ASH Draft Recommendations for Acute Myeloid Leukemia in Older Adults

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please visit **https://ashaml.questionpro.com.** Only comments submitted via the online survey will be reviewed by the guideline panel.

The public comment period for these draft recommendations is **November 27 – December 20, 2019.**

RECOMMENDATIONS

- **Question 1:** Should older adults with newly diagnosed AML who are candidates for antileukemic therapy be offered antileukemic therapy instead of best supportive care only?

  The ASH guideline panel *recommends* offering antileukemic therapy over best supportive care to older adults with newly diagnosed AML who are candidates for such therapy (strong recommendation, moderate quality evidence)

  Remarks: This recommendation includes both, intensive and less intensive antileukemic therapy.

- **Question 2:** Should intensive antileukemic therapy vs. less intensive antileukemic therapy be used for older adults with newly diagnosed AML considered candidates for antileukemic therapy?

  The ASH guideline panel *suggests* intensive antileukemic therapy over less intensive antileukemic therapy in older adults with newly diagnosed AML considered candidates for intensive antileukemic therapy (conditional recommendation, low quality evidence).

- **Question 3:** Should post-remission therapy vs. no additional therapy be used for older adults with newly diagnosed AML who achieve remission after at least 1 cycle of intensive antileukemic therapy?

  The ASH guideline panel suggests post-remission therapy over no additional therapy in older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy, and who are not candidates for allo-HSCT (conditional recommendation, low quality evidence)

- **Question 4:** Should older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy receive gemtuzumab ozogamicin, low-dose cytarabine, azacitidine, 5-day decitabine, or 10-day decitabine monotherapy or in combination?

  When choosing between hypomethylating agents monotherapy and low-dose cytarabine monotherapy, the ASH guideline panel suggests using either of the options in older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy (conditional recommendation, moderate quality evidence).

  When choosing between hypomethylating agents (azacytidine and decitabine) or low-dose cytarabine as a monotherapy and in combination with other agents, the ASH guideline panel suggests using monotherapy over combination in older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy (conditional recommendation, low quality evidence).

- **Question 5:** Should continuing therapy indefinitely until progression/ toxicity vs. giving therapy for a finite number of cycles be used for older adults with AML who received less intensive antileukemic therapy and who achieved a response?

  The ASH guideline panel suggests continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy in older adults with AML who achieve a response after receiving less-intensive therapy. (conditional recommendation based on very low certainty evidence).

- **Question 6:** Should red blood cells (RBC) transfusions, platelet transfusions, or both, vs. no transfusions be used for older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life or hospice care)?

  The ASH guideline panel suggests RBC transfusions and platelet transfusions be available over not having transfusions available for older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life care or hospice care) (conditional recommendation, based on very low certainty evidence).

QUESTION 1A

Should intensive antileukemic therapy vs. best supportive care be used for older adults with newly diagnosed AML?	
POPULATION:	older adults with newly diagnosed AML
INTERVENTION:	intensive antileukemic therapy
COMPARISON:	best supportive care
MAIN OUTCOMES:	Mortality; Serious adverse events: Pneumonia; Serious adverse events: Febrile neutropenia; Complete remission; Quality of life impairment; Functional impairment; Burden on caregivers; Allogeneic hematopoietic stem cell transplant; Hospitalization; Serious adverse events: Septic shock; Serious adverse events: Intensive care unit admission; Serious adverse events: Multi-organ failure; Serious adverse events: Acute respiratory failure;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel prioritized this question, recognizing the importance of guidance for front-line clinicians regarding whether antileukemic therapy should be routinely offered for older adults with AML.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know		The panel judged that the magnitude of the potential benefits of intensive antileukemic therapy on mortality was large.

Outcomes	With best supportive care	With intensive antileukemic therapy	Difference	Relative effect (95% CI)
Mortality assessed with: Proportion of patients who died follow up: 30 days	453 per 1,000	**127 per 1,000** (63 to 263)	**326 fewer per 1,000** (390 fewer to 190 fewer)	**RR 0.28** (0.14 to 0.58)
Mortality assessed with: Proportion of patients	804 per 1,000	**458 per 1,000** (362 to 579)	**346 fewer per 1,000**	**RR 0.57** (0.45 to 0.72)

who died follow up: 6 months			(442 fewer to 225 fewer)	
Mortality assessed with: Proportion of patients who died follow up: 1 years	800 per 1,000	**504 per 1,000** (360 to 696)	**296 fewer per 1,000** (440 fewer to 104 fewer)	**RR 0.63** (0.45 to 0.87)
Mortality assessed with: Proportion of patients who died follow up: 1 years	889 per 1,000	**631 per 1,000** (533 to 738)	**258 fewer per 1,000** (356 fewer to 151 fewer)	**RR 0.71** (0.60 to 0.83)
Mortality assessed with: Risk of death	889 per 1,000	**998 per 1,000** (988 to 1,000)	**109 more per 1,000** (99 more to 111 more)	**HR 2.80** (2.01 to 3.90)
Complete remission assessed with: duration of complete remission	There was 1 study reporting this outcome. The difference in complete remission duration was 2.1 months shorter when patients received intensive antileukemic therapy versus best supportive care.			
Serious adverse events: Pneumonia assessed with: Proportion of patients experiencing Grade 3+ AE follow up: median 24.4 months	50 per 1,000	**48 per 1,000** (7 to 322)	**3 fewer per 1,000** (43 fewer to 272 more)	**RR 0.95** (0.14 to 6.44)
Serious adverse events: Febrile neutropenia assessed with: Proportion of patients experiencing Grade 3+ AE follow up: median 24.4 months	275 per 1,000	**311 per 1,000** (157 to 608)	**36 more per 1,000** (118 fewer to 333 more)	**RR 1.13** (0.57 to 2.21)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See table above and evidence profile 1a.	The panel judged that the magnitude of the potential increase of febrile neutropenia with intensive antileukemic therapy was small.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence for the critical outcomes is low.	The panel judged that mortality was the critical outcome of interest. The evidence for this outcomes is low-quality. The panel discussion focused on residual confounding and selection bias inherent to the observational studies that formed the majority of the evidence base for this question. Based on this and additional risk of bias considerations, the certainty of the evidence for critical outcomes was deemed to be low for critical outcomes.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	There were 3 studies that provided evidence regarding how patients value the outcomes.[1-3] In the first study, researchers assessed the heath state of different outcomes in 125 participants with AML in the UK, whose age ranged from 18 to 87 (mean 50 years), and found - Remission (median, IQR), 0.70, 0.50 to 0.90 - Relapse (median, IQR), 0.10, -0.10 to 50 - Functional status (functionally cured) (median, IQR), 0.80, 0.70 to 0.90 - There were no statistical differences between men and women In the second study, researchers assessed the health state of treatment failure/ relapse/ refractory disease in 210 participants, from whom 24.3% were 55 or older. The median (IQR) was 0.50 (0.45 to 0.57)	The panel discussed that most patients are likely to place a high value on any therapeutic interventions that offers possibility of remission and improvement in functional status.

