National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Lymphoblastic Leukemia

NCCN Evidence Blocks™

Version 2.2025 — June 27, 2025

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Evidence Blocks™

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Acute Lymphoblastic Leukemia
NCCN Evidence Blocks™

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

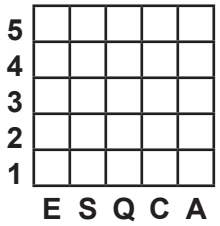
See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

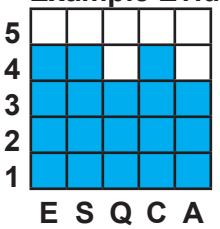
NCCN Guidelines for Patients® available at www.nccn.org/patients

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**

DIAGNOSIS

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

Patients should be referred to specialized centers for evaluation, diagnosis, and treatment of ALL throughout the continuum of care.

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts[d,e,f] on hematopathology review of bone marrow aspirate and biopsy materials, which includes:

- **Morphologic assessment of Wright-Giemsa–stained bone marrow aspirate smears, and hematoxylin and eosin (H&E)–stained core biopsy and clot sections**
- **Comprehensive flow cytometric immunophenotyping[c,g]**
- **Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal/measurable residual disease (MRD) analysis (ALL-F)**
- **Karyotyping of G-banded metaphase chromosomes**

MOLECULAR CHARACTERIZATION

- **Cytogenetic and molecular prognostic risk stratification for B-cell ALL (B-ALL) (ALL-2)**
- **Optimal risk stratification and treatment planning require testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:**
  - **Interphase fluorescence in situ hybridization (FISH) testing, including probes capable of detecting the major recurrent genetic abnormalities**
  - **Reverse transcriptase polymerase chain reaction (RT-PCR) testing for *BCR::ABL1* in B-ALL, including determination of transcript size (ie, p190 vs. p210)**
  - **Comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended.**
- **Additional optional tests include:**
  - **Assessment with chromosomal microarray (CMA)/array comparative genomic hybridization (cGH) in cases of aneuploidy or inadequate karyotype.**

CLASSIFICATION

Together, these studies allow determination of the World Health Organization (WHO) and International Consensus Classification (ICC) ALL subtypes and cytogenetic and clinical risk groups.

Workup ALL-3

Footnotes on ALL-1A

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.

FOOTNOTES FOR DIAGNOSIS

[a] Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2022 and ICC 2022 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.

[b] Burkitt leukemia/lymphoma, see the NCCN Guidelines for B-Cell Lymphomas.

[c] T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) subtypes include T-ALL/T-LBL, not otherwise specified (NOS), cortical type, mature type, and early T-cell precursor (ETP) lymphoblastic leukemia/lymphoma; ETP-ALL typically lacks expression of CD5, CD8, and CD1a and expresses one or more myeloid/stem cell markers. The mature subtype often also lacks expression of CD1a and frequently is accompanied by T-ALL11 or T-ALL12 rearrangement.

[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 1000 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 presence of an immunophenotypically clonal lymphoblast population <20% can be considered ALL in appropriate circumstances.

[g] The following immunophenotypic findings are particularly notable: CD10 negativity correlates with *KMT2A* rearrangement; CD20 positivity: definition not clear, most studies have used >20% of blasts expressing CD20. See Discussion.

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CYTOGENETIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL[h]

RISK GROUPS	CYTOGENETIC AND MOLECULAR ALTERATIONS
Standard 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*[i] • t(1;19)(q23;p13.3): *TCF3::PBX1* • *DUX4* rearranged • *PAX5* P80R • t(9;22)(q34;q11.2): *BCR::ABL1*[j] without *IKZF1* plus[k] and without antecedent chronic myeloid leukemia (CML)
Poor risk	• Hypodiploidy[l,m] (<44 chromosomes) • Low hypodiploidy (30–39 chromosomes) • Near triploidy (60–78 chromosomes) • *TP53* mutation[n] • *KMT2A* rearranged (t[4;11] or others) • *IgH* rearranged[o] • *HLF* rearranged • *ZNF384* rearranged • *MEF2D* rearranged • *MYC* rearranged • *BCR::ABL1*-like (Philadelphia chromosome [Ph]-like) ALL ▸ JAK-STAT (*CRLF2r*,[p] *EPORr*, *JAK1/2/3r*, *TYK2r*, mutations of *SH2B3*, *IL7R*, *JAK1/2/3*) ▸ ABL class (rearrangements of *ABL1*, *ABL2*, *PDGFRA*, *PDGFRB*, *FGFR*) ▸ Other (*NTRKr*, *FLT3r*, *LYNr*, *PTK2Br*) • *PAX5alt* • t(9;22)(q34;q11.2): *BCR::ABL1*[j] with *IKZF1* plus[k] and/or antecedent CML • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of *IKZF1*[k,q,r] • Complex karyotype (5 or more chromosomal abnormalities)

Workup ALL-3
Footnotes ALL-2A

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All recommendations are category 2A unless otherwise indicated.

FOOTNOTES FOR CYTOGENIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL

[h] FISH probes that may be useful include: centromeric probes for chromosomes 4, 10, and 17 to detect hyperdiploidy; dual-color probe set to detect cryptic t(12;21), which will also allow detection of iAMP21 (when ≥5 copies of the *RUNX1* gene are detected); probes to detect *BCR::ABL1* and *KMT2A* rearrangements; probes to detect *ABL1, ABL2*, and *PDGFRB* rearrangements; probes for *CDKN2A* at 9p21.3 to detect deletions; probes to detect cryptic t(X;14)(p22;q32)/t(Y;14)(p11;q32) *IGH*::*CRLF2* rearrangements; and probes to detect *JAK2* rearrangements. Multiplex gene panels may be considered in the absence of targeted probes.

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

[j] Interphase FISH for the detection of *BCR::ABL1* transcript on blood granulocytes is recommended to differentiate between de novo blast phase CML (BP-CML) and de novo Ph-positive ALL. See NCCN Guidelines for Chronic Myeloid Leukemia for the management of BP-CML.

[k] *IKZF1* deletions with co-occurring deletions in *CDKN2A, CDKN2B, PAX5*, or *PAR1* in the absence of *ERG* deletion, which are called *IKZF1* plus, as well as those with concomitant 22q11.22 deletions, are especially associated with worse outcomes in pediatric patients with B-ALL.

[l] There are other results that are not < 44 chromosomes that may be equivalent to hypodiploidy and have the same implications. It is important to distinguish true hypodiploidy from masked hypodiploidy, which results from the doubling of hypodiploid clones. Carroll AJ, et al. Cancer Genet 2019;238:62-68.

[m] Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone. Patients with hypodiploid ALL should be considered for germline testing, as hypodiploid ALL may be associated with Li-Fraumeni syndrome.

[n] Saygin C, et al. Blood Cancer Discov 2024;5:164-179.

[o] Includes *IGH::IL3* rearrangement.

[p] Jain N, et al. Blood 2017;129:572-581; Roberts KG, et al. N Engl J Med 2014;371:1005-1015.

[q] Mullighan CG, et al. N Engl J Med 2009;360:470-480; Stanulla M, et al. J Clin Oncol 2018;36:1240-1249.

[r] Emerging evidence suggests *DUX4*r ALL is favorable. Additionally in cases of *DUX4*r, *IKZF1* alterations do not confer poor prognosis.

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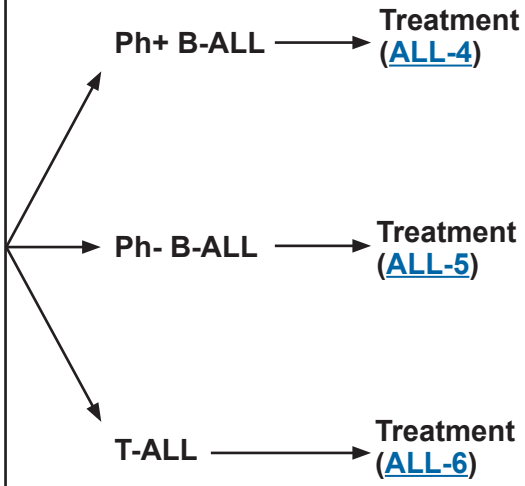
WORKUP[s]

- History and physical examination (H&P)
- Complete blood count (CBC), differential, chemistry profile, liver function tests (LFTs)
- Disseminated intravascular coagulation (DIC) panel: d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Tumor lysis syndrome (TLS) panel: lactate dehydrogenase (LDH), uric acid, potassium, calcium, phosphorus (See Tumor Lysis Syndrome in the NCCN Guidelines for B-Cell Lymphomas)
- Hepatitis B/C, human immunodeficiency virus (HIV) testing
- Pregnancy testing, fertility counseling, and preservation
- CT/MRI of head with contrast, if neurologic symptoms[t]
- Lumbar puncture (LP)[t,u] with intrathecal (IT) therapy
  - Evaluation and Treatment of Extramedullary Involvement (ALL-B)
- CT of neck/chest/abdomen/pelvis with IV contrast, as indicated for symptoms
  - Recommend PET/CT if lymphomatous involvement is suspected and/or confirmed by CT imaging
- Testicular examination, including scrotal ultrasound as indicated
- Infection evaluation:
  - Screen for opportunistic infections, as appropriate (NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)
- Echocardiogram or cardiac nuclear medicine scan should be considered in all patients, since anthracyclines are important components of ALL therapy, but especially in patients with prior cardiac history and prior anthracycline exposure or clinical symptoms suggestive of cardiac dysfunction.
- Central venous access device of choice
- Strongly consider early transplant evaluation and donor search.
- For patients with possible cancer predisposition syndromes, principles of cancer risk assessment and counseling should be taken into consideration (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and ALL-A)

ALL SUBTYPE



[s] The following list represents minimal recommendations; other testing may be warranted according to clinical symptoms and discretion of the clinician.
[t] 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).
[u] The Panel recommends first LP be performed at time of initial scheduled IT therapy unless directed by symptoms to perform earlier.

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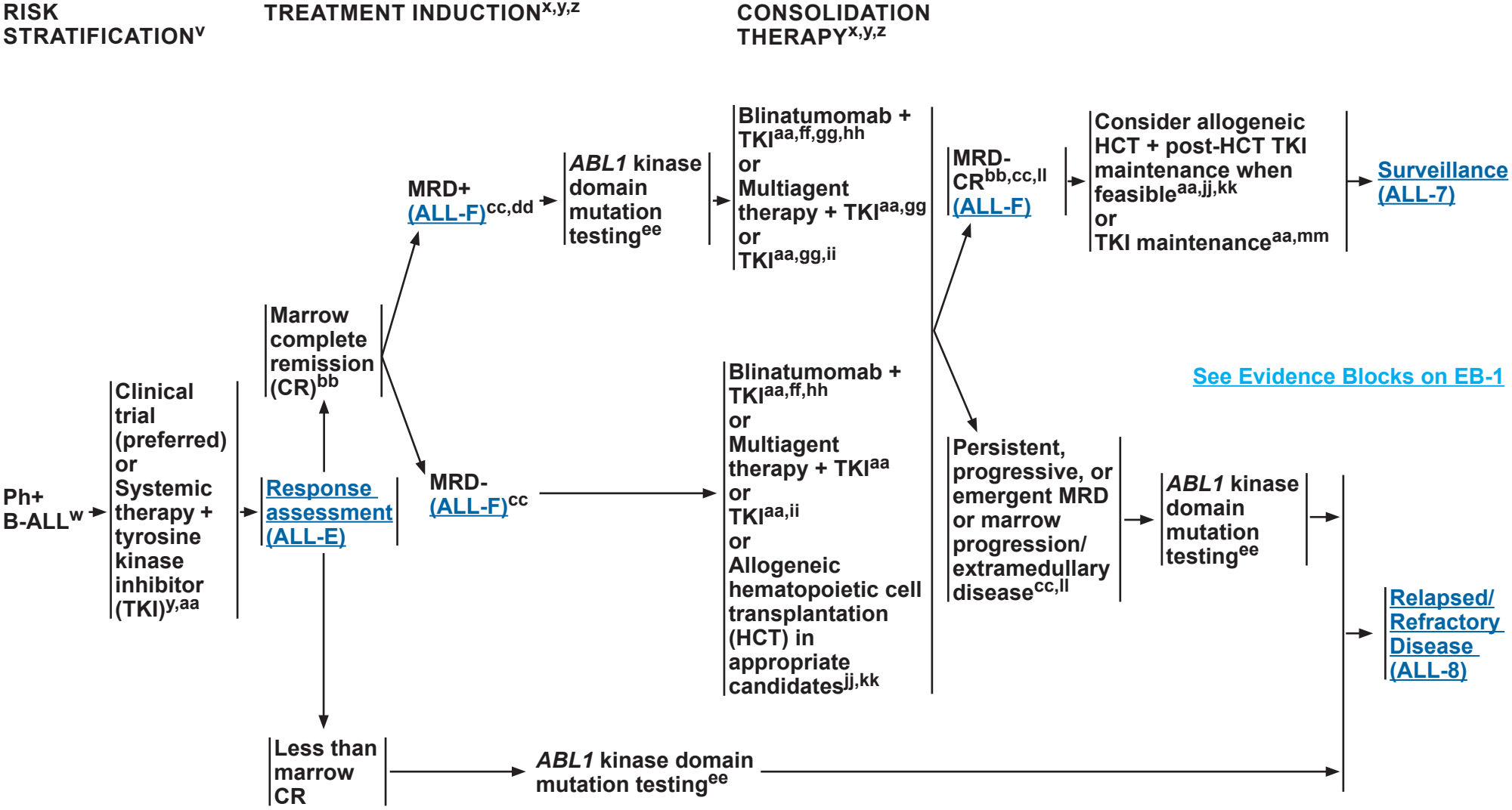

See Evidence Blocks on EB-1

Footnotes on ALL-4A

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FOOTNOTES FOR Ph+ B-ALL TREATMENT INDUCTION AND CONSOLIDATION THERAPY

[v] Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (ALL-2).
[w] It is reasonable to approach the initial treatment of BP-CML with similar strategies to Ph+ ALL, with a goal of proceeding to HCT.
[x] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.
[y] ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B).
[z] Principles of Supportive Care (ALL-C).
[aa] Principles of Systemic Therapy (ALL-D).
[bb] Adequate count recovery per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted. Assess for myelosuppression secondary to TKI and consider dose reduction.
[cc] The preferred method of MRD quantification is an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in immunoglobulin (Ig) and T-cell receptor (TCR) loci (does not require patient-specific primers), if available. Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for any patient with ALL with MRD positivity.
[dd] *BCR::ABL1* quantitative RT-PCR (qPCR) positivity may reflect persistence in the myeloid compartment. Where feasible, flow sorting to isolate myeloid versus lymphoid cells for FISH/qPCR studies and/or NGS MRD may help to resolve. Of note, the presence of the Philadelphia chromosome in the myeloid compartment does not necessarily imply a diagnosis of CML with lymphoid blast transformation.
[ee] See ALL-D 1 of 27 for treatment options based on *BCR::ABL1* mutation profile.
[ff] Principles of Supportive Care: Toxicity Management (ALL-C 2 of 6).
[gg] Consider using an alternative and more broadly acting TKI. See Treatment options based on *BCR::ABL1* mutation profile (ALL-D 1 of 27).
[hh] Blinatumomab + TKI is preferred in consolidation regardless of MRD status for those who have not previously received blinatumomab.
[ii] TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies.
[jj] Data suggest that for patients aged ≤21 years, particularly for those who achieve MRD negativity, allogeneic HCT may not offer an advantage over chemotherapy + TKI. Schultz KR, et al. J Clin Oncol 2009;27:5175-5181; Schultz KR, et al. Leukemia 2014;28:1467-1471.
[kk] Favored for poor risk B-ALL (ALL-2) and/or slow/incomplete MRD clearance.
[ll] Consider sequential MRD monitoring for patients with complete molecular remission (undetectable levels). Increased frequency may be indicated for detectable levels or for those discontinuing TKI.
[mm] May include other elements of maintenance therapy, such as vincristine, corticosteroids, and IT therapy.

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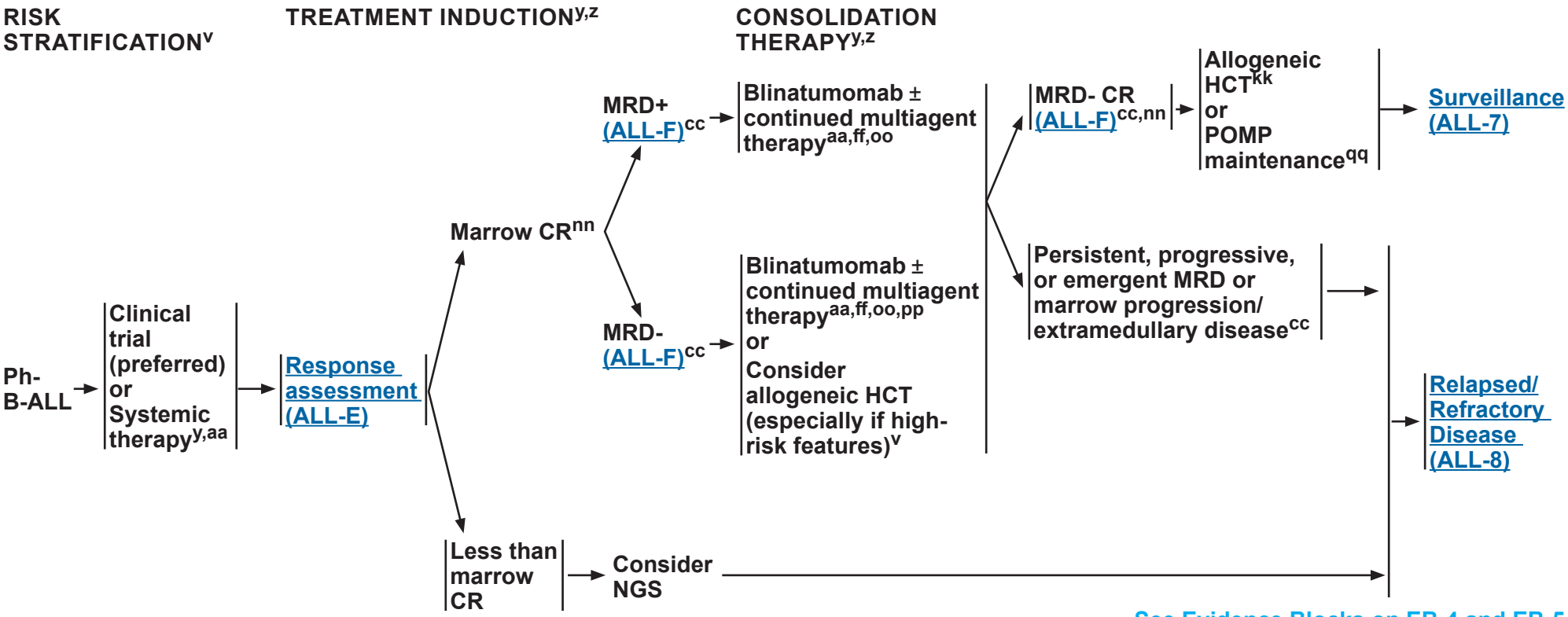

See Evidence Blocks on EB-4 and EB-5

[v] Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (ALL-2).
[y] ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B).
[z] Principles of Supportive Care (ALL-C).
[aa] Principles of Systemic Therapy (ALL-D).
[cc] The preferred method of MRD quantification is an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and TCR loci (does not require patient-specific primers), if available. Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for patients with ALL with MRD positivity.
[ff] Principles of Supportive Care: Toxicity Management (ALL-C 2 of 6).
[kk] Favored for poor risk B-ALL (ALL-2) and/or slow/incomplete MRD clearance.
[nn] Adequate count recovery per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted.
[oo] Blinatumomab can be considered for consolidation in patients for whom multiagent therapy is contraindicated.
[pp] Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910.
[qq] May include other elements of maintenance therapy, such as blinatumomab and IT therapy.

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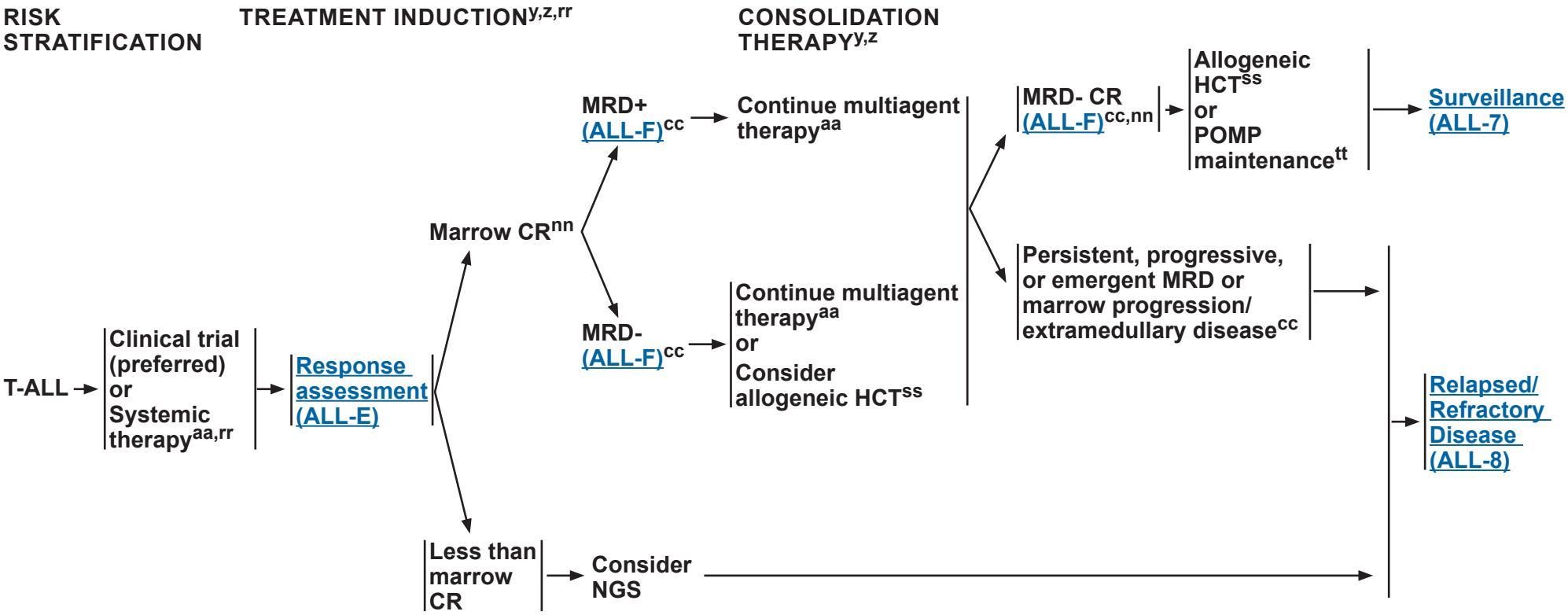

See Evidence Blocks on EB-8 and EB-9

[y] ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B).
[z] Principles of Supportive Care (ALL-C).
[aa] Principles of Systemic Therapy (ALL-D).
[cc] The preferred method of MRD quantification is an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and TCR loci (does not require patient-specific primers), if available. Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for patients with ALL with MRD positivity.
[nn] Adequate count recovery per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted.
[rr] The addition of nelarabine to selected induction regimens may be beneficial (ALL-D 19 of 27).
[ss] Favored for high-risk T-ALL (Simonin M, et al. Blood 2024;144:1570-1580) and/or slow/incomplete MRD clearance. High-risk features include ETP-phenotype or *RAS*/*PTEN* and/or *NOTCH1/FBXW7* wild-type classifier.
[tt] May include other elements of maintenance therapy, such as IT therapy.

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SURVEILLANCE[uu]

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

→ Relapsed/Refractory Disease (ALL-8)

Other General Measures

- Bone marrow aspirate can be considered as clinically indicated at a frequency of up to 3 to 6 months for at least 5 years[vv]
  - If bone marrow aspirate is done: Flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular testing, and MRD assessment [Minimal/Measurable Residual Disease Assessment (ALL-F)]
- 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/

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

[vv] While there is insufficient evidence to guide MRD monitoring for patients with Ph-negative disease 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 and ALL-3 as applicable.

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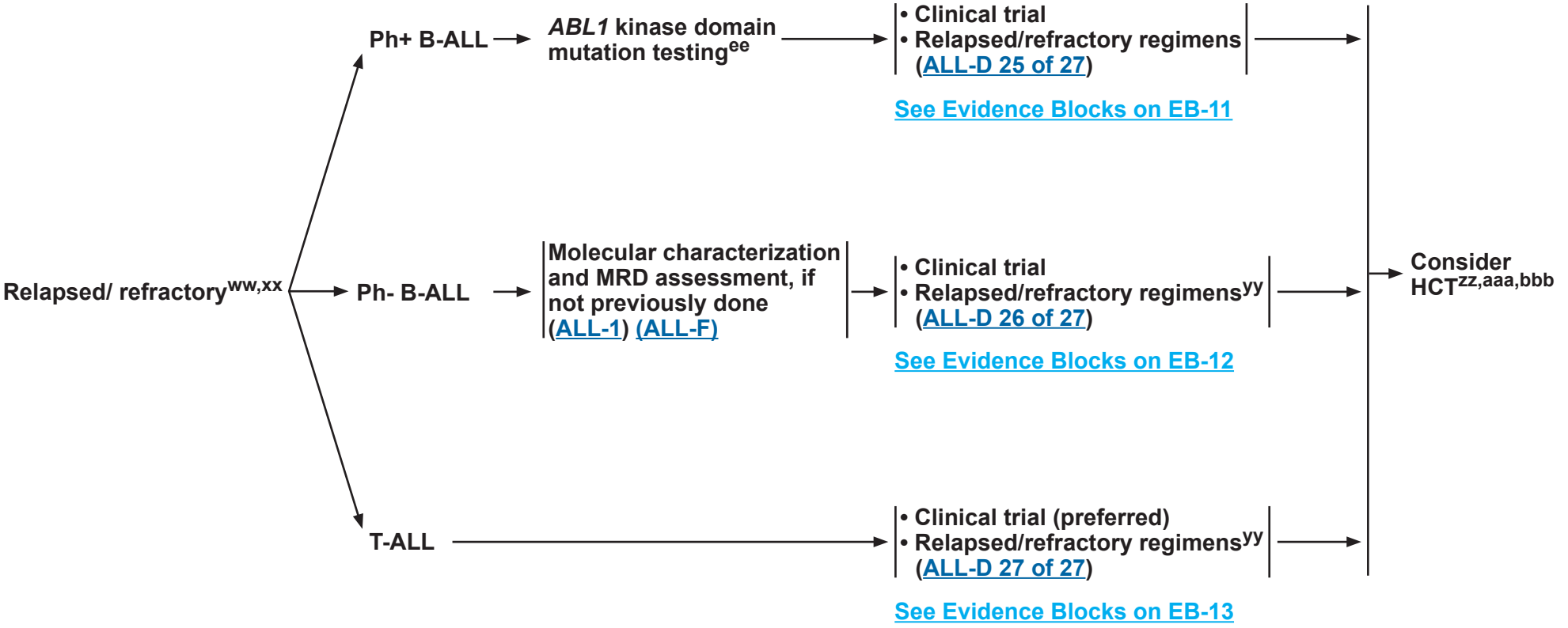
RELAPSED/REFRACTORY DISEASE

TREATMENT



ee See ALL-D 1 of 27 for treatment options based on *BCR::ABL1* mutation profile.
ww Isolated extramedullary relapse (including CNS and testicular) requires systemic therapy to prevent relapse in marrow. Consider CNS prophylaxis for relapsed/refractory disease. The role of CNS prophylaxis in the setting of cellular therapy is still being studied.
xx NCCN Guidelines for Palliative Care.
yy For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same regimen used at initial diagnosis (for Ph-negative B-ALL, see ALL-D 9 of 27; for T-ALL, see ALL-D 18 of 27).
zz The role of allogeneic HCT following cellular therapy is unclear.
aaa If second remission is achieved prior to HCT and patient has not had a prior HCT, consolidative HCT is recommended.
bbb For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.

