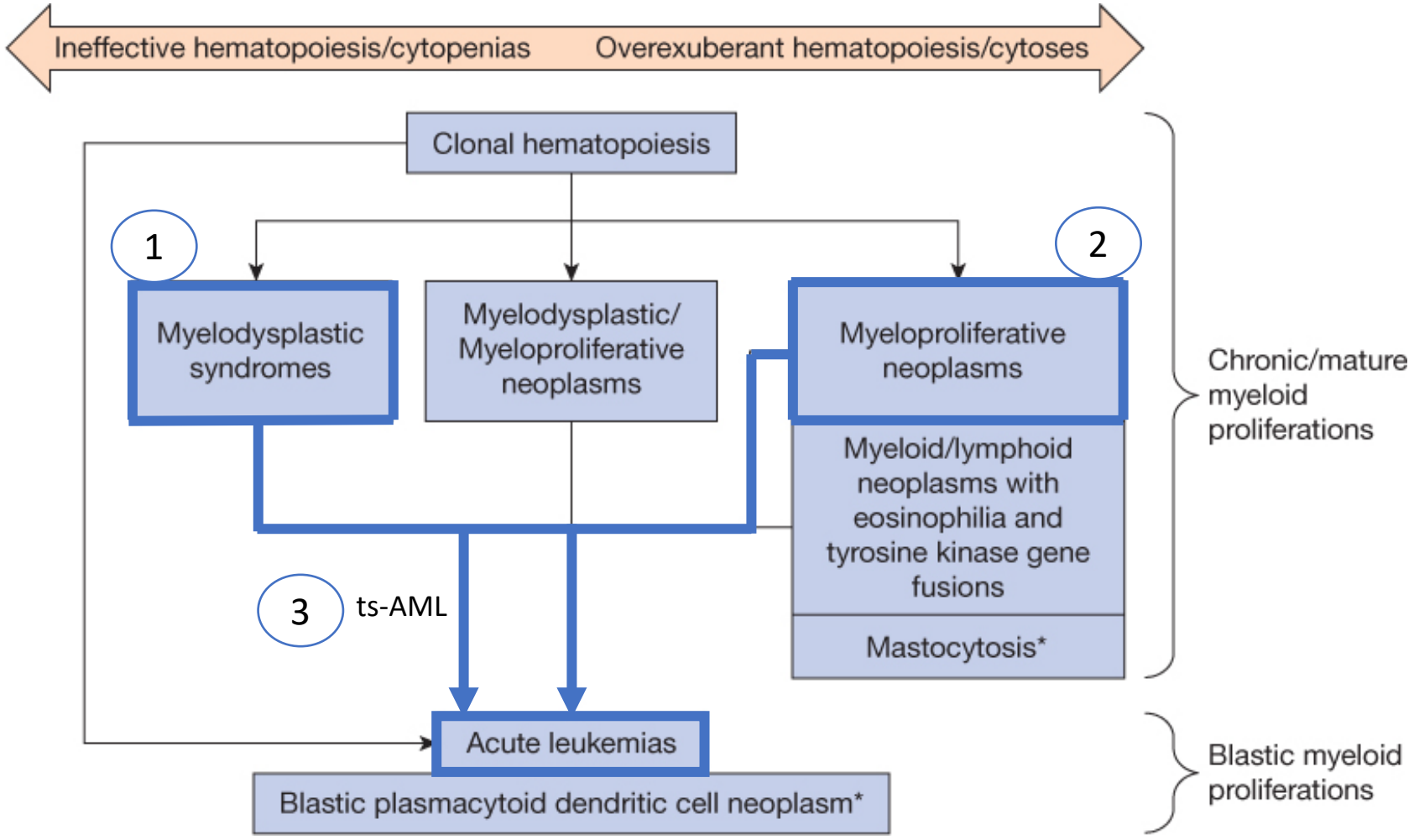
Semi-intensive therapy for secondary AML