	In the third study, researchers assessed the utility of different health states in 300 participants who did not necessarily has AML, and whose mean age was 44 years. The results showed - Complete remission, 0.88 - Relapse, 0.36 - Serious infection, -0.22 (from complete remission) - Abnormally low blood counts, -0.10 (from complete remission) Health states and utilities range from 0 to 1, where 0 represents death and 1 optimal health.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is low quality evidence of large benefits and small harms. Patients seem to value the benefits that intensive therapy can potentially achieve.	The panel judged that the benefits of offering antileukemic therapy on health outcomes are likely to outweigh the harms of doing so, even when accounting for the uncertainty in the evidence. Given the value attached to benefits associated with intensive therapy, the panel judged that the balance of effects probably favoured the intervention. The panel also considered the evidence of the comparison between less intensive therapy versus best supportive care. Given that there is moderate quality evidence for superiority of less intensive therapy when compared to best supportive care, and that there is no convincing evidence of non-inferiority when comparing intensive to less intensive antileukemic therapy, it was inferred that intensive therapy is also likely to be superior than best supportive care.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There was 1 systematic review in which researchers explored costs drivers relevant to this question.[4]The researchers describe that - Cost drivers for BSC: drugs (15%), support staff (10%), monitoring tests (1%) and transfusions (70%) - Costs were $4685 for patients who receive BSC Another study, conducted in France, showed[5] - Median use of packed red blood cells, 22 for intensive therapy and 7.5 for BSC - Median use of platelet concentrates, 18 for intensive therapy and 2 for BSC - Median use of frozen plasma, 0 for both groups	The panel noted that costs of antileukemic therapies and best supportive care interventions may vary across institutions and regions, and that resources may be limited institutionally or at a health systems level. Costs associated with antileukemic therapy were generally considered to be large; the panel did not consider this a primary consideration. Best supportive care costs may also be substantial, and variable depending on a given patient's care needs.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	There are issues regarding applicability for the identified studies, and thus the evidence was considered not relevant.	Intensive antileukemic therapy is more expensive than best supportive care. This factor did not have substantial bearing in the recommendation.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not find any research evidence	This factor did not have substantial bearing in the recommendation. However, the panel discussed that because there may be more benefits with intensive therapy than with best supportive care, the former is favores regardless of the added costs.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	One study in which researchers used data from 61,775 patients with AML from the USA National Cancer Database,[6]in which more than 70% were older than 55 years showed - Males are more likely to receive treatment than females (OR, 1.07; 95% CI 1.03 to 1.12) - African American are less likely to receive treatment than whites (OR 0.84, 95% CI, 0.73 to 0.96) and others (OR, 0.85; 95% CI, 0.78 to 0.93) - Lower median household incomes are less likely to receive treatment than higher median household income (ORs vary from 0.80 to 0.90)	This factor did not have substantial bearing in the recommendation.

	- Distance traveled was associated with receiving treatment (less distance less likely to receive therapy) - Likelihood of treatment decreased with uninsured status. - Treatment at academic centers increased likelihood of receiving therapy Another study in which researchers included data from 2,134 patients > 60 years showed that patients with lower education were less likely to receive high intensive therapy (OR, 0.65; 95% CI 0.44 to 0.98[7] A third study[8]in which researchers included data from approximately 6500 patients older than 60 years from California showed - Older patients less likely to receive treatment than 40-50 year old patients (OR for 60 to 75, 95% CI 0.80 to 0.86; OR for 76+, 0.43, 95% CI 0.41 to 0.46) - Females may be less likely to receive treatment than males (OR, 0.98, 95% CI 0.94 to 1) - No statistical differences between races/ethnicities (asian, hispanic, and black compared to white. - Likelihood of treatment decreases with nSES (OR 0.89 to 0.91) - Patients with favorable cytogenetics more likely to receive treatment (OR, 1.15; 95% CI 1.09 to 1.22) A fourth study[9]in which researchers included data from 11088 patients from California from whom 61% were 60 years or older showed - Black people less likely to receive treatment than white people (OR, 0.74; 05% CI, 0.61 to 0.91); but no differences between hispanics and whites. - Females may be less likely to receive treatment than males (OR, 1.10; 95% CI 0.99 to 1.20) - Older patients less likely to receive treatment - Patients with more comorbidities less likely to receive treatment (OR varies from 0.71 to 0.52)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A study in which researchers included 125 participants with a mean age of 50 years, in the UK showed that the health state median (IQR) of receiving treatment with chemotherapy is 0.50 (0 to 0.60). Health states range from 0 to 1, where 0 represents death and 1 optimal health.[1]	The panel had uniform agreement that patients with AML likely place high value on being considered for antileukemic therapy as appropriate. The panel discussed that most patients are likely to place a high value on having the option to access therapeutic interventions they may be considered for, especially where the risk-benefit balance may be unclear.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	This factor did not have substantial bearing in the recommendation.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

The ASH guideline panel suggests offering intensive antileukemic therapy over offering best supportive care only to older adults with newly diagnosed AML (conditional recommendation, based on low certainty evidence).

Related recommendation(s)

1. Should less intensive antileukemic therapy vs. best supportive care be used in older adults with newly diagnosed AML?
The ASH guideline panel recommends offering less intensive antileukemic therapy over offering best supportive care only to older adults with newly diagnosed AML (strong recommendation, moderate certainty evidence).

Justification

This recommendation places high value on the potential benefits of offering intensive antileukemic therapy to all AML patients who are candidates for this treatment, and how important patients and clinicians perceive the treatment itself as well as the potential benefits. The potential burden, costs, and feasibility concerns were judged to be less important, and the desirable consequences of offering antileukemic therapy were judged to outweigh the undesirable consequences.

Subgroup considerations

This recommendation applies to patients who are perceived to likely benefit from antileukemic therapy, in terms of clinical considerations such as baseline functional status and likelihood of remission.

Implementation considerations

No major concerns were identified with regards to implementation as per the panel's judgement.

Research priorities

There is a need for comparative studies addressing this question, with more rigorous evaluation of associated benefits and harms. The optimal study design to inform this recommendation question is a well designed randomized clinical trial comparing the options of interest. Observational studies in which similar groups of older adults with AML receive antileukemic therapy and best supportive care may also be valuable.

References

[1] Castejon N, Cappelleri JC, Cuervo J, Lang K, Mehta P, Mokgokong R, et al. Social preferences for health states associated with acute myeloid leukemia for patients undergoing treatment in the United Kingdom. Health Qual Life Outcomes. 2018;16:66.

