



Precision in Myeloid Malignancies

Are We There Yet?

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What Precision Medicine Promised

Molecular subclassification → tailored therapy → improved outcomes.

WHO 2022 / ICC 2022: myeloid neoplasms redefined by genotype, not morphology alone.

ELN 2022/2024 risk stratification: mutation-driven treatment allocation now standard of care.

NGS and MRD moved from prognostic curiosities to actionable, real-time clinical inputs.

Today's question:

has this genomic revolution changed what we DO at the bedside — or mostly how we CLASSIFY and PREDICT?

The Genomic Foundation

- Four frameworks now define how we classify, risk-stratify, and monitor myeloid neoplasms.
- Each one has genuinely changed a real clinical decision, not just a label.

WHO 2022 / ICC 2022

Genotype defines the entity now

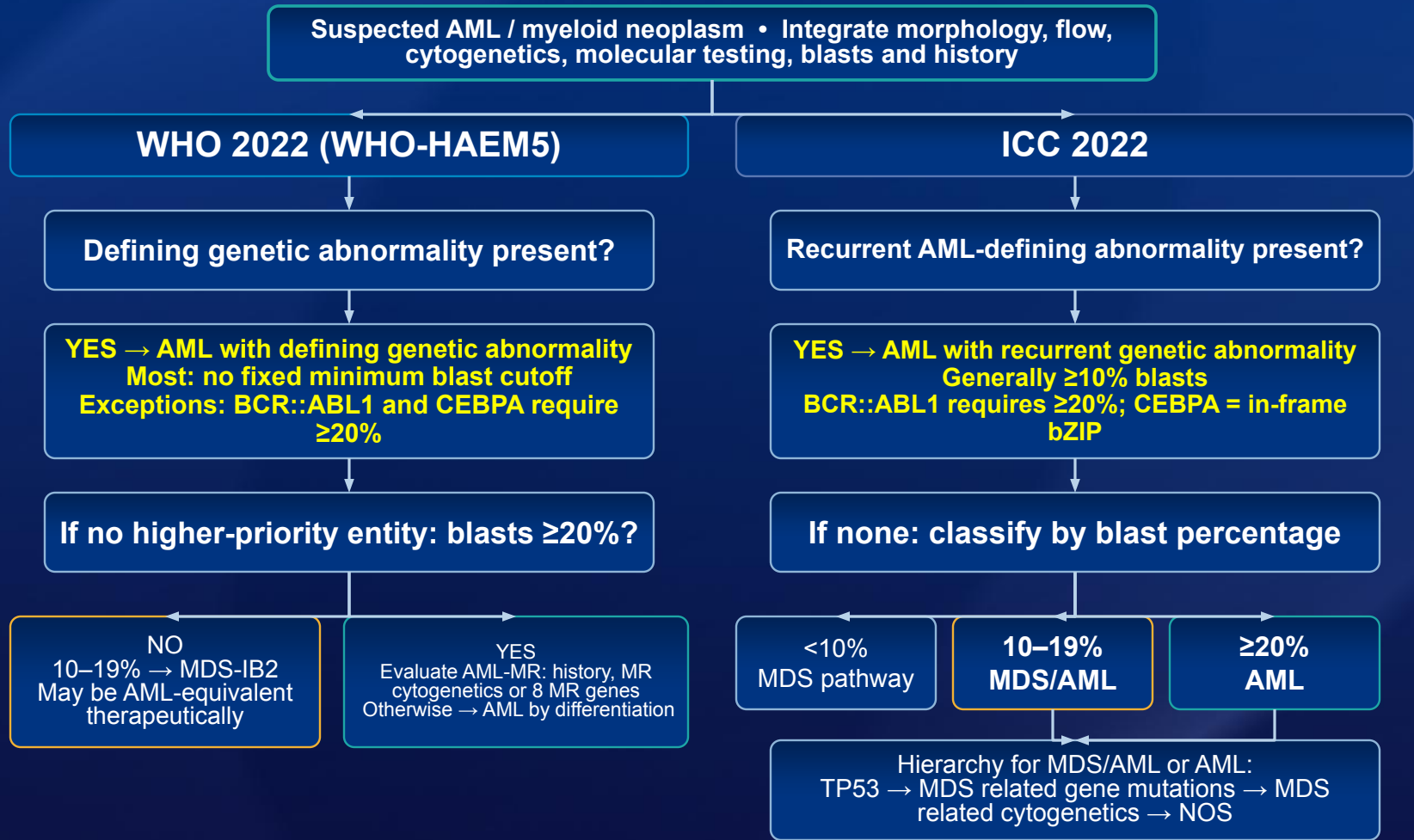
ELN 2022/24 + IPSS-M

Mutation-driven risk allocation

NGS + MRD

Now drive real treatment decisions

WHO 2022 and ICC 2022 classification of AML

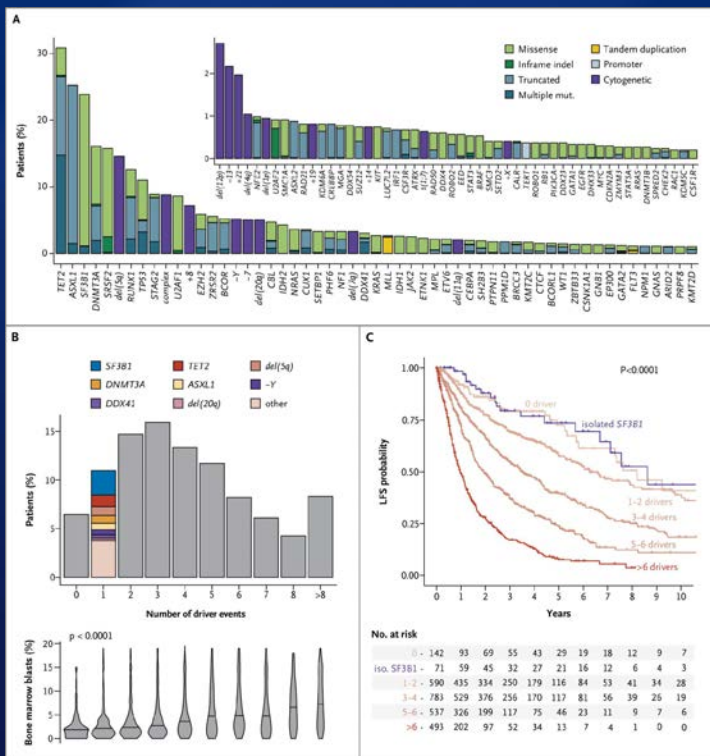


High-yield differences

Feature	WHO 2022	ICC 2022
Genetic AML threshold	<u>No fixed minimum for most defining genetic entities;</u> increased blasts and clinicopathologic correlation required	<u>≥10% for recurrent genetic entities;</u> BCR::ABL1 remains ≥20%
NPM1	<u>No fixed minimum blast cutoff</u>	<u>≥10% blasts</u>
CEBPA	Biallelic or single bZIP mutation; ≥20% blasts	In-frame bZIP mutation; ≥10% blasts
TP53	No separate AML entity	Distinct AML entity at ≥20% blasts and VAF >10%; MDS/AML at 10–19%
MR definition	8 MR genes; prior MDS/MDS-MPN can define AML-MR	9 MR genes (adds RUNX1); prior disease is a qualifier
10–19% blasts	MDS-IB2 if no defining AML genotype	MDS/AML if no recurrent AML-defining genotype
Secondary disease	Post-cytotoxic therapy and germline predisposition are disease families/attributes	Appended diagnostic qualifiers

IPSS-M, ELN 2022 and ELN 2024

Mutation-driven risk allocation

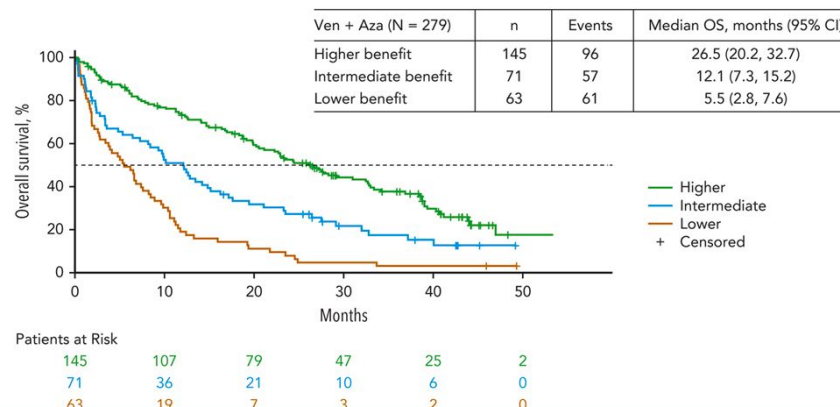


Bernard et al. NEJM Evidence. 2022;1(7)

Risk category	Defining genetic abnormalities
FAVORABLE	- RUNX1::RUNX1T1; CBFβ::MYH11 - NPM1-mutated without FLT3-ITD - CEBPA bZIP in-frame mutation
INTERMEDIATE	- NPM1-mutated with FLT3-ITD - NPM1 wild-type with FLT3-ITD, without adverse-risk lesions - MLLT3::KMT2A - Other abnormalities not classified as favorable or adverse
ADVERSE	- DEK::NUP214; KMT2A rearrangements; BCR::ABL1; KAT6A::CREBBP; MECOM rearrangements -5/del(5q), -7, -17/abn(17p); complex or monosomal karyotype - Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 and/or TP53

Döhner H, et al. Blood. 2022;140:1345–1377

Four-gene prognostic risk classifier:



Döhner H, et al. Blood. 2024;144:2211–2222

AML Survival Gains: The Big Picture

OS in patients <65 improved from 8 mo (1975–1979) to 46 mo (2010–2014)' largely before most targeted agents existed.

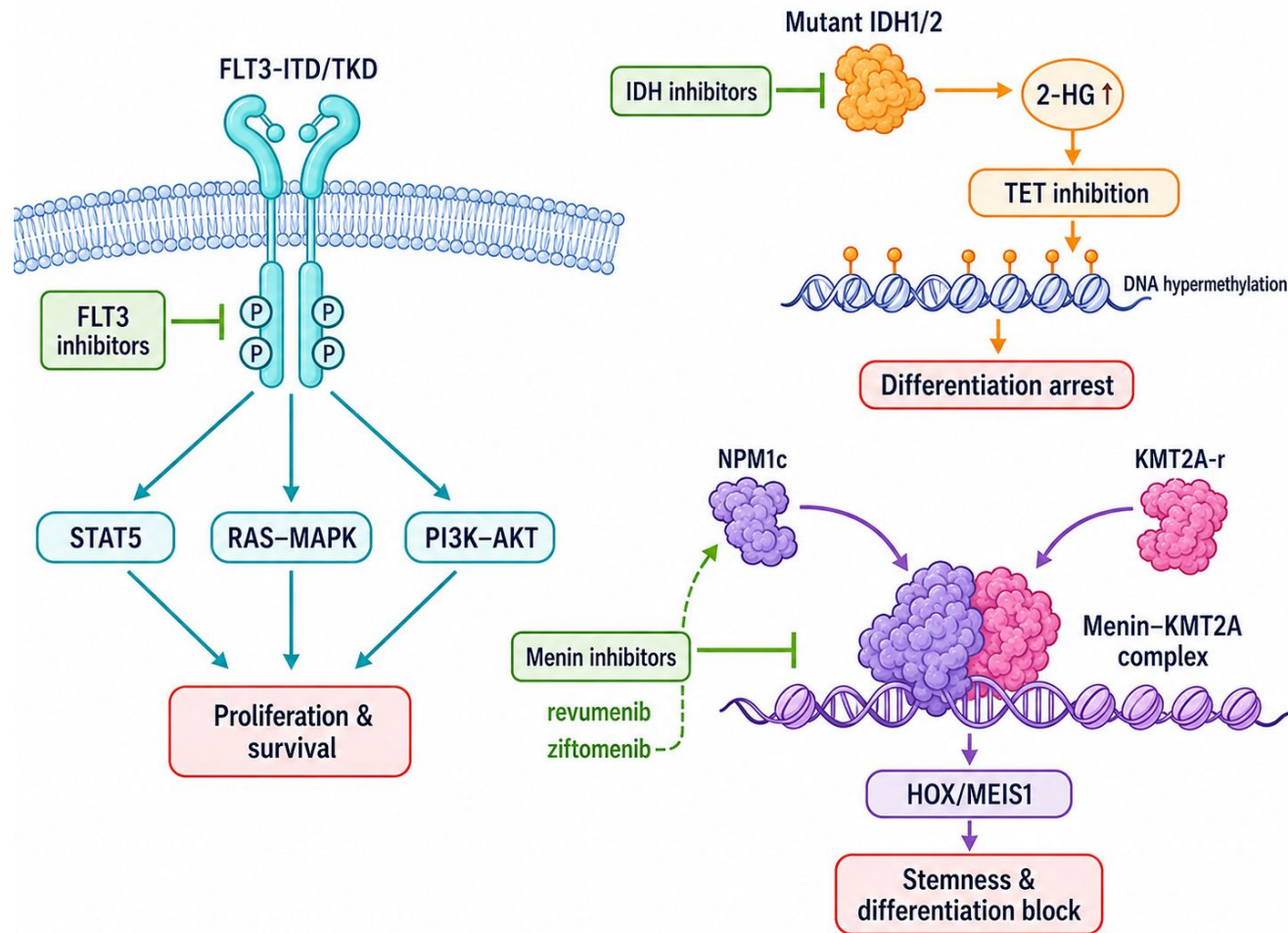
Since 2017, 14 targeted/novel agents have been FDA-approved for AML, more than the prior four decades.

Favorable AML; APL, CBF AML, 5-yr OS of 75–90%+

But older/unfit, secondary, complex-karyotype, or TP53-mutated AML still has 5-year OS below 20%

**The gains are real — and uneven.
The next few slides walk through where targeted therapy has
delivered — mutation by mutation.**

Targetable pathways in AML



**TP53 / IMMUNE
ESCAPE**

**APR-246
(eprenetapopt)**

**Mutant-p53
reactivation
→ apoptosis**

**MAGROLIMAB
anti-CD47**

**Blocks 'don't-eat-me'
signal →
macrophage
phagocytosis**

**INVESTIGATIONAL
No approved
TP53-directed therapy**

APL — The Original Success Story

PML-RAR α fusion defines the disease and IS the drug target; the template precision medicine has chased ever since.

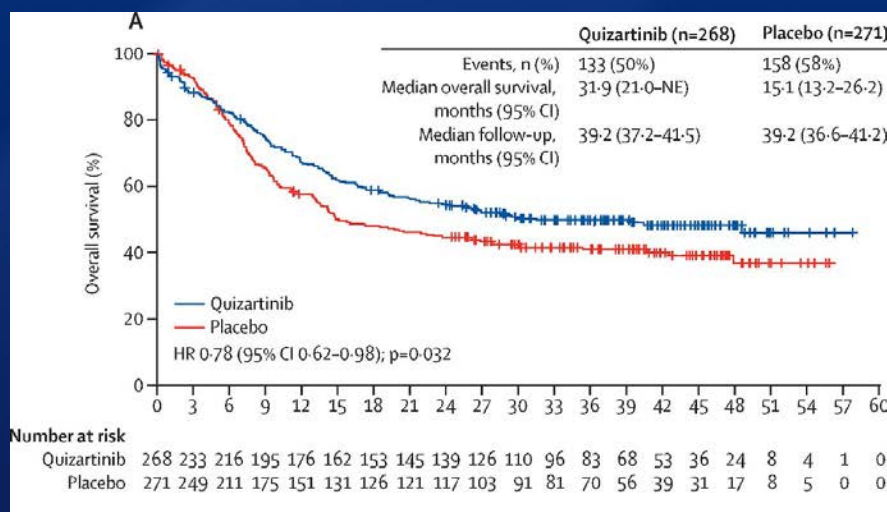
ATRA + ATO: chemo-free induction, cure rates now > 90% in low/int-risk disease.

Rarer RAR α fusion partners (ZBTB16, STAT5B, NUMA1) retain ATRA/ATO resistance; a reminder molecular precision still has exceptions.

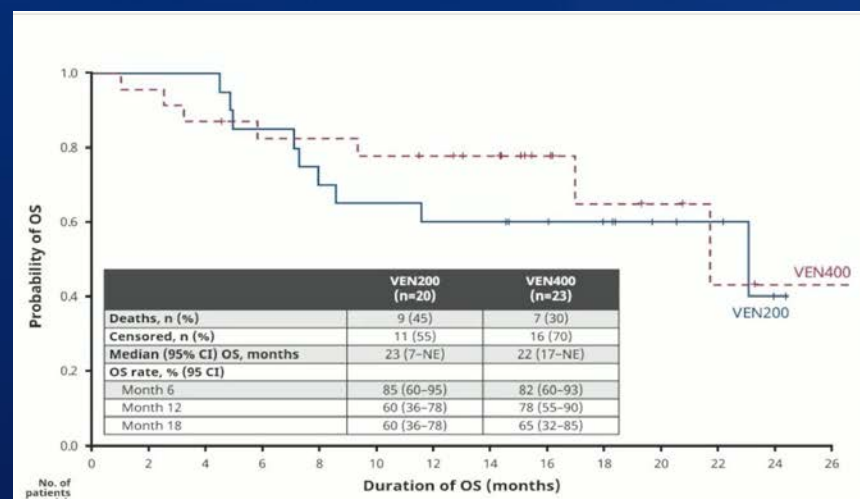
APL proves the model works

when target, drug, and biomarker align perfectly. The rest of AML has been trying to replicate this for 20 years.

FLT3-Mutated AML



QuANTUM-First trial



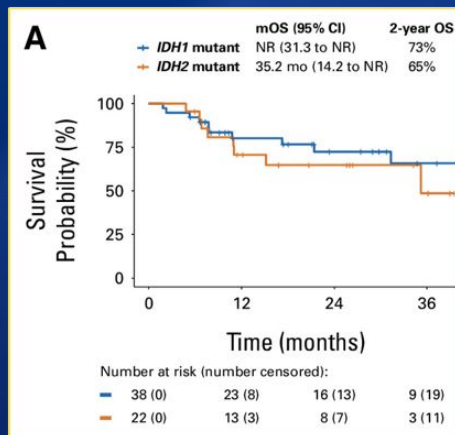
Viceroy trial; AZA+VEN+Gilt

Challenges: (a) tolerability in older adults with triplet combinations — myelosuppression, infections; (b) resistance mutations

Key takeaway: better sequencing of treatment based on tolerability, guided by day 21 bone marrow biopsy

IDH-Mutated AML

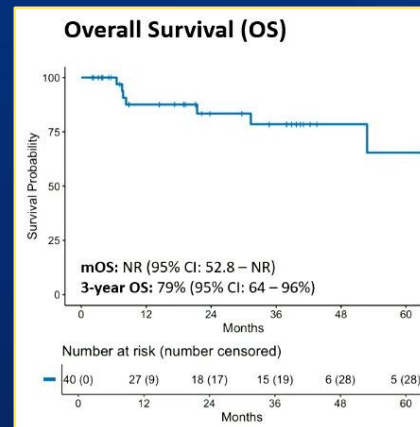
Inqovi + VEN + IDH1/2 i



92% cCR — 2-yr OS 73%/65%; 2-yr OS by IDH1/IDH2 mutant

DiNardo et al. JCO 2025;43(24):2692-2699

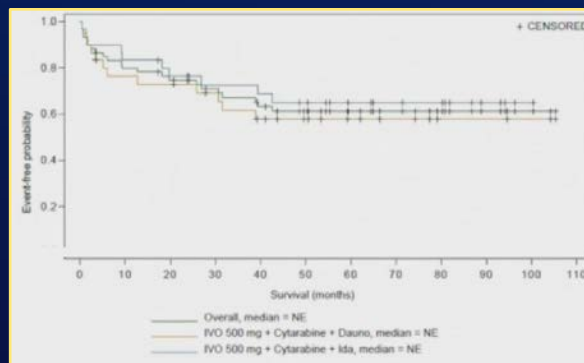
IVO + VEN + AZA TRIPLET



>90% cCR — 3-yr OS 79%
Frontline triplet, IDH1-mutated AML

Marvin-Peek et al. EHA 2026

3+7 + IVOSIDENIB



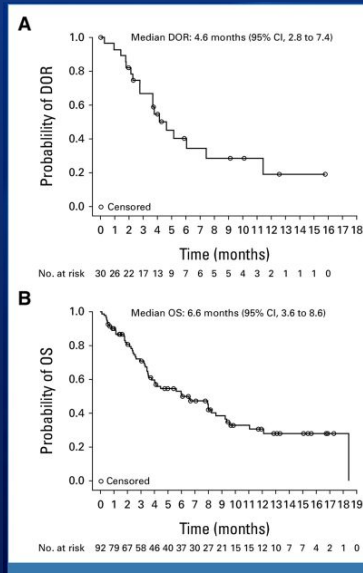
>75% cCR — 3-yr OS 67%
3+7 induction + ivosidenib, older/unfit IDH1-mutated AML

Stein et al. ASH 2025

IDH inhibitors show precision medicine can work even in older, unfit patients — not just as a relapsed/refractory rescue strategy.
Randomized studies are needed to establish true benefit.

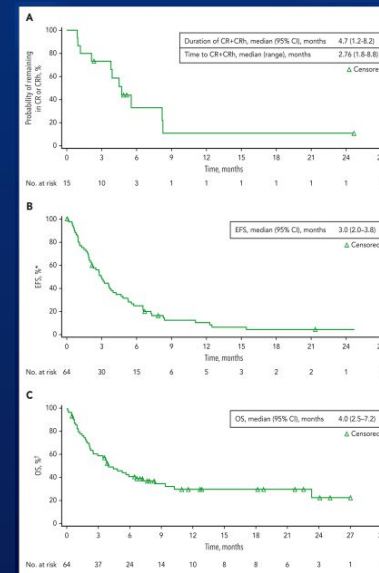
Menin inhibitors: a new AML target

Ziftomenib • NPM1-mutated AML



CR/CRh 22% | MRD- 61% | mDOR 4.6 mo

Revumenib • NPM1m / KMT2A-r



CR/CRh 23.4% | mDOR 4.7 mo | mOS 4.0 mo

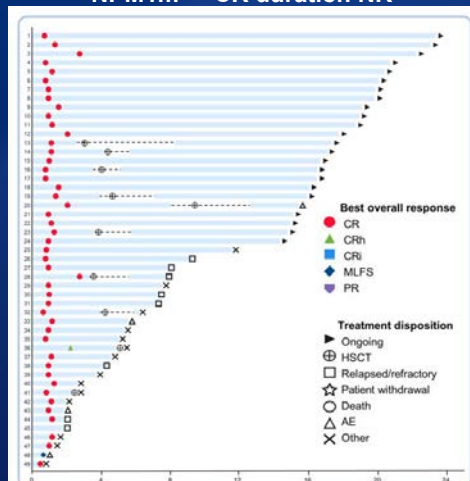
THE NEWEST GENOTYPE-DIRECTED AML CLASS

Menin inhibition targets the HOX/MEIS1 dependency—activity is meaningful, but durability remains the next challenge.

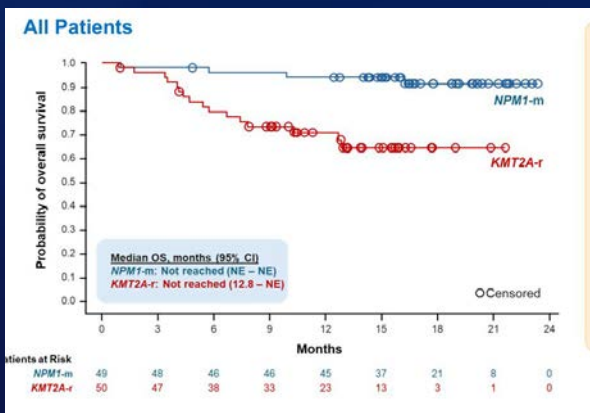
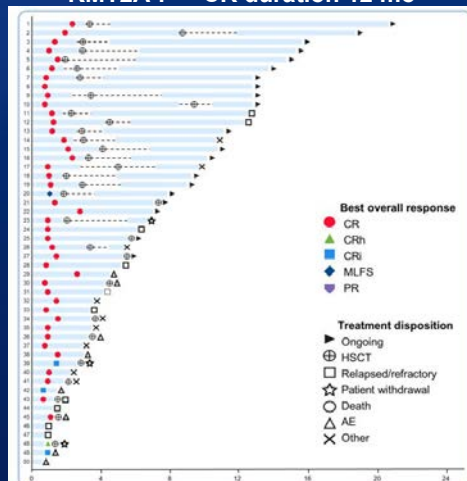
Moving menin inhibition upfront

ZIFTOMENIB + 7+3

NPM1m • CR duration NR

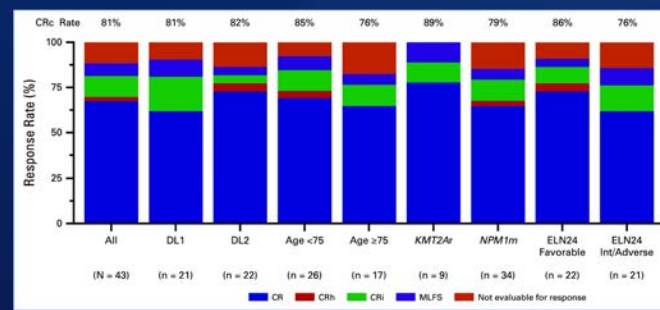
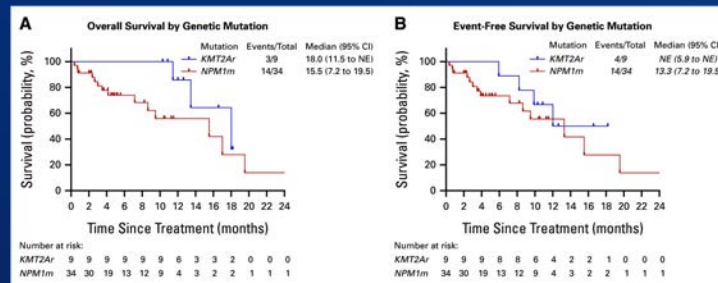


KMT2A-r • CR duration 12 mo



12-mo OS: 94% NPM1m | 71% KMT2A-r

AZA + VEN + REVUMENIB

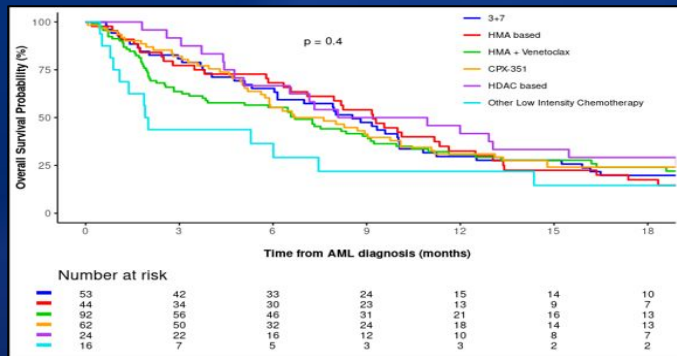


CRc 81% overall
89% KMT2A-r | 79% NPM1m

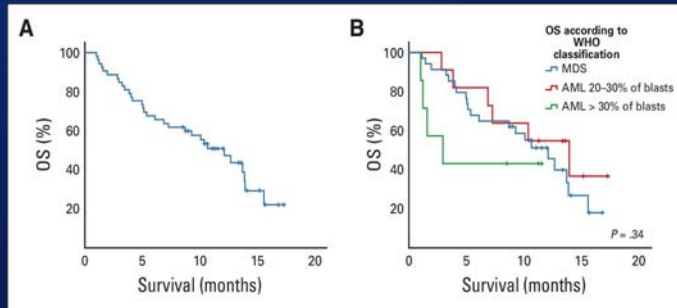
Median OS: 18.0 mo KMT2A-r
15.5 mo NPM1m

Early frontline efficacy is encouraging; follow-up remains immature.

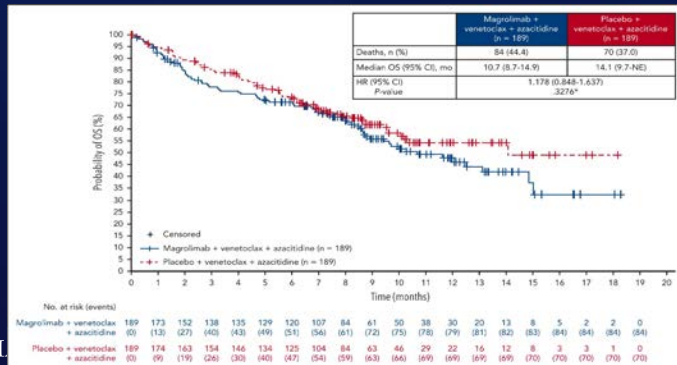
TP53: Precision in Prognosis, Not Yet Therapy



TP53-m AML/MDS is precisely classified but remains therapeutically unresolved, with mOS of 6–9 mo across treatment groups.



Eprenetapopt (APR-246) + AZA: promising phase II, did not confirm benefit in phase III.



Magrolimab and other immune-checkpoint strategies: largely negative or inconclusive to date

OPTI-AML: The First Randomized Test of Ven Duration

175 randomized → 169 started treatment · Age ≥60, unfit for intensive chemo · stratified by age <75 vs ≥75

AV28 — 28-Day Venetoclax

Ven days 1–28 + Aza 75 mg/m² × 7 days

n = 83 patients

AV14 — 14-Day Venetoclax

Ven days 1–14 + Aza 75 mg/m² × 7 days

n = 86 patients

PRIMARY ENDPOINT: CR RATE ACROSS 2 CYCLES

49.4%

AV28 · CR (41/83)

43.0%

AV14 · CR (37/86)

Δ 6.4% [90% CI: –6.1% to 19.0%] — upper bound exceeds 10% margin: non-inferiority NOT met

The first prospective randomized answer
to a question the field had only been guessing at from retrospective data.

OPTI-AML: Full-Duration Benefit Is Concentrated in *NPM1/IDH2*

NPM1 / IDH2-Mutated AML

~23% of cohort

60.9%

AV28 CR

33.3%

AV14 CR

Large CR gap favors full 28-day dosing

Non-NPM1/IDH2 AML

~70% of cohort

45.0%

AV28 CR

45.1%

AV14 CR

Shorter 14-day dosing may be reasonable here

Overall survival: 21.4 mo (AV28) vs 13.6 mo (AV14), $p=0.07$ — confounded by baseline TP53 imbalance (19 vs 13); treatment arm not independently associated with OS after adjustment (HR 1.33, $p=0.23$).
Grade ≥ 3 AEs and early mortality were similar between arms.

This is PRECISE-VEN's premise, now with prospective evidence
Venetoclax duration may need to be molecularly tailored, not one-size-fits-all.

NGS-Based MRD: 2025 ELN-DAVID Update

56 recommendations, genotype-tailored to ELN 2022 risk

New qualitative MRD response — replaces binary positive/negative

OPTIMAL

MRD-negative — continue
planned therapy

WARNING

MRD-LL — repeat testing
in ~4 weeks

HIGH RISK

Treatment failure — urgent
intervention

Genotype-specific assay changes

FLT3-ITD

UHS-NGS now preferred over-flow

LOD $\geq 0.01\%$ VAF — tested after 2 cycles
and pre-alloHCT

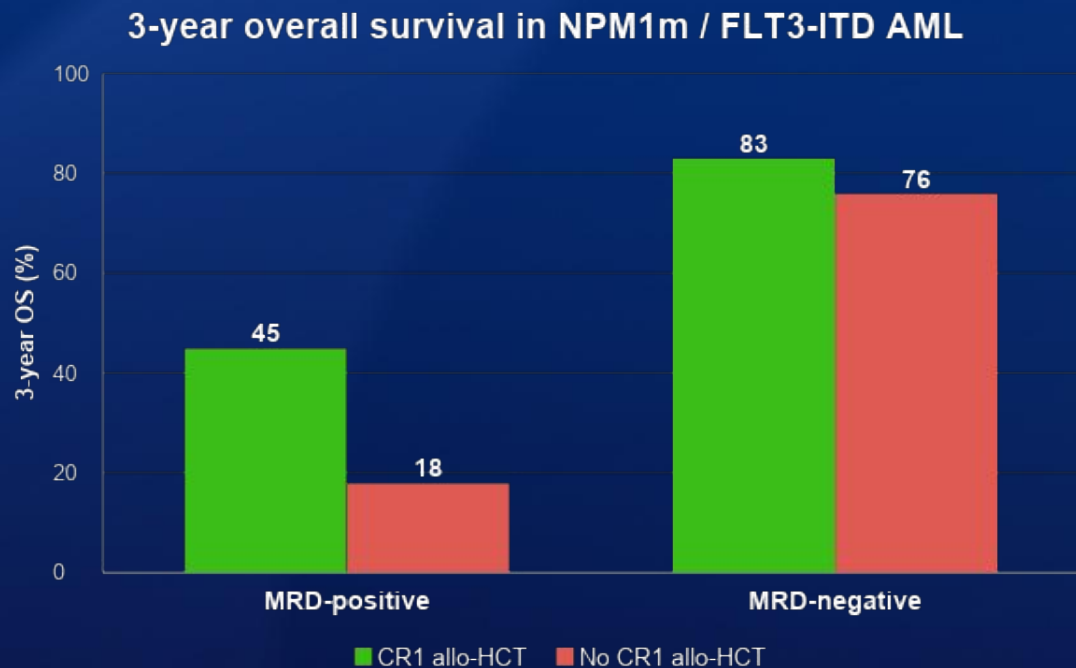
NPM1-MT

20× lower EOT threshold

Positivity cutoff: 2% → 0.1% *NPM1/ABL1*
in bone marrow

NPM1 MRD identifies who benefits from CR1 transplant

UK NCRI AML17/AML19 • PB NPM1 RT-qPCR after course 2 • 737 patients in remission



**MRD-POSITIVE
TRANSPLANT BENEFIT**
45% vs 18%
3-year OS: CR1 allo-HCT vs
no allo-HCT

**MRD-NEGATIVE
NO TRANSPLANT BENEFIT**
83% vs 76%
3-year OS: CR1 allo-HCT vs
no allo-HCT

Clinical implication

Baseline FLT3-ITD should not automatically mandate CR1 allo-HCT when postinduction NPM1 MRD is negative; FLT3-ITD allelic ratio did not modify the MRD-guided result.

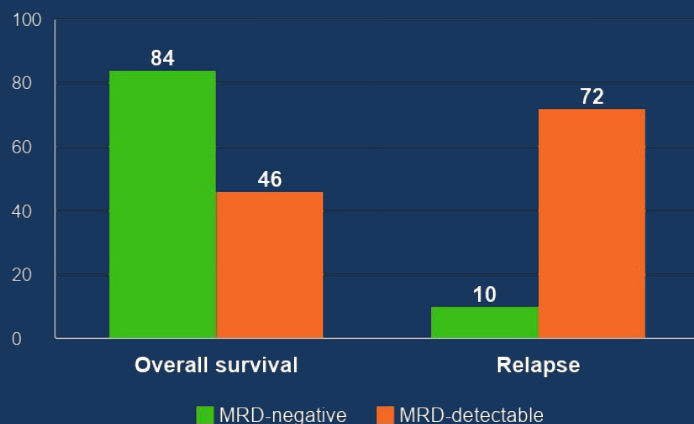
MRD remains prognostic with venetoclax-based therapy

Complementary evidence: molecular NPM1 RT-qPCR and VIALE-A flow cytometric MRD

Othman et al. • NPM1m • VEN-based therapy • n=76

58% achieved bone-marrow MRD negativity

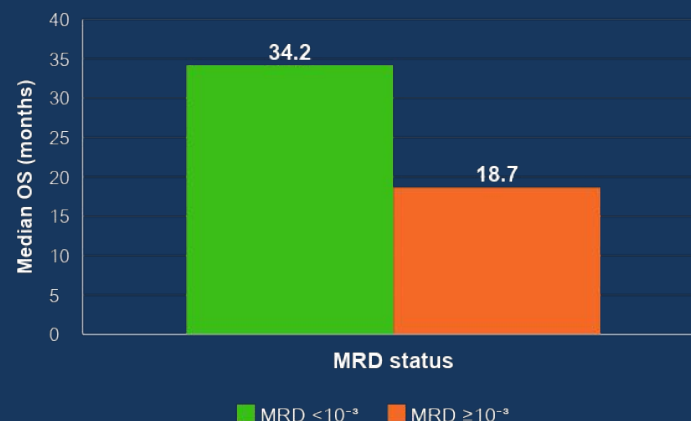
24-month outcomes by NPM1 MRD



VIALE-A • VEN+AZA • flow MRD • n=431

Overall OS: 14.7 vs 9.6 mo • HR 0.58

Median OS among VEN+AZA responders



Clinical implication

Across molecular and flow-based assays, early MRD clearance identifies durable remission and substantially lower relapse risk.

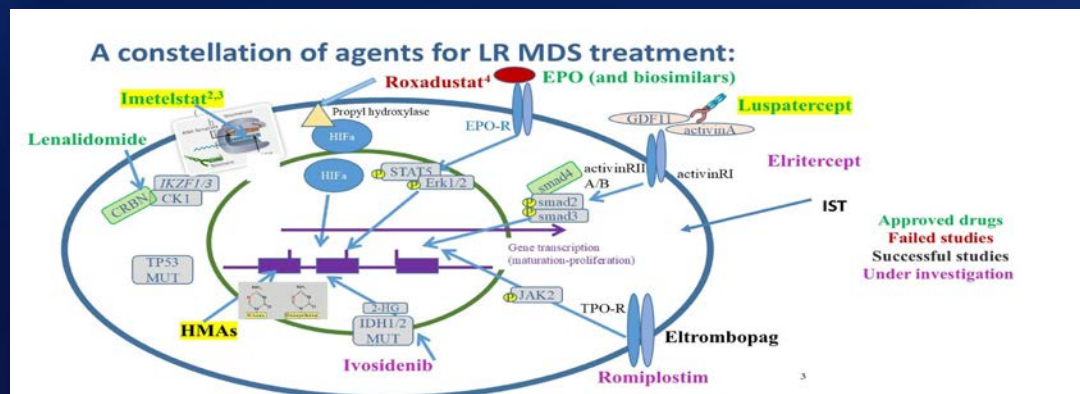
MRD is prognostic—but prospective trials are still needed before using it as a treatment-stopping rule.

MDS: Molecular Risk Outrunning Molecular Therapy

IPSS-M reclassifies ~40–46% vs. IPSS-R, changing intended management in ~17% — *a genuine precision upgrade*

Access tracks with insurance status and practice setting; Medicare covers NGS only when tied to an FDA-approved companion diagnostic, and testing lags in rural/community vs. academic settings

Few MDS-specific targeted agents exist outside *IDH1/SF3B1* niches



Precision diagnostics without precision access

is precision on paper only — IPSS-M's own validation studies flag cost and infrastructure as the limiting step.

IDH1-Mutated MDS: Rationale & Early Efficacy

All MDS Patients

IDH1-mutated (~3%)

Enriched with neutropenia —
regardless of IPSS-R

Phase I Dose Escalation

n=16 · ivosidenib 500 mg daily

44%

CR rate

60%

maintained response
@ 1 yr

Early proof of concept, first-in-human

IDIOME Phase II

n=32 · HMA-failure or HR-MDS

69%

ORR

7.4 mo

DOR

46%

CR

14 mo

OS

Up to 91% response in treatment-naïve HR-MDS

A narrow but real target

IDH1 mutations are rare in MDS — but where present, response rates rival
anything else in this space.

Ivosidenib: FDA-Approved for R/R IDH1-Mutated MDS

1

Breakthrough Designation

Accelerated review pathway granted

2

Expanded Enrollment

n=19 · 78.9% prior HMA failure

3

Efficacy Confirmed

CR 39% · mOS 35.7 mo · mDOR not reached

4

FDA Approval

October 24, 2023

15/18 evaluable patients responded — all responses were complete responses

Small sample size and IDH1m present in only 3–4% of MDS — but ORR up to 90% in treatment-naïve disease

A genuine, if narrow, precision approval

One of very few MDS-specific targeted agents to reach approval — proof the model can work outside AML too.

The Access Gap

Real-world eligibility for “precision” trials is far narrower than practice — REVIVE: mandatory MRD assessment completed in a minority of real-world venetoclax-treated patients.

NGS/cytogenetics turnaround often exceeds the window for a timely frontline decision, especially in community settings.

Clonal evolution and resistance under targeted-therapy pressure mean today's target may not be tomorrow's!

Genomically-defined disease ≠
genomically-matched, equitably delivered care.

Four Conditions for Getting “There”

- 1 Real-time NGS turnaround** — Built into frontline treatment decision windows, not after them.
- 2 Combination strategies** — Matched to molecular markers, rather than conventional approaches.
- 3 MRD-adapted consolidation** — Validated in prospective, randomized trials — not just retrospective signal.
- 4 Equitable access** — Molecular testing and matched agents reach academic and community settings alike.

Precision has changed how we diagnose MN: hasn't yet completely changed how we treat them.

- **Match.** Close the biology-to-therapy gap where diagnosis still outruns drugs e.g. *TP53*-mutated disease, HR MDS.
- **Tailor.** Move dosing and duration from empiric to molecularly-guided therapy — OPTI-AML is a first step, not the finish line.
- **Deliver.** Get these advances into community practice, not just academic centers.

Thank you



Rochester,
Minnesota



Phoenix/
Scottsdale,
Arizona



Jacksonville,
Florida

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