Lymphoma · Leukemia & Myeloma Congress

From Mutation to Remission: Integrating Menin Inhibitors and MRD Monitoring into Optimizing Outcomes in AML

Eunice S. Wang, MD

Roswell Park Comprehensive Cancer Center

Eytan Stein, MD

Memorial Sloan Kettering Cancer Center

Supported by educational grants from Syndax Pharmaceuticals and Kura Oncology, Inc.

Lymphoma • Leukemia & Myeloma Congress

Disclosures

- **Eunice Wang, MD:** Consultant – Cullinan, Stemline; Speaker's Bureau – Astellas, Kura, Taiho; Advisory Board – AbbVie, Amgen, Astellas, Cullinan, Daiichi Sankyo, Geron, Johnson & Johnson, Kura, Novartis, Servier, Stemline; Other – UpToDate (section editor)

- **Eytan Stein, MD:** Advisory Board – Charm Therapeutics, Johnson & Johnson, Kura, Syndax Pharmaceuticals

This activity may include discussion of off-label, investigational, or unapproved uses of drugs.

Lymphoma · Leukemia & Myeloma Congress

Learning Objectives

- Summarize current diagnostic strategies, risk stratification methods, and biomarker considerations that inform the use of menin inhibitors in AML treatment protocols
- Evaluate the safety, efficacy, and clinical implications of newly approved and investigational menin inhibitors within the context of targeted therapy for AML
- Integrate recent clinical trial data and treatment guidelines to select menin inhibitor-based regimens, manage treatment-related adverse events (TRAEs) effectively, and collaborate with multidisciplinary teams to improve patient outcomes and QoL in AML care

AML = acute myeloid leukemia; QoL = quality of life.

Lymphoma · Leukemia & Myeloma Congress

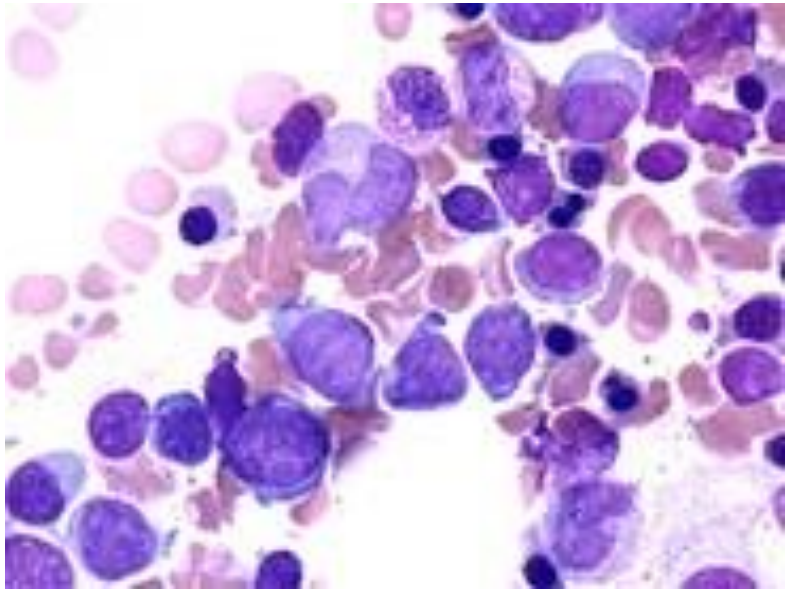
The Evolving Treatment Landscape and Unmet Needs in AML

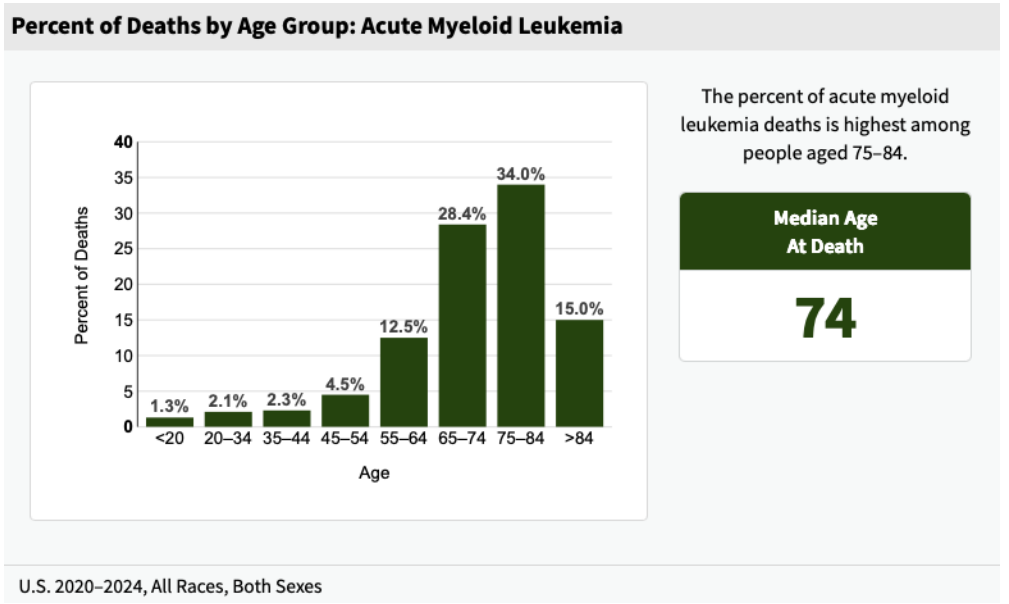
Eunice S. Wang, MD

Lymphoma · Leukemia & Myeloma Congress

Overview of Acute Myeloid Leukemia (AML)

- Disease of older adults (median age at diagnosis: 70)
- Biologically diverse (karyotype, mutations, antigens)
- Clinically aggressive disease with survival in weeks to months if untreated
- Estimated deaths in 2026: 11,500

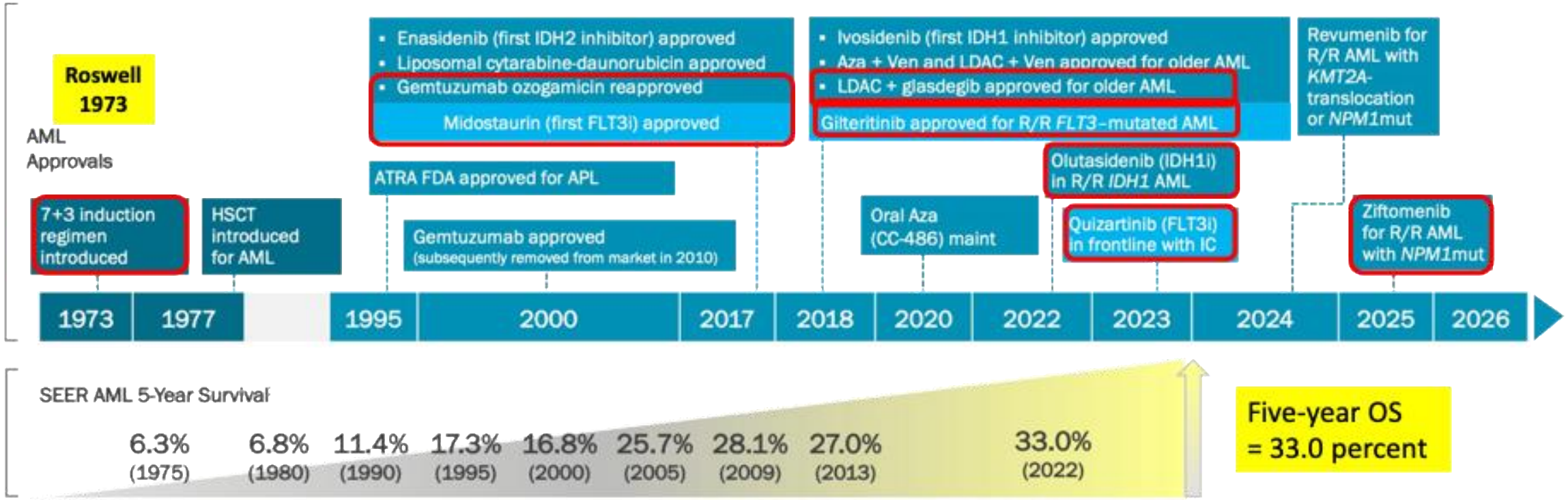




Surveillance, Epidemiology, and End Results (SEER). Accessed October 6, 2026. https://seer.cancer.gov/statfacts/html/amyl.html.

Outcomes of Current AML Therapy and Persistent Gaps

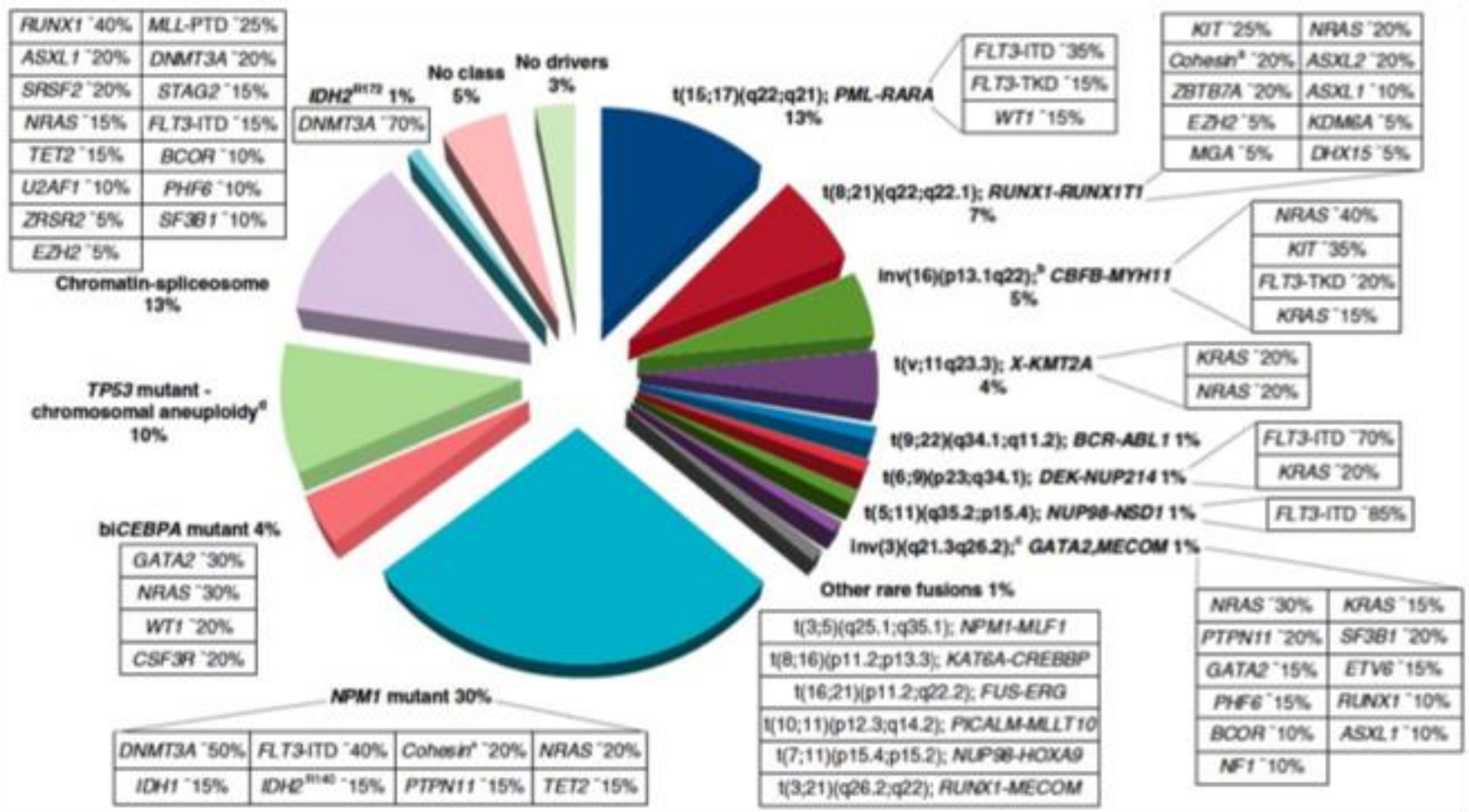
Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care induction regimen for newly diagnosed AML



OS = overall survival.

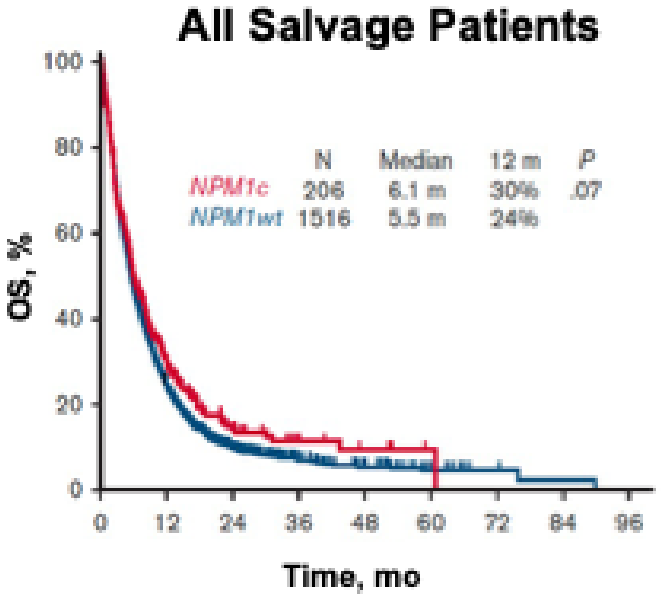
Drugs@FDA. Accessed January 27, 2026. https://www.accessdata.fda.gov/scripts/cder/daf/. SEER. Accessed January 27, 2026. https://seer.cancer.gov/statfacts/html/amyl.html.

Acute Myeloid Leukemia: Biological Heterogeneity



Döhner H, et al. *Blood*. 2017;129(4):424-447.

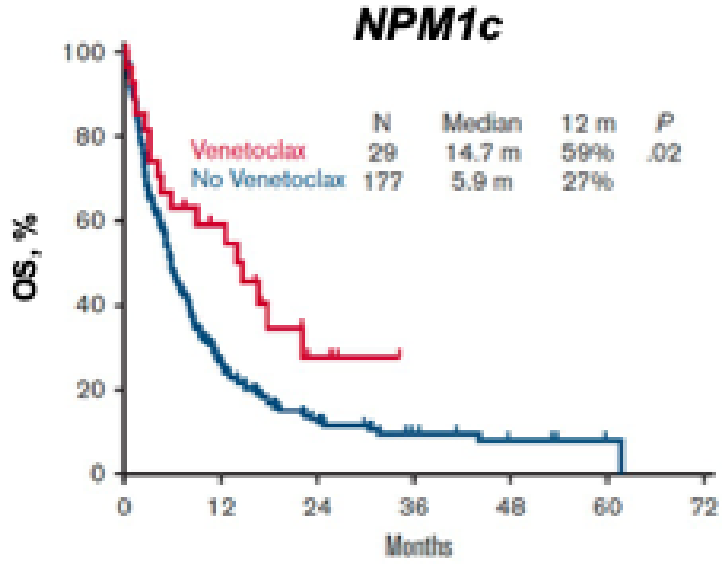
Impact of *NPM1* Mutations on R/R AML Prognosis



Median OS for *NPM1*m vs NPM1wt	*NPM1*m had no impact on risk of relapse or death
After salvage 1	7.8 vs 6.0 mos
After salvage 2	5.3 vs 4.1 mos
After salvage 3	3.5 vs 3.6 mos

Venetoclax still beneficial in R/R AML with *NPM1*m

(role for combos)

