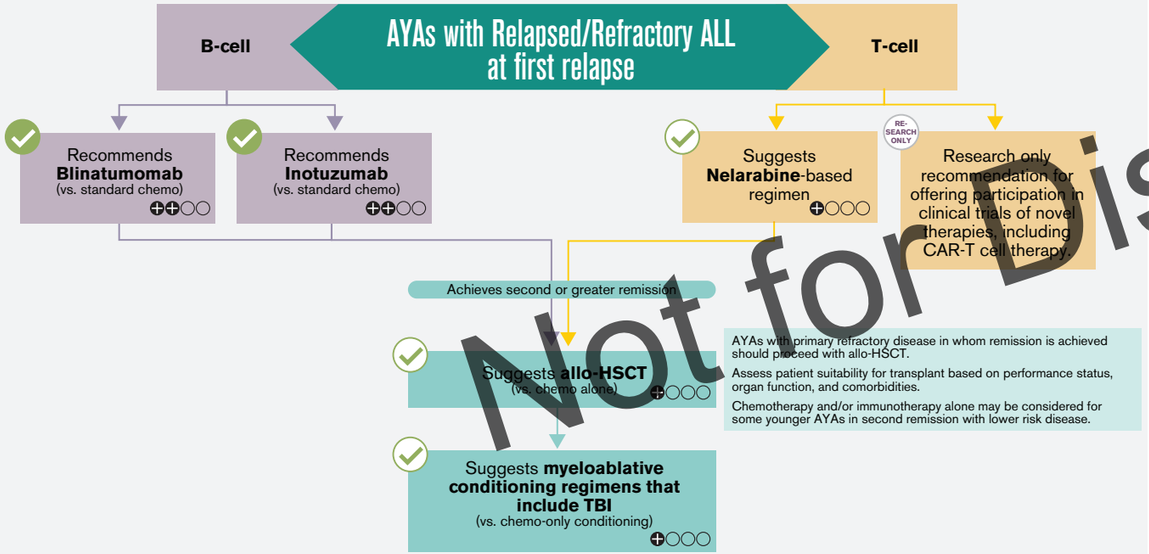
Relapsed or Refractory Management of ALL in AYAs

Therapeutic Approaches



ALL: Acute lymphoblastic leukemia; **Allo-HSCT:** Allogeneic hematopoietic stem cell transplant; **AYAs:** Adolescents and young adults; **CAR-T:** Chimeric antigen receptor T-cell **CNS:** Central nervous system; **TBI:** Total body irradiation

Research Only: A research only recommendation is a recommendation that confines the use of intervention options in a specific population to a research setting.

Strong Recommendations		Conditional Recommendations	
Recommends... ✓	Recommends against... ✗	Suggests... ✓	Suggests against... ✗
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.	

Evidence Certainty	
High Certainty	
⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate Certainty	
⊕⊕⊕◯	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low Certainty	
⊕⊕◯◯	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low Certainty	
⊕◯◯◯	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Access additional tools and resources at *hematology.org/ALLguidelines*:

- Visual Summaries
- Teaching slides
- Infographics
- Snapshots
- Patient resources
- Additional pocket guides

Reference: O'Dwyer, K.*‡, Winestone, L.*, Cheung, M.C., Benitez, L., Buldini, B., Cole, P., Damlaj, M., Dholaria, B., Dias, A., Dils, A., Fritsch, M., Greer, J., Hayes-Lattin, B., Henry, M., Jaffe, A., Jamy, O., Kebriaei, P., Mehrtens, I., Shah, N., Wilde, L., Young, P., Mai, H.J., Kanaan, G., Sereda, Y., Saldanha, I., Balk, E., Gupta, S‡. American Society of Hematology 2026 guidelines for Relapsed/Refractory Management of Acute Lymphoblastic Leukemia in Adolescents and Young Adults (ALL in AYAs). *Blood Advances*. doi: *https://doi.org/10.1182/bloodadvances.2025006479*.

* O'Dwyer, K. and Winestone, L. contributed equally to this work and share co-first authorship as co-writers of the guideline panel.

