

American Society of Hematology 2025 guidelines for treating newly diagnosed acute myeloid leukemia in older adults

Mikhael A. Sekeres,¹ Ryan Mattison,² Andrew Artz,³ Maria R. Baer,⁴ Chong Chyn Chua,⁵ Roberta Demichelis-Gómez,⁶ Pamela C. Egan,⁷ Luke Fletcher,⁸ Charles Foucar,⁹ Jacqueline S. Garcia,¹⁰ Linda Gilberto,¹¹ Andres Gómez de León,¹² Jeffrey Lancet,¹³ Kah Poh Loh,¹⁴ Luca Malcovati,¹⁵ Bernard Marini,¹⁶ Uwe Platzbecker,¹⁷ Mohamed L. Sorror,¹⁸ Sara Tinsley-Vance,¹³ John Treitz,¹⁹ Maria Jose Oliveros,^{20,21} Sara Ibrahim,²⁰ Yetiani Roldan,²⁰ Gordon Guyatt,²⁰ and Romina Brignardello-Petersen²⁰

¹Division of Hematology, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; ²Division of Hematology, Medical Oncology and Palliative Care, University of Wisconsin-Madison, Madison, WI; ³Division of Leukemia, Department of Hematology & Hematopoietic Cell Transplantation, City of Hope, Duarte, CA; ⁴Division of Hematology/Oncology, University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; ⁵Division of Hematology, Monash Hospital, Monash University and Northern Hospital Melbourne, Melbourne, Australia; ⁶Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador, Mexico City, Mexico; ⁷Department of Medicine, MaineHealth Cancer Center, South Portland, ME; ⁸Division of Medical Oncology, Willamette Valley Cancer Institute, Eugene, OR; ⁹Department of Internal Medicine, Division of Hematology and Oncology, The University of New Mexico, Albuquerque, NM; ¹⁰Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; ¹¹Jacksonville, FL; ¹²Division of Hematology, Department of Internal Medicine, Universidad Autónoma de Nuevo León, Monterrey, Mexico; ¹³Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL; ¹⁴Division of Hematology and Oncology, University of Rochester Medical Center, Rochester, NY; ¹⁵Department of Molecular Medicine, University of Pavia and San Matteo University Hospital Foundation, Pavia, Italy; ¹⁶Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI; ¹⁷Department of Internal Medicine, University Hospital Carl Gustav Carus, Dresden, Germany; ¹⁸Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA; ¹⁹Louisville, KY; ²⁰Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; and ²¹Departamento de Ciencias de la Rehabilitación, Facultad de Medicina, Universidad de La Frontera, Temuco, Chile

Background: Older adults with acute myeloid leukemia (AML) represent a cancer population in which disease-based risk factors, comorbidities, patient goals, and treatment risks and benefits influence treatment recommendations.

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

Methods: ASH formed a multidisciplinary guideline panel, including patient representatives, that minimized bias from conflicts of interest. Clarity Research Group at McMaster University supported the guideline development process, including updating or performing systematic evidence reviews. The panel prioritized questions and outcomes according to their importance for clinicians and patients. The panel used the grading of recommendations assessment, development and evaluation approach, including evidence-to-decision frameworks, to assess evidence and make recommendations.

Results: The panel agreed on 9 critical clinical recommendations for managing AML in older adults, mirroring real-time practitioner-patient conversations: the decision to pursue antileukemic treatment vs best supportive management; traditional induction and postremission therapy vs hypomethylating agent or low-dose cytarabine, or combinations with venetoclax; the role and duration of postremission therapy; combinations with venetoclax vs monotherapy; the use of targeted therapy, including isocitrate dehydrogenase and FMS-like tyrosine kinase 3 (FLT3) inhibitors, in appropriate patients; the role of hematopoietic stem cell transplantation in unfavorable prognosis AML; and the role of transfusion support for patients no longer receiving antileukemic therapy.

Conclusions: Key recommendations of these guidelines include treatment over best supportive care; venetoclax-based regimens over monotherapies; and incorporation of FLT3 inhibitors into traditional induction and postremission therapy.

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The full-text version of this article contains a data supplement.

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Summary of recommendations

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of Clarity Research Group at McMaster 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 GRADE (grading of recommendations assessment, development, and evaluation) approach⁴⁻¹⁰ to assess the certainty in the evidence and formulate recommendations.

The following criteria were used to identify older adults with acute myeloid leukemia (AML) included in the clinical trials forming the basis for these recommendations.

Inclusion criteria:

1. Newly diagnosed de novo, treatment-related, and secondary AML (ie, not relapsed or refractory AML);
2. Patients aged ≥ 55 years;
3. Patients had to have received definitive antileukemic therapy (ALT) depending on the specific question being addressed;
4. Patients were treated as part of randomized controlled trials (RCTs; which were prioritized) and nonrandomized studies (NRSs); and
5. Studies had to include ≥ 20 patients.

Exclusion criteria:

1. Acute promyelocytic leukemia;
2. Myeloid neoplasms associated with Down syndrome; and
3. Studies in which $>75\%$ of patients did not meet an eligibility criterion based on characteristics of the patients or the intervention, or in which the results were not reported separately for those who met the criteria.

Note that, compared with the 2020 American Society of Hematology (ASH) guidelines for treating newly diagnosed AML in older adults, the 2025 guidelines no longer use the terms “intensive” and “nonintensive” therapy, because the panel judged that venetoclax-based therapies were not truly “nonintensive.” Instead, the 2025 ASH guidelines have adopted the terms “conventional induction and postremission therapy” and hypomethylating agents (HMA) or low-dose cytarabine (LDAC) in combination with venetoclax.

The panel judged that, although certain studies included patients treated with either azacitidine- or decitabine-based therapy, 7-day dosing of azacitidine and 5-day dosing of decitabine are generally considered interchangeable.

Also of note, the studies used heterogeneous approaches to cytogenetic risk classification; details are provided in supplemental Appendices 4-10.

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.			
	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.

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:

Recommendations

Recommendation 1. For older adults with newly diagnosed AML who are candidates for ALT, the ASH guideline panel *recommends* offering ALT over best supportive care (strong recommendation based on moderate certainty in the evidence of effects $\oplus\oplus\oplus\circ$).

- This recommendation is from the ASH 2020 Guidelines for Treating Acute Myeloid Leukemia in Older Adults. The evidence for this recommendation was not rereviewed for this guideline.

Recommendation 2a. For older adults with newly diagnosed AML considered candidates for intensive ALT, the ASH guideline panel *suggests* conventional induction and postremission therapy over HMA or LDAC monotherapy induction and postremission therapy (conditional recommendation based on low certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 2b. For older adults with newly diagnosed AML considered candidates for intensive ALT, the ASH guideline panel *suggests* using either conventional induction and postremission therapy or HMA- or LDAC-based induction and postremission therapy in combination with venetoclax (conditional recommendation based on very low certainty in the evidence of effects $\oplus\circ\circ\circ$).

Remarks:

- Conventional induction and postremission therapy may be preferred for patients who have favorable risk cytogenetic or molecular mutations and for those for whom a long hospital stay would not be a deterrent. Furthermore, "younger" older adults (eg, sexagenarians) may better tolerate conventional induction and postremission chemotherapy.
- HMA- or LDAC-based induction and postremission therapy in combination with venetoclax may be preferred for patients who are older (eg, aged ≥ 70 years) or with certain poor-risk cytogenetic or mutations that may compromise response to conventional therapy. Furthermore, those patients who wish to avoid admission to the hospital may prefer this treatment approach.

Recommendation 3. For older adults with AML who achieve remission after at least a single cycle of conventional induction therapy and who are not candidates for allogeneic hematopoietic stem cell transplantation (allo-HCT), the ASH guideline panel *recommends* postremission therapy over no additional therapy (strong recommendation based on low certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 4a. For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy or for HMA-based combination therapy, the ASH guideline panel *suggests* azacitidine monotherapy over LDAC monotherapy (conditional recommendation based on low certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 4b. For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy or for HMA-based combination therapy, the ASH guideline panel *suggests* 5-day decitabine monotherapy over 10-day decitabine monotherapy (conditional recommendation based on low certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 4c. For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* HMA in combination with venetoclax over HMA alone (conditional recommendation based on moderate certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 4d. For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy or for HMA-based combination therapy, the ASH guideline panel *suggests* LDAC in combination with venetoclax over LDAC monotherapy (conditional recommendation based on low certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 5a. For older adults with newly diagnosed AML and an *isocitrate dehydrogenase 1 (IDH1)* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* azacitidine in combination with ivosidenib over azacitidine monotherapy (conditional recommendation based on low certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 5b. For older adults with newly diagnosed AML and an *IDH1* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* using either HMA in combination with ivosidenib or HMA in combination with venetoclax (conditional recommendation based on very low certainty in the evidence of effects $\oplus\circ\circ\circ$).

Recommendation 5c. For older adults with newly diagnosed AML and an *IDH2* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* azacitidine monotherapy over azacitidine in combination with enasidenib (conditional recommendation based on low certainty in the evidence of effects $\oplus\oplus\circ\circ$).

Recommendation 5d. For older adults with newly diagnosed AML and an *IDH2* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* HMA in combination with venetoclax over HMA in combination with enasidenib (conditional recommendation based on very low certainty in the evidence of effects $\oplus\circ\circ\circ$).

Recommendation 6. For older adults with AML who achieve a response after receiving HMA- or LDAC-based induction and postremission therapy, the ASH guideline panel *suggests* continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy after a finite number of cycles (conditional recommendation based on very low certainty in the evidence of effects $\oplus\circ\circ\circ$).

Recommendation 7. For older adults with newly diagnosed AML who have an FMS-like tyrosine kinase 3 (*FLT3*) mutation, the ASH guideline panel *suggests* ALT in combination with an *FLT3* inhibitor over ALT alone (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remark:

- This recommendation applies primarily to patients receiving conventional induction and postremission therapy, and may or may not apply to patients receiving HMA or LDAC plus venetoclax, or HMA or LDAC monotherapy. The panel is less confident about the addition of *FLT3* inhibitors resulting in net benefit for patients who receive HMA or LDAC plus venetoclax, or HMA or LDAC monotherapy.

Recommendation 8. For older adults with newly diagnosed AML who have responded to initial ALT, who are candidates for an allo-HCT during first remission, and who have unfavorable prognosis based on karyotypic and molecular characteristics, the ASH guideline panel *suggests* an allo-HCT over no transplantation (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Recommendation 9. For older adults with AML who are no longer receiving ALT (including those receiving end-of-life care or hospice care), the ASH guideline panel *suggests* having red blood cell (RBC) transfusions be available over not having transfusions be available (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- There may be rare instances in which platelet transfusions may be of benefit in the event of bleeding, but there are even less data to support this practice and it is anticipated that platelet transfusions will have little or no role in end-of-life or hospice care.

This recommendation is from the ASH 2020 guidelines on AML in older adults. The evidence for this recommendation was not rereviewed for this guideline.

Values and preferences

The panel reviewed the available evidence on how patients value and prioritize key health outcomes. These recommendations place a relatively higher value on outcomes that reflect survival and disease control, and a relatively lower value on avoiding burdens such as treatment-related toxicity, prolonged hospital stays, or temporary reductions in quality of life (QoL). However, the panel recognized important variability and uncertainty in how different patients weigh these outcomes. This underscores the need for shared decision-making to ensure that care aligns with individual values and preferences.

Explanations and other considerations

In developing these recommendations, the panel judged, in addition to net benefit and values and preferences, cost-effectiveness, equity, acceptability, and feasibility. However, given the global scope of this guideline, variability in feasibility and resource use across settings did not substantially influence the direction or strength of the recommendations.

Introduction

Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations for the management of newly diagnosed AML in older adults, from the time of diagnosis through postremission therapy, and considerations for end-of-life/hospice care. The primary goals of these guidelines are to review, critically appraise, and implement evidence-based recommendations that will inform decisions made in real time, mirroring discussions that occur between practitioners and patients with AML, and the disease natural history. Through improved provider and patient education on the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision-making that will result in treatment decisions reflecting patient goals of care.

The target audience includes patients, hematologists, oncologists, geriatric specialists, 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 providing optimal management of older adults with AML. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

The median age at AML diagnosis in the United States is 68 years, with >75% of cases diagnosed in those aged ≥55 years.¹¹ AML can thus be considered a cancer of older adults, with “older” defined in clinical studies starting at ages 55 to 65 years. Naturally, age cutoffs that distinguish older adults with AML from younger adults are inherently somewhat arbitrary, as disease characteristics, functional status, and comorbidities evolve continuously, and may differ in an older adult in the current era from someone the same age in an era decades earlier.

Although AML in younger adults is frequently thought to be a medical emergency due to its rapid proliferation and consequent sequelae of infections, bleeding complications, leukostasis, and tumor lysis syndrome (TLS), in older adults AML tends to be somewhat more indolent, likely as a consequence of its evolution from an antecedent hematologic disorder in many cases.¹²⁻¹⁵ This biologic and genetic basis for the clinical behavior of AML in older adults also explains its relative resistance to chemotherapy, shorter duration of response, and grim overall survival. Patient factors, such as accumulated comorbidities and the effects of aging on physiologic and functional status, contribute to the untoward outcomes and limitations in tolerance of intensive, cytotoxic therapy.

Given the limitations imposed by the recalcitrance of the disease and other factors inherent in the person diagnosed with AML, informed discussions regarding goals of care and the relative balance of risks and benefits of any therapeutic intervention are critical at the time of diagnosis. Initial options may include no therapy at all, hospice care, supportive care only, outpatient-based treatment approaches, or inpatient-based approaches. An important component of this decision involves assessing social support from family and friends, and any existing caregiver responsibilities, particularly given the burden of both the treatment itself and supportive care needs, such as transfusions and transitions from inpatient to outpatient settings. Because cure for AML in older adults is relatively uncommon, enrollment in a clinical trial should be considered for all patients.

It is also important to acknowledge that it may be overly reductionist to divide the entirety of AML into a disease that affects older adults distinctly from younger adults. There are older adults whose disease behaves like, and has biologic characteristics of, AML that we typically associate with someone who is younger, and vice versa. Particularly for patients in a “younger older” category with better-risk disease characteristics, survival is better, and initial treatment discussions may be less driven by QoL considerations.¹⁶

These guidelines were developed with these complicated factors influencing treatment decisions in mind, mirroring the conversations that should be occurring between practitioners and patients from the initial consideration of therapy, through treatment continuation, and invocation of palliative care and hospice.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.⁴⁻¹⁰ ASH guided the overall guideline development process, including project funding, panel formation, conflict-of-interest management, internal and external review, and organizational approval, based on policies and procedures from the GIN-McMaster guideline development checklist (<http://cebgrade.mcmaster.ca/guidecheck.html>).¹⁷ The process followed standards for trustworthy guideline development established by the Institute of Medicine and the GIN.¹⁻³

Organization, panel composition, planning, and coordination

ASH, in collaboration with the Clarity Research Group at McMaster University (funded by ASH under a paid agreement) coordinated the work of this panel. The ASH guideline oversight subcommittee oversaw the project and reported to the ASH committee on quality. ASH vetted and appointed individuals to the guideline panel. The Clarity Research Group vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process including the use of the GRADE approach. Supplement 2 describes the membership of the panels and the Clarity Research Group.