Andrew Wei

Peter MacCallum Cancer Centre and Royal Melbourne Hospital

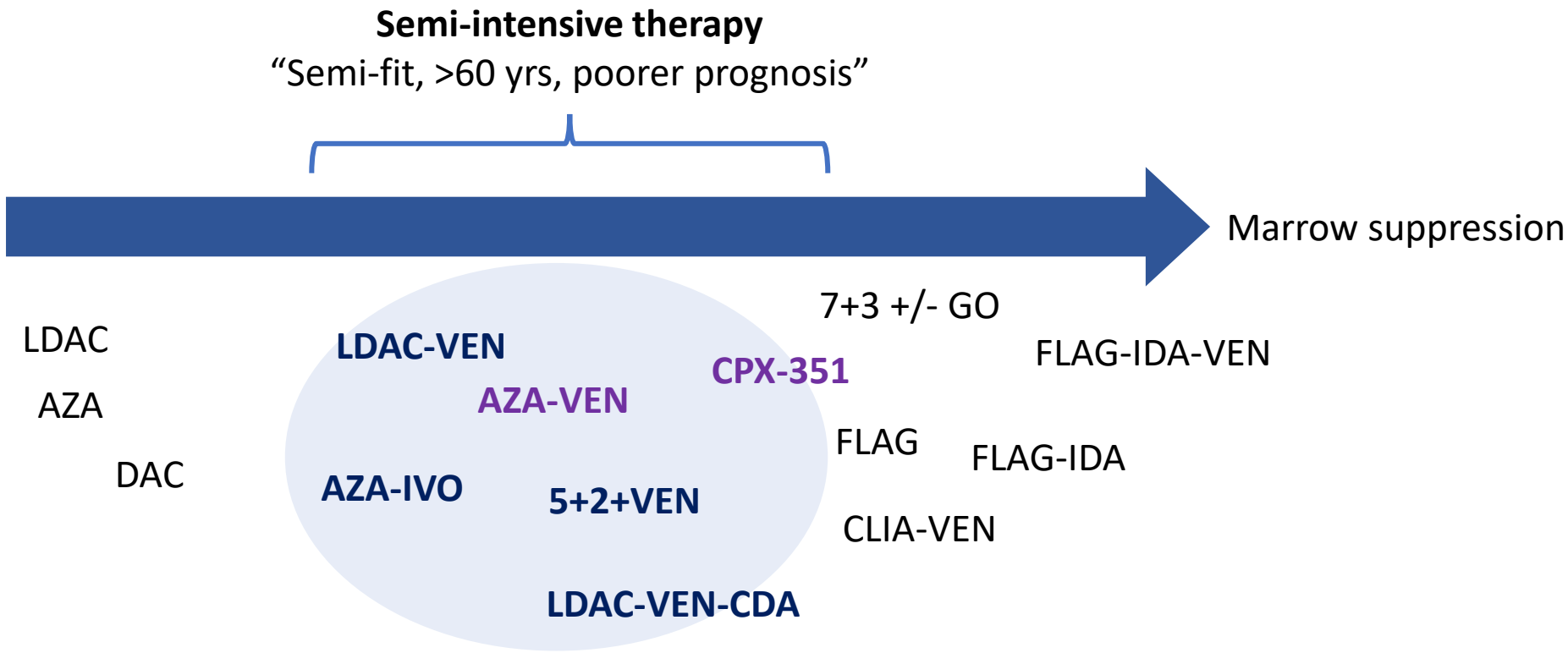
Walter and Eliza Hall Institute of Medical Research

AML with antecedent hematologic disease



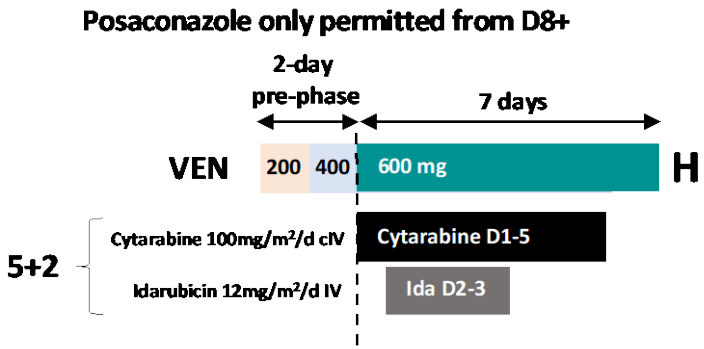
Arber, Daniel, A. et al. The International Consensus Classification of Myeloid and Lymphoid Neoplasms. Wolters Kluwer Health, 2024

