National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Lymphoblastic Leukemia

NCCN Evidence Blocks™

Version 2.2019 — May 15, 2019

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Acute Lymphoblastic Leukemia
NCCN Evidence Blocks™

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

Bhavana Bhatnagar, DO ‡ † Þ
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

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

Teresa Bryan, MD Þ
University of Alabama at Birmingham Comprehensive Cancer Center

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

Ryan D. Cassaday, MD † ‡ Þ
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Peter F. Coccia, MD € ≠
Fred & Pamela Buffett Cancer Center

Steven E. Coutre, MD ‡
Stanford Cancer Institute

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

Amir Fathi, MD † ‡ Þ
Massachusetts General Hospital Cancer Center

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

Suzanne Kirby, MD ‡
Duke Cancer Institute

Mark Litzow, MD ‡
Mayo Clinic Cancer Center

Arthur Liu, MD, PhD §
University of Colorado Cancer Center

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

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

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

Olalekan Oluwole, MD ‡
Vanderbilt-Ingram Cancer Center

Nikolaos Papadantonakis, MD, PhD †
University of Alabama at Birmingham Comprehensive Cancer Center

Jae Park, MD †
Memorial Sloan Kettering Cancer Center

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

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

Eunice S. Wang, MD † ‡ Þ
Roswell Park Cancer Institute

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

NCCN
Kristina Gregory, RN, MSN, OCN
Ndiya Ogba, PhD

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

NCCN Guidelines Panel Disclosures

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Acute Lymphoblastic Leukemia
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

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/clinicians.aspx.

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

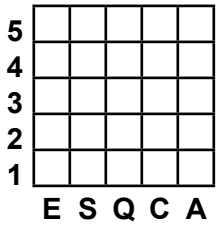
See NCCN Categories of Evidence and Consensus.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Acute Lymphoblastic Leukemia
NCCN Evidence Blocks™

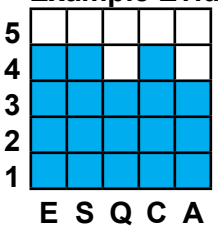
NCCN Guidelines Index
Table of Contents
Discussion

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

Acute lymphoblastic leukemia (ALL)[a,b,c] →

Patients should undergo evaluation and treatment at specialized centers

DIAGNOSIS

The diagnosis of ALL generally requires demonstration of ≥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 minimal/measurable residual disease (MRD) characterization of leukemic clone to facilitate subsequent MRD analysis (see AML-F)**
- **Karyotyping of G-banded metaphase chromosomes**

MOLECULAR CHARACTERIZATION

Optimal risk stratification and treatment planning requires 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)**
- **Testing is encouraged for gene fusions and pathogenic mutations, particulary if known to be *BCR-ABL1* negative[g]**

Additional optional tests include:

- **Assessment (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 risk group[h]

→ **See Workup and Risk Stratification (ALL-2)**

[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; 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.

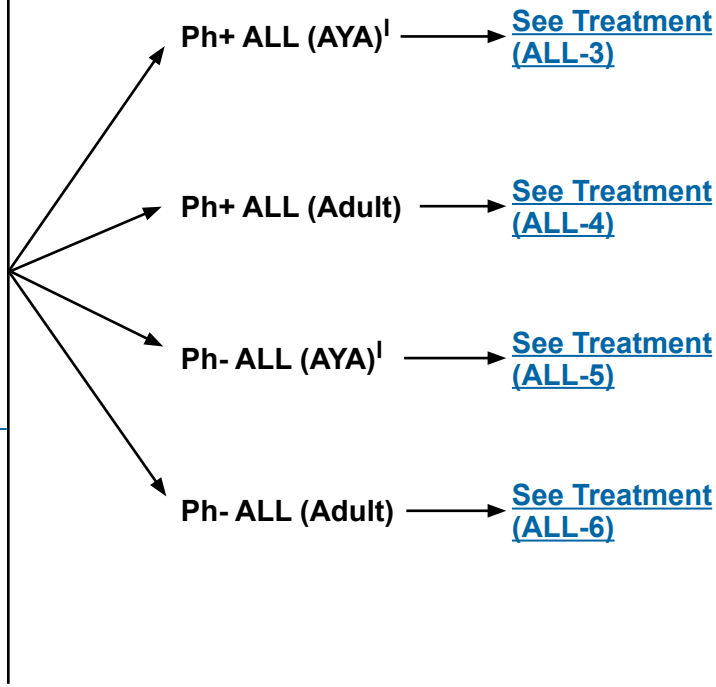
[h]See Cytogenetic Risk Groups for B-ALL (ALL-A).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

WORKUP[i]

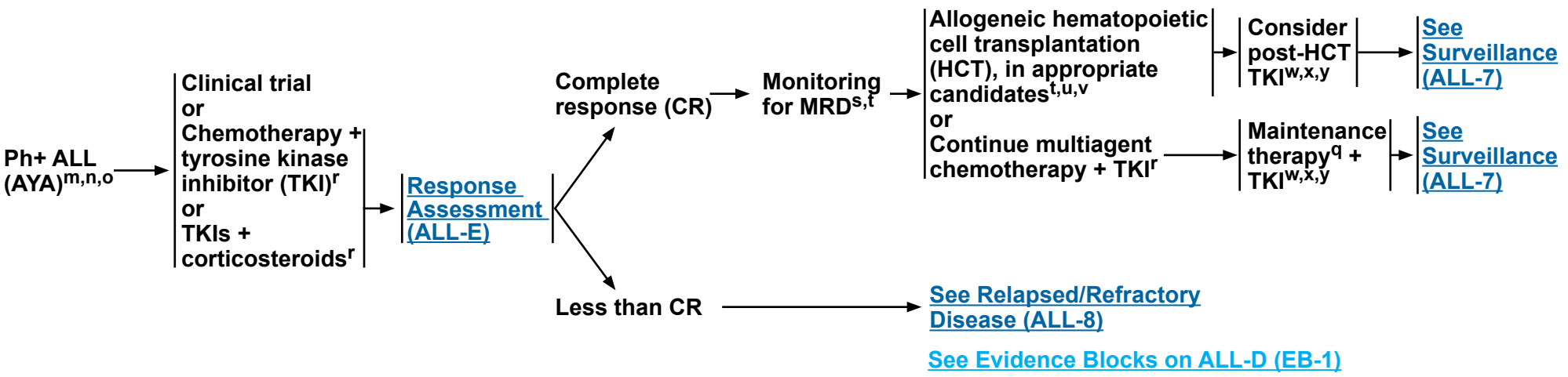
- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, chemistry profile, liver function tests (LFTs)
- Disseminated intravascular coagulation (DIC) panel: d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Tumor lysis syndrome (TLS) panel: Lactate dehydrogenase (LDH), uric acid, K, Ca, Phos (See Tumor Lysis Syndrome in the NCCN Guidelines for B-Cell Lymphomas.)
- Urinalysis
- Hepatitis B/C, HIV, CMV Ab testing
- Pregnancy testing, fertility counseling, and preservation
- CT/MRI of head with contrast, if neurologic symptoms[i]
- Lumbar puncture (LP)[j,k] 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 human leukocyte antigen (HLA) typing and early evaluation and search for family or an alternative donor

RISK STRATIFICATION



[i]The following list represents minimal recommendations; other testing may be warranted according to clinical symptoms and discretion of the clinician.
[j]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).
[k]The panel recommends first LP be performed at time of initial scheduled IT therapy unless directed by symptoms to perform earlier.
[l]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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.



[m]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.

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

[o]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.

[p]All ALL treatment regimens include CNS prophylaxis.

[q]See Principles of Supportive Care (ALL-C).

[r]See Principles of Systemic Therapy (ALL-D).

[s]See Minimal/Measurable Residual Disease Assessment (ALL-F).

[t]Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplant.

[u]Data suggest that for younger patients (aged ≤21 y), allogeneic HCT may not offer an advantage over chemotherapy + TKIs. Schultz KR, 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; Schultz KR, 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.

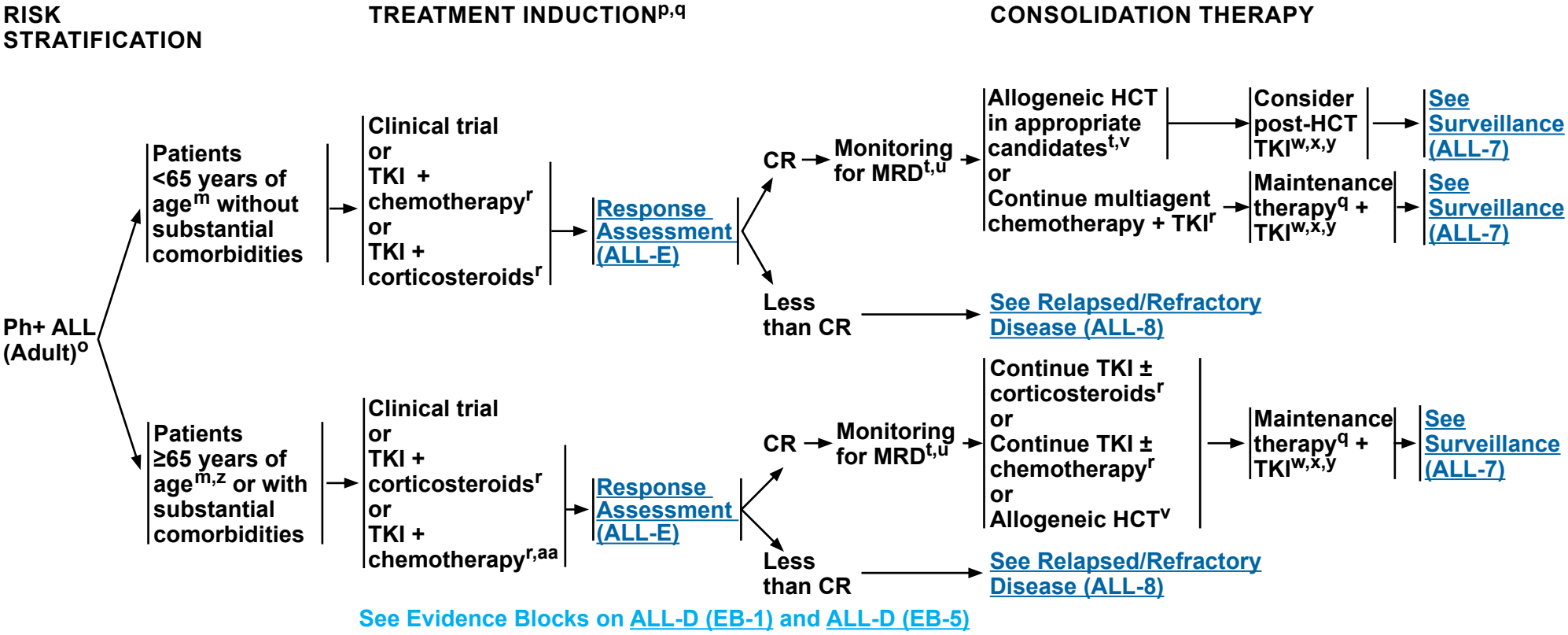
[v]Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.

[w]See Discussion for use of different TKIs in this setting.

[x]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.

[y]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.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.



See Evidence Blocks on ALL-D (EB-1) and ALL-D (EB-5)

[m]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.

[o]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.

[p]All ALL treatment regimens include CNS prophylaxis.

[q]See Principles of Supportive Care (ALL-C).

[r]See Principles of Systemic Therapy (ALL-D).

[s]See Minimal/Measurable Residual Disease Assessment (ALL-F).

[t]Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplant.

[v]Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.

[w]See Discussion for use of different TKIs in this setting.

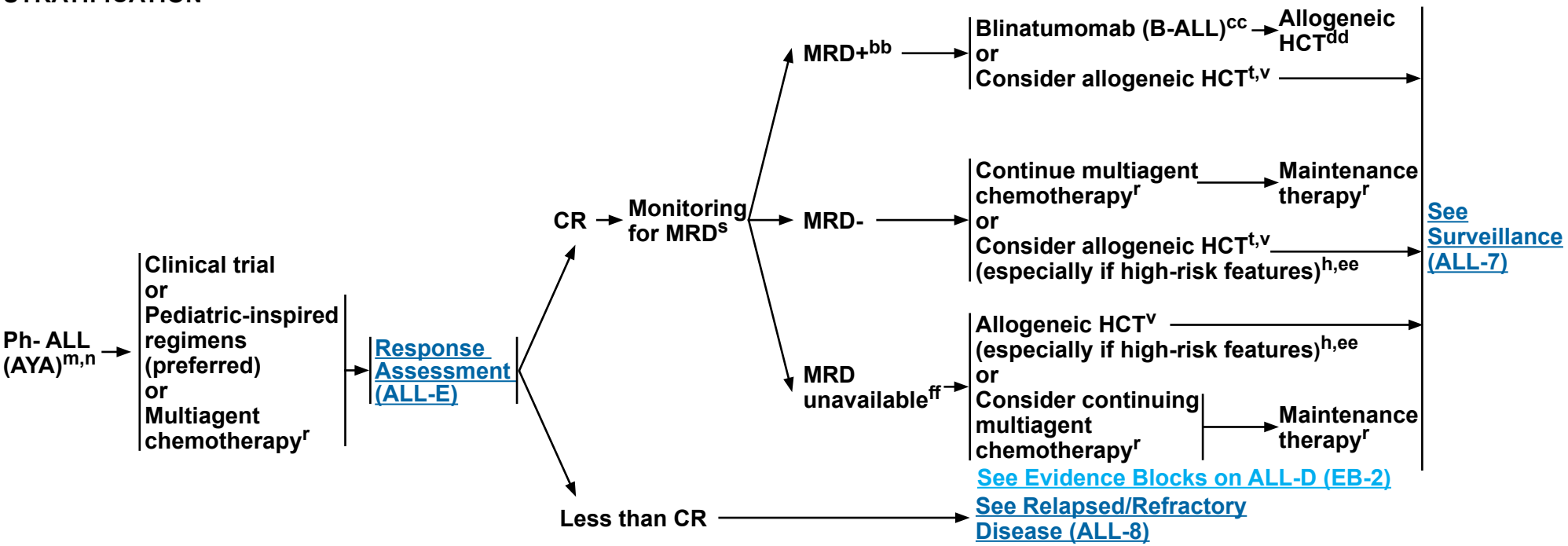
[x]The recommended duration of TKI after HCT is at least one year. The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy. The optimal duration of TKI is unknown in both settings.

