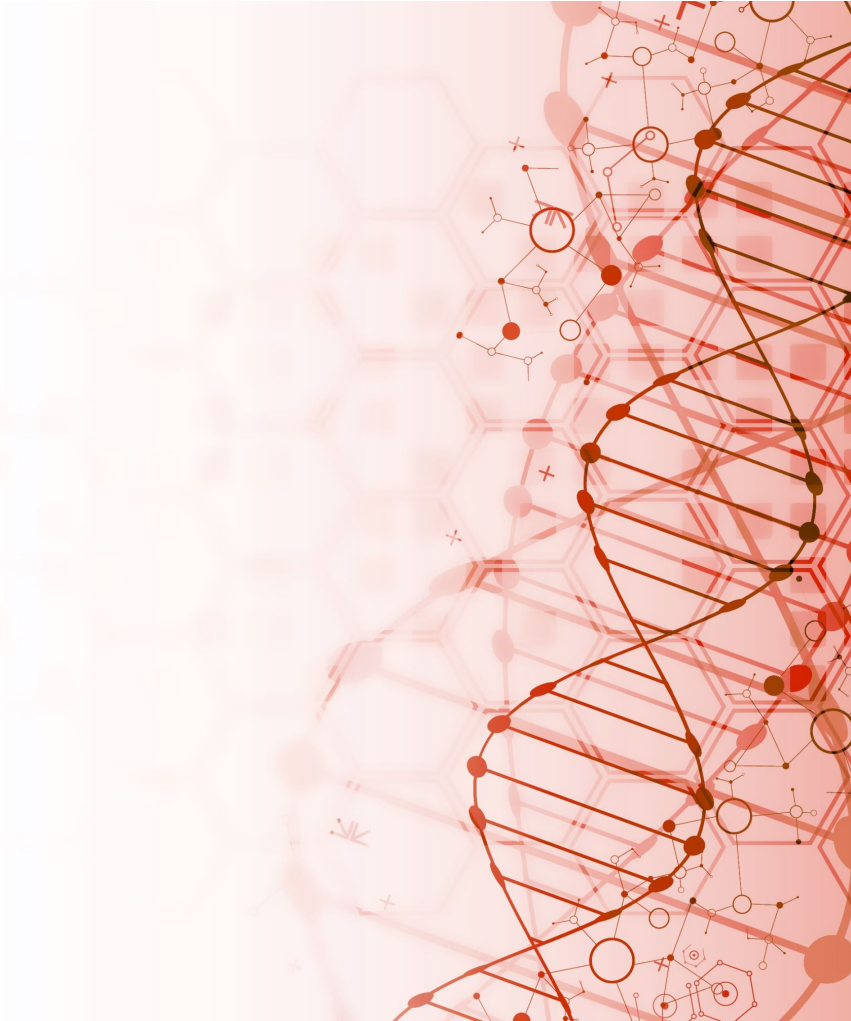


AML in 2026: Genomics & Hereditary Predisposition

Courtney DiNardo, MD

Department of Leukemia
UT MD Anderson Cancer Center





Disclosures:

Research Support (to institution):

Abbvie, Aprea, Astex, BMS, Foghorn,
ImmuneOnc, Jazz, Remix, Rigel, Servier,
Schrodinger, Systimmune

Consultant/Advisory Boards:

Abbvie, Astellas, AZD, BMS, Daiichi Sankyo,
Ellipses, GenMab, GSK, MPI, Rigel,
Schrodinger, Servier, Syndax

AML is not one disease: Varied outcomes with Intensive Chemotherapy (IC)

ELN 2022¹

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*

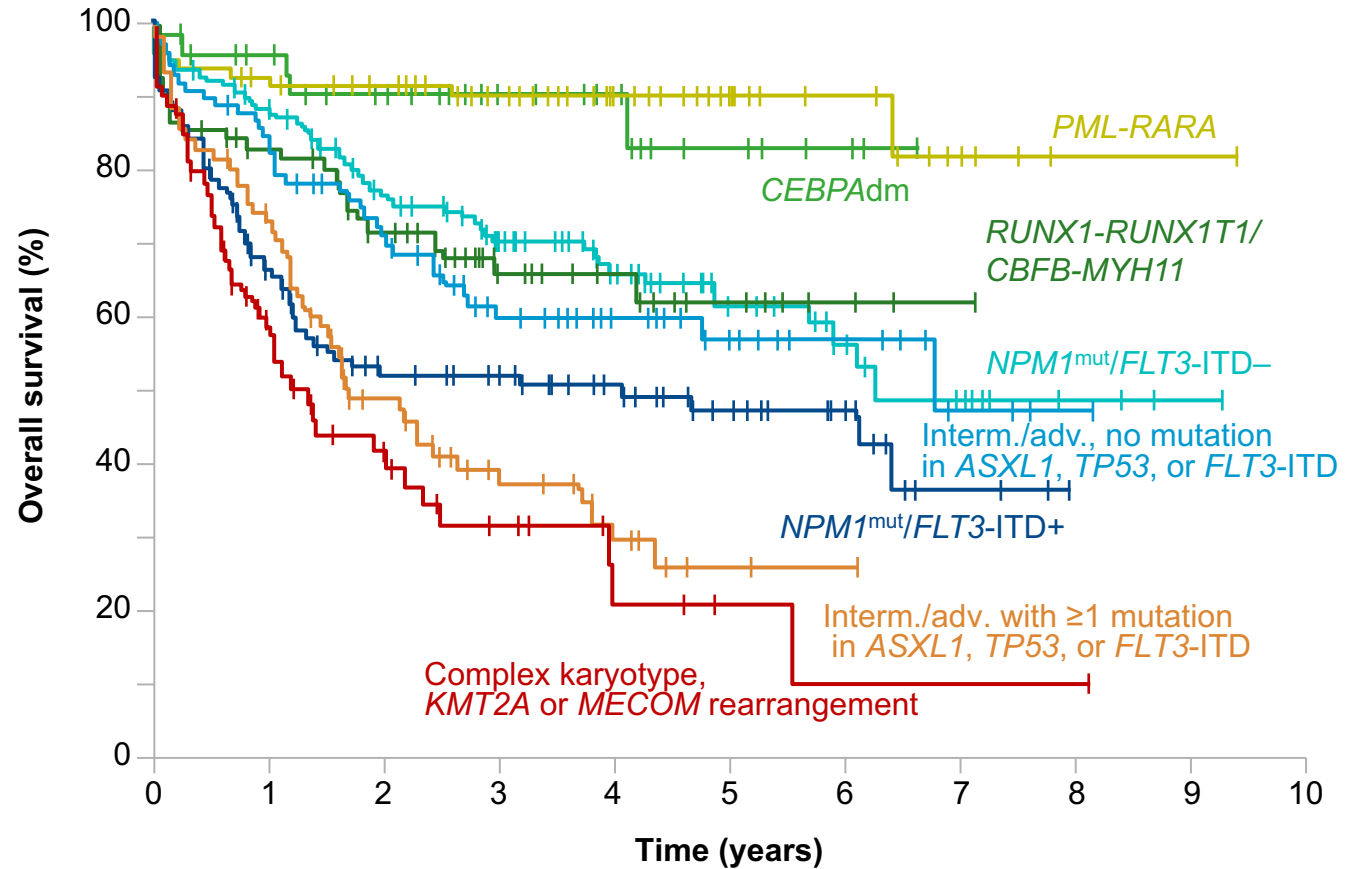
Intermediate

- Mut *NPM1* with *FLT3*-ITD
- Wt *NPM1* with *FLT3*-ITD
- t(9;11)(p21.3;q23.3)/*MLL3::KMT2A*
- Cytogenetic and/or molecular

Adverse

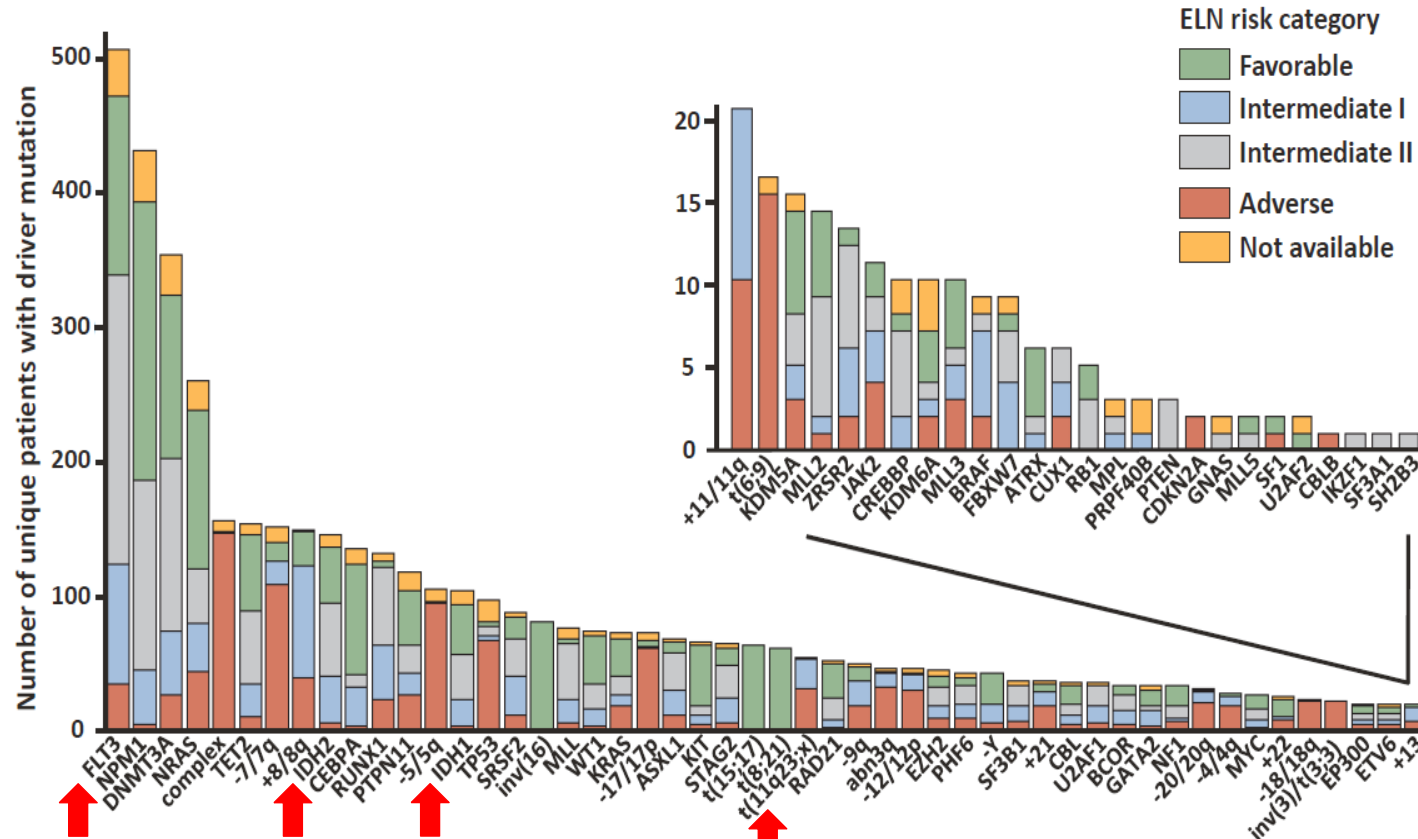
- t(6;9)(p23.3;q34.1)/*DEK::NUP214*
- t(v;11q23.3)/*KMT2A*-rearr
- t(9;22)(q34.1;q11.2)/*BCR::ABL1*
- t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
- t(3q26.2;v)/*MECOM(EVI1)*-rearr
- -5 or del(5q); -7; -17/abn(17p)
- Complex/monosomal karyotype
- Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*
- Mut *TP53*

OS in patients aged <60 years with *de novo* AML* (N=867)²

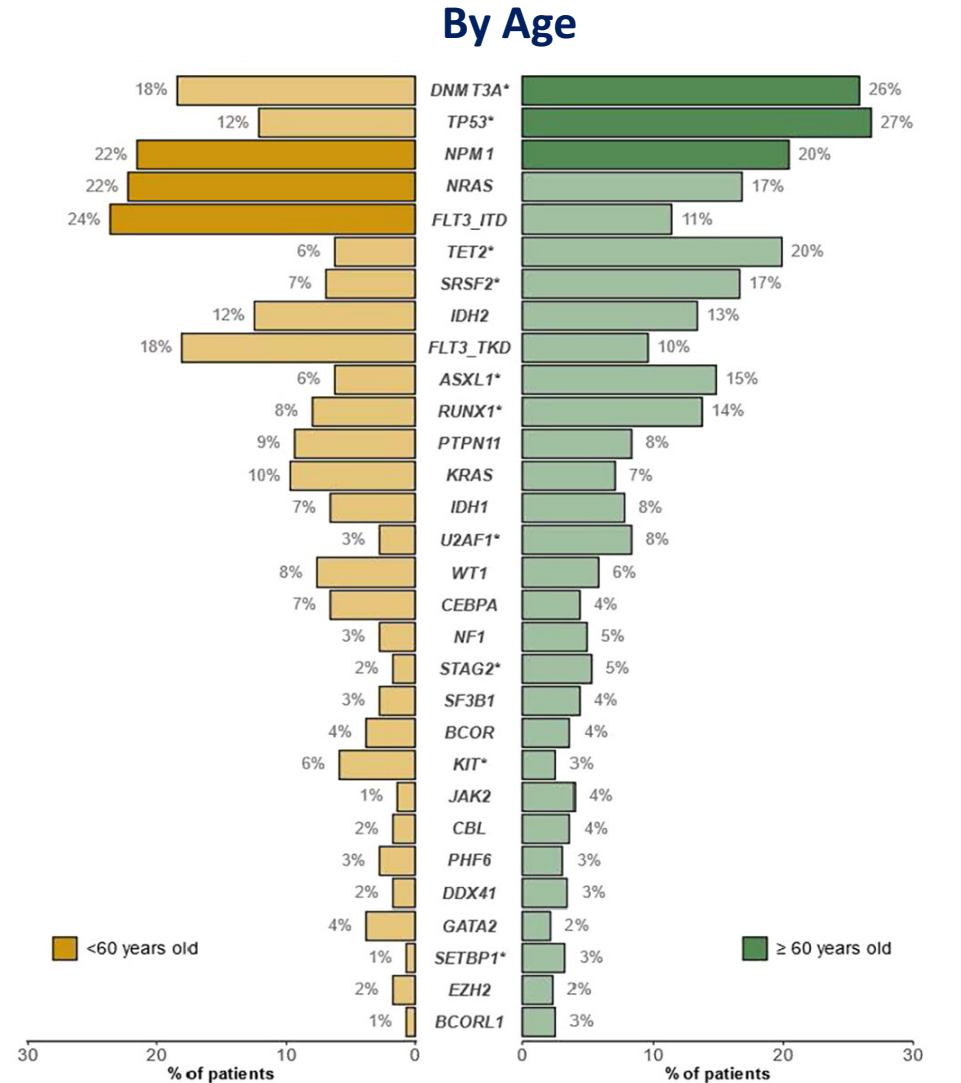


* This population of patients had been treated with standard intensive chemotherapy.