[2] Joshi N, Hensen M, Patel S, Xu W, Lasch K, Stolk E. Health State Utilities for Acute Myeloid Leukaemia: A Time Trade-off Study. Pharmacoeconomics. 2019;37:85-92.
[3] Stein EM, Yang M, Guerin A, Gao W, Galebach P, Xiang CQ, et al. Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. Health and Quality of Life Outcomes. 2018;16 (1) (no pagination).
[4] Bosshard R, O'Reilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. Cancer Treatment Reviews. 2018;69:224-32.
[5] Cannas G, Fattoum J, Boukhit M, Thomas X. Economic analysis of blood product transfusions according to the treatment of acute myeloid leukemia in the elderly. Transfusion Clinique et Biologique. 2015;22:341-7.
[6] Bhatt VR, Shostrom V, Gundabolu K, Armitage JO. Utilization of initial chemotherapy for newly diagnosed acute myeloid leukemia in the United States. Blood Adv. 2018;2:1277-82.
[7] Ostgard LSG, Norgaard M, Medeiros BC, Friis LS, Schoellkopf C, Severinsen MT, et al. Effects of Education and Income on Treatment and Outcome in Patients With Acute Myeloid Leukemia in a Tax-Supported Health Care System: A National Population-Based Cohort Study. J Clin Oncol. 2017;35:3678-87.
[8] Jabo B, Morgan JW, Martinez ME, Ghamsary M, Wieduwilt MJ. Sociodemographic disparities in chemotherapy and hematopoietic cell transplantation utilization among adult acute lymphoblastic and acute myeloid leukemia patients. PLoS ONE. 2017;12:e0174760.
[9] Patel MI, Ma Y, Mitchell B, Rhoads KF. How do differences in treatment impact racial and ethnic disparities in acute myeloid leukemia? Cancer Epidemiol Biomarkers Prev. 2015;24:344-9.

QUESTION 1B

Should less intensive antileukemic therapy vs. best supportive care be used for older adults with newly diagnosed AML?	
POPULATION:	older adults with newly diagnosed AML
INTERVENTION:	less intensive antileukemic therapy
COMPARISON:	best supportive care
MAIN OUTCOMES:	Mortality; Hospitalization; Serious adverse events: Febrile neutropenia; Serious adverse events: Febrile neutropenia; Serious adverse events: Pneumonia; Serious adverse events: Septic shock; Complete remission; Burden on caregivers; Quality of life impairment; Functional impairment; Allogeneic hematopoietic stem cell transplant; Serious adverse events: Intensive care unit admission; Serious adverse events: Multi-organ failure; Serious adverse events: Acute respiratory failure;

ASSESSMENT

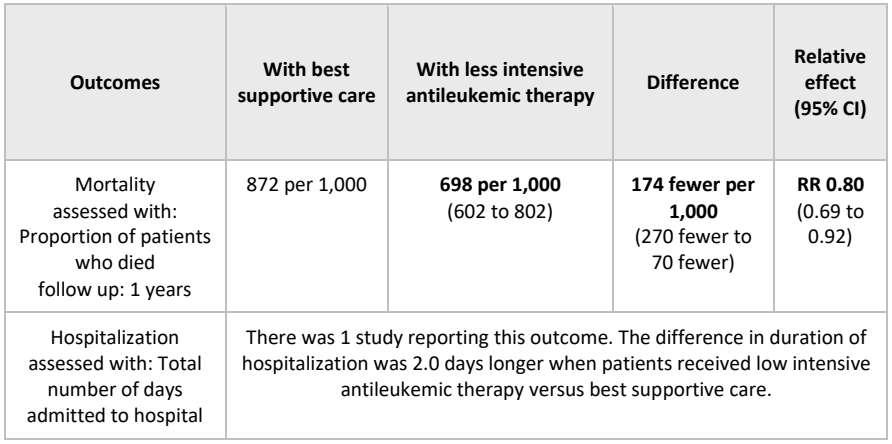
Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel prioritized this question, recognizing the importance of guidance for front-line clinicians regarding whether antileukemic therapy should be routinely offered for older adults with AML.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		The panel judged that the magnitude of the potential benefits of less-intensive antileukemic therapy on mortality was moderate.

Outcomes	With best supportive care	With less intensive antileukemic therapy	Difference	Relative effect (95% CI)
Mortality assessed with: Proportion of patients who died follow up: 1 years	872 per 1,000	**698 per 1,000** (602 to 802)	**174 fewer per 1,000** (270 fewer to 70 fewer)	**RR 0.80** (0.69 to 0.92)
Hospitalization assessed with: Total number of days admitted to hospital	There was 1 study reporting this outcome. The difference in duration of hospitalization was 2.0 days longer when patients received low intensive antileukemic therapy versus best supportive care.			

follow up: range 6 months to NA months				
Serious adverse events: Febrile neutropenia assessed with: Proportion of patients experiencing Grade 3+ AE follow up: range 18.5 months to 30.0 months	172 per 1,000	**235 per 1,000** (103 to 541)	**64 more per 1,000** (69 fewer to 369 more)	**RR 1.37** (0.60 to 3.15)
Serious adverse events: Pneumonia assessed with: Proportion of patients experiencing Grade 3+ AE follow up: range 18.5 months to 24.4 months	50 per 1,000	**190 per 1,000** (49 to 746)	**140 more per 1,000** (2 fewer to 696 more)	**RR 3.80** (0.97 to 14.92)
Mortality assessed with: Proportion of patients who died follow up: 30 days	158 per 1,000	**175 per 1,000** (125 to 247)	**17 more per 1,000** (33 fewer to 89 more)	**RR 1.11** (0.79 to 1.56)
Mortality assessed with: Proportion of patients who died follow up: 30 days	462 per 1,000	**208 per 1,000** (115 to 374)	**254 fewer per 1,000** (346 fewer to 88 fewer)	**RR 0.45** (0.25 to 0.81)
Mortality assessed with: Proportion of patients who died follow up: 6 months	656 per 1,000	**498 per 1,000** (413 to 603)	**157 fewer per 1,000** (243 fewer to 52 fewer)	**RR 0.76** (0.63 to 0.92)
Mortality assessed with: Proportion of patients who died follow up: 1 years	877 per 1,000	**561 per 1,000** (360 to 886)	**316 fewer per 1,000** (518 fewer to 9 more)	**RR 0.64** (0.41 to 1.01)
Mortality assessed with: Risk of death follow up: range 18.5 months to 30.0 months	842 per 1,000	**803 per 1,000** (715 to 866)	**39 fewer per 1,000** (127 fewer to 24 more)	**HR 0.88** (0.68 to 1.09)

Mortality assessed with: Risk of death follow up: median 35 months	877 per 1,000	**369 per 1,000** (285 to 455)	**508 fewer per 1,000** (592 fewer to 422 fewer)	**HR 0.22** (0.16 to 0.29)
Serious adverse events: Septic shock assessed with: Proportion of patients experiencing Grade 3+ AE follow up: median 18.5 months	83 per 1,000	**142 per 1,000** (83 to 243)	**59 more per 1,000** (0 fewer to 160 more)	**RR 1.71** (1.00 to 2.93)
Complete remission - not reported	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	-