[y]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.

[z]For additional considerations in the management of older adult patients with ALL, see the NCCN Guidelines for Older Adult Oncology.

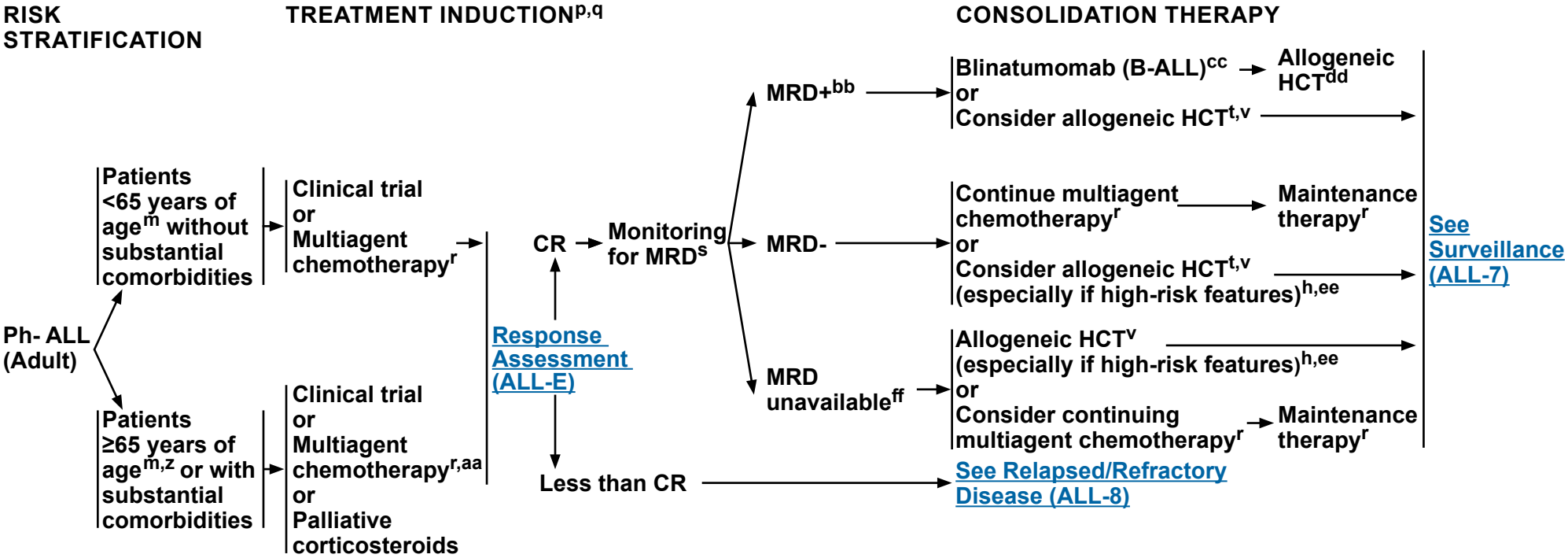
[aa]Consider dose modifications appropriate for patient age and performance status. See Principles of Systemic Therapy - Treatment of Older Adults with ALL (ALL-D 7 of 8).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.



[h]See Cytogenetic Risk Groups for B-ALL (ALL-A).
[m]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.
[n]For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.
[p]All ALL treatment regimens include CNS prophylaxis.
[q]See Principles of Supportive Care (ALL-C).
[r]See Principles of Systemic Therapy (ALL-D).
[s]See Minimal/Measurable Residual Disease Assessment (ALL-F).
[t]Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplant.
[v]Many variables determine eligibility for allogeneic HCT including donor availabiltiy, depth of remission, comorbidities, and social support.
[bb]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 evalution for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible. (See Discussion)
[cc]See Supportive Care: Toxicity Management (ALL-C 2 of 4).
[dd]Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.
[ee]High WBC count (≥30 x 10^9/L for B lineage or ≥100 x 10^9/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population and likely superseded by MRD quantification after treatment.
[ff]Consider retesting for MRD at first available opportunity.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.



See Evidence Blocks on ALL-D (EB-2) and ALL-D (EB-5)

[h]See Cytogenetic Risk Groups for B-ALL (ALL-A).
[m]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]All ALL treatment regimens include CNS prophylaxis.
[q]See Principles of Supportive Care (ALL-C).
[r]See Principles of Systemic Therapy (ALL-D).
[s]See Minimal/Measurable Residual Disease Assessment (ALL-F).
[t]Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplant.
[v]Many variables determine eligibility for allogeneic HCT including donor availabiltiy, depth of remission, comorbidities, and social support.
[z]For additional considerations in the management of older adult patients with ALL, see the NCCN Guidelines for Older Adult Oncology.
[aa]Consider dose modifications appropriate for patient age and performance status. See Principles of Systemic Therapy - Treatment of Older Adults with ALL (ALL-D 7 of 8).
[bb]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 evalution for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible. (See Discussion)
[cc]See Supportive Care: Toxicity Management (ALL-C 2 of 4).
[dd]Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.
[ee]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 is less firmly established for adults than for the pediatric population and likely superseded by MRD quantification after treatment.
[ff]Consider retesting for MRD at first available opportunity.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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[gg]

- **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 as clinically indicated every 3–6 months for at least 5 years[hh]**
  - **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/**

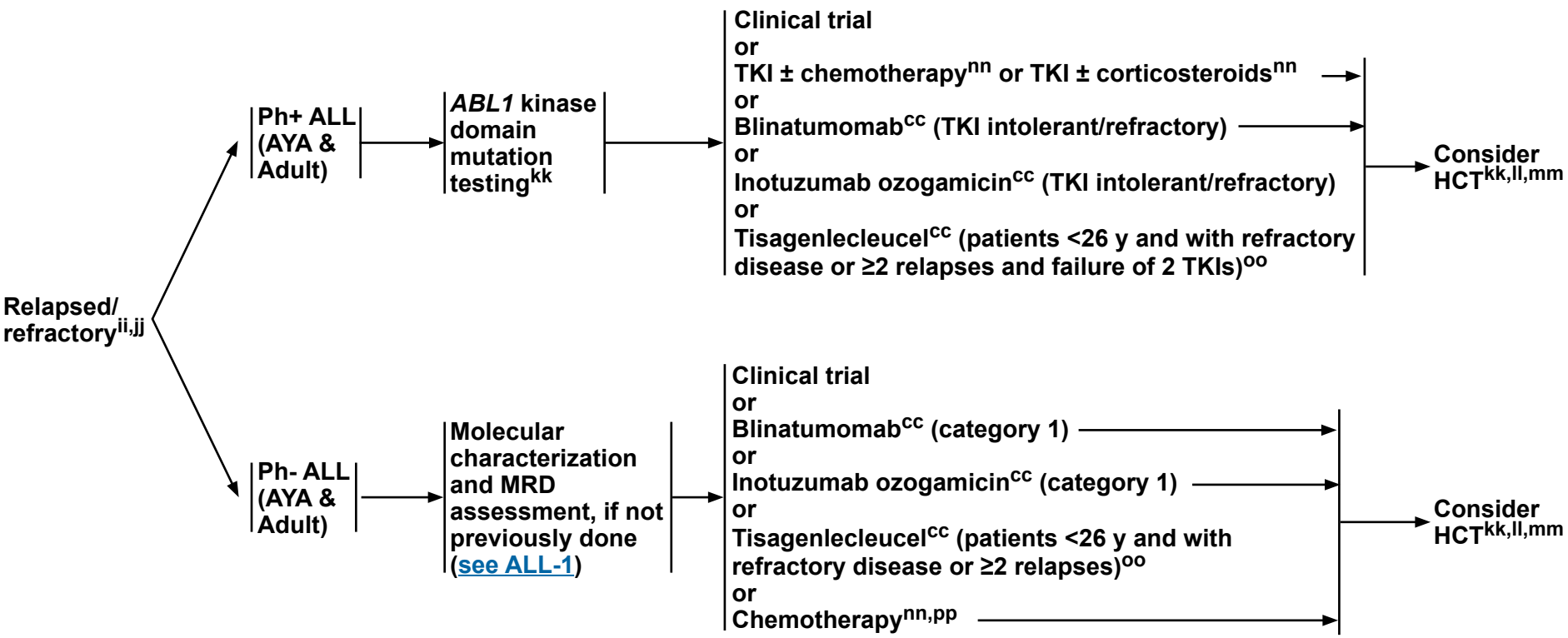
→ See Relapsed/Refractory Disease (ALL-8)

[gg]Surveillance recommendations apply after completion of chemotherapy, including maintenance.

[hh]While there are 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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

RELAPSED/REFRACTORY DISEASE | **TREATMENT[ll,mm]**



See Evidence Blocks on ALL-D (EB-3) and ALL-D (EB-4)

[cc] See Supportive Care: Toxicity Management (ALL-C 2 of 4).
[ii] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.
[jj] See NCCN Guidelines for Palliative Care.
[kk] See Treatment Options Based on BCR-ABL1 Mutation Profile (ALL-D 3 of 8).
[ll] See Principles of Systemic Therapy (ALL-D 3 of 8 and ALL-D 4 of 8).
[mm] If second remission is achieved prior to transplant and patient has not had a prior HCT, consolidative HCT is recommended.
[nn] For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.
[oo] 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.
[pp] For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See ALL-D 2 of 8).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

CYTOGENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	CYTOGENETICS
Good risk	Hyperdiploidy (51–65 chromosomes; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): *ETV6-RUNX1*
Poor risk	Hypodiploidy (<44 chromosomes); *KMT2A* rearranged (t[4;11] or others); t(v;14q32)/IgH; t(9;22)(q34;q11.2): *BCR-ABL1* (defined as high risk in the pre-TKI era); complex karyotype (5 or more chromosomal abnormalities); Ph-like ALL; intrachromosomal amplification of chromosome 21 (iAMP21)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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 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 LP be done concurrently with initial IT therapy.
- Classification of CNS status:
  - CNS-1: No lymphoblasts in cerebrospinal fluid (CSF) regardless of white blood cell (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, corticosteroids), 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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

SUPPORTIVE CARE

Best supportive care

- Infection control (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)
- Acute TLS (See Tumor Lysis Syndrome in the NCCN Guidelines for B-Cell Lymphomas)
- Toxicity Management for Inotuzumab, 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
  - 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 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 Cancer Pain)

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

SUPPORTIVE CARE
Toxicity Management for Inotuzumab, Blinatumomab, and Tisagenlecleucel

Inotuzumab:

- 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 stem cell transplantation [SCT]), those whose treatment extends beyond two cycles, and/or those who previously received or will receive double alkylator conditioning prior to allogeneic SCT. 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.
- 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.

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

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 three formulations of asparaginase in clinical use: 1) pegaspargase (PEG), 2) Calaspargase pegol-mknl (Cal-PEG), and 3) asparaginase Erwinia chrysanthemi (Erwinia). 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.**
- **For more detailed information, refer to 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. 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.**
- **Erwinia is commonly 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, diphenhydramine, and acetaminophen).**
- **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.[1]**

[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.

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

SUPPORTIVE CARE

Asparaginase Toxicity Managment (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 very close monitoring.
- For Grade 3 AST or ALT elevation, hold until Grade 1, then resume. For Grade 4 AST or ALT elevation, hold until Grade 1. If resolution to Grade 1 takes 1 week or less, then resume. Otherwise, either discontinue or resume with very close monitoring.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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

INDUCTION REGIMENS FOR Ph-POSITIVE ALL[a]

See Evidence Blocks on ALL-D (EB-1)

Protocols for AYA patients:

- **EsPhALL regimen: (imatinib, dasatinib); and a backbone of the Berlin-Frankfurt-Münster regimen[2,3]**
- **TKIs (ponatinib, imatinib, dasatinib) + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[4–8]**
- **TKIs (imatinib, nilotinib, dasatinib) + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)[9-13]**
- **TKIs (imatinib, dasatinib, nilotinib)[14,15] + corticosteroids[b]**
- **TKIs (imatinib, dasatinib, nilotinib) + vincristine + dexamethasone[16,b]**

Adult patients:

- **TKIs (ponatinib, imatinib, dasatinib) + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[4–8]**
- **TKIs (imatinib, nilotinib) + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)[9-13]**
- **TKIs (imatinib, dasatinib, nilotinib)[14,15] + corticosteroids[b]**
- **TKIs (imatinib, dasatinib, nilotinib) + vincristine + dexamethasone[16,17,b]**

Treatment of Older Patients (≥65 y) with ALL

Maintenance regimens:

- **Add TKIs (imatinib, dasatinib, nilotinib, ponatinib) 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.[c,d]**

Induction Regimens for Ph-Negative ALL
References

[a]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).
[b]These regimens are used for induction therapy and additional therapy is needed.
[c]For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP.
[d]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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

EVIDENCE BLOCKS FOR INDUCTION REGIMENS FOR Ph-POSITIVE ALL

Protocols for AYA Patients	Induction	Consolidation
EsPhALL regimen		
TKI (ponatinib, imatinib, dasatinib)/hyper-CVAD/alternating with high-dose methotrexate/cytarabine		
TKI (imatinib, nilotinib, dasatinib)/multiagent chemotherapy (daunorubicin/ vincristine/prednisone/cyclophosphamide)		
TKI (imatinib, dasatinib, nilotinib)/corticosteroids		—
TKI (imatinib, dasatinib, nilotinib)/vincristine/dexamethasone		

