ACUTE MYELOID LEUKEMIA
NATIONAL CLINICAL PRACTICE GUIDELINES

NATIONAL INTEGRATED CANCER CONTROL PROGRAM

Acute Myeloid Leukemia National Clinical Practice Guidelines

Published by
National Integrated Cancer Control Program
Disease Prevention and Control Bureau
Department of Health
San Lazaro Compound, Rizal Avenue, Sta. Cruz
Manila 1003, Philippines

An electronic copy of this publication can be downloaded at: www.doh.gov.ph

Suggested citation. Department of Health. (2022). *Acute Myeloid Leukemia National Clinical Practice Guidelines*. Manila, Philippines.

General disclaimers

This document has been produced with the assistance of the Department of Health. The contents of this publication are the sole responsibility of the Guideline Development Group, and does not necessarily reflect the opinions, recommendations, or advice of the Department of Health.

Editorial and Publication Team

Acute Myeloid Leukemia Guideline Development Group

Technical Advisory Group

Chair:	Dr. Nilo C. de los Santos East Avenue Medical Center
Co-chair:	Dr. Clarito U. Cairo, Jr. Department of Health
Members:	Ms. Alma B. Abainza-Sanchez Philippine Health Insurance Corporation
	Dr. Allan Troy D. Baquir East Avenue Medical Center
	Dr. Samuel S. Duran East Avenue Medical Center

Steering Committee

Chair:	Dr. Lucille Osias
Members:	Dr. Lynn Bonifacio Dr. Prerna Vaswani Dr. Chrystal Catli-Burog Dr. Ma. Clariza Santos Dr. Camille Ariadne Tanchanco Dr. Mary Shayrel Lagan-Ragas Dr. Ma. Regina De Leon Dr. Alma Calavera Dr. Roxan Perez Dr. Alejandro Arevalo Dr. Rose Lou Marie Agbay

Consensus Panel

Chair:	Dr. Lucille Osias
Members:	Dr. Milflordeliza Gonzaga

Dr. Connie Rose Benjamin
Dr. Karen Kate Tobias
Dr. Noel Pingoy
Dr. Haidee Michelle Lim-Chua
Dr. Januario Veloso
Dr. Marjorie Rose Bravo

Lead Guideline Development Team

Principal Investigator:	Dr. Lucille Osias
Principal Co-investigator:	Dr. Lynn Bonifacio
Technical Lead:	Dr. Ian Theodore Cabaluna
Technical Co-lead:	Mr. Teddy Dizon
Support Team:	Dr. Jeriel De Silos Ms. Hygeia Grace C. Agosto Ms. Jessica A. Hernandez

Implementing Agencies

East Avenue Medical Center
Healthcare Practice and Policy Management (HPPM), Inc.

Funding Agency

Department of Health

Supporting Agency

East Avenue Medical Center

Partner Agencies and Societies

Table of Contents

Abbreviation and Acronym

AML	Acute Myeloid Leukemia
AGREE	Appraisal of Guidelines for Research and Evaluation
COI	Conflict of Interest
CP	Consensus Panel
ICPG	Interim Clinical Practice Guideline
ERE	Evidence Review Experts
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
PG	Practice Guideline
NCPG	National Clinical Practice Guideline
PICO	Population, Intervention, Comparison, Outcome
PIPOH	Population, Interventions, Professionals, Outcome, Healthcare Setting
QoE	Quality of Evidence
SC	Steering Committee
SoR	Strength of Recommendation
TAG	Technical Advisory Group

Acknowledgements

The Department of Health (DOH) with technical assistance from East Avenue Medical Center (EAMC) and Healthcare Practice and Policy Management, Inc. developed the Acute Myeloid Leukemia (AML) National Clinical Practice Guideline.

The Technical Advisory Group composed of EAMC, DOH, and PhilHealth representatives serves as the oversight committee ensuring quality and inclusive development of the guideline.

EAMC contracted Healthcare Practice and Policy Management, Inc. (HPPM) as an independent study group to provide highly technical assistance to develop the AML NCPG through a series of consultations and evidence reviews.

The following partner organizations contributed to the success of this publication:

- East Avenue Medical Center
- National Kidney and Transplant Institute (NKTI)
- Philippine College of Hematology and Transfusion Medicine (PCHTM)
- Philippine Society for Blood and Marrow Transplantation (PSBMT)
- Philippine Society of Pathologists (PSP)
- Philippine College of Physicians (PCP)

Contributors

In collaboration with members of the medical community, national government agencies, and clinical experts we developed the Acute Myeloid Leukemia National Clinical Practice Guidelines (AML NCPG). The Consensus Panel (CP) includes hematologists, pathologists, policy program managers, and primary health care providers. All contributors completed the declaration of interest form.

The Technical Advisory Group (TAG) was composed of the following representatives: Dr. Nilo C. de los Santos (EAMC), Dr. Clarito U. Cairo, Jr. (DOH), Ms. Alma B. Abainza-Sanchez (PhilHealth), Dr. Allan Troy D. Baquir (EAMC) and Dr. Samuel S. Duran (EAMC).

The Steering Committee (SC) was composed of the following representatives: Dr. Lucille Osias (EAMC), Dr. Lynn Bonifacio (NKTI), Dr. Prerna Vaswani (PCHTM), Dr. Chrystal Catli-Burog (PCHTM), Dr. Ma. Clariza Santos (PCHTM), Dr. Camille Ariadne Tanchanco (PCHTM), Dr. Mary Shayrel Lagan-Ragas (PCHTM), Dr. Ma. Regina De Leon (PSBMT), Dr. Alma Calavera (PSBMT), Dr. Roxan Perez (PSBMT), Dr. Alejandro Arevalo (PSP), and Dr. Rose Lou Marie Agbay (PSP).

The Evidence Review Experts (ERE) included the following representatives: Dr. Ian Theodore G, Cabaluna, Dr. Jeriel de Silos, Mr. Teddy S. Dizon, Ms. Hygeia C. Agosto, Ms. Jessica A. Hernandez, Dr. Howell Bayona, and Dr. Flordeluna Mesina.

The Consensus Panel was composed of the following representatives: Dr. Lucille Osias (EAMC)[1], Dr. Milflordeliza Gonzaga (PCHTM), Dr. Connie Rose Benjamin (PCHTM), Dr. Karen Kate Tobias (PCHTM), Dr. Noel Pingoy (PCHTM), Dr. Haidee Michelle Lim-Chua (PCHTM), Dr. Januario Veloso (PSP) and Dr. Marjorie Rose Bravo (PSBMT).

[1] Non-voting member

Executive Summary

Acute Myeloid Leukemia (AML) is a common type of leukemia among the adult population. Delayed treatment and diagnosis of AML result in life-limiting and life-threatening conditions.

The AML National Clinical Practice Guidelines (NCPG) aim to provide evidence-based standards of diagnosis and treatment that meet all the quality requirements stipulated in the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. It includes high-priority questions on the diagnosis and treatment protocol for this disease.

The Guideline Development Group (GDG) employed the ADAPTE process in developing this NCPG. The Technical Advisory Group (TAG) provided the Population, Intervention, Professionals, Outcomes, and Healthcare setting (PIPOH) framework for selecting and framing clinical questions. The Steering Committee used this framework in developing, prioritizing, and rationalizing the practice guideline questions.

The Evidence Review Experts (ERE) conducted evidence-gathering, appraisal, and synthesis to answer the priority practice guideline questions. Finally, the Consensus Panel (CP) scrutinized the summary of evidence and participated in the eDelphi consensus-building process to finalize the recommendation for each practice guideline question.

Acute Myeloid Leukemia NCPG Summary

The Guideline Development Group used the ADAPTE methodology to generate and finalize the recommendations for AML NCPG, covering diagnosis and clinical management. The ADAPTE process results in the adoption and adaption of recommendations from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Acute Myeloid Leukemia and supplemented from The National Institute for Health and Care Excellence (NICE), American Society of Hematology (ASH), Japanese Society of Hematology (JSH), Medical Journal of Australia (MJA), American College of Physicians (ACP), and American Society of Clinical Oncology (ASCO).

Table 1. Acute Myeloid Leukemia NCPG Summary

Clinical Questions	Recommendations	SoR	QoE
Diagnosis			
Among patients suspected to have AML, can histopathology (bone marrow core biopsy and aspirate smears) with immunohistochemical (IHC) staining of blasts for *MPO, CD34, CD117 and CD68* alone be a surrogate test to diagnose AML compared to histopathology (bone marrow core biopsy and aspirate smears) with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD56, CD4, CD14*)?	If available, multiparameter flow cytometry, a laser-based technique, should be offered. Immunohistochemistry, a microscopy-based technique, is recommended as auxiliary to diagnose patients suspected to have AML.	Strong	Low
Among newly diagnosed AML patients, should conventional karyotyping compared to FISH *[inversion 3 (GATA2/MECOM), 5q del, 7q del, t(6;9), 11q23 (MLL) or KMT2A, del17p, trisomy 8, BCR ABL1, t(8;21) (RUNX1/RUNX1T1, t(15;17)*	We recommend the use of cytogenetic study using conventional karyotyping for risk stratification of patients and to guide individualized therapy. In cases with inadequate karyotype analysis, we	Strong	Low

(PML/RARA), inv 16, t(16;16) (CBFB)] be used to risk stratify patients with AML?	recommend addition of fluorescence in situ hybridization (FISH).		
Among newly diagnosed AML patients, should a baseline screening with molecular analysis (*FLT3-ITD, c-KIT, ASXL1, FLT-3 TKD, CEBPA, RUNX1, NPM1, TP53, IDH1, IDH2*) be done to risk stratify patients and guide treatment plan?	We suggest testing for baseline molecular analysis of c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1, IDH2, RUNX1, ASXL1, and TP53 for gene mutations to risk stratify patients and guide individualized therapy.	Weak	Low
Among newly diagnosed AML patients who will undergo chemotherapy, should HBsAg, anti HBc total, anti HBs, anti HCV, and HIV testing be done for all patients to improve patient outcomes (i.e., decrease infectious complications)?	We suggest testing for HBsAg, anti-HBc total, anti-HBs, anti-HCV, and HIV especially among high-risk population group.	Good Practice Statement	
Among patients who have undergone induction chemotherapy, can histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD117, CD68* with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14* be a surrogate to detect minimal residual disease in AML compared to bone marrow aspirate alone for multi-color (8 color) flow cytometry with BULK lysis?	We suggest offering multi-color flow cytometry among post-induction patients with AML to monitor for minimal residual disease, if available.	Weak	Low
Treatment			
Among AML patients who are fit to receive intensive therapy, should we use doxorubicin with cytarabine compared to idarubicin with cytarabine for frontline induction treatment to improve patient	We recommend standard dose cytarabine with either idarubicin or daunorubicin* or doxorubicin among patients less than 60 years old with favorable or intermediate risk cytogenetics, if available.	Strong	High

outcomes (i.e., remission rate, disease-free survival, overall survival)?			
Among AML patients with intermediate or high-risk cytogenetics in first remission, should we do allogeneic hematopoietic stem cell transplant compared to consolidation chemotherapy to improve patient outcomes (i.e., disease-free survival, overall survival)?	For patients age <60 years with intermediate-risk cytogenetics and/or molecular abnormalities (including MRD positive), we suggest the following options: a. matched sibling or alternative donor HCT; b. HIDAC with or without oral Midostaurin; c. Cytarabine on days one to four + daunorubicin* on day one (1st cycle) or days one to two (2nd cycle) + gemtuzumab ozogamicin* on day one x two cycles (CD33-positive); d. Maintenance therapy with oral azacitidine PO OD on days one to 14 of each 28-day cycle until progression or unacceptable toxicity (if patients decline or not fit/eligible for allogenic HCT).	Weak	Low
	For patients age <60 years with unfavorable cytogenetics, we suggest the following options: a. Matched sibling or alternative donor HCT; b. HIDAC with or without oral Midostaurin; c. Dual-drug liposomal encapsulation* of cytarabine and daunorubicin on days and three x q12 hours; d. Maintenance therapy with oral azacitidine PO OD on days one to 14 of each 28-day cycle until progression or unacceptable toxicity (if patients decline or not fit/eligible for allogenic HCT).	Weak	Low

Among newly diagnosed patients unfit for intensive induction chemotherapy, how effective is HMA monotherapy compared to HMA plus Venetoclax or LDAC plus Venetoclax in improving clinical outcomes (i.e., overall survival)?	We recommend the use of either hypomethylating-agent monotherapy with Venetoclax or low-dose-cytarabine with Venetoclax for older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy.	Strong	Low
Among newly diagnosed AML patients with FLT3-ITD mutation, how effective is standard chemotherapy compared to standard chemotherapy with FLT3 inhibitor in achieving complete remission?	We recommend addition of FLT3-inhibitor in the management of newly diagnosed adults with acute FLT3-mutation-positive myeloid leukemia.	Strong	Low
Among patients who are undergoing induction chemotherapy, how accurate is a day 14 to 21 bone marrow histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD 117, CD 68* with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14*) compared to bone marrow aspirate alone for multi-color flow cytometry (8 color) with BULK lysis in predicting clinical outcome (i.e. remission rate, overall survival) and treatment modification?	We suggest offering a bone marrow evaluation (bone marrow aspirate with multicolor flow cytometry) 14 to 21 post-therapy to categorize the patient according to the presence of blasts or hypoplasia.	Weak	Low

Background

Introduction

Leukemia begins in one of the bone marrow's immature cells, wherein a cell's DNA undergoes one or more mutations, transforming into a type of cancer cell known as a "leukemia cell" (Leukemia & Lymphoma Society (LLS), 2021). Classification of leukemia subtypes is according to the rate of progression and the type of cells involved in the disease.

