

Current AML Treatment Algorithms and Key Phase III Clinical Trials: A Clinician's Resource

Acute myeloid leukemia (AML) represents the most common type of acute leukemia in adults, with 19,940 Americans estimated to be diagnosed with AML in 2020.^[1] The median age at diagnosis of AML is 68 years with incidence increasing with age.^[2] The prevalence of AML appears to be increasing, particularly in the population older than 60 years of age. This resource focuses on the current treatment algorithms for patients with newly diagnosed or relapsed/refractory AML and provides a listing of select ongoing phase III trials for patients with AML as of December 2020. This resource has been developed to assist you in providing the best possible care for your patients with AML.

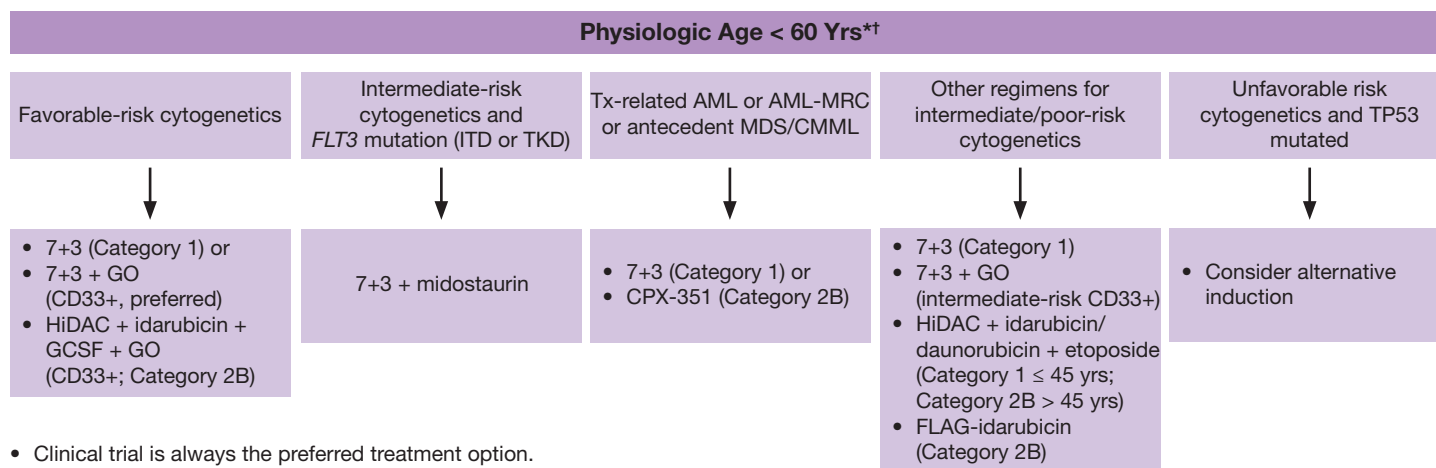
MOLECULAR ANALYSIS

Chemotherapy regimens cure only a minority of patients with AML, leading to a search for meaningful biomarkers to facilitate a risk-adapted stratification approach to treatment. Molecular analysis has become a key component of AML diagnosis, stratification, and treatment, enabling clinicians to classify their patient's AML by risk group: favorable, intermediate, or adverse (Table 1).