Protocols for Adult Patients	Induction	Consolidation
TKI (ponatinib, imatinib, dasatinib)/hyper-CVAD/alternating with high-dose methotrexate/ cytarabine		
TKI (imatinib, nilotinib)/multiagent chemotherapy (daunorubicin/vincristine/ prednisone/ cyclophosphamide)		
TKI (imatinib, dasatinib, nilotinib)/corticosteroids		—
TKI (imatinib, dasatinib, nilotinib)/vincristine/dexamethasone		

Maintenance Regimens	
TKI (imatinib, dasatinib, nilotinib, ponatinib for ≥ 1 year)/monthly vincristine/prednisone pulses (for 2–3 years)	
TKI (imatinib, dasatinib, nilotinib, ponatinib for ≥ 1 year)/monthly vincristine/prednisone pulses (for 2–3 years)/ weekly methotrexate/daily 6-mercaptopurine (6-MP)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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

INDUCTION REGIMENS FOR Ph-NEGATIVE ALL[a,e]

See Evidence Blocks on ALL-D (EB-2)

AYA patients:

- **Regimens based on data from multi-institutional or cooperative group studies:**
  - **CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase[f] (ongoing study in patients aged <40 years)[18,e,g]**
  - **COG AALL0232 regimen: daunorubicin, vincristine, prednisone, and pegaspargase[f] (patients aged ≤21 years)[19,e,g]**
  - **COG AALL0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegaspargase;[f] nelarabine added to consolidation regimen[20,g]**
  - **DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase[f] (ongoing study in patients aged <50 years)[21,e,g]**
  - **GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase,[f] and cyclophosphamide (patients aged <60 years), with rituximab for CD20-positive disease[22,e,g]**
  - **PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase,[f] and cyclophosphamide (patients aged <30 years)[23,e,g]**
- **Regimens based on data from single-institution studies:**
  - **Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with or without rituximab for CD20-positive disease[24,e]**
  - **USC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged 18–57 years)[25,e,g]**
  - **Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase[26,e]**

Adult patients: for treatment of older patients (≥65 y) with ALL see ALL-D 7 of 8

- **CALGB 8811 Larson regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide; for patients aged ≥60 years, reduced doses for cyclophosphamide, daunorubicin, and prednisone[27,28,e]**
- **GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <60 years) with rituximab for CD20-positive disease[22,e]**
- **Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with or without rituximab for CD20-positive disease[24,29,e]:**
- **Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase (patients aged <60 years)[26,e]**
- **MRC UKALLXII/ECOG2993 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (induction phase I); and cyclophosphamide, cytarabine, and 6-MP[c] (induction phase II)[30,e]**

Induction Regimens for Ph-Positive ALL
References

Maintenance regimen:

- **Weekly methotrexate + daily 6-MP[c] + monthly vincristine/prednisone pulses (duration based on regimen)**

[a]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]For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP.
[e]There are data to support the benefit of rituximab in addition to chemotherapy for CD20-positive patients (especially in patients <60 years). Refer to the GRAALL-2005 study for timing and frequency of administration.
[f]Pegaspargase 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.
[g]Pediatric-inspired regimen.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

EVIDENCE BLOCKS FOR INDUCTION REGIMENS FOR Ph-NEGATIVE ALL

Protocols for AYA Patients		
Regimens based on data from multi-institutional or cooperative group studies	**Induction**	**Consolidation**
CALGB 10403 regimen		
COG AALL0232 regimen		
COG AALL0434 regimen		
DFCI ALL regimen		
GRAALL-2005 regimen		
GRAALL-2005 regimen/rituximab (for CD20-positive disease)		
PETHEMA ALL-96 regimen		
Regimens based on data from single-institution studies	**Induction**	**Consolidation**
Hyper-CVAD		
Hyper-CVAD/rituximab (for CD20-positive disease)		
USC ALL regimen (based on CCG-1882 regimen)		
Linker 4-drug regimen		

Protocols for Adult Patients		
Regimens based on data from multi-institutional or cooperative group studies	**Induction**	**Consolidation**
CALGB 8811 Larson regimen		
GRAALL-2005 regimen		
GRAALL-2005 regimen/rituximab (for CD20-positive disease)		
Hyper-CVAD		
Hyper-CVAD/rituximab (for CD20-positive disease)		
Linker 4-drug regimen		
MRC UKALLXII/ECOG2993 regimen		

Consolidation for Ph-Negative ALL (if MRD positive after CR)	
Blinatumomab	

Maintenance Regimen	
Weekly methotrexate/daily 6-MP/monthly vincristine/ prednisone pulses (duration based on regimen)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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

REGIMENS FOR RELAPSED OR REFRACTORY ALL[a,h]

See Evidence Blocks on ALL-D (EB-3)

Ph-positive ALL:

- **Dasatinib[31,32]**
- **Imatinib[33]**
- **Ponatinib[34,i]**
- **Nilotinib[35]**
- **Bosutinib[36]**
- **The TKIs noted above may also be used in combination with any of the induction regimens noted on ALL-D 1 of 8 that were not previously given.**
- **Blinatumomab (for B-ALL) (TKI intolerant/refractory)[37,j]**
- **Inotuzumab ozogamicin (for B-ALL) (TKI intolerant/refractory)[38,j]**
- **Tisagenlecleucel (for B-ALL) (patients <26 y and with refractory disease or ≥2 relapses and failure of 2 TKIs)[39,j]**
- **MOpAD regimen (category 2B): methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease and TKI.[40]**
- **The regimens listed on ALL-D 4 of 8 for Ph-negative ALL may be considered for Ph-positive ALL refractory to TKIs.**

TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

Mutation	Treatment Recommendation
Y253H, E255K/V, or F359V/C/I	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib

Regimens for Relapsed/Refractory Ph-Negative ALL
References

[a]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).

[h]The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established. Please see ALL-D 7 of 8 for additional information.

[i]Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). The FDA indications are for the treatment of adult patients with T315I-positive, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of adult patients with Ph+ ALL for whom no other TKI therapy is indicated. For details, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203469s007s008lbl.pdf.

[j]See Supportive Care: Toxicity Management (ALL-C 2 of 4).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

EVIDENCE BLOCKS FOR REGIMENS FOR RELAPSED OR REFRACTORY Ph-POSITIVE ALL

Dasatinib	
Imatinib	
Ponatinib	
Nilotinib	
Bosutinib	
Blinatumomab (TKI intolerant/refractory)	
Inotuzumab ozogamicin (TKI intolerant/refractory)	
Tisagenlecleucel (patients <26 y & with refractory disease or ≥2 relapses and failure of 2 TKIs)	
MOpAD regimen/TKI/rituximab (for CD20-positive disease)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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

REGIMENS FOR RELAPSED OR REFRACTORY ALL[a,h,k]

See Evidence Blocks on ALL-D (EB-4)

Ph-negative ALL:

- **B-ALL**
  - **Blinatumomab (category 1)[41]**
  - **Inotuzumab ozogamicin (category 1)[38]**
  - **Tisagenlecleucel (patients <26 y and with refractory disease or ≥2 relapses)[39]**
- **T-ALL**
  - **Nelarabine[42,43]**
  - **Nelarabine, etoposide, cyclophosphamide (young and fit patients)[44,45]**
- **B-ALL or T-ALL**
  - **Augmented hyper-CVAD: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase; alternating with high-dose methotrexate and cytarabine[46]**
  - **Vincristine sulfate liposome injection (VSLI)[47,48]**
  - **Clofarabine[49,50]**
  - **Clofarabine-containing regimens: eg, clofarabine, cyclophosphamide, etoposide[51]**
  - **MOpAD regimen: methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease[40]**
  - **Fludarabine-based regimens**
    - ◊ **FLAG-IDA: fludarabine, cytarabine, granulocyte colony-stimulating factor, ± idarubicin[52]**
    - ◊ **FLAM: fludarabine, cytarabine, and mitoxantrone[53]**
  - **Cytarabine-containing regimens: eg, high-dose cytarabine, idarubicin, IT methotrexate[54]**
  - **Alkylator combination regimens: eg, etoposide, ifosfamide, mitoxantrone[55]**

Regimens for Relapsed/Refractory Ph-Positive ALL
References

[a]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).
[h]The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established. Please see ALL-D 7 of 8 for additional information.
[j]See Supportive Care: Toxicity Management (ALL-C 2 of 4).
[k]For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See ALL-D 2 of 8).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

EVIDENCE BLOCKS FOR REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE ALL

B-ALL	
Blinatumomab (for B-ALL)	
Inotuzumab ozogamicin (for B-ALL)	
Tisagenlecleucel (for B-ALL; patients <26 years and with refractory disease or ≥2 relapses)	
T-ALL	
Nelarabine (for T-ALL)	
Nelarabine, etoposide, cyclophosphamide (young and fit patients)	
B-ALL or T-ALL	
Augmented hyper-CVAD	
Vincristine sulfate liposome injection	
Clofarabine	
Clofarabine-containing regimens (for B-ALL; eg, clofarabine, cyclophosphamide, etoposide)	
MOpAD regimen	
MOpAD regimen/rituximab (for CD20-positive disease)	
FLAG-IDA regimen (fludarabine, cytarabine, G-CSF ± idarubicin)	
FLAM regimen (fludarabine, cytarabine, mitoxantrone)	
Cytarabine-containing regimens (eg, high-dose cytarabine, idarubicin, IT methotrexate)	
Alkylator combination regimens (eg, etoposide, ifosfamide, mitoxantrone)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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

[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]Hunger SP, SahaV, Devidas M, et al. CA 180-372; 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.
[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]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.
[18]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.
[19]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.
[20]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.
[21]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.
[22]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.
[23]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.
[24]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.
[25]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.
[26]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.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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

[27]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.
[28]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.
[29]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.
[30]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.
[31]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.
[32]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 2014;110:2309-2315.
[33]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.
[34]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.
[35]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.
[36]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:
[37]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.
[38]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.
[39]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.
[40]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.
[41]Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376: 836-847.
[42]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.
[43]Zwaan CM, Kowalczyk J, Schmitt C, et al. Safety amd 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.
[44]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.
[45]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.
[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]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.
[52]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.
[53]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.
[54]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.
[55]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.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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 - Treatment of Older Adults with ALL

- 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.
- Dose reduction of pegylated asparaginase (1000 IU/m^2), 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.

See the NCCN Guidelines for Older Adult Oncology. Discussion of ALL in the elderly can be found on OAO-C page 2 of 7.

INDUCTION REGIMENS for Ph-negative ALL – Adults aged ≥65 y

- Low intensity
  - Vincristine + prednisone[1]
  - Prednisone, vincristine, methotrexate, and 6-mercaptopurine (POMP)[2]
- Moderate intensity
  - GMALL: Idarubicin + dexamethasone + vincristine + cyclophosphamide + cytarabine ± rituximab[3]
  - PETHEMA-based regimen[4]
    - ◊ ALLOLD07 regimen: vincristine, dexamethasone, idarubicin, cyclophosphamide, cytarabine, methotrexate, and L-asparaginase
  - GRAALL: doxorubicin + vincristine + dexamethasone + cytarabine + cyclophosphamide[5]
  - Modified DFCI 91-01 protocol: dexamethasone, doxorubicin, vincristine, methotrexate, cytarabine, L-asparaginase, and IT chemotherapy[6]
- High intensity
  - Hyper-CVAD[7] with dose-reduced cytarabine to 1 g/m^2
  - CALGB 9111[8] (cyclophosphamide, daunorubicin, vincristine, prednisone, and pegaspargase)

INDUCTION REGIMENS for Ph-positive ALL – Adults aged ≥65 y

- Low intensity
  - TKI (imatinib, dasatinib, nilotinib) ± corticosteroids[9-12]
  - TKI (dasatinib, imatinib) + vincristine + dexamethasone[13-15]
- Moderate intensity
  - EWALL: TKI (dasatinib, nilotinib) with multiagent chemotherapy (vincristine, dexamethasone, methotrexate, cytarabine, asparaginase)[16]
- High intensity[17,18]
  - TKI (dasatinib, ponatinib) + HyperCVAD with dose-reduced cytarabine to 1 g/m^2

References

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

EVIDENCE BLOCKS FOR INDUCTION REGIMENS FOR OLDER ADULT PATIENTS WITH ALL

Protocols for Older Adult Patients with Ph-Negative ALL According to Intensity	
Low Intensity	
Vincristine/prednisone	
Prednisone/vincristine/methotrexate/6-mercaptopurine (POMP)	
Moderate Intensity	
GMALL regimen: idarubicin/dexamethasone/vincristine/cyclophosphamide/cytarabine ± rituximab	
PETHEMA ALLOLD07 regimen: vincristine/dexamethasone/idarubicin/cyclophosphamide/cytarabine/methotrexate/L-asparaginase	
GRAALL regimen: doxorubicin/vincristine/dexamethasone/cytarabine/cyclophosphamide	
Modified DFCI 91-01 protocol: dexamethasone/doxorubicin/vincristine/methotrexate/cytarabine/L-asparaginase/IT chemotherapy	
High Intensity	
Hyper-CVAD with dose-reduced cytarabine to 1 g/m^2	
CALGB 9111 regimen: cyclophosphamide/daunorubicin/vincristine/prednisone/pegaspargase	
Protocols for Older Adult Patients with Ph-Positive ALL According to Intensity	
Low Intensity	
TKI (imatinib, dasatinib, nilotinib)	
TKI (imatinib, dasatinib, nilotinib)/corticosteroids	
TKI (dasatinib, imatinib)/vincristine/dexamethasone	
Moderate Intensity	
EWALL regimen: TKI (dasatinib, nilotinib)/multiagent chemotherapy (vincristine/dexamethasone/methotrexate/cytarabine/asparaginase)	
High Intensity	
TKI (dasatinib, ponatinib)/hyper-CVAD with dose-reduced cytarabine to 1 g/m^2	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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 - Treatment of Older Adults with ALL
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]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.
[8]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.
[9]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.
[10]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.
[11]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.
[12]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.
[13]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.
[14]Rousselot P, Coude MM, Huguet 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.
[15]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.
[16]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.
[17]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.
[18]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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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 optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate.**
- **MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.**
- **MRD is an essential component of patient evaluation over the course of sequential therapy. If patient is not treated in an academic center, there are commercially available tests available that should be used for MRD assessment.**
- **Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurements during and after initial induction therapy.[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 next-generation sequencing (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.**
  - **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.**

[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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise indicated.