The panel included hematologists, geriatric specialists, community-based physicians, a clinical pharmacist, a nurse practitioner, oncologists, and patients. Clinician members had research expertise relevant to the guideline topic, including expertise in leukemia, epidemiology, palliative medicine, and geriatric oncology. One cochair served as a content expert, whereas the other provided expertise in guideline development methodology.

In addition to synthesizing evidence systematically, the Clarity Research Group supported the guideline development process, including determining methods, preparing meeting materials, and facilitating panel discussions. The panel conducted its work using web-based tools (www.limesurvey.org and www.gradeapro.org), along with face-to-face and virtual meetings.

Guideline funding and management of conflicts of interest

ASH, a nonprofit medical specialty society representing hematologists, fully funded the development of these guidelines. ASH did not accept direct funding from other organizations including from

any for-profit companies for the development of these guidelines. ASH staff and ASH committees including the ASH executive committee reviewed the guidelines but had no role in 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 Clarity Research Group, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

ASH managed all participants' conflicts of interest according to its policies, which follow recommendations from the Institute of Medicine¹⁸ and the GIN.³ The guideline panel included individuals with diverse perspectives and experience. During the guideline development process, all panelists avoided significant direct financial relationships with for-profit health care companies. Many panelists had relevant nonfinancial interests, such as published opinions on the guideline topic. None of the researchers from Clarity Research Group who contributed to the systematic reviews or who supported the guideline development process had any direct or indirect financial relationships with for-profit health care companies relevant to the guideline topic.

Recusal was used to manage certain conflicts.^{5,19-21} For 3 recommendations, 2 panelists (C.F. for recommendation 2 and C.C.C. for recommendations 6 and 7) were recused because of leadership role in relevant research; that is, they participated in group discussions about evidence but they did not participate in making judgments about the evidence or in group discussions about the direction and strength of recommendations. The GRADE “evidence-to-decision” (EtD) tables for each recommendation describe any instance in which ≥ 1 panel members were recused.

Supplement 3 provides complete disclosure forms for all panel members and a record of ASH's conflict management decisions. Supplement 4 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 committee on quality convened a working group, composed of 3 original guideline authors. Based on recent clinical advances and emerging evidence, the group reviewed the 2020 guideline to identify which questions remained relevant and which required revision. The panel brainstormed and then prioritized new questions using a survey form, with questions in the brainstorming session generated from actual decisions that arise in the clinical care of patients with AML. Panelists also decided that it was important to address questions that arise in a variety of settings globally, some of which may not provide access to specialty drugs such as venetoclax, or may use LDAC instead of an HMA. As a consequence, questions were generated and recommendations provided without the mandate that a regimen be approved by a regulatory authority, as practice patterns vary globally. The final list including both revised and new recommendation questions is available in [Table 1](#).

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.²² They

Table 1. Clinical questions formulated and prioritized

Recommendation questions	Priority
Should older adults with newly diagnosed AML who are candidates for ALT receive ALT instead of best supportive care only?	Original 2020 question with unchanged recommendation
Should older adults with newly diagnosed AML considered candidates for ALT receive conventional induction and postremission therapy vs HMA or LDAC monotherapy vs HMA or LDAC in combination with venetoclax?	Original 2020 question with updated terminology and recommendation
Should older adults with newly diagnosed AML who achieve remission after at least 1 cycle of conventional induction therapy receive postremission therapy vs no additional therapy?	Original 2020 question with updated terminology and recommendation
Should older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy receive gemtuzumab ozogamicin, LDAC, azacitidine, 5-day decitabine, or 10-day decitabine as monotherapy or in combination?	Original 2020 question
Should older adults with newly diagnosed AML and actionable/targetable mutations considered appropriate for ALT but not for conventional induction and postremission therapy, receive HMA monotherapy, HMA plus venetoclax, HMA plus venetoclax plus additional targeted therapy, HMA plus targeted therapy, or targeted therapy alone?	New question
Should older adults with newly diagnosed AML who received HMA- or LDAC-based induction and postremission therapy and who achieved a response continue therapy indefinitely until progression/toxicity or be given therapy for a finite number of cycles?	Original 2020 question with updated terminology and recommendation
Should older adults with newly diagnosed AML who have an <i>FLT3</i> mutation be offered an <i>FLT3</i> inhibitor in combination with ALT vs ALT alone?	New question
Should older adults with newly diagnosed AML who have responded to initial ALT, who are candidates for an all-HCT during first remission, and who have nonfavorable prognosis based on molecular and karyotypic characteristics, receive an allo-HCT vs not?	New question
Should older adults with AML who are no longer receiving ALT (including those receiving end-of-life or hospice care) receive RBC transfusions, platelet transfusions, or both, vs no transfusions?	Original 2020 question with original recommendation

began with the comprehensive list of questions generated during the 2020 guideline development and brainstormed additional outcomes. The panel then rated the relative importance of each outcome for decision-making, following the GRADE approach.²² While acknowledging considerable variation in the impact on patient outcomes, the panel rated the outcomes listed in [Table 2](#) as critical for clinical decision-making.

Evidence review and development of recommendations

For each guideline question, Clarity Research Group prepared ≥ 1 GRADE EtD frameworks, using the GRADEpro Guideline Development Tool (www.grade-pro.org).^{4,5,10} These tables present summaries of the results of systematic reviews on intervention effects, certainty in the evidence, and values and preferences, alongside structured considerations of cost-effectiveness, equity, acceptability, and feasibility to inform panel judgments. Although global applicability was assessed, setting variability did not drive recommendations. The panel reviewed and revised the draft tables to address corrections and gaps.

Under the direction of the Clarity Research Group, researchers followed the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org)²³ to conduct both updated and newly developed systematic reviews of intervention effects. For details on the systematic reviews methods, see supplement 1, appendix 1. For details on eligibility criteria for each question, see supplement 1, appendix 2. For recommendation questions being updated, the team conducted literature searches from January 2019 to 16 February 2024 (supplement 1, appendix 3). For new questions, the team searched from database inception to the following dates: 14 March 2024, for recommendation question 7; 21 March 2024, for recommendation question 5; and

16 April 2024, for recommendation question 8 (supplement 1, appendix 4). To ensure that the systematic reviews captured studies published between the last date of search and the guideline recommendation development meeting (in November 2024), the team asked panel members to suggest any newly published studies that met eligibility criteria. For details on study selection question process, see supplement 1, appendices 5-8.

For each included study, the Clarity Research Group team assessed risk of bias at the outcome level, grouping outcomes as objective or nonobjective. For randomized trials, the team used an adapted version of the Cochrane Risk of Bias 2.0 tool²⁴ and for NRSs, they applied the ROBINS-I tool.²⁵ For each effect estimate of the outcomes of interest, the team assessed the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimates of effects) using the GRADE approach. This assessment included the following domains: risk of bias, imprecision, inconsistency indirectness, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.^{6,26} Within this report, these categories are represented by the symbols, as described in [Table 3](#).

In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence on values and preferences, acceptability, and equity, and summarized the findings within the EtD frameworks.^{4,5,10}

At a 2-day in-person meeting, the panel used EtD tables to develop clinical recommendations from a population perspective, reaching consensus on evidence certainty, benefit-harm balance, and assumed values. The panel also assessed equity and acceptability. The panel agreed on the recommendations (including direction and strength) and remarks by consensus based on the balance of all

Table 2. Critical outcomes for decision-making

Outcomes
Q1
Mortality/survival
QoL impairment
Functional status impairment
Severe toxicity
Morphologic complete remission (CR) or CR
Allo-HCT
Hospitalization (non-intensive care unit)
Burden on caregivers
Q2
Mortality/survival
QoL impairment
Functional status impairment
Recurrence or duration of response
Morphologic CR (or CR)
Allo-HCT
Severe toxicity
Burden on caregivers
Q3
Mortality/survival
QoL impairment
Functional status impairment
Recurrence or duration of response
Severe toxicity
Hospitalization (non-intensive care unit)
Q4
Mortality/survival
QoL impairment
Functional status impairment
Recurrence or duration of response
Morphologic CR (or CR)
Severe toxicity
Burden on caregivers
Q5
Mortality/survival
QoL impairment
Morphologic CR/responses less than morphologic CR
Recurrence
Severe toxicity
Hospitalization
Allo-HCT
Q6
Mortality/survival
QoL impairment
Functional status impairment
Severe toxicity
Burden on caregivers

Table 2 (continued)

Outcomes
Q7
Mortality/survival
Morphologic CR
Recurrence
Severe toxicity
Allo-HCT
Functional status impairment
QoL impairment
Q8
Mortality/survival
Functional status impairment
Recurrence
Severe toxicity
QoL impairment
Burden on caregivers
Hospitalization
Q9
Mortality/survival
Functional status impairment
Burden on caregivers
Hospice care
Major bleeding
Platelet transfusion refractoriness

desirable and undesirable consequences. All panel members reviewed and approved the final guidelines, including the recommendations.

Interpretation of strong and conditional recommendations

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

Document review

All members of the panel reviewed the draft recommendations. ASH posted a revised version online from 17 March 2025 to 14 April 2025 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. In response to the feedback, ASH revised the document to address pertinent comments but made no changes to the recommendations.

The ASH guideline oversight subcommittee and the ASH committee on quality confirmed that the guidelines followed the

Table 3. Certainty of body of evidence for effect estimates of outcomes of interest

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.

defined development process. On 23 July 2025, the officers of the ASH executive committee approved the submission of the guidelines for publication under the imprimatur of ASH. *Blood Advances* then conducted peer review of the guidelines.

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. Policymakers, including payers, may use guidelines to inform decisions about allocation of health care resources, for example, coverage decisions. Such decisions should be consistent with the intended interpretation of strong and conditional recommendations (Figure 1). It is the position of ASH that patients should have access to all safe and effective treatment options recommended by the individual patient's physician. 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. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aid. 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

Should older adults with newly diagnosed AML who are candidates for ALT receive ALT instead of best supportive care only?

Recommendation 1

For older adults with newly diagnosed AML who are candidates for ALT, the ASH guideline panel *recommends* offering ALT over best supportive care (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

This recommendation is from the ASH 2020 guidelines on AML in older adults. The evidence for this recommendation was not rereviewed for this guideline. Note that a candidate for therapy means that the patient desires therapy, therapy aligns with patient goals, the physician recommends therapy, and the benefit of therapy outweighs the risk. Please review the [2020 ASH AML in Older Adults guidelines](#).

Should older adults with newly diagnosed AML considered candidates for ALT receive conventional induction and postremission therapy vs HMA- or LDAC-based induction and postremission therapy?

Recommendation 2a

For older adults with newly diagnosed AML considered candidates for intensive ALT, the ASH guideline panel *suggests* conventional induction and postremission therapy over HMA or LDAC monotherapy induction and postremission therapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Recommendation 2b

For older adults with newly diagnosed AML considered candidates for intensive ALT, the ASH guideline panel *suggests* using either conventional induction and postremission therapy or HMA- or LDAC-based induction and postremission therapy in combination with venetoclax (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- Conventional induction and postremission therapy may be preferred for patients who have favorable-risk cytogenetics or molecular mutations and for those for whom a long

hospital stay would not be a deterrent. Furthermore, “younger” older adults (eg, sexagenarians) may better tolerate conventional induction and postremission chemotherapy.

- HMA- or LDAC-based induction and postremission therapy in combination with venetoclax may be preferred for patients who are older (eg, aged ≥ 70 years) or with certain poor-risk cytogenetics or molecular mutations that may compromise response to conventional therapy. Furthermore, those patients who wish to avoid admission to the hospital may prefer this treatment approach.

Summary of the evidence

We updated the systematic review conducted for the previous version of the guideline and used the most current relevant evidence for this question. There were 21 studies (3 RCTs and 18 NRSs) addressing this question.²⁷⁻⁴⁷

Recommendation 2a. One RCT provided evidence comparing conventional induction and postremission therapy with azacitidine or LDAC as monotherapy as reported in the previous guideline³⁴; 1 new RCT compared conventional induction and postremission therapy with 10-day decitabine³⁹; and 1 RCT compared conventional induction and postremission therapy with 5-day decitabine in combination with homoharringtonine, cytarabine, and granulocyte-colony stimulate factor.⁴⁷ The 3 RCTs enrolled 1099 older adults at least 60 years of age.^{34,39,47} The mean age across studies was 70.6 years (standard deviation [SD], 5.1 years), the mean percentage of male participants was 56%.^{34,39,47} There was variability across studies in risk classification system used to stratify patients.

Recommendation 2b. A total of 18 NRSs compared conventional induction and postremission therapy with HMA- or LDAC-based therapy combined with venetoclax; we did not identify any randomized trials.^{27-33,35-38,40-46} The NRSs enrolled 6770 older adults.^{27-33,35-38,40-46} The mean age across studies was 67.1 ± 5.04 years, the mean percentage of male participants was 58.3%. Across studies, participants were stratified with different risk classification systems.^{27-33,35-38,40-46}

Supplement 1, appendix 9 presents the characteristics of all included studies.

The evidence profile and EtD framework for recommendation 2a are available online at <https://guidelines.ash.gradepro.org/profile/Q5GycakUXIM>.

The evidence profile and EtD framework for recommendation 2b are available online at <https://guidelines.ash.gradepro.org/profile/sabOEx5rrE0>.

Benefits

Recommendation 2a. When conventional induction and postremission therapy is compared with HMA- or LDAC-based monotherapy, low certainty in evidence *suggests* that patients who receive conventional therapy may have a lower risk of death at the longest follow-up (relative risk [RR], 0.94; 95% confidence interval

[CI], 0.85- 1.04; 48 months follow-up).³⁹ Conventional therapy increases CR rates (odds ratio, 1.75; 95% CI, 1.25-2.38; high certainty in evidence)³⁹ and may reduce recurrence at 12 months (RR, 0.69; 95% CI, 0.48-1.00; low certainty in evidence)³⁹ and at the longest follow-up (RR, 0.81; 95% CI, 0.64-1.04; 48 months follow-up; low certainty in evidence).³⁹ HMA- or LDAC-based monotherapy, as opposed to combination therapy with venetoclax, is a valid comparison to conventional induction therapy in select subgroups, such as patients whose AML has a *TP53* mutation or in areas of the world in which venetoclax may not be available.

Recommendation 2b. When conventional induction and postremission therapy is compared with HMA- or LDAC-based therapy plus venetoclax, low certainty in evidence *suggests* that patients who receive conventional therapy may have a lower risk of death at 1 year (RR, 0.72; 95% CI, 0.60-0.87).^{29,30,32,33,41,42,44,45} Receipt of conventional therapy may also be associated with a higher likelihood of undergoing allo-HCT (RR, 2.28; 95% CI, 1.70-3.06; range, 6-60 months follow-up; low-certainty evidence).^{27,31,33,35,41,46} The very low certainty in evidence does not allow for definitive conclusions about other potential benefits.