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FAMILIAL GENETIC ALTERATIONS IN ALL

- **Hereditary predisposition to ALL is increasingly recognized.[1,2] As many as 4% of children with ALL carry a germline cancer predisposition gene mutation.[3]**
- **Referral for genetic counseling, germline tissue testing, and potential extension of these services to appropriate family members should be considered in select patients (eg, those with a suggestive family history of leukemia, other hematologic cancers, the associated conditions listed in the table below). See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.**
- **Hereditary forms of ALL may impact HCT donor and regimen selection.[4] Therefore, an expeditious evaluation for germline ALL predisposition mutations is of particular importance prior to allogeneic transplantation.**

Name of Syndrome[a]	Causative Gene(s)	Pattern of Inheritance	Characteristic Malignancy	Other Hematopoietic Abnormalities	Other Associated Conditions	Recommended Diagnostic Test
Familial platelet disorder with propensity to myeloid malignancies (OMIM 601399)	*RUNX1*	Autosomal dominant	• Myelodysplastic syndrome (MDS) • Acute myeloid leukemia (AML) • T-ALL	Thrombocytopenia Platelet dysfunction		Exon sequencing and gene rearrangement testing for *RUNX1*
Thrombocytopenia 5 (OMIM 616216)	*ETV6*	Autosomal dominant	• MDS • AML • Chronic myelomonocytic leukemia (CMML) • B-ALL • Multiple myeloma	Thrombocytopenia Platelet dysfunction		Exon sequencing and gene rearrangement testing for *ETV6*
PAX5-associated leukemia predisposition (OMIM 615545)	*PAX5*	Autosomal dominant	• B-ALL			Exon sequencing and gene rearrangement testing for *PAX5*
IKZF1-associated leukemia predisposition (OMIM 613067)	*IKZF1*	Autosomal dominant	• B-ALL • T-ALL		Immunodeficiency	Exon sequencing for *IKZF1*
Li-Fraumeni syndrome (OMIM 151623)	*TP53*	Autosomal dominant	• MDS • AML • Low-hypodiploid ALL		Adrenocortical carcinoma, osteosarcoma, brain cancer, breast cancer, choroid plexus carcinoma, colon cancer, lung carcinoma, sarcoma, other tumors; therapy-related neoplasms may emerge after treatment for solid tumors	Exon sequencing for *TP53*

[a] Other syndromes have rarely been associated with ALL. For a full list, see references 1-4.

References on ALL-A 2 OF 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.

FAMILIAL GENETIC ALTERATIONS IN ALL REFERENCES

[1] Pui CH, Nichols KE, Yang JJ. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. Nat Rev Clin Oncol 2019;16:227-240.
[2] Klco JM, Mullighan CG. Advances in germline predisposition to acute leukaemias and myeloid neoplasms. Nat Rev Cancer 2021;21:122-137.
[3] Bloom M, Maciaszek JL, Clark ME, et al. Recent advances in genetic predisposition to pediatric acute lymphoblastic leukemia. Expert Rev Hematol 2020;13:55-70.
[4] Furutani E, Shimamura A. Germline genetic predisposition to hematologic malignancy. J Clin Oncol 2017;35:1018-1028.

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EVALUATION AND TREATMENT OF EXTRAMEDULLARY INVOLVEMENT

- **The aim of central nervous system (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.**
- **CNS involvement should be evaluated (by LP) at the appropriate timing:**
  - **Timing of LP should be consistent with the chosen treatment regimen.**
  - **Pediatric-inspired regimens typically include LP at the time of diagnostic workup.**
  - **The Panel recommends that IT therapy be administered with initial LP.**
- **Classification of CNS status:**
  - **CNS-1: No lymphoblasts in cerebrospinal fluid (CSF) regardless of white blood cell (WBC) count.[a]**
  - **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, 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 therapy (eg, methotrexate, cytarabine, corticosteroid), and/or systemic chemotherapy (eg, high-dose methotrexate, intermediate or high-dose cytarabine, pegaspargase [PEG]). 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 1.8–2.0 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 therapy 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. Use of irradiation should be reserved for resistant CNS disease.**
- **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.**

[a] Flow cytometry may be considered. Patients who have CNS-1 disease with leukemia detected only by flow cytometry may be at higher risk but evidence is limited to retrospective analyses.

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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE

Best Supportive Care

- Infection control (NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)
  - For infection risk, monitoring, and prophylaxis recommendations for immune-targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections
- Acute TLS (See Tumor Lysis Syndrome on NHODG-B in the NCCN Guidelines for B-Cell Lymphomas)
- Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, Tisagenlecleucel, Brexucabtagene Autoleucel and Obecabtagene Autoleucel (ALL-C 2 of 6)
- Asparaginase Toxicity Management (ALL-C 3 of 6)
- Methotrexate and Glucarpidase
  - Trimethoprim/sulfamethoxazole may be held when high-dose methotrexate is administered and restarted when methotrexate clearance is achieved per protocol or institutional guidelines.
  - If a patient receiving high-dose methotrexate experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended when:
    - ◊ plasma methotrexate concentrations are two standard deviations above the mean expected plasma concentration as determined by MTXPK.org

    or
    - ◊ plasma methotrexate level is >30 µM at 36 hours, >10 µM at 42 hours, or >5 µM at 48 hours.
  - Optimal administration of glucarpidase is within 48 to 60 hours from the start of methotrexate infusion. Leucovorin should be continued for at least 2 days following glucarpidase administration and should be administered at least 2 hours before or 2 hours after glucarpidase.
- 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 (Discussion)
      - – Obtain vitamin D and calcium status and replete as needed.
      - – Consider radiographic evaluation with x-rays 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 NCCN Guidelines for Acute Myeloid Leukemia).
- Antiemetics (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 greater than 10% weight loss.
- Palliative treatment for pain (NCCN Guidelines for Adult 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.

PRINCIPLES OF SUPPORTIVE CARE

Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, Tisagenlecleucel, Brexucabtagene Autoleucel, and Obecabtagene Autoleucel

Inotuzumab Ozogamicin:
- Cytoreduction should be considered for those with absolute blast count ≥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 used.
- Liver enzymes, and particularly bilirubin, should be closely monitored, as SOS (sinusoidal obstruction syndrome; or veno-occlusive disease [VOD]) may occur, particularly among patients at higher risk (including those who are status-post allogeneic HCT, those whose treatment extends beyond two cycles, and/or those who previously received or will receive double alkylator conditioning prior to allogeneic HCT). For those patients receiving inotuzumab ozogamicin as a bridge to allogeneic HCT, double alkylator conditioning is strongly discouraged. Ursodiol may be considered for SOS prophylaxis.
- Consider defibrotide for patients who develop SOS related to inotuzumab ozogamicin toxicity.[1,2]

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

Tisagenlecleucel/Brexucabtagene Autoleucel/Obecabtagene Autoleucel:
- Severe CRS and/or neurologic toxicity may accompany therapy, Tisagenlecleucel and brexucabtagene autoleucel 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). Obecabtagene autoleucel is not associated with a REMS program. Please see obecabtagene autoleucel prescribing information and follow institutional guidelines for supportive care measures.
- Prophylaxis with anti-seizure medication may be considered during the first month after chimeric antigen receptor [CAR] T-cell infusion.
- Severe neutropenia, T-cell depletion, and B-cell aplasia can occur, for which growth factor, prophylactic antimicrobial therapy, and IV immunoglobulin (Ig) administration should be considered, in accordance with institutional practice (NCCN Guidelines for Management of Immunotherapy-Related Toxicities).

Continued
References on ALL-C 6 of 6

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.

PRINCIPLES OF SUPPORTIVE CARE

Asparaginase Toxicity Management[3]

- **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) PEG, 2) calaspargase pegol-mknl (Cal-PEG[a]) (in patients aged 1 to ≤21 years), and 3) asparaginase Erwinia chrysanthemi (recombinant)-rywn (ERW-rywn).[b] PEG is a common component of therapy for children and AYAs with ALL. The preferred route for administration for both PEG and Cal-PEG is IV. The toxicity profile of these asparaginase products presents significant challenges in clinical management. The following guidelines are intended to help providers address these challenges.**
- **The Panel recommends that the dose of PEG or Cal-PEG should be capped at one vial (3750 IU).**
- **All toxicity grades refer to CTCAE v5.0.[c]**
- **For ERW-rywn, a phase 2/3 study supports a new IM dosing schedule of 25 mg/m² Monday/Wednesday, 50 mg/m² Friday based on positive risk:benefit ratio.[4]**
- **Consider anticoagulation prophylaxis if no contraindications.[5]**

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. Therapeutic drug monitoring (TDM) can be considered for patients with low-grade systemic reactions to confirm efficacy and allow continuation of asparaginase. Patients who experience a grade 1 or 2 reaction but demonstrate adequate asparaginase activity can be considered for rechallenge.

- **ERW-rywn should be used as a second-line agent in patients who have developed a systemic allergic reaction or anaphylaxis due to PEG hypersensitivity.**
- **Anaphylaxis or other allergic reactions of Grade 3–4 severity (CTCAE v5.0)[c] merit permanent discontinuation of the type of asparaginase that caused the reaction.**
- **For Grade 1 reactions and Grade 2 reactions (rash, flushing, urticaria, and drug fever ≥38°C) without bronchospasm, hypotension, edema, or need for parenteral intervention, the asparaginase that caused the reaction may be continued, with consideration for anti-allergy premedication (such as hydrocortisone, famotidine or ranitidine, diphenhydramine or cetirizine, and acetaminophen).**
- **Measures that can be considered for preventing or limiting severity of infusion reactions or hypersensitivity reactions include slowing the infusion to ≥ 2 hours, infusing normal saline concurrently, and use of premedications provided above.**
- **If anti-allergy premedication is used prior to PEG or ERW-rywn administration, TDM using commercially available asparaginase activity assays is highly recommended, since premedication may "mask" the systemic allergic reactions that can indicate the development of neutralizing antibodies.[6]**
  - **TDM for asparaginase therapy using the serum asparaginase activity (SAA) is available as a CLIA-certified test with a turnaround time of less than 1 week, allowing real-time decision-making and therapeutic adjustments. Generally accepted SAA assay targets include a minimum trough of greater than or equal to 0.1 IU/mL. However, data indicate that when SAA levels fall below 0.4 IU/mL, asparagine is no longer completely depleted, and begins to rebound, suggesting an optimal trough of ≥ 0.4 IU/mL.[7] The optimal timing for PEG trough is 14 days, for Cal-PEG trough is 21 days, and for ERW-rywn trough is 48 hours.**

[a] In the setting of AYA/Adult ALL, Cal-PEG is substituted for PEG in patients aged 15 to ≤21 years for more sustained asparaginase activity.
[b] ERW-rywn is for patients who had an allergic reaction to *E. coli*-derived asparaginase.
[c] National Institutes of Health; National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Continued
References on ALL-C 6 of 6

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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PRINCIPLES OF SUPPORTIVE CARE
Asparaginase Toxicity Management (continued)

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

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 and treat with appropriate antithrombotic therapy. Upon resolution of symptoms and antithrombotic therapy stable, consider resuming asparaginase.
- Consider checking antithrombin (AT) III 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.
- Perform magnetic resonance angiography (MRA)/magnetic resonance venography (MRV) to rule out bleeding associated with venous sinus thrombosis.

Cerebral Thrombosis, Ischemia, or Stroke
- Discontinue asparaginase. Consider antithrombotic therapy. For Grade 3, if symptoms/signs fully resolve, consider risk/benefit ratio of resuming asparaginase. For Grade 4, permanently discontinue asparaginase.

Hypofibrinogenemia
- Prophylactic repletion with fibrinogen concentrates for asparaginase-induced-hypofibrinogenemia in the absence of bleeding increases the risk of clotting.[8]
- Prophylactic repletion is recommended in the setting of full dose anticoagulation.

Continued

References on ALL-C 6 of 6

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.

PRINCIPLES OF SUPPORTIVE CARE
Asparaginase Toxicity Management (continued)

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

Note: 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.

PRINCIPLES OF SUPPORTIVE CARE REFERENCES

[1] Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant 2018;53:449-456.
[2] Giglio F, Xue E, Greco R, et al. Defibrotide Prophylaxis of Sinusoidal Obstruction Syndrome in Adults Treated With Inotuzumab Ozogamicin Prior to Hematopoietic Stem Cell Transplantation. Front Oncol 2022;12:933317.
[3] 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.
[4] Maese LD, Loh ML, Choi MR, et al. Recombinant erwinia asparaginase (JZP458) in acute lymphoblastic leukemia: Results from the phase 2/3 AALL1931 study. Blood 2023;141:704-712.
[5] Hu Z, Persaud Y, Ahuja S. A systematic review and meta-analysis of the effectiveness of primary thromboprophylaxis in acute lymphoblastic leukemia during early-phase therapy including asparaginase or its prolonged form. Crit Rev Oncol Hematol 2024;197:104347.
[6] 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.
[7] Kloos RQH, Pieters R, Jumelet FMV, et al. Individualized asparaginase dosing in childhood acute lymphoblastic leukemia. J Clin Oncol 2020;38:715-724.
[8] Orvain C, Balsat M, Tavernier E, et al. Thromboembolism prophylaxis in adult patients with acute lymphoblastic leukemia treated in the GRAALL-2005 study. Blood 2020;136:328-338.

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PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL

Ph-NEGATIVE B-ALL

T-ALL

REGIMENS FOR RELAPSED OR REFRACTORY

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.

PRINCIPLES OF SYSTEMIC THERAPY

GENERAL CONSIDERATIONS

- **The ALL Panel considers adolescent and young adult (AYA) to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages. For additional considerations in the care of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.**
- **For infection risk, monitoring, and prophylaxis recommendations for immune and targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**
- **For toxicity management for blinatumomab, inotuzumab ozogamicin, brexucabtagene autoleucel, tisagenlecleucel, and obecabtagene autoleucel, see Principles of Supportive Care ALL C 2 of 6.**
- **Although there are limited data, the Panel recommends waiting at least 4 weeks from the completion of inotuzumab ozogamicin monotherapy and the start of conditioning therapy for allogeneic HCT to minimize risk of SOS. SOS occurred less frequently when fewer alkylators were used as part of the conditioning regimen. Kantarjian H, et al. Cancer 2013;119:2728-2736**
- **Leucovorin is always used in combination with high-dose methotrexate.**
- **Mesna is always used in combination with ifosfamide and used in combination with cyclophosphamide as clinically indicated.**
- **An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. Tbo-filgrastim is also an appropriate substitute for G-CSF.**

Mutation Profile Principles

TREATMENT OPTIONS BASED ON *BCR::ABL1* MUTATION PROFILE

Therapy	Contraindicated Mutations
Asciminib	*A337T, P465S, M244V,* or *F359V/I/C*
Bosutinib	*T315I, V299L, G250E*, or *F317L*
Dasatinib	*T315I/A, F317L/V/I/C*, or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, or F359V/C/I* or *G250E*
Ponatinib	None

- **Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.**
- **Nilotinib may be preferred over bosutinib in patients with *F317L* mutation.**
- **Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or progressive disease (PD) on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.**

Continued

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PRINCIPLES OF SYSTEMIC THERAPY

GENERAL CONSIDERATIONS

- **For patients receiving mercaptopurine (6-MP), consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both *TPMT* and *NUDT15* variant status should be considered, especially for patients of East Asian descent. Relling MV, et al. Clin Pharmacol Ther 2019;105:1095-1105.**

Maintenance Principles

- **Ph+ B-ALL**
  - **The optimal duration of TKI maintenance is unknown.**
    - ◊ **The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy.**
    - ◊ **TKI should be continued for at least 2 years post-HCT.**
- **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.**

CNS Prophylaxis Principles

- **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).**
- **Refer to specific references/protocols, and/or chemotherapy order templates (where available) for appropriate timing in phases of treatment.**

Adults ≥65 Years or Adults with Substantial Comorbidities

- **Adults who are ≥65 years benefit from therapy, despite higher treatment-related morbidity and mortality.**
- **Chronological age is a poor surrogate for fitness of therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.**
- **Careful assessment of comorbid conditions, performance status, and ability to attend to activities of daily living (ADLs) and instrumental ADLs (IADLs) is important when deciding treatment intensity.**
- **For tools to aid optimal assessment and care of adults ≥65 years with cancer, see the NCCN Guidelines for Older Adult Oncology.**
- **Dose reduction of pegylated asparaginase (1000 IU/m^2), anthracycline (50% dose), and/or other myelosuppressive agents may be warranted.[a]**
- **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 allogeneic HCT may be appropriate.**

[a] Patel AA, Heng J, Dworkin E, et al. Efficacy and tolerability of a modified pediatric-inspired intensive regimen for acute lymphoblastic leukemia in older adults. EJHaem 2021;2:413-420.

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PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL INDUCTION REGIMENS[b]

AYA Patients and Adults <65 years without Substantial Comorbidities: Frontline	Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
Preferred • Clinical trial **Other Recommended Regimens** • TKI[c,d] in combination with: ▸ Blinatumomab[e,1-3] ▸ HyperCVAD[4-8] **Useful in certain circumstances** • TKI[c,d] in combination with: ▸ Corticosteroid[f,9,10] ▸ Vincristine + dexamethasone[11]	**Preferred** • Clinical trial **Other Recommended Regimens** • Low intensity ▸ TKI[c,d] in combination with: ◊ Blinatumomab[e,1-3] ◊ Corticosteroid[f,9,10,12-14] ◊ Vincristine + dexamethasone[11] • Moderate intensity ▸ TKI[c,d] + mini-hyperCVD[15]

See Evidence Blocks on EB-1
Regimen components on ALL-D 4 of 27

[b] There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.
[d] Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.
[e] Prior to blinatumomab initiation, cytoreduce with TKI plus corticosteroid to a peripheral WBC count of <10 x 10^9/L. Foà R, et al. J Clin Oncol 2024;42:881-885.
[f] TKI + corticosteroid as induction should be followed by TKI + multiagent therapy or TKI + blinatumomab consolidation unless TKI + corticosteroid is used in a palliative manner.

References on ALL-D 8 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL INDUCTION COMPONENTS[b,g,h,i]

AYA Patients and Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **Blinatumomab[e] + TKI[c,d,1-3]** • **HyperCVAD[4-8] + TKI[c,d]:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine **Useful in certain circumstances** • **Corticosteroid + TKI[c,d,f,9,10]** • **Vincristine + dexamethasone + TKI[c,d,11]**
Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
Other Recommended Regimens • **Low intensity** ▸ **Blinatumomab[e] + TKI[c,d,1-3]** ▸ **Corticosteroid + TKI[c,d,f,9,10,12-14]** ▸ **Vincristine + dexamethasone + TKI[c,d,11]** • **Moderate intensity** ▸ **Mini-hyperCVD[15] + TKI[c,d]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine

Footnotes on ALL-D 4A of 27

References on ALL-D 8 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL INDUCTION COMPONENTS FOOTNOTES

[b] There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).

[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.

[d] Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.

[e] Prior to blinatumomab initiation, cytoreduce with TKI plus corticosteroid to a peripheral WBC count of <10 x 10^9/L. Foà R, et al. J Clin Oncol 2024;42:881-885.

[f] TKI + corticosteroid as induction should be followed by TKI + multiagent therapy or TKI + blinatumomab consolidation unless TKI + corticosteroid is used in a palliative manner.

[g] 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] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.

[i] For patients who develop hypersensitivity to *Escherichia coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL CONSOLIDATION REGIMENS[b]

- **Blinatumomab + TKI[c,d,j,1-3]**
- **Multiagent therapy[k] + TKI[c,d,4-8,11,15] (see ALL-D 6 of 27)**
- **TKI[c,d,l,9,10,12-14]**

Regimen components on ALL-D 6 of 27

See Evidence Blocks on EB-2

[b] There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.
[d] Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.
[j] Blinatumomab + TKI is preferred in consolidation regardless of MRD status for those who have not previously received blinatumomab.
[k] Refer to induction regimen references, consolidation components on ALL-D 6 of 27, or chemotherapy order templates (where available), for components if not listed.
[l] TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies.

References on ALL-D 8 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL CONSOLIDATION COMPONENTS[b,g,h,i]

AYA Patients without Substantial Comorbidities	Adults <65 years without Substantial Comorbidities	Adults ≥65 Years or Adults with Substantial Comorbidities
HyperCVAD[4-8] + TKI[c,d]: Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine		**Mini-hyperCVD[15] + TKI[c,d]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine
Vincristine + dexamethasone + TKI[c,d,11]: Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, high-dose methotrexate, vincristine		**Vincristine + dexamethasone + TKI[c,d,11]:** May use mini-hyperCVD[15] + TKI

[b] There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.
[d] Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.
[g] 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] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
[i] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.

References on ALL-D 8 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL MAINTENANCE THERAPY[b,m]

- **POMP (mercaptopurine, vincristine, methotrexate, prednisone) + TKI[c,d]**
- **Vincristine + prednisone + TKI[c,d]**
- **TKI[c,d,l,n] monotherapy (if post-HCT or previously received blinatumomab + TKI)**

See Evidence Blocks on EB-3

[b] There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.
[d] Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.
[l] TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies.
[m] Refer to induction regimen references or chemotherapy order templates (where available), for components. Include IT chemotherapy per protocol, or as clinically indicated.
[n] TKI should be continued for at least 2 years post-HCT. See Discussion for use of different TKIs in this setting. 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.

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL REFERENCES

[1] Foa R, Bassan R, Elia L, et al. Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. J Clin Oncol 2024;42:881-885.
[2] Gökbuget N, Zugmaier G, Dombret H, et al. Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. Leuk Lymphoma 2020;61:2665-2673.
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[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.
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[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(Suppl 11):Abstract 2931.
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[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;16:1547-1555.
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[10] 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.
[11] 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.
[12] 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.
[13] Papayannidis C, Fazi P, Piciocchi A, et al. Treating Ph+ acute lymphoblastic leukemia (ALL) in the elderly: the sequence of two tyrosine kinase inhibitors (TKI) (nilotinib and imatinib) does not prevent mutations and relapse. Blood 2012;120:Abstract 2601.
[14] Martinelli G, Piciocchi A, Papayannidis C, et al. First report of the GIMEMA LAL 1811 prospective study of the combination of steroids with ponatinib as frontline therapy of elderly or unfit patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2017;139:99.
[15] Jen WY, Jabbour E, Short NJ, et al. A phase 2 trial of mini-hyper-CVD, blinatumomab, and ponatinib in Philadelphia positive acute lymphoblastic leukemia. Am J Hematol 2024;99:2229-2232.

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL INDUCTION REGIMENS[a]

Only for AYA Patients without Substantial Comorbidities: Frontline	For both AYA Patients & Adults <65 years without Substantial Comorbidities: Frontline	Only for Adults <65 years without Substantial Comorbidities: Frontline	Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
Preferred • Clinical trial • CALGB 10403[b,1] • DFCI ALL regimen based on DFCI Protocol 00-01[b,2]	**Preferred** • Clinical trial **Other Recommended Regimens** • ECOG 1910[3] • HyperCVAD[4-6] • MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 to <60 years)[b,7,8]	**Preferred** • Clinical trial **Other Recommended Regimens** • Inotuzumab ozogamicin + mini-hyperCVD[9-11]	**Preferred** • Clinical trial **Other Recommended Regimens** • Low Intensity ▸ Vincristine + prednisone[12] ▸ POMP[13]: mercaptopurine, vincristine, methotrexate, prednisone • Moderate Intensity ▸ ALL-INITIAL-1[14]: Inotuzumab ozogamicin/ dexamethasone (category 2B) ▸ ALLIANCE A041703[15]: Inotuzumab ozogamicin (category 2B) ▸ Inotuzumab ozogamicin + mini-hyperCVD[9-11] ▸ Modified DFCI 91-01 protocol[16] ▸ Mini-hyperCVD[17,18] ▸ Mini-hyperCVD + venetoclax[17] • High Intensity ▸ ECOG 1910[3] **Useful in certain circumstances** • ALLOLD07 (PETHEMA-based regimen)[19] • CALGB 9111[20] • EWALL[21] • GMALL[22] + rituximab for CD20-positive disease • GRAALL[23]

[a] There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).

[b] Pediatric-inspired regimen.

See Evidence Blocks on EB-4 and EB-5
Regimen components on ALL-D 10 of 27

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.

References on ALL-D 16 of 27

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL INDUCTION COMPONENTS[a,c,d,e,f]

AYA Patients without Substantial Comorbidities: Frontline
Preferred Regimens • **CALGB 10403[b,1]:** Daunorubicin, pegaspargase, prednisone, vincristine • **DFCI ALL regimen based on DFCI Protocol 00-01[b,2]:** Doxorubicin, high-dose methotrexate, pegaspargase, prednisone, vincristine
For both AYA Patients and Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **ECOG 1910[3]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, mercaptopurine, pegaspargase, vincristine, rituximab for CD20-positive disease • **HyperCVAD[4-6]:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine, rituximab for CD20-positive disease • **MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 to <60 years)[b,7,8]:** Cyclophosphamide, cytarabine, daunorubicin, mercaptopurine, pegaspargase, prednisone, vincristine
Only for Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **Inotuzumab ozogamicin + mini-hyperCVD[9-11]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin

Continued

Footnotes on ALL-D 11A of 27

References on ALL-D 16 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL INDUCTION COMPONENTS[c,d,e,f]

Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline and Relapsed/Refractory

Other Recommended Regimens

- **Low intensity**
  - **Vincristine + prednisone[12]**
  - **POMP[13]:** Mercaptopurine, vincristine, methotrexate, prednisone

- **Moderate intensity**
  - **ALL-INITIAL-1[14]: Inotuzumab ozogamicin/Dexamethasone (category 2B)**
  - **ALLIANCE A041703[15]: Inotuzumab ozogamicin (category 2B)**
  - **Inotuzumab ozogamicin + mini-hyperCVD[9-11]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin
  - **Modified DFCI 91-01 protocol[16]:** Dexamethasone, doxorubicin, methotrexate, pegaspargase, vincristine
  - **Mini-hyperCVD[17,18]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine, rituximab for CD20-positive disease
  - **Mini-hyperCVD + venetoclax[17]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine; venetoclax

- **High intensity**
  - **ECOG 1910[3]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, mercaptopurine, pegaspargase (age <55 years), vincristine, rituximab for CD20-positive disease

Useful in certain circumstances

- **ALLOLD07 (PETHEMA-based regimen)[19]:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine
- **CALGB 9111[20]:** Cyclophosphamide, daunorubicin, prednisone, pegaspargase, vincristine
- **EWALL[21]:** Cyclophosphamide, dexamethasone, vincristine
- **GMALL[22]:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine, rituximab for CD20-positive disease
- **GRAALL[23]:** Cyclophosphamide, dexamethasone, doxorubicin, vincristine

Footnotes on ALL-D 11A of 27

References on ALL-D 16 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL INDUCTION COMPONENTS FOOTNOTES

[a] There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[b] Pediatric-inspired regimen.
[c] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[d] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
[e] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[f] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤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.