Table of Contents

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 1.38 per 100,000 individuals per year,[2] with approximately 5,930 new cases and 1,500 deaths estimated in 2019.[3] The median age at diagnosis for ALL is 15 years[4] with 55.4% of patients diagnosed at younger than 20 years of age.[5] In contrast, 28% of cases are diagnosed at 45 years or older and only approximately 12.3% of patients are diagnosed at 65 years or older.[5] ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults.[1,6]

Risk factors for developing ALL include older age (>70 years), exposure to chemotherapy or radiation therapy, and genetic disorders, particularly Down syndrome.[7,8] Although rare, other genetic conditions have been categorized as a risk factor for ALL and include neurofibromatosis,[9] Klinefelter syndrome,[10-12] Fanconi anemia,[13,14] Shwachman-Diamond syndrome,[15,16] Bloom syndrome,[17] and ataxia telangiectasia.[18]

The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children.[19] Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of risk-adapted therapy, the advent of new targeted agents, and the use of allogeneic hematopoietic 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.[19,20] However, survival rates for adult patients remains low at approximately 20% to 40%.[21-23] Survival rates are especially poor in older adult patients at approximately 20%.[22,24,25] 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.[22] 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%[19] (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 recent adoption of pediatric treatment regimens.[26] AYA patients represent a unique population, because they may receive treatment based on either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. Favorable cytogenetic subtypes, such as *ETV6-RUNX1* ALL and hyperploidy, occur less frequently among AYA patients compared with children, whereas the incidence of ALL with *BCR-ABL* (Ph-positive ALL) is higher in AYA patients.

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 term: acute lymphoblastic leukemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only 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; 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 have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 https://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.[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 ≥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's 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; comprehensive immunophenotyping with flow cytometry (see

Immunophenotyping); and baseline characterization of leukemic clone(s) to facilitate subsequent analysis of minimal/measurable residual disease (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-cell 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-cell 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: early T-cell precursor (ETP) lymphoblastic leukemia and natural killer (NK) cell lymphoblastic leukemia/lymphoma.[34] The Ph-like ALL, B-cell 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-cell ALL. If samples are *BCR-ABL1*–negative, testing for other gene fusions and mutations associated with Ph-like ALL is essential. In cases of aneuploidy or failed karyotype, additional assessment may include array comparative genomic hybridization (aCGH).

Immunophenotyping

Immunophenotypic classification of ALL involves flow cytometry to determine the presence of cell surface antigens on lymphocytes. ALL can be broadly classified into 3 groups based on immunophenotype, which include precursor B-cell ALL, mature B-cell ALL, and T-cell ALL.[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-cell 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-cell ALL. Early pre-B-cell ALL is characterized by the presence of terminal deoxynucleotidyl transferase (TdT), the expression of CD19/CD22/CD79a, and the absence of CD10 (formerly termed *common ALL antigen*) or surface immunoglobulins. CD10 negativity correlates with *KMT2A* rearrangement and poor prognosis.[41,42] Pre-B-cell 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-cell ALL due to the expression of CD10 at diagnosis. Mature B-cell ALL shows positivity for surface immunoglobulins and clonal lambda or kappa light chains, and is negative for TdT.[1] 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-cell ALL.[43,44]

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 to 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-cell 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 al[46] 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 bilineage leukemias, in which 2 distinct populations of lymphoblasts are identified, with 1 meeting the criteria for acute myeloid leukemia. Biphenotypic MPAL is defined as a single population of lymphoblasts that expresses markers consistent with B-cell or T-cell ALL, in addition to expressing myeloid or monocytic markers. Notably, myeloid-associated markers such as CD13 and CD33 may be expressed in ALL, and the presence of these markers does not exclude this diagnosis, 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 nonlineage antigens; these are useful in classification, particularly for MPAL.

Cytogenetic and Molecular Subtypes

Recurrent chromosomal and molecular abnormalities characterize ALL subtypes in both adults and children (Table 1), and often provide prognostic information that may weigh into risk stratification and treatment decisions. The frequency of certain subtypes differs between adult and childhood ALL, which partially explains the difference in clinical outcomes between patient populations. Among children with ALL, the most common chromosomal abnormality is hyperdiploidy (>50 chromosomes; 25% of cases) seen in B-cell lineage ALL compared to 7% in the adult ALL patient

population.[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 with favorable outcomes in ALL.[48-50] Ph-positive ALL, associated with poor prognosis, is relatively uncommon among childhood ALL (3%), whereas this abnormality is the most common subtype among adults (25%).[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]

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)	*BCR-ABL1*	25%	2%–4%
t(12;21)(p13;q22)	*ETV6-RUNX1 (TEL-AML1)*	2%	22%
t(v;11q23) [eg, t(4;11) and others], t(11;19)	*KMT2A rearranged*	10%	8%
t(1;19)(q23;p13)	*TCF3-PBX1 (E2A-PBX1)*	3%	6%
t(5;14)(q31;q32)	*IL3-IGH*	<1%	<1%
t(8;14), t(2;8), t(8;22)	*c-MYC*	4%	2%
t(1;14)(p32;q11)	*TAL-1*[a]	12%	7%
t(10;14)(q24;q11)	*HOX11 (TLX1)*[a]	8%	1%
t(5;14)(q35;q32)	*HOX11L2*[a]	1%	3%
t(11;14)(q11) [eg, (p13;q11), (p15;q11)]	*TCRα and TCRδ*	20%–25%	10%–20%
BCR-ABL1-like/Ph-like	*various*[b]	10%–30%	15%
B-ALL with *iAMP21*	*RUNX1*	--	2%
ETP	*various*[b]	2%	2%
Ikaros	*IKZF1*	25%–35%	12%–17%

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

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, PDGFRβ*, *EBF1*, *FLT3*, *IL7R*, *NTRK3*, and *SH2B3* genes.[35,55-57] A genomic profiling study found kinase-activating alternations in 91% of Ph-like ALL cases,[56] suggesting potential for *ABL*-class tyrosine kinase inhibitors (TKIs) or other targeted therapies to significantly improve patient outcomes in this subgroup.[58]

B-ALL with *iAMP21* is characterized by amplification of a portion of chromosome 21, detected by FISH with a probe for the *RUNX1* gene.[59,60] Occurring in approximately 2% of children with ALL, B-ALL with *iAMP21* is associated with adverse prognosis.[59,60] 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.[61]

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.[26,44] Hypodiploidy is associated with poor prognosis and is observed in 1% to 2% of patients.[26,62] 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.[63,64]

In B-cell ALL, mutations in the Ikaros gene (*IKZF1*) are associated with a poor prognosis and a greater incidence of relapse.[65] *IKZF1* mutations are seen in approximately 15% to 20% of pediatric B-cell ALL[66,67] and at a higher frequency of greater than 75% in patients who are also *BCR-ABL* positive.[55,67] Incidence in adults is about 25% to 35% in B-cell ALL[68-71] and about 65% in patients who are *BCR-ABL* positive.[72,73] 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.[74] The presence of either mutation was indicative of poor prognosis and was independent of conventional risk factors. Both mutations are considered strong independent risk factors for B-cell ALL and are applicable across a broad range of stratified ALL including patients with intermediate MRD.

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, phosphates, and calcium). Other recommended tests include a urinalysis and 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-cell 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 cardiac scan should be considered for all patients due to the use of anthracyclines as the backbone of nearly all treatment regimens. Assessment of cardiac function is particularly important for patients with prior cardiac history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction, and for elderly patients. Human leukocyte antigen (HLA) typing should be performed at workup, and an early evaluation and search for family or an alternative donor should be strongly considered.

Appropriate imaging studies (eg, CT/MRI scan of the head with contrast) should be performed to detect meningeal disease, chloromas, or central nervous system (CNS) bleeding for patients with major neurologic signs or symptoms at diagnosis. CNS involvement should be evaluated through

lumbar puncture at timing that is consistent with the treatment protocol. Pediatric-inspired regimens typically include lumbar puncture at diagnostic workup; the NCCN ALL Panel recommends that the first lumbar puncture be performed at the time of initial scheduled intrathecal therapy unless directed by symptoms to perform earlier (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 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

Initially, risk assessment for childhood ALL was individually determined by the institution, complicating the interpretation of data. However, in 1993, a common set of risk criteria was established by the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) at an international conference hosted by the NCI.[75] 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-cell ALL (regardless of age or WBC count), were considered high risk.[62] It should be noted that despite exclusion from this report, patients younger than age 1 should also be considered very high risk.[76,77] 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-cell ALL, to further refine therapy. Specifically, in B-cell ALL, a group identified as very high risk was defined as patients with any of the following characteristics: t(9;22) chromosomal translocation (ie, Ph-positive ALL) and/or presence of *BCR-ABL1* fusion protein; hypodiploidy (<44 chromosomes);[78] *BCR-ABL1*–like or Ph-like ALL;[79] *iAMP21*;[77] or failure to achieve remission with induction therapy.[26,62] *KMT2A* rearrangements and a poor response to induction chemotherapy also re-categorized patients into this group.[80-82] Conversely, criteria were refined for lower risk and included patients with hyperploidy, the t(12;21) chromosomal translocation (*ETV6-RUNX1* subtype),[83] or simultaneous trisomies of chromosomes 4, 10, and 17.[62,84] Presence of extramedullary disease and the early response to treatment also modified risk. Early marrow response to therapy was a strong positive prognostic factor while the presence of extramedullary disease at diagnosis was correlated with a poorer prognosis. Using the refined risk assessment, four risk categories for B-cell ALL, designated as low risk, standard risk, high risk, and very high risk were identified encompassing 27%, 32%, 27%, and 4% of cases, respectively.[62]

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

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.[26,50] Comparison of adult and pediatric protocols has shown that adults received lower doses of nonmyelosuppressive chemotherapy and less intense intrathecal chemotherapy regimens.[85,86] Adult protocols also entail a greater use of allogeneic HCT compared to pediatric protocols, but the benefits of HCT in the AYA population have not been sufficiently studied, and the available data have conflicting findings.[87-91] However, this is a significant difference between the way adults and pediatric patients are treated and may be a variable in the treatment of AYA patients. Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.

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.[92] 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*[93] and a greater incidence of poor-risk cytogenetics including Ph-positive ALL, hypodiploidy, and complex karyotype,[94] and a higher incidence of ETP-ALL.[45,95] Furthermore, the positive prognostic values of the *ETV6-RUNX1* mutation and hyperdiploidy are greater in the pediatric population, suggesting that the benefits decline with age.[94] The effects of the treatment are also shown to be different in the AYA population compared to the pediatric population. *In vitro* studies showed that ALL cells from children older than 10 years are more resistant to chemotherapy compared to the cells from children younger than 10 years.[96] The COG AALL0232 study reported an initial delay in response to induction therapy in older AYA patients (ages 16–30 years) compared to younger patients (1–15 years).[97] 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;[98] however, only 2% of AYA patients enroll in clinical trials compared to the 60% enrollment of pediatric patients.[99] Pediatric patients have been shown to be more compliant to treatment protocols compared to AYA patients,[100] which may be due to greater parental supervision of the treatment and better insurance.[101]

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 × 10^9/L for B-cell lineage; >100 x 10^9/L for T-cell lineage) that were predictive of significantly decreased remission duration.[102,103] Subsequent studies have confirmed the prognostic importance of these clinical parameters, although the cutoff values differed between studies.[38,44]

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 × 10^9/L for B-cell lineage; >100 × 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.[104] 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.[104] Among patients with Ph-negative ALL, those older than 35 years or with elevated WBC count (>30 × 10^9/L for B-cell lineage; >100 × 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.[104] 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.[104]

In a subsequent analysis from this MRC UKALL XII/ECOG E2993 study, cytogenetic data were evaluated in approximately 1000 patients.[105] 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).[105] 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%).[105] 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.[106] 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.[105]

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.[107] In this study, the prognostic impact of the different cytogenetic categories outweighed that of the more traditional factors, such as age and WBC count; in multivariate analysis for both relapse-free survival (RFS) and OS, cytogenetics remained a significant independent predictor of outcomes, whereas factors such as age and WBC count lost prognostic significance.[107] Moreover, the subgroup (n = 19) of patients with “very high risk” cytogenetic features [identified based on outcomes from the MRC/ECOG study mentioned earlier: presence of t(4;11) *MLL* translocation; t(8;14); complex karyotype; or low hypodiploidy] had substantially decreased 5-year RFS and OS rates (22%, for both endpoints). Analysis by ploidy status was not possible because only 2 patients were considered to have low hypodiploidy/near triploidy. The 5-

year RFS and OS rates among patients with Ph-positive ALL (n = 36) were 0% and 8%, respectively.[107]

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. Because AYA patients may benefit from pediatric-inspired ALL treatment protocols, this 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 (≥30 × 10^9/L for B-cell lineage; ≥100 × 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 (≥30 × 10^9/L for B-cell lineage; ≥100 × 10^9/L for T-cell lineage) has been considered a high-risk factor based on some earlier studies. However, more recent studies in adult patients have demonstrated that WBC counts may lose independent prognostic significance when cytogenetic factors 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. Therefore, adult patients with ALL may not necessarily be classified as high risk based on high WBC count alone.