Acute Myeloid Leukemia (AML) evolved from a single acute leukemia entity to a complex array of AML sub-entities. AML has distinct pathophysiologic, clinical, cytogenetic, and molecular characteristics (Kantarjian et al., 2021).

Additionally, AML is a heterogeneous malignancy defined by clonal proliferation and improper differentiation of myeloid precursors (Yang & Wang, 2018). There are well-known chromosomal translocations, such as t(8:21) in core-binding factor AML (CBF-AML) and t(15:17) in Acute Promyelocytic Leukemia (APL). These result in chimeric proteins – RUNX1-RUNX1T1 and PML-RARA, respectively – that disrupt the normal maturation process of myeloid precursor cells (De Kouchkovsky & Abdul-Hay, 2016).

Patients diagnosed with AML often experience non-specific symptoms such as fatigue, weight loss, fever, night sweats, and loss of appetite (Leukemia & Lymphoma Society (LLS), 2021). These symptoms generally appear over a few weeks and become more severe as the number of immature white blood cells increases (National Health Service, 2019). Other signs or symptoms such as but are not limited to include pale or "washed-out" skin, exhaustion, breathlessness, fever, excessive sweating, weight loss, frequent infections, unusual and frequent bleeding, easily bruised skin, flat red or purple spots on the skin, bone and joint pain, a feeling of fullness or discomfort in the tummy, and swollen glands in the neck (National Health Service, 2019).

A lack of normal blood cells causes many signs and symptoms of AML. It occurs when the leukemia cells in the bone marrow crowd out the normal blood-making cells. As a result, normal red blood cells, white blood cells, and blood platelets are in short supply. While individuals with AML may have elevated white blood cell counts due to an overabundance of leukemia cells, these cells may not provide the same level of protection against infection that normal white blood cells do (American Cancer Society, 2018).

Myelodysplastic syndrome, myelofibrosis, aplastic anemia, Down's syndrome, Bloom syndrome, and exposure to radiation, tobacco, and benzene are risk factors for AML (Vakiti & Mewawalla, 2019).

The Global Cancer Observatory (2020a) identified leukemia as the 10th leading cause of cancer death worldwide, with up to 311,594 of all deaths. The global incidence of

AML has risen steadily over the last 28 years, from 63,840 cases in 1990 to 119,570 cases in 2017 (Yi et al., 2020). Subgroup analysis by geographical zone revealed the highest prevalence of AML in Western Europe and South Asia (Yi et al., 2020).

In the Philippines, cancer is among the top three leading causes of mortality (Philippine Statistics Authority, 2021). Leukemia ranks 5th among all cases of cancer-related mortalities, with up to 4,370 deaths (Globocan, 2020b).

The five-year survival rate of AML for individuals under 20 years old is only 68%; this rate decreases to 26% for those 20 years old and above (American Society of Clinical Oncology, 2021).

Guideline Development Process

Phase 1 – Preparation Phase

Establishment of the Guideline Development Group

The guideline development group was composed of policy makers, program managers, hematologists, blood and bone marrow transplant specialists, and pathologists. The multidisciplinary and multispecialty professionals composed the relevant working groups of the AML NCPG, the Technical Advisory Group (TAG), the Steering Committee (SC), the Evidence Review Experts (ERE), and the Consensus Panel (CP).

The TAG and the SC comprised the lead NCPG developers. The TAG has the oversight function to ensure a quality and inclusive NCPG development process. Nominated members for the TAG included representatives from East Avenue Medical Center, the Department of Health, and the Philippine Health Insurance Corporation.

The multidisciplinary SC drafted the scope and target audience of the NCPG. They also identified, ranked, and finalized the clinical questions on diagnosis and clinical management of AML in the Philippines. The SC identified, invited, reviewed, and managed the COI of the relevant working groups, such as the steering committee, evidence reviewers, consensus panelists, and facilitators.

The ERE provided technical assistance in evidence review ranging from the development of the clinical questions, search and identification of evidence, appraisal of relevant literature to answer clinical questions, and synthesis of evidence summaries as the basis of recommendation statements. The ERE for this Guideline included consultants with backgrounds in clinical epidemiology, information specialists, medical informatics, and public health.

The CP was a wider group of AML stakeholders. Establishing a more open and diverse group of stakeholders for the CP — including multidisciplinary healthcare practitioners, patient advocates, DOH program managers, and other technical content experts — was aimed at promoting transparency, introducing different perspectives to AML management, and safeguarding against conflicts of interest. The CP reviewed and revised the recommendation statements and voted on adopting these statements into the Guideline.

Declaration and Management of Conflicts of Interest

The AML NCPG Guideline Development Group utilized the PhP 1,000,000 DOH sub-allotment to develop the guideline. The stakeholder of the working groups that composed the Guideline Development Group (GDG) declared no true conflict interests related to this material. The stakeholders included in the guideline development groups were requested to provide a summary of their conflicts of interest (COI) related to AML. These COIs may be classified into financial and non-financial (or intellectual) COI. COIs were reviewed by the ERE, and admission of a stakeholder to the GDG was contingent on the stakeholder having no or minimal COI, following recommendations in the DOH CPG Manual (DOH [Philippines] 2018). Conflicts of interest(s) and how COIs were managed are presented in Annex A.

Identification of the Scope of the NCPG

The PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes and Health Care Setting (ADAPTE Collaboration, 2009). These five items aided the selection and framing of clinical questions on Population; Intervention of interest – screening, diagnostics, and treatment/management; Professionals to whom the guideline will be targeted; specific Outcomes; and Health care setting and context that the guideline will be implemented.

Generation of NCPG questions

The methodology of clinical question generation is based on frameworks of clinical practice guidelines (CPG), agenda-setting, and consensus-building (Murphy et al, 1998; The James Lind Alliance, 2020; WHO, 2014). For CPG question development guidelines, we specifically referred to guidance published by the WHO in 2014. Due to the COVID-19 pandemic and mobility restrictions at the time of guideline development, all methods of communication were virtual; no face-to-face, physical gatherings were conducted.

PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes, and Health Care Setting (ADAPTE Collaboration, 2009).

Table 2. PIPOH Framework for the AML NCPG Development

Population	Adult (19 years old and above), including elderly, newly diagnosed, not relapse patients
Intervention	Diagnostics, treatment and management
Professionals	Medical specialist and allied health professionals

Outcomes	Overall survival rate, disease-free survival, recurrence, and remission
Healthcare Setting	Tertiary level of care (hospital or medical centers)

These guidelines included relevant questions on diagnosis and treatment of AML. The objectives are the following:

1. To present and synthesize the best available evidence on the diagnosis and treatment of Acute Myeloid Leukemia;
2. To standardize the diagnosis and treatment of Acute Myeloid Leukemia in the Philippines for the reduction of the burden of disease; and,
3. To complement the existing DOH program mandates on cancer control by providing evidence to its statements for policy implementation.

The generation of CPG questions is an essential early step in CPG development. These questions were used as the basis for the subsequent systematic review of the evidence base on AML (WHO, 2014). CPG questions generated by the SC were agreed to focus on evidence uncertainties, areas of controversy in the management of AML and known variations of clinical practice and care especially in the resources available in the Philippine setting. The SC was then convened in virtual workshops where the final questions were formulated in PICO (Population, Intervention, Comparator, and Outcome) format, reviewed, and prioritized according to a consensus. Technical working groups were assigned for further review and revision to reach the final PICO format of the clinical questions. The final list of PICO elements for each CPG question is located in Annex C.

Phase 2 – Evidence synthesis

Overview of evidence synthesis methods

Considering the time and resources to produce quality CPGs, it is recommended that existing guidelines be adapted to reduce duplication of effort and update existing guidelines in a shorter period of time. In this CPG development process, guideline adaptation by the ADAPTE method was considered to address specific health questions generated. Independent methodologists and reviewers determined if adaptation of any existing CPG was feasible and consequently created the evidence base and recommendation matrix.

The ERE utilized the ADAPTE method to review existing guidelines for inclusion in the evidence base and drafting of recommendation matrix. The ADAPTE collaboration has developed a systematic approach to aid in the adaptation of guidelines (ADAPTE Collaboration, 2009). The systematic approach aids in the use and modification of existing guidelines to customize an existing guideline to suit the local context while

addressing relevant health questions. A systematic search of existing guidelines in multiple databases, including PubMed, Google Scholar and Scopus®. Search terms and limits are provided in Annex B. Updated versions of the guidelines were also searched to ensure currency of the recommendations. Assessment of the guidelines yielded from the systemic search were then given consideration for adaptation by assessment if it meets the qualities of a high-quality guideline using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument as well as if it can address the specific clinical questions. The AGREE II instrument provides a framework for assessing the quality of CPGs (Brouwers et al, 2013). The 23 items in the AGREE instrument assess the methods used for developing the guideline and quality of reporting. Assessment is focused on the rigor and overall score. The domains and criteria for the AGREE II tool are shown in Annex B. The guidelines were assessed for guideline quality, currency, content, consistency, and applicability (ADAPTE Collaboration, 2009). The characteristics and contents of the source guidelines are summarized in Annex B.

Phase 3 – Evidence to Recommendation

The ERE drafted the initial recommendation statements to include level of evidence based on the source guidelines and its references. All guidelines included utilized by recommended Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for evaluation of level of evidence (Schünemann et al, 2013). This is the tool developed by the GRADE working group in evaluating the quality of the evidence and is summarized and defined in Table 3 below.

Table 3. Quality of Evidence Grades (Schünemann et al, 2013)

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

The recommendation matrix developed was for finalization of the CP who were provided by the ERE with a guide on determining the strengths of recommendation (Schünemann et al, 2013). Recommendations may either be strong or weak. Strong recommendations refer to issues where the guideline development group may be confident that the benefits outweigh the risks or costs of an intervention, or vice versa, whereas weak recommendations are those where there is appreciable uncertainty on

the calculus of benefits and risks. A summary of the implication of recommendation strength on each type of guideline user based on WHO which is reproduced in full in Table 4.

Table 4. Implications of Strong and Weak Recommendations for Different Users of Guidelines (WHO, 2014)

Guideline Users	Strong Recommendation	Weak Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Phase 4 – Consensus Development

The consensus panel facilitator led the asynchronous consensus-building process through the eDelphi process. The facilitator sent out the two batches of recommendations from the ADAPTE evidence evaluation and synthesis for scrutiny by the consensus panelists. There are three iterations for comments discussions

followed by a presentation of the evidence and nominal group technique discussions (NGT) of recommendations (Delbecq et al., 1986).

Following the NGT discussions, the CP was allowed to revise the recommendation statements for adaptation and contextualization within reasonable limits as long as the revision did not alter the value of the underlying evidence. The facilitator was allowed only to clarify the comments by asking probing exploratory questions. There were no leading questions asked.

The CP set the 80% consensus agreement on every content and strength of each recommendation. The CP repeated the cycle of discussions for content and strength and recommendations that could not reach the consensus marker.

The invited patient and advocacy group did not attend any consensus panel meeting. To ensure inclusivity, the SC and CP provided email updates and encouraged email comments or feedback through the project management team.

Patient Values, Preferences, and Other Considerations

As there are no patient nor patient groups present within the SC or CP, results based on a systematic review of patient or family values, was assessed vis-à-vis the recommendations of the GDG after consensus made.

The SC and CP thoroughly discussed the applicability of the recommendations using several criteria, such as improvement of treatment outcomes through availability of quality affordable drugs and medicines, acceptability to local professional practice, public health impact, and cost of specialist care based on lived experiences.

Ethics review was sought and approved by the DOH Single Joint Review Board.

External evaluation was sought by the guideline development group through a public forum with the hematologists where feedbacks were documented and directly incorporated in the final manuscript.

The DOH as funding agency and EAMC as fund manager did not influence the editorial independence of the GDG.

Dissemination and Use of the Guideline

The value of a CPG is fully appreciated when it is widely adopted, and adoption is contingent on access and distribution of the CPG to its target audience. This clinical practice guideline is available on the DOH website.

The GDG will work closely with DOH and other partners to ensure wide dissemination of the guideline through different events: (1) Presentation in professional society's

scientific fora; (2) Distribution of the guideline will be done electronically through DOH and partner society websites; (3) Monitoring/assessment on the uptake of the guideline will be done through monitoring the number of downloads and request for distribution, and; (4) Health outcomes will be monitored during the first three years of guideline distribution specifically on number of cases identified, treated and surveillance for recurrence reported.

The NCPG recommendations are valid until new significant evidence emerges that would require a change in recommendation. The ERE recommends revisiting the Guidelines regularly every three years. The research recommendations may be considered by policymakers and program managers for future research funding as part of the continuous quality improvement of healthcare services in the country.

References

ADAPTE Collaboration. (2009). *The ADAPTE Process: Resource Toolkit for Guideline Adaptation*. Version 2.0, 1–95. http://www.g-i-n.net

American Cancer Society (ACS). (2018). Acute Myeloid Leukemia - Signs and Symptoms of Acute Myeloid Leukemia (AML). *American Cancer Society*, August 2018, 1–21.

American Society of Clinical Oncology. (2021). Leukemia - Acute Myeloid - AML: Statistics | Cancer.Net.

Brouwers, M., Kho, M., Browman, G., Cluzeau, F., Feder, G., Fervers, B., Hanna, S., & Makarski, J. (2013). Appraisal of Guidelines for Research & Evaluation II: AGREE II Instrument. https://doi.org/10.1503/cmaj.090449

De Kouchkovsky, I., & Abdul-Hay, M. (2016). 'Acute myeloid leukemia: A comprehensive review and 2016 update.' *Blood Cancer Journal*, *6*(7). https://doi.org/10.1038/bcj.2016.50

Delbecq, A.L., Van de Ven, A.H., & Gustafson, D.H. (1986). *Group techniques for program planning: A guide to nominal group and Delphi processes*. Green Briar Press.