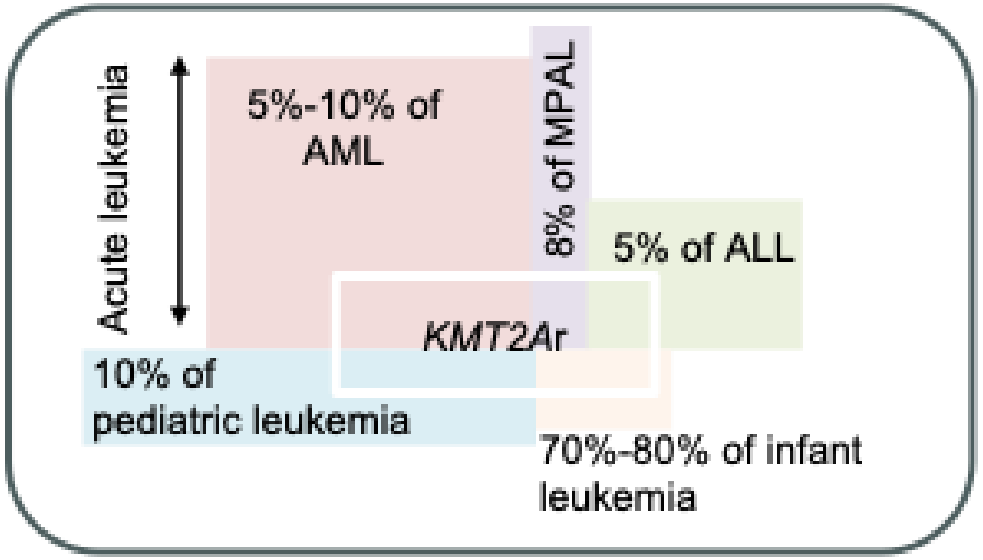


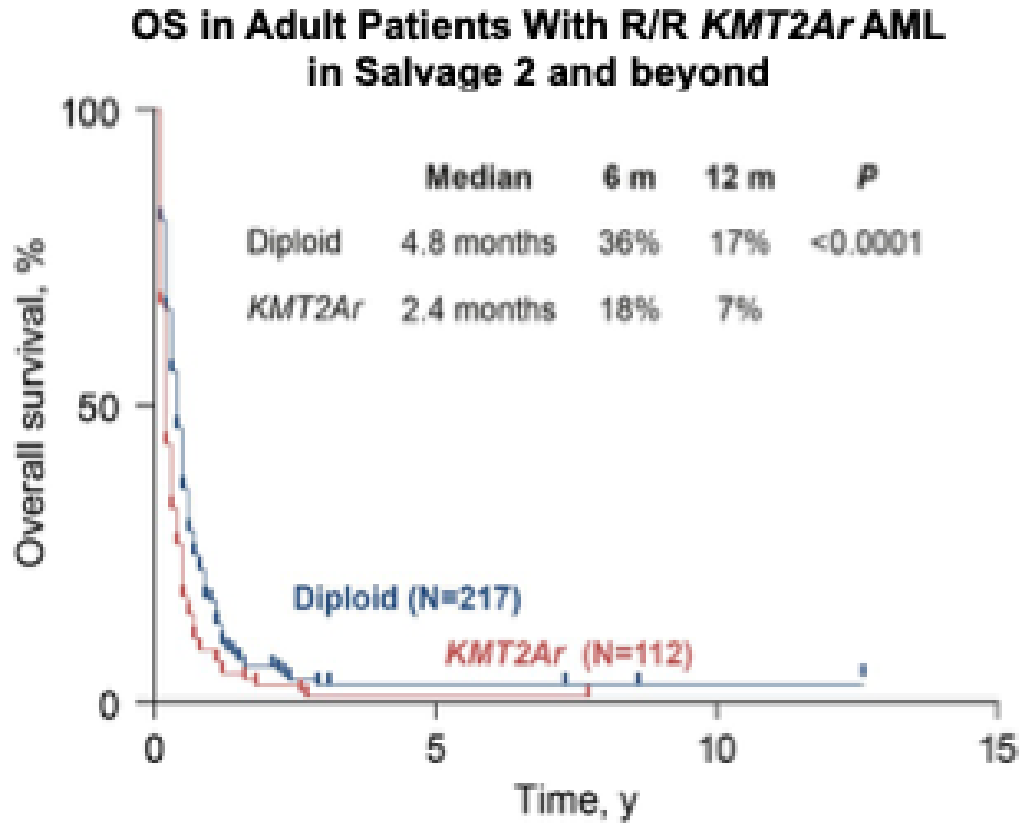
R/R = relapsed/refractory.

Issa GC, et al. *Blood Adv*. 2023;7(6):933-942.

Impact of *KMT2Ar* on AML Prognosis and Resistance

- Many patients relapse after frontline chemotherapy and/or HSCT
- In adults, remission rates after relapse (CR, 5%) and median OS (2.4 months) in salvage 2 and beyond remain low
- Outcomes in infants/children after relapse also remain poor





HSCT = hematopoietic stem cell transplantation; CR = complete response; MPAL = mixed-phenotype acute leukemia; ALL = acute lymphoblastic leukemia.

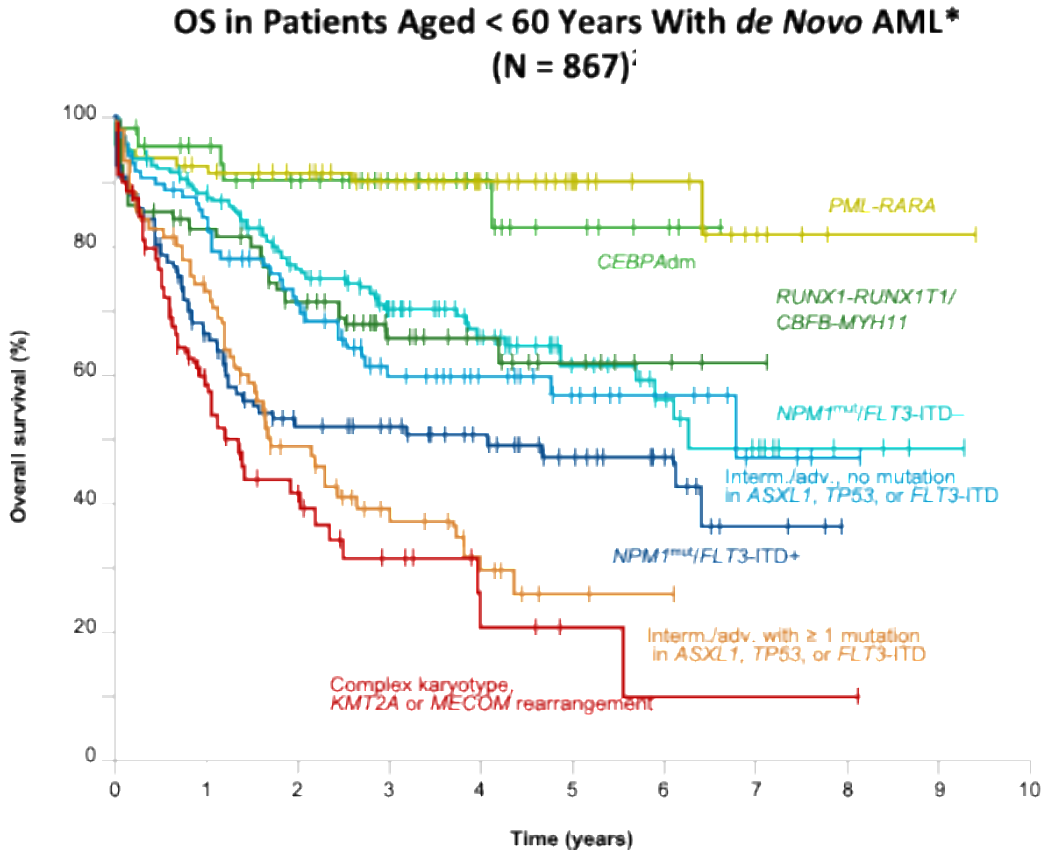
Figure reproduced from Issa GC, et al. *Blood Cancer J*. 2021;11(9):162. Creative Commons Attribution (CC BY) license. http://creativecommons.org/licenses/by/4.0/.

Limitations of Conventional 7+3: ELN 2022 Risk Categories

EUROPEAN LEUKEMIA NET 2022

Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • Mut *NPM1* w/o *FLT3*-ITD • bZIP in-frame mut *CEBPA*
Intermediate	• Mut *NPM1* with ***FLT3*-ITD** • Wt *NPM1* with ***FLT3*-ITD** • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Cytogenetic and/or molecular
Adverse	• t(6;9)(p23.3;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearr • 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)*-rearr • –5 or del(5q); –7; –17/abn(17p) • Complex/monosomal karyotype • Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2* • Mut *TP53*

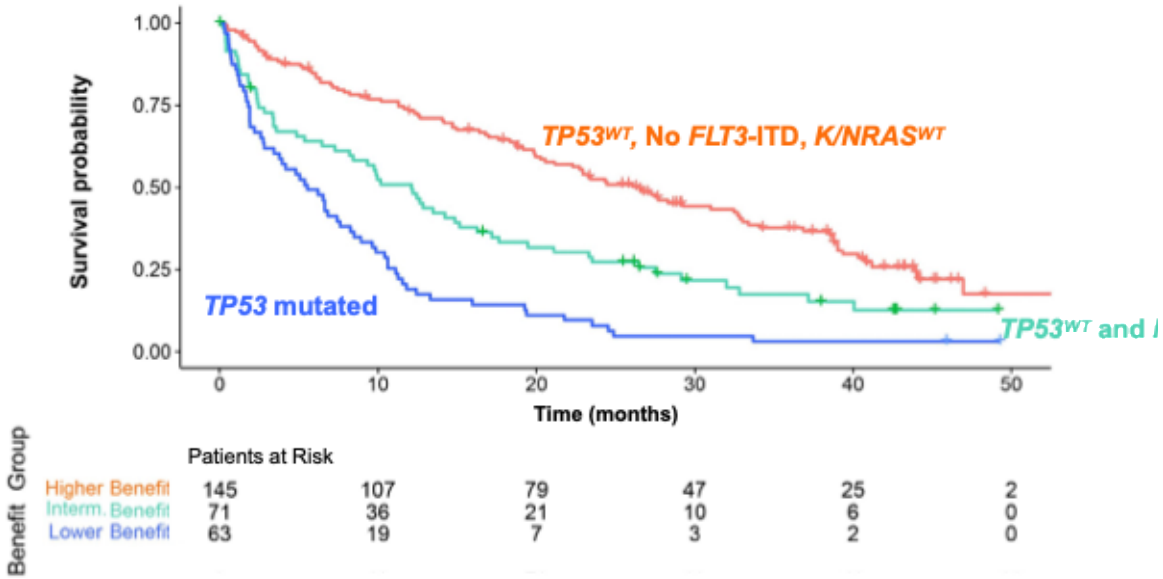
* This population of patients had been treated with standard intensive chemotherapy.



ELN = European LeukemiaNet.

Döhner H, et al. *Blood*. 2022;140(12):1345-1377. Adapted from Haferlach C, et al. *Blood*. 2016;128(22):286.

Limitations of Venetoclax/HMA Regimens: ELN 2024

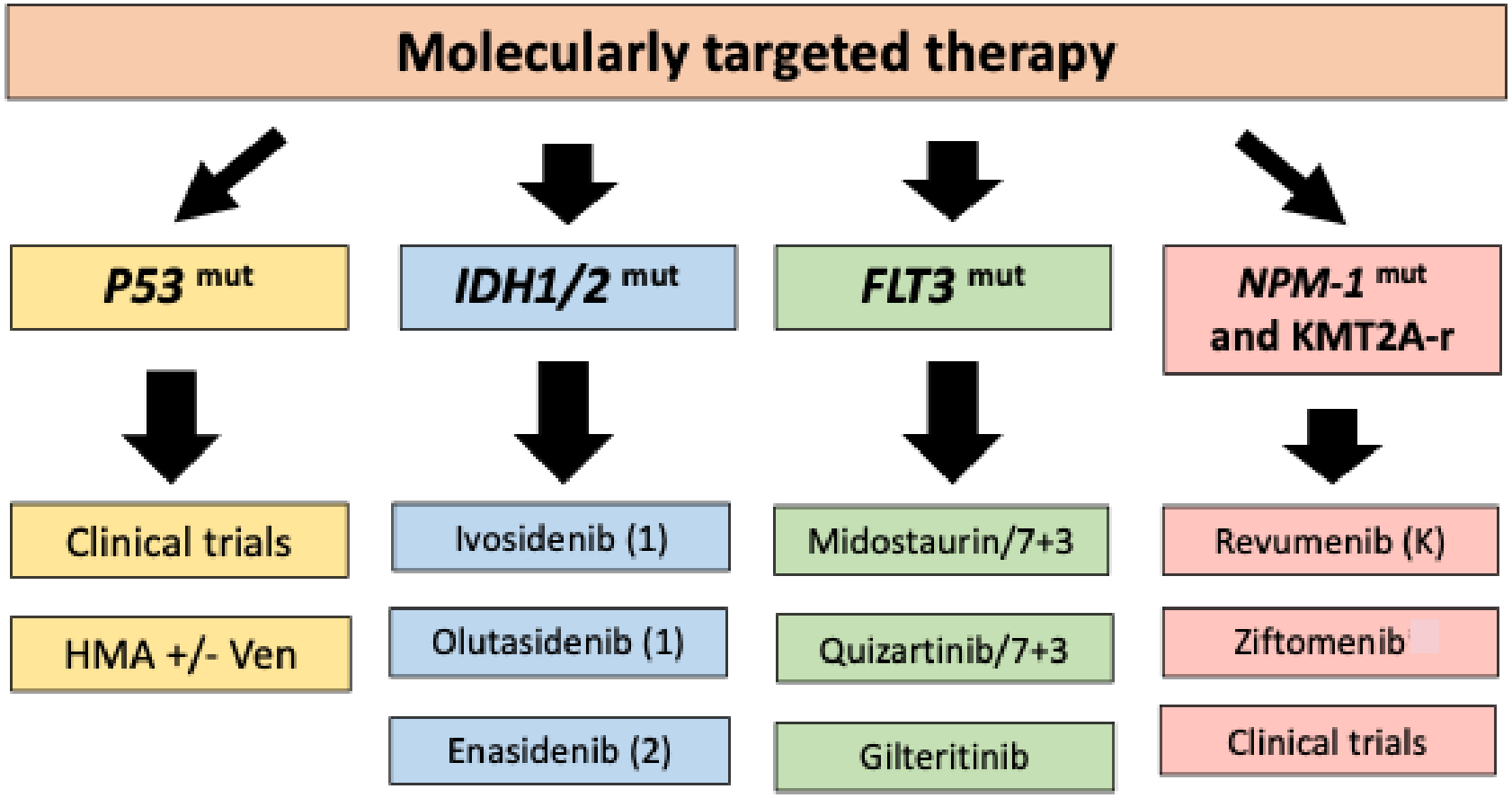


Genetic marker	Median OS, mo
Favorable-risk group	
Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39
Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37
Mutated *IDH1** (*TP53*^{wt})	29
Mutated *DDX41*	>24
AML with MR gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23
Intermediate-risk group	
AML with MR gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13
Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12
Adverse-risk group	
Mutated *TP53*	5-8

HMA = hypomethylating agent.

Döhner H, et al. *Blood*. 2024;144(21):2169-2173.

Key Genetic Mutations and Druggable Targets in AML



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

Lymphoma · Leukemia & Myeloma Congress

Key Learning Points

- AML is an aggressive blood cancer primarily diagnosed in older adults
- Biological heterogeneity dictates response to 7+3 and Ven/HMA
- KMT2A rearrangement associated with poor prognosis
- NPM1 mutations favorable at diagnosis but not at relapse
- Key genetic mutations are druggable targets in AML
  - FLT3 muts → FLT3 inhibitors
  - IDH1/2 muts → IDH1/2 inhibitors
  - NPM1 mut and KMT2A rearrangements → menin inhibitors

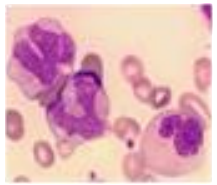
Lymphoma · Leukemia & Myeloma Congress

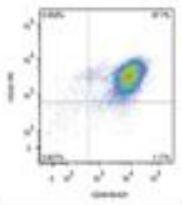
Genomic Profiling and Measurable Residual Disease (MRD) in AML

Eunice S. Wang, MD

Lymphoma · Leukemia & Myeloma Congress

Comprehensive Molecular Testing and Optimal Turnaround





Same day → Morphology (BM, PB), Flow cytometry (CD33)

5-7 days → Conventional cytogenetics, FISH (per request), marrow IHC



3-5 days → Mutation results (diagnostic, actionable therapeutic target)

REQUIRED (3-5 days)

- *FLT3, IDH1, IDH2, NPM1*
- *CEBPA, DDX41, TP53, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*

RECOMMENDED (1st cycle)

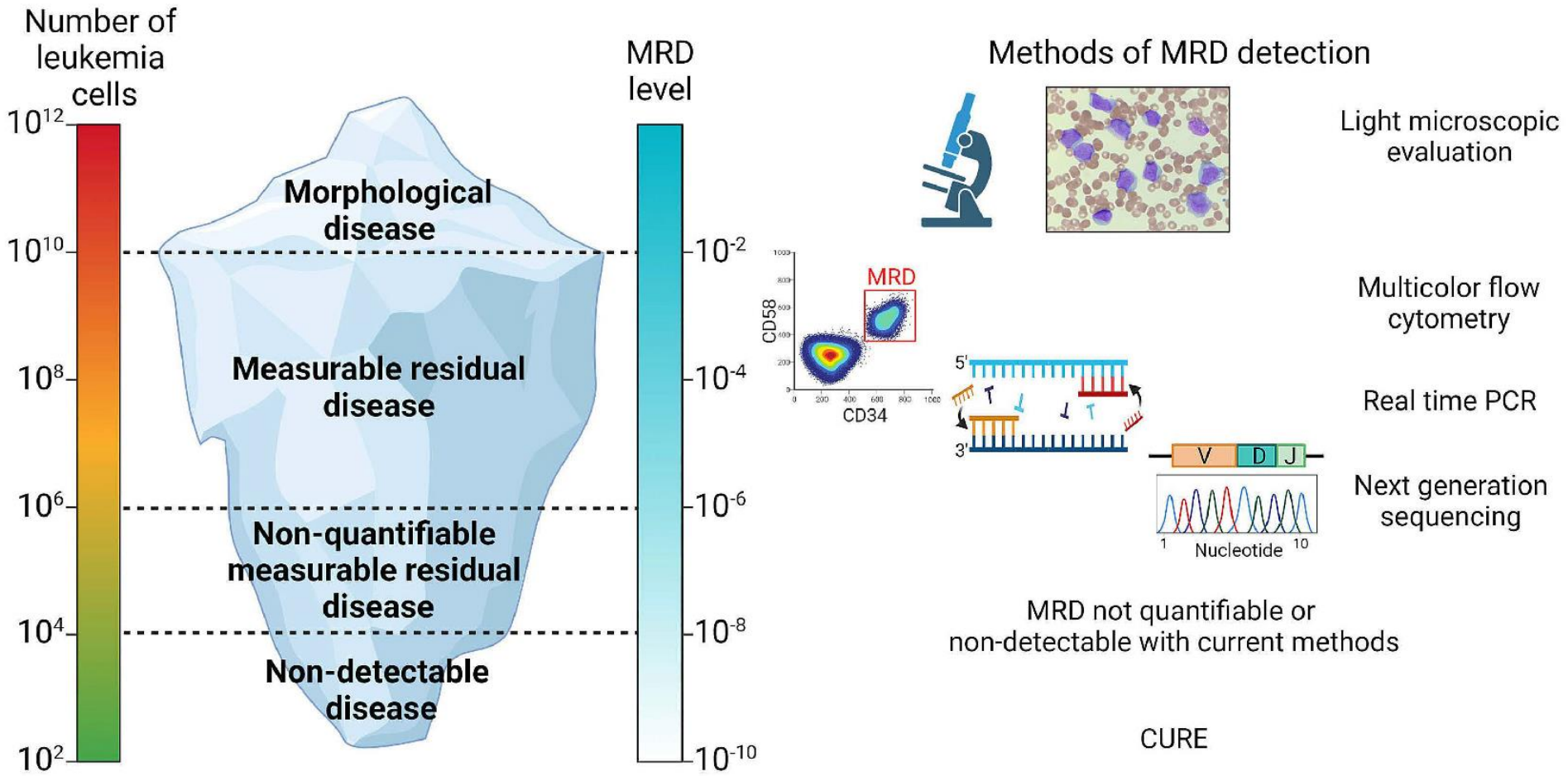
- *ANKRD26, BCOR1, BRAF, CBL, CSF3R, DNMT3A ETV6, GATA2, JAK2, KIT, KRAS, NRAS, NF1, PHF6, PPM1D, PTPN11 RAD21, SETBP1, TET2, WT1*

BM = bone marrow; PB = peripheral blood; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry.