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION REGIMENS[a,g]

- **Blinatumomab (preferred) + continued multiagent therapy[h]**
- **Blinatumomab[i]**

See Evidence Blocks on EB-6

Regimen components on ALL-D 13 of 27

[a] There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[g] Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673. Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. N Engl J Med 2024;391:320-333.
[h] Refer to induction regimen references, consolidation components (ALL-D 13 of 27), or chemotherapy order templates, where available, for components if not listed.
[i] Blinatumomab can be considered for consolidation in patients for whom multiagent therapy is contraindicated.

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION COMPONENTS[a,c,d,e,f,g]

AYA Patients without Substantial Comorbidities
Preferred Regimens • **CALGB 10403[b,1]:** Cyclophosphamide, cytarabine, mercaptopurine, pegaspargase, vincristine • **DFCI ALL regimen based on DFCI Protocol 00-01[b,2]:** Dexamethasone, doxorubicin, mercaptopurine, methotrexate, pegaspargase, vincristine
For both AYA Patients and Adults <65 years without Substantial Comorbidities
Other Recommended Regimens • **ECOG 1910[3]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, pegaspargase, vincristine, rituximab for CD20-positive disease, alternating with blinatumomab • **HyperCVAD[4-6]:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine, rituximab for CD20-positive disease, with sequential blinatumomab • **MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 to <60 years)[b,7,8]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, high-dose methotrexate, pegaspargase, prednisone, thioguanine, vincristine
Only for Adults <65 years without Substantial Comorbidities
Other Recommended Regimens • **Inotuzumab ozogamicin + mini-hyperCVD[9-11]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin, with sequential blinatumomab

Continued

Footnotes on ALL-D 14A of 27

References on ALL-D 16 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION COMPONENTS[c,d,e,f,g]

Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline and Relapsed/Refractory

Other Recommended Regimens

- **Low intensity**
  - **Vincristine + prednisone**[12]
  - **POMP**[13]**:** mercaptopurine, vincristine, methotrexate, prednisone

- **Moderate intensity**
  - **ALL-INITIAL-1**[14]**:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, high-dose methotrexate, pegaspargase, vincristine, with rituximab for CD20-positive disease
  - **ALLIANCE A041703**[15]**:** Blinatumomab
  - **Inotuzumab ozogamicin + mini-hyperCVD**[9-11]**:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin, with sequential blinatumomab
  - **Modified DFCI 91-01 protocol**[16]**:** Dexamethasone, doxorubicin, mercaptopurine, pegaspargase, vincristine
  - **Mini-hyperCVD**[17,18]**:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine, rituximab for CD20-positive disease, with sequential blinatumomab
  - **Mini-hyperCVD + venetoclax**[17]**:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine; venetoclax

- **High intensity**
  - **ECOG 1910**[3]**:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, pegaspargase, vincristine, rituximab for CD20-positive disease, alternating with blinatumomab

Useful in certain circumstances

- **ALLOLD07 (PETHEMA-based regimen)**[19]**:** Cytarabine, high-dose methotrexate, pegaspargase
- **CALGB 9111**[20]**:** Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, mercaptopurine, pegaspargase, thioguanine, vincristine
- **EWALL**[21]**:** Cytarabine, high-dose methotrexate, pegaspargase
- **GMALL**[22]**:** Cytarabine, methotrexate, rituximab for CD20-positive disease
- **GRAALL**[23]**:** Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, mercaptopurine, vincristine

Footnotes on ALL-D 14A of 27

References on ALL-D 16 of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION COMPONENTS FOOTNOTES

[a] There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[b] Pediatric-inspired regimen.
[c] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[d] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
[e] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[f] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤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] Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673. Topp MS, et al. J Clin Oncol 2011;29:2493-2498. Litzow MR, et al. N Engl J Med 2024;391:320-333.

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PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL MAINTENANCE THERAPY[a,j]

- POMP (mercaptopurine, vincristine, methotrexate, prednisone)
- Blinatumomab alternating with POMP[k]

See Evidence Blocks on EB-7

[a] There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
[j] Refer to induction regimen references, or chemotherapy order templates (where available), for components. Include IT chemotherapy per protocol, or as clinically indicated.
[k] For maintenance in patients induced with inotuzumab ozogamicin + mini-hyperCVD + blinatumomab regimen or hyperCVAD + blinatumomab regimen.

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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL REFERENCES

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Continued

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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL REFERENCES

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PRINCIPLES OF SYSTEMIC THERAPY

T-ALL INDUCTION REGIMENS[a]

Only for AYA Patients without Substantial Comorbidities: Frontline	For both AYA Patients & Adults <65 years without Substantial Comorbidities: Frontline	Only for Adults <65 years without Substantial Comorbidities: Frontline	Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
Preferred • Clinical trial • CALGB 10403[b,1] • COG AALL 0434[b,2-4] **Other Recommended Regimens** • DFCI ALL regimen based on DFCI Protocol 00-01[b,5] • MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 years)[b,6,7]	**Preferred** • Clinical trial **Other Recommended Regimens** • HyperCVAD[8]	**Preferred** • Clinical trial **Other Recommended Regimens** • Dose-adjusted GRAALL-2014[9-11]	**Preferred** • Clinical trial **Other Recommended Regimens** • Low Intensity ▸ Vincristine + prednisone[12] ▸ POMP: mercaptopurine, methotrexate, prednisone, vincristine[13] • Moderate Intensity ▸ ALLOLD07 (PETHEMA-based regimen)[14] ▸ GMALL[15] ▸ GRAALL[16] ▸ Mini-hyperCVD[17,18] ▸ Modified DFCI 91-01 protocol[19]

See Evidence Blocks on EB-8 and EB-9

Regimen components on ALL-D 19 of 27

[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] Pediatric-inspired regimen.

References on ALL-D 24 of 27

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PRINCIPLES OF SYSTEMIC THERAPY

T-ALL INDUCTION COMPONENTS[a,c]

Only AYA Patients without Substantial Comorbidities: Frontline
Preferred Regimens • **CALGB 10403[b,1]:** Daunorubicin, pegaspargase, prednisone, vincristine • **COG AALL 0434[b,2-4]:** Daunorubicin, pegaspargase, prednisone, vincristine **Other Recommended Regimens** • **DFCI ALL regimen based on DFCI Protocol 00-01[b,5]:** Doxorubicin, methotrexate, pegaspargase, prednisone, vincristine • **MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 years)[b,6,7]:** Cyclophosphamide, cytarabine, daunorubicin, mercaptopurine, pegaspargase, prednisone, vincristine
For both AYA Patients & Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **HyperCVAD[8]:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine +/- nelarabine
Only for Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **Dose-adjusted GRAALL-2014[9-11]:** Cyclophosphamide, daunorubicin, pegaspargase, prednisone, vincristine

Continued

[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] Pediatric-inspired regimen.
[c] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.

References on ALL-D 24 of 27

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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

T-ALL INDUCTION COMPONENTS[a,c,d]

Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline and Relapsed/Refractory

Other Recommended Regimens

- **Low intensity**
  - **Vincristine + prednisone**[12]
  - **POMP**[13]**:** mercaptopurine, vincristine, methotrexate, prednisone

- **Moderate intensity**
  - **ALLOLD07 (PETHEMA-based regimen)**[14]**:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine
  - **GMALL**[15]**:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine
  - **GRAALL**[16]**:** Cyclophosphamide, dexamethasone, doxorubicin, vincristine
  - **Mini-hyperCVD**[17,18]**:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine ± nelarabine
  - **Modified DFCI 91-01 protocol**[19]**:** Dexamethasone, doxorubicin, methotrexate, pegaspargase, vincristine

[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 who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[d] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤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.

References on ALL-D 24 of 27

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PRINCIPLES OF SYSTEMIC THERAPY

T-ALL CONSOLIDATION COMPONENTS[a,c,d]

Only AYA Patients without Substantial Comorbidities: Frontline
Preferred Regimens • **CALGB 10403[b,1]:** Cyclophosphamide, cytarabine, mercaptopurine, pegaspargase, vincristine • **COG AALL 0434[b,2-4]:** Cyclophosphamide, cytarabine, mercaptopurine, pegaspargase, vincristine, ± nelarabine **Other Recommended Regimens** • **DFCI ALL regimen based on DFCI Protocol 00-01[b,5]:** Dexamethasone, doxorubicin, mercaptopurine, methotrexate, pegaspargase, vincristine • **MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 years)[b,6,7]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, high-dose methotrexate, pegaspargase, prednisone, thioguanine, vincristine
For both AYA Patients & Adults <65 Years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **HyperCVAD[8]:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine, ± nelarabine
Only for Adults <65 Years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **Dose-adjusted GRAALL-2014[9-11]:** Cyclophosphamide, cytarabine, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, pegaspargase, vincristine ± nelarabine

Continued

[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] Pediatric-inspired regimen.
[c] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[d] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤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.

References on ALL-D 24 of 27

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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

T-ALL CONSOLIDATION COMPONENTS[a,c,d]

Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline and Relapsed/Refractory

Other Recommended Regimens

- **Low intensity**
  - **Vincristine + prednisone**[12]
  - **POMP**[13]**:** mercaptopurine, vincristine, methotrexate, prednisone

- **Moderate intensity**
  - **ALLOLD07 (PETHEMA-based regimen)**[14]**:** Cytarabine, high-dose methotrexate, pegaspargase
  - **GMALL**[15]**:** Cytarabine, methotrexate
  - **GRAALL**[16]**:** Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, mercaptopurine, vincristine
  - **Mini-hyperCVD**[17,18]**:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine, ± nelarabine
  - **Modified DFCI 91-01 protocol**[19]**:** Dexamethasone, doxorubicin, mercaptopurine, pegaspargase, vincristine

[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 who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[d] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤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.

References on ALL-D 24 of 27

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PRINCIPLES OF SYSTEMIC THERAPY

T-ALL MAINTENANCE COMPONENTS[c,d,e]

Maintenance Regimen (if not already included in a multi-part regimen)
• Weekly methotrexate + daily mercaptopurine + monthly vincristine/prednisone pulses (duration based on regimen)
Specific Maintenance Regimens
• **COG AALL 0434[b,2-4] (AYA without substantial comorbidities):** Mercaptopurine, methotrexate, prednisone, vincristine, ± nelarabine • **HyperCVAD[8]:** Hyperfractionated cyclophosphamide, doxorubicin, dexamethasone, mercaptopurine, methotrexate, pegaspargase, prednisone, vincristine, ± nelarabine • **Dose-adjusted GRAALL-2014[9-11] (Adults <65 years without substantial comorbidities):** Mercaptopurine, methotrexate, prednisone, vincristine, ± nelarabine

See Evidence Blocks on EB-10

[b] Pediatric-inspired regimen.
[c] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[d] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤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.
[e] Refer to induction regimen references or chemotherapy order templates, where available, for components. Include IT chemotherapy per protocol, or as clinically indicated.

References on ALL-D 24 of 27

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PRINCIPLES OF SYSTEMIC THERAPY

T-ALL REFERENCES

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PRINCIPLES OF SYSTEMIC THERAPY

REGIMENS FOR RELAPSED OR REFRACTORY Ph-POSITIVE B-ALL[a,b]

Other Recommended Regimens

- **TKI[c] (dasatinib,[1,2] imatinib,[3] ponatinib,[4] nilotinib,[5] or bosutinib[6])**
  - **The TKIs noted above may also be used in combination with any of the regimens noted on ALL-D 3 of 27 that were not previously given.**
- **Asciminib + dasatinib[7]**
- **Blinatumomab ± TKI[8,9]**
- **Inotuzumab ozogamicin ± TKI[10,11]**
- **Tisagenlecleucel (patients aged <26 years and with refractory disease or ≥2 relapses and following therapy that has included 2 TKIs)[12]**
- **Brexucabtagene autoleucel (following therapy that has included TKIs)[13]**
- **Obecabtagene autoleucel (following therapy that has included TKIs)[14]**
- **The regimens listed on ALL-D 26 of 27 for Ph-negative B-ALL may be considered for Ph-positive B-ALL refractory to TKIs.**

See Evidence Blocks on EB-11

[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] The safety of relapsed/refractory regimens in adults ≥65 years or adults with substantial comorbidities has not been established. Please see ALL-D 2 of 27 for additional information.
[c] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, BCR::ABL1 mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.

References on ALL-D 25A of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

REFERENCES FOR REGIMENS FOR RELAPSED OR REFRACTORY Ph-POSITIVE B-ALL

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[14] Roddie C, Sandhu KS, Tholouli E, et al. Obecabtagene autoleucel in adults with B-cell acute lymphoblastic leukemia. N Engl J Med 2024;391:2219-2230.

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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE B-ALL[a,b,c,d]

Preferred Regimens

- **Blinatumomab (CD19 antigen directed) (category 1)[1] ± multiagent therapy**
- **Inotuzumab ozogamicin (CD22 antigen directed) (category 1)[2]**
- **Tisagenlecleucel (CD19 antigen directed) (patients aged <26 years and with refractory disease or ≥2 relapses)[3]**
- **Brexucabtagene autoleucel (CD19 antigen directed)[4]**
- **Obecabtagene autoleucel (CD19 antigen directed)[5]**

Other Recommended Regimens[e]

- **Inotuzumab ozogamicin + mini-hyperCVD with or without sequential blinatumomab (**hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine)[6,7]
- **Augmented HyperCVAD:** hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, pegaspargase; alternating with high-dose methotrexate, cytarabine[8]
- **Clofarabine alone[9-12] or in combination (**eg, clofarabine, cyclophosphamide, etoposide)[10,13,14]
- **MOpAD regimen:** methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease[15]
- **Fludarabine-based regimens**
  - **FLAG-IDA:** fludarabine, cytarabine, G-CSF ± idarubicin[16]
  - **FLAM:** fludarabine, cytarabine, mitoxantrone[17]
- **Cytarabine-containing regimens:** eg, high-dose cytarabine, idarubicin, IT methotrexate[18]
- **Alkylator combination regimens:** eg, etoposide, ifosfamide, mitoxantrone[19]
- **Revumenib (*KMT2A* rearranged)[f,20]**

See Evidence Blocks on EB-12

[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] For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same regimen used at initial diagnosis (see ALL-D 9 of 27).
[c] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[d] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in patients aged 15 to ≤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.
[e] The safety of relapsed/refractory regimens in adults ≥65 years or adults with substantial comorbidities has not been established. Please see ALL-D 2 of 27 for additional information.
[f] Revumenib can cause fatal or life-threatening differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

References on ALL-D 26A of 27

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.

PRINCIPLES OF SYSTEMIC THERAPY

REFERENCES FOR REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE B-ALL

[1] Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-847.
[2] 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.
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[14] 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.
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[16] 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.
[17] 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.
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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

REGIMENS FOR RELAPSED OR REFRACTORY T-ALL[a,b,c,d,e,f]

Preferred Regimens

- **Clinical trial**

Other Recommended Regimens

- **Bortezomib-containing regimen**[1]
- **Daratumumab-containing regimen (category 2B)**[2-6]
- **High-dose cytarabine-containing regimen**[7,8]
- **Mitoxantrone, etoposide, cytarabine**[9]
- **Revumenib (*KMT2A* rearranged)**[g,10]
- **Nelarabine**[11-14] **± etoposide, cyclophosphamide**[15-17]
- **Venetoclax-containing regimen (eg, HMA [azacitidine or decitabine], hyperCVAD, nelarabine, mini-hyperCVD) (category 2B)**[18-21]

The following regimens for relapsed/refractory Ph-negative B-ALL may be appropriate/considered for relapsed/refractory T-ALL:

- **Augmented HyperCVAD:** hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, pegaspargase; alternating with high-dose methotrexate, cytarabine[22]
- **Clofarabine alone**[23-26] **or in combination (**eg, clofarabine, cyclophosphamide, etoposide**)**[24,27,28]
- **MOpAD regimen:** methotrexate, vincristine, pegaspargase, dexamethasone
- **Fludarabine-based regimens**
  - **FLAG-IDA:** fludarabine, cytarabine, G-CSF ± idarubicin[29]
  - **FLAM:** fludarabine, cytarabine, mitoxantrone[30]
- **Cytarabine-containing regimens:** eg, high-dose cytarabine, idarubicin, IT methotrexate[31]
- **Alkylator combination regimens:** eg, etoposide, ifosfamide, mitoxantrone[32]

See Evidence Blocks on EB-13

[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] The safety of relapsed/refractory regimens in adults ≥65 years or adults with substantial comorbidities has not been established. Please see ALL-D 2 of 27 for additional information.
[c] For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same regimen used at initial diagnosis (see ALL-D 18 of 27).
[d] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
[e] PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in patients aged 15 to ≤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.
[f] Based on limited case report data, there may be a role for targeted therapy in relapsed or refractory T-ALL based on molecular mutational status in appropriate situations (see Discussion).
[g] Revumenib can cause fatal or life-threatening differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

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All recommendations are category 2A unless otherwise indicated.

References on ALL-D 27A of 27

PRINCIPLES OF SYSTEMIC THERAPY

REFERENCES FOR REGIMENS FOR RELAPSED OR REFRACTORY T-ALL

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Continued

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PRINCIPLES OF SYSTEMIC THERAPY

REFERENCES FOR REGIMENS FOR RELAPSED OR REFRACTORY T-ALL

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RESPONSE ASSESSMENT

Response Criteria for Blood and Bone Marrow[a,1-3]	
Complete remission (CR)	• No circulating lymphoblasts or extramedullary disease ▸ No lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, CNS involvement, or other extramedullary involvement • Trilineage hematopoiesis (TLH) and <5% leukemic blasts • Absolute neutrophil count (ANC) ≥1000/microL • Platelets ≥100,000/microL
CR with partial hematologic recovery (CRh)	• Meets all criteria for CR except with partial recovery of peripheral blood counts (platelets ≥50,000/microL and ANC ≥500/microL)
CR with incomplete hematologic recovery (CRi)	• Meets all criteria for CR except without recovery of platelet count or without recovery of ANC (platelets <100,000/microL and ANC ≥1000/microL or platelets ≥100,000/microL and ANC <1000/microL)

Response assessment for those not achieving CR[a,1-3]	
Morphologic leukemia-free state (MLFS)	• Leukemic blasts <5% and no measurable extramedullary leukemia • ANC <500/microL and platelets <50/microL • The marrow shows ≥10% cellularity, with at least 200 cells enumerated from an aspirate that contains spicules
Aplastic marrow[b]	• All criteria for MLFS are met, but with <10% cellularity and/or an aspicular aspirate with <200 cells that can be enumerated
Refractory disease	• CR not achieved at the end of induction
Progressive disease (PD)	• Appearance of circulating leukemic blasts or an 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 and Lymphomatous Extramedullary Disease (ALL-E 2 of 2)

[a] MRD assessment is not included in morphologic assessment and should be obtained (ALL-F).
[b] This entity may not be consistent with a response.

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RESPONSE ASSESSMENT

Response Criteria for CNS Disease	
CNS remission	• Achievement of CNS-1 status (ALL-B) in a patient with CNS-2 or CNS-3 status at diagnosis.
CNS relapse	• New development of CNS-2 or 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 if lymphomatous involvement is suspected and/or confirmed by CT, imaging 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.
Partial remission (PR)	• >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the lymphomatous 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 lymphomatous 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)	• Does not meet criteria for either PR or PD.
Relapse	• Recurrence of lymphomatous enlargement after achieving CR.

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MEASURABLE (MINIMAL) RESIDUAL DISEASE ASSESSMENT

- MRD refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods or standard immunophenotyping.
- MRD quantification is an essential component of patient evaluation over the course of sequential ALL therapy.
- Studies in children and adults with ALL have demonstrated a strong correlation between the presence of MRD during remission and risk for relapse, as well as the prognostic significance of MRD measurements after induction and consolidation therapy.[1]
- 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. Referral to or consultation with a center with expertise is recommended due to the complexity of MRD assessment and monitoring.
- The preferred sample for MRD assessment is the first small volume (of up to 3 mL) pull of the bone marrow aspirate, if feasible.
- If validated MRD assessment technology with appropriate sensitivity (at least 10^{-4}) is not available locally, there are commercially available tests.
- The most frequently used methods for MRD quantification include an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and T-cell receptor (TCR) loci (does not require patient-specific primers) (preferred), flow cytometry assays[2,3] specifically designed to detect abnormal MRD immunophenotypes at low frequency, real-time quantitative PCR (RQ-PCR) assays (eg, clonally rearranged Ig, TCR genes), and quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) assays (eg, *BCR::ABL1*).
- High-sensitivity flow cytometry with validated analysis algorithms or PCR methods can quantify leukemic cells at a sensitivity threshold of 1×10^{-4} (0.01%) bone marrow mononuclear cells (MNCs).[2,3] NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of 1×10^{-6} (0.0001%) MNCs.[4,5]
  - If MRD is negative by flow cytometry, an FDA-approved NGS assay should be considered to confirm negativity.
- For flow cytometric quantification of MRD, notify laboratory performing the assay if the patient has received immunotherapy (such as monoclonal antibodies, bispecific antibodies, or CAR T cells) or HCT as these treatments can affect interpretation. Such testing should be performed in a laboratory with experience performing MRD testing in this clinical setting.
- For MRD assessment of *BCR::ABL1*, RT-qPCR is sensitive but in some cases lacks specificity, possibly due to multilineage involvement. Other MRD techniques, including flow cytometry and NGS, may be more specific.
- Timing of MRD assessment:
  - Upon completion of initial induction.
  - End of consolidation
  - Additional time points should be guided by the regimen used and risk features.
  - Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.
  - For some techniques, a baseline sample (ie, prior to treatment) is needed to characterize the leukemic clone for subsequent MRD assessment.

[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;97:1582-1593.
[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.

EVIDENCE BLOCKS FOR Ph-POSITIVE B-ALL INDUCTION REGIMENS

	AYA Patients without Substantial Comorbidities: Frontline	Adults <65 Years without Substantial Comorbidities: Frontline
Other Recommended Regimens		
Blinatumomab + TKI†		
HyperCVAD + TKI†		
Corticosteroid + TKI†		
Vincristine/dexamethasone + TKI†		

EVIDENCE BLOCKS FOR FRONTLINE AND RELAPSED/ REFRACTORY REGIMENS FOR ADULTS ≥65 YEARS OR ADULTS WITH SUBSTANTIAL COMORBIDITIES

Regimens for Ph-Positive B-ALL According to Intensity	
Other Recommended Regimens	
Low Intensity	
Blinatumumab + TKI†	
Corticosteroid + TKI†	
Vincristine/dexamethasone + TKI†	
Moderate Intensity	
Mini-hyperCVD + TKI†	

†TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.

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

EVIDENCE BLOCKS FOR Ph-POSITIVE B-ALL CONSOLIDATION REGIMENS

	MRD Positive	MRD Negative
Blinatumomab + TKI†		
TKI†		

†TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.

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

EVIDENCE BLOCKS FOR Ph-POSITIVE B-ALL MAINTENANCE REGIMENS

POMP + TKI†	
Vincristine/prednisone + TKI†	
TKI† monotherapy (if post-HCT or previously received blinatumomab + TKI)	

†TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.

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

EVIDENCE BLOCKS FOR Ph-NEGATIVE B-ALL INDUCTION REGIMENS

AYA Patients without Substantial Comorbidities	
Preferred Regimens	
CALGB 10403 regimen	
DFCI ALL regimen (based on DFCI Protocol 00-01)	
Other Recommended Regimens	
ECOG1910	
ECOG1910/rituximab (for CD20-positive disease)	
HyperCVAD	
HyperCVAD/rituximab (for CD20-positive disease)	
MSKCC ALL regimen (based on CCG-1882 regimen)	

Adult Patients <65 years without Substantial Comorbidities	
Other Recommended Regimens	
ECOG1910	
ECOG1910/rituximab (for CD20-positive disease)	
GRAALL-2005	
GRAALL-2005/rituximab (for CD20-positive disease)	
HyperCVAD	
HyperCVAD/rituximab (for CD20-positive disease)	
Inotuzumab ozogamicin/mini-hyperCVD	
MSKCC ALL regimen (based on CCG-1882 regimen)	

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

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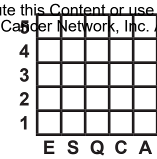
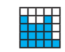


EVIDENCE BLOCKS FOR FRONTLINE AND RELAPSED/REFRACTORY REGIMENS FOR ADULTS ≥65 YEARS OR ADULTS WITH SUBSTANTIAL COMORBIDITIES

Regimens for Ph-Negative B-ALL According to Intensity	
Other Recommended Regimens	
Low Intensity	
Vincristine/prednisone	
POMP	
Moderate Intensity	
ALL-INITIAL-1: Inotuzumab ozogamicin/dexamethasone	
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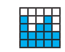
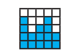
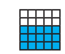
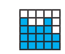
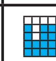
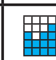
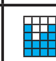
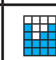
Inotuzumab ozogamicin/mini-hyper-CVD	
Modified DFCI 91-01 protocol	
Mini-hyperCVD	
Mini-hyperCVD/venetoclax	
High Intensity	
ECOG 1910	
Useful in Certain Circumstances	
ALLOLD07 (PETHEMA-based regimen)	
CALGB 9111	
EWALL	
GMALL	
GMALL + rituximab (for CD20-positive disease)	
GRAALL	

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

EVIDENCE BLOCKS FOR Ph-NEGATIVE B-ALL MAINTENANCE REGIMENS

	MRD Positive	MRD Negative
Blinatumomab		
Blinatumomab + continued multiagent therapy		

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

EVIDENCE BLOCKS FOR Ph-NEGATIVE B-ALL CONSOLIDATION REGIMENS

Ph-Negative B-ALL Maintenance Therapy Regimens	
POMP	
Blinatumumab alternating with POMP	

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

EVIDENCE BLOCKS FOR FRONTLINE REGIMENS FOR T-ALL

AYA Patients without Substantial Comorbidities	
Preferred Regimens	
CALGB 10403	
COG AALL0434	
COG AALL0434/nelarabine	
Other Recommended Regimens	
DFCI ALL regimen (based on DFCI Protocol 00-01)	
HyperCVAD	
HyperCVAD/nelarabine	
MSKCC ALL (based on CCG-1882)	

Adult Patients <65 y and without Substantial Comorbidities	
Other Recommended Regimens	
Dose-adjusted GRAALL-2014	
Dose-adjusted GRAALL-2014/nelarabine	
HyperCVAD	
HyperCVAD/nelarabine	

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

(continued)

EVIDENCE BLOCKS FOR FRONTLINE AND RELAPSED/REFRACTORY REGIMENS FOR ADULTS ≥65 YEARS OR ADULTS WITH SUBSTANTIAL COMORBIDITIES

Regimens for T-ALL According to Intensity	
Other Recommended Regimens	
Low Intensity	
Vincristine/prednisone	
POMP	
Moderate Intensity	
ALLOLD07 (PETHEMA-based regimen)	
GMALL	
GRAALL	
Mini-hyperCVD	
Mini-hyperCVD/nelarabine	
Modified DFCI 91-01	

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

EVIDENCE BLOCKS FOR MAINTENANCE REGIMENS FOR T-ALL

Maintenance Regimen (if not already included in a multi-part regimen)	
Weekly methotrexate/daily 6-MP/monthly vincristine/ prednisone pulses (duration based on regimen)	

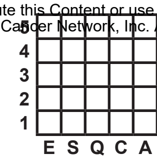
Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

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

Other Recommended Regimens	
Dasatinib	
Imatinib	
Ponatinib	
Nilotinib	
Bosutinib	
Asciminib + dasatinib	
Blinatumomab	
Blinatumomab + TKI†	
Inotuzumab ozogamicin	
Inotuzumab ozogamicin + bosutinib	
Inotuzumab ozogamicin + dasatinib, imatinib, nilotinib, or ponatinib	
Tisagenlecleucel (patients <26 y & with refractory disease or ≥2 relapses and following therapy that has included 2 TKIs)	
Brexucabtagene autoleucel (following therapy that has included TKIs)	
Obecabtagene autoleucel (following therapy that has included TKIs)	

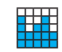
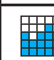
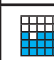
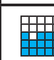
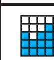
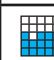
†TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see ALL-D 1 of 27.