AML induction options

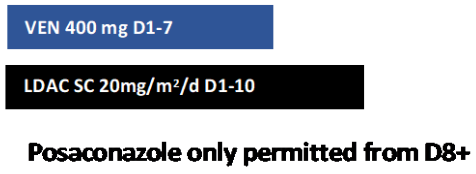


5+2+VEN (CAVEAT)

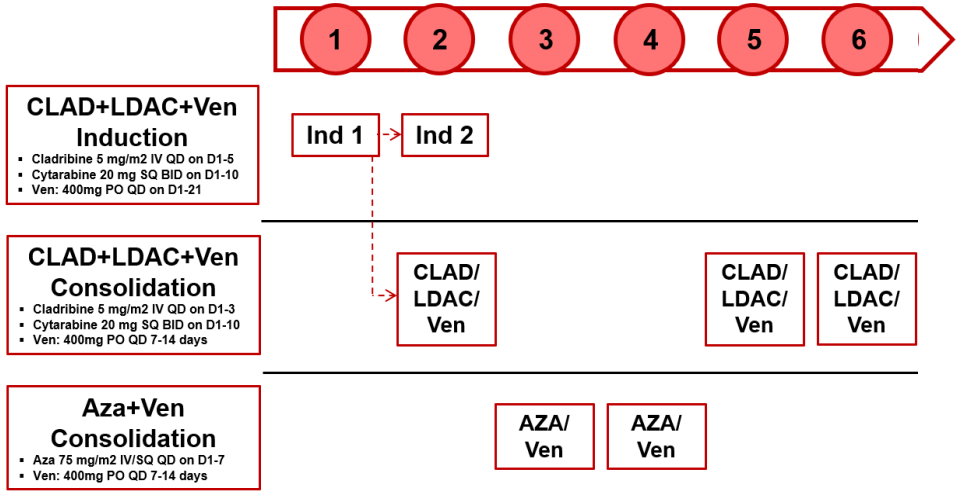
Induction (1 cycle)



Consolidation (up to 4 cycles)



2-CDA-LDAC-VEN/AZA-VEN



Parameters	5+2+VEN (CAVEAT)	2-CDA-LDAC-VEN/AZA-VEN
Age	71 (63-80)	68 (47-84)
Secondary AML	**39%**	21%
Prior HMA	**19%**	**0%**
FLT3-ITD	7%	4%
NPM1 mut	24%	23%
TP53 mut	18%	17%
Median cycles	3	2
HCT rate	6%	**44%**