Döhner H, et al. *Blood*. 2022;140(12):1345-1377. Adapted from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.5.2026.

© 2026 National Comprehensive Cancer Network, Inc. All rights reserved. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. 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.

Measurable/Minimal Residual Disease in AML



PCR = polymerase chain reaction.

Saygin C, et al. *Haematologica*. 2022;107(12):2783-2793.

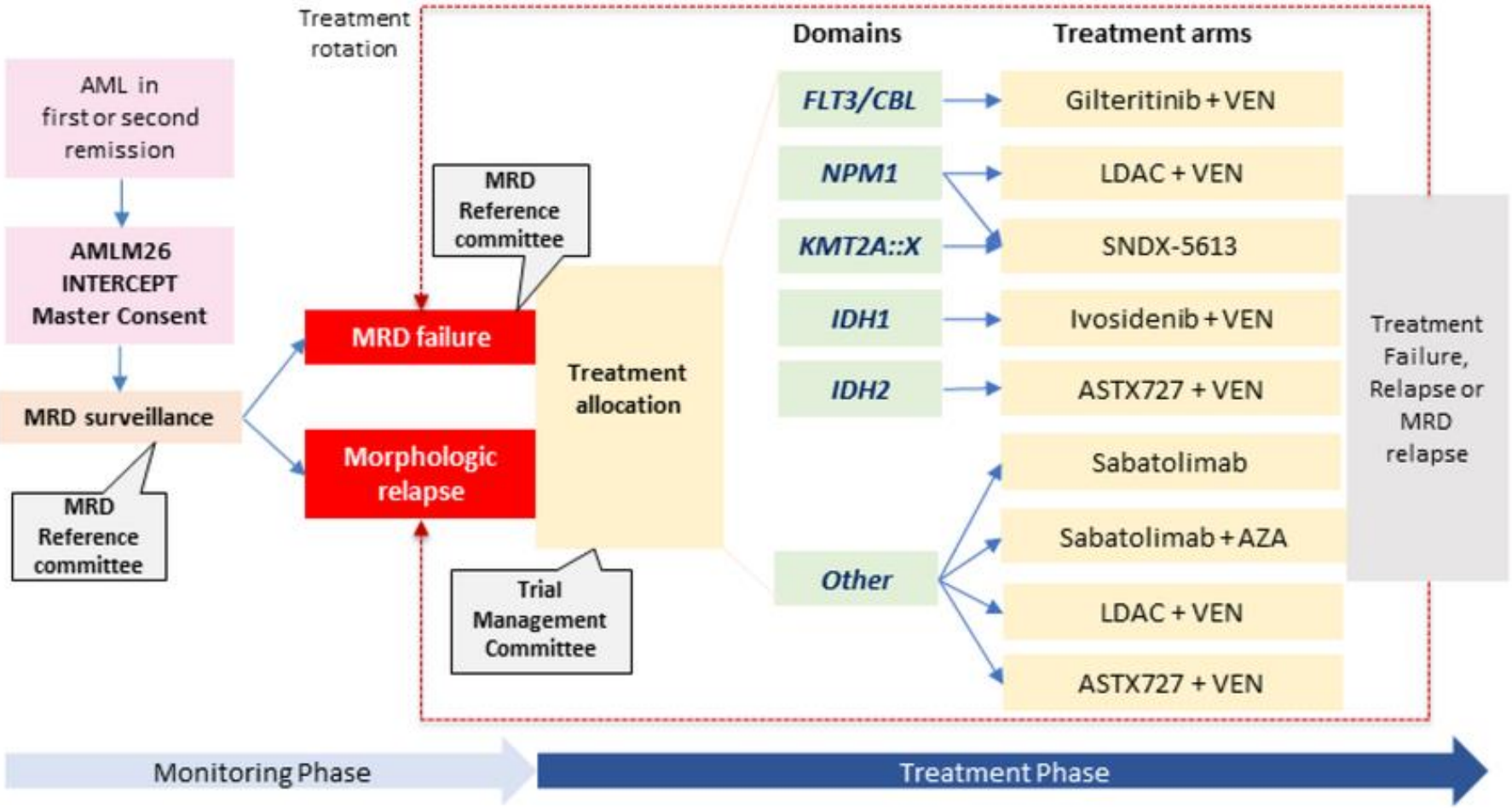
Validated MRD in AML: *NPM1, RUNX1-RUNX1T1, CBF-MYH11*

ELN risk	Subgroup	Assay	Diagnosis	After 2 cycles or before HCT	EOT	Follow-up (see footnotes for frequency and duration during follow-up)
Favorable	mut*NPM1* without *FLT3*-ITD	qPCR	PB (if blasts ≥20%) or BM*	PB	BM	PB or BM†
	RUNX1::*RUNX1T1*	qPCR	BM‡	BM	BM	PB or BM§
	CBFB::*MYH11*	qPCR	BM‡	BM	BM	PB or BM§
	PML::*RARA*	qPCR	PB (if blasts ≥20%) or BM*	Not recommended	BM‖	Only if MRD positive at EOT, and in chemotherapy-treated high-risk APL even when MRD negative; BM*,‖
	CEBPA bZIP in-frame	MFC	PB (if blasts ≥20%) or BM*	See recommendation B13		

*If a rare MRD marker is to be used for monitoring (eg, non-type A, B, or D NPM1 mutations, very large FLT3-ITD insertions, or uncommon noncanonical PML::RARA transcripts), analyte detectability should be confirmed at diagnosis using the established MRD assay to ensure its suitability for subsequent monitoring; ‡The analyte's baseline level must be established in the BM at time of diagnosis to enable comparison with MRD levels after 2 cycles and at EOT; ‖PB is not recommended for monitoring because PB usually becomes MRD positive only at frank APL relapse; †Frequency and duration of monitoring in follow-up: PB, every 4 to 6 weeks for 24 months; BM, every 3 months for at least 24 months if not indicated otherwise; §Due to rapid relapses during the first 12 months, monitoring from PB every 4 to 6 weeks is preferred.

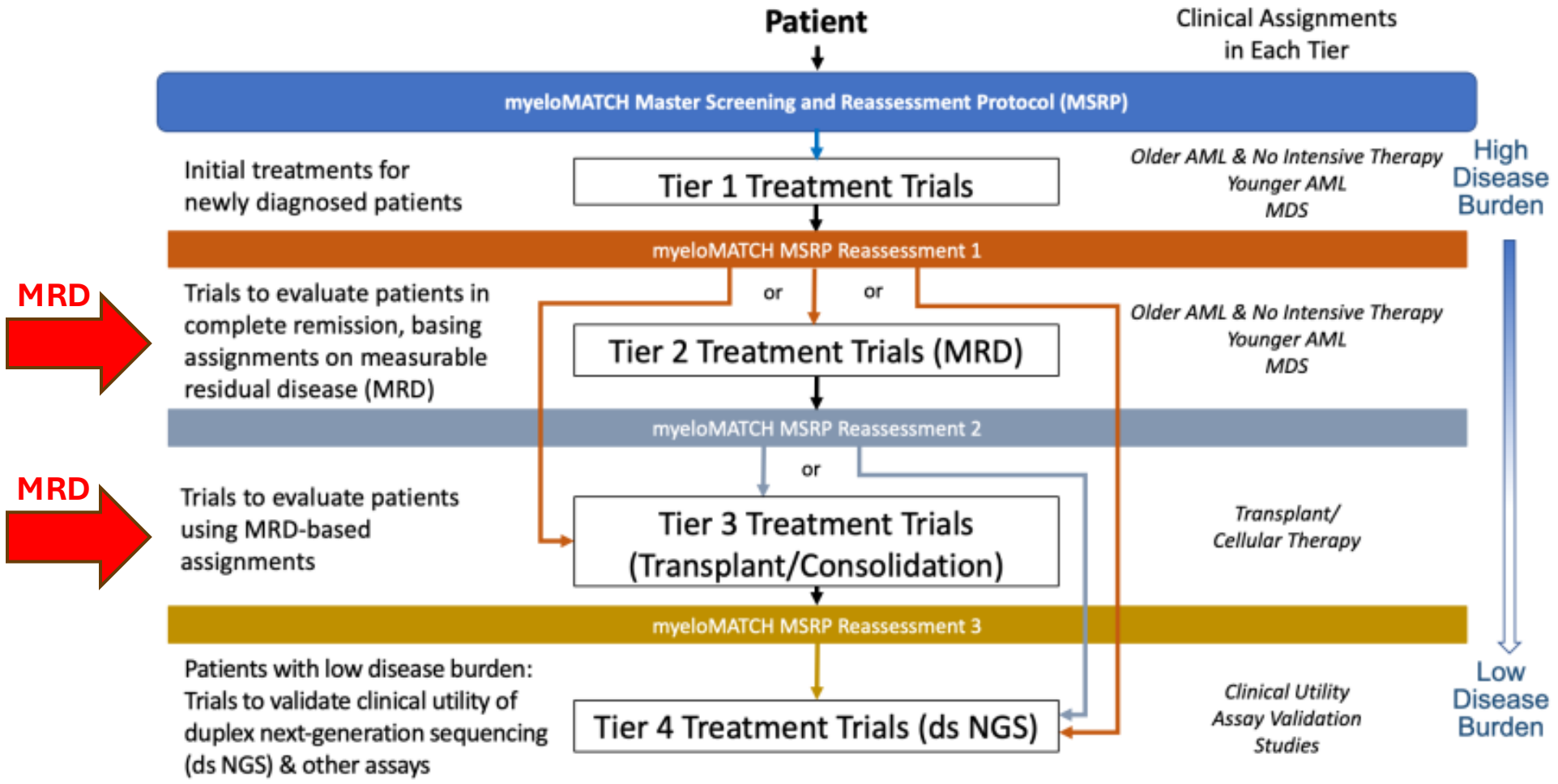
Cloos J, et al. *Blood*. 2026;147(11):1147-1167.

Emerging MRD-Directed Trial Designs: ALLG AMLM26 INTERCEPT



ClinicalTrials.gov. Accessed October 6, 2026. https://clinicaltrials.gov/study/NCT06664879.

Emerging MRD-Directed Trial Designs: NCI myeloMATCH



ds NGS = duplex sequencing next-generation sequencing.

ClinicalTrials.gov. Accessed October 6, 2026. https://clinicaltrials.gov/study/NCT05564390.

Lymphoma · Leukemia & Myeloma Congress

Key Learning Points

- AML diagnosis in 2026 requires genomic/molecular characterization
- Measurable residual disease (MRD): Key predictor of therapy response and risk of inevitable relapse in some AML subtypes
- Molecular MRD validated in specific AML genotypes

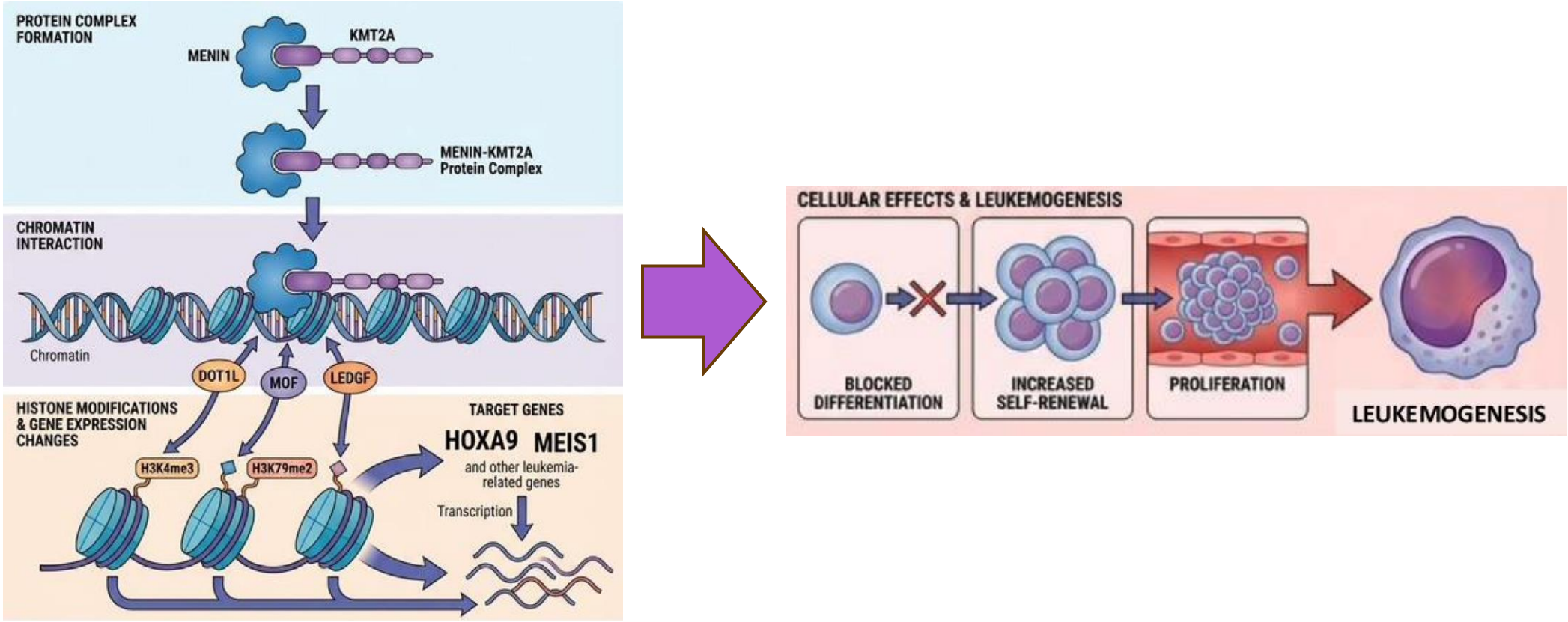
- Eradication of AML MRD+ disease is being investigated in clinical trials
  - INTERCEPT: Targeted therapies
  - myeloMATCH: Treatment groups assigned by MRD status