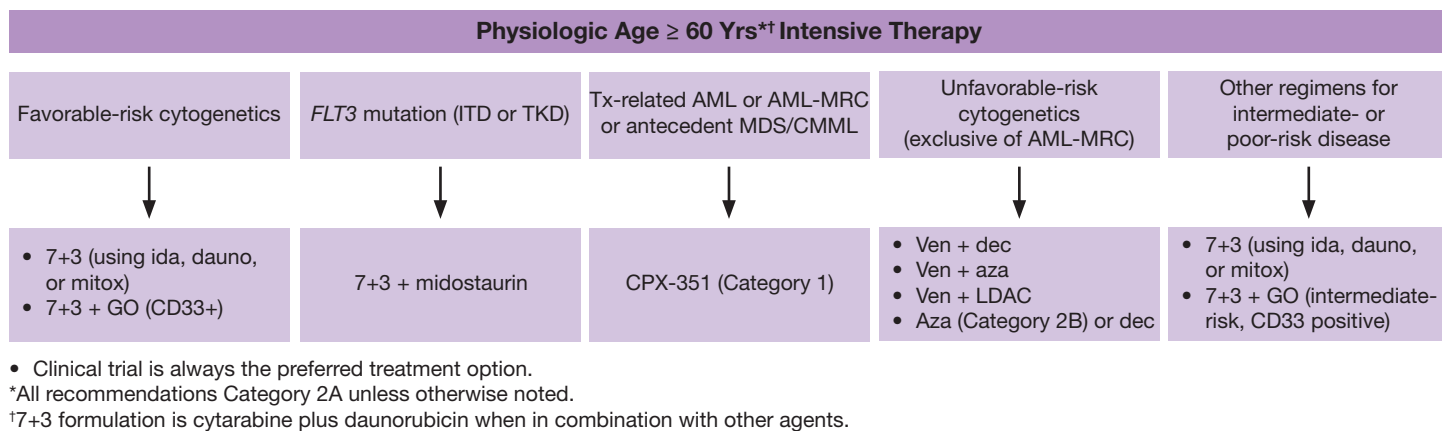
Table 1. Correlation of Cytogenetic and Genetic/Mutation Data With Risk in AML^[3]

Risk Status	Cytogenetics	Molecular Abnormalities
Favorable	t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i> inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i>	Mutated <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> ^{low} or biallelic-mutated <i>CEBPA</i>
Intermediate	t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i> Cytogenetic abnormalities not classified as favorable or adverse	Mutated <i>NPM1</i> and <i>FLT3-ITD</i> ^{high} Wild-type <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> ^{low} (without adverse risk genetic lesions)
Adverse	t(6;9)(p23;q34.1); <i>DEK-NUP214</i> t(v;11q23.3); <i>KMT2A</i> rearranged t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i> inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2, MECOM(EVI1)</i> -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype	Wild-type <i>NPM1</i> and <i>FLT3-ITD</i> ^{high} Mutated <i>RUNX1</i> Mutated <i>ASXL1</i> Mutated <i>TP53</i>

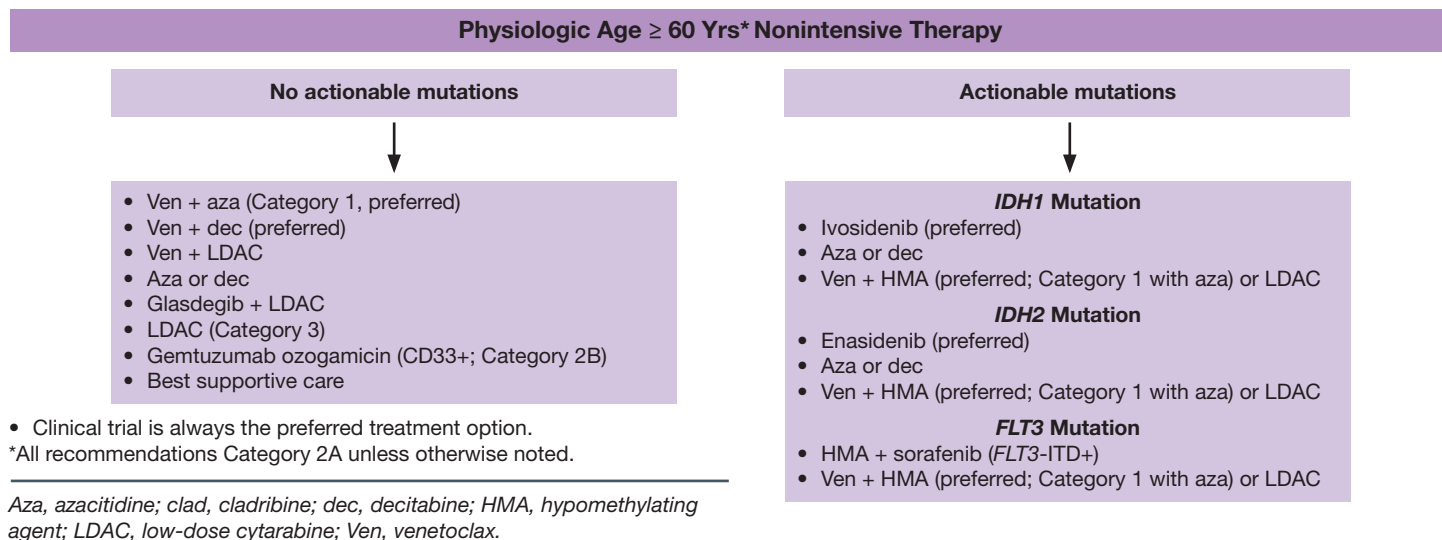
Figure 1. Treatment algorithms for newly diagnosed AML.^[4] (All Algorithms Adapted From NCCN Guidelines®)