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See table above and Evidence Profile 1b	The panel judged that the magnitude of the potential harms on adverse events was small.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ● Moderate ○ High ○ No included studies	The quality of the evidence for the critical outcomes is moderate.	The panel judged that mortality was the critical outcome of interest. One-year mortality was prioritized. Moderate-quality evidence from randomized trials and very low-quality evidence from observational studies was available for this comparison.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	There were 3 studies that provided evidence regarding how patients value the outcomes.[1-3] In the first study, researchers assessed the heath state of different outcomes in 125 participants with AML in the UK, whose age ranged from 18 to 87 (mean 50 years), and found - Remission (median, IQR), 0.70, 0.50 to 0.90 - Relapse (median, IQR), 0.10, -0.10 to 50 - Functional status (functionally cured) (median, IQR), 0.80, 0.70 to 0.90 - There were no statistical differences between men and women In the second study, researchers assessed the health state of treatment failure/ relapse/ refractory disease in 210 participants, from whom 24.3% were 55 or older. The median (IQR) was 0.50 (0.45 to 0.57) In the third study, researchers assessed the utility of different health states in 300 participants who did not necessarily has AML, and whose mean age was 44 years. The results showed - Complete remission, 0.88 - Relapse, 0.36 - Serious infection, -0.22 (from complete remission) - Abnormally low blood counts, -0.10 (from complete remission) Health states and utilities range from 0 to 1, where 0 represents death and 1 optimal health.	The panel discussed that patients place a high value on any therapeutic interventions that offers possibility of remission and improvement in functional status, and likeihood of relapse.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	There is moderate quality evidence of moderate benefits and harms. Patients seem to value the benefits that less intensive therapy can potentially achieve more than potential harms.	The panel judged that the benefits of offering less-intensive antileukemic therapy on health outcomes are likely to outweigh the harms of doing so, even when accounting for the uncertainty in the evidence. Given the value attached to benefits associated with less intensive therapy, the panel judged that the balance of effects probably favoured the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There was 1 systematic review in which researchers explored costs drivers relevant to this question.[4] The researchers describe that - cost drivers for less-intensive antileukemic therapy: drugs (86%), support staff (4%), monitoring tests (1%) and transfusions (9%) - cost drivers for BSC: drugs (15%), support staff (10%), monitoring tests (1%) and transfusions (70%) - Costs were 36,801 USD for patients who receive low intensity therapy, and 4685 for patients who receive BSC - Transfusions costs were similar for less intensive therapy and BSC Another study, conducted in France, showed [6] - Median use of packed red blood cells, 15 for less intensive therapy and 7.5 for BSC - Median use of platelet concentrates, 5 for less intensive therapy and 2 for BSC - Median use of frozen plasma, 0 for both groups	The panel noted that costs of antileukemic therapies and best supportive care interventions may vary across institutions and regions, and that resources may be limited institutionally or at a health systems level. Costs associated with antileukemic therapy were generally considered to be moderate; the panel did not consider this important enough to have a bearing in the recommendation. Best supportive care costs may also be substantial, and variable depending on a given patient's care needs.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	There are issues regarding applicability for the identified studies, and thus the evidence was not considered to be relevant	Certain studies were excluded due to inclusion of interventions that were not formally approved for use as indicated (e.g., tipifarnib). This factor did not have substantial bearing in the recommendation otherwise.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Although less intensive therapy seems to have more important benefits on health outcomes that best supportive care, there are also larger costs.	This factor did not have substantial bearing in the recommendation.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	One study in which researchers used data from 61,775 patients with AML from the USA National Cancer Database, in which more than 70% were older than 55 years showed (Bhatt 2018) - Males are more likely to receive treatment than females (OR, 1.07; 95% CI 1.03 to 1.12) - African American are less likely to receive treatment than whites (OR 0.84, 95% CI, 0.73 to 0.96) and others (OR, 0.85; 95% CI, 0.78 to 0.93) - Lower median household incomes are less likely to receive treatment than higher median household income (ORs vary from 0.80 to 0.90) - Distance traveled was associated with receiving treatment (less distance less likely to receive therapy) - Likelihood of treatment decreased with uninsured status. - Treatment at academic centers increased likelihood of receiving therapy Another study in which researchers included data from 2,134 patients > 60 years showed that patients with lower education were less likely to receive high intensive therapy (OR, 0.65; 95% CI 0.44 to 0.98 A third study (Jabo) in which researchers included data from approximately 6500 patients older than 60 years from California showed - Older patients less likely to receive treatment than 40-50 year old patients (OR for 60 to 75, 95% CI 0.80 to 0.86; OR for 76+, 0.43, 95% CI 0.41 to 0.46) - Females may be less likely to receive treatment than males (OR, 0.98, 95% CI 0.94 to 1) - No statistical differences between races/ethnicities (asian, hispanic, and black compared to white. - Likelihood of treatment decreases with nSES (OR 0.89 to 0.91) - Patients with favorable cytogenetics more likely to receive treatment (OR, 1.15; 95% CI 1.09 to 1.22) A fourth study (Patel) in which researchers included data from 11088 patients from California from whom 61% were 60 years or older showed	This factor did not have substantial bearing in the recommendation.

	- Black people less likely to receive treatment than white people (OR, 0.74; 05% CI, 0.61 to 0.91); but no differences between hispanics and whites. - Females may be less likely to receive treatment than males (OR, 1.10; 95% CI 0.99 to 1.20) - Older patients less likely to receive treatment - Patients with more comorbidities less likely to receive treatment (OR varies from 0.71 to 0.52)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A study in which researchers included 125 participants with a mean age of 50 years, in the UK showed that (Castejon 2018) the health state median (IQR) of receiving treatment with chemotherapy is 0.50 (0 to 0.60). Health states range from 0 to 1, where 0 represents death and 1 optimal health.	The panel had uniform agreement that patients with AML likely place high value on being considered for antileukemic therapy as appropriate. The panel discussed that patients place a high value on having the option to access therapeutic interventions they may be considered for, especially where the risk-benefit balance may be unclear.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence found	This factor did not have substantial bearing in the recommendation.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know

RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

QUESTION 2

Should intensive antileukemic therapy vs. less intensive antileukemic therapy be used for older adults with newly diagnosed AML considered candidates for antileukemic therapy?	
POPULATION:	older adults with newly diagnosed AML considered candidates for antileukemic therapy
INTERVENTION:	intensive antileukemic therapy
COMPARISON:	less intensive antileukemic therapy
MAIN OUTCOMES:	Mortality; Allogeneic hematopoietic stem cell transplantation; Serious adverse events;; ICU hospitalization (Serious adverse events); Hospitalization (Serious adverse events); Complete remission; Quality of life impairment; Functional status impairment; Burden on caregivers

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is no research evidence	The panel judged that this questions was a priority

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		The evidence suggests that when comparing intensive to less-intensive antileukemic therapy - There is a lower risk of death over time - There is a higher probability of receiving an allo-transplant - There is a lower risk of experiencing pneumonia

		This potential benefits were judged to be of moderate importance

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		The evidence suggests that when comparing intensive to less-intensive antileukemic therapy - There is a higher risk of treatment emergent adverse events - There is a higher risk of intensive care unit hospital admission - There is a longer duration of hospitalization These potential harms were judged of small importance

Outcomes	With less intensive antileukemic therapy	With intensive antileukemic therapy	Difference	Relative effect (95% CI)
Mortality assessed with: Risk of death follow up: range 7.7 months to 60 months	578 per 1,000	**490 per 1,000** (449 to 536)	**88 fewer per 1,000** (129 fewer to 42 fewer)	**HR 0.78** (0.69 to 0.89) [Mortality]
Mortality (sensitivity analyses by including non significance studies, taking HR as 1) assessed with: Risk of death follow up: range 6 months to 60 months	578 per 1,000	**520 per 1,000** (485 to 556)	**58 fewer per 1,000** (93 fewer to 22 fewer)	**HR 0.85** (0.77 to 0.94) [Mortality (sensitivity analyses by including non significance studies, taking HR as 1)]
Mortality assessed with: Proportion of people who died follow up: 30 days	83 per 1,000	**100 per 1,000** (61 to 164)	**17 more per 1,000** (21 fewer to 82 more)	**RR 1.21** (0.74 to 1.99)