Overview of Treatment Phases in ALL Management

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations differ between AYA patients and adults, and among different subtypes of ALL, the basic treatment principles are similar. The most common treatment regimens used in patients with ALL include modifications or variations of multiagent chemotherapy regimens originally developed by the Berlin-Frankfurt-Münster Group (BFM) for pediatric patients (eg, regimens used by COG for children and AYA patients, or the CALGB regimen for adult patients), and the hyper-CVAD regimen 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.[1,26,38,44,50]

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.[108-112] Some studies from the CALGB group have utilized a 5-drug regimen, which adds cyclophosphamide to the above 4-drug combination.[113] 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.[114,115] The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of dexamethasone into the CNS.[116] 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).[117] 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.[117] 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 8 alternating treatment cycles with the “A” regimen (hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and the “B” regimen (high-dose methotrexate and cytarabine).[21,118,119] 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).[1,50,116] CNS prophylaxis is typically given to all patients throughout the entire course of ALL therapy, from induction, to consolidation, to the maintenance phases of treatment.

Consolidation

The intent of postinduction consolidation is to eliminate any leukemic cells potentially remaining after induction therapy, further eradicating residual disease. The postremission induction phase of treatment (but before long-term maintenance therapy) may also be described as *intensification therapy*. The combination of drugs and duration of therapy for consolidation regimens vary largely among studies and patient populations

but can comprise combinations of drugs similar to those used during the induction phase. High-dose methotrexate, cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, vincristine, corticosteroids and L-asparaginase are frequently incorporated into consolidation/intensification regimens.[28,38,44,50,111,112]

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.[26,38,44,50] Maintenance therapy is omitted for patients with mature B-cell 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.[38,120]

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.[121,122] Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.[123-125] The concomitant use of other chemotherapeutic agents such as methotrexate can alter toxicity.[126] 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.[127,128] Diet has been shown to affect absorption of 6-MP.[129,130] 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.[131] 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.[132,133] Heterozygosity at the *TPMT* gene locus occurs in 5% to 10% of the population and has been shown to have intermediate enzyme activity.[131,134,135] Therefore, a 10% to 15% reduction in 6-MP dose is necessary in these patients to prevent toxicity.[136,137] Determination of patient TPMT genotype using genomic DNA is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses.[138,139]

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.[140] This may be especially beneficial for dose adjustment in pediatric patients.[141] Outcomes are better in patients who achieve myelosuppression during maintenance compared with patients who have higher neutrophil counts,[100,142] 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.[126] 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, and ponatinib, represents an important advancement in ALL therapy.[143-151] Incorporation of TKIs into treatment regimens should include evaluation of clinical pharmacokinetics.[152] 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-cell ALL).[153,154] 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.[155-157] 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,[105,112] 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-cell 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 5-year EFS (calculated from time of diagnosis) and OS rates were 28% and 40%, respectively, for the entire patient cohort.[54] The 7-year EFS and OS rates were 25% and 36%, respectively. Even among the subgroup of patients considered to have a better prognosis (ie, WBC count $<50 \times 10^9$/L and age <10 years), the 5-year DFS rate (calculated from time of first CR) was only 49%.[54] Compared with patients who received only chemotherapy, the subgroup of patients who underwent allogeneic HCT with an HLA-matched related donor (n = 38) had significantly higher 5-year DFS (65% vs. 25%; $P < .001$) and OS (72% vs. 42%; $P = .002$) rates. This benefit with HCT versus chemotherapy alone was not observed with autologous HCT or with HCT from matched URDs. This study showed that allogeneic HCT from a matched related donor offered improvements in outcomes over chemotherapy alone.

In a subsequent analysis of outcomes in children with Ph-positive ALL treated between 1995 and 2005 but also without targeted TKIs, the 7-year EFS and OS rates were 32% and 45%, respectively.[158] Outcomes with allogeneic HCT from either matched related donors or URDs appeared similar, and HCT improved disease control over intensive chemotherapy alone.[158] 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; age 1–21 years) was treated with an intensive chemotherapy regimen combined with imatinib (340 mg/m^2/d; given during postremission induction therapy and maintenance).[159] 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).[159] 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.[159] Subsequent follow-up after 5 years confirmed these outcomes.[160] In a phase II single-arm COG trial (AALL-0622) of children and young adults with Ph-positive ALL (n = 60; age 1–30 years), imatinib was replaced with dasatinib on induction day 15 and combined with the same chemotherapy used in AALL-0031.[161] The 5-year overall OS and EFS rates (± Standard Deviation [SD]) were 86% ± 5% and 60% ± 7%, respectively, and outcomes were similar to those observed in AALL-0031.[161]

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.[162] 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).[162] 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.[163] 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.[162,163] Additionally, a phase II trial evaluated the safety and efficacy of adding continuous dasatinib at day 15 to the intensive BFM regimen in pediatric patients with newly diagnosed Ph-positive ALL (n = 109 enrolled; age

range, 1–17 years).[164] 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).[164]

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.[150] The 3-year OS rate with this regimen was 54%. Among the patients aged 40 years or younger (n = 16), a strong trend was observed for OS benefit with allogeneic HCT (3-year OS rate, 90% vs. 33%; *P* = .05).[150] Among patients aged 60 years or younger, no statistically significant difference was observed in the 3-year OS rate between patients who received HCT and those who did not (77% vs. 57%).

Studies have shown the promising activity of other TKIs, including dasatinib and ponatinib when incorporated into frontline regimens for patients with ALL. In a phase II study from MDACC, dasatinib was combined with hyper-CVAD and subsequent maintenance therapy in patients with previously untreated Ph-positive ALL (n = 35; median age, 53 years; range, 21–79 years; 31% were older than 60 years); 4 of the patients received allogeneic HCT in CR1.[165] 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; age ≥18 years; median age, 51 years; 12 patients were ≥60 years) in a phase II prospective trial.[144] 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.[144] However, it is worth noting that only half of the patients ≥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%.[166]

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.[167,168] 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%.[168] 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).[169] 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).[169] 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.[169]

In a phase II study from the Spanish Cooperative Group, patients with Ph-positive ALL (n = 30; median age, 42 years; range, 8–62 years; only 1 patient was <15 years of age) were treated with intensive chemotherapy combined with imatinib, followed by HCT and imatinib maintenance.[170] Overall, 53% of patients proceeded to allogeneic HCT and 17% received autologous HCT. At a median follow-up of 4.1 years, the OS and DFS rates were both 30%. The incidence of transplant-related mortality was 27%.[170] Post-transplant maintenance with imatinib was not feasible in most patients, primarily because of transplant-related complications.

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.[171,172] 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.[172] 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).[171] 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).[171]

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).[173] 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%.[173]

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%.[174]

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%[175,176] and 3-year OS rates of 36% to 44%.[88,171] 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.[177] 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.[177] 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).[177] The incorporation of imatinib in the treatment regimen for Ph-positive ALL has led to improvements in outcomes over chemotherapy alone.[150,172,174]

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.[178-180] 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).[178] 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).[178]

TKIs Combined With Hyper-CVAD

Studies evaluating TKIs plus hyper-CVAD have included both AYA and adult patients.[144,150,165] 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[167-171,173] (see *Initial Treatment in AYA Patients with Ph-positive AYA patients*). Several studies evaluating the efficacy of TKIs combined with multi-agent chemotherapy in patients with previously untreated ALL have shown improved outcomes, particularly when treatment was followed by allogeneic HCT.[147,169,171,172] A multicenter trial from the European Working Group for Adult ALL (EWALL; EWALL-PH02) evaluated the efficacy and safety of nilotinib with multi-agent chemotherapy in older patients with Ph-positive ALL (n = 79 [72 evaluable]; age range, 55–85 years).[147] The CR rate was 94.4% and the MRD response (*BCR-ABL*/*ABL* ratio ≤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.[181] 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.[182] The median OS was numerically higher (but not statistically significant) among patients who received imatinib induction compared with those randomized to chemotherapy induction (23.5 vs. 12 months). However, the incidence of severe adverse events was significantly lower with imatinib induction (39% vs. 90%; *P* = .005), which suggested that induction therapy with imatinib may be better tolerated than chemotherapy in older patients with Ph-positive ALL.[182]

In a study from GIMEMA (LAL-1205), patients with Ph-positive ALL (n = 53 evaluable; median age, 54 years; range, 24–76.5 years) received induction therapy with dasatinib and prednisone.[143] 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.[143] 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.[183] 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).[183] 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).[184] 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.[184] 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.[143] 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.[143]

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.[185,186] 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 polymerase chain reaction [PCR]) after induction/consolidation. In an early report from this study (n = 118; n = 83 evaluable; median age 42 years), 52 patients proceeded to 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).[185] 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 2 cycles of therapy were similar between arm A and arm B (66.1% vs. 64.5%).[187] 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.[187] Among patients who proceeded to allogeneic HCT or autologous HCT after MRD response, the outcomes were similar in terms of the 5-year posttransplant 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.[187]

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.[188] 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.[188] 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 engraftment until 1 year after HCT.[189] 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 1 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.[189] 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).[190] 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.[190] 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.[190]

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.[191] 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.[191] 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%).[191] 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. not reached [NR]; 4-year EFS, 39% vs. 65%; P = .037).[191] 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.

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%.[192-195] 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 Hematologia) 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).[193] 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).[192] 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.[192,194]

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.[196,197] 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.[198,199] 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.[200-202] Moreover, case reports have described using newer TKIs, such as dasatinib and nilotinib, along with DLI to manage relapse after allogeneic HCT.[203,204] 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

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.[205-208] 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.[206,208] 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.[207] Patients with imatinib-resistant disease who developed CNS disease rapidly died from progressive disease (PD); conversely, patients with imatinib-sensitive disease who developed isolated CNS relapse could be successfully treated with intrathecal therapy with or without cranial irradiation.[205,207]

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.[209-211] The former has been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy.[212,213] Moreover, *ABL* kinase domain mutations may be present in a small group of imatinib-naïve patients even before initiation of any TKI therapy.[214,215]

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.[148,216-218] Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL that is resistant to imatinib treatment.[219-221] 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;[220] 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).[220] 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) chronic myelogenous leukemia (CML) (n = 15).[222] 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 9 patients who went on to receive allogeneic HCT, including 2 patients with ALL. In the patients with relapsed ALL, 30% remained in complete remission at 3 years with a 3-year OS of 26%. At the median follow-up of 52 months (range, 45–59 months), 2 patients (11%) with ALL were still alive.

Bosutinib, a second-generation TKI that acts as a dual inhibitor of *BCR-ABL* and SRC family kinases,[223,224] 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.[224] Efficacy and safety analyses of bosutinib monotherapy included patients with advanced leukemia [AP CML (n = 79), BP CML (n = 64), or ALL (n = 24)] previously

treated with at least one TKI.[225,226] Of the 22 evaluable patients with ALL, 2 patients (9%) attained or maintained a confirmed overall hematologic response by 4 years.[225] Common overall treatment-related adverse events reported in patients with advanced leukemia included diarrhea (74%), nausea (48%), and vomiting (44%).[225,226]

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.[227] 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.[228] Major hematologic response was observed in 41% of the subgroup with Ph-positive ALL (n = 32). In the subset of patients with Ph-positive ALL with *ABL* T315I mutation (n = 22), major hematologic response was observed in 36%.[228] 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,[228] 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.[211,217,229,230] 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.[231] (See *Principles of Systemic Therapy* in the algorithm for *TKI treatment options for Treatment Options Based on BCR-ABL Mutation Profile*).

Blinatumomab

In December 2014, the FDA approved blinatumomab for the treatment of relapsed or refractory Ph-negative precursor B-cell 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-cell 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).[232] During the first two cycles of blinatumomab, 36% achieved complete remission or complete remission with partial hematologic recovery, and 88% of the latter responders achieved a complete MRD response.[232] 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,[233] a randomized study was conducted comparing InO with standard intensive chemotherapy regimens in Ph-negative or Ph-positive ALL in first or second relapse, defined as >5% marrow blasts (n = 326). Compared 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).[234] 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).[234] In August 2017, InO received full approval from the FDA for the treatment of R/R precursor B-cell 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.[235] 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 remission status have a CR and ultimately transplantation. CAR T-cell therapy relies on the genetic manipulation of a patients' T-cells to engender a response against a leukemic cell-surface antigen, most commonly CD19.[236] (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-cell ALL.

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.[237] A phase II trial incorporated a new PEGylated formulation of L-asparaginase due to improved tolerability,[238] 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).[239] For patients with Ph-positive ALL, TKIs (ie, imatinib, dasatinib, nilotinib) were added to the regimen and if patients had CD20-positive B-cell 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.[239] Patients with Ph-positive ALL had CR and ORR rates of 50% and 67%, respectively.[239] This regimen may be considered in patients who have received a maximal dose of anthracycline and have cardiac dysfunction and limited performance status.

NCCN Recommendations for Ph-Positive ALL

AYA Patients with Ph-Positive ALL

The panel recommends that AYA patients with Ph-positive ALL 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. Treatment regimens should include adequate CNS prophylaxis for all patients. It is also important to adhere to the treatment regimens for a given protocol in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. For AYA patients experiencing a CR after initial induction therapy, 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.[240] The

optimal time for a patient to receive allogeneic HCT is unclear; however, for fit patients, additional therapy may be considered to eliminate MRD before transplant. In younger AYA patients (aged ≤21 years), emerging data suggest that allogeneic HCT may not confer an advantage over chemotherapy combined with TKIs.[159] 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 without a donor, consolidation therapy after a CR should comprise a continuation of multiagent chemotherapy combined with a TKI. These patients should continue to receive post-consolidation maintenance therapy with a regimen that includes a TKI. 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 of developing hematopoietic toxicity (in particular, severe neutropenia) after treatment with 6-MP.[137] 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 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 with Ph-Positive ALL

For adult patients with Ph-positive ALL, 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 performance status, end-organ function, and end-organ reserve.