Department of Health (DOH) & Philippine Health Insurance Corporation (PhilHealth). (2018). *Manual for Clinical Practice Guideline Development* (1st ed.). Manila, Philippines: Department of Health and PhilHealth.

Global Cancer Observatory, The (Globocan). (2020a). *Leukaemia* [Fact sheet]. International Agency for Research on Cancer. https://gco.iarc.fr/today/data/factsheets/cancers/36-Leukaemia-fact-sheet.pdf

Globocan. (2020b). *Philippine Fact Sheets (Cancer)* [Fact sheet]. Global Cancer Statistics, *163*, 1–2. https://gco.iarc.fr/today/data/factsheets/populations/608-philippines-fact-sheets.pdf

James Lind Alliance, The. (2020). *The James Lind Alliance Guidebook* (9th ed.). http://www.jla.nihr.ac.uk/jla-guideb

Kantarjian, H., Kadia, T., DiNardo, C., Daver, N., Borthakur, G., Jabbour, E., Garcia-Manero, G., Konopleva, M., & Ravandi, F. (2021). Acute myeloid leukemia: Current progress and future directions. *Blood Cancer Journal*, *11*(2). https://doi.org/10.1038/s41408-021-00425-3

Leukemia & Lymphoma Society (LLS). (2021). Acute myeloid leukemia in adults. In M. Eunice S. Wang (Ed.), Wintrobe's Clinical Hematology: Fourteenth Edition.

Murphy, M., Black, N., Lamping, D., McKee, C., Sanderson, C., Askham, J., & Marteau, T. (1998). Consensus development methods, and their use in clinical

guideline development. *Health Technology Assessment*, *2*(3). https://doi.org/10.4135/9781848608344.n24

National Health Service. (2019). Acute myeloid leukaemia. https://doi.org/10.1093/med/9780199299676.003.27

National Institute for Health and Care Excellence. (2014). Developing NICE guidelines: The manual. www.nice.org.uk/process/pmg20

Oxman, A. D. (2004). Grading quality of evidence and strength of recommendations. In *British Medical Journal* (Vol. 328, Issue 7454, pp. 1490–1494). BMJ Publishing Group. https://doi.org/10.1136/bmj.328.7454.1490

Pandya, B. J., Chen, C. C., Medeiros, B. C., McGuiness, C. B., Wilson, S. D., Walsh, E. H., & Wade, R. L. (2020). Economic and clinical burden of acute myeloid leukemia episodes of care in the United States: A retrospective analysis of a commercial payer database. *Journal of Managed Care and Specialty Pharmacy*, *26*(7), 849–859. https://doi.org/10.18553/jmcp.2020.19220

Philippine Statistics Authority. (2021). Causes of Deaths in the Philippines (Preliminary): January to December 2020.

Redaniel, M.T., Laudico, A., Mirasol-Lumague, M. R., Alcasabas, A.P., Pulte, D., & Brenner, H. (2010). Geographic and ethnic differences in childhood leukaemia and lymphoma survival: Comparisons of Philippine residents, Asian Americans and Caucasians in the United States. *British Journal of Cancer*, *103*(1), 149–154. https://doi.org/10.1038/sj.bjc.6605703

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013, October). *GRADE Handbook*. https://gdt.gradepro.org/app/handbook/handbook.html

Schünemann, H., Wiercioch, W., Brozek, J., Etxeandia-Ikobaltzeta, I., Mustafa, R. A., Manja, V., Brignardello- Petersen, R., Neumann, I., Falavigna, M., Alhazzani, W., Santesso, N., Zhang, Y., Meerpohl, J. J., Morgan, R. L., Rochwerg, B., Darzi, A., Rojas, M. X., Carrasco-Labra, A., Adi, Y., … Akl, E. A. (2017). GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *Journal of Clinical Epidemiology*, *81*, 101–110. https://doi.org/10.1016/j.jclinepi.2016.09.009

Scottish Intercollegiate Guidelines Network (SIGN). (2015, November). *SIGN 50: a guideline developer's handbook*. Edinburgh. http://www.sign.ac.uk

Shallis, R.M., Wang, R., Davidoff, A., Ma, X., & Zeidan, A. M. (2019). Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. *Blood Reviews*, *36*, 70–87. https://doi.org/10.1016/j.blre.2019.04.005

Vakiti, A., & Mewawalla, P. (2019). Cancer, Acute Myeloid Leukemia (AML, Erythroid Leukemia, Myelodysplasia-Related Leukemia, BCR-ABL Chronic Leukemia). In StatPearls. StatPearls Publishing.

Wang, Z., Norris, S.L., & Bero, L. (2018). The advantages and limitations of guideline adaptation frameworks. *Implementation Science*, *13*(1), 72. https://doi.org/10.1186/s13012-018-0763-4

World Health Organization. (2014). *Handbook for guideline development* (2nd ed.). http://www.who.int/kms/handbook_2nd_ed.pdf

Yang, X., & Wang, J. (2018). Precision therapy for acute myeloid leukemia. *Journal of Hematology and Oncology*, *11*(1), 1–11. https://doi.org/10.1186/s13045-017-0543-7

Yi, M., Li, A., Zhou, L., Chu, Q., Song, Y., Wu, K., & Wu, K. (2020). The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: Estimates based on the global burden of disease study 2017. *Journal of Hematology and Oncology*, *13*(1), 1–16. https://doi.org/10.1186/s13045-020-00908-z

Clinical Practice Guidelines

Acute Myeloid Leukemia National Clinical Practice Guidelines Recommendations

Diagnosis

Question 1. Among patients suspected to have AML, should histopathology (bone marrow core biopsy and aspirate smears) with Immunohistochemical (IHC) staining of blasts for *MPO, CD34, CD117, CD68* alone be a surrogate test to diagnose AML compared to histopathology (bone marrow core biopsy and aspirate smears) with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD56, CD4, CD14*)?

Recommendation 1a.

If available, multiparameter flow cytometry, a laser-based technique, should be offered.

Immunohistochemistry, a microscopy-based technique, is recommended as auxiliary to diagnose patients suspected to have AML.

Strong recommendation, Low quality of evidence

Consensus Issues

The Consensus Panel (CP) voted to adapt and modify the recommendations. A suggestion was made to indicate the number of white blood cells (WBC) or percent blasts in the peripheral blood that is considered suitable or acceptable for immunotyping and cytogenetic testing.

Summary of Evidence

As stated in the National Comprehensive Cancer Network (NCCN) guidelines, bone marrow core biopsy, aspirate analyses (including immunophenotyping and cytochemistry), and cytogenetic analyses are useful procedures in planning treatment for AML patients. Döhner et al. (2017), Ley et al. (2013), and Papaemmanuil et al. (2016) have demonstrated that gene mutations are associated with prognoses for certain patients, which have implications in their management.

The application of circulating leukemic blasts from peripheral blood may also be an alternative specimen in detecting molecular abnormalities. According to the 2016 World Health Organization (WHO) classification, AML diagnosis is established on the presence of ≥20% blasts in the marrow or peripheral blood. In a clinical setting, it may

be with <20% blasts in patients with recurrent cytogenetic abnormalities including *t(15;17), t(8;21), t(16;16), or inv(16)* or the corresponding transcript.

With this, the NCCN AML Panel advocated for complementary diagnostic techniques to be utilized at the discretion of the pathology unit in the institution. Multidisciplinary diagnostic studies (e.g., immunohistochemistry, cytochemistry, or both), together with molecular genetics analysis, are necessary in the accurate classification of AML (NCCN, 2019).

Research Recommendation

The GDG recommended no additional research.

References

Cancer Genome Atlas Research Network. (2013). Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *New England Journal of Medicine*, *368*(22), 2059-2074.

Döhner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F.R., Büchner, T., ... & Bloomfield, C.D. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood, The Journal of the American Society of Hematology*, *129*(4), 424-447.

National Comprehensive Cancer Network. (2019). Acute Myeloid Leukemia Version 3.2019. *Journal of the National Comprehensive Cancer Network* (JNCCN), *17*(6). United States, Pennsylvania.

Papaemmanuil, E., Gerstung, M., Bullinger, L., Gaidzik, V. I., Paschka, P., Roberts, N. D., ... & Campbell, P. J. (2016). Genomic classification and prognosis in acute myeloid leukemia. *New England Journal of Medicine*, *374*(23), 2209-2221.

Question 2. Among newly diagnosed AML patients, should conventional karyotyping compared to FISH *[inversion 3 (GATA2/MECOM), 5q del, 7q del, t(6;9), 11q23 (MLL) or KMT2A, del17p, trisomy 8, BCR ABL1, t(8;21) (RUNX1/RUNX1T1, t(15;17) (PML/RARA), inv 16, t(16;16) (CBFB)]* be used to risk stratify patients with AML?

Recommendation 2a.

We recommend the use of cytogenetic study using conventional karyotyping for risk stratification of patients and to guide individualized therapy. In cases with inadequate karyotype analysis, we recommend addition of fluorescence in situ hybridization (FISH).

Strong recommendation, Low quality of evidence

Consensus Issues

The Panel members adapted the recommendation but specified that there are areas in the country with inadequate resources/facilities for investigating genetic abnormalities in AML.

Summary of Evidence

The molecular pathogenesis of AML has been determined by cytogenetic analysis. It has been shown that recurrent chromosomal structural variations denote diagnostic and prognostic markers, implying the significant role of acquired genetic abnormalities (i.e., somatic mutations) in pathogenesis. (Mrózek et al., 2004; Rowley, 2008). As such, the WHO 2016 Classification of AML highlighted the importance of testing AML patients for genetic abnormalities to correctly classify AML (Arber et al, 2016).

Together with molecular testing, cytogenetic analyses (karyotype with fluorescence in situ hybridization) are beneficial in stratification and treatment guidance among AML cases (NCCN, 2019). Depending on the genetic abnormalities, the prognosis and management may differ.

Aside from the above, the 2016 WHO Classification of AML also incorporated all diagnostic approaches of clinical history, cytogenetics, molecular genetics, morphology and immunophenotype. Additionally, it included two full entities regarding specific gene mutations – AML with mutated *NPM1* and AML with biallelic mutations of *CEBPA* – which are usually early events that are disease-defining.

Data obtained from the said diagnostic strategies are currently important to properly classify cases of AML, as the collaboration among hematologists, pathologists, reference laboratories, cytogeneticists and/or molecular pathologists is needed. This

ensures diagnoses that have clearer definitions of disease groups, including prognostic features and potential new targets for treatment (Arber, 2019).

Research Recommendation

The GDG recommended no additional research.

References

Arber, D. (2019). The 2016 WHO classification of acute myeloid leukemia: What the practicing clinician needs to know. *Seminars in Hematology*, *56*(2), 90-95. https://doi.org/10.1053/j.seminhematol.2018.08.002

National Comprehensive Cancer Network. (2019). Acute Myeloid Leukemia Version 3.2019. *Journal of the National Comprehensive Cancer Network* (JNCCN), *17*(6). United States, Pennsylvania.

Rowley, J. D. (2008). Chromosomal translocations: Revisited yet again. *Blood, The Journal of the American Society of Hematology*, *112*(6), 2183-2189.

Mrózek, K., Heerema, N. A., & Bloomfield, C. D. (2004). Cytogenetics in acute leukemia. *Blood reviews*, *18*(2), 115-136.

Question 3. Among newly diagnosed AML patients, should a baseline screening with molecular analysis (*FLT3-ITD, c-KIT, ASXL1, FLT-3 ITD, CEBPA, RUNX1, NPM1, TP53, IDH1, IDH2*) be done to risk stratify patients and guide treatment plan?

Recommendation 3a.

We suggest testing for baseline molecular analysis of *c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1, IDH2, RUNX1, ASXL1*, and *TP53* for gene mutations to risk stratify patients and guide individualized therapy.

Weak recommendation, Low quality of evidence

Consensus Issues

The Panel members adapted the recommendation on using molecular testing in stratifying patients. This was based on the NCCN guidelines in testing for gene mutation to stratify and guide recommendations. The Panel also noted that this recommendation is subject to the availability of tests.

Summary of Evidence

According to NCCN and European LeukemiaNet (ELN), all AML cases should be assessed for the following gene mutations: *c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1, IDH2, RUNX1, ASXL1, and TP53*. Multiple studies have demonstrated that mutations in these genes, along with multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis, are beneficial for the management of various phases of treatment among patients. (Döhner et al., 2017; Lindsley et al., 2015; Papaemmanuil et al., 2016).

Genetic analysis among AML patients undergoing intensive therapy showed that the above gene mutations and their interactions were drivers of pathogenesis and clinical prognosis. Döhner et al. (2017) stratified the genetic abnormalities among AML patients according to their prognosis derived from several studies (Bullinger et al., 2017; Meyer et al., 2014; Papaemmanuil, 2016; Patel et al., 2012). These may change as new treatment protocols emerge.

Table 2. Genetic abnormalities and their prognosis (adapted from Döhner et al., 2017)

Favorable	Intermediate	Adverse/Unfavorable
t(8;21)(q22;q22.1); RUNX1-RUNX1T1	Mutated *NPM1* and *FLT3-ITDhigh*†	*t(6;9)(p23;q34.1); DEK-NUP214*
inv(16)(p13.1q22) or *t(16;16)(p13.1;q22); CBFB-MYH1*	Wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITDlow*† (without	*t(v;11q23.3); KMT2A* rearranged

	adverse-risk genetic lesions)	
Mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITDlow*	*t(9;11)(p21.3;q23.3); MLLT3-KMT2A*	*t(9;22)(q34.1;q11.2); BCR-ABL1*
Biallelic mutated CEBPA	Cytogenetic abnormalities not classified as favorable or adverse	*inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)*
		−5 or del(5q); −7; −17/abn(17p)
		Complex karyotype monosomal karyotype
		Wild-type NPM1 and FLT3-ITD high
		Mutated RUNX1
		Mutated ASXL1
		Mutated TP53

Research Recommendation

The GDG recommended no additional research.