Mortality assessed with: Proportion of people who died follow up: 1 years	578 per 1,000	**538 per 1,000** (492 to 584)	**40 fewer per 1,000** (87 fewer to 6 more)	**RR 0.93** (0.85 to 1.01)	
Mortality assessed with: Proportion of people who died follow up: 1 years	558 per 1,000	**463 per 1,000** (340 to 631)	**95 fewer per 1,000** (218 fewer to 73 more)	**RR 0.83** (0.61 to 1.13)	
Allogeneic hematopoietic stem cell transplantation assessed with: Proportion of people who received AlloHCT/AlloSCT follow up: range 8.5 months to 60 months	31 per 1,000	**207 per 1,000** (129 to 334)	**176 more per 1,000** (97 more to 302 more)	**RR 6.65** (4.13 to 10.71)	
Serious adverse events assessed with: Proportion of people who had Treatment emergent adverse events follow up: median 5 years	463 per 1,000	**537 per 1,000** (472 to 602)	**74 more per 1,000** (9 more to 139 more)	**RR 1.16** (1.02 to 1.30)	
Serious adverse events assessed with: Proportion of people who had	349 per 1,000	**143 per 1,000** (63 to 331)	**206 fewer per 1,000** (286	**RR 0.41** (0.18 to 0.95)	

Treatment emergent adverse events follow up: median 24.4 months			fewer to 17 fewer)	
Serious adverse events assessed with: Proportion of people who had febrile neutropenia follow up: range 20 months to 24.4 months	337 per 1,000	**350 per 1,000** (313 to 388)	**13 more per 1,000** (24 fewer to 51 more)	**RR 1.04** (0.93 to 1.15)
Serious adverse events assessed with: Proportion of people who had anemia follow up: median 24.4 months	185 per 1,000	**139 per 1,000** (65 to 302)	**46 fewer per 1,000** (120 fewer to 117 more)	**RR 0.75** (0.35 to 1.63)
Serious adverse events assessed with: Proportion of people who had anemia follow up: median 20.1 months	620 per 1,000	**372 per 1,000** (174 to 812)	**248 fewer per 1,000** (446 fewer to 192 more)	**RR 0.60** (0.28 to 1.31)
Serious adverse events assessed with: Proportion of people who had neutropenia follow up: median 24.4 months	257 per 1,000	**334 per 1,000** (211 to 532)	**77 more per 1,000** (46 fewer to 275 more)	**RR 1.30** (0.82 to 2.07)

Serious adverse events assessed with: Proportion of people who had neutropenia follow up: median 20.1 months	930 per 1,000	**893 per 1,000** (716 to 1,116)	**37 fewer per 1,000** (241 fewer to 186 more)	**RR 0.96** (0.77 to 1.20)	
Serious adverse events assessed with: Proportion of people who had thrombocytopenia follow up: median 24.4 months	252 per 1,000	**217 per 1,000** (118 to 393)	**35 fewer per 1,000** (134 fewer to 141 more)	**RR 0.86** (0.47 to 1.56)	
Serious adverse events assessed with: Proportion of people who had thrombocytopenia follow up: median 20.1 months	930 per 1,000	**874 per 1,000** (660 to 1,153)	**56 fewer per 1,000** (270 fewer to 223 more)	**RR 0.94** (0.71 to 1.24)	
Serious adverse events assessed with: Proportion of people who had pneumonia follow up: median 24.4 months	190 per 1,000	**48 per 1,000** (11 to 186)	**143 fewer per 1,000** (179 fewer to 4 fewer)	**RR 0.25** (0.06 to 0.98)	
Serious adverse events assessed with: Proportion of people who admitted to ICU due to therapy follow up: median 2 years	176 per 1,000	**420 per 1,000** (288 to 613)	**244 more per 1,000** (112 more to 438 more)	**RR 2.39** (1.64 to 3.49)	

ICU hospitalization (Serious adverse events) assessed with: Duration in days follow up: median 20 months	The mean ICU hospitalization (Serious adverse events) was **2.33** days	The mean ICU hospitalization (Serious adverse events) in the intervention group was 6.84 days higher (3.44 higher to 10.24 higher)	MD **6.84 days higher** (3.44 higher to 10.24 higher)	-
Hospitalization (Serious adverse events) assessed with: Duration in days of hospitalization follow up: range 20 months to 60 months	The mean hospitalization (Serious adverse events) was **24.36** days	The mean hospitalization (Serious adverse events) in the intervention group was 12.96 days higher (16.23 lower to 42.15 higher)	MD **12.96 days higher** (16.23 lower to 42.15 higher)	-
Overall survival assessed with: Duration in months follow up: range 6 months to 60 months	There were 14 studies (16 arm-level comparisons) reporting this outcome. Near half of the comparisons (7) reported a shorter overall survival (OS) with IC, half (8) reported a longer OS with IC and 1 reported the same OS durations between the two groups. The difference in OS duration ranged from 3.5 months shorter to 7.6 months longer when patients received IC versus less-intensive therapy.			
Overall survival assessed with: Duration in months follow up: range 20.1 months to 24.4 months	There were 2 studies (4 arm-level comparisons) reporting this outcome. 3 reported a shorter overall survival (OS) with IC and 1 reported a longer OS with IC. The difference in OS duration ranged from 10.3 months shorter to 5.8 months longer when patients received IC versus less-intensive therapy.			
Complete remission assessed with: Duration in months (or time	There were 4 studies reporting this outcome. Most of them (3) reported a shorter remission with IC. The difference in CR duration ranged from 3.1 months shorter to 0.03 months longer when patients received IC versus less-intensive therapy.			

	to relapse) follow up: range 13.3 months to 60 months	
	Complete remission assessed with: Duration in months (or time to relapse) follow up: median 24.4 months	There was 1 study reporting this outcome. The difference in CR duration was 2.5 months shorter when patients received IC versus less-intensive therapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	There is low quality evidence for the critical outcomes	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or	There were 3 studies that provided evidence regarding how patients value the outcomes (Castejon 2018, Joshi 2018, Stein 2018)	Panel noted that majority of patients will place more value on the uncertain benefit on survival over the uncertain harm in adverse events and hospitalization, but this will possibly vary.