Lymphoma · Leukemia & Myeloma Congress

Targeted Therapy in AML: Focus on Menin Inhibitors

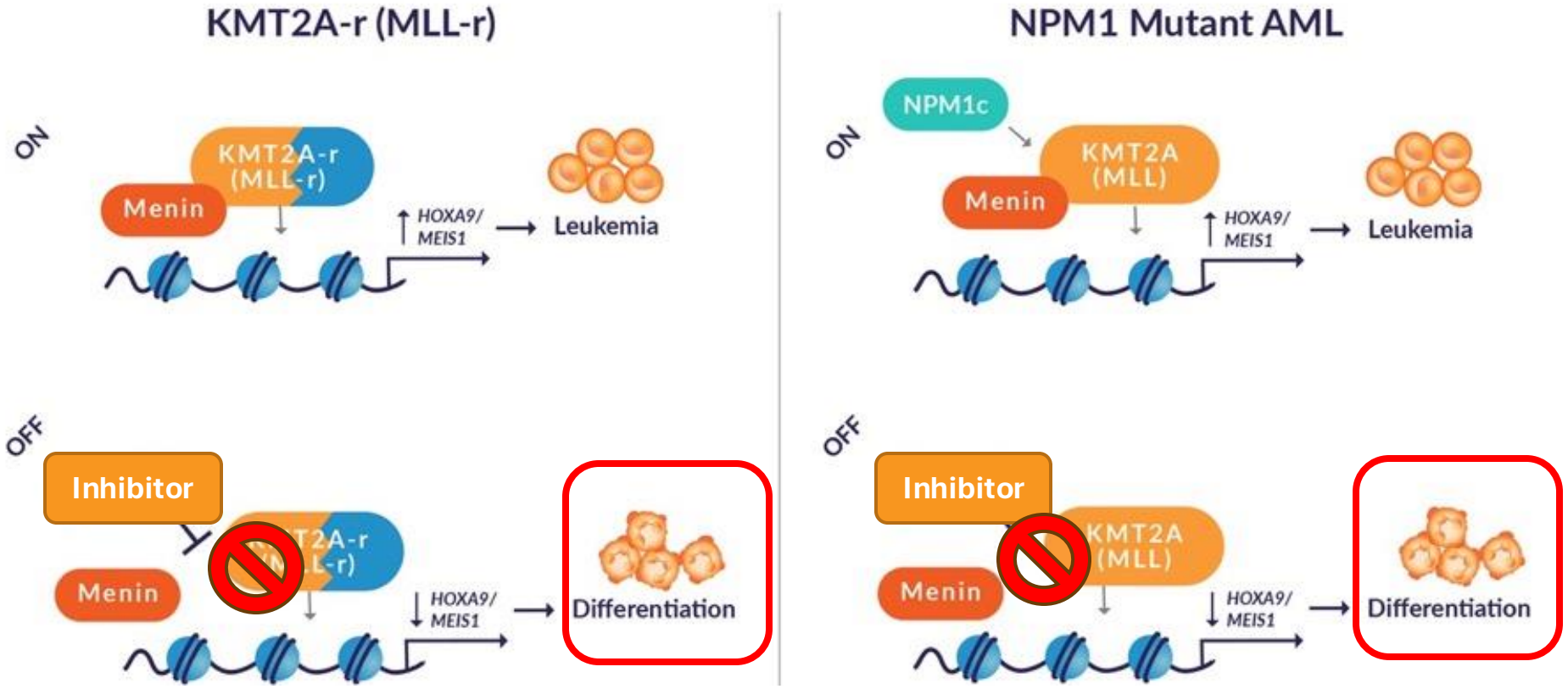
Eunice S. Wang, MD

The Menin-KMT2A Interaction Drives Leukemogenesis in Specific AML Subtypes



Bruzzese A, et al. *Eur J Haematol*. 2026;117(1):132-143.

Biological Rationale for Targeting *NPM1m* and *KMT2Ar* AML

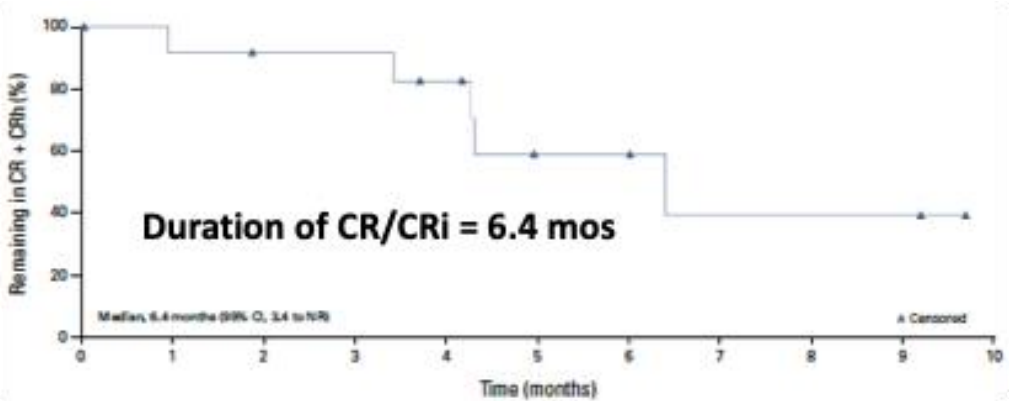


Kühn MWM, et al. *Cancer Discov*. 2016;6(10):1166-1181. Thorsteinsdottir U, et al. *Mol Cell Biol*. 2001;21(1):224-234. Patel SS, et al. *Curr Hematol Malig Rep*. 2020;15(4):350-359. Brunetti L, et al. *Cancer Cell*. 2018;34(3):499-512.e9.

Lymphoma · Leukemia & Myeloma Congress

FDA-Approved Menin Inhibitor: Revumenib in R/R *KMT2Ar* AML

Parameter	Efficacy population (n=97)
ORR, n (%)	**62 (63.9)**
CR+CRh rate, n (%)	22 (22.7)
95% CI	14.8–32.3
CRc, n (%)	41 (42.3)
95% CI	32.3–52.7
Negative MRD status, n (%)[a]	
CR+CRh	11/18 (61.1)
CRc	21/36 (58.3)



Any grade TEAEs that occurred in ≥25% patients

All terms, n (%)	Safety population (n=94)[a]
Nausea	42 (45)
Febrile neutropenia	36 (38)
Diarrhea	33 (35)
Vomiting	29 (31)
Differentiation syndrome	26 (28)
Hypokalemia	26 (28)
Epistaxis	25 (27)
QTc prolongation	24 (26)

All terms, n (%)	Safety population (n=94)[a]
Febrile neutropenia	35 (37)
Decreased neutrophil count	15 (16)
Decreased white blood cell count	15 (16)
Decreased platelet count	14 (15)
Anemia	17 (18)
Differentiation syndrome	15 (16)
QTc prolongation	13 (14)
Sepsis	11 (12)
Hypokalemia	10 (11)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

No patients discontinued due to differentiation syndrome, QTc prolongation, or cytopenias

Note: 50% dose reduction in presence of azoles

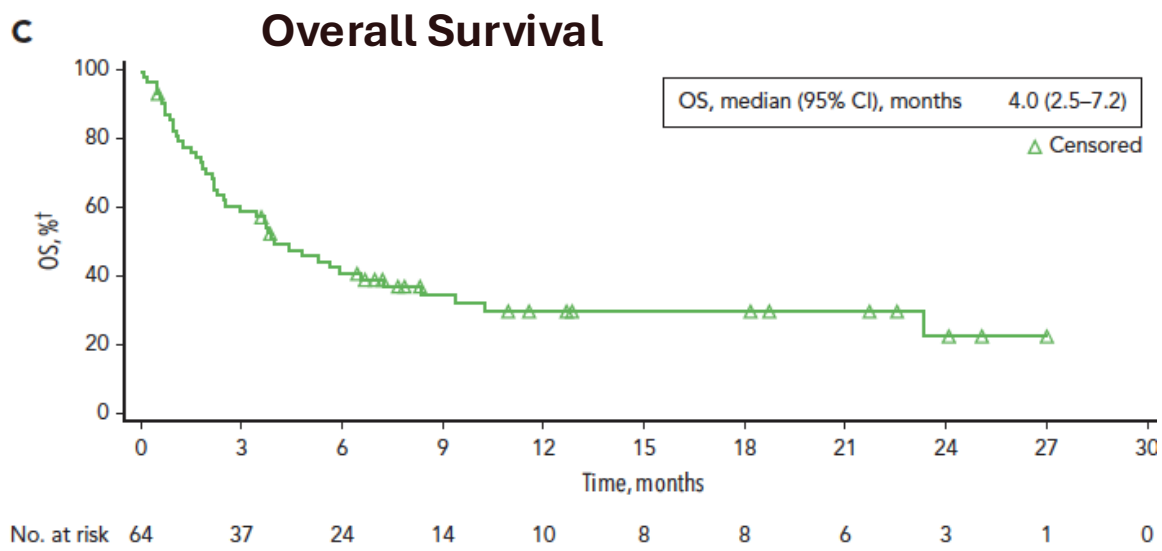
Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.

Lymphoma · Leukemia & Myeloma Congress

FDA-Approved Menin Inhibitor: Revumenib in R/R *NPM1m* AML

Clinical Responses

Parameter	Adult efficacy-evaluable population (n = 64)
ORR, n (%)	30 (46.9)
95% CI	34.3-59.8
Time to first response, median (range), mo	1.84 (0.9-4.6)
Duration of first response, median (95% CI), mo	4.4 (1.2-5.6)
CR + CRh rate, n (%)	15 (23.4)
95% CI	13.8-35.7
P value, 1-sided	.0014
Time to first CR + CRh, median (range), mo	2.76 (1.8-8.8)
Duration of CR + CRh, median (95% CI), mo	4.7 (1.2-8.2)



Adverse Events

Differentiation syndrome (any): 19%; Grade >= 3: 13%
QTcF prolongation (any): 43%; Grade >= 3: 22.6%

Arellano ML, et al. *Blood*. 2025;146(9):1065-1077.

Lymphoma · Leukemia & Myeloma Congress

FDA-Approved Menin Inhibitor: Ziftomenib in R/R *NPM1m* AML

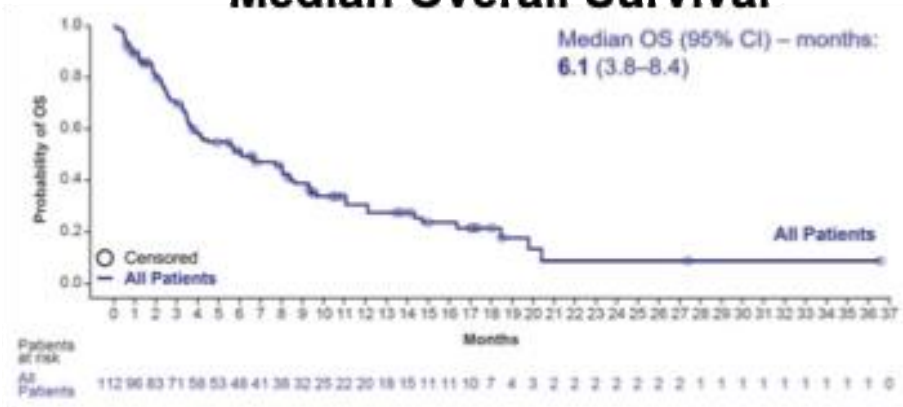
Primary Phase 2 endpoint was met (*P*-value = 0.0058)* vs. 12% historical control rate

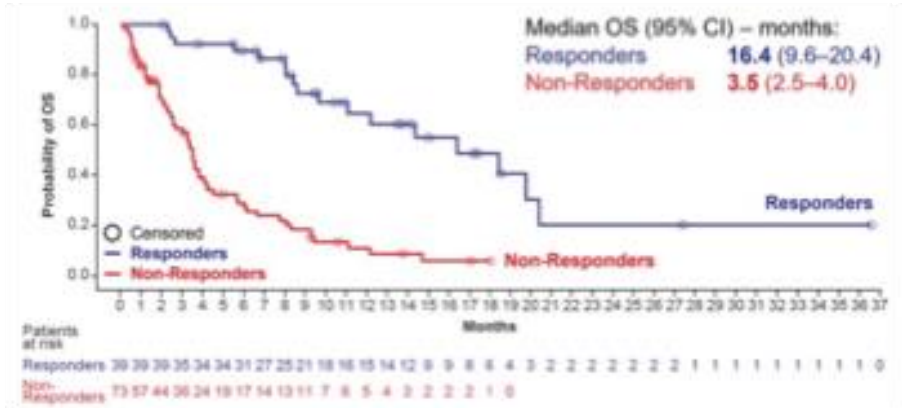
n (%) Overall Response Rate	Ziftomenib RP2D 600 mg QD	
	Phase 2 (N = 92)	Pooled Phase 1b/2 (N = 112)
CR/CRh	**21 (23)**	**28 (25)**
Overall response	**30 (33)**	**39 (35)**
CR	13 (14)	20 (18)
CRh	8 (9)	8 (7)
CRi/CRp	3 (3)	4 (4)
MLFS	5 (5)	6 (5)
PR	1 (1)	1 (1)
Other[a]	62 (67)	73 (65)
Median duration of response, months (95% CI)		
CR/CRh	3.7 (1.9–NE)	3.7 (1.9–7.7)
CRc	4.6 (2.8–11.4)	5.1 (2.8–8.1)
ORR	4.6 (2.8–11.4)	4.6 (3.6–7.7)
Restricted mean duration of response[b], months (95% CI)		
CR/CRh	4.3 (3.1–5.6)	5.2 (3.6–6.7)
CRc	5.9 (4.0–7.7)	6.4 (4.6–8.1)
ORR	5.9 (4.4–7.5)	6.5 (4.9–8.1)
MRD negativity, n/N[c] (%)	**12/19 (63)**	**17/26 (65)**

*Based on primary analysis data cut (Oct 28, 2024).
[a]Stable disease/no response/clinical benefit/progressive disease/not evaluable.
[b]Defined as the expected duration of response (area under the Kaplan-Meier curve, up to the time point when ≥ 10% of patients remain at risk).
[c]Among CR/CRh responders evaluated for MRD (centrally tested).

For Ph 2 pts, median time to CR/CRh = 2.8 months

Median Overall Survival





Wang ES, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 30-June 3, 2025; Chicago, IL. Oral presentation #6505.
Wang ES, et al. *J Clin Oncol*. 2025;43(31):3381-3390.

Lymphoma · Leukemia & Myeloma Congress

FDA-Approved Menin Inhibitor: Ziftomenib in R/R *NPM1m* AML

Ziftomenib-Related AEs in ≥ 5% of All Patients

Event, n (%)	Ziftomenib RP2D 600 mg QD			
	Phase 2 (N = 92)		Pooled Phase 1b/2 (N = 112)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any ziftomenib-related AE	64 (70)	37 (40)	77 (69)	45 (40)
Hematologic AEs				
Anemia	5 (5)	5 (5)	6 (5)	6 (5)
Neutropenia	6 (7)	6 (7)	6 (5)	6 (5)
Nonhematologic AEs				
Differentiation syndrome	**22 (24)**	**14 (15)[a]**	**26 (23)**	**15 (13)[a]**
Pruritus	15 (16)	0	16 (14)	0
Nausea	8 (9)	0	13 (12)	0
Diarrhea	8 (9)	0	10 (9)	2 (2)
Alanine aminotransferase increased	6 (7)	2 (2)	7 (6)	2 (2)
Decreased appetite	5 (5)	0	6 (5)	0

[a]No patients had Grade 4–5 differentiation syndrome.

*All 3 patients were on additional medications associated with QTc prolongation: 2 patients had electrolyte abnormalities and 1 patient had prior diagnosis of atrial fibrillation.

Ziftomenib was well tolerated, with a safety profile consistent with previous studies, including:

- Low rates of ziftomenib-related myelosuppression
- No clinically significant QTc prolongation:
  - 3 (3%) Patients*: 1 Gr2, 2 Gr3 (all investigator-assessed)
- Differentiation syndrome: 15 (13%) Gr3; no Gr4–5 events
- 3% Discontinuations due to ziftomenib-related AEs

Wang ES, et al. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, IL. Oral presentation #6505. Wang ES, et al. *J Clin Oncol*. 2025;43(31):3381-3390.

Lymphoma · Leukemia & Myeloma Congress

Targeted Therapy in AML: Focus on Menin Inhibitors

Eytan Stein, MD

Generative AI was used in the preparation of some slides in this presentation. Any AI-generated content was reviewed and verified by the presenter, who accepts full responsibility for the accuracy, completeness, and integrity of all content presented.