7+3, cytarabine plus idarubicin or daunorubicin; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; FLAG, fludarabine, high-dose cytarabine; G-CSF, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; HiDAC, high-dose cytarabine; MDS, myelodysplastic syndrome; MRC, myelodysplastic-related changes; Tx, treatment.

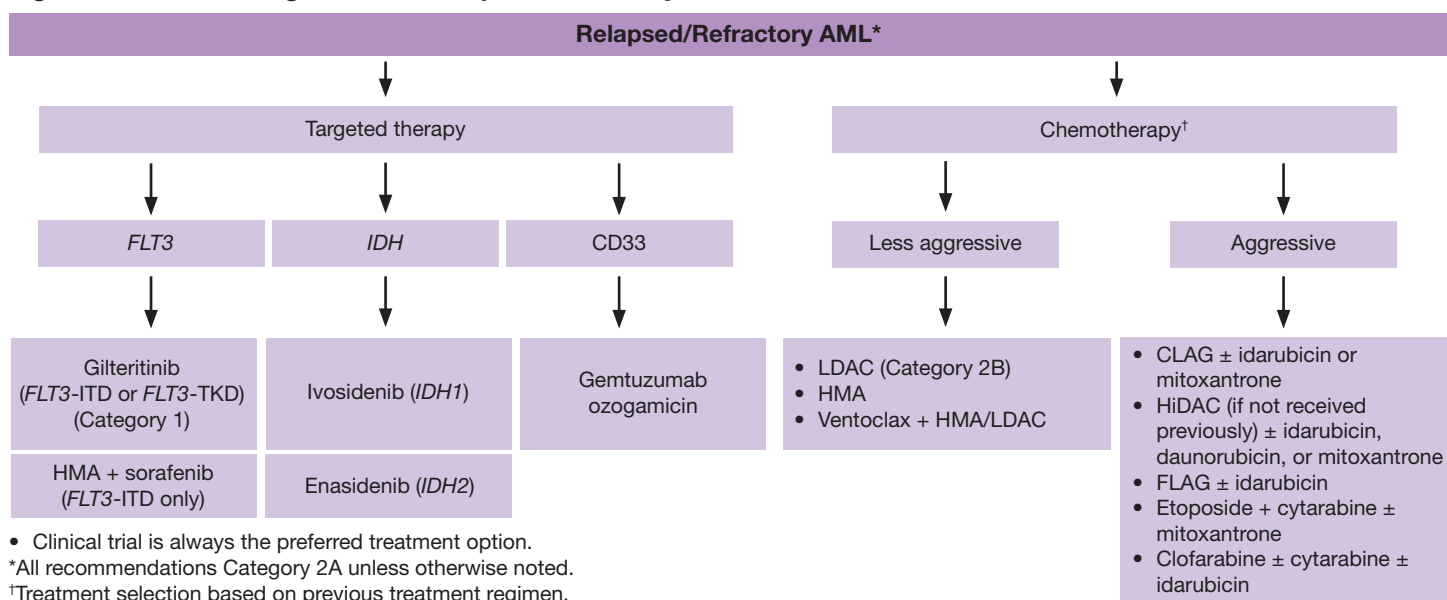


AML, acute myeloid leukemia; aza, azacitidine; clad, cladribine; CMML, chronic myelomonocytic leukemia; dauno, daunorubicin; dec, decitabine; ida, idarubicin; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; MRC, myelodysplasia-related changes; mitox, mitoxantrone; Tx, treatment; Ven, venetoclax.



Patients with remission should be considered for consolidation treatment with hematopoietic stem cell transplantation or other therapy. See NCCN Guidelines® at nccn.org for additional information.

