale GA, Coustan-Smith E, Stow P, et al. Comparative analysis of flow cytometry and polymerase chain reaction for the detection of minimal residual disease in childhood acute lymphoblastic leukemia. *Leukemia*

2004;18:934-938. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15029212>.

383. Wu D, Emerson RO, Sherwood A, et al. Detection of minimal residual disease in B lymphoblastic leukemia by high-throughput sequencing of IGH. *Clin Cancer Res* 2014;20:4540-4548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24970842>.

384. Wu D, Sherwood A, Fromm JR, et al. High-throughput sequencing detects minimal residual disease in acute T lymphoblastic leukemia. *Sci Transl Med* 2012;4:134ra163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22593176>.

385. Kerst G, Kreyenberg H, Roth C, et al. Concurrent detection of minimal residual disease (MRD) in childhood acute lymphoblastic leukaemia by flow cytometry and real-time PCR. *Br J Haematol* 2005;128:774-782. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15755280>.

386. Coustan-Smith E, Sancho J, Behm FG, et al. Prognostic importance of measuring early clearance of leukemic cells by flow cytometry in childhood acute lymphoblastic leukemia. *Blood* 2002;100:52-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12070008>.

387. Coustan-Smith E, Sancho J, Hancock ML, et al. Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. *Blood* 2000;96:2691-2696. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11023499>.

388. Cave H, van der Werff ten Bosch J, Suciu S, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European Organization for Research and Treatment of Cancer--Childhood Leukemia Cooperative Group. *N Engl J Med* 1998;339:591-598. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9718378>.

389. Coustan-Smith E, Behm FG, Sanchez J, et al. Immunological detection of minimal residual disease in children with acute lymphoblastic



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

leukaemia. Lancet 1998;351:550-554. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9492773>.

390. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010;115:3206-3214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20154213>.

391. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol 2013;14:199-209. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23395119>.

392. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol 2014;15:809-818. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24924991>.

393. Eckert C, Henze G, Seeger K, et al. Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group. J Clin Oncol 2013;31:2736-2742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23775972>.

394. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet 2010;376:2009-2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21131038>.

395. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol 2010;28:648-654. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19841326>.

396. Coustan-Smith E, Gajjar A, Hijiya N, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia after first relapse. Leukemia 2004;18:499-504. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14981525>.

397. Paganin M, Zecca M, Fabbri G, et al. Minimal residual disease is an important predictive factor of outcome in children with relapsed 'high-risk' acute lymphoblastic leukemia. Leukemia 2008;22:2193-2200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18754029>.

398. Basso G, Veltroni M, Valsecchi MG, et al. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow cytometric measurement of residual disease on day 15 bone marrow. J Clin Oncol 2009;27:5168-5174. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19805690>.

399. Panzer-Grumayer ER, Schneider M, Panzer S, et al. Rapid molecular response during early induction chemotherapy predicts a good outcome in childhood acute lymphoblastic leukemia. Blood 2000;95:790-794. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10648387>.

400. Bruggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood 2006;107:1116-1123. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16195338>.

401. Holowiecki J, Krawczyk-Kulis M, Giebel S, et al. Status of minimal residual disease after induction predicts outcome in both standard and high-risk Ph-negative adult acute lymphoblastic leukaemia. The Polish Adult Leukemia Group ALL 4-2002 MRD Study. Br J Haematol 2008;142:227-237. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18492099>.

402. Patel B, Rai L, Buck G, et al. Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993. Br J Haematol 2010;148:80-89. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19863538>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

403. Vidriales MB, Perez JJ, Lopez-Berges MC, et al. Minimal residual disease in adolescent (older than 14 years) and adult acute lymphoblastic leukemias: early immunophenotypic evaluation has high clinical value. *Blood* 2003;101:4695-4700. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12586618>.

404. Ravandi F, Jorgensen JL, O'Brien SM, et al. Minimal residual disease assessed by multi-parameter flow cytometry is highly prognostic in adult patients with acute lymphoblastic leukaemia. *Br J Haematol* 2016;172:392-400. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26492205>.

405. Nagafuji K, Miyamoto T, Eto T, et al. Monitoring of minimal residual disease (MRD) is useful to predict prognosis of adult patients with Ph-negative ALL: results of a prospective study (ALL MRD2002 Study). *J Hematol Oncol* 2013;6:14. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23388549>.

406. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood* 2009;113:4153-4162. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19141862>.

407. Raff T, Gokbuget N, Luschen S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. *Blood* 2007;109:910-915. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17023577>.

408. Gokbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood* 2012;120:1868-1876. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22442346>.

409. Dworzak MN, Froschl G, Printz D, et al. Prognostic significance and modalities of flow cytometric minimal residual disease detection in

childhood acute lymphoblastic leukemia. *Blood* 2002;99:1952-1958. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11877265>.

410. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20033054>.

411. Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program* 2010;2010:7-12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21239764>.

412. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* 2015;126:964-971. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26124497>.

413. O'Connor D, Enshaei A, Bartram J, et al. Genotype-specific minimal residual disease interpretation improves stratification in pediatric acute lymphoblastic leukemia. *J Clin Oncol* 2018;36:34-43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29131699>.

414. Wood BL, Winter SS, Dunsmore KP, et al. T-lymphoblastic leukemia (T-ALL) shows excellent outcome, lack of significance of the early thymic precursor (ETP) immunophenotype, and validation of the prognostic value of end-induction minimal residual disease (MRD) in Children's Oncology Group (COG) Study AALL0434. *Blood* 2014;124:1. Available at: <http://www.bloodjournal.org/content/124/21/1>.