References

Arber, D.A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M.J., Le Beau, M.M., Bloomfield, C.D., Cazzola, M., & Vardiman, J.W. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*, *127*(20), 2391–2405. https://doi-org.ezp-prod1.hul.harvard.edu/10.1182/blood-2016-03-643544

Bullinger, L., Döhner, K., & Döhner, H. (2017). Genomics of acute myeloid leukemia diagnosis and pathways. *Journal of Clinical Oncology*, *35*(9), 934-946.

Döhner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F.R., Büchner, T., ... & Bloomfield, C.D. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood, The Journal of the American Society of Hematology*, *129*(4), 424-447.

Grimwade, D., Ivey, A., & Huntly, B. J. (2016). Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. *Blood, The Journal of the American Society of Hematology*, *127*(1), 29-41.

Lindsley, R. C., Mar, B. G., Mazzola, E., Grauman, P. V., Shareef, S., Allen, S. L., ... & Ebert, B. L. (2015). Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood, The Journal of the American Society of Hematology*, *125*(9), 1367-1376. https://www.ncbi.nlm.nih.gov/pubmed/25550361

Meyer, S. C., & Levine, R. L. (2014). Translational implications of somatic genomics in acute myeloid leukaemia. *The Lancet Oncology*, *15*(9), e382-e394.

National Comprehensive Cancer Network. (2019). Acute Myeloid Leukemia Version 3.2019. *Journal of the National Comprehensive Cancer Network* (JNCCN), *17*(6). United States, Pennsylvania.

Papaemmanuil, E., Gerstung, M., Bullinger, L., Gaidzik, V. I., Paschka, P., Roberts, N. D., ... & Campbell, P. J. (2016). Genomic classification and prognosis in acute myeloid leukemia. *New England Journal of Medicine*, *374*(23), 2209-2221.

Patel, J. P., Gönen, M., Figueroa, M. E., Fernandez, H., Sun, Z., Racevskis, J., ... & Levine, R. L. (2012). Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *New England Journal of Medicine*, *366*(12), 1079-1089.

Question 4. Among newly diagnosed AML patients who will undergo chemotherapy, should HBsAg, anti HBc total, anti HBs, anti HCV, and HIV testing be done for all patients to improve patient outcomes (i.e., decrease infectious complications)?

Recommendation 4a.

We suggest testing for HBsAg, anti-HBc total, anti-HBs, anti-HCV, and HIV especially among high-risk population group[2].

Good Practice Statement

Consensus Issues

The CP members adapted the recommendation of providing hepatitis B surface antigen (HBsAg), anti-hepatitis B core antibody (HBc) total, anti-hepatitis B surface antibody (HBs), anti-hepatitis C virus (HCV), and human immunodeficiency virus (HIV) testing to patients, particularly those who belong in high-risk population groups.

Summary of Evidence

Based on several studies (Bruix, 2011; Terrault, 2016), the American College of Physicians (ACP) Guidelines (2017) stated that it is best practice for patients with chronic hepatitis B virus (HBV) infection to be routinely tested. Patients who are given this type of care can have significant reductions in HBV-associated morbidity and mortality (Cohen et al., 2017; Gordon et al., 2014; Lai et al., 2013; Ward et al., 2012).

Research Recommendation

The GDG recommended no additional research.

[2] Men who have sex with men, persons who inject drugs, HIV-positive persons, household and sexual contacts of HBV-infected persons, persons requiring immunosuppressive therapy.

References

Abara, W. E., Qaseem, A., Schillie, S., McMahon, B. J., Harris, A. M., & High Value Care Task Force of the American College of Physicians and the Centers for Disease Control and Prevention. (2017). Hepatitis B vaccination, screening, and linkage to care: best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. *Annals of Internal Medicine*, *167*(11), 794-804. doi: 10.7326/M17-1106

Bruix, J., & Sherman, M. (2011). Management of hepatocellular carcinoma: A update. *Hepatology (Baltimore, Md.)*, *53*(3), 1020. doi: 10.1002/hep.24199

Cohen, C., Holmberg, S. D., McMahon, B. J., Block, J. M., Brosgart, C. L., Gish, R. G., ... & Block, T. M. (2011). Is chronic hepatitis B being undertreated in the United States? *Journal of Viral Hepatitis*, *18*(6), 377-383. doi: 10.1111/j.1365-2893.2010.01401.x

Gordon, S. C., Lamerato, L. E., Rupp, L. B., Li, J., Holmberg, S. D., Moorman, A. C., ... & CHeCS Investigators. (2014). Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. *Clinical Gastroenterology and Hepatology*, *12*(5), 885-893. doi: 10.1016/j.cgh.2013.09.062

Lai, C. L., & Yuen, M. F. (2013). Prevention of hepatitis B virus–related hepatocellular carcinoma with antiviral therapy. *Hepatology*, *57*(1), 399-408. doi: 10.1002/hep.25937

Lok, A. S., McMahon, B. J., Brown Jr, R. S., Wong, J. B., Ahmed, A. T., Farah, W., ... & Mohammed, K. (2016). Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. *Hepatology*, *63*(1), 284-306. doi: 10.1002/hep.28280

Lok, A. S., & McMahon, B. J. (2007). Chronic hepatitis B. *HEPATOLOGY-BALTIMORE THEN ORLANDO-*, *45*(2), 507

Mast, E. E., Margolis, H. S., Fiore, A. E., Brink, E. W., Goldstein, S. T., Wang, S. A., ... & Alter, M. J. (2005). A Comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States; recommendations of the Advisory Committee on Immunization Practices (ACIP); Immunization of infants, children and adolescents; Part I.

Terrault, N. A., Bzowej, N. H., Chang, K. M., Hwang, J. P., Jonas, M. M., & Murad, M. H. (2016). AASLD guidelines for treatment of chronic hepatitis B. *Hepatology (Baltimore, Md.)*, *63*(1), 261. doi: 10.1002/hep.28156

Ward, J. W., Lok, A. S., Thomas, D. L., El-Serag, H. B., & Kim, W. R. (2012). Report on a single-topic conference on “Chronic Viral Hepatitis–Strategies to Improve Effectiveness of Screening and Treatment.” *Hepatology*, *55*(1), 307-315. doi: 10.1002/hep.24797

Question 5. Among patients who have undergone induction chemotherapy, can histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD117, CD68* with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14*) be a surrogate to detect minimal residual disease in AML compared to bone marrow aspirate alone for multi-color (8 color) flow cytometry with BULK lysis?

Recommendation 5a.

We suggest offering multi-color flow cytometry among post-induction patients with AML to monitor for minimal residual disease, if available.

Weak recommendation, Low quality of evidence

Consensus Issues

The CP adapted the recommendation of the Japan Society of Hematology (JSH), wherein the use of multi-color flow cytometry on bone marrow aspirate was an option due to emerging evidence.

Summary of Evidence

The JSH cited a sub-study of the COG AAML03P1 study, which is a prospective cohort study involving 340 children and young adults with AML. The presence of residual disease post-induction as detected by multi-color flow cytometry was a significant prognostic factor for overall survival (OS) and residual-free survival (RFS) [OS HR 2.46 (95%CI, 1.35 to 4.47) and RFS HR 2.38 (95%CI, 2.46 (1.51 to 3.97) (Loken et al., 2012). Patients with positive minimal residual disease (MRD) had lower OS and RFS.

In another study conducted among 202 children and adolescents, presence of MRD detected by flow cytometry of bone marrow specimens after induction therapy was correlated with a much lower five-year event free survival compared to those without (Inaba et al., 2012).

A recent systematic review including 24 studies (n=11,151 patients) showed a significantly higher five-year OS and disease-free survival (DFS) among those who are MRD-negative. MRD-negative had a pooled OS of 68% whereas MRD-positive patients only had 34% OS rate (Short et al., 2020).

Research Recommendation

The GDG recommended no additional research.

References

Inaba, H., Coustan-Smith, E., Cao, X., Pounds, S.B., Shurtleff, S.A., Wang, K.Y., ... & Campana, D. (2012). Comparative analysis of different approaches to measure treatment response in acute myeloid leukemia. *Journal of Clinical Oncology*, *30*(29), 3625. https://doi.org/10.1200/JCO.2011.41.5323

Loken, M.R., Alonzo, T.A., Pardo, L., Gerbing, R.B., Raimondi, S.C., Hirsch, B.A., ... & Meshinchi, S. (2012). Residual disease detected by multidimensional flow cytometry signifies high relapse risk in patients with de novo acute myeloid leukemia: a report from Children's Oncology Group. *Blood, The Journal of the American Society of Hematology*, *120*(8), 1581-1588. https://doi.org/10.1182/blood-2012-02-408336

Short, N.J., Zhou, S., Fu, C., Berry, D.A., Walter, R.B., Freeman, S.D., ... & Ravandi, F. (2020). Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncology*, *6*(12), 1890-1899. https://doi.org/10.1001/jamaoncol.2020.4600

Treatment and Care

Question 6. Among AML patients who are fit to receive intensive therapy, should we use Doxorubicin with cytarabine compared to idarubicin with cytarabine for frontline induction treatment to improve patient outcomes (i.e., remission rate, disease-free survival, overall survival)?

Recommendation 6a.

We recommend standard dose cytarabine with either idarubicin or daunorubicin or doxorubicin among patients less than 60 years old with favorable or intermediate risk cytogenetics, if available.

Strong recommendation, High quality evidence

Consensus Issues

The CP members adapted the recommendation but raised the concern on the cost of idarubicin and availability of daunorubicin in the Philippines. Doxorubicin more accessible hence is also prescribed to AML patients.

Although the recommendation is applicable and acceptable to both patients and clinicians, it must be considered that idarubicin is more costly compared to doxorubicin. In cases where cost is an issue (i.e., resources of patient are limited), an alternative anthracycline should be offered.

Summary of Evidence

The standard induction treatment for patients less than 60 years old is formed on a combination of cytarabine and anthracycline. The anthracycline regimen that is used frequently is daunorubicin with a dosage of 45 to 60 mg/m^2 for three days. Nevertheless, idarubicin with a dosage of 12 mg/m^2 for three days has equivalent outcomes with fewer patients needing another treatment at the 15th day to complete remission (CR).

For patients less than 60 years old with previously untreated AML, a study done by the Eastern Cooperative Oncology Group (ECOG) showed significant increases in CR rate (71% vs 57%; P<0.001) and median OS (vs 16 months; P=0.003) for those given daunorubicin at a dosage of 90 mg/m^2 for three days (n=327) compared to those who took it for 45 mg/m^2 in three days (n=330). However, the advantage in survival was seen among patients with favorable and intermediate-risk cytogenetics.

Moreover, studies including a phase III trial conducted in newly diagnosed AML patients aged 15 to 65 years old, imply that a higher dose of daunorubicin (90 mg/m^2)

provides improved OS and event-free survival (EFS) rates for FLT3-ITD mutation-positive cases (Burnett et al., 2016; Lee et al., 2011, 2017).

On a retrospective study of Sherif et.al (2021), 143 patients with de novo AML received full dose of standard induction therapy using anthracyclines and cytarabine, idarubicin did not provide a clear advantage over doxorubicin in achieving complete remission.

Research Recommendation

The GDG recommended the conduct of a costing study on the anthracycline regimen that will be used for each AML patient, considering their financial capability and age.

References

Burnett, A.K., Russell, N.H., & Hills, R.K. (2016). United Kingdom National Cancer Research Institute Acute Myeloid Leukemia Study Group. Higher daunorubicin exposure benefits FLT3 mutated acute myeloid leukemia. *Blood*, *128*(3), 449-452.

Fernandez, H.F., Sun, Z., Yao, X., Litzow, M.R., Luger, S.M., Paietta, E.M., ... & Tallman, M.S. (2009). Anthracycline dose intensification in acute myeloid leukemia. *New England Journal of Medicine*, *361*(13), 1249-1259.

Fischer, T., Stone, R.M., DeAngelo, D.J., Galinsky, I., Estey, E., Lanza, C., ... & Giles, F.J. (2010). Phase IIB trial of oral Midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. *Journal of Clinical Oncology*, *28*(28), 4339.

Lee, J.H., Joo, Y.D., Kim, H., Bae, S.H., Kim, M.K., Zang, D.Y., ... & Cooperative Study Group A for Hematology. (2011). A randomized trial comparing standard versus high dose daunorubicin induction in patients with acute myeloid leukemia. *Blood, The Journal of the American Society of Hematology*, *118*(14), 3832-3841.

Lee, J.H., Kim, H., Joo, Y.D., Lee, W.S., Bae, S.H., Zang, D.Y., ... & Cooperative Study Group A for Hematology. (2017). Prospective randomized comparison of idarubicin and high dose daunorubicin in induction chemotherapy for newly diagnosed acute myeloid leukemia. *Journal of Clinical Oncology*, *35*(24), 2754-2763.

National Comprehensive Cancer Network. (2019). Acute Myeloid Leukemia Version 3.2019. *Journal of the National Comprehensive Cancer Network* (JNCCN), *17*(6). United States, Pennsylvania.

Sherif, H. A., Magdy, A., Elshesheni, H. A., Ramadan, S. M., & Rashed, R. A. (2021). Treatment outcome of doxorubicin versus idarubicin in adult acute myeloid leukemia. *Leukemia research reports*, *16*, 100272. https://doi.org/10.1016/j.lrr.2021.100272

Stone, R.M., Fischer, T., Paquette, R., Schiller, G., Schiffer, C.A., Ehninger, G., ... & Giles, F. (2012). Phase IB study of the FLT3 kinase inhibitor Midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. *Leukemia*, *26*(9), 2061-2068.

