



Multidisciplinary Approaches to Cancer Symposium

Role of Genomics & Pathology in Acute Myeloid Leukemia (AML)

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City of Hope

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Racial and ancestry-based disparities in AML genomics. Genomic reference databases (TCGA, BEAT-AML) overrepresent European-ancestry patients, limiting variant interpretation for Black, Hispanic, Asian, and Indigenous patients. I will also note differences in mutation frequencies and outcomes across groups, plus language and health-literacy barriers around consent for somatic and germline sequencing.*
- Black, Hispanic, older, rural, non-English-speaking, and under-insured patients experience disparities in AML care. Bias affects who gets comprehensive NGS at diagnosis, who is offered targeted therapy (FLT3, IDH1/2, menin inhibitors), who is referred for allogeneic transplant, and who is enrolled on trials. I will discuss how assumptions about frailty and "fitness for intensive therapy" can drive undertreatment, and offer mitigations (reflex molecular testing, standardized geriatric assessment, structured trial screening).*

Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Two patients. One diagnosis.

Dana, 38

Preschool teacher. Three weeks of bruising, WBC 62,000, 80% blasts. Fit, no comorbidities.

MOLECULAR REPORT

NPM1 mut	FLT3-ITD	DNMT3A
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Normal karyotype. Intermediate risk. Every decision ahead of her — the added drug, the transplant question, the follow-up schedule — comes off these three lines.

Walter, 71

Retired machinist. Two years of “anemia of aging,” now 30% marrow blasts. COPD, prior MI.

MOLECULAR REPORT

TP53 VAF 42%	SRSF2	ASXL1
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Complex karyotype. Adverse risk. The report tells you he is not an induction candidate, and it tells you roughly how much time you are working with.

What I want you to leave with

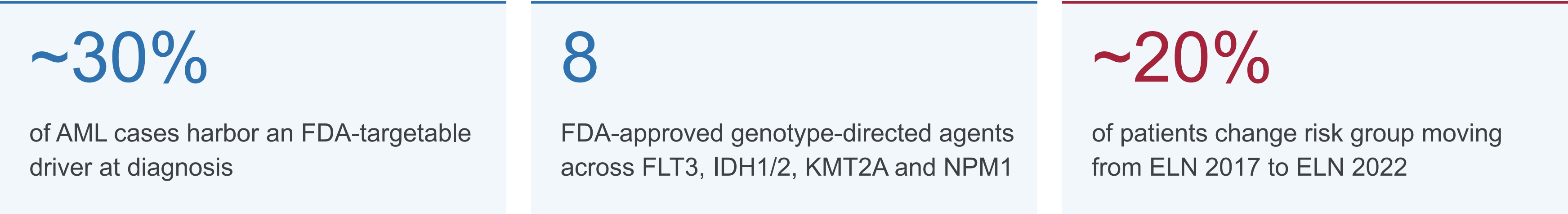
- 1 Genomic profiling at diagnosis**
What to send, when, and why it shapes every downstream decision
 - 2 ELN 2022 risk stratification**
What changed from ELN 2017, and where the framework breaks down
 - 3 The targeted therapy menu**
FLT3, IDH1/2, and the menin inhibitors for KMT2A-r and NPM1-mutant disease
 - 4 MRD as a clinical tool**
Methods, timing, and what to do with the answer
 - 5 Practical take-aways**
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What the report says

Why a mutation panel is not a research test.

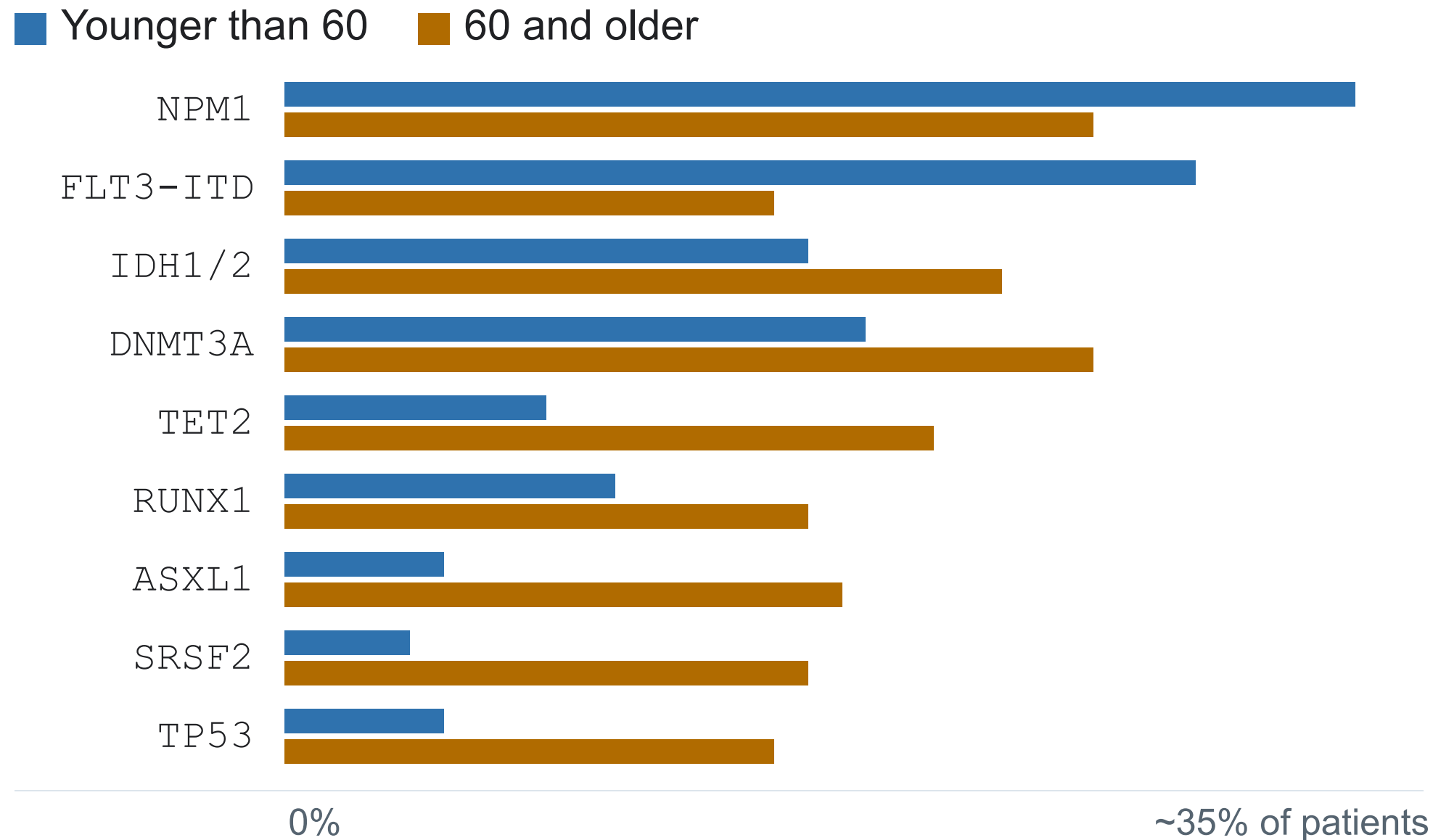
Why molecular profiling at diagnosis is essential



Diagnosis	WHO 2022 and ICC 2022 define many AML subtypes by molecular events — <i>NPM1</i> , <i>KMT2A</i> , <i>MECOM</i> , <i>CEBPA</i> bZIP, <i>TP53</i> , and the MDS-related mutations.
Treatment	Frontline regimen, transplant decision, and relapse therapy are all driven by the mutation profile.
Monitoring	MRD by RT-qPCR or NGS detects relapse earlier than morphology — and changes management.

Venugopal S, Sekeres MA. *JAMA Oncol.* 2024;10(10):1417. Döhner H et al. *Blood.* 2022;140(12):1345. Khoury JD et al. *Leukemia.* 2022;36:1703. Arber DA et al. *Blood.* 2022;140:1200.

Common AML mutations vary with age

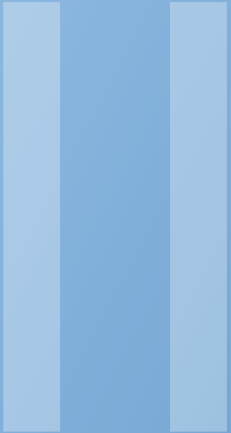


Clinical implications

Older AML is enriched for **DNMT3A**, **TET2**, **ASXL1**, **SRSF2**, **RUNX1** and **TP53** — the secondary-AML and MDS-related signature.

Younger AML more often carries **NPM1 + FLT3-ITD** , or a core-binding factor lesion: *KMT2A*-r, t(8;21), inv(16).

These differences drive different ELN risk groups, different fitness for intensive therapy, and a different targeted-therapy menu at diagnosis.



What the risk group means

ELN 2022 sorts patients better than ELN 2017.

What changed from ELN 2017

FLT3-ITD allelic ratio is gone

All FLT3-ITD AML is now intermediate risk, regardless of allelic ratio or *NPM1* status. Removes a number that labs reported inconsistently.

***CEBPA*: in-frame bZIP only**

Only in-frame bZIP mutations confer favorable risk. The mono- versus biallelic distinction is no longer used.

MDS-related mutations are adverse

ASXL1, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*. Seven of the nine — all but *ASXL1* and *RUNX1* — are new in 2022. Not adverse when they co-occur with a favorable subtype.

***TP53* defined at VAF $\geq 10\%$**

Allelic status is no longer required. A single *TP53* mutation at VAF $\geq 10\%$ is sufficient for adverse classification.

ELN 2022 risk groups — intensive-therapy candidates

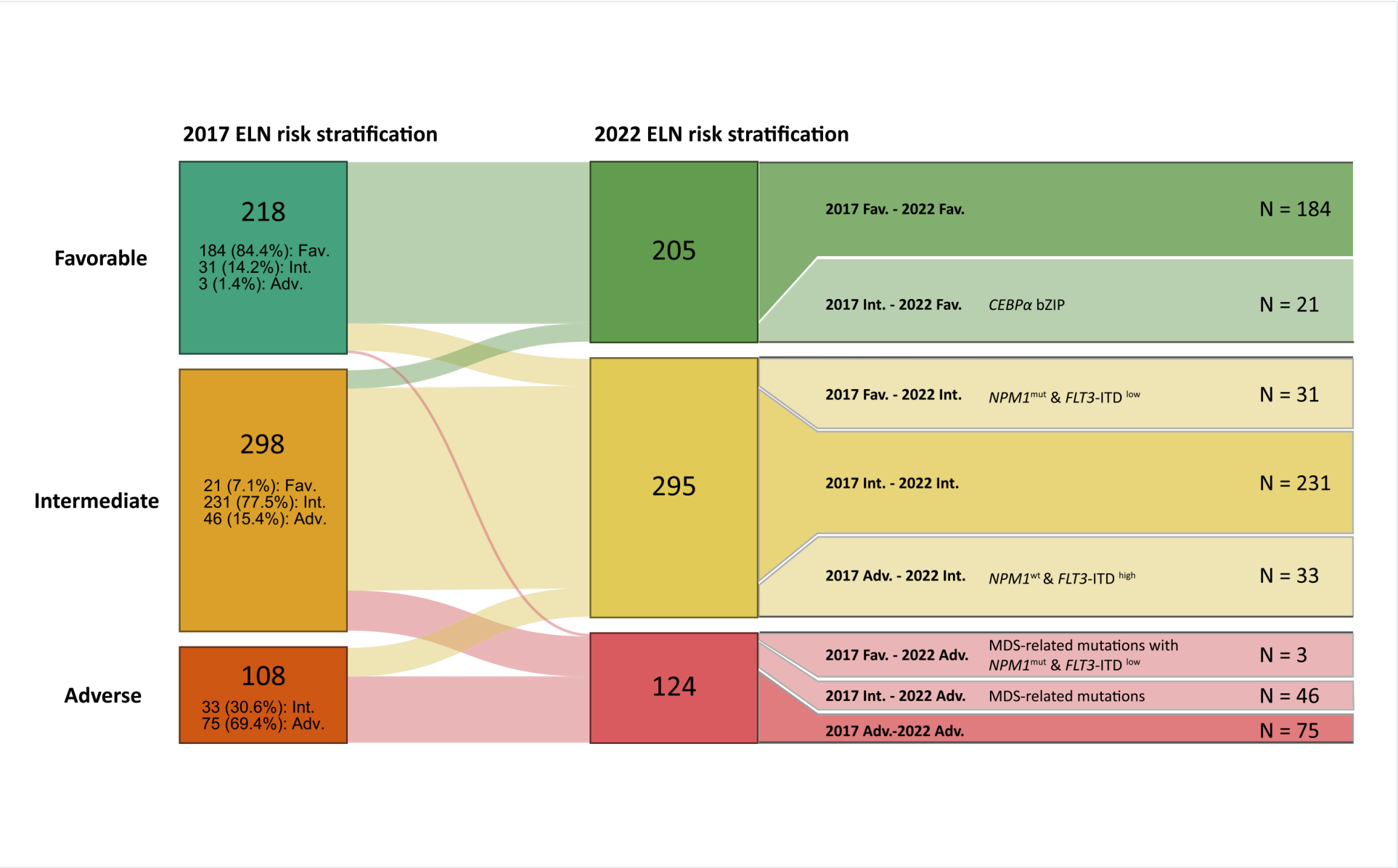
Favorable	Intermediate	Adverse
t(8;21) / <i>RUNX1::RUNX1T1</i> inv(16) or t(16;16) / <i>CBFB::MYH11</i> Mutated <i>NPM1</i> without FLT3-ITD <i>CEBPA</i> in-frame bZIP mutation	Mutated <i>NPM1</i> with FLT3-ITD Wild-type <i>NPM1</i> with FLT3-ITD, without an adverse lesion t(9;11) / <i>KMT2A::MLLT3</i> Cytogenetic or molecular abnormalities not classified as favorable or adverse	t(6;9), t(v;11q23.3) other than t(9;11), t(9;22), inv(3) / t(3;3), t(8;16) −5 / del(5q), −7, −17 / abn(17p) Complex (≥ 3 abnormalities), monosomal karyotype Mutated <i>ASXL1</i>, <i>BCOR</i>, <i>EZH2</i>, <i>RUNX1</i>, <i>SF3B1</i>, <i>SRSF2</i>, <i>STAG2</i>, <i>U2AF1</i>, <i>ZRSR2</i> * Mutated <i>TP53</i> at VAF ≥ 10%

Note: this framework was derived in patients receiving intensive induction. A separate ELN 2024 classification exists for less-intensive therapy — see the next two slides.

* MDS-related mutations are not adverse when co-occurring with a favorable subtype. Adapted from Döhner H et al. *Blood*. 2022;140(12):1345. ELN 2024 less-intensive classification: Döhner H et al. *Blood*. 2024;144:2169.

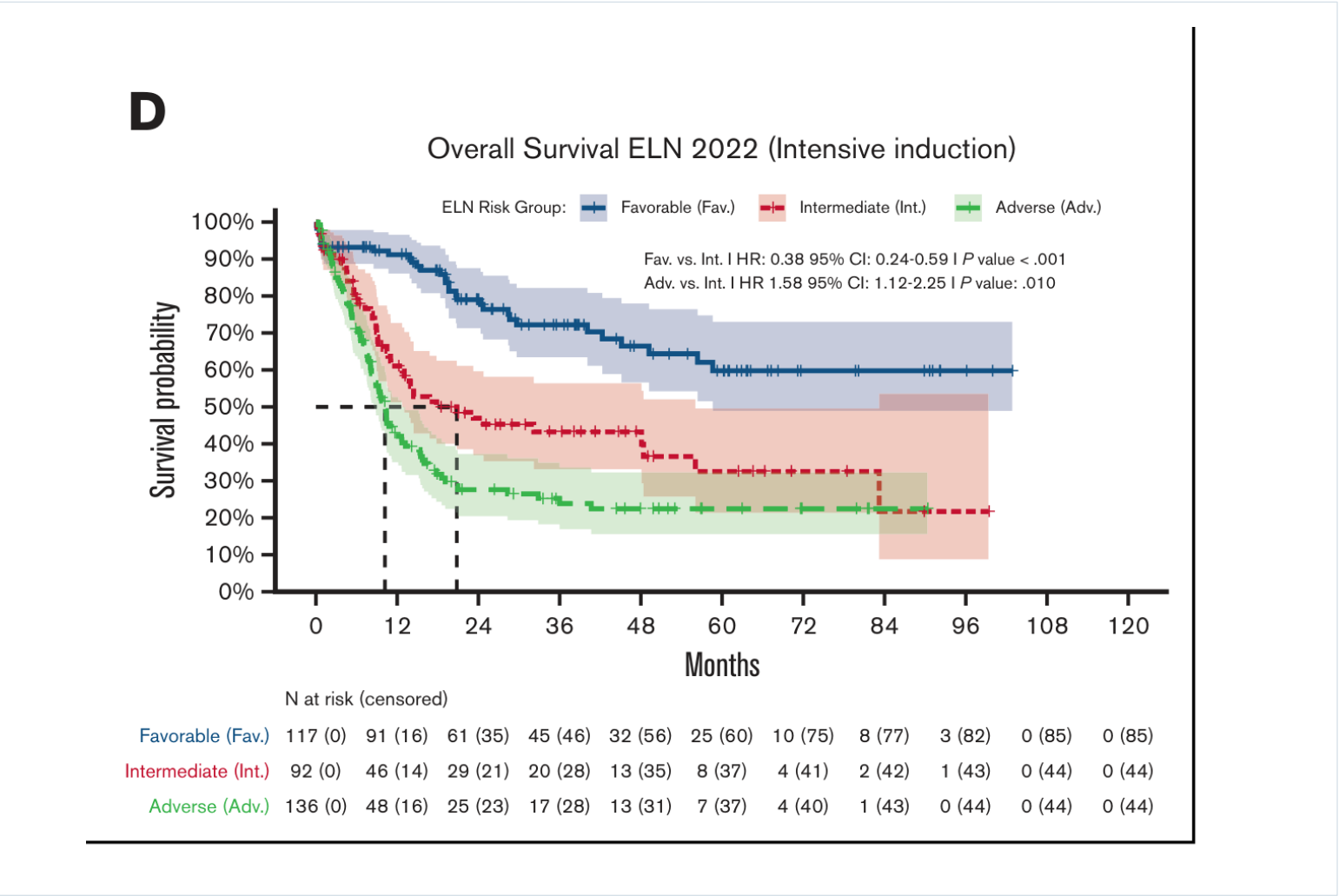
Validation: meaningful re-classification, sharper survival separation

Re-classification, ELN 2017 → ELN 2022 (n = 624)



21% changed risk group (134 of 624). Net movement is intermediate → adverse, driven by the MDS-related gene mutations and the updated *TP53* rule.

Overall survival by ELN 2022, intensive induction (n = 345)



ELN 2022 separates adverse from intermediate (HR 1.58, 95% CI 1.12–2.25, *P* = .010). ELN 2017 did not (HR 1.27, 95% CI 0.89–1.85, *P* = .20).

ELN 2022 under-performs with venetoclax + azacitidine

OS with venetoclax + azacitidine by ELN risk group (VIALE-A + M14-358, n = 279)

What actually predicts outcome

Higher benefit

52% of patients

TP53 wild-type, *RAS* wild-type, no *FLT3*-ITD — median OS **26.5 months**

Intermediate benefit

25%

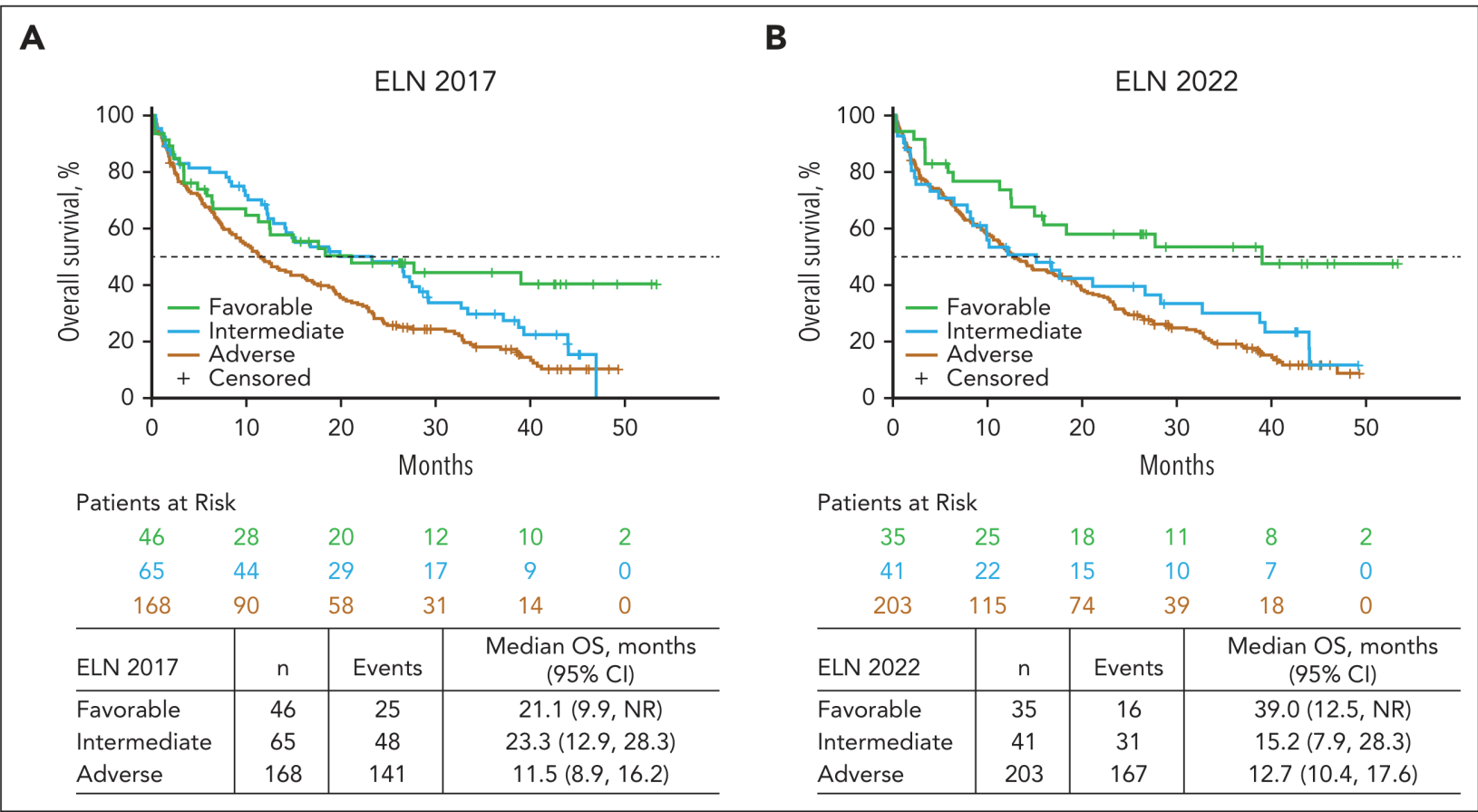
TP53 wild-type with *FLT3*-ITD and/or *KRAS/NRAS* mutation — median OS **12.1 months**

Lower benefit

23%

TP53 mutated — median OS **5.5 months**

Take-home: on an HMA + venetoclax track the ELN bucket is a starting point. *TP53*, *FLT3*-ITD and *RAS* carry the prognostic signal.



Döhner H, Pratz KW, DiNardo CD, et al. *Blood*. 2024;144(21):2211-2222, Figure 2. Companion ELN 2024 less-intensive classification: Döhner H et al. *Blood*. 2024;144(21):2169-2173.



What you can target

FDA-approved genotype-directed agents in AML

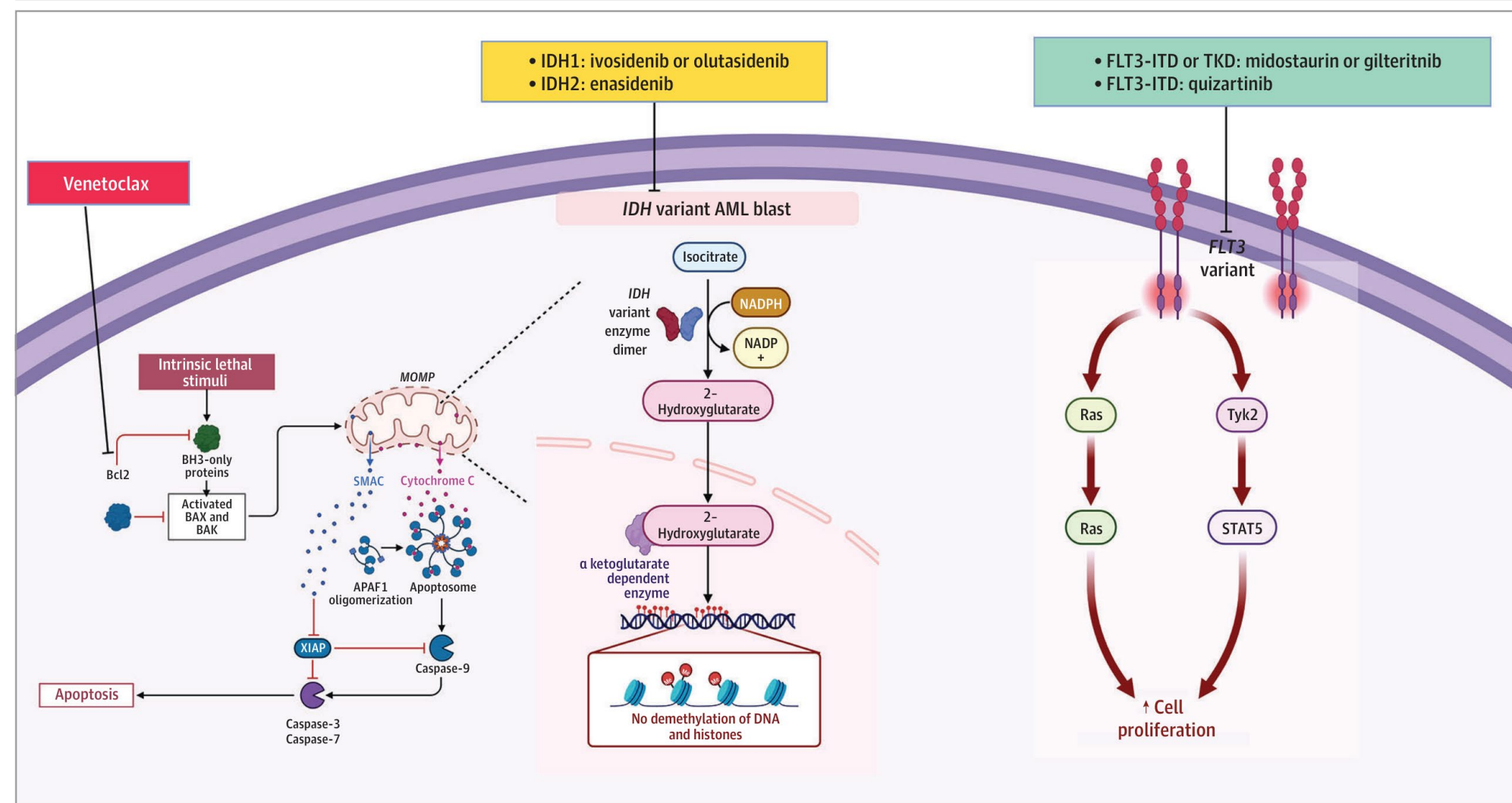
TARGET	AGENT	SETTING	PRACTICAL NOTE
FLT3-ITD / TKD	Midostaurin	Frontline with 7+3	Category 1; covers ITD or TKD
FLT3-ITD	Quizartinib	Frontline + maintenance	ITD only; QTc monitoring
FLT3-ITD / TKD	Gilteritinib	R/R; post-HCT maintenance	ITD or TKD; oral, once daily
IDH1	Ivosidenib	Frontline with aza; R/R	Category 1 with aza; differentiation syndrome
IDH1	Olutasidenib	R/R	Alternative if QTc concerns
IDH2	Enasidenib	R/R	100 mg daily; differentiation syndrome
KMT2A rearranged	Revumenib	R/R — FDA Nov 2024	Menin inhibitor; QTc monitoring
NPM1 mutated	Revumenib	R/R — expanded Oct 2025	Menin inhibitor; QTc monitoring
NPM1 mutated	Ziftomenib	R/R — FDA Nov 2025	Menin inhibitor; differentiation syndrome ~25%

Approval status as of August 2026. Selection should also account for co-mutations, prior therapy and drug interactions — especially azoles.

TOPIC 3 · TARGETED THERAPY

How the agents work

Figure 1. Mechanism of Action of Commonly Used Drugs in Acute Myeloid Leukemia (AML)



Mechanism in one line

FLT3 inhibitors

Block constitutively active FLT3 receptor signaling

IDH inhibitors

Shut down 2-hydroxyglutarate production, restoring differentiation

Venetoclax

Displaces pro-apoptotic proteins from BCL-2, lowering the apoptotic threshold

Menin inhibitors

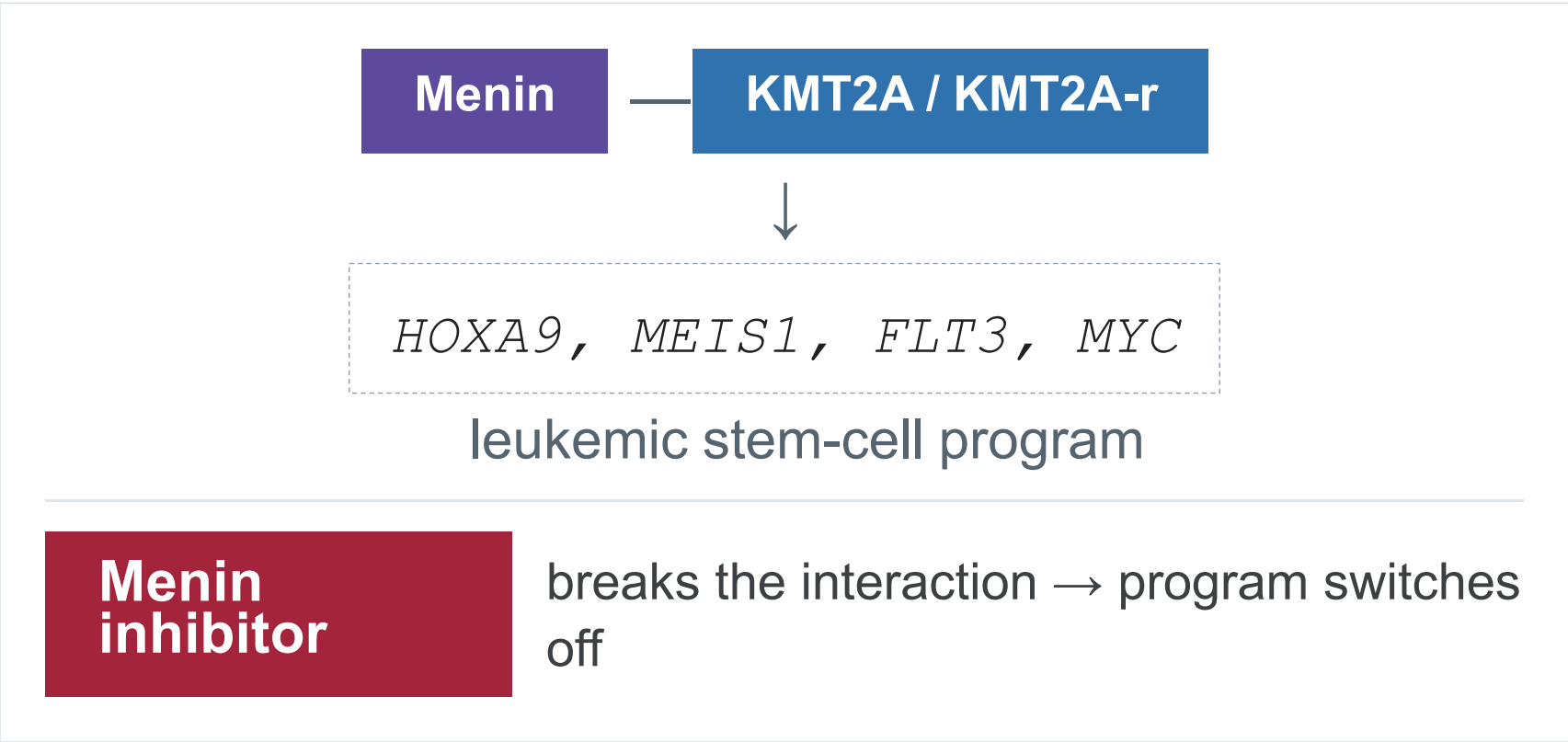
Disrupt menin–KMT2A binding, turning off the HOXA9 / MEIS1 program

Hypomethylating agents

Hypomethylate and sensitize to apoptosis — synergistic with venetoclax

Why menin matters in *NPM1*-mutant and *KMT2A*-rearranged AML

Menin–KMT2A drives leukemic transcription



~10%

of AML is *KMT2A*-rearranged

~30%

of AML is *NPM1*-mutant

Why this matters clinically

Up to **40% of AML is potentially menin-actionable** — the first drug class with activity in chemotherapy-refractory *NPM1* - mutant and *KMT2A*-rearranged disease.

Class effects to know

- **Differentiation syndrome** — similar to APL and the IDH inhibitors; steroids and dose interruption
- **QTc prolongation** — reported with both agents; monitor ECGs
- **CYP3A4 interactions** — especially with azole antifungals

Resistance

On-target *MEN1* mutations emerge at progression with menin inhibitors. Reported rates differ between trials, but assays and denominators are not comparable — treat cross-trial comparisons with caution.

Revumenib (AUGMENT-101): *KMT2A*-r and *NPM1*-mutant AML

R/R *KMT2A*-rearranged acute leukemia n = 57

22.8%

CR + CRh

63.2%

overall response

6.4_{mo}

median DOR

MRD-negative in 68% of composite CR. FDA approved 15 Nov 2024 for adults and children ≥ 1 year.

R/R *NPM1*-mutant AML n = 64

23.4%

CR + CRh

46.9%

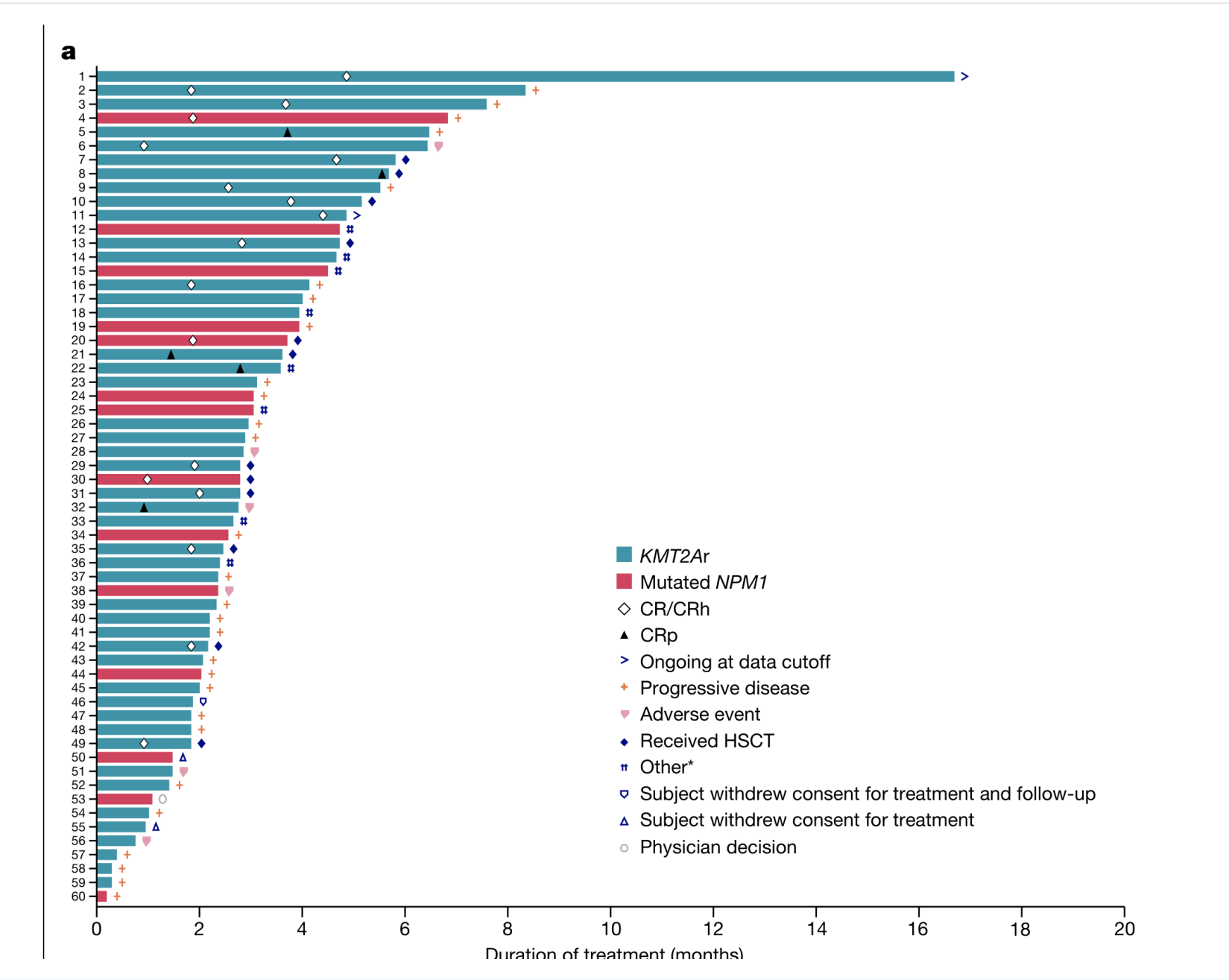
overall response

4.7_{mo}

median DOR

Heavily pre-treated, largely venetoclax-exposed population. FDA approved 24 Oct 2025.

Duration of treatment and response, phase 1 (n = 60)



Phase 1: Issa GC et al. *Nature*. 2023;615:920-924, Figure 2a. Pivotal *KMT2A*-r cohort: Issa GC et al. *J Clin Oncol*. 2025;43(1):75-84. *NPM1* -mutant cohort: Arellano ML et al. *Blood*. 2025;146(9):1065-1077.

Ziftomenib (KOMET-001): R/R *NPM1*-mutant AML

22%

CR / CRh rate

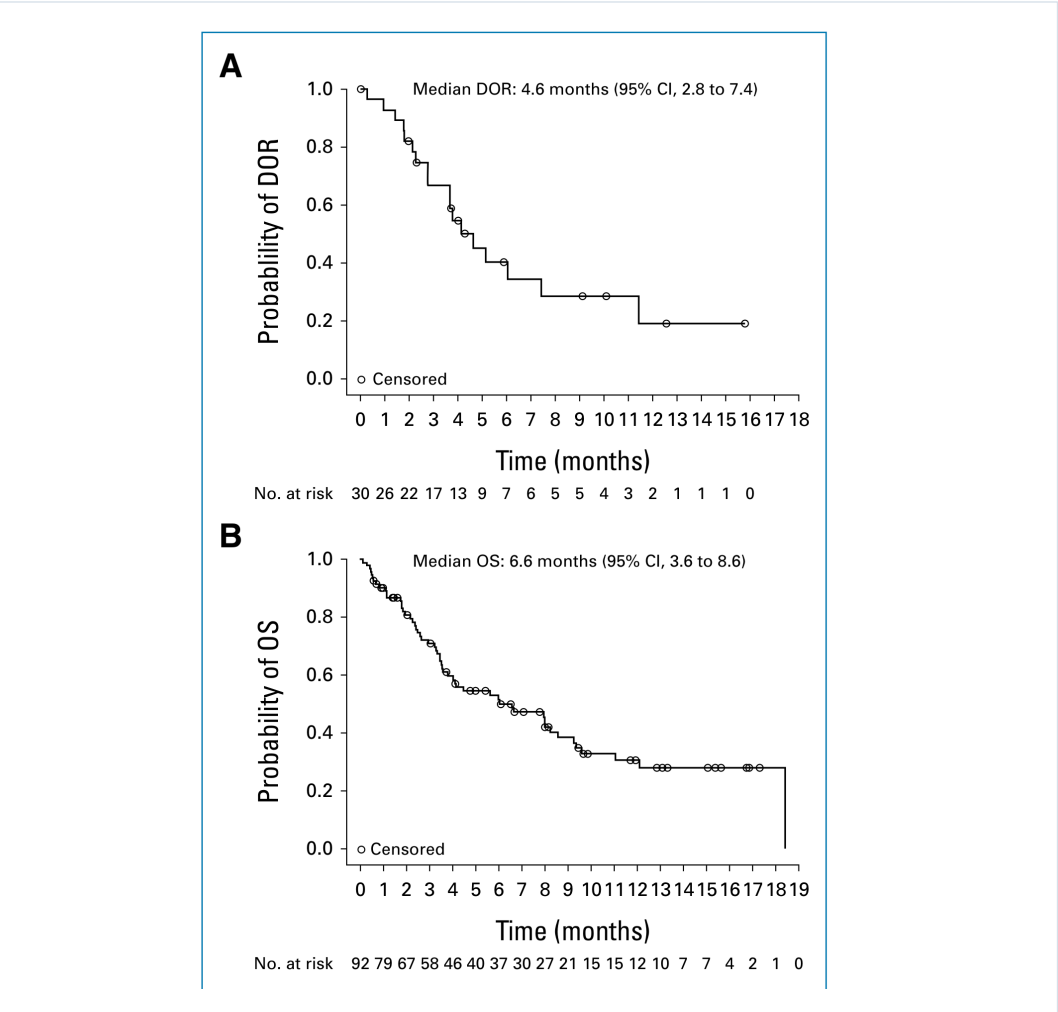
61%

MRD-negative among responders

6.6_{mo}

median overall survival

Duration of response and OS



How does it compare to revumenib?

Comparable CR/CRh rate in R/R *NPM1* -mutant AML — **22% vs 23%** — but from separate single-arm trials. There is no head-to-head comparison.

Cross-trial claims about differing rates of on-target *MEN1* resistance mutations are **not supported** by published comparative data.

Approved 13 Nov 2025 as KOMZIFTI for adults with R/R *NPM1*-mutant AML.

Key toxicities to watch

Differentiation syndrome

25% all grades, 15% grade ≥ 3. Steroids and dose interruption, as for IDH inhibitors.

QTc prolongation

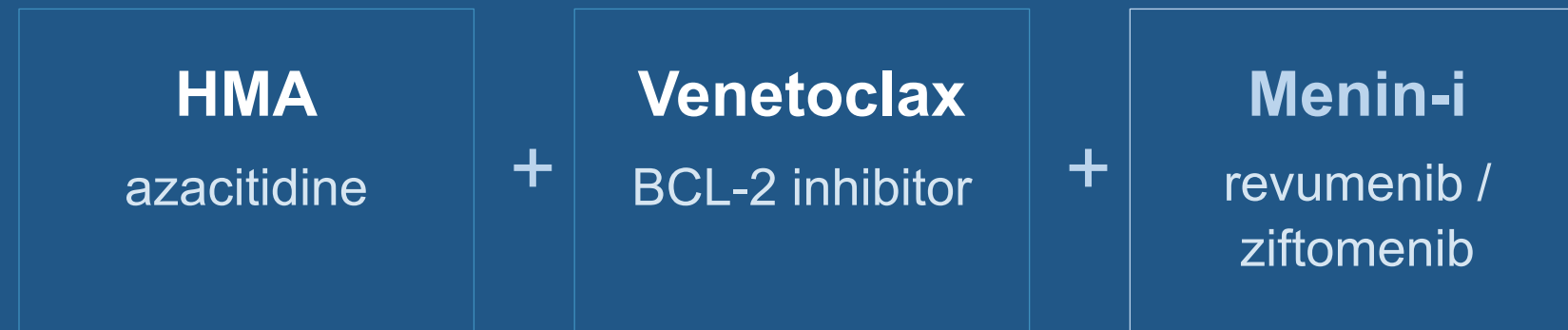
12% all grades, 8% grade 3–4 per label. Monitor ECGs — do not assume this class is QT-neutral.

Cytopenias and CYP3A4

Expect transfusion support; adjust dosing with azole antifungals.

Wang ES, Montesinos P, Foran J, et al. Ziftomenib in relapsed or refractory *NPM1*-mutated AML (KOMET-001). *J Clin Oncol*. 2025;43(31):3381-3390. Safety rates from KOMET-001 and the US prescribing information.

What's coming: triplet combinations



88%

overall response rate — frontline azacitidine + venetoclax + revumenib, phase 1 (n = 43)

85% in *NPM1*-mutant and 100% in *KMT2A* -rearranged disease. Composite CR 81%. All 37 MRD-evaluable responders were MRD-negative, and 84% responded within cycle 1.

Why triplets, why now

Each agent hits a non-overlapping pathway in *NPM1*-mutant or *KMT2A* -rearranged AML: the HMA primes apoptosis, venetoclax executes it, and the menin inhibitor shuts off the leukemic transcription program.

Open questions

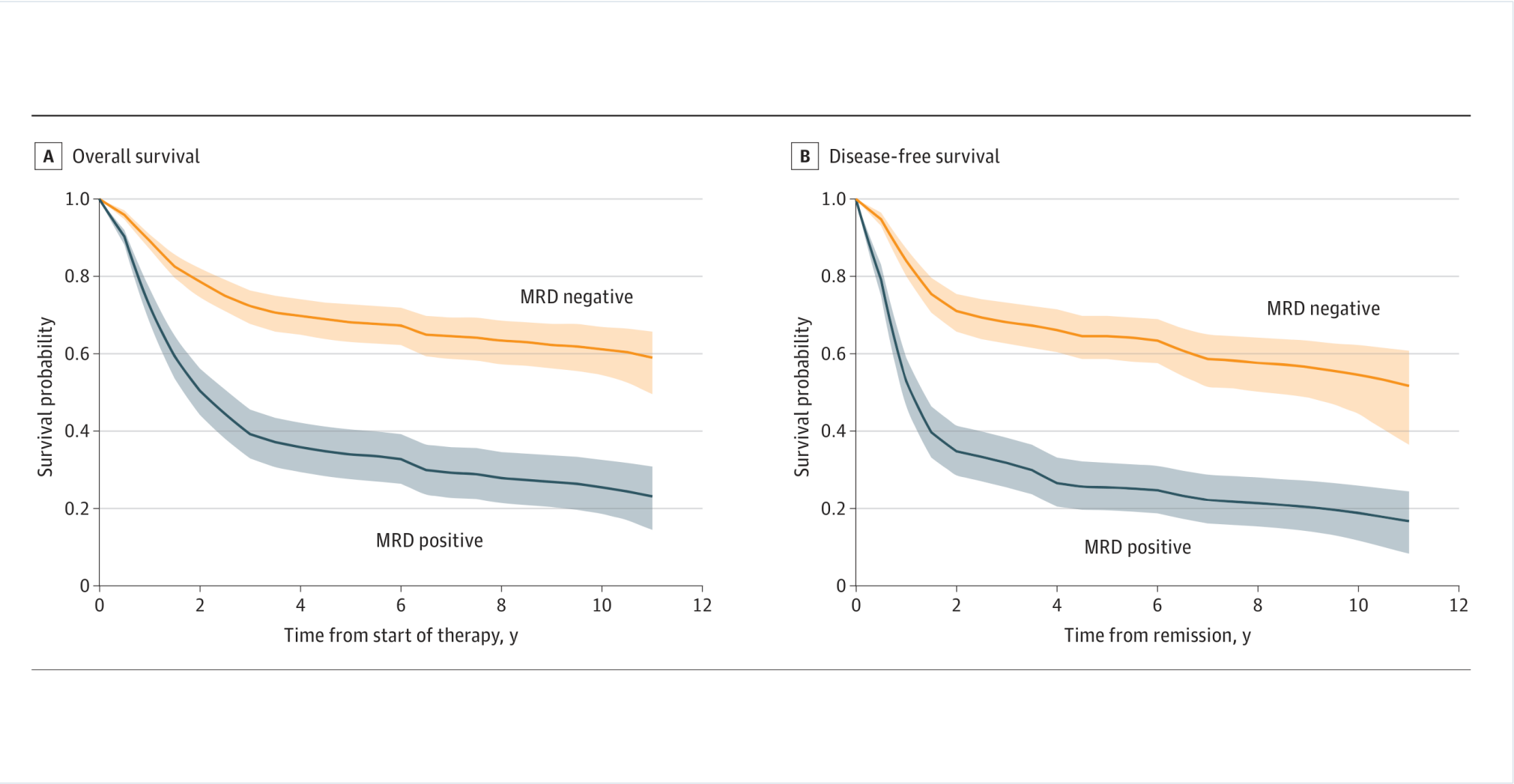
- Cytopenias stack, so duration and dosing are unsettled
- Sequencing versus up-front combination is untested
- No randomized data yet, and no overall survival benefit demonstrated
- Ziftomenib triplets (KOMET-007) are so far reported in abstract form only

IV

How you know it worked

MRD negativity is the strongest post-induction prognostic marker

Overall survival (A) and disease-free survival (B) by MRD status in CR



Bayesian hierarchical meta-analysis of 81 studies and more than 11,000 patients. The separation appears within the first two years and does not converge with longer follow-up.

5-year overall survival

68% MRD-negative vs 34% MRD-positive

5-year disease-free survival

64% vs 25%

Hazard ratios

OS 0.36 (95% CrI 0.33–0.39); DFS 0.37 (0.34–0.40)

Consistent across

age, AML subtype, timepoint and MRD method — except cytogenetics / FISH, which was not prognostic.

Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with AML: a systematic review and meta-analysis. *JAMA Oncol.* 2020;6(12):1890-1899, Figure 2.

Practical MRD: what to send, and when

Don't track DTA mutations

DNMT3A, *TET2* and *ASXL1* reflect age-related clonal hematopoiesis, not residual leukemia. Excluding them is what makes molecular MRD prognostic.

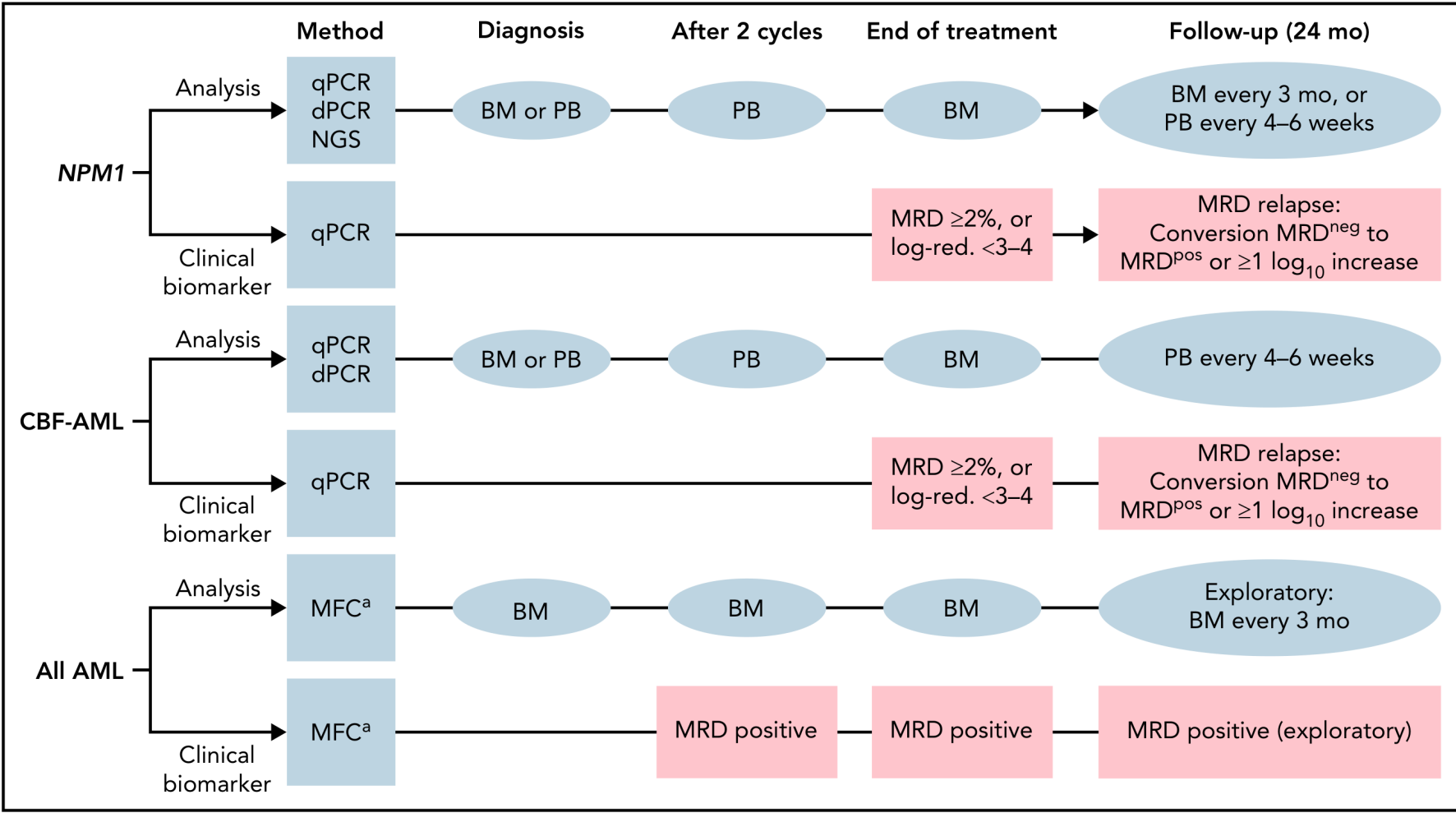
Timing in *NPM1* and CBF AML

Marrow at remission and end of treatment, then blood every 4–6 weeks (or marrow every 3 months) for 2 years. A rising transcript is a relapse warning.

MRD positive: what to do

Move toward allogeneic transplant, a clinical trial, or targeted therapy. Post-transplant FLT3-ITD MRD at 10^{-6} identified the patients who benefited from gilteritinib maintenance in MORPHO.

ELN algorithm: MRD method, sample and timing



Döhner H et al. *Blood*. 2022;140(12):1345, Figure 2. Current MRD consensus: Cloos J et al. *Blood*. 2026;147(11):1147-1167. Levis MJ et al. *J Clin Oncol*. 2024;42(15):1766-1775 (MORPHO / BMT CTN 1506).

What the report actually did for Dana and Walter

Dana, 38 NPM1 / FLT3-ITD

Diagnosis	Intermediate risk. 7+3 with midostaurin — because of the FLT3 line on the report.
End of consolidation	CR, <i>NPM1</i> transcript undetectable. Blood MRD every 6 weeks.
Month 14	Transcript returns. Normal counts, unremarkable marrow. Molecular relapse.
Outcome	To transplant in second molecular remission — months before she would have relapsed on morphology.

Walter, 71 TP53 / SRSF2

Diagnosis	Adverse risk, and in the lower-benefit venetoclax group — median OS 5.5 months.
Treatment	Azacitidine + venetoclax. No induction, no transplant workup.
Cycle 1	Palliative care involved early — not at the last admission. Goals set while he could set them.
Outcome	Seven months, most of them at home.

Risk groups per Döhner H et al. *Blood*. 2022;140(12):1345. Venetoclax benefit groups per Döhner H et al. *Blood*. 2024;144(21):2211.

Take-aways

01 **Order comprehensive NGS at diagnosis on every patient**

Bone marrow and peripheral blood.

02 **Re-test at relapse**

Mutations shift. New FLT3, IDH, *KMT2A* or *NPM1* lesions can open targeted-therapy options that weren't there at diagnosis.

03 **Use ELN 2022 as a starting point**

In the older patient on HMA + venetoclax, *TP53*, FLT3-ITD and *RAS* carry more prognostic weight than the ELN bucket. A separate ELN 2024 classification exists for less-intensive therapy.

04 **MRD-negative CR is the goal**

Track *NPM1* and CBF transcripts by qPCR and FLT3-ITD by NGS. Use rising MRD to trigger transplant or maintenance discussions before morphologic relapse.

05 **Refer early for transplant and trials**

Adverse-risk disease, MRD-positive CR1, relapsed/refractory disease, and *KMT2A*-r or *NPM1* -mutant patients should reach a transplant or trial center early — not at first relapse.

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Thank You

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