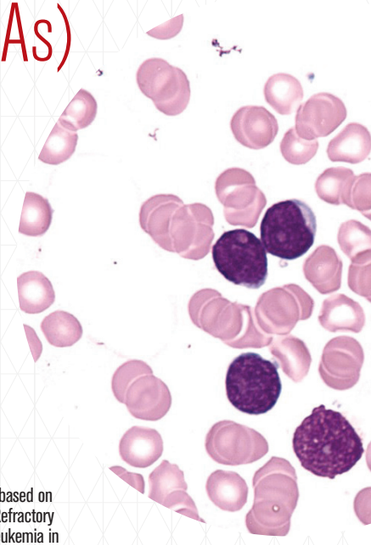
‡ O'Dwyer, K. and Gupta, S. contributed equally to this work and share co-senior authorship as co-chairs of the guideline panel.

ASH CLINICAL PRACTICE GUIDELINES
ACUTE LYMPHOBLASTIC LEUKEMIA

POCKET GUIDE

Relapsed/Refractory Management of Acute Lymphoblastic Leukemia in Adolescents and Young Adults (ALL in AYAs)

POCKET GUIDE
2026



The recommendations in this guide are based on the ASH 2026 Guidelines for Relapsed/Refractory Management of Acute Lymphoblastic Leukemia in Adolescents and Young Adults (ALL in AYAs).

Isolated CNS Relapse

Recommends **CNS-directed therapy** (intrathecal chemotherapy) in the context of systemic therapy ⊕○○○

and

Recommends against **CNS radiation alone** (without systemic chemotherapy with intrathecal chemotherapy) ⊕○○○

Consolidation After CAR-T Therapy

AYAs with Relapsed B- cell ALL → **Achieving 2nd or greater remission with CAR-T*** → **HSCT-Naive** → Suggests **further consolidation with allo-HSCT** ⊕○○○

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

* with FDA approved autologous CD19 CAR-T products (tisagenlecleucel and brexucabtagene autoleucel)

Minimal Residual Disease

GOOD PRACTICE

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

Good Practice: Good practice statements (GPS) are ungraded recommendations that reflect what the guideline panel considers to be an uncontested marker of good care. While not fully supported by systematic evidence, GPS are strong, actionable, and widely accepted as beneficial best practices.

*For more information on the MRD approach, refer to the ALL in AYAs Frontline Management Manuscript Recommendation 15.

MRD: Minimal residual disease

Evidence Gaps

CNS Relapse

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

Blinatumomab vs. Inotuzumab vs. CAR-T

There are nearly no head- to-head comparisons of these three therapies 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 ofdisease, and candidacy for future consolidative therapy including allo-HSCT.

CAR-T vs. Other Therapies

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

Psychosocial Care for AYAs

GOOD PRACTICE STATEMENTS

Specialized care

AYAs with ALL require person-centered and specialized healthcare.

Psychological Needs

Routinely assess psychosocial functioning and implement multidisciplinary psychosocial support from diagnosis and into survivorship.

Social Support

Assess existing social supports and encourage connection to supportive communities and resources as needed.

Financial Needs

Assess financial needs and encourage connection to institutional and/or regional financial counseling supports, resources, and organizations.

Goals of Care

Goals of care and end-of-life concepts should be addressed early in treatment and readdressed throughout treatment, particularly at transitional points during care (e.g., relapse).

Clinical Trials

Offer eligible AYAs enrollment in an appropriate clinical trial, as they are underrepresented in trials and have seen slower improvements in survival.

Palliative care

Interdisciplinary and/or primary palliative care should be provided throughout treatment starting at the time of diagnosis.

Fertility

Multidisciplinary and comprehensive fertility consultation and care should be provided prior to diagnosis and throughout treatment and into survivorship.

Sexual Health

Sexual health and relevant identities should be discussed with each individual patient at diagnosis and through treatment and survivorship.

Developmental Needs

Deliver service flexibly in consideration of each patient's developmental needs, preferences, and goals for treatment.