415. Pemmaraju N, Kantarjian H, Jorgensen JL, et al. Significance of recurrence of minimal residual disease detected by multi-parameter flow cytometry in patients with acute lymphoblastic leukemia in morphological remission. *Am J Hematol* 2017;92:279-285. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28052371>.

416. Hamid M, Lashari B, Ahsan I, et al. A deadly prescription: combination of methotrexate and trimethoprim-sulfamethoxazole. *J*



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

Community Hosp Intern Med Perspect 2018;8:149-151. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29915656>.

417. Ducore JM, Waller DA, Emslie G, Bertolone SJ. Acute psychosis complicating induction therapy for acute lymphoblastic leukemia. J Pediatr 1983;103:477-480. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6577167>.

418. Friedenbergr WR, Kyle RA, Knospe WH, et al. High-dose dexamethasone for refractory or relapsing multiple myeloma. Am J Hematol 1991;36:171-175. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1996557>.

419. Jenkins CA, Bruera E. Difficulties in diagnosing neuropsychiatric complications of corticosteroids in advanced cancer patients: two case reports. J Pain Symptom Manage 2000;19:309-317. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10799797>.

420. Stiefel FC, Breitbart WS, Holland JC. Corticosteroids in cancer: neuropsychiatric complications. Cancer Invest 1989;7:479-491. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2695230>.

421. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. Blood 2011;117:2340-2347; quiz 2556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21148812>.

422. Patel B, Richards SM, Rowe JM, et al. High incidence of avascular necrosis in adolescents with acute lymphoblastic leukaemia: a UKALL XII analysis. Leukemia 2008;22:308-312. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17989709>.

423. Mattano LA, Jr., Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. Lancet Oncol 2012;13:906-915. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22901620>.

424. Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000;18:3262-3272. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10986059>.

425. te Winkel ML, Pieters R, Hop WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. J Clin Oncol 2011;29:4143-4150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21947829>.

426. Vora A. Management of osteonecrosis in children and young adults with acute lymphoblastic leukaemia. Br J Haematol 2011;155:549-560. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22077340>.

427. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol 2013;31:1202-1210. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23358966>.

428. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer 2019;125:2474-2487. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30920645>.

429. George B, Kantarjian H, Jabbour E, Jain N. Role of inotuzumab ozogamicin in the treatment of relapsed/refractory acute lymphoblastic leukemia. Immunotherapy 2016;8:135-143. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26780449>.

430. Kebriaei P, Wilhelm K, Ravandi F, et al. Feasibility of allografting in patients with advanced acute lymphoblastic leukemia after salvage therapy with inotuzumab ozogamicin. Clin Lymphoma Myeloma Leuk 2013;13:296-301. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23313065>.



NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

431. Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. *Bone Marrow Transplant* 2018;53:449-456. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29330398>.

432. Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program* 2016;2016:567-572. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27913530>.

433. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol* 2018;15:47-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28925994>.

434. Neelapu SS, Tummala S, Kebriaei P, et al. Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. *Nat Rev Clin Oncol* 2018;15:218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29434334>.

435. Angiolillo AL, Schore RJ, Devidas M, et al. Pharmacokinetic and pharmacodynamic properties of calaspargase pegol *Escherichia coli* L-asparaginase in the treatment of patients with acute lymphoblastic leukemia: results from Children's Oncology Group Study AALL07P4. *J Clin Oncol* 2014;32:3874-3882. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25348002>.

436. Asselin BL. The three asparaginases. Comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol* 1999;457:621-629. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10500842>.

437. Pieters R, Hunger SP, Boos J, et al. L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase. *Cancer* 2011;117:238-249. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20824725>.

438. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21827361>.

439. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood* 2002;99:1986-1994. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11877270>.

440. Wang B, Relling MV, Storm MC, et al. Evaluation of immunologic crossreaction of anti-asparaginase antibodies in acute lymphoblastic leukemia (ALL) and lymphoma patients. *Leukemia* 2003;17:1583-1588. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12886246>.

441. Zalewska-Szewczyk B, Gach A, Wyka K, et al. The cross-reactivity of anti-asparaginase antibodies against different L-asparaginase preparations. *Clin Exp Med* 2009;9:113-116. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19184328>.

442. Willer A, Gerss J, Konig T, et al. Anti-*Escherichia coli* asparaginase antibody levels determine the activity of second-line treatment with pegylated *E coli* asparaginase: a retrospective analysis within the ALL-BFM trials. *Blood* 2011;118:5774-5782. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21940824>.

443. Vrooman LM, Supko JG, Neuberg DS, et al. Erwinia asparaginase after allergy to *E. coli* asparaginase in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2010;54:199-205. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19672973>.

444. Silverman LB, Blonquist TM, Hunt SK, et al. Randomized study of pegasparagase (SS-PEG) and calaspargase pegol (SC-PEG) in pediatric patients with newly diagnosed acute lymphoblastic leukemia or lymphoblastic lymphoma: Results of DFCL ALL Consortium Protocol 11-001. *Blood* 2016;128:175-175. Available at: <http://www.bloodjournal.org/content/128/22/175?sso-checked=true>.



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021

Acute Lymphoblastic Leukemia

445. Bleyer A, Asselin BL, Koontz SE, Hunger SP. Clinical application of asparaginase activity levels following treatment with pegaspargase. *Pediatr Blood Cancer* 2015;62:1102-1105. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25393506>.