Harms and burden

Recommendation 2a. When conventional induction and postremission therapy is compared with HMA- or LDAC-based monotherapy, conventional chemotherapy probably increases hospital length of stay (mean difference [MD], 11.7; 95% CI, 3.8-18.6; median, 48 months follow-up; moderate certainty in evidence),³⁹ multiple organ failure (RR, 2.33; 95% CI, 0.78-6.34; moderate certainty in evidence),³⁹ and sepsis (RR, 1.65; 95% CI, 1.05-2.59; moderate certainty in evidence).³⁹

Recommendation 2b. The evidence is very uncertain about the harms of conventional induction and postremission therapy compared with HMA- or LDAC-based therapy plus venetoclax. Very low certainty in evidence *suggests* that patients who receive conventional therapy may have a higher risk of death at 1 month (RR, 1.34; 95% CI, 0.61-2.95)^{31,40-42,45} and may have lower CR rates (RR, 0.95; 95% CI, 0.80-1.12; range, 18-80 months follow-up).^{27,28,30,31,36,38,40,42-46} Additionally, when conventional therapy is compared with HMA- or LDAC-based therapy plus venetoclax, conventional therapy may increase hospital length of stay (MD, 26 days; 95% CI, 19.6-32.4; 40 months follow-up; very low certainty in evidence).⁴²

Other EtD criteria and considerations

Regarding values and preferences, the panel reviewed evidence suggesting that patients may prioritize survival over severe toxicities, including prolonged hospital stays. However, the panel also recognized important uncertainty and variability in how patients trade off critical outcomes, such as remission, survival, QoL, and functional status. With regard to acceptability, the panel agreed that conventional induction and postremission therapy is frequently used, and therefore, it is probably acceptable to all relevant stakeholders. Additionally, and acknowledged by patient representative panelists, qualitative evidence indicates that patients value the controlled environment and convenience of inpatient care, although hospitalization might limit acceptability in some contexts.⁴⁸

The panel agreed that resource requirements vary widely, with costs differing across settings and between patients. This variability, along with the absence of a systematic search for cost or cost-effectiveness studies, limited the influence of this criterion on the recommendation. The panel also discussed the impact on health equity, recognizing that access to treatment may increase for some equity-deserving groups but decrease for others depending on the context; therefore, equity did not play an important role in these recommendations. However, the panel acknowledged that cost and access to care may affect the choice of the preferred treatment modality for an individual patient. Feasibility was similarly discussed, with the panel noting that conventional induction and postremission therapy is frequently implemented and has been a historic standard, suggesting feasibility in most health care systems. However, differences in infrastructure across regions could affect feasibility, particularly in those without capacity for comprehensive supportive care delivery that may lead to increased risk of complications and adverse outcomes.

Conclusions and research needs for this recommendation

The panel determined that conventional induction and postremission therapy may offer a net benefit over HMA or LDAC monotherapy for older adults with AML who are candidates for conventional therapy. This recommendation places value on the survival benefits (low certainty in evidence) and the higher CR rates (high certainty in evidence) associated with conventional therapy.

When comparing conventional induction and postremission therapy with HMA- or LDAC-based induction and postremission therapy in combination with venetoclax, the panel judged that the net benefit does not favor either conventional induction and postremission therapy or HMA- or LDAC-based combined with venetoclax. Very low-certainty evidence suggests that conventional therapy increases the probability of receiving allo-HCT and improves some outcomes such as death at 1-year follow-up but also may increase early mortality and toxicity risks. The fitness eligibility for conventional therapy for older adults with AML considering age and/or other health conditions remained poorly defined, substantially hindering generalization to patients with more advanced age (eg, ≥ 75 years and/or health impairments). Given the important uncertainty or variability in patient selection, patient values, and patient preferences, as well as the very low certainty in evidence for all critical outcomes, the panel emphasized the importance of shared decision-making and tailoring treatment to individual patient contexts.

Conventional induction and postremission therapy is widely used and probably acceptable to stakeholders when feasible, although variability in infrastructure may limit its implementation in some regions.

The panel highlighted the importance of future research focusing on HMA- or LDAC-based therapies combined with venetoclax. Objective and reproducible fitness eligibility for conventional induction and postremission therapy is necessary. Such studies should assess critical outcomes, including survival, QoL, remission rates, and toxicity. Additionally, research should address outcomes that are not being measured adequately, such as caregiver burden

and nonhematologic adverse events, to provide a more comprehensive understanding to harmonize with patient values and preferences. Finally, as use of venetoclax-based regimens is expanding to younger populations and those “fit” for conventional induction chemotherapy, results from studies enrolling these populations not included in the previous randomized trials that justified their use will be increasingly important.

The current evidence includes patients with favorable, intermediate, and adverse prognoses; however, subgroup-specific data were unavailable due to variability in how outcomes were reported in the studies and limited molecular data.³⁹ This context should be taken into consideration with treatment selection. Specifically, mutational data to refine risk groups may enhance prediction for response both to conventional induction and postremission therapy and in HMA- or LDAC-based approaches as well as survival.⁴⁹⁻⁵¹ The implications are substantial because patients with genetically defined favorable-risk AML may achieve long-term disease control without the need for allo-HCT. Conversely, select patients with AML and adverse-risk characteristics may not respond as well to conventional chemotherapy, and HMA- or LDAC-based therapies, either as monotherapies for select patient subsets (such as those with TP53 mutations) or combined with venetoclax may be more appropriate in those scenarios, followed by allo-HCT when feasible. Although study-level analyses suggest no important differences in outcomes between risk groups, the panel highlighted the need for further research.

Should older adults with newly diagnosed AML who achieve remission after at least 1 cycle of conventional induction therapy receive postremission therapy vs no additional therapy?

Recommendation 3

For older adults with AML who achieve remission after at least a single cycle of conventional induction therapy and who are not candidates for allo-HCT, the ASH guideline panel *recommends* postremission therapy over no additional therapy (strong recommendation based on low certainty in the evidence of effects $\oplus\oplus\bigcirc\bigcirc$).

Summary of the evidence

We updated the systematic review from the previous version of the guideline with the most current and relevant evidence to address this question. There were 4 RCTs identified.⁵²⁻⁵⁵ These studies provided evidence comparing no additional therapy or placebo vs postremission therapy with oral azacitidine,⁵⁵ subcutaneous/IV azacitidine,^{52,54} and gemtuzumab ozogamicin,⁵³ with a mean average duration of treatment of 9 months. The panel judged that the recommendations could also be applied to postremission cytarabine-based therapy and applied to both consolidation and maintenance regimens. The included RCTs enrolled 874 older adults, with a mean age of 68.16 years (SD, 5.1 years).⁵²⁻⁵⁵ Discontinuation criteria varied by drug and/or trial, including relapse or toxicity,⁵⁵ therapy for up to 54 months,⁵⁴ therapy until relapse or 12 months,⁵² and a maximum of 3 cycles for gemtuzumab ozogamicin.⁵³

Online supplement 1, appendix 10 presents the characteristics of all included studies.

The evidence profile and EtD framework for this recommendation are available online at <https://guidelines.ash.gradepro.org/profile/YVoywdz8jEs>.

Benefits

The panel judged that postremission therapy provides moderate benefit over no additional therapy. Postremission therapy vs no additional therapy probably reduces mortality at 12 months (RR, 0.67; 95% CI, 0.54-0.84; moderate certainty in evidence),^{52,53,55} and probably increases survival time, with a median of 24.7 months for patients receiving postremission therapy (95% CI, 18.7-30.5) vs 14.8 months for patients not receiving postremission therapy (95% CI, 11.7-17.6; moderate certainty in evidence).⁵⁵

Postremission therapy compared with no additional therapy probably increases disease-free survival at 12 months (RR, 1.61; 95% CI, 1.31-1.98; moderate certainty in evidence)^{52,55} and may increase the rate of disease-free survival over time (HR, 0.59; 95% CI, 0.42-0.84; mean, 51 months follow-up; low certainty in evidence).⁵² Postremission therapy probably decreases relapse at the longest follow-up (RR, 0.83; 95% CI, 0.70-0.98; mean, 51 months follow-up; moderate certainty in evidence),⁵²⁻⁵⁵ and probably increases time to relapse, with a median of 10.2 months (95% CI, 8.3-13.4) compared with 4.9 months (95% CI, 4.6-6.4; moderate certainty in evidence).⁵⁵

Moderate certainty in evidence from 2 studies^{54,55} suggests longer median relapse-free survival time among patients receiving postremission therapy compared with those not receiving additional therapy at 10.2 months (95% CI, 7.9-12.9) and 10.8 months (95% CI, 1.9-19.6), compared with those with no additional therapy at 4.8 months (95% CI, 4.6-6.4) and 6.0 months (95% CI, 0.2-11.7), respectively.

Low certainty in evidence suggests that postremission therapy compared with no additional therapy may reduce mortality at the longest follow-up (RR, 0.93; 95% CI, 0.86-1.02; mean, 58 months follow-up)^{53,55} and may also reduce the rate of mortality over time (HR, 0.74; 95% CI, 0.59-0.92; mean, 76 months follow-up; low certainty in evidence).^{52,55}

Harms and burden

The panel judged the harms to be trivial. Compared with no therapy, postremission therapy may increase relevant adverse events including grade 3/4 pneumonia (RR, 1.37; 95% CI, 0.54-3.46; low certainty in evidence).^{54,55} Other adverse events based on very low certainty in evidence suggest an increase in rates of hospitalization (RR, 1.08; 95% CI, 0.54-3.46).^{52,54,55} Additionally, the panel judged that gastrointestinal adverse events, particularly with oral therapy, would probably be important to patients; however, due to feasibility, these were not included in this systematic review.

Very low certainty in evidence suggests that patients receiving postremission therapy may experience a decrease in QoL compared with those receiving no additional therapy, with a mean change of -9.63 and 5.13, respectively.⁵⁴ QoL was assessed using the Quality of Life-E scale, in which higher scores indicate better QoL (measured on a scale from 0 to 100).⁵⁴ Additionally, very low certainty in evidence suggests that postremission therapy

may decrease functional status across multiple subdomains: physical function (MD, -5.71; 95% CI, -11.42 to 0), cognitive function (MD, -6.67; 95% CI, -20.67 to 7.33), and social function (MD, -13.57; 95% CI, -36.59 to 9.45), noting that these were from a single study examining subcutaneous/IV azacitidine as postremission therapy.⁵⁴

Other EtD criteria and considerations

Four studies evaluated the values and preferences of adult patients with AML.⁵⁶⁻⁵⁹ Across studies, patients place the highest value on attaining remission. There is variability in how patients placed value on survival and QoL. The panel judged that most older adults with newly diagnosed AML probably place a higher value on survival and preventing relapse (patients are considered to have achieved CR at this stage) over severe toxicities, particularly grade 3/4 pneumonia and hospitalizations, with probably no important uncertainty or variability in how patients trade off the critical outcomes. However, the panel acknowledged that some patients may value life-prolonging and QoL considerations equally or may trade length of life for QoL, or vice versa. Due to the large variability in treatment costs across settings, as well as the wide range of expenses incurred by patients within and between settings, cost-effectiveness was not a major factor influencing the recommendation.

Focusing on equity, a Cleveland Clinic study (1997-2008)⁶⁰ found that the proportion of patients receiving postremission therapy was similar (Black, 56%; White, 58%), but Black patients experienced a longer median time to therapy initiation (31 vs 23 days). At any given time point, Black patients were less likely to start therapy than White patients (HR, 0.25; $P = .016$). However, drug intensity and the median number of cycles were comparable between groups (2.36 vs 2.06), and overall survival did not differ significantly. The panel noted that, "some disadvantaged groups at higher risk of being lost to follow-up, whether that is due to economic, health literacy, or access to care reasons," and may face challenges in receiving adequate postremission therapy. The panel acknowledged that treatment access may vary among equity-deserving groups based on context and, as such, equity was not a decisive factor in these recommendations. The panel discussed that postremission therapy is commonly administered to patients with newly diagnosed AML in their first CR, suggesting that its implementation is likely feasible.

Postremission therapy is generally regarded as acceptable by all relevant stakeholders. However, the panel acknowledged that variability across different settings could affect the intervention's acceptability. There is an increasing number of postremission therapeutic options after conventional intensive chemotherapy, including more conventional consolidation chemotherapy, oral HMAs, reduced-intensity HCT and, more recently, targeted therapies. The included studies do not differentiate between the effects of postremission chemotherapy alone and those of combined consolidation chemotherapy and maintenance therapy. There are limited data on older patients with AML to provide guidance on the number of postremission conventional chemotherapy cycles that should be administered beyond 1 cycle. In addition, over two-thirds of patients included in these studies had intermediate-risk AML as assessed by cytogenetics. Thus, the data and conclusions may not be as applicable to patients with favorable- or adverse-risk cytogenetics. Although gemtuzumab ozogamicin was included in these analyses, the drug did not result in

significant improvement in survival or reduced relapses, and the panel does not recommend routine use of gemtuzumab ozogamicin alone as postremission therapy.⁵³

Conclusions and research needs for this recommendation

The panel recommends postremission therapy over no additional therapy for older adults with newly diagnosed AML who achieve remission after at least 1 cycle of conventional induction therapy (strong recommendation, low certainty in evidence). This recommendation reflects a paradigmatic situation, in which the panel placed a high value on preventing catastrophic outcomes, such as mortality and relapse, for which further treatment is less effective or may not be offered.⁶¹

Despite the overall low certainty in evidence, the panel considered the moderate-certainty evidence of moderate benefits, the low-certainty evidence of trivial harms, and their collective experience indicating that long-term survival is rare without postremission therapy. Given that most patients would prioritize survival and minimizing the risk of relapse, with probably no important uncertainty or variability in how they trade off the critical outcomes, the panel determined that the benefits outweigh the harms, favoring postremission therapy.

With improving prognostic tools, remission-inducing therapies, and supportive care, there is a steady increase in older patients with AML undergoing HCT.⁶² However, to date, there are no RCTs comparing HCT with postremission therapy, including chemotherapy, HMAs, or targeted approaches, in older patients with AML. For older patients ineligible for HCT,⁵⁵ and who did not receive any other postremission therapy such as conventional chemotherapy, oral azacitidine therapy is an appropriate maintenance strategy after remission is achieved with initial intensive chemotherapy. The panel underscores the need for high-certainty evidence from future research directly comparing standardized postremission therapy regimens. RCTs, comparative observational studies, and systematic reviews with individual patient data could address this gap, offering valuable insights to refine these recommendations in the future.

*Should older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy receive gemtuzumab ozogamicin, LDAC, azacitidine, 5-day decitabine, or 10-day decitabine as monotherapy or in combination?**

Recommendation 4a

For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy or for HMA-based combination therapy, the ASH guideline panel *suggests* azacitidine monotherapy over LDAC monotherapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Recommendation 4b

For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and

postremission therapy or for HMA-based combination therapy, the ASH guideline panel *suggests* 5-day decitabine monotherapy over 10-day decitabine monotherapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Recommendation 4c

For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* HMA in combination with venetoclax over HMA alone (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Recommendation 4d

For older adults with newly diagnosed AML considered appropriate for ALT but not for conventional induction and postremission therapy or for HMA-based combination therapy, the ASH guideline panel *suggests* LDAC in combination with venetoclax over LDAC monotherapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

*There is no evidence addressing the comparative effects of gemtuzumab ozogamicin with other regimens; therefore, the ASH guideline panel did not make a recommendation.

Summary of the evidence

We identified 47 studies to inform this question (30 RCTs^{34,26,63-91} and 17 NRSs^{28,30,33,36,43,44,82,92-101}). The panel considered only studies that addressed comparisons judged to be clinically relevant or commonly used in practice. As such, studies evaluating combinations of regimens not routinely used were not included in the formulation of the recommendations (Supplement 1, Appendix 5). Therefore, the evidence from 5 RCTs^{34,70,74,87,90} and 2 NRS^{82,99} informed these recommendations.

Recommendation 4a. We identified 2 RCTs that evaluated azacitidine monotherapy compared with LDAC monotherapy for older adults with newly diagnosed AML who were considered appropriate for ALT but ineligible for conventional induction and postremission therapy.^{34,74} The trials included 433 participants with a median age of 71 years (overall age range: 50-89 years), and 60.3% were male.^{34,74} Studies used different risk classification systems to stratify patients.

Recommendation 4b. We identified 1 RCT comparing 5-day decitabine monotherapy with 10-day decitabine monotherapy.⁸⁷ The trial included 71 participants, with a mean age of 76.1 years (SD, 10.4 years), with 53% of participants having adverse cytogenetic risk.⁸⁷

Recommendation 4c. We identified 1 RCT⁷⁰ and 2 NRSs⁹⁹ comparing azacitidine monotherapy with azacitidine in combination with venetoclax. The RCT included 431 participants, with a median

age of 76 years (range, 49-91).⁷⁰ Participants were classified based on cytogenetic risk, with 39.9% having intermediate risk and 37.1% having adverse risk.⁷⁰ The NRS included 397 participants, with a median age of 76.4 years (range, 49-91).⁹⁹ In this study, 61.7% had intermediate risk, whereas 40.3% had adverse risk.⁹⁹

Recommendation 4d. We identified 1 RCT comparing LDAC plus venetoclax with LDAC monotherapy for older adults with newly diagnosed AML who were considered appropriate for ALT but ineligible for conventional induction and postremission therapy.⁹⁰ The trial included 211 participants, with a median age of 76 years (range, 36-93), and 55.45% were male.⁹⁰ Participants were classified based on cytogenetic risk, with 1.9% favorable risk, 63 % intermediate risk, and 31.8% poor risk.⁹⁰

Online supplement 1, appendix 11 presents the characteristics of all included studies.

The evidence profile and EtD framework for recommendation 4a are available online at <https://guidelines.ash.gradepro.org/profile/IgxvewAlbMY>.

The evidence profile and EtD framework for recommendation 4b are available online at <https://guidelines.ash.gradepro.org/profile/EYZWiKcM14w>.

The evidence profile and EtD framework for recommendation 4c are available online at <https://guidelines.ash.gradepro.org/profile/Y0MRhThqnWw>.

The evidence profile and EtD framework for recommendation 4d are available online at <https://guidelines.ash.gradepro.org/profile/uRYdYNEeGOM>.

Benefits

Recommendation 4a. The evidence did not demonstrate any desirable effects of LDAC over azacitidine.^{34,74} Therefore, the panel judged the benefits to be trivial.

Recommendation 4b. When compared with 5-day decitabine, 10-day decitabine may have trivial to no effect on mortality at 12 months (RR, 0.99; 95% CI, 0.73-1.34; low-certainty evidence).⁸⁷ Very low-certainty evidence suggests that 10-day decitabine may increase CR at the longest follow-up (RR, 1.30; 95% CI, 0.12-13.69).⁸⁷ Similarly, very low-certainty evidence suggests that 10-day decitabine may reduce relapse at the longest follow-up (RR, 0.97; 95% CI, 0.57-1.65).⁸⁷ The panel considered the increase in CR and reduction in relapse as the key benefits of 10-day decitabine. Given the large uncertainty and the minimal differences, however, the panel judged these benefits to be trivial. HMA-based monotherapy, as opposed to combination therapy with venetoclax, may be equiefficacious with respect to survival in select subgroups, such as patients whose AML has a *TP53* mutation or in areas of the world in which venetoclax may not be available.

Recommendation 4c. When compared with HMA monotherapy, HMA in combination with venetoclax probably reduces mortality at 12 months (RR, 0.84; 95% CI, 0.71-1.01; moderate-certainty evidence) and reduces mortality rate over time (HR, 0.66; 95% CI, 0.52-0.84; high-certainty evidence).⁷⁰ Very low-certainty

evidence from 1 NRS study reported similar findings for mortality at 12 months.⁸²

Additionally, this combination probably increases CR at the longest follow-up (RR, 2.05; 95% CI, 1.40-2.99; moderate-certainty evidence),⁷⁰ and very low-certainty evidence from 1 NRS reported similar findings.⁹⁹ Moreover, it probably improves QoL (RR, 1.25; 95% CI, 0.96-1.62; moderate-certainty evidence).⁷⁰

Low-certainty evidence suggests that HMA in combination with venetoclax may reduce sepsis (RR, 0.68; 95% CI, 0.33-1.40).⁷⁰ Very low certainty in evidence suggests that HMA in combination with venetoclax may improve physical functioning at the longest follow-up (RR, 1.14; 95% CI, 0.82-1.59).⁷⁰ The panel judged the key benefits of HMA in combination with venetoclax to be the reduction in mortality rate over time (high-certainty evidence) and the likely increase in CR at the longest follow-up (moderate-certainty evidence). They also noted that a reduction in mortality at 12 months and an improvement in QoL are likely (moderate-certainty evidence), whereas low-certainty evidence suggests that there may be improvements in physical functioning and a reduction in severe toxicities, although the certainty of these effects is low. Given the moderate certainty in evidence for key benefits and the magnitude of effects on mortality rate over time and CR, the panel judged the desirable effects of HMA in combination with venetoclax to be moderate.

Although the panel planned to explore subgroup effects for patients with *TP53* mutation, this was not possible due to insufficient data. During discussions,¹⁰²⁻¹⁰⁴ the panel members referenced a study of a pooled analysis of 2 RCTs¹⁰⁴ on patients with *TP53* mutation comparing HMA in combination with venetoclax and HMA monotherapy. The study reported a complete remission composite rate of 41% for patients receiving HMA in combination with venetoclax, compared with 17% for patients receiving HMA monotherapy.¹⁰⁴ Despite these differences in response rates, the study showed similar duration of response (6.5 vs 6.7 months) and median overall survival (5.2 vs 4.9 months) between the 2 groups.¹⁰⁴ These outcomes did not appear to differ by *TP53* variant allelic frequency. Therefore, uncertainty remains regarding whether to use HMA in combination with venetoclax or HMA alone.

Recommendation 4d. When compared with LDAC monotherapy, LDAC in combination with venetoclax may reduce mortality at 30 days (RR, 0.78; 95% CI, 0.39-1.57; low-certainty evidence) and probably reduces the mortality rate over time (HR, 0.70; 95% CI, 0.50-0.98; moderate-certainty evidence).⁹⁰

Low-certainty evidence suggests that LDAC in combination with venetoclax may improve QoL at the longest follow-up (RR, 1.82; 95% CI, 1.04-3.21; 18 months follow-up) and may improve physical functioning at the same time point (RR, 1.99; 95% CI, 1.10-3.59).⁹⁰ Additionally, this combination may increase CR at the longest follow-up (RR, 3.80; 95% CI, 1.57-9.21; 24 months follow-up; low certainty in evidence).⁹⁰

LDAC in combination with venetoclax may have trivial to no effect on sepsis at the longest follow-up (RR, 0.96; 95% CI, 0.30-3.07; 24 months follow-up; low-certainty evidence) compared with LDAC monotherapy.⁹⁰

The panel judged the likely reduction in mortality rate over time (moderate-certainty evidence) to be the key benefit of LDAC in combination with venetoclax. They also acknowledged

improvements in physical functioning, QoL, and CR at the longest follow-up, although the certainty of these effects remains low. The panel judged these benefits to be small but important.

Harms and burden

Recommendation 4a. When compared with azacitidine, LDAC probably reduces CR at the longest follow-up (RR, 0.60; 95% CI, 0.29-1.24; moderate-certainty evidence).³⁴ Low-certainty evidence suggests that LDAC may increase mortality at 12 months (RR, 1.28; 95% CI, 1.06-1.55)³⁴ and may also increase the rate of mortality over time (HR, 1.45; 95% CI, 0.65-3.24).^{34,74} Additionally, LDAC may increase Centers for Disease Control (CDC) grade 3/4 pneumonia at the longest follow-up (RR, 1.54; 95% CI, 0.39-6.08; low-certainty evidence).³⁴

Although the certainty in the evidence is low to moderate, the panel considered these harms, particularly the increased mortality and severe toxicities, as important factors in decision-making.

Recommendation 4b. When compared with 5-day decitabine, 10-day decitabine may increase mortality at 30 days (RR, 2.60; 95% CI, 0.31-22.12; low-certainty evidence) and CDC grade 3/4 infections (RR, 2.08; 95% CI, 0.86-5.04; low-certainty evidence).⁸⁷

The panel discussed that other toxicities, such as treatment-related hospitalizations, were not captured in this systematic review due to feasibility but could still be clinically relevant. Given the important uncertainty in the evidence, the panel judged these harms as small but important.

Recommendation 4c. When compared with HMA monotherapy, the evidence does not demonstrate any undesirable effects of HMA in combination with venetoclax. However, the panel acknowledged that clinically relevant toxicities may not have been captured in this systematic review due to feasibility. These include prolonged myelosuppression, increased risk of infections, and TLS, which may lead to prolonged hospitalizations and intensive supportive care.

Given these considerations, the panel judged the harms to be small but important.

Recommendation 4d. The evidence does not demonstrate any undesirable effects of LDAC in combination with venetoclax compared with LDAC monotherapy. However, the panel recognized that some clinically relevant toxicities commonly associated with venetoclax-based regimens, such as prolonged myelosuppression, infections, and TLS, were not captured in the systematic review due to feasibility. Despite this, they emphasized that these toxicities are generally manageable with appropriate monitoring and supportive care. Additionally, the panel noted that the available evidence suggests trivial to no effect on sepsis.⁹⁰ Considering the large uncertainty in the evidence and the manageable nature of toxicities, the panel judged the harms to be trivial.

Other EtD criteria and considerations

The panel judged that most older adults with newly diagnosed AML eligible for ALT but ineligible for conventional induction and postremission therapy would likely prioritize mortality and CR over

other outcomes including severe toxicities. There is also variability in how patients placed value on QoL and physical functioning. However, the panel acknowledged that some patients may prioritize differently. Therefore, the panel judged that there is probably no important uncertainty or variability in how patients trade off the critical outcomes, in the setting of these antileukemic therapies.

Given the wide variation in treatment costs across different settings and the substantial differences in out-of-pocket expenses for patients within and across health care systems, cost and cost-effectiveness did not play a significant role in shaping the recommendations.

Regarding equity, access to treatment varies significantly among equity-deserving groups across different settings. Depending on regional health care resources and availability of treatment options, equity may be reduced in some groups and settings whereas improving in others. Therefore, this criterion did not have a significant impact on the recommendation.

Acceptability of LDAC compared with azacitidine is likely lower. Azacitidine is more frequently used and can be administered subcutaneously or IV, making it a convenient and acceptable option for both patients and providers. In contrast, LDAC requires more frequent dosing, which may be perceived as less convenient. Given these factors, the panel judged that LDAC is probably not acceptable to all stakeholders, although acceptability may vary depending on individual circumstances and health care system considerations. Similarly, this applies to 10-day decitabine vs 5-day decitabine. Although both require frequent administration, 10-day decitabine has a longer treatment duration, which may increase the treatment burden on patients, caregivers, and health care systems. Given this, the panel judged that 10-day decitabine is probably not acceptable to all stakeholders.

From a patient perspective, both HMA with venetoclax and HMA monotherapy are most commonly outpatient-based regimens, which aligns with the preferences of older adults seeking less burdensome therapy. From a clinician's perspective, HMA with venetoclax has become a widely used standard of care, further reinforcing its acceptability. However, the need for close monitoring of toxicities, such as prolonged myelosuppression and TLS, may require dose adjustments, treatment interruptions, additional supportive care, or hospitalizations. These factors could reduce acceptability in certain settings, particularly those with limited resources. Given these considerations, the panel judged that HMA in combination with venetoclax is probably acceptable to most stakeholders, although acceptability may vary depending on treatment burden and health care infrastructure. For patients who are frail or prefer to avoid additional risks of toxicities and hospitalizations, HMA monotherapy may be considered.

When discussing LDAC combined with venetoclax compared with LDAC monotherapy, the panel judged that LDAC in combination with venetoclax is probably acceptable for all stakeholders. Although LDAC requires subcutaneous or IV administration, venetoclax is an oral medication, which may increase its acceptability. Both regimens are delivered in an outpatient setting, making them more convenient for patients. Additionally, LDAC combined with venetoclax is already in clinical use, further reinforcing its acceptability among clinicians. The panel also noted that some patients enrolled in the randomized

trial had been treated previously with HMAs for myelodysplastic syndromes/neoplasms. However, this regimen requires frequent monitoring, supportive care, dose adjustments, and hospitalizations, which may limit acceptability in certain settings, especially for patients who prioritize minimizing treatment burden or have limited access to health care services.

The panel discussed that the feasibility of implementing LDAC compared with azacitidine varies across health care settings. Both treatments require frequent administration, but LDAC's twice-daily dosing over multiple days may pose a greater logistical burden, particularly for outpatient care or patients with limited health care access. However, in settings in which azacitidine is unavailable or cost-prohibitive, or with alternative dosing strategies, LDAC may be a more feasible alternative.

Similarly, the panel judged that feasibility varies across settings when comparing 10-day and 5-day decitabine. For 10-day vs 5-day decitabine, the longer treatment schedule of 10-day decitabine requires more frequent clinic visits, prolonged hospital stays, or increased outpatient support and monitoring. This could be a barrier in resource-limited settings in which health care infrastructure is constrained.

Conclusions and research needs for these recommendations

The ASH guideline panel suggests azacitidine over LDAC (4a), 5-day decitabine over 10-day decitabine (4b), HMA in combination with venetoclax over HMA monotherapy (4c), and LDAC in combination with venetoclax over LDAC monotherapy (4d) for older adults with newly diagnosed AML who are considered appropriate for ALT but not for conventional induction and postremission therapy. These recommendations reflect the panel's emphasis on benefits, the certainty in the evidence, and the balance of effects across treatment options.

Recommendation 4a. The panel placed a higher value on the absence of benefits and moderate harms of LDAC, including increased mortality and reduced CR (low-certainty evidence). Because most patients prioritize survival and remission, and acceptability of LDAC is likely lower than that of azacitidine, the balance of effects probably favors azacitidine over LDAC.

Recommendation 4b. The panel placed a higher value on the small but important harms of 10-day decitabine, including increased 30-day mortality and severe infections (low-certainty evidence). Given that 5-day decitabine offers a similar efficacy profile with a shorter treatment duration and potentially fewer toxicities, the balance of effects probably favors 5-day decitabine. Acceptability is probably lower for 10-day decitabine due to its longer schedule and uncertain benefits, whereas feasibility varies across settings.

Recommendation 4c. The panel placed a higher value on the benefits of HMA in combination with venetoclax, including a reduction in mortality rate over time and increased CR (moderate-certainty evidence), which the panel identified as key outcomes. Additionally, QoL probably improves with this regimen. Although no additional harms were identified, the panel acknowledged that

some toxicities, such as prolonged myelosuppression, infections, and TLS, may not have been captured in the systematic review. The balance of effects probably favors HMA with venetoclax over HMA monotherapy, with high acceptability but some feasibility challenges in resource-limited settings. Due to insufficient evidence for patients with *TP53*-mutated AML, the panel could not determine whether the effects of HMA in combination with venetoclax differ in this subgroup. The choice of HMA in combination with venetoclax or HMA monotherapy for patients with *TP53*-mutated AML should strongly consider the balance of risks and harms, patient preferences, alternative options, and the availability of clinical trials. Future research, including randomized trials and high-quality observational studies, is needed to evaluate whether treatment effects vary for patients with *TP53* mutations.

Recommendation 4d. The panel placed a higher value on the benefits of LDAC in combination with venetoclax, particularly the likely reduction in mortality rate over time, and improvements in QoL, physical functioning, and CR (low-certainty evidence). The panel judged these benefits as small but important. Because the evidence did not demonstrate additional harms and toxicities, such as myelosuppression, infections, and TLS, are clinically manageable, the balance of effects probably favors LDAC with venetoclax over LDAC monotherapy. Although acceptability is likely high, feasibility may vary across health care settings based on resource availability, monitoring capacity, and access to supportive care.

To date, a number of combination approaches have been evaluated in randomized trials. These include HMA or LDAC in combination with another agent (eg, immune checkpoint inhibitor, histone deacetylase inhibitor). The addition of any agent in combination with an HMA or LDAC, or in combination with venetoclax and an HMA or LDAC, may lead to harm, and should be explored within the context of a clinical trial.

A randomized phase 2 study assessing LDAC in combination with glasdegib compared with LDAC monotherapy suggests that the combination may increase survival.¹⁰⁵ However, future research with RCTs or high-quality NRSs should assess the efficacy and safety of this and other potential combinations.

The available evidence includes patients aged ≥ 55 years with favorable, intermediate, and adverse prognosis. However, data stratified by risk or age subgroups (<70 vs ≥ 70 years) were not available due to the way outcomes were reported in the studies. Although study-level analyses suggest no major differences in outcomes between these groups, the panel believes that further research is needed to clarify potential subgroup variations.

Future RCTs and comparative observational studies with proper subgroup analyses, as well as systematic reviews incorporating individual patient data, would help refine these recommendations.

Should older adults with newly diagnosed AML and actionable/targetable mutations considered appropriate for ALT, but not for conventional induction and postremission therapy, receive HMA monotherapy, HMA in combination with venetoclax, HMA in combination with venetoclax and an additional targeted therapy, HMA in combination with a targeted therapy, or targeted therapy alone?

Recommendation 5a

For older adults with newly diagnosed AML and an *IDH1* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* azacitidine in combination with ivosidenib over azacitidine monotherapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Recommendation 5b

For older adults with newly diagnosed AML and an *IDH1* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* using either azacitidine in combination with ivosidenib or an HMA in combination with venetoclax (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Recommendation 5c

For older adults with newly diagnosed AML and an *IDH2* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* azacitidine monotherapy over azacitidine in combination with enasidenib (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Recommendation 5d

For older adults with newly diagnosed AML and an *IDH2* mutation considered appropriate for ALT but not for conventional induction and postremission therapy, the ASH guideline panel *suggests* an HMA in combination with venetoclax over HMA in combination with enasidenib (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

ASH guideline panel will monitor the evidence and issue recommendations for additional targeted therapies for mutations in genes such as *TP53*, *KMT2A*, and *NPM1* when more evidence becomes available.

Summary of the evidence

We found 2 RCTs to inform this question.^{71,80}

For recommendation 5a, for patients with *IDH1*-mutated AML, we identified 1 RCT that compared ivosidenib combined with azacitidine with azacitidine alone.⁸⁰ This trial enrolled 146 older adults with a mean age of 75 years (SD, 8.2 years).⁸⁰ Among participants, 6.9% had favorable cytogenetics, 63% were classified as intermediate risk, 24.6% as adverse risk, and 5.5% had an unknown risk classification as defined by the National Comprehensive Cancer Network clinical practice guidelines in oncology for AML.⁸⁰ Because no study has prospectively compared targeted therapy with HMA therapy combined with venetoclax for

patients with an *IDH1* mutation, we used the same RCT⁸⁰ to indirectly inform recommendation 5b.

For recommendation 5c, for patients with *IDH2*-mutated AML, we identified 1 RCT comparing enasidenib combined with azacitidine with azacitidine alone.⁷¹ This RCT enrolled 101 older adults with a mean age of 75 years (SD, 5.3 years).⁷¹ Among participants, 8% had favorable cytogenetics, 64% were classified as intermediate risk, and 28% as adverse risk according to the European LeukemiaNet (ELN) 2017 classification.^{71,106} The same RCT⁷¹ indirectly informed recommendation 5d, because no study has prospectively compared targeted therapy with an HMA combined with venetoclax for *IDH2* mutations. HMA-based monotherapy, as opposed to combination therapy with venetoclax, may be equivocal with respect to survival in select subgroups, such as patients whose AML has a *TP53* mutation or in areas of the world in which venetoclax may not be available.

We did not identify randomized studies evaluating triplet therapy composed of an HMA, venetoclax, and an US Food and Drug Administration-approved targeted therapy in our systematic review. Additionally, no randomized studies addressed US Food and Drug Administration-approved targeted therapies for the other mutations of interest (*TP53*, *KMT2A*, and *NPM1*).

Online supplement 1, appendix 12 presents the characteristics of all included studies.

The evidence profile and EtD framework for recommendation 5a are available online at <https://guidelines.ash.gradepro.org/profile/rRzm23TIVYk>.

The evidence profile and EtD framework for recommendation 5b are available online at <https://guidelines.ash.gradepro.org/profile/Euwq4iSnkNA>.

The evidence profile and EtD framework for recommendation 5c are available online at https://guidelines.ash.gradepro.org/profile/QJ_J4UWgvMk.

The evidence profile and EtD framework for recommendation 5d are available online at <https://guidelines.ash.gradepro.org/profile/TIVNQM-Rh2w>.

Benefits

Recommendation 5a. There is moderate-certainty evidence suggesting that azacitidine combined with ivosidenib, when compared with azacitidine alone, probably increases CR or CR with incomplete hematologic recovery (CRI) at the longest follow-up of the included study (RR, 3.34; 95% CI, 1.91-5.85; median, 15 months follow-up).⁸⁰ This combination may also reduce mortality at 12 months (RR, 0.64; 95% CI, 0.46-0.88; low-certainty evidence) and may further decrease the rate of mortality over time (HR, 0.44; 95% CI, 0.27-0.71; median, 15 months follow-up; very low-certainty evidence).⁸⁰ It may also increase survival time at the longest follow-up (36 months), with a median of 24 months compared with 7.9 months (very low-certainty evidence).⁸⁰

Additionally, azacitidine combined with ivosidenib may improve QoL at the longest follow-up (19 cycles), as most subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 scale remained stable or improved from

baseline starting at cycle 5 through cycle 19, whereas no such improvement was observed in the azacitidine monotherapy group (low-certainty evidence).⁸⁰ This combination may also reduce recurrence at the longest follow-up (median, 15 months), with a longer median duration of response of 22 months (95% CI, 13 to not estimable) compared with 9.2 months (95% CI, 6.6-14.1; low certainty in evidence).⁸⁰

Regarding safety outcomes, this combination may reduce severe toxicity, including CDC grade 3/4 pneumonia (RR, 0.78; 95% CI, 0.45-1.38; median, 15 months follow-up; low-certainty evidence) and CDC grade 3/4 infections at the longest follow-up (RR, 70; 95% CI, 0.40-1.24; median, 15 months follow-up; low-certainty evidence).⁸⁰

Although there is large uncertainty in the evidence, the panel judged the benefits of azacitidine in combination with ivosidenib, including a reduction in mortality at 12 months and the longest follow-up, as well as a probable increase in CR/CRi at the longest follow-up, to be of moderate magnitude.

Recommendation 5b. The evidence presented to inform recommendation 5a also informed recommendation 5b on the use of HMA in combination with ivosidenib or venetoclax; however, for this recommendation, the evidence was further downgraded by 1 level due to indirectness, because the comparator in this question was HMA combined with venetoclax, whereas the available evidence was derived from comparing azacitidine alone. When compared with HMA combined with venetoclax, azacitidine in combination with ivosidenib may increase CR/CRi at the longest follow-up (low certainty in evidence).⁸⁰ Very low-certainty evidence suggests that when azacitidine is combined with ivosidenib, it may reduce mortality at 12 months, decrease the rate of mortality over time, and increase survival.⁸⁰ Additionally, very low-certainty evidence suggests that azacitidine combined with ivosidenib may improve QoL, may reduce AML recurrence, and may lower the risk of severe toxicities, such as CDC grade 3/4 pneumonia and infections, although uncertainty remains.⁸⁰

To further inform this question, we conducted a survey to systematically collect the experience of the panel members in using (any) targeted therapy (supplement 1, appendix 16). The results indicate that most use HMA plus venetoclax, followed by triple therapy (HMA plus venetoclax plus targeted therapy) or HMA plus targeted therapy in their practices. Some panelists also use targeted therapy alone. Based on the outcomes observed in their practices, there is little to no difference in CR/CRi, mortality, or survival between patients receiving HMA plus venetoclax compared with those receiving HMA plus targeted therapy.

The panel discussed that, according to the indirect evidence, the key benefits of HMA in combination with targeted therapy may include a reduction in mortality and an increase in survival. However, the panel was very uncertain about these effects.

After considering all aforementioned factors, the panel judged the benefits of HMA in combination with ivosidenib compared with HMA in combination with venetoclax to be trivial.

Recommendation 5c. The evidence from 1 RCT comparing enasidenib combined with azacitidine with azacitidine alone,

suggests that azacitidine in combination with enasidenib probably increases CR/CRi at the longest follow-up (RR, 2.09; 95% CI, 1.21-3.61; median, 15 months follow-up; moderate-certainty evidence).⁷¹ This combination may reduce mortality at 12 months (RR, 0.94; 95% CI, 0.48-1.82; low-certainty evidence) and may increase survival time at the longest follow-up (42 months), with a median of 22 (95% CI, 14.6-37.2) compared with 18.6 months (95% CI, 11.9-25.7; low-certainty evidence).⁷¹ However, it may have trivial to no effect on the rate of mortality over time, although there is uncertainty (HR, 0.99; 95% CI, 0.52-1.87; very low-certainty evidence).⁷¹ Additionally, azacitidine combined with enasidenib may reduce severe toxicity, including CDC grade 3/4 pneumonia at the longest follow-up (20 fewer per 1000 (95% CI, 120 fewer to 80 more; low-certainty evidence).⁷¹ The panel placed a higher value on mortality outcomes, particularly on the rate of mortality over time; therefore, the panel judged the benefits of azacitidine in combination with enasidenib as trivial.

Recommendation 5d. No direct evidence was found comparing HMA combined with targeted therapy with HMA combined with venetoclax for *IDH2* mutations. Therefore, this recommendation on the comparison of HMA combined with enasidenib vs HMA combined with venetoclax was indirectly informed by the same evidence used in recommendation 5c. Consequently, we further downgraded the evidence due to indirectness.

Low-certainty evidence suggests that azacitidine in combination with enasidenib may increase CR/CRi at the longest follow-up.⁷¹ Very low-certainty evidence suggests that this combination may reduce mortality at 12 months, may increase survival time, and may have little to no effect on the rate of mortality over time.⁷¹ The combination may reduce CDC grade 3/4 pneumonia; however, we are very uncertain about this effect.⁷¹

To inform this decision, the panel used the evidence from the survey on the experience of the panel members in using targeted therapy (supplement 1, appendix 16), as described in recommendation 5b. The panel discussed that the benefits of HMA in combination with enasidenib were likely smaller when compared with those of azacitidine in combination with venetoclax (the comparator in the indirect evidence). This is supported by evidence that azacitidine in combination with venetoclax (the comparator in this question) provides moderate benefits compared with azacitidine monotherapy (the comparator in the indirect evidence), as discussed for recommendation 4c. Based on these considerations, the panel judged the benefits of HMA in combination with enasidenib compared with HMA in combination with venetoclax to be trivial.

Harms and burden

Recommendation 5a. When compared with azacitidine monotherapy, azacitidine in combination with ivosidenib may have trivial to no effect on severe toxicity, particularly differentiation syndrome (low-certainty evidence).⁸⁰ The panel acknowledged, based on their clinical experience, that there may be additional severe toxicities not included in this systematic review due to feasibility. Given the uncertainty in the evidence, the panel judged these harms as small but important.

Recommendation 5b. The evidence on the undesirable effects of azacitidine in combination with ivosidenib compared with HMA in combination with venetoclax is indirect and of very low certainty. It suggests that azacitidine combined with ivosidenib may have trivial to no effect on differentiation syndrome (very low-certainty evidence).⁸⁰ The panel discussed that differentiation syndrome, although serious, is typically manageable, whereas HMA combined with venetoclax carries a risk of TLS, which can also be mitigated with prophylaxis and close monitoring. Both regimens share common toxicities such as myelosuppression, fatigue, and infections, and the overall toxicity burden is unlikely to differ meaningfully when appropriate mitigation strategies are in place. Given the very low certainty in the evidence, the panel judged the harms to be trivial.

Recommendation 5c. The estimates about the potential harms of azacitidine in combination with enasidenib, when compared with azacitidine monotherapy, suggest that the combination may increase mortality at the longest follow-up and may also increase the risk of severe toxicity differentiation syndrome (low-certainty evidence).⁷¹ Additionally, it may have trivial to no effect on the likelihood of receiving a transplant (low-certainty evidence).⁷¹ The panel recognized that additional severe toxicities may not have been captured in the systematic review due to feasibility. The panel also recognized that treatment with enasidenib can be associated with the development of differentiation syndrome. The panel discussed that differentiation syndrome, although serious, is typically manageable. Both regimens share common toxicities such as myelosuppression, fatigue, and infections, and the overall toxicity burden is unlikely to differ meaningfully when appropriate mitigation strategies are in place. Given the very low certainty in the evidence, the panel judged the harms to be trivial. Given the uncertainty in the evidence and the panel's experience, they judged these harms as small but important.

Recommendation 5d. The undesirable effects of azacitidine in combination with enasidenib compared with HMA in combination with venetoclax were assessed using indirect evidence. Very low certainty in evidence suggests that azacitidine with enasidenib may increase mortality at the longest follow-up and may increase the risk of differentiation syndrome.⁷¹ The panel discussed that differentiation syndrome, although serious, is typically manageable, whereas HMA combined with venetoclax carries a risk of TLS, which can also be mitigated with prophylaxis and close monitoring. Both regimens share common toxicities such as myelosuppression, fatigue, and infections, and the overall toxicity burden is unlikely to differ meaningfully when appropriate mitigation strategies are in place. Given the very low certainty in the evidence, the panel judged the harms to be trivial.

Other EtD criteria and considerations

Regarding values and preferences, the panel judged that most older adults with newly diagnosed AML and an actionable *IDH1* or *IDH2* mutation would probably prioritize reducing mortality and increasing CR/CRi over concerns about severe toxicity. Additionally, as oral or outpatient-based therapies, they do not require extensive hospitalization, aligning with the priorities of older adults and those seeking less burdensome treatment options. Although some individual variability exists, the panel agreed that there is probably no important uncertainty or variability in how patients trade off these critical outcomes.

Due to large variability in treatment costs across settings and significant differences in patient-incurred expenses within and between health care systems, cost-effectiveness was difficult to assess and thus was not a major factor influencing the recommendations. Regarding equity, access to treatment may be improved for some equity-deserving groups but reduced for others, depending on regional health care resources and access to molecular diagnostics. Given this variability in access to molecular diagnostics and targeted therapies, equity was not a decisive factor in the recommendations.

In terms of acceptability, ivosidenib is generally acceptable to patients due its oral administration. However, concerns about adverse effects, financial burden, and logistical barriers, such as access to mutation testing and regular monitoring, may limit its acceptability in certain settings. Despite these challenges, the panel judged that it is still probably acceptable overall. Similarly, the oral administration of enasidenib may improve its acceptability among patients. However, from a clinician's perspective, although azacitidine in combination with enasidenib is a treatment option for patients with *IDH2* mutations, its use is less common outside specialized centers. This lower exposure and familiarity with targeted therapies may reduce its acceptability among clinicians. Therefore, when compared with azacitidine alone, the acceptability of azacitidine combined with enasidenib may vary, as its relative novelty and monitoring requirements could pose challenges. Moreover, when compared with azacitidine combined with venetoclax, the acceptability of azacitidine with enasidenib is probably lower. Azacitidine with venetoclax is widely used in clinical practice and has a broader evidence base supporting its efficacy, particularly when compared with azacitidine monotherapy, contributing to a higher level of confidence in its administration and toxicity management.

Feasibility was similarly discussed, with the panel noting that access to *IDH* mutation testing, monitoring requirements, and drug availability are key factors influencing the feasibility of implementing ivosidenib and enasidenib. Given these considerations, the panel judged that feasibility varies depending on health care infrastructure and access to supportive care. The panel also acknowledged that mutation testing may return after a treatment regimen, such as venetoclax combined with an HMA, has already been started. In these scenarios, there are no data supporting switching regimens to a more targeted treatment approach.

Considerations for implementing the use of targeted therapies for patients with *IDH1* and *IDH2* mutations include provider education and training to manage adverse effects. Patient education is equally important to promote informed decision-making adherence to therapy, and timely recognition of side effects. A robust supply chain and equitable distribution are necessary to prevent access disparities, especially in rural or resource-constrained settings. Financial assistance programs or reimbursement strategies may also be required to address the high cost of therapy and ensure affordability.

Conclusions and research needs for these recommendations

The panel suggests azacitidine in combination with ivosidenib over azacitidine monotherapy (5a) and either HMA with ivosidenib or HMA with venetoclax (5b) for older adults with newly diagnosed

AML and an *IDH1* mutation who are ineligible for conventional induction and postremission therapy. These recommendations reflect the panel's emphasis on the benefits of treatment and the uncertainty in the evidence.

- Recommendation 5a. The panel placed a higher value on the benefits of azacitidine with ivosidenib and the lack of important variability in patient values and preferences. Therefore, the balance of effects probably favors azacitidine with ivosidenib over azacitidine monotherapy.
- Recommendation 5b. The panel placed a higher value on the very low certainty in the evidence regarding the relative effects of the options, which was supported by their clinical experience. Therefore, the panel concluded that the balance of effects does not favor either HMA in combination with ivosidenib or HMA in combination with venetoclax. In addition, although both HMA combined with ivosidenib and HMA combined with venetoclax are appropriate treatment options, the toxicity profile in relation to the patient's comorbidities and functional status may help guide the choice between them.

For older adults with newly diagnosed AML and an *IDH2* mutation who are ineligible for conventional induction and postremission therapy, the panel suggests azacitidine monotherapy over azacitidine with enasidenib (5c) and HMA with venetoclax over azacitidine with enasidenib (5d).

- Recommendation 5c. The panel placed a higher value on feasibility, resource use, and acceptability concerns, given the low-certainty evidence supporting trivial benefits of azacitidine in combination with enasidenib compared with azacitidine monotherapy. As a result, the balance of the effects does not favor either azacitidine in combination with enasidenib or azacitidine monotherapy. Although CR/CRi may increase, and mortality at 12 months may be reduced, concerns about increased severe toxicities and trivial long-term mortality effects did not support either regimen.
- Recommendation 5d. This recommendation places a high value on the trivial differences in the net benefits, the very low certainty in the evidence, and the greater clinical experience and acceptability of azacitidine with venetoclax. Although patient values and preferences were expected to have no important variability, the trivial differences in the outcomes and the uncertainty of the benefits made it unlikely that the broader evidence supporting HMA in combination with venetoclax would support either regimen. As a result, values and preferences have little to no bearing in this recommendation. Although the balance of the effects favors neither the intervention nor the comparison, the panel conditionally *suggests* HMA with venetoclax over HMA with enasidenib, placing a higher value on the greater clinical experience and acceptability of HMA in combination with venetoclax.

The panel acknowledges the possible added value of triplet therapies (HMA combined with venetoclax and combined with targeted therapy). However, because clinical trials are still ongoing, it is not yet possible to make definitive treatment recommendations at this time.

This section specifically discussed *IDH1* and *IDH2* mutations. However, other molecular subgroups may also benefit from

targeted therapies incorporated into treatment regimens for newly diagnosed AML in older adults, such as *NPM1*-mutated AML or *KMT2A*-rearranged AML, for which emerging therapies such as menin inhibitors are currently under clinical investigation in this setting.

The panel emphasizes the need for high-certainty evidence to clarify the comparative effectiveness and safety of these regimens. Future RCTs (eg, comparing HMA combined with venetoclax with HMA combined with ivosidenib), comparative observational studies, and systematic reviews incorporating individual patient data would help better define the benefits, risks, and patient-relevant trade-offs between these treatment options. Specifically, further research should evaluate long-term survival, remission duration, QoL, and the incidence and management of key toxicities, such as differentiation syndrome and myelosuppression.

Given the clinical perspective of the guidelines and the goal of ensuring applicability across diverse health care settings, secondary factors such as cost, cost-effectiveness, and equity did not play a decisive role in these recommendations.

Should older adults with AML who received HMA- or LDAC-based induction and postremission therapy and who achieved a response continue therapy indefinitely until progression or unacceptable toxicity or stop therapy after a finite number of cycles?

Recommendation 6

For older adults with AML who achieve a response after receiving HMA- or LDAC-based induction and postremission therapy, the ASH guideline panel *suggests* continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy after a finite number of cycles (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence

This systematic review updates a previous recommendation, incorporating evidence from 2 observational studies with a total of 70 older adults.^{107,108} Continuous therapy regimens included LDAC plus venetoclax, azacitidine plus venetoclax or decitabine plus venetoclax (median duration: 28 months),¹⁰⁷ and azacitidine or decitabine monotherapy (median duration: 17 months).¹⁰⁸ Finite therapy regimens involved LDAC plus venetoclax or decitabine plus venetoclax (median duration: 17 months)¹⁰⁷ and azacitidine or decitabine monotherapy (median duration: 3 months).¹⁰⁸ In the included studies, although they used different risk classification systems, most participants had intermediate or unfavorable cytogenetic risk.^{107,108} Male participants represented 55.2% of the population.^{107,108} Online supplement 1, appendix 13 presents the characteristics of all included studies.

The evidence profile and EtD framework for this recommendation are available online at https://guidelines.ash.gradepro.org/profile/q_QfbXQWInk.

Benefits

The panel judged that continuing therapy indefinitely until progression or unacceptable toxicity, compared with stopping therapy after a finite number of cycles, provides a benefit.

When compared with stopping therapy, very low certainty in evidence suggests that continuing therapy with azacitidine or decitabine may reduce mortality at 12 months (odds ratio, 0.03; 95% CI, 0.02-3.67; very low certainty in evidence).¹⁰⁸ The panel did express concerns about the applicability of this study to real-world treatment recommendations, because the treatment given in the intervention group (6+3 cycles of HMA monotherapy) is not generally used in clinical practice. Additionally, the evidence suggests that continuing therapy with azacitidine or decitabine may increase survival time at the longest follow-up (MD, 3.45; 95% CI, 1.36-5.54; 15 months follow-up; very low certainty in evidence).¹⁰⁸

Panelists referenced the VIALE-A study⁷⁰ during discussions to contextualize current clinical practice. Clinical experts on the panel unanimously agree on the benefits of postremission therapy until progression or toxicity, highlighting that, in their experience, discontinuing treatment often results in poor outcomes. The VIALE-A trial evidence supporting the use of HMA plus venetoclax for older adults with AML led to the widespread adoption of indefinite therapy per the study protocol but did not specifically address the utility or optimal duration of postremission HMA plus venetoclax therapy.⁷⁰ The panel experts have cared for numerous patients who have been on HMA plus venetoclax for extended periods of time and are able to tolerate ongoing therapy with appropriate dose reductions or cycle adjustments. Although the panel experts acknowledge that there appear to be some patients who have therapy stopped for toxicities and appear to maintain a durable response off therapy and acknowledge increasing reports of selected patients with durable relapse-free survival after discontinuation of HMA plus venetoclax after 12 months, it is not possible to identify who those patients will be prospectively. The members of the guideline panel strongly recommend following published guidelines for dose modification to allow patients to safely remain on indefinite therapy. This view aligns with that of patient panel members, who emphasized that ongoing therapy is acceptable as long as side effects remain mild and it allows them to maintain QoL and continue daily activities.

Due to very low certainty, the evidence does not support definitive conclusions about other benefits. Despite this uncertainty, the panel judged the benefits to be moderate, citing the uniformity of clinical practice among clinician panel members and their shared experience.

Harms and burden

When comparing HMA- or LDAC-based induction and postremission therapy given indefinitely until progression or unacceptable toxicity over stopping therapy after a finite number of cycles, the panel identified severe toxicities as the primary harm of continuing therapy, in those who have had a response, until progression or toxicity. Although these outcomes were not reported in the included studies, clinical experts agreed that most patients experience mild but manageable toxicities. They emphasized that these toxicities are often cumulative, frequently necessitating dose reductions, particularly with azacitidine or decitabine combined with venetoclax. The patient partner's experience supported this perspective, because they maintained a good QoL with mild toxicities. However, the panel acknowledged that individual patients may perceive and tolerate toxicities related to therapy differently. In addition, a small number of patients will experience severe toxicities that prohibit or delay further therapy.

Because of the important uncertainty in the evidence about the key harms and the likely variability in how patients feel about toxicities, the panel judged these harms as small but important.

Other EtD criteria and considerations

Considering the variability in values and preferences reported in the evidence,⁵⁶⁻⁵⁹ as previously described in recommendation 3, and the clinical experience of the panel members, the panel judged that there is probably no important uncertainty or variability in how patients trade off the critical outcomes. Based on shared clinical experience, the panel believes that most patients probably place a higher value on survival over the risk of severe toxicities, although the panel acknowledged that some patients may have different priorities and goals of care. Taking this into consideration, along with the overall very low certainty in the evidence, the panel concluded that the balance of effects likely favors therapy until progression or unacceptable toxicity over stopping therapy after a finite number of cycles.

The panel recognized that resource requirements and the costs of treatment vary widely across settings and patient populations. Therefore, there is large variability in cost-effectiveness within and across health care settings. The panel evaluated the impact on health equity, acknowledging that access to treatment could improve for some equity-deserving groups but worsen for others, depending on the context. However, studies addressing health equity in the context of finite vs indefinite therapy using HMA plus venetoclax have not been performed. As a result, equity did not play a decisive role in these recommendations. The main limitation to the acceptability of therapy until progression or toxicity is the need for hospitalization or frequent travel to outpatient clinics for treatment and supportive care. Although such resource use is common among newly diagnosed patients with AML who received HMA- or LDAC-based induction and postremission therapy, the financial burden to patients and payers with respect to actual quality-adjusted life-years gained from this treatment will need to be considered with more in-depth studies and analyses to assist decision-making in the long term. The panel noted that therapy until progression or toxicity is feasible to implement, because it is the preferred and most commonly used approach for older adults with AML.

Conclusions and research needs for this recommendation

The guideline panel determined that continuing therapy indefinitely until progression or unacceptable toxicity may offer a net benefit over stopping therapy after a finite number of cycles for older adults with AML who achieve a response after receiving HMA- or LDAC-based induction and postremission therapy. This recommendation places a high weight on the benefits. It takes into consideration the very low certainty in evidence of moderate benefits, very low certainty of small but important harms, the collective experience of the guideline panel, and the uniformity of clinical practice among clinician experts who recommend continuing therapy until progression/toxicity. Because most patients are likely to place a higher value on the benefits of therapy compared with the harms with probably no important uncertainty and variability in how they trade off the outcomes, the balance of effects probably favors therapy until progression/toxicity over stopping therapy.

Considering the clinical focus of the guidelines and the goal of ensuring applicability across diverse settings, secondary factors such as cost-effectiveness, equity, acceptability, and feasibility had limited influence on this recommendation. The evidence included regimens that may have limited applicability, because they are not commonly used in current practice. The panel highlighted the need for further research on methods to identify patients receiving HMA- or LDAC-based regimens for whom therapy can be safely stopped and acknowledged that there are currently prospective clinical trials underway examining this clinical question.^{109,110} RCTs, comparative observational studies with moderate or high-certainty evidence, and systematic reviews with individual patient data could address this gap and guide future updates to the recommendations.

Should older adults with newly diagnosed AML who have an FLT3 mutation be offered an FLT3 inhibitor in combination with ALT vs ALT alone?

Recommendation 7

For older adults with newly diagnosed AML who have an *FLT3* mutation, the ASH guideline panel *suggests* ALT in combination with an *FLT3* inhibitor over ALT alone (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remark:

- This recommendation applies primarily to patients receiving conventional induction and postremission therapy, and may or may not apply to patients receiving HMA or LDAC plus venetoclax, or HMA or LDAC monotherapy. The panel is less confident about the addition of *FLT3* inhibitors resulting in net benefit for patients who receive HMA or LDAC plus venetoclax, or HMA or LDAC monotherapy.

Summary of the evidence

Five studies addressed this question, including 3 RCTs^{69,89,111} and 2 NRSs,^{112,113} with a total of 729 participants. In the first RCT ($n = 216$ participants met inclusion criteria for this question), quizartinib was administered at 40 mg orally once daily for 14 days during conventional 7+3 induction chemotherapy and each high-dose cytarabine postremission cycle, followed by maintenance therapy at 30 to 60 mg orally once daily for up to 36 months.¹¹¹ In the second RCT ($n = 27$ participants), quizartinib was combined with LDAC and given at a dose of 90 mg or 60 mg orally once daily for 21 days in each cycle.⁶⁹ A third RCT (123 participants) compared azacitidine combined with gilteritinib vs azacitidine alone for patients with AML with *FLT3* internal tandem duplication (ITD) or *FLT3* tyrosine kinase domain (TKD) point mutations.⁸⁹ Gilteritinib was administered at 120 mg orally once daily throughout each 28-day cycle, with treatment continuing until loss of benefit, toxicity, or until discontinuation criteria were met.⁸⁹

One NRS, involving 191 participants with AML with *FLT3*-ITD, compared conventional 7+3 induction chemotherapy plus midostaurin with 7+3 chemotherapy alone.¹¹³ Midostaurin was administered at 50 mg orally twice daily from day 8 until 48 hours before the start of the next cycle of therapy.¹¹³ All patients were intended to receive allo-HCT in remission; those who were not

candidates for allo-HCT received up to 4 cycles of consolidation with high dose cytarabine in combination with midostaurin (starting on day 6 until 48 hours before the start of the next cycle of therapy).¹¹³ Maintenance therapy with midostaurin was intended for all patients at the same dose for 12 months.¹¹³ The second NRS was a retrospective analysis of 395 participants with *FLT3*-ITD, assessing the impact of *FLT3* inhibitors in clinical outcomes.¹¹² This analysis included 172 participants with AML with *FLT3*-ITD who received lower-intensity therapy (HMA or LDAC) with or without an *FLT3* inhibitor.¹¹² The *FLT3* inhibitors included quizartinib, sorafenib, midostaurin, or axitinib.¹¹²

The RATIFY RCT, which evaluated the addition of midostaurin to conventional 7+3 induction chemotherapy to conventional induction chemotherapy alone, was not included, because this trial did not enroll older adults.¹¹⁴ Furthermore, the systematic review did not identify any comparative studies assessing the benefit of the addition of *FLT3* inhibitors to venetoclax-based combinations.

The mean average age across included studies was 65.2 ± 10.3 years, and the mean percentage of male participants was 52%.^{69,89,111-113} Among 729 included participants, 95.9% had an *FLT3*-ITD mutation, 2.9% had *FLT3*-TKD mutation, and 1.2% had both mutations.^{69,89,111-113}

Online supplement 1, appendix 14, presents the characteristics of all included studies.

The evidence profile and EtD framework for this recommendation are available online at <https://guidelines.ash.gradepro.org/profile/SHuDIGR2k-Q>.

Benefits

When compared with conventional 7+3 induction chemotherapy alone, the addition of quizartinib to 7+3 for patients with AML with *FLT3*-ITD may reduce mortality at 12 months (RR, 0.88; 95% CI, 0.63-1.21; low-certainty evidence) and the rate of mortality over time (HR, 0.91; 95% CI, 0.66-1.26; 39 months follow-up; low-certainty evidence).¹¹¹ It may also increase survival time at the longest follow-up (39 months), with a median of 17.5 months compared with 14.2 months (low-certainty evidence).¹¹¹ Benefits from the addition of quizartinib to conventional induction therapy appeared lower in subgroup analyses that included older adults.

When compared with conventional 7+3 induction chemotherapy alone, very low-certainty evidence suggests that the addition of midostaurin to conventional 7+3 induction chemotherapy for patients with AML with *FLT3*-ITD may decrease mortality at 12 months (RR, 0.60; 95% CI, 0.46-0.78) and may reduce the rate of mortality over time (HR, 0.47; 95% CI, 0.33-0.67; 40 months follow-up).¹¹³ It may also increase survival time at the longest follow-up, with a median of 22.7 months compared with 8.4 months (very low-certainty evidence).¹¹³ Additionally, midostaurin in combination with conventional 7+3 induction chemotherapy, when compared with conventional 7+3 induction chemotherapy alone, may increase CR/CRi at the longest follow-up (RR, 1.33; 95% CI, 1.03-1.71; 96 months follow-up; very low-certainty evidence) and may increase the proportion of patients receiving allogeneic transplants (RR, 3.62; 95% CI, 1.58-8.32; 96 months follow-up; very low-certainty evidence).¹¹³

When compared with azacitidine alone, the combination of gilteritinib and azacitidine for patients with *FLT3*-ITD or *FLT3*-TKD

mutations probably results in no difference in mortality at the longest follow-up (RR, 1.00; 95% CI, 0.82-1.47; 30 months follow-up; moderate-certainty evidence).⁸⁹ However, it may reduce mortality at 1 month (RR, 0.79; 95% CI, 0.28-2.22; low-certainty evidence).⁸⁹ This combination, when compared with azacitidine monotherapy, may also increase CR/CRi at the longest follow-up (RR, 1.88; 95% CI, 1.12-3.17; 10 months follow-up; low-certainty evidence) and may increase the duration of CR, because the median duration was not reached in the combination group, compared with 8.57 months in those receiving azacitidine alone.⁸⁹ Additionally, gilteritinib in combination with azacitidine may reduce the incidence of sepsis at the longest follow-up (RR, 0.52; 95% CI, 0.15-1.82; 10 months follow-up; low-certainty evidence).⁸⁹

When compared with LDAC alone, quizartinib in combination with LDAC for patients with AML with *FLT3*-ITD may reduce mortality at the longest follow-up (RR, 0.99; 95% CI, 0.85-1.15; 30 months follow-up; low-certainty evidence).⁶⁹ Very low certainty in evidence suggests that mortality may also decrease at 1 month; because no events were reported in the group receiving quizartinib, the relative effect is not estimable, but the absolute effect suggests a reduction in mortality by 210 fewer deaths per 1000 (95% CI, 450 fewer to 20 more).⁶⁹ At 12 months, quizartinib plus LDAC, when compared with LDAC monotherapy, may further decrease mortality (RR, 0.41; 95% CI, 0.21-0.84; very low-certainty evidence) and may lower the rate of mortality over time (HR, 0.33; 95% CI, 0.14-0.76; very low-certainty evidence).⁶⁹ This combination may also increase survival time at the longest follow-up, with a median of 17.5 months compared with 5.1 months (very low-certainty evidence).⁶⁹ Additionally, quizartinib in combination with LDAC, compared with LDAC monotherapy, may improve CR/CRi at the longest follow-up; because no events were observed in the comparison group, the relative effect is not estimable, but the absolute effect indicates an increase of 380 more CRs/CRis per 1000 (95% CI, 110 more to 660 more; 13 months follow-up; very low-certainty evidence).⁶⁹

Overall, the evidence is of very low certainty. When comparing quizartinib combined with HMA or LDAC with HMA or LDAC alone, the combination may reduce the rate of mortality over time (HR, 0.44; 95% CI, 0.20-0.96; 60 months follow-up; low-certainty evidence).¹¹² It may also decrease mortality at 12 months (RR, 0.38; 95% CI, 0.11-1.36; very low-certainty evidence) and at the longest follow-up (RR, 0.96; 95% CI, 0.81-1.12; 60 months follow-up; very low-certainty evidence).¹¹² Additionally, quizartinib combined with HMA or LDAC compared with HMA or LDAC monotherapy may increase survival time at the longest follow-up, with a median of 20.4 months compared with 11.4 months (very low-certainty evidence).¹¹²

Harms and burden

When compared with azacitidine alone, the combination of gilteritinib and azacitidine may increase mortality at 12 months (RR, 1.10; 95% CI, 0.82-1.47; very low-certainty evidence).⁸⁹ It may also increase severe toxicities, such as pneumonia, at the longest follow-up (10 months; RR, 1.21; 95% CI, 0.56-1.82; 10 months follow-up; low-certainty evidence).⁸⁹

The panel noted that the observed harms of *FLT3* inhibitors, particularly gilteritinib, in combination with ALT, were based on very low-certainty evidence. Additionally, study limitations prevented the assessment of toxicities in the RCTs and NRSs

assessing other *FLT3* inhibitors (quizartinib and midostaurin). For instance, the study assessing the addition of quizartinib to 7 +3 chemotherapy did not analyze toxicities in the subset of older patients in the trials.¹¹¹ The panel acknowledged that there may be additional severe toxicities resulting from the addition of *FLT3* inhibitors to ALT, such as gastrointestinal symptoms, QT prolongation, prolonged cytopenias, and infections, that were not captured in this systematic review. The panel further highlighted the variability in toxicity profiles among *FLT3* inhibitors, including possible higher rates of gastrointestinal symptoms with midostaurin, cytopenias and QT prolongation with quizartinib, and mild liver function test elevations with gilteritinib. Additionally, they emphasized that patient perception of treatment toxicities can vary. Given the significant uncertainty in the evidence about key harms and the likely variability in how patients perceive toxicities, the panel judged these harms as small but important.

Other EtD criteria and considerations

Regarding values and preferences, the panel judged that most older adults with newly diagnosed AML and an *FLT3* mutation probably place a higher value on reducing mortality, achieving CR, and increasing survival over avoiding severe toxicities. Although they recognized that some patients may prioritize differently depending on their individual circumstances and tolerance for treatment-related harms, the panel ultimately judged that there is probably no important variability in how patients trade off these critical outcomes.

The panel agreed that resource requirements for offering an *FLT3* inhibitor in combination with ALT vs ALT alone vary widely, with costs differing significantly across health care settings and patient populations. This variability, combined with the lack of a systematic search for cost or cost-effectiveness studies, limited the influence of resource use on the recommendation. The panel also judged the impact on health equity, noting that access to *FLT3* inhibitors may vary across equity-deserving groups, with some facing increased barriers depending on the context. As a result, equity did not play a decisive role in formulating this recommendation. With regard to acceptability, 1 study reported that patients often considered the distance to the cancer center when choosing between intensive and less-intensive treatments, with some preferring inpatient care to avoid long commutes and to benefit from a controlled environment with easy access to medical staff.⁴⁸ The panel noted that, because all approved *FLT3* inhibitors are oral medications, these barriers are more relevant to the choice of primary ALT rather than to the *FLT3* inhibitors themselves. They judged *FLT3* inhibitors to be convenient for outpatient use and likely acceptable to most stakeholders, although they acknowledged variability across settings that could affect acceptability.

Feasibility was similarly discussed, with the panel noting that although ALT (conventional therapy and HMA- or LDAC-based therapies) is frequently used for patients with newly diagnosed AML, the implementation of *FLT3* inhibitors may vary depending on the setting and health care system. *FLT3* inhibitors are feasible to implement in settings with adequate diagnostic infrastructure, access to drugs, and capacity for toxicity management. However, factors such as cost, availability, and resource constraints may limit feasibility in certain regions.

Conclusions and research needs for this recommendation

The panel determined that FLT3 inhibitors in combination with ALT may offer a net benefit over ALT alone for older adults with newly diagnosed AML who have an *FLT3* mutation. This recommendation places value on benefits, such as a possible reduction in mortality and increased rates of CR, despite the low to very low certainty in evidence. The panel also acknowledged small but important harms, including increased severe toxicities, such as pneumonia, length of hospitalization, or gastrointestinal side effects. Based on their judgment, most patients are likely to prioritize these benefits over the harms, with probably no important uncertainty or variability in how they trade off these outcomes. Consequently, the balance of effects probably favors the combination of an FLT3 inhibitor with ALT over ALT alone.

The panel discussed that the benefit of FLT3 inhibitors applies primarily to patients receiving conventional induction and postremission therapy. In this setting, the optimal FLT3 inhibitor in combination with ALT has not been established; thus, differences in toxicity profiles, medication access, and patient preference play a role in the agent selection. Type 1 FLT3 inhibitors (eg, midostaurin and gilteritinib) have efficacy in AML with both *FLT3*-ITD and *FLT3*-TKD mutations, whereas type 2 FLT3 inhibitors (eg, quizartinib and sorafenib) have efficacy only in AML with *FLT3*-ITD mutations.

For patients who are not candidates for conventional induction and postremission therapy, the benefit of FLT3 inhibitors added to HMA or LDAC monotherapy, or to venetoclax-based combination therapies, which have become the standard of care in this setting, has not been definitively established. Clinical trials are ongoing, evaluating triplet therapy with FLT3 inhibitors in addition to HMA and venetoclax. Given the clinical focus of the guidelines and the goal of ensuring applicability across various settings, secondary factors such as cost, cost-effectiveness, equity, acceptability, and feasibility were not key determinants in this recommendation.

The panel emphasized the need for further research to evaluate the effectiveness and safety of different FLT3 inhibitors in combination with ALT for AML with *FLT3*-ITD or *FLT3*-TKD mutations. They highlighted the importance of conducting RCTs and comparative observational studies that generate moderate- or high-certainty evidence. Additionally, systematic reviews incorporating individual patient data could offer valuable insights into patient-specific outcomes, including variations in benefits and harms across subgroups. Such research is essential to refine these recommendations and better inform clinical decision-making in the future.

Should older adults with newly diagnosed AML who have responded to initial ALT, who are candidates for an allo-HCT during first remission, and who have nonfavorable prognosis based on molecular and karyotypic characteristics, receive an allo-HCT vs not?

Recommendation 8

For older adults with newly diagnosed AML who have responded to initial ALT, who are candidates for an allo-HCT during first remission, and who have nonfavorable prognosis based on molecular and karyotypic characteristics, the ASH guideline panel suggests an allo-HCT over no transplantation

(conditional recommendation based on very low certainty in the evidence of effects ⊕○○○)

Summary of the evidence

We included 1 RCT and 13 observational studies addressing this question. Four observational studies compared allo-HCT with no transplant (unspecified treatment).^{59,115-117} One RCT¹¹⁸ (Niederwieser et al) and 10 observational studies^{117,119-127} compared allo-HCT with ALT.

The included studies enrolled 4348 older adults, with a mean average age of 64 years. The mean percentage of male participants was 54.2%.^{59,115-119,121,124,125,127-131} Although participants were classified using different risk stratification systems (ELN 2010, ELN 2017, Southwest Oncology Group, National Comprehensive Cancer Network, Medical Research Council),^{106,132-135} most were categorized as having intermediate or unfavorable cytogenetic risk.^{59,115-119,121,124,125,127-131} Seven studies reported Eastern Cooperative Oncology Group performance status at baseline, with most of the participants having a score of 0 to 2.^{59,119,121,124,127,130,131} Across studies, participants received different induction therapy regimens, including conventional chemotherapy-based therapy and HMA- or LDAC-based therapies.^{59,115-119,121,124,125,127-131} All participants achieved first CR and received different conditioning regimens before allo-HCT, including myeloablative, nonmyeloablative, reduced intensity, and targeted conditioning.^{59,115-119,121,124,125,127-131} Donor types included matched related donor in 43% of participants and unrelated donor in 57%.^{59,115-119,121,124,125,127-131}

Online supplement 1, appendix 15, presents the characteristics of all included studies.

The evidence profile and EtD framework for this recommendation are available online at <https://guidelines.ash.gradepro.org/profile/HvGdnZnRnPo>.