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



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

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

Preferred Regimens	
Blinatumomab (CD19 antigen directed)	
Blinatumomab + multiagent therapy	
Inotuzumab ozogamicin (CD22 antigen directed)	
Tisagenlecleucel (CD19 antigen directed; patients <26 years and with refractory disease or ≥2 relapses)	
Brexucabtagene autoleucel (CD19 antigen directed)	
Obecabtagene autoleucel (following therapy that has included TKIs)	
Other Recommended Regimens	
Inotuzumab ozogamicin + mini-hyperCVD	
Inotuzumab ozogamicin + mini-hyperCVD + sequential blinatumumab	
Augmented hyper-CVAD	
Clofarabine	
Clofarabine, cyclophosphamide, etoposide	
MOpAD	
MOpAD regimen/rituximab (for CD20-positive disease)	
FLAG	
FLAG-IDA	
FLAM	
Cytarabine-containing regimens (eg, high-dose cytarabine, idarubicin, IT methotrexate)	
Alkylator combination regimens (eg, etoposide, ifosfamide, mitoxantrone)	
Revumenib (*KMT2A* rearranged)	

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

EVIDENCE BLOCKS FOR REGIMENS FOR RELAPSED OR REFRACTORY T-ALL

Preferred Regimens	
Nelarabine	
Nelarabine + etoposide and cyclophosphamide	
Other Recommended Regimens	
Bortezomib containing regimen	
Daratumumab containing regimen	
High-dose cytarabine containing regimen	
Mitoxantrone, etoposide, cytarabine	
Revumenib (*KMT2A* rearranged)	
Venetoclax containing regimen (eg, HMA [azacitidine or decitabine], hyper-CVAD, nelarabine, mini-hyper-CVD)	

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

ABBREVIATIONS

ADL	activities of daily living
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	antithrombin
AYA	adolescent and young adult
B-ALL	B-cell acute lymphoblastic leukemia
BP-CML	blast phase chronic myeloid leukemia
CAR	chimeric antigen receptor
CBC	complete blood count
CGH	comparative genomic hybridization
CMA	chromosome microarray analysis
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
COG	Children's Oncology Group
CR	complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
DIC	disseminated intravascular coagulation
DLI	donor lymphocyte infusion
ETP	early T-cell precursor
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
H&E	hematoxylin and eosin
H&P	history and physical
HCT	hematopoietic cell transplant
HIV	human immunodeficiency virus
IADL	instrumental activities of daily living
iAMP21	intrachromosomal amplification of chromosome 21
ICC	International Consensus Classification
Ig	immunoglobulin
IT	intrathecal
LDH	lactate dehydrogenase
LFT	liver function test
LL	lymphoblastic lymphoma
LP	lumbar puncture
MDS	myelodysplastic syndrome
MLFS	morphologic leukemia-free state
MNC	mononuclear cell
MPAL	mixed phenotype acute leukemia
MRA	magnetic resonance angiography
MRD	measurable (minimal) residual disease
MRV	magnetic resonance venogram
NGS	next-generation sequencing
NOS	not otherwise specified
NR	no response
PCR	polymerase chain reaction
PD	progressive disease
PEG	pegaspargase
Ph	Philadelphia chromosome
PPI	proton pump inhibitor
PR	partial remission

Continued

ABBREVIATIONS

PT	**prothrombin time**
PTT	**partial thromboplastin time**
qPCR	**quantitative RT-PCR**
RBC	**red blood cell**
REMS	**risk evaluation and mitigation strategy**
RQ-PCR	**real-time quantitative PCR**
RT-PCR	**reverse transcriptase polymerase chain reaction**
RT-qPCR	**quantitative reverse transcriptase polymerase chain reaction**
SAA	**serum asparaginase activity**
SOS	**sinusoidal obstruction syndrome**
SPD	**sum of product of greatest perpendicular diameters**
T-ALL/T-LBL	**T-cell acute lymphoblastic leukemia/lymphoma**
TCR	**T-cell receptor**
TDM	**therapeutic drug monitoring**
TKI	**tyrosine kinase inhibitor**
TLH	**trilineage hematopoiesis**
TLS	**tumor lysis syndrome**
VOD	**veno-occlusive disease**
WBC	**white blood cell**

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Acute Lymphoblastic Leukemia

Discussion

This discussion corresponds to the NCCN Guidelines for Acute Lymphoblastic Leukemia. Last updated: June 27, 2025

Table of Contents

Overview

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.[1] The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year,[2] with approximately 6100 new cases and 1400 deaths estimated in 2025.[3] The median age at diagnosis for ALL is 17 years, with 53.5% of patients diagnosed at <20 years of age.[2] In contrast, 29.6% of patients are diagnosed at ≥45 years of age and only approximately 13.7% of patients are diagnosed at ≥65 years of age.[2] ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults.[1,4]

Risk factors for developing ALL include age >70 years, exposure to chemotherapy or radiation therapy, and genetic disorders, particularly Down syndrome.[5,6] Although rare, other genetic conditions have been categorized as a risk factor for ALL and include Li-Fraumeni syndrome,[7] neurofibromatosis,[8] Klinefelter syndrome,[9-11] Fanconi anemia,[12,13] Shwachman-Diamond syndrome,[14,15] Bloom syndrome,[16] and ataxia telangiectasia.[17]

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

Analyses from the SEER database have shown improvements in survival for pediatric and adolescent and young adult (AYA) patients with 5-year overall survival (OS) rates of 89% and 61%, respectively.[18,19] However, survival rates for adult patients remain low at approximately 20% to 40%.[20-22] Survival rates are especially poor in adult patients who are older, at approximately 20%.[21,23,24] Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA, and adult patients, the trend is nonetheless clear that OS decreases substantially with increased age.[21] The exception is infants <1 year of age, which is an age group that has not seen any improvement in survival over the last 30 years. The 5-year OS in this population is 55.8%[18] (see *Cytogenetic and Molecular Subtypes*). Cure rates for AYA patients with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the adoption of pediatric treatment regimens.[25] AYA patients represent a unique population, because they may receive treatment based on either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. Favorable cytogenetic subtypes, such as *ETV6::RUNX1* ALL and hyperdiploidy, occur less frequently among AYA patients compared with children, whereas the incidence of ALL in high-risk subgroups such as *BCR::ABL* (Philadelphia chromosome [Ph]-positive ALL) or with Ph-like ALL[26] is higher in AYA patients.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia 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 Ph-positive and Ph-negative ALL for both 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 referred to specialized

cancer centers with expertise in the management of ALL for evaluation, diagnosis, and treatment of ALL throughout the continuum of care.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Acute Lymphoblastic Leukemia, an electronic search of the PubMed database was performed to obtain key literature in acute lymphoblastic leukemia published since the previous Guidelines update, using the following search terms: acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia, and T-cell acute lymphoblastic anemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[27] Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice 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 during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

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 (GI) involvement, or chin numbness resulting from cranial nerve involvement, are more suggestive of mature B-cell ALL (B-ALL).[1,28]

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. The presence of an immunophenotypically clonal lymphoblast population of <20% can be considered ALL in appropriate circumstances. 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 ≥1000 circulating lymphoblasts per microliter. The WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease.[31] 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] Lymphoblastic lymphoma was previously categorized with non-Hodgkin lymphoma (NHL) 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 flow cytometric and/or molecular characterization of leukemic clone(s) to facilitate subsequent analysis of MRD.

Identification of specific recurrent genetic abnormalities is critical for disease evaluation, optimal risk stratification, and treatment planning (see *Cytogenetic and Molecular Subtypes*). Subtypes of B-ALL with recurrent genetic abnormalities include the following: hyperdiploidy (51–65 chromosomes); hypodiploidy (<44 chromosomes); t(9;22)(q34;q11.2), *BCR::ABL1*; t(4;11) and other *KMT2A rearranged*, t(v;11q23); t(12;21)(p13;q22), *ETV6::RUNX1*; t(1;19)(q23;p13.3), *TCF3::PBX1*; and t(5;14)(q31;q32), *IL3::IGH*.[31] During the 2016 WHO classification update, two new provisional entities were added to the B-ALL classification: B-lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases or cytokine receptors (*BCR::ABL1*–like ALL or Ph-like ALL)[32-34] and B-lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (iAMP21).[32,35] Two new provisional entities were also added to T-cell ALL (T-ALL): early T-cell precursor (ETP) lymphoblastic leukemia and natural killer (NK) cell lymphoblastic leukemia/lymphoma.[32] The Ph-like ALL, B-ALL with iAMP21 and ETP T-ALL subtypes are no longer considered provisional entities.

With the 2022 WHO classification update, two new entities were added to the B-ALL classification: B-ALL with *TCF3::HLF* fusion and B-ALL with *ETV6::RUNX1*-like features.[31] In addition, multiple subtypes were added to the classification of B-ALL with other defined genetic abnormalities, including B-ALL with rearrangements in *DUX4*, *MEF2D*, or *ZNF384*, B-ALL with *IG::MYC* fusion, and B-ALL with *PAX5alt* or *PAX5* p.P80R.

Presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics), 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 for *BCR::ABL1* in B-ALL, including determination of transcript size (ie, p190 vs. p210). Multiplex gene panels may be considered in the absence of targeted FISH probes. Comprehensive testing by next-generation sequencing (NGS) for other gene fusions is recommended. In cases of aneuploidy or inadequate karyotype, additional assessment may include chromosomal microarray (CMA)/array comparative genomic hybridization

(aCGH). The translocation t(12;21)(p13;q22) is typically cryptic by karyotyping and requires FISH or PCR to be identified.

Immunophenotyping

Immunophenotypic classification of ALL involves flow cytometry to determine the presence of cell surface antigens on lymphocytes. ALL can be broadly classified into three groups based on immunophenotype, which include precursor B-ALL, mature B-ALL, and T-ALL.[1,36] Among children, B-cell lineage ALL constitutes approximately 88% of cases[37]; in adult patients, subtypes of B-cell lineage ALL represent approximately 75% of cases (including mature B-ALL that constitutes 5% of adult ALL), whereas the remaining 25% comprise T-cell lineage ALL.[37,38] Within the B-cell lineage, the profile of cell surface markers differs according to the stage of B-cell maturation, which includes early precursor B-cell (early pre-B-cell), pre–B-cell, and mature B-ALL. Early pre–B-ALL is characterized by the presence of terminal deoxynucleotidyl transferase (TdT), the expression of CD19/CD22/CD79a, and the absence of CD10 (formerly termed *common ALL antigen*) or surface immunoglobulins (Igs). CD10 negativity correlates with *KMT2A* rearrangement and poor prognosis.[39,40] Pre–B-ALL is characterized by the presence of cytoplasmic Igs and CD10/CD19/CD22/CD79a expression[1,28,31,38,41] and was previously termed common B-ALL due to the expression of CD10 at diagnosis. Mature B-ALL shows positivity for surface Igs 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% of blasts expressing CD20.[42] CD20 may be expressed in approximately 50% of B-cell lineage ALL in adults, with a higher frequency (>80%) observed in cases of mature B-ALL.[42,43]

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.[1,28,31,41] CD52 may be expressed in 30% to 50% of T-cell lineage ALL in adults.[1] Combined data from the German Multicenter Study Group for Adult ALL (GMALL) 06/99 study and the GMALL 07/03 study revealed a distribution of T-cell lineage ALL among three subgroups: cortical/thymic (56%), medullary/mature (21%), and early (23%) T-ALL.[36] 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-ALL (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.[44] The mature subtype, on the other hand, often lacks expression of CD1a and frequently is accompanied by T-ALL11 or T-ALL12 rearrangement.

A pivotal study from Zhang et al[45] 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.[46]

Hematologic malignancies related to ALL include acute leukemias with ambiguous lineage (ALALs), such as the mixed phenotype acute leukemias (MPALs). MPALs include bi-lineage leukemias, in which two distinct populations of lymphoblasts are identified, with one meeting the criteria for acute myeloid leukemia (AML). Bi-phenotypic MPAL is defined as a single population of lymphoblasts that expresses markers consistent with B-cell or T-ALL, in addition to expressing myeloid or monocytic markers. Notably, myeloid-associated markers such as CD13 and CD33 may be expressed in ALL, and the presence of these markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis.[31] The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype that may include expression of non-lineage antigens; these are useful in classification, particularly for MPAL. In the 2022 update of the WHO classification of hematolymphoid tumors, ALALs/MPALs were separated into those with defining genetic abnormalities and those defined based on immunophenotyping alone.[47] Lineage assignment criteria were refined to highlight principles of intensity and pattern.

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.[37,48] 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%).[37] Both hyperdiploidy and *ETV6::RUNX1* subtypes are associated

Table 1: Common Chromosomal and Molecular Abnormalities in ALL

Cytogenetics	***Gene***	***Frequency in Adults***	***Frequency in Children***
Hyperdiploidy (>50 chromosomes)	--	7%	25%
Hypodiploidy (<44 chromosomes)	--	2%	1%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	*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.

with favorable outcomes in ALL.[48-50] Emerging evidence suggests t(1;19)(q23;p13.3): *TCF3::PBX1*, *DUX4r,* and *PAX5* P80R are also associated with favorable outcomes in ALL.[51] Ph-positive ALL has been historically associated with poor prognosis; however, the NCCN Panel now considers Ph-positive ALL without *IKZF1* plus and without antecedent chronic myeloid leukemia (CML) as standard risk. Ph-positive ALL is relatively uncommon among childhood ALL (3%), whereas this abnormality is the most common subtype among adults (25%).[37] The frequency of Ph-positive ALL increases with age (10%, patients 15–39 years; 25%, patients 40–49 years; 20%–40%, patients >50 years).[49,52-54] Moreover, children aged 1 to 9 years with Ph-positive ALL have a better prognosis than adolescents with this subtype.[55]

BCR::ABL1–like or Ph–like ALL is a subgroup of B-cell lineage ALL associated with unfavorable prognosis.[33,34] 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%.[33] In adult patients with *BCR::ABL1*–like ALL, the 5-year event-free survival (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%).[34] 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.[56] Genomically, this subtype is typically associated with gene fusions and mutations that activate tyrosine kinase pathways as the common mechanism of transformation. These gene fusions and mutations include *ABL1*, *ABL2, CRLF2, CSF1R, EPOR*, *JAK1, JAK2*, *JAK3, TYK2, PDGFRβ, PDGFRα, FGFR*, *EBF1*, *FLT3*, *IL7R*, *NTRK3*, *PTL2B,* and *SH2B3* genes.[33,56-59] A genomic profiling study found kinase-activating alternations in 91% of Ph-like ALL cases,[57] suggesting potential for *ABL*-class tyrosine kinase inhibitors (TKIs) or other targeted therapies to significantly improve patient outcomes in this subgroup.[60]

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

Other cytogenetic and molecular subtypes are associated with ALL and prognosis. Although not as common, translocations in the *KMT2A* gene [in particular, cases with t(4;11) translocation] are known to have poor prognosis.[25,43] Hypodiploidy, alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone, is associated with poor prognosis and is observed in 1% to 2% of cases.[25,64] Low hypodiploidy (30–39 chromosomes)/near triploidy (60–78 chromosomes) and complex karyotype (≥5 chromosome abnormalities) are also associated with poor prognosis, and occur more frequently with increasing age (1%–3%, patients 15–29 years; 3%–6%, patients 30–59 years; 5%–11%, patients >60 years).[49] Of note, low hypodiploidy is associated with a high frequency of *TP53* alterations.[65-67] Patients with hypodiploid ALL should be considered for germline testing as hypodiploid ALL may be associated with Li-Fraumeni syndrome.[65] In addition, masked hypodiploidy, which results from a doubling of hypodiploid clones, needs to be distinguished from true hyperdiploidy to allow appropriate treatment selection.[68]

In B-ALL, mutations in the Ikaros gene (*IKZF1*) are associated with a poor prognosis and a greater incidence of relapse.[69] *IKZF1* mutations are seen in approximately 15% to 20% cases of pediatric B-ALL[70,71] and at a higher frequency of >75% in patients who also have *BCR::ABL* positive disease.[56,71,72] Incidence in adults with B-ALL is about 25% to 35%[73-76] and about 65% in patients with *BCR::ABL* positive disease.[77,78] 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.[79] The presence of either mutation was indicative of poor prognosis and was independent of conventional risk factors.[56] Both mutations are considered strong independent risk factors for B-ALL and are applicable across a broad range of stratified ALL including the setting of intermediate MRD. *IKZF1* deletions with co-occurring deletions in *CDKN2A, CDKN2B, PAX5*, or *PAR1* in the absence of *ERG* deletion, which are called *IKZF1* plus, as well as those with concomitant 22q11.22 deletions, are especially associated with worse outcomes in pediatric patients with B-ALL. However, *DUX4* rearrangements with *IKZF1* alterations do not confer poor prognosis.[56,72,80]

A genomic analysis of patients treated on the UKALLXII/ES992 trial revealed that patients with *MYC* rearranged ALL had significantly worse outcomes than patients with *DUX4* rearranged (standard-risk) ALL.[51] Patients with PAX5alt, *ZNF384* rearranged, and *MEF2D* rearranged ALL had inferior RFS compared to patients with *DUX4* rearranged ALL, but with a lower level of significance.

The hematopathology review and molecular characterization studies described above allow determination of the WHO[31] and International Consensus Classification (ICC)[81] ALL subtypes and cytogenetic and clinical risk groups.

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 differential, a blood chemistry profile, liver function tests, a disseminated intravascular coagulation panel (including measurements for D-dimer, fibrinogen, prothrombin time, and partial thromboplastin time), and a tumor lysis syndrome (TLS) panel (including measurements for serum lactate dehydrogenase [LDH], uric acid, potassium, phosphate, and calcium). Other recommended tests include hepatitis B/C and HIV evaluations. Individuals of childbearing potential should undergo pregnancy testing and all patients with testes should be evaluated for testicular involvement of disease, including a scrotal ultrasound as indicated; testicular involvement is especially common in cases of T-ALL. Fertility counseling and preservation options should be presented to all patients. CT scans of the neck, chest, abdomen, and pelvis with IV contrast are recommended as indicated by symptoms, and if any extramedullary involvement is suspected, a PET/CT is recommended 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, available at www.NCCN.org). In addition, an echocardiogram or multigated acquisition (MUGA) scan should be obtained for all patients due to the use of anthracyclines as the backbone of nearly all treatment regimens. Assessment of cardiac function is particularly important for patients with prior cardiac history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction, and for patients who are older. An early transplant evaluation and donor search should be strongly considered.

Appropriate imaging studies (eg, CT/MRI scan of the head with contrast) should be performed to detect meningeal disease, chloromas, or central nervous system (CNS) bleeding for patients with major neurologic signs or symptoms at diagnosis. CNS involvement should be evaluated through lumbar puncture (LP) at timing that is consistent with the treatment protocol. Pediatric-inspired regimens typically include LP at diagnostic workup; the NCCN ALL Panel recommends that the first LP be performed at the time of initial scheduled intrathecal (IT) 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 and molecular subtype, presence of CNS disease, and response to induction/consolidation therapy have been identified as important factors in defining risk and assessing prognosis for both adult and childhood ALL.

Prognostic Factors in AYA Patients with ALL

In 1993, a common set of risk criteria was established by the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) at an international conference hosted by the National Cancer Institute (NCI).[82] In this system, two risk groups were designated: those with standard risk and those with high-risk disease. Standard-risk disease was assigned to patients 1 to <10 years of age and with a WBC count <50 × 10^9 cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered to have high-risk disease.[64] It should be noted that despite exclusion from this report, patients <1 year of age should also be considered to have very high-risk disease.[83,84] The POG and CCG have since merged to form the Children's Oncology Group (COG) and subsequent risk assessment has produced additional risk factors, particularly in precursor B-ALL, to further refine therapy. Specifically, in B-ALL, a group identified as having very high-risk disease was defined as having 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)[85]; *BCR::ABL1*–like or Ph-like ALL[86]; *iAMP21*[84]; or inability to achieve remission with induction therapy.[25,64] *KMT2A* rearrangements and a poor response to induction chemotherapy also re-categorized patients into this group.[87-89] Conversely, criteria were refined for lower risk and included hyperploidy, the t(12;21) chromosomal translocation (*ETV6::RUNX1* subtype),[90] or simultaneous trisomies of chromosomes 4, 10, and 17.[64,91] Presence of extramedullary disease and early response to treatment also modified risk. Early marrow response to therapy was a strong positive prognostic factor while the presence of extramedullary disease at diagnosis was correlated with a poorer prognosis. Using the refined risk assessment, four risk categories for B-ALL, designated as low risk, standard risk, high risk, and very high risk, were identified encompassing 27%, 32%, 27%, and 4% of cases, respectively.[64]

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

Historically, the AYA population has been treated on either a pediatric or an adult ALL regimen, depending on referral patterns and the institution. Over the last two decades, several retrospective studies from both the United States and Europe have shown that AYA patients (15–21 years of age) treated on a pediatric protocol have substantially improved EFS compared to same-aged patients treated on adult ALL regimens.[25,50] Comparison of adult and pediatric protocols has shown that adults received lower doses of nonmyelosuppressive chemotherapy and less

intense IT chemotherapy regimens.[92,93] Adult protocols are also more likely to include allogeneic HCT compared to pediatric protocols, but the benefits of HCT in the AYA population have not been sufficiently studied, and the available data include conflicting findings.[94-98] There is clearly a significant difference between the way adults and pediatric patients are treated and this may be a variable in the treatment of AYA patients. Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.

Despite improved outcomes for AYA patients treated on pediatric-inspired regimens versus adult ALL regimens, studies have shown poorer outcomes among patients in the AYA group compared with children <10 years of age.[99] 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*,[100] and a greater incidence of poor-risk cytogenetics including Ph-positive ALL, Ph-like ALL, hypodiploidy, and complex karyotype,[101] and a higher incidence of ETP-ALL.[44,102] Furthermore, the positive prognostic values of the *ETV6::RUNX1* mutation and hyperdiploidy are greater in patients <10 years of age, suggesting that the benefits decline with age.[101] The effects of treatment are also shown to be different in the AYA population compared to the pediatric population. *In vitro* studies showed that ALL cells from children >10 years of age are more resistant to chemotherapy compared to the cells from children <10 years of age.[103] The COG AALL0232 study reported an initial delay in response to induction therapy in AYA patients aged 16 to 30 years compared to patients aged 1 to 15 years.[104] There was a statistically significant reduction in the number of patients in the aged 16 to 30 year cohort who experienced negative end-induction MRD compared to the aged 1 to 15 year 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[105]; however, only 2% of AYA patients enroll in clinical trials compared to the 60% enrollment of pediatric patients.[106] Pediatric patients have been shown to be more adherent to treatment protocols compared to AYA patients,[107] which may be due to greater parental supervision of the treatment and better insurance.[108]

Prognostic Factors in Adults with ALL

Both age and initial WBC count have historically been considered clinically significant prognostic factors in adults with ALL.[36,43] Early prospective multicenter studies defined values for 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.[109,110] Subsequent studies have confirmed the prognostic importance of these clinical parameters, although the cutoff values differed between studies.[36,43]

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.[111] All patients, regardless of Ph status, had received induction therapy followed by intensification (for patients who achieved a complete response [CR] postinduction) with contemporary chemotherapy combination regimens. Patients who achieved a CR after induction received allogeneic HCT (for patients <50 years of age and with human leukocyte antigen [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.[111] Among patients with Ph-negative ALL, those >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 having high-risk disease, whereas all others were classified as having standard-risk disease. The 5-year OS rates for the Ph-negative high-risk and standard-risk subgroups were 29% and 54%, respectively.[111] Further analysis of the Ph-negative population according to risk factors showed that patients could be categorized as having low-risk disease (no risk factors based on age or WBC count), intermediate-risk disease (either age >35 years or elevated WBC count), or high-risk disease (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.[111]

In a subsequent analysis from this MRC UKALL XII/ECOG E2993 study, cytogenetic data were evaluated in approximately 1000 patients.[112] 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).[112] 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%).[112] 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.[113] 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.[112]

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.[114] 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.[114] Moreover, the subgroup (n = 19) of patients with disease with very-high-risk cytogenetic features [identified based on outcomes from the MRC/ECOG study mentioned earlier: presence of t(4;11) *KMT2A* (*MLL)* translocation; t(8;14); complex karyotype; or low hypodiploidy] had substantially decreased 5-year RFS and OS rates (22%, for both endpoints). Analysis by ploidy status was not possible because there were only two cases of low hypodiploidy/near triploidy. The 5-year RFS and OS rates among patients with Ph-positive ALL (n = 36) were 0% and 8%, respectively.[114]

Emerging evidence suggests that ALL with myeloid clonal hematopoiesis mutations also portends high-risk disease.[115]

As previously discussed in *Immunophenotyping* regarding patients with T-ALL, ETP-ALL is associated with poor clinical outcomes even with contemporary treatment regimens. In a study of 239 patients with T-ALL, gene expression profiling, flow cytometry, and single nucleotide polymorphism array analysis were used to identify patients with ETP-ALL.[44] ETP-ALL was associated with a 10-year OS of 19% (95% CI, 0%–92%) compared with 84% (95% CI, 72%–96%) in patients with non–ETP-ALL. The 10-year EFS was similarly poor in patients with ETP-ALL (22%; 95% CI, 5%–49%) compared with patients with non–ETP-ALL (69%; 95% CI, 53%–84%). Inability to achieve remission and hematologic relapse were significantly higher for patients with ETP-ALL ($P < .0001$).[44]

A Group for Research in Adult Acute Lymphoblastic Leukemia (GRAALL) study found that the presence of *RAS/PTEN* mutations and/or *NOTCH1/FBXW7* wild type was associated with poor prognosis and that the favorable prognostic significance of mutations in *NOTCH1/FBXW7* was only seen in the absence of *RAS/PTEN* mutations.[116] Estimated 5-year cumulative incidence of relapse (CIR) was 15% in patients with mutations in *NOTCH1/FBXW7* compared to 50% in those with *NOTCH1/FBXW7* wildtype ($P < .001$). Conversely, in those with *RAS/PTEN* mutations, estimated 5-year CIR was similar in patients with mutations in *NOTCH1/*FBXW7 and in those with *NOTCH1/FBXW7* wildtype (58% vs. 57%; $P = .78$). Estimated 5-year RFS and OS rates for patients with mutations in *NOTCH1/*FBXW7 were 85% and 82% compared to 45% and 37% in those with *NOTCH1/FBXW7* wildtype ($P < .001$ for both RFS and OS). Conversely, in those with *RAS/PTEN* mutations, estimated 5-year RFS (36% vs. 43%; $P = .78$) and OS (49% vs. 32%; $P = .43$) were similarly poor in patients with mutations in *NOTCH1/*FBXW7 and in those with *NOTCH1/FBXW7* wildtype.