Chua et al, Blood Adv 2025

Bataller et al, ASH 2024

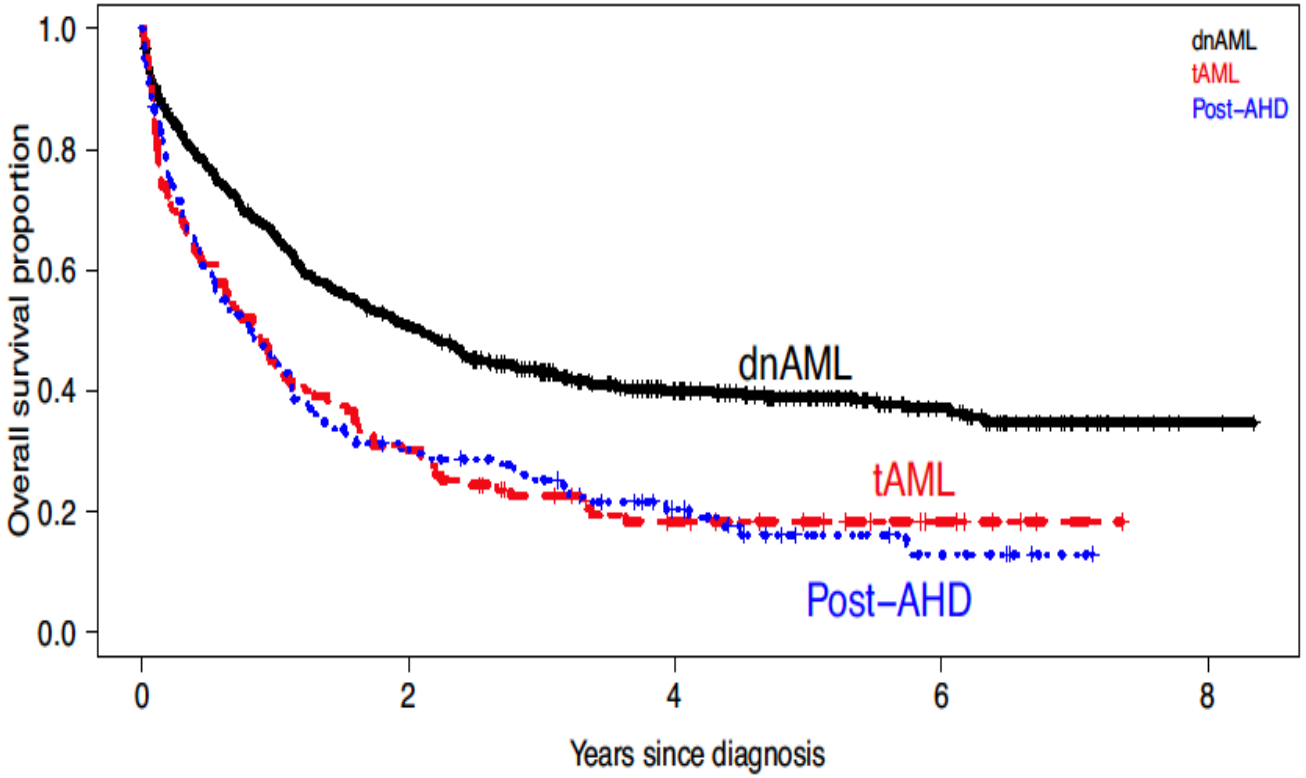
Frontline outcomes with “semi-intensive” therapies

					Secondary AML					
		Overall			No prior HMA			Prior HMA (ts-AML)		
Regimen	**Age (range)**	**N**	**CR+CRi**	**Median OS**	**N**	**CR+CRi**	**Median OS**	**N**	**CR+CRi**	**Median OS**
AZA-VEN[1]	**76** (49-91)	286	66%	14.7 mo	72	66%	**16.4 mo**	-	-	-
LDAC-VEN[2]	**76** (36-93)	143	48%	8.4 mo	30	47%	NA	28	25%	**5.5 mo**
CPX-351[3]	**68** (64-71)	153	48%	9.6 mo	21	67%	**15.7 mo**	50	36%	**5.7 mo**
5+2 plus VEN[4]	**72** (63-80)	81	75%	15.4 mo	17	65%	**15.1 mo**	16	44%	**5.7 mo**
CDA-LDAC-VEN/ AZA-VEN[5]	**68** (57-84)	60	93%	64% at 2y	14	93%	**69% at 2y**	-	-	-

1. DiNardo et al, NEJM 2020
2. Wei et al, Blood 2020
3. Lancet at al, Lancet Hematology 2021
4. Chua et al, Blood Adv 2025
5. Kadia et al, J Clin Oncol. 2022

Clinical or genetic factors to define secondary AML?

734 ND pts with AML from JH or MGH



Number at Risk

488	240	126	51	3	dnAML
123	37	16	7		tAML
123	36	16	4		Post–AHD

Hochman et al, Leukemia 2023

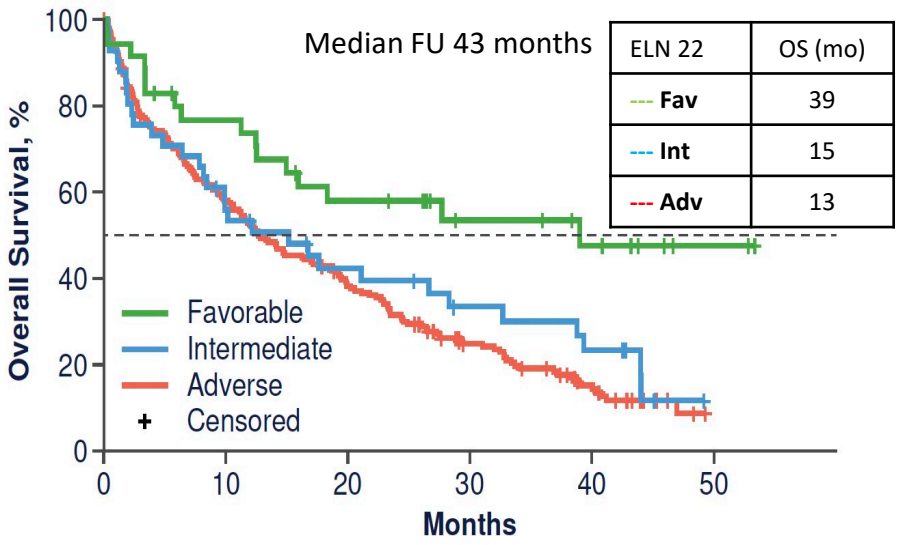
Clinical or genetic factors to define secondary AML?

	Univariate HR (95% CI)	Multivariable HR (95% CI)
ELN22 adverse	3.05 (2.30–4.05)	2.71 (2.00–3.68)
Poor PS	3.10 (2.51–3.82)	2.39 (1.91–2.98)
ELN22 intermediate	1.52 (1.07–2.17)	1.90 (1.32–2.73)
TP53 mutant	3.15 (2.55–3.89)	1.74 (1.38–2.20)
tAML	1.77 (1.41–2.23)	1.21 (0.95–1.53)
Post-AHD sAML	1.81 (1.44–2.27)	1.12 (0.88–1.42)
Age (per 10 years)	1.30 (1.21–1.39)	1.11 (1.03–1.20)
Transplant	0.38 (0.31–0.47)	0.45 (0.36–0.56)

Hochman et al, Leukemia 2023

Semi-intensive options for elderly ELN 2022 adverse risk

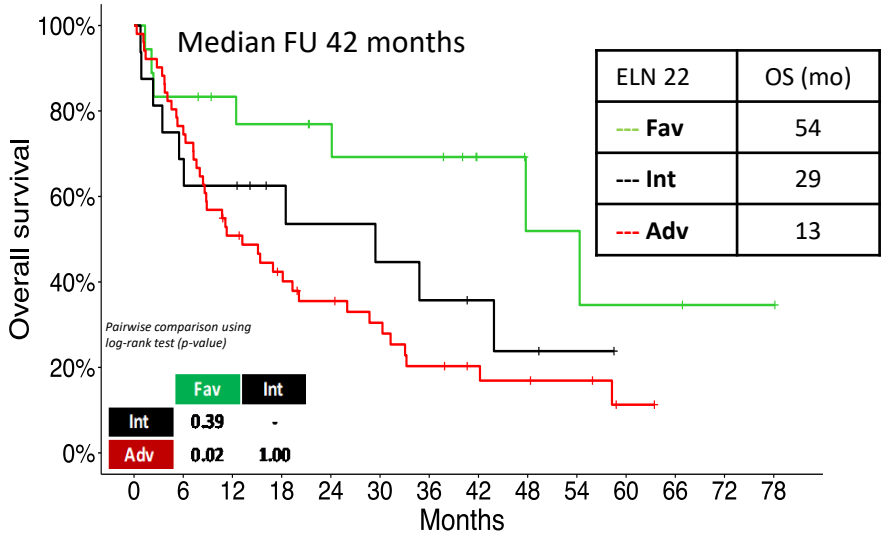
AZA-VEN



ELN 22	OS (mo)
Fav	39
Int	15
Adv	13

Döhner et al, Blood 2024

5+2+VEN

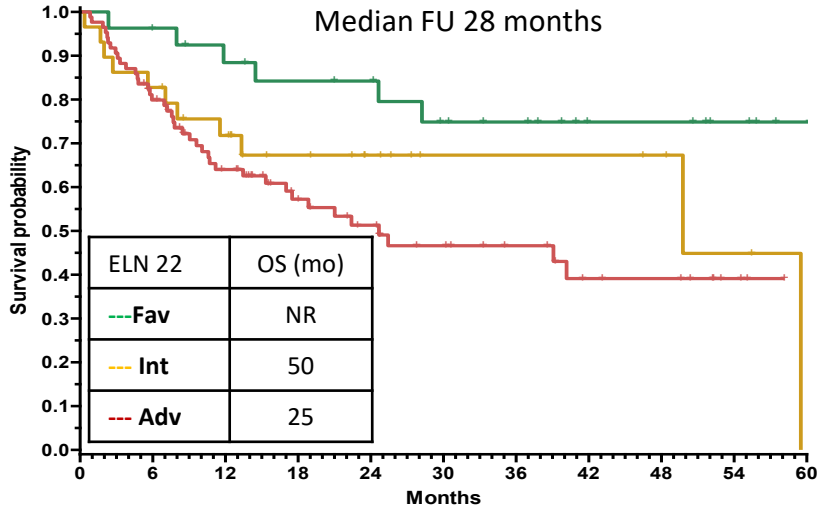


ELN 22	OS (mo)
Fav	54
Int	29
Adv	13

Chua et al, unpublished

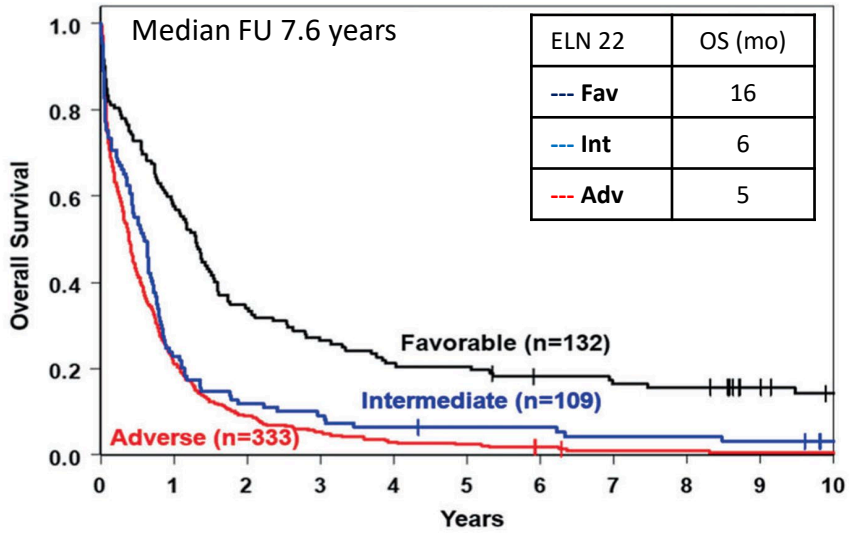
2-CDA-LDAC-VEN/AZA-VEN

Median FU 28 months



ELN 22	OS (mo)
Fav	NR
Int	50
Adv	25

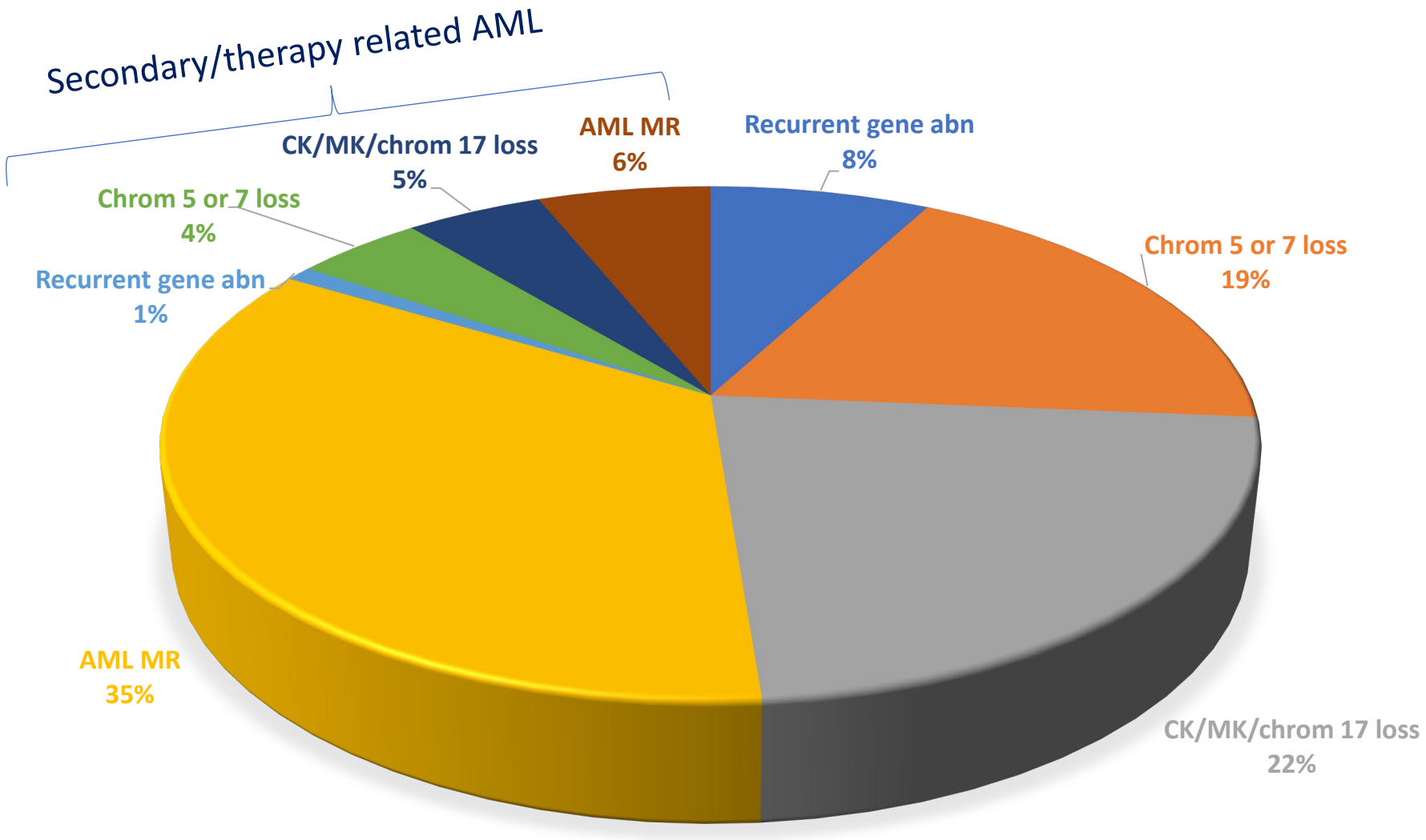
7+3 based (>60 years)



ELN 22	OS (mo)
Fav	16
Int	6
Adv	5

Krzysztof Mrózek, Leukemia (2023) 37:788–798

ELN 2022 adverse risk AML



Fleming *et al*, Blood, 2023

TP53 mut associations in adverse ELN 2022 risk group

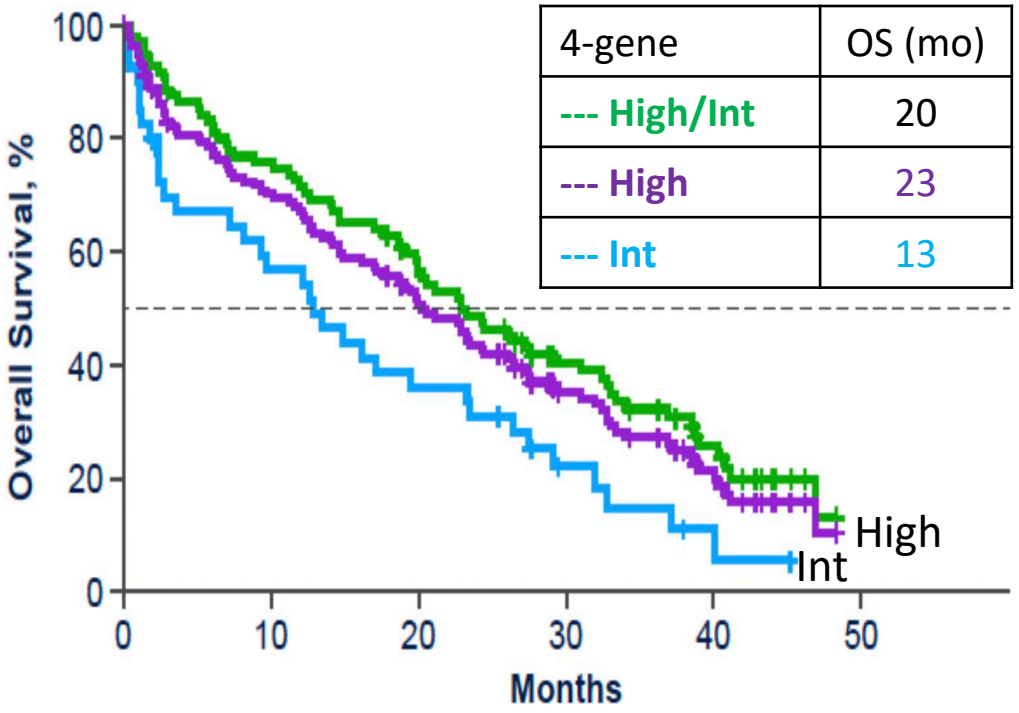
Classifier	*De novo AML*	*TP53* mutated (%)	*TP53* wild-type (%)	Secondary/therapy related AML	*TP53* mutated (%)	*TP53* wild-type (%)
Adverse risk	1063	200 (18.8)	863 (81.0)	191	50 (26.2)	141 (73.8)
DEK::*NUP214*	25	0 (0)	25 (100)	0	0 (0)	0 (0)
KMT2A-rearranged	63	2 (3.2)	60 (96.8)	4	0 (0)	4 (100)
BCR::*ABL1*	9	1 (11.1)	8 (88.9)	2	0 (0)	2 (100)
KAT6A::*CREBBP*	0	0	0	0	0 (0)	0 (0)
GATA2, *MECOM(EVI1)*	34	2 (5.9)	32 (94.1)	2	0 (0)	2 (100)
MECOM(EVI1)-rearranged	10	1 (10.0)	9 (90.0)	9	4 (44.4)	5 (63.6)
Monosomy 5 or del(5q)	198	133 (67.2)	65 (32.8)	51	29 (56.8)	12 (23.5)
Monosomy 7	141	52 (36.9)	89 (63.1)	31	13 (41.9)	18 (58.1)
Monosomy 17/abn(17p)	115	86 (70.4)	34 (29.6)	21	11 (52.4)	10 (47.6)
Complex and/or monosomal karyotype	293	159 (54.2)	134 (45.7)	67	39 (58.2)	28 (41.8)
AML with myelodysplasia related gene mutations	635	**37 (5.8)**	598 (94.2)	111	**5 (4.5)**	106 (95.5)
ASXL1	214	9 (4.2)	205 (95.8)	46	1 (2.2)	45 (97.8)
BCOR	61	5 (8.2)	56 (91.8)	13	0 (0)	13 (100)
EZH2	45	3 (6.7)	42 (93.3)	9	0 (0)	9 (100)
RUNX1	284	8 (2.8)	276 (97.2)	40	1 (2.5)	39 (97.5)
SF3B1	68	5 (7.4)	63 (92.6)	17	1 (5.9)	16 (94.1)
SRSF2	103	0 (0)	103 (100)	29	1 (3.4)	28 (96.6)
STAG2	106	3 (2.8)	103 (97.2)	22	0 (0)	22 (100)
U2AF1	83	4 (4.8)	79 (95.1)	23	2 (8.7)	21 (91.3)
ZRSR2	28	2 (7.1)	26 (92.9)	7	1 (14.3)	6 (85.7)
Insufficient data to classify by ELN 2022	212	0 (0)	212 (100)	4	0 (0)	4 (100)

AML MR

Fleming *et al*, Blood, 2023

AML with MDS related mutations

