KMT2Ar and *NPM1m* Acute Leukemias Disease State Overview

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MED-REV-240049 02/2025

Objectives

- Communicate current clinical unmet needs and the need for targeted, highly effective, and well-tolerated interventions for patients with R/R acute leukemias with *KMT2Ar* and *NPM1m*

- Describe the mechanisms underlying the pathophysiology of R/R acute leukemias with *KMT2Ar* and *NPM1m*

KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, mutated nucleophosmin 1; R/R, relapsed/refractory.

Acute Leukemia Pathophysiology

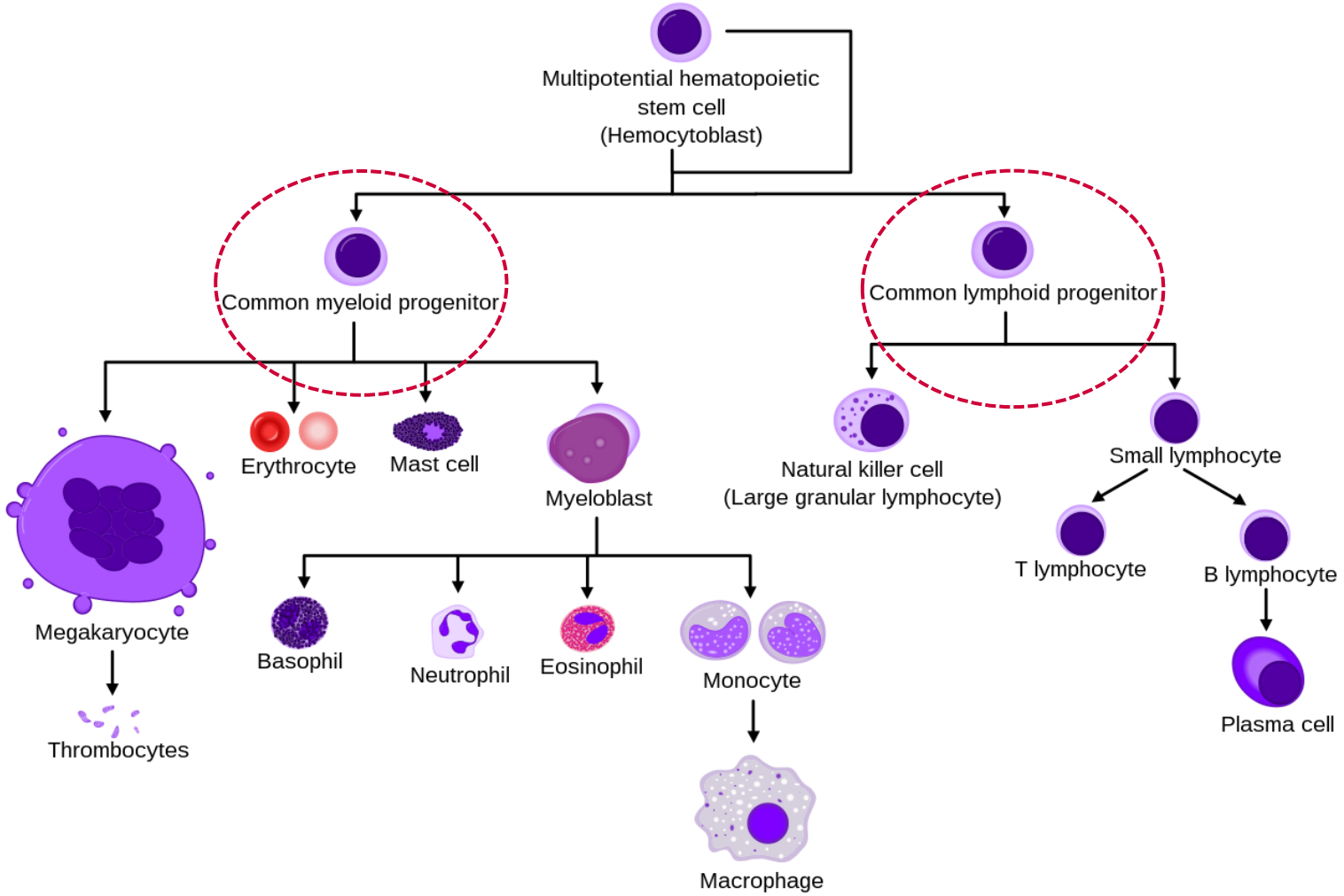

Image by A. Rad and Mikael Häggström, MD. CC-BY-SA 3.0

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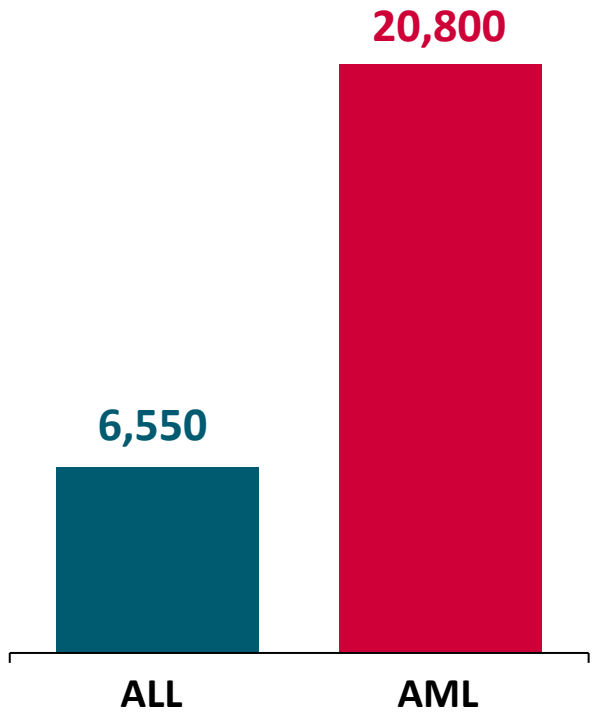
Incidence and Prevalence of Acute Leukemias

- Acute leukemias are characterized by uncontrolled blast proliferation in the bone marrow[1-3]
  - The incidence of ALL follows a bimodal distribution; the first peak occurs in childhood (<5 years) and the second peak occurs in adulthood (>50 years)[4]
  - AML is more common in adults than children, with an average age at diagnosis of 68 years[5]
- Patients with acute leukemias commonly present with thrombocytopenia, anemia, and leukopenia, which result in infections, bruising/bleeding, and weakness[2,3,6]

Estimated number of new cases in 2024 in the United States[7,8]



ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

1. Puckett Y, Chan O. Acute Lymphocytic Leukemia. 2022. In: StatPearls [Internet]. StatPearls Publishing; 2023. **2.** PDQ Adult Treatment Editorial Board. https://www.cancer.gov/types/leukemia/hp/adult-all-treatment-pdq. Accessed July 10, 2023. **3.** PDQ Adult Treatment Editorial Board. https://www.cancer.gov/types/leukemia/hp/adult-aml-treatment-pdq. Accessed July 10, 2023. **4.** American Cancer Society. https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/about/key-statistics.html. Accessed July 10, 2023. **5.** American Cancer Society. https://www.cancer.org/cancer/types/acute-myeloid-leukemia/about/key-statistics.html. Accessed July 10, 2023. **6.** Hansen et al. *Mediterr J Hematol Infect Dis*. 2020;12:e2020009. **7.** National Cancer Institute. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed November 12, 2024. **8.** National Cancer Institute. https://seer.cancer.gov/statfacts/html/alyl.html. Accessed November 12, 2024.

AML Risk Stratification

Risk Category[*,†]	Genetic abnormality
Favorable (low risk)	t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[†,‡]
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[†,‡]
	Mutated *NPM1*[†,§] without *FLT3-ITD*
	bZIP in-frame mutated *CEBPA*[‖]
Intermediate (intermediate risk)	**Mutated *NPM1*[†,§] with *FLT3-ITD***
	Wild-type *NPM1* with *FLT3-ITD* (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[†,¶]
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Unfavorable (adverse/high risk)	t(6;9)(p23.3;q34.1)/*DEK::NUP214*
	t(v;11q23.3)/*KMT2A*-rearranged[#]
	t(9;22)(q34.1;q11.2)/*BCR::ABL1*
	t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
	t(3q26.2;v)/*MECOM(EVI1)*-rearranged
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype,** monosomal karyotype[††]
	Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, and/or *ZRSR2*[‡‡]
	Mutated *TP53*[a]

Footnotes are in speaker notes

Dohner H, et al. *Blood*. 2022;140(12):1345-1377.

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Adult B-Cell ALL Cytogenic Risk Stratification

Risk Groups	Gene Mutation
Good Risk	Hyperdiploidy (51-65 chromosomes) ○ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome
	t(12;21)(p13;q22): *ETV6-RUNX1*
Poor Risk	Hypodiploidy (<44 chromosomes)
	***KMT2A* rearranged (t[4;11] or others)**
	t(v;14q32)/IgH
	t(9;22)(q34;q11.2): *BCR-ABL1* (defined as “high risk” in the pre-TKI era)
	Complex karyotype (5 or more chromosomal abnormalities)
	BCR-ABL1-like (Ph-like) ALL ○ JAK-STAT (*CFLF2r, EPORr, JAK1/2/3r, TYK2r,* mutations of *SH2B3, IL7R, JAK1/2/3*) ○ ABL class (rearrangements of *ABL1, ABL2, PDGFRA, PDGFRB, FGFR*) ○ Other (*NTRKr, FLT3r, LYNr, PTK2Br*)
	Intrachromosomal amplification of chromosome 21 (iAMP21)
	t(17;19): *TCF3-HLF* fusion
	Alterations of *IKZF1*

Cytogenetic Risk Groups for B-Cell ALL- Leukemia and Lymphoma Society PS33 3/24. Accessed January 23, 2025. Available at: https://www.lls.org/booklet/acute-lymphoblastic-leukemia-all-adults

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KMT2Ar Acute Leukemia

Incidence, Prevalence, Burden, Mechanism of Disease, and Diagnosis

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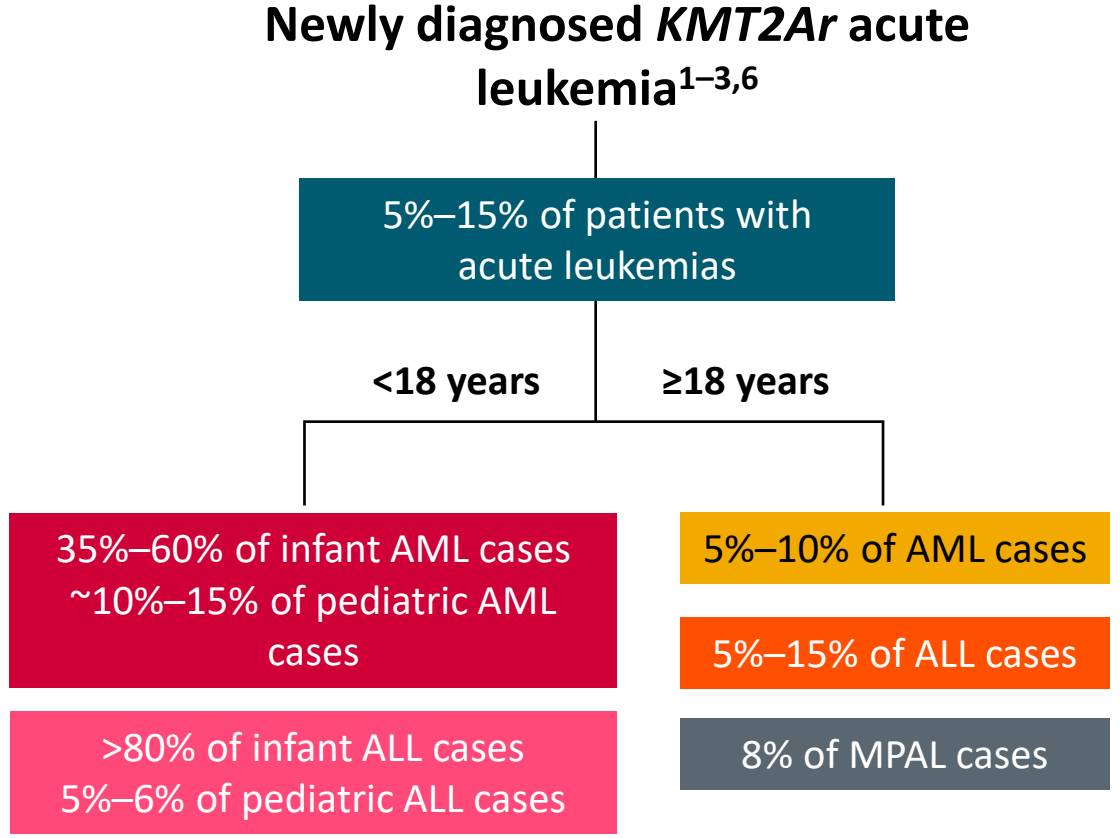
Incidence and Prevalence of *KMT2Ar* Acute Leukemia

- Rearrangements of the *KMT2A* gene are associated with acute leukemia[1]
- *KMT2Ar* is detected in 35%–60% of new AML diagnoses in infants, ~10%–15% in childhood and adolescence, and 5%–10% in adults[1,3]
  - The median age at diagnosis for *KMT2Ar* AML (52 years) is lower than for AML in general (68 years)[4,5]
- *KMT2Ar* is detected in >80% of new ALL diagnoses in infants, 5%–6% of pediatric cases, and 5%–15% of adult cases[1,6]
- The estimated annual incidence is ~1,500 patients with R/R *KMT2Ar* ALL or AML in the United States[1,3,4,7–16]



ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MPAL, mixed-phenotype acute leukemia.

1. Issa et al. *Leukemia.* 2021;35:2482-2495. **2.** Issa et al. *Nature.* 2023;615:920-924. **3.** Conneely and Rau. *Cancer Metastasis Rev*. 2020;39(1):189-209. **4.** Issa et al. *Blood Cancer J*. 2021;11:162. **5.** Appelbaum et al. *Blood*. 2006;107:3481-3485. **6.** Górecki et al. *Biomedicines*. 2023;11:821. **7.** National Cancer Institute. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed October 2, 2023. **8.** National Cancer Institute. https://seer.cancer.gov/statfacts/html/alyl.html. Accessed October 2. 2023. **9.** Pieters et al. Lancet 2007; 370: 240–50; **10.** Larsen et al. J Clin Oncol 34:2380-2388; **11.** Richard-Carpentier et al. *Blood Adv.* 2021;5(23):5415-5419; **12.** Arber et al. *Blood.* 2016;127(20):2391-2405; **14.** Schlenk et al. *N Engl J Med.* 2008;358:1909-1918; **14.** Brown et al. *Blood.* 2019;133(3):205-214; **15.** Moorman et al. *Blood.* 2007;109(8):3189-3197; **16.** Lafage-Pochitaloff et al. *Blood.* 2017;130(16):1832-1844.

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Burden of Newly Diagnosed *KMT2Ar* AML

- *KMT2Ar* AML is associated with poor overall survival, disease outcomes, and is commonly resistant to currently used standard of care therapies[1,2]
- Adults with newly diagnosed *KMT2Ar* AML had:
  - Lower rates of response to therapy compared with diploid AML
    - CR/CRi rate of 72% (*KMT2Ar* AML) vs 81% (diploid AML) (*P*=0.01)[2]
  - A higher risk of relapse compared with diploid AML[2]

Survival Outcomes in Adult Patients With Newly Diagnosed *KMT2Ar* AML After First-Line Therapy[2]

	KMT2Ar (N=172)	Diploid (N=522)	*P* value
Median OS, months	10.8	25.2	<0.0001
1-year OS, %	47.0	67.0	
5-year OS, %	20.0	34.0	
5-year CIR, %	66.0	62.0	0.04

AML, acute myeloid leukemia; CIR, cumulative incidence of relapse; CR, complete remission; CRi, complete remission with incomplete count recovery; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; OS, overall survival.

1. Issa et al. *Leukemia*. 2021;35:2482-2495. **2.** Issa et al. *Blood Cancer J*. 2021;11:162.

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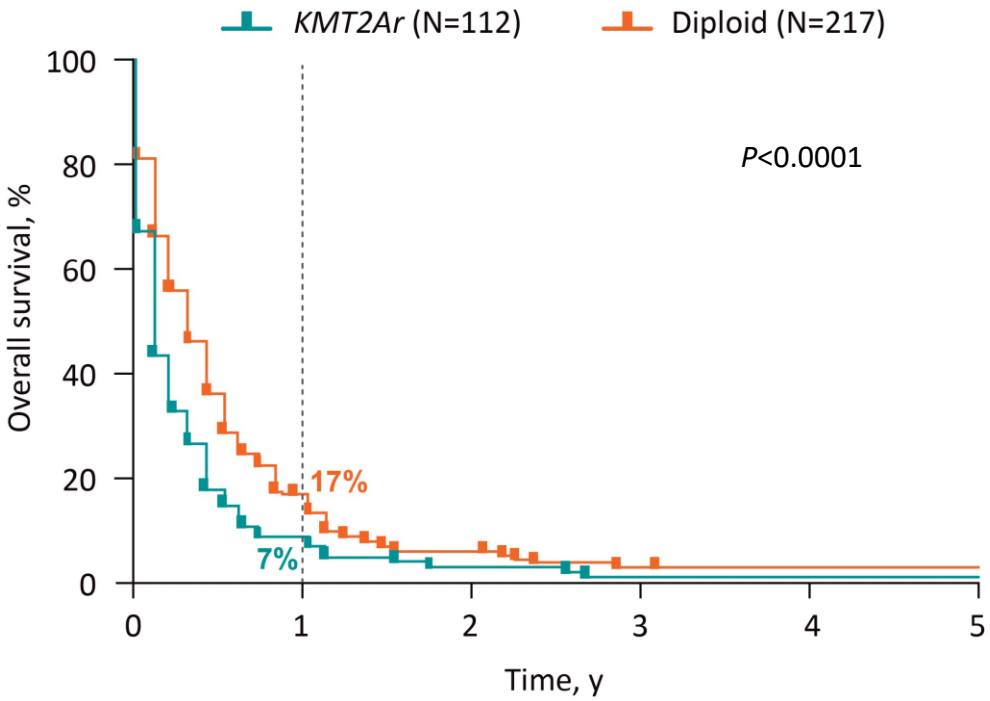
Burden of R/R *KMT2Ar* AML

- Patients with *KMT2Ar* AML have poor outcomes following relapse
- After receiving ≥ 3 lines of therapy, patients with *KMT2Ar* AML (N=112) had:
  - Lower rates of response compared with diploid AML
    - CR/CRi rate of 9% (*KMT2Ar* AML) vs 31% (diploid AML) (*P*<0.001)
  - Higher rates of relapse compared with diploid AML[1]
    - CIR at 12 months of 85% (*KMT2Ar* AML) vs 68% (diploid AML) (*P*=0.6)
  - Lower median OS rate (2.4 months) compared with diploid AML (4.8 months) (*P*<0.0001)

OS in Adult Patients With R/R *KMT2Ar* AML After ≥ 3 Lines of Therapy



Modified from Issa et al. *Blood Cancer* J. 2021;11:162. Creative Commons Attribution (CC BY) license https://creativecommons.org/licenses/by/4.0/.

AML, acute myeloid leukemia; CIR, cumulative incidence of relapse; CR, complete remission; CRi, complete remission with incomplete count recovery; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; OS, overall survival; R/R, relapsed/refractory.

Issa et al. *Blood Cancer J*. 2021;11:162.

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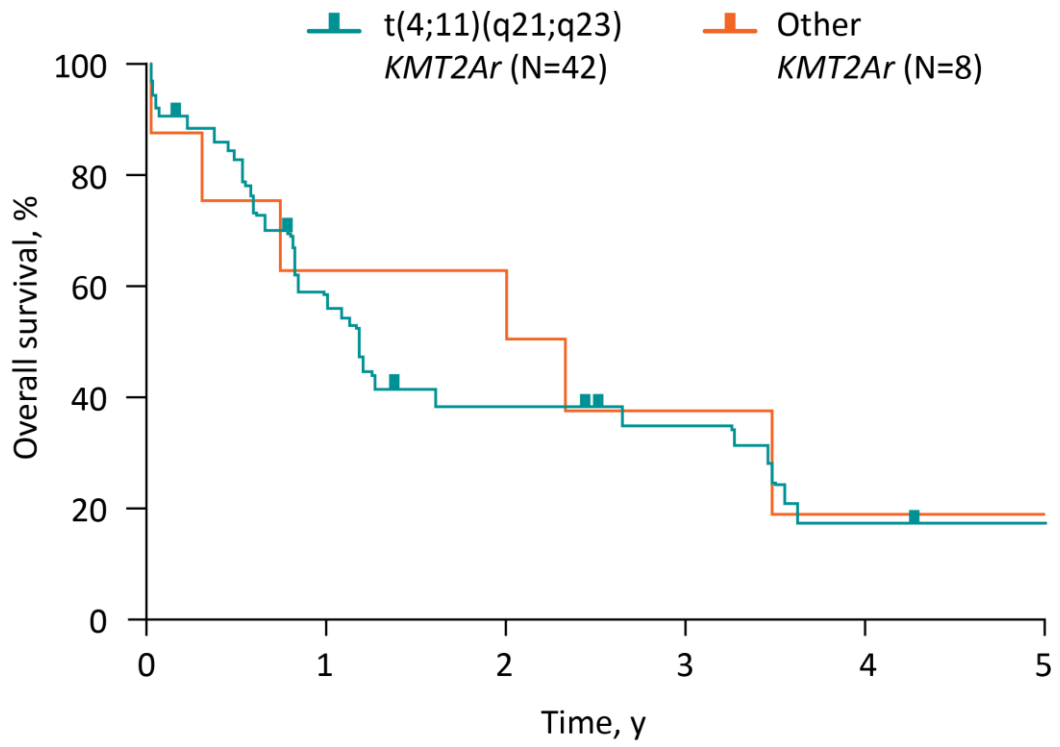
Burden of Newly Diagnosed *KMT2Ar* ALL

- *KMT2Ar* ALL is a rare subtype of ALL that is associated with poor overall survival and disease outcomes
- In a retrospective analysis of newly diagnosed adult patients with *KMT2Ar* ALL (n=50)
  - The overall CR rate was 88%
    - CR rate was 90% (38/42) among patients with t(4;11)(q21;q23) *KMT2Ar* and was 75% (6/8) among patients with other *KMT2Ar*
    - The rate of MRD negativity at CR was 41%
  - The estimated 5-year OS and RFS rates were 18% and 15%, respectively

OS in Adult Patients With Newly Diagnosed *KMT2Ar* ALL[a]



[a]No significant difference in OS (*P*=0.8700) was observed according to *KMT2A* rearrangements.

ALL, acute lymphoblastic leukemia; CR, complete remission; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MRD, minimal residual disease; OS, overall survival; R/R, relapsed/refractory; RFS, relapse-free survival.

Richard-Carpentier et al. *Blood Adv*. 2021;5:5415-5419.

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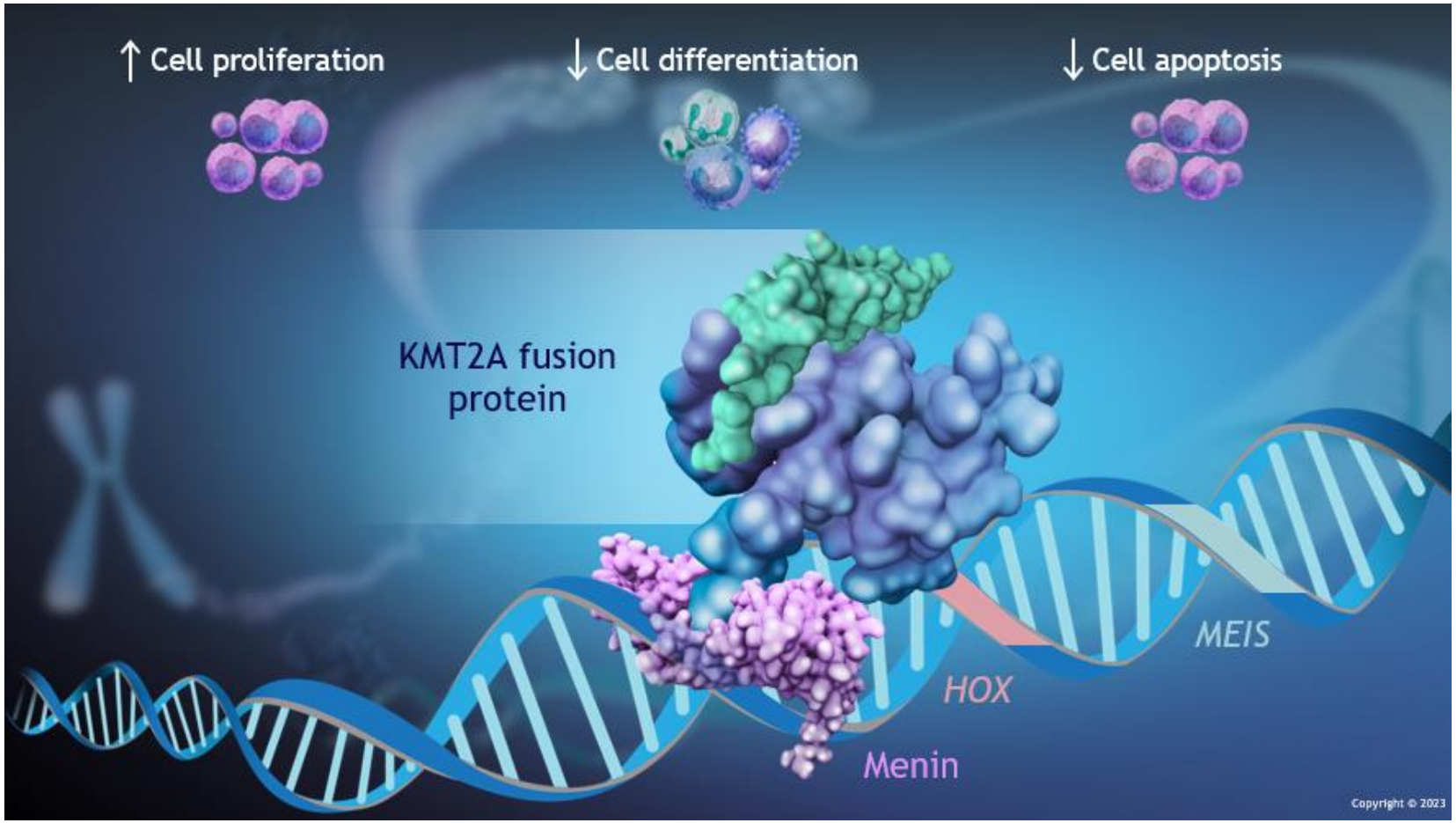
Menin-KMT2A Interaction Is a Critical Leukemogenic Driver in *KMT2Ar* Acute Leukemia[1-3]

- In *KMT2Ar* acute leukemia, the interaction of menin with KMT2A fusion proteins drives upregulation of *HOX*/*MEIS1* leukemic gene expression
- This interaction leads to hematopoietic differentiation arrest and leukemogenesis



HOX, homeobox; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements;; *MEIS1*, Meis homeobox 1.

1. Harada et al. *Genes Dev.* 2022;36:368-389. **2.** Issa et al. *Leukemia.* 2021;35:2482-2495. **3.** Issa et al. *Nature.* 2023;615:920-924.

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Diagnostic Tests for *KMT2Ar* Acute Leukemia[1-4]

Patients with acute leukemia undergo cytogenetic and molecular testing for risk profiling

FISH

- Usually detects chromosome 11q23.3 rearrangements indicative of a *KMT2A* fusion
- Results are usually obtained in 1-3 days after sampling[a]
- The only FDA-cleared *KMT2Ar* detection kit employs FISH
  - Analytical sensitivity: >95%
  - Analytical specificity: 100%

Conventional cytogenetics

- ≥20 bone marrow metaphases are required to define a normal karyotype and recommended to define an abnormal karyotype
- Results are usually obtained in 7-14 days after sampling[a]
- Often cannot identify cryptic rearrangements

[a]Timing may vary based on specific laboratories.

AML, acute myeloid leukemia; FISH, fluorescence in situ hybridization; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements.

1. Döhner et al. *Blood.* 2022;140:1345-1377. **2.** Afrin et al. *Mol Cancer Res*. 2018;16:279-285. **3.** Nucleic Acid Based Tests. US Food and Drug Administration. https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. Accessed August 12, 2023. **4.** Decision Summary. Evaluation of automatic class III designation for Cytocell FISH probe kits for AML and MDS. https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170070.pdf. Accessed August 12, 2023.

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NPM1m Acute Myeloid Leukemia

Incidence, Prevalence, Burden, Mechanism of Disease, and Diagnosis

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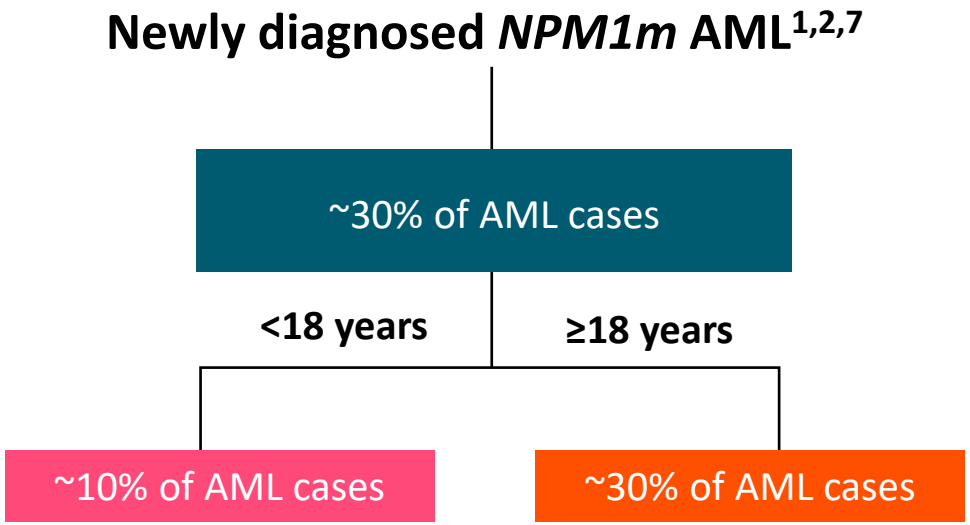
Incidence and Prevalence of *NPM1m* AML

- *NPM1m* is a critical driver mutation and the single most common genetic abnormality in AML, present in ~30% of patients at initial diagnosis[1-3]
- In the newly diagnosed setting, *NPM1m* AML is generally associated with a favorable prognosis[4]
- *NPM1m* commonly occurs with co-mutations such as *FLT3*-ITD, *DNMT3A*, and *IDH1/2*[5]
  - *FLT3*-ITD, which worsens prognosis, has been reported in ~40% of patients with *NPM1m* AML[6]
- There are no FDA-approved targeted therapies for *NPM1m* AML[8]
- In recent retrospective studies, the incidence of R/R *NPM1m* AML was reported as 12%-28% of the study populations[9,10]
  - The estimated annual incidence is ~3,600 patients with R/R *NPM1m* AML in the United States[5,11,12]



AML, acute myeloid leukemia; *DNMT3A*, DNA methyltransferase 3 alpha; *FLT3*-ITD, FMS-related receptor tyrosine kinase 3 internal tandem duplication; *IDH1/2*, isocitrate dehydrogenase 1 and 2; *NPM1m*, mutated nucleophosmin 1; R/R, relapsed/refractory.

1. Issa et al. *Leukemia.* 2021;35:2482-2495. **2.** Papaemmanuil et al. *N Engl J Med.* 2016;374:2209-2221. **3.** Issa et al. *Nature.* 2023;615:920-924. **4.** Issa et al. *Blood Adv.* 2023;7:933-942. **5.** Falini. *Am J Hematol*. 2023;98:1452-1464**. 6.** Thiede et al. *Blood*. 2006;107:4011-20. **7.** Braoudaki et al. *J Hematol Oncol.* 2010:41. **8.** Fareed et al. *Rare Tumors*. 2023;15:20363613231183785. **9.** Piccini et al. *J Clin Med*. 2021;10:1684. **10.** Venugopal et al. *Blood*. 2021;138:2287. 11. Dohner et al. *The Lancet Haematology.* 2023; 10(7):E495-509. 12. National Cancer Institute. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed October 2, 2023..

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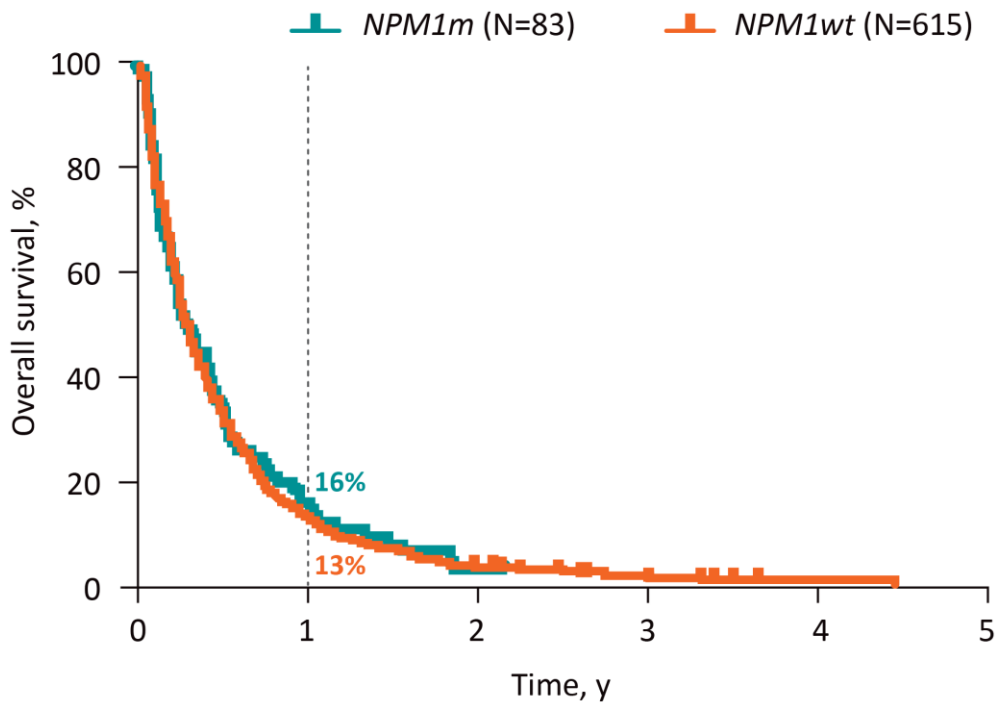
Burden of R/R *NPM1m* AML

- Unlike in the newly diagnosed setting, *NPM1m* is associated with a poor prognosis in patients with R/R AML[1]
- In a retrospective analysis of patients with R/R *NPM1m* AML (n=206)[2]
  - 76% of the evaluable patients showed remission following first-line therapy
  - The duration of first remission was ≤6 months in 41% of patients
  - Although there were higher CR/CRi rates after salvage therapy in *NPM1m* vs *NPM1wt*, there was no impact on RFS and OS

Survival Outcomes in Adult Patients With R/R *NPM1m* AML[2]

	Median RFS, months	Median OS, months
Aggregate population	5.5	6.1
Outcome after therapy		
Salvage 1	8.3	7.8
Salvage 2	3.3	5.3

OS in Adult Patients With R/R *NPM1m* AML After ≥3 Salvage Therapies[2,a]



[a]No significant difference in OS (*P*=0.7000) was observed in patients with *NPM1m* AML compared with *NPM1wt* AML.

AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete count recovery; *NPM1m*, mutated nucleophosmin 1; *NPM1wt*, wild-type *NPM1*; OS, overall survival; R/R, relapsed/refractory; RFS, relapse-free survival.

1. Venugopal et al. *Blood*. 2021;138:2287. **2.** Issa et al. *Blood Adv*. 2023;7:933-942.

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Burden of R/R *NPM1m* AML With *FLT3*-ITD

- Approximately 50% of patients with R/R *NPM1m* AML have a *FLT3*-ITD co-mutation[1]
- In a retrospective analysis of adult patients with R/R *NPM1m* AML (n=206), patients with *FLT3*-ITD mutations had poorer overall survival as compared with patients with *FLT3wt*[2]

Clinical Outcomes in Adult Patients With R/R *NPM1m* AML after first salvage treatment[2]

	FLT3-ITD^{pos} (n=56)	*FLT3wt* (n=65)
CR, %	23	40
CRi, %	32	18
CR/CRi, %	55	58
Median OS, months	5.8	8.6

AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete count recovery; *FLT3*-ITD, FMS-related receptor tyrosine kinase 3 internal tandem duplication; FLT3-ITD^{pos}, FLT3-ITD–positive mutations; *FLT3wt*, wild-type FMS-related receptor tyrosine kinase 3; *NPM1m*, mutated nucleophosmin 1; OS, overall survival; R/R, relapsed/refractory.

1. Venugopal et al. *Blood*. 2021;138(suppl 1):2287. **2.** Issa et al. *Blood Adv*. 2023;7:933-942.

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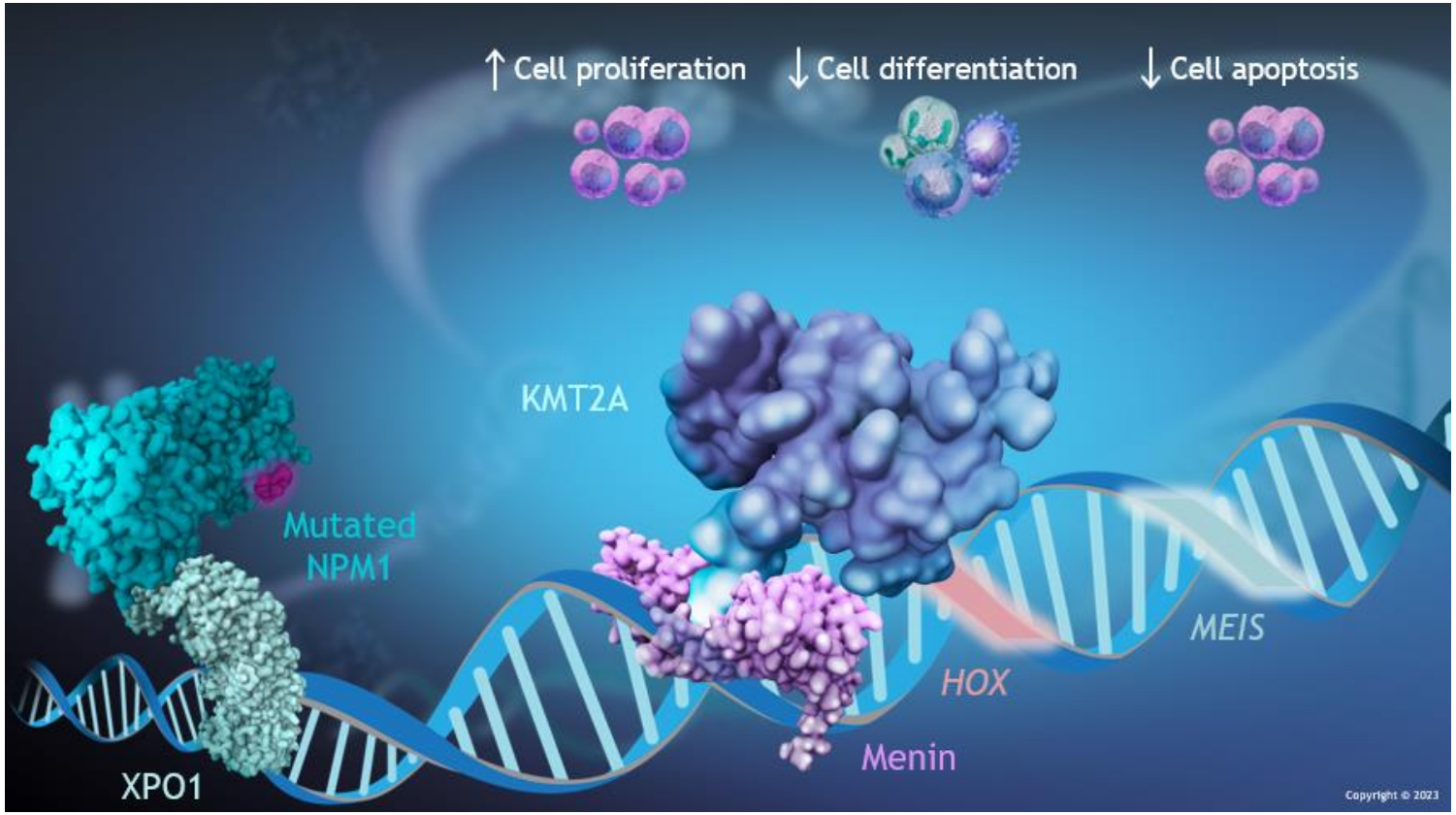
Menin-KMT2A Interaction Is a Critical Leukemogenic Driver in *NPM1m* AML[1,2]

NPM1m, in association with the nuclear export protein XPO1, binds to and induces chromatin changes, exposing start sites for menin-KMT2A binding, leading to aberrant transcription of leukemia-driving genes such as *HOX* and *MEIS1*



AML, acute myeloid leukemia; *HOXA/B*, homeobox A/B; KMT2A, histone-lysine N-methyltransferase 2Ar; *MEIS1*, Meis homeobox 1; *NPM1m*, mutated nucleophosmin 1; XPO1, nuclear export protein.

1. Wang et al. *Cancer Discov*. 2023;13:724-745. **2.** Issa et al. *Leukemia.* 2021;35:2482-2495.

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Diagnostic Tests for *NPM1m* AML[1-3]

Patients with acute leukemia undergo cytogenetic and molecular testing for risk profiling

PCR

- High analytical sensitivity (1:1,000)
- Detects >95% of known *NPM1* mutations
- Turnaround time of 1 day[a]

NGS

- Similar sensitivity to the RT-qPCR assay
- Commercially available molecular panels are designed to detect majority of *NPM1* mutations

[a]Timing may vary based on specific laboratories.

AML, acute myeloid leukemia; NGS, next-generation sequencing; *NPM1m*, mutated nucleophosmin 1; PCR; polymerase chain reaction; RT-qPCR, real-time quantitative PCR.

1. Döhner et al. *Blood.* 2022;140:1345-1377. **2.** Barakat et al. *Arch Pathol Lab Med*. 2011;135:994-1000. **3.** Blombery et al. *Arch Pathol Lab Med*. 2018;142:606-612.

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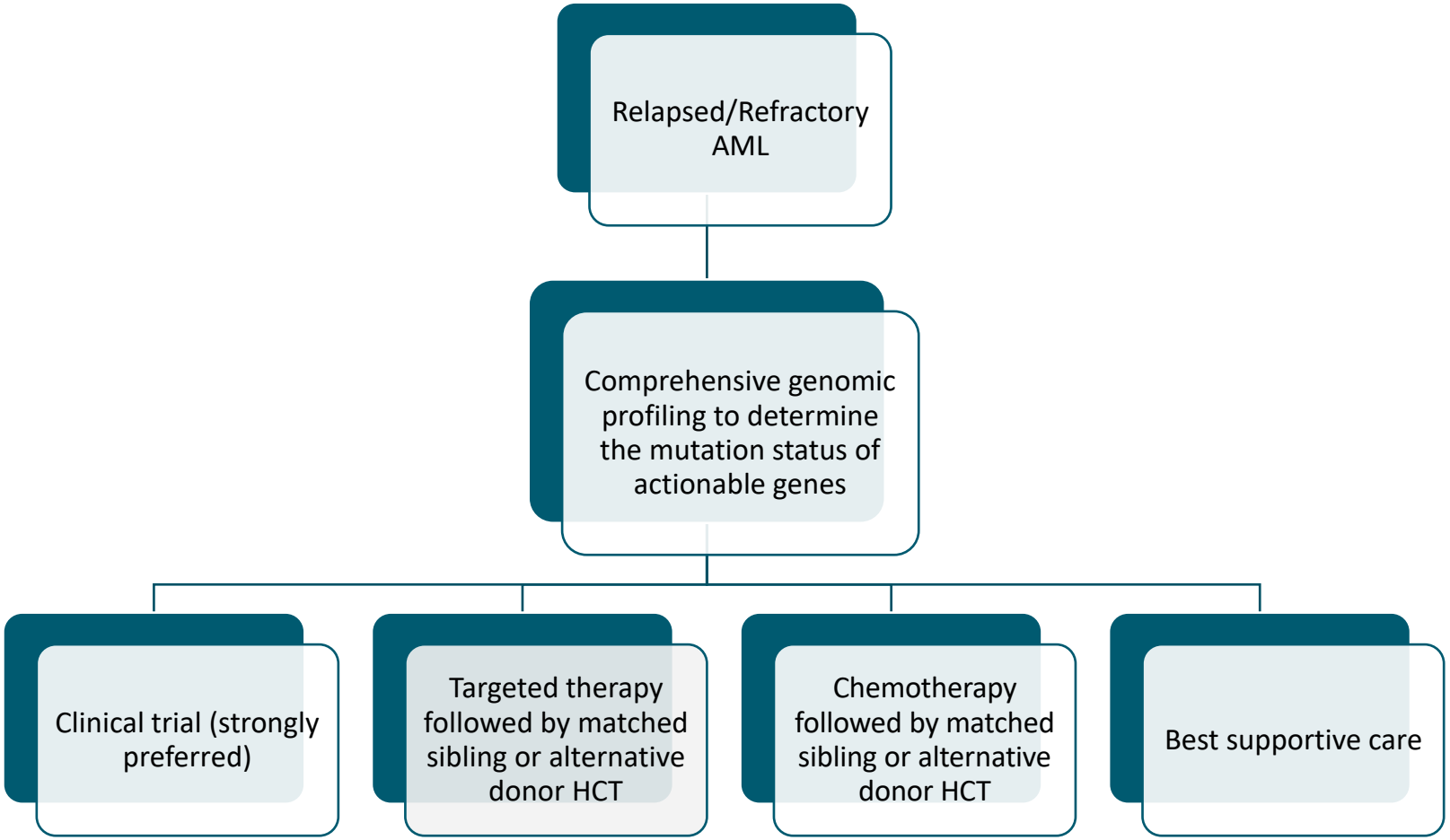
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Therapy for R/R AML (Age ≥18 Years)



AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; NCCN, National Comprehensive Cancer Network; R/R, relapsed/refractory.

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NCCN Guidelines®
Considerations for Therapy for R/R AML (Ages ≥18 Years)

- Multigene molecular profiling/targeted NGS (including *IDH1*/*IDH2*, *FLT3* mutations) is suggested, as it may assist with selection of therapy and appropriate clinical trials
  - Molecular testing should be repeated at each relapse or progression
- Reinduction therapy may be appropriate in certain circumstances, such as in patients with long first remission (there are no data regarding reinduction with dual-drug liposomal encapsulation of cytarabine and daunorubicin)
  - This strategy primarily applies to cytotoxic chemotherapy and excludes the re-use of targeted agents due to the potential development of resistance
  - Targeted therapies may be retried if agents were not administered continuously and not stopped due to development of clinical resistance
  - If a second CR is achieved, then consolidation with allogeneic HCT should be considered
- All recommendations are NCCN category 2A unless otherwise indicated
  - NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

CR, complete response; *FLT3*, fms related receptor tyrosine kinase 3; HCT, hematopoietic cell transplant; *IDH*, isocitrate dehydrogenase; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; R/R, relapsed/refractory.

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Treatment Strategy Overview for R/R ALL

Goal: To induce subsequent remission, with consolidative cell therapy approach (alloHCT or CAR-T)[1,2]

1. There is no current standard-of-care regimen in R/R ALL; treatment is very heterogenous[1,3,4]
2. Mutation testing for specific recurrent genetic abnormalities is required for optimal risk stratification and treatment planning[5]
3. Pediatric patients would commonly be treated in a clinical trial through one of the cooperative groups[6]
4. AYA and adult patients can be treated with a combination of chemotherapy, immunotherapy, and novel therapies[7,8]
5. Further drug development is required to improve survival outcomes for patients with R/R ALL[1]

ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic cell transplant; AYA, adolescent and young adult; B-ALL; B cell ALL; CAR-T, chimeric antigen receptor T cells; T-ALL; T cell ALL; NCCN, National Comprehensive Cancer Network; Ph, Philadelphia chromosome; R/R, relapsed/refractory; TKI, tyrosine kinase inhibitor.

1. DuVall et al. *JCO Oncol Pract.* 2022;18:479-487. **2.** Sheykhhasan et al. *Cancer Gene Ther*. 2022;29(8-9):1080-1096. **3.** Ravandi. *Blood.* 2019;133(2):130-136. **4.** Frey NV, Luger SM. *Blood*. 2015;126:589-96. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia, V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed December 20, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **6.** Maloney et al. *J Clin Oncol*. 2020;38:602-612. **7.** PDQ Adult Treatment Editorial Board. https://www.cancer.gov/types/leukemia/hp/adult-all-treatment-pdq. Accessed July 10, 2023. **8.** Rytting et al. *Cancer*. 2017;123:2398-2403.

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Challenges in Treatment of *KMT2Ar* and *NPM1m* Acute Leukemias

- Despite the advances in the management of acute leukemias[1,2]
  - Patients with *KMT2Ar* AML experience higher rates of early mortality compared with those with diploid AML (60-day mortality rate of 15% vs 7%, respectively)[3]
  - The estimated 5-year OS of patients with *KMT2Ar* ALL is 18% (95% confidence interval, 9%-35%)[4]
  - Approximately 50% of patients with *NPM1m* AML experience progressive disease leading to death[1]

AML, acute myeloid leukemia; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, mutated nucleophosmin 1; R/R, relapsed/refractory.

1. Ranieri et al. *Leukemia.* 2022;36:2351-2367. **2.** DeAngelo et al. *Am Soc Clin Oncol Educ Book.* 2020;40:330-342. **3.** Issa et al. *Blood Cancer J.* 2021;11:162. **4.** Richard-Carpentier et al. *Blood Adv*. 2021;5:5415-5419.

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Summary

1. Patients with relapsed *KMT2Ar* and *NPM1m* AML experience poor survival and disease outcomes[1,2]
2. The KMT2A-menin interaction is a critical leukemogenic driver in both R/R *KMT2Ar* and *NPM1m* acute leukemias[3]
3. Patients with R/R *KMT2Ar* and *NPM1m* acute leukemias have considerable clinical unmet needs[4]

AML, acute myeloid leukemia; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, mutated nucleophosmin 1; R/R, relapsed/refractory.

1. Issa et al. *Blood Cancer J.* 2021;11:162. **2.** Issa et al. *Blood Adv.* 2023;7:933-942. **3.** Issa et al. *Leukemia.* 2021;35:2482-2495. **4.** Issa et al. *Nature.* 2023;615:920-924.

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