NCCN Recommendations for Risk Assessment in ALL

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

The NCI defines the age range for AYA patients as 15 to 39 years. For Ph-positive B-ALL, the AYA patient population is grouped with fit, adult patients <65 years of age. However, additional considerations for the management of ALL in AYA can be found in the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology (available at www.NCCN.org). For Ph-negative B-ALL and T-ALL, the AYA patient population is considered separately from the adult population (defined as age ≥40 years). Given the poor prognosis associated with Ph-positive B-ALL and the wide availability of agents that specifically target the *BCR::ABL* kinase, initial risk stratification for all patients with B-ALL (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 B-ALL (Ph-positive or Ph-negative) and T-ALL, 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 <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 as having high-risk disease if their disease is MRD positive, they have an elevated WBC count (>30 × 10^9/L for B-cell lineage; >100 ×

10^9/L for T-cell lineage), or 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 ≥65 years of age (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, studies in adult patients have demonstrated that WBC counts may lose independent prognostic significance when cytogenetic factors and MRD assessments are considered. Data showing the effect of WBC counts on prognosis in adult patients with ALL are less firmly established than in the pediatric population and likely superseded by MRD quantification after treatment. Therefore, adult patients with ALL may not necessarily be classified as high risk based on high WBC count alone.

Overview of Treatment Phases in ALL Management

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations 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 therapy regimens originally developed by the Berlin-Frankfurt-Münster (BFM) group for pediatric patients (eg, regimens used by COG for children and AYA patients, or the CALGB regimen for adult patients), and the hyperCVAD regimen developed at MD Anderson Cancer Center (MDACC). In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. All treatment regimens for ALL include CNS prophylaxis and/or treatment.

Induction

The intent of initial induction therapy is to reduce tumor burden by clearing as many leukemic cells as possible from the bone marrow. Induction regimens are typically based on a backbone that includes a combination of vincristine, anthracyclines (eg, daunorubicin, doxorubicin), and corticosteroids (eg, prednisone, dexamethasone) with or without L-asparaginase and/or cyclophosphamide.[1,25,36,43,50]

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.[117-121] Some studies from the CALGB group have utilized a 5-drug regimen, which adds cyclophosphamide to the above 4-drug combination.[122] 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.[123,124] The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of dexamethasone into the CNS.[125] 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).[126] 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.[126] 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 hyperCVAD regimen may be considered a less complex treatment regimen compared with the CALGB regimen, and comprises eight alternating treatment cycles with the "A" regimen (hyperCVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and the "B" regimen (high-dose methotrexate and cytarabine).[20,127,128] CNS prophylaxis and/or CNS-directed treatment (which may include IT chemotherapy, cranial irradiation, and/or systemic therapy for patients with CNS leukemia at diagnosis) and maintenance treatment are also used with the hyperCVAD 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, IT chemotherapy (eg, methotrexate, cytarabine, corticosteroids), and/or systemic chemotherapy (eg, high-dose methotrexate, intermediate-/high-dose cytarabine, L-asparaginase).[1,50,125] 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. CNS prophylaxis should be considered for relapsed/refractory disease as well. The role of CNS prophylaxis in the setting of cellular therapy is still being studied.

Consolidation

The intent of postinduction consolidation is to eliminate any leukemic cells potentially remaining after induction therapy, further eradicating residual disease. The postremission induction phase of treatment (but before long-term maintenance therapy) may also be described as intensification therapy. The combination of drugs and duration of therapy for consolidation regimens vary largely among studies and patient populations but can comprise combinations of drugs similar to those used during the induction phase. Methotrexate, cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, vincristine, corticosteroids, and asparaginase are frequently incorporated into consolidation/intensification regimens.[28,36,43,50,120,121]

Hematopoietic Stem Cell Transplantation

As part of postremission consolidative therapy, the decision to proceed with allogeneic 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 disease with evidence of high-risk features (including 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 patients with newly diagnosed disease and patients with relapsed disease who have not yet undergone transplant to facilitate timely donor identification, and ultimately allogeneic transplant if warranted.

Maintenance

The goal of extended maintenance therapy is to prevent disease relapse after postremission induction and consolidation therapy. Most maintenance regimens are based on a backbone of daily 6-MP and weekly methotrexate (typically with the addition of periodic vincristine and corticosteroids) for 2 to 3 years.[25,36,43,50] Maintenance therapy is omitted for patients with mature B-ALL (see the NCCN Guidelines for B-Cell Lymphomas: Burkitt Lymphoma, available at www.NCCN.org), given that long-term remissions are seen early with short courses of intensive

therapy in these patients, with relapses rarely occurring beyond 12 months.[36,129]

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.[130,131] Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.[132-134] The concomitant use of other chemotherapeutic agents such as methotrexate can alter toxicity.[135] 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.[136,137] Diet has been shown to affect absorption of 6-MP.[138,139] 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.[140] 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.[141,142] Heterozygosity at the *TPMT* gene locus occurs in 5% to 10% of the population and has been shown to have intermediate enzyme activity.[140,143,144] Therefore, a 10% to 15% reduction in 6-MP dose is necessary in these patients to prevent toxicity.[145,146] Determination of patient TPMT genotype using genomic DNA is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses.[147-149]

Dose reductions may be necessary if patients have genetic polymorphisms and/or experience hepatotoxicity, whereas dose escalation may be necessary in patients who do not experience 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 >1500 is observed for >6 weeks. In 2014, the U.S. Food and Drug Administration (FDA) approved an oral suspension of 6-MP, which may be more amenable to dose adjustments than the tablet form.[150] This may be especially beneficial for dose adjustment in pediatric patients.[151] Outcomes are better in patients who achieve myelosuppression during maintenance compared with patients who have higher neutrophil counts,[107,152] emphasizing the need for optimal dosing of 6-MP.

Nonadherence also results in undertreatment, particularly in the AYA population. Adherence 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 nonadherence.[135] Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to nonadherence or hypermetabolism.

Targeted Agents

The emergence of targeted therapies for hematologic malignancies, including the treatment of Ph-positive disorders with TKIs, including imatinib, dasatinib, nilotinib, ponatinib, and bosutinib represents an important advancement in ALL therapy.[153-161] Incorporation of TKIs into treatment regimens should include evaluation of clinical pharmacokinetics.[162] Clinicians should be aware of variation among the TKIs relating to absorption from the GI tract. Additionally, histamine-2 antagonists or proton pump inhibitors can affect the bioavailability of some TKIs.

Other targeted agents include an anti-CD20 monoclonal antibody (eg, rituximab) for CD20-expressing B-cell lineage ALL (especially for mature B-ALL).[163,164] 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.[165-167] 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 B-ALL

Initial Treatment in AYA Patients with Ph-Positive B-ALL

Ph-positive ALL is rare in children with ALL, occurring in only approximately 3% of pediatric cases compared with 25% of adult cases.[37] The frequency of Ph-positive ALL among AYA patients ranges from 5% to 25% and increases with age,[112,121] although this subtype is still uncommon relative to the incidence in adults who are older. Historically, children and adolescents with Ph-positive disease had a poorer prognosis compared with patients with Ph-negative B-ALL. However, improvements in the treatment options are closing this gap.

Hematopoietic Cell Transplant

In a retrospective analysis of children with Ph-positive ALL treated between 1986 and 1996 (n = 326) with intensive chemotherapy regimens with or without allogeneic HCT, the 7-year EFS and OS rates were 25% and 36%, respectively.[55] 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.[168] Outcomes with allogeneic HCT from either matched related donors or URDs appeared similar, and HCT improved disease control over intensive chemotherapy alone.[168] 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.

Blinatumomab

Treatment of adults with newly diagnosed Ph-positive ALL was evaluated in a phase II single-group trial using dasatinib chemotherapy-free induction followed by first-line consolidation therapy with blinatumomab.[169] Sixty-three patients, aged 24 to 84 years, were enrolled. At the end of induction, 29% of patients achieved a molecular response, which increased to 60% after 2 cycles of blinatumomab. *ABL1* mutations occurred in six patients who experienced an increase in MRD, however were cleared upon treatment with blinatumomab. Few toxic effects of grade 3 or higher were observed, with CMV reactivation or infection occurring in six patients. As a result of high molecular response, OS and DFS at a median follow-up of 18 months was achieved in 95% and 88% (95% CI, 90–100; 80–97) of patients, respectively.[170] DFS was lower in the setting of *IKZF1* deletions.

The safety and efficacy of blinatumomab in combination with TKIs has been evaluated in the treatment of Ph-positive ALL.[171-173] In a small retrospective study, adults with R/R Ph+ ALL (n = 9) and CML (n = 3) who had previously been treated with one line of chemotherapy and one class of TKIs were treated with the combination blinatumomab and a TKI (ponatinib, dasatinib, or bosutinib). Of the 12 total patients, 75% (9/12)

achieved complete molecular responses with no cardiovascular adverse events.[171]

A single arm phase II study explored the chemotherapy free combination of blinatumomab plus ponatinib in 54 patients ≥18 years of age with newly diagnosed Ph-positive ALL.[174] With a median follow up of 24 months, complete molecular response rate by RT-PCR was 83%, with 98% achieving MRD negativity utilizing a highly sensitive NGS-based assay. Estimated 3-year OS and EFS were 91% and 77%, respectively. Only two patients went on to allogeneic HCT. Three patients had to discontinue blinatumomab secondary to adverse events, while nine patients discontinued ponatinib secondary to adverse events, including but not limited to coronary artery stenosis, cerebrovascular ischemia, and arterial thrombus.

TKIs Combined with HyperCVAD

A phase II study at MDACC evaluated imatinib combined with the hyperCVAD 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.[160] The 3-year OS rate for this regimen was 54%. Among the patients ≤40 years of age (n = 16), a strong trend was observed for OS benefit with allogeneic HCT (3-year OS rate, 90% vs. 33%; *P* = .05).[160] Among patients ≤60 years of age, 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 hyperCVAD and subsequent maintenance therapy in patients with previously untreated Ph-positive ALL (n = 35; median age, 53 years; range, 21–79 years; 31% were >60 years); four of the patients received allogeneic HCT in CR1.[175] The 2-year OS and EFS rates were 64% and 57%, respectively. The efficacy and safety of ponatinib combined with hyperCVAD was examined in patients with Ph-positive ALL (n = 37; aged ≥18 years; median age, 51 years; 12 patients were ≥60 years) in a phase II prospective trial.[154] Of the 32 patients with disease with Ph-positive metaphases at the start of therapy, all 32 patients (100%) achieved an overall complete cytogenetic response. By multiparametric flow cytometry, 35 of 37 patients (95%) achieved MRD negativity after a median of 3 weeks of therapy.[154] However, it is worth noting that only half of the patients ≥60 years of age completed 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 hyperCVAD with a 3-year EFS rate of 70%.[176]

Initial Treatment in Adults with Ph-Positive B-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 <20%.[179]

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%[180,181] and 3-year OS rates of 36% to 44%.[95,182] 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 <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.[183] Among the Ph-positive 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.[183] 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).[183] The incorporation of imatinib in the treatment regimen for Ph-positive ALL has led to improvements in outcomes over chemotherapy alone.[160,179,184]

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.[185-187] 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).[185] 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).[185]

TKIs Combined with HyperCVAD

Studies evaluating TKIs plus hyperCVAD have included both AYA and adult patients.[154,160,175] For discussion of these studies, refer to the previous section (see *Initial Treatment in AYA Patients with Ph-Positive ALL*).

In a phase II trial, the combination of lower intensity mini-hyperCVD, ponatinib, and blinatumomab was evaluated among 12 patients ≥18 years of age with newly diagnosed Ph-positive ALL.[188] Induction consisted of 4 cycles of ponatinib and mini-hyperCVD alternating with mini-methotrexate and cytarabine, with blinatumomab utilized in consolidation. Among patients with evaluable data, 78% achieved complete molecular remission. Three-year OS was 72%. Of note, 50% of patients were in CR at time of enrollment.

TKIs Combined with Multiagent Therapy

Several studies evaluating the efficacy of TKIs combined with multiagent therapy in patients with previously untreated ALL have shown improved outcomes, particularly when treatment was followed by allogeneic HCT.[157,182,184,189,190]

PhALLCON is an ongoing phase III study comparing ponatinib versus imatinib combined with reduced-intensity chemotherapy in 245 patients (median age, 54 years) with newly diagnosed Ph-positive ALL.[191] Treatment was continued for 20 cycles, through induction, consolidation, and post-consolidation. Following 20 cycles, single agent ponatinib or imatinib was continued until disease progression or unacceptable toxicity. Many patients discontinued study treatment, with the most common reasons being the decision to proceed with HCT, adverse events, and lack of efficacy. Seventy-eight patients remained on protocol at the time of data cutoff. Among these 78 patients, MRD negative CR rates were significantly higher among the ponatinib cohort compared to the imatinib cohort (34.4% vs. 16.7%; *P* = .002). Median follow up was 20.1 months. There was also a trend towards improved EFS (hazard ratio [HR] = 0.652; 95% CI, 0.385–1.104) and time to treatment failure with ponatinib (HR = 0.455), though survival data was not mature. Rates of treatment-emergent adverse events of any grade were comparable between the two cohorts. Based on this data, the FDA approved ponatinib with chemotherapy for adult patients with newly diagnosed Ph+ ALL on March 19, 2024.[178]

TKIs Combined with Corticosteroids

The treatment of patients who are older with Ph-positive ALL may pose a challenge, because patients who are older or those with comorbidities may

not tolerate aggressive regimens with multiagent therapy combined with TKIs.[192] Several studies have evaluated outcomes with imatinib induction, with or without concurrent corticosteroids, in adults who are older with Ph-positive ALL. In a study that randomly assigned patients aged 54 to 79 years with Ph-positive ALL (n = 55; median age, 68 years; 94.5% were ≥60 years of age) 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.[193] The median OS was numerically higher (but not statistically significant) among patients who received imatinib induction compared with those randomized to receive chemotherapy induction (23.5 vs. 12 months). However, the incidence of severe adverse events was significantly lower with imatinib induction (39% vs. 90%; *P* = .005), which suggested that induction therapy with imatinib may be better tolerated than chemotherapy in patients in this age group with Ph-positive ALL.[193]

In a study by GIMEMA (LAL-1205), patients with Ph-positive ALL (n = 53 evaluable; median age, 54 years; range, 24–76.5 years) received induction therapy with dasatinib and prednisone.[153] Twelve patients were >60 years of age. 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.[153] *T315I* mutation was detected in 12 of 17 cases of relapsed disease (71%).

In a small phase II study from GRAALL (AFR-09 study), patients ≥55 years of age 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.[194] 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).[194] A phase II study by GIMEMA (LAL0201-B study) also evaluated imatinib combined with corticosteroids in patients >60 years of age with Ph-positive ALL (n = 29 evaluable; median age, 69 years).[195] 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.[195] 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.[153] 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.[153]

A phase II study from GIMEMA (LAL1811) also evaluated the efficacy and safety of ponatinib and prednisone in adult patients aged 27 to 85 years with untreated Ph-positive ALL (n = 42 evaluable; median age, 68 years).[196] Dose reduction of ponatinib was allowed for adverse events. At week 24, the primary endpoint of the study, complete hematologic response, was prematurely reached in 75% of patients. During the study, 75 adverse events were reported; 36 were related to ponatinib.[196]

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 hyperCVAD (arm B) in patients <60 years of age with previously untreated Ph-positive ALL.[197,198] Eligible patients proceeded to HCT (allogeneic or autologous) after induction/consolidation phases. The primary endpoint was noninferiority of the less intensive arm A regimen in terms of MRD response (*BCR::ABL*/*ABL* ratio <0.1% by quantitative PCR) after induction/consolidation. In an early report from this study (n = 118; n = 83 evaluable; median age, 42 years), 52 patients proceeded to HCT (allogeneic, n = 41; autologous, n = 11). The estimated 2-year OS rate was 62%, with no significant difference between patients who received imatinib with vincristine and dexamethasone and those who received imatinib with hyperCVAD (68% vs. 54%, respectively).[197] 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%).[199] 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.[199] Among patients who proceeded to allogeneic HCT or autologous HCT after MRD response, the outcomes were similar in terms of the 5-year post-transplant RFS (48.3% vs. 46.1%) and OS (56.7% vs. 55.1%) rates. This study suggests that outcomes with less intensive chemotherapy regimens (using high-dose imatinib) may offer similar benefits to more intensive imatinib-containing chemotherapy regimens.[199]

In the EWALL-Ph-01 study, induction therapy with dasatinib combined with low-intensity chemotherapy (vincristine and dexamethasone) was evaluated in patients ≥55 years of age 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::ABL1*/*ABL1* ratio ≤0.1%) was observed in 65% of patients.[200] 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.[200] At 5 years, the cumulative incidence of relapse was 54% (95% CI, 42%–66%). These studies suggest that the use of TKIs in combination with less intensive therapies (eg, corticosteroids with or without vincristine) may provide an alternative treatment option for patients who are older 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.[201] The median time after HCT until initiation of imatinib was short, at 27 days (range, 21–39 days). Molecular remission (by PCR) was observed in 46% of patients (6 of 13) prior to HCT and 80% (12 of 15) after HCT. Two patients died after hematologic relapse and one patient died due to acute respiratory distress syndrome approximately 1 year post-HCT. At a median follow-up of 1.3 years, 12 patients (80%) were alive without detectable disease.[201] 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).[202] 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.[202] 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.[202]

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.[203] 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.[203] 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%).[203] 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 achieved MRD negativity (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%; $P = .037$).[203] 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 B-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 adults with relapsed disease have reported a median OS of 4.5 to 6 months, and a 5-year OS rate of 3% to 10%.[204-207] 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 >2 years after frontline therapy had significantly higher 5-year OS rates than the groups

with disease that relapsed within 1 to 2 years or within 1 year of frontline therapy (31% vs. 15% vs. 2%; $P < .001$).[205] Similarly, in the MRC UKALL XII/ECOG E2993 trial, patients with disease that relapsed >2 years after initial diagnosis and frontline therapy had a significantly higher 5-year OS rate than those whose disease relapsed within 2 years (11% vs. 5%; $P < .001$).[204] In the pre-imatinib era, patients with Ph-positive B-ALL who experienced relapse after frontline therapy had dismal outcomes; subgroup data from the large, prospective trials LALA-94 and MRC UK XII/ECOG E2993 showed a median OS of 5 months and a 5-year OS rate of 3% to 6% among patients subsequently treated for relapsed Ph-positive B-ALL.[204,206]

Hematopoietic Cell Transplant

Treatment options are extremely limited for patients with Ph-positive B-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.[208,209] Studies that include donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in those who experience relapse after allogeneic HCT have reported little to no benefit, though it has been suggested that this is due to excessively high leukemic burden.[210,211] 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.[212-214] Moreover, case reports have described using newer TKIs, such as dasatinib and nilotinib, along with DLI to manage relapse after allogeneic HCT.[215,216] Although these approaches are promising, only limited data are available. Evidence from prospective studies is needed to establish the role of DLI, with or without TKIs, in the treatment of relapsed disease.

Tyrosine Kinase Inhibitors

The emergence of resistance poses a challenge for patients who experience relapse 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.[217-219] The former has been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy.[220,221] Moreover, *ABL* kinase domain mutations may be present in a small group of patients not yet treated with imatinib even before initiation of any TKI therapy.[222,223]

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.[224-227] 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.[225,227] A study showed that among patients with ALL treated with imatinib and who did not receive routine prophylactic IT therapy or cranial irradiation, 12% developed CNS leukemia.[226] 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 IT therapy with or without cranial irradiation.[224,226]

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.[158,228-230] In addition, dasatinib has better CNS penetration than imatinib, and therefore may have advantages in preventing CNS relapse. Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL that is resistant to imatinib treatment.[231-233] 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[232]; 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).[232] These differences in outcomes between the dosing arms were not statistically significant.

Dasatinib in combination with the hyperCVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was investigated in a phase II trial that included patients with Ph-positive relapsed ALL (n = 19) and lymphoid blast phase (BP) CML (n = 15).[234] An overall response rate (ORR) of 91% was obtained, with 26 patients (84%) achieving complete cytogenetic remission, 13 patients (42%) achieving a complete molecular response, and 11 patients (35%) achieving a major molecular response. There were nine patients who went on to receive allogeneic HCT, including two patients with ALL. In the patients with relapsed ALL, 30% remained in complete remission at 3 years with a 3-year OS of 26%. At the median follow-up of 52 months (range, 45–59 months), two patients (11%) with ALL were still alive.

Bosutinib, a second-generation TKI that acts as a dual inhibitor of *BCR::ABL* and SRC family kinases,[235,236] 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 disease resistant to prior TKI treatment based on an open-label, multicenter phase I/II trial.[236] Efficacy and safety analyses of bosutinib monotherapy included patients with advanced leukemia [AP CML (n = 79), BP CML (n = 64), or ALL (n = 24)] who were previously treated with at least one TKI.[237,238] Of the 22 evaluable patients with ALL, two patients (9%) attained or maintained a confirmed overall hematologic response by 4 years.[237] Common overall treatment-related adverse events reported in patients with advanced leukemia included diarrhea (74%), nausea (48%), and vomiting (44%).[237,238]

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.[239] 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.[240] 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%.[240] 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,[240] 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*.[219,229,241,242] 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.[243] (See *Principles of Systemic Therapy* in the algorithm for TKI treatment options for *Treatment Options Based on BCR::ABL1 Mutation Profile*).

Asciminib plus Dasatinib

Asciminib is an allosteric inhibitor of *BCR::ABL1* currently FDA approved for the treatment of chronic phase (CP) Ph-positive CML with *T315I* mutation or CP Ph-positive CML without *T315I* mutation that has previously been treated with TKIs. In a phase I study including 24 patients with Ph-positive ALL, the combination of asciminib with dasatinib was evaluated.[244] Patients received a 28-day course of induction consisting of asciminib, dasatinib, and prednisone, followed by asciminib and dasatinib indefinitely or until allogeneic HCT. Eighty-four percent of patients achieved complete hematologic remission at day 28. By day 84, the complete hematologic remission rate had improved to 100%, with 89% achieving MRD negativity by multicolor flow cytometry.

Blinatumomab

In December 2014, the FDA approved blinatumomab for the treatment of relapsed or refractory Ph-negative precursor B-ALL (see *Treatment of Relapsed Ph-Negative ALL* for a detailed discussion of blinatumomab). In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-ALL (Ph-negative and Ph-positive). A follow-up, open-label, single-arm, multicenter, phase II study evaluated the efficacy and safety of blinatumomab in patients with R/R Ph-positive ALL who experienced disease progression after imatinib and at least one second- or third-generation TKI (n = 45).[245] During the first 2 cycles of blinatumomab, 36% achieved complete remission or complete remission with partial hematologic recovery, and 88% of these responders achieved a complete MRD response.[245] Notably, responses were independent of *T315I* mutation status (see *Initial Treatment in AYA Patients with Ph-Negative ALL* for a discussion of studies related to blinatumomab and chemotherapy-resistant MRD).

In a phase II study that included 14 patients with R/R Ph-positive ALL, the chemotherapy free combination of blinatumomab plus ponatinib was evaluated.[246] Patients received up to 5 cycles of ponatinib and continuous IV blinatumomab, followed by single agent ponatinib. Among patients with R/R disease with evaluable data, 92% achieved an overall response, with 79% achieving a complete molecular response.

Inotuzumab Ozogamicin

Following the generation of encouraging single-agent phase II data,[247] a randomized study was conducted comparing inotuzumab ozogamicin (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%; $P < .001$).[248] Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with Ph-positive leukemia. The overall incidence of severe adverse events was similar across treatment arms, with a higher incidence of hepatic sinusoidal obstruction syndrome (SOS), observed in the InO 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; $P = .005$).[248] In August 2017, InO received full approval from the FDA for the treatment of R/R precursor B-ALL.

CAR T Cells

Currently, HCT 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.[249] Pre-treatment with CAR T cells has served as a bridge for transplant, and patients who were formerly unable to be transplanted due to poor remission status achieve a CR and ultimately proceed to transplantation. CAR T-cell therapy relies on the genetic manipulation of a patients' T cells to engender a response against a leukemic cell-surface antigen, most commonly CD19[250] (see *Treatment of Relapsed Ph-Negative ALL* for a detailed discussion of CAR T cells). CAR T-cell therapy with 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 <26 years of age with R/R precursor B-ALL. In October 2021, the FDA approved the second CAR T-cell therapy for adults with relapsed or refractory B-ALL: brexucabtagene autoleucel. This treatment is the first CAR T-cell therapy for patients ≥26 years of age in this setting. The 3rd CAR T-cell therapy for adults with relapsed or refractory B-ALL, obecabtagene autoleucel, was approved on November 8, 2024.