Cytogenetic and Mutational Landscape of AML

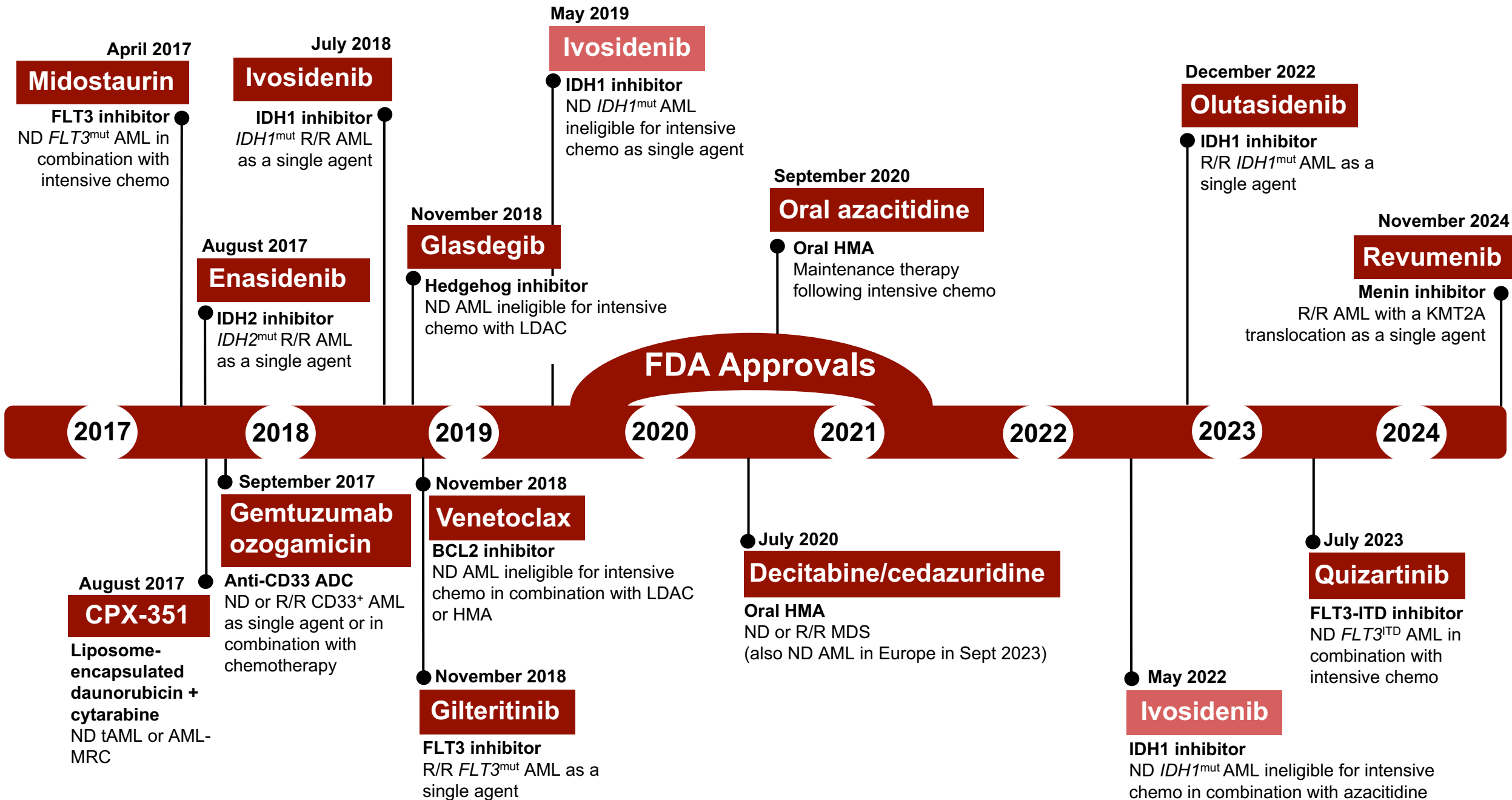


- Targeted resequencing of 111 myeloid cancer genes (combined with cytogenetic profiles) in 1540 AML
- 5236 driver mutations (i.e., fusion genes, copy number alterations, gene mutations) involving 77 loci
- 6 genes mutated in >10% pts; 13 genes 5–10% pts; 24 genes 2–5% pts; 37 genes <2% pts

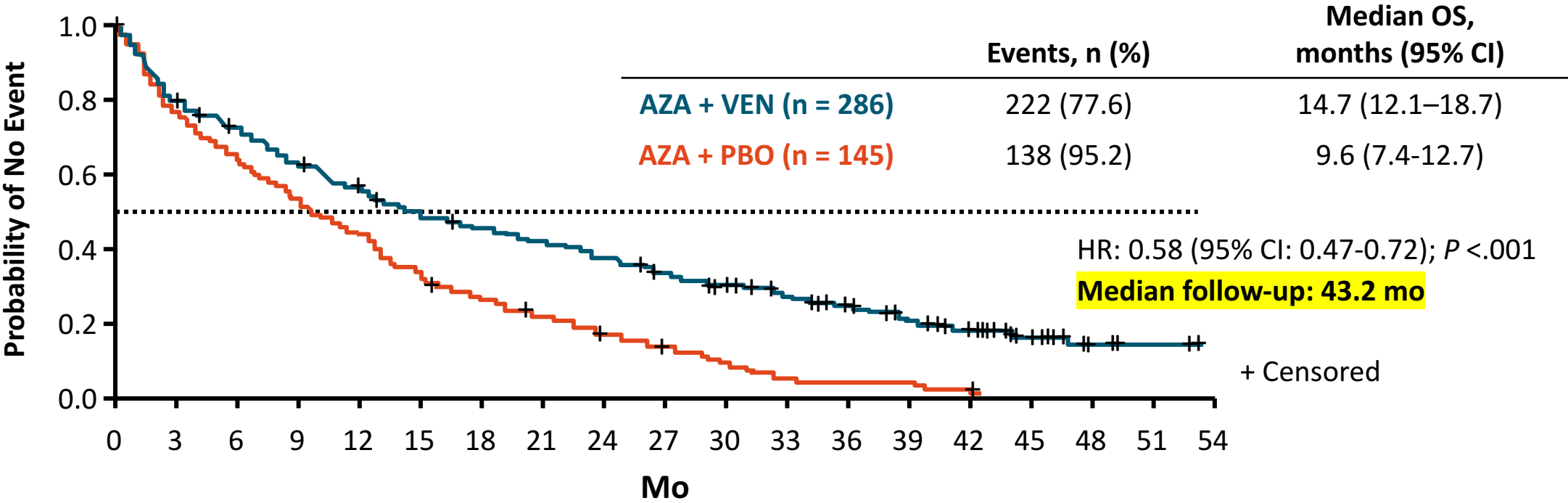


*indicates mutations with significantly different incidence by age group

The Rapidly Evolving Treatment Landscape of AML



VIALE-A : AZA + VEN for older IC-ineligible AML

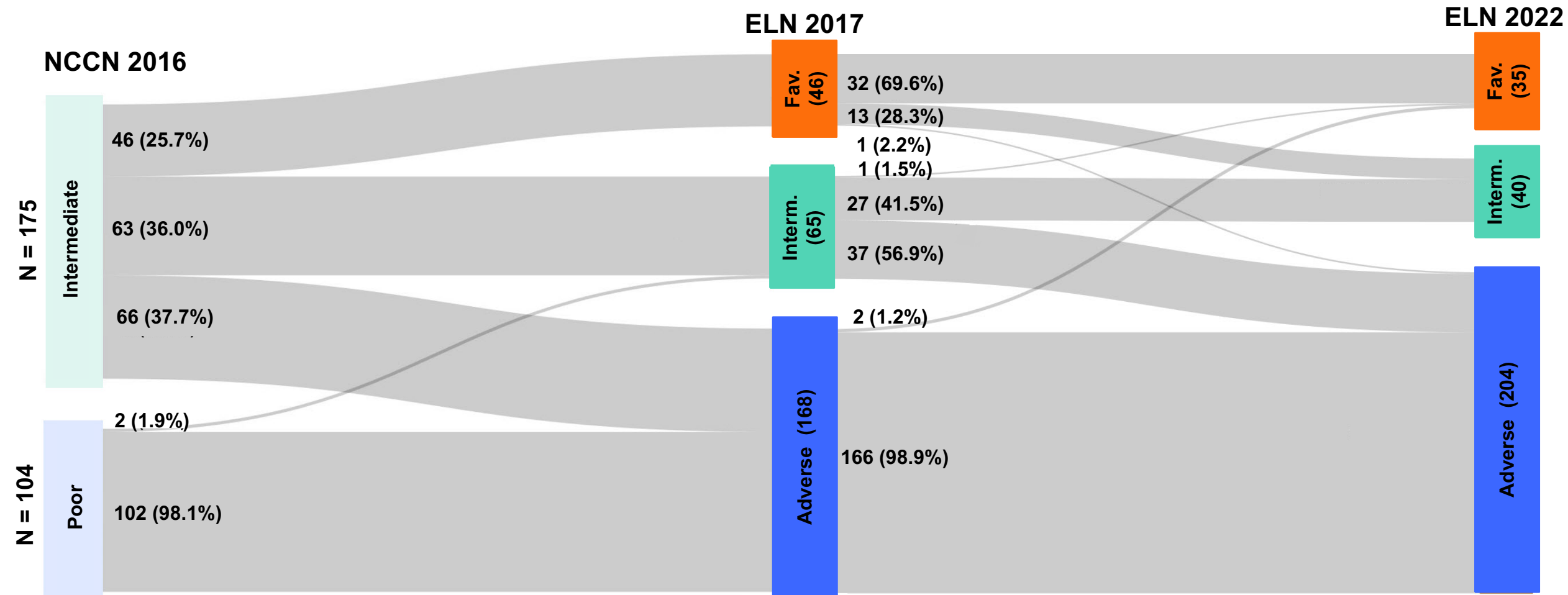


	Events, n (%)	Median OS, months (95% CI)
AZA + VEN (n = 286)	222 (77.6)	14.7 (12.1–18.7)
AZA + PBO (n = 145)	138 (95.2)	9.6 (7.4-12.7)

Patients at Risk, n

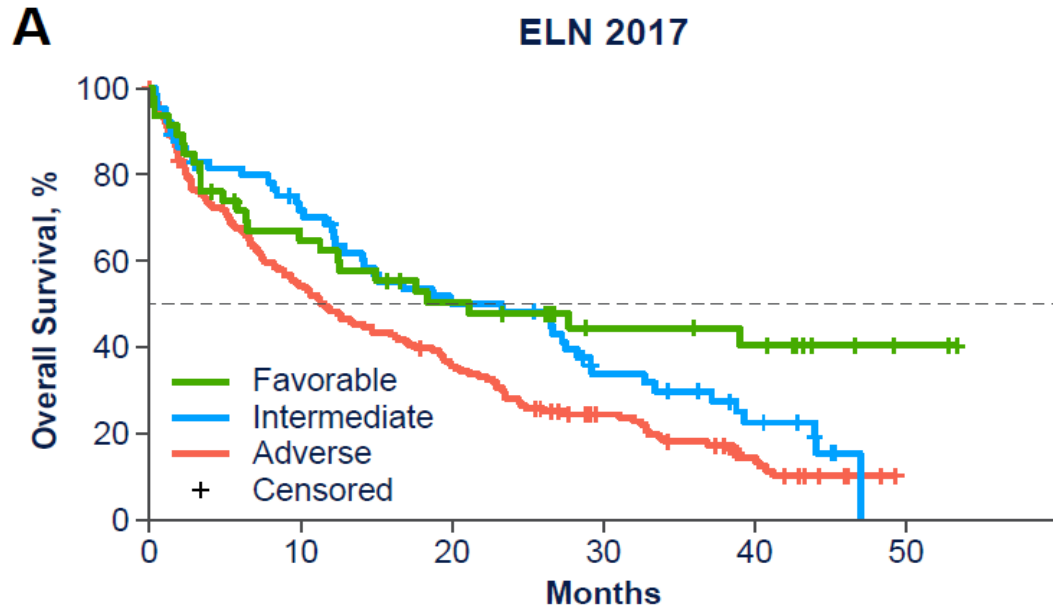
AZA + PBO	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0			
AZA + VEN	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0

By ELN 2017 or 2022 recommendations, most patients are categorized as adverse risk group



- Favorable-risk patients in ELN 2022 are primarily those with an *NPM1* mutation. **Patients with favorable-risk cytogenetics such as t(8;21), inv(16), t(16;16) or t(15;17) were excluded from the trials**
- The increase in the adverse-risk group is largely driven by myelodysplasia-related genetic signature genes: *RUNX1*, *ASXL1* (ELN 2017); *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2* (ELN 2022)

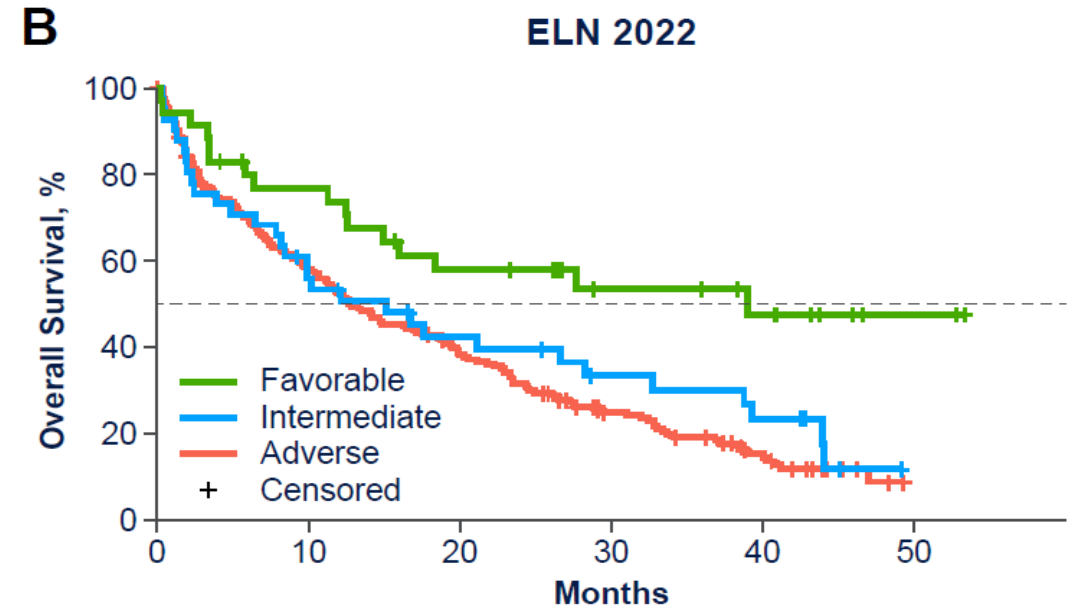
Neither ELN 2017 nor 2022 discriminate optimally for patients receiving VEN-based therapies



Patients at Risk

46	28	20	12	10	2
65	44	29	17	9	0
168	90	58	31	14	0

ELN 2017	n	Events	Median OS, months (95% CI)
Favorable	46	25	21.1 (9.9, NR)
Intermediate	65	48	23.3 (12.9, 28.3)
Adverse	168	141	11.5 (8.9, 16.2)