For relatively fit adult patients (age <65 years without substantial comorbidities), the recommended treatment approach is similar to that for AYA patients. Induction therapy would comprise multiagent chemotherapy or corticosteroids combined with a TKI. For patients experiencing a CR after induction, an MRD assessment should be performed prior to consolidation with allogeneic HCT if a matched donor is available. Similar to the treatment strategy for AYA patients, the optimal time for a patient to receive allogeneic HCT is unclear; however, for fit patients, additional therapy may be considered to eliminate MRD before transplant. Maintenance therapy with a TKI, with or without monthly pulses of vincristine/prednisone for 2 to 3 years is recommended. As previously mentioned, although the optimal duration of post-transplant 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 without a donor, consolidation therapy after a CR should comprise a continuation of multiagent chemotherapy combined with a TKI.

These patients should continue to receive post-consolidation maintenance therapy with a regimen that includes a TKI. 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. Again, testing for *TPMT* gene polymorphism should be considered for patients receiving 6-MP as part of maintenance therapy, especially those who develop severe bone marrow toxicities after its initiation. For patients with less than a CR after induction, the treatment approach would be similar to that for patients with R/R disease (see *Patients with Relapsed/Refractory Ph-Positive ALL*).

For adult patients who are less fit (aged ≥65 years or with substantial comorbidities), the recommended induction therapy options include a TKI with corticosteroids or with low-intensity chemotherapy regimens. Dose modifications may be required for chemotherapy agents, as needed. In patients with a CR after induction, an MRD assessment should be performed prior to consolidation therapy including continuing therapy with a TKI with or without corticosteroids or low-intensity chemotherapy. Allogeneic HCT may be considered based on performance status, donor availability, and transplant center expertise in treating older patients with allogeneic HCT. Post-consolidation maintenance TKI therapy is recommended for at least 2 to 3 years with or without monthly pulses of vincristine/prednisone. Weekly methotrexate and daily 6-MP may be added to the maintenance regimen, as tolerated; however, the doses of antimetabolites may need to be reduced in the setting of hepatotoxicity or myelosuppression. As previously mentioned, although the optimal duration of post-transplant TKI is unknown, the minimum suggested duration is 1 year. Adult patients with less than a CR after induction should be managed similarly to those with R/R disease (see *Patients with Relapsed/Refractory Ph-Positive ALL*).

Patients with Relapsed/Refractory Ph-Positive ALL

Mutation testing for the *ABL1* kinase domain is recommended in patients with Ph+ ALL that has relapsed after or is 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.[231] 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*. Due to the high frequency of serious vascular events with ponatinib therapy, the FDA indication is restricted to the treatment of patients with the T315I mutation or in patients with disease resistant to other TKI therapies.

For all patients with R/R Ph-positive 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 and InO are treatment options if the patient is refractory or intolerant to TKIs. Compared to standard care, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease, and increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality.[241] Tisagenlecleucel is also an option for patients up to age 25 years (aged <26 years) and with refractory disease or ≥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 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.[242] For patients with Ph-positive 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.[85,86,112,243,244] 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.[112] 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.[112] 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, *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).[88] Patients were stratified into 4 risk groups: 1) Ph-negative standard-risk disease [defined as achievement of CR after 1 course of chemotherapy; absence of CNS disease; absence of t(4;11), t(1;19), or other 11q23 rearrangements; WBC count $<30 \times 10^9$/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.[88] 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%).[88]

Outcomes were improved in patients with Ph-negative high-risk ALL and those with CNS involvement allocated to allogeneic HCT. The median DFS was 21 months for these patients, and the median OS has not yet been reached; the 5-year OS rate was 51%.[88] Thus, it appears that in patients with Ph-negative high-risk disease, allogeneic HCT in first CR improved DFS outcomes, whereas autologous HCT did not result in significant benefit compared with chemotherapy alone.

In the PETHEMA ALL-93 trial, adult patients with high-risk ALL [defined as having at least one of the following criteria: 30–50 years of age; WBC count ≥25 × 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).[245] 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).[245]

The role of allogeneic HCT in adults with ALL was also evaluated in the large multicenter MRC UKALL XII/ECOG E2993 study (n = 1913; age 15–59 years).[89] 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 × 10^9/L for B-cell ALL; >100 × 10^9/L for T-cell 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%).[89] 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).[89] 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.[246] In the donor group, the non-relapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.[246]

As evidenced by the previously described studies, matched sibling HCT has been established as a valuable treatment strategy for patients with high-risk Ph-negative ALL, but more recently studies have examined the role of URD transplants. In a retrospective analysis of 169 patients who underwent URD HCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57%) had multiple risk factors. The 5-year survival was 39%, which is higher than survival reported in studies of high-risk patients receiving chemotherapy alone.[247] 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.[248] RIC conditioning most commonly comprised busulfan (9 mg/kg or less), melphalan (150 mg/m^2), low-dose total body irradiation (TBI) (less than 500 cGy single dose or less than 800 cGy fractionated), or fludarabine plus TBI of 200 cGy. RIC is more prominent in the treatment of older patients; therefore, the median age for patients receiving full-intensity (FI) conditioning was 28 years (range, 16–62 years), and for patients receiving RIC, the median age was 45 years (range, 17–66 years). Despite the variation in age, results from the study have shown no difference in relapse (35% vs. 26%, *P* = .08) or in treatment-related mortality (FI, 33%; 95% CI, 31%–36% vs. RIC, 32%; 95% CI, 23%–43%; *P* = .86) at 3 years.[248] 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%).[248]

A systematic review and meta-analysis of published randomized trials on postremission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HCT in first CR (RR, 0.88; 95% CI, 0.80–0.97) compared with autologous HCT or chemotherapy.[249] 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.[249] Autologous HCT in first remission was not shown to be beneficial relative to chemotherapy in several large studies and meta-analyses.[88,89,249,250]

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).[251] 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 (≥50 × 10^9/L) or in older children and adolescents aged 10 to 21 years.[111] 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.[111] In the subgroup of AYA patients (age 16–21 years; n = 262) from the CCG 1961 study treated with either augmented or standard-intensity regimens, the 5-year EFS and OS rates were 71.5% and 77.5%, respectively.[252] Among the AYA patients who were considered

rapid early responders, the augmented-intensity (n = 88) and standard-intensity (n = 76) arms showed no statistically significant differences in rates of 5-year EFS (82% vs. 67%, respectively) or OS (83% vs. 76%, respectively). For the AYA patients who were considered slow early responders (all of whom received the augmented-intensity regimen), the 5-year EFS rate was 71%.[252]

COG AALL0232

The AALL0232 trial enrolled 2154 patients between the ages of 1 and 30 years who were diagnosed with high-risk B-cell ALL.[253] In this study patients were randomly assigned to receive dexamethasone versus prednisone during induction and high-dose methotrexate versus Capizzi escalating-dose methotrexate plus pegaspargase (PEG) during interim maintenance 1. High-dose methotrexate showed improved 5-year EFS (80% vs. 75%; *P* = .008) and OS (88.9% ± 1.2% vs. 86.1% ± 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/m^2/d for 14 days to 60 mg/m^2/d 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 10 years of age or older. These data suggest that age may be an important factor for the selection of a corticosteroid.[253]

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 × 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.[254] 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%).[254] 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).[254]

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.[255] 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.[255] 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%).[255] 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%).[256] A phase II successor trial was initiated to determine whether pegylated-asparaginase could be substituted for L-asparaginase in this regimen.[257] A high frequency of asparaginase toxicities precipitated reverting to L-

asparaginase during induction and a dose-reduction of pegylated-asparaginase during consolidation. After 4 weeks, the CR rate was 89%, and with a median follow-up of 39 months, the estimated 3-year DFS and OS rates are 73% and 75%, respectively.[257] 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).[258] 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.[258] 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%).[258] 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).[259] 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).[259]

USC 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 57 years of age with newly diagnosed ALL (n = 51).[260] The augmented arm included one long-lasting PEG dose in each cycle of the 6 total scheduled doses. Each dose of PEG (2000 IU/m^2 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/m^2 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) is currently ongoing to evaluate a pediatric-inspired regimen in the treatment of AYA patients with Ph-negative ALL. One of the study objectives is to compare the outcomes of patients treated in this trial with those of a similar group of

patients (in regard to age and disease characteristics) treated by pediatric oncologists in the COG trial (AALL-0232). The treatment protocol includes a 4-drug induction regimen with intrathecal cytarabine and intrathecal methotrexate, consolidation, interim maintenance, delayed intensification, maintenance (for 2–3 years), and radiotherapy (for patients with testicular or CNS disease or those with T-cell ALL). Results from 295 evaluable patients (median age, 24 years; range 17–39 years) report 2 post-remission deaths and 3% overall treatment-related mortality.[261] The median EFS is 78.1 months (95% CI, 41.8 months to NR) and the 3-year EFS rate is 59% (95% CI, 54%–65%). The estimated 3-year OS rate is 73% (95% CI, 68%–78%).[261] It was also noted that Ph-like gene expression signatures and obesity were associate with worse treatment outcomes.[261]

COG AALL0434 Regimen

Nelarabine is a nucleoside metabolic inhibitor and a prodrug of ara-G, approved for the treatment of patients with T-cell ALL with disease that has not responded to or that has relapsed after at least 2 chemotherapy regimens. The randomized phase III COG study (AALL0434) evaluated the safety of nelarabine as part of frontline therapy, using the augmented BFM chemotherapy regimen, with or without nelarabine, and showed that the toxicity profiles were similar between patients with high-risk T-cell ALL who received nelarabine (n = 47) and those who did not (n = 47).[262] 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.[262]

Results from the efficacy phase of this study evaluated data from 1,895 patients with newly diagnosed T-ALL and T-LL.[263] 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 randomized into arms with or without nelarabine (650 mg/m^2/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).[263] Compared to the high-dose methotrexate and nelarabine arm, use of escalating dose methotrexate and nelarabine appeared to enhance the 4-year DFS rates.[263] 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.[264]

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-cell ALL (n = 23).[265] 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.[265] 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.[266] These studies suggest that for patients with T-cell ALL, the addition of nelarabine to frontline therapy may be a promising approach.

Hyper-CVAD with or without Rituximab

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

untreated ALL (n = 288; median age, 40 years; range, 15–92 years; Ph-positive in 17%).[21] 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%.[21] Among patients who experienced a CR (92% of all patients), the 5-year CR duration rate was 38%.[21] Death during induction therapy occurred in 5% of patients, and was more frequent among patients aged 60 years or older. Notably, this was not associated with an increase in 5-year OS (17%).[21] 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%).[267]

Based on retrospective analyses of data from adults with B-cell ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on >20% of blasts) was found to be associated with adverse outcomes measured by a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.[43,268] 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).[154] 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.[154] 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.[269]

Linker 4-Drug Regimen

Linker et al[270] evaluated an intensified chemotherapy regimen that incorporated a 4-drug induction regimen (comprising vincristine, daunorubicin, prednisone, and asparaginase) in adolescent and adult patients with ALL (n = 84; Ph-positive in 16%; median age, 27 years; range, 16–59 years). The 5-year EFS and OS rates for all patients were 48% and 47%, respectively. Among the patients who experienced a CR (93% of all patients), the 5-year EFS rate was 52%. The 5-year EFS rate was 60% for the subgroup of patients without high-risk features (n = 53).[270]

Blinatumomab

Blinatumomab first showed promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multi-center, single-arm, phase II study, Topp et al[271] evaluated the efficacy of blinatumomab in MRD-positive patients with Ph-negative B-ALL (n = 21; age range, 20–77 years). Patients were considered MRD-positive if they had never achieved MRD negativity before blinatumomab, or had experienced a hematologic CR with MRD $\geq 10^{-4}$. After blinatumomab treatment, 16 of 20 evaluable patients were determined to be MRD-negative at a detection threshold of 10^{-4}.[271] After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.[272] Gökbuget et al[273] 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%.[273] In both of these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HCT,

establishing blinatumomab as an effective "bridge to transplant" in MRD-positive patients. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in patients with R/R B-precursor ALL.[274-276] In March 2018, the FDA approved blinatumomab use for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR with MRD defined as disease ≥0.1% (see *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 AYAs 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.[180] 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.[180]

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).[113] Patients aged ≥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 ≥60 years, contributing to a median OS of 1 month in this population.[113] 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%.[113]

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).[277] 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.[277] Among the 41 patients aged ≥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%.[277]

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.[258,259] 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.[278] 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 ≥55 years.[278]

Linker 4-Drug Regimen

The referenced study evaluating linker 4-drug regimen included both AYA and adult patients.[270] For a summary of this study, refer to the previous section (*see Initial Treatment in AYA Patients with Ph-Negative ALL*).

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; age 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).[104] After completion of induction therapy, patients who experienced a CR received intensification therapy with 3 cycles of high-dose methotrexate (with standard leucovorin rescue) and L-asparaginase. After intensification, those younger than 50 years who had an HLA-compatible sibling underwent allogeneic HCT; all others were randomized to receive autologous HCT or consolidation/maintenance treatment.[104] For Ph-negative disease, high risk was defined as having any of the following factors: age 35 years or older; time to CR greater than 4 weeks; or elevated WBC count (>30 × 10^9/L for B-cell lineage; >100 × 10^9/L for T-cell lineage). All other Ph-negative patients were considered to have standard-risk disease. The 5-year OS rate for all patients with Ph-negative ALL was 41%; the OS rates for the subgroups with standard risk (n = 533) and high risk (n = 590) were 54% and 29%, respectively.[104] In the subgroup of patients with T-cell ALL (n = 356), the 5-year OS rate was 48%; the OS rate was improved to 61% for those with a matched sibling donor, primarily because of a lower incidence of cumulative relapse.[279] Among the patients with T-cell 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.[21,154] For discussion of these studies, refer to the previous section (see *Initial Treatment of AYAs with Ph-Negative ALL*).

