ASH® CLINICAL PRACTICE GUIDELINES

Treating newly diagnosed acute myeloid leukemia in older adults

An Educational Slide Set

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

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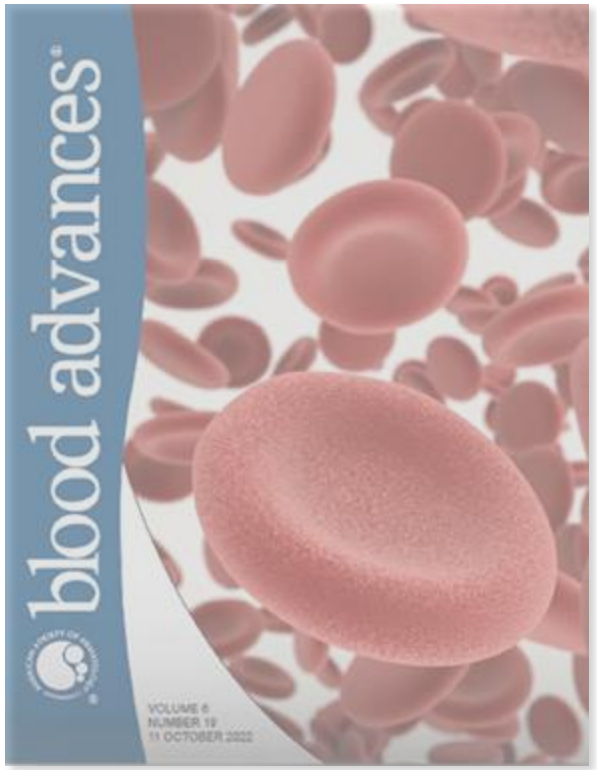


How were these guidelines updated?

PANEL FORMATION

The **guideline panel** was formed following these key criteria:

- Balance of expertise
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

9 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

Example PICO question:
"Should older adults with newly diagnosed AML who are candidates for antileukemic therapy receive antileukemic therapy instead of best supportive care only?"

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed routinely by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

How patients and clinicians should use these recommendations

	Strong Recommendation		Conditional Recommendation	
	"The panel recommends…"	"The panel recommends against…"	"The panel suggests…"	"The panel suggests against…"
				
	Interpretation of Strong Recommendations		**Interpretation of Conditional Recommendations**	
For 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.	
For clinicians	Most individuals should follow the recommended course of action.		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.	

Objectives

By the end of this session, you should be able to

1. Describe recommendations for post-remission therapy for older adults with AML in three settings
    - Candidates for allogeneic stem cell transplantation (allo-HCT)
    - Not candidates for allo-HCT post conventional induction therapy
    - Not candidates for allo-HCT and responding to HMA- or LDAC-based therapy
2. Describe recommendations for targeted therapy for older adults with AML

Case 1A: Post remission management for older adults with AML

68M with AML

- 80% bone marrow blasts at diagnosis
  - Normal karyotype
  - Mutations in *ASXL1, RUNX1, EZH2, TET2*
- Achieved remission (bone marrow blasts <5%) after 1 cycle of '7+3' induction
  - Complications: febrile neutropenia, mucositis, neutropenic colitis
- Minimal comorbidities, ECOG 0

Case 1A: Post remission management for older adults with AML

68M in morphological remission after 1 cycle of conventional intensive induction chemotherapy.

AML is adverse risk by European LeukemiaNet (ELN) 2022 risk stratification.

What would you do next?

A. No further therapy as the patient is already in remission

B. Work up / refer patient for consideration of allogeneic stem cell transplantation

C. Switch to azacitidine-venetoclax

Recommendation 8

- For older adults with newly diagnosed AML who have responded to initial antileukemic therapy, who are candidates for an allo-HCT during first remission, and who have non-favorable 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 ⨁◯◯◯).

*Goldenberg N, et al; *JAMA*, 2022

Recommendation

Recommendation is based on 1 randomized controlled trial (RCT) and 13 observational studies comparing allo-HCT to no allo-HCT. [1-14]

Total of 4348 older adults, most with intermediate or adverse risk disease

BENEFITS allo-HCT

- Reduces rate of mortality over time (HR 0.74, 95% CI 0.58-0.93)
- Reduces rate of leukemia recurrence over time (HR 0.46, 95% CI 0.33-0.64)

Most older adults with non-favorable prognosis AML are not cured, will relapse and die from AML. Allo-HCT represent a potentially curative treatment alternative.