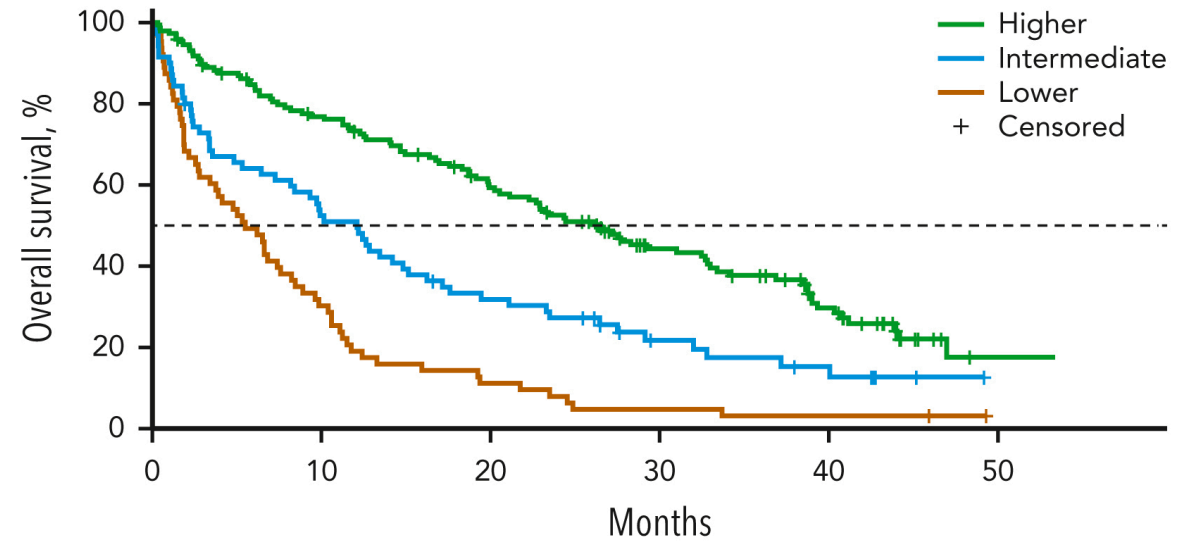
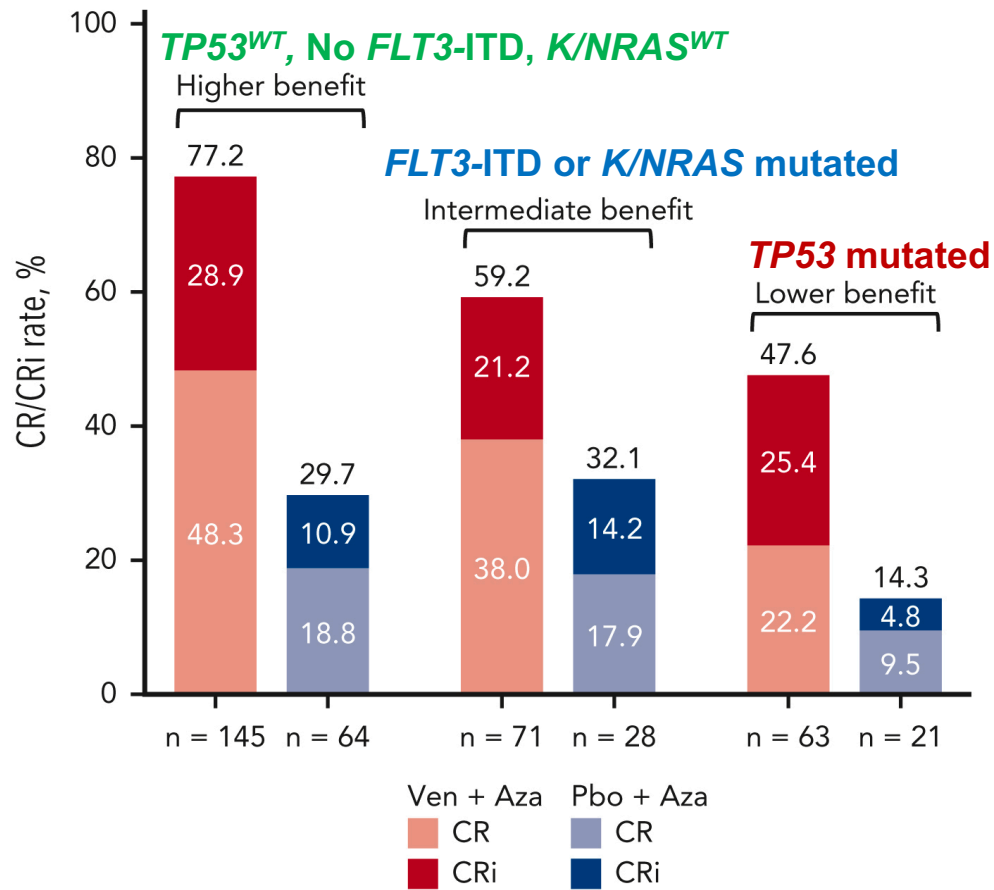


Patients at Risk

35	25	18	11	8	2
41	22	15	10	7	0
203	115	74	39	18	0

ELN 2022	n	Events	Median OS, months (95% CI)
Favorable	35	16	39.0 (12.5, NR)
Intermediate	41	31	15.2 (7.9, 28.3)
Adverse	203	167	12.7 (10.4, 17.6)

Some genomically defined groups do better than others : but better treatment outcomes are needed for most, if not all, transplant-ineligible pts

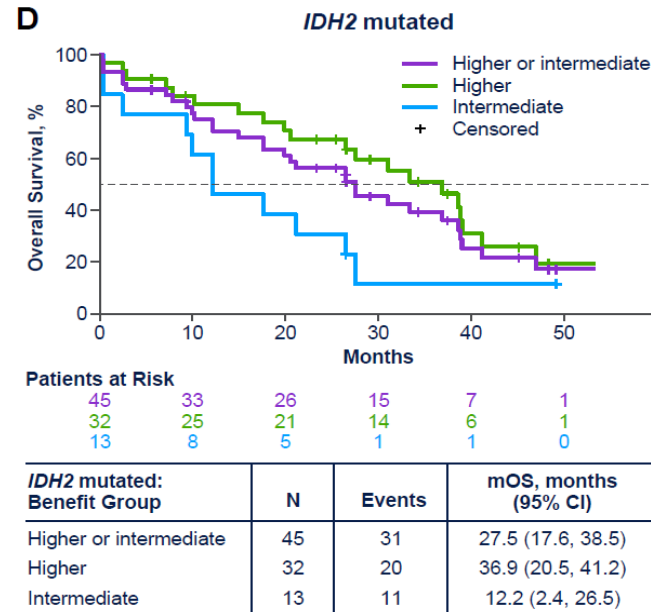
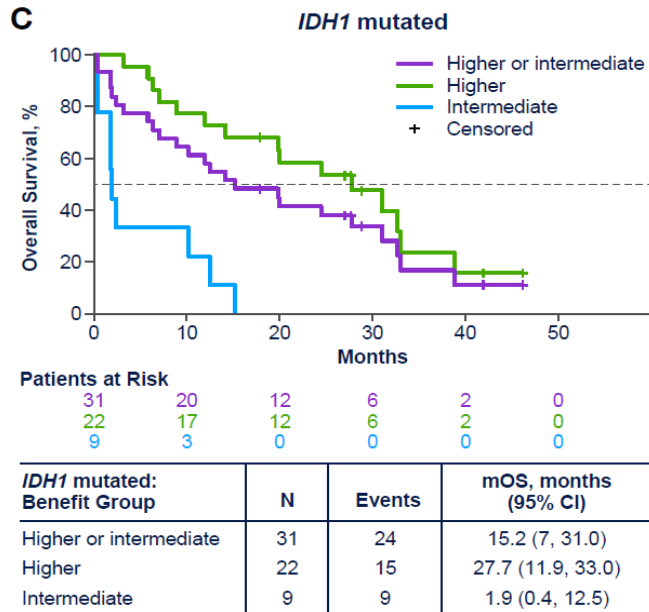
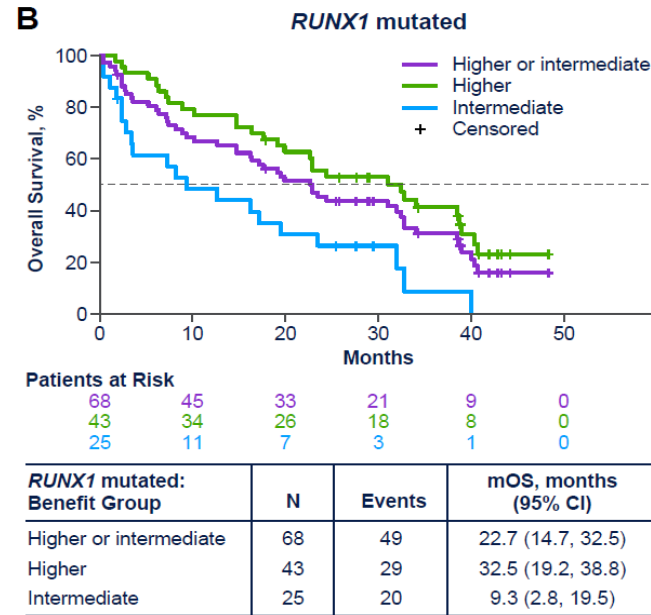
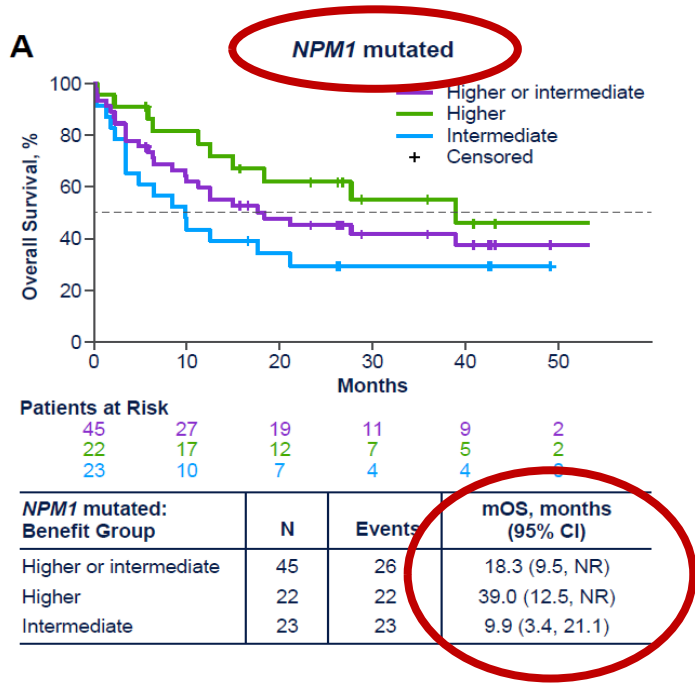


Patients at Risk

145	107	79	47	25	2
71	36	21	10	6	0
63	19	7	3	2	0

Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher benefit	145	96	26.5 (20.2, 32.7)
Intermediate benefit	71	57	12.1 (7.3, 15.2)
Lower benefit	63	61	5.5 (2.8, 7.6)

mPRS = modified prognostic risk signature



Outcomes with HMA+VEN in more “favorable” subgroups like *NPM1*, *IDH1*, *IDH2* and *RUNX1* all depend on presence/absence of the signaling mutations *FLT3-ITD* and *N/KRAS*

- Green = no signaling mutation
- Blue = signaling mutation (either *FLT3-ITD*, *KRAS* or *NRAS*)
- Purple = all together

Updated AML classifications reflect the impact on genomics associated with DIFFERENT AML therapies

ELN 2022¹

(Intensive treated patients)

- 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***

ELN 2024²

(Less-intensive therapies)

- Favorable**
- Mutated *NPM1* (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)
 - Mutated *IDH2* (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)
 - **Mutated *IDH1** (*TP53* wild type)**
 - Mutated *DDX41*†
 - Other cytogenetic and/or molecular abnormalities (wild-type *FLT3-ITD, NRAS, KRAS, TP53*)‡

- Intermediate**
- **Mutated *FLT3-ITD* and/or Mutated *NRAS* and/or *KRAS* (*TP53* wild-type)**

- Adverse**
- **Mutated *TP53***

❖ This classification does not apply to pts that have received a prior HMA

* **Favorable mutated *IDH1* risk applies specifically to patients treated with AZA + IVO and appears irrespective of signaling gene mutations**

† Identification of a *DDX41* mutation (especially VAF ~ 50%) should prompt consideration of a germline mutation

‡ For many genomic abnormalities, not enough data is currently available

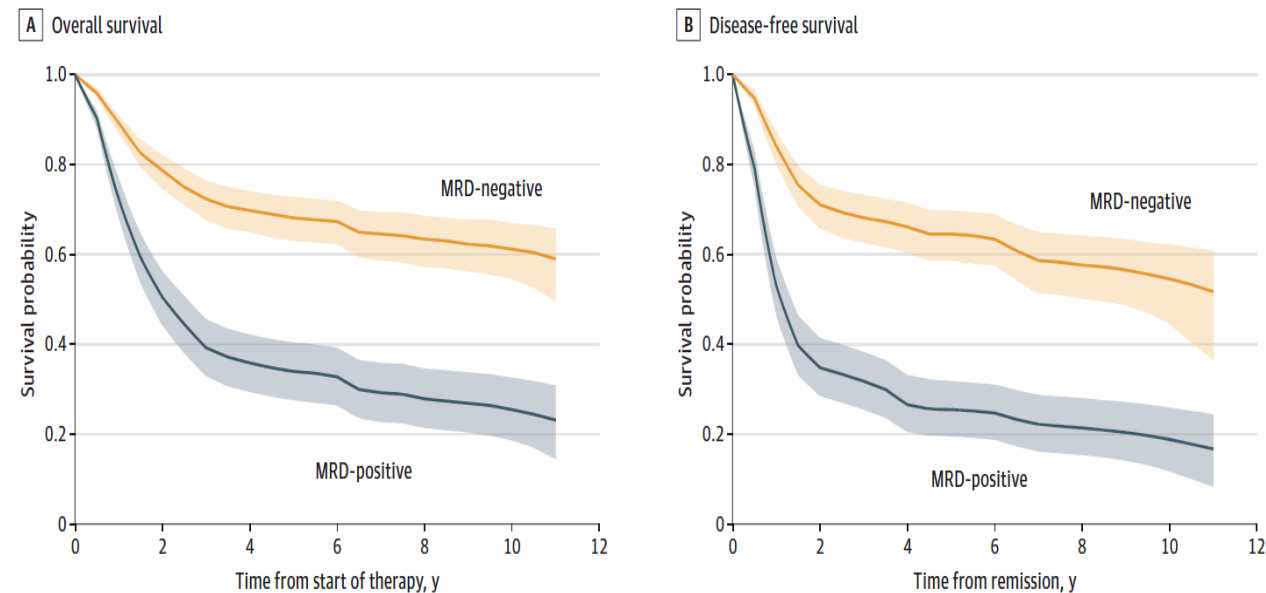
Minimal/Measurable Residual Disease (MRD)

- Quantification of MRD increasingly important in patients achieving CR to better assess risk of relapse

METHOD	TARGET	SENSITIVITY	PROS/CONS
Cytogenetics	Chromosomal abnormalities	1 in 20 (5%)	Cheap, readily available Applicable for ~50% AML
Flow Cytometry	Leukemia-associated aberrant immunophenotype (LAIP) or Different from Normal (DFN)	1 in 10,000 (0.01%)	Applicable to most AML Relatively cheap & fast (2-3d) Not easily standardized Subject to expertise & interpretation
Quantitative PCR (qPCR)	Fusion transcripts (CBFs), gene mutations (NPM1)	Up to 1 in 100,000 (0.001%)	Highly sensitive Very standardized Applicable for ~30-40% AML
NGS (mutation analysis)	Any somatic mutations	Up to 1 in 10,000 (0.01%) But typically ~1%	Genetic heterogeneity, clonal architecture complicate analysis. Long TAT (5-14 days)

MRD has a strong predictive value for survival in patients undergoing intensive chemotherapy

Figure 2. Estimated Survival Curves, Stratified by Measurable Residual Disease (MRD) Status