Figure 2. Treatment algorithm for relapsed/refractory AML.^[4]



CLAG, cladribine + cytarabine + G-CSF; FLAG, fludarabine + cytarabine + G-CSF; HiDAC, high-dose cytarabine; HMA, hypomethylating agent; LDAC, low-dose cytarabine.

Table 2. Selected Ongoing Phase III Clinical Trials in AML^[5]

Study	Patient Population	N*	Status	Treatment Arms
NEWLY DIAGNOSED AML				
NCT03512197	ND <i>FLT3</i> -negative AML	513	Accrued	Chemo ± midostaurin induction and post consolidation
NCT04293562	ND <i>FLT3</i> -negative or -positive AML	1400	Enrolling	CPX-351 ± gilteritinib vs standard chemotherapy
NCT02752035 (II/III)	ND <i>FLT3</i> AML ineligible for intensive chemo	250	Enrolling	Gilteritinib ± azacitidine vs azacitidine
NCT03416179 BRIGHT AML1019	Tx-naïve AML	730	Accrued	Intensive chemo or azacitidine ± glasdegib
NCT03173248 AGILE	Tx-naïve <i>IDH1</i> AML	200	Enrolling	Ivosidenib + azacitidine vs placebo + azacitidine
NCT02668653 QuANTUM-First	ND <i>FLT3</i> -ITD AML	539	Accrued	Quizartinib with standard-of-care chemo and as maintenance Tx
NCT03701308 (II/III)	Older patients with AML receiving intensive induction Tx	670	Enrolling	Uproleselan + 7+3 vs 7+3
NCT03069352 M16-043	Tx-naïve AML ineligible for intensive chemo	211	Accrued	Venetoclax + cytarabine vs cytarabine
NCT02993523	Tx-naïve AML ineligible for standard induction	443	Accrued	Venetoclax + azacitidine vs azacitidine
NCT03941964 (IIIb)	Age ≥ 12 yrs with Tx-naïve AML ineligible for intensive chemo	60	Enrolling	Venetoclax + azacitidine or decitabine (single arm, outpatient Tx)
NCT01721876	Age ≥ 65 yrs with Tx-naïve AML ineligible for intensive chemo	666	Accrued	Volasertib + LDAC vs LDAC
MAINTENANCE THERAPY				
NCT01757535 QUAZAR AML-001	AML in CR1	472	Accrued	Azacitidine + best supportive care vs best supportive care
NCT02927262	<i>FLT3</i> -ITD AML in CR1 post induction	98	Accrued	Gilteritinib vs placebo
NCT02997202	<i>FLT3</i> -ITD AML in CR1 post ASCT	356	Accrued	Gilteritinib vs placebo
RELAPSED/REFRACTORY AML				
NCT03250338	Age ≤ 75 yrs with R/R <i>FLT3</i> AML	322	Enrolling	Chemo ± crenolanib
NCT03616470	Age ≤ 75 yrs with R/R AML	380	Enrolling	Chemo ± uproleselan
NCT02577406 IDENTIFY	Older subjects with late-stage R/R <i>IDH2</i> AML	319	Accrued	Enasidenib vs CCR
NCT03504410	Older subjects with R/R AML	500	Enrolling	HiDAC + mitoxantrone ± CPI-613
NCT02665065 SIERRA	Older subjects with R/R AML + CD45 expression	150	Enrolling	Iodine-131 apamistamab + RIC prior to allo-HSCT vs allo-HSCT after further leukemic reduction (CCR)

Allo-HSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukemia; ASCT, autologous stem cell transplant; CCR, conventional care regimens; HiDAC, high-dose cytarabine; LDAC, low-dose cytarabine; RIC, reduced-intensity conditioning; R/R, relapsed/refractory; Tx, treatment.

*Actual or planned N.

References

1. Siegel. CA Cancer J Clin. 2020;70:7-34. 2. SEER data. <http://seer.cancer.gov/statfacts/html/amyl.html>. 3. Döhner. Blood.2017; 129:424. 4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for AML V2.2021. ©National Comprehensive Cancer Network, Inc 2020. All rights reserved. Accessed November 16, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. 5. ClinicalTrials.gov.