Stone, R.M., Mandrekar, S.J., Sanford, B.L., Laumann, K., Geyer, S., Bloomfield, C. D., ... & Döhner, H. (2017). Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *New England Journal of Medicine*, *377*(5), 454-464.

Question 7. Among AML patients with intermediate or high-risk cytogenetics in first remission, should allogeneic hematopoietic stem cell transplant compared to consolidation chemotherapy be done to improve patient outcomes (i.e., disease-free survival, overall survival)?

Recommendation 7a.

For patients age <60 years with intermediate-risk cytogenetics and/ or molecular abnormalities (including MRD positive), we suggest the following options:

a. matched sibling or alternative donor HCT;

b. HIDAC with or without oral Midostaurin;

c. Cytarabine on days 1-4 + daunorubicin* on day one (1st cycle) or days one to two (2nd cycle) + gemtuzumab ozogamicin* on day one x two cycles (CD33-positive);

d. Maintenance therapy with oral azacitidine PO OD on days one to 14 of each 28-day cycle until progression or unacceptable toxicity (if patients decline or not fit/ eligible for allogenic HCT).

Weak recommendation, Low quality evidence

Recommendation 7b.

For patients age <60 years with unfavorable cytogenetics, we suggest the following options:

a. Matched sibling or alternative donor HCT;

b. HIDAC with or without oral Midostaurin;

c. Dual-drug liposomal encapsulation* of cytarabine and daunorubicin* on days and three x q12 hours;

d. Maintenance therapy with oral azacitidine PO OD on days one to 14 of each 28-day cycle until progression or unacceptable toxicity (if patients decline or not fit/ eligible for allogenic HCT).

Weak recommendation, Low quality evidence

Consensus Issues

Consolidation chemotherapy (patients <60 years old)

The CP adapted the NCCN recommendation on the use of consolidation chemotherapy among patients less than 60 years old with complete response after therapy. This included the use of Allogeneic HCT, or chemotherapy, for patients over 60 years old who have had a complete response to previous intensive therapy.

In addition, it was noted that daunorubicin, gemtuzumab ozogamicin, midostaurin and oral azacitidine are not readily available.

Patients <60 years old with intermediate-risk or unfavorable cytogenetics

The CP adapted the NCCN recommendation for people less than 60 years old with intermediate, and unfavorable cytogenetics.

In addition, it was noted that dual-drug liposomal encapsulation of cytarabine, daunorubicin, midostaurin and oral azacitidine are not readily available.

Summary of Evidence

Post-remission Therapy and Intensive Antileukemic Therapy

According to the ASH, patients receiving more post-remission therapy seem to do better than those who receive less therapy. In the clinical trial of Büchner et al. (2003), which consisted of 832 patients with de novo AML, 69.2% of the patients went into CR. Although no statistically significant survival benefit was observed in CR patients (P=0.085), it was discovered that more patients in the maintenance arm than in the S-HAM arm remained in initial CR (P=0.026).

Consolidation chemotherapy (patients <60 years old)

In the clinical trial of Willemze et al., (2014), CR patients underwent a single consolidation cycle consisting of daunorubicin and intermediate dose cytarabine (500 mg/m^2 every 12 hours for six days). Those who were assigned randomly to standard-dose cytarabine had a 38.7% OS rate, while patients assigned randomly to high-dose (HD) cytarabine had a 42.5% OS rate (log-rank test P =0.06). Survival rates were 43.3% and 51.9%, respectively, for patients less than 46 years old (P=0.009; multivariable analysis P=0.003), and 33.9% and 32.9%, respectively, for patients 46 to 60 years old (P=0.91).

Mayer et al. (1994) treated 1,088 newly diagnosed AML individuals aged 16 and up with daunorubicin for three days, cytarabine for seven days, and assigned randomly

patients who had a CR to receive four sessions of cytarabine at one of three doses. After 52 months of follow-up, 693 patients had achieved CR, whereas 596 were given post-remission cytarabine, and the DFS rates in the three groups were considerably different. The likelihood of remaining alive and disease-free after four years was 21% in the 100-mg group (95% CI, 15-26%), 25% in the 400-mg group (95% CI, 19-32%), and 39% in the 3-g group for the 596 patients who were assigned randomly to the medication (95% CI 32-46%). Furthermore, in each of the three post-remission cytarabine groups, patients aged 60 and higher had a 16% or lower likelihood of remaining disease-free after four years.

Patients <60 years old with intermediate-risk or unfavorable cytogenetics

Cairoli et al. (2006) conducted an Italian retrospective analysis to examine the prognostic significance of 67 adult patients with the c-KIT mutation. When compared to the 17 c-KIT unmutated (c-KIT) patients, the 12 TKD816 (tyrosine kinase domain) mutant patients had a significantly higher recurrence rate and lower OS at 24 months. There was no difference in relapse rate or OS between c-KIT patients with mutations other than TKD816 (n = 7) and c-KIT patients without mutations.

To assess the prognostic significance of mutant KIT in core-binding factor acute myeloid leukemia (AML), 110 patients with de novo CBF AML from Cancer and Leukemia Group B (CALGB) were studied (Paschka et al., 2006). The study revealed that KIT mutations were found in 29.5% of the inv(16) and 22% of the t(8;21) AML participants. For those with mutKIT (P 0.05; 5-year cumulative incidence of relapse (CIR), 56% v 29%) and mutKIT17 (P=0.002; 5-year cumulative incidence of relapse (CIR), 80% v 29%) had a greater CIR than wtKIT patients in inv(16). It was observed that after adjusting for sex, mutKIT predicted a worse OS rate. This confirmed that those with mutKIT17 had a higher relapse risk.

Chen et al. (2015) conducted a study evaluating the impact of KIT (a proto-oncogene) mutations on CBF-AML CR and recurrence, as well as the OS and mentioned that KIT mutations in CBF-AML should be considered in the initial diagnostic workup and classification of patients with t(8,21) AMP. The probability of relapse in CBF-AML and t(8;21) AML was shown to be negative. KIT mutations had a deleterious influence on non-Caucasians' CR (OR, 2.03; 95% CI: 1.02–4.05), relapse risk (RR, 1.89; 95% CI: 1.51–2.37), and OS (RR, 2.26; 95% CI: 1.35–3,78). However, it was also stated that larger prospective clinical studies are required to assess their findings.

In the prospective study of Jourdan et al. (2013), on days one to three, a 30-minute IV infusion of daunorubicin (DNR) at 60 mg/m^2/d was given, followed by a continuous IV infusion of cytarabine. On days eight and nine, DNR at 35 mg/m^2/d by 30-minute IV infusion was followed by cytarabine at 1000 mg/m^2/12 h by 2-hour IV infusion. For treatment B, on days one to three, DNR was administered IV for 30 minutes, and cytarabine was given IV daily from days one to seven. On day 15, patients in arm B

had a blood and BM test. Chemotherapy was restarted on day 16 for patients with more than 5% marrow blasts or Auer rods on day 15. Despite a faster drop in MRD, reinforced induction had no effect on RFS (64% in both groups; P=0.91). At 36 months, patients who had a 3-log MRD drop had a 22% recurrence rate and a 73% RFS rate, respectively. These findings imply that MRD, rather than gene mutations, should be employed to stratify individuals with CBF-AML in the future.

Based on the systematic review of Dholaria et.al (2020) allo-HCT offers survival benefit in patients with intermediate- and high-risk AML. On a meta-analysis of 4 intent-to treat AML-CR1 trials with over 3500 allo-HCT recipients and showed significant relapse-free survival for those whose cytogenetics were adverse risk (HR, 0.76; 95% CI, 0.68 to 0.85) rather than favorable risk (HR, 1.06; 95% CI, 0.80 to 1.42) the same with the overall survival.

Research Recommendation

The GDG recommended no additional research.

References

Post-remission Therapy and Intensive Antileukemic Therapy

Büchner, T., Hiddemann, W., Berdel, W. E., Wormann, B., Schoch, C., Fonatsch, C., ... & Heinecke, A. (2003). 6-Thioguanine, cytarabine, and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) for induction, TAD for consolidation, and either prolonged maintenance by reduced monthly TAD or TAD-HAM-TAD and one course of intensive consolidation by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia (AML): a randomized trial of the German AML Cooperative Group. *Journal of Clinical Oncology*, *21*(24), 4496-4504.

Gardin, C., Turlure, P., Fagot, T., Thomas, X., Terre, C., Contentin, N., ... & Dombret, H. (2007). Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood, The Journal of the American Society of Hematology*, *109*(12), 5129-5135.

Sekeres, M. A., Guyatt, G., Abel, G., Alibhai, S., Altman, J. K., Buckstein, R., ... & Brignardello-Petersen, R. (2020). American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. *Blood advances*, *4*(15), 3528-3549. doi: 10.1182/bloodadvances. 2020.

Consolidation chemotherapy (patients <60 years old)

Mayer, R. J., Davis, R. B., Schiffer, C. A., Berg, D. T., Powell, B. L., Schulman, P., ... & Frei, E. (1994). Intensive postremission chemotherapy in adults with acute myeloid leukemia. *New England Journal of Medicine*, *331*(14), 896-903.

National Comprehensive Cancer Network. (2019). Acute Myeloid Leukemia Version 3.2019. *Journal of the National Comprehensive Cancer Network* (JNCCN), *17*(6). United States, Pennsylvania.

Willemze, R., Suciu, S., Meloni, G. R., Labar, B., Marie, J. P., Halkes, C. J., ... & De Witte, T. (2014). High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. Journal of Clinical Oncology, *32*, 219–228.

Patients <60 years old with intermediate-risk or unfavorable cytogenetics

Cairoli, R., Beghini, A., Grillo, G., Nadali, G., Elice, F., Ripamonti, C.B., ... & Morra, E. (2006). Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. *Blood*, *107*(9), 3463-3468.

Chen, W., Xie, H., Wang, H., Chen, L., Sun, Y., Chen, Z., & Li, Q. (2016). Prognostic significance of KIT mutations in core-binding factor acute myeloid leukemia: a systematic review and meta-analysis. *PloS One*, *11*(1), e0146614.

Dholaria, B., Savani, B., Hamilton, B… Hamandi, M., Carpenter, P., & Nagler, A. (2020). Hematopoietic Cell Transplantation in the Treatment of Newly Diagnosed Adult Acute Myeloid Leukemia: An Evidence-Based Review from the American Society of Transplantation and Cellular Therapy. Transplantation and Cellular Therapy, 27(1), 6–20. https://doi.org/10.1016/j.bbmt.2020.09.020

Jourdan, E., Boissel, N., Chevret, S., Delabesse, E., Renneville, A., Cornillet, P., ... & Dombret, H. (2013). Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. *Blood, The Journal of the American Society of Hematology*, *121*(12), 2213-2223.

Paschka, P., Marcucci, G., Ruppert, A.S., Mrózek, K., Chen, H., Kittles, R.A., ... & Bloomfield, C.D. (2006). Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv (16) and t (8; 21): A Cancer and Leukemia Group B Study. *Journal of Clinical Oncology*, *24*(24), 3904-3911.

Question 8. Among newly diagnosed patients unfit for intensive induction chemotherapy, how effective is HMA monotherapy compared to HMA plus Venetoclax or LDAC plus Venetoclax in improving clinical outcomes (i.e., overall survival)?

Recommendation 8a.

We recommend the use of either hypomethylating-agent with Venetoclax or low-dose-cytarabine with Venetoclax for older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy.

Strong recommendation, Low quality evidence

Consensus Issues

The CP decided to recognize the AML-ASH2020 guidelines recommending the use of hypomethylating agents (HMA; monotherapy) or low-dose cytarabine (LDAC; monotherapy).

In addition, the CP considered and preferred the addition of Venetoclax to standard HMA or LDAC for older adults considered appropriate for antileukemic therapy but not for intensive therapy.

Summary of Evidence

Based on the ASH recommendation, giving HMAs or LDAC in combination with other drugs do not give any significant benefit over HMA or LDAC monotherapy.

In a study comparing the use of LDAC plus arsenic trioxide (ATO) against LDAC monotherapy among AML patients (median age = 74 years, range 36-86 years), no significant difference was noted in terms of CR between the LDAC + ATO and LDAC groups (LDAC + ATO 12% vs LDAC 15%, OR = 1.25, 95% CI [0.51, 3.06]; *P*=0.6), as well as in terms of 12-month OS (HR = 1.17, 95% CI [0.83, 1.65]; *P*=0.4) (Burnett et al., 2011). One RCT compared the effect of gemtuzumab ozogamicin (GO) + LDAC to LDAC alone in older patients with AML.

In terms of remission rate, GO + LDAC has a significantly better outcome (GO + LDAC 30% vs LDAC 17%, OR = 0.48, 95% CI [0.32, 0.73]; *P*=0.006). However, the 12-month OS rate between the two groups is not significant (GO + LDAC 27% vs LDAC 25%, HR = 0.99, 95% CI [0.83, 1.16]) (Burnett et al., 2012).

Vosaroxin + LDAC has no significant benefit against LDAC, both in terms of 12-month survival (Vosaroxin + LDAC 33% vs LDAC 37%, HR = 1.30, 95% CI [0.81, 2.07], *P* = 0.3) and response rate (Vosaroxin + LDAC 38% vs LDAC 34%, OR = 0.83, 95% CI [0.37, 1.84], *P* = 0.6). A reason to this lack of benefit was the Vosaroxin + LDAC

group's excess early mortality, most notably in the second month following randomization (Dennis et al., 2015).

A randomized, Phase II trial of LDAC and LDAC + volasertib in AML patients (median age = 75 years) resulted to a significantly higher EFS for LDAC + volasertib (LDAC + volasertib 5.6 months vs LDAC 2.3 months, HR = 0.57, 95% CI [0.35, 0.92], *P* = 0.021). The median OS is also higher for LDAC + volasertib (LDAC + volasertib 8.0 months vs LDAC 5.2 months, HR = 0.63, 95% CI [0.40, 1.00], *P* = 0.47) Response rate is also higher (but insignificant) for LDAC + volasertib (LDAC + volasertib 31.0% vs LDAC 13.3%, OR = 2.91, *P* = 0.052) (Döhner et al., 2014).