HARMS allo-HCT

- Increases mortality at 12 months (RR 1.76, 95% CI 0.99-3.15)
- Increases duration of hospitalization

Harms are not well measured in these studies: severe toxicities relating to conditioning regimen, non-relapse mortality, organ injury, impact on quality of life and costs implications

Summary of Case 1A

- Caution should be exercised in interpreting these results as patients selected for allo-HCT are in general healthier, more fit with less aggressive AML features.
- There is a lack of well-designed randomized trials to help guide the decision of allo-HCT versus no allo-HCT in this patient population.
- This recommendation places a high value on the potential survival benefits of allo-HCT. Although the certainty of 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.

Summary of Case 1A

The potential value of allo-HCT and the decision whether to recommend the procedure is complicated, modulated by multiple factors and should be a shared decision between the patients and their clinicians.

http://hematology.org/decisionaids

Case 1B: Post remission management for older adults with AML

68M with AML in remission after 1 cycle of '7+3' induction

AML is adverse risk by European LeukemiaNet (ELN) 2022 risk stratification.

Further work up found not to be a candidate for allo-HCT

What would you do next?

A. No further therapy as the patient is already in remission
B. Repeat conventional intensive induction chemotherapy
C. Post-remission therapy
D. Switch to azacitidine-venetoclax

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 post-remission therapy*** over no additional therapy (strong recommendation based on low certainty in the evidence of effects ⨁⨁◯◯).

Recommendation

Recommendation is based on 4 RCTs comparing no additional therapy / placebo vs:

- oral azacitidine,[15] SC/IV azacitidine,[16,17] gemtuzumab ozogamicin[18]

On pooled analysis, receiving additional therapy has the following benefits:

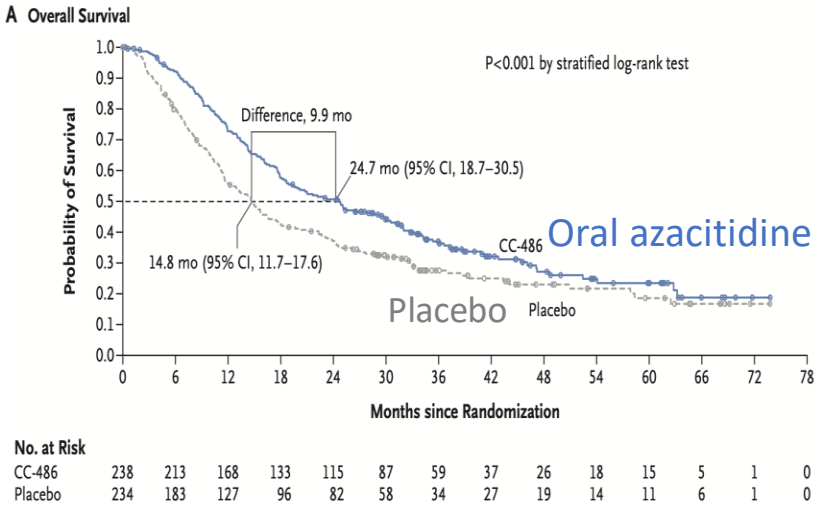
- Reduces mortality at 12 months: RR 0.67, 95% CI 0.54-0.84
- Increases survival time at longest follow-up (41 months): median difference 9.9 months
- Increases disease-free survival at 12 months: RR 1.61, 95% CI 1.31-1.98
- Decreases relapse at longest follow-up (mean 51 months): RR 0.83, 95% CI 0.70-0.98

Main harm relates to treatment-related adverse events and resultant hospitalization.

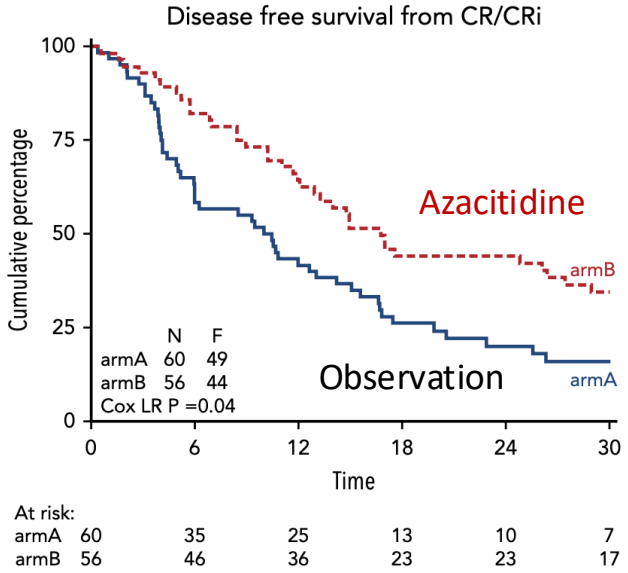
Recommendation

Survival benefit mainly reflects azacitidine maintenance

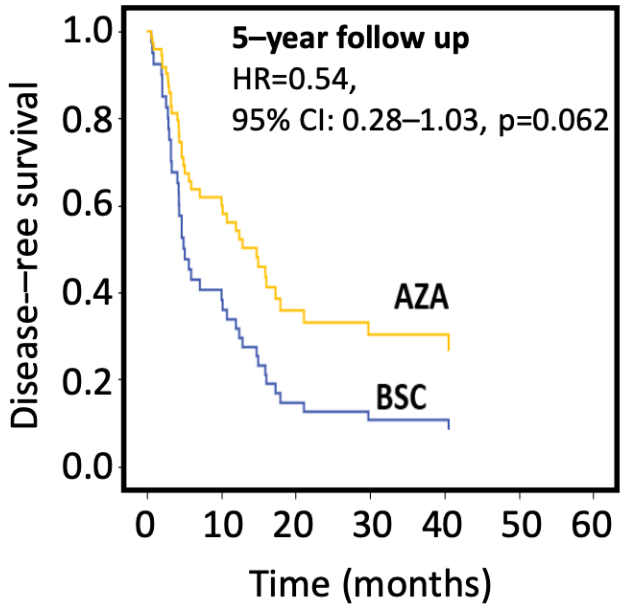
Oral azacitidine (Wei et al.)[15]



SC azacitidine (Hul et al.)[16]



SC/IV azacitidine (Oliva et al.)[17]



Summary of Case 1B

Overall, the panel determined that potential benefits of survival outweigh the harms, favoring post-remission therapy.

Important caveats:

- Post-remission therapy can consist of cytarabine-based treatment or azacitidine-based treatment
- Gemtuzumab ozogamicin alone in the post-remission setting did not result in significant improvement in survival or relapses
- Insufficient data for maintenance therapy in patients with core binding factor AML
- Limited data on the number of post remission conventional chemotherapy cycles that should be administered beyond one cycle
- Optimal duration of post-remission therapy still needs to be further studied

Case 2: Post remission management for older adults with AML

76M with AML

- 45% bone marrow blasts at diagnosis
  - Normal karyotype
  - Mutations in *NPM1, SRSF2, TET2*
- Achieved remission (bone marrow blasts <5%) after 1 cycle of Azacitidine-Venetoclax (AZA-VEN)
  - Complications: febrile neutropenia
- ECOG 1, Comorbidities: T2DM, IHD, HTN, HChol, OSA

Case 2: Post remission management for older adults with AML

76M with AML in remission after 1 cycle of Azacitidine-Venetoclax

AML is favorable risk by European LeukemiaNet (ELN) 2024 risk stratification for less-intensive therapies.

Continued treatment for a total of 6 months with minimal complications.

NPM1 measurable residual disease (MRD) at 4 and 6 months (by RT-qPCR) were undetectable.

Patient is feeling good and now asking “Doc, how long do I need to continue AZA-VEN for?”

Case 2: Post remission management for older adults with AML

76M with AML in MRD negative remission, completed 6 months of AZA-VEN.

AML is favorable risk by European LeukemiaNet (ELN) 2024 risk stratification.

Patient asking re: duration of AZA-VEN therapy.

What would you do next?

A. Stop now, no further therapy
B. Continue AZA-VEN until progression or unacceptable toxicity
C. Continue AZA-VEN until 12 months total then cease
D. Switch to VEN alone
E. Switch to AZA alone

Recommendation 6

- For older adults with AML who achieve a response after receiving HMA- or LDAC-based induction and post-remission 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 ⊕◯◯◯).

Recommendation

- Systematic review identified only two retrospective observational studies comparing continuous vs finite duration of therapy. [19-20]
  - One study compared patients receiving ≥12 months of venetoclax-based combinations (with LDAC, azacitidine or decitabine) and reported that a subset of patients can experience durable treatment-free remission after ceasing therapy with trivial to no effect on mortality[19]
  - One study compared HMA monotherapy (6+3 schedule) and reported that continuing HMA until progression/toxicity is associated with improved overall survival (increase in survival time at longest follow-up (15 months): MD 3.45 months higher (95% CI: 1.36 higher to 5.54 higher)[20]

Summary of Case 2

- Overall, the panel judged that currently there is insufficient evidence to guide routine cessation of therapy after a defined period → ***conditional recommendation for continuing therapy***
  - Being retrospective and observational with small patient numbers, the studies provided very low certainty of evidence
  - Main harm of continuous treatment are treatment-related toxicities, which should be managed with dose modifications following published guidelines to allow patients to safely remain on therapy
- Prospective studies are underway to identify patients receiving HMA- or LDAC- based regimens in whom therapy can be safely stopped[21,22]

Case 3: AML with IDH1 mutation

77M with AML

- 44% bone marrow blasts at diagnosis
  - Normal karyotype
  - Mutation in *IDH1*
- ECOG 1, Comorbidities: T2DM, CKD3, HTN

Case 3: Treatment for older adults with IDH1 mutations

Patient is wondering about next step for treatment

What would you do next?

A. Ivosidenib alone
B. Azacitidine + ivosidenib
C. Azacitidine + venetoclax
D. Azacitidine alone
E. B or C

Recommendation 5

- A: For older adults with newly diagnosed AML and an IDH1 mutation considered appropriate for antileukemic therapy but not for conventional induction and post-remission 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 ⨁⨁◯◯).

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

Recommendation

- Systematic review identified only one randomized control trials to answer question of IDH1 therapy[23]
  - Agile study: 146 patients mean age 75 years, HMA + ivosidenib vs HMA alone
  - Results:
    - Probably increases CR/CRi (RR, 3.34; 95% CI, 1.91 to 5.85; median 15 months follow-up)
    - Reduce mortality at 12 months (RR, 0.64; 95% CI, 0.46 to 0.88; low certainty evidence)
    - May increase survival time: median of 24 months compared to 7.9 months (very low certainty evidence)

Recommendation

- In answering question of HMA therapy + venetoclax vs. azacitidine + ivosidenib therapy, there were no direct trials comparing these head-to-head. Data was indirectly extrapolated from AGILE study but also from a guideline panel survey.
  - 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.
  - Per survey of full panel, panel judged the benefits of HMA in combination with ivosidenib compared to HMA in combination with venetoclax to be trivial.

Harms

- When compared to azacitidine monotherapy, azacitidine in combination with ivosidenib may have trivial to no effect on severe toxicity, particularly differentiation syndrome (low-certainty evidence)
  - Given the uncertainty in the evidence, the panel judged these harms as small but important.
- The evidence on the undesirable effects of azacitidine in combination with ivosidenib compared to HMA in combination with venetoclax is indirect and of very low certainty.
  - Both regimens share common toxicities, and the overall toxicity burden is unlikely to differ meaningfully with supportive care.
  - Given the very low certainty of the evidence, the panel judged the harms to be trivial.

Summary of Case 3

- Overall, the panel judged that while there was uncertainty in evidence, 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.
  - The panel placed a higher value on the benefits of azacitidine with ivosidenib and the lack of important variability in patient values and preferences.
- After considering all factors of HMA plus ivosidenib versus HMA plus venetoclax versus, the panel judged the benefits to be trivial.
  - 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.
  - Toxicity profile in relation to the patient's comorbidities and functional status may help guide the choice between them.

Case 4: AML with IDH2 mutation

79M with AML

- 54% bone marrow blasts at diagnosis
  - Normal karyotype
  - Mutation in *IDH2, DNMT3A*
- ECOG 2, Comorbidities: OSA, HLD, HTN, CHF (stable)

Case 4: Treatment for older adults with IDH2 mutations

What therapy do you recommend?

A. Azacitidine monotherapy

B. Azacitidine + venetoclax

C. Azacitidine + enasidenib

D. Conventional induction (7+3)

E. Enasidenib alone

Recommendation 5D

- For older adults with newly diagnosed AML and an IDH2 mutation considered appropriate for antileukemic therapy but not for conventional induction and post-remission 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 ⨁◯◯◯).

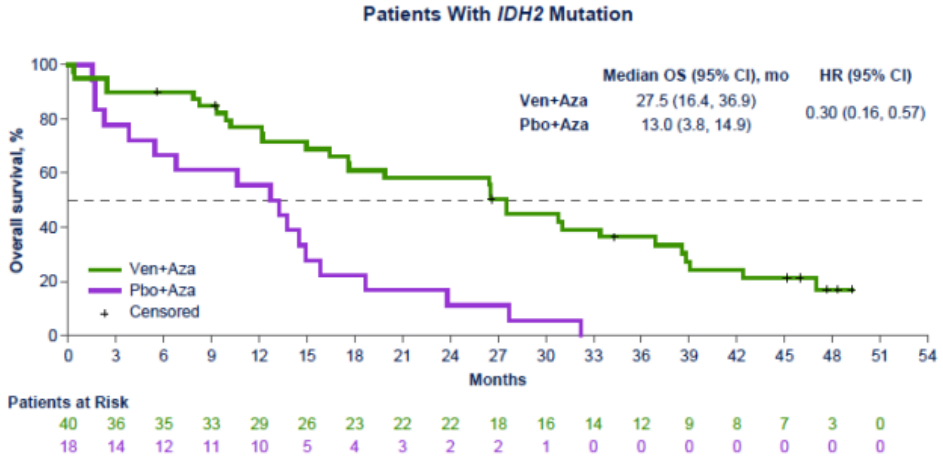
Recommendation

- We identified one RCT comparing enasidenib combined with azacitidine to azacitidine alone.[24] This RCT enrolled 101 older adults with a mean age of 75 years (SD 5.3)

- Low certainty evidence suggests that azacitidine in combination with enasidenib may increase CR/CRi at the longest follow-up (RR, 2.09; 95% CI, 1.21 to 3.61. with a median of 22 (95% CI, 14.6 to 37.2) compared to 18.6 months (95% CI, 11.9 to 25.7), but trivial to no effect on the rate of mortality over time, though there is uncertainty (HR, 0.99; 95% CI, 0.52 to 1.87; very low certainty evidence.

Recommendation

- To answer question of enasidenib + azacitidine vs. HMA + venetoclax though, there again was no direct head-to-head comparisons and indirect evidence required along with panel.
- Indirect evidence : Panel survey, VIALE-A study, with IDH2 specific data with CRc rate of 86.0% and mOS not reached in longterm data[25,26]



(Pratz et al Am J Hematol 2024)

Harms

- The undesirable effects of azacitidine in combination with enasidenib compared to HMA in combination with venetoclax were assessed using indirect evidence.
  - 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 of the evidence, the panel judged the harms to be trivial.

Summary of Case 4

- The panel discussed that the benefits of HMA in combination with enasidenib were likely smaller when compared to those of azacitidine in combination with venetoclax. This is supported by evidence that azacitidine in combination with venetoclax provides moderate benefits compared to azacitidine monotherapy.
  - 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.
- HMA-based monotherapy, as opposed to combination therapy with venetoclax, may be equi-efficacious in select subgroups, such as patients whose AML has a TP53 mutation or in areas of the world where venetoclax may not be available.

Case 5: FLT3

72M with AML with new diagnosis of FLT3 ITD mutated AML. Very fit, ECOG 1 without significant comorbidities including cardiac disease, renal disease, or liver disease. He is motivated for aggressive therapy.

What would you do next?

A. Standard induction chemotherapy (ie 7+3) alone
B. 7+3 plus FLT3 inhibitor (midostaurin or quizartinib)
C. Azacitidine alone
D. Gilteritinib alone

Recommendation 7

- For older adults with newly diagnosed AML who have a FLT3 mutation, the ASH guideline panel ***suggests antileukemic therapy in combination with a FLT3 inhibitor over antileukemic therapy alone*** (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯).

- Remark: This recommendation applies primarily to patients receiving conventional induction and post-remission 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 in patients who receive HMA or LDAC plus venetoclax, or HMA or LDAC monotherapy.

Recommendation

- Five studies addressed this question, including three RCTs[27-29] and two NRSs[30-31] and a total of 729 participants.
- First RCT (27): quizartinib once daily for 14 days + conventional 7+3 and in ARA-C consolidation, then maintenance for u pto 36 months
  - Results: may reduce mortality at 12 months (RR, 0.88; 95% CI, 0.63 to 1.21), increase median of 17.5 months compared to 14.2 months (low certainty evidence).
- Second RCT (28) quizartinib + low dose cytarabine
  - Very low certainty evidence: may reduce 12-month mortality (RR, 0.41; 95% CI, 0.21 to 0.84; very low certainty evidence), may also increase survival time at the longest follow-up, with a median of 17.5 months compared to 5.1 months (very low certainty evidence).
- Third RCT (29) azacitidine combined with gilteritinib vs. azacitidine alone
  - Results: no difference in mortality at the longest follow-up (RR, 1.00; 95% CI, 0.82 to 1.47; 30 months follow-up; moderate certainty evidence).

Recommendation

- Non-randomized study (30): 191 patients midostaurin vs. 7+3 chemotherapy alone
  - Very low certainty evidence suggests that the addition of midostaurin may decrease mortality at 12 months (RR, 0.60; 95% CI, 0.46 to 0.78) and may reduce the rate of mortality over time (HR, 0.47; 95% CI, 0.33 to 0.67)
- Last study (31): 395 participants with FLT3-ITD, assessing the impact of FLT3-inhibitors in clinical outcomes

Harms

- The panel noted that the observed harms of FLT3 inhibitors were based on very low certainty evidence.

- 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.

- 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.

Recommendation

- Panel determined that FLT3 inhibitors in combination with antileukemic therapy may offer a net benefit over antileukemic therapy alone in older adults with newly diagnosed AML who have a FLT3 mutation.
  - This recommendation places value on benefits, such as a possible reduction in mortality and increased rates of complete remission, despite the low to very low certainty of evidence.
  - The panel also acknowledged small but important harms, including the for increased severe toxicities, such as pneumonia, length of hospitalization, or gastrointestinal side effects.
- The panel discussed that the benefit of FLT3 inhibitors applies primarily to patients receiving conventional induction and post-remission therapy.

Recommendation

- Optimal FLT3 inhibitor in combination with antileukemic therapy has not been established; thus, differences in toxicity profiles, medication access, and patient preference play a role in the agent selection.
  - Type I FLT3 inhibitors (e.g., midostaurin, gilteritinib) have efficacy in AML with both FLT3-ITD and FLT3 TKD mutations, whereas Type II FLT3 inhibitors (e.g., quizartinib, sorafenib) have efficacy only in AML with FLT3-ITD mutations.
- Benefit of FLT3 inhibitors added to HMA or LDAC monotherapy, or to venetoclax-based combination therapies, has not been definitively established.
  - Clinical trials are ongoing evaluating triplet therapy with FLT3 inhibitors in addition to HMA and venetoclax.

In Summary: Back to our Objectives

1. Describe recommendations for post-remission therapy for older adults with AML in three settings

Candidates for allogeneic stem cell transplantation (allo-HCT)

- ✓ **Rec 8: For older adults with newly diagnosed AML who have responded to initial antileukemic therapy and who have non-favorable prognosis based on molecular and karyotypic characteristics, the ASH guideline panel suggests an allo-HCT over no transplantation.**

Not candidates for allo-HCT post conventional induction therapy

- ✓ **Rec 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 post-remission therapy over no additional therapy.**

In Summary: Back to our Objectives

1. Describe recommendations for post-remission therapy for older adults with AML in three settings

   Not candidates for allo-HCT and responding to HMA- or LDAC-based therapy

   - ✓ **Rec 6: For older adults with AML who achieve a response after receiving HMA- or LDAC-based induction and post-remission therapy, the ASH guideline panel *suggests continuing therapy indefinitely until progression or unacceptable toxicity* over stopping therapy after a finite number of cycles**

Objectives:

2. Describe recommendations for targeted therapy for older adults with AML

IDH1

- ✓ **Rec 5A: For older adults with newly diagnosed AML and an IDH1 mutation considered appropriate for antileukemic therapy but not for conventional induction and post-remission therapy, the ASH guideline panel suggests azacitidine in combination with ivosidenib over azacitidine monotherapy.**
- ✓ **Rec 5B: For older adults with newly diagnosed AML and an IDH1 mutation considered appropriate for antileukemic therapy but not for conventional induction and post-remission therapy, the ASH guideline panel suggests using either HMA in combination with ivosidenib or HMA in combination with venetoclax.**

Objectives

2. Describe recommendations for targeted therapy for older adults with AML

IDH2

- ✓ **For older adults with newly diagnosed AML and an IDH2 mutation considered appropriate for antileukemic therapy but not for conventional induction and post-remission therapy, the ASH guideline panel suggests HMA in combination with venetoclax over HMA in combination with enasidenib.**

FLT3

- ✓ **Rec 7: For older adults with newly diagnosed AML who have a FLT3 mutation, the ASH guideline panel suggests antileukemic therapy in combination with a FLT3 inhibitor over antileukemic therapy alone.**

Acknowledgements

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See more about the **ASH AML guidelines** at *hematology.org/amlguidelines*

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