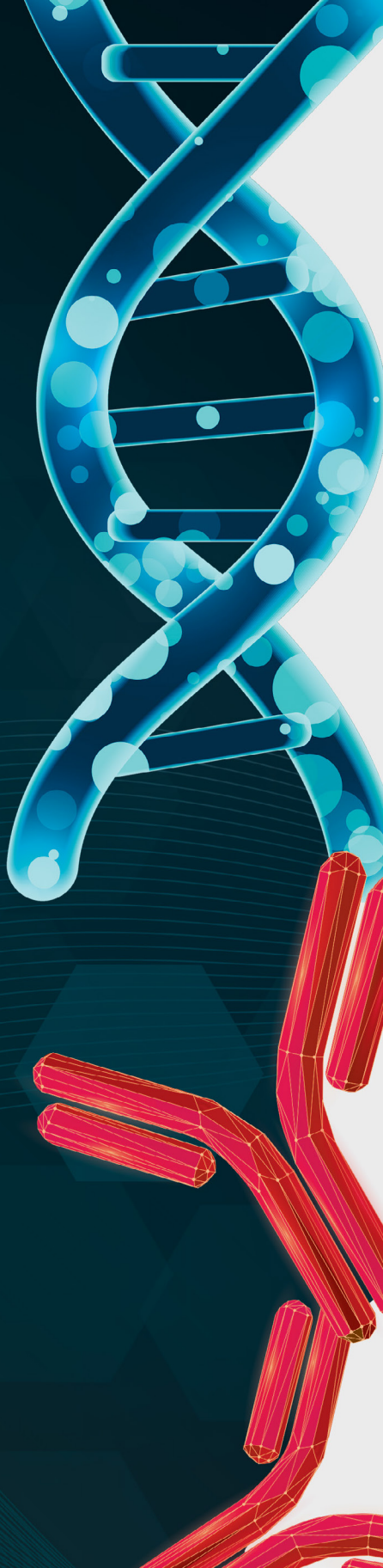
INFORMED TREATMENT DECISIONS:

Molecular Profiling in Acute Myeloid Leukemia (AML)[1]

Genetic and molecular analyses are becoming increasingly important to inform prognoses and the selection of therapeutic options for patients with AML.

The European LeukemiaNet (ELN) recommends that patients with AML should be tested for genetic mutations at initial diagnosis and the relapsed/refractory stage. This tool presents selected treatment options from the ELN recommendations. Please refer to the ELN recommendations for complete details.



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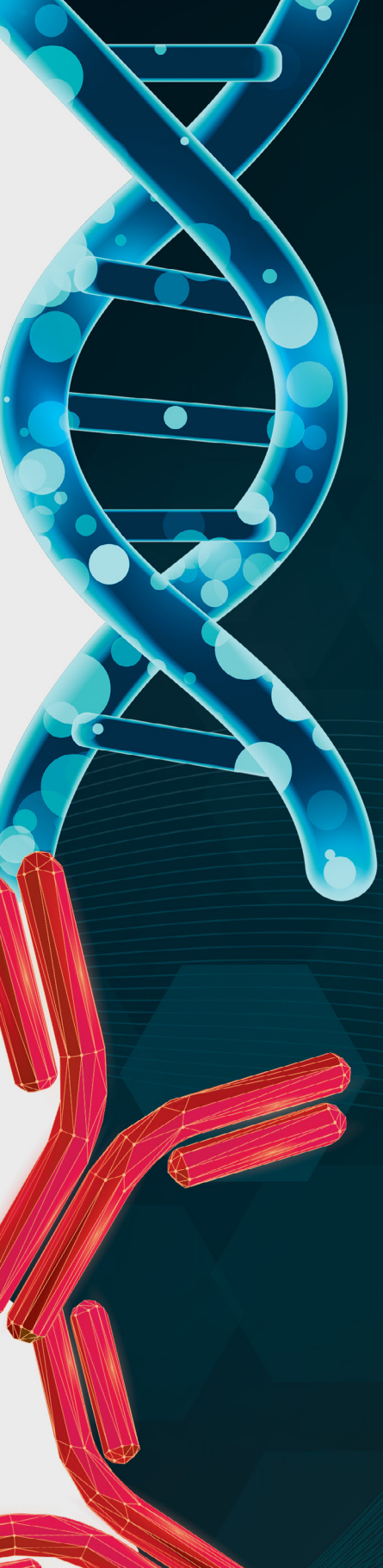


