

American Society of Hematology 2026 guidelines for frontline management of acute lymphoblastic leukemia in adolescents and young adults

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Background: Adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL) represent a unique population. Treatment regimens can vary significantly depending on whether they receive care in a pediatric or in an adult setting. They also have distinctive care needs, social risk factors, and disease behavior compared with other age groups.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about the frontline management of ALL in AYAs.

Methods: ASH formed a multidisciplinary guideline panel including hematologists, AYA psychosocial care specialists, pharmacists, methodologists, and patient representatives with efforts to minimize bias from conflicts of interest. An evidence review team at Brown University supported guideline development, including performing systematic evidence reviews up to November 2023. The panel prioritized clinical questions and outcomes according to importance for clinicians and patients. The panel used grading of recommendations assessment, development, and evaluation (GRADE), including GRADE evidence-to-decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 15 recommendations and several good practice statements.

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Conclusions: Pediatric-inspired regimens containing asparaginase are recommended as frontline therapy compared with more traditional adult-inspired protocols, requiring significant supportive care and close follow-up. Allogeneic hematopoietic stem cell transplantation is not routinely recommended in first remission but may be indicated for higher-risk subsets or those with suboptimal responses to initial therapy. The use of targeted agents in frontline therapy is increasingly supported, although further research is needed to optimize this strategy.

Summary of recommendations

These guidelines are based on original systematic reviews of evidence conducted under the direction of the methods team from Brown University. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.¹⁻³ The panel used the grading of recommendations assessment, development, and evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations.⁴⁻¹⁰

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong (“the guideline panel recommends...”), or conditional (“the guideline panel suggests...”) and should be interpreted as described in [Figure 1](#).

Interpretation of good practice statements

As described by the GRADE guidance group, good practice statements endorse interventions or practices that the guideline

Recommendation strength				
	“Recommends...”	“Recommends against...”	“Suggests...”	“Suggests against...”
				
	Interpretation of strong recommendations		Interpretation of conditional recommendations	
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.		Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.	
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.		Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with the patient’s values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.	
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.		Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision-making is appropriate.	
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.		The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.	

Figure 1. Interpretations of strong and conditional recommendations for patients, clinicians, policymakers, and researchers.

panel agreed have unequivocal net benefit yet may not be widely recognized or used.⁴ Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Recommendations

Frontline treatment approach

RECOMMENDATION 1. For adolescents and young adults (AYAs) with B-cell or T-cell acute lymphoblastic leukemia (B-ALL/T-ALL) or T-cell acute lymphoblastic lymphoma (T-LBL/LLy) receiving frontline therapy, the American Society of Hematology (ASH) guideline panel *recommends* pediatric-inspired (asparaginase-containing) regimens (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Asparaginase management: dosing

RECOMMENDATION 2. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel *suggests* that empiric dose capping and dose reductions are reasonable strategies to mitigate asparaginase-induced toxicities in AYAs without evidence of adversely affecting disease outcomes (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).*

Remarks:

- The panel defines dose capping as a maximum pegylated asparaginase (PEG-Asp) dose of 3750 international units (IU).
- The panel defines reduced dosing of PEG-Asp as any weight-based dose of <2500 IU/m² for individuals aged <22 years, or <2000 IU/m² for individuals aged ≥22 years.
- *See “Good practice statement for recommendations 2 and 3” under “Asparaginase management” for therapeutic drug monitoring (TDM) guidance related to dose capping or reduction.

Asparaginase management: premedication

RECOMMENDATION 3. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel *recommends* the use of prophylactic premedication to prevent hypersensitivity reactions (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).*

Remarks:

- Premedication is defined at a minimum as IV steroid premedication and may also include antihistamines and/or acetaminophen.
- *See “Good practice statement for recommendations 2 and 3” under “Asparaginase management” for TDM guidance related to dose capping or reduction.

GOOD PRACTICE STATEMENT FOR RECOMMENDATIONS 2 AND 3. The panel considers it good practice to use TDM to ensure adequate asparagine depletion when dose capping and dose reductions are undertaken. TDM should also be used in the context of premedication to determine whether hypersensitivity

reactions are associated with antibody-mediated inactivation (ie, undetectable nadir serum asparaginase activity levels) or to identify silent inactivation.

Remark:

- The panel recognizes that there is some heterogeneity in the target asparaginase activity levels across studies and when and how levels should be monitored. An in-depth discussion and evaluation of the optimal asparaginase activity level is beyond the scope of this effort. However, based on pharmacokinetic and clinical outcomes data, activity levels of ≥0.1 IU/mL for at least 14 days are recommended to ensure adequate asparagine depletion.

Asparaginase management: venous thromboembolism (VTE) prophylaxis

RECOMMENDATION 4. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel *recommends against* the routine use of cryoprecipitate replacement (or fibrinogen concentrate) outside the context of active bleeding (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 5. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel *recommends against* the routine use of unfractionated heparin (UFH) for VTE prophylaxis (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).

NO RECOMMENDATION. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against routine VTE prophylaxis with low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs).

NO RECOMMENDATION. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against routine antithrombin (AT) replacement.

Remark (for this group of recommendations for VTE prophylaxis with asparaginase):

- The panel recognizes there is uncertainty in the timing and duration of VTE prophylaxis (induction, consolidation, intensification), LMWH dosing, and AT replacement targets. They also highlight the importance of risk models to identify patients at high risk for developing VTE.

Asparaginase management: alternative formulations

RECOMMENDATION 6. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens who develop an asparaginase-related allergic/hypersensitivity reaction with PEG-Asp, the ASH guideline panel *recommends* that patients switch to an *Erwinia*-based asparaginase formulation over discontinuation of asparaginase therapy (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- The panel was unable to provide a recommendation related to desensitization due to the lack of evidence comparing the effects of desensitization vs alternative asparaginase products.
- The ASH guideline panel concluded that the benefits, such as improved survival and disease control, outweighed the drawbacks, including the high costs and resources for *Erwinia*-based treatments.

Asparaginase management: rechallenging after toxicity

NO RECOMMENDATION. For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens who have a nonhypersensitivity asparaginase-related toxicity, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation on resuming asparaginase therapy.

Allogeneic transplant in first complete remission (CR1)

RECOMMENDATION 7. For AYAs with ALL receiving frontline therapy and in CR1, the ASH guideline panel *suggests against* routinely proceeding with allogeneic hematopoietic stem cell transplantation (allo-HSCT) as consolidation (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- For specific high-risk subgroups (especially those with minimal residual disease [MRD] persistence, induction failure, and high-risk biologic subsets), there may be a survival benefit from allo-HSCT in CR1.

Additional therapies for specific subsets: rituximab

RECOMMENDATION 8. For AYAs with CD20⁺ B-ALL receiving frontline therapy, the ASH guideline panel *suggests* the addition of rituximab to standard chemotherapy (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- The panel recognizes the considerable uncertainty associated with rituximab dosing, frequency and timing of administration, the minimum required level of CD20 expression, and the lack of data specific to younger AYA individuals.

Additional therapies for specific subsets: blinatumomab

RECOMMENDATION 9. For AYAs with B-ALL receiving frontline therapy, the ASH guideline panel *suggests* the addition of blinatumomab for those who achieve morphologic remission, regardless of MRD status (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- The panel recognizes there are limited data using blinatumomab within conventional pediatric-inspired (asparaginase-containing) chemotherapy backbones in AYAs.

- The panel further recognizes the evolution of evidence in this space, and that the recommendation may change with the availability of more data.
- Guidance for individuals with MRD persistence is addressed in Recommendation 15.

Additional therapies for specific subsets: inotuzumab ozogamicin (inotuzumab)

NO RECOMMENDATION. For AYAs with B-ALL receiving frontline therapy, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against the addition of inotuzumab.

Additional therapies for specific subsets: nelarabine

NO RECOMMENDATION. For AYAs with T-ALL receiving frontline therapy with all planned doses of asparaginase (including Capizzi methotrexate-based interim maintenance), the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against the addition of nelarabine.

Remark:

- The panel noted that incorporating nelarabine may provide benefit among subgroups of AYAs including those with non-early T-cell precursor (non-ETP) subtype, central nervous system 3 (CNS3) disease, and/or others who receive a high-dose methotrexate-based interim maintenance regimen.

RECOMMENDATION 10. For AYAs with T-LBL/LLy receiving frontline therapy, the ASH guideline panel *suggests against* the addition of nelarabine, due to insufficient evidence demonstrating efficacy for nelarabine in these patients (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Additional therapies for specific subsets: bortezomib

RECOMMENDATION 11. For AYAs with T-ALL receiving frontline therapy, the ASH guideline panel *suggests against* the addition of bortezomib into treatment regimens (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

NO RECOMMENDATION. For AYAs with T-LBL/LLy, the ASH guideline panel determined the evidence is insufficient to recommend for or against addition of bortezomib.

Remark:

- The panel noted that incorporating bortezomib may provide benefit among the youngest adolescents of the AYA population.

Treatment for Ph⁺ ALL

RECOMMENDATION 12. For AYAs with Philadelphia chromosome-positive (Ph⁺) ALL, the ASH guideline panel *suggests* reduced-intensity therapy (RIT) with a tyrosine kinase inhibitor (TKI) for remission induction over intensive chemotherapy (IC) with a TKI. This should be followed by postremission therapy. Options include IC plus a TKI and/or immunotherapy plus a TKI. Either of these approaches may be consolidated by allo-HSCT in CR1 (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- All patients with Ph⁺ ALL must receive CNS prophylaxis with concurrent intrathecal (IT) chemotherapy (see Recommendation 13).
- The panel recognizes that postremission therapies (including allo-HSCT) are evolving given emerging data surrounding next-generation TKIs and novel/targeted immunotherapies.
- This recommendation may not be as applicable to the youngest AYA subgroup in which pediatric-inspired (asparaginase-containing) regimens would be applied; the panel appreciates that studies of pediatric-inspired backbones were not captured within the available data set.

CNS prophylaxis: IT chemotherapy regimens

RECOMMENDATION 13. For AYAs with ALL receiving frontline therapy, the ASH guideline panel *suggests* the use of either IT methotrexate or triple IT therapy (TIT) for CNS prophylaxis (conditional recommendation for either the intervention or comparison based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- Hydrocortisone can be used (in conjunction with IT methotrexate) for prevention of chemical arachnoiditis.

CNS prophylaxis: cranial radiation

RECOMMENDATION 14. For AYAs with ALL receiving frontline therapy, the ASH guideline panel *suggests* against the routine use of cranial radiation for CNS prophylaxis for patients treated on a pediatric-inspired (asparaginase-containing) backbone (conditional recommendation against the intervention based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- There is uncertainty with respect to the use of cranial radiation for CNS prophylaxis for AYA individuals with T-ALL who are unable to receive nelarabine.

Approach for MRD

RECOMMENDATION 15. For patients with ALL with persistent MRD after ≥3 months of frontline therapy (induction plus a minimum of 1 block of postremission therapy), the ASH guideline panel *recommends* a change in approach to treatment (see Recommendation 9) (strong recommendation for the intervention based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- The change in therapy could include several approaches including immunotherapy or allo-HSCT. The optimal timing, choice of intervention(s), order, or combination of these approaches has not been defined.
- Although T-ALL has not been studied individually, patients with T-ALL were included in the studies, demonstrating the benefit of transplant for patients with MRD positivity.

GOOD PRACTICE STATEMENT FOR RECOMMENDATION 15. Measurement of disease response using MRD is considered standard

of care in AYA ALL for both prognostic value and, in some cases, determination of treatment intensity.

Good practice statements

Good practice statement. Given the unique challenges of cancer in adolescence and young adulthood, it is good practice for AYAs with ALL to have their developmental needs evaluated, and their preferences and goals for treatment assessed within their unique developmental context. Whenever possible, their treatment should be delivered with these considerations in mind, providing scheduling flexibility when not otherwise contraindicated.

Good practice statement. Given the risk and prevalence of psychological comorbidities and adverse psychosocial outcomes during the cancer experience of AYAs with ALL, it is good practice to routinely screen for depression, anxiety, and other psychological comorbidities and implement multidisciplinary psychosocial support.

Good practice statement. Given the unique social needs of AYAs with ALL, it is good practice to assess and evaluate each patient's existing social supports and encourage connection with supportive communities when possible, through organized care coordination and resource navigation from a multidisciplinary team experienced in working with AYAs.

Good practice statement. Given the financial toxicity experienced by AYAs with ALL, it is good practice to provide financial counseling, resource navigation, and concrete resources through institutional means and/or in collaboration with larger regional/national organizations.

Good practice statement. Given the importance of sexual health and sexuality for AYAs with ALL, along with the dynamic changes experienced in these areas over time, it is good practice to discuss sexual health, sexual orientation, sexual preferences, and gender identity of each individual patient from the onset of diagnosis, again throughout the course of the individual's treatment, and into survivorship.

Good practice statement. Given the importance of fertility and how it is affected by cancer and its therapy, it is good practice to provide AYAs with ALL access to comprehensive fertility care and consultation from, but not limited to, their oncology provider, fertility specialist, and fertility counselors before the initiation of therapy whenever possible, with continued involvement and care from this multidisciplinary team throughout therapy and into survivorship.

Good practice statement. Given that AYAs are underrepresented in cancer clinical trials, and improvement in survival over time has lagged in underrepresented populations of AYAs, it is good practice to offer AYAs treatment in appropriate clinical trials.

Good practice statement. It is good practice to introduce interdisciplinary palliative care teams as early as possible during treatment. Interdisciplinary and/or primary (ie, delivered by the treating oncology team) palliative care should remain a focus of care throughout the care continuum, regardless of disease status.

Good practice statement. It is good practice to discuss goals of care and end-of-life concepts earlier in treatment, and before disease- or symptom-related crises arise. These discussions should be ongoing, tailored to the AYAs developmental and cognitive level, centered on the AYAs wishes, and should involve families and/or caregivers to the extent desired by the AYA. End-of-life care goals should be readdressed at key transition points during care (eg, relapse).

Good practice statement. Considering differential outcomes for AYAs by location of care, in the context of their unique medical and developmental needs and the recommendations and statements included here, it is good practice to ensure AYAs with ALL have access to specialized care with professionals and institutions well versed in AYA ALL, whenever feasible.

Introduction

Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations on the frontline treatment of ALL in AYAs. The primary goals of these guidelines are to review, critically appraise, and implement evidence-based recommendations that address ongoing questions related to several aspects of treatment approach, disease assessment, and supportive care for this specific patient population. The appraisal and interpretation of available literature was conducted in the context of rapidly evolving diagnostic, monitoring, and therapeutic options. Through improved provider and patient education of the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision-making between clinicians and patients that will result in optimal treatment choices.

The target audience includes patients, hematologists, general practitioners, internists, other clinicians, and decision-makers. Policy makers interested in these guidelines include those involved in developing local, national, or international plans with the goal of optimizing approaches to AYAs with ALL, given their unique circumstances; these include disease biology, therapeutic options, susceptibility to toxicities, and psychosocial challenges specific to AYAs with a new diagnosis of ALL. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

AYA ALL remains a challenging malignancy to manage and although survival rates have significantly improved, a single standardized frontline treatment has not been established for treatment of ALL in AYAs. The National Cancer Institute defines AYAs with cancer as individuals diagnosed with cancer between the ages of 15 and 39 years (<https://www.cancer.gov/types/aya>). Considerable uncertainty persists regarding the optimal therapeutic approach to the AYA patient, with varying approaches between pediatric and adult practitioners. Regardless, treatment is intensive and lasts a long time, with tremendous demands on the patient, caregivers, and families. This adds to the significant short- and long-term psychosocial and socioeconomic burden caused by the disease itself. It is also crucial to consider the treatment-related toxicities and late effects of these treatments, although related survival outcomes have improved.

Despite significant advancements in treatment, which have included the introduction of immunotherapy into frontline regimens, it is crucial to engage in a rigorous evaluation of the optimal approach and management of AYAs with ALL. ALL treatment backbones have evolved over the course of several decades, with differences in approach not only related to pediatric-style or adult-style therapies but also the incorporation of allo-HSCT, novel therapies, and measurement of MRD response.

Nevertheless, distinctions between the approaches used more commonly by pediatric or adult hematologist-oncologists highlight an urgent need for harmonized, evidence-based guidelines to address gaps and inconsistencies in care for the AYA age group. This guideline attempts to focus on approaches tailored for AYAs, addressing the complexities of disease biology, treatment responses, psychosocial, and health system-related factors unique to this age group. By leveraging recent advancements in the field ranging from allo-HSCT and targeted therapies to detection of MRD, the panel aims to provide a framework for improving outcomes in this vulnerable population. By actively bridging adult and pediatric expertise and literature, the panel aims to ensure equitable access to novel therapies and provide a clearer road map for the frontline treatment of ALL in the unique AYA population.