variability ○ No important uncertainty or variability	In the first study, researchers assessed the heath state of different outcomes in 125 participants with AML in the UK, whose age ranged from 18 to 87 (mean 50 years), and found - Remission (median, IQR), 0.70, 0.50 to 0.90 - Relapse (median, IQR), 0.10, -0.10 to 50 - Functional status (functionally cured) (median, IQR), 0.80, 0.70 to 0.90 - There were no statistical differences between men and women In the second study, researchers assessed the health state of treatment failure/ relapse/ refractory disease in 210 participants, from whom 24.3% were 55 or older. The median (IQR) was 0.50 (0.45 to 0.57) In the third study, researchers assessed the utility of different health states in 300 participants who did not necessarily has AML, and whose mean age was 44 years. The results showed - Complete remission, 0.88 - Relapse, 0.36 - Serious infection, -0.22 (from complete remission) - Abnormally low blood counts, -0.10 (from complete remission) Health states and utilities range from 0 to 1, where 0 represents death and 1 optimal health.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is low quality evidence suggesting a small benefit in Mortality when using intensive versus less intensive therapy. Intensive therapy, however, also results in more severe adverse effects. Given that the decision may depend on the patient, both the intervention or the comparison may be favor depending on the case.	There is low to very low quality of a benefit of intensive over less-intensive antileukemic therapy in mortality, which the panel judged to be of moderate importance. Given than there is also very low quality of potential harms, which were considered of small importance by the panel; and that patients are more likely to value the potential benefits, the balance of effects probably favors intensive antileukemic therapy.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There were 3 studies providing information on costs for these patients (Bosshard 2018, Cannas 2015, Batty 2013). The first study describes that patients receiving intensive chemotherapy require more transfusions than those receiving low intensity therapy, for no significant survival advantage. The second study describes that - Median use of packed red blood cell: 22 for intensive and 15 for less intensive therapy - Median use of platelet concentrate: 18 for intensive, 5 for less intensive therapy - Median use of fresh frozen plasma: 0 for both groups The third study describes that the incremental cost effectiveness ratio was -170,503 favoring decitabine compared to intensive therapy (QUALY, 0.18 for	The panel did not consider this to be a factor that had an important bearing in the recommendation.

	intensive therapy and 0.60 for decitabine; costs, 127,867 for intensive therapy and 55,777 for decitabine).	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The studies may not be applicable to most patients.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		The panel did not consider this to be a factor that had an important bearing in the recommendation.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	There was 1 study providing evidence for this question (Ostgart, 2017). Researchers included data from 2,134 patients with AML who were 60 years or older, and found that patients with lower education were less likely to receive high intensive therapy than less-intensive therapy or BSC (OR, 0.65; 95% CI 0.44 to 0.98)	The panel did not consider this to be a factor that had an important bearing in the recommendation.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There was 1 study providing research evidence for this question (Bories, 2016). Researchers surveyed 230 physicians who treated older adults with AML. The results are: - Ambiguity tolerant physicians are less likely to prescribe intensive than less intensive therapy or BSC (OR, 0.87; 95% CI 0.77 to 0.99)	Intensive antileukemic therapy is an option used in several patients, which supports its acceptability by all relevant stakeholders.

	- Physicians not conforming to expected utilities may be more likely to recommend intensive than less intensive therapy or BSC (OR, 1.85; 95% CI, 0.92 to 3.73) - Females may be more likely to recommend intensive than less intensive therapy or BSC (OR, 0.58; 95% CI, 0.28 to 1.20)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not find any research evidence	Intensive antileukemic therapy is commonly done in patients who are candidates for it, which demosntrated that it is feasible to implement.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests intensive antileukemic therapy over less intensive antileukemic therapy in older adults with newly diagnosed AML considered candidates for intensive antileukemic therapy (conditional recommendation, low quality evidence).

Justification

This recommendation places a high value on the potential benefits of intensive over less-intensive antileukemic therapy. Even though there is low to very low quality evidence of such benefits, there is no higher quality evidence that less-intensive antileukemic therapy results in better health outcomes. Although values and preferences are likely to vary, it is likely that most patients value the uncertain benefits more than the uncertain harms. Intensive antileukemic therapy is an option likely to be acceptable to stakeholders and there are no issues related to its implementation. Costs did not have a bearing in this recommendation.

Subgroup considerations

Implementation considerations

Research priorities

The evidence includes patients with both, intermediate and poor prognosis. Because of the way in which studies are reported, we could not separate these subgroups. Even though at the study level there seem to be no differences in outcomes between them, the panel believes that studies that explore this issue at a patients level (RCTs and OSs with proper subgroup analyses, and systematic reviews with individual patient data) may help informing this question when revising and updating these recommendations.

QUESTION 3

Should post-remission therapy vs. no additional therapy be used for older adults with newly diagnosed AML who achieve remission after at least 1 cycle of intensive antileukemic therapy?	
POPULATION:	older adults with newly diagnosed AML who achieve remission after at least 1 cycle of intensive antileukemic therapy
INTERVENTION:	post-remission therapy
COMPARISON:	no additional therapy
MAIN OUTCOMES:	Mortality; Quality of life; Functional status; Recurrence; Severe toxicity; Hospitalization

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence.	The panel considers this is a relevant issues to address

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See evidence profiles 1 to 6	After reviewing the evidence, the panel judged that there seem to be moderate benefits of post-remission therapy

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See evidence profiles 1 to 6	The panel judged that the potential harms of post-remission therapy are small

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall quality of the evidence varies from moderate to very low across comparisons.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or	One study[1] in which researchers included information from 125 participants, whose mean age was 50 years showed that	The panle discussed that it is likely that most patients value prolonged survival and remaining in remission similarly, and that

variability ○ No important uncertainty or variability	- Health state mean (95% CI), median (IQR): relapse, 0.12 (0.03 to 0.22) and 0.10 (-0.10 to 0.50). No statistical differences between men and women. - Health state mean (95% CI), median (IQR): Functionality cured, 0.75 (0.71 to 0.79) and 0.80 (0.70 to 0.90). No statistical differences between men and women. In a second study, researchers assessed the health state of treatment failure/ relapse/ refractory disease in 210 participants, from whom 24.3% were 55 or older. The median (IQR) was 0.50 (0.45 to 0.57)[2] In a third study,[3] researchers assessed the utility of different health states in 300 participants who did not necessarily has AML, and whose mean age was 44 years. The results showed - Complete remission, 0.88 - Relapse, 0.36 - Serious infection, -0.22 (from complete remission) - Abnormally low blood counts, -0.10 (from complete remission)	they are likely to place more value on these outcomes than in the potential adverse effects.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Moderate to very low quality evidence suggests that there may be moderate benefits of post-remission therapy. Very low quality evidence suggests that there may be toxicity. Patients are likely value the benefits.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There is no research evidence	The panel discussed that post-remission therapy is likely to result in more costs than no-postremission therapy

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There is no research evidence	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no research evidence	The panel discussed that the potential benefits of post-remission therapy are wirth the added costs.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	One study [4] in which researchers included information from 421 patients from the Cleveland Clinic, whose mean age was 55 years, showed that white patients are more likely to have a shorter time to initiation of post-remission therapy (HR, 0.25; 95% CI 0.06 to 0.77; median for whites 1.07 months, for black 2.73 months) than black patients.	This factor did not have a bearing in this recommendation

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One study [1] in which researchers included information from 125 participants, whose mean age was 50 years showed that the health state mean (95% CI), median (IQR) for consolidation was 0.47 (0.41 to 0.53) and 0.50 (0.20 to 0.70). There were no statistical differences between men and women. Another study [2] in which researchers assessed the health state in 210 participants, from whom 24.3% were 55 or older showed that	The panel discussed that post-remission therapy is likely to be acceptable to all stakeholders.