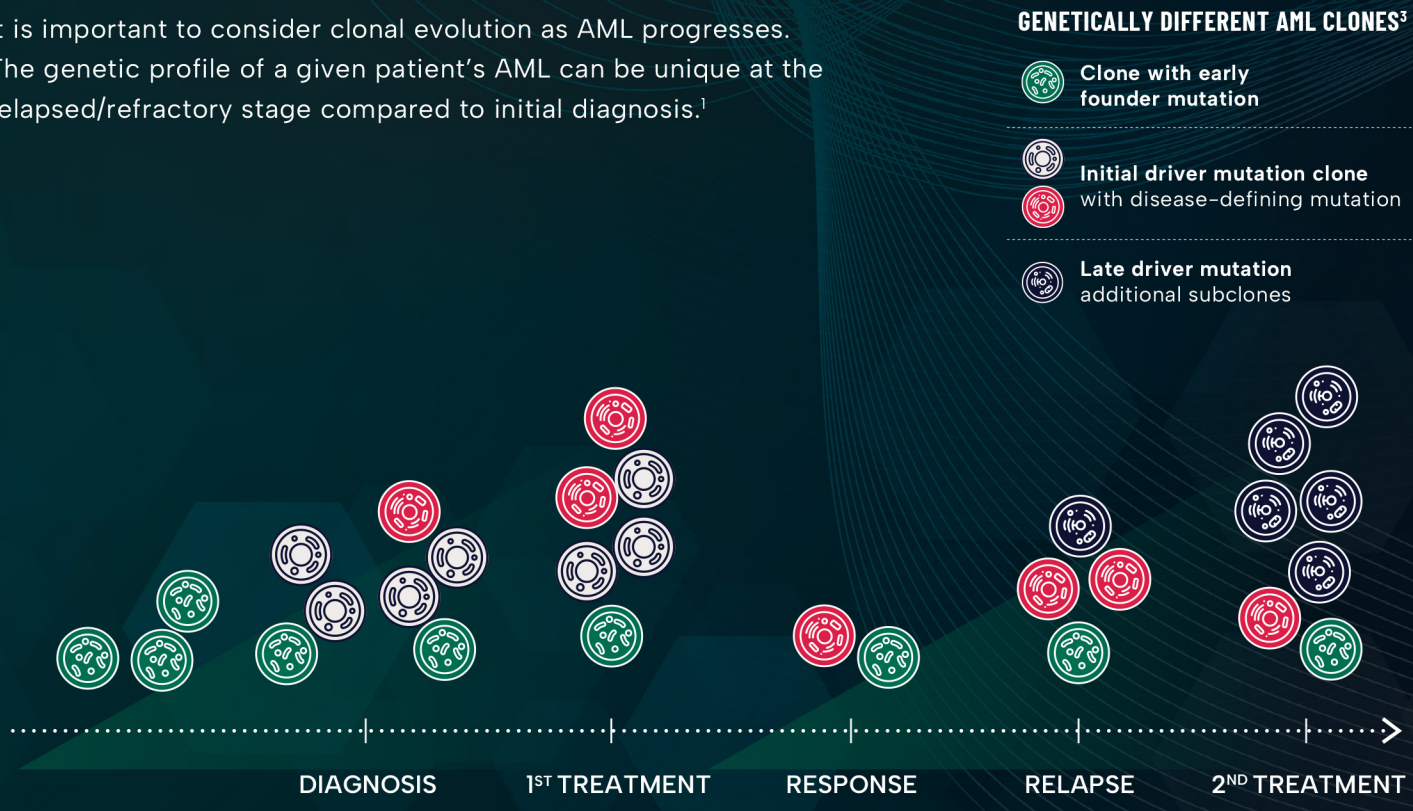
Molecular Profiling of Select Genetic Mutations in AML[2]

Genetic testing is becoming increasingly important for patients with AML, and several mutations are associated with specific prognoses in different subsets of patients. The rates of mutations in specific genes are as follows:

ASXL1	Approximately **5% to 36%** of *de novo* AML cases
c-KIT	Approximately **20%** of patients with core binding factor AML
CEBPA (biallelic)	**7% to 11%** of AML cases
DNMT3A	**18% to 22%** of AML cases
FLT3-ITD	Approximately **30%** of AML cases
FLT3-TKD	Approximately **10%** of AML cases
IDH1	**6% to 9%** of AML cases
IDH2	**8% to 12%** of AML cases
KMT2A rearrangements	Approximately **3%** of *de novo* AML cases and **9%** of t-AML cases
NPM1	**28% to 35%** of AML cases
RUNX1	Approximately **10%** of *de novo* AML cases
TP53	Approximately **12% to 13%** of AML cases

Clonal Evolution During Therapy Can Lead to a Change in Mutational Status

It is important to consider clonal evolution as AML progresses. The genetic profile of a given patient's AML can be unique at the relapsed/refractory stage compared to initial diagnosis.[1]



- **AML cells often gain or lose mutations** and these cells can proliferate[4]
- Some clones may become dominant, while others may emerge, leading to a **change in mutation status**[4]

At clinical progression, it is important to highlight the potential for clonal evolution and emergence of actionable targets not detected at diagnosis. Currently, these include emergence of *IDH1*/*IDH2* mutations or new or expanded *FLT3*-ITD or *FLT3*-TKD clones. Therefore, molecular re-evaluation at relapse is important to identify patients who may be suitable for targeted salvage options. In the interest of therapeutic progress, it is recommended to enter these patients into clinical trials whenever possible.[1]

Selected Treatment Options for Patients Fit for Intensive Chemotherapy: ELN RECOMMENDATIONS[1]

The key components of initial diagnosis include physical examination, medical history, complete blood counts, bone marrow assessment, cytogenetic tests, and genetic profiling.*,[1]

***ASXL1, BCOR, CEBPA, DDX41, EZH2, FLT3-ITD, FLT3-TKD, IDH1, IDH2, NPM1, RUNX1, SF3B1, SRSF2, STAG2, TP53, U2AF1, ZRSR2* gene mutations and *BCR::ABL1, CBFB::MYH11, KMT2A, PML::RAR alpha*, and *RUNX1::RUNX1T1* gene rearrangements, in addition to molecular markers, should be analyzed in the initial workup for all patients with AML.*,†,[1]**

Fit for intensive chemotherapy	Induction	Consolidation‡	Maintenance
AML with *FLT3* mutation	• Daunorubicin IV; or idarubicin IV; and cytarabine CIV; plus midostaurin PO • Re-induction: either 2nd cycle "7+3" or regimen containing higher dose of cytarabine, each plus midostaurin, preferable the latter in patients with no response to 1st cycle	• 3–4 cycles of IDAC IV; plus midostaurin PO§	Midostaurin PO‖
Non-*FLT3* mutant¶	• Daunorubicin IV, idarubicin IV, or mitoxantrone IV; and cytarabine CIV • Re-induction: either 2nd cycle "7+3" or regimen containing higher dose of cytarabine, preferable the latter in patients with no response	• 3–4 cycles of IDAC IV	Oral azacitidine PO, until disease progression#
Other options#			
GO for CD33-positive AML, favourable (or intermediate) cytogenetic risk	• Daunorubicin IV and cytarabine CIV; plus GO IV • Re-induction (if not in CR/CRh/CRi) may be with daunorubicin IV and cytarabine IV without GO	• 2–4 cycles of IDAC IV, GO may be added on • Consider omitting GO if allogeneic HSCT is planned to reduce the risk of veno-occlusive disease	
CPX-351 for AML with myelodysplasia-related changes or therapy-related AML**	• CPX-351 IV • Re-induction (if not in CR/CRh/CRi): CPX-351 IV	• 1–2 cycles of CPX-351 IV	
Common salvage regimens in patients not responding to initial induction or with relapsed disease who are candidates for intensive therapy			
Gilteritinib (AML with *FLT3* mutation)	• Gilteritinib PO, until disease progression		
Intermediate-dose cytarabine†† (with or without anthracycline)	• Cytarabine IV; with or without daunorubicin IV; idarubicin IV; or mitoxantrone IV		
FLAG-IDA‡‡	• Fludarabine IV; cytarabine IV; idarubicin IV; G-CSF SC; additional G-CSF may be administered after end of chemotherapy until WBC count > 0.5 x 10^9/L • Consider dose reduction in patients ≥ 60 years: fludarabine; cytarabine; idarubicin		
MEC	• Mitoxantrone IV; etoposide IV; cytarabine IV		
CLAG-M	• Cladribine IV; cytarabine IV; mitoxantrone IV; G-CSF SC		
Allogeneic HSCT	• Consider transplantation for patients with primary refractory disease, for patients in second CR (or CRh, CRi) or with major cytoreduction but still active disease following salvage therapy. Consider second transplantation under certain conditions. Perform early HLA typing.		
Salvage options if not a candidate for intensive chemotherapy			
Gilteritinib (AML with *FLT3* mutation)§§	• PO, until disease progression		
Ivosidenib (AML with *IDH1* mutation)‖‖	• PO, until disease progression		
Enasidenib (AML with *IDH2* mutation)¶¶	• PO, until disease progression		