The GRADE approach was used to systematically rate the quality of evidence and the strength of recommendations. A significant challenge was posed by the indirectness of the existing data; specifically, much of the evidence for AYA ALL is derived from studies focused on either pediatric or adult populations, with limited representation of AYAs. The lack of dedicated AYA-focused studies (described in more detail hereafter) introduced uncertainty when extrapolating benefits and harms to the unique AYA population. Nonetheless, considering the importance of this issue, the panel attempted to use the best available evidence, albeit indirect, to appropriately tailor recommendations to the specific clinical niche of AYAs with ALL.

Although the panel used the widely accepted National Cancer Institute definition of AYA, including patients aged 15 to 39 years at leukemia diagnosis, our group recognized that there were limited data that spanned the full AYA age range; thus, there were nuances in considering regimens for the youngest AYA patients. For special populations, these nuances are noted in the sections hereafter as relevant. The term “pediatric-inspired” regimen is used throughout the recommendations hereafter; this refers to the implementation of a pediatric regimen in an adult population in which there have been subtle adaptations to the pediatric regimen over time. Furthermore, when using this term, the panel is referring to both this adaptation and traditional high-risk pediatric regimens. For brevity, the abbreviation B-ALL within this document is used to represent Philadelphia chromosome-negative (Ph⁻) ALL.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.⁵⁻¹¹ The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the Guideline International Network—

McMaster guideline development checklist (<http://cebgrade.mcmaster.ca/guidecheck.html>)¹² and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.¹⁻³

Organization, panel composition, planning, and coordination

The work of the 2 ALL in AYA panels was coordinated by the ASH and the Brown University School of Public Health (funded by ASH under a paid agreement). Project oversight for both panels was provided by the ASH guideline oversight subcommittee (represented by M.C.C., the ex officio member of the panel), which reported to the ASH committee on quality. The ASH vetted and appointed individuals to the guideline panels. The 2 panels worked in parallel and collaborated in protocol development and other aspects of guideline development. The Brown University School of Public Health vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process including the use of the GRADE approach. The membership of the panels and the methods team is described in supplement 1.

The frontline panel included hematologists/oncologists specializing in either pediatric or adult ALL, or both, each with relevant clinical and research experience, alongside pharmacists, a social worker, a clinical psychologist, and individuals with lived experience of ALL during the AYA period. One pediatric and 1 adult hematologist served as clinical cochairs of the panel.

In addition to synthesizing evidence systematically, the Brown University School of Public Health, in collaboration with ASH staff, helped to train the panel members in guideline and systematic review methodology, led research question and protocol development discussions, organized research question eligibility criteria, coordinated outcome prioritization, developed summary tables, and participated in panel discussions, synthesizing the evidence and developing recommendations and good practice statements (primarily to ensure that recommendations aligned with the evidence). The panel's work was done using web-based tools (www.questionpro.com and www.gradeapro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by the ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of the ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings. The panelists received no other payments. Through the Brown University School of Public Health, researchers who contributed to the systematic evidence reviews received salary support or direct payment.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine¹³ and the Guidelines International Network.² Participants disclosed all financial and nonfinancial interests with for-profit health

care companies, regardless of relevance to the guideline topic. ASH staff and the ASH guideline oversight subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. During the guideline development process, panelists avoided significant direct financial relationships with for-profit health care companies, agreeing to keep the total value of all direct financial conflicts under \$7500 per year (excluding travel support for educational or academic purposes). Many panelists had relevant nonfinancial interests, such as published opinions on the guideline topic. None of the Brown University School of Public Health researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

Recusal was used to manage certain conflicts.^{5,14-16} During discussions about recommendations, any panel member who was a current lead principal investigator in relevant research could participate in evidence and clinical context discussions; however, they were recused from making judgments or voting about individual domains (eg, magnitude of desirable consequences) and the direction and strength of the recommendation. The "evidence-to-decision" (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

On 30 June 2025, 1 panel member, (L.I.) disclosed that during the guideline development process they had received direct payments or other transfers of value from companies that could be affected by the guidelines in excess of the amount allowable. These disclosures occurred after the panel had agreed on recommendation statements. ASH staff and our ex officio representative from the Guideline Oversight Subcommittee reviewed the guidelines in relation to these late disclosures and agreed that conflicts were unlikely to have influenced any of the recommendations.

Supplement 2 provides the complete disclosure-of-interests forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years before appointment; in part B, indirect financial interests; and in part C, not mainly financial interests. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplement 3 provides the complete disclosure-of-interest forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel formulated a preliminary list of research topics for both the frontline management and relapsed/refractory panels starting in August 2022. Based on this list, the methods team reformulated research topics into formal population, intervention, comparator, and outcomes questions and drafted preliminary eligibility criteria for each question. Through a series of regular Zoom conference calls with the full panel, calls with the cochairs, and email communications, together with the methods team and ASH staff, the panels developed a list of 33 research questions (21 for the frontline management panel, 8 for the relapse/

refractory management panel, and 4 for both panels) with detailed eligibility criteria.

We originally planned to draft recommendations during a 2-day in-person meeting in October 2023; however, the methods team instead presented evidence from randomized controlled trials (RCTs) and existing systematic reviews to the panels. Because up to ~600 additional studies were potentially eligible across all topics, the coauthors instead reprioritized the research questions to a more feasible scope, focusing on topics that were likely to be most impactful for patient care. The final prioritized clinical questions for frontline management are presented in Table 1, derived from the original list determined by the panel, with minor wording changes.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.^{8,17} In brief, the panels prioritized outcomes in 3 steps. The coauthors and methods team initially brainstormed all possible outcomes for each clinical question. Then, all panel members rated the relative importance of outcomes for decision-making via a QuestionPro survey in April 2023, focusing attention on those considered most important for clinicians and patients, following the GRADE approach.⁸ While acknowledging considerable variation in the impact on patient outcomes, the panel considered the outcomes listed as critical for clinical decision-making (Table 1). The outcomes rated highly by the panel and those identified as important based on the literature reviews were further refined and finalized during panel meetings until June 2023. When questions were reprioritized in October 2023 in in-person meetings, the outcomes of importance remained the same as originally prioritized.

Evidence review and development of recommendations

Under the direction of the Brown University School of Public Health, researchers followed standard, current methodology from the Agency for Healthcare Research and Quality and outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting systematic reviews and evaluating the evidence base.^{4-6,8-10,18} The methodology team conducted a broad search for all 33 original research questions across both frontline management and relapsed/refractory panels. All research questions were initially addressed by new systematic reviews. Literature searches were conducted in PubMed, Embase, PsycINFO, and CINAHL. The final searches were run on 29 November 2023, but additional studies were sought from reference lists of existing systematic reviews. Panel members also suggested additional potentially eligible studies through August 2024. Citations were screened in duplicate using Abstrackr (<https://abstrackr.com/>), an abstract screening tool that uses machine learning to prioritize most-relevant studies based on the accept and reject labels provided by human screeners. Conflicts were adjudicated in team meetings. The full texts of potentially eligible studies were rescreened in duplicate, with conflicts adjudicated by a senior researcher.

For each prioritized research question, the methods team prepared ≥1 GRADE evidence tables, using the GRADEpro guideline development tool (<https://gradepro.org>). Separate rows (and, thus, summaries of evidence and determination of certainty in evidence) were included for each outcome and reported separately at

Table 1. Clinical questions formulated and prioritized

Questions determined by the panel	Outcomes
For AYAs with B-ALL/T-ALL or T-LBL/Ly receiving frontline therapy, what are the comparative benefits and harms of asparaginase-containing regimens (eg, CALGB 10403) vs non-asparaginase-containing regimens (eg, hyper-CVAD) for frontline therapy?	OS RFS/EFS/DFS/PFS/relapse CR MRD-negative status Fertility QOL Allo-HSCT Toxicity
For patients (of any age) with ALL receiving frontline asparaginase, what are the comparative benefits and harms of changing asparaginase dose by: (1) following asparaginase levels (including monitoring frequency and timing) and changing asparaginase doses in response to those levels, (2) dose capping, (3) dose lowering (per BSA per square meter)?	OS RFS/EFS/DFS/PFS/relapse CR MRD-negative status QOL Hospital admission Toxicity
For patients with ALL receiving asparaginase, what are the comparative benefits and harms of prophylactic premedication to prevent infusion reactions?	RFS/EFS/DFS/PFS/relapse Silent inactivation Switches or discontinuation Hospital admission Toxicity
For patients with ALL receiving frontline asparaginase therapy, what are the comparative benefits and harms of different prophylaxis regimens to prevent hypercoagulation including (1) anticoagulation for VTE prophylaxis (thromboprophylaxis), and (2) monitoring (eg, PT/PTT/INR/ATIII and fibrinogen levels) with reflex product replacement administration (or replacement recombinant AT)?	Hospital admission Toxicity
For AYAs with ALL receiving frontline asparaginase who have an asparaginase-related reaction (allergic-type reaction), what are the comparative benefits and harms of desensitization vs use of alternative asparaginase products (<i>Erwinia</i> , Rylaze)?	OS RFS/EFS/DFS/PFS/relapse Asparaginase activity levels QOL Hospital admission Toxicity
For AYAs with ALL receiving frontline asparaginase who have an asparaginase-related toxicity (eg, coagulation-related side effect, pancreatitis, or hepatotoxicity), what are the comparative benefits and harms of resuming (or changing) asparaginase therapy?	OS RFS/EFS/DFS/PFS/relapse QOL Hospital admission Toxicity
For AYAs with ALL being treated with frontline therapy, what are the comparative benefits and harms of allo-HSCT vs no transplant (in CR1)?	OS RFS/EFS/DFS/PFS/relapse
For patients with B-ALL or T-ALL or T-LBL/Ly in frontline therapy, what are the comparative benefits and harms of inclusion (vs no inclusion) of targeted therapies (eg, inotuzumab, blinatumomab, rituximab, nelarabine, and bortezomib)?	OS RFS/EFS/DFS/PFS/relapse MRD-negative status Fertility QOL Allo-HSCT Financial toxicity Toxicity
For patients with Ph ⁺ ALL, what are the comparative benefits and harms of frontline treatment consisting of (1) IC plus a TKI, (2) reduced-intensity chemotherapy plus a TKI, or (3) targeted immunotherapy (eg, blinatumomab, inotuzumab) plus a TKI?	OS RFS/EFS/DFS/PFS/relapse MRD-negative status QOL Adherence Allo-HSCT Financial toxicity Toxicity

ATIII, antithrombin III; BSA, body surface area; INR, International normalized ratio; PFS, progression-free survival; PT, prothrombin time; PTT, partial thromboplastin time.

Table 1 (continued)

Questions determined by the panel	Outcomes
For patients with ALL without CNS involvement at diagnosis, what are the comparative benefits and harms of different CNS prophylaxis regimens, including (1) IT chemotherapy regimens, and (2) cranial radiation?	OS
	RFS/EFS/DFS/PFS/relapse
	CNS recurrence
	Neurocognitive impact
	QOL
	Caregiver burden
For patients with ALL receiving frontline therapy and being assessed for MRD, what are the comparative benefits and harms of changing the treatment regimen due to the detection of MRD, including incorporation of immunotherapy?	Toxicity
	OS
	RFS/EFS/DFS/PFS/relapse
	Complete remission
	MRD-negative status
	QOL
	Allo-HSCT
	Toxicity

ATIII, antithrombin III; BSA, body surface area; INR, International normalized ratio; PFS, progression-free survival; PT, prothrombin time; PTT, partial thromboplastin time.

different time points. In addition, studies reporting different effect size measures (typically relative risks or hazard ratios [HRs]) were summarized separately. For the purpose of entering data into the GRADE software, the methods team conducted restricted maximum likelihood meta-analyses when at least 2 studies had similar comparisons at the same time point using the same effect size measure. Proportions were meta-analyzed after double arcsine transformation. The methods team also assessed clarity and accuracy of study eligibility criteria, interventions, outcomes, and results reporting.

The certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed by the GRADE software (based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding) for each evaluated outcome (split by follow-up time and/or analytic measure). Study risk of bias was evaluated with the Cochrane collaboration's risk of bias tool for RCTs,¹⁸ and additional selected questions that addressed selection and analytic methods from ROBINS-I (risk of bias in nonrandomized studies of interventions).¹⁹ To evaluate directness of the evidence and standardize/rationalize eligibility criteria across topics, the coauthors for the frontline management

and relapse/refractory panels defined 6 tiers of evidence that were agreed upon by the panels (Table 2).

Interested readers may find more explanation about the GRADE approach to assessing and rating certainty in a body of evidence in other publications.^{7,9,20}

The panel began drafting clinical recommendations with a 2-day in-person meeting in October 2023, followed by a series of video conference calls to review evidence for the reprioritized research questions between February 2024 and September 2024. In separate virtual calls for each research question, the Brown University School of Public Health methods team leads presented the summarized data and GRADE evidence profiles to panel members, who provided feedback on clarity, completeness, and accuracy of the summarized data. For each question, the panel decided which tiers of studies would be included, dependent on how many higher tier studies were identified (Table 3).

The panel took a population perspective (considering a broad, well-resourced population) and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly considered the extent of resource use associated with alternative management options. The panel prepared a GRADE EtD framework, using the GRADEpro guideline development tool (<https://gradepro.org>).^{5,6,11} The EtD table addressed effects of interventions, resource use, values and preferences (relative importance of benefits and harms), equity, acceptability, and feasibility. The panel did not explicitly solicit judgments for the certainty in evidence underlying resource requirements (costs) and cost-effectiveness unless the panel raised these issues for discussion.

The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in 1 instance, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. Between October 2024 to May 2025, the cowriters and coauthors, with support from the methodology team, refined the manuscript sections drafted by panel members. The panel developed recommendations when feasible and appropriate based on the evidence and discussion among panel members. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Table 2. Categorization of evidence by tier

Tiers	Publication year	Sample size	Age, y	Directness
Tier 1	≥2000	N ≥ 10	AYA	Direct
Tier 2	≥2000	N ≥ 10	Median, 15-39	Serious indirect
Tier 3	≥2014	N ≥ 25	Median, 10-14 or 40-65	Very serious indirect
Tier 4	≥2000	N ≥ 25	Median, 10-14 or 40-65	Very serious indirect
Tier 5	≥2014	N ≥ 25	Median, <10 or >65	Very serious indirect
Tier 6	≥2000	N ≥ 25	Median, <10 or >65	Very serious indirect

The certainty was categorized into 4 levels ranging from very low to high.^{7,9,20} Within this report, these categories are represented by symbols, as described in Figure 2.

Table 3. Eligibility criteria by research question

Topic	Eligible study designs	Studies, N	Eligible study tiers (included tiers)
1. Pediatric-inspired vs adult-inspired regimens	Comparative; prospective single-group	24	1 (1)
2. Changing asparaginase dose by (1) monitoring asparaginase levels, (2) dose capping, or (3) dose lowering	Comparative; single-group	9	1-6 (1, 2, 4, 5)
3. Prophylactic premedication to prevent asparaginase infusion reactions	Comparative	6	1-6 (1, 5*)
4. Prophylaxis against hypercoagulation, including (1) anticoagulation and (2) hypercoagulation monitoring	Comparative	14	1-6 (2, 3, 5, 6)
5. After asparaginase-related reaction, desensitization vs alternative asparaginase product	Comparative; single-group	7	1-6 (3, 4, 5)
6. After asparaginase-related toxicity, resuming or changing asparaginase product	Comparative	0	1-6
7. Allo-HSCT vs no transplant	Comparative	7	1, 2 (1, 2)
8. Targeted therapies (eg, inotuzumab, blinatumomab, rituximab, nelarabine, or bortezomib)	Comparative; single-group	15	1-4
Blinatumomab		2	(3, 4)
Nelarabine		8	(1, 2, 3, 4)
Bortezomib		1	(3)
Rituximab		4	(2, 3, 4)
9. Ph+ treatments: reduced vs IC, with a TKI	Comparative; single-group	25	1-3 (1, 2, 3)
10. CNS prophylaxis regimens, including (1) IT chemotherapy regimens and (2) cranial radiation	Comparative	15	1-6
IT chemotherapy		2	(5, 6)
Cranial radiation		13	(3, 5, 6)
11. Changing the treatment regimen due to the detection of MRD	Comparative	5	1-6 (1, 2, 3)

*One study did not report participant age data, so the tier could not be determined.

Interpretation of strong and conditional recommendations

The recommendations are labeled as either “strong” or “conditional” according to the GRADE approach. The words “the guideline panel recommends” are used for strong recommendations, and “the guideline panel suggests” for conditional recommendations. Figure 1 provides GRADE’s interpretation of strong and conditional recommendations by patients, clinicians, health care policymakers, and researchers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online from 27 September to 29 October 2024, for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Two individuals or organizations submitted comments across both guideline panels: frontline and relapsed/refractory management. Six individuals or organizations submitted comments specifically for the frontline management panel. The document and deliverables were revised to address relevant comments, and any changes were communicated to each commenter between November 2024 and January 2025.

One comment suggested reconsidering the nelarabine recommendation in T-ALL and prompted extensive discussion; in particular, the comment highlighted the dearth of data that were AYA-specific data or in the setting of Capizzi-methotrexate,

coupled with toxicity and cost. In response, the panel reviewed the data again in detail and adjusted the strength of the recommendation to reflect the uncertainty in the data, expanding on this in the remarks and further discussion. Consequently, the panel also reconsidered the AYA-specific data regarding bortezomib in

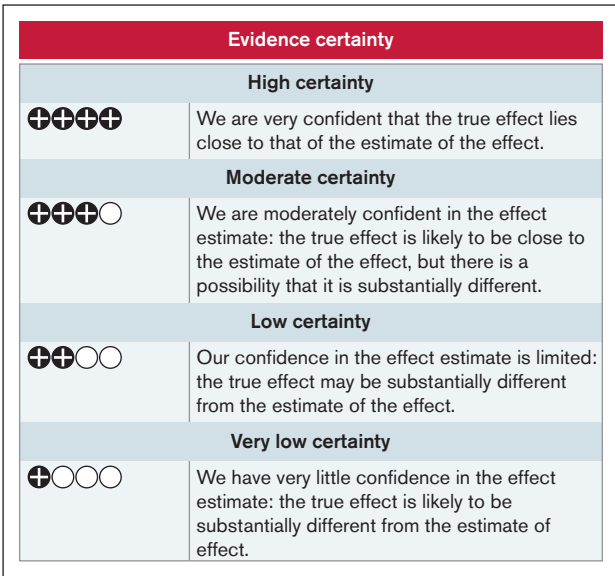


Figure 2. Certainty of evidence for outcomes of interest.

T-LBL and revised this recommendation. Due to insufficient evidence both yielded “no recommendation” statements within the final publication. In a full panel meeting (20 November 2024), the frontline management panel reviewed and approved the changes, which were then communicated to the relevant commenter.

By 23 September 2025, the ASH guideline oversight subcommittee and the ASH committee on quality approved that the defined guideline development process was followed, and on 1 October 2025, the officers of the ASH executive committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians and patients make shared decisions about diagnostic and treatment alternatives, with the goal of improving quality of patient care. Other purposes are to inform policy, education, and advocacy, and to state future research needs.

These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, or availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary of findings tables in each section.

Recommendations

Frontline treatment approach

For AYAs with B-ALL/T-ALL or T-LBL/LLy receiving frontline therapy, what are the comparative benefits and harms of asparaginase-containing regimens (eg, CALGB 10403) vs non-asparaginase-containing regimens (eg, hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone]) for frontline therapy?

Recommendation 1

For AYAs with B-ALL/T-ALL or T-LBL/LLy receiving frontline therapy, the ASH guideline panel *recommends* pediatric-inspired (asparaginase-containing) regimens (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Summary of the evidence. The panel considered a total of 24 studies for review,²¹⁻⁴⁷ all of which were tier 1 and had a median patients age range in the AYA age, including 1 RCT and other comparative analyses of prospective and retrospective comparative cohorts. The definitions of therapeutic approaches (pediatric-inspired and adult-inspired) were established by the authors of the primary manuscripts. In general, pediatric-inspired regimens are those typically administered in a largely outpatient setting and include intensive asparaginase, whereas adult-style regimens are historically non-asparaginase-including (or not containing intensive asparaginase) regimens that rely primarily on repeated inpatient hospitalizations for infusional myelosuppressive chemotherapy administration. The panel acknowledges that the available evidence lacks some of the most recent data on incorporation of targeted immunotherapy into frontline regimens for AYAs, although all efforts were made to incorporate newer data as they emerged.

The critical outcome was identified to be overall survival (OS), with event-free survival (EFS), and disease-free survival (DFS) also clinically important outcomes. Although toxicities were considered important, limited data are available on comparative outcomes of toxicity; the panel also acknowledges that the data set may not capture data on all outcomes of importance, including hospitalizations and quality of life (QOL). A total of 23 included studies reported OS (or death),^{21-23,25-47} 13 of which were comparative and 10 of which were single-group. Eight comparative studies reported EFS (or an event),^{22,24,25,28,33,34,41,44} and 6 included comparisons of DFS or relapse-free survival (RFS).^{22,25,29,37,43,46} Given lack of direct evidence in the form of RCTs, the data from the comparative studies on the outcomes of interest were pooled to generate effect sizes of the impact of pediatric-inspired vs adult-inspired regimens. The evidence profile and EtD framework are available online at https://guidelines.ash.gradepro.org/profile/8_VaFSTb_s.

Benefits. The evidence reviewed by the panel demonstrates a significant decrease in mortality at 7 years (HR, 0.53; 95% confidence interval [CI], 0.37- 0.77) with pediatric-inspired regimens. Analyzing 2-year mortality with available studies, the HR nonsignificantly favored pediatric-inspired protocols, suggesting late toxicity and/or relapse may play a role as well (HR, 0.89; 95% CI, 0.47-1.69). EFS at 7 years also significantly favored pediatric-inspired therapy (HR, 0.45; 95% CI, 0.33-0.63), with a nonsignificant decrease in relapse at 2 years (HR, 0.74; 95% CI, 0.40-1.30).

Overall, the estimated desirable effects are large. Although the certainty in the evidence is very low (as per GRADE) owing to the sparseness of RCTs, the large number of comparative studies (most of which leveraged RCTs to make retrospective comparisons) and the median age of individuals within the studies (AYA range) were compelling for the panel. In particular, the panel considered the consistency of the results strongly favoring pediatric-inspired regimens and the low likelihood that additional future studies would change the results; as such, the panel decided to formally upgrade the certainty in evidence within the EtD framework to moderate certainty. The overwhelming majority of the panel felt a strong recommendation for pediatric-inspired therapy was warranted, whereas 1 dissenting voice felt a

conditional recommendation was appropriate given the potential difficulty of implementing the recommendation in all settings. All panelists agreed that the potential magnitude of survival benefits is substantial and clinically meaningful to patients. Patient representatives on the panel placed the highest value on OS and mortality relative to other outcomes, with toxicity as an additional important outcome. The panel felt confident that the available effect estimates were representative of the true effect and that there was a low likelihood that future evidence would change the effect estimates. Although understanding that some uncertainty regarding the strength of the evidence remains, they highlighted the difficulty of conducting an RCT comparing these approaches in the context of the current data and the low likelihood that future RCTs will be conducted in this area.

Harms and burden. In considering the potential harms or undesirable effects of pediatric-inspired therapy for AYAs with ALL, toxic mortality, pancreatitis, and fertility were specifically considered of particular interest. Toxic mortality was included in only 2 comparative studies^{24,33} and pancreatitis in 1,³³ and fertility rates were not addressed at all. Considering overall toxicity, there was no statistically significant difference between regimens, but the HR for treatment-related mortality (TRM) favored pediatric-inspired therapy (HR, 0.68; 95% CI, 0.10-4.41).

The burden of therapy in AYAs with ALL is difficult to measure objectively. All current intensive ALL regimens, regardless of approach (pediatric-inspired vs adult-inspired) are long and arduous, require intensive supportive care from the health care team, and may incur significant debt on the patients and their caregivers due to out-of-pocket costs for prescriptions, travel, and lost productivity and job revenue. Implementation of pediatric-inspired regimens requires additional health system resources and infrastructure to ensure the safe and timely delivery of treatment modules in the outpatient setting; in contrast, adult-inspired regimens are associated with different burdens, including repeated planned hospitalizations and similar challenges relating to delivering care on prescribed schedules. Although both approaches pose challenges, in part due to the unique patient population and the prolonged treatment (nearly 3 years), with strong outcomes weighing in its favor, the panel ultimately recommends the use of pediatric-inspired therapy for AYAs with ALL.

Other EtD criteria and considerations. Survival outcomes (OS, EFS) were identified as the outcomes of utmost importance by both health care professionals and patient representatives on the panel, with a focus on toxicity as well. As described earlier, access to care, feasibility, and equity were also considered and discussed at length.

The evidence includes only a single RCT, and relies largely on retrospective comparisons, some of which compare outcomes on pediatric vs adult trials that were prospectively conducted, and some compare single-institution/single-group outcomes with historical data. The panel recognizes this limitation, which led to a prolonged consideration toward the weight of the recommendation, but given the consistent directionality of the available data, the panel decided a strong recommendation was warranted. There is also a lack of dedicated evidence on toxicity comparisons between regimens. The panel identified not only pancreatitis as a specific

toxicity of interest, but also other asparaginase-related toxicity such as thrombosis and hypersensitivity. Also considered were fertility, steroid-associated toxicities, infectious complications, avascular necrosis, and unplanned hospitalizations. Some of these would be unlikely to be compared between pediatric- and adult-inspired regimens given less usage of certain agents (for example, asparaginase would unlikely be a component in most adult-inspired regimens). However, for toxicities that would be expected regardless of regimen, such as unplanned hospitalizations, the data do not currently exist.

An important area in which the current guidelines are lacking is the impact of immunotherapies on the outcomes of interest. Some of these agents will be discussed in other sections of these guidelines but given differential access to, and uptake of, these agents within pediatric vs adult studies, few comparative outcomes exist. This will be discussed in later sections. The panel acknowledges that these agents have the potential to dramatically reshape our approach to ALL in general, including in the AYA population. However, it should be noted that there is a lack of data integrating immunotherapy with pediatric-based regimens in the AYA population. It should also be noted that the ability to deliver these therapies to all patients may highlight further inequities in access to care.

Conclusions and research needs for this recommendation. Prioritizing survival outcomes (OS, EFS, and DFS) as critically important and considering toxicity as an important outcome, the panel concludes that the use of pediatric-inspired therapy results in superior outcomes for AYAs with newly diagnosed ALL. The certainty in evidence is low to very low, with the largest limitation being the lack of RCTs, whereas the age specificity (AYAs) and comparative nature (including retrospective comparisons of RCTs) somewhat muted the limitations. The setting in which therapy is given is critical, because the burden on patients is high, with frequent trips to the treatment center for outpatient chemotherapy, as well as a need for high adherence to oral medications.

Implementation of such regimens without proper support structures in place introduces a risk of health inequities within an already at-risk population. Despite this, the panel concluded that the magnitude of survival benefits is substantial and clinically meaningful to patients and felt confident that the effect estimates were reflective of true benefits. The composition of the panel was key for this discussion, because it included both pediatric and adult hematologist-oncologists and transplant physicians, pharmacists, social workers, and patients, and professionals who represented not only urban academic centers but also community and rural settings. The prioritization of survival benefit is likely to be acceptable to stakeholders and advocates as a rationale to dedicate system resources to enable hospitals, health systems, and health care professionals to accept and adopt pediatric-inspired regimens.

Future research in this area has the potential to address knowledge gaps related to outcomes of interest for which data do not currently exist, ranging from late effects of therapy and psychosocial outcomes (including fertility and health-related QOL) to care delivery outcomes (unplanned hospitalization rates, and the impact of social determinants of health). Given the formative time during which AYAs are undergoing treatment, considerations for short- and long-term

health, both physical and mental, are paramount. Furthermore, the panel acknowledges that the landscape of ALL treatment is changing rapidly and dramatically, with increasing roles of immunotherapies and other targeted agents within (and perhaps in place of) chemotherapy backbones. Modifications of current regimens may increase survival rates and change toxicity profiles, potentially providing great benefit to patients.

Asparaginase management

For the asparaginase management sections that follow, the data presented and recommendations are related to PEG-Asp, and not calaspargase pegol.

Good practice statement for recommendations 2 and 3

The panel considers it good practice to use TDM to ensure adequate asparagine depletion when dose capping and dose reductions are undertaken. TDM should also be used in the context of premedication to determine whether hypersensitivity reactions are associated with antibody-mediated inactivation (ie, undetectable nadir serum asparaginase activity levels) or to identify silent inactivation.

Remark:

- The panel recognizes that there is some heterogeneity in the target asparaginase activity levels across studies and when and how levels should be monitored. An in-depth discussion and evaluation of the optimal asparaginase activity level is beyond the scope of this effort. However, based on pharmacokinetic and clinical outcomes data, activity levels of ≥ 0.1 IU/mL for at least 14 days are recommended to ensure adequate asparagine depletion.

Asparaginase dosing. For all patients (of any age) with ALL receiving frontline asparaginase, what are the comparative benefits and harms of changing asparaginase dose by (1) following asparaginase levels (including monitoring frequency and timing) and changing asparaginase doses in response to those levels, (2) dose capping, or (3) dose lowering?

Recommendation 2

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel suggests that empiric dose capping and dose reductions are reasonable strategies to mitigate asparaginase-induced toxicities in AYAs without evidence of adversely affecting disease outcomes (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).*

Remarks:

- The panel defines dose capping as a maximum PEG-Asp dose of 3750 IU.
- The panel defines reduced dosing of PEG-Asp as any weight-based dose of <2500 IU/m² for individuals aged <22 years or <2000 IU/m² for individuals aged ≥ 22 years.⁴⁸

- *See “Good practice statement for recommendations 2 and 3” under “Asparaginase management” for TDM guidance related to dose capping or reduction.

Summary of the evidence. The panel reviewed a total of 9 comparative studies ranging from tiers 1 to 5 to evaluate the benefits and harms of PEG-Asp dose capping and reduced dosing of PEG-Asp in AYA patients receiving upfront treatment on a pediatric-inspired (asparaginase-containing) protocol,^{23,30,43,45,49-53} among which 7 had a median patients age within the AYA age range. Among the comparative studies included, 1 was an RCT⁵⁰ and 3 were single-center retrospective reviews.^{49,52,53} The remaining 5 noncomparative studies were taken into consideration to further support the panel's recommendations.^{23,30,43,45,51} The evidence profile and EtD framework are available online at https://guidelines.ash.gradepro.org/profile/jiscxt3g_wl.

Five studies provided direct evidence for the AYA population. The certainty in evidence was very low due to indirectness, imprecision, and risk of bias. The potential benefit of dose modification is mitigating toxicity, whereas the potential harm of this as an intervention is decreasing efficacy.

From the perspective of dose modification as an intervention, the potential benefit of the intervention is mitigating toxicity whereas the potential harm is decreasing efficacy. Overall, the panel felt the evidence available did not indicate any negative impact on survival outcomes when using dose-capped or reduced-dose PEG-Asp. Notably, TDM was used in most, if not all, of the studies cited here, supporting the recommendation that when using a dose-capping or dose-reduction strategy, it would be recommended to also pair that with TDM.

Benefits. The evidence reviewed by the panel did not demonstrate significant differences in rates of PEG-Asp induced toxicities in AYA patients treated on pediatric-inspired regimens with reduced dose PEG-Asp or capped dose PEG-Asp compared with conventional dose PEG-Asp.^{49,50,52,53} In the noncomparative studies, rates of grade 3 or 4 toxicities, hepatotoxicity, pancreatitis and thrombosis were not significantly different when comparing low-dose PEG-Asp 1000 IU/m² vs PEG-Asp 2500 IU/m² (capped at 3750 IU) vs PEG-Asp 2500 IU/m² (without dose capping).^{30,43,45,51}

Comparison of rates of toxicity were difficult for the panel to assess given population heterogeneity and differences in adverse event (AE) definitions and reporting requirements between studies. The panel also notes that several studies used clinical characteristics such as older age, baseline liver dysfunction, diabetes, and obesity to determine PEG-Asp dosing.^{49,52} The selection of patients with these “at risk” specific clinical characteristics for dose reduction/capping may indicate that giving high-risk patients lower PEG-Asp doses may reduce the risk of toxicity because toxicity rates were no different from those among patients without risk factors who did not get PEG-Asp dose reductions.

Overall, the benefits of decreased toxicity were considered moderate although the certainty in evidence was very low. The

heterogeneity of patient populations and AE reporting made it difficult for the panel to draw conclusions on toxicity rates with various PEG-Asp dosing strategies. Given the available evidence, the panel felt that dose-capped and reduced-dose PEG-Asp may help mitigate toxicities in AYA patients, especially in older AYAs and those with obesity, diabetes, or underlying liver disease.

Harms and burden. Evidence reviewed by the panel did not demonstrate a difference in OS or EFS for patients treated with reduced-dose PEG-Asp or for patients who received capped-dose PEG-Asp compared with patients treated with conventional dosing.^{49,50} Subgroup analyses did not identify any differences in treatment outcomes when looking at various clinical and biological subsets of patients.

Several large prospective European trials that included AYA patients used lower doses of PEG-Asp (1000 IU/m²) within pediatric-inspired regimens and reported survival outcomes comparable with those in prospective North American trials in AYA patients using higher doses of PEG-Asp (2500 IU/m²) within similar regimens.^{23,30,43,45,51} Among studies that evaluated differing dose strategies of asparaginase, there were no significant difference in survival outcomes between low-dose PEG-Asp (1000 IU/m²), dose-capped PEG-Asp (3750 IU), or conventional-dose PEG-Asp (2500 IU/m² with no cap).^{49,50}

Other EtD criteria and considerations. The panel placed a high value on OS and CR rates balanced with toxicities and QOL. Although the available evidence did not capture all these outcomes, the panel did not feel this warranted a change in the strength or direction of the overall recommendation. The panel recognizes the very low certainty in evidence used to support this recommendation, and that the available data that are representative of the AYA population are sparse.

The panel felt reassured that the available evidence did not signal an adverse impact on survival outcomes such as OS and EFS. Furthermore, the data demonstrated that lower doses of PEG-Asp achieve therapeutic asparaginase activity levels and asparagine depletion. Several additional single-center retrospective reviews and prospective trials have also reported success with reduced-dose PEG-Asp achieving therapeutic asparaginase activity levels.⁵⁴⁻⁵⁷ Based on these data and the expert opinion of the panel, it was felt that reducing PEG-Asp dose to as low as 1000 IU/m² is reasonable, especially when TDM is implemented.

Conclusions and research needs for this recommendation.

The panel determined that there may be a benefit of PEG-Asp dose capping or reduction in AYA patients. The panel recognizes the very low certainty in evidence but that based on the available evidence, it is reasonable to dose reduce or dose cap PEG-Asp to mitigate toxicity without a detriment to survival or remission rates. This should especially be considered for patients who have risk factors for toxicity such as obesity, underlying liver dysfunction, and older age. TDM is encouraged if dose reductions or dose-capping is used to confirm adequate asparaginase activity levels for asparagine depletion.

Further research is needed to determine the optimal exposure to asparaginase and duration of asparagine depletion to maximize outcomes and minimize toxicity. This is true across all age groups but is of particular importance in the AYA population given the

differences in disease biology and patient characteristics compared with pediatric and older adult patients. Asparaginase has proven to be highly efficacious but with a significant risk of serious toxicity, and validating this information is of utmost importance for patient care, including the risks and benefits of prolonged asparagine depletion. Ongoing studies are evaluating calaspargase for patients aged >18 years ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT04817761) identifier: NCT04817761, NCT05581030). However, these are only single-arm studies and will not provide comparative evidence on the benefits and harms of calaspargase compared with PEG-Asp. Given the longer half-life of calaspargase and attendant potential for increased toxicities, clear understanding of any potential benefits and harms of this newer asparaginase preparation in the AYA population is needed.⁵⁸

Lastly, further research is needed on prevention and treatment of asparaginase induced toxicities as well as rechallenging with asparaginase after toxicity. Current evidence is sparse and primarily retrospective.⁵⁹⁻⁶⁷ Most data focus on the use of levocarnitine with or without vitamin B complex for prevention or treatment of hepatotoxicity.⁶²⁻⁶⁷ A phase 3 trial comparing levocarnitine with no levocarnitine as hepatotoxicity prophylaxis is currently underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT05602194) identifier: NCT05602194).

Asparaginase premedication. For patients with ALL receiving asparaginase, what are the comparative benefits and harms of prophylactic premedication to prevent infusion reactions?

Recommendation 3

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel *recommends* the use of prophylactic premedication to prevent hypersensitivity reactions (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).*

Remarks:

- Premedication is defined at a minimum as IV steroid premedication and may also include antihistamines and/or acetaminophen.
- *See “Good practice statement for recommendations 2 and 3” under “Asparaginase management” for TDM guidance related to dose capping or reduction.

Summary of the evidence. The panel considered a total of 6 comparative studies for review,^{45,68-72} which ranged from tiers 1 to 5; 1 study included only AYAs,⁴⁵ whereas the median patient age for 4 other studies were younger, and 1 was not reported. There were limited data overall with only 2 studies evaluating rates of switching asparaginase products to *Erwinia*-based treatments on premedication (vs none),^{45,69} only 1 study directly comparing premedication vs none, 1 simply reporting rates of silent inactivation with premedication,⁶⁹ 1 addressing serum asparaginase activity,⁶⁹ 1 evaluating the cost associated with implementing premedication,⁶⁸ and 2 regarding cost savings associated with avoiding a switch to *Erwinia*-based treatments as a consequence of a hypersensitivity reaction.^{45,68} The evidence profile and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/7j6NAdBsfn0>.

Benefits. Evidence reviewed by the panel demonstrated a reduction in the numbers of patients having asparaginase-related hypersensitivity reactions with premedication that included at least IV corticosteroid.^{45,68,69} Moreover, the systematic review of grade 3 to 4 hypersensitivity reactions per patient demonstrated a statistically significant reduction in reactions with premedication (risk ratio [RR], 0.24; 95% CI, 0.10-0.58).

The panel considered whether premedication could prevent hypersensitivity reactions that necessitated a switch to *Erwinia*-based treatments, given the cost and inconvenience associated with *Erwinia*-based treatment administration.^{69,72} The evidence reviewed revealed decreased rates of *Erwinia*-based treatment substitution with premedication with concurrent TDM (RR, 0.40; 95% CI, 0.27-0.59).^{69,72} In addition, by avoiding *Erwinia*-based treatment substitution, premedication was associated with a cost savings ranging from US \$12 402 per premedicated patient⁶⁹ to US \$106 550.⁷¹ Considering that premedication would also lead to fewer reaction-related hospital admissions and avoiding *Erwinia*-based treatment would lead to fewer chemotherapy clinic visits, cost savings were projected to be larger than these estimates.

Overall, the estimated desirable effects are moderate although the certainty in evidence is very low owing to indirect evidence leading to a risk of bias. More specifically, 5 of 6 studies in this review evaluated non-AYAs, none were randomized, and the chemotherapy backbones varied between studies. Despite these limitations, the panel felt that the moderate desirable effects favor premedication compared with no premedication to prevent asparaginase reactions.

Harms and burden. The panel determined that there is low-quality evidence to argue against the implementation of premedication before asparaginase administration to prevent infusion reactions. Four studies in this review evaluated silent inactivation, with 2 of these studies reporting no instances of silent inactivation^{68,72} and 2 studies each identifying a single episode in a patient receiving premedication.^{45,69} As outlined in the good practice statement, TDM should be made readily available as a tool to avoid missing silent inactivation of PEG-Asp in the context of premedication.

Although the estimated undesirable effects are trivial, the panel acknowledges the very low certainty in evidence owing to an indirect evidence base and risk of bias. Although these studies included non-AYAs and were not randomized, the panel felt that these undesirable effects were unlikely to be different in AYAs.

Other EtD criteria and considerations. The panel acknowledges that although there is no research evidence on patient values, preferences, and acceptability of premedication to prevent asparaginase hypersensitivity reactions, many of the potential benefits are aligned with patient values. In addition to reduced rates of hypersensitivity reactions, decreasing the need for *Erwinia*-based treatment substitution is of particular importance given the burden of increased clinic visits and injections. Moreover, the resources required for premedication were deemed acceptable and feasible for implementation, with the potential for cost savings as reported in 2 of the noncomparative studies.^{45,68} It should be noted that although several studies did not show an increase in silent inactivation with premedication, TDM is important to detect silent inactivation, which may be masked by premedication. If TDM is unavailable, consideration should be given to administering

asparaginase without premedication to allow for the detection of hypersensitivity and silent inactivation.

Conclusions and research needs for this recommendation. The panel determined that there is a net benefit of premedication to prevent asparaginase hypersensitivity reactions and that this includes at least IV corticosteroids but may also contain antihistamines and/or acetaminophen. The panel recognized that the evidence was of very low certainty. Despite this, the panel was compelled by the many desirable effects including a lower incidence of hypersensitivity reactions and the associated cost savings. Moreover, there did not appear to be a significant adverse impact with the use of premedication. Following the considered judgment process of the panel and the recognition that the intervention could mitigate a life-threatening situation (hypersensitivity reaction), the panel supported a strong recommendation in favor of premedication despite the very low certainty in evidence.⁷³

Prophylaxis of VTE in the setting of asparaginase. For patients with ALL receiving frontline asparaginase therapy, what are the comparative benefits and harms of different prophylaxis regimens to prevent hypercoagulation including (1) anticoagulation for VTE prophylaxis (thromboprophylaxis), and (2) monitoring (eg, prothrombin time/partial thromboplastin time/international normalized ratio/antithrombin III, and fibrinogen levels) with reflex product replacement administration (or replacement recombinant AT)?

Recommendation 4

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel *recommends against* the routine use of cryoprecipitate replacement (or fibrinogen concentrate) outside the context of active bleeding (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).

Recommendation 5

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel *recommends against* the routine use of UFH for VTE prophylaxis (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).

No recommendation

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against routine VTE prophylaxis with LMWH or DOACs.

No recommendation

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against routine AT replacement.

Remark (for this group of VTE prophylaxis with asparaginase recommendations):

- The panel recognizes uncertainty in timing or duration of VTE prophylaxis (induction, consolidation, intensification), LMWH dosing, and AT replacement targets, and importance of risk models to identify high-risk patients.

Summary of the evidence. The panel considered a total of 14 comparative studies for review,⁷⁴⁻⁸⁷ including 3 RCTs; the studies ranged from tiers 2 to 6. Seven studies had a median patient age within the pediatric range, and 6 studies had a median patient age between 30-41 years. There was 1 study with a median patient age in the AYA range. There was a great deal of heterogeneity in the evidence in terms of antithrombotic therapy (in addition to heterogeneity in duration and timing of such therapy), clinical features (type of thromboses), and sociodemographic characteristics of the study populations. The heterogeneity and limited data made it difficult for the panel to endorse strong conclusions. The evidence profile and EtD framework are available online at https://guidelines.ash.gradepro.org/profile/Sj_DjDua_Cl.

Benefits. Evidence reviewed by the panel was insufficient to routinely recommend routine VTE prophylaxis with LMWH. LMWH prophylaxis after asparaginase was associated with significantly decreased rates of VTE both when compared with UFH (RR, 0.37; 95% CI, 0.14-0.96) and with no prophylaxis (RR, 0.54; 95% CI, 0.36-0.83). However, the heterogeneity and imprecision in the studies was too great to support specific recommendations. There was a nonsignificant decrease in VTEs with the DOAC, apixaban (RR, 0.69; 95% CI, 0.45-1.05) compared with no prophylaxis; similarly, the panel concluded there was no recommendation for using this class of agents in this situation.

The evidence reviewed by the panel was insufficient for routine recommendation of AT replacement in the setting of asparaginase. Although the systematic review of 3 studies comparing AT replacement with no prophylaxis demonstrated a decreased incidence of VTE (RR, 0.57; 95% CI, 0.35-0.92), the studies used different AT dosing, monitoring, replacement schedules, as well as varying replacement thresholds.^{74,75,78} Due to this substantial heterogeneity and the retrospective nature of the studies, the panel was unable to support specific recommendations for AT replacement in this situation.

Harms and burden. Despite the paucity of data, the panel recommends against the routine use of cryoprecipitate (or fibrinogen concentrate) based on a retrospective adult study in which both fresh frozen plasma or fibrinogen concentrates and AT replacement were recommended as routine practice during treatment,⁸⁴ and patients receiving fibrinogen concentrate outside the context of grade 3/4 bleeding had a higher incidence of VTE (17% vs 9%; odds ratio [OR], 2.2; 95% CI, 1.1-4.3; $P = .02$).⁸⁴

With the evidence reviewed, the panel recommends against the use of UFH for VTE prophylaxis. In an RCT (THROMBOTECT),

UFH was inferior to both AT replacement and LMWH,⁸⁰ and in a retrospective study,⁸⁴ UFH was unexpectedly associated with an increased risk of VTE (13% vs 7%; OR, 1.92; 95% CI, 1.03-3.58; $P = .04$) and a lower risk of grade 3/4 bleeding (OR, 0.51; 95% CI, 0.35-0.75).

Although bleeding poses a potential harm with any VTE prophylaxis, the studies reviewed inconsistently reported bleeding and its clinical significance but did not reveal an increase in significant bleeding events for either LMWH (RR, 0.43; 95% CI, 0.05-3.83) or DOACs (RR, 2.60; 95% CI, 0.94-7.19).

Other EtD criteria and considerations. The panel acknowledges that there is limited research evidence on patient values, preferences, and acceptability of VTE prophylaxis. Although the THROMBOTECT RCT randomized pediatric patients to LMWH, AT replacement, and UFH arms during induction,⁸⁰ 3% of patients refused randomization to AT replacement and UFH arms, and 33% refused LMWH randomization. It is key to consider that this may potentially be due, in part, to injection-associated discomfort. Regardless, adding another agent to an already complex regimen for a fragile population merits close consideration. The panel strongly endorses shared decision-making in discussion of VTE prophylaxis, particularly in outpatient setting in which patients may be asked to inject themselves.

Conclusions and research needs for these recommendations. The panel was compelled to issue a strong recommendation against the routine use of cryoprecipitate or fibrinogen concentrate replacement (outside the context of active bleeding), despite the very low certainty in underlying evidence. In weighing the potential desirable and undesirable effects of cryoprecipitate (or fibrinogen concentrate) replacement, the panel was specifically concerned with an increased risk of thrombosis documented in the 1 available study.⁸⁴ Following the considered judgment process of the panel and the recognition that the intervention (cryoprecipitate or fibrinogen concentrate) might be associated with greater harm, the panel supported a strong recommendation against the use of cryoprecipitate or fibrinogen concentrate outside the context of bleeding.⁷³ Similarly, the panel issued a strong recommendation against the use of UFH for VTE prophylaxis, despite the very low certainty evidence. Again, the balance of desirable and undesirable effects were considered by the panel; although there was a paucity of data, the available evidence did not support any reduction in the risk of VTE (compared with AT replacement and LMWH), and in 1 retrospective study, UFH was associated with an increased VTE risk. Following the considered judgment process of the panel and the recognition that the intervention (UFH) might be associated with greater harm, the panel supported a strong recommendation against the use of UFH.⁷³

Despite not providing a recommendation on VTE prophylaxis with LMWH, DOAC, or AT replacement, the panel recognizes the need for guidance in this patient population and situation. We also recognize that the care of a hospitalized patient may be different than in the outpatient setting with respect to treatment decisions regarding VTE prophylaxis. Identification of higher-risk populations and/or treatment protocols is a useful step in assessing risk/benefit of routine prophylaxis. The VTE risks in the studies varied

and included presence of central venous catheter, asparaginase administration, induction vs other treatment phases, age, and patient body mass index. For patients at higher risk for VTE, additional decisions include timing and dosing of VTE prophylaxis. VTE incidence is highest during, and immediately after, induction, particularly for cerebral venous sinus thromboses, but is not negligible in subsequent phases of intensive treatment (excluding maintenance). Although the use of DOACs has expanded in oncology, their use as VTE prophylaxis in ALL is limited. In the PREVAPIX-ALL study, pediatric patients were only treated for 28 days, so the results may not be generalizable to the AYA population or for treatment periods beyond induction.⁸⁵ At this juncture, we endorse individualized shared decision-making and consideration of VTE prophylaxis for higher-risk patients.

Alternative asparaginase formulations. For AYAs with ALL receiving frontline asparaginase who have an asparaginase-related reaction (allergic-type reaction), what are the comparative benefits and harms of desensitization vs use of alternative asparaginase products (Erwinia, Rylaze)?

Recommendation 6

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens who develop an asparaginase-related allergic/hypersensitivity reaction with PEG-Asp, the ASH guideline panel *recommends* that patients switch to an *Erwinia*-based asparaginase formulation over discontinuation of asparaginase therapy (strong recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- The panel was unable to provide a recommendation related to desensitization due to the lack of evidence comparing effects of desensitization vs alternative asparaginase products.
- The ASH guideline panel concluded that the benefits, such as improved survival and disease control, outweighed the drawbacks, including the high costs and resources for *Erwinia*-based treatments.

Summary of the evidence. The panel considered 1 nonrandomized comparative study (Gupta et al) and 6 additional noncomparative single-group studies, all with a median patient age of ≤10 years.⁸⁸ The overall body of evidence was consistent, but the certainty in the evidence was very low due to indirectness and imprecision. The panel explored whether it was possible to make a recommendation regarding desensitization vs switching to *Erwinia*-based treatment, but due to very low certainty in the evidence and the lack of comparative studies, the panel was unable to provide a recommendation relating to desensitization. The evidence profile and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/EuVECNpYS3c>.

Benefits. Switching to *Erwinia*-based treatment was not associated with differences in survival compared with those who completed all of their intended asparaginase doses (HR, 0.8; 95% CI, 0.4-1.4).⁸⁸ However, missing PEG-Asp doses without *Erwinia*-based treatment substitution resulted in an inferior DFS

(HR, 1.5; 95% CI, 1.1-1.9; $P = .002$) compared with receiving all PEG-Asp doses and this decrease in DFS was mitigated by substitution with *Erwinia*-based treatment (HR, 1.1; 95% CI, 0.8-1.7; vs receiving all PEG-Asp doses).⁸⁸ Although the certainty in evidence regarding survival benefit was considered low, the panel felt that the desirable effects were of critical importance. Although not included in the summary of evidence considered due to indirectness of the research question, the panel placed high relevance on reports of poor outcomes for patients who have early discontinuation of PEG-Asp rather than using alternative formulations.⁸⁹

The systematic review demonstrated clearly that adequate asparagine depletion is achieved with *Erwinia chrysanthemi*-based asparaginase products, with very few cases of silent inactivation. Overall, the certainty in these estimated effects is very low owing to indirectness in the studies, a small total body of evidence, and imprecision of the estimates.

Harms and burden. The panel recognized that patients receiving *E chrysanthemi*-based asparaginase formulations remain at risk for serious toxicities associated with asparaginase therapy including pancreatitis, thrombosis, hypersensitivity/anaphylaxis, and hepatotoxicity. In addition to adverse effects associated with *E chrysanthemi*-based asparaginase products, the panel recognizes the increased burden associated with inconvenience of multiple weekly injections that must be administered in a health care setting. Additionally, there is an increased cost associated with *E chrysanthemi*-based formulations, with studies demonstrating a cost benefit when a premedication strategy before PEG-Asp is implemented along with careful stewardship of individual cases to avoid unnecessary switching of asparaginase formulations.

Given that the data presented were pooled from single-group analyses, there is a low certainty in the estimate of the risk of adverse effects. However, given the available evidence, the guideline panel considered the risk of adverse effects and burdens of alternative asparaginase formulations to be outweighed by the survival benefits achieved when switching to an alternative formulation rather than discontinuing asparaginase in this patient population.

Other EtD criteria and considerations. The panel places a high importance on the availability of continued access to the currently available alternative asparaginase formulation, Rylaze (*E chrysanthemi* [recombinant-rywn]) given adverse outcomes during a time period in which *Erwinia*-based treatment was not reliably available.⁸⁸ The panel also acknowledges that the preponderance of the evidence available to drive this recommendation is based on older noncommercially available products, and that the currently available product, Rylaze, is a different formulation for which comparative outcomes data are limited. Nonetheless, adequate asparagine depletion has been reported with Rylaze.⁹⁰

Conclusions and research needs for this recommendation. The guideline panel determined that there is a very low certainty to the evidence for a net health benefit/harm from using alternative asparaginase formulations, namely Rylaze. However, based on the body of available evidence, and the high value placed on DFS outcomes in the high-risk population that is represented by AYAs, the panel judged that there is a strong potential for improved outcomes (including survival) without an appreciable

difference in AEs. Following the considered judgment process of the panel and the recognition that the intervention (switch to an *Erwinia*-based asparaginase formulation) might offer benefit in a life-threatening situation, and weighing the potential substantial desirable effects (improved DFS) over minimal undesirable effects, the panel decided to issue a strong recommendation despite the very low certainty evidence.⁷³

The panel identified the following research needs: additional data regarding tolerability of the commercially available product, Rylaze, in the AYA population given the product was studied in mostly young children; and additional data regarding comparative effects of desensitization and/or rechallenge compared with switching formulations.

Rechallenging after asparaginase toxicity. For AYAs with ALL receiving frontline asparaginase who have a non-hypersensitivity asparaginase-related toxicity (eg, coagulation-related side effect, pancreatitis, or hepatotoxicity), what are the comparative benefits and harms of resuming (or changing) asparaginase therapy?

No recommendation

For AYAs with ALL receiving frontline pediatric-inspired (asparaginase-containing) regimens who have a non-hypersensitivity asparaginase-related toxicity, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation on resuming asparaginase therapy.

The panel recognizes that in the absence of a recommendation, clinicians will need to rely on existing guidance on toxicity management; potential resources for clinicians at present include published treatment protocols, product monographs, and narrative/consensus guidance documents.⁹¹⁻⁹⁴

Allogeneic transplant in CR1

For AYAs with ALL being treated with frontline therapy, what are the comparative benefits and harms of allo-HSCT vs no transplant in CR1?

Recommendation 7

For AYAs with ALL receiving frontline therapy and in CR1, the ASH guideline panel *suggests against* routinely proceeding with allo-HSCT as consolidation (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- For specific high-risk subgroups (especially those with MRD persistence, induction failure, high-risk biologic subsets), there may be a survival benefit from allo-HSCT in CR1.

Summary of the evidence. The panel considered a total of 7 comparative studies (none were RCTs) for review,⁹⁵⁻¹⁰¹ all of which were tier 1 or 2 (with a median patient age all within or near the AYA

range) for evaluating the benefit and harms of allo-HSCT vs no allo-HSCT in AYA patients with ALL in CR1. One study evaluated patients with Ph⁺ ALL¹⁰¹; the other 6 evaluated patients with Ph⁻ ALL. Ph⁺ ALL is separately addressed in “Treatment for Ph⁺ ALL” and Recommendation 12, and is not considered part of the high-risk subgroups defined here. MRD persistence is further defined and addressed in “Approach to MRD” and Recommendation 15.

Among these 6 studies reporting Ph⁻ ALL, all reported on the effect of allo-HSCT on mortality or OS,⁹⁵⁻¹⁰⁰ on EFS,⁹⁸ 5 on DFS or RFS,^{95,96,98-100} and 5 on relapse.^{95,96,98-100} Ph⁺ ALL is addressed in Recommendation 12 and the evidence profiles and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/bxJabROu5Ac>.

Benefits. Evidence reviewed by the panel demonstrates a significant survival benefit in AYA patients with ALL who did not undergo an allo-HSCT (5-year OS: HR, 0.48; 95% CI, 0.24-0.95), with 262 fewer deaths estimated per 1000 patients. The survival benefit noted for those who did not receive allo-HSCT in CR1 was largely due to an increased risk of TRM for those receiving allo-HSCT, with a significantly higher 4-year risk of TRM (HR, 6.88, 95% CI, 3.02-15.7) and higher nonrelapse mortality (all cause) at 3, 5, and 6 years.⁹⁹ After 6 years, 553 more patients per 1000 who underwent allo-HSCT in CR1 suffered nonrelapse mortality compared with those AYAs who did not receive a transplant in CR1 (HR, 5.41; 95% CI, 3.23-9.06).

The panel recognizes both the scarcity of data and the low-quality data specifically comparing OS and EFS in allo-HSCT compared with no allo-HSCT in CR1 among AYAs with ALL, largely limited by the lack of RCTs with this focus. These data are also limited by the definition of CR1 and lack of availability of MRD status in older studies, thus limiting any outcomes specific to MRD status and allo-HSCT in the AYA ALL population. The panel acknowledges that high-risk subgroups (eg, MRD persistence, *KMT2A* rearranged, Ph-like ALL, hypodiploid ALL, TP53-mutant ALL, and ETP ALL) may benefit from allo-HSCT in CR1. Unfortunately, because little data exist on these high-risk subgroups, the desirable effects of transplant in CR1 are unknown and may be further tempered by the current strategies to attempt to “eradicate” MRD with targeted antibody therapy before moving forward with allo-HSCT in CR1.

Harms and burden. The most undesirable effect from the intervention (allo-HSCT) is TRM (specifically transplant-related mortality) leading to worse OS, compared with relatively less TRM noted in the chemotherapy regimens alone. Mortality at 6 years was significantly higher for AYAs who received allo-HSCT in CR1 (HR, 2.00; 95% CI, 1.5-2.66), with 228 more deaths estimated per 1000 patients among patients who received a transplant.

Although beyond the scope of the systematic review, the panel also considered the significant long-term morbidities specifically associated with transplantation including infertility, graft-versus-host disease, organ toxicity, and secondary malignancies that are particularly relevant to the AYA population. Similarly, the panel acknowledges the long-term effects of chemotherapy, including second cancers, which require more focused study in the AYA population.

Other EtD criteria and considerations. The panel acknowledges that underrepresented/disadvantaged populations are less likely to find a matched unrelated donor. Even patients with matched donors experience disparities; certain aspects of allo-HSCT may make outcomes strongly linked to racial disparities (donor availability), to socioeconomic factors such as the expense and complexities of the procedures, as well as other potential social barriers (need for caregivers, transportation, etc). The panel further acknowledges that access to allo-HSCT and to intensive pediatric regimens is not universal and that geographically, economically, and socially isolated populations are more likely to experience greater barriers to access highly specialized comprehensive care essential to the successful treatment of AYAs with ALL.

Conclusions and research needs for this recommendation. For AYA patients with ALL in CR1 and receiving pediatric regimens as frontline therapy, the ASH guideline panel suggests not to routinely proceed with allo-HSCT in CR1, while recognizing there are data lacking for specific high-risk subgroups (eg, MRD persistence, *KMT2A* rearranged, Ph-like ALL, hypodiploid ALL, TP53-mutant ALL, and ETP ALL) for whom the benefits may outweigh the harms. In light of the scarcity and low certainty in the evidence regarding this outcome in AYAs with ALL, and the fact that some patient subgroups may benefit from allo-HSCT, the panel's recommendation against this intervention is conditional.

The panel recognizes the urgent need for additional clinical trials focused on allo-HSCT in the aforementioned high-risk populations, including attention to long-term outcomes and late effects. Similarly, long-term follow-up to assess the late effects of an intensive pediatric regimen is essential. Future studies are also needed to evaluate the impact of newer targeted therapies (including antigen-directed therapies such as blinatumomab and inotuzumab), TKIs, and new molecular-based therapies (eg, menin inhibitors, B-cell lymphoma 2 homology 3 mimetics) on early MRD eradication and the subsequent benefit of allo-HSCT in CR1. Prospective studies evaluating access to centers of excellence for AYA ALL care and allo-HSCT, are urgently needed to further inform this recommendation, because such access is often determined by factors including insurance status, socioeconomic status, and other social determinants of health.

Additional therapies for specific subsets

For patients with B-ALL/T-ALL or T-LBL/LLy in frontline therapy, what are the comparative benefits and harms of inclusion (vs no inclusion) of targeted therapies (eg, inotuzumab, blinatumomab, rituximab, nelarabine, and bortezomib)?

Rituximab

Recommendation 8

For AYAs with CD20⁺ B-ALL receiving frontline therapy, the ASH guideline panel *suggests* the addition of rituximab to standard chemotherapy (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- The panel recognizes the considerable uncertainty associated with rituximab dosing frequency and timing of administration, the minimum required level of CD20 expression, and the lack of data specific to younger AYA individuals.

Summary of the evidence. Among the publications that evaluated the efficacy of rituximab in combination with chemotherapy for frontline management of pre-B-cell ALL, 4 comparative studies met criteria for review by the panel; 2 were RCTs, 1 was a single-group study, and 1 was a nonrandomized comparative study.¹⁰²⁻¹⁰⁵ The studies ranged from tiers 2 to 4, with a median patient age ranging from 37 to 46 years; 3 of 4 studies reviewed had a median patient age outside the AYA age range. The prioritized outcomes of interest included EFS, OS, and allo-HSCT. The evidence profile and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/deBc3uGzTEI>.

Benefits. The panel noted superior EFS at 2 years, 30 months, and 4 years (HR, 0.66; 95% CI, 0.45-0.98) with the addition of rituximab to standard chemotherapy in CD20⁺ ALL in 1 RCT,¹⁰² whereas differences in EFS in the other RCT were not statistically significant.¹⁰³ Although the median patient age in the former trial was 40 years, in subgroup analyses there were no significant differences based on age (age of <40 or >40 years). There was a lower risk of relapse in both an RCT (HR, 0.52; 95% CI, 0.31-0.89)¹⁰² and in the nonrandomized prospective study with a median patient age of 41 years (RR, 0.55; 95% CI, 0.41-0.72).¹⁰⁵ Although there were no statistically significant differences in OS in the RCTs, there was a lower hazard of death after allo-HSCT for patients who received rituximab (HR, 0.55, 95% CI, 0.34-0.91).^{102,103}

No studies demonstrated significant differences in CR rates or MRD negativity after first induction or first consolidation.

Harms and burden. Adding rituximab to chemotherapy did not significantly increase toxicity in frontline management of ALL; in particular, there was no statistically significant increased risk of infections or cytopenias.^{102,103} Nevertheless, the panel highlighted that the addition of rituximab to standard therapy may be associated with some undesirable effects, including infusion reactions, prolonged immunosuppression (including hypogammaglobulinemia and delayed-onset neutropenia), and loss of vaccine efficacy.

The addition of rituximab to various chemotherapy backbones has the potential to increase costs and impose additional burden on patients by increasing the number and duration of infusion appointments.

Other EtD criteria and considerations. The certainty in evidence for critical outcomes related to rituximab (including EFS and OS), were considered low to very low. The panel acknowledged that differences in the study designs (including dosing frequency and timing of rituximab administration and level of CD20

expression level of enrolled patients) may explain the differences in results (ie, studies that use more doses showed more benefit whereas the only study that used 4 doses did not find a benefit).¹⁰³

The recommendation was informed by the patient panelists, who placed the highest value on OS/mortality relative to other outcomes. Thus, although the panel acknowledged that the available data set may not have captured all outcomes of value for patients, the uncertainty was not felt to likely change the direction or strength of the recommendation.

The panel acknowledges that underrepresented/disadvantaged populations may be disproportionately affected by the high costs associated with the potential cost/resource implications associated with novel/targeted immunotherapies, including rituximab. The panel noted that some institutions may face barriers to providing inpatient novel therapies (including rituximab).

Conclusions and research needs for this recommendation. For AYA patients with CD20⁺ ALL receiving frontline therapy, the potential benefit of rituximab appears to outweigh the risks. In particular, rituximab appears to decrease the risk of relapse. This recommendation is based on data that include, but are not limited to, an AYA population. Future studies that include AYAs (ideally with age-based subanalyses) regarding the minimal threshold of CD20 expression, the optimal timing and dosing of rituximab, and the role of rituximab in the context of other evolving immune-based therapies would enhance the management of AYA patients with ALL.

Blinatumomab

Recommendation 9

For AYAs with B-ALL receiving frontline therapy, the ASH guideline panel *suggests* the addition of blinatumomab for those who achieve morphologic remission, regardless of MRD status (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- The panel recognizes there are limited data using blinatumomab within conventional pediatric-inspired chemotherapy backbones.
- The panel further recognizes the evolution of evidence in this space, and that the recommendation may change with the availability of more data.
- Guidance for individuals with MRD persistence is addressed in Recommendation 15.

Summary of the evidence. Two comparative studies met criteria for the panel to review regarding the role of blinatumomab in frontline management of MRD-negative B-ALL^{106,107}; the studies were within tiers 3 to 4, with median patient age ranging from 37 to 55 years. Although one of these studies was prospective with a subset analysis restricted to individuals aged <55

years with MRD-negative disease, younger AYAs (aged <29 years) were excluded.¹⁰⁷ Importantly, the panel acknowledges that prospective randomized comparative studies are lacking for the use of blinatumomab.¹⁰⁸ Considerations related to MRD-positive disease are addressed in Recommendation 15. The evidence profile and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/VtHyq5pflfg>.

Benefits. The panel noted the 2 referenced studies demonstrated improvement in RFS and OS with the addition of blinatumomab to an IC backbone. At 3.5 years, there was superior OS (lower hazard of death; HR, 0.16; 95% CI, 0.05-0.47) and DFS (lower hazard of relapse/death; HR, 0.53; 95% CI, 0.32-0.87). The only study to evaluate a solely AYA population was a small non-randomized single-institution study with an AYA subset (n = 22; age range, 18-39 years), in which a 3-year RFS of 77% and OS of 86% were observed in interim analysis.¹⁰⁷

Harms and burden. The panel highlighted that blinatumomab is associated with notable toxicities. In the relevant RCT considered by the panel, the only statistically significant toxicity identified was grade ≥3 neurologic events (RR, 4.20; 95% CI, 1.79-9.85) with blinatumomab.¹⁰⁷ Other reported toxicities included infusion-related reactions, cytokine release syndrome, and development of hypogammaglobulinemia.

Other EtD criteria and considerations. The certainty in evidence in support of blinatumomab in the frontline setting was felt to be very low in the AYA setting.

The panel noted the potential substantial cost and resource implications associated with blinatumomab, including the requirement for hospitalization at the time of drug initiation, the need for 28-day continuous infusion cycles, and the potential of increasing the overall duration of therapy compared with regimens that do not include blinatumomab. In addition, the panel recognized that some institutions may face barriers to providing both inpatient immunotherapies as well as home health care infrastructure required for prolonged continuous IV infusion. The panel also recognized that patient acceptance and adherence to novel targeted therapies may be multifactorial, with these and similar considerations contributing to the overall therapeutic burden. The panel acknowledges that underrepresented and disadvantaged populations may also be disproportionately affected by the high costs and complexity of blinatumomab administration.

The panel recognized that this guideline is principally focused on management of AYA ALL in well-resourced countries and wished to highlight the potential for variable and inequitable global access to blinatumomab within clinical trials or as a component of standard therapy.

Conclusions and research needs for this recommendation. The panel acknowledges encouraging improvements in RFS and OS with the incorporation of blinatumomab within consolidation treatment for patients, regardless of MRD status. This includes patients who do not undergo allo-HSCT and patients with high-risk genomic features. The use of blinatumomab in MRD-positive disease is addressed with a later recommendation (see Recommendation 15).

Further prospective randomized studies specific to the AYA population and including pediatric-inspired chemotherapy backbones are required to establish definitive real-world evidence that supports the use of blinatumomab in the frontline management of ALL in AYA populations. The panel also acknowledges that formulations of blinatumomab that may improve equity of access and deliverability of therapy are desirable.

Inotuzumab

No recommendation

For AYAs with B-ALL receiving frontline therapy, the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against the addition of inotuzumab.

Although 2 manuscripts were identified at the time the panel was convened, neither met criteria for review by the panel; 1 was below tier 6 (<25 patients) and the other was tier 5 (median patient age of 68 years).^{109,110} There were insufficient data to further consider the addition of inotuzumab in CR1.

The panel recognizes that data in this area are emerging, including studies that may further clarify the toxicities associated with the addition of inotuzumab to multiagent chemotherapy (including trials NCT03150693 and NCT03959085), and that with time this recommendation may evolve.

Nelarabine

No recommendation

For AYAs with T-ALL receiving frontline therapy with all planned doses of asparaginase (including Capizzi methotrexate–based interim maintenance), the ASH guideline panel determined that the evidence is insufficient to issue a recommendation for or against the addition of nelarabine.

Remark:

- The panel noted that incorporating nelarabine may provide benefit among subgroups of AYAs including those with non-ETP subtype, CNS3 disease, and/or others who receive a high-dose methotrexate–based interim maintenance regimen.

Recommendation 10

For AYAs with T-LBL/LLy receiving frontline therapy, the ASH guideline panel *suggests against* the addition of nelarabine, due to insufficient evidence demonstrating efficacy for nelarabine in these patients (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. The panel considered 8 comparative studies that incorporated nelarabine into frontline therapy for T-ALL or T-LBL/LLy.¹¹¹⁻¹¹⁸ The studies ranged from tiers 1 to 4, with a median patient age ranging from 10 to 46 years; although 1

study had a median patient age >40 years and 3 studies had median patient ages of <14 years, one of the “younger” studies had an AYA-only subanalysis, and an additional 3 studies had median patient ages between 15 and 39 years. The evidence profile and EtD framework are available online at https://guidelines.ash.gradepro.org/profile/ly9b_Czxjs.

Benefits. Among patients with T-ALL enrolled on an RCT with an asparaginase-containing chemotherapy backbone, a significant 5-year DFS benefit (RR, 1.07; 95% CI, 1.01-1.15) was observed for those randomized to receive nelarabine.¹¹⁹ However, there was no OS benefit; the median patient age was young; and in the AYA subgroup, the DFS advantage was not maintained (survival ratio, 0.96; 95% CI, 0.67-1.39; $P = .81$).¹¹⁶ Although patients assigned to receive nelarabine across all arms in this trial were observed to have a significantly lower risk of CNS relapse (1.3% vs 6.9%), the panel recognized uncertainty related to whether patients benefited from nelarabine or the study-allocated approach to methotrexate treatment. In particular, although all patients were randomized to receive (or not receive) nelarabine, all patients with CNS3 disease were nonrandomly assigned to high-dose methotrexate, whereas those with CNS1-2 disease were randomized to either high-dose or escalating (Capizzi) methotrexate. Although patients with CNS3 disease randomized to nelarabine (all receiving high-dose methotrexate) had fewer CNS relapses (3.4% vs 21.4%) and superior DFS (93.1% vs 67.9%, $P = .014$) than those who did not receive nelarabine, the cumulative incidence of CNS relapse among all patients was lower among those assigned to Capizzi (0.2%) than high-dose (2.1%) methotrexate.

With this in mind, the panel determined that the evidence was insufficient to issue a recommendation for or against the addition of nelarabine for AYAs with T-ALL receiving frontline therapy with all planned doses of asparaginase (including Capizzi methotrexate–based interim maintenance), while noting that some subgroups of AYAs may see some benefit to including nelarabine (non-ETP subtype, CNS3 disease, and/or others who receive a high-dose methotrexate–based interim maintenance regimen).

Among patients with T-LBL/LLy receiving nelarabine, neither an OS nor DFS benefit was observed.^{111,112,118}

Harms and burden. In the studies reviewed, no statistically significant differences in neurotoxicity were observed between cohorts receiving or not receiving nelarabine.^{112,114,118} Nevertheless, the panel recognizes both a “black box” warning for nelarabine regarding neurotoxicity based on historical data,¹¹⁹ and cases of nelarabine-associated rhabdomyolysis noted in post-marketing surveillance.^{120,121}

Other EtD criteria and considerations. The patient panelists discussed the high value that patients place on OS/mortality, rendering it of higher value than other outcomes. In addition, toxicities were considered important by patient panelists, even independent of long-term impact on QOL.

Considering the way in which it is administered (eg, IV for 5 consecutive days), the incorporation of nelarabine into frontline therapy increases overall health care resource use. Additionally, use of these therapies requires increased financial burden on

patients/families both for the therapy itself and for travel and other potential costs.

Conclusions and research needs for this recommendation. After review of the outlined evidence and feedback from public comment, the panel determined that the evidence is insufficient to issue a recommendation for or against the addition of nelarabine to frontline therapy for AYAs with T-ALL, while noting that there may be potential benefit among subgroups such as those with non-ETP T-ALL, CNS3 disease, and/or any others receiving a high-dose methotrexate-based interim maintenance regimen. The panel suggests against incorporating nelarabine into treatment regimens for patients with T-LBL/LLy.

For more definitive evidence, future work is necessary, including RCTs incorporating nelarabine into T-ALL therapy for the AYA population.

Bortezomib

Recommendation 11

For AYAs with T-ALL receiving frontline therapy, the ASH guideline panel *suggests against* the addition of bortezomib into treatment regimens (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

No recommendation

For AYAs with T-LBL/LLy, the ASH guideline panel determined the evidence is insufficient to recommend for or against addition of bortezomib.

Remark:

- The panel noted that incorporating bortezomib may provide benefit among the youngest adolescents of the AYA population.

Summary of the evidence. One comparative study was eligible for panel consideration; this was a tier 3 study with a median patient age of 12 years and reported an RCT that incorporated bortezomib into an asparaginase-containing regimen for patients with T-ALL or T-LBL/LLy.¹²² The benefits of bortezomib were considered as a whole and separately for patients with T-ALL and T-LBL/LLy. The evidence profile and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/jxDJFpHxG0>.

Benefits. When considering T-ALL and T-LBL/LLy together, or T-ALL alone, there was not a statistically significant survival benefit for bortezomib (OS or DFS). Although both 4-year OS (RR, 1.13; 95% CI, 1.03-1.24) and EFS (RR, 1.12; 95% CI, 1.01-1.27) were improved with the addition of bortezomib when considering T-LBL/LLy alone, the lack of enrollment of older AYAs coupled with the young median age (12 years) precluded a recommendation specific to the AYA population.

Harms and burden. There were no significant differences with respect to toxicities between patients receiving and not receiving bortezomib (overall AEs, grade ≥3; RR, 1.05; 95% CI, 0.97-1.12),

including neuropathy and pulmonary toxicities.¹²² When considering neuropathy in particular, which is known to be associated with bortezomib, there also was no significant difference between randomized groups.¹²² Patients randomized to bortezomib were no more likely to experience grade 3/4 peripheral motor neuropathy than those randomized to chemotherapy alone (RR, 0.66; 95% CI, 0.4-1.06). Similarly, grade 3/4 peripheral sensory neuropathy was no more likely in those randomized to bortezomib (RR, 1.31; 95% CI, 0.82-2.11). Nevertheless, the panel acknowledges the known association between bortezomib and both neuropathy and pulmonary complications. These are more common with increasing age, especially when bortezomib is combined with vincristine. Given this concern of increasing toxicity with age and lack of data across the AYA age range, the panel could not issue a recommendation for AYAs with T-LBL/LLy of all ages but acknowledged that there may be benefit in the youngest AYAs with T-LBL/LLy.

Other EtD criteria and considerations. The patient panelist emphasized the high value placed on OS/mortality relative to other outcomes; this informed the recommendation against bortezomib in T-ALL and the lack of a recommendation in T-LBL/LLy.

Conclusions and research needs for this recommendation. For patients with T-ALL, the panel suggests against incorporating bortezomib into frontline therapy. For AYAs with T-LBL/LLy, the panel concluded that the evidence was insufficient to recommend for or against addition of bortezomib to frontline therapy for all AYAs. The panel recognized that the available study did not include older AYAs and, thus, efficacy and toxicity in this population is unknown. Incorporating bortezomib into treatment for the youngest adolescents with T-LBL/LLy, however, may provide benefit among the youngest adolescents of the AYA population with T-LBL/LLy.

Future research is needed to evaluate the optimal treatment of AYA patients with T-ALL. It is imperative that this research includes AYA patients of the entire age spectrum, between the ages of 15 and 39 years.

Treatment for Ph⁺ ALL

For patients with Ph⁺ ALL, what are the comparative benefits and harms of frontline treatment consisting of (1) IC plus a TKI, (2) reduced-intensity chemotherapy plus a TKI, and (3) targeted immunotherapy (eg, blinatumomab, inotuzumab) plus a TKI?

Recommendation 12

For AYAs with Ph⁺ ALL, the ASH guideline panel *suggests* RIT with a TKI for remission induction over IC with a TKI. This should be followed by postremission therapy. Options include IC plus a TKI and/or immunotherapy plus a TKI. Either of these approaches may be consolidated by allo-HSCT in CR1 (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- All patients with Ph⁺ ALL must receive CNS prophylaxis with concurrent IT chemotherapy (see Recommendation 13).

- The panel recognizes that postremission therapies (including allo-HSCT) are evolving, given emerging data surrounding next-generation TKIs and novel/targeted immunotherapies.
- This recommendation may not be as applicable to the youngest AYA subgroup in which pediatric-inspired (asparaginase-containing) regimens would be applied; the panel appreciates that studies of pediatric-inspired backbones were not captured within the available data set.

Summary of the evidence. The panel considered a total of 25 studies for review,¹²³⁻¹⁴⁷ ranging from tiers 1 to 3. Three comparative studies with median patient age range of 40 to 47 years evaluated a TKI combined with either RIT or IC during remission induction.¹⁴⁵⁻¹⁴⁷ These included 1 RCT comparing RIT plus the first-generation TKI imatinib with standard hyper-CVAD chemotherapy during induction.¹⁴⁵ An additional 22 non-comparative single-group studies were reviewed. Two had a median patient age in the AYA range, 2 had a median patient age of 10 years, and the remainder had median patient ages between 30 and 55 years. The indirect evidence of these studies was taken into consideration to further support the panel's recommendations. The evidence profiles and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/CRFhtO0fWU>.

Benefits. The bulk of the evidence reviewed by the panel did not focus solely on an AYA population and specifically did not include AYAs aged <18 years. Nevertheless, the studies reviewed by the panel demonstrated that induction with RIT plus a TKI appears to be associated with reduced early TRM and improved OS compared with IC with a TKI. Specifically, patients treated with RIT plus a TKI are less at risk for death within 60 days compared with those treated with a standard chemotherapy regimen (RR, 0.25; 95% CI, 0.07-0.85), and there is a trend toward higher likelihood of OS at 5 years using a RIT regimen (HR, 1.17; 95% CI, 0.84-1.62).¹⁴⁵ The panel determined that there is low certainty evidence suggesting potential decreased short-term infections and AEs in AYA patients with Ph⁺ ALL treated with reduced-intensity conditioning plus a TKI compared with IC plus a TKI. The first induction cycle carries less infectious risk when RIT is used rather than IC (RR, 0.64; 95% CI, 0.49-0.83), and is accompanied by a trend toward lower rates of other grade 3/4 AEs during induction with RIT plus a TKI compared with IC plus a TKI (RR, 0.90; 95% CI, 0.69-1.19).¹⁴⁵

Overall, the estimated desirable effects are moderate although the certainty in the evidence is very low owing to the indirect evidence base and imprecision of the estimates including wide CIs. Additionally, the studies reviewed included patient populations that were not AYAs, and only 1 study was an RCT. Most patients received postremission therapy with chemotherapy, and many followed this by allo-HSCT; however, it was not possible to determine the relative effect of allo-HSCT on clinical outcomes. Nevertheless, given the benefits of desirable effects including reduced mortality and improved EFS and OS, the panel felt that the evidence most likely favors the use of RIT plus a TKI over IC plus a TKI during remission induction. The panel recognizes that

postremission therapies (including allo-HSCT) are evolving given emerging data surrounding next-generation TKIs and novel/targeted immunotherapies.

Harms and burden. With an RIT regimen, the panel considered the risk of higher relapse rates. The data suggest, however, that RIT is not associated with an increased rate of early relapse in studies evaluating this outcome. There is a nonsignificant trend toward lower rates of pre- and post-allo-HSCT relapse rates with RIT plus a TKI than with IC plus a TKI (pre-allo-HSCT RR of 0.26 [95% CI, 0.03-2.18]; post-allo-HSCT RR of 0.65 [95% CI, 0.2-2.11]). Patients who received reduced-intensity conditioning plus a TKI also trend toward reduced transplant-related mortality than those who received IC plus a TKI (RR, 0.35; 95% CI, 0.1-1.18).

The panel acknowledges that there is very low certainty regarding these data owing to indirectness, imprecision, and risk of bias. Comparisons between RIT and IC with respect to long-term toxicity and AEs following the remission induction period are limited by introduction of postremission therapy and transplantation. Furthermore, conclusions regarding harm from the intervention of RIT rather than IC were limited by the lack of RCT or observational data addressing other important AEs considered by the panel, namely organ-specific side effects, QOL, time spent in the inpatient setting and rate of hospitalization, and financial toxicity, among others.

Contextualizing the implications of 1 therapeutic strategy compared with another is essential to the understanding of potential harms despite the lack of direct evidence. The panel acknowledges that other factors also appear to favor the use of RIT plus a TKI for induction, but these may not easily be quantitatively measured. These include the increased risk of infertility with high-dose chemotherapy (such as hyper-CVAD) and the potential for cardiac toxicity from higher doses of anthracycline-based therapy. Both risks could possibly be lowered with reduced intensity regimens, although they are not eliminated. As data evolve regarding novel strategies for RIT, such as incorporation of targeted agents or transplant-sparing immunotherapy combinations, new approaches may further reduce the risk of chemotherapy-related toxicity during chemotherapy cycles beyond remission induction (consolidation and maintenance).

Other EtD criteria and considerations. OS and ability to achieve CR were recognized by the panel to be of highest value to patients in balance with toxicities and QOL. Although the available data did not capture all outcomes of value for patients, namely QOL, the panel did not believe this uncertainty was enough to change the strength or direction of the recommendation. With the promising results of combined second-generation (and now third-generation) TKIs with blinatumomab and response-adapted transplant approaches,^{142,109,148} the panel recognized that these approaches are likely to support the values important to patients.

The panel acknowledged that the comparison of chemotherapy intensity did not include intensive pediatric-inspired asparaginase-containing regimens or the incorporation of blinatumomab into these regimens, now used by national and international cooperative groups for the treatment of pediatric Ph⁺ ALL. The intensive pediatric treatment approach uses an MRD-guided postremission risk-stratification strategy that results in fewer pediatric patients undergoing allo-HSCT compared with the adult RIT trials that

informed our recommendation. Therefore, the recommendation may not be directly applicable to younger AYA patients or acceptable to clinicians treating this subgroup of patients.

Most patients in the available comparative studies received the first-generation TKI, imatinib, thereby limiting the panel's ability to analyze comparative efficacy, drug accessibility, or cost among TKI generations. In 1 retrospective study reviewed,¹⁴⁷ some patients received the second-generation TKIs, dasatinib and nilotinib. The third-generation TKI, ponatinib, may further avoid emergence of treatment resistance in Ph⁺ ALL, but results of treatment regimens incorporating ponatinib were not yet available during the generation of this guideline. The panel acknowledges that disadvantaged populations may be disproportionately affected by higher costs of second- and third-generation TKIs, limiting their broad access. The same limitations apply to consolidative treatment with targeted immunotherapies such as blinatumomab.

Conclusions and research needs for this recommendation. This panel determined that there may be a net benefit of RIT plus a TKI over IC plus a TKI for remission induction in AYA patients with Ph⁺ ALL. This recommendation places a high value on the potential benefits of RIT over more IC. All patients should receive CNS prophylaxis as part of their treatment, with frequency and intensity depending on the type of regimen used, and with particular attention to those receiving a reduced-intensity approach.

Future research is needed to evaluate the optimal treatment of AYA patients with Ph⁺ ALL and efforts among pediatric and adult hematology cooperative groups should be made to broaden prospective studies to include the entire AYA age range. Although the induction question is relatively straightforward (despite low-grade evidence), the best postremission therapy approach is evolving. Excellent survival rates using a TKI with blinatumomab without allo-HSCT have recently been reported in adults with Ph⁺ ALL.¹⁴³ Longer-term follow-up of this study as well as results of ongoing prospective studies that include AYAs, and are testing third-generation TKIs, targeted immunotherapy, with minimal or no traditional chemotherapy and no allo-HSCT, will be critical to strengthen our current guidelines. The role of chimeric antigen receptor T-cell therapy in frontline treatment of Ph⁺ ALL also remains to be elucidated. Improved risk-stratification models to identify high-risk patients who might benefit from allo-HSCT in CR1 will also be helpful.

CNS prophylaxis

For patients with ALL without CNS involvement at diagnosis, what are the comparative benefits and harms of different CNS prophylaxis regimens, including (1) IT chemotherapy regimens and (2) cranial radiation?

IT chemotherapy regimens

Recommendation 13

For AYAs with ALL receiving frontline therapy, the ASH guideline panel suggests the use of either IT methotrexate or TIT for CNS prophylaxis (conditional recommendation for

either the intervention or comparison based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- Hydrocortisone can be used (in conjunction with IT methotrexate) for prevention of chemical arachnoiditis.

Summary of the evidence. The panel reviewed 14 comparative studies that evaluated CNS prophylaxis regimens, ranging from tiers 3 to 6, with a median patient age of <10 years in all but 1 study. Among these, 2 RCTs compared TIT (IT methotrexate, cytarabine, and hydrocortisone) with single-agent IT therapy (SIT; methotrexate) as postinduction CNS prophylaxis among patients without CNS involvement,¹⁴⁹⁻¹⁵¹ with a median follow-up of 5 to 6 years. One of these compared neurocognitive outcomes at 6 years between TIT and SIT.¹⁴⁹

For all outcomes, the certainty in the evidence was considered low to very low due to indirectness and imprecision of the data. Generalizability to the AYA population cannot be precisely determined because most patients included in the analysis were younger than AYA age. The evidence profile and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/k4oMgZsVBLQ>.

Benefits. A meta-analysis comparing the benefits of TIT vs SIT showed no differences in OS (RR, 0.98; 95% CI, 0.94-1.03), DFS (RR, 0.97; 95% CI, 0.71-1.33), or EFS (RR, 0.98; 95% CI, 0.94-1.02) but did reveal a lower rate of isolated CNS relapse favoring TIT (RR, 0.58; 95% CI, 0.40-0.83). One trial found higher rates of systemic relapse for patients receiving TIT with relapses that were generally harder to salvage.¹⁵⁰ The panel noted challenges in interpreting these results, however, because at least 1 was an older study using a chemotherapy backbone with less systemic intensity than what is currently used.

The panel highlighted that the consequences of CNS relapse, and its treatment, are likely to be significant and underrecognized. Therefore, isolated CNS relapse was considered an important outcome independent of EFS and OS. Despite the lower risk of CNS relapse seen with TIT, however, the panel could not conclude that TIT is clearly superior to SIT due to the lack of difference in EFS or OS.

Harms and burden. The panel was concerned about the potential for increased neurological toxicities and long-term cognitive impairment with the use of TIT compared with SIT. In studies directly comparing TIT with SIT, there were no significant differences in encephalopathy, neurotoxicity, or CNS toxicity outcomes while on treatment.^{149,151} Long-term follow-up of neurocognitive function found no meaningful differences between treatment arms across many measured metrics. There was a small difference noted in cognitive processing speed in favor of TIT. However, it is unclear whether this outcome is clinically relevant and representative of actual neurocognitive function. In addition, these studies only included patients between the age of 1 and 9.9 years, so the data were indirect for the AYA population. The panel recognized the importance of neurocognitive and neurotoxicity

outcomes and their impact on future QOL and work productivity. The panel highlighted that these concerns are often underrecognized and not routinely discussed at the outset of treatment. In our literature search, comparative and prospective studies in AYA patients with ALL focusing on the effects of CNS-directed therapies on long-term neurocognition were lacking.

The panel raised concerns about the more immediate side effects of IT therapy, including chemical arachnoiditis. Although the scope of this systematic review did not establish strategies that clearly reduce the risk of chemical arachnoiditis, the panel recognizes that there is a long-standing practice, particularly among adult oncology centers, to administer IT hydrocortisone in addition to IT methotrexate and/or IT cytarabine for this purpose. The panel felt it was reasonable to consider the addition of hydrocortisone to IT therapy. In addition, IT cytarabine can be used as an alternative for patients exhibiting intolerance to IT methotrexate, although there are no data to clearly determine whether it is noninferior. The panel also raised some concerns about the need for repeated sedation/anesthesia in younger AYA patients and its cumulative effects, including neurocognition. The consequences of these exposures were not captured in this analysis.

Conclusions and research needs for this recommendation. For AYA patients with ALL receiving frontline therapy, the ASH guidelines panel suggests the use of either SIT therapy (methotrexate) or TIT therapy for CNS prophylaxis. The analysis did not demonstrate an EFS or OS benefit from TIT compared with SIT. There were also no clear differences in encephalopathy, neurotoxicity, CNS toxicity, and neurocognition. The panel felt that the available data favored neither intervention nor comparator.

Additional research studies in the AYA population directly comparing TIT with SIT would be beneficial, especially in the context of the evolving incorporation of immunotherapy into ALL treatment regimens. Analyzed outcomes should not only include CNS relapse, OS, and EFS, but also short-term and long-term neurologic toxicities. Comparative studies looking at the long-term neurocognitive effects of therapy (and subsequent impact of CNS relapse) are lacking and should be considered a research priority.

Cranial radiation

Recommendation 14

For AYAs with ALL receiving frontline therapy, the ASH guideline panel *suggests against* the routine use of cranial radiation for CNS prophylaxis for patients treated on a pediatric-inspired (asparaginase-containing) backbone (conditional recommendation against the intervention based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- There is uncertainty with respect to the use of cranial radiation for CNS prophylaxis for AYA individuals with T-ALL who are unable to receive nelarabine.

Summary of the evidence. The panel reviewed 12 studies^{122,152-164} that evaluated cranial radiation therapy (CRT) for

CNS prophylaxis, with a median patient age of <10 years in all but 1 study. Only 3 studies provided randomized evidence comparing CRT use with no CRT use.^{153,160,161} Overall, the panel recognized that there is considerable heterogeneity in the studies included with respect to other CNS-directed therapies, such as IT and systemic (eg, high-dose methotrexate) treatments. This heterogeneity limits the strength of the pooled analyses. Some studies were based on systemic backbone regimens that are less relevant to current practice (and not all of which were pediatric-inspired). The panel also noted that many of these studies were conducted in children aged <10 years, rendering the evidence even more indirect. In all but 1 of the studies evaluated, risk of bias was serious to very serious, and all studies provided indirect evidence due to the ages of patients included. The evidence profile and EtD framework are available online at <https://guidelines.ash.gradeapro.org/profile/QELaX1fLG70>.

Benefits. Among 3 randomized studies included in the meta-analysis, there was no difference in OS, DFS, or EFS for patients who did and did not receive CRT; of note, patients who did not receive CRT were treated with intensive IT therapy and systemic chemotherapy that provides some CNS penetration.^{153,160,161} Specifically, there was no OS difference between groups receiving or not receiving CRT at 8 to 10 years^{153,161} (RR, 1.02; 95% CI, 0.97-1.07) or 25 years from diagnosis⁹ (CRT, 78.5% vs no CRT, 78.1%; HR, 1.00; 95% CI, 0.53-1.88)^{122,157,158} In 2 nonrandomized comparative studies there was also no benefit to OS (RR, 1.00; 95% CI, 0.99-1.01),^{122,158} nor EFS or DFS with use of CRT. Overall, the panel agreed that there were no clear benefits to administering prophylactic CRT to patients without CNS involvement compared with the use of IT chemotherapy and treatment regimens with systemic chemotherapy that provides CNS coverage.

Harms and burden. A significant concern with CRT use is the risk of poor neurocognitive outcomes. Eight studies described such outcomes and generally suggest that CRT use leads to worse function in this area. Domains of concern for deterioration included attention, processing speed, neuromotor abilities, visual learning and motor integration, and general academic achievement.^{152,154-156,163,164} Importantly, these studies primarily included younger patients (aged <15 years) during the period of CRT exposure. The panel recognized that the risks and burdens of neurocognitive deficits may be different among AYAs receiving CRT; however, data on both short- and long-term burdens of CRT use among AYAs are lacking. Nonetheless, given the lack of benefit coupled with potential harms associated with CRT use, the panel does not recommend routine use of prophylactic CRT among AYAs with ALL without CNS involvement.

Other EtD criteria and considerations. Of particular consideration is the evolving role of CRT as CNS prophylaxis in T-ALL, especially because most patients in the included studies were treated for B-ALL. All patients with T-ALL enrolled on CALGB 10403⁴⁵ and all intermediate- and high-risk patients enrolled on COG AALL0434 were nonrandomly assigned to receive prophylactic CRT as part of protocol therapy¹¹⁴ and experienced favorable outcomes. However, the AALL0434 trial additionally randomized these patients to nelarabine or no nelarabine, and to high-dose or escalating (Capizzi-style) methotrexate (see

“Additional therapies for specific subsets: nelarabine” for additional detail regarding the role of nelarabine in CNS relapse).¹¹⁴ The panel expressed uncertainty with respect to the role of CRT for CNS prophylaxis in T-ALL in the setting of nelarabine (either its use or omission), because treatment with and without CRT has not been formally tested. The panel also expressed uncertainty about the role of CRT for AYAs with T-ALL who are unable to receive nelarabine due to toxicity or other comorbidities.

Conclusions and research needs for this recommendation. When taken as a whole, the studies showed no clear benefit to administering prophylactic CRT to patients without CNS involvement, with the caveat that most of the patients considered in these studies were treated for B-ALL. Furthermore, although the risk of cognitive impairment due to CRT exposure is well described among younger patients, the burden of this risk is less described among AYAs. As a result, studies describing late effects from CRT exposure may not be representative of the impact on AYAs, or the risk-to-benefit ratio that AYA patients may place on the use of CRT to reduce CNS relapse risk. Finally, current radiation doses, protocols, and techniques may result in different toxicity rates and cognitive outcomes than those documented in the summarized older studies. Considerations for future work should include dedicated work on neurocognitive outcomes for patients undergoing CRT during the AYA years and could include prospective studies of the efficacy of nelarabine without CRT to prevent CNS relapses.

Approach to MRD

For patients with ALL receiving frontline therapy and being assessed for MRD, what are the comparative benefits and harms of changing the treatment regimen due to the detection of MRD, including incorporation of immunotherapy?

Recommendation 15

For patients with ALL with persistent MRD after ≥ 3 months of frontline therapy (induction plus a minimum of 1 block of postremission therapy), the ASH guideline panel *recommends* a change in approach to treatment (see Recommendation 9) (strong recommendation for the intervention based on very low certainty in the evidence of effects $\oplus\bigcirc\bigcirc\bigcirc$).

Remarks:

- The change in therapy could include several approaches including immunotherapy or allo-HSCT. The optimal timing, choice of intervention(s), order, or combination of these approaches has not been defined.
- Although T-ALL has not been studied individually, patients with T-ALL were included in the studies demonstrating the benefit of transplant for patients with MRD-positivity.

Good practice statement for Recommendation 15

Measurement of disease response using MRD is considered standard of care in AYA ALL for both prognostic value and, in some cases, determination of treatment intensity.

Background. Quantitative measurement of MRD has both prognostic and therapeutic implications in ALL and is now considered a standard of care for disease assessment for patients with ALL. There are different methods of MRD measurement, and prognostic implications of MRD levels are dependent on treatment approach and treatment time point. A few general definitions may be helpful. In most studies, the definition of MRD-positive disease is $\geq 0.01\%$ when using quantitative flow cytometric or clone-specific MRD measurement. Conversely, MRD-negative disease is defined as $< 0.01\%$ using these methods. Next-generation sequencing techniques for MRD measurement are more sensitive than flow by ~ 2 logs (eg, $< 0.0001\%$) and report an absolute copy number of the leukemia-specific immunoglobulin H or T-cell receptor clonally rearranged cells representing the leukemia clone. The AYA guideline panel is aware of a forthcoming guideline from the College of American Pathologists and systematic review with expert recommendations in the application, interpretation, and actionability of MRD for pediatric and adult B-ALL (<https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/evaluation-of-mrd-testing-in-all>).

Although this recommendation focused on the decision to alter therapy in MRD-positive patients after initial therapy, there are parallel considerations for MRD-negative patients addressed in aforementioned recommendations and these are referenced hereafter.

Summary of the evidence. To determine the effects of changes in therapy based on MRD status in AYA patients with ALL, the panel reviewed a total of 5 comparative studies from tiers 2 to 3, with a median patient age ranging from 31 to 55 years.^{100,107,165-167}

Indirect evidence from an additional 9 noncomparative studies that are not included in the evidence profiles was discussed and taken into consideration by the panel.^{110,168-175}

The evidence profiles for MRD-positivity and MRD-negativity in CR1 and EtD framework are available online at <https://guidelines.ash.gradepro.org/profile/juHAYkZOB0w>.

Benefits. The panel reviewed 5 comparative studies that evaluated changes to therapy based on MRD-positivity after both induction therapy and at least 1 cycle of consolidation therapy in AYA ALL.^{100,107,165-167}

First, data were considered surrounding the addition of blinatumomab to therapy for patients in an MRD-positive remission. With the addition of blinatumomab in MRD-positivity, there was a decreased risk of relapse or death at 2.5 years adjusting for allo-HSCT (HR, 0.47; 95% CI, 0.30-0.73)¹⁷⁰ and MRD-positive patients were more likely to be able to receive an allo-HSCT (44% vs 78.5%; HR, 1.78; 95% CI, 1.46-2.19). This was not accompanied by a statistically significant difference in OS (HR, 0.68; 95% CI, 0.42-1.09).

Data were also considered surrounding the receipt of allo-HSCT in MRD-positive patients. With allo-HSCT, there was a decreased risk of relapse (HR, 0.34; 95% CI, 0.20-0.58),^{100,167} improved RFS at 5 years (HR, 0.41; 95% CI, 0.26-0.66),^{100,167} improved DFS at 6 years (RR, 7.19; 95% CI, 1.02-50.74),¹⁶⁷ and improved

OS at 5 years (HR, 0.40; 95% CI, 0.25-0.64).^{100,167} However, nonrelapse mortality was higher for MRD-positive patients who received an allo-HSCT (HR, 2.39; 95% CI, 1.03-5.58).¹⁶⁶

Although evidence was sought to evaluate other changes to therapy based on MRD status (including inotuzumab), there were no additional data. Overall, the panel felt there was minimal comparative evidence for specific therapy augmentation approaches, and due to the uncertainty raised with study designs and indirectness, the overall certainty in the evidence was very low.

Therapy augmentation for MRD-negative patients is addressed in other recommendations. Specifically, Recommendation 9 addresses the addition of blinatumomab to postremission therapy for MRD-negative patients, and Recommendation 7 addresses allo-HSCT in MRD-negative patients in CR1.^{100,107}

Harms and burden. Unfortunately, changes in therapy can result in undesirable effects (including serious toxicities and death), which must be considered. Patients receiving blinatumomab had increased grade ≥ 3 neurologic or psychiatric AEs (RR, 4.2, 95% CI, 1.79-9.85), but less grade ≥ 3 thrombocytopenia (RR, 0.71; 95% CI, 0.55-0.92) than patients who received chemotherapy alone. MRD-positive patients who received an allo-HSCT experienced higher rates of nonrelapse mortality (11.8% vs 4.9%; HR, 2.39; 95% CI, 1.03-5.58) than those who did not receive an allo-HSCT.¹⁶⁶ Nevertheless, given the poor prognosis associated with persistent MRD-positivity, the improved RFS with blinatumomab and improved RFS and OS with allo-HSCT as highlighted earlier were felt to outweigh potential undesirable effects.

Other EtD criteria and considerations. For changes in therapy guided by MRD status, the panel recognized mortality and OS as the highest value relative to other outcomes, while also acknowledging the importance of added toxicities for patients and the potential impact of any intervention on long-term QOL. The available studies to examine changing therapy in the setting of MRD-positivity may not have captured all outcomes valuable to patients outside short-term AE and mortality, especially due to lack of data on QOL. Nevertheless, this uncertainty was not considered robust enough to change the strength or direction of the panel's recommendation regarding changes to treatment in the setting of persistent MRD-positivity. Although long-term effects of these therapies may become evident over time, it would not modify the value placed on the OS benefit in making this recommendation, given the strength of the negative prognosis associated with MRD-positivity.

The totality of the evidence reviewed by the panel highlighted the need to escalate or change therapy from standard chemotherapy-based approaches for patients who remain MRD-positive while acknowledging that uncertainty remains as to the optimal approach to changing therapy in this situation. There was very low certainty regarding blinatumomab and allo-HSCT as interventions in light of minimal comparative evidence, single-arm and historical control study designs, and the indirectness of the study population. For other potential interventions, such as inotuzumab, no prospective, comparative data from frontline studies are available. In addition, there was high uncertainty with respect to whether there is a specific treatment time point or MRD threshold level that

would warrant escalation. There was also heterogeneity in the MRD assessment approach and technique. Furthermore, there was no evidence surrounding the optimal number of postremission cycles of blinatumomab, the best timing or sequence of blinatumomab and allo-HSCT as interventions, and/or how to incorporate other potential approaches to MRD-positivity after these interventions.

The panel noted the cost and resource implications associated with MRD testing and the incorporation of subsequent therapies including blinatumomab and/or allo-HSCT. In addition, the panel acknowledges that underrepresented or disadvantaged populations may be disproportionately negatively affected by the high costs associated with MRD testing and subsequent escalation of care, including access to antibody-based or immunotherapies and/or pursuit of allo-HSCT. Although this guideline is focused on the management of AYAs with ALL in well-resourced countries, the panel recognizes the potential for variable and inequitable access to MRD testing, novel targeted therapies, immunotherapies, and HSCT in other parts of the world.

Conclusions and research needs for this recommendation. The panel determined that there is a net benefit to changing the approach to treatment after ≥ 3 blocks of front-line therapy in AYA patients with ALL who have persistent MRD. This approach could include blinatumomab, inotuzumab, or allo-HSCT. This recommendation places a high value on the potential benefits of changing the treatment approach. Although the grade of available evidence is of very low certainty, there are comparative studies demonstrating improved RFS and/or OS with both blinatumomab and allo-HSCT. Undesirable effects with this approach include toxicities related to these treatments: cytokine release syndrome and neurotoxicity with blinatumomab, cytopenias and hepatotoxicity with inotuzumab, and infections and graft-versus-host disease with allo-HSCT. Although values and preferences are likely to vary, given the poor prognosis associated with persistent MRD and the fact that patients place the highest value on OS relative to other outcomes, it is likely that most patients value the uncertain benefits more than the uncertain harms. Following the considered judgment process of the panel and the recognition that the intervention (change in approach to therapy for persistent MRD) may offer benefit in a life-threatening situation (relapse), the panel supported a strong recommendation for this approach despite the very low certainty in evidence.⁷³ Changing treatment after ≥ 3 blocks of frontline therapy for patients with persistent MRD is an option likely to be acceptable to stakeholders. The optimal order or combination of these approaches is unknown. Implementation of these changes may be challenging in underresourced populations due to cost and access.

Future research is needed to better determine the optimal timing and choice of alternate therapies, as well as the order in which these treatments should be given. It remains unclear which patients still benefit from allo-HSCT if their MRD is cleared with blinatumomab or inotuzumab, and whether the aforementioned data are relevant to patients with low levels of MRD (measured by CloneSeq).

A new era is emerging suggesting a significant survival benefit with the addition of blinatumomab to postremission frontline chemotherapy for MRD-negative as well as MRD-positive disease (see Recommendation 9), and the panel recommendations are reflective

of these developments. The issues of equitable access and financial toxicity that are highlighted for MRD-positive patients as described earlier apply, perhaps even more strongly, to the application of targeted immunotherapies in the MRD-negative frontline setting. Similarly, it is still unknown whether blinatumomab can or should be combined with other targeted agents and other immunotherapies, how treatment should be sequenced, how many cycles of blinatumomab are optimal and practical, the impact of these targeted immunotherapies on particular high-risk molecular cytogenetic subsets (eg, Ph-like and TP53-mutant disease), how best to apply CNS-directed therapy, whether or not there are still patients who will benefit from allo-HSCT in CR1, and whether IC and/or maintenance therapy can be shortened to potentially minimize treatment duration and long-term toxicities. Finally, the first studies addressing new targeting strategies for T-ALL in the front line across the AYA age range are now underway or imminent, and this remains an important area of research for the future. These questions are mandates for this next exciting era in AYA ALL research.

Good practice statements

Good practice statement

Given the unique challenges of cancer in adolescence and young adulthood, it is good practice for AYAs with ALL to have their developmental needs evaluated, and their preferences and goals for treatment assessed within their unique developmental context. Whenever possible, their treatment should be delivered with consideration of their unique developmental stage, providing scheduling flexibility when not otherwise contraindicated.

Good practice statement

Given the risk and prevalence of psychological comorbidities and adverse psychosocial outcomes during the cancer experience of AYAs with ALL, it is good practice to routinely screen for depression, anxiety, and other psychological comorbidities and implement multidisciplinary psychosocial support.

Good practice statement

Given the unique social needs of AYAs with ALL, it is good practice to assess and evaluate each patient's existing social supports and encourage connection with supportive communities, when possible, through organized care coordination and resource navigation from a multidisciplinary team experienced in working with AYAs.

Good practice statement

Given the financial toxicity experienced by AYAs with ALL, it is good practice to provide financial counseling, resource navigation, and concrete resources through institutional means and/or in collaboration with larger regional and national organizations.

Good practice statement

Given the importance of sexual health and sexuality for AYAs with ALL along with the dynamic changes experienced in these areas over time, it is good practice to discuss sexual health, sexual orientation, sexual preferences, and gender identity of each individual patient from the onset of diagnosis, throughout the course of the individual's treatment, and into survivorship.

Good practice statement

Given the importance of fertility and how it is affected by cancer and its therapy, it is good practice to provide AYAs with ALL access to comprehensive fertility care in consultation with, but not limited to, their oncology provider, fertility specialist, and fertility counselors before the initiation of therapy whenever possible, with continued involvement and care from this multidisciplinary team throughout therapy and into survivorship.

Good practice statement

Given that AYAs are underrepresented in cancer clinical trials, and improvement in survival over time has lagged in underrepresented populations of AYAs, it is good practice to offer AYAs treatment in an appropriate clinical trial.

Good practice statement

It is good practice to introduce interdisciplinary palliative care teams as early as possible in treatment. Interdisciplinary and/or primary (ie, delivered by the treating oncology team) palliative care should remain a focus of care throughout the care continuum, regardless of disease status.

Good practice statement

It is good practice to discuss goals of care and end-of-life concepts early in treatment, and before disease- or symptom-related crises arise. These discussions should be ongoing, tailored to the AYAs developmental and cognitive level, center on the AYAs wishes, and involve families and/or caregivers to the extent desired by the AYA. End-of-life care goals should be readdressed at key transition points during care (eg, relapse).

Good practice statement

Considering differential outcomes for AYAs by location of care, in the context of their unique medical and developmental needs and the statements included here, it is good practice to ensure AYAs with ALL have access to specialized care with professionals and institutions well versed in AYA ALL when feasible.

See the [Appendix](#) for expanded content related to these statements.

These statements are also published in the ASH guidelines for management of relapsed/refractory ALL in AYAs to ensure consistency across AYA guidance.¹⁷⁶

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence we identified for many of the questions. In particular, most of the existing data were considered indirect to the AYA population of interest for this guideline. The paucity of AYA-focused studies required the guideline panel to extrapolate estimates of benefits and harms from data that were more specific to either pediatric or adult populations and resulted in the lower certainty ratings associated with our recommendations.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.¹⁷⁷

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.¹⁷⁸

Priorities for research

Throughout the aforementioned discussions, the panel made distinct recommendations for research. However, beyond those specific recommendations there are some more pervasive gaps in evidence that were identified during the guideline development process. Considering these, the panel highlights further priorities for research.

Understanding the psychosocial impacts of therapy and therapy settings should be a priority, because AYAs are at a unique time in their social, emotional, and physical development from both the older adult population and pediatric population. AYAs also represent an overwhelming majority of patients with ALL who are of reproductive age. There is a paucity of data regarding therapy-related toxicity related to reproductive organs; much of these data require decades to document, which renders decision-making among AYAs and leukemia clinicians incredibly challenging. There are advocacy efforts to encourage collection of relevant reproductive data points during oncology drug development, but it is crucial to consider collecting these data points at any point along the trajectory of evaluating therapy outcomes.¹⁷⁹ Specifically considering patients with ovaries who are diagnosed with ALL, there is controversy regarding the infiltration of the ovaries and whether it is safe or wise to harvest ovarian tissue and/or oocytes. Providers make recommendations regarding pregnancy and fertility without substantial data; although it is key that clinicians rely on the expertise of our colleagues in maternal fetal medicine and reproductive endocrinology and infertility, it is also vital to collect robust data to inform clinical management. Providers also make varying recommendations regarding sexual practices without robust assessments of sexual health or evidence regarding potential risks, and there are a lack of data in this area. The unique position of AYAs in terms of the health system and how their care

is delivered puts them at risk of financial toxicity and nonadherence to treatment recommendations, especially in the context of prolonged outpatient therapy. Research in these areas is desperately needed as well. Finally, the underlying theme to all the gaps in research noted and the overwhelming indirectness of the vast majority of the evidence leveraged for this endeavor, is the need for AYA-specific data in ALL. The panel recognizes that conducting AYA-specific studies may not always be plausible, and encourages all investigators to strongly consider reporting AYA subgroups of patients within their analyses and reports such that AYA clinicians and researchers can better understand the relevance of an intervention or outcome among AYAs and, at minimum, to facilitate future meta-analyses that may improve our understanding and ability to identify the best approach to care for AYAs with ALL.

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Authorship

Contribution: All guideline panel members contributed to specific subsections of the text for the recommendations; M.C.C., W.S., J.A.W., J.M., and A.S.D. organized and then revised these subsections into the first draft of the manuscript, and subsequently revised the manuscript based on authors' suggestions; all guideline panel members critically reviewed the manuscript and provided suggestions for improvement to strengthen the final version; H.J.M., G.K., Y.S., I.J.S., and E.M.B., the members of the knowledge synthesis team, contributed evidence summaries to the guidelines; J.A.W. and W.S. were coauthors of the guideline panel and led panel meetings; M.C.C. was the ex officio representative from the American Society of Hematology clinical practice guidelines oversight committee; and all authors approved of the content.

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Appendix: a broader look at psychosocial care for AYAs

To comprehensively treat all AYAs with ALL, it is important to consider the domains of health beyond medical complexity including the developmental, psychological, and social domains unique to this population. In general, psychosocial support for individuals coping with cancer is associated with improved emotional distress and QOL.^{180,181} Below, we outline important practice considerations across key domains (this should not be considered an exhaustive list); these prioritize holistic treatment to improve function during treatment and maximize positive outcomes immediately after treatment and into survivorship.

Developmental needs of AYAs

Adolescence and young adulthood comprise a critical stage of human development that is characterized by rapid cognitive, emotional, and social growth. During this transition from childhood to adulthood, young people are tasked with navigating pubertal changes and cognitive development; exploring sexuality; developing a healthy body image; renegotiating boundaries with parents while increasing reliance on peers; forming a cohesive identity; achieving important legal milestones; and making decisions about employment, education, and/or family.¹⁸²

A cancer diagnosis, although impactful at any age, can be particularly disruptive to typical development during the AYA period. AYAs who are diagnosed with cancer must navigate the same developmental tasks as any other AYA, while also managing treatment-related disruptions across nearly every domain of development (eg, educational/vocational, independence from parents, peer and dating relationships, sexual functioning, and family planning). AYAs with cancer also face many developmentally incongruent tasks, such as relinquishing newly found independence and bodily autonomy, moving back into their parents' homes, relying on parents or partners for caretaking tasks, pausing educational and vocational aspirations, and confronting mortality, often for the first time.

AYA oncology is a unique discipline, as the psychosocial and developmental needs of this population is equivalent in importance to the biology of the disease itself. We acknowledge the significant individual variability in development between AYA patients, and we emphasize that the unique developmental needs differ from the needs of other adult or pediatric patients.

Psychological needs of AYAs

AYAs with ALL and other cancers are at highest risk of psychological distress relative to those with cancer who are younger or older in age.⁴⁻⁶ They are more likely to endorse clinically significant symptoms of anxiety, depression, posttraumatic stress, and other mental health diagnoses, with symptoms often persisting well into survivorship.¹⁸² The increased risk of psychological distress among AYAs has been attributed to the disruption that cancer and its therapy has on important unique developmental time periods

leading to difficulty in mastering critical traumatic exposures during the treatment process and difficulty in understanding the severity of their illness while sometimes lacking fully developed cognitive and emotional coping abilities.^{178,183} AYAs also endorse psychological adjustment difficulties such as delayed social maturation, disrupted educational attainment and vocational pursuits, job and insurance discrimination, financial difficulties, and relationship and intimacy problems, all of which negatively affect broader psychosocial functioning.^{184,185} Furthermore, the AYA period intersects with a critical time point in the development of severe psychopathology such as schizophrenia or bipolar disorder. For these disorders, symptoms may emerge between the late teens and mid-30s, with the peak age of onset occurring in the early to mid-20s. Collectively, these factors contribute to worsened psychosocial outcomes that are observed among AYA patients. Importantly, psychosocial functioning may adversely affect treatment outcomes because it may affect the patient's interest, willingness, or ability to access and/or complete oncology treatment, which may increase their risk of treatment failure.

Despite the risk for adverse outcomes, it is also important to note that AYAs have remarkable capacity for posttraumatic growth and resilience, particularly when they are provided appropriate supports throughout treatment and survivorship.¹⁸⁶ However, few seek out psychosocial supports when needed due to significant stigma that can lead to embarrassment or unwillingness to report their concerns to providers without significant prompting, whereas many of those who do seek out supports report experiencing difficulties obtaining assistance.¹⁸⁷

Social needs of AYAs

The social needs of AYAs with ALL are intrinsically linked to both the developmental and psychological needs of this population. For AYAs, their developmental need for social connection and belongingness are in direct contradiction with the demands of treatment, which often calls for social isolation and separation. Additionally, treatment may prevent an AYA from achieving or participating in important social (eg, proms or friends' weddings), educational (eg, graduations), or vocational (eg, advancing careers) milestones. Collectively, the impact of cancer and its treatment on social development may contribute to, or exacerbate, psychological adjustment difficulties; flexibility in health care delivery that affords AYAs as much opportunity to live as normal as possible and participate in as many developmental milestones as possible is beneficial.

Financial needs of AYAs

An oncologic diagnosis during the AYA period intersects with a time in which most AYAs are building resources and learning financial independence. Such a diagnosis puts AYAs at a greater risk for insufficient insurance coverage and limited access to financial supports.¹⁸⁸ There is significant individual variability across AYAs in the amount and type of financial resources due to the broad age and developmental range included in the AYA population. Although the Affordable Care Act has expanded insurance coverage for some in the AYA group, AYAs (especially those aged 19-34 years) remain the most uninsured group in the United States (<https://www.census.gov/content/dam/Census/library/visualizations/2022/demo/p60-278/figure2.pdf>). Beyond

the feasibility and cost of insurance, AYAs must also manage the burden of insurance copayments, meeting deductibles, and navigating the limitations of individual insurance plans for comprehensive oncology care (eg, fertility preservation and family planning, mental health care, and treatment-related travel costs). Although AYAs may initially find conversations regarding the finances to be overwhelming, it is important that all AYAs have access to information regarding the financial toxicities associated with treatment.

Sexual health and sexuality

Sexual health and sexuality are complicated but vital parts of human existence that involve interactions between biopsychosocial, environmental, developmental, and physical domains. Cancer and its therapy significantly affect both sexual functioning and nonsexual physical intimacy of AYAs including self-image, physical desire, physical pain and comfort, fatigue, and uncertainty of what may be safe for them and others throughout diagnosis and therapy. However, discussions regarding sexual

health and sexuality can be embarrassing for anyone of any age and oncology providers report little training in these areas.^{189,190} Additionally, with their age and development, there may be changes to the AYAs sexual functioning, desires, and preferences throughout diagnosis, treatment, and into survivorship.

Fertility preservation

Cancer and its therapy can significantly affect an AYAs ability to build their family in their chosen manner through their impact on fertility. Additionally, each individual patient's hopes and desires and the impact of different therapies are unique, at times uncertain, and can also change over time. However, it has been demonstrated that even discussions surrounding the impact of cancer and its therapy on fertility can ultimately reduce distress and improve QOL. Unfortunately, fertility preservation is not always possible with acute leukemias such as ALL given the level of illness on presentation requiring emergent therapy and/or financial or social barriers that are unable to be overcome.

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