NCCN Recommendations for Ph-Positive B-ALL

AYA and Adult Patients with Ph-Positive B-ALL

The Panel recommends that Ph-positive B-ALL AYA and adult patients <65 years of age and no substantial comorbidities be treated in a clinical trial, when possible. In the absence of an appropriate clinical trial, other recommended induction therapy options include would comprise multiagent therapy, blinatumomab, or corticosteroids blinatumomab or hyperCVAD combined with a TKI. Prior to initiation of blinatumomab, cytoreduction to a peripheral WBC count of <10 x 10^9/L is recommended, which can frequently be achieved with a TKI plus corticosteroid.[170] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. However, the Panel notes that not all TKIs have been studied within the context of each regimen, and there are limited data for bosutinib in Ph-positive B-ALL. Use of a specific TKI should account for anticipated or prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. The PhALLCON study suggests improved MRD responses with ponatinib compared to imatinib.[191] Imatinib use in first-line treatment should be restricted to patients who cannot tolerate broader acting TKIs. Additional induction options that may be useful in certain circumstances include a TKI in combination with either a corticosteroid or with vincristine and dexamethasone.

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 and adults <65 years without substantial comorbidities, there are data to support the benefit of rituximab in addition to multiagent therapy (excluding immunotherapy) in the setting of CD20-positive disease.

For AYA and adult (<65 years of age) patients experiencing a marrow CR after initial induction therapy, an MRD assessment should be performed prior to consideration of consolidation therapy (see *NCCN Recommendations for MRD Assessment*). Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for any patient with ALL with MRD positivity. *BCR::ABL1* qPCR positivity may reflect persistence in the myeloid compartment. Where feasible, flow sorting to isolate myeloid versus lymphoid cells for FISH/qPCR studies and/or NGS MRD may help to resolve. Of note, the presence of the Philadelphia chromosome in the myeloid compartment does not necessarily imply a diagnosis of CML with lymphoid blast transformation.

Adequate count recovery per protocol is necessary before transitioning to post remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow up for MRD may be warranted. Myelosuppression secondary to TKI should also be assessed, and consideration should be made for dose reduction.

Consolidation therapy options in the setting of MRD positivity or negativity may include blinatumomab combined with a TKI,[170,246] continuation of multiagent therapy or corticosteroid combined with a TKI, or single agent TKI. In cases of MRD positivity, using an alternative and more broadly acting TKI is recommended. *ABL1* kinase domain mutation testing is also recommended, though mutations associated with asciminib resistance can occur outside of the kinase domain. Relevant *BCR::ABL1* mutations should be considered as outlined in the algorithm table titled, *Treatment Options Based on BCR::ABL1 Mutation Profile*. Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs; however, it is associated with a high frequency of serious vascular events, such as stroke, heart attack, or tissue ischemia (see package insert for more details).

Allogeneic HCT is another consolidation option in the setting of MRD negativity for appropriate candidates. Many variables determine eligibility for allogeneic HCT, including donor availability, depth of remission, comorbidities, and social support.[251] The optimal time for a patient to receive allogeneic HCT is unclear; however, proceeding to allogenic HCT with MRD is not optimal. In AYA patients ≤21 years of age, emerging data suggest that allogeneic HCT may not confer an advantage over multiagent combined with TKIs.[252]

Following consolidation therapy, repeat MRD assessment is recommended (see *NCCN Recommendations for MRD Assessment*). If MRD negativity is achieved following consolidation, options include maintenance TKI or allogeneic HCT followed by post-HCT TKI. TKI should be started as soon as feasible post-transplant. Although the optimal duration of post-transplant or maintenance TKI is unknown, TKI should be continued for at least 2 years post-transplant. Sequential MRD assessments should be considered for patients who have achieved a complete molecular remission (undetectable levels). The frequency may be increased if MRD levels are detectable or for those discontinuing TKI.

For patients receiving a maintenance 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.[146] 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*).

In the setting of persistent, progressive, or emergent MRD, marrow progression, or development of extramedullary disease following consolidation therapy, *ABL1* kinase domain mutation testing is recommended, followed by treatment for R/R disease (see *Patients with Relapsed/Refractory Ph-Positive B-ALL*). As note previously, mutations associated with asciminib resistance can occur outside of the kinase domain.

Adult Patients ≥65 Years of Age with Ph-Positive B-ALL

For adult patients with Ph-positive B-ALL ≥65 years of age or with substantial comorbidities, the Panel recommends treatment in a clinical trial, when possible. In the absence of an appropriate clinical trial, other recommended therapies can be broken down into low and moderate intensity categories. Low intensity induction therapy options include TKI in combination with either blinatumomab, a corticosteroid, or vincristine and

dexamethasone. A moderate intensity induction therapy option is TKI combined with mini-hyperCVD rather than hyperCVAD. Treatment regimens should include adequate CNS prophylaxis for all patients, and a given treatment protocol should be followed in its entirety. Although the age cutoff indicated in the guidelines has been set at 65 years, it should be noted that chronologic age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as age, performance status, end-organ function, and end-organ reserve. Dose modifications for patients age and performance status should also be considered.

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

Patients with Relapsed/Refractory Ph-Positive B-ALL

Mutation testing for the *ABL1* kinase domain is recommended in patients with Ph+ B-ALL that have experienced relapse after or have disease 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.[243] If not administered during initial induction, TKIs (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) are recommended options for patients with R/R Ph+ B-ALL. The PhALLCON study suggests improved MRD responses with ponatinib compared to imatinib.[177]

For second- and third-generation TKIs, relevant *BCR::ABL1* mutations should be considered as outlined in the algorithm table titled, *Treatment Options Based on BCR::ABL1 Mutation Profile*.

For all patients with R/R Ph-positive B-ALL, participation in a clinical trial is preferred. In the absence of an appropriate trial, patients may be considered for second-line therapy with an alternative TKI (ie, different from the TKI used as part of induction therapy) alone, TKI combined with systemic therapy regimens as previously discussed in the frontline setting, or TKI combined with corticosteroids (especially for patients who are older who may not tolerate multiagent combination therapy). Other options include asciminib plus dasatinib or blinatumomab or InO with or without a TKI. Compared to standard care, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic SOS, and increased risk of post-HCT non-relapse mortality.[253] Although there are limited data, it is recommended to wait at least 4 weeks from InO monotherapy and the start of conditioning for allogeneic HCT to minimize risk of SOS. SOS has been shown to occur less frequently when less alkylators are used as part of the conditioning regimen.[254]

Brexucabtagene autoleucel and obecabtagene autoleucel are CAR-T cell therapy options for AYA and adult patients with R/R Ph-positive B-ALL following therapy that has included TKIs. Tisagenlecleucel is also an option for patients <26 years of age and with refractory disease or ≥2 relapses and following therapy that has included 2 TKIs.

If patients who have not yet undergone transplant 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. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT. In the global registration trial, estimated 3-year RFS rates were 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients

proceeding to HCT.[255] Further study will be required before conclusive recommendations can be made. In the absence of an appropriate clinical trial, for patients with T-ALL that is refractory to TKIs, regimens for R/R Ph-negative ALL can be considered. (*See Treatment of Relapsed Ph-Negative ALL*).

Management of Ph-Negative ALL

Initial Treatment in AYA Patients with Ph-Negative ALL

The AYA population with ALL can pose a unique challenge given that patients may be treated with either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. The NCCN Guidelines for ALL are intended to apply to AYA patients treated in an adult oncology setting. For recommendations and discussion regarding the treatment of AYA patients with ALL in a pediatric oncology setting, see the NCCN Guidelines for Pediatric ALL (available at www.NCCN.org).

Retrospective analyses based on cooperative group studies from both the United States and Europe have consistently shown the superior outcomes for AYA patients (age range, 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.[92,93,121,256,257] In a retrospective comparative study that analyzed outcomes of AYA patients (age range, 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.[121] 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.[121] Given the success seen with multiagent intensive therapy regimens for pediatric patients with ALL, several clinical trials have evaluated pediatric-inspired regimens for the AYA patient population.

Hematopoietic Cell Transplant

For AYA patients with Ph-negative ALL in first CR, allogeneic HCT may be considered for high-risk cases—particularly for patients with disease that is MRD positive any time after induction; or patients with elevated WBC counts; or patients with B-ALL and poor-risk cytogenetics [eg, hypodiploidy, *KTM2A (MLL)* rearrangement] at diagnosis. A large multicenter trial (LALA-94 study) evaluated the role of postinduction HCT as one of the study objectives in adolescent and adult patients with ALL receiving therapy for previously untreated ALL (n = 922; median age, 33 years; range, 15–55 years).[95] Patients were stratified into four risk groups: 1) Ph-negative standard-risk disease [defined as achievement of CR after 1 course of chemotherapy; absence of CNS disease; absence of t(4;11), t(1;19), or other 11q23 rearrangements; WBC count $<30 \times 10^9$/L]; 2) Ph-negative high-risk ALL (defined as patients with non–standard-risk disease and without CNS involvement); 3) Ph-positive ALL; and 4) evidence of CNS disease. After induction therapy, patients with Ph-negative high-risk ALL were eligible to undergo allogeneic HCT if a matched sibling donor was available; those without a sibling donor were randomized to undergo autologous HCT or chemotherapy alone.[95] 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%).[95] 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%.[95] 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).[258] Based on intent-to-treat analysis of data from patients with Ph-negative high-risk disease, no significant advantage was observed in a donor versus no-donor comparison of median DFS (21 vs. 38 months), median OS (32 vs. 67 months), 5-year DFS rate (37% vs. 46%), or 5-year OS rate (40% vs. 49%). In addition, when the analysis was conducted based on the actual postremission treatment received, no significant differences were noted between treatment arms for 5-year DFS rates (50% for allogeneic HCT; 55% for autologous HCT; and 54% for chemotherapy alone).[258]

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 range, 15–59 years).[96] In this study, high risk was defined as ≥35 years of age; time to CR >4 weeks from induction; elevated WBC counts (>30 × 10^9/L for B-ALL; >100 × 10^9/L for T-ALL); or the presence of Ph chromosome. All other patients were considered to have standard-risk disease. 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 disease (62% vs. 52%; P = .02) but not for those with Ph-negative high-risk disease (41% vs. 35%).[96] 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 disease, 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 disease (24% vs. 49%; P < .001) and those with high-risk disease (37% vs. 63%; P < .001).[96] 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 adults 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.[259] In the donor group, the non-relapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.[259]

As evidenced by the previously described studies, matched sibling HCT has been established as a valuable treatment strategy for patients with both standard and high-risk Ph-negative ALL, but subsequent studies have examined the role of URD transplants in high-risk Ph-negative ALL. In a retrospective analysis of 169 patients who underwent URD HCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57%) had multiple risk factors. The 5-year survival rate was 39%, which is higher than survival rates reported in studies of patients with high-risk disease receiving chemotherapy alone.[260] 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 patients <35 years of age and patients >35 years of age, suggesting that URD transplants may be an option for patients who are older. In a follow-up retrospective study by the same group, RIC was evaluated to lower treatment-related mortality.[261] RIC conditioning most commonly comprised busulfan (≤9 mg/kg), melphalan (150 mg/m^2), low-dose total body irradiation (TBI) (<500 cGy single dose or <800 cGy fractionated), or fludarabine plus TBI of 200 cGy. RIC is more prominent in the treatment of patients who are older; 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.[261] 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%).[261]

A systematic review and meta-analysis of published randomized trials on post-remission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HCT in first CR (RR, 0.88; 95% CI, 0.80–0.97) compared with autologous HCT or chemotherapy.[262] 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.[262] Autologous HCT in first remission was not shown to be beneficial relative to chemotherapy in several large studies and meta-analyses.[95,96,262,263]

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.[264] The treatment regimen comprised induction (vincristine, doxorubicin, prednisone, L-asparaginase, and high-dose methotrexate), triple IT 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.[264] Adverse events included one death from sepsis (during induction), pancreatitis in nine patients (12%; including 1 death), osteonecrosis in two patients (3%), thrombosis/embolism in 14 patients (19%), and neutropenic infection in 23 patients (31%).[264] 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%).[265] A phase II successor trial was initiated to determine whether PEG could be substituted for L-asparaginase in this regimen.[266] A high frequency of

asparaginase toxicities precipitated reverting to L-asparaginase during induction and a dose-reduction of PEG during consolidation. After 4 weeks, the CR rate was 89%, and with a median follow-up of 39 months, the estimated 3-year DFS and OS rates were 73% and 75%, respectively.[266] 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.

MSKCC ALL Regimen Based on CCG-1882 Regimen

The MSKCC 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 18 and 60 years of age with newly diagnosed ALL (n = 51).[267,268] 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 had Ph-negative disease) 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 ≥4 weeks. This deviated from the pediatric protocol to account for the difference in drug enzymatic activity in adults. Study data suggest that adaptation of the pediatric regimen to the adult population may be feasible with modifications to reduce toxicity.

CALGB 10403 Regimen

A multicenter phase II Intergroup study (CALGB 10403) was conducted to evaluate a pediatric-inspired regimen in the treatment of AYA patients with Ph-negative ALL. One of the study objectives was to compare the outcomes of patients treated in this trial with those of a similar group of patients (in regard to age and disease characteristics) treated by pediatric oncologists in the COG trial (AALL-0232). The treatment protocol included a 4-drug induction regimen with IT cytarabine and IT methotrexate, consolidation, interim maintenance, delayed intensification, maintenance (for 2–3 years), and radiotherapy (for patients with testicular or CNS disease or those with T-ALL). Results from 295 patients with evaluable data (median age, 24 years; range 17–39 years) reported two post-remission deaths and 3% overall treatment-related mortality.[269] The median EFS was 78.1 months (95% CI, 41.8 months – NR) and the 3-year EFS rate was 59% (95% CI, 54%–65%). The estimated 3-year OS rate was 73% (95% CI, 68%–78%).[269] It was also noted that post-induction MRD positivity, Ph-like gene expression signatures, and obesity were associated with worse treatment outcomes.[269]

COG AALL0434 Regimen

Nelarabine is a nucleoside metabolic inhibitor and a prodrug of ara-G, approved for the treatment of patients with T-ALL with disease that has not responded to or that has relapsed after at least 2 chemotherapy regimens. The randomized phase III COG study (AALL0434) evaluated the safety of nelarabine as part of frontline therapy, using the augmented BFM chemotherapy regimen, with or without nelarabine, and showed that the toxicity profiles were similar between patients with high-risk T-ALL who received nelarabine (n = 47) and those who did not (n = 47).[270] 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.[270]

Results from the efficacy phase of this study evaluated data from 1895 patients with newly diagnosed T-ALL and T-LL.[271] Patients were randomized to receive escalating dose methotrexate without leucovorin rescue and PEG or high-dose methotrexate with leucovorin rescue. Patients with intermediate and high-risk T-ALL and T-LL all received prophylactic or therapeutic cranial irradiation and were randomized into arms with or without nelarabine (650 mg/m^2/day). The 4-year DFS rate for patients with T-ALL in the nelarabine arm (n = 323) versus those who did not receive nelarabine (n = 336) was 88.9% ± 2.2% and 83.3% ± 2.5%, respectively (*P* = .0332).[271] Compared to the high-dose methotrexate and nelarabine arm, use of escalating-dose methotrexate and nelarabine appeared to enhance the 4-year DFS rates.[271] 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.[272]

A single-arm phase II study from the MDACC evaluated the efficacy of hyperCVAD plus nelarabine as frontline therapy in adults with T-ALL (n = 23).[273] 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.[273] 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.[274] These studies suggest that for patients with T-ALL, the addition of nelarabine to frontline therapy may be a promising approach.

HyperCVAD with or without Rituximab or Blinatumomab

The hyperCVAD regimen constitutes another commonly used ALL treatment regimen for adults. A phase II study from MDACC evaluated hyperCVAD in adolescents and adults with previously untreated ALL (n = 288; median age, 40 years; range, 15–92 years; Ph-positive in 17%).[20] The median OS for all patients was 32 months and the 5-year OS rate was 38%, with a median follow-up of 63 months. Among the patients with Ph-negative ALL (n = 234), the 5-year OS rate was 42%.[20] Among patients who experienced a CR (92% of all patients), the 5-year CR duration rate was 38%.[20] Death during induction therapy occurred in 5% of patients, and was more frequent among patients ≥60 years of age. The 5-year OS in patients ≥60 years of age was 17%.[20] A subsequent retrospective review from the same institution suggested that this may be related to higher rates of death in remission (34%) relative to patients <60 years of age (7%).[275]

Based on retrospective analyses of data from adults with B-ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on >20% of blasts) was found to be associated with adverse outcomes measured by a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.[42,276] 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 patients with newly diagnosed Ph-negative B-lineage ALL (n = 282; median age, 41 years; range, 13–83 years).[164] Among the subgroup of patients with CD20-positive ALL who were treated with hyperCVAD combined with rituximab, the 3-year CR duration and OS rates were 67% and 61%, respectively. In addition, among patients <60 years of age with CD20-positive disease, modified hyperCVAD 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 hyperCVAD regimen without rituximab.[164] No significant differences in outcomes with the addition of rituximab were noted for the subgroup of patients with CD20-negative disease. Notably, patients ≥60 years of age 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 patients ≥60 years of age may relate to anthracycline intensification as opposed to rituximab.[277]

Another phase II study from MDACC evaluated hyperCVAD and sequential blinatumomab in patients with newly diagnosed Ph-negative B-ALL (n = 38; median age, 37 years).[278] Treatment consisted of 4 cycles of hyperCVAD followed by 4 cycles of blinatumomab consolidation. Maintenance consisted of 15 cycles of alternating POMP for 3 cycles and blinatumomab for 1 cycle. Three-year RFS was estimated at 73%, with no relapses >2 years from the start of therapy. Grade 3 CRS occurred in one patient (3%), while four patients (11%) had grade 3 neurological events related to blinatumomab.

Blinatumomab

Blinatumomab has shown promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multicenter, single-arm, phase II study, Topp et al[279] evaluated the efficacy of blinatumomab in patients with MRD-positive Ph-negative B-ALL (n = 21; age range, 20–77 years). Patients were considered to have MRD-positive disease if they had never achieved MRD negativity before blinatumomab or had experienced a hematologic CR with MRD ≥10^{-4}. After blinatumomab treatment, 16 of 20 patients with evaluable data were determined to have achieved MRD negativity at a detection threshold of 10^{-4}.[279] After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.[280] Gökbuget et al[281] examined the efficacy of blinatumomab in an expanded cohort (n = 116) using a higher threshold for MRD positivity (hematologic CR with MRD ≥10^{-3}). After one 28-day cycle of blinatumomab, 88 of 113 patients with evaluable data achieved a complete MRD response, and the RFS rate at 18 months was 54%.[281] 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 patients with MRD-positive disease. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in patients with R/R B-precursor ALL.[282-284] 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 B-ALL* for discussion of studies related to blinatumomab use in R/R B-ALL).

Initial Treatment in Adults with Ph-Negative ALL

Hematopoietic Cell Transplant

Studies evaluating HCT in first CR for AYA patients with Ph-negative ALL have generally been inclusive of adult patients and therefore have been discussed previously (see *Initial Treatment in AYA Patients with Ph-Negative ALL*). More aggressive therapies are being considered for patients who are older or less fit. A retrospective study of 576 adults ≥45 years of age compared RIC or MAC allogeneic HCT from HLA-matched siblings.[187] Patients who received RIC (n = 127) versus MAC (n = 449) showed no statistically significant difference in leukemia-free survival (P = .23; HR, 0.84), thereby supporting the incorporation of more aggressive treatments for this population.[187]

CALGB 9111 Regimen

The CALGB 9111 study evaluated the impact of adding granulocyte colony-stimulating factor (G-CSF) after intensive therapy (CALGB 8811 Larson regimen; a 5-drug induction regimen comprising vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide) on neutrophil recovery in adults with ALL (n = 198; median age, 35 years; range, 16–83 years).[285] 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.[285] Among the 41 patients ≥60 years of age randomized to G-CSF (n = 21) or placebo (n = 20), G-CSF use was associated with lower induction mortality (10% vs. 25%); however, this did not 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* = .1). For the entire group ≥60 years of age, median OS was improved to 12 months, but 3-year OS remained poor at 17%.[285]

GRAALL- 2014 Regimen

Studies involving the GRAALL-2005 regimen investigated the addition of rituximab for CD20-positive disease in both AYA and adult patients.[286,287] 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.[288] 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 ≥55 years of age.[288]

The GRAALL-2014 study aimed to improve outcomes of the GRAALL-2005 by reducing chemotherapy intensity in patients aged 45 to 59 years and modifying the indication for HCT to only a post-induction MRD $\geq 10^{-3}$ and/or a post-consolidation MRD $\geq 10^{-4}$.[289] Compared to GRAALL-2005, induction death rate was significantly reduced in GRAALL-2014 among patients aged 45 to 59 years (3% vs. 11%; *P* = .001). CR rate was also higher in this age group in GRAALL-2014 (92% vs. 86%; *P* = .05), attributed to a higher need for second induction due to the reduced-intensity of first induction. In light of MRD-based HCT indication, fewer patients proceeded to HCT on GRAALL-2014, leading to an increase in 3-year CIR (35% vs. 28%; *P* = .01), though a reduction in 3-year cumulative incidence of transplant related mortality (5% vs. 11%; *P* < .001) and OS (71% vs. 64%; *P* = .002).

In the phase II GRAALL-2014 T ATRIALL study of adult patients with T-ALL, patients were deemed to be at high risk based on the presence of *RAS/PTEN* alterations or lack of *NOTCH1/FBXW7* mutations.[116,290] Patients in the high risk group were offered 2 cycles of nelarabine combined with etoposide and cyclophosphamide during consolidation and another 3 cycles during maintenance, though some received standard of care without nelarabine.[290] Following 1 cycle, patients with MRD $\geq 10^{-3}$ and/or post-consolidation MRD $\geq 10^{-4}$ were eligible for HCT. When censored at time of transplant, the addition of nelarabine was associated with a significant reduction in CIR (*P* = .045) and a non-significant prolongation of DFS (*P* = .075). The benefit of nelarabine was similar in patients in the high-risk group who were not eligible for transplant, with a significant reduction in CIR (*P* = .045) and a non-significant prolongation of DFS (*P* = .06). While patients with ETP-ALL did not benefit from nelarabine, the addition of nelarabine in patients with non-ETP ALL led to significant improvements in both CIR (*P* = .025) and DFS (*P* = .048).

MSKCC ALL Regimen Based on CCG-1882 Regimen

Studies evaluating MSKCC ALL regimen have included both AYA and adult patients.[267,268] For discussion of these studies, refer to the previous section (see *Initial Treatment in AYA Patients with Ph-Negative ALL*).

HyperCVAD with or without Rituximab or Blinatumomab

Studies evaluating hyperCVAD with or without rituximab or blinatumomab have included both AYA and adult patients.[20,164,278] For discussion of these studies, refer to the previous section (see *Initial Treatment in AYA Patients with Ph-Negative ALL*).

A separate phase II MDACC study evaluated the use of hyperCVAD with or without blinatumomab in patients ≥60 years of age with newly diagnosed Ph-negative B-ALL.[291] Treatment consisted of 4 cycles of mini-hyperCVD followed by 4 cycles of blinatumomab consolidation. Maintenance therapy consisted of 3 cycles of POMP alternating with 1 cycle of blinatumomab for a total of 12 cycles. Five-year PFS was 44%. The most common grade 3–4 events were hematological. Six patients (8%) developed SOS, four of which were fatal.

Mini-hyperCVD plus Venetoclax

Venetoclax is a selective BCL2 inhibitor that is currently FDA approved for treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) as well as in combination with hypomethylating agents (HMAs) or low-dose cytarabine for treatment of newly diagnosed AML in those ≥75 years or those with comorbidities precluding intensive induction chemotherapy. It has also been studied in the treatment of R/R T-ALL.

An ongoing phase Ib/II study is investigating the combination of venetoclax with mini-hyperCVD in the treatment of patients ≥55 years or ≥50 years with BMI ≥35 kg/m^2 with newly diagnosed Ph-negative B-ALL or T-ALL (n = 30; median age, 68 years).[292] Patients received hyperCVAD along with venetoclax (with ramp up for cycle 1) for 21 days out of a 28-day cycle for up to 8 cycles or until allogeneic HCT, followed by venetoclax in addition to POMP maintenance for up to 2 years. Eighty-three percent of patients achieved MRD-negative CR by a median of 1 cycle). Among those who achieved CR, 44% proceeded to allogeneic HCT in CR1. With a median follow-up of 16.4 months, estimated 12-month OS and EFS were 82.1% and 82.9%, respectively. Estimated 24-month OS and RFS were 74.6% and 67.8%, respectively. The addition of venetoclax did not slow count recovery, with a median time of 34 days between the 1st and 2nd cycles of therapy.

Inotuzumab Ozogamicin

In a phase II study, the efficacy and safety of InO combined with low-intensity chemotherapy (mini-hyperCVD) was evaluated in adults with a median age of 68 years with newly diagnosed Ph-negative ALL and an ECOG performance status ≤3 (n = 52; interquartile range, 64–72 years).[293] Compared to hyperCVAD, mini-hyperCVD has no anthracycline and is composed of reduced doses of dexamethasone (50% reduction), methotrexate (75% reduction), and cytarabine (given every 12 hours at 0.5 g/m^2 on days 2 and 3). In this study, InO was given on day 3 of the first 4 courses at 1.3–1.8 mg/m^2 for cycle 1, followed by 1.0–1.3 mg/m^2 for subsequent cycles.[293] In addition, maintenance therapy with dose-reduced POMP (6-MP, vincristine sulfate, methotrexate, and prednisone) was given for 3 years. With a median follow-up of 29 months, the 2-year PFS was 59% (95% CI, 43%–72%).[293] Some of the most frequent grade 3 and 4 adverse events were prolonged thrombocytopenia (81%), infections during induction and consolidation (52% and 69%, respectively), and hyperglycemia (54%).[293] In this study, SOS occurred in four patients (8%).

A phase II study evaluated InO monotherapy in 26 patients (median age, 46 years; range, 19–70 years) with B-cell ALL in CR1 or beyond with positive MRD (≥1x10^{-4}).[294] After a median of 3 cycles (range, 1–6 cycles; 69% of patients achieved MRD negativity. Two-year RFS and OS rates were 54% and 60%, respectively. Eight percent of patients developed SOS and the remainder of adverse events were noted to be low grade.

In the ongoing phase II INITIAL-1 trial, InO combined with dexamethasone is being investigated as an induction regimen for patients ≥55 years of age (n = 43; median age, 64 years; age range, 56–80 years) with newly diagnosed Ph-negative B-ALL.[295] Up to 3 cycles of InO/dexamethasone induction were given, followed by up to 6 cycles of GMALL consolidation adapted by age and maintenance therapy. All

patients achieved CR/CRi following 2 to 3 cycles of InO/dex. Following cycle 2, 53% of patients achieved MRD negativity, while 30% achieved MRD negativity following cycle 3. With a median follow-up of 2.7 years, 1-year EFS and OS were 88% and 91%, respectively. Three-year EFS and OS were 55% and 73%, respectively.