Short NJ et al., *JAMA Oncol.* 2020;6(12):1890-1899
 Freeman SD et al., *J Clin Oncol.*, 2018 May 20;36(15):1486-1497
 Ivey A et al., *N Engl J Med.*, 2016 Feb 4;374(5):422-33
 Othman J et al., *Blood.* 2024 May 9;143(19):1931-1936
 Rucker FG et al., *Blood*, 2019 Nov 7;134(19):1608-1618
 Puckrin R et al., *Haematologica.* 2021 Jan 1;106(1):56-63

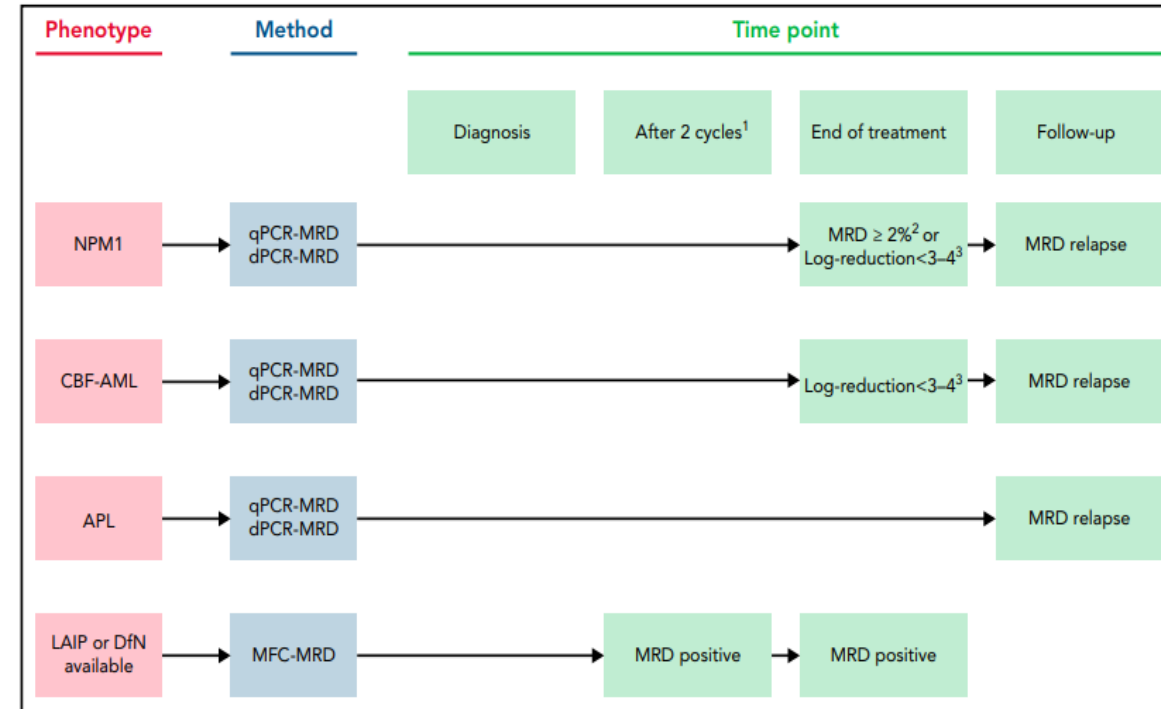


Figure 2. Time points at which MRD is considered a clinically relevant biomarker. The time points and MRD cutoffs are indicated at which an MRD result may influence the therapeutic decision for a given patient. For example, in a patient with AML carrying an *NPM1* mutation, who is monitored by qPCR, MRD persistence at ≥2% *NPM1* mutant copies/*ABL1* copies at the end of chemotherapy may trigger the decision to consider allo-HCT for this patient. ¹After 2 cycles of chemotherapy (either 2 induction cycles or 1 induction and 1 consolidation cycle), which includes the time point before allo-HCT. ²Percentage *NPM1* mutant copies per *ABL1* copies measured in BM. ³Log reduction of the ratio of target copies/*ABL1* copies between the sample at diagnosis and the sample at end of treatment, measured in the same tissue (preferably BM).

Heuser M et al., *Blood.* 2021 Dec 30;138(26):2753-2767

New ELN MRD Guidance (and there's an app for that!)



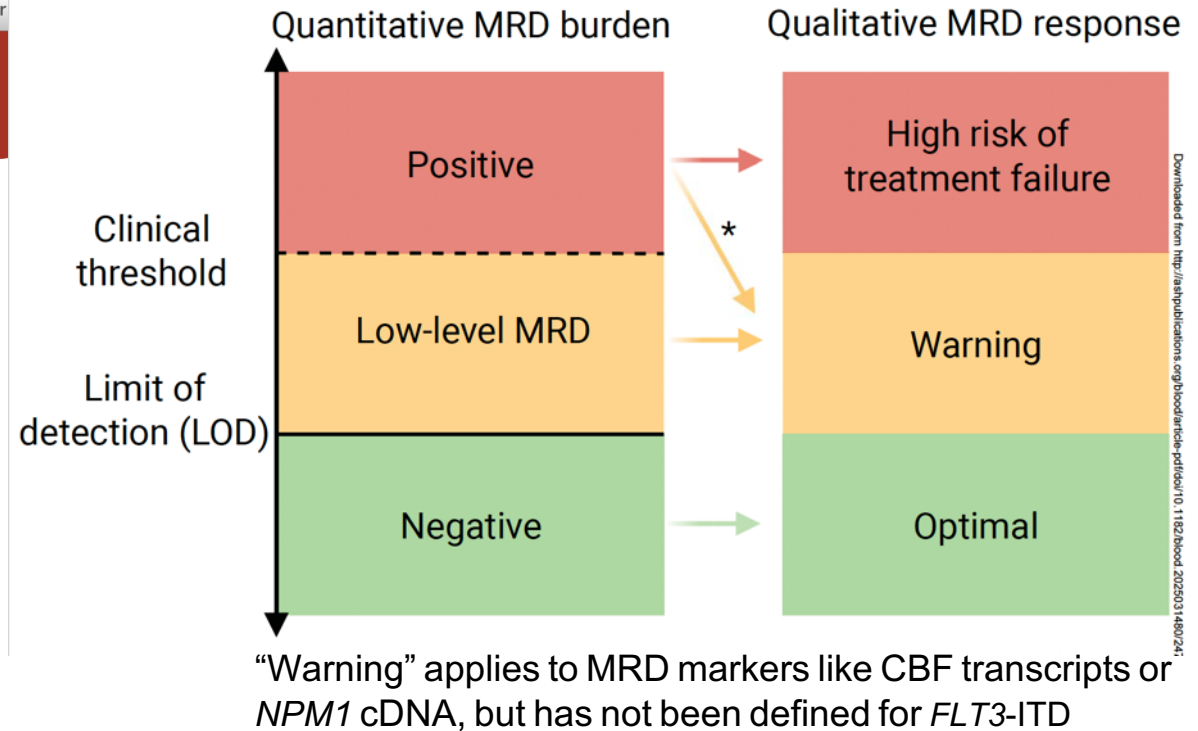
2025 update on MRD in acute myeloid leukemia: a consensus document from the ELN-DAVID MRD Working Party

Jacqueline Cloos,^{1,2} Peter J. M. Valk,³ Christian Thiede,^{4,5} Konstanze Döhner,⁶ Gail J. Roboz,^{7,8} Brent L. Wood,^{9,10} Roland B. Walter,¹¹⁻¹³ Sa Wang,¹⁴ Agnieszka Wierzbowska,^{15,16} Andrew H. Wei,¹⁷⁻¹⁹ David Wu,¹³ François Vergez,²⁰⁻²² Adriano Venditti,²³ Bert A. van der Reijden,²⁴ Arjan A. van de Loosdrecht,^{1,2} Ing Soo Tiong,²⁵ Felicitas R. Thol,²⁶ Marion Subklewe,²⁷⁻²⁹ Christophe Roumier,³⁰ Tom Reuvekamp,^{1,2} Farhad Ravandi,³¹ Claude Preudhomme,^{30,32} Adriana Plesa,³³ Jad Othman,^{34,35} Gert J. Ossenkoppele,^{1,2} Yishai Ofran,^{36,37} Aguirre Mimoun,³⁸ Luca Maurillo,²³ Agata Majchrzak,³⁹ David de Leeuw,^{1,2} Wolfgang Kern,⁴⁰ Dennis Dong Hwan Kim,^{41,42} Maura R. V. Ikoma-Colturato,⁴³ Lukas H. Haaksma,^{1,2} Monica L. Guzman,⁷ Michaela Feuring,⁶ Barbara Depreter,^{44,45} Anna Cysz,⁴⁶ Veit Bücklein,^{27,29} Constance Baer,⁴⁰ Costa Bachas,^{1,2} Sylvie D. Freeman,⁴⁷ Francesco Buccisano,²³ Christopher S. Hourigan,⁴⁸ Richard Dillon,⁴⁹ and Michael Heuser^{26,50}

56 new recommendations!!!

High level > two main new ones

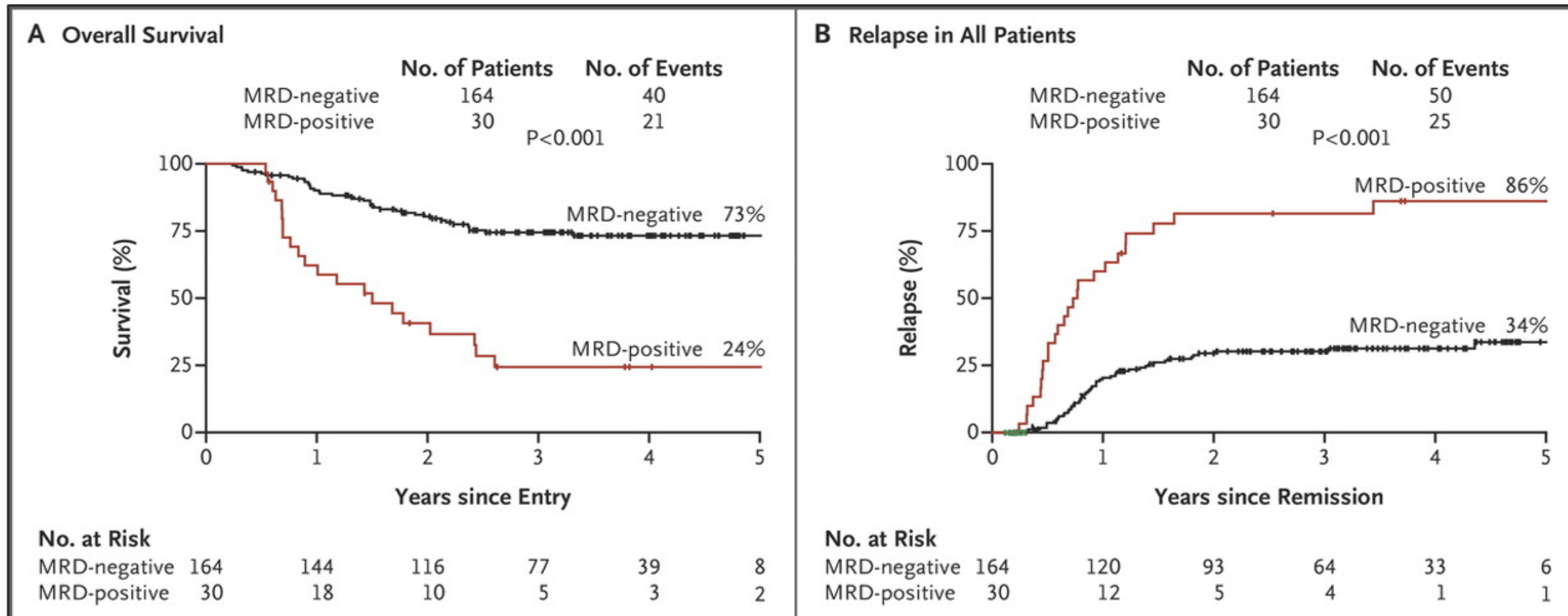
- 1) Moving away from just MRD +/-
- 2) *FLT3*-ITD NGS-MRD as a prognostic and predictive biomarker



Targeted <i>FLT3</i> -ITD UHS-NGS (<i>FLT3</i> -ITD positive/mut <i>NPM1</i> or <i>FLT3</i> -ITD positive/ <i>NPM1</i> wild type) (LOD measured as VAF ⁹ %)				
2 cycles of intensive chemotherapy or pre-alloHCT	BM or PB	<LOD ⁹	Negative	Optimal
		≥LOD ⁹	Positive	High risk of treatment failure
End of Treatment (after consolidation/ after alloHCT)	BM or PB	<LOD ⁹	Negative	Optimal
		≥LOD ⁹	Positive	High risk of treatment failure
Follow-up	PB or BM	<LOD ⁹	Negative	Optimal
		≥LOD ^{9,10}	MRD relapse	MRD relapse

PCR based MRD for AML in CR1 with NPM1 mutation impacts RFS and OS – **Standard of Care Monitoring**

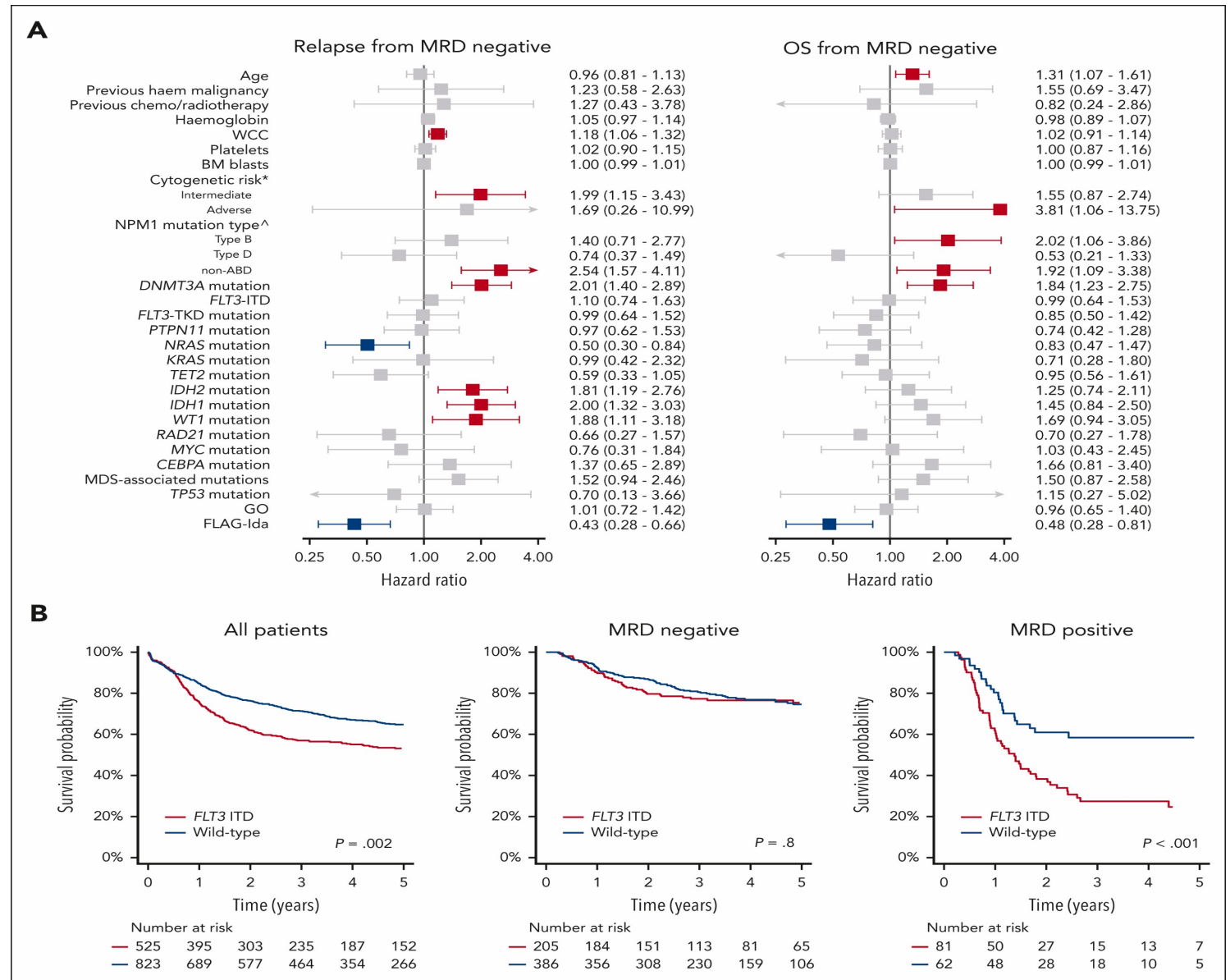
Most prognostic time-point was after 2nd cycle