Selected Treatment Options for Patients Not Suitable for Intensive Chemotherapy: ELN RECOMMENDATIONS##,1

Regimen	Recommended dosing
Azacitidine or decitabine + venetoclax***,†††	Azacitidine SC/IV or decitabine IV; venetoclax dose ramp up PO • Adjust venetoclax dose if concurrent strong CYP3A4 inhibitors • For venetoclax dose modifications and management of myelosuppression please refer to the ELN recommendations
Low-dose cytarabine + venetoclax***,†††	Cytarabine SC; venetoclax dose ramp up PO • Adjust venetoclax dose if concurrent strong CYP3A4 inhibitors • For venetoclax dose modifications and management of myelosuppression please refer to the ELN recommendations
Azacitidine + ivosidenib (AML with *IDH1* mutation)	Azacitidine SC/IV; ivosidenib PO; until progression
Ivosidenib (AML with *IDH1* mutation)	For very frail patients, ivosidenib PO as monotherapy, until progression may be considered
Best supportive care	Including hydroxyurea; for patients who cannot tolerate any anti-leukemic therapy, or who do not wish any therapy

Treatment options are based on ELN recommendations; please refer to the ELN recommendations for complete dosing information.

Treatments listed may not be available in Canada, and treatments available in Canada may not be included in these tables.

* Additional tests may be required; please refer to the ELN recommendations for complete details.

† Therapeutic options are not available for all genetic abnormalities.

‡ Results from assessment of MRD should be taken into account for selecting the appropriate consolidation therapy.

§ In the trial that led to the regulatory approval of midostaurin for *FLT3*-mutated AML, consolidation cycles included high-dose cytarabine at 3000 mg/m^2, whereas intermediate dose levels of cytarabine (1000–1500 mg/m^2) are nowadays more commonly applied in AML therapeutics.

‖ The value of maintenance treatment with midostaurin remains uncertain.

¶ Alternative active frontline induction regimens that are sometimes used include FLAG-IDA (defined below under common salvage regimens).

Data regarding the role of oral azacitidine maintenance therapy in younger patients (< 55 years) or patients with core-binding factor AML are lacking; in addition, data are lacking for oral azacitidine after GO-based or CPX-351 induction/consolidation therapy.

** Data in younger adult patients (< 60 years) and for AML post myeloproliferative neoplasm are lacking. No benefit compared with "7+3" induction was shown in patients with antecedent MDS with prior hypomethylating agent exposure.

†† Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of "7+3." Single-agent IDAC should not be used in patients relapsing within 6 months following consolidation with higher doses of cytarabine.

‡‡ Idarubicin may be replaced by mitoxantrone 10 mg/m^2 IV day 2–4 (FLAG-MITO); or by amsacrine 100 mg/m^2 IV day 2–4 (FLAG-AMSA).

§§ Gilteritinib as a salvage option has only been validated in a randomized trial after prior intensive chemotherapy.

‖‖ Based on single-arm data.

¶¶ Although enasidenib did not show improved overall survival in a randomized study in comparison with conventional therapy in late-stage *IDH2*-mutant AML, clinically useful single-agent anti-leukemic activity has been demonstrated.

For instance, criteria that have been used in clinical trials to select patients not suitable for intensive chemotherapy have been as follows: (1) age ≥ 75 years (however, this cannot be an absolute criterion; for instance, patients with more favourable disease and without relevant comorbidities may derive benefit from intensive chemotherapy) or (2) ECOG performance status > 2 and/or age-related comorbidities, such as severe cardiac disorder (e.g., congestive heart failure requiring treatment, ejection fraction ≤ 50%, or chronic stable angina), severe pulmonary disorder (e.g., DLCO ≤ 65% or FEV1 ≤ 65%), creatinine clearance < 45 mL/min, hepatic disorder with total bilirubin > 1.5 times the upper limit of normal, or any other comorbidity that the physician assesses to be incompatible with intensive chemotherapy.

*** To reduce the risk of tumor lysis syndrome, the prophylactic use of uric acid lowering drugs, close electrolyte monitoring and cytoreduction of the WBC to < 25 x 10^9/L or even lower, for patients with high bone marrow blast burden, elevated LDH is recommended.

††† In the VIALE-A and VIALE-C trials, an adjusted venetoclax dose of 50 mg was used in the presence of a strong CYP3A4 inhibitor. This venetoclax dose is supported by a pharmacokinetic study examining venetoclax in the presence of posaconazole.

Abbreviations:

7+3 = 7 days of standard-dose cytarabine, and 3 days of an anthracycline antibiotic or an anthracenedione; AML = acute myeloid leukemia; ASXL1 = additional sex combs-like 1; BCOR = B-cell lymphoma 6 co-repressor; BCR::ABL = breakpoint cluster region protein / tyrosine-protein kinase ABL1; c-KIT = tyrosine-protein kinase KIT; CBFB = core binding factor beta; CEBPA = CCAAT enhancer-binding protein alpha; CIV = continuous intravenous; CLAG-M = cladribine, cytarabine, granulocyte colony-stimulating factor, mitoxantrone; CPX-351 = daunorubicin and cytarabine liposome for injection; CR = complete remission; CRh = complete remission with incomplete hematologic improvement; CRi = complete remission with incomplete count recovery; CYP3A4 = cytochrome P450 3A4; DDX41 = DEAD-box helicase 1; DLCO = diffusing capacity of the lungs for carbon monoxide; DNMT3A = DNA (cytosine-5)-methyltransferase 3A; ECOG = Eastern Cooperative Oncology Group; ELN = European LeukemiaNet; EZH2 = enhancer of zeste homolog 2; FEV1 = forced expiratory volume in 1 second; FLAG-AMSA = fludarabine, cytarabine, granulocyte colony-stimulating factor, amsacrine; FLAG-IDA = fludarabine, cytarabine, granulocyte colony-stimulating factor, idarubicin; FLAG-MITO = fludarabine, cytarabine, granulocyte colony-stimulating factor, mitoxantrone; FLT3 = FMS-like tyrosine kinase 3; G-CSF = granulocyte colony-stimulating factor; GO = gemtuzumab ozogamicin; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; IDAC = intermediate-dose cytarabine; IDH1/2 = isocitrate dehydrogenase 1/2; ITD = internal tandem duplication; IV = intravenous; LDH = lactate dehydrogenase; MEC = mitoxantrone, etoposide, cytarabine; MRD = minimal residual disease; MYH11 = myosin heavy chain 11; NPM1 = nucleophosmin 1; PML::RAR = promyelocytic leukemia / retinoic acid receptor; PO = by mouth; RUNX1 = runt-related transcription factor 1; RUNX1T1 = partner transcriptional co-repressor 1; SC = subcutaneous; SF3B1 = splicing factor 3b subunit 1; SRSF2 = serine and arginine-rich splicing factor; STAG2 = stromal antigen 2; t-AML = therapy-related acute myeloid leukemia; TKD = tyrosine kinase domain; TP53 = cellular tumour antigen p53; U2AF1 = U2 small nuclear RNA auxiliary factor 1; WBC = white blood cell count; ZRSR2 = zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2.

References:

1. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377. **2.** National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Myeloid Leukemia. Version 3.2023. April 5, 2023. **3.** Leisch M, Jansko B, Zaborsky N, et al. Next generation sequencing in AML-on the way to becoming a new standard for treatment initiation and/or modulation? *Cancers*. 2019;11:252; doi:10.3390/cancers11020252. **4.** Morita K, Wang F, Jahn K, et al. Clonal evolution of acute myeloid leukemia revealed by high-throughput single-cell genomics. *Nature Commun*. 2020;11:5327; doi:10.1038/s41467-020-19119-8.

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