In a randomized, Phase IIb study of LDAC + lintuzumab against LDAC + placebo, adding lintuzumab to LDAC did not improve survival (LDAC + lintuzumab 14%, LDAC + placebo 9%, HR = 0.96, 95% CI [0.72, 1.28], *P* = 0.7585) (Sekeres et al., 2013).

Combining glasdegib with LDAC for patients with newly diagnosed AML resulted to a higher median OS (glasdegib + LDAC 8.8 months vs LDAC 4.9 months, HR = 0.51, 80% CI [0.39-0.67], *P* = 0.0004) and CR (glasdegib + LDAC 17% vs LDAC 2.3%, OR = 5.03, 80% CI [1.59-15.88], *P* = 0.0152, and can be an option for AML patients unsuitable for intensive chemotherapy (Cortes et al., 2019).

In an RCT comparing azacitidine (AZA) + vorinostat (VOR) versus AZA alone, no difference was seen in the overall response rate (AZA + VOR 42% vs AZA 41%, OR = 1.05, 95% CI [0.64, 1.72]); *P* = 0.84) and in the median OS (AZA + VOR 11.0 months vs AZA 9.6 months, HR = 1.15, 95% CI [0.87, 1.51]; *P* = 0.32) (Craddock et al., 2017).

A randomized Phase II trial comparing ten days of decitabine with bortezomib against decitabine alone among elderly patients with AML (median age = 72.4 years, range = 60.5-92.3 years) did not show any improvement in terms of median OS (decitabine + bortezomib 9.3 months vs 8.9 months, HR = 1.7, 95% CI [0.84, 1.63]; *P* = 0.18).

Currently, gemtuzumab ozogamicin, vosaroxin, volsertab, vorinostat, and lintuzumab are not available in the local market, while arsenic trioxide is formerly available but is no longer distributed in the country.

Bewersdorf et.al (2020) systematic review and meta-analysis, the addition of Venetoclax has demonstrated promising outcomes but inconclusive.

Research Recommendation

The GDG recommended no additional research.

References

Bewersdorf, J. P., Giri, S., Wang, R., Williams, R. T., Tallman, M. S., Zeidan, A. M., & Stahl, M. (2020). Venetoclax as monotherapy and in combination with hypomethylating agents or low dose cytarabine in relapsed and treatment refractory acute myeloid leukemia: a systematic review and meta-analysis. *Haematologica*, *105*(11), 2659–2663. https://doi.org/10.3324/haematol.2019.242826

Burnett, A.K., Hills, R.K., Hunter, A.E., Milligan, D., Kell, W.J., Wheatley, K., Yin, J., McMullin, M.F., Dignum, H., Bowen, D., & Russell, N.H. (2012). The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: Results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. *Leukemia*, *27*(1), 75–81. https://doi.org/10.1038/leu.2012.229

Burnett, A.K., Hills, R.K., Hunter, A., Milligan, D., Kell, J., Wheatley, K., Yin, J., McMullin, M.F., Cahalin, P., Craig, J., Bowen, D., & Russell, N. (2011). The addition of arsenic trioxide to low dose ara-C in older patients with AML does not improve outcome. *Leukemia*, *25*(7), 1122. https://doi.org/10.1038/LEU.2011.59

Cortes, J.E., Heidel, F.H., Hellmann, A., Fiedler, W., Smith, B.D., Robak, T., Montesinos, P., Pollyea, D.A., DesJardins, P., Ottmann, O., Ma, W.W., Shaik, M.N., Laird, A.D., Zeremski, M., O'Connell, A., Chan, G., & Heuser, M. (2019). Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*, *33*(2), 379–389. https://doi.org/10.1038/S41375-018-0312-9

Craddock, C.F., Houlton, A.E., Quek, L.S., Ferguson, P., Gbandi, E., Roberts, C., Metzner, M., Garcia-Martin, N., Kennedy, A., Hamblin, A., Raghavan, M., Nagra, S., Dudley, L., Wheatley, K., McMullin, M.F., Pillai, S.P., Kelly, R.J., Siddique, S., Dennis, M., … Vyas, P. (2017). Outcome of azacitidine therapy in acute myeloid leukemia is not improved by concurrent vorinostat therapy but is predicted by a diagnostic molecular signature. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *23*(21), 6430–6440. https://doi.org/10.1158/1078-0432.CCR-17-1423

Dennis, M., Russell, N., Hills, R.K., Hemmaway, C., Panoskaltsis, N., McMullin, M.F., Kjeldsen, L., Dignum, H., Thomas, I.F., Clark, R.E., Milligan, D., & Burnett, A.K. (2015). Vosaroxin and vosaroxin plus low-dose Ara-C (LDAC) vs low-dose Ara-C alone in older patients with acute myeloid leukemia. *Blood*, *125*(19), 2923–2932. https://doi.org/10.1182/BLOOD-2014-10-608117

Döhner, H., Lübbert, M., Fiedler, W., Fouillard, L., Haaland, A., Brandwein, J.M., Lepretre, S., Reman, O., Turlure, P., Ottmann, O.G., Müller-Tidow, C., Krämer, A., Raffoux, E., Döhner, K., Schlenk, R.F., Voss, F., Taube, T., Fritsch, H., & Maertens, J. (2014). Randomized, phase 2 trial of low dose cytarabine with or without volasertib in AML patients not suitable for induction therapy. *Blood*, *124*(9), 1426–1433. https://doi.org/10.1182/BLOOD-2014-03-560557

Sekeres, M.A., Lancet, J.E., Wood, B.L., Grove, L.E., Sandalic, L., Sievers, E.L., & Jurcic, J.G. (2013). Randomized phase IIb study of low-dose cytarabine and lintuzumab versus low-dose cytarabine and placebo in older adults with untreated acute myeloid leukemia. *Haematologica*, *98*(1), 119–128. https://doi.org/10.3324/HAEMATOL.2012.066613

Question 9. Among newly diagnosed AML patients with FLT3-ITD mutation, how effective is standard chemotherapy compared to standard chemotherapy with FLT3 inhibitor in achieving complete remission?

Recommendation 9a.

We recommend addition of FLT3-inhibitor in the management of newly diagnosed adults with acute FLT3-mutation-positive myeloid leukemia.

Strong recommendation, Low quality evidence

Consensus Issues

The CP voted to adopt the recommendation, with a suggestion to include other FLT3 inhibitors aside from Midostaurin, such as in Wei et al. (2020). Sorafenib did not improve EFS when combined with intensive chemotherapy in adults with newly diagnosed FLT3-ITD AML. Although not powered for significance, sorafenib showed a trend for improved OS among patients with higher FLT3-ITD AR or receiving HCT in CR1.

Summary of Evidence

According to the NICE guidelines (2021), evidence from RATIFY indicated that individuals taking Midostaurin with chemotherapy live longer than those given chemotherapy alone. It compared Midostaurin with intensive chemotherapy (daunorubicin plus cytarabine), followed by Midostaurin monotherapy (n=360) with chemotherapy alone (n=357).

In the said trial, participants aged 18 to 59 years old were randomized to receive standard cytarabine therapy (200 mg/m^2 daily for seven days via continuous infusion) and daunorubicin (60 mg/m^2 on days one to three) with placebo or Midostaurin (50 mg, twice daily on days eight to 21).

Patients who experienced CR were given four 28-day cycles of HiDAC (3 g/m^2 every 12 hours on days one, three, and five) with placebo or Midostaurin (50 mg, twice a day on days eight to 21), followed by a year of maintenance therapy with placebo or Midostaurin (50 mg twice a day) (Tallman et al., 2019). The median OS was 74.7 months (95% CI, 31.5–not reached [NR]) in the Midostaurin group and 25.6 months (95% CI, 18.6–42.9) in the placebo group (P=0.009). It was also found that patients who were provided with Midostaurin with standard induction and consolidation therapy had significant improvement in OS (HR for death, 0.78; P=0.009) and EFS (HR for event or death, 0.78; P=0.002) compared to the placebo group.

Studies such as Fischer et al. (2010) and Stone et al. (2012, 2017) have demonstrated the advantage of including Midostaurin to standard chemotherapy as part of frontline treatment for patients with newly diagnosed FLT3-mutation-positive AML. Based on the cost-effectiveness analysis done by NICE, Midostaurin plus chemotherapy compared with chemotherapy alone are considered an efficient use of resources, as such Midostaurin is recommended.

In FLT3-mutant cases, of whom majority are found in patients with intermediate-risk cytogenetics, findings show that the inclusion of Midostaurin to standard chemotherapy as frontline treatment improved survival, particularly for newly diagnosed cases. Results of the CALGB 10603/RATIFY Alliance trial (n=717), which was done in patients aged 18 to 59 years old indicated that those who received Midostaurin with standard induction and consolidation therapy had significant improvements in OS (HR for death, 0.78; P=0.009) and EFS (HR for event or death, 0.78; P=0.002), compared to those given placebo (Stone et al., 2017).

Research Recommendation

The GDG recommended no additional research.

References

Fischer, T., Stone, R. M., DeAngelo, D. J., Galinsky, I., Estey, E., Lanza, C., ... & Giles, F. J. (2010). Phase IIB trial of oral Midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. *Journal of Clinical Oncology*, *28*(28), 4339.

National Institute for Health and Care Excellence (NICE). 2021. *Myeloid Leukemia*. London, United Kingdom.

Stone, R.M., Fischer, T., Paquette, R., Schiller, G., Schiffer, C.A., Ehninger, G., ... & Giles, F. (2012). Phase IB study of the FLT3 kinase inhibitor Midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. *Leukemia*, *26*(9), 2061-2068.

Stone, R.M., Mandrekar, S.J., Sanford, B.L., Laumann, K., Geyer, S., Bloomfield, C. D., ... & Döhner, H. (2017). Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *New England Journal of Medicine*, *377*(5), 454-464.

Tallman, M. S., Wang, E. S., Altman, J. K., Appelbaum, F. R., Bhatt, V. R., Bixby, D., ... & Ogba, N. (2019). Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, *17*(6), 721-749.

Wei, A. H., Kennedy, G. A., Morris, K. L., Grigg, A., He, S., Schwarer, A., ... & Roberts, A. W. (2020). Results of a phase 2, randomized, double-blind study of sorafenib versus placebo in combination with intensive chemotherapy in previously untreated patients with FLT3-ITD acute myeloid leukemia (ALLG AMLM16). *Blood*, *136*, 36-38.

Post-treatment Evaluation

Question 10. Among patients who are undergoing induction chemotherapy, how accurate is a day 14 to 21 bone marrow histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD117, CD68* with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14*) compared to bone marrow aspirate alone for multi-color flow cytometry (8 color) with BULK lysis in predicting clinical outcome (i.e. remission rate, overall survival) and treatment modification?

Recommendation 10a.

We suggest offering a bone marrow evaluation (bone marrow aspirate with multicolor flow cytometry) 14 to 21 days post-therapy to categorize the patient according to the presence of blasts or hypoplasia.

Weak recommendation, Low quality evidence

Consensus Issues

The CP decided to adapt the recommendation from NCCN, Acute Myeloid Leukemia, Version 3.2019. No suggestions or issues from the Panel members were documented.

Summary of Evidence

The NCCN recommended a bone marrow evaluation 14 to 21 days post-therapy (i.e., standard cytarabine/anthracycline induction with or without Midostaurin or GO, or a dual-drug encapsulation of daunorubicin and cytarabine) to categorize the patient based on the presence of blasts or hyperplasia.

A retrospective analysis of 194 untreated AML patients found that a day-14 marrow had a 90% sensitivity in predicting CR on day 28 but had a rather low 43% specificity and 29% negative predictive value (NPV) (Hussein et al., 2008).

In another retrospective study involving 74 patients, the 14-day bone marrow biopsy was assessed as to whether it was accurate in determining a patient's need for re-induction chemotherapy. Results showed a positive predictive value (PPV) of 15% (95% CI [0.02; 0.45]) and an NPV of 93% (95% CI [0.81, 0.98]) for the 14-day bone marrow biopsy. The sensitivity and specificity are observed to be at 40% (95% CI [0.05, 0.85]) and 79% (95% CI [0.66, 0.89]), respectively (Morris et al., 2013).

A more recent retrospective study about 84 AML patients treated with standard chemotherapy showed that the 14-day bone marrow biopsy had an 82% sensitivity in

predicting CR on Day 28. It also had a specificity of 60% in predicting failure of CR (Alsaleh et al., 2018).

Research Recommendation

The GDG recommended no additional research.

References

Alsaleh, K., Aleem, A., Almomen, A., Anjum, F., & Alotaibi, G.S. (2018). Impact of Day 14 Bone Marrow Biopsy on Re-Induction Decisions and Prediction of a Complete Response in Acute Myeloid Leukemia Cases. *Asian Pacific Journal of Cancer Prevention : APJCP*, *19*(2), 421–425. https://doi.org/10.22034/APJCP.2018.19.2.421

Hussein, K., Jahagirdar, B., Gupta, P., Burns, L., Larsen, K., & Weisdorf, D. (2008). Day 14 bone marrow biopsy in predicting complete remission and survival in acute myeloid leukemia. *American Journal of Hematology*, *83*(6), 446–450. https://doi.org/10.1002/AJH.21133

Morris, T.A., DeCastro, C.M., Diehl, L.F., Gockerman, J.P., Lagoo, A.S., Li, Z., ... & Rao, A.V. (2013). Re-induction therapy decisions based on day 14 bone marrow biopsy in acute myeloid leukemia. *Leukemia Research*, *37*(1), 28-31. https://doi.org/10.1016/J.LEUKRES.2012.09.016

National Comprehensive Cancer Network. (2019). Acute Myeloid Leukemia Version 3.2019. *Journal of the National Comprehensive Cancer Network* (JNCCN), *17*(6). United States, Pennsylvania.