Benefits

When compared with no treatment, low certainty in evidence suggests that allo-HCT may reduce the rate of mortality over time (HR, 0.74; 95% CI, 0.58-0.93; 60 months follow-up)^{59,117} and rate of recurrence of leukemia over time (HR, 0.46; 95% CI, 0.33-0.64; 60 months follow-up).¹¹⁷ Additionally, very low certainty in evidence suggests that allo-HCT may reduce mortality at 12 months (RR, 1.02; 95% CI, 0.76-1.38) and at longest follow-up (RR, 0.82; 95% CI, 0.70-0.95; 60 months follow-up).¹¹⁷ Allo-HCT may also decrease recurrence at 12 months (RR, 0.75; 95% CI, 0.56-1.01; very low certainty in evidence) and at longest follow-up (RR, 0.63; 95% CI, 0.51-0.79; 60 months follow-up; very low certainty in evidence) and increasing the time to recurrence (median difference of 37.93 months; very low certainty in evidence).¹¹⁷

Compared with no transplant (unspecified treatment), allo-HCT at the longest follow-up may reduce the rate of mortality over time (HR, 0.56; 95% CI, 0.42-0.76; median, 52 months follow-up; low certainty in evidence) and the rate of recurrence of leukemia over time (HR, 0.27; 95% CI, 0.19-0.38; median, 52 months follow-up; low certainty in evidence).¹¹⁵ Very low certainty in evidence suggests that allo-HCT may reduce mortality at 12 months (RR, 0.19; 95% CI,

0.08-0.46) and at the longest follow-up (RR, 0.62; 95% CI, 0.48-0.79; mean, 90 months follow-up).¹¹⁶ Allo-HCT may also increase survival time at longest follow-up (median difference, 49 months; very low certainty in evidence; 90 months follow-up), and decrease recurrence at longest follow-up (RR, 0.27; 95% CI, 0.14-0.53; very low certainty in evidence; median, 22 months follow-up).¹¹⁶

Low certainty in evidence suggests that, at the longest follow-up (mean, 60 months), there may be a reduction in mortality (RR, 0.74; 95% CI, 0.64-0.86)^{117,119,121,124,125,127-129,131} and recurrence (RR, 0.43; 95% CI, 0.32-0.58)^{117,119,124,125,127-131} for patients who receive allo-HCT compared with those who receive ALT alone. Additionally, allo-HCT may reduce recurrence at 12 months (RR, 0.41; 95% CI, 0.22-0.77; very low certainty in evidence)^{117,125,127,129,131} and the rate of recurrence of leukemia over time (HR, 0.32; 95% CI, 0.20-0.52; 60 months follow-up; very low certainty in evidence).¹¹⁸

Low to very low certainty in evidence suggests that patients receiving allo-HCT may experience benefits, particularly in reducing mortality and recurrence at longest follow-up. The panel emphasized that the primary goal of allo-HCT is to increase survival; therefore, they judged the benefit in reducing mortality and possibility of cure to be more critical than the benefit in reducing recurrence. Moreover, the clinical experts noted that, in their experience, patients who respond to initial ALT, who are candidates for allo-HCT during first remission, and have nonfavorable prognosis, benefit from allo-HCT. Caution should be exercised in interpreting these results as patients selected for allo-HCT are, in general, healthier, more fit, and with less aggressive AML features than those selected not to receive an allo-HCT. Experts highlight the lack of well-designed randomized trials to help guide the decision of allo-HCT vs no allo-HCT for this population. This large gap in evidence needs to be fulfilled to better guide clinical decisions about choice of therapies for future patients.

Considering the large uncertainty in the evidence and panel's clinical experience, the panel judged the benefits to be small but important.

Harms and burden

Compared with ALT, allo-HCT may increase mortality at 12 months (RR, 1.76; 95% CI, 0.99-3.15; very low certainty in evidence)¹¹⁸ and duration of hospitalization at longest follow-up (MD, 65 months; 95% CI, 51.68-78.44; very low certainty in evidence; median, 77.7 months follow-up).¹¹⁹

The panel acknowledged, based on their clinical experience, that there are likely additional undesirable effects, particularly severe toxicities such as those related to the conditioning regimen, with early and delayed organ injury, and nonrelapse mortality, that were not measured in the included studies. The panel also noted that transplant-related toxicities are often unavoidable and can have a significant impact on patients, particularly those who are older, less fit, or who have comorbidities. Additionally, the long-term QoL after transplant may vary widely due to complications such as graft-versus-host disease, infections, graft function issues, psychosocial harms, frailty, disability, psychological health, financial and time toxicity, and other treatment-related harms, and allo-HCT may have a negative impact on donors and caregivers. Although cost considerations and data on QoL were not available in the included studies, the panel judged the undesirable effects of allo-HCT to be moderate.

Other EtD criteria and considerations

Four studies addressed values and preferences of patients regarding the critical outcomes.⁵⁶⁻⁵⁹ For details on the description of the studies, please refer to the section on Population, Intervention, Comparator, Outcome 2. One study⁵⁷ found that patients aged >60 years generally have a stronger preference to avoid short-term side effects compared with those aged <60 years. Based on this evidence and their clinical experience, the panel believes that most patients would prioritize reductions in mortality and recurrence over harms such as severe toxicities and QoL impairment. However, they acknowledged that a significant proportion of patients (eg, those aged ≥70 years) might prioritize differently, leading the panel to conclude that there may be important uncertainty or variability in patient values and preferences. Taking this into consideration, along with the overall low certainty in the evidence for the critical outcomes, the panel judged that the balance of the effects probably favors allo-HCT over no transplantation.

In evaluating equity, a multicenter study presented preliminary results,¹³⁶ evaluating differences in access to allo-HCT in 695 patients. The study reported that people with lower education levels were less likely to receive allo-HCT compared with those with education beyond high school (HR, 0.68; 95% CI, 0.55-0.84).¹³⁶ Similarly, individuals living in neighborhoods with higher rates of supplemental nutrition assistance program usage, as a surrogate for poverty, were less likely to receive allo-HCT (HR, 0.86; 95% CI, 0.74-1.00).¹³⁶ Although an increase in median income (\$25 000) was associated with an increase in allo-HCT use (HR, 1.05; 95% CI, 0.94-1.18), individuals in neighborhoods with more households below the poverty level (HR, 0.85; 95% CI, 0.70-1.03 per 10% increase) or receiving supplemental security income (HR, 0.66; 95% CI, 0.39-1.11) might have been less likely to receive allo-HCT.¹³⁶ The panel judged that the impact of allo-HCT on health equity varies due to differences in access to treatment among equity-deserving groups across settings. These disparities may reduce equity in some groups and settings while increasing it in others. Therefore, although this criterion did not have an important bearing in the recommendation, experts strongly emphasized the importance of implementing intervention studies to enhance access to allo-HCT for older patients with AML from diverse backgrounds.

Allo-HCT is likely to be acceptable to all relevant stakeholders. However, its acceptability may vary across settings due to differences in health care systems, cultural norms, and associated costs. In some settings, the high cost of the procedure, both for patients and health care systems, may limit its acceptability. Moreover, stakeholder perceptions of the trade-offs between the benefits and risks, including severe toxicities and QoL implications, can further influence its acceptability.

The feasibility of allo-HCT also varies depending on health care infrastructure, resource availability, and health care expertise. In high-resource settings, specialized transplant centers and trained teams facilitate its implementation. However, in resource-limited settings, challenges such as insufficient facilities, difficulties in donor matching, and logistical constraints create significant barriers. Furthermore, the high financial burden of the procedure and associated post-transplant care can make implementation challenging. Patient-specific factors, including comorbidities, geriatric health, and age, are essential in determining whether allo-HCT is feasible.

Conclusions and research needs for this recommendation

The ASH guideline panel suggests allo-HCT over no transplantation for older adults with newly diagnosed AML who have responded to initial ALT, who are candidates for an allo-HCT during first remission, and who have nonfavorable prognosis based on molecular and karyotypic characteristics (conditional recommendation, low certainty in evidence). Studies suggest that most older adults with nonfavorable prognoses in remission are not cured, will relapse, and die of complications of AML. Allo-HCT can represent a potentially curative treatment alternative that can be safely performed in an increasingly higher number of older adults after continuing improvements in patient selection, conditioning regimen intensity tailoring, and a larger alternative donor pool through the increased use of mismatched unrelated and haploidentical donors.^{131,137,138}

The value of allo-HCT and the decision whether to recommend the procedure for older adults with AML is modulated by multiple factors including comorbidities and fitness more than a specific age threshold and the presence of a suitable social support network. Specific genetic characteristics of the disease within nonfavorable disease subgroups can also predict outcomes after allo-HCT. For example, studies suggest that patients with TP53 mutations have a high likelihood of relapse despite receiving allo-HCT in remission, whereas patients classified in the intermediate-risk category may have distinctly better outcomes after the procedure. In contrast, allo-HCT probably offers increased probabilities of survival for patients with adverse risk, whereas its efficacy for patients with intermediate risk is less certain.^{51,59,118,139,140}

The presence of measurable residual disease is another strong prognostic factor that can affect outcome after allo-HCT.¹⁴¹⁻¹⁴⁶ Lastly, the intensity of the conditioning regimen planned and the characteristics of the available donors (including age, HLA matching, ABO and cytomegalovirus status, among other factors), can modulate the harms of the procedure, including QoL and the likelihood of nonrelapse mortality.¹⁴⁷⁻¹⁴⁹

This recommendation places a high value on the benefits of allo-HCT. Although the certainty in the evidence is very low and does not capture the heterogeneity of the disease, the panel makes a conditional recommendation based on the overall small, but important, benefits observed in the evidence and their clinical experience. Additionally, the panel judged that many patients would likely place a higher value on survival and avoiding mortality and relapse over the harms, including increased severe toxicity, prolonged hospitalizations, and impacts on QoL, particularly for older adults or those with comorbidities. The panel believes that these benefits outweigh the harms. However, they acknowledged that there is possibly important uncertainty or variability in how patients trade off the critical outcomes, because some may prioritize avoiding severe toxicities or preserving QoL. Given this variability, the balance of effects probably favors allo-HCT over no transplantation.

The panel also expressed concerns regarding the control groups in the included studies, particularly lack of details on options for alternative nontransplant treatments. These groups may not reflect the current standard of care due to changes in practice over time. Similarly, the regimens used in some control groups may lack

applicability to contemporary clinical settings. To address these limitations, the panel strongly emphasized the need for further research, including RCTs, comparative observational studies yielding moderate- or high-certainty evidence, and systematic reviews with individual patient data. These studies should evaluate regimens in control groups that better represent current standards of care to provide valuable insights for future updates to the recommendations. Similarly, well-designed studies are needed to ensure equitable levels of care for older patients with AML from underrepresented minorities or adverse social determinants of health groups. Such studies should focus on reducing risks of mortality overall and increasing access to allo-HCT for this marginalized group of older adults with AML.

Contextual factors such as health care infrastructure, resource availability, and financial costs also play a significant role in the implementation of allo-HCT. High-resource settings with specialized transplant centers and trained teams are better equipped to offer this procedure, whereas resource-limited settings face challenges such as inadequate facilities, donor availability issues, and logistical constraints. Disparities in access to treatment among equity-deserving groups may further reduce or enhance equity depending on the context. However, given the clinical perspective of these guidelines and the aim of ensuring applicability across different settings, secondary factors such as cost, cost-effectiveness, equity, acceptability, and feasibility did not have a major bearing on this recommendation.

Should older adults with AML who are no longer receiving ALT (including those receiving end-of-life or hospice care) receive RBC transfusions, platelet transfusions, or both, vs no transfusions?

Recommendation 9

For older adults with AML who are no longer receiving ALT (including those receiving end-of-life care or hospice care), the ASH guideline panel *suggests* having RBC transfusions be available over not having transfusions be available (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remark:

- There may be rare instances in which platelet transfusions may be of benefit in the event of bleeding, but there are even less data to support this practice and it is anticipated that platelet transfusions will have little or no role in end-of-life or hospice care.

This recommendation is from the ASH 2020 guidelines on AML in older adults. The evidence for this recommendation was not rereviewed for this guideline. Please review the [ASH 2020 AML in Older Adults guidelines](#).

What is new in these guidelines?

The ASH 2025 guidelines for treating newly diagnosed AML in older adults update the 2020 ASH guidelines in important ways. Notably, we have updated terminology to eliminate arbitrary definitions for what constitutes “intensive” and “nonintensive” therapy, instead distinguishing treatment approaches by being “traditional 7+3-type” therapy vs therapy that is HMA- or LDAC-based. Although the 2020

guidelines alluded to impending RCT results with HMA- or LDAC-based combinations with venetoclax, the 2025 guidelines could formally interpret those trials and make recommendations favoring combinations over monotherapy. We were able to make recommendations comparing HMA- or LDAC-based combinations with venetoclax vs other treatment options. We added questions to the 2025 recommendations focusing on actionable/targetable mutations, including *IDH* and *FLT3* mutations, and make a recommendation regarding allo-HCT for patients with nonfavorable prognoses based on molecular and karyotypic characteristics.

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.

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.

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.¹⁵⁰

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Authorship

Contribution: M.A.S., M.J.O., Y.R., S.I., R.B.-P., R.M., A.A., M.R.B., C.C.C., R.D.-G., P.C.E., L.F., C.F., J.S.G., L.G., A.G.d.L., J.L., K.P.L., L.M., B.M., U.P., M.L.S., S.T.-V., J.T., and G.G. wrote the first draft of the manuscript and revised it based on authors' suggestions; guideline panel members critically reviewed the manuscript and provided suggestions for improvement; members of the evidence synthesis team (M.J.O., Y.R., S.I., and R.B.-P.) contributed evidence summaries to the guideline; M.A.S. and R.B.-P. served as coauthors of the panel and led the panel meeting; and all authors approved the content.

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John Treitz died on 8 August 2025.

ORCID profiles: M.A.S., [0000-0003-2009-6524](https://orcid.org/0000-0003-2009-6524); R.M., [0000-0001-8574-8365](https://orcid.org/0000-0001-8574-8365); A.A., [0000-0003-0803-9607](https://orcid.org/0000-0003-0803-9607); M.R.B., [0000-0002-9499-1348](https://orcid.org/0000-0002-9499-1348); C.C.C., [0000-0002-2162-3288](https://orcid.org/0000-0002-2162-3288); R.D.-G., [0000-0003-0258-7397](https://orcid.org/0000-0003-0258-7397); P.C.E., [0000-0001-8590-2916](https://orcid.org/0000-0001-8590-2916); L.F., [0000-0002-2384-536X](https://orcid.org/0000-0002-2384-536X); C.F., [0009-0006-8678-9656](https://orcid.org/0009-0006-8678-9656); J.S.G., [0000-0003-2118-6302](https://orcid.org/0000-0003-2118-6302); A.G.d.L., [0000-0001-6904-9345](https://orcid.org/0000-0001-6904-9345); J.L., [0000-0002-7751-7310](https://orcid.org/0000-0002-7751-7310); K.P.L., [0000-0002-6978-0418](https://orcid.org/0000-0002-6978-0418); L.M., [0000-0002-1460-1611](https://orcid.org/0000-0002-1460-1611); B.M., [0000-0003-0436-8948](https://orcid.org/0000-0003-0436-8948); U.P., [0000-0003-1863-3239](https://orcid.org/0000-0003-1863-3239); M.L.S., [0000-0001-5260-1981](https://orcid.org/0000-0001-5260-1981); S.T.-V., [0000-0003-3012-7398](https://orcid.org/0000-0003-3012-7398); M.J.O., [0000-0002-9327-6844](https://orcid.org/0000-0002-9327-6844); S.I., [0000-0002-7713-6171](https://orcid.org/0000-0002-7713-6171); Y.R., [0009-0009-4564-5973](https://orcid.org/0009-0009-4564-5973); G.G., [0000-0003-2352-5718](https://orcid.org/0000-0003-2352-5718); R.B.-P., [0000-0002-6010-9900](https://orcid.org/0000-0002-6010-9900).

Correspondence: Mikkael A. Sekeres, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, 1120 NW 14th St, Suite 610M, Miami, FL 33136; email: msekeres@med.miami.edu.

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