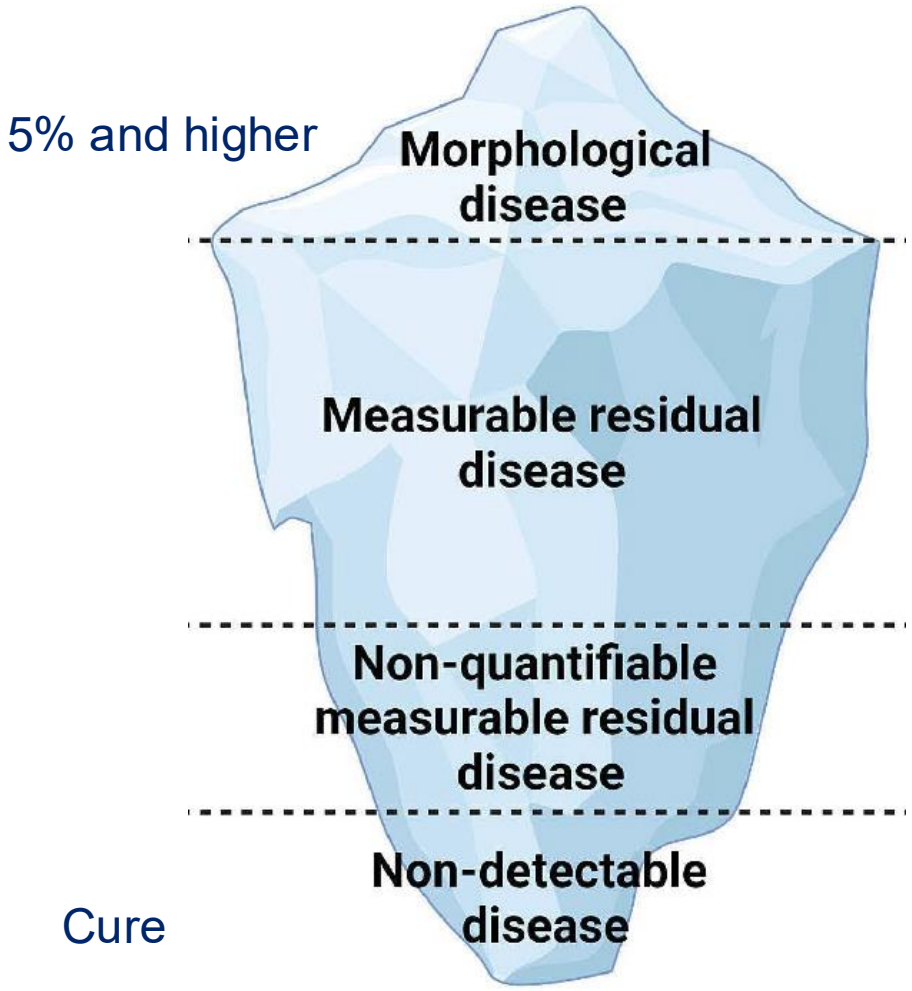
Two Cases from My Clinical Practice

- 55-year-old man with AML associated with a normal karyotype and an NPM1 mutation without a FLT3-ITD; what is the optimal induction regimen?

- 34-year-old woman with KMT2A-rearranged AML who receives intensive induction chemotherapy with 7+3 → CR → HIDAC consolidation x 1; on her pre-transplant bone marrow biopsy, she has MRD at a level of 0.75%; she proceeds with an allo-transplant

Lymphoma · Leukemia & Myeloma Congress

Principles of MRD Testing in AML



Methods of MRD Detection

Multiparameter flow cytometry (MFC)
Next-generation sequencing (NGS)
RT-PCR (most sensitive)

Issues with Above Methods

MFC – operator-dependent, monocytic leukemias
NGS – need a gene to follow; mutations associated with clonal hematopoiesis
RT-PCR – good for diseases with single/predominant driver mutation (APL, core-binding factor, ? NPM1)

Regulatory Considerations (FDA)

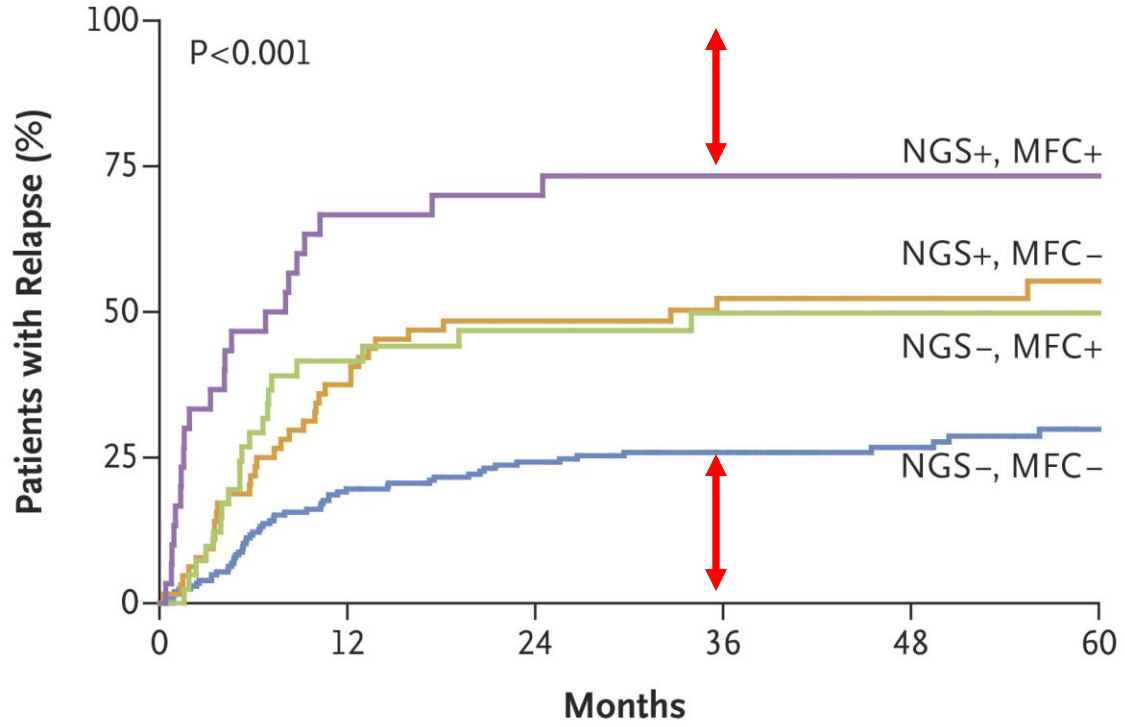
MRD not considered a surrogate of overall survival and not currently used for approvals
Combination of MRD negativity and EFS in intensively treated pts has possibility of use as a surrogate for OS (but has never been done)

EFS = event-free survival.

Saygin C, et al. *Haematologica*. 2022;107(12):2783-2793.

Lymphoma · Leukemia & Myeloma Congress

MRD in Intensively Treated Patients



No. at Risk						
NGS+, MFC+	30	8	7	5	4	4
NGS–, MFC+	41	22	18	14	11	7
NGS+, MFC–	64	39	30	22	15	11
NGS–, MFC–	205	153	130	101	69	42

- **No relapse when MRD is positive**
  - Kinetics of MRD eradication
    - The MRD is eventually cleared subsequent to the measurement
- **Relapse when MRD is negative**
  - Sampling error
  - MRD below limit of detection

Jongen-Lavrencic M, et al. *N Engl J Med*. 2018;378(13):1189-1199.

Lymphoma · Leukemia & Myeloma Congress

Kinetics of MRD Clearance – QUAZAR CC-486 Maintenance

Eligibility Criteria
- **AML with intermediate/poor risk cytogenetics**
- **Age ≥55 years**
- **Within 90 days of first CR/CRi following induction ± consolidation**

R 1:1

CC-486 maintenance
300 mg daily x 14 days/28-day cycle + BSC

PBO maintenance
Daily x 14 days/28-day cycle + BSC

Maintain CR/CRi:
Continue treatment

Relapse with >5%–15% BM blasts:
Dose-escalate to CC-486 300 mg or PBO daily x 21 days

Relapse with ≥16% BM blasts:
Discontinue treatment

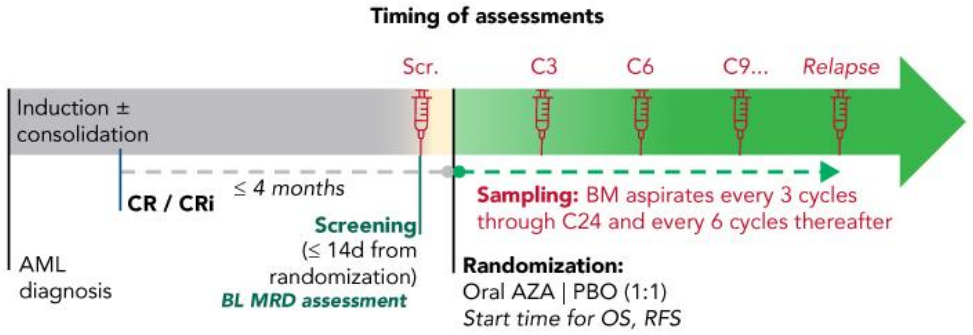


Table 4. Achievement of MRD response (MRD⁻ at ≥2 consecutive assessments) among patients who were MRD⁺ at baseline

Placebo	Oral-AZA	Placebo
MRD⁺ at baseline, N	103	116
MRD responders,* n (%)	38/103 (37)	22/116 (19)
OR [95% CI], Oral-AZA vs placebo	2.50 [1.35, 4.61]	
Time to MRD response,*† n (%)		
≤3 mo	22/38 (58)	15/22 (68)
>3 to ≤6 mo	7/38 (18)	6/22 (27)
>6 mo	9/38 (24)	1/22 (5)

*MRD response was defined as patients who were MRD1 at baseline and became MRD2 on treatment; †Time from randomization.

Roboz GJ, et al. *Blood*. 2022;139(14):2145-2155.

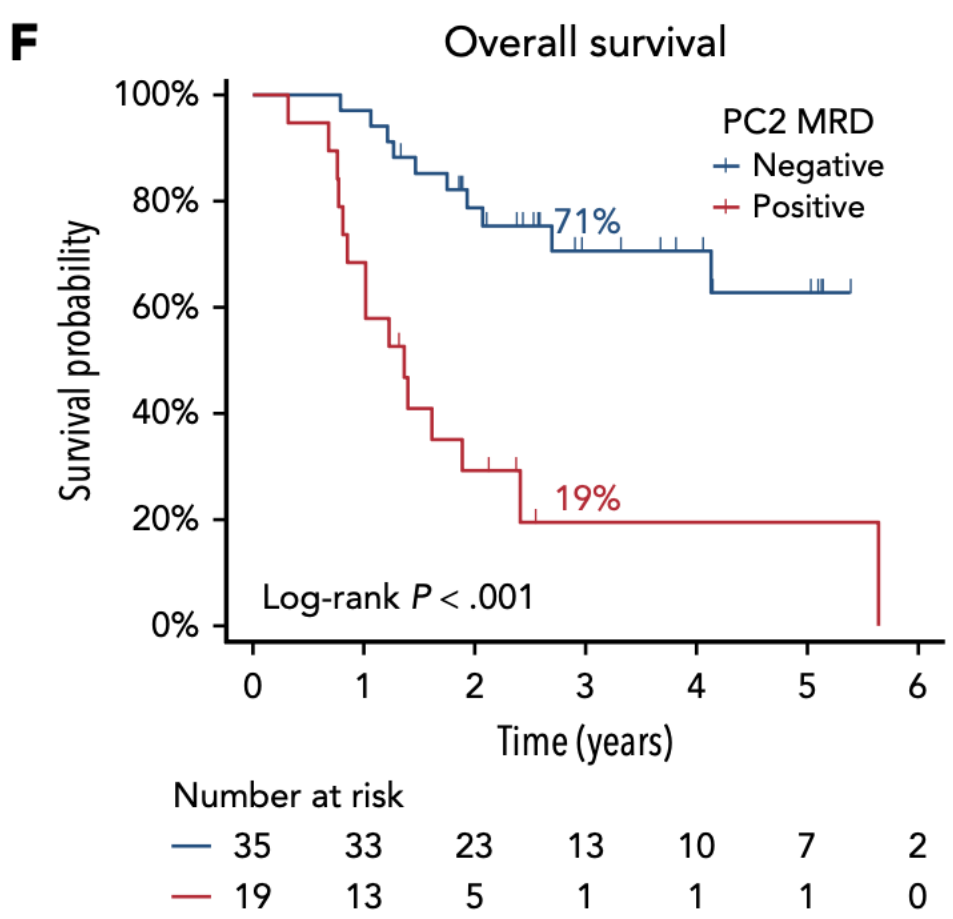
Lymphoma · Leukemia & Myeloma Congress

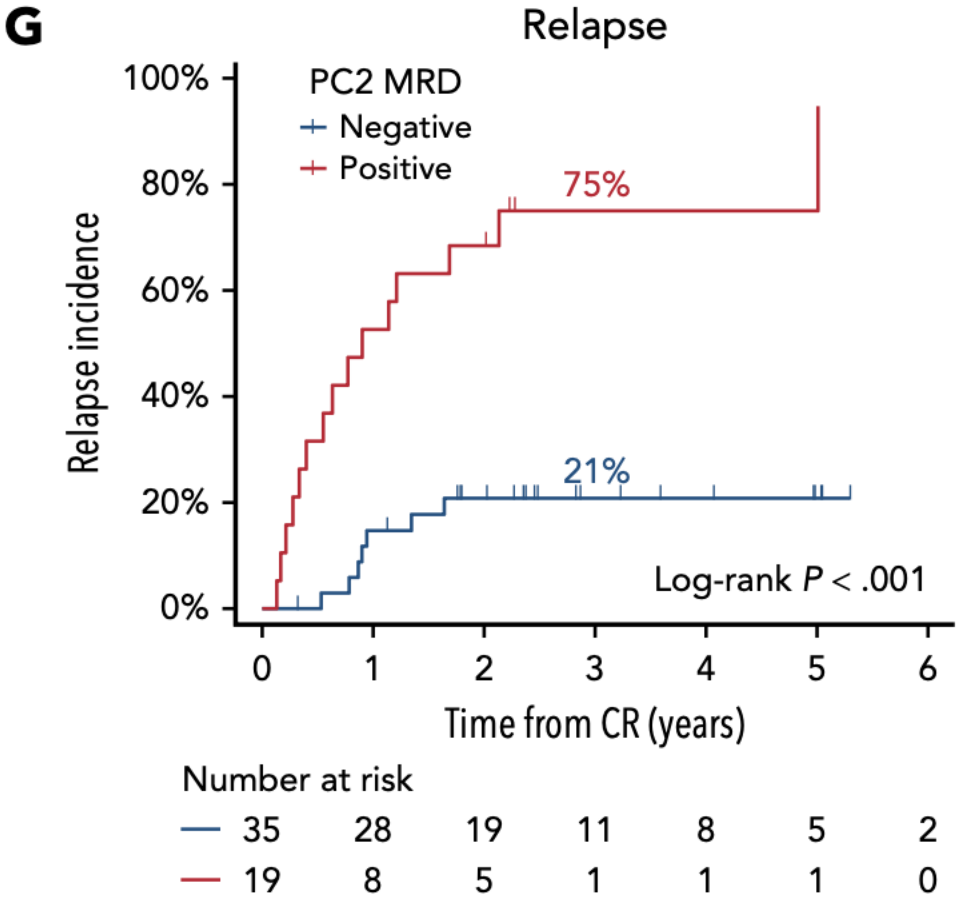
Does the Presence of MRD = We Must Eliminate the MRD?

- Assumes you can eliminate MRD with currently available agents and that the MRD population is not the resistant population
- Benefit of MRD elimination > risk of toxicity from MRD eliminating agents (most/all of which are myelosuppressive)
- Transplant or non-transplant candidate
- Goals of therapy for the patient

Lymphoma · Leukemia & Myeloma Congress

MRD in KMT2Ar AML after Chemotherapy Predicts Survival



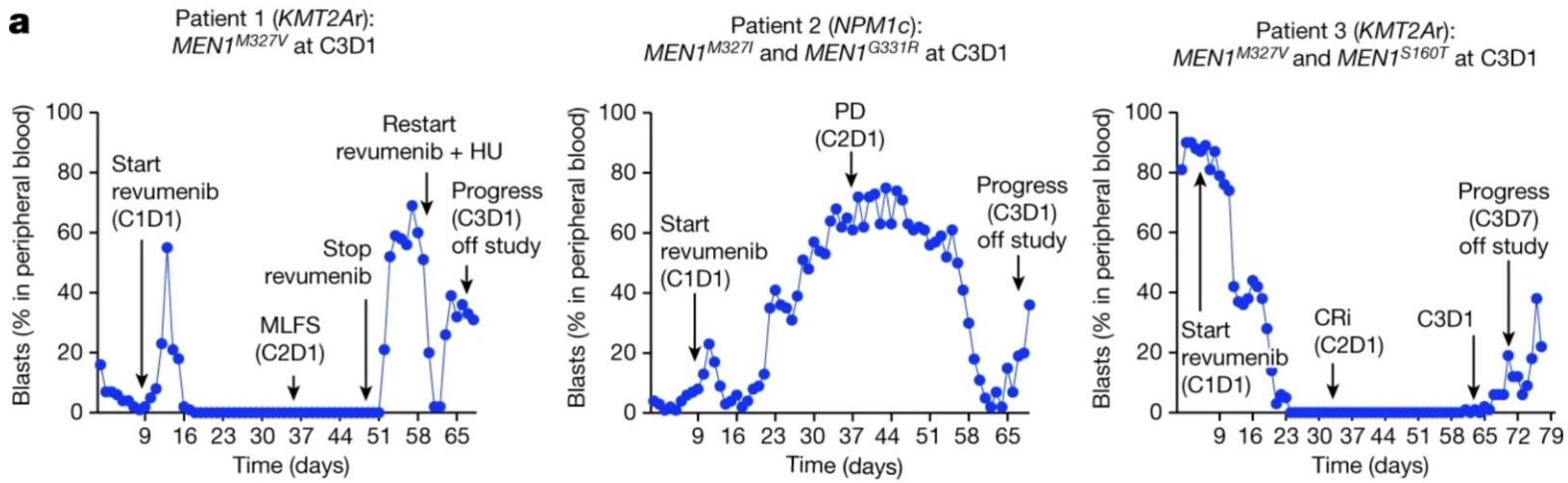


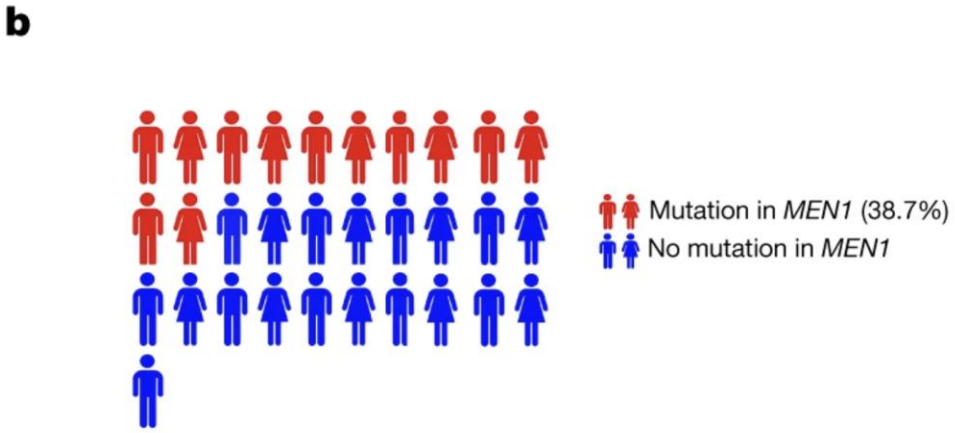
Othman J, et al. *Blood*. 2025;146(15):1862-1867.

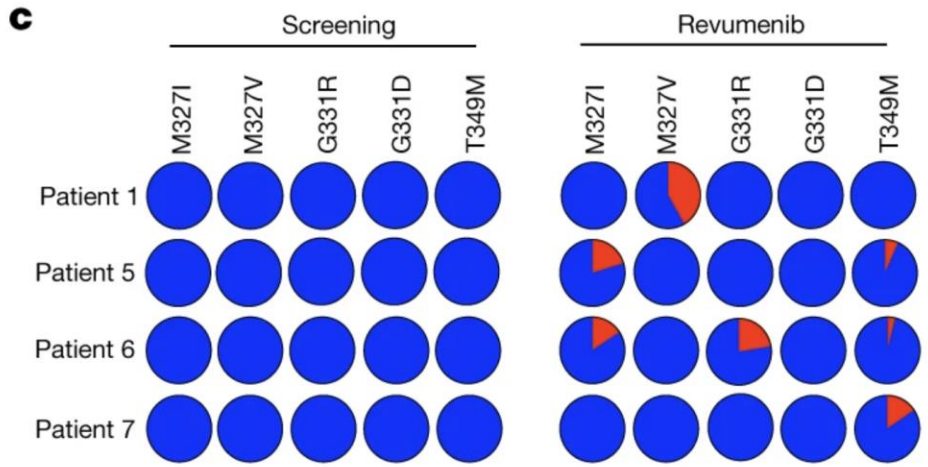
Case 2

- 34-year-old woman with KMT2A-rearranged AML who receives intensive induction chemotherapy with 7+3 → CR → HIDAC consolidation x 1; on her pre-transplant bone marrow biopsy, she has MRD at a level of 0.75%; she proceeds with an allo-transplant
- Relapses at 6 months and placed on single-agent revumenib for R/R KMT2Ar AML
- Achieves a complete remission on revumenib…and relapses (see next slide)

Resistance to Single-Agent Revumenib







Perner F, et al. *Nature*. 2023;615(7954):913-919.

Revumenib Escape Is Mediated by Clonal Acquisition of Canonical MEN1 M327I

SNDX-5613 (Revumenib) Relapse Course

- **Long-term exposure duration:** Remained in an MRD-negative complete remission (CR) for **17 cycles (68 weeks)** of revumenib monotherapy
- **Acquired clinical relapse:** Developed progressive cytopenias and an elevation in peripheral blood myeloblasts (30-40% bone marrow blasts)
- **Structural mechanism of escape:** Revumenib binds in an *extended conformation* across the Met327 residue toward the distal pocket; the mutant Ile327 introduces a bulky, branching beta-methyl group that sterically clashes with revumenib
- **Leukemogenic reactivation:** Steric clash dramatically lowers revumenib binding affinity without disrupting the menin-KMT2A binding, restoring the pathologic HOX/MEIS1 transcription network

Genomic Relapse Panel (MSK-IMPACT)

MEN1 p.M327I — 23.1% VAF

The primary driver of drug resistance; bulky methyl group sterically displaces revumenib and ziftomenib, but spares bleximenib's compact, curved binding pose

MSH3 p.D362H — 20.3% VAF

An emergent somatic mismatch-repair alteration; the clinical and therapeutic significance of this co-mutational clone remains uncertain in this context

Note: Chimerism studies at relapse confirmed 52% donor status, indicating partial host-clone re-emergence.

VAF = variant allele frequency.

Chin KK, et al. *Leukemia*. 2026;40:1331-1334.

Lymphoma · Leukemia & Myeloma Congress

Resistance to Other Menin Inhibitors – Enzomenib

Figure 4: E368 is the dominant *MEN1*m after enzomenib

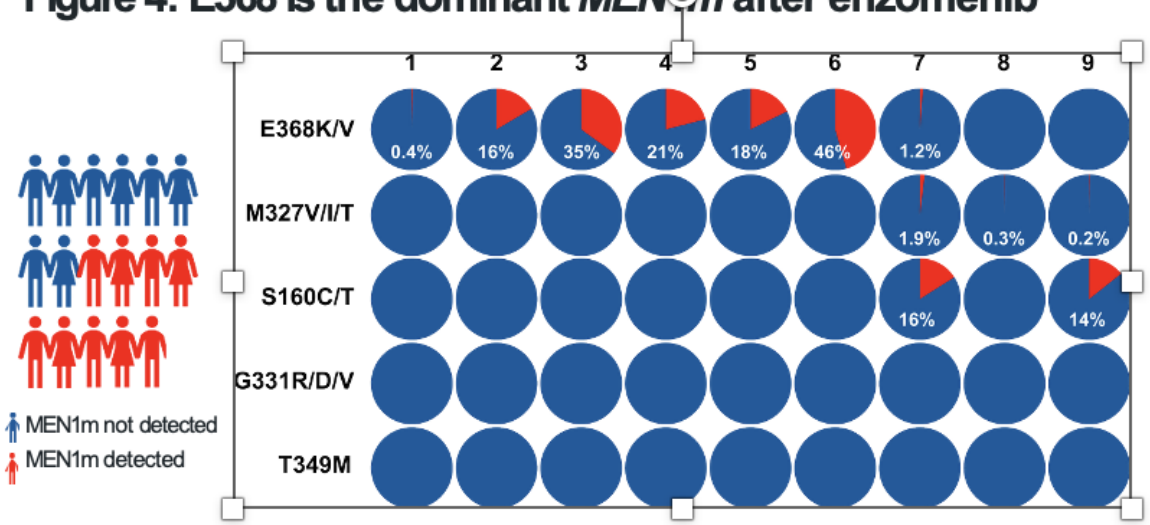


Figure 4. 9/17 (53%) of patients tested had detectable MEN1m at relapse. Mutations to E368 were detected in 7, including 1 pt with concomitant M327T (1.9%) and S160C (16%) mutations, suggesting E368 is the likely predominant acquired mutation associated with enzomenib resistance.

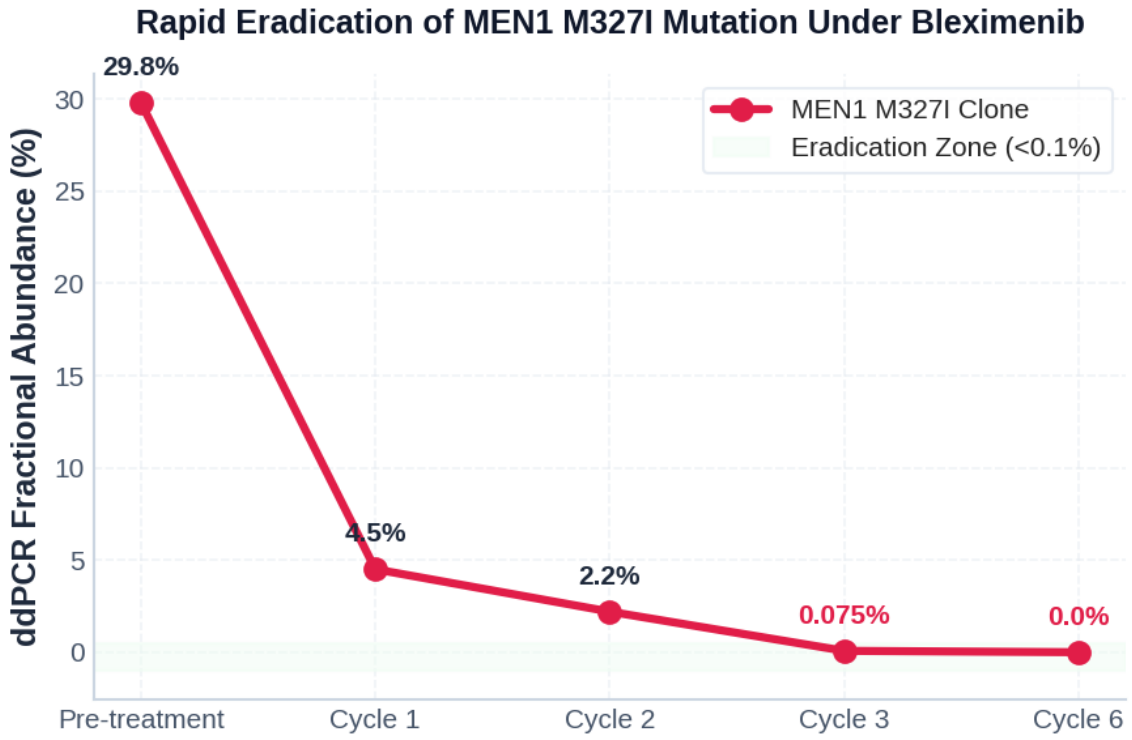
Table 4: Summary of patient characteristics and *MEN1*m data

Patient	Target	Starting Dose	Dose Notes	Mutation Detected at relapse	Sampled Visit
1	MLLr	140mg BID	DI (200mg) C3	**E368K (0.35%)**	C3D1
2	MLLr	120mg BID	DR (100mg) C3-C6	**E368K (16.48%)**	C9D1
3	MLLr	200mg BID	MD (6d) C2 DR (100mg) C2-C5	**E368K (35%)**	C5D1
4	MLLr	300mg BID	MD (8d) C1 & (7d) C2	**E368K (21%)**	C3D1
5	NPM1m	300mg BID	MD (13d) C1 & (8d) C2 DR (100 QD) C2-C3	**E368K (17.53%)** **E368V (0.15%)**	C7D1
6	NPM1m	200mg BID	MD (4-7d) C1-C4	**E368K (45.61%)**	C5D1
7	NPM1m	200mg BID	MD (3d) C1	**E368K (1.2%)** **M327T (1.9%)** **S160C (16%)**	C11D1
8	MLLr	300mg BID	n/a	**M327I (0.34%)**	C7D1
9	Other	200mg BID	n/a	**M327T (0.21%)** **S160T(14.33%)**	C13D1
10	NPM1m	200mg BID	n/a	ND	C3D1
11	NPM1m	200mg BID	n/a	ND	C3D1
12	MLLr	300mg BID	n/a	ND	C3D1
13	MLLr	400mg BID	n/a	ND	C3D1
14	Other	300mg BID	n/a	ND	C5D1
15	MLLr	400mg BID	MD (12d) C1 DR (200mg) C2-C3	ND	C3D1
16	MLLr	400mg BID	MD (14d) C1, 58d hold C3 DR (200mg) C2	ND	C3D1
17	MLLr	300mg BID	MD (3d) C2	ND	C3D1

n/a - Not Applicable, ND – None Detected, MD – Missed Doses, DI – Dose Increased, DR – Dose Reduced

Cutler J, et al. Presented at: European Hematology Association (EHA) Congress; June 11-14, 2026; Stockholm, Sweden.

Switching to Bleximenib Rapidly Eradicates the Dominant MEN1 M327I Clone



Targeted Bleximenib Salvage and Outcomes

- **Rational treatment switch:** Based on pre-clinical data that bleximenib retains activity against M327I, the patient was initiated on bleximenib (100 mg orally BID)
- **Deep molecular response:** Droplet digital PCR (ddPCR) tracked a massive log-fold decline in MEN1 M327I fractional abundance: from **29.8% pre-treatment** to **4.5%** (Cycle 1), **2.2%** (Cycle 2), **0.075%** (Cycle 3), and complete eradication (**0.000%**) by Cycle 6
- **MRD-negative cleared state:** Achieved a flow-MRD-negative complete remission (CR) after Cycle 3 and confirmed complete eradication of the M327I mutant clone pre-transplant
- **Curative consolidation:** Following Cycle 6, she was successfully consolidated with a **third, curative allogeneic hematopoietic stem cell transplant (alloHSCT)** from a first-degree haploidentical donor

Chin KK, et al. *Leukemia*. 2026;40:1331-1334.

Lymphoma · Leukemia & Myeloma Congress

The Emerging MEN1 “Map”

A simplified way of thinking about the major mutations is:

MEN1 mutation	Revumenib	Ziftomenib	Bleximenib	Enzomenib
M327I/V/T	🔴 strong	🔴 strong	🟠 moderate	🟠 moderate/lower
G331D	🔴 strong	🔴 strong	🟠	🟡/🟠
G331R	🔴/🟠	🟢 relatively preserved	🟢 relatively preserved	🟢 preserved
T349M	🔴/🟠	🟢 relatively preserved	🟠	🟡
E368K/V	🟢	🟢	🟢	🔴 **strong/selective**
V372A	🟢	🔴 **strong/selective**	🟢	🟢
D290H	limited effect	limited effect	🔴 relatively selective	limited effect

Lymphoma · Leukemia & Myeloma Congress

Doublet of Bleximenib and Venetoclax in R/R AML

Figure 1: ALE1002 (NCT05453903) study design

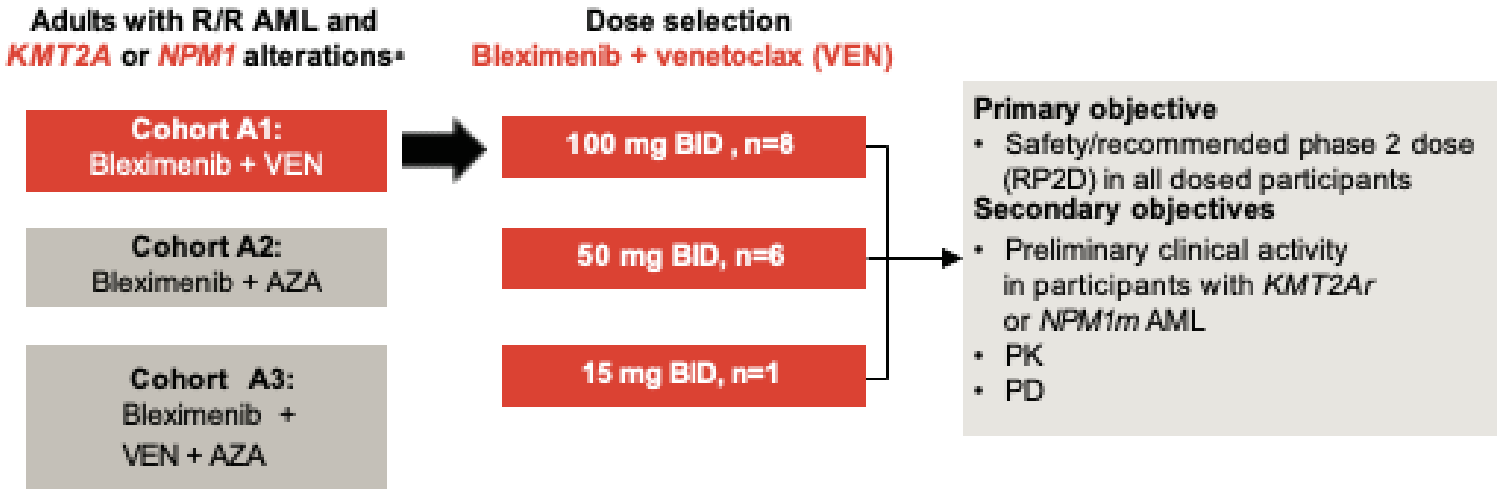
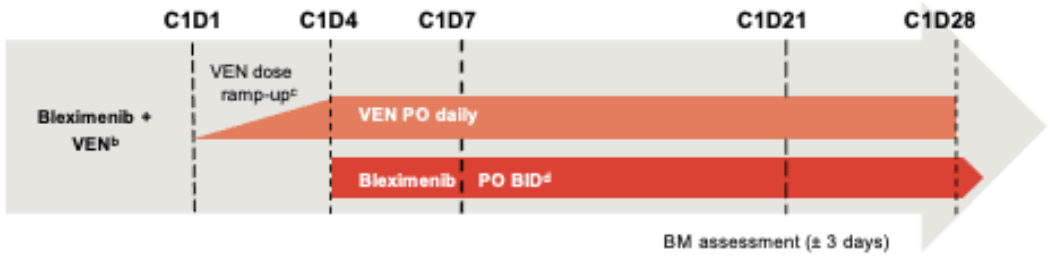


Figure 2: Dosing schedule[a]

Participants received increasing doses of bleximenib (15–100 mg BID) in combination with VEN



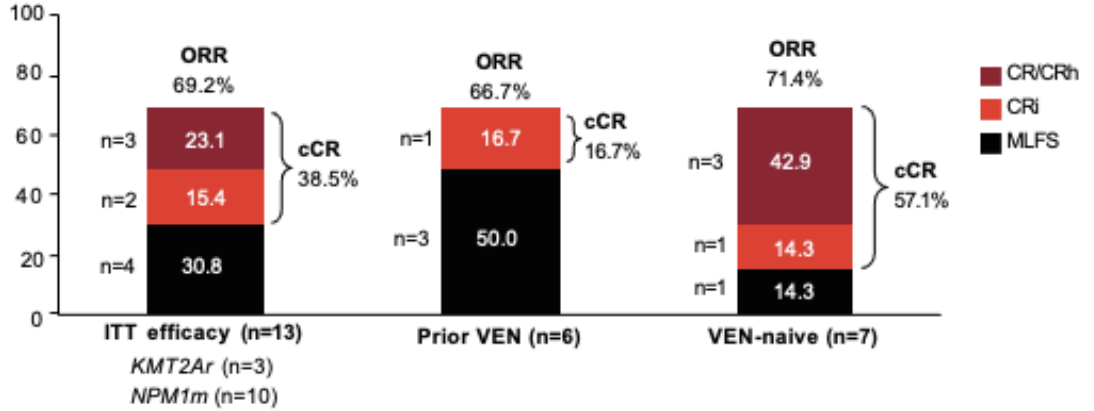
O'nions J, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; December 6-9, 2025; Orlando, FL.

Lymphoma · Leukemia & Myeloma Congress

Doublet of Bleximenib and Venetoclax in R/R AML

Efficacy

Figure 3: Best overall response in the intention-to-treat (ITT) efficacy population[a]



	Responders in the ITT population N=9
Time to first response, median (range), days	22 (19–56)

Data cutoff: October 2025.

[a]ITT population comprised participants with *KMT2Ar* or *NPM1m* R/R AML who received bleximenib 50 mg BID or 100 mg BID in combination with VEN, including those who discontinued prior to the first disease evaluation; 2 participants were excluded from efficacy analysis (bleximenib 15 mg BID and prior menin inhibitor in 1 participant each).

- Responses were observed in most participants, including those with prior VEN exposure, although interpretation of these data is limited by the small sample size (**Figure 3**)

O'nions J, et al. Presented at: ASH Annual Meeting; December 6-9, 2025; Orlando, FL.

Triplet Regimens in R/R Disease May Suppress the Emergence of Resistant MEN1 Clones

Rational triplet combination raises the genetic barrier to acquired resistance.

Multi-pathway blockade: The combination of the menin-KMT2A inhibitor revumenib with the hypomethylating agent decitabine/cedazuridine (ASTX727) and the BCL2 inhibitor venetoclax forces concurrent cytotoxic and differentiation-inducing pressures, preventing single-node clonal escape.

Deep molecular clearance: Sustained, deep clearances of mutated NPM1 (VAF <0.005%) and multiparameter flow cytometry MRD-negativity reduce the absolute leukemic cell reservoir. This significantly narrows the genetic target area from which a spontaneous resistant subclone can emerge.

Diminished clonal dominance: Clinically, emergent menin-binding site mutations are observed at a substantially lower frequency under this upfront triplet combination than the 38.7-40% rate documented under single-agent revumenib monotherapy.

Clinical Parameter	Revumenib Monotherapy	SAVE Triplet Regimen
Efficacy (CR/CRh)	21-23% in R/R cohort	**71% (composite CR)**
MEN1 mutation rate	38.7-40% at relapse	**Significantly lower frequency**
Primary resistance	Single-node MEN1 mutations	**Multi-pathway clonal selection**
Response duration	Median 4.4-6.0 months	**Not reached (KMT2Ar) / 10.7 mo**

Issa GC, et al. *J Clin Oncol*. 2026;44(22):2110-2120.

Polyclonal Kinetics of Acquired MEN1 Mutations in Triplet Relapses

In rare events where triplet therapy fails to prevent relapse, serial ddPCR reveals highly complex, polyclonal, and rapid clonal expansion of specific menin-binding pocket mutations.

MDA15 (44yo Male, KMT2Ar)

HYPER-ACUTE POLYCLONAL RELAPSE

Experienced exceptionally rapid disease progression at day ~20

Identified Mutational Clones

- **M327V / M327I (A & C):** Multiple distinct variants emerging at the same codon
- **G331D / G331R:** Pan-resistance clones emerging in lockstep

Clinical insight: Demonstrates that highly aggressive KMT2Ar clones can utilize immediate, highly complex polyclonal escape, driving concurrent rebound of blast counts and variant allele frequencies (VAFs)

MDA24 (73yo Male, NUP98r)

INTERMEDIATE CLONAL REMODELING

Developed gradual disease relapse after Day 75 of treatment

Identified Mutational Clones

- **M327I (A & C alleles):** Emergent binding-site mutations driving late resistance
- **T349M / G331R:** Co-emerging clones remodel the KMT2A-binding pocket

Clinical insight: Highlights NUP98-rearranged AML escaping through gradual, synchronized subclonal emergence, suggesting a need for routine mutational monitoring throughout treatment

MDA56 (66yo Male, NUP98r)

LATE-STAGE MONOCLONAL SELECTION

Relapsed after Day 140 of sustained therapy on study

Identified Mutational Clones

- **T349M:** Highly selective, dominant mutant clone outgrowth
- **Monoclonal escape:** No other binding-pocket variants detected

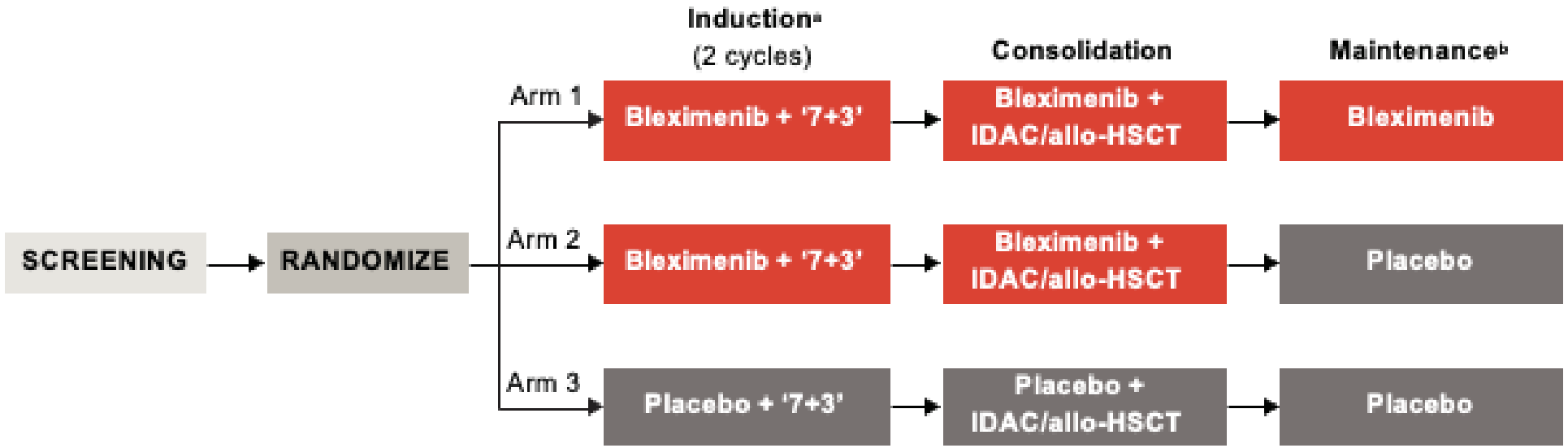
Clinical insight: Illustrates that even under prolonged multi-agent pressure, single-clone escape (particularly via the T349M residue, which retains MLL1 affinity) remains a primary mechanism of late relapse

Issa GC, et al. *J Clin Oncol*. 2026;44(22):2110-2120.

Lymphoma · Leukemia & Myeloma Congress

Pivotal Phase III Study – Blexi with Intensive Chemotherapy

Figure 2: HOVON 181 AML / AMLSG 37-25 study design



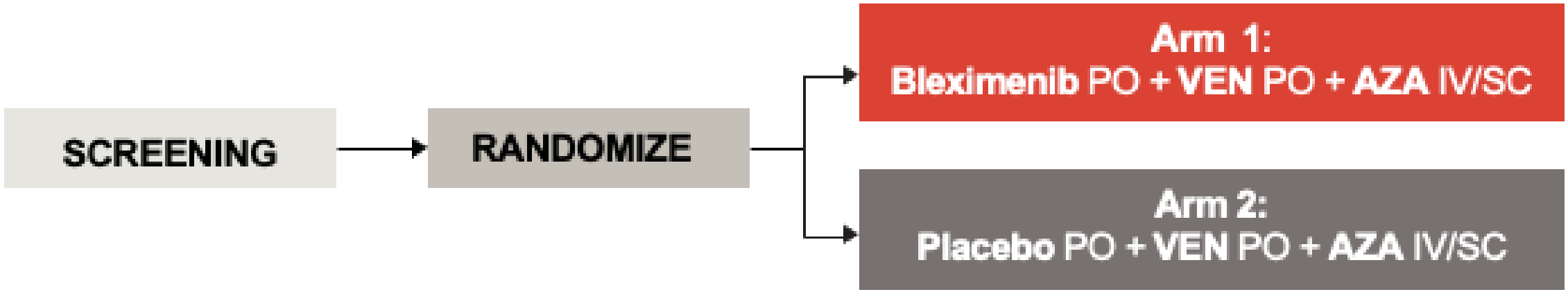
[a]Second induction cycle: IDAC ± anthracycline.
[b]All participants eligible for maintenance, regardless of allo-HSCT status.

Raaijmakers M, et al. Presented at: ASH Annual Meeting; December 6-9, 2025; Orlando, FL.

Lymphoma · Leukemia & Myeloma Congress

Lower-Intensity Therapy Randomized Study

Figure 2: cAMeLot-2 study design



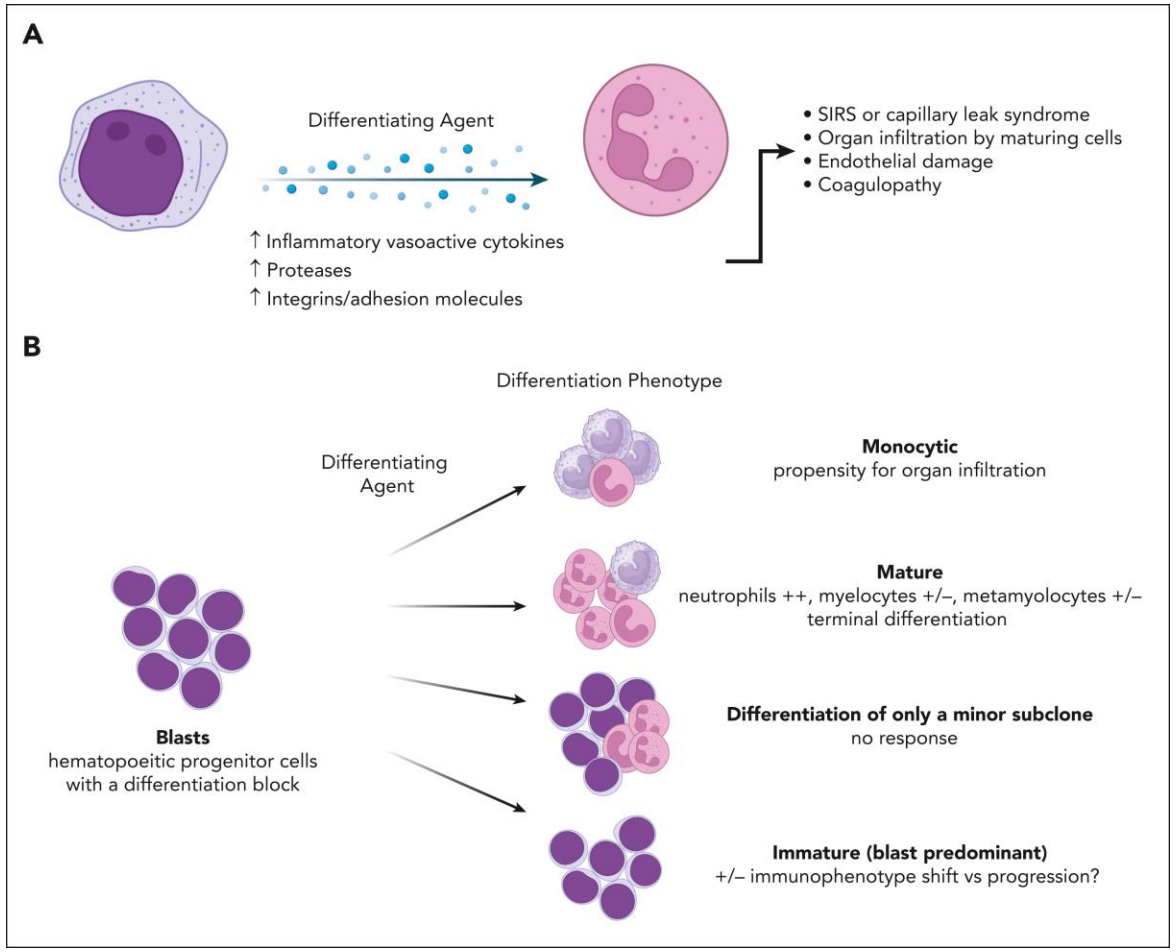
Jabbour E, et al. Presented at: ASH Annual Meeting; December 6-9, 2025; Orlando, FL.

Case 2

- 34-year-old woman with KMT2A-rearranged AML who receives intensive induction chemotherapy with 7+3 → CR → HIDAC consolidation x 1; on her pre-transplant bone marrow biopsy, she has MRD at a level of 0.75%; she proceeds with an allo-transplant
- Relapses at 6 months and placed on single-agent revumenib for R/R KMT2Ar AML
- Achieves a complete remission on revumenib…and relapses
- **Starts bleximenib and develops shortness of breath and lower extremity edema**

Lymphoma · Leukemia & Myeloma Congress

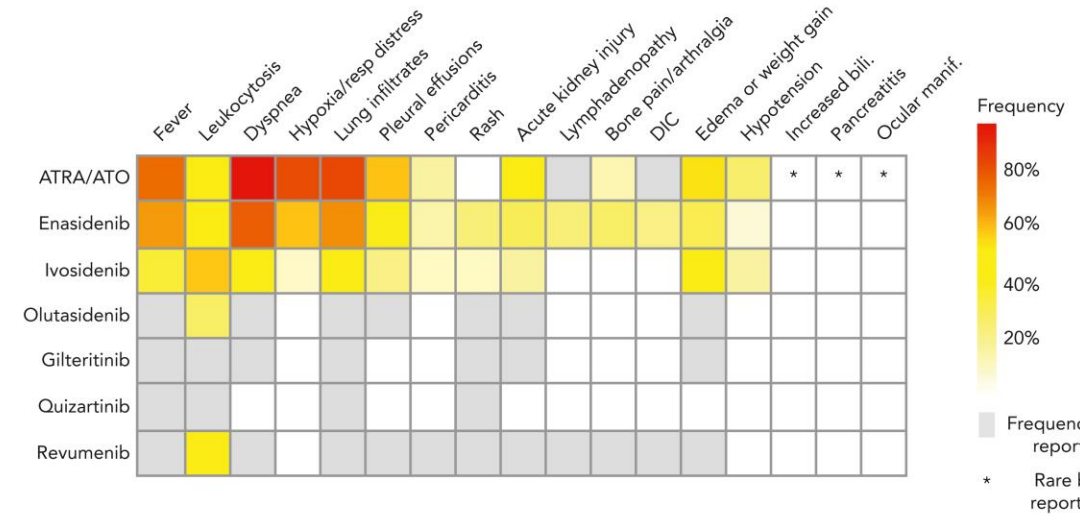
Phenotypes of Differentiation and Frequency of DS



A

DS Characteristics	ATRA/ATO	IDH-I			FLT3-I		Menin-I
		Ena	Ivo	Olu	Gilt	Quiz	Rev
Rate (%)	19-25%	12-19%	11-19%	14%	3%	5%	16-26%
Median time to onset (range), days	12 (0-46)	19 (1-86)	20 (1-78)	18 (1-561)	- (2-75)		18 (5-41)
Recurrence (%)	Rare	15%	12%				
Severe DS (%)	6-12%	7%	4%	7%	Rare		0-16%

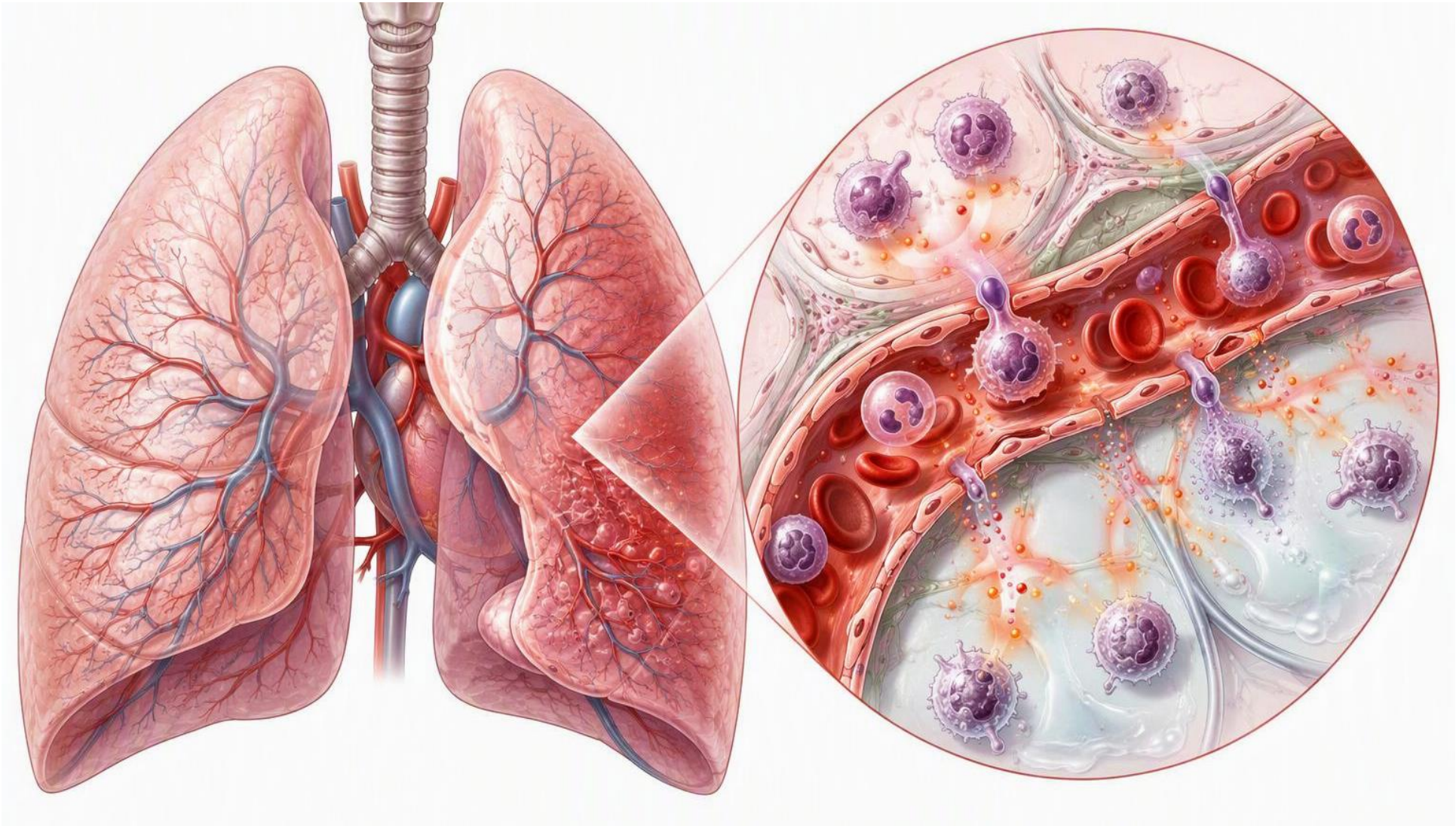
B



Issa GC, et al. *Blood*. 2025;145(12):1251-1259.

Lymphoma · Leukemia & Myeloma Congress

Differentiation Syndrome (DS)



Fathi AT, et al. *JAMA Oncol*. 2018;4(8):1106-1110.

Treatment of DS

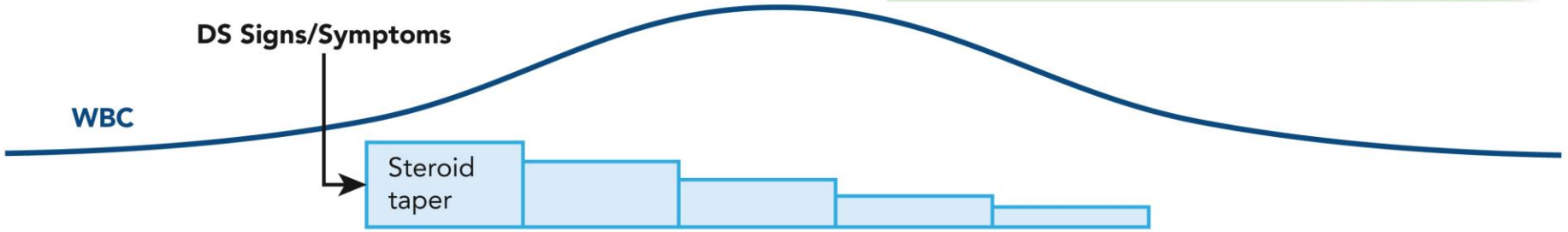
Inform patient and monitor diligently for signs/symptoms DS
High index of suspicion during cycle 1-2
High risk of severe DS if high burden or rapidly proliferative disease

Monitoring tests
CBC, electrolytes, creatinine, LDH, LFTs, PT, PTT, fibrinogen

If chest pain/dyspnea/hypoxia → chest imaging (lung infiltrates, pleuropericardial effusions) +/– EKG, TTE (pericarditis)

Supportive treatment
Hospitalization for most cases
Diuresis if edema/weight gain
Blood cultures, empiric antibiotics and rule out infection

Cytoreduction for leukocytosis (**hydroxyurea**, Ara-C, GO)
Monitor and manage TLS



Any sign/symptom of DS → **Dexamethasone** 10 mg PO twice daily for 3 days followed by tapering doses if improvement
Consider holding differentiating agent for severe cases

Cycle 1 | Cycle 2

Issa GC, et al. *Blood*. 2025;145(12):1251-1259.

Lymphoma · Leukemia & Myeloma Congress

Atypical Menin-DS?

A provocative case of steroid-refractory inflammation

Baseline
- 40F w prior Burkitt lymphoma and therapy-related AML with t(11;19) *KMT2A:ELL* and *FLT3*-ITD s/p alloHCT experiences relapse and starts revumenib 163 mg Q12H (12 months after alloHCT)

D16
- She's admitted for fevers and hypoxia consistent with menin-DS, which responds to steroids and cytoreduction

D37
- She improves clinically and D37 BmBx shows MLFS (MRD indeterminate by flow)

D40+
- Steroid-refractory fevers, hypoxemia, and hypotension with resumption of revumenib; marked elevated inflammatory markers (see next slide)

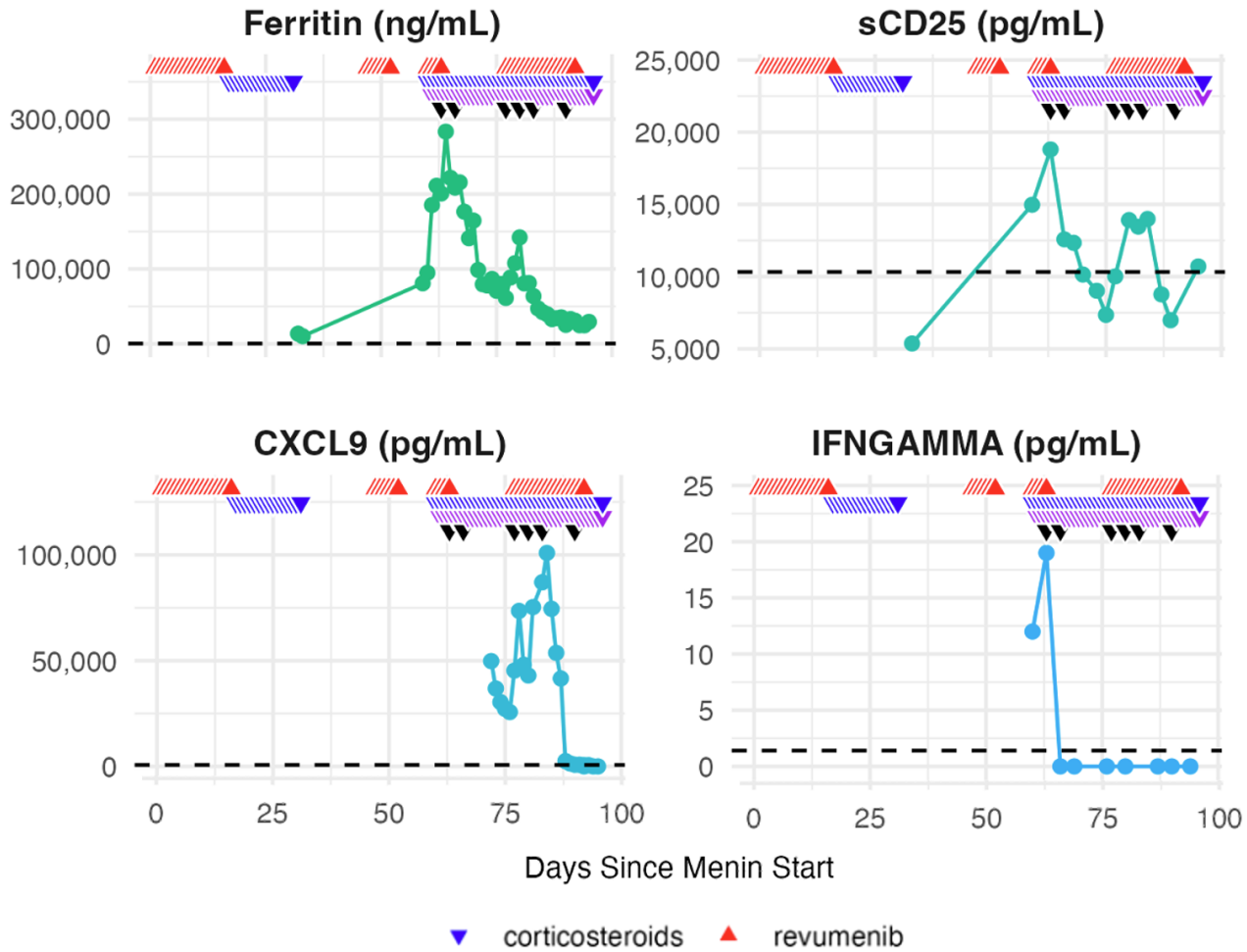
MLFS = morphologic leukemia-free state.
Courtesy: Chin KK, et al. *Haematologica*. 2026 [Epub ahead of print].

Lymphoma · Leukemia & Myeloma Congress

Markedly Elevated Inflammatory Markers with MENINi

D59 labs

- **WBC** 0.1×10^3/μL, **HgB** 8.6 g/dL, **PLT** 36×10^3/μL
- **Ferritin** 80,867 ng/mL
- **sCD25** (sIL2) 3,482 U/mL
- **Serum CXCL9** 49,778 pg/mL (normal ≤669 pg/mL)
- **Serum IFNγ** 2,069 pg/mL (normal ≤1.4)



WBC = white blood cell; Hgb = hemoglobin; PLT = platelet; IFN = interferon.
Courtesy: Chin KK, et al. *Haematologica*. 2026 [Epub ahead of print].

Lymphoma · Leukemia & Myeloma Congress

Evidence of Hemophagocytosis in Leukemia-Derived Histiocytes

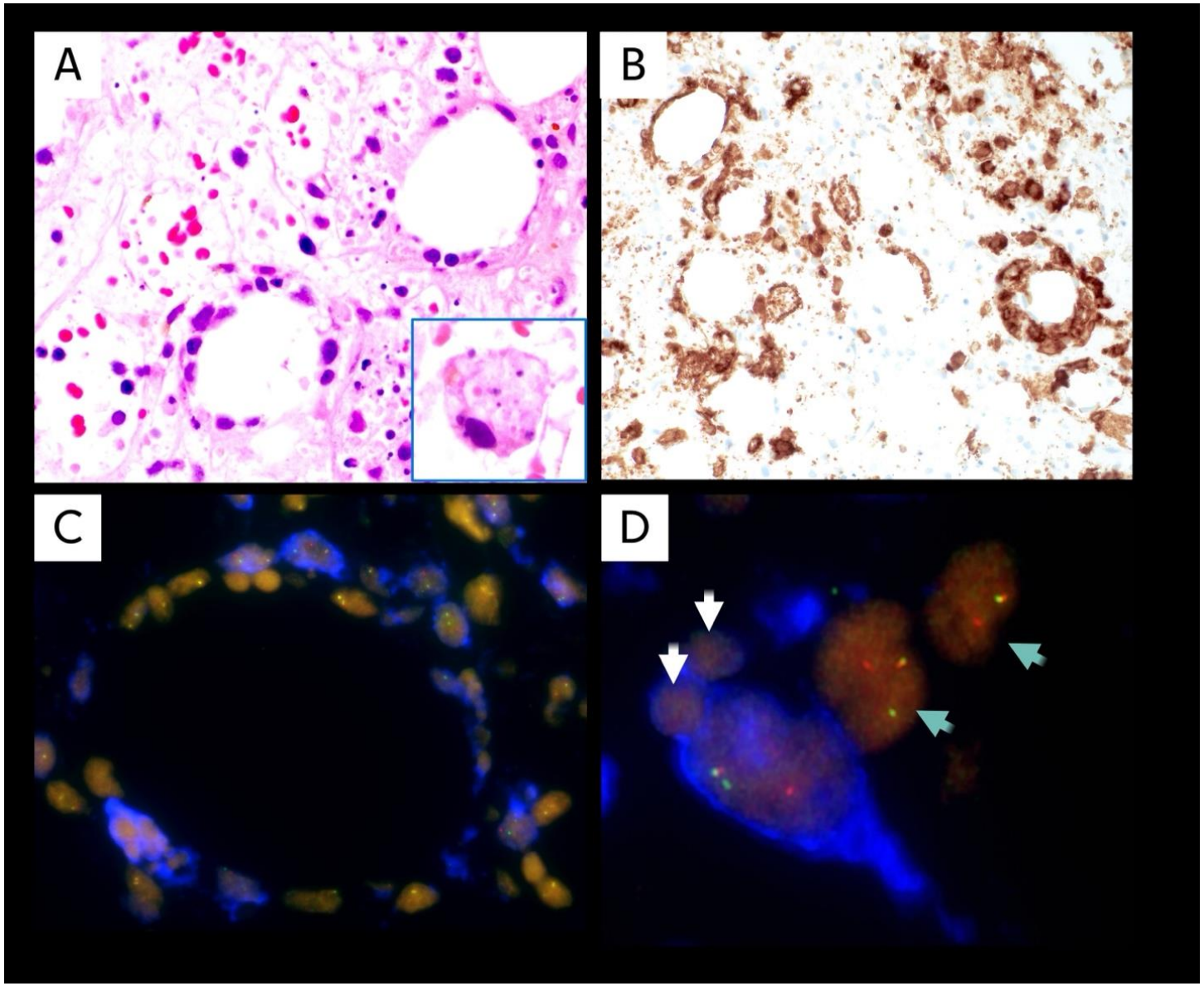
D64 BmBx

A. H&E section (x600) of bone marrow biopsy shows an increase in histiocytes, including hemophagocytic histiocytes (inset)

B. Immunohistochemical staining for CD163 (brown, x400) highlights an increase in histiocytes on the bone marrow biopsy with strong membranous and cytoplasmic staining

C. Combined immunophenotyping using CD163 (aqua), and FISH testing using *KMT2A* break-apart probes (5'MLL in green and 3' MLL in orange); most CD163-positive cells are positive for *KMT2A* translocation, eg, t(11;19)

D. CD163-positive cells show *KMT2A* split signal pattern, with evidence of hemophagocytic feature, eg, two red blood cells (white arrows) in the cytoplasm; two CD163-negative cells (green arrows) are also positive for *KMT2A* translocation



H&E = hematoxylin and eosin.

Courtesy: Chin KK, et al. *Haematologica*. 2026 [Epub ahead of print].

Lymphoma · Leukemia & Myeloma Congress

Monitoring While on Revumenib or Ziftomenib

- Both revumenib and ziftomenib may cause QTc prolongation
  - Monitor QTc as per FDA label for each agent
  - Be careful co-administering other QT-prolonging agents with revumenib or ziftomenib; not an absolute contraindication, but needs increased monitoring
  - Maintain K over 4.0 and Mg over 2.0

Drugs@FDA. Accessed October 9, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218944s003lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220305s000lbl.pdf.

Lymphoma · Leukemia & Myeloma Congress

Key Learning Points

- Many menin inhibitors in various stages of clinical development or FDA-approved: Revumenib, ziftomenib, bleximenib, enzomenib
- Clinical trials with other agents
- MEN1 resistance mutations are a significant cause of disease relapse in patients on single-agent menin inhibitors
- Combinations of menin inhibitors with SOC agents may abrogate the frequency of MEN1 resistance mutations
- Differentiation syndrome and QT prolongation are major side effects of menin inhibitors
- Many novel combinations with menin inhibitors coming to an academic medical center near you!

SOC = standard-of-care.

Lymphoma · Leukemia & Myeloma Congress

Thank You!



David H. Koch Center for Cancer Care, Memorial Sloan Kettering Cancer Center

Email: steine@mskcc.org
WhatsApp: +1 312 513 6830