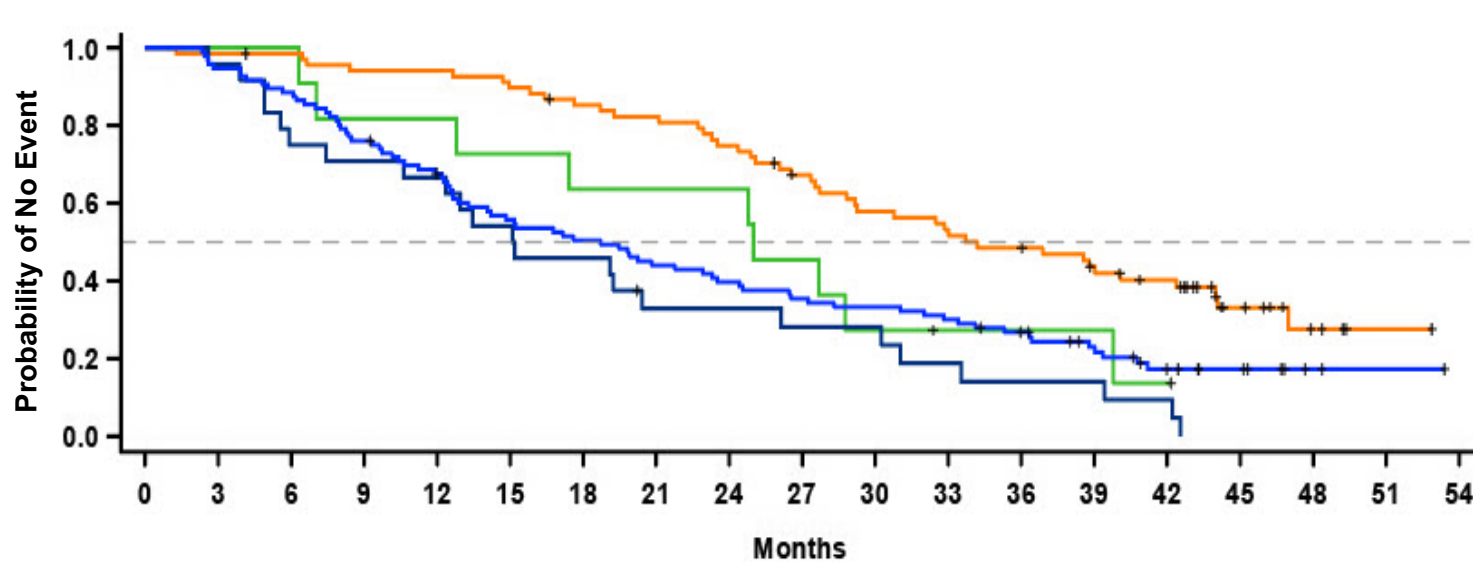
***Strongly supports consideration of transplant in “favorable” risk patients who do not attain MRD negative CR1**

NPM1m AML: Decisions must integrate MRD

- **N=1357 NPM1-mut AML** from AML17 or AML19 NCRI studies
- **MRD negativity after 2 treatment courses remains the major determinant of outcome (even in FLT3-ITD mutated pts)**
- **Intensified chemotx with FLAG-IDA was associated with improved outcomes, especially in high-risk molecular subgroups (>50% reduction in risk of relapse)**



Median OS is ~3 yrs for flow cytometric MRD < 10⁻³ CR/CRi patients on Ven+Aza



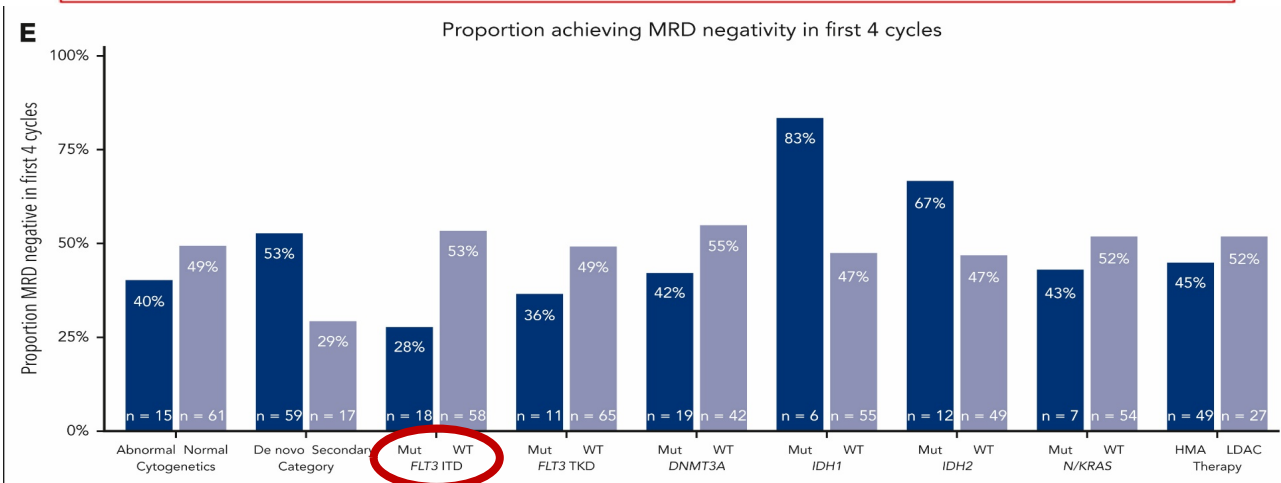
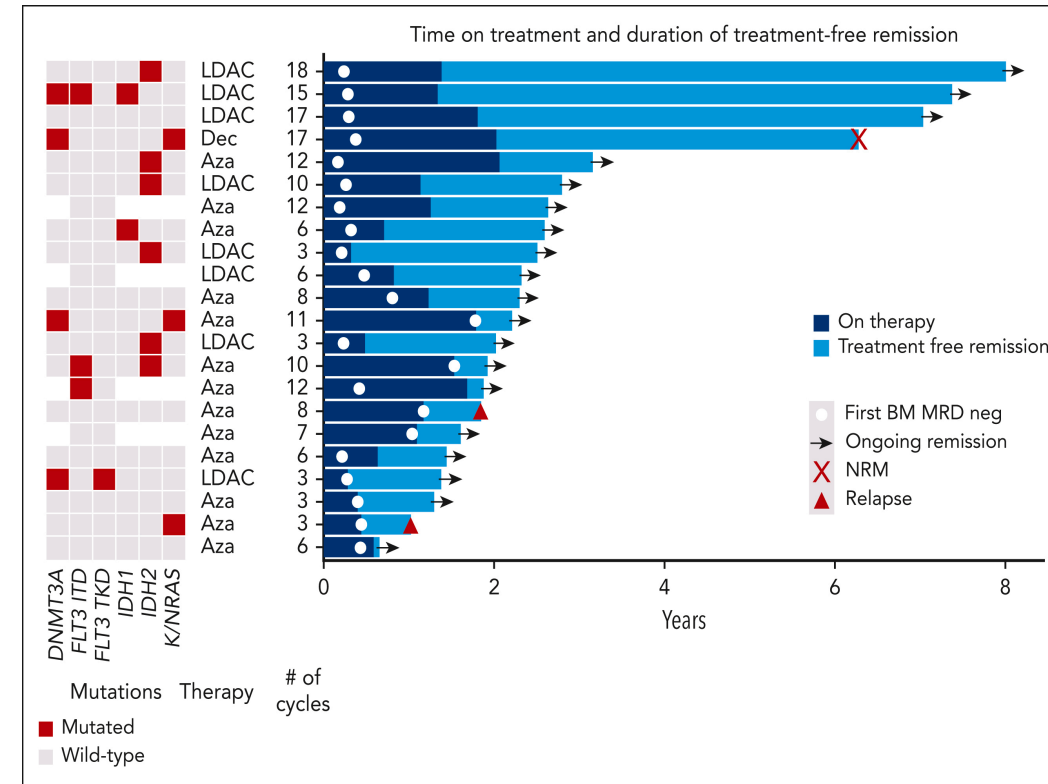
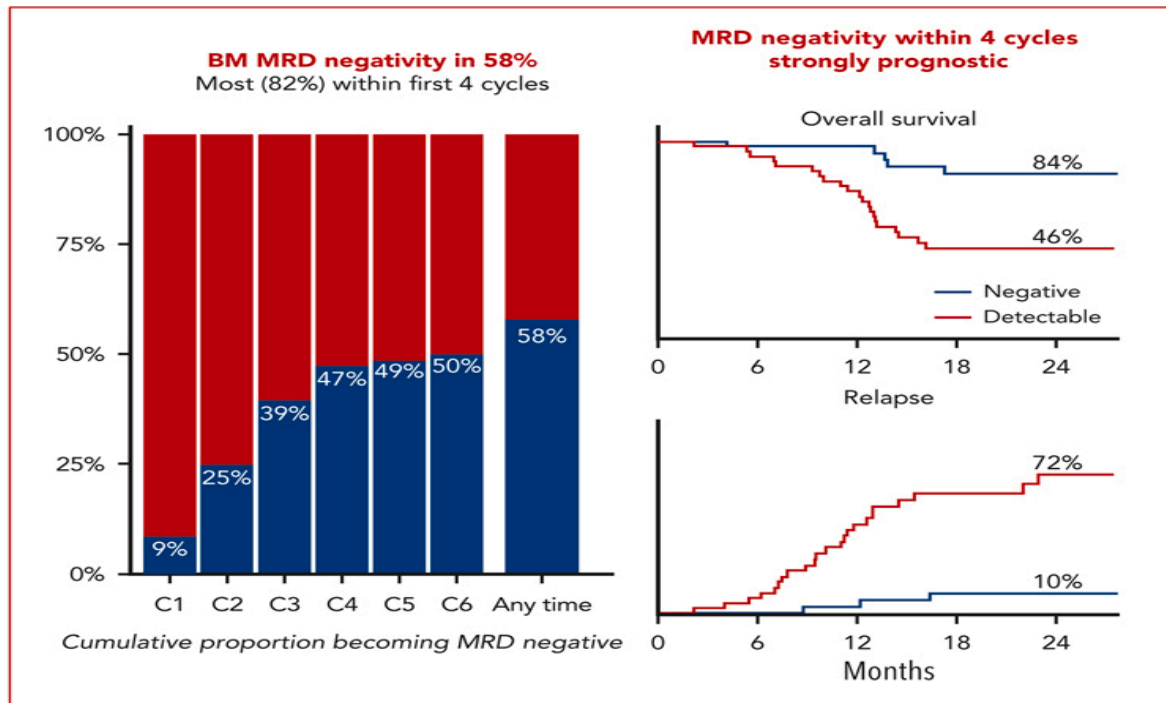
	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza MRD < 10 ⁻³	43/69 (62)	34.2 (27.7, 44.0)
Ven+Aza MRD ≥ 10 ⁻³	76/96 (79)	18.7 (12.9, 23.5)
Pbo+Aza MRD < 10 ⁻³	9/11 (82)	25.0 (7.0, 39.8)
Pbo+Aza MRD ≥ 10 ⁻³	23/24 (96)	15.1 (7.4, 26.4)

Patients at Risk

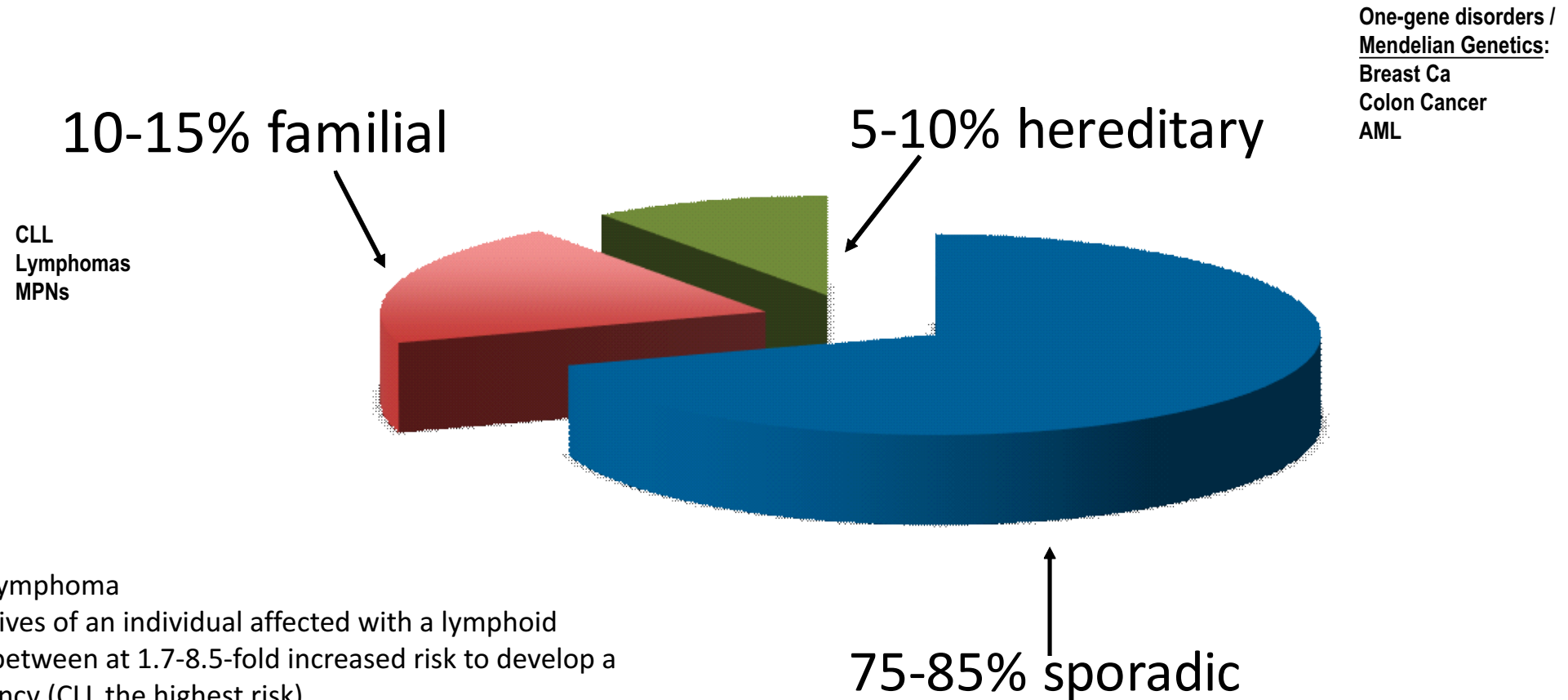
Ven+Aza MRD < 10 ⁻³	69	68	67	64	64	61	57	55	50	43	37	34	31	26	22	10	4	1	0
Ven+Aza MRD ≥ 10 ⁻³	96	91	85	73	63	52	47	41	37	33	31	28	23	17	10	7	2	1	0
Pbo+Aza MRD < 10 ⁻³	11	11	11	9	9	8	7	7	7	5	3	2	2	2	1	0			
Pbo+Aza MRD ≥ 10 ⁻³	24	23	18	17	16	13	11	7	7	6	6	4	3	3	2	0			

* **41%** of CR/CRi pts (67 of 164) attained MRD < 10⁻³ by centralized flow cytometry

NPM1 MRD Neg status by RT-qPCR provides valuable prognostic information (n=76 patients with NPM1m AML attaining CR/CRi w frontline VEN + LDAC or HMA)



Most cancers are NOT hereditary : but a substantial minority are!