	- Health state mean (95% CI), median (IQR): Consolidation, 0.57 (0.51 to 0.63) and 0.70 (0.50 to 0.90). - Health state mean (95% CI), median (IQR): Maintenance, 0.89 (0.88 to 0.89) and 0.95 (0.85 to 1.00).	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is no research evidence	Post-remission therapy is already implemented in many settings.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests post-remission therapy over no additional therapy in older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy, and who are not candidates for allo-HSCT (conditional recommendation, low quality evidence)

Remarks: In some settings, patients may receive 2 cycles of intensive antileukemic therapy even if they achieve remission after the first one. In those settings, the second cycle can be considered post-remission therapy.

Justification

The panel determined that there may be a benefit of post-remission therapy over no additional therapy in older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy, and who are not candidates for allo-HSCT. It is likely that there is little variability among patients in the value of prolonged survival and remaining in remission for a longer time. Post-remission therapy is likely to be accepted by all stakeholders. This recommendation places a high value on the potential benefits of post-remission therapy.

The panel acknowledged that the evidence is not sufficient to make a recommendation for a specific number of cycles.

Subgroup considerations

Implementation considerations

Research priorities

The EtDs for question 4 will be posted the first week of December.

QUESTION 5

Should continuing therapy indefinitely until progression/ toxicity vs. giving therapy for a finite number of cycles be used for older adults with AML who received less-intensive antileukemic therapy and who achieved a response?	
POPULATION:	older adults with AML who received less-intensive antileukemic therapy and who achieved a response
INTERVENTION:	continuing therapy indefinitely until progression/ toxicity
COMPARISON:	giving therapy for a finite number of cycles
MAIN OUTCOMES:	Mortality, quality of life impairment, functional status impairment, burden on caregivers, severe toxicities

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is no research evidence	There is a lack of guidance regarding what to do in older adults with AML who achieve a response after treatment with less-intensive antileukemic therapy.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	There were no comparative studies addressing this question. The panel used two sources of indirect evidence to inform the judgments regarding desirable and undesirable effects. First, there were 2 randomized clinical trials in which researchers compared the outcomes of patients who received less-intensive antileukemic therapy with those of patients who received best supportive care.[1, 2] In both studies, the researchers describe that patients received at least 6 cycles of Azacitidine for 7 consecutive days (each cycle was 28 days). The researchers do not describe how many patients achieved a response after a specific number of cycles, and	The panel discussed that there seemed to be an approximate 10% difference in the absolute risk of death between the alternatives, favoring continuing therapy. The panel discussed at the meeting that, according to their experience, the 2 year survival is ~10% (5-10 but not more than 10) when continuing treatment, and ~0% (about 0 to 1%) when stopping treatment.

	only describe that, overall, 27.8% of patients achieved a hematologic response in one study[1] and 18% did in the other study.[2] Second, we conducted a survey among the panel members to systematically collect their experiences. The survey was based on the panelist's best recollection of experiences, because it was not feasible to collect information from clinical records given the timelines for the development of these guidelines. The results are: - Number of experts who responded: 10 - 100% continue therapy indefinitely until progression or severe toxicity, 80% do it in all patients - Similar results between strategies, but much less data for the second - Survival may be slightly better in patients that continue therapy indefinitely than in those who stop Experience with patients who continue indefinitely: - Percentage of patients alive at 3 months: median, 61; IQR, 60-66; range, 40 to 90 - Percentage of patients alive at 6 months: median, 50; IQR, 37-50; range, 12.5 to 75 - Percentage of patients alive at 1 year: median, 25; IQR, 20-27; range, 0 to 40 - Average survival in months; median, 7.25 ; IQR, 6- 7.9; range, 3 to 10 - Percentage of patients with severe toxicity: median, 17; IQR, 10-33; range, 4 to 50 - Percentage of patients with good QoL: median, 30; IQR, 20-32; range, 17-38 - Percentage of patients with acceptable QoL: median, 40; IQR, 33-40; range, 12.5-50 - Percentage of patients with poor QoL: median, 30; IQR, 28-40; range, 20-66.7 - Percentage of patients with good, acceptable, and poor functional status similar to that of QoL - Percentage of patients with acceptable burden on caregivers: median, 52; IQR 40 to 75 - Percentage of patients with unacceptable burden on caregivers: median, 48; IQR 25 to 60 Experience with patients who stop therapy: - Percentage of patients alive at 3 months: median, 60; IQR, 50-70; range, 40 to 80 - Percentage of patients alive at 6 months: median, 40; IQR, 35-45; range, 30 to 50 - Percentage of patients alive at 1 year: median, 15; IQR, 12.5- 17.5; range, 10 to 20 - Average survival in months; median, 7.5; IQR, 6.75- 8.25; range, 6 to 9	

	- Percentage of patients with good, acceptable, and poor QoL or functional status similar to that of the patients who continue indefinitely - Percentage of patients with acceptable and unacceptable burden on caregivers similar to that of the patients who continue indefinitely	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See evidence summary above (in “desirable effects”)	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The data was obtained from a survey to panel members. Panel members were asked to recall the proportions of patients with specific outcomes with both options, and thus there are very serious limitations owing to risk of bias. Even though this is evidence is very low certainty, it is the best evidence available to inform this recommendation.	The panel discussed and acknowledged the limitations of the evidence. The evidence from the randomized clinical trials was very serious limitations related to indirectness, because these do not address the question of interest and were only used to get a better understanding of what could be the standard. Second, the panel acknowledged the very serious risk of biases (recall and confounding) of the data.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was found	The panel discussed that patients who are likely to accept burden of treatment are likely to favour intervention. Patients who are likely to be toxicity-averse or treatment burden-averse with uncertain benefit will likely favour control. However, given the experience of the panel members, it seems that most patients do not place a high value on the burden of treatment and care more about the potential benefits on survival.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Very low quality evidence suggests that there may be a longer survival when patients continue therapy indefinitely, and patients are likely to value this outcome over the potential burden of continuing therapy indefinitely. The quality of life and functional status seems to be similar between the groups.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence found	Continuing therapy is more likely to be more expensive than stopping it. This factor, however, did not have a bearing in the recommendation

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There were no included studies and thus the quality of the evidence could not be assessed	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence found	The panel discussed that patients who continue therapy indefinitely may have more expenses related to the continued use of drugs. At the same time, they may have a longer survival.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No research evidence found	This factor did not have a bearing in the recommendation

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	From the survey conducted, we can infer that continuing therapy indefinitely is acceptable to most stakeholders: all experts use this option most of the time, which implies that this option is acceptable to most patients and caregivers (regardless of the fact that the burden on caregivers seem to be higher than when stopping therapy)	The panel discussed examples of when the burden may make continuing therapy unacceptable (i.e. patients and caregivers who have to drive long distances to get the continued therapy once a month). This is why they judged that it is likely that this option is acceptable for most, but not definitely.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes	The survey reflects that continuing therapy indefinitely is feasible to implement, because all experts use this option most of the time	

● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy in older adults with AML who achieve a response after receiving less-intensive therapy. (conditional recommendation, based on very low certainty evidence).