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.[280] In this moderate-intensity regimen containing vincristine, dexamethasone, and cyclophosphamide, patients were randomized to receive either CI-Dox (n = 31; 12 mg/m^2/day), or Peg-Dox (n = 29; 40 mg/m^2).[280] 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).[280] 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.[280]

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).[281] 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/m^2 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.[281] The 5-year OS rate was 23%, and the 2-year OS rates observed in groups 1 and 2 were 33% and 52%, respectively.[281] 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 ≥2 correlated with higher induction mortality rates compared to those with an ECOGb score of 0 to 1 (53% vs. 7%, respectively; $P < .0001$).[281] 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.[281]

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).[282,283] 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.[283]

Modified DFCI 91-01 Protocol

A retrospective analysis examined the efficacy of a modified version of a Dana Farber Cancer Institute (DFCI) pediatric protocol, DFCI 91-01,[251,284] in adult patients with newly diagnosed ALL (n = 51; age range, 60–79 years).[285] 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).[285] 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.[285] 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%).[285]

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.[286] Attempts to identify optimal therapy in this population have included adaptations of palliative regimens including vincristine and corticosteroids, and POMP (6-MP, vincristine, methotrexate, and prednisone).[287-290] 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.[271-273] 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.[291-293] Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.[155,294,295] 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%.[291] For cases of isolated bone marrow relapse, the 5-year survival estimates among early (n = 412), intermediate (n = 324), and late (n = 387) relapsing disease were 11.5%, 18.0%, and 43.5%, respectively (P < .0001). Intermediate relapse was defined as relapse occurring between 18 and 36 months from time of diagnosis; late cases were defined as relapse occurring 36 months or more from time of diagnosis. For cases of isolated CNS relapse, the 5-year survival estimates among early (n = 175), intermediate (n = 180), and late (n = 54) relapsing disease were 43.5%, 68.0%, and 78.0%, respectively (P < .0001).[291] 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.[291] In a separate analysis of data from one of the above COG studies (CCG-1952), the timing and site of first relapse were significantly predictive of EFS and OS outcomes, even among the patients with standard-risk ALL (n = 347; based on NCI criteria: age 1 to <10 years of age and WBC count <50 × 10^9/L).[296] 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.[296] 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.[296]

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%.[192,193] Approximately 20% to 30% of patients experience a second CR with second-line therapies.[193,195] Factors predictive of more favorable outcomes after subsequent therapies included younger age and a first CR duration of more than 2 years.[177,193] Among younger patients (age <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%.[193]

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.[297] 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.[294,295,298] 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 (age 1 to <10 years of age and WBC count <50 × 10^9/L) remained poor with no apparent advantage of HCT, regardless of timing (ie, early or late) of bone marrow relapse.[296] 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.[192] Patients treated with HCT demonstrated a superior OS at 5 years compared to those treated with chemotherapy alone.[192] 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.[299] At 3 years, OS rates were 16% (95% CI, 13%–20%).[299] 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.[179]

Blinatumomab

A component of the growing arsenal of immunotherapies for cancer treatment, blinatumomab is a bispecific anti-CD3/CD19 monoclonal antibody that showed high CR rates (69%; including rapid MRD-negative responses) in patients with R/R B-precursor ALL (n = 25).[276,300] 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-cell ALL that demonstrated a CR or CR without platelet recovery (CRp) in 43% of patients within the first 2 cycles of treatment.[275,301] 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).[274] 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).[274] 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).[274] Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.[274]

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.[302] CRS typically occurs within the first 2 days following initiation of blinatumomab infusion.[302] 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.[233,234] For discussion of these studies, see *Treatment of Relapsed Ph-Positive ALL*.

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.[235,303,304] The pre-treatment of patients with CAR T cells has served as a bridge for transplant, and patients who were formerly unable to receive a transplant due to poor remission status have a CR and ultimately transplantation. CAR T-cell therapy relies on the genetic manipulation of a patients' T-cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.[236] 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.[236] 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.[305] 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. The modified receptor, 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-cell ALL following infusion with CAR T cells.[306] 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%).[192,306-308] Furthermore, 7 out of 16 patients were able to receive an allogeneic HCT, suggesting that CAR T cells may provide a bridge to transplant.[306] 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 a 83% CR rate after the infusion and 32 patients achieved an MRD-negative CR.[309] 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.[309] KTE-C19 uses a similar anti-CD19 CAR construct, and demonstrated an MRD-negative CR in 6 of 8 efficacy-evaluable adult patients with R/R ALL.[310]

A second receptor construct defined by the attachment of an alternative costimulatory protein, 4-1BB, to the CD19 binding protein has shown similar results to the 19-28z CAR T cells in terms of overall CR.[311] These cells, more simply referred to as CTL019, were infused into 16 children and 4 adults with R/R ALL; a CR following therapy was achieved in 14 patients.[311] There was no response of the disease to treatment in 3 patients and disease response to therapy was still under evaluation for 3 patients.[311] A follow-up study of 25 children and 5 adults showed a morphologic CR of 90% (27 out of 30) patients within a month of treatment and an OS of 78% (95% CI, 65%–95%) and EFS of 78% (95% CI, 51%–88%) at 6 months.[312] There were 19 patients in sustained remission, of which 15 received no further therapy. Together these data inspired the development of larger multicenter trials of CAR T-cell therapy.[313] 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.[242] This high response rate was associated with OS rates of 90% and 76% at 6 and 12 months, respectively. As with blinatumomab, T-cell activation was accompanied by severe CRS and neurologic toxicity, as well as higher infectious risks—though treatment-related mortality remains low.[242] Given these data, CTL019/tisagenlecleucel was recommended for accelerated approval by the FDA oncologic drug advisory committee in July 2017 and fully approved by the FDA in August 2017 for the treatment of patients up to age 25 years (aged <26 years) with R/R precursor B-cell ALL.

There are fewer side effects to this treatment compared to the current standard-of-care regimens; while side effects from CAR T cells may be severe, they have been reversible. Adverse events are attributed to CRS and macrophage activation that occur in direct response to adoptive cell transplant resulting in high fever, hypotension, breathing difficulties, delirium, aphasia, and neurologic complications. Improvement in patient monitoring has shown successful treatment of these symptoms with the monoclonal antibody tocilizumab, an antagonist of interleukin-6.[306]

Nelarabine

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-cell ALL who have unresponsive or relapsed disease after at least 2 chemotherapy regimens. A phase II study of nelarabine monotherapy in children and adolescents with R/R T-cell ALL or T-cell non-Hodgkin's lymphoma (n = 121) showed a 55% response rate among the subgroup with T-cell ALL with first bone marrow relapse (n = 34) and a 27% response rate in the subgroup with a second or greater bone marrow relapse (n = 36).[155] 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-cell ALL or T-cell lymphoblastic leukemia in a phase II study (n = 39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-cell ALL, n = 26).[157] 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.[157]

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).[314] 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.[314]

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.[315,316] 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).[308] 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.[308] The incidence of early induction death (30-day mortality rate) was 12%.[308]

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%).[308,317] The most common grade 3 or greater treatment-related toxicities with VSLI included neuropathy (23%), neutropenia (15%), and thrombocytopenia (6%).[308] 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-cell ALL in second or greater relapse. Confirmation of benefit from phase III studies is pending.

Clofarabine

Clofarabine is a nucleoside analog approved for the treatment of pediatric patients (aged 1–21 years) with ALL that is relapsed or refractory after at least 2 prior regimens. In a phase II study of single-agent clofarabine in heavily pretreated pediatric patients with R/R ALL (n = 61; median age, 12 years; range, 1–20 years), the response rate (CR + CRp) was 20%.[318] 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.[318] 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%.[319,320] 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).[319]

There are limited studies of clofarabine combination regimens in adults with R/R disease. In a study by Miano et al,[321] 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%.[321] In a study from GRAALL, adult patients with R/R ALL (n = 55) were treated with clofarabine in combination with conventional chemotherapy (cyclophosphamide [ENDEVOL cohort; median age, 53 years; range, 18–78 years], or a more intensive regimen with dexamethasone, mitoxantrone, etoposide, and PEG-asparaginase [VANDEVOL cohort; median age, 34 years; range, 19–67 years]). Patients in the ENDEVOL cohort achieved a CR of 50% (9 of 18) and patients in the VANDEVOL cohort yielded a CR rate of 41% (15 of 37); the median OS was 6.5 months after a median follow-up of 6 months.[322] The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%), with an early death rate of 11%.[322] 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

Clinical studies described earlier include patients with relapsed or refractory Ph-positive and Ph-negative ALL.[237-239] For discussion of these studies, see *Treatment of Relapsed Ph-Positive ALL*.

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-cell 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.[154] 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.

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. 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 may be considered 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 relapsed/refractory ALL (see *Patients with R/R Ph-Negative 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), 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.

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

For recommendations on the treatment of adult patients with mature B-cell ALL, refer to the NCCN Guidelines for B-Cell Lymphomas.

Patients with Relapsed/Refractory Ph-Negative ALL

For patients with R/R Ph-negative 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-cell 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.[241]

Tisagenlecleucel is also an option for patients up to age 25 years/age <26 years and with refractory disease or ≥2 relapses. Other options that may be considered include subsequent chemotherapy, with regimens containing clofarabine, nelarabine [for T-cell ALL], VSLI, augmented hyper-CVAD, MOpAD regimen, or other cytarabine- or alkylator-containing regimens. 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.[242]

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.[323] 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 regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other CHOP-like regimens.[324,325] 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%.[149] 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.[110,326,327] 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.[116] 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.[328,329] CNS leukemia at diagnosis was associated with a significantly decreased 5-year OS rate in one trial (29% vs. 38%; *P* = .03)[328] but not in another trial (35% vs. 31%).[329] 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.[44,328] 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).[1,50,116]

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.[1,116] 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.[108,327]

Data from the most recent 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.[327,330] The 5-year EFS rate for the AYA population (age 15–18 years; n = 45) was 86% (95% CI, 72%–94%), which was not significantly different from the 87% EFS rate (95% CI, 84%–90%; *P* = .61) observed for the younger patients (n = 448). The 5-year OS rates for the AYA patients and younger patients were 88% and 94%, respectively (*P* = not significant).[327,330] The favorable EFS and OS outcomes in AYA patients in this study were attributed partly to the use of intensive dexamethasone, vincristine, and asparaginase, in addition to early intrathecal therapy (ie, triple intrathecal chemotherapy with cytarabine, hydrocortisone, and methotrexate) for CNS-directed therapy. In addition, the use of prophylactic cranial irradiation was safely omitted in this study; the 5-year cumulative incidence of isolated CNS relapse and any CNS relapse was 3% and 4%, respectively, for the entire study population (n = 498).[327] 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.[327,330]

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%.[21,118,331,332] 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 to the specific treatment protocol used for each patient. Pediatric-inspired treatment regimens typically include lumbar puncture at diagnostic workup. The panel recommends that lumbar puncture, if performed, be conducted concomitantly with initial intrathecal therapy. All patients being treated for ALL should receive adequate CNS prophylaxis with intrathecal therapy and/or systemic therapy that incorporates methotrexate.

The classification of CNS status includes the following: CNS-1 refers to no lymphoblasts in the CSF regardless of WBC count; CNS-2 is defined as a WBC count less than 5 leukocytes/mcL in the CSF with the presence of blasts; and CNS-3 is defined as a WBC count of 5 leukocytes/mcL or greater with the presence of blasts. If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic (containing ≥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-cell ALL. Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of induction therapy should be considered for radiation to 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).

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, or 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 1.0×10^9/L and platelet counts should be greater than 100×10^9/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 1.0×10^9/L or the platelet count remains less than 100×10^9/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 should be performed as clinically indicated; if a bone marrow aspirate is performed, flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests, and MRD assessments should be 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 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.[333] 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.[38,334]

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 next-generation sequencing (NGS)-based assays to detect clonal rearrangements in immunoglobulin and/or T-cell receptor genes.[335-342] 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 recent 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.[336,338,341,342] 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.[337,339,342-346] 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%.[344] 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.[342] At the 0.01% threshold, the concordance between both methods was high, but high-throughput sequencing was able to detect MRD at lower thresholds.[342] The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.[338,344,347] 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).[348,349] An early study in children with ALL (n = 178) showed that patients with detectable MRD after initial induction therapy (42% of patients) had significantly shorter time to relapse than patients with MRD-negative status ($P < .001$), defined by a PCR sensitivity level of less than 1.5×10^{-4}.[350] 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}.[350] In another study in children with ALL (n = 158),

patients with detectable MRD (flow cytometry sensitivity level <1 × 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).[351] 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 x 10^{-4}) versus those without detectable disease (43% vs. 10%; *P* < .001).[349] 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).[349] 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 × 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).[348] The prognostic significance of MRD detection at lower levels (sensitivity threshold, ≤1 × 10^{-5}, or ≤0.001%, according to PCR measurements) was evaluated in children with B-cell lineage ALL treated with contemporary regimens.[341] 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 ≥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).[341] Furthermore, the 5-year cumulative incidence of relapse was higher among the subgroup of patients with MRD less than 0.01% (but ≥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 ≥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.[341]

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 ≤0.01%) at 2 time points (days 33 and 78), which were used to guide postinduction treatment.[352] Patients were considered standard risk if MRD negativity (≤0.01%) was achieved at both days 33 and 78, intermediate risk if MRD was greater than 0.01% (but <0.1%) on either day 33 or 78 (the other time point being MRD-negative) or on both days 33 and 78, and high risk if MRD was 0.1% or greater on day 78. Nearly all patients with favorable cytogenetic/molecular markers such as the *ETV6-RUNX1* subtype or hyperdiploidy were either standard risk or intermediate risk based on MRD evaluation.[352] 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.[352]

A randomized controlled trial in children and young adults with low-risk ALL according to MRD compared treatment reduction to standard induction (n = 521).[353] 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.[354] 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}.[355] 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% ± 5%) versus patients remaining on chemotherapy (24% ± 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 allogenic HCT. There was no significant difference in EFS between these two groups (66% ± 6% vs. 80% ± 9%; *P* = .45). Results indicate that MRD can be useful to further risk stratify patients with intermediate risk of relapse to the appropriate treatment regimen. However, the study acknowledges that 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.[356] Therefore, MRD levels may influence treatment decisions, but the application of this prognostic factor must be carefully evaluated on a regimen-by-regimen basis.