In the ongoing phase II Alliance A041703 trial, the chemotherapy-free regimen of inotuzumab ozogamicin for induction followed by blinatumomab consolidation is being investigated in patients ≥60 years of age (n = 33; median age, 71 years; range, 60–84 years) with newly diagnosed Ph-negative B-ALL with no plans for allogeneic HCT.[296] Induction course IA included InO at a dose of 0.8 mg/m^2 on day 1 followed by 0.5 mg/m^2 on days 8 and 15 of a 21-day cycle. Those with adequate cytoreduction, defined as bone marrow (BM) blasts ≥50% or cellularity ≤20%, went on to receive either induction IB (InO, 0.5 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) if CR/CRi was achieved or induction IC (InO, 0.8 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) if having not achieved CR/complete remission with incomplete hematologic recovery (CRi). Those with inadequate cytoreduction to induction IA or those without events in induction IA, IB, or IC began blinatumomab consolidation. Those achieving CR/CRi with InO received a total of three 28-day cycles of blinatumomab, while all others received a total of 4 cycles. The cumulative CR rate through induction InO courses was 85% and for blinatumomab consolidation was 97%. With a 22-month median follow-up, 1-year EFS was 75% (95% CI, 61%–92%) and 1-year OS was 84% (95% CI, 72%–98%).

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 patients ≥55 years of age with ALL.[297] 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).[297] 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).[297] 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.[297]

GMALL Regimen

In a prospective trial, the GMALL group evaluated the efficacy of a moderate-intensity regimen in adults aged 55 to 85 years with Ph-negative ALL (n = 268).[298] 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, 1 cycle with 500 U/m^2 PEG 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.[298] The 5-year OS rate was 23%, and the 2-year OS rates observed in groups 1 and 2 were 33% and 52%, respectively.[298] 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).[298] In addition, the study

showed that consolidation with native *Escherichia coli* asparaginase and PEG was feasible and well tolerated, and was associated with improvements in CR rates and 2-year OS in this aged 55 to 85 years patient subset.[298]

PETHEMA-Based Regimen

The Spanish PETHEMA group conducted phase II prospective studies in patients aged 56 to 79 years with Ph-negative ALL (ALLOLD07; n = 56).[299,300] 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.[300]

Modified DFCI 91-01 Protocol

A retrospective analysis examined the efficacy of a modified version of a DFCI pediatric protocol, DFCI 91-01,[301,302] in adults with newly diagnosed ALL (n = 51; age range, 60–79 years).[303] 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).[303] 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.[303] 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%).[303]

Low-Intensity Chemotherapy and Corticosteroids

For adults who are older 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.[304] Attempts to identify optimal therapy in this population have included adaptations of palliative regimens including vincristine and corticosteroids, and POMP.[305-308] 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 adults who are older 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 therapy included both AYA and adult patients.[279-281] For a discussion of these studies, refer to the previous section (*see Initial Treatment in AYA Patients with Ph-Negative ALL*).

ECOG-ACRIN E1910 Regimen

In contrast to prior studies investigating blinatumomab as a means of eradicating MRD during or after multiagent therapy, this phase III trial investigated whether blinatumomab could improve outcomes in patients receiving chemotherapy who had achieved MRD negativity (<0.01%).[309] Patients with newly diagnosed Ph-negative B-ALL between the ages of 30 to 70 years initially received multiagent induction therapy with a BFM-like regimen adapted from E2993/UKALLXII. PEG was added for patients <55 years of age and rituximab was added for CD20 positivity. Following induction, patients who achieved a CR/CRi remained on study and proceeded to intensification with high dose methotrexate and pegaspargase for CNS prophylaxis. Thereafter, MRD status was assessed

by 6-color flow cytometry. Patients were randomized to receive either 4 cycles of consolidation chemotherapy or 2 cycles of blinatumomab followed by 3 cycles of consolidation chemotherapy, followed by a 3rd cycle of blinatumomab, followed by another cycle of consolidation chemotherapy, and finally a 4th cycle of blinatumomab. However, following the FDA approval of blinatumomab for patients with MRD positive disease, those with MRD positivity in the trial were no longer randomized and assigned to the blinatumomab arm. All patients received POMP maintenance therapy for a total of 2.5 years. Patients were referred for allogeneic HCT at provider discretion. For the entire cohort, CR/CRi rate following induction was 81%. For those who achieved MRD negativity, the addition of blinatumomab led to significant improvement on OS. With a median follow-up of 43 months, 3-year OS was 85% for the blinatumomab arm compared to 68% for the consolidation chemotherapy arm (95% CI, 0.23–0.73; *P* =.002). Three-year RFS also favored the blinatumomab arm, at 80% vs. 64% (95% CI, 0.32–0.87).

Based on initial data, in June 2024, the FDA expanded the approval of blinatumomab to include adult and pediatric patients ≥1 month with Ph-negative B-ALL in the consolidation phase of multiphase chemotherapy.

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.[310-312] Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.[165,313,314] 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%.[310] 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 18 to 36 months from time of diagnosis; late cases were defined as relapse occurring ≥36 months 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).[310] 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.[310] In a separate analysis of data from one of the above COG studies (CCG-1952), the timing and site of first relapse were significantly predictive of EFS and OS outcomes, even among the patients with standard-risk ALL (n = 347; based on NCI criteria: aged 1 to <10 years and WBC count <50 × 10^9/L).[315] 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.[315] 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.[315]

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%.[204,205] Approximately 20% to 30% of patients experience a second CR with second-line therapies.[205,207] Factors predictive of more favorable outcomes after subsequent therapies included younger age and

a first CR duration of more than 2 years.[183,205] Among younger patients (aged <30 years) whose disease relapsed after experiencing a first CR duration longer than 2 years with frontline treatment in PETHEMA trials, the 5-year OS rate from the time of first relapse was 38%.[205]

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 adults with ALL experiencing a second CR.[316] 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.[313,314,317] Seemingly contradictory data were reported in the COG CCG-1952 study that showed prognosis after early bone marrow relapse in patients with standard-risk ALL (aged 1 to <10 years and WBC count <50 × 10^9/L) remained poor with no apparent advantage of HCT, regardless of timing (ie, early or late) of bone marrow relapse.[315] 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.[204] Patients treated with HCT demonstrated a superior OS at 5 years compared to those treated with chemotherapy alone.[204] The CIBMTR group conducted an analysis of outcomes of patients with ALL (n = 582; median age, 29 years; range, <1 to 60 years) who underwent transplant during relapse.[318] At 3 years, OS rates were 16% (95% CI, 13%–20%).[318] Response to therapy for relapsed/refractory disease 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.[186]

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).[284,319] Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 patients with R/R Ph-negative B-ALL that demonstrated a CR or CR with incomplete platelet recovery (CRp) in 43% of patients within the first 2 cycles of treatment.[283,320] 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).[282] 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).[282] 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, CR with partial hematologic recovery [CRh], or CRi, 44% vs. 25%; P < .001).[282] Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.[282]

There are significant and unique side effects to blinatumomab treatment compared to other established 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.[321] CRS typically occurs within the first 2 days following initiation of blinatumomab infusion.[321] 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.[247,248] For discussion of these studies, see *Treatment of Relapsed Ph-Positive ALL*.

In a phase II study, the efficacy and safety of InO combined with low-intensity chemotherapy (mini-hyperCVD) was evaluated in adults with R/R B-ALL (n = 59; median age, 35 years; range, 18–87 years).[322] The response rate was 78%, with 35 of these patients achieving CR (59%).[322] The overall MRD negativity rate among responders was 82%. With a median follow-up of 24 months, the median RFS and OS were 8 and 11 months, respectively. The 1-year RFS and OS rates were 40% and 46%, respectively. When using this regimen, the risk of SOS should be considered in patients with previous liver damage and among transplant candidates. In this study, SOS occurred in 9 patients (15%).[322]

In a subsequent report, to reduce the risk of SOS and improve outcomes, the investigators amended the protocol by lowering the weekly InO doses and including 4 cycles of blinatumomab in the consolidation phase.[323] In a cohort of adults with Ph-negative B-ALL treated in first relapse (n = 48; median age, 39 years; range, 18–87 years), the rates of SOS prior to the protocol amendment and after the protocol amendment were 13% (n = 5 of 38) and 0% (n = 0 of 10), respectively.[323] In addition, based on propensity score matching, the combination of InO with mini-hyperCVD with or without blinatumomab resulted in better outcomes than inotuzumab alone or intensive chemotherapy for relapsed/refractory disease.[323] Long-term follow up data from a total of 96 patients revealed an ORR of 80%, with 57% achieving a CR. Among responders, the overall MRD negativity rate was 83%.[324] Patients treated at first relapse had better outcomes than patients treated at second relapse or 3rd relapse and beyond, with ORR rates of 91%, 59%, and 57%, respectively. Similarly, rates of MRD negativity were higher among patients treated at first relapse compared to those treated at second relapse or beyond, at 88% and 67%, respectively. Forty-six percent of patients ultimately went on to allogeneic HCT. Estimated 3-year OS was 33% in the entire cohort and 48% among patients who proceeded to allogeneic HCT. Sixteen percent of patients underwent allogeneic HCT developed SOS compared to 6% of patients who did not proceed to allogeneic HCT.

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.[249,325,326] CAR T-cell therapy relies on the genetic manipulation of a patient's T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.[250] 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.[250] 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.[327] Following infusion, debulking of tumors occurs in <1 week and these cells may remain in the body for extended periods of time to provide immunosurveillance against relapse.

There are several clinical trials using CAR T cells that differ in the receptor construct for patients with relapsed or refractory ALL. One of the first CAR constructs to be investigated, termed 19-28z—which links the CD19 binding receptor to the costimulatory protein CD28—demonstrated an overall CR in 14 out of 16 patients with relapsed or refractory B-ALL following infusion with CAR T cells.[328] 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%).[204,328-330] Furthermore, 7 out of 16 patients were able to receive an allogeneic HCT, suggesting that CAR T cells may provide a bridge to transplant.[328] No relapse has been seen in patients who underwent allogeneic HCT (follow-up, 2–24 months); however, 2 deaths occurred from transplant complications. Follow-up data of adults enrolled on this trial (n = 53) showed an 83% CR rate after the infusion and 32 patients achieved an MRD-negative CR.[331] At a median follow-up of 29 months (range, 1–65 months), the median OS was 12.9 months (95% CI, 8.7–23.4 months) and subsequent allogeneic HCT did not appear to improve survival.[331] In contrast, data in children and young adults treated on another clinical trial at the National Institutes of Health/National Cancer Institute with a similar CAR construct suggested consolidative allogeneic HCT post-CAR T-cell therapy might be associated with superior outcomes (2-year cumulative incidence of relapse post-transplant, 9.5%; 5-year EFS post-transplant, 62%).[332]

Other CD19-targeted constructs have been investigated—some comprising an alternative costimulatory protein, 4-1BB—have shown similar results to the 19-28z CAR T cells in terms of overall CR.[333] 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.[334] These results led to the approval of CTL019 by the FDA in August 2017 for the treatment of patients <26 years of age with R/R precursor B-ALL. The efficacy of CTL019 in children and young adults with R/R B-ALL in the non-trial setting was recently confirmed using registry data from the CIBMTR. This retrospective analysis showed morphologic CR in 85% of patients.[335] MRD negativity was reported in 99% of patients who had achieved a CR with available data. A comparable proportion of patients experienced durable responses at 12 months in the CIBMTR cohort compared to patients treated on the ELIANA clinical trial (61% and 67%, respectively). At the last update of the ELIANA data at the 2019 American Society of Transplantation and Cellular Therapy (ASTCT) Annual Meeting (median follow-up, 24 months), the median duration of remission and OS was NR and the 24-month RFS probability in responders was 62%. Survival probability curves plateaued after 1 year. Consolidation with allo-HCT after CTL019 was reported in only 9% of patients who had achieved a CR. These updated results suggest treatment with CTL019 in children and young adults with R/R B-ALL could be curative in a subset of patients in the absence of consolidative allo-HCT.[336]

The single-arm, open-label, international multicenter phase 2 ZUMA-3 clinical trial assessed the efficacy of the CAR T-cell product KTE X19 (brexucabtagene autoleucel) in 71 adults with R/R B-ALL.[337] The primary endpoint, the rate of overall CR or CRi by central assessment, was met (71%; 95% CI, 57–82; $P < .0001$). Secondary endpoints were also met: 76% of patients experienced MRD-negative CR, the median duration of remission was 12.8 months, the median RFS was 11.6 months, and the median OS was 18.2 months.[337] Brexucabtagene autoleucel had a manageable safety profile. The most common grade 3 or higher adverse

events were anemia (49%) and pyrexia (36%). It is also being evaluated in children and young adults ≤21 years of age with R/R ALL in the ZUMA-4 trial (NCT02625480).

A phase Ib/II multicenter study investigated the anti-CD19 CAR T-cell therapy obecabtagene autoleucel in adults ≥18 years with R/R B-ALL (n = 127 with evaluable data; median age, 47 years).[338,339] All patients had received at least two prior lines of therapy. In a cohort of patients with morphologic disease, the ORR was 77%, with 55% achieving CR. Among all patients who received obecabtagene autoleucel, including patients with both morphologic disease and MRD, ORR was 78% and median EFS and OS were 11.9 months and 15.6 months, respectively. Among those who achieved response, 17% proceeded to allogeneic HCT in MRD-negative CR. Grade ≥3 CRS or immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 2.4% and 7.1% of patients, respectively.

As with blinatumomab, T-cell and CAR T-cell activation can be accompanied by severe CRS and neurologic toxicity (ICANS), as well as infectious risks—though treatment-related mortality remains low.[334] While side effects from CAR T cells can be severe, they are reversible in most cases. CRS is clinically characterized by high fever, hypotension, tachycardia, and hypoxia; ICANS includes delirium, aphasia, headaches, tremor, focal deficits, and cerebral edema. Higher CRS and ICANS severity have been reported in patients with B-ALL compared to patients with NHL after CD19 CAR T-cell therapy.[340] It is recommended to evaluate CRS and ICANS severity using the ASTCT consensus criteria.[341] Tocilizumab (interleukin-6 receptor antagonist) and corticosteroids are the cornerstone of CRS and ICANS management. An FDA-approved biosimilar is an appropriate substitute for tocilizumab. Expert consensus clinical guidelines were recently published by the Society of Immunotherapy of Cancer to guide toxicity management.[342]

Nelarabine

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-ALL who have unresponsive or relapsed disease after at least two chemotherapy regimens. A phase II study of nelarabine monotherapy in children and adolescents with R/R T-ALL or T-cell NHL (n = 121) showed a 55% response rate among the subgroup with T-ALL with first bone marrow relapse (n = 34) and a 27% response rate in the subgroup with a second or greater bone marrow relapse (n = 36).[165] Major toxicities included grade 3 or higher neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single-agent therapy was also evaluated in adults with R/R T-ALL or T-cell lymphoblastic leukemia in a phase II study (n = 39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, n = 26).[167] 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.[167]

There are limited studies of nelarabine combination regimens in adults with R/R T-ALL. In a study by Commander et al, pediatric patients with R/R T-ALL (n = 7; range, 1–19 years) were treated with nelarabine, etoposide, and cyclophosphamide.[343] In addition, all patients received IT prophylaxis with methotrexate or triple IT therapy with methotrexate, cytarabine, and hydrocortisone. All patients experienced a CR after 1 or 2 courses of therapy. The most common adverse events attributed to nelarabine were grade 2 and 3 sensory and motor neuropathy and musculoskeletal pain.[343] In phase I of the NECTAR trial, pediatric patients with R/R T-ALL and T-LL (range, 1–21 years) were also treated with nelarabine, etoposide, and cyclophosphamide.[344] Of nine patients with T-ALL with evaluable data, there were two CRs, one partial CR, and one CR in the bone marrow/partial response (PR) in an extramedullary site for a response rate of 44%.[344]

Augmented HyperCVAD

A phase II study from the MDACC evaluated an augmented hyperCVAD 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).[345] Among patients with evaluable data (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 patients with evaluable data 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.[345]

Clofarabine

Clofarabine is a nucleoside analog approved for the treatment of pediatric patients (aged 1–21 years) with ALL that is relapsed or refractory after at least two prior regimens. In a phase II study of single-agent clofarabine in pediatric patients who have undergone heavy pretreatment with R/R ALL (n = 61; median age, 12 years; range, 1–20 years), the response rate (CR + CRp) was 20%.[346] 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.[346] 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%.[347,348] 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 SOS (the latter occurring in the post-allogeneic HCT setting).[347]

There are limited studies of clofarabine combination regimens in adults with R/R disease. In a study by Miano et al,[349] 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 experienced treatment response, with a 24-month OS rate of 25%.[349] In a study from GRAALL, adults 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 [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.[350] The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%), with an early death rate of 11%.[350] Because the use of clofarabine-containing regimens require close monitoring and intensive supportive care measures, patients should only be treated in centers with expertise in the management of ALL, preferably in the context of a clinical trial.

MOpAD Regimen

A single-arm trial evaluating the efficacy of the MOAD regimen (methotrexate, vincristine, L-asparaginase, and dexamethasone) in adults with newly diagnosed ALL (n = 55) demonstrated a CR rate of 76% with a median CR duration of over 12 months.[351] A phase II trial incorporated a new PEGylated formulation of L-asparaginase due to improved tolerability,[352] 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).[353] For patients with Ph-positive ALL, TKIs (ie, imatinib, dasatinib, nilotinib) were added to the regimen and if patients had CD20-positive B-ALL, rituximab was added to the regimen. The CR and ORR rates were 28% and 39%, respectively, with a median duration of response of 4.3 months.[353] Patients with Ph-positive ALL achieved CR and ORR rates of 50% and

67%, respectively.[353] This regimen may be considered in patients who have received a maximal dose of anthracycline and have cardiac dysfunction and limited performance status.

TKIs

Studies evaluating other novel TKIs in targeting specific genetic subtypes have been evaluated for the treatment of R/R T-ALL disease. While daratumumab has efficacy in its application for MRD, it has been reported to have potential preclinical benefit in T-ALL with positive CD38 expression.[354] The use of the selective BCL2 inhibitor, venetoclax, has been retrospectively analyzed in the treatment of R/R T-ALL. In this analysis, 60% of patients receiving venetoclax plus various chemotherapeutic agents such as hyperCVAD, nelarabine, or decitabine, achieved remission in marrow blasts, with the median OS of 7.7 months.[355] Proteasome inhibition with the use of bortezomib in combination with chemotherapeutic agents has been suggested to improved relapse response rates in patients with T-ALL. In a phase II COG study, patients with ALL were treated with reinduction chemotherapy plus bortezomib.[356] Patients with relapsed T-ALL showed a CR rate of 68%, with end of induction MRD significantly predicting survival.[356]

Revumenib

In the ongoing phase II AUGMENT-101 study the safety and efficacy of the oral menin inhibitor revumenib was evaluated in adult and pediatric patients ≥30 days old (n = 94; 57 with efficacy-evaluable data) with primary refractory or relapsed *KMT2Ar* acute leukemia, including 14 patients with ALL.[357] Many patients (43.6%) had received ≥3 prior lines of therapy and 50% of patients had undergone prior allogeneic HCT.

Patients received revumenib 163 mg (or 95 mg/m^2 for those weighing <40 kg) every 12 hours in 28-day continuous cycles. Dose of revumenib could be increased to 276 mg (or 160 mg/m^2 if weight <40 kg) if no concomitant strong CYP3A4 inhibitor was being utilized; however, this did not occur on study and is rare in R/R acute leukemia, as most patients require fungal prophylaxis with azoles. Among patients with evaluable data, the CR/CRh rate was 22.8%. ORR was 63.2% with 68.2% of patients achieving MRD negativity. Among those who achieved response, 38.9% were able to proceed to allogeneic HCT and half of these patients receive revumenib maintenance therapy following HCT.

The most common adverse effects were nausea/vomiting/diarrhea, febrile neutropenia (grade ≥3 in 37.2% of patients), and edema. Grade ≥3 differentiation syndrome occurred in 16% of patients and grade ≥3 QTc prolongation occurred in 13.8% of patients.

Based on this data, the FDA approved revumenib for R/R acute leukemia with a KMT2A translocation in adult and pediatric patients ≥1 year.

NCCN Recommendations for Ph-Negative B-ALL

AYA and Adult Patients<65 Years without Substantial Comorbidities with Ph-Negative B-ALL

The Panel recommends that AYA and adult patients <65 years without substantial comorbidities with Ph-negative B-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 systemic therapy regimens.

For AYA patients, preferred systemic therapy regimens are regimens based on pediatric-inspired protocols, the DFCI-00-01 and CALGB 10403 regimens. Multiagent therapy protocols based on data from multi-institution studies such as ECOG1910 and single-institution studies, including CCG-1882 (if ≥18 years) and hyperCVAD (with or without rituximab), are also recommended.

For patients <65 years of age and without substantial comorbidities, recommended systemic therapy regimens include multiagent therapy such as those based on protocols from the ECOG1910 regimen, hyperCVAD with or without sequential blinatumomab (with or without rituximab), the MSKCC ALL regimen (CCG-1882 regimen; if <60 years), and InO with mini-hyperCVD with or without blinatumomab.

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.

Following induction, a response assessment is recommended. For patients experiencing less than a marrow CR, NGS testing may be considered prior to therapy for R/R disease. For patients experiencing a marrow CR following initial induction therapy, MRD status should be assessed (see *NCCN Recommendations for MRD Assessment*). If the resulting MRD status is negative, continuation of the multiagent therapy protocol with blinatumomab or blinatumomab monotherapy for consolidation may be considered. Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910.[309]Consolidation with allogeneic HCT may also be considered, especially in the setting of high-risk features If MRD is positive following treatment induction, blinatumomab with or without continued multiagent therapy is recommended. Adequate count recovery per protocol is necessary before transitioning to post remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted.

Following consolidation therapy, repeat MRD assessment is recommended. In the setting of MRD negative CR following consolidation, POMP maintenance therapy or allogeneic HCT are recommended.

Allogeneic HCT is favored for individuals with B-ALL with poor risk cytogenetic and molecular alterations, or in the setting of slow or incomplete MRD clearance. In the setting of persistent progressive, or emergent MRD, marrow progression, or new extramedullary disease, treatment for R/R disease is recommended (see *Patients with Relapsed/Refractory Ph-Negative B-ALL*).

Adults ≥65 Years or Patients with Substantial Comorbidities with Ph-Negative B-ALL

For adults ≥65 years of age or patients with substantial comorbidities with Ph-negative B-ALL, the Panel recommends treatment in a clinical trial, where possible. 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 patients ≥65 years of age or patients with substantial comorbidities, other recommended induction therapy options can be broken down by intensity. Low-intensity options include vincristine with prednisone or POMP. Moderate intensity options include InO monotherapy (a category 2B option based on ALLIANCE A041703), InO combined with dexamethasone (a category 2B option based on ALL-INITIAL-1), InO combined with mini-hyperCVD, the modified DFCI 91-01 protocol, and mini-hyperCVD with or without venetoclax. ECOG1910 is a high-intensity option. Other regimens that may be useful in certain circumstances include the PETHEMA-based regimen ALLOLD07, CALGB9111, EWALL, GMALL with rituximab for CD20-positive disease, and GRAALL.

Dose modifications may be required for systemic therapy agents, as needed. MRD assessment and consolidation approach after initial treatment induction would be similar to that for AYA and adult patients <65 years without substantial comorbidities with Ph-B-ALL, with appropriate

dose modifications (see *AYA and Adult Patients <65 Years without Substantial Comorbidities with Ph-Negative B-ALL).*

For recommendations on the treatment of adults with mature B-ALL, refer to the NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org).

Patients with Relapsed/Refractory Ph-Negative B-ALL

For patients with R/R Ph-negative B-ALL, molecular characterization and MRD assessment are recommended, if not previously done. The approach to second-line treatment may depend on the duration of the initial response. For late relapses (ie, relapses occurring ≥3 years from initial diagnosis), retreatment with the same induction regimen is a reasonable option. For other patients, participation in a clinical trial is preferred, when possible. In the absence of an appropriate trial, for patients with R/R Ph-negative precursor B-ALL, recommended category 1 options include blinatumomab with or without multiagent therapy or InO. As previously mentioned, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic SOS, and increased risk of post-HCT non-relapse mortality.[253]

Brexucabtagene autoleucel and obecabtagene autoleucel are additional options for AYA and adult patients with R/R Ph-negative B-ALL. Tisagenlecleucel is also an option for patients <26 years of age and with refractory disease or ≥2 relapses. Other options that may be considered include subsequent multiagent therapy, with regimens containing clofarabine, InO with mini-hyperCVD with or without sequential blinatumomab, augmented hyperCVAD, MOpAD regimen, or other fludarabine-, cytarabine-, or alkylator-containing regimens.[324,358-361] Revumenib is a targeted therapy option for those with R/R *KMT2A* rearranged Ph-negative B-ALL. If patients who have not yet undergone transplant 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. As previously discussed, persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT.[255]

NCCN Recommendations for T-ALL

AYA and Adult Patients <65 Years without Substantial Comorbidities with Ph-Negative T-ALL

The Panel recommends that AYA and adult patients <65 years without substantial comorbidities with T-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 systemic therapy regimens. For AYA patients, preferred induction regimens are the CALGB 10403 and COG ALL0434 regimens, which are pediatric-inspired protocols. Other recommended regimens are based on data from multi-institutional studies, such as the DFCI ALL regimen based on the DFCI-00-01 protocol or multiagent therapy protocols based on data from single-institution studies, including the MSKC ALL regimen, based on CCG-1882 (for those ≥18 years) and hyperCVAD. For adult patients <65 years without substantial comorbidities, hyperCVAD and dose-adjusted GRAALL-2014 are other recommended treatment regimens. The addition of nelarabine to COG AALL0434 and hyperCVAD may be beneficial.

Following induction therapy, a response assessment is recommended. For patients experiencing less than a marrow CR, NGS should be considered prior to treatment for R/R therapy. For patients achieving a marrow CR, an MRD assessment should be performed. Regardless of MRD response, continuation of multiagent therapy for consolidation is recommended, though consideration of allogeneic HCT is an alternative consolidative measure for those achieving MRD negative CR. Adequate count recovery

per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted.

Following consolidation therapy, repeat MRD assessment is recommended (see *NCCN Recommendations for MRD Assessment*). For those experiencing persistent, progressive, or emergent MRD, marrow progression, or development of extramedullary disease, treatment for R/R is recommended (see *Patients with Relapsed/Refractory T-ALL*). For those achieving MRD negative CR, POMP maintenance or allogeneic HCT are recommended. Allogeneic HCT is favored for those with slow/incomplete MRD clearance or those with disease with high-risk features such as ETP-phenotype or *RAS/PTEN* and/or *NOTCH1/FBXW7* wild-type classifier.

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.