ANNEXES

Annex A: GDG COI Declaration and Management

Annex A.1. Technical Advisory Group COI Declaration and Management

Name	Affiliation	Conflict of Interest		
		Intellectual	Financial	Management
Dr. Nilo C. de los Santos	East Avenue Medical Center	None	None	May participate in the NCPG development
Dr. Clarito U. Cairo, Jr.	Department of Health	None	None	May participate in the NCPG development
Ms. Alma B. Abainza-Sanchez	PhilHealth	None	None	May participate in the NCPG development
Dr. Samuel S. Duran	East Avenue Medical Center	None	None	May participate in the NCPG development
Dr. Allan Troy D. Baquir	East Avenue Medical Center	None	None	May participate in the NCPG development

Annex A.2. Steering Committee COI Declaration and Management

Name	Qualifications	Conflict of Interest		
		Intellectual	Financial	Management
Dr. Lucille Osias	East Avenue Medical Center	None	None	May participate in the NCPG development
Dr. Lynn Bonifacio	National Kidney and Transplant Institute	None	None	May participate in the NCPG development
Dr. Prerna Vaswani	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Chrystal Catli-Burog	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Ma. Clariza Santos	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Camille Ariadne Tanchanco	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Mary Shayrel Lagan-Ragas	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Ma. Regina De Leon	Philippine Society for Blood and Marrow Transplantation	None	None	May participate in the NCPG development
Dr. Alma Calavera	Philippine Society for Blood and Marrow Transplantation	None	None	May participate in the NCPG development

Dr. Roxan Perez	Philippine Society for Blood and Marrow Transplantation	None	None	May participate in the NCPG development
Dr. Alejandro Arevalo	Philippine Society of Pathologists	None	None	May participate in the NCPG development
Dr. Rose Lou Marie Agbay	Philippine Society of Pathologists	None	None	May participate in the NCPG development

Annex A.3. Consensus Panel COI Declaration and Management

Name	Qualifications	Conflict of Interest		
		Intellectual	Financial	Management
Dr. Milflordeliza Gonzaga	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Connie Rose Benjamin	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Karen Kate Tobias	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Noel Pingoy	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Haidee Michelle Lim-Chua	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Januario Veloso	Philippine Society of Pathologists	None	None	May participate in the NCPG development
Dr. Marjorie Rose Bravo	Philippine Society for Blood and Marrow Transplantation	None	None	May participate in the NCPG development

Annex B: Summary of ADAPTE evidence

During the development of the Acute Myeloid Leukemia National Clinical Practice Guideline (AML NCPG), ADAPTE methodology was used to take advantage of the existing high-quality guidelines that can be modified or customized to suit the local context while addressing relevant health questions This is a systematic approach that was designed to aid in the adaptation of guidelines by the ADAPTE collaboration using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. This, in turn, provides a framework for assessing the quality of clinical practice guidelines ensuring that high quality guidelines are used for adaptation.

Annex B.1. NCPG PIPOH framework

Population	Adult (19 years old and above), including elderly, newly diagnosed, not relapse patients
Intervention	Diagnostics and Management
Professionals	Medical Specialist and Allied Health Professionals
Outcomes	Overall survival rate, disease-free survival, recurrence, and remission
Healthcare setting	Tertiary Level of Care (Hospital or Medical Centers)

Annex B.2. Search Terms and Search Criteria

The eight previously identified databases were systematically searched for guidelines on AML. The following were the inclusion criteria used for selection of applicable guidelines:

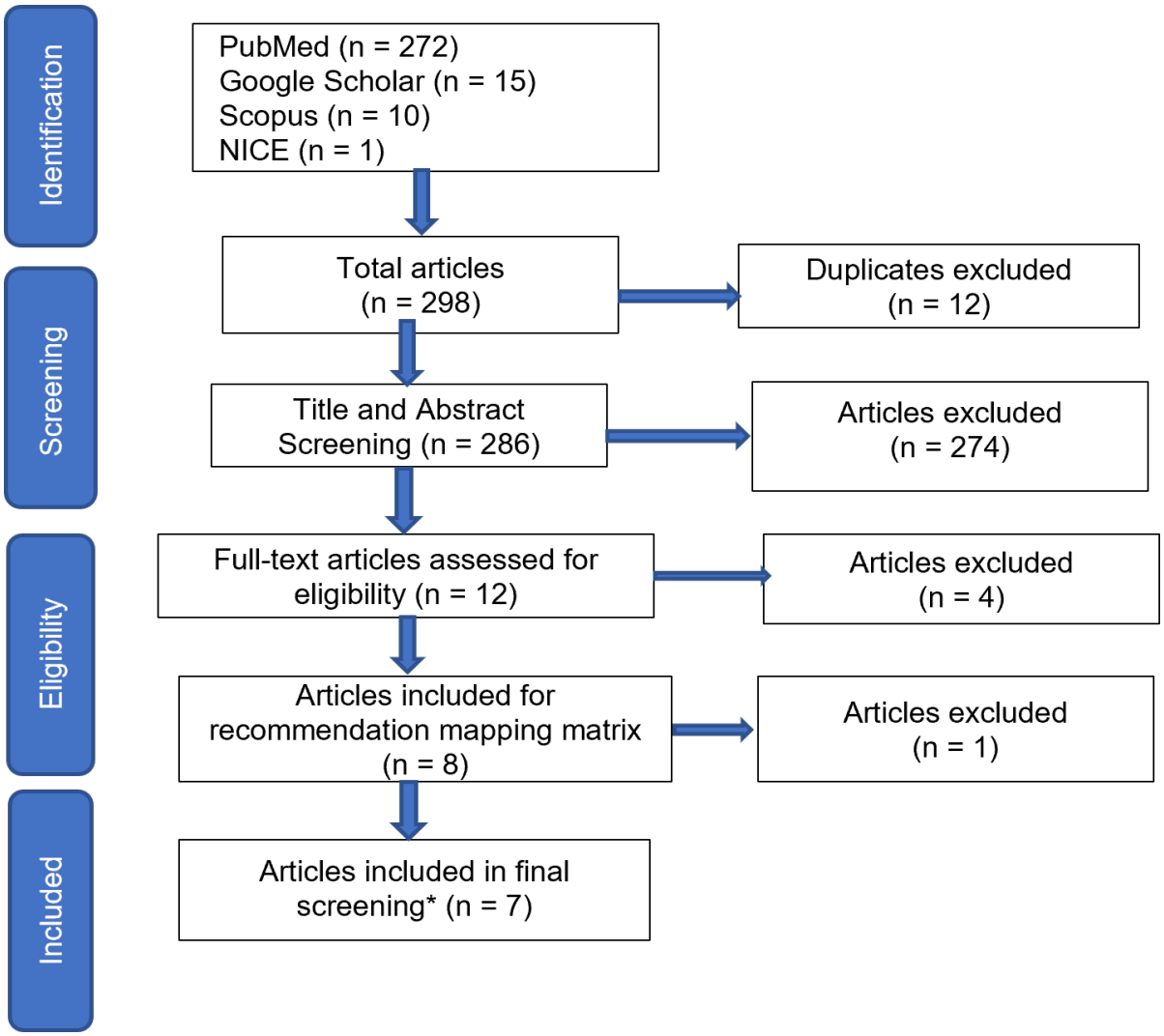
Database	Search String Used
PubMed	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]
Scopus	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]
Google Scholar	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]

Guidelines International Network (GIN)	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]
The National Institute for Health and Care Excellence (NICE)	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]
Scottish Intercollegiate Guidelines Network (SIGN)	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]
EMBASE	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]
Cochrane	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Leukemia, Myeloid, Acute"[MeSH Terms]

Search Criteria in Scoping Review

Inclusion Criteria	Exclusion Criteria
1. Clinical practice guidelines for Acute Myeloid Leukemia published in the last 10 years (2011 – present)	1. Articles with no available full-text access 2. Articles not written in English and without English translation

Annex B.3. PRISMA Flow



**6 with AGREE II score on RIGOR Domain >75%, 1 with <75% AGREE II score*

Annex B.4. Guideline Characteristics

Guideline	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence	OVERALL SCORE
AML-ASH2020	100	97.2	100	100	77.1	100	91.7
AML-NCCN2019	91.7	66.7	87.5	83.3	68.8	87.5	75
AML-NICE2021	94.4	100	85.4	100	100	79.2	83.3
AML-NCCN2021	91.7	66.7	87.5	83.3	68.8	87.5	75
AML-JSH2018	47.2	11.1	18.8	72.2	39.6	33.3	33.3
AML-ACP2017	97.2	77.8	81.3	100	77.1	91.7	83.3
AML-NCCN2022	91.7	66.7	87.5	83.3	68.8	87.5	75

Annex B.5. Guideline Assessment and Selection

The tables below summarize the characteristics of the included guidelines that were evaluated for adaptation. The rigor dimension of the AGREE II instrument was completed by two appraisers who were members of the ERE team for the seven guidelines.

Title	Publisher	Country/ Language	Publication Date	Search Duration	Recommendation Standards	AGREE II Score (Rigor)
NCCN Acute Myeloid Leukemia, Version 3.2019	National Comprehensive Cancer Network	Plymouth Meeting, Pennsylvania/ English	2019	07/21 to 05/22	NCCN Categories of Evidence and Consensus	87.5
NCCN Acute Myeloid Leukemia, Version 2.2021	National Comprehensive Cancer Network	Plymouth Meeting, Pennsylvania/ English	2021	07/21 to 05/22	NCCN Categories of Evidence and Consensus	85.4
NCCN Acute Myeloid Leukemia, Version 1.2022	National Comprehensive Cancer Network	Plymouth Meeting, Pennsylvania/ English	2021	07/21 to 05/22	NCCN Categories of Evidence and Consensus	87.5
JSH Practical Guidelines For Hematological Malignancies, 2018: I. Leukemia1. Acute Myeloid Leukemia (AML)	Japanese Society of Hematology	Japan/ English	2020	07/21 to 05/22	N/A	18.8

American Society Of Hematology 2020 Guidelines For Treating Newly Diagnosed Acute Myeloid Leukemia In Older Adults	American Society of Hematology	Washington, D.C., United States/ English	March 25, 2020	07/21 to 05/22	GRADE	100
Myeloid Leukemia	National Institute for Health and Care Excellence	London, United Kingdom/ English	July 14, 2021	07/21 to 05/22	N/A	85.4
Hepatitis B Vaccination, Screening, And Linkage To Care: Best Practice Advice From The American College Of Physicians And The Centers For Disease Control And Prevention	American College of Physicians	Philadelphia PA/ English	December 5, 2017	07/21 to 05/22	N/A	81.3

Annex C. CPG Questions in PICO Framework

Annex C.1. Diagnosis

1. Among patients suspected to have AML, can histopathology (bone marrow core biopsy and aspirate smears) with Immunohistochemical (IHC) staining of blasts for *MPO, CD34, CD117, CD68* alone be a surrogate test to diagnose AML compared to histopathology (bone marrow core biopsy and aspirate smears) with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD56, CD4, CD14*)?

Population	Intervention	Comparator	Outcomes
Patients suspected to have AML	Histopathology (bone marrow core biopsy and aspirate smear) with flow cytometry (*CD45, CD34, HLADR, CD117, MPO, CD13, CD33, CD56, CD4, CD14*)	Histopathology (bone marrow core biopsy and aspirate smear) with IHC staining of blasts for *MPO, CD34, CD 117, CD 68*	Accuracy, Overall survival rate, disease-free survival

2. Among newly diagnosed AML patients, should conventional karyotyping compared to FISH *[inversion 3 (GATA2/MECOM), 5q del, 7q del, t(6;9), 11q23 (MLL) or KMT2A, del17p, trisomy 8, BCR ABL1, t(8;21) (RUNX1/RUNX1T1, t(15;17) (PML/RARA), inv 16, t(16;16) (CBFB)]* be used to risk stratify patients with AML?

    - NON-FAVORABLE: *inversion 3 (GATA2/MECOM), 5q del, 7q del, t(6;9), 11q23 (MLL) or KMT2A, del17p, trisomy 8, BCR ABL1*
    - FAVORABLE: *t(8;21) (RUNX1/RUNX1T1, t(15;17) (PML/RARA), inv 16, t(16;16) (CBFB)*.

Population	Intervention	Comparator	Outcomes
Newly diagnosed AML patients	FISH *[inversion 3 (GATA2/MECOM), 5q del, 7q del, t(6;9), 11q23 (MLL) or KMT2A, del17p, trisomy 8, BCR ABL1, t(8;21) (RUNX1/RUNX1T1, t(15;17) (PML/RARA), inv 16, t(16;16) (CBFB)]*	Conventional Karyotyping	Accuracy for risk stratification, Overall survival rate, disease-free survival

3. Among newly diagnosed AML patients, should a baseline screening with molecular analysis (*FLT3-ITD, c-KIT, ASXL1, FLT-3 TKD, CEBPA, RUNX1, NPM1, TP53, IDH1, IDH2*) be done to risk stratify patients and guide treatment plan?

Population	Intervention	Comparator	Outcomes
Newly diagnosed AML patients	Baseline screening with molecular analysis	No screening with molecular analysis	Accuracy for risk stratification, Overall survival rate, disease-free survival

4. Among newly diagnosed AML patients who will undergo chemotherapy, should HBsAg, anti HBc total, anti HBs, anti HCV, and HIV testing be done for all patients to improve patient outcomes (i.e., decrease infectious complications)?