Approximately 20% of children treated with intensive therapies for ALL will ultimately experience disease relapse.[357] MRD assessment may play a prognostic role in the management of patients in the relapsed setting.[358,359] 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).[358] 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.[358] 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.[359] 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).[359] 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.[360,361] 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.[334,362-365] 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).[365] 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.[365] 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).[364] 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).[364]

Postinduction MRD can serve as an independent predictor of relapse even among adult patients considered to be standard risk based on traditional prognostic factors. In a study of adult patients with Ph-negative ALL (n = 116), MRD status after induction therapy (flow cytometry sensitivity level <0.1%) was significantly predictive of relapse regardless of whether the patient was standard risk or high risk at initial evaluation.[363] 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.[363] 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.[362] Only patients with ALL who met all of

the following criteria for standard risk were enrolled in this study: absence of t(4;11) *MLL* translocation or t(9;22) *BCR-ABL* translocation; WBC count less than 30 × 10^9/L for B-cell lineage ALL or less than 100 × 10^9/L for T-cell lineage ALL; age 15 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%.[362] 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.[362] 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 recent prospective study from the MDACC, adult patients with B-cell 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.[366] MRD negative status at CR significantly correlated with improved DFS and OS, and was an independent predictor of DFS (P < .05).[366]

A recent prospective study (Japan ALL MRD2002) evaluated outcomes by MRD status in adult patients with Ph-negative ALL.[367] 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.[367]

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.[368] 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).[368] In a follow-up to the GMALL 06/99 study mentioned earlier, patients with standard-risk ALL (as defined by Bruggemann et al[362]) who experienced MRD negativity (PCR sensitivity <0.01% leukemic cells) during the first year of treatment underwent sequential MRD monitoring during maintenance therapy and follow-up.[369] 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.[369] 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.[369] 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 ≥0.01%).[370] 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).[370] 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.[370] 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).[341,348-351,371] In one study, nearly 50% of children had MRD clearance (<0.01% by flow cytometry) at day 19 of induction therapy.[348] 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.[362,365] 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.[334,362] 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 optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate. 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 at a sensitivity threshold of fewer than 1×10^{-6} (<0.0001%) bone marrow MNCs.[336,338,372,373] The concordance rate for detecting MRD between these methods is generally high.

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.[372,373] 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.[370,374-376] 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.[377] 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 (eg, risks for hypersensitivity reactions, hyperglycemia, coagulopathy, hepatotoxicity, and/or pancreatitis). Supportive care measures should be tailored to meet the individual needs of each patient based on factors such as age, performance status, extent of cytopenias before and during therapy, risks for infectious complications, disease status, and the specific agents used in the ALL treatment regimen.

NCCN Recommendations for Supportive Care

Most chemotherapy regimens used in ALL contain agents that are at least moderately emetogenic, which may necessitate antiemetic support before initiating emetogenic chemotherapy. Antiemesis prophylaxis may include the use of agents such as serotonin receptor antagonists, corticosteroids, and/or neurokinin-1–receptor antagonists. Recommendations for antiemetic support for patients receiving chemotherapy are available in the NCCN Guidelines for Antiemesis. 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 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 standard deviations 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).

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 × 10^9/L) and symptoms of decreased tissue perfusion that often affect respiratory and CNS function. Although leukapheresis is not typically recommended in the routine management of patients with high WBC counts, it can be considered with caution in cases of leukostasis that is unresponsive to other interventions.

Key components of the ALL treatment regimen, such as corticosteroids and asparaginase, are associated with unique toxicities that require close monitoring and management. Corticosteroids, such as prednisone and dexamethasone, constitute a core component of nearly 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 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;[378-381] 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.[382,383] 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.[382,384-388] 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.[384,385] 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.[382] 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.[382]

In a recent DFCI ALL Consortium study in children and adolescents that included randomization to postinduction therapy with dexamethasone versus prednisone, dexamethasone was associated with a significantly increased 5-year EFS but, in older children, the increased cumulative incidence of osteonecrosis was comparable with prednisone.[388] 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).[385] 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; age 1–21 years) to postinduction intensification treatment with intermittent dose scheduling of dexamethasone (10 mg/m^2 daily on days 0–6 and days 14–20) versus continuous doses of dexamethasone (10 mg/m^2 daily on days 0–20).[384] Among older children and adolescents (age ≥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.[384] 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.

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) native *E. coli*-derived asparaginase (*E coli* asparaginase); 2) asparaginase derived from *E. coli* that has been modified with a covalent linkage to PEG; 3) asparaginase derived from a different Gram-negative bacteria *Erwinia chrysanthemi* (*Erwinia* asparaginase); and 4) calaspargase pegol. These formulations differ in their pharmacologic properties, and may also differ in terms of immunogenicity.[389-392] 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.[393] However, cross-reactivity between neutralizing antibodies against native *E. coli* asparaginase and pegaspargase has been reported.[394,395] 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.[396] In contrast, no cross-reactivity between antibodies

against native *E. coli* asparaginase and *Erwinia* asparaginase was reported,[394,395] and enzyme activity of *Erwinia* asparaginase was not affected by the presence of anti–*E coli* asparaginase antibodies.[396] 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.[397]

Similar to PEG, calaspargase pegol is a newer asparaginase enzyme formulation with a different linker molecule that enhances its hydrolytic stability.[389] 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.[389] 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).[398] In this study, patients with newly diagnosed ALL (n = 230; age range, 1–21 years) were randomized to receive an intravenous dose (2500 IU/m^2) 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.[398] However, longer follow-up is needed to 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 should be substituted (see *Supportive Care: Asparaginase Toxicity Management* in the algorithm). *Erwinia* asparaginase is 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 ≥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, diphenhydramine, and acetaminophen). 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.[399] 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,[392] 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.

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. National Cancer Institute. SEER cancer statistics review, 1975-2015: Leukemia, annual incidence rates (acute lymphocytic leukemia). 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed January 31, 2019.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30620402.

4. National Cancer Institute. SEER cancer statistics review, 1975-2015: Overview, median age at diagnosis. 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed January 31, 2019.

5. National Cancer Institute. SEER cancer statistics review, 1975-2015: Overview, age distribution of incidence cases by site. 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed January 31, 2019.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. Passarge E. Bloom's syndrome: the German experience. Ann Genet 1991;34:179-197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1809225.

18. 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.

19. Ma H, Sun H, Sun X. Survival improvement by decade of patients aged 0-14 years with acute lymphoblastic leukemia: a SEER analysis. Sci Rep 2014;4:4227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24572378.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

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

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

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. 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.

59. 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.

60. 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.

61. 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.

62. 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.

63. 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.

64. 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.

65. 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.

66. 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.

67. 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.

68. 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.

69. Dupuis A, Gaub MP, Legrain M, et al. Biclonal 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.

70. 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.

71. 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.

72. 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.

73. 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.

74. 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 2013;122:2622-2629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23974192.

75. 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.

76. 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.

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

83. 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.

84. 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.

85. 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.

86. 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.

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

88. 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.

89. 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.

90. 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.

91. 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.

92. 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.

93. 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.

94. 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.

95. 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.

96. 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.

97. 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.

98. 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.

99. 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.

100. 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.

101. Martin S, Ulrich C, Munsell M, et al. Delays in cancer diagnosis in underinsured young adults and older adolescents. Oncologist 2007;12:816-824. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17673613.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

107. 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.

108. 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.

109. 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.

110. 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.

111. 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.

112. 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.

113. 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.

114. 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.

115. 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.

116. 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.

117. 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.

118. 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.

119. 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.

120. 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.

121. 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.

122. 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.

123. 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.

124. 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.

125. 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.

126. 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.

127. 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.

128. 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.

129. 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.

130. 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.

131. 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.

132. 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.

133. 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.

134. 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.

135. 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.

136. 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.

137. 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.

138. 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.

139. 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.

140. 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.

141. 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.

142. 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.

143. 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.

144. 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.

145. 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.

146. 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.

147. 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.

148. 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.

149. 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.

150. 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.

151. 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.

152. 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.

153. 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.

154. 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.

155. 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.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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.

161. 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.

162. 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.

163. 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.

164. 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.

165. 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.

166. 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://www.ncbi.nlm.nih.gov/pubmed/30501869.

167. 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.

168. 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.

169. 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.

170. 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.

171. 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.

172. 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.

173. 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.

174. 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.

175. 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 outcome. Blood 2001;97:1572-1577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11238093.

176. 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.

177. 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.

178. 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.

179. 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.

180. 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.

181. 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.

182. 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.

183. 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.

184. 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.

185. Chalandon Y, Thomas X, Hayette S, et al. First results of the GRAAPH-2005 study in younger adult patients with de novo Philadelphia positive acute lymphoblastic leukemia [abstract]. Blood 2008;112:Abstract 12. Available at: http://www.bloodjournal.org/content/112/11/12.

186. 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.

187. 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.

188. 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.

189. 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.

190. 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 lymphobla stic leukemia. J Hematol Oncol 2012;5:29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22682059.

191. 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.

192. 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.

193. 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.

194. 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.

195. 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.

196. 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.

197. 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.

198. Collins RH, Jr., Goldstein S, Giralt 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.

199. Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood 1995;86:2041-2050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7655033.

200. 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.

201. 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.

202. 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.

203. 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.

204. 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.

205. 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 2004;45:401-403. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15101732.

206. 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.

207. 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.

208. 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.

209. 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.

210. 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.

211. 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.

212. 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.

213. 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.

214. 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.

215. 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.

216. 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.

217. 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.

218. Verstovsek S, Golemovic 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.

219. 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.

220. 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.

221. 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.

222. 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.

223. 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.

224. 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.

225. 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.

226. 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.

227. 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.

228. 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.

229. 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.

230. 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.

231. 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.

232. 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.

233. 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.

234. 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.

235. 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.

236. 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.

237. 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.

238. 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.

239. 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.

240. 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.

241. 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.

242. 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.

243. 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.

244. 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.

245. 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.

246. 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.

247. 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.

248. 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.

249. 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.

250. 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.

251. 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.

252. 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.

253. 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.

254. 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.

255. 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.

256. 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.

257. 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.

258. 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.

259. 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.

260. 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.

261. 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.

262. 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.

263. Dunsmore KP, Winter S, Devidas M, et al. COG AALL0434: A randomized trial testing nelarabine in newly diagnosed t-cell malignancy. Journal of Clinical Oncology 2018;36:10500-10500. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.10500.

264. 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.

265. 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.

266. 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.

267. 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.

268. 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.

269. 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.

270. 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.

271. 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.

272. 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.

273. 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.

274. 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.

275. 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.

276. 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.

277. 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.

278. 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.

279. 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.

280. 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.

281. 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.

282. 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 thyrosine 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.

283. 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.

284. Storring 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.

285. 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.

286. 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.

287. 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.

288. 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.

289. 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.

290. 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.

291. 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.

292. 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.

293. 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.

294. Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: 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.

295. 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.

296. 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.

297. 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.

298. 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.

299. 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.

300. 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.

301. 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.

302. 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.

303. 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.

304. 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.

305. 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.

306. 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.

307. 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.

308. 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.

309. 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.

310. Shah BD, Wierda WG, Schiller GJ, et al. Updated results from ZUMA-3, a phase 1/2 study of KTE-C19 chimeric antigen receptor (CAR) T cell therapy, in adults with high-burden relapsed/refractory acute lymphoblastic leukemia (R/R ALL). Journal of Clinical Oncology 2017;35:3024-3024. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.3024.

311. 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.

312. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-1517. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25317870.

313. Shah B, Huynh V, Sender LS, et al. High Rates of Minimal Residual Disease-Negative (MRD−) Complete Responses (CR) in Adult and Pediatric and Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) Treated With KTE-C19 (Anti-CD19 Chimeric Antigen

Receptor [CAR] T Cells): Preliminary Results of the ZUMA-3 and ZUMA-4 Trials. Blood 2016;128:2803. Available at: http://www.bloodjournal.org/content/128/22/2803.

314. 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.

315. 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.

316. 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.

317. 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.

318. 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.

319. 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.

320. 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.

321. 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.

322. 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.

323. 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.

324. 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.

325. 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.

326. 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.

327. 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.

328. 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.

329. 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.

330. 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.

331. 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.

332. 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.

333. 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.

334. 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.

335. 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.

336. 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.

337. Faham M, Zheng J, Moorhead M, et al. Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia. Blood 2012;120:5173-5180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23074282.

338. 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.

339. 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.

340. 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.

341. 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.

342. 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.

343. 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.

344. 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.

345. 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.

346. 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.

347. 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.

348. 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.

349. 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.

350. 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.

351. Coustan-Smith E, Behm FG, Sanchez J, et al. Immunological detection of minimal residual disease in children with acute lymphoblastic leukaemia. Lancet 1998;351:550-554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9492773.

352. 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.

353. 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.

354. 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.

355. 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.

356. 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.

357. 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.

358. 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.

359. 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.

360. 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.

361. 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.

362. 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.

363. 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.

364. 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.

365. 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.

366. 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.

367. 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.

368. 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.

369. 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.

370. 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.

371. 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.

372. 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.

373. 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.

374. 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.

375. 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.

376. 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.

377. 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.

378. 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.

379. Friedenberg 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.

380. 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.

381. 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.

382. 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.

383. 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.

384. 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.

385. 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.

386. 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.

387. 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.

388. 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.

389. 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.

390. 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.

391. 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.

392. 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.

393. 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.

394. Wang B, Relling MV, Storm MC, et al. Evaluation of immunologic crossreaction of antiasparaginase antibodies in acute lymphoblastic leukemia (ALL) and lymphoma patients. Leukemia 2003;17:1583-1588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12886246.

395. 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.

396. 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.

397. 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.

398. 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 DFCI ALL Consortium Protocol 11-001. Blood 2016;128:175-175. Available at: http://www.bloodjournal.org/content/128/22/175?sso-checked=true.

399. 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.