Adults ≥65 Years or Patients with Substantial Comorbidities with Ph-Negative T-ALL

For adults ≥65 years or patients with substantial comorbidities with T-ALL, the Panel recommends treatment in a clinical trial, where possible. In the absence of an appropriate clinical trial, other recommended treatment regimens can be broken down by intensity. Low intensity induction options include vincristine + prednisone or POMP. Moderate intensity induction regimens include the PETHEMA-based ALLOLD07 regimen, GMALL, GRAAL, modified DFCI91-01, and mini-hyperCVD regimens. The addition of nelarabine to GRALL-2014 and hyperCVAD may be beneficial.

Dose modifications may be required for systemic therapy agents, as needed. MRD assessment and consolidation approach after initial treatment induction would be similar to that for AYA and adult patients <65 years without substantial comorbidities with T-ALL, with appropriate dose modifications (see *AYA and Adult Patients without Substantial Comorbidities with T-ALL).*

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.

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.

Patients with Relapsed/Refractory T-ALL

For patients with R/R T-ALL, the approach to second-line treatment may depend on the duration of the initial response. For late relapses (ie, relapses occurring ≥3 years 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, the regimens listed for R/R Ph-negative B-ALL may be appropriate for R/R T-ALL. Other recommended treatment options include nelarabine[167,362,363] in combination with etoposide and cyclophosphamide,[343,344] HiDAC, regimens containing daratumumab,[364-366] mitoxantrone-, etoposide-, cytarabine,[367] venetoclax-containing regimens (a category 2B recommendation),[355,368,369] or bortezomib-containing regimens.[356]

Based on limited case report data, there may be a role for targeted therapy in R/R T-ALL based on molecular mutational status in appropriate situations.[370]

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.[371] 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.[372,373] HyperCVAD (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%.[159] However, it should be noted that 40% to 60% of adults experience 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 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.[119,374,375] 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.[125] 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.[376,377] CNS leukemia at diagnosis was associated with a significantly decreased 5-year OS rate in one trial (29% vs. 38%; $P = .03$)[376] but not in another trial (35% vs. 31%).[377] 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.[43,376] CNS-directed therapy may include cranial irradiation, IT therapy (eg, methotrexate, cytarabine, corticosteroids), and/or high-dose systemic chemotherapy (eg, methotrexate, cytarabine, 6-MP, asparaginase).[1,50,125]

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.[1,125] With the increasing use of effective IT therapy 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 IT 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.[117,375]

Data from the Total Therapy (XV) study by the St. Jude Children's Research Hospital showed dramatic improvements in survival outcomes for the AYA population. In this study, patients were primarily risk-stratified based on treatment response; patients were treated according to risk-adjusted intensive chemotherapy, with the incorporation of MRD

evaluation during induction (day 19) to determine the need for additional doses of asparaginase.[375,378] The 5-year EFS rate for the AYA population (aged 15–18 years; n = 45) was 86% (95% CI, 72%–94%), which was not significantly different from the 87% EFS rate (95% CI, 84%–90%; *P* = .61) observed for patients <15 years of age (n = 448). The 5-year OS rates for the AYA patients and patients <15 years of age were 88% and 94%, respectively (*P* = not significant).[375,378] 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 IT therapy (ie, triple IT therapy 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).[375] Moreover, all 11 patients with isolated CNS relapse were children <12 years of age. This study showed that, with intensive risk-adjusted therapy and effective CNS-directed IT regimens, AYA patients can obtain long-term EFS without the need for cranial irradiation or routine allogeneic HCT.[375,378]

In adults with ALL who received IT therapy and intensive systemic chemotherapy for CNS prophylaxis, the overall CNS relapse rate was 2% to 6%.[20,127,379,380] Therefore, with the incorporation of adequate systemic chemotherapy (eg, high-dose methotrexate and cytarabine) and IT therapy regimens (eg, methotrexate alone or with cytarabine and corticosteroid, which constitutes the triple IT regimen), it may be possible to avoid the use of upfront cranial irradiation. The use of irradiation should be reserved for resistant CNS 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 LP at timing in accordance with the specific treatment protocol used for each patient. Pediatric-inspired treatment regimens typically include LP at diagnostic workup. The Panel recommends that IT therapy be administered with initial LP. All patients being treated for ALL should receive adequate CNS prophylaxis with IT 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 <5 leukocytes/mcL in the CSF with the presence of blasts; and CNS-3 is defined as a WBC count of ≥5 leukocytes/mcL with the presence of blasts. If leukemic cells are present in the peripheral blood and the LP 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). Flow cytometry may be considered in the setting of CNS-1 status. Patients who have CNS-1 disease with leukemia detected only by flow cytometry may be at higher risk but evidence is limited to retrospective analyses.

In general, patients with CNS involvement at diagnosis (ie, CNS-3 and/or cranial nerve involvement) or with CNS disease that does not clear after induction IT 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 treatment 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 IT therapy containing methotrexate throughout the treatment course. Adequate systemic therapy should also be given during the management of isolated CNS relapse.

A testicular examination should be performed for all patients with testes at diagnostic workup; testicular involvement is especially common among patients with T-ALL. Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of induction therapy should be considered for radiation to both testes in the scrotal sac. Radiation therapy is typically performed concurrently with the first cycle of maintenance chemotherapy. Testicular total dose should be 24 Gy (in 2.0 Gy/fraction).

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 extramedullary involvement). A bone marrow assessment should show trilineage hematopoiesis and <5% blasts. For a CR, absolute neutrophil counts (ANCs) should be >1.0 × 10^9/L and platelet counts should be >100 × 10^9/L. In addition, no recurrence should be observed for at least 4 weeks. A patient is considered to have achieved a CRi if all criteria for CR are met except the ANC remains <1.0 × 10^9/L or the platelet count remains <100 × 10^9/L. A patient is considered to have achieved a CRh if all criteria for CR are met and peripheral blood counts have partially recovered (ANC $\geq$0.5 × 10^9/L and platelet count $\geq$50 × 10^9/L.

Refractory disease is defined as having not achieved 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-2 or 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 PR is defined as a >50% decrease in the sum product of the greatest perpendicular diameters (SPD) of the lymphomatous enlargement. PD is defined as a >25% increase in the SPD. No response indicates that neither criteria for a PR or PD (as defined earlier) are met. For patients with a previous positive PET scan, the post-treatment PET must be positive in at least one previously involved site. Relapse is defined as recurrence of mediastinal lymphomatous enlargement after achieving CR.

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) every 1 to 3 months. Liver function tests should be performed every 1 to 3 months until normal values are achieved. During the second year, a physical exam and CBC with differential can be performed every 3 to 6 months and these can be further spaced out to every 6 to 12 months or as indicated from the 3rd year and beyond. An assessment of bone marrow aspirate can be considered as clinically indicated at a frequency of 3 to 6 months for the first 5 years; if a bone marrow aspirate is performed, flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests, and MRD assessments should be carried out. While there is insufficient evidence to guide MRD monitoring for patients with Ph-negative disease following completion of maintenance therapy, the approval of blinatumomab, and potentially future therapies for MRD-positive relapse, may warrant testing in this regard.

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 (available at www.NCCN.org) and NCCN Guidelines for Survivorship (available at www.NCCN.org).

The COG has published guidelines on long-term survivorship issues for survivors of childhood cancers.[381] 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.[36,382]

The most frequently used methods for MRD quantification include an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and TCR loci (preferred; does not require patient-specific primers), multiparameter flow cytometry (eg, 6-color or higher) to detect leukemia-associated immunophenotypes, real-time quantitative PCR assays to detect fusion genes (eg, *BCR::ABL1*).[383-390]

Current multi-parameter flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 10^{-4} (<0.01%) bone marrow mononuclear cells (MNCs), and NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 10^{-6} (<0.0001%) bone marrow MNCs.[384,386,389,390] 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.[385,387,390-394] 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%.[392] 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.[390] At the 0.01% threshold, the concordance between both methods was high, but high-throughput sequencing was able to detect MRD at lower thresholds.[390] The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.[386,392,395] 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.

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).[396,397] 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 who achieved MRD-negative status ($P <$ .001), defined by a PCR sensitivity level of $<1.5 \times 10^{-4}$.[398] 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 $\geq 1 \times 10^{-2}$ had a 16-fold higher risk of relapse compared with those who had MRD levels $<1 \times 10^{-3}$.[398] In another study in children with ALL (n = 158), patients with detectable MRD (flow cytometry sensitivity level $<1 \times 10^{-4}$) at the end of induction therapy had a significantly higher 3-year cumulative incidence of relapse than those who were MRD negative (33% vs. 7.5%; $P <$ .001).[399] Subsequent studies have confirmed these findings. In a study of 165 patients, the 5-year relapse rate was significantly higher among patients with MRD (flow cytometry sensitivity $<1 \times 10^{-4}$) versus those without detectable disease (43% vs. 10%; $P <$ .001).[397] 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 achieved MRD-negativity by 14 weeks (68% vs. 7%; $P =$ .035).[397] 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 achieved MRD clearance (MRD $<1 \times 10^{-4}$ by flow cytometry) before day 19 of induction therapy (about 2–3 weeks from initiation of induction); the 5-year cumulative incidence of relapse was significantly higher among patients with MRD at day 19 of treatment than those without detectable MRD (33% vs. 6%; $P <$ .001).[396] The prognostic significance of MRD detection at lower levels (sensitivity threshold, $\leq 1 \times 10^{-5}$, or ≤0.001%, according to PCR measurements) was evaluated in children with B-cell lineage ALL treated with contemporary regimens.[389] 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%, 14% had <0.01% (but ≥0.001%), and 11% had <0.001%. The 5-year cumulative incidence of relapse was significantly higher among patients with MRD of ≥0.01% versus patients with <0.01% or undetectable disease (23% vs. 6%; $P <$ .001).[389] Furthermore, the 5-year cumulative incidence of relapse was higher among the subgroup of patients with MRD <0.01% (but ≥0.001%) versus those with MRD <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% at the end of induction had MRD of ≥0.01% 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.[389]

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 two time points (days 33 and 78), which were used to guide postinduction treatment.[400] Patients were considered at standard risk if MRD negativity (≤0.01%) was achieved at both days 33 and 78, at intermediate risk if MRD was >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 at high risk if MRD was ≥0.1% on day 78. Nearly all patients with favorable cytogenetic/molecular markers such as the *ETV6::RUNX1* subtype or hyperdiploidy were either considered at standard risk or intermediate risk based on MRD evaluation.[400] The 5-year EFS rate was 92% for patients categorized as at 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 disease 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.[400]

A randomized controlled trial in children and young adults with low-risk ALL according to MRD compared treatment reduction to standard induction (n = 521).[401] 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.[402] In this trial, 533 patients with a high risk of MRD (defined as clinical standard-risk and intermediate-risk with MRD of ≥0.01% 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}.[403] Patients with 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 experienced a low level of MRD ($<10^{-3}$) received 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.[404] 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.[405] MRD assessment may play a prognostic role in the treatment of patients in the relapsed setting.[406,407] 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% versus 28% among those with MRD <0.01% (*P* = .008).[406] 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% versus 0% for those with MRD <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.[406] In another study, MRD (PCR sensitivity level <0.01%) was evaluated in children with high-risk ALL (n = 60) who experienced first relapse within 30 months from the time of diagnosis.[407] 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%. The 3-year EFS rates based on these MRD categories were 73%, 45%, and 19%, respectively (*P* < .05).[407] 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.[408,409] 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.[382,410-413] 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 <0.05% at day 35 compared with those with MRD of ≥0.05% (42 vs. 16 months; *P* = .001).[413] A similar pattern emerged when only the subgroup of patients who achieved morphologic CR at day 35 was included in the MRD evaluation. Although patient numbers were

limited, 90% of patients with MRD <0.03% at an earlier time point (day 14 during induction therapy) remained relapse-free at 5 years.[413] 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).[412] The 5-year RFS rate was significantly higher in patients with MRD negativity versus those with MRD of ≥0.01% (71% vs. 15%; *P* = .0002).[412]

Postinduction MRD can serve as an independent predictor of relapse even among adult patients considered to be at standard risk based on traditional prognostic factors. In a study of adult patients with Ph-negative ALL (n = 116), MRD status after induction therapy (flow cytometry sensitivity level <0.1%) was significantly predictive of relapse regardless of whether the patient was considered to be at standard risk or high risk at initial evaluation.[411] Among patients who were initially classified as at standard risk, those with MRD of <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.[411] 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.[410] Only patients with ALL who met all of the following criteria for standard-risk disease were enrolled in this study: absence of t(4;11) *MLL* translocation or t(9;22) *BCR::ABL* translocation; WBC count <30 × 10^9/L for B-cell lineage ALL or <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% had a 2.4-fold higher risk (95% CI, 1.3–4.2) of relapse than those with MRD of <0.01%.[410] Moreover, this study identified distinct risk groups according to MRD status at various time points. Patients categorized as at low risk (10% of study patients) had MRD of <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% persisting through week 16, and 3-year DFS and OS rates of 6% and 45%, respectively. All other patients (67%) categorized as at intermediate risk had 3-year DFS and OS rates of 53% and 70%, respectively.[410] Importantly, MRD was the only independently significant predictor of outcome in a multivariate Cox regression analysis that included gender, age, WBC count, B- or T-cell lineage, and MRD. In a prospective study from the MDACC, adult patients with B-ALL (n = 340; median age, 52 years; range, 15–84 years) were monitored for MRD by multi-parameter flow cytometry (sensitivity level = 0.01%) at CR and at approximately 3-month intervals after CR.[414] MRD negative status at CR significantly correlated with improved DFS and OS, and was an independent predictor of DFS (*P* < .05).[414]

A prospective study (Japan ALL MRD2002) evaluated outcomes by MRD status in adult patients with Ph-negative ALL.[415] Among the patients who achieved a CR after induction/consolidation (n = 39), those who achieved MRD negativity (<0.1%) after induction had a significantly higher 3-year DFS (69% vs. 31%; *P* = .004) compared with patients with MRD; 3-year OS was higher among patients who achieved MRD-negative status after induction, although the difference was not statistically significant (85% vs. 59%). Based on multivariate Cox regression analysis, 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.[415]

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

<0.01% (n = 58) were primarily allotted to receive maintenance chemotherapy for 2 years, whereas those with MRD of ≥0.01% (n = 54) were eligible to undergo allogeneic HCT after high-dose therapy.[416] The 5-year DFS rate was significantly higher among patients who achieved MRD negativity versus those with MRD of ≥0.01% (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).[416] In a follow-up to the GMALL 06/99 study mentioned earlier, patients with standard-risk ALL (as defined by Bruggemann et al[410]) 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.[417] Among the patients included in this analysis (n = 105), 28 (27%) experienced MRD-positivity after the first year of therapy; MRD was detected before hematologic relapse in 17 of these patients.[417] The median RFS was 18 months (calculated from the end of initial treatment) among the subgroup that experienced MRD positivity, 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.[417] 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 persistent quantifiable MRD positivity (MRD ≥10^{-4}).[418] 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).[418] 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.[418] This analysis showed that MRD status following consolidation was an independent risk factor for poorer outcomes in adults with ALL, and may identify patients at high-risk who could potentially benefit from allogeneic HCT.

Studies in children and adults 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).[389,396-399,419] In one study, nearly 50% of children had MRD clearance (<0.01% by flow cytometry) at day 19 of induction therapy.[396] Adults seem to have a slower rate of leukemic cell clearance compared with children, with 30% to 50% of adults achieving MRD negativity after initial induction.[410,413] Approximately 50% of patients experienced persistent MRD positivity at 2 months after initiation of induction, with further reductions in the proportion of MRD-positive cases occurring beyond 3 to 5 months.[382,410] 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. Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for any patient with ALL with MRD positive disease.

The preferred sample for MRD assessment is the first small-volume (up to 3 mL) pull or early pull of the bone marrow aspirate, if feasible. Validated MRD assessment technology with appropriate sensitivity (at least 10^{-4} [<0.01%]), 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 $<1 \times 10^{-4}$ (<0.01%) bone marrow MNCs, and PCR or NGS methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-6}$ (<0.0001%) bone marrow MNCs.[384,386,420,421] If MRD is negative by flow cytometry, an FDA-approved NGS assay should be considered to confirm negativity. For flow cytometric analysis of MRD, if immunotherapy has been used (eg, rituximab, blinatumomab, InO, tisagenlecleucel, or brexucabtagene autoleucel), the lab performing the MRD assessment should be notified. For MRD assessment of *BCR::ABL1*, RT-qPCR is sensitive but in some cases lacks specificity, possibly due to multilineage involvement. Other MRD techniques, including flow cytometry and NGS, may be more specific.

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 and end of consolidation; additional time points for MRD evaluation should be guided by the treatment protocol or regimen used and risk features.[420,421] 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.[418,422-424] This further highlights the importance of referring to the protocol or regimen being used when interpreting MRD results. For some techniques, a baseline sample (ie, prior to treatment) is needed to characterize the leukemic clone for subsequent MRD assessment.

An increase in the frequency of serial monitoring of MRD may be useful in patients experiencing molecular relapse and low-level disease[425] or for those with Ph-positive ALL discontinuing a TKI. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt an evaluation for allogeneic HCT. When possible, therapy aimed at eliminating MRD prior to allogeneic HCT is preferred.

Supportive Care for Patients with ALL

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

before and during therapy, risks for infectious complications, disease status, and the specific agents used in the ALL treatment regimen.

NCCN Recommendations for Supportive Care

Most chemotherapy regimens used in ALL contain agents that are at least moderately emetogenic, which may necessitate antiemetic support before initiating emetogenic chemotherapy. Antiemesis prophylaxis may include the use of agents such as serotonin receptor antagonists, corticosteroids, and/or neurokinin-1–receptor antagonists. Recommendations for antiemetic support for patients receiving chemotherapy are available in the NCCN Guidelines for Antiemesis (available at www.NCCN.org). For patients with ALL, the routine use of corticosteroids as part of antiemetic therapy should be avoided given that steroids constitute a major component of ALL regimens. For patients experiencing >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, available at www.NCCN.org).

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 (available at www.NCCN.org).

High doses of methotrexate can result in toxic plasma methotrexate concentrations in patients with significant renal dysfunction, large effusions/ascites, and delayed methotrexate clearance (plasma methotrexate concentrations >2 SDs of the mean methotrexate excretion curve specific for the dose of methotrexate administered). Toxic plasma methotrexate concentrations in patients may also be observed due to other interacting medications. While this is more commonly seen in osteosarcoma and soft-tissue tumors due to the higher dose of methotrexate in treatment, the FDA has approved the use of glucarpidase as a rescue product in patients with ALL. If a patient receiving high dose methotrexate experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended either when plasma methotrexate concentrations are 2 SDs above the mean expected plasma concentration as determined by MTXPK.org or when plasma methotrexate level is >30 µM at 36 hours, >10 µM at 42 hours, or >5 µM at 48 hours. Optimal administration of glucarpidase is within 48 to 60 hours from the start of methotrexate infusion.[426,427] Leucovorin should also be given as part of the treatment of methotrexate toxicity and should be continued for at least 2 days following glucarpidase administration and should be administered at least 2 hours before or 2 hours after glucarpidase (see *Supportive Care* in the algorithm). Drug interactions with trimethoprim-sulfamethoxazole (TMP/SMX) and methotrexate can worsen methotrexate toxicity,[428] so the Panel recommends holding TMP/SMX when high-dose methotrexate is administered, and re-starting when methotrexate clearance is achieved per treatment protocol or institutional guidelines.

Patients with ALL may be at high risk for developing acute TLS, particularly those with highly elevated WBC counts before induction

chemotherapy. TLS is characterized by metabolic abnormalities stemming from the sudden release of intracellular contents into the peripheral blood because of cellular disintegration induced by chemotherapy. If left untreated, TLS can result in profound metabolic changes leading to cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death. Recommendations for the management of TLS are available in the *Tumor Lysis Syndrome* section of the NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org). Standard prophylaxis for TLS includes hydration with diuresis, alkalinization of the urine, and treatment with allopurinol or rasburicase. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function. Although relatively uncommon in patients with ALL, symptomatic hyperleukocytosis (leukostasis) constitutes a medical emergency and requires immediate treatment, as recommended in the NCCN Guidelines for Acute Myeloid Leukemia (available at www.NCCN.org). 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 treatment of patients with high WBC counts, it can be considered with caution in cases of leukostasis that is unresponsive to other interventions.

Key components of the ALL treatment regimen, such as corticosteroids, immunotherapies, and asparaginase, are associated with unique toxicities that require close monitoring and management. Corticosteroids, such as prednisone and dexamethasone, constitute a core component of nearly every ALL induction regimen, and are frequently incorporated into consolidation and/or maintenance regimens. Acute side effects of steroids may include hyperglycemia and steroid-induced diabetes mellitus. Patients should be monitored for glucose control to minimize the risk of developing 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 proton pump inhibitors (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[429-432]; 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.[433,434] 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.[433,435-439] 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 <10 years of age, to 10% to 13.5% in patients between 10 and 15 years of age, to 18% to 20% in patients ≥16 years of age.[435,436] 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.[433] Children >10 years of age had a significantly higher cumulative incidence of osteonecrosis (45% vs. 10%; $P < .001$) compared with children ≤10 years of age. In this study, factors such as age >10 years, 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.[433]

In a DFCI ALL Consortium study in children and adolescents that included randomization to postinduction therapy with dexamethasone versus

prednisone, dexamethasone was associated with a significantly increased 5-year EFS but, in children 10 to 18 years of age, the increased cumulative incidence of osteonecrosis was comparable with prednisone.[439] 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).[436] These studies appeared to suggest that dexamethasone, particularly in higher doses, may be associated with increased risks for osteonecrosis in children who are older and adolescents. To further investigate these findings, the CCG-1961 trial randomized patients (n = 2056; aged 1–21 years) to postinduction intensification treatment with intermittent dose scheduling of dexamethasone (10 mg/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).[435] Among children and adolescents ≥10 years of age who experienced a 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 adolescents ≥16 years of age (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.[435] 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.

When patients are treated with InO, liver enzymes— especially bilirubin— should be closely monitored because SOS may occur.[440] Ursodiol may be considered for SOS prophylaxis.[441,442] Defibrotide may be considered for patients who develop SOS related to InO toxicity.[443,444] If InO is being given as a bridge to allogeneic HCT, double alkylator conditioning is strongly discouraged, as SOS has been shown to occur less frequently when alkylators are used as part of the conditioning regimen.[441,442] Although there is limited data, it is recommended to wait at least 4 weeks from InO monotherapy and the start of conditioning for allogeneic HCT to minimize risk of SOS.

Patients treated with blinatumomab and tisagenlecleucel should be monitored for CRS and neurologic toxicity. For CRS (including refractory CRS), tocilizumab should be considered.[445] An FDA-approved biosimilar is an appropriate substitute for tocilizumab. Upon development of CRS, the Panel recommends holding blinatumomab infusions with consideration for steroids and/or vasopressors for patients with severe symptoms according to manufacturer guidelines and prescribing information. Signs and symptoms neurologic toxicity include confusion, word-finding difficulty, somnolence, ataxia, tremor, seizure, or syncope. Severe neurotoxicity related to blinatumomab. During the first month after tisagenlecleucel infusion, prophylaxis with anti-seizure medication may be considered.[446,447] A retrospective study investigating the safety of administering IT chemotherapy during blinatumomab infusion in patients with ALL and found no statistically significant difference in incidence of neurotoxicity between patients treated or not treated with IT chemotherapy during blinatumomab infusion (18.4% vs. 27.2%, respectively; *P* = .37).[448] For additional information regarding guidelines for immunotherapy-related toxicities, see NCCN Guidelines for Management of Immunotherapy-Related Toxicities (available at www.NCCN.org).

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. Three different formulations of the enzyme are in clinical use: 1) PEG; 2) calaspargase pegol-mknl (cal-PEG) (in patients ≤21 years); and 3) asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (ERW-rywn).These formulations differ in their pharmacologic properties, and may also differ in terms of immunogenicity.[449-453] Asparaginase products are associated with potentially severe hypersensitivity reactions (including anaphylaxis) due to anti-asparaginase or anti-PEG antibodies.[454,455] PEG seems to be associated with a lower incidence of neutralizing antibodies compared with native asparaginase.[456] However, cross-reactivity between neutralizing antibodies against native *E. coli* asparaginase and pegaspargase has been reported.[457,458] 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 PEG.[459] Therapeutic drug monitoring (TDM) can be considered for patients with low-grade systemic reactions to confirm efficacy and allow continuation of asparaginase. Patients who experience a grade 1 or 2 reaction but demonstrate adequate asparaginase activity can be considered for rechallenge.[460-463]

Similar to PEG, cal-PEG is a newer asparaginase enzyme formulation with a different linker molecule that enhances its hydrolytic stability.[449] A multicenter, open-label, randomized study determined the pharmacokinetic and pharmacodynamic profiles of PEG and cal-PEG 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.[449] 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).[464] 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 cal-PEG. The SAA was similar for both enzymes 18 days after the induction dose, but the SAA was higher for cal-PEG 25 days after induction, suggesting the potential for this enzyme to be given less frequently than PEG. Additionally, the two enzymes had similar efficacy. 99% of patients in the PEG arm achieved a CR compared to 95% in the cal-PEG arm (P = .12), and there was no difference in the frequency of end of induction MRD between the two groups. The 5-year EFS (± SE) of 84.9% (± 3.4%) was for PEG and 88.1% (± 3.0%) for cal-PEG (P = .65).[464] The FDA approved cal-PEG in December 2018 for use as part of multiagent therapy in pediatric and AYA patients (aged ≤21 years) with ALL. PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤21 years for more sustained asparaginase activity. [449,465]

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, ERW-rywn, which has a more frequent administration schedule, should be substituted, and is currently approved by the FDA for patients with ALL who have developed hypersensitivity to *E. coli*-derived asparaginase (see *Supportive Care: Asparaginase Toxicity Management* in the algorithm). A phase 2/3 study[453] supports a new intramuscular (IM) dosing scheduling for ERW-rywn of 25 mg/m^2 Monday/Wednesday, 50 mg/m^2 Friday based on positive risk:benefit ratio.

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, famotidine or ranitidine, diphenhydramine or cetirizine, and acetaminophen). Measures can be considered for preventing or limiting severity of infusion reactions or hypersensitivity including slowing infusion to ≥2 hours, infusing normal saline concurrently, and use of premedications. If anti-allergy medication is

used prior to PEG or ERW-rywn administration, TDM using commercially available asparaginase activity assays is highly recommended, since premedication may “mask” the systemic allergic reactions that can indicate the development of neutralizing antibodies.[460] However, if the patient experiences anaphylaxis or other allergic reactions of grade 3 or 4 severity (common terminology criteria for adverse events [CTCAE] 5.0[466]), 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,[452] and have been incorporated into the NCCN Guidelines for ALL (see *Supportive Care: Asparaginase Toxicity Management* in the algorithm).

Pain management should be used 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 (available at www.NCCN.org).

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