Justification

This recommendation places a high value on the potential benefits of survival when continuing therapy indefinitely, and in the acceptability of the intervention from clinicians and researchers who seem to continue therapy as the default option. It also places a low value on the moderate costs that are likely to result from continuing therapy indefinitely. Values and preferences of patients are likely to play an important role: patients who are likely to accept burden of treatment are likely to benefit more from continuing over stopping therapy. Patients who are likely to be toxicity-averse or treatment burden-averse with uncertain benefit will likely benefit more from stopping therapy.

Subgroup considerations

Implementation considerations

Research priorities

There is a need for comparative studies addressing this question.

QUESTION 6

Should red blood cells transfusions, platelet transfusions, or both, vs. no transfusions be used for older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life or hospice care)?	
POPULATION:	Older adults with AML who are not receiving antileukemic therapy (including those receiving end-of-life or hospice care)
INTERVENTION:	Red blood cells (RBC) transfusion, platelet transfusions, both
COMPARISON:	no transfusion
MAIN OUTCOMES:	Mortality; Functional status impairment; Quality of life impairment; Fatigue; Burden on caregivers; Hospice care; Hospitalization; Major bleeding; Transfusion refractoriness

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence	The panel discussed that this question is relevant to address given the lack of understanding of the importance from such stakeholders, such as hospital administrators, of the matter.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Outcomes** / **Impact** Mortality assessed with: Time from transfusion to death — The median or mean survival after transfusion ranged from 42 days to 3 months; however, three out of the four studies reported a time < 50 days. Mortality assessed with: Survival within 15 days of transfusion — Adjusted analysis showed that transfusion was not associated with survival within 15 days of transfusion	The panel judged that the magnitude of the potential benefits was moderate.

Functional status impairment assessed with: Scores of different instruments follow up: 1 weeks	Two studies showed that physical function decreased one week after transfusion. One study showed a reduction from 70 in the Barthel index score, to 66. Another study showed a reduction from 59.2 in the Australia-modified Karnofsky Performance Scale, to 46.3.
Quality of life impairment assessed with: Scores of different instruments to measure wellbeing follow up: 2 weeks	Two studies reported improvement in wellbeing scores. One study reported a change from 4.2 to 5.8, and another from 3.9 to 6.0 (measured using a visual analogue scale)
Quality of life impairment assessed with: Perception of improvement in wellbeing	The proportion of patients who (themselves or the clinicians) reported an improvement in wellbeing was 65% in one study and 51.4% in another.
Quality of life impairment assessed with: Perception of quality of life improvement	One study reported that quality of life improved by 68%. Another reported that the index improved, but there were no values provided in the systematic review.
Fatigue assessed with: Scores of different instruments to measure fatigue	One study reported that median FACT-F scores changed from 12.5 before transfusion to 23.5 after. Another reported very small changes, from 4.8 before transfusion to 4.9 after 7 days.
Fatigue assessed with: Perception of improvement	One study reported that 70% of patients perceived an improvement in fatigue after transfusion.
Fatigue assessed with: Scores using a visual analogue scale 0-100	Scores were 35.9 in patients who received transfusions and 29.4 in those who did not. Differences seem to be not statistically significant.
Burden on caregivers	Not reported
Hospice care	Not reported
Hospitalization	Not reported
Major bleeding	Not reported
Transfusion refractoriness	Not reported

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See table in "Desirable effects" section and Evidence Profile in Appendix X.	The panel discussed that there may be additional downsides of transfusions not captured in the studies, such as: - complications after transfusion that would lead to hospitalization - burden to patients and caregivers receiving transfusions

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence for the critical outcomes is very low	The panel discussion focused on the very serious indirectness of the evidence. The systematic reviews used to inform this question, given the lack of direct evidence after our systematic review, did not provide details regarding the types of malignancies included in the studies, yet it is likely that these were mostly solid tumours. The panel believes that the potential benefits of transfusion may be importantly different in older adults with AML.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	There is no research evidence	The panel discussed that patients place a high value on avoiding bleeding, which they believe is achieved through the transfusions. Moreover, those who put high value in possible increases in well-being with transfusion more likely, those who are burdened by accessing transfusions in health care setting with unclear likelihood of benefit are less likely

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Even though there is very low quality evidence, there seem to be moderate benefits of red cell transfusions. There is also no evidence of harms.	The panel judged that the benefits of transfusions on health outcomes are likely to outweigh the harms, even when accounting for the uncertainty in the evidence.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There is no research evidence	The panel noted potential impact on blood blanks, cost of transfusions and that transfusion resources are not unlimited. They also noted that, in patients in hospice, the resources required for transfusions are considerable. However, if transfusions are made available in hospice there are potential savings given that some patients who require or desire these transfusions could be transferred from a hospital to a hospice.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There is no research evidence	This factor did not have any bearing in the recommendation

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no research evidence	This factor did not have any bearing in the recommendation

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	There is no research evidence	This factor did not have any bearing in the recommendation

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	One survey of 348 physicians reported that transfusions are acceptable to them, regardless of the cost, and that most believe that transfusions should not be withheld from terminal patients	The panel had uniform agreement that patients with AML place high value on receiving transfusions near the end of life.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There were 6 studies providing information regarding feasibility. Transfusions seem feasible, given that they can be performed at home in many patients.	The panel discussed some issues that may threaten the feasibility of transfusions, for example, - Inability to receive transfusions because of systemic obstacles (e.g. ineligibility for hospice care). - in some settings patients need to check into hospital and wait for transfusion Nevertheless, they stilt judged that it is likely that transfusions are feasible.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests RBC transfusions and platelet transfusions be available over not having transfusions available for older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life care or hospice care) (conditional recommendation, based on very low certainty evidence).

Remarks:
- the decision to give RBC transfusions or platelet transfusions should not substitute end of life discussions

Justification

This recommendation places high value on the potential benefits of RBC and platelet transfusions on health-related quality of life, and how important patients and clinicians perceive the treatment itself as well as the potential benefits are. The potential burden, costs, and feasibility concerns were judged to be less important than the desirable consequences mentioned above.

Subgroup considerations

This recommendation applies to patients who are perceived to likely benefit from RBC transfusions or platelet transfusions, such as those with with symptomatic anemia or active bleeding

Implementation considerations

Research priorities

There is a need for comparative studies addressing this question. The optimal study design to inform this recommendation question is a well designed randomized clinical trial comparing the options of interest (including a no-transfusion arm), and measuring the outcomes that are important to patients (particularly, health-related quality of life). Observational studies in which similar groups of older adults with AML received transfusions and others did not could also be useful.

1: Chin-Yee N, Taylor J, Rourke K, Faig D, Davis A, Fergusson D, Saidenberg E.
Red blood cell transfusion in adult palliative care: a systematic review.
Transfusion. 2018 Jan;58(1):233-241. doi: 10.1111/trf.14413. Epub 2017 Dec 1.
Review. PubMed PMID: 29194669.

2: Uceda Torres ME, Rodríguez Rodríguez JN, Sánchez Ramos JL, Alvarado Gómez F.
Transfusion in palliative cancer patients: a review of the literature. J Palliat
Med. 2014 Jan;17(1):88-104. doi: 10.1089/jpm.2013.0387. Epub 2013 Dec 10. Review.
PubMed PMID: 24325560.