

Dr. Jekyll and Mr. Hyde in AML: Understanding the *NPM1* Mutation

Jeffrey Lancet, MD

Chair, Department of Malignant Hematology

Moffitt Cancer Center

Tampa, FL

Disclosures

- Consulting: Treadwell Therapeutics, Bristol Myers Squibb, Moderna, AbbVie
- Research Funding: AbbVie

Dr. Jekyll and Mr. Hyde



Jekyll vs Hyde

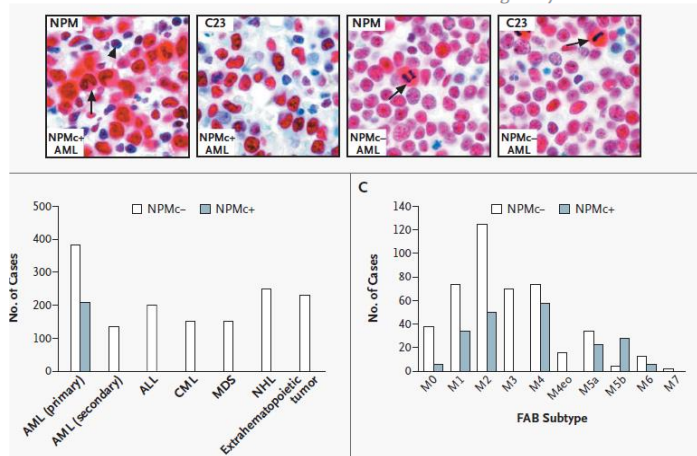


- Age
- Classification
- Outcomes with various chemotherapeutic approaches
- Impact as in setting of mutations (including FLT3)
- Impact in setting of MRD positivity or negativity
- Efficacy with maintenance therapy
- Pertinence to novel therapeutics

ORIGINAL ARTICLE

Cytoplasmic Nucleophosmin in Acute Myelogenous Leukemia with a Normal Karyotype

Brunangelo Falini, M.D., Cristina Mecucci, M.D., Ph.D., Enrico Tiacci, M.D., Myriam Alcalay, M.D., Ph.D., Roberto Rosati, Ph.D., Laura Pasqualucci, M.D., Roberta La Starza, M.D., Ph.D., Daniela Diverio, M.D., Emanuela Colombo, Ph.D., Antonella Santucci, M.D., Barbara Bigerna, Roberta Pacini, Alessandra Pucciarini, Ph.D., Arcangelo Liso, M.D., Marco Vignetti, M.D., Paola Fazi, M.D., Natalia Meani, Ph.D., Valentina Pettirossi, Ph.D., Giuseppe Saglio, M.D., Franco Mandelli, M.D., Francesco Lo-Coco, M.D., Pier-Giuseppe Pelicci, M.D., Ph.D., and Massimo F. Martelli, M.D., for the GIMEMA Acute Leukemia Working Party*



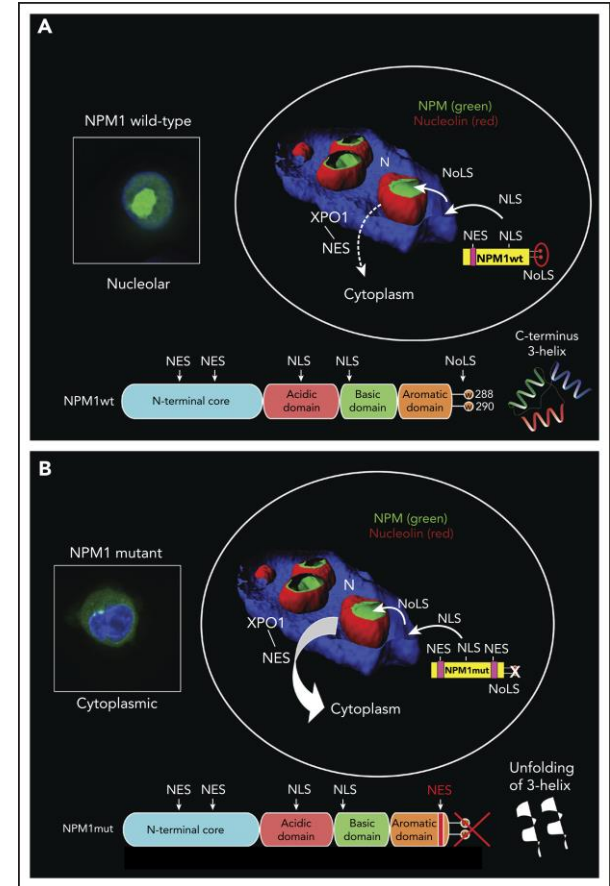
NPM1 structure, function, features

Biology and Function

- Multifunctional ubiquitous shuttling protein
- Primarily localized to nucleolus in WT form
- Mutant form relocalized to cytosol

Features in AML

- Most common genetic lesion in adult AML (30-40%)
- Typically associates with normal karyotype
- Genetically defined AML subtype per ICC-2022 and WHO 2022, irrespective of blast %
- AML driver mutation, not observed in clonal hematopoiesis
- Frequently co-occurs with mutant *FLT3*, *IDH1/2*, *DNMT3A*

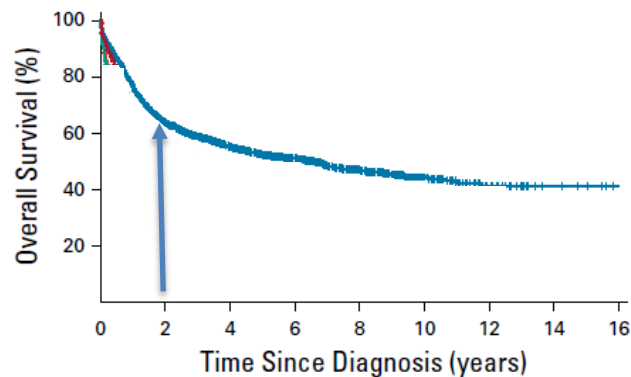


NPM1m AML Generally Considered Favorable Risk

Table 6. 2022 ELN risk classification by genetics at initial diagnosis*

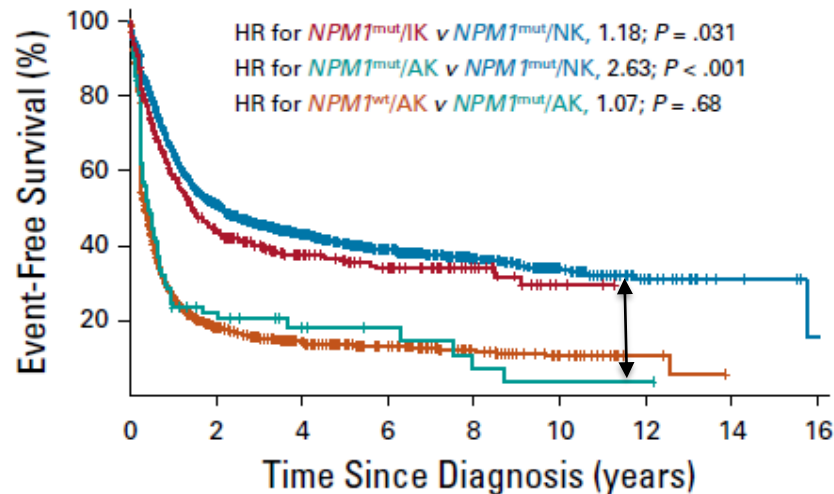
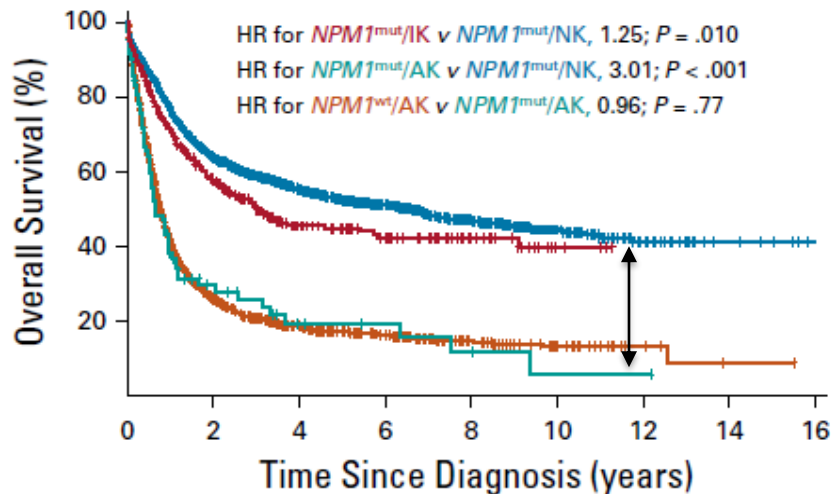
Risk category†	Genetic abnormality
Favorable	<ul style="list-style-type: none"> t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡ inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/CBFB::MYH11†,‡ Mutated NPM1†,§ without FLT3-ITD bZIP in-frame mutated CEBPA
Intermediate	<ul style="list-style-type: none"> Mutated NPM1†,§ with FLT3-ITD Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/MLL3::KMT2A†,¶ Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	<ul style="list-style-type: none"> t(6;9)(p23.3;q34.1)/DEK::NUP214 t(v;11q23.3)/KMT2A-rearranged# t(9;22)(q34.1;q11.2)/BCR::ABL1 t(8;16)(p11.2;p13.3)/KAT6A::CREBBP inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1) t(3q26.2;v)/MECOM(EVI1)-rearranged -5 or del(5q); -7; -17/abn(17p) Complex karyotype,** monosomal karyotype†† Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡ Mutated TP53^a

NPM1m, normal karyotype, FLT3 neg/low



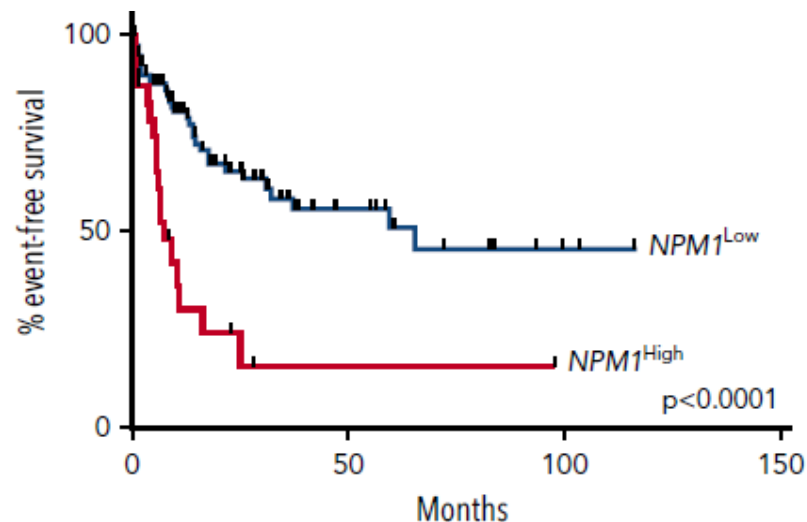
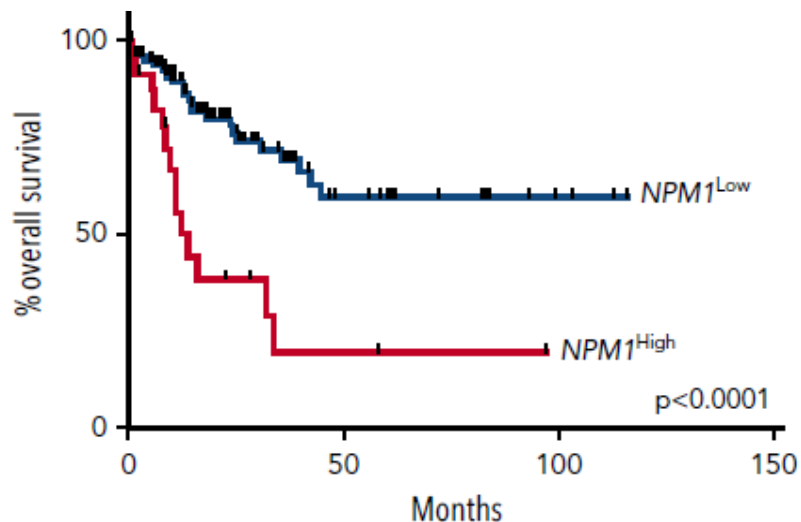
*NPM1*m AML with Adverse Cytogenetics

(*FLT3-ITD* negative or low)

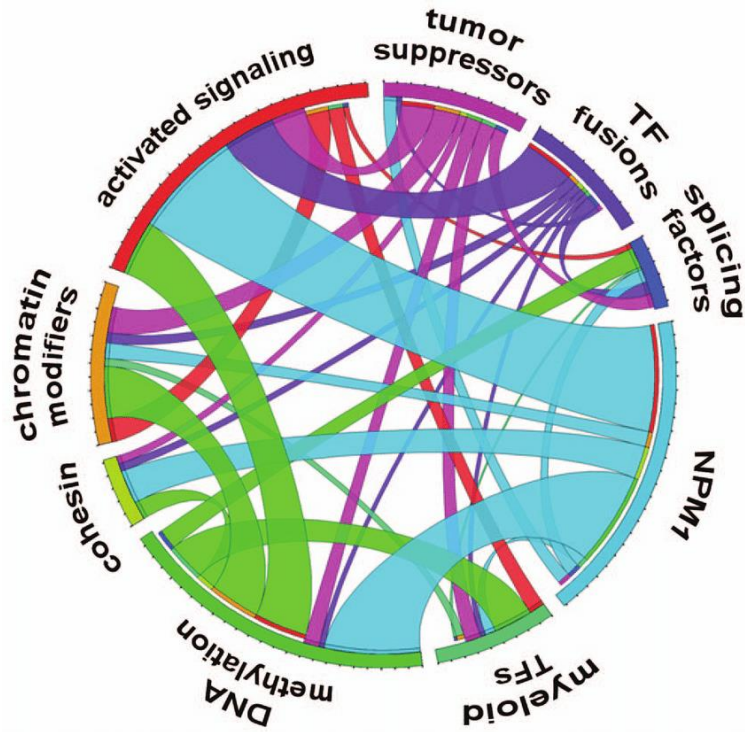


NPM1 Mutation Burden May Associate with Adverse Outcomes

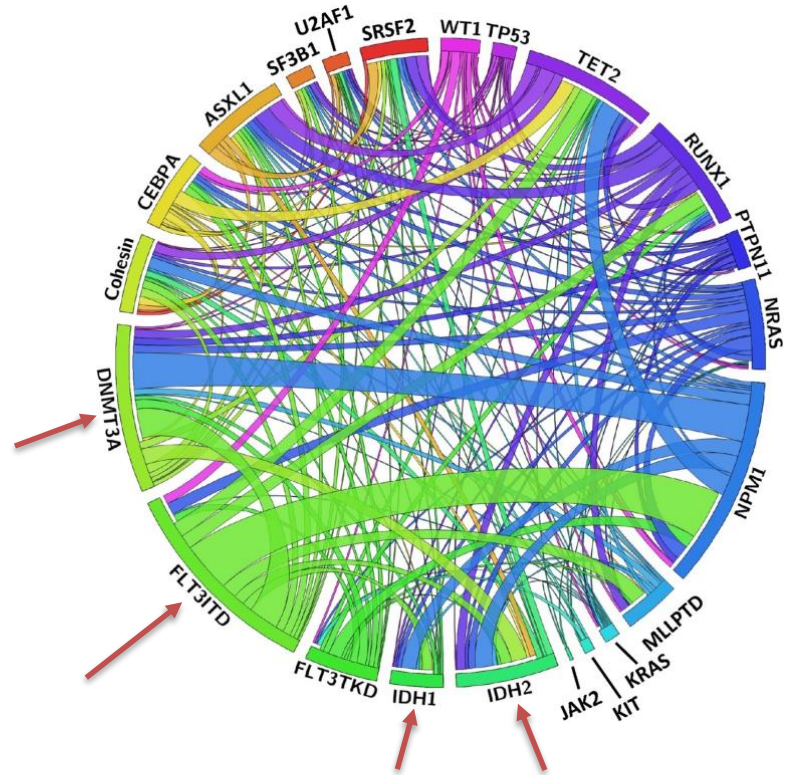
VAF ≥ 0.44 (high) vs < 0.44 (low)



NPM1 Mutational Co-occurences

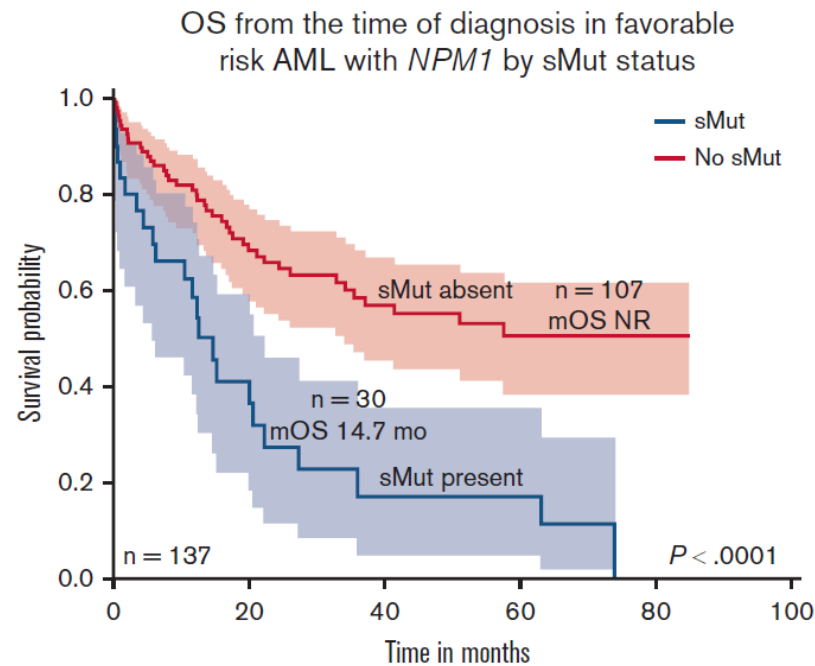
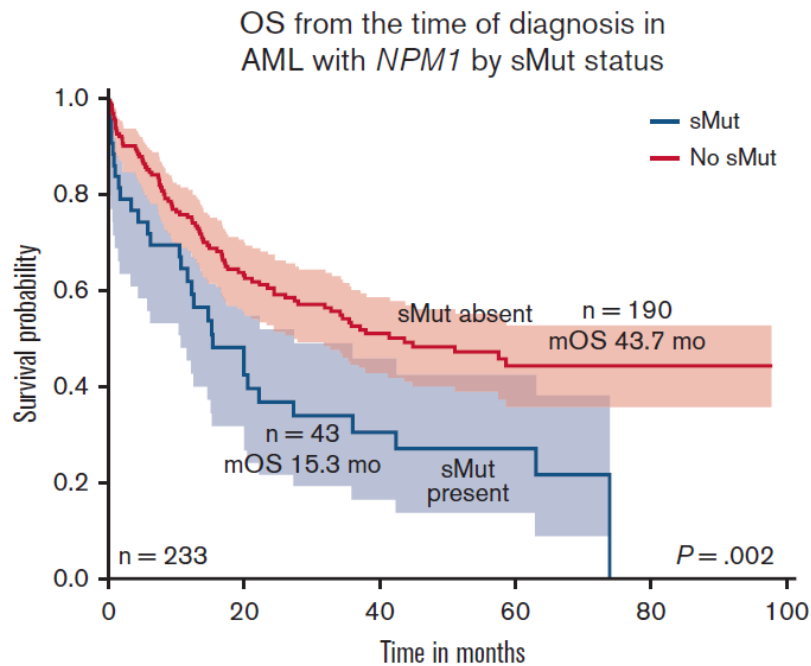


Fathi, et al. ASCO Educ 2014

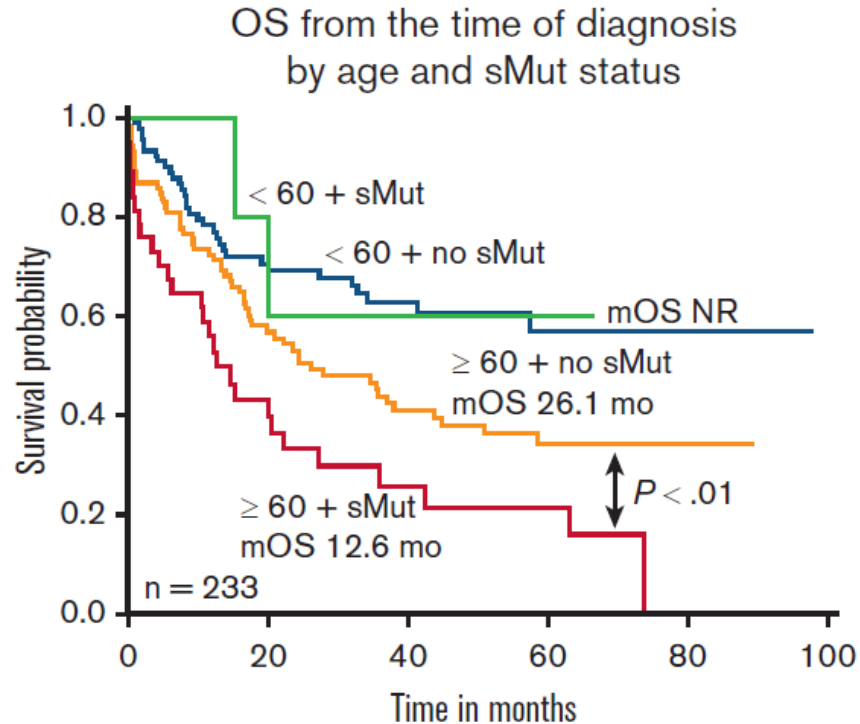


Hou and Tien, J Biomed Sci 2020; 27:81

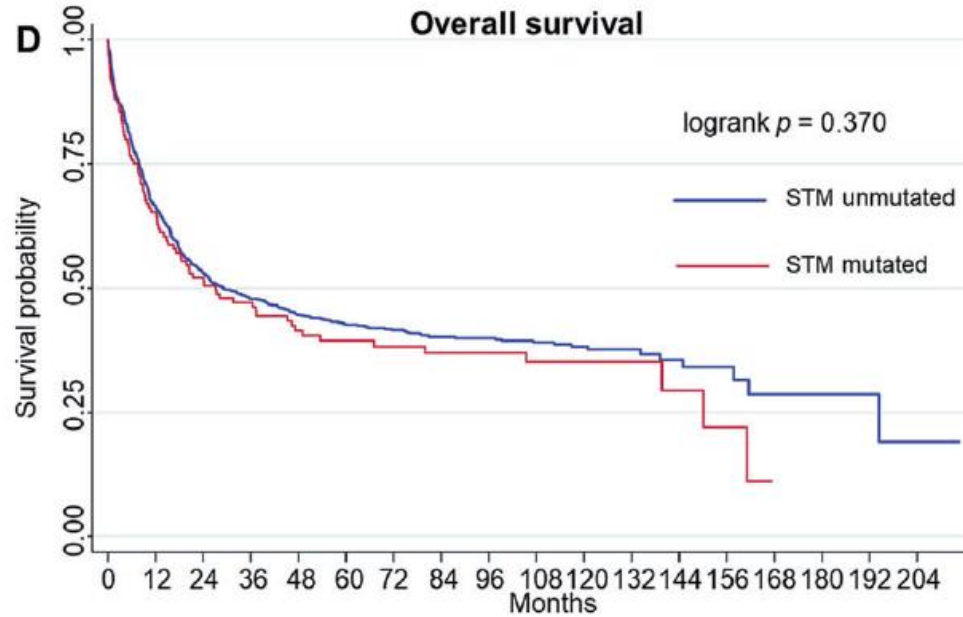
Secondary Mutations in Presence of *NPM1m* Associate with Inferior Outcomes



Effect of Secondary Mutations on Outcome in *NPM1m* AML by Age

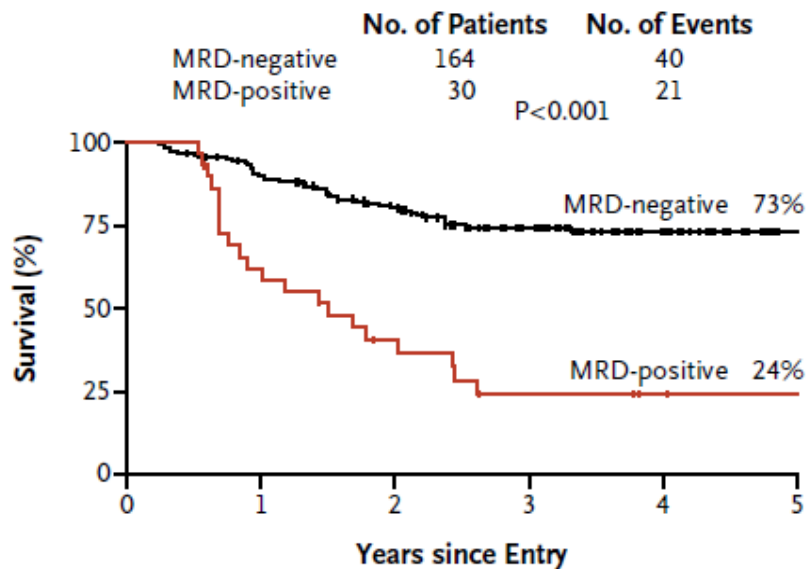


Or Do They?



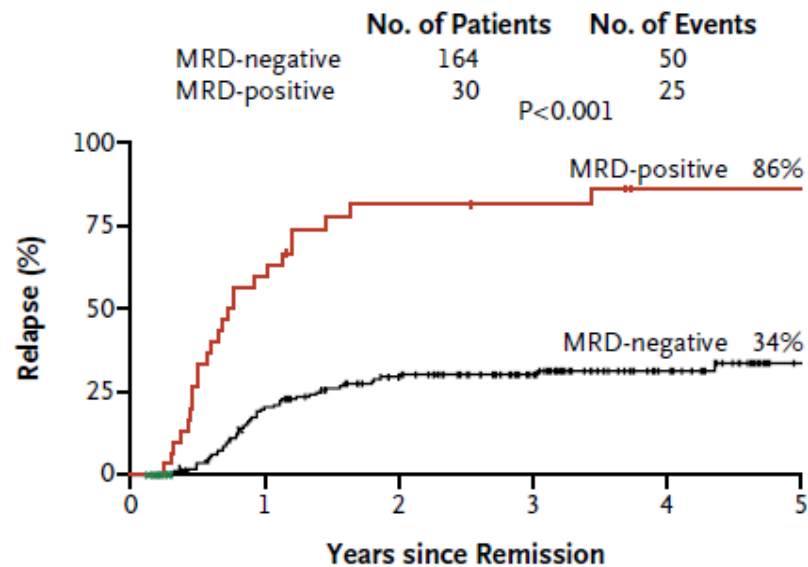
Effect of MRD in *NPM1m* AML

- qPCR after 2 cycles of chemotherapy



No. at Risk

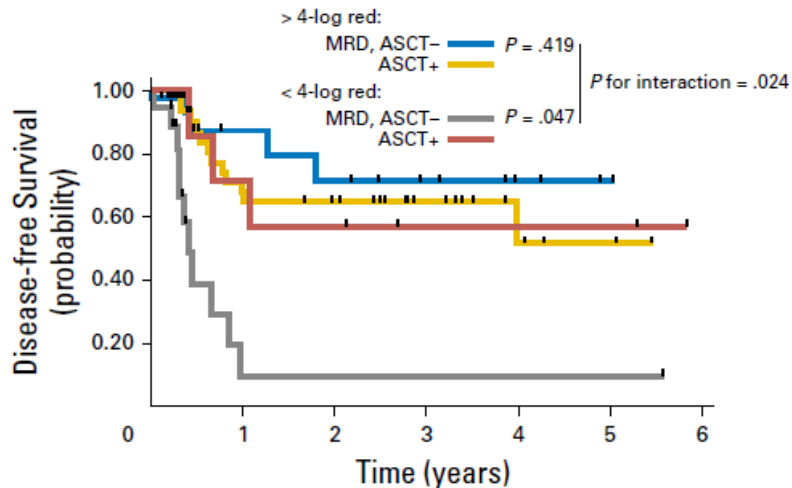
MRD-negative	164	144	116	77	39	8
MRD-positive	30	18	10	5	3	2



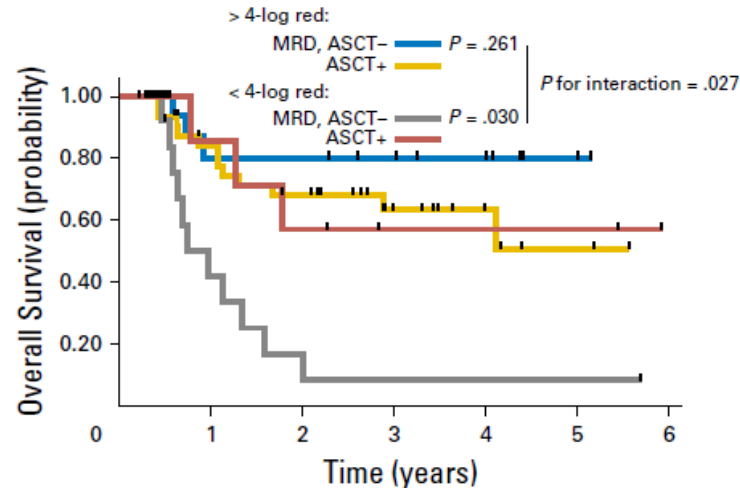
No. at Risk

MRD-negative	164	120	93	64	33	6
MRD-positive	30	12	5	4	1	1

NPM1 MRD Overcome with Allo HCT?



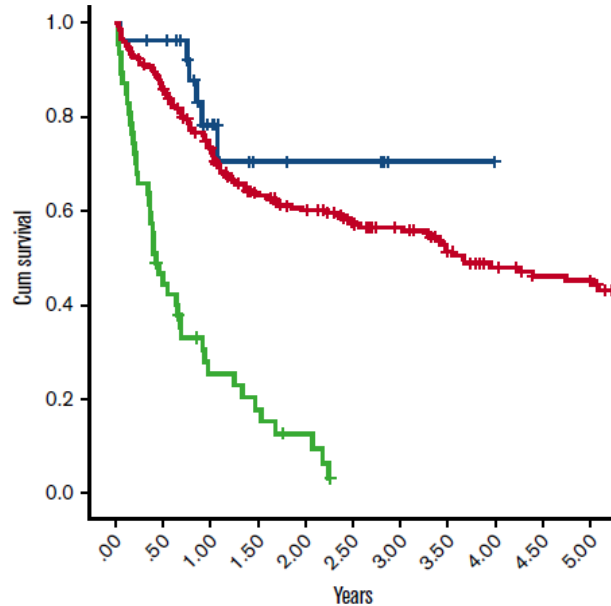
No. at risk:	0	1	2	3	4	5	6
> 4-log red: 45	11	9	6	3	1	0	
MRD, ASCT-							
ASCT+	0	21	19	10	4	2	0
< 4-log red: 19	1	1	1	1	1	0	
MRD, ASCT-							
ASCT+	0	5	4	2	2	2	0



No. at risk:	0	1	2	3	4	5	6
> 4-log red: 45	11	11	8	5	1	0	
MRD, ASCT-							
ASCT+	0	27	21	10	5	2	0
< 4-log red: 19	5	2	1	1	1	0	
MRD, ASCT-							
ASCT+	0	6	4	2	2	2	0

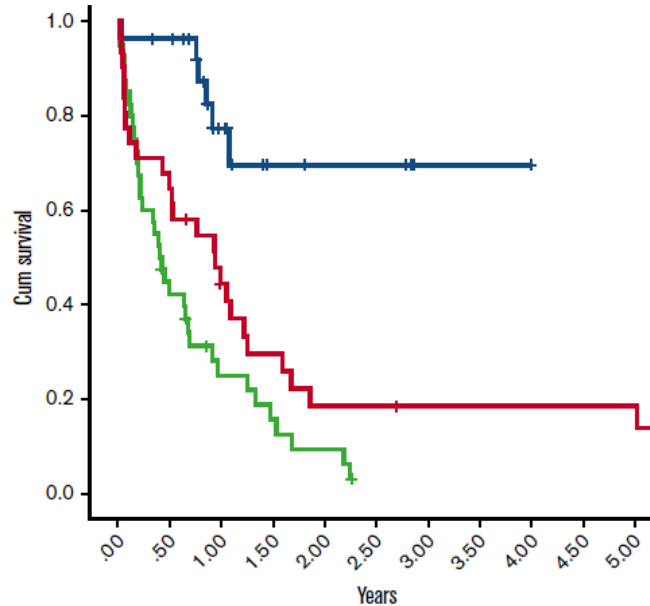
HMA/Ven outcomes with *NPM1m*

All Patients



Treatment Group	Median OS (years)	p-value
HMA+Ven (n=28)	NR	-
HMA (n=47)	0.4 (.29-.56)	< 0.001
IC (n=228)	3.7 (2.5-4.8)	0.292

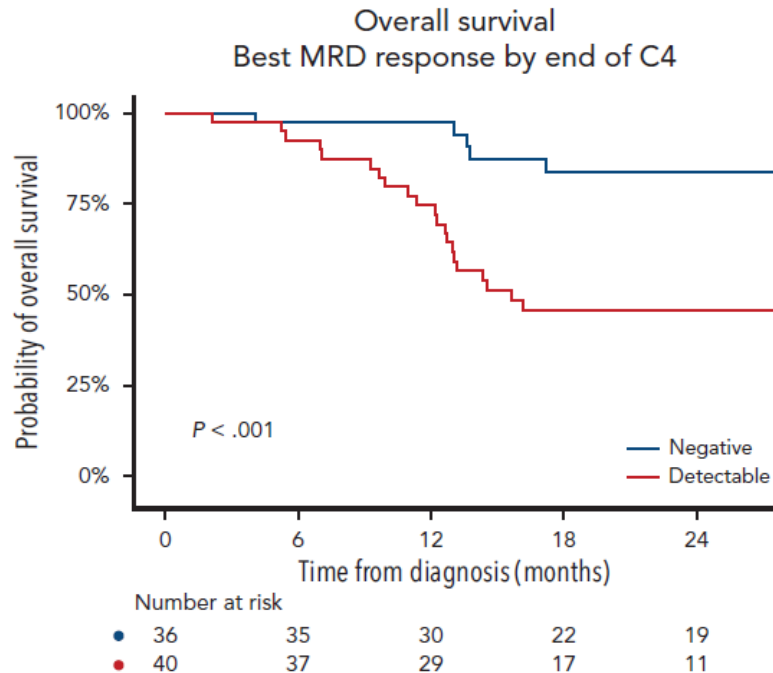
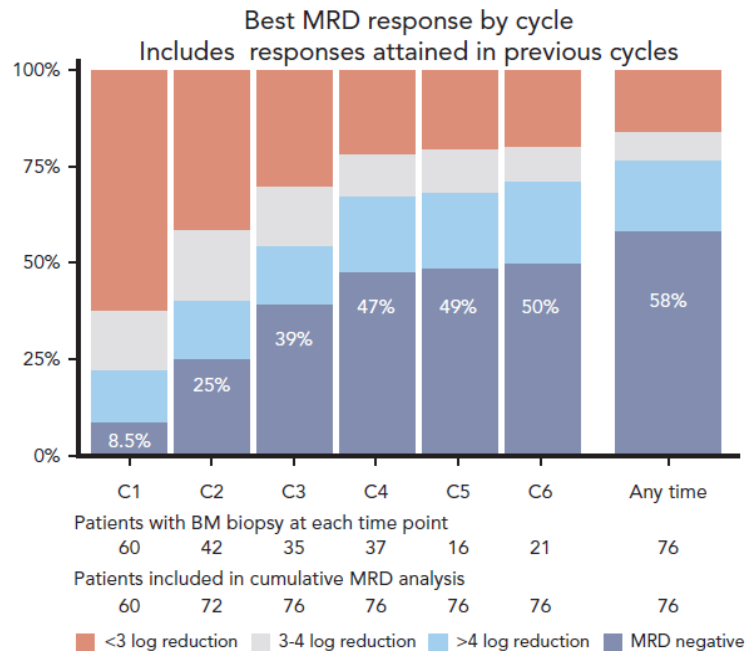
Age > 65



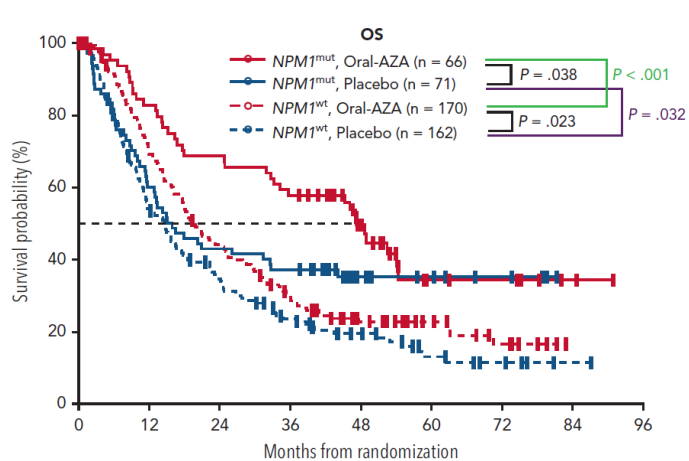
Treatment Group	Median OS (years)	p-value
HMA+Ven (n=26)	NR	-
HMA (n=39)	0.4 (.25-.56)	< 0.001
IC (n=25)	0.9 (0.3-1.5)	< 0.001

CR_c = 96%

NPM1m MRD in HMA/Ven Treated Patients

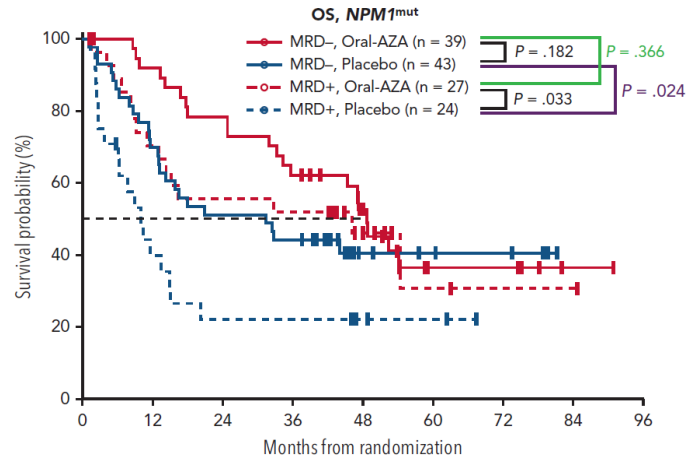


Beneficial Effect of Oral Azacitidine Maintenance in *NPM1m* AML



Median OS, months

<i>NPM1</i> ^{mut} , Oral-AZA	47.2	<i>NPM1</i> ^{wt} , Oral-AZA	19.6
<i>NPM1</i> ^{mut} , Placebo	15.9	<i>NPM1</i> ^{wt} , Placebo	14.6



Median OS, months

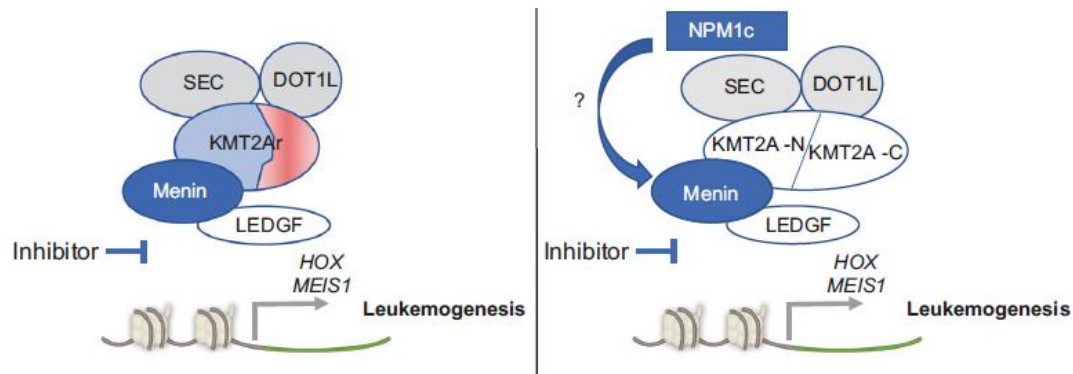
MRD-, Oral-AZA	48.6	MRD+, Oral-AZA	46.1
MRD-, Placebo	31.4	MRD+, Placebo	10.0

MRD+ to MRD- conversion rate in *NPM1m* patients:

63% with oral Aza

33% with placebo

Menin Inhibitors – Role in *NPM1m* AML?



Alterations with upregulated *HOX*

Alteration/Mutation

KMT2A-PTD
NPM1-MLF1
NUP98r
SET-NUP214
RUNX1-EVI1
MYST3-CREBBP
CDX2-ETV6
CALM-AF10
MN1-ETV6

Cytogenetics

Normal karyotype
 t(3;5)(q25;q34)
 11p15 rearrangements
 t(9;9)(q34;q34)
 t(3;21)(q26;q22)
 t(8;16)(p11;p13)
 t(12;13)(p13;q12)
 t(10;11)(p13;q14-21)
 t(12;22)(p13;q12)

Phase 1 Menin Inhibitor Ziftomenib (KO-539)

Best Overall Response N (%)	200 mg	600 mg
<i>NPM1-m</i> Phase 1a + 1b	(n=6)	(n=20)
CR	1 (16.7)	7 (35.0)
CR/CRh	1 (16.7)	7 (35.0)
CRc	1 (16.7)	8 (40.0)
MRD negativity	1 (100.0)	4/6 (67) ¹
ORR	2 (33.3)	9 (45.0)
<i>KMT2A-r</i> Phase 1a + 1b	(n=14)	(n=18)
CR/CRh	0	1 (5.6)
CRc	0	2 (11.1)
MRD negativity	0	2 (100.0)
ORR	0	3 (16.7)

Age >18 years, AML only, Ph1 included all genotypes, Ph1b (*KMT2Ar*, *NPM1m*)

TRAEs: DS (25% G3, DLT), febrile neutropenia (13% G3 TEAEs)

RP2D (*NPM1-m*): 600 mg daily

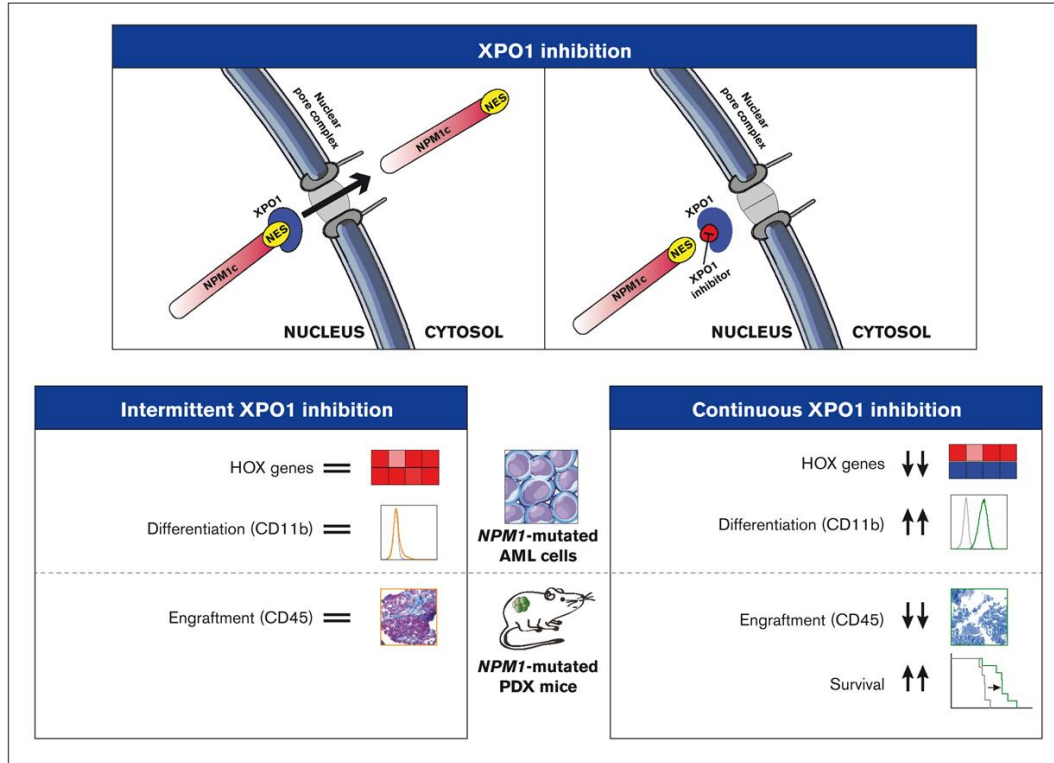
Current development for *KMT2Ar* in combination not as single-agent

***NPM1-m*:** median DoR 8.2 months (95% CI: 1.0 to NE)

¹ MRD was assessed for 5/7 CRc patients; 3 of those 5 patients (60%) tested were MRD negative
 CRc includes CR, CRh, CRi, CRp
 ORR includes CR, CRh, CRi, CRp, MLFS, DoR, duration of response

Data Cut
KMT2Ar: 24-Oct-2022
NPM1-m: 12-Apr-2023

Other Potential Interventions for *NPM1m* AML



Summary

- *NPM1m* AML is clinically heterogeneous
- Key adverse co-occurring factors include
 - Poor-risk cytogenetics
 - *FLT3* ITD mutations
 - ? Secondary-like mutations
- MRD monitoring in *NPM1m* AML is relevant and useful
- HMA/Ven regimens appear effective in *NPM1m* AML
- Novel therapies being developed to target *NPM1m* AML



THANK YOU

Jeffrey.Lancet@moffitt.org