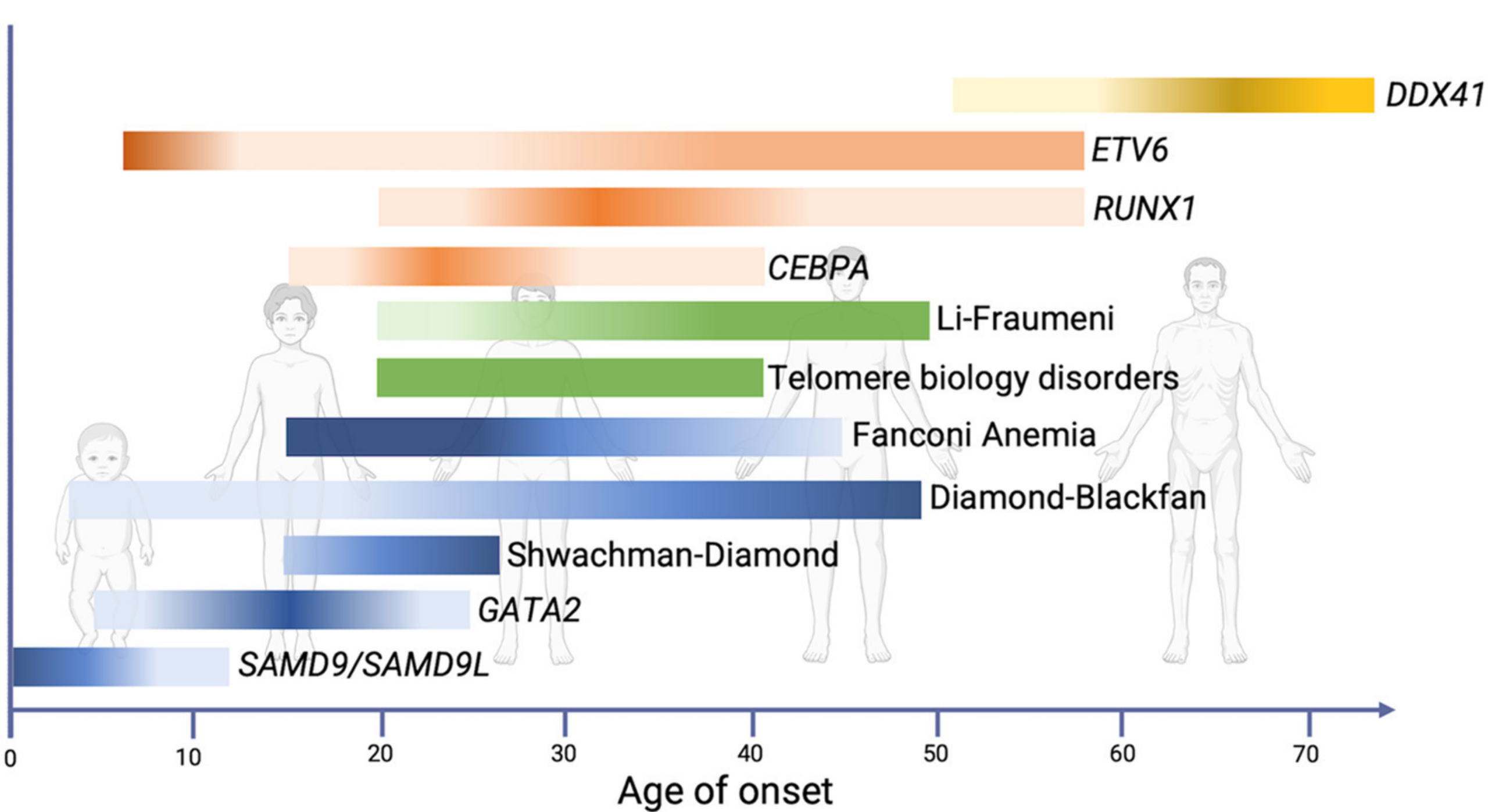
Example: Familial lymphoma

- First degree relatives of an individual affected with a lymphoid malignancy have between at 1.7-8.5-fold increased risk to develop a lymphoid malignancy (CLL the highest risk)
- Twin studies of monozygotic twins show 100-fold increased risk for HL
- But very few causative single genes identified

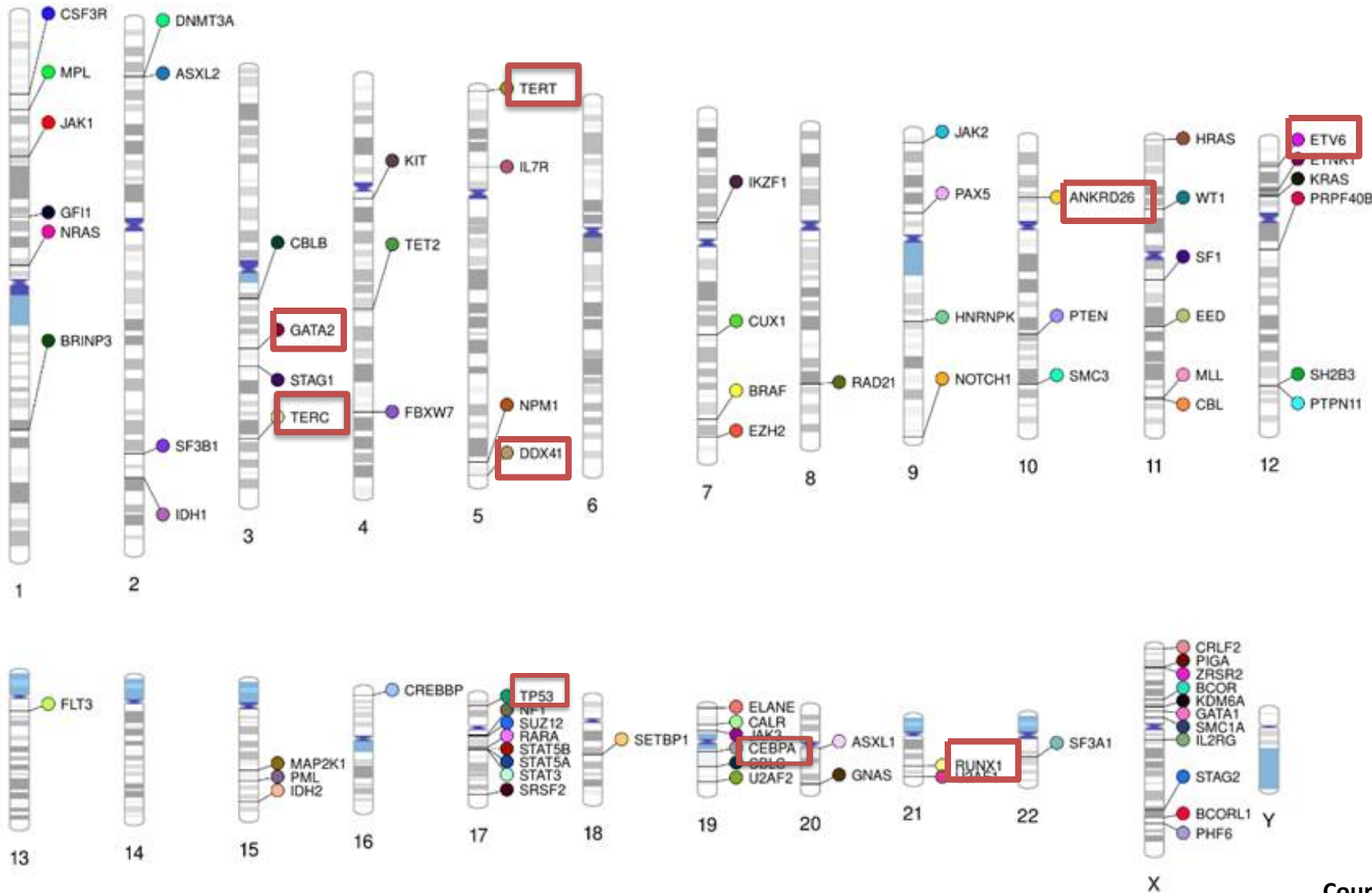
Clinical Features Prompting Consideration of Genetic Testing

Clinical features
Personal history of ≥ 2 cancers, 1 of which is a hematopoietic malignancy (order does not matter)
Personal history of a hematopoietic malignancy plus: <ul style="list-style-type: none">• Another relative within two generations with another hematopoietic malignancy, or• Another relative within two generations with a solid tumor diagnosed at age 50 or younger, or• Another relative within two generations with other hematopoietic abnormalities
Presence of a deleterious gene variant in tumor profiling that could be a germline allele, especially if that variant is present during remission*
Age of diagnosis of hematopoietic malignancy at an earlier age than average (eg, MDS diagnosed ≤ 40 y)
Germline status of a variant is confirmed by:
Its presence in DNA derived from a tissue source not likely to undergo somatic mutation frequently (eg, cultured skin fibroblasts or hair follicles) AND at a variant allele frequency consistent with the germline (generally considered between 30-60%), or
Its presence in at least two relatives at a variant allele frequency consistent with the germline

***Certain gene alleles (i.e. *DDX41* truncating variants) are overwhelmingly likely to be germline and should prompt consideration of germline testing**



Our MDACC Heme Malignancy NGS “EndLeukemia” Panel (designed for somatic mutations)



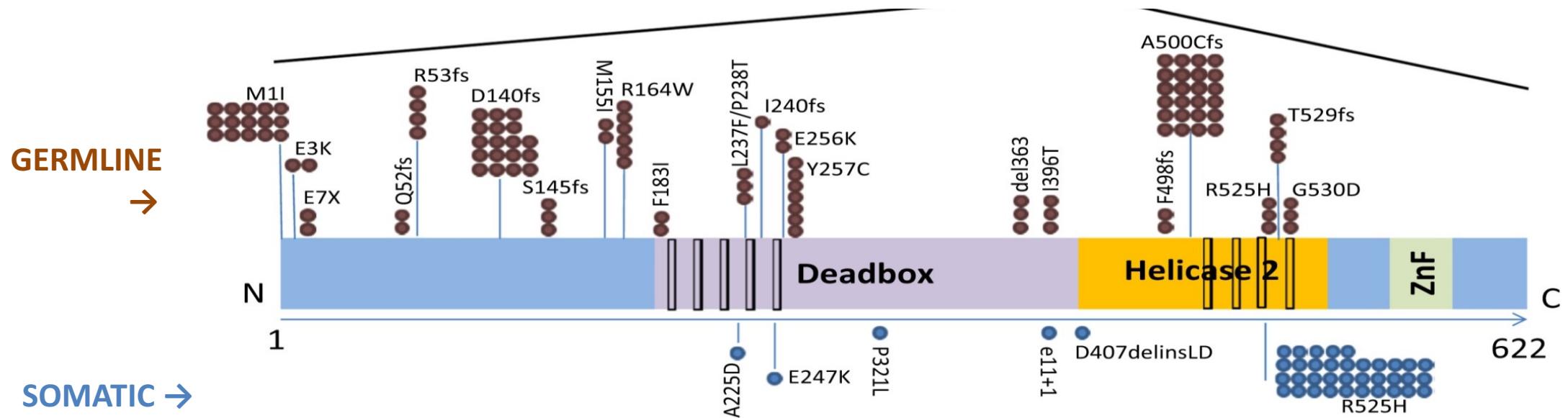
- Identification of a pathogenic mutation at heterozygous frequency (VAF ~50%) in a “red-box” gene(s) should prompt *consideration* of germline status
- **But this does not replace genetic testing!** Many NGS panels do NOT sequence the entire gene, do not test promoter and intron regions, will miss small deletions, and does not test all relevant HMM genes

How do you order genetic testing?

1. You shouldn't perform genetic testing on peripheral blood or buccal or saliva samples in patients with active heme malignancy
... you will NOT be able to tell what is somatic and what is germline since you are testing the circulating tumor !
2. Cultured skin fibroblasts from a skin **punch** biopsy (not a shave biopsy) is the gold standard.
3. Many clinical genetic testing labs do **not** have ability to process skin samples (and these procedures take time and planning)
4. Nail clippings and hair follicles also provide appropriate germline DNA - but very small amounts and not routine for most labs (yet)

DDX41-associated susceptibility to heme malignancies

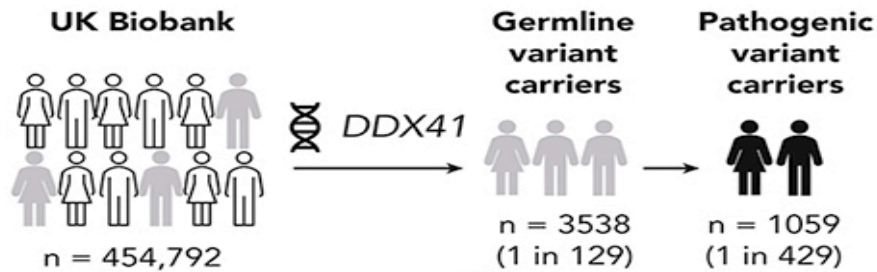
- Autosomal dominant MDS/AML often presenting at older age (median 65 yrs) often with hypocellularity and diploid cytogenetics
- RNA helicase enzyme involved in RNA metabolism, spliceosome function, ribosome biogenesis and innate immune regulation



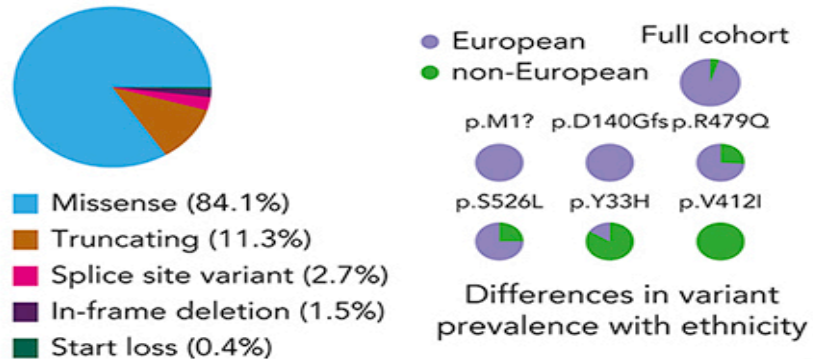
Prevalence and significance of DDX41 variants in the general population

DDX41 Germline Variants: Prevalence and Associated Phenotypes

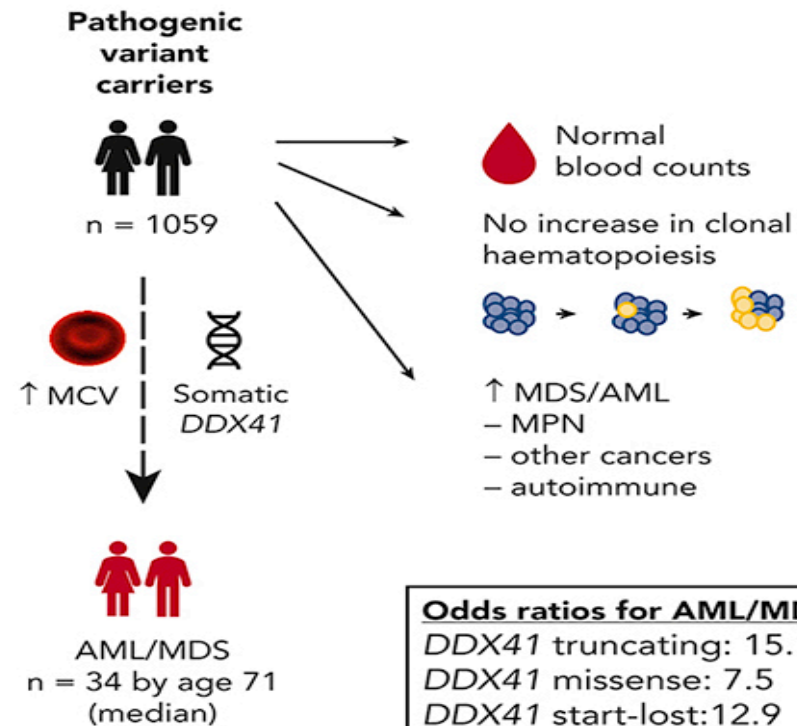
DDX41 germline variant prevalence



DDX41 variant characteristics



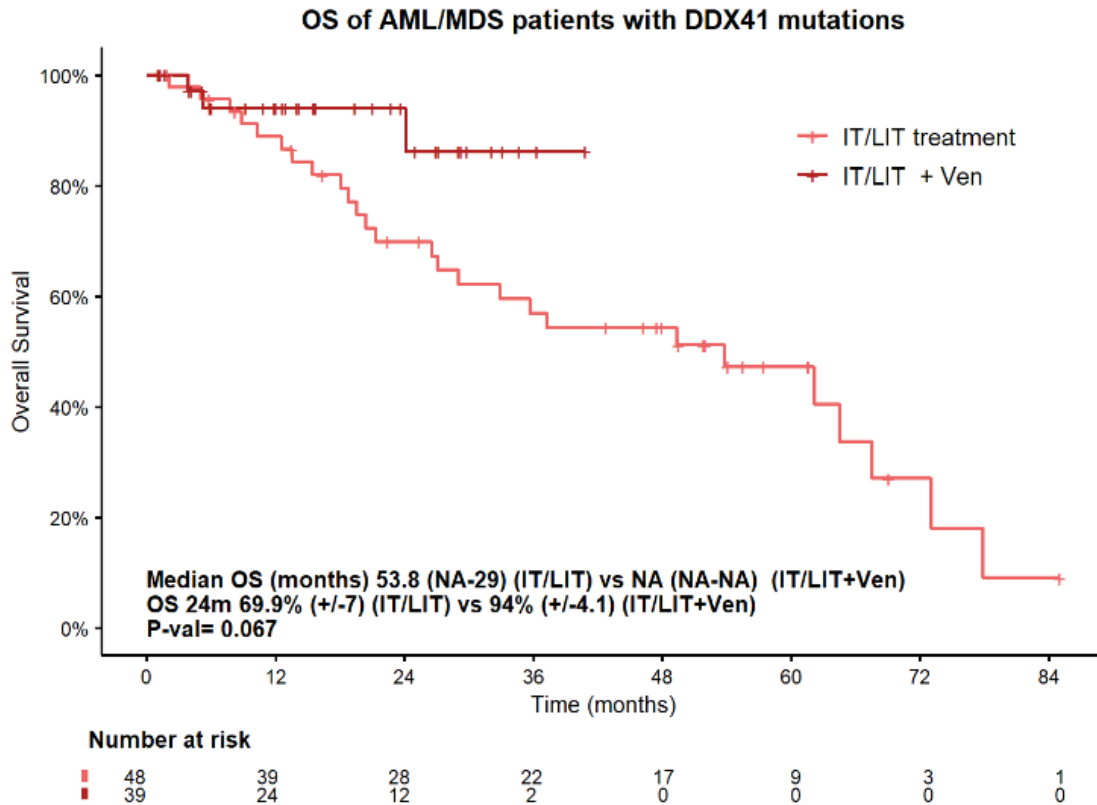
MDS/AML risk and other phenotypes in DDX41 germline pathogenic variant carriers



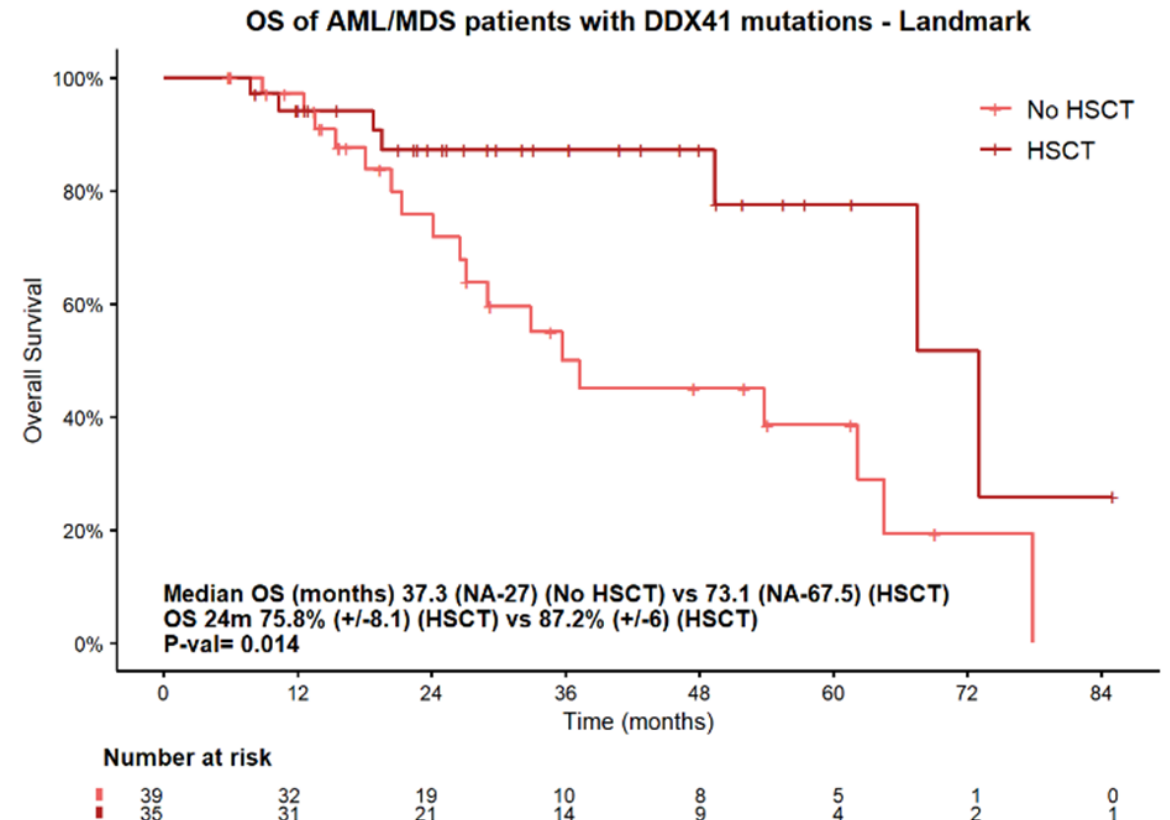
- DDX41 germline variants common in general population (1 in 129 individuals)
- **DDX41 germline PATHOGENIC variants relatively common (1 in 429 individuals)**

MDACC Experience: Improved OS with Venetoclax and HSCT

Improved Outcomes with addition of VEN

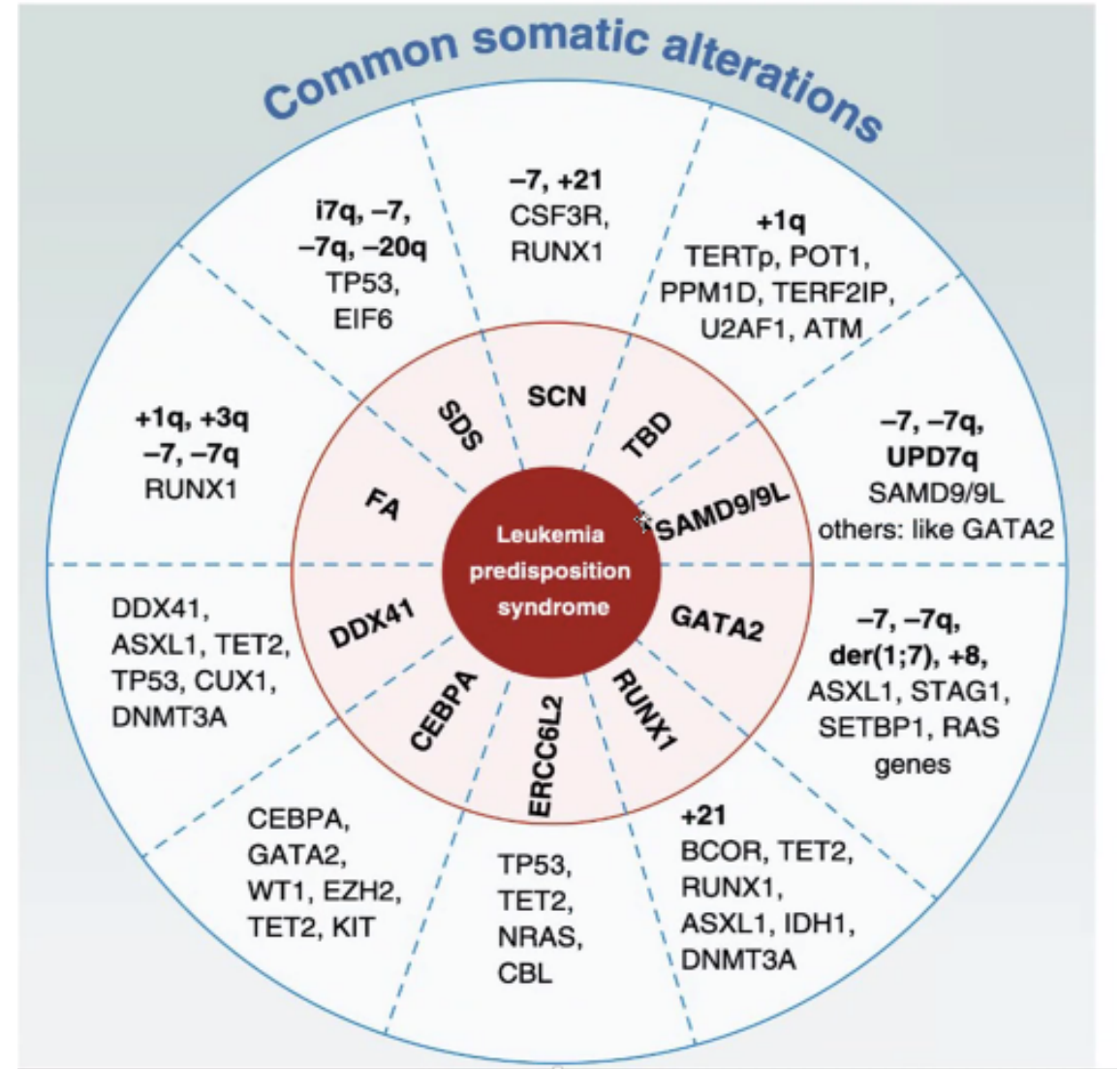


Improved Outcomes with HSCT*



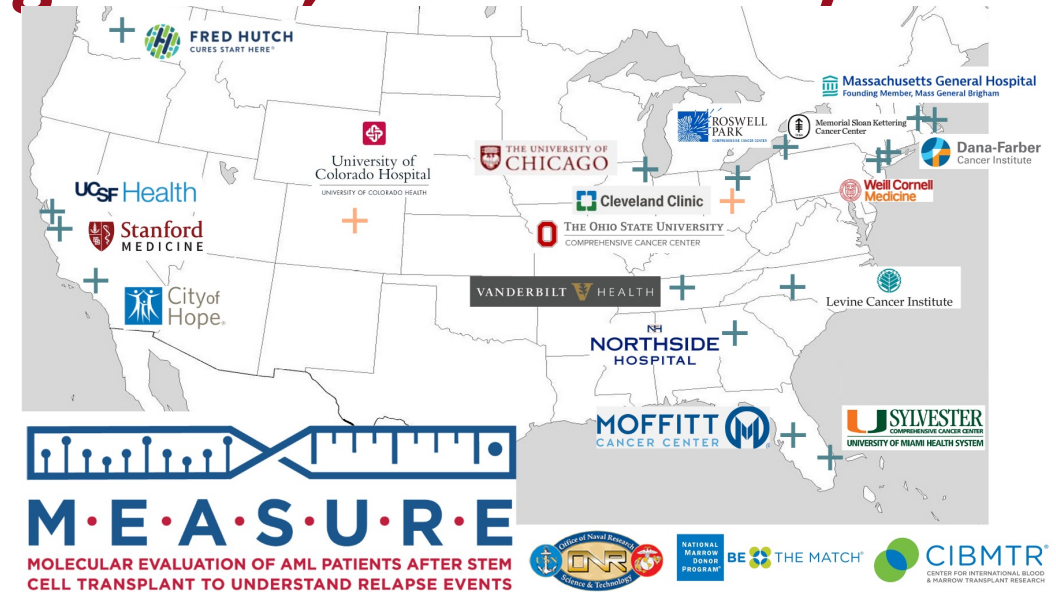
* post-transplant cyclophosphamide as standard of care

Common somatic alterations in pts with HHMs



The MEASURE Genome Atlas (Hourigan Lab; Yu #455 ASH)

- MEASURE clinical protocol (NCT05224661)
- 18 high-volume transplant centers in the US
- Adult with AML undergoing Allogeneic hematopoietic cell transplantation (alloHCT) in CR
- **N=255 patients included**
- AML Temporal Landscape Analysis by Sequencing (“ATLAS”)
- **Samples:**
 - Time of diagnosis (TOD)
 - Complete Remission (CR)
- **WGS on Illumina platform**
 - TOD: 59-300X (median=117X)
 - CR: 24-89X (median=37X)
- **Bioinformatics framework:**
 - DRAGEN Heme WGS Tumor Only analysis
 - DRAGEN Tumor/CR paired analysis
 - Other secondary analysis as indicated

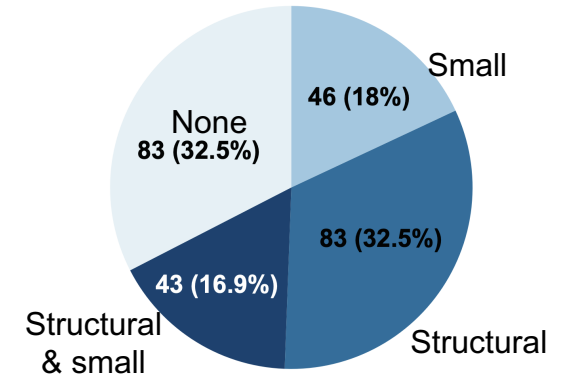


Total patients (n=255)			
Age		CR sample collection to tumor sample collection	
median: 59 (19-79)		median: 110 days (38-1983)	
Sex		Tumor Sample Type	
Female	119 (47%)	BM	180 (71%)
Male	136 (53%)	PB	75 (29%)
Ethnic		ELN 2022	
Hispanic or Latino	23 (9%)	Favorable	36 (14%)
Not Hispanic or Latino	222 (87%)	Intermediate	72 (28%)
Not reported/Unknown	10 (4%)	Adverse	147 (58%)
Race			
White	189 (74%)		
Native Hawaiian or Other Pacific Islander	3 (1%)		
Black or African American	16 (6%)		
Asian	20 (8%)		
American Indian or Alaska Native	4 (2%)		

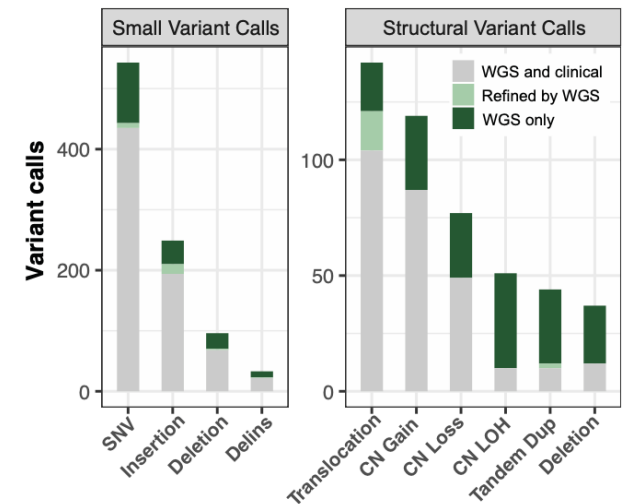
~70% pts had AML/cancer-related features identified by WGS



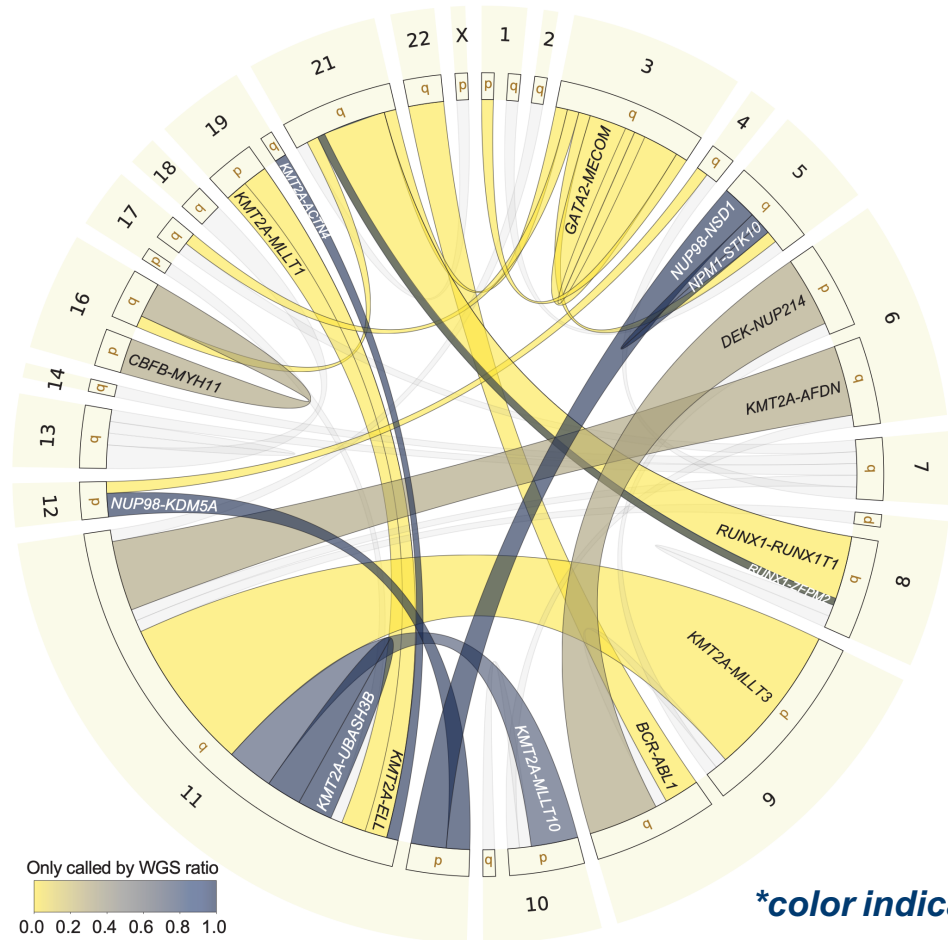
Patients with novel genomic findings by WGS (Oncogenic variants)



Additional findings in each category

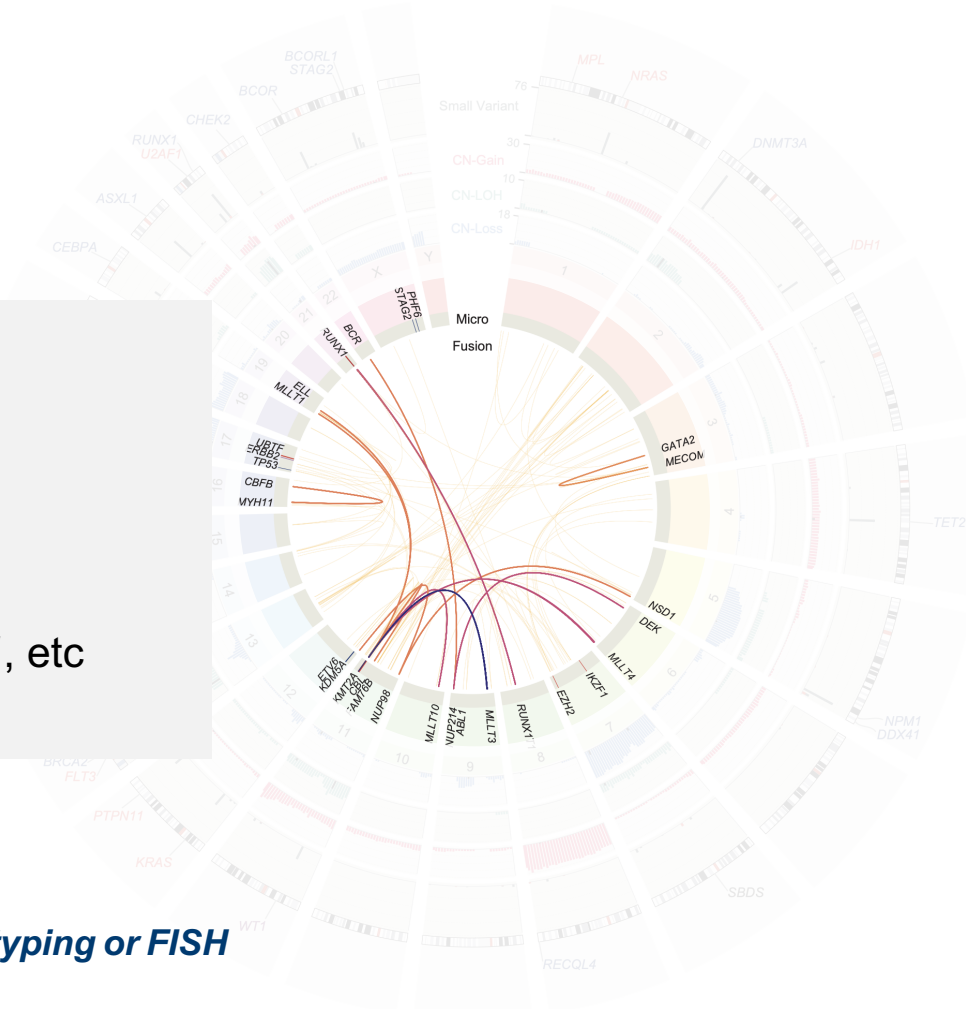


Driver fusion genes missed by standard cytogenetics

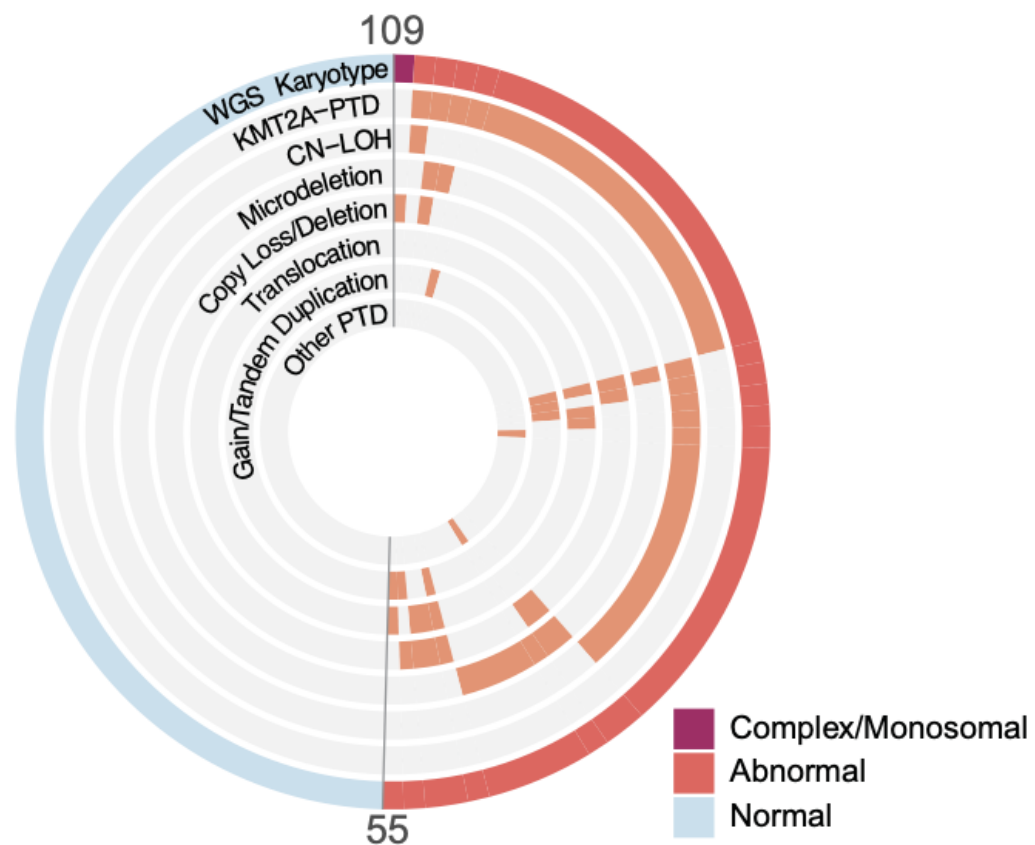


- *NUP98-r*
- Atypical *MECOM-r*
- Other cryptic fusions:
KMT2A, *RUNX1*, *NPM1*, etc

**color indicates the fraction missed by karyotyping or FISH*



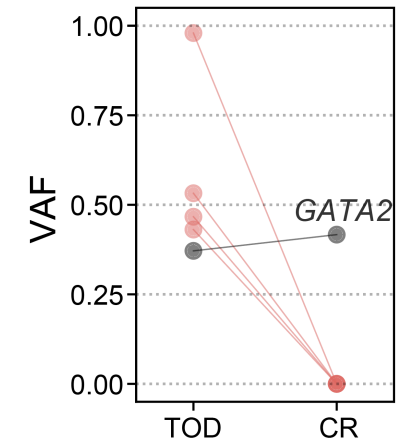
WGS reveals hidden genomics of normal karyotype AML



More than half of patients determined to be normal karyotype by metaphase cytogenetics are not normal by WGS

WGS at CR helps identify potential inherited myeloid malignancy predisposition variants

- WGS in CR identified oncogenic variants likely to be germline.
- **~10% of patients carry a likely germline variant that could cause autosomal dominant myeloid-predisposition syndrome.**
- >50% of these germline-risk patients would have been missed by routine clinical testing



AD myeloid neoplasm (n=25)	AR myeloid neoplasm (n=15)	Other cancer (n=6)
<i>DDX41</i> (n=6) <i>CHEK2</i> (n=5) <i>RUNX1</i> (n=4) <i>BRCA1</i> (n=2) <i>BRCA2</i> (n=2) <i>MPL</i> (n=2) <i>ATM</i> (n=1) <i>GATA2</i> (n=1) <i>MSH6</i> (n=1) <i>RTEL1</i> (n=1)	<i>SBDS</i> (n=5) <i>RECQL4</i> (n=2) <i>FANCA</i> (n=2) <i>FANCC</i> (n=1) <i>FANCE</i> (n=1) <i>FANCI</i> (n=1) <i>FANCD2</i> (n=1) <i>NBN</i> (n=1) <i>RAD51C</i> (n=1)	<i>CDKN2A</i> (n=1) <i>ERCC2</i> (n=1) <i>ERCC3</i> (n=1) <i>MSH3</i> (n=1) <i>RAD50</i> (n=1) <i>RAD51B</i> (n=1)

AD: Autosomal dominant

AR: Autosomal-recessive

Prognostic or potentially therapeutic significance from ATLAS genomes (n=255)

- WGS can recapitulate standard AML clinical diagnostic workup
- Enhanced resolution and coverage empowered to capture additional variant types
- WGS at CR allows further refinement, interpretation, and discovery of oncogenic variants.

Feature	Total cases (WGS only)	Potential clinical significance	Citation
Potentially germline AD predisposition myeloid neoplasm	25 (14)	Practice guidelines on disease management and risk assessment	NCCN Guidelines; PMID: 35797463
Additional ELN prognostic/predictive	N/A (31)	Risk stratification and targeted therapy selection	PMID: 35797463
<i>KMT2A-r</i>	27 (1)	Risk stratification and targeted therapy (including Menin inhibitors)	PMID: 35797463, 39121437
<i>KMT2A-PTD</i>	34 (24)	High-risk marker and on-going investigation into targeted therapies	PMID: 36725100, 40361241
<i>RUNX1-PTD/MD</i>	4 (4)	Potential risk stratification	PMID: 35797463
<i>NUP98-r</i>	5 (3)	High-risk marker and on-going investigation into targeted therapies	PMID: 38744828, 38890447, 40700635
<i>UBTF-ITD</i>	3 (3)	Pre-clinical evidence of sensitivity to menin inhibitors	PMID: 37890156
<i>SETD2</i>	5 (3)	Resistance to cytarabine-based chemotherapy, potentially overcome by combination with S & G2/M checkpoint inhibition	PMID: 30967619
<i>RIT1</i>	5 (4)	Evidence of sensitivity to SHP2 inhibitors, RAS nucleotide exchange inhibition, RAS tri-complex inhibitors in lung cancer	PMID: 40644578
<i>POLE, LRP1B, ARID1A</i>	3 (3)	Clinical association with sensitivity to immune checkpoint inhibitors	PMID: 31415061, 33653800, 32111729
<i>BAP1</i>	1 (1)	Evidence of sensitivity to PARP inhibitors in multiple tumor types	PMID: 39626160
<i>SOS1</i>	1 (1)	On-going investigation into targeted therapies in multiple tumor types	PMID: 39488215, NCT06104488, NCT05578092

Conclusions

- AML therapeutic options continue to improve, with increasingly individualized and effective treatments
- Awareness of genomics (cytogenetics and mutational data) are essential to determine optimal treatment
- MRD testing is critical to guide post-remission decisions: MRD standardization approaches have expanded access
- Inherited predispositions to heme malignancy are not so rare! Requires attention and often additional work-up and evaluation