Population	Intervention	Comparator	Outcomes
Newly diagnosed AML patients	HBsAg, anti HBc total, anti HBs, anti HCV, and HIV testing	No HBsAg, anti HBc total, anti HBs, anti HCV, and HIV testing	Overall survival rate, disease-free survival

5. Among patients who have undergone induction chemotherapy, can histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD117, CD68* with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14*) be a surrogate to detect minimal residual disease in AML compared to bone marrow aspirate alone for multi-color (8 color) flow cytometry with BULK lysis?

Population	Intervention	Comparator	Outcomes
Newly diagnosed AML patients	Submitting bone marrow aspirate alone for multi-color (8 color) flow cytometry using BULK lysis technique	Histopathology with IHC or Histopathology with tri-color flow	Accuracy, Overall survival rate, disease-free survival

Annex C.2. Treatment and Care

6. Among AML patients who are fit to receive intensive therapy, should we use Doxorubicin with cytarabine compared to idarubicin with cytarabine for frontline induction treatment to improve patient outcomes (i.e., remission rate, disease-free survival, overall survival)?

Population	Intervention	Comparator	Outcomes
AML patients fit to receive intensive therapy	Doxorubicin with cytarabine	Idarubicin with cytarabine	Overall survival rate, disease-free survival, remission rate

7. Among AML patients with intermediate or high-risk cytogenetics in first remission, should we do allogeneic hematopoietic stem cell transplant compared to consolidation chemotherapy to improve patient outcomes (i.e., disease-free survival, overall survival)?

Population	Intervention	Comparator	Outcomes
AML patients with intermediate or high-risk cytogenetics in first remission	Allogeneic hematopoietic stem cell transplant	Consolidation chemotherapy	Overall survival rate, disease-free survival

8. Among newly diagnosed patients unfit for intensive induction chemotherapy, how effective is HMA monotherapy compared to HMA plus Venetoclax or LDAC plus Venetoclax in improving clinical outcomes (i.e., overall survival)?

Population	Intervention	Comparator	Outcomes
Newly diagnosed patients unfit for intensive induction chemotherapy	Hypomethylating agent (Azacitidine or Decitabine) monotherapy	Hypomethylating agent (Azacitidine or Decitabine) plus Venetoclax or Low dose cytarabine (LDAC) plus Venetoclax	Overall survival rate

9. Among newly diagnosed AML patients with FLT3-ITD mutation, how effective is standard chemotherapy compared to standard chemotherapy with FLT3 inhibitor in achieving complete remission?

Population	Intervention	Comparator	Outcomes
Newly diagnosed AML patients with FLT3-ITD mutation	Standard chemotherapy	Standard chemotherapy with FLT3 inhibitor	Complete remission, overall survival

Annex C.3. Post-treatment Evaluation

10. Among patients who are undergoing induction chemotherapy, how accurate is a day 14 to 21 bone marrow histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD117, CD68* with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14*) compared to bone marrow aspirate alone for multi-color flow cytometry (8 color) with BULK lysis in predicting clinical outcome (i.e. remission rate, overall survival) and treatment modification?

Population	Intervention	Comparator	Outcomes
Patients undergoing induction chemotherapy	Day 14 to 21 bone marrow assessment using option 1: bone marrow histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD117, CD68* and tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14*) VERSUS option 2: bone marrow aspirate alone for multi-color flow cytometry (8 color) with BULK lysis	No day 14 to 21 bone marrow assessment	Overall survival, remission rate

Annex C.4. Source Guideline Content Comparison

AML NCPG Questions and Recommendations	Content Comparison A check (✓) indicates inclusion of the relevant discussion in the guideline						
	AML-NCCN 2019	**AML-NCCN 2021**	**AML-JSH 2020**	**AML-ASH 2020**	**AML-NICE 2021**	**AML-ACP 2017**	AML-NCCN 2022
Diagnosis							
Among patients suspected to have AML, can histopathology (bone marrow core biopsy and aspirate smears) with immunohistochemical (IHC) staining of blasts for *MPO, CD34, CD117, CD68* alone be a surrogate test to diagnose AML compared to histopathology (bone marrow core biopsy and aspirate smears) with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD56, CD4, CD14*)?	✓						✓
Among newly diagnosed AML patients, should conventional karyotyping compared to FISH *[inversion 3 (GATA2/MECOM), 5q del, 7q del, t(6;9), 11q23 (MLL) or KMT2A, del17p, trisomy 8, BCR ABL1, t(8;21) (RUNX1/RUNX1T1, t(15;17) (PML/RARA), inv 16, t(16;16) (CBFB)]* be used to risk stratify patients with AML? • NON-FAVORABLE: *inversion 3 (GATA2/MECOM), 5q del, 7q del, t(6;9), 11q23 (MLL) or KMT2A, del17p, trisomy 8, BCR ABL1*	✓						

• FAVORABLE: *t(8;21) (RUNX1/RUNX1T1, t(15;17) (PML/RARA), inv 16, t(16;16) (CBFB)*							
Among newly diagnosed AML patients, should a baseline screening with molecular analysis *(FLT3-ITD, c-KIT, ASXL1, FLT-3 TKD, CEBPA, RUNX1, NPM1, TP53, IDH1, IDH2)* be done to risk stratify patients and guide treatment plan?	✓						
Among newly diagnosed AML patients who will undergo chemotherapy, should HBsAg, anti HBc total, anti HBs, anti HCV, and HIV testing be done for all patients to improve patient outcomes (i.e., decrease infectious complications)?						✓	
Among patients who have undergone induction chemotherapy, can histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD 117, CD 68 with tri-color flow cytometry (CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14* be a surrogate to detect minimal residual disease in AML compared to bone marrow aspirate alone for multi-color (8 color) flow cytometry with BULK lysis?			✓				
Treatment and Care							
Among AML patients who are fit to receive intensive therapy, should we use Doxorubicin with cytarabine compared to idarubicin with cytarabine for frontline induction treatment to improve patient outcomes	✓						

(i.e., remission rate, disease-free survival, overall survival)?							
Among AML patients with intermediate or high-risk cytogenetics in first remission, should we do allogeneic hematopoietic stem cell transplant compared to consolidation chemotherapy to improve patient outcomes (i.e., disease-free survival, overall survival)?	✓	✓		✓			
Among newly diagnosed patients unfit for intensive induction chemotherapy, how effective is HMA monotherapy compared to HMA plus Venetoclax or LDAC plus Venetoclax in improving clinical outcomes (i.e., overall survival)?		✓					
Among newly diagnosed AML patients with FLT3-ITD mutation, how effective is standard chemotherapy compared to standard chemotherapy with FLT3 inhibitor in achieving complete remission?					✓		
Post-treatment Evaluation							
Among patients who are undergoing induction chemotherapy, how accurate is a day 14 to 21 bone marrow histopathology (bone marrow core biopsy and aspirate smears) with IHC staining of blasts for *MPO, CD34, CD117, CD68* with tri-color flow cytometry (*CD45, CD34, HLADR, CD45, CD117, MPO, CD13, CD33, CD, CD 56, CD4, CD14*) compared to bone marrow aspirate alone for multi-color flow cytometry (8 color) with BULK lysis	✓						

in predicting clinical outcome (i.e. remission rate, overall survival) and treatment modification?							

Annex D: AGREE II Reporting Checklist (Self Evaluation)

TITLE OF CPG: _____

EVALUATOR: _____ **DATE:** _____

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
DOMAIN 1. SCOPE AND PURPOSE			
1. THE OVERALL OBJECTIVE(S) OF THE GUIDELINES IS (ARE) SPECIFICALLY DESCRIBED.	□ Health intent □ Expected benefit or outcome □ Target		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
2. THE HEALTH QUESTION(S) COVERED BY THE GUIDELINE IS (ARE) SPECIFICALLY DESCRIBED)	□ Target population □ Intervention or exposure □ Comparisons □ Outcomes □ Health care setting or context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
3. THE POPULATION (PATIENT, PUBLIC, ETC.) TO WHOM THE GUIDELINE IS MEANT TO APPLY IS SPECIFICALLY DESCRIBED.	□ Target population □ Clinical condition □ Severity/stage □ Comorbidities □ Excluded populations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 2. STAKEHOLDER INVOLVEMENT			
4. THE GUIDELINE DEVELOPMENT GROUP INCLUDES INDIVIDUALS FROM ALL RELEVANT PROFESSIONAL GROUPS.	□ Name of participant □ Discipline/content expertise □ Institution □ Geographical location □ A description of the member's role in the guideline development		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
5. THE VIEWS AND PREFERENCES OF THE TARGET POPULATION (PATIENTS, PUBLIC, ETC.) HAVE BEEN SOUGHT.	□ Statement of type of strategy used to capture patient/public views and preferences □ Methods by which preferences and views were sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Outcomes/ information gathered on patient/public information □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations		
6. THE TARGET USERS OF THE GUIDELINE ARE CLEARLY DEFINED.	□ The intended guideline audience □ How the guideline may be used by its target audience		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 3. RIGOUR OF DEVELOPMENT			
7. SYSTEMATIC METHODS WERE USED TO SEARCH FOR EVIDENCE.	□ Named electronic databases or evidence source where the search was performed □ Time periods searched □ Search terms used □ Full search strategy included		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
8. THE CRITERIA FOR SELECTING THE EVIDENCE ARE CLEARLY DESCRIBED.	□ Target population □ Study design □ Comparisons □ Outcomes □ Language □ Context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
9. THE STRENGTHS AND LIMITATIONS OF THE BODY OF EVIDENCE ARE CLEARLY DESCRIBED. TOOLS EXIST THAT CAN FACILITATE THE REPORTING OF THIS CONCEPT.	□ Study design included in body of evidence □ Study methodology limitations □ Appropriateness/ relevance of primary and secondary outcomes considered □ Consistency of results across studies		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Direction of results across studies □ Magnitude of benefit vs magnitude of harm □ Applicability to practice context.		
10, THE METHODS FOR FORMULATING THE RECOMMENDATIONS ARE CLEARLY DESCRIBED. SPECIFY AREAS OF DISAGREEMENTS AND METHODS USED TO RESOLVE THEM.	□ Recommendation development process □ Outcomes of the recommendation development process □ How the process influenced the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
11. THE HEALTH BENEFITS, SIDE EFFECTS, AND RISKS HAVE BEEN CONSIDERED IN FORMULATING THE RECOMMENDATIONS.	□ Supporting data and report of benefits □ Supporting data and report of harms/side effects/ risks □ Reporting of the balance/trade-off between benefits and harms/side effects/risks □ Recommendations reflect considerations of both benefits and harms/side effects/risks		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
12. THERE IS AN EXPLICIT LINK BETWEEN THE RECOMMENDATIONS AND THE SUPPORTING EVIDENCE.	□ How the guideline development group linked and used the evidence to inform recommendations. □ Link between each recommendation and key evidence □ Link between recommendations and evidence summaries/or evidence tables in the results section of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
13. THE GUIDELINE HAS BEEN EXTERNALLY REVIEWED BY EXPERTS PRIOR TO ITS PUBLICATION.	□ Purpose and intent of the external review □ Methods taken to undertake the external review		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Description of the external reviewers □ Outcomes/information gathered from the external review □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		Comments:
14. A PROCEDURE FOR UPDATING THE GUIDELINE IS PROVIDED.	□ A statement that the guideline will be updated □ Explicit time interval or explicit criteria to guide decisions about when an update will occur □ Methodology for the updating procedure		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 4. CLARITY OF PRESENTATION			
15. THE RECOMMENDATIONS ARE SPECIFIC AND UNAMBIGUOUS.	□ A statement of the recommended action □ Intent or purpose of the recommended action □ Relevant population □ Caveats or qualifying statements, if relevant □ If there is uncertainty about the best care option, the uncertainty should be stated in the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
16. THE DIFFERENT OPTIONS FOR MANAGEMENT OF THE CONDITION OR HEALTH ISSUE ARE CLEARLY PRESENTED.	□ Description of management options □ Population or clinical situation most appropriate to each option		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
17. KEY RECOMMENDATIONS ARE EASILY IDENTIFIABLE.	□ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms □ Specific recommendations grouped together in one section		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 5. APPLICABILITY			
18. THE GUIDELINE DESCRIBES FACILITATORS AND BARRIERS TO ITS APPLICATION.	□ Types of facilitators and barriers that were considered □ Method by which information regarding the facilitators and barriers to implementing recommendations were sought. □ Information/ description of the types of facilitators and barriers that emerged from the injury □ How the information influenced the guideline development process and/or formation of the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
19. THE GUIDELINE PROVIDES ADVICE AND/OR TOOLS ON HOW THE RECOMMENDATIONS CAN BE PUT INTO PRACTICE.	□ Additional materials to support the implementation		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
20. THE POTENTIAL SOURCE IMPLICATIONS OF APPLYING THE RECOMMENDATIONS HAVE BEEN CONSIDERED.	□ Types of cost information that were considered □ Methods by which the cost information was sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Information/ description of the cost information that emerged from the inquiry □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		
21. THE GUIDELINE PRESENTS MONITORING AND/OR AUDITING CRITERIA.	□ Criteria to assess guideline implementation or adherence to recommendations □ Criteria for assessing impact of implementing the recommendations □ Advice on the frequency and interval of measurement □ Operational definitions of how the criteria should be measured.		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 6. EDITORIAL INDEPENDENCE			
22. THE VIEWS OF THE FUNDING BODY HAVE NOT INFLUENCED THE CONTENT OF THE GUIDELINE.	□ The name of the funding body or source of funding □ A statement that the funding body did not influence the content of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
23. COMPETING INTERESTS OF GUIDELINE DEVELOPMENT GROUP MEMBERS HAVE BEEN RECORDED AND ADDRESSESD.	□ Types of competing interests considered □ Methods by which potential competing interests were sought □ a description of the competing interests □ How the competing interests influenced the guideline process and		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments: