

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

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Background: Adolescents and young adults (AYAs) with relapsed/refractory acute lymphoblastic leukemia (ALL) face unique challenges as they experience greater treatment resistance, higher rates of toxicity, and present at a specific life stage with distinct priorities.

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

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 8 recommendations and 1 research-only recommendation, covering remission reinduction and consolidation. They focused on the following treatment modalities: immunotherapy, targeted therapies, allogeneic hematopoietic stem cell transplant, and central nervous system (CNS)-directed therapy.

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Conclusions: Key recommendations include the use of blinatumomab and/or inotuzumab over chemotherapy for reinduction. Additional management of ALL subsets (T-cell ALL), CNS relapse, and the role of consolidation with allogeneic transplant are addressed. Future research should evaluate these approaches with special attention to the unique AYA population, and should evaluate quality of life outcomes.

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 (GIN).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 panel agreed have unequivocal net benefit yet may not be widely recognized or used.¹¹ Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Interpretation of research-only recommendations

A research-only recommendation is an actionable guideline, explicitly based on available evidence, that confines the use of an intervention within a specific population strictly to a research setting.

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.

It is considered appropriate when the certainty in existing evidence is insufficient for a guideline panel to issue a formal recommendation, but where feasible and acceptable future research has the potential to significantly reduce uncertainty regarding the intervention's desirable or undesirable consequences. Unlike a formal recommendation for clinical practice, public health, or policy, this guidance aims to direct further investigation.¹²

Recommendations

B-ALL immunotherapies

RECOMMENDATION 1. For adolescents and young adults (AYAs) with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL), the American Society of Hematology (ASH) guideline panel *recommends* the use of blinatumomab over chemotherapy (strong recommendation based on low certainty in the evidence of effects $\oplus\oplus\bigcirc\bigcirc$).

Remark:

- The panel highlighted the potential need to debulk before proceeding with blinatumomab for individuals with high blast counts at relapse.

RECOMMENDATION 2. For AYAs with relapsed/refractory B-ALL, the ASH guideline panel *recommends* the use of inotuzumab over chemotherapy (strong recommendation based on low certainty in the evidence of effects $\oplus\oplus\bigcirc\bigcirc$).

Remark:

- The panel highlighted the need to consider the risk of veno-occlusive disease (VOD) in individuals intended to proceed with allogeneic hematopoietic stem cell transplant (allo-HSCT) following inotuzumab ozogamicin (InO).

NO RECOMMENDATION. With minimal comparative data to review, the panel was unable to make a recommendation between chimeric antigen receptor (CAR) T-cell therapy and chemotherapy or other immune-based therapies. However, the ASH guideline panel recognizes the notable utility of CAR T-cell therapy following relapse based on existing single-arm studies.

NO RECOMMENDATION. There are almost no head-to-head comparisons of these 3 therapies (blinatumomab, inotuzumab vs CAR T-cell therapy), and the best sequence of their use is not yet understood. Therefore, the ASH guideline panel was unable to make a recommendation for one agent over the other. The choice should be made based on individual patient assessment, burden of disease, and candidacy for future consolidative therapy including allo-HSCT.

Approaches to consolidative therapy: role of allo-HSCT following CAR T-cell therapy

RECOMMENDATION 3. For AYAs who are HSCT naïve with relapsed B-ALL who achieve a second (or greater) remission (CR2) with US Food and Drug Administration (FDA)-approved autologous CD19 CAR T-cell products (tisagenlecleucel and brexucabtagene autoleucel), the ASH guideline panel *suggests* further consolidation with allo-HSCT (conditional recommendation based on very low certainty in the evidence of effects $\oplus\bigcirc\bigcirc\bigcirc$).

Remark:

- The panel recognizes emerging evidence that could aid in identifying individuals and clinical scenarios in which CAR T-cell therapy alone is sufficient, and in which the risks of transplant might outweigh the benefit. Individualized patient assessment and shared decision-making are warranted.

Approaches to consolidative therapy: role of definitive chemotherapy vs allo-HSCT

RECOMMENDATION 4. For AYAs with relapsed B-ALL who achieve a CR2 (or greater), the ASH guideline panel *suggests* allo-HSCT over chemotherapy alone as definitive consolidation treatment (conditional recommendation based on very low certainty in the evidence of effects $\oplus\bigcirc\bigcirc\bigcirc$).

Remarks:

- AYAs with primary refractory disease in whom remission is achieved should proceed with allo-HSCT.
- The recommendation for allo-HSCT must be balanced with systematic assessments of patient suitability for transplant, including performance status, organ function, and comorbidities as considerations.
- The panel recognizes that pediatric data indicate that some younger AYAs in CR2 with lower risk disease (defined by late relapse with low minimal residual disease [MRD] after reinduction therapy) may be considered for chemotherapy and/or immunotherapy alone.

Allo-HSCT conditioning regimens: role of TBI

RECOMMENDATION 5. For AYAs with relapsed/refractory ALL proceeding with allo-HSCT, the ASH guideline panel *suggests* myeloablative conditioning regimens that include total body irradiation (TBI), rather than chemotherapy alone (conditional recommendation based on very low certainty in the evidence of effects $\oplus\bigcirc\bigcirc\bigcirc$).

CNS relapse

RECOMMENDATION 6. For AYAs with isolated central nervous system (CNS) relapse of ALL, the ASH guideline panel *recommends* that patients receive CNS-directed therapy (intrathecal chemotherapy) in the context of systemic therapy (strong recommendation based on very low certainty in the evidence of effects $\oplus\bigcirc\bigcirc\bigcirc$).

RECOMMENDATION 7. For AYAs with isolated CNS relapse of ALL, the ASH guideline panel *recommends against* patients receiving CNS radiation alone (without systemic chemotherapy with intrathecal chemotherapy) (strong recommendation against the intervention based on very low certainty in the evidence of effects $\oplus\bigcirc\bigcirc\bigcirc$).

NO RECOMMENDATION. There are insufficient data to support a recommendation regarding the additional benefit of radiation when combined with other CNS-directed therapy.

NO RECOMMENDATION. The ASH guideline panel recognized promising emerging data for the use of CAR T-cell therapy in the

management of isolated CNS relapse; however, the data are insufficient to support a recommendation at this time.

T-ALL therapies

RECOMMENDATION 8. For AYAs with relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL), the ASH guideline panel *suggests* the use of a nelarabine-based regimen (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- The panel noted that many AYAs are receiving nelarabine as part of frontline treatment. There are no data to suggest that AYAs who have received nelarabine previously in the frontline setting should be precluded from receiving nelarabine again.

RESEARCH-ONLY RECOMMENDATION. There is limited available evidence for novel therapies, including CAR T-cell therapy, in relapsed/refractory T-ALL. As such, the ASH guideline panel is currently unable to issue a formal recommendation regarding these treatment approaches, despite recognizing that early phase data appear promising. The panel thus issues a research-only recommendation that if available and feasible, individuals with relapsed/refractory T-ALL should be offered participation in clinical trials of novel therapies, including CAR T-cell therapy.

Good practice statements

GOOD PRACTICE STATEMENT. 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. For more information on the MRD approach, refer to the Recommendation 15 in DuVall et al.¹³⁶

GOOD PRACTICE STATEMENT. Given the unique challenges of cancer in AYA, 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, where 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, 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 an appropriate clinical trial.

GOOD PRACTICE STATEMENT. It is good practice to introduce interdisciplinary palliative care teams as early as possible in the 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 AYA's developmental and cognitive level, and centered on the wishes of the AYA, and they 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 where feasible.

Values and preferences. These recommendations place a relatively higher value on overall survival (OS) than on other outcomes, and a relatively lower value on minimizing toxicities, regardless of their long-term impact on quality of life. This value judgment reflects the panel's prioritization, including that of patient representatives, of survival, and informed the development of the recommendations across sections.

Introduction

Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations on the management of relapsed/refractory ALL in AYAs. The primary goals of these guidelines are to review, critically appraise, and implement evidence-based recommendations that

address the most important questions related to treatment approaches for these patients. The appraisal and interpretation of available literature was conducted in the context of rapidly evolving therapeutic options available to this population. 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 (adult and pediatric specialists), 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 that include disease biology, therapeutic options, susceptibility to toxicities, and the specific psychosocial challenges. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

ALL is a challenging malignancy to manage, particularly in AYAs, a demographic that bridges pediatric and adult oncology. 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>). Although significant strides have been made in frontline treatment approaches that decrease the risk of recurrence, relapse remains a critical concern with overall poor prognosis, underscoring the need for effective interventions that treat relapse. For relapsed ALL, the goal of achieving a CR2 historically has guided therapeutic strategies, often as a bridge to allo-HSCT.

Despite advancements in treatment including immunotherapy, significant differences remain between pediatric and adult approaches to relapsed/refractory ALL. These differences potentially stem from variations in disease biology, therapeutic tolerance, and long-term outcome priorities. Pediatric protocols emphasize achieving durable remissions tailoring interventions based on risk stratification. In contrast, adult strategies often prioritize early transplant due to higher relapse risks and poorer outcomes after achieving a CR2. Young adults also face greater challenges with chemotherapy resistance and tolerability relative to their adolescent counterparts.

These distinctions between the pediatric and adult approaches 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, and psychosocial factors unique to this age group. By critically assessing evidence related to new targeted therapies and longstanding treatments like transplant, the panel aims to provide a framework for improving outcomes in this vulnerable population. By bridging adult and pediatric expertise and literature, the panel aims to provide a clearer roadmap for managing relapsed 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 is the indirectness of the existing data for this population, as much of the evidence is derived from studies focused on either pediatric or adult populations, with limited representation of AYAs. The lack of dedicated AYA-focused studies (tier 1 evidence,

Table 2) introduced uncertainty when extrapolating benefits and harms to the AYA population. Efforts focused on leveraging the best available data to tailor specific recommendations for this population.

Methods

The guideline panel developed and graded the recommendations, and assessed the certainty in the supporting evidence following the GRADE approach.⁴⁻¹⁰ 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 GIN-McMaster Guideline Development Checklist (<http://cebgrade.mcmaster.ca/guidecheck.html>),¹³ and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.¹⁻³

Organization, panel composition, planning, and coordination

The work of the 2 ALL in AYA panels was coordinated by ASH and 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 Matthew Cheung, the Ex Officio member of the panel), which reported to the ASH Committee on Quality. 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 relapsed/refractory panel included hematologists/oncologists specializing in either pediatric or adult ALL or both, each with relevant clinical and research experience, alongside a pharmacist, social workers, a clinical psychologist, and individuals with lived experience of ALL during the AYA period. One pediatric and 1 adult hematologist served as clinical coauthors of the panel.

In addition to synthesizing evidence systematically, 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 ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of 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, some 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 Medicine and the GIN.^{3,14} 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.^{4,15-17} During deliberations 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.

Supplement 2 provides the complete disclosure-of-interest forms of all panel members. In part A of the forms, individuals disclosed direct financial interests 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 ASH guideline panelists formulated a preliminary list of research topics for both the Frontline Management and Relapsed/Refractory Management of ALL in AYA starting in August 2022; thereafter, the Frontline and Relapsed/Refractory panels conducted separate but parallel guideline processes, with coordination from ASH staff and the ex officio member to ensure

consistency in the recommendations, terminology, and the application of ASH policies and procedures. 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 guideline panel, calls with the coauthors, 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 Relapsed/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. Since 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 management of relapsed/refractory disease 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.^{7,18} 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.⁷ 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-person, 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.^{4,5,7-10,19} The methodology team conducted a broad search for 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 the most-relevant studies based on the accept and reject labels provided by human screeners.

Table 1. Clinical questions and outcomes formulated and prioritized

Questions determined by the panel	Outcomes
For patients with first relapse or refractory B-ALL, what are the comparative benefits and harms of intensive chemotherapy (whether asparaginase-containing or nonasparaginase-containing regimens) vs immunotherapy (including CD19-directed antibody [blinatumomab], CD22-directed antibody [InO], or CAR T-cell therapy)?	OS RFS/EFS/DFS/PFS/relapse CR MRD-negative status Fertility Quality of life Allo-HSCT Toxicity
For patients with relapsed/refractory B-ALL who achieve a CR2 with CAR T-cell therapy, what are the comparative benefits and harms of additional consolidation vs no additional therapy (or nontransplant therapies)?	OS RFS/EFS/DFS/PFS/relapse TRM MRD-negative status Infections GVHD GRFS Quality of life
For patients with relapsed/refractory B-ALL who achieve a CR2, what are the comparative benefits and harms of: (1) chemotherapy only, and (2) allo-HSCT as definitive consolidation treatment?	OS RFS/EFS/DFS/PFS/relapse TRM MRD-negative status Infections GVHD GRFS Quality of life
For patients with relapsed/refractory ALL who undergo allo-HSCT, what are the comparative benefits and harms of myeloablative preparative regimens using: (1) TBI in addition to chemotherapy, and (2) chemotherapy alone?	OS RFS/EFS/DFS/PFS/relapse TRM Infections GVHD GRFS Quality of life
For patients with ALL with isolated CNS relapse, what are the comparative benefits and harms of: (1) CAR T-cell therapy, (2) CNS-directed chemotherapy, (3) CNS radiation as monotherapy, and (4) CNS radiation in combination?	OS RFS/EFS/DFS/PFS/relapse CR CNS recurrence Neurocognitive impact Quality of life Allo-HSCT Toxicity
For patients with relapsed/refractory T-ALL, what are the comparative benefits and harms of: (1) chemotherapy, (2) novel agents, (3) targeted therapies (nelarabine, venetoclax, navitoclax, TKIs), and (4) immunotherapy?	OS RFS/EFS/DFS/PFS/relapse CR MRD-negative status Fertility Quality of life Allo-HSCT Toxicity

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://gradeepro.org>). Separate rows (and, thus, summaries of evidence and determination of certainty in evidence) were included for each outcome and reported separately at different time points. In addition, studies reporting different effect size measures (typically relative risks [RRs] 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 ≥ 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 Risk of Bias tool for RCTs,²⁰ and additional selected questions that addressed selection and analytic methods from ROBINS-I (Risk of bias in non-randomized studies of interventions).²¹ To evaluate the 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.⁶⁻⁸

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://gradeepro.org>).^{4,5,10} The EtD table addressed effects of interventions, resource utilization, 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

Table 2. Categorization of evidence by tier

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

The certainty was categorized into 4 levels ranging from very low to high.⁶⁻⁸ Within this report, these categories are represented by symbols, as shown in Figure 2.

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 and May 2025, the cowriters and cochairs, with support from the methodology team, refined the manuscript sections drafted by panel members. The panel developed recommendations where 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.

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 policy-makers, and researchers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online from 27 September 2024 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. Five individuals or organizations submitted comments specifically for the Relapsed/Refractory 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 called for further discussion, suggesting that blinatumomab, CAR T-cell therapy, and inotuzumab should be presented without hierarchy, as the optimal sequencing remains undetermined, and recommended revising the statement to note that there are no head-to-head comparisons of these therapies. In response to this feedback, we reorganized the relevant section to include a separate “no recommendation” statement for CAR T-cell therapy, rather than grouping it under the general “no recommendation” for immunotherapy comparisons, and added a summary of the existing single-arm studies related to CAR T-cell therapy in the recommendation section. These revisions are

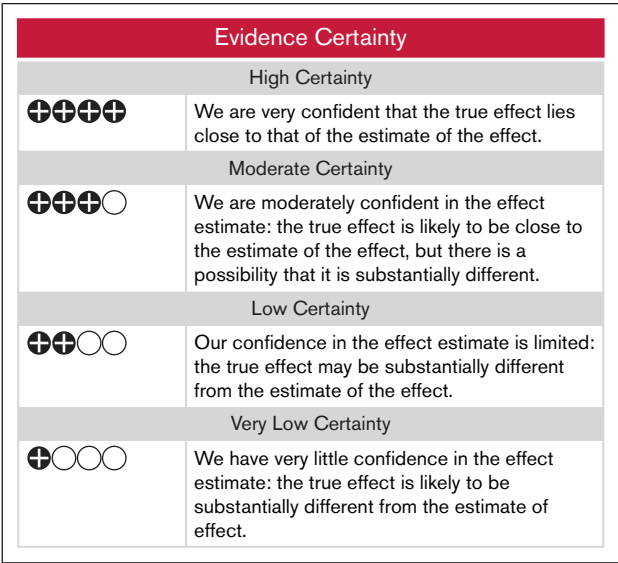


Figure 2. Certainty of evidence for outcomes of interest.

Table 3. Eligibility criteria by research question

Topic	Eligible study designs	Studies (N)	Study tiers
B-ALL: intensive chemotherapy vs immunotherapy	Comparative studies; prospective single-group studies	46	1-3
B-ALL (CR2 with CAR T-cell therapy): additional consolidation vs no additional therapy (or nontransplant therapies)	Comparative studies; prospective single group studies	18	1-3
B-ALL (CR2): (1) chemotherapy only, (2) allo-HSCT	Comparative studies; prospective single group studies	5	1-5
Allo-HSCT myeloablative regimens: (1) TBI + chemotherapy, (2) chemotherapy alone	Comparative studies; prospective single group studies	11	1-3
CNS relapse: (1) CAR T-cell therapy, (2) CNS-directed chemotherapy, (3) CNS radiation (monotherapy), (4) CNS radiation in combination	Comparative studies; prospective single group studies	4	1-3
T-ALL: (1) chemotherapy, (2) novel agents, (3) targeted therapies, (4) immunotherapy	Comparative studies; prospective single group studies	11	1-4

reflected in the final publication recommendation statements. The panel reviewed and approved the adjustments to the “no recommendation statement” via email communications, 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

B-ALL immunotherapies

For patients with first relapse/refractory B-ALL, what are the comparative benefits and harms of intensive chemotherapy (whether asparaginase-containing or nonasparaginase-containing regimens) vs immunotherapy (including CD19-directed antibody [blinatumomab], CD22-directed antibody [inotuzumab], or CAR T-cell therapy)?

Blinatumomab vs chemotherapy

Recommendation 1

For AYAs with relapsed/refractory B-ALL, the ASH guideline panel *recommends* the use of blinatumomab over chemotherapy (strong recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remark:

- The panel highlighted the potential need to debulk before proceeding with blinatumomab for individuals with high blast counts at relapse.

Summary of the evidence. The panel included 14 studies in the blinatumomab vs chemotherapy evidence analysis.²²⁻³⁵ The evidence was limited by the lack of studies intentionally conducted for relapsed/refractory ALL in the AYA age group (15-39 years), and therefore analyzed indirect data from pediatric studies (age 0-21 years) or adult studies (age >18 years) to inform this question (though many of the studies reported important outcomes for patients aged 18-35 years). As noted in “Methods,” the indirect evidence led to low-quality and very low-quality evidence, with an overall low certainty in the evidence of effects. The panel prioritized the following outcomes as most important for this question: survival/mortality, complete remission (CR) and MRD-negative rates, rates of allo-HSCT following blinatumomab-induced remission, and severe toxicity. Ten studies addressed the comparison between blinatumomab and standard of care chemotherapy, 1 of which was a RCT,³³ and 4 of which described secondary analyses

from the RCT,³⁶⁻³⁹ including evidence for survival outcomes,^{36,37} serious adverse events,³⁸ and health-related quality of life (HRQL).³⁹ Five studies retrospectively compared blinatumomab with historical standard chemotherapy.^{22-24,32,35} The remaining 4 studies were single-arm, prospective phase 1/2 studies of blinatumomab. These studies provided evidence for survival outcomes, response rates, and serious adverse events for blinatumomab.^{25-27,31} The evidence profile and EtD framework is available online at <https://guidelines.ash.gradepro.org/profile/ho6a54LqfQE>. Two additional studies describing 1 RCT were reviewed but excluded from the analysis due to the recognition that blinatumomab therapy was administered as consolidation treatment (following an intensive 4-drug salvage chemotherapy regimen).^{40,41}

Benefits. The evidence reviewed by the panel shows that blinatumomab therapy for first relapse or refractory Philadelphia chromosome-negative (Ph⁻) and Ph⁺ B-ALL provides a survival benefit over standard chemotherapy. Low-quality evidence from a RCT³³ and very low-quality evidence from comparative trials^{22-24,32,35} suggest that the hazard of death for patients that receive blinatumomab therapy is 38% lower over time (HR, 0.62; 95% confidence interval [CI], 0.49-0.79)).

Low-quality evidence suggests that the risk of death for patients who receive blinatumomab may be lower than for patients who received chemotherapy at 6 months (HR, 0.75).³³ Very low-quality evidence shows that the risk of death for patients who receive blinatumomab may be lower at 6 months,²² 12 months,^{22-24,35} and 3 years³² (RR, 0.62 at 6 months; 0.44-0.86 at 12 months; and 0.78 at 3 years).

Low-quality evidence from the RCT and very low-quality evidence from comparative trials shows that the CR rates and MRD-negative remission rates are higher for patients that receive blinatumomab therapy (RR, 2.14; 95% CI, 1.40-3.28; RR, 1.71; 95% CI, 0.78-3.78). Very low-quality evidence from comparative studies and single-arm studies shows that patients who receive blinatumomab therapy have comparable likelihood of proceeding to an alloHSCT (RR, 1.19; 95% CI, 0.44-3.22). There is low-quality evidence from the RCT that both cohorts of patients proceeded to allo-HSCT at equal rates (RR, 1.00; 95% CI, 0.69-1.45).

Low-quality evidence from the RCT and very low-quality evidence from the comparative and single-arm studies show that patients receiving blinatumomab therapy have a lower risk of infection during treatment (RR, 0.65; 95% CI, 0.51-0.83).³³

Very low-quality evidence from single-arm prospective phase 1/2 trials consistently showed that blinatumomab resulted in high remission rates and MRD-negative responses, as well as low treatment-related mortality (TRM).^{25-27,31} Likewise, the 2 studies describing the RCT from the Children's Oncology Group trial (AALL1331) that were excluded from this analysis reported outcomes for pediatric, adolescent, and young adult patients similar to those described in the evidence base for this recommendation.^{40,41}

Overall, the certainty in the estimated effects is low because of the lack of studies designed specifically for the AYA population, and the need to generalize the findings from studies of pediatric patients or older adults. Despite these limitations, the benefits of blinatumomab as monotherapy for patients receiving their first salvage regimen were consistently superior to standard chemotherapy. Similarly for

patients who had received ≥ 2 previous salvage treatments as well as for patients whose disease relapsed following allo-HSCT, the superior efficacy of blinatumomab compared with standard chemotherapy was noted across all age groups. In particular, the single RCT was a well-designed direct comparison of blinatumomab vs salvage chemotherapy that showed its benefits, including superior OS specifically for patients aged 18 to 35 years (HR, 0.7; 95% CI, 0.46-1.06).³³ Of note, during the second planned interim analysis of the RCT, the independent data safety monitoring committee recommended the trial be stopped early because of the OS benefit observed with blinatumomab as compared with chemotherapy. Moreover, the historical data from decades of salvage chemotherapy regimens before the introduction of blinatumomab into clinical practice show that the survival outcomes, remission rates, allo-HSCT rates, and toxicity profiles are inferior for almost all adult patients, except perhaps for some low-risk younger adolescent patients who may be cured with chemotherapy alone.⁴²⁻⁴⁵ Finally, the patient-reported outcomes (PROs) collected as part of the study showed that patients who received blinatumomab had superior posttreatment HRQL and significantly delayed time to quality of life deterioration compared with patients who received chemotherapy, offering further support for the meaningful benefit of blinatumomab in relapsed/refractory B-ALL.³⁹ Considering the totality of the evidence, the panel judged that blinatumomab's benefits were significant and applicable to the AYA population.

Harms and burden. The panel recognized there is evidence for undesirable anticipated toxicities following blinatumomab therapy, including cytokine release syndrome (CRS) and neurotoxicity. Other toxicities the panel considered included adverse events grade ≥ 3 , infections during treatment, febrile neutropenia/sepsis, toxic mortality, and impact on fertility.

Low-quality evidence from the RCT and very low-quality evidence from comparative and single-arm studies reveals that most patients experienced adverse events of grade ≥ 3 (RR, 0.94; 95% CI, 0.88-1.02). More patients discontinued therapy due to adverse events when receiving blinatumomab compared with chemotherapy (RR, 1.50; 95% CI, 0.74-3.02).³³ Very low-quality evidence from single-arm prospective phase 1/2 trials showed that ~9% of patients treated with blinatumomab discontinued therapy due to adverse events.^{25,27,31}

Low-quality evidence from the RCT shows that risk of infection and febrile neutropenia during treatment were lower for patients receiving blinatumomab than with chemotherapy (RR, 0.65; 95% CI, 0.51-0.83; RR, 0.61; 95% CI, 0.43-0.86). Very low-quality evidence from comparative and single-arm studies confirms the rates of infection and febrile neutropenia during blinatumomab treatment reported in the RCT.^{25,26,31,32,35} Fatal adverse events during blinatumomab treatment were rare events in all studies reviewed (<3%).

The rates of grade ≥ 3 CRS and neurotoxicity reported in the RCT were 4.9% and 9.4%, respectively. Neurologic events were reported in 8.3% of patients treated with chemotherapy in the RCT.³³ In comparative and single-arm studies, grade ≥ 3 CRS associated with blinatumomab was reported in 4% to 6% of patients, and neurotoxicity was reported in 4% to 8% of patients.^{25-27,31}

The impact of blinatumomab treatment on fertility was not reported in any of the studies used in the evidence profile.

Other EtD criteria and considerations. The panel recognized the importance of immunophenotypic confirmation that the leukemic blasts express the relevant antigen target (CD19).

OS was recognized by the panel, and in particular by the patient advocate members of the panel, to be the highest priority relative to other outcomes. Toxicities were considered of importance to patients, independent of long-term impact on HRQL. The unique toxicities of blinatumomab treatment were judged to be acceptable to patients, given specific standard management currently implemented for the management of CRS and neurotoxicity (ie, step-up dosing of blinatumomab, dexamethasone, tocilizumab, and anakinra). Because efficacy and toxicity from blinatumomab have been correlated with degree of disease burden, the panel highlighted the importance of debulking the leukemia burden before proceeding with blinatumomab for individuals with marrow blast counts >50% at time of relapse. In a real-world multicenter study evaluating tumor debulking before blinatumomab in relapsed/refractory B-ALL, this strategy demonstrated enhanced responses to blinatumomab compared with historic studies, though the sample size was small ($n = 34$).⁴⁶ The specific cytoreductive strategy (chemotherapy, steroids, and tyrosine kinase inhibitors [TKI] alone or in combination) is best determined by the treating physician and individualized to each patient. The panel also discussed the importance of continuing CNS prophylaxis with intrathecal chemotherapy throughout the blinatumomab salvage treatment given the lack of CNS penetration.

One study addressed PROs from the phase 3 RCT to determine the impact of blinatumomab therapy compared with salvage chemotherapy on HRQL.³⁹ The HRQL assessment was made using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) core questionnaire. The prespecified HRQL secondary end point for the RCT was the time to a ≥ 10 -point decrease from baseline in HRQL or death. Patients completed questionnaires on day 1 (baseline), day 8 (cycle 1 only), and days 15 and 29 of each cycle of investigational therapy. Overall, the patients receiving blinatumomab reported stable or improved HRQL measures from baseline, regardless of response to treatment, as compared with stable or worsening HRQL measures for patients receiving chemotherapy, especially for patients who did not respond to chemotherapy. Additionally, blinatumomab therapy was associated with a delay in time to clinically meaningful deterioration in HRQL or death across all the EORTC QLQ-C30 scales as compared with chemotherapy ($HR < 1.0$; $P < .05$), except for financial difficulties, insomnia, and social functioning.

The panel considered the substantial costs, resource implications, and burden on patients and caregivers associated with blinatumomab infusion, which requires hospitalization for drug initiation, a 4-week continuous infusion, and need for home health care infrastructure. The financial burden, one of the items that did not improve with blinatumomab,³⁹ and lost workdays for patients and caregivers, especially those who must travel to a center with the ability to deliver therapy, serve as potential barriers to universal access in comparison to chemotherapy-based salvage regimens. Along with these considerations, the panel also notes that historically marginalized and disadvantaged populations may be disproportionately affected

by the high costs and logistical burden associated with blinatumomab. These barriers will need to be addressed to prevent already existing disparities in ALL outcomes from persisting or widening.

Conclusions and research needs for this recommendation. The panel concluded that the benefits of blinatumomab including prolonged survival and higher CR rates outweighed the harms and burdens, including the toxicity profile of blinatumomab. The certainty in the estimated effects is rated as low because of the lack of studies designed specifically for the AYA population, and the need to generalize the findings from studies of pediatric patients or older adults. Despite these limitations, the benefits of blinatumomab as monotherapy were consistently superior for patients receiving their first salvage regimen than for patients who had received ≥ 2 previous salvage treatments, and patients who had relapsed following allo-HSCT.

The panel recognizes that the available data did not capture all valued outcomes for patients, including time spent in the hospital or in the outpatient clinic, fertility, and rare or evolving toxicities associated with novel therapies. This uncertainty, however, was not judged to change the direction or strength of the recommendation. Following the considered judgment process of the panel and the recognition that the intervention (blinatumomab over chemotherapy) could mitigate a life-threatening situation (and prolong survival), the panel supported a strong recommendation in favor of blinatumomab despite the low certainty in evidence.⁴⁷ Consideration of CD19-directed CAR T-cell therapy for patients previously treated with blinatumomab also did not change the recommendation for blinatumomab therapy in the relapsed or refractory setting.

Inotuzumab vs chemotherapy

Recommendation 2

For AYAs with relapsed/refractory B-ALL, the ASH guideline panel *recommends* the use of inotuzumab over chemotherapy (strong recommendation based on low certainty in the evidence of effects $\oplus\oplus\bigcirc\bigcirc$).

Remark:

- The panel highlighted the need to consider the risk of VOD in individuals intended to proceed with allo-HSCT following InO.

Summary of the evidence. The panel included 10 studies in the InO vs chemotherapy evidence analysis.^{24,28-30,34,48-52} No studies specifically conducted for the AYA age group were identified to inform the evidence profile, though a secondary analysis of the single RCT did report results for a subgroup of AYA patients.⁵³ Two studies reporting the phase 1B pediatric trial testing InO in relapsed/refractory B-ALL (ITCC-059 trial) were reviewed and excluded from the evidence profile because they did not meet the defined tier criteria for inclusion (Table 2).^{54,55} The certainty in the evidence of effects is graded as low because of the indirectness of the age group in the comparative studies, particularly in the overall RCT, which reported a median age of 46 years (range, 18-78 years). The panel prioritized the following outcomes as most important for this question: survival/mortality, CR and

MRD-negative rates, rates of allo-HSCT following inotuzumab-induced remission, and severe toxicity.

The results of a single RCT (INO-VATE) were reported in 7 studies that informed the comparison between InO and standard of care chemotherapy. After the primary study,⁴⁸ a second reported long-term survival,⁵⁶ and 5 described secondary analyses of the same RCT,^{53,57-60} including the outcomes of InO for patients with Ph⁺ B-ALL,⁵⁷ the role of disease burden at the time of relapse in efficacy,⁶⁰ serious hepatic adverse events,⁵⁸ and HRQL.⁵⁹ Of particular interest was the secondary analysis describing the impact of age on inotuzumab efficacy.⁵³ A separate retrospective observational study reported on 108 patients with Ph⁻ B-ALL who underwent allo-HSCT after achieving remission with different immunotherapies, including 14 of 108 patients who received inotuzumab.²⁴ Three studies were single-arm, prospective phase 1/2 studies of InO for relapsed/refractory B-ALL. These studies provided evidence for response rates, survival outcomes, and serious adverse events for inotuzumab.^{49,50,52} The remaining 4 studies provided evidence for response rates, survival outcomes, and serious adverse events from standard salvage chemotherapy regimens.^{28-30,34} The evidence profile and EtD framework for this recommendation is available online at <https://guidelines.ash.gradepro.org/profile/h2pxukYV-RQ>.

Benefits. The evidence reviewed by the panel indicates that InO produces higher response rates and provides a survival benefit compared with standard salvage chemotherapy for adult patients with relapsed/refractory Ph⁻ and Ph⁺ B-ALL. Very low-quality evidence (due to indirectness) from an RCT shows the CR or CR with incomplete count recovery rates (RR, 2.39; 95% CI, 1.87-3.06), and MRD-negative remission rates are higher for patients that receive InO therapy than for patients receiving salvage chemotherapy (RR, 1.79; 95% CI, 0.74-4.30).^{48,56} Very low-quality evidence from the RCT shows that 4 times as many patients proceeded directly to allo-HSCT before receiving any further therapy. Patients treated with InO who proceeded to transplant had a median OS of 12.6 months vs 7.1 months for those who did not (HR, 0.55; 95% CI, 0.36-0.84). Very low-quality evidence from noncomparative single-arm prospective phase 1/2 trials showed that InO resulted in high CR rates (58%-68%), MRD-negative responses (63%-84%), and allo-HSCT rates (33%-45%).^{49,50}

Very low-quality evidence from the RCT suggests that there is a 55% reduction in the risk of leukemia progression or mortality at 1 year for patients who received InO compared with patients who received chemotherapy (HR, 0.45; 95% CI, 0.34-0.60).⁴⁸ Further, patients who received InO had a 25% lower risk of death at 1 year than patients who received chemotherapy (HR, 0.75; 95% CI, 0.57-0.99). The rate of 2-year survival was 23% for patients who received InO compared with 10% for patients who received chemotherapy. Very low-quality evidence from noncomparative single-arm phase 1/2 studies of InO suggested a rate of 1-year survival of ~20% to 30%.^{50,51} Survival outcomes for patients who received salvage chemotherapy in the RCT were similar to survival reported in noncomparative studies of salvage chemotherapy evaluated by the panel.^{28-30,34}

As noted above, a secondary analysis of the RCT reported several outcomes by subgroups defined by age.⁵³ Though most of the analyses focused on patients aged >55 years vs <55 years at diagnosis, several outcomes were reported for younger AYAs aged 18 to 29 years. For example, among this group of younger AYAs, those who received InO experienced CR/CR with incomplete hematologic recovery (CRi) rate of 77% (36%/41%) vs 19% (6%/14%) among those receiving standard chemotherapy ($P < .005$). Among responders, the MRD negativity rate was also higher among patients aged 18 to 29 years receiving InO (77% vs 43%, $P < .003$). The median survival was also longer (11.1 months vs 9.1 months; HR, 0.53; 95% CI, 0.30-0.92).

In contrast, very low-quality evidence from the retrospective comparative study of InO as a pretransplant salvage regimen suggests that the hazard of death for patients who receive InO and proceed to allo-HSCT may be higher at 1 year than for patients who received chemotherapy as a salvage regimen before allo-HSCT (HR, 2.14; 95% CI, 1.01-4.55).²⁴ Patients who received InO as a salvage regimen before allo-HSCT also had inferior relapse-free survival at 1 year compared with patients who received chemotherapy and proceed to allo-HSCT (HR, 3.41; 95% CI, 1.66-7.02).²⁴ The panel noted substantial selection bias in this study due to differences in the clinical characteristics of patients who received InO, including older median age, more previous salvage therapy regimens, and higher likelihood of receiving a reduced intensity or nonmyeloablative preparative regimen for allo-HSCT. These differences in patient population and allo-HSCT approach likely contributed to the 1-year relapse rate of 57% for the InO group vs 7% in the chemotherapy group. Given these substantial differences, the small number of patients in the InO cohort ($n = 14$) and the fact that all patients in this retrospective observational study underwent an allo-HSCT, the panel judged that these data should not outweigh the survival benefit demonstrated in the RCT.⁵⁹

Harms and burden. The panel recognized evidence for undesirable toxicities following InO therapy, specifically liver toxicities and VOD/sinusoidal obstructive syndrome (SOS). Other toxicities of importance to the panel included infections during treatment, febrile neutropenia/sepsis, impact on fertility, any adverse events grade ≥ 3 , and toxic mortality.

Very low-quality evidence (due to indirectness) from the RCT suggests that adverse events grade ≥ 3 were similar between patients who received InO (52%) and salvage chemotherapy (50%). More patients who received InO, however, discontinued treatment compared with patients who received chemotherapy (temporary discontinuation 44% vs 12%, and permanent discontinuation of treatment 19% vs 7.4%; RR, 2.55 [95% CI, 1.36-4.79]).⁴⁸

Very low-quality evidence from the RCT shows that risk of infection and febrile neutropenia during treatment were similar for patients receiving InO compared with chemotherapy (RR, 0.62; 95% CI, 0.32-1.18; RR, 0.61; 95% CI, 0.36-1.06). Very low-quality evidence from comparative and single-group studies showed that the rates of infection and febrile neutropenia during InO treatment were comparable to that reported in the RCT.^{49,50} Fatal adverse event deaths during InO treatment were estimated at 4.9% compared with 1.4% during chemotherapy treatment.

Rates of hepatic toxicities (all grades) in the RCT were higher for patients receiving InO (83/164; 51%) than for patients receiving chemotherapy (49/143; 34%). The rates of grade ≥ 3 VOD/SOS reported for patients receiving InO vs chemotherapy in the RCT were 14% and 2%, respectively (RR, 5.5; 95% CI, 1.7-18.3). For patients who received InO and proceeded to allo-HSCT ($n = 77$), the incidence of VOD/SOS was 23% ($n = 18$).⁴⁸ Five patients had fatal adverse events due to VOD/SOS deemed related to InO treatment. Of patients receiving chemotherapy and proceeding to allo-HSCT ($n = 32$), 1 developed VOD/SOS and fatal septic shock. In other comparative and single-arm studies, VOD/SOS associated with InO was reported in 35% of patients, and 4.4% of patients receiving chemotherapy.²⁴

Additional high-grade toxicities (hematologic and nonhematologic) evaluated by the panel were similar between InO and chemotherapy, with grade ≥ 3 cytopenias frequently reported but not significantly different between the groups. The impact of InO treatment on fertility was not reported in any of the studies used in the evidence profile.

The panel recognized that VOD/SOS is a serious complication of InO treatment, particularly for patients who proceed to allo-HSCT. Risk factors include previous allo-HSCT, a transplant preparative regimen that includes 2 alkylating agents, bilirubin concentration of greater than or equal to the upper limit of normal before allo-HSCT, a history of liver disease or hepatitis, and greater total number of cycles of InO received. Of note, age ≥ 55 years was also a risk factor for VOD/SOS, suggesting that perhaps the risk of this serious complication is lower among AYAs.

Other EtD criteria and considerations. The panel recognized the importance of immunophenotypic confirmation that the leukemic blasts express the relevant antigen target (CD22).

The certainty in the estimated effects is rated as low because of the lack of studies designed specifically for the AYA population and the need to generalize the findings from studies predominantly of older adults. Although some AYA-specific outcomes were provided, the majority of patients included in the INO-VATE RCT were not AYA. The benefits of InO as first or second salvage compared with salvage chemotherapy were judged by the panel to be relevant and applicable to AYAs with relapsed/refractory B-ALL. Follow-up analysis of the RCT supports improved response rates (CR/CRi and MRD negative) and survival benefits irrespective of disease burden (measured by the percentage of marrow blasts at time of relapse)⁶⁰ and patient age.⁵³ Moreover, though not all outcomes were provided, CR/CRi, MRD-negative remission among responders, and OS were superior among younger AYAs (18-29 years at diagnosis) who received InO compared with those who received standard chemotherapy.

One study addressed PROs from the RCT to determine the impact of InO therapy compared with salvage chemotherapy on HRQL as assessed by the EORTC QLQ-C30.⁵⁹ Patients receiving InO reported better HRQL and symptom scores, except for constipation and emotional functioning. Additionally, patients receiving InO reported significantly better appetite, physical functioning, and ability to perform strenuous activities, while reporting fewer limitations in their activities of daily living.

Though toxicities were considered of importance to patient advocates on the panel, OS was recognized by the panel and patient advocates to be the highest priority relative to other outcomes. The panel recognizes that the available data did not capture all valued outcomes for patients, including time in the hospital, fertility, and rare or evolving toxicities associated with novel therapies. This uncertainty, however, was not felt likely to change the direction or strength of the recommendation. The panel acknowledges the high costs and resources needed to deliver InO and its supportive care may limit the access of this treatment by historically marginally and disadvantaged populations. The panel recognized that certain populations may not have been adequately represented in the studies that defined the evidence for this recommendation. These barriers will need to be studied further to prevent already existing disparities in ALL outcomes from persisting or widening.

Conclusions and research needs for this recommendation. The panel concluded that the benefits of InO including improved response rates, the significant proportion of responders who were able to proceed to allo-HSCT, and prolonged survival outweighed the undesirable effects, including the hepatic toxicity profile and risk of VOD/SOS associated with the use of InO. Following the considered judgment process of the panel and the recognition that the intervention (inotuzumab over chemotherapy) could mitigate a life-threatening situation (and prolong survival), the panel supported a strong recommendation in favor of inotuzumab despite the low certainty in evidence.⁴⁷ The panel acknowledged the importance of evaluating individual patient risk of VOD/SOS when considering this intervention, especially for patients proceeding to allo-HSCT.

CAR T-cell therapy

No recommendation

With minimal comparative data to review, the panel was unable to make a recommendation between CAR T-cell therapy and chemotherapy or other immune-based therapies. However, the panel recognizes the notable utility of CAR T-cell therapy following relapse based on existing single-arm studies.

Studies of CAR T-cell therapy were restricted to those studying constructs currently licensed for clinical use or closely related agents. Two single-center retrospective comparative studies were reviewed,^{61,62} along with several secondary analyses of primary publications.⁶³⁻⁷⁶ Although the comparative studies suggested superior outcomes in those patients receiving CAR T-cell therapy vs those receiving chemotherapy, both studies were substantially affected by bias in which patients received each modality.^{61,62} Two of the prospective single-cohort studies presented subgroups of AYA patients.^{65,75} Although the panel felt that together these studies provided substantial evidence of the efficacy of CAR T-cell therapy and thus its role in the treatment of AYA with relapsed/refractory B-ALL, the panel was unable to make a recommendation for CAR T-cell therapy over other treatment modalities due to the lack of comparative studies.

Inotuzumab vs blinatumomab vs CAR T-cell therapy

No recommendation

There are almost no head-to-head comparisons of these 3 therapies (blinatumomab, inotuzumab vs CAR T-cell therapy), and the best sequence of their use is not yet understood. Therefore, the panel was unable to make a recommendation for 1 agent over the other. The choice should be made based on individual patient assessment, burden of disease, and candidacy for future consolidative therapy including allo-HSCT.

Only 1 small single-center study from China retrospectively compared outcomes of patients receiving blinatumomab vs those receiving CAR T-cell therapy, which was affected by significant selection bias.⁶¹ Given the lack of comparative studies, the panel was unable to make any recommendation for 1 immunotherapeutic agent over another. The panel strongly encouraged the conduct of studies comparing the efficacy of these modalities in AYAs with relapsed or refractory disease. The panel also noted that given the current lack of evidence, the decision of which immunotherapeutic agent to use should be made with consideration of multiple factors, including previous exposure to frontline or salvage immunotherapy, previous toxicities, leukemia immunophenotype at time of relapse, current comorbidities, the availability of and suitability for subsequent allo-HSCT, and the availability/eligibility for subsequent immunotherapies should the initial choice of immunotherapy be unsuccessful. Of note, when considering CD19-directed therapies (CAR T cells and blinatumomab), debulking therapy to reduce disease burden and optimize response is an important consideration. Finally, the panel recognized the importance of immunophenotypic confirmation that the leukemic blasts express the relevant antigen target (CD19 or CD22).

Approaches to consolidative therapy: role of allo-HSCT following CAR T-cell therapy

For patients with relapsed/refractory B-ALL who achieve a CR2 with CAR T-cell therapy, what are the comparative benefits and harms of additional consolidation vs no additional therapy (or nontransplant therapies)?

Recommendation 3

For AYAs who were HSCT naïve with relapsed B-ALL who achieve a CR2 (or greater) with FDA-approved autologous CD19 CAR T-cell products (tisagenlecleucel and brexucabtagene autoleucel), the ASH guideline panel *suggests* further consolidation with allo-HSCT (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- The panel recognizes that evolving evidence may aid in identifying individuals and clinical scenarios in which CAR T-cell therapy alone is sufficient, and in which the risks of transplant might outweigh the benefit. Individualized patient assessment and shared decision-making are warranted.

Summary of the evidence. The panel reviewed 22 studies for the comparison of allo-HSCT consolidation following CD19-directed CAR T-cell therapy vs no allo-HSCT consolidation in AYA patients with relapsed B-ALL. No studies intentionally conducted for the AYA age group (Tier 1) were identified to inform the evidence profile. No studies in the evidence profiles were RCTs. Four studies reporting novel CAR T-cell constructs for relapsed/refractory B-ALL were reviewed and discussed, but were experimental and not accessible for generalized use, and thus excluded from the evidence profile.⁷⁷⁻⁸⁰ While acknowledging the merit of the novel studies, the panel judged that CAR T-cell constructs used in the studies to inform this evidence base should resemble those used in phase 1/2 trials that led to the FDA- and European Medicines Agency-approved CAR T-cell products, tisagenlecleucel and brexucabtagene autoleucel.^{71,72,81} One study of a CAR T-cell product that is now FDA approved for adult patients (>18 years) with relapsed/refractory B-ALL based on the results of the phase 1b-2 multicenter study of obecabtagene autoleucel was not included in the panel deliberation because it was not published at the time of the systematic review.⁸² Similarly, a real-world study of outcomes following brexucabtagene autoleucel as standard therapy for adult patients was not included in the evidence base because these data were not published at the time of the systematic review.⁸³

Eighteen studies informed the final evidence analysis.^{63,65-69,71-73,75,84-91} Ten studies informed the comparison of CAR T-cell therapy followed by allo-HSCT consolidation vs CAR T-cell therapy without allo-HSCT consolidation.^{65-68,85,86,88,89,91,92} Seven studies were single-arm, prospective phase 1/2 studies of CAR T-cell therapy; 1 of the 7 studies reported on patients who received CAR T-cell therapy and all patients proceeded to allo-HSCT,⁹⁰ and 6 studies reported on patients who received CAR T-cell therapy and the majority of patients did not receive consolidative allo-HSCT.^{63,71-73,75,87} In these 6 studies, the data were censored at the time of allo-HSCT, and informed the evidence for survival outcomes and serious adverse events for CAR T-cell therapy without consolidative allo-HSCT. One study reported the quality of life following CAR T-cell therapy without allo-HSCT.⁶⁹ For survival, the panel focused on 2-year outcomes as this reporting period was complete for most studies in the evidence profile. The certainty in the evidence was graded as low to very low due to the indirectness of the age group in the comparative and single-group phase 1/2 studies (most of the CD19 CAR T-cell treated patients were in the pediatric age range) and the lack of prospective randomized trials comparing allo-HSCT consolidation following CAR T-cell therapy with no allo-HSCT consolidation. The panel prioritized the following outcomes as most important for this question: OS, leukemia-free survival, RFS, and event-free survival (EFS), severe toxicity (transplant-related mortality, acute and chronic graft-versus-host disease [GVHD], infections), and quality of life. The evidence profile and EtD framework for this recommendation is available online at <https://guidelines.ash.gradepro.org/profile/xQqM90HwQTK>.

Benefits. The evidence reviewed by the panel shows that CAR T-cell therapy followed by allo-HSCT for patients with relapsed/refractory B-ALL provides a survival benefit compared with CAR T-cell therapy without allo-HSCT consolidation. Very low-quality

evidence from 2 comparative, nonrandomized trials suggests that the hazard of death may be 12 times higher for patients who did not receive consolidative allo-HSCT (HR, 12.25; 95% CI, 4.77-31.44)⁸⁴ and, likewise, that the hazard of death is 81% lower for patients who received CAR T-cell therapy followed by consolidative allo-HSCT compared with patients who did not receive consolidative allo-HSCT (HR, 0.19; 95% CI, 0.03-1.42).⁸⁵ Additional very low-quality evidence from 2 comparative trials suggests that CAR T-cell therapy followed by consolidative allo-HSCT provides a survival benefit at 1 year (80% vs 34%)⁸⁶ and 2 years (81.8% vs 65.6%)⁹¹ compared with CAR T-cell therapy without consolidative allo-HSCT. In contrast, very low-quality evidence from 2 comparative trials suggests that CAR T-cell therapy alone can provide a superior OS benefit at 1 and 2 years for some patients without allo-HSCT.^{65,88} Very low-quality evidence from single-group studies suggested that patients who receive CAR T-cell therapy and do not receive consolidative allo-HSCT have 6-month OS that ranges from 78% to 90%,^{71,72} 1-year OS of 80%,^{72,75,87} and 2-year OS of 81%.^{63,87}

Low-quality evidence from 1 comparative study suggests the risk of leukemia relapse or death for patients who received consolidative allo-HSCT may be 84% lower (HR, 0.16; 95% CI, 0.05-0.48) than for patients who did not receive consolidative allo-HSCT following CAR T-cell therapy.⁸⁶ Low-quality evidence from another comparative study suggests that the risk of leukemia relapse or death within the first year is 47% lower for patients who received CAR T-cell therapy followed by allo-HSCT than for patients who did not receive allo-HSCT following CAR T-cell therapy (HR, 0.53; 95% CI, 0.17-1.69).⁸⁵ Very low-quality evidence from 1 comparative study suggests that patients who received consolidative allo-HSCT following CAR T-cell therapy had a 26.43 times lower risk of leukemia recurrence or death within the first year compared with patients who did not receive allo-HSCT following CAR T-cell therapy (HR, 26.43; 95% CI, 7.29-95.79).⁸⁴ Very low-quality evidence from 3 comparative studies suggests that the risk of relapse or death is less likely at 2 years for patients who received consolidative allo-HSCT following CAR T-cell therapy compared with patients who did not receive consolidative allo-HSCT following CAR T-cell therapy (RR, 0.29; 95% CI, 0.06-0.52).^{65,89,91}

Very low-quality evidence from 2 comparative studies suggests that RFS at 2 years is superior for patients who receive consolidative allo-HSCT following CAR T-cell therapy than for patients who do not receive consolidative allo-HSCT, ranging from 72.7% to 74% vs 16% to 40%, respectively.^{65,86} Very low-quality data from a phase 1/2 single-arm study for patients who received consolidative allo-HSCT following CAR T-cell therapy reported a 1-year RFS of 46.4%.⁷⁵

Very low-quality evidence from 1 comparative study suggests that the risk of no response, leukemia relapse, or death (defined events for analysis of EFS) is 61% lower for patients who received consolidative allo-HSCT following CAR T-cell therapy than for patients who did not proceed to allo-HSCT following CAR T-cell therapy (HR, 0.39; 95% CI, 0.13-1.15).⁶⁶ Very low-quality evidence from 1 comparative study suggests that EFS at 1 and 2 years is superior for patients who receive consolidative allo-HSCT following CAR T-cell therapy compared with patients who do not receive consolidative allo-HSCT, 76.4% vs 39.7%, and 54% vs 23.4%,

respectively.⁶⁷ One comparative study reported inferior 2-year EFS for patients who receive consolidative allo-HSCT following CAR T-cell therapy compared with patients who did not receive consolidative allo-HSCT, 23.0% vs 27.1%, respectively.⁸⁸ Very low-quality evidence from single-arm, phase 1/2 trials of patients who received CAR T-cell therapy and did not receive consolidative allo-HSCT (or data were censored for those who received a subsequent transplant) reported 6-month EFS of 67% and 73%,^{71,72} 1 year EFS of 56.1%,^{72,73,87} 1.5 year EFS of 43.1%,⁶³ and 2-year EFS 68.6%.⁸⁷

Harms and burden. The panel recognized there is evidence for undesirable anticipated toxicities following allo-HSCT, including transplant-related mortality, acute and chronic GVHD. Other toxicities of importance included rates of adverse events grade ≥ 3 , infections following transplant, and impact of treatment on fertility. Very low-quality evidence from 1 single-arm prospective study in which all patients received consolidation with allo-HSCT following CAR T-cell therapy reported the rates for acute GVHD, grades 2 to 4 and 3 to 4, were 48.1% and 11.1%, respectively.⁹⁰ Very low-quality evidence from 1 comparative study suggests that patients who received consolidation with allo-HSCT following CAR T-cell therapy have a 3.5-fold higher risk of TRM at 2 years than patients who did not receive transplant following CAR T-cell therapy (RR, 3.50; 95% CI, 0.15-81.99).⁸⁹

Very low-quality evidence from 1 single-arm, phase 1/2 trial of patients who received CAR T-cell therapy and did not receive consolidative allo-HSCT (or data were censored for those who received a subsequent transplant) reported grade 3 to 4 infection rates of 24%. Very low-quality evidence from 1 single-arm prospective study in which all patients received consolidation with allo-HSCT following CAR T-cell therapy reported cytomegalovirus reactivation rates in 52% of patients.

The impact of CAR T-cell therapy on fertility or CAR T-cell therapy followed by consolidative allo-HSCT on fertility was not reported in any of the studies used in the evidence profile.

Other EtD criteria and considerations. One study addressed patient-reported quality of life outcomes following CAR T-cell therapy for patients enrolled on the international, single-arm, phase 2 ELIANA trial.⁶⁹ Overall, although the patients reported improvements in quality of life scores for all measures at month 3 after the CAR T-cell infusion, quality of life following consolidative allo-HSCT was not evaluated. The panel recognized the need for more data assessing PROs and quality of life in this setting.

There was no research evidence regarding cost or feasibility for the intervention. The panel recognized the considerable cost and resource implications associated with CAR T-cell therapy and allo-HSCT, particularly the potential for significant financial burden and costs borne by patients and their caregivers. These costs can be exacerbated for those patients and caregivers who must travel long distances to a transplant center or who experience loss of work and productivity due to the treatment(s). The panel acknowledged that access to cellular therapies may not be universal due to insurance coverage, donor availability, and patient-related comorbidities that could render the tandem approach of CAR T-cell therapy followed by allo-HSCT less feasible, with

underrepresented and disadvantaged populations disproportionately affected.

The panel concluded that for most AYAs with relapsed/refractory B-ALL who have an appropriate matched donor, and who remain eligible and fit for allo-HSCT, the intervention of the allo-HSCT following CAR T-cell therapy would be a beneficial treatment and 1 that is likely acceptable to patients, their families, and health care providers. The panel noted that individualized risks and benefits of allo-HSCT should be discussed with each patient.

Conclusions and research needs for this recommendation. The panel concluded that there is a net benefit of consolidation with allo-HSCT following CAR T-cell therapy compared with no consolidation in AYA patients with relapsed/refractory B-ALL who are in a CR2 or greater. The survival benefits demonstrated in the evidence review were observed irrespective of CAR T-cell product or manufacturing platform. Although the panel acknowledged that durable remissions are reached in pediatric patients without consolidative allo-HSCT, they nonetheless concluded that the benefits of improved survival and decreased rates of relapse demonstrated in most of the studies using consolidation with allo-HSCT warranted strong consideration, particularly for patients who were allo-HSCT naïve.

The panel recognized 3 substantial limitations in the data. First, reporting of short- and long-term toxicities associated with allo-HSCT was rare and should be discussed with patients. Second, most data pertained to studies with median ages in the pediatric age range. Third, no randomized data were available. Despite these limitations, the panel judged that the results are likely relevant and applicable to AYAs with relapsed/refractory B-ALL. This conditional recommendation placed a high value on the critical outcomes of OS, long-term remission, and cure. The AYA patients on the guideline panel valued the improved outcomes over the concerns of toxicity associated with stem cell transplant, including GVHD, infections, and infertility.

The panel highlighted that understanding the optimal role for allo-HSCT consolidation after CAR T-cell therapy is a high-priority research need for the field. Because durable remissions can be reached without allo-HSCT consolidation in some pediatric patients and using allo-HSCT has known associated long-term adverse effects, well-designed studies focused on risk-stratification, based on patient and disease characteristics before and after CAR T-cell infusion, are needed to determine more precisely for whom transplant consolidation is beneficial despite the associated toxicities. Studies of HRQL for patients who do and do not proceed to transplant consolidation of health disparities related to both CAR T-cell and/or transplant access are also warranted. Finally, with 3 different CAR T-cell products now available for AYAs, further comparative studies should focus on determining which CAR T-cell product will be most effective in each patient population.

Approaches to consolidative therapy: role of definitive chemotherapy vs allo-HSCT

For patients with relapsed/refractory B-ALL who achieve a CR2, what are the comparative benefits and harms of: (1) chemotherapy only, and (2) allo-HSCT as definitive consolidation treatment?

Recommendation 4

For AYAs with relapsed B-ALL who achieve a CR2 (or greater), the ASH guideline panel *suggests* allo-HSCT over chemotherapy alone as definitive consolidation treatment (conditional recommendation based on very low certainty in the evidence of effect ⊕○○○).

Remarks:

- AYAs with primary refractory disease in whom remission is achieved should proceed with allo-HSCT.
- The recommendation for allo-HSCT must be balanced with systematic assessments of patient suitability for transplant, including performance status, organ function, and comorbidities as considerations.
- The panel recognizes that pediatric data indicate that some younger AYAs in CR2 with lower risk disease (defined by late relapse with low MRD after reinduction therapy) may be considered for chemotherapy and/or immunotherapy alone.

Summary of the evidence. In adult practice, allo-HSCT historically has been the recommended course of postremission treatment for all adult patients with ALL with relapsed disease who achieve a CR2. Prospective clinical trials from international study groups and large individual treatment center trials conducted during the 1980s through early 2000s (before the development of immunotherapy) demonstrated that following achievement of CR, subsequent allo-HSCT in CR2 increased OS, and confirmed that long-term survival is determined by whether or not a patient receives allo-HSCT.^{42,43,93-95} The historically poor outcomes following ALL relapse among AYAs were well characterized by a retrospective analysis of 1706 patients (aged ≥15 years) with relapsed/refractory Ph⁺ B-ALL diagnosed between 1990 and 2013 from 11 study groups in Europe and the United States, and treated with standard of care chemotherapy before the introduction of new targeted therapies, including blinatumomab: 3-year OS for patients aged 15 to 17 years and 18 to 34 years was 16% and 15%, respectively.²²

In pediatric practice, however, prospective clinical trials have identified a subset of patients who can be maintained in a CR2 with chemotherapy with or without CNS radiotherapy, but without allo-HSCT consolidation.⁹⁶⁻⁹⁸ Pediatric patients who relapse late (variably defined, but, eg, >36 months after the first diagnosis) and who have low MRD (defined as <10⁻³ cells) at the end of an intensive 4-drug reinduction regimen are considered low risk, and receive chemotherapy for 2 years as definitive consolidation therapy. In contrast, among adult patients, there is no established “cut point” for CR duration or MRD value after reinduction therapy that predicts long-term survival. Thus, a low-risk adult patient population for whom a chemotherapy-based curative consolidation regimen in CR2 can be justified has not been defined or identified.

With this historical context in mind, the panel sought to identify comparative evidence, either prospective or retrospective studies, to evaluate the current standard practice that proceeds with allo-

HSCT during CR2 for the majority of AYAs who experience first relapse of B-ALL.

Tier 1 to 5 studies were included (ie, median age of study participants between 0 and 65 years). No comparative studies addressed this question in the AYA population. No trials compared allo-HSCT with chemotherapy in CR2 in a randomized manner; rather, patients were stratified to allo-HSCT or chemotherapy and/or immunotherapy alone based on site of relapse, time to first relapse, and MRD following reinduction chemotherapy. The panel thus only identified indirect evidence from 3 studies (4 publications)^{40,41,99,100} to inform this recommendation. One prospective study (Children's Oncology Group trial AALL1331) was reported in 2 publications, and provided data for survival outcomes for the pediatric approach: chemotherapy vs chemoimmunotherapy without allo-HSCT for low-risk patients,⁴¹ and chemotherapy vs chemoimmunotherapy followed by allo-HSCT for high-risk patients.⁴⁰ A second prospective trial conducted in children and adolescents with late bone marrow relapses of B-ALL provided data on long-term outcomes following a similar risk-adapted assessment based again on duration of CR1 and end of reinduction MRD.¹⁰⁰ The final study was a prospective multicenter single-arm study of allo-HSCT in CR2, and provided data on survival outcomes and rates of acute and chronic GVHD and transplant-related mortality.⁹⁹ The panel prioritized the following outcomes as the most important for this question: OS, composite outcome measures that incorporated relapse (eg, RFS, EFS, disease-free survival [DFS], progression-free survival [PFS]), risk of relapse, TRM, infections, GVHD, GVHD-free and relapse-free survival (GRFS), and quality of life. No studies reported on quality of life or the composite end point of GRFS. The evidence profile and EtD framework for this recommendation is available online at <https://guidelines.ash.gradepro.org/profile/KYkYibFJ1fM>.

Benefits. The evidence reviewed by the panel shows that pediatric and young AYAs with a late first marrow relapse (>36 months after diagnosis) and low MRD (<0.1%) following reinduction treatment have favorable OS with consolidation chemotherapy and immunotherapy without undergoing allo-HSCT, but patients with early relapse or high MRD (>0.1%) following reinduction benefit from allo-HSCT. Very low-quality evidence from 2 large international prospective trials suggests that the 4-year and 7-year OS is estimated at 90% and 84%, respectively, for children and young AYAs who met low-risk criteria and received chemotherapy with or without blinatumomab without allo-HSCT.^{41,100} Very low-quality evidence from a large prospective trial that examined the high MRD cohort suggests that receiving allo-HSCT significantly reduced the risk of relapse (HR, 0.36; 95% CI, 0.16-0.83).¹⁰⁰ Very low-quality evidence from a second prospective study that evaluated an intermediate and high-risk relapse cohort with chemotherapy treatment with or without blinatumomab followed by allo-HSCT favored blinatumomab as part of consolidation therapy, with 2-year OS estimated at 71% for the blinatumomab group compared with 58% for the chemotherapy group.⁴⁰ The hazard of death for patients that receive blinatumomab is 38% lower over time (HR, 0.62; 95% CI, 0.39-0.98), and the survival benefit was derived from the patients who were able to proceed with allo-HSCT. Very low-quality evidence from a prospective study evaluating a nonmyeloablative preparative regimen for allo-HSCT in

CR2 was included in the evidence profile, but the survival outcomes were not considered by the panel given that non-myeloablative preparative regimens are not recommended for an AYA population in current practice.⁹⁹

The panel noted the strong and inherent bias in comparing outcomes for AYAs with relapsed ALL nonrandomly receiving allo-HSCT vs chemotherapy ± immunotherapy. For example, proceeding to allo-HSCT is contingent on sufficient disease control. Conversely, those selected to receive chemotherapy alone in the studies included were a particular group of patients deemed to be low risk by explicitly defined criteria from several large pediatric trials.

Crucially, no studies of older AYA who were treated without allo-HSCT after first relapse could be identified. The study populations in the included studies were comprised of majority populations whose initial diagnosis occurred in the pediatric age range. For example, in the Hogan et al study, although 34 patients (13.3%) were aged ≥18 years at the time of relapse, only 3 patients (1.2%) were aged ≥18 years at the time of initial ALL diagnosis.⁴¹

Harms and burden. The panel recognized evidence for undesirable short- and long-term toxicities, GVHD, TRM, severe infections, and increased patient and caregiver burden with allo-HSCT when compared with treatment with chemotherapy. Very low-quality evidence from the single-arm study testing a non-myeloablative preparative regimen for allo-HSCT revealed an acute GVHD rate of 23%, chronic GVHD rate of 19%, and transplant-related mortality of 21%.⁹⁹ The remaining 3 studies included in the evidence profile did not report the anticipated transplant-related toxicities. Alternatively, 1 study did provide evidence that the intensity of the salvage chemotherapy regimen resulted in significant toxicity for the AYA patients.⁴⁰ No studies measured the burden on patients and caregivers.

The panel noted historic data that myeloablative allo-HSCT carries significant TRM, estimated at 10% to 30%,¹⁰¹ compared with <5% with chemotherapy or immunotherapy. The panel also acknowledged that the risk of GVHD is a major limitation of allo-HSCT, affecting 30% to 50% of patients acutely and up to 50% chronically, and can lead to substantial long-term effects on skin, lungs, liver, and joints, and higher risks of opportunistic infections secondary to prolonged immunosuppression. Conditioning regimens (eg, TBI, cyclophosphamide, busulfan) used in preparation for allo-HSCT are also associated with significant short- and long-term morbidity. Compared with chemotherapy and CAR T-cell therapy, where toxicities are often transient or reversible, allo-HSCT results in higher chronic health complications.¹⁰²

Other EtD criteria and considerations. AYA patients, including those on the panel, value the critical outcomes of OS and long-term remission; many will prioritize these outcomes over the concerns of toxicity, including acute toxicities, the risk of GVHD, and late effects including infertility associated with allo-HSCT. However, the panel recognized 2 situations where the above must be balanced. First, the panel recognized that factors such as performance score, organ function, and comorbidities may increase the risk of transplant-related mortality and morbidity. The panel

recommended the use of evidence-based and validated tools (ie, www.hctci.org) that can guide individualized assessments of transplant risk.¹⁰³ Second, the panel recognized that for individual patients, their specific values and preferences may inform decision-making around transplant. Acknowledging the above considerations, however, the panel, including patient advocates, determined that among AYAs with relapsed B-ALL who have an appropriate donor match and are eligible for allo-HSCT in CR2, allo-HSCT would be acceptable and recommended to most patients. The panel also noted that PROs and quality of life measures should be included in future trials to better inform these discussions.

The panel acknowledges that access to allo-HSCT may not be universal, and that underserved populations may experience greater barriers to accessing transplant care. The panel recognizes that underrepresented populations are less likely to find a matched unrelated donor. Even underserved patients with matched donors may experience disparities, and factors including health insurance access and other socioeconomic factors are particularly salient given the expense and complexity of the procedures, as well as the requirement for a dedicated caregiver and frequent and prolonged follow-up. Finally, the panel discussed the costs and resource implications of allo-HSCT, which are considerable. The panel also recognized the potential for significant financial burden and costs borne by patients given the lost productivity due to treatment and subsequent isolation, especially for individuals (and caregivers) who must travel long distances to a transplant center.

Conclusions and research needs for this recommendation. The panel determined that there is a net benefit of allo-HSCT for AYAs with relapsed B-ALL in CR2 who have not previously received an allo-HSCT as part of frontline treatment. The panel also recognized that there is an evidence base from the pediatric literature for AYAs with defined low-risk relapse features that supports a curative potential with chemoimmunotherapy without allo-HSCT in CR2. This is particularly relevant for patients whose relapse occurred in the AYA age range, but whose initial diagnosis of B-ALL occurred at age <15 years. In such patients, the panel recommends that the treating physician develop a care plan in coordination with pediatric leukemia and transplant teams. There is inadequate evidence, however, to support risk stratification and identification of a subgroup across the full AYA age range for whom transplant can be omitted in CR2. With the absence of more definitive evidence about a low-risk subgroup in the overall AYA population, AYAs in CR2 should be informed of the survival benefit of allo-HSCT but also the toxicities, acknowledging limited AYA-specific toxicity data. Finally, the panel recognized that there is considerable uncertainty around the impact of immunotherapy on the role of allo-HSCT, and emerging evidence may require a future revision of this recommendation. The panel supports future research that addresses immunotherapy as definitive consolidation along with research on patient preferences and PROs, including financial toxicity.

Allo-HSCT conditioning regimens: role of TBI

For patients with relapsed/refractory ALL who undergo allo-HSCT, what are the comparative benefits and harms of myeloablative preparative regimens using: (1) TBI in addition to chemotherapy, or (2) chemotherapy alone?

Recommendation 5

For AYAs with relapsed/refractory ALL proceeding with allo-HSCT, the ASH guideline panel *suggests* myeloablative conditioning regimens that include TBI, rather than chemotherapy alone (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. For this question, the panel included comparative studies that were either prospective or retrospective, as well as prospective single-group studies. Tier 1 to 3 studies were included (ie, median age of study participants between 10 and 65 years, published after 2010). The panel limited inclusion to studies that used TBI at myeloablative doses (defined as ≥ 8 Gy). The panel prioritized the following outcomes as the most important for this question: OS, composite outcome measures that incorporated relapse (eg, RFS/EFS/DFS/PFS), TRM, GVHD, GRFS, infections, and quality of life.

Eleven studies informed this panel recommendation. Two studies were RCTs,^{104,105} 8 were retrospective comparative studies,¹⁰⁶⁻¹¹³ and 1 study was a single-group prospective trial.¹¹⁴ No studies were designed specifically for the AYA population, though all included AYA patients.

All studies reported OS and nonrelapse mortality or transplant-related mortality/TRM. Six studies reported RFS, DFS, or EFS.^{104-106,109,113,114} Nine studies assessed the risk of relapse.^{104-108,110-113} Ten studies reported incidence of acute and chronic GVHD.^{104-108,110-114} Three studies reported GRFS.^{104,111,112} Three studies reported the risk of infections.^{105,107,109} No study reported HRQL measures, fertility, neurocognitive outcomes, or secondary malignancies. The evidence profile and EtD framework for this recommendation is available online at <https://guidelines.ash.gradepro.org/profile/pMesyOZ7g1E>.

Benefits. Multiple studies found improved survival and/or measures of long-term disease control to be associated with TBI use compared with chemotherapy-based preparative regimens. Very low-quality evidence from a European multi-institutional RCT in children and adolescents showed that inclusion of TBI as part of a myeloablative preparative regimen was associated with improved OS at 2 years (RR, 1.21; 95% CI, 1.11-1.33). Improved EFS (RR, 1.47; 95% CI, 1.3-1.68) at 2 years was also reported in the same RCT.¹⁰⁴ RFS at 5 years was also higher with the use of TBI (RR, 1.34; 95% CI, 1.06-1.69) in 1 retrospective comparative study among adults in Japan.¹¹³ Very low-quality evidence from 2 retrospective comparative studies demonstrated decreased risk of leukemia or death with inclusion of TBI (adjusted HR [aHR], 0.71; 95% CI, 0.52-0.98; aHR, 0.55; 95% CI, 0.34-0.86).^{110,112} Reduced risk of relapse (RR, 0.36; 95% CI, 0.24-0.55) was identified among those who received TBI in the European pediatric RCT.¹⁰⁴ Very low-quality evidence from 4 retrospective comparative studies^{106,110,111,113} also confirmed reduced relapse risk with inclusion of TBI. One RCT¹⁰⁴ found an improvement in GRFS at 2 years with use of TBI (RR, 1.41; 95% CI, 1.2-1.65), whereas 2 retrospective comparative studies did not find any significant difference.^{108,112}

The remaining studies, including low-quality evidence from 1 RCT among adolescents and adults in China,¹⁰⁵ did not find significant differences in survival outcomes (OS, RFS/EFS/DFS/PFS, GRFS) when compared with chemotherapy-based preparative regimens.

Harms and burden. In 1 RCT among children and adolescents, the risk of transplant-related mortality at 2 years with TBI-based preparative regimens was decreased compared with chemotherapy-based preparative regimens (RR, 0.21; 95% CI, 0.07-0.61).¹⁰⁴ One retrospective comparative study also found a decrease in the risk of nonrelapse mortality at 2 years with TBI-based preparative regimens (aHR, 0.53; 95% CI, 0.33-0.86).¹¹² However, another retrospective comparative study found an increased risk of transplant-related mortality at 3 years with use of TBI (RR, 1.31; 95% CI, 1.01-1.71), but with no significant difference at 5 years.¹⁰⁶ The remaining studies did not find a significant difference in nonrelapse or transplant-related mortality between the TBI-based and chemotherapy-based preparative regimens.

No study found a significant difference in risk of developing acute GVHD between TBI-based and chemotherapy-based preparative regimens. Of the 10 studies that evaluated the risk of developing chronic GVHD,^{104-108,110-114} 1 retrospective comparative study reported an increased risk of chronic GVHD at 5 years (RR, 1.47; 95% CI, 1.03-2.09) with the use of TBI.¹¹⁰ In the remainder of the studies, no significant difference was found in risk of developing chronic GVHD based on the preparative regimen.

In terms of risk of infection, 1 retrospective comparative study found a decreased risk of development of any grade ≥ 3 infection with the use of TBI (RR, 0.69; 95% CI, 0.5-0.96).¹⁰⁹ Another retrospective comparative study found an increased risk of cytomegalovirus infection or other viremia with the use of TBI (RR, 3.06; 95% CI, 1.65-5.68).¹⁰⁷ One RCT reported no significant difference in risk of infections between those who received TBI and those who received chemotherapy-based preparative regimens.¹⁰⁵

Other EtD criteria and considerations. The panel reached a consensus on the benefit of TBI-based myeloablative preparative regimens based on improved OS, improved EFS, reduced relapse risk, and improved GRFS. The risk of toxicities of allo-HSCT, including GVHD and infection, were not consistently different between TBI-based and chemotherapy-based preparative strategies in the reviewed studies.

The studies included in the evidence profile did not report on long-term toxicities known to be associated with TBI, such as secondary malignancies,¹¹⁵ infertility, growth impairment, or neurocognitive effects. The panel noted that the risk and impact of these late effects should be considered in the decision to incorporate TBI in preparative regimens, especially for younger AYA patients. The importance of weighing the undesirable long-term effects of TBI against the survival benefits using individualized shared decision-making was emphasized by patient representatives on the panel. Emerging evidence suggests MRD status before HSCT affects risk of relapse, and may inform the decision to include TBI in preparative regimens for patients who are at higher risk of relapse going into allo-HSCT.¹¹⁶⁻¹¹⁹

The panel also acknowledged that access to TBI may not be available to all patients at their primary treatment center, and that arranging access to radiation oncology centers may add to the logistical and financial burden on patients and their families, with disadvantaged groups affected differentially.

Conclusions and research needs for this recommendation. The panel determined that the benefits of TBI-based myeloablative preparative regimens outweighed the harms when compared with chemotherapy-based myeloablative preparative regimens in AYAs with relapsed/refractory ALL proceeding to allo-HSCT. The panel issued a conditional and not a strong recommendation due to the low to very low certainty in the data. The low certainty was again due to the need to extrapolate data from pediatric or adult populations as no study focused specifically on the AYA population. The available evidence, however, suggests that inclusion of TBI in preparative regimens improves OS and reduces relapse risk in AYAs. The risk of acute and chronic GVHD and infection appeared similar between TBI-based and chemotherapy-based preparative regimens; however, the panel noted that approaches to GVHD prophylaxis are evolving and may affect future assessments of the evidence for this question.

The panel identified the need for additional future research, including the following: (1) randomized data regarding the role that MRD status going into allo-HSCT may have in the use of myeloablative TBI-based preparative regimens compared with chemotherapy-based preparative regimens for AYA patients; (2) randomized trials that include prespecified HRQL end points and long-term follow-up to evaluate late effects; and (3) the evolving impact of posttransplant maintenance strategies on risk of relapse.

CNS relapse

For patients with ALL with isolated CNS relapse, what are the comparative benefits and harms of: (1) CAR T-cell therapy, (2) CNS-directed chemotherapy, (3) CNS radiation as monotherapy, and (4) CNS radiation in combination?

CAR T-cell therapy

No recommendation

The ASH guideline panel recognized promising emerging data for the use of CAR T-cell therapy in the management of isolated CNS relapse; however, the data are insufficient to support a recommendation at this time.

CNS-directed chemotherapy

Recommendation 6

For AYAs with isolated CNS relapse of ALL, the ASH guideline panel *recommends* that patients receive CNS-directed therapy (intrathecal chemotherapy) in the context of systemic therapy (strong recommendation based on very low certainty in the evidence of effects $\oplus\circ\circ\circ$).

CNS radiation as monotherapy

Recommendation 7

For AYAs with isolated CNS relapse of ALL, the ASH guideline panel *recommends against* patients receiving CNS radiation alone (without systemic chemotherapy with intrathecal chemotherapy) (strong recommendation against the intervention based on very low certainty in the evidence of effects ⊕○○○).

CNS radiation in combination

No recommendation

There are insufficient data to support a recommendation regarding the additional benefit of radiation when combined with other CNS-directed therapy.

Summary of the evidence. For this question, the panel included comparative studies that were either prospective or retrospective, as well as prospective single-group studies. Tier 1 to 3 studies were included (ie, median age of study participants between 10 and 65 years, published after 2014). The panel prioritized the following outcomes as the most important for this question: OS, composite outcome measures that incorporated relapse (eg, RFS/EFS/DFS/PFS), relapse (both overall and involving the CNS), CR, rates of allo-HSCT, toxicity, neurocognitive impact, and quality of life. Only 4 studies met inclusion criteria and were considered by the panel for this question. One retrospective comparative study¹²⁰ and 1 single-arm study within the broader context of an RCT⁴¹ addressed the use of systemic and intrathecal chemotherapy with or without cranial radiation. The evidence profile and EtD framework for Recommendations 6 and 7 are available online at <https://guidelines.ash.gradepro.org/profile/lBwZ6-YZkvc>. One retrospective comparative study¹²¹ addressed the role of cranial radiation boost, though this was not one of the primary comparisons of interest in this question (<https://guidelines.ash.gradepro.org/profile/4hHEzbPBdbk>). One prospective single-group study addressed the role of CAR T-cell therapy (<https://guidelines.ash.gradepro.org/profile/hVoMhIEnuvv>).¹²²

Benefits. The panel noted that all identified studies of patients with isolated CNS relapse were treated with a combination of systemic chemotherapy (often including agents with CNS activity) and intrathecal therapy. No studies were identified that used CNS radiation alone to treat such patients with curative intent. Thus, the panel recommended that such patients should receive CNS-directed therapy (intrathecal chemotherapy) in the context of systemic therapy, and that such patients should not receive cranial radiation alone (both strong recommendations based on very low certainty evidence). Given the limited and heterogeneous literature, no recommendations could be made for specific treatment regimens.

Very low-quality evidence from a retrospective comparative study indicated that adult patients with ALL with relapses involving the CNS who received systemic chemotherapy and intrathecal chemotherapy and radiation therapy were more likely to achieve CR than

those who received systemic and intrathecal therapy but no radiation (12/17; 70% vs 13/31; 42%; RR, 1.68; 95% CI, 1.01-2.82).¹²⁰ This study was limited by heterogeneity in population (eg, both B- and T-lineage disease) and systemic treatment regimens. It was also limited by its retrospective nature, with the indication for cranial radiation unclear. The 1 single-group prospective study was an arm of the pediatric RCT Children's Oncology Group trial AALL1331, in which some patients with late isolated CNS relapses received systemic and intrathecal chemotherapy plus cranial radiation.⁴¹ The 4-year DFS was 24.0% and 4-year OS was 60.3%, though panel members noted that these outcomes were substantially inferior to past studies in this population, possibly due to a de-intensification of systemic therapy with CNS activity.¹²³ Based on this evidence, the panel was unable to make a recommendation on the addition of cranial radiation to AYAs with isolated CNS relapse who are already receiving systemic and intrathecal therapy.

One retrospective comparative study examined the role of cranial boost among patients with ALL who were undergoing allo-HSCT.¹²¹ As this was a heterogeneous population, including both those with de novo and relapsed disease, and who may or may not have received cranial radiation before allo-HSCT, the panel determined that the study did not address the intent of the proposed question, and this study was not considered in the evidence profile. The panel recognized that decisions around pre-allo-HSCT cranial radiation and cranial boost in the context of allo-HSCT conditioning are linked in many clinical situations.

Finally, 1 prospective single-arm study (comprising of pooling several prospective single-arm trials) was identified that examined the role of CAR T-cell therapy for patients with relapses involving the CNS, including 43 pediatric patients with isolated CNS relapses.¹²² CR rates following CAR T-cell infusion were 97.7%, although, of note, most patients received systemic agents with CNS activity and intrathecal therapy between relapse and infusion. Indeed, 38 (88%) were CNS1 at the time of infusion. Among these 43 patients, 2-year RFS was 66% and 2-year OS was 91%. Though the panel considered this evidence promising for pediatric patients (median age 10.2 years at CAR T-cell infusion), it is unknown whether CAR T-cell therapy would be as effective in the AYA population with isolated CNS relapse, particularly older AYA (recent evidence in adults was not available at the time of panel deliberations).¹²⁴ The panel thus felt the evidence base was insufficient to make a recommendation for CAR T-cell therapy as routine therapy for this patient population at this time.

Harms and burden. The panel recognized that many of the considered interventions (intrathecal therapy, CNS-directed systemic therapy, cranial radiation) are associated with short-term and long-term toxicities. Indeed, several outcomes prioritized by the panel (toxicities, neurocognition, quality of life) were usually not reported by the included studies. As an exception, toxicity data were available on the cohort of pediatric patients treated with CAR T cells; the incidence of neurotoxicity or CRS was not different between patients with CNS positive and CNS negative. The panel also recognized the associated burden on patients and caregivers, particularly that involved with cranial radiation, which is typically administered over 2 to 3 weeks. Despite these potential toxicities and burden, the panel made the above recommendations prioritizing outcomes such as OS and DFS/EFS/LFS/RFS.

Other EtD criteria and considerations. The panel discussed several other important considerations when arriving at the above recommendations. First, the panel acknowledged that the above questions do not consider the optimal consolidative therapy for patients with isolated CNS relapse. The panel felt that the recommendations regarding consolidative therapy for all patients with relapsed/refractory disease were appropriate for this population as well.

Second, the panel discussed at length the promise of CAR T-cell therapy for this population. In addition to the Leahy study described earlier,¹²² a noncomparative retrospective study only available in abstract form showed a favorable safety profile and high CNS disease response rates among 28 patients with CNS2/3 disease who received brexucabtagene autoleucel.¹²⁵ Although unable to make a recommendation for CAR T-cell therapy for this indication, the panel recognized the potential for it to spare some patients from cranial radiation and perhaps allo-HSCT, particularly in younger AYA. The panel also recognized differences in access to CAR T-cell therapy across populations and locations.

Conclusions and research needs for these recommendations. The panel recommends that all AYAs with isolated CNS relapse should receive CNS-directed chemotherapy (intrathecal) and systemic chemotherapy following the considered judgment process that the benefits of this approach (OS, DFS) outweighed potential harms; in this context, the panel supported a strong recommendation in favor of CNS-directed chemotherapy and systemic therapy despite the very low certainty in evidence.⁴⁷ The panel does not recommend that radiation therapy be used alone in this context due to the risk of subsequent marrow relapse. During the considered judgment process, the panel acknowledged that there were no studies that supported the use of CNS radiation alone, and noted that well-established toxicity associated with radiation.⁴⁷ With this balance, the panel issued a strong recommendation despite the very low certainty in evidence.

As described above in the summary of the evidence, the recommendations were made based on nonrandomized studies with very low certainty. Outcome measures including acute toxicity, quality of life, and long-term cognitive function could not be addressed. In addition, the evidence was not specific to the AYA age group. The panel was not able to make a recommendation for or against the use of either radiation therapy (in the context of systemic and intrathecal therapy) or CAR T-cell therapy in this population. The panel was therefore left with uncertainty regarding the following questions: (1) whether the addition of radiation provides additional benefit over CNS-directed chemotherapy alone, (2) which consolidation therapy provides the best outcome after a CR2 is achieved, and (3) the role of CAR T-cell therapy for this population. The panel encourages the conduct of prospective trials for AYAs with the aim of answering these questions.

T-cell therapies

For AYAs with relapsed/refractory T-ALL, what are the comparative benefits and harms of (1) chemotherapy, (2) novel agents, (3) targeted therapies (nelarabine, venetoclax, navitoclax, TKIs), and (4) immunotherapy?

Recommendation 8

For AYAs with relapsed/refractory T-ALL, the ASH guideline panel *suggests* the use of a nelarabine-based regimen (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- The panel noted that many AYAs are receiving nelarabine as part of frontline treatment. There are no data to suggest that AYAs who have received nelarabine previously in the frontline setting should be precluded from receiving nelarabine again.

Research-only recommendation

There is limited available evidence for novel therapies, including CAR T-cell therapy, in relapsed/refractory T-ALL. As such, the ASH guideline panel is currently unable to issue a formal recommendation regarding these treatment approaches, despite recognizing that early phase data appear promising. The panel thus issues a research-only recommendation that if available and feasible, individuals with relapsed/refractory T-ALL should be offered participation in clinical trials of novel therapies, including CAR T-cell therapy.

Summary of the evidence. For this question, the panel included comparative studies that were either prospective or retrospective, as well as prospective noncomparative, single-group studies. Tier 1 to 4 studies were included (ie, median age of study participants between 10 and 65 years, published after 2000). The panel prioritized the following outcomes as the most important for this question: OS, composite outcome measures that incorporated relapse (eg, RFS/EFS/DFS/PFS), relapse (both overall and involving the CNS), CR, rates of MRD negativity, rates of allo-HSCT, toxicity, fertility, and quality of life. Ten studies met the defined inclusion criteria and were considered by the panel for this question; this included 1 abstract (complete manuscript subsequently published) that the panel felt warranted inclusion given its focus on an agent of particular interest, daratumumab,¹²⁶ 1 retrospective comparative study,¹²⁷ and 5 prospective single-arm studies¹²⁸⁻¹³² that addressed the use of nelarabine. The evidence profile and EtD framework is available online at <https://guidelines.ash.gradepro.org/profile/D7RUziMJ44>. The remaining single-arm prospective studies examined the role of CAR T-cell therapy,¹³³ or chemotherapy alone.^{93,134}

Benefits. The panel first reviewed the evidence pertaining to the use of nelarabine. Although all 6 studies included AYAs, none was designed to specifically address the use of nelarabine in this population. The sole comparative study was comprised of pediatric and AYAs with primary induction failure identified from 2 multinational randomized trials in the United Kingdom, UKALL2003 and UKALL2001, who were subsequently treated “off protocol.”¹²⁷ Additional data were obtained about nontrial therapy from the treating centers. Patients with induction failure subsequently treated with nelarabine (as a single agent or as

combination therapy followed by allo-HSCT) did not experience improved 5-year OS compared with those who did not receive nelarabine as a salvage regimen (39.1% vs 59.2%; HR, 1.72; $P = .11$). These data were considered to be very low certainty evidence. The remaining 5 single-arm prospective studies testing nelarabine in relapsed/refractory T-ALL were comprised of pediatric^{128,131,132} or adult^{129,130} cohorts. Of note, although the Children's Oncology Group study AALL0434¹³² was comprised of newly diagnosed patients with T-ALL, outcomes for patients with induction failure nonrandomly assigned to receive nelarabine were reported and included in the panel's deliberation. All studies were considered very low certainty evidence given heterogeneity in patient populations and the lack of AYA-specific data, with the exception of the CALGB 19801 study that was considered of higher but still low certainty due to a median age (34 years) within the AYA range.¹²⁹ The panel acknowledged that outcomes including OS, RFS/EFS/DFS/PFS, and CR, while promising were not clearly superior when comparing studies of nelarabine vs studies that used chemotherapy only.^{93,134} Outcomes for these patients are reported in the EtD.

The panel was also aware of a multicenter retrospective study of adult patients with relapsed/refractory T-ALL who received nelarabine in Italy.¹³⁵ Although this study cohort was large ($n = 118$) and had a median age within the AYA range (37 years), it did not meet inclusion criteria based on its retrospective noncomparative design. The panel nonetheless discussed this study and noted that its reported outcomes were generally consistent with the included studies described above.

Hogan et al described the results of a phase 2 single-arm study of daratumumab (DELPHINUS trial) in 29 children and AYAs with relapsed/refractory T-ALL in abstract form. This trial was subsequently published in full.¹²⁶ Although the final manuscript was not available to the ASH guideline panel at the time of the evidence review discussion, the outcomes are included in the text here. The CR rate among patients who received daratumumab was 16 of 29 (55.2%). The 2-year EFS among the pediatric and AYA subgroups were 36.1% and 20.0%, respectively, whereas 2-year OS was 41.3% and 25.0%. Allo-HSCT rates were 75.0% and 60.0%, respectively.

Zhang et al described a series of phase 1/2 trials conducted in China of CD7-directed CAR T-cell therapy with which 60 pediatric and adult patients had been treated.¹³³ CR rates were an impressive 94.4%, whereas 2-year PFS and OS were 53.7% and 63.5%, respectively. The panel noted the encouraging progress of CAR T-cell therapy for T-ALL/lymphoblastic lymphoma, and highlighted the unmet need of immunotherapy for relapsed/refractory T-ALL, but acknowledged that the evidence is not sufficient to make a recommendation for CAR T-cell therapy over other salvage treatments.

Harms and burden. The panel noted that the reported toxicities associated with nelarabine (see EtD) were generally of low incidence and manageable compared with those associated with intensive chemotherapy. Specifically, although the panel acknowledged the FDA's black box warning regarding

neurotoxicity, the incidence of nelarabine-associated neurotoxicity in the included studies was deemed to be acceptable. The toxicities associated with both daratumumab¹²⁶ and CAR T cells¹³³ were also deemed to be expected and acceptable. The panel recognized the associated burden on patients and caregivers of any of these agents, while also noting the burden associated with intensive chemotherapy and allo-HSCT. Outcomes such as fertility and HRQL were not reported in any of the included studies.

Other EtD criteria and considerations. As noted above, the panel acknowledged that despite the increasing use of nelarabine over time for relapsed/refractory T-ALL, the included data did not provide clear evidence for the superiority of nelarabine as compared with chemotherapy alone regarding the outcome that patients generally consider of highest value: OS. The panel also acknowledged the burden associated with nelarabine administration, which requires 3 to 5 days of outpatient administration, and may present challenges to access particularly for disadvantaged populations. The panel, however, also noted reasonable evidence of disease response in noncomparative studies, acceptable rates of toxicity, the FDA approval for this agent in this patient population, existent widespread clinical use, and the poor outcome of relapsed/refractory T-ALL in general. Weighing these considerations, the panel issued a conditional recommendation that suggests the use of nelarabine-based regimens for this population, while acknowledging the very low certainty in the underlying evidence. The panel noted the lack of any data to suggest that AYAs who had received nelarabine as frontline therapy should not also receive nelarabine in the relapse setting.

Conclusions and research needs for these recommendations. The panel suggests that AYA with relapsed/refractory T-ALL use a nelarabine-based regimen based on very low certainty evidence but also upon other considerations as outlined above. Although other agents, particularly daratumumab and CD7-directed CAR T cells, show promising activity, the panel was unable to make a recommendation regarding these agents based on current evidence. The panel encourages the conduct of prospective trials in AYAs regarding the efficacy of nelarabine in relapsed/refractory T-ALL for patients who were nelarabine exposed and nelarabine naïve.

The panel noted the encouraging progress of immunotherapy for relapsed/refractory T-ALL, specifically the data for daratumumab and CD7-directed CAR T-cell therapy. At present, there is insufficient evidence to recommend these agents outside of a clinical trial. The panel also highlighted the unmet need for access to immunotherapy clinical trials for AYAs with relapsed/refractory T-ALL as these trials are offered at only a limited number of academic centers and thus unavailable to the majority of patients. The panel thus issued a research-only recommendation that if available and feasible, individuals with relapsed/refractory T-ALL should be offered participation in clinical trials of daratumumab, CAR T-cell therapy, BCL-2 inhibitors, TKIs, and other novel agents. Finally, the panel encouraged the conduct of studies examining the impact of all these agents on short- and long-term toxicity, fertility, and HRQL.

Good practice statements

Good practice statement

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.

For more information on the MRD approach, refer to Recommendation 15 in DuVall et al.¹³⁶

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, where 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 developmental and cognitive level of the AYAs, and centered on the wishes of the AYAs, and they 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 statements included here, it is good practice to ensure that AYAs with ALL have access to specialized care with professionals and institutions well versed in AYA ALL where feasible.

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

These statements are also published in the guidelines for frontline management of ALL in AYAs to ensure consistency across AYA guidance.¹³⁶

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, the majority 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.¹³⁷

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.¹³⁸

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Authorship

Contribution: All guideline panel members contributed to specific subsections of the text for the recommendations; M.C.C., K.O., S.G., and L.E.W. 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; K.O.

and S.G. 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 quality of life.^{139,140} 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.¹⁴¹

A cancer diagnosis, while 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 are equivalent in importance to the biology of the disease itself. We acknowledge the significant individual variability in development between AYA patients, and we emphasize 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.¹⁴²⁻¹⁴⁴ 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.¹⁴⁵ 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.^{141,146} 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.^{147,148} 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 as 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.¹⁴⁹ 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, and many of those who do seek out supports report experiencing difficulties obtaining assistance.¹⁵⁰

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 where 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.¹⁵¹ 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 burdens 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.^{152,153} Additionally, with their age and development, there may be changes to AYAs' sexual functioning, desires, and preferences throughout diagnosis, treatment, and into survivorship.

Fertility preservation

Cancer and its therapy can significantly affect an AYA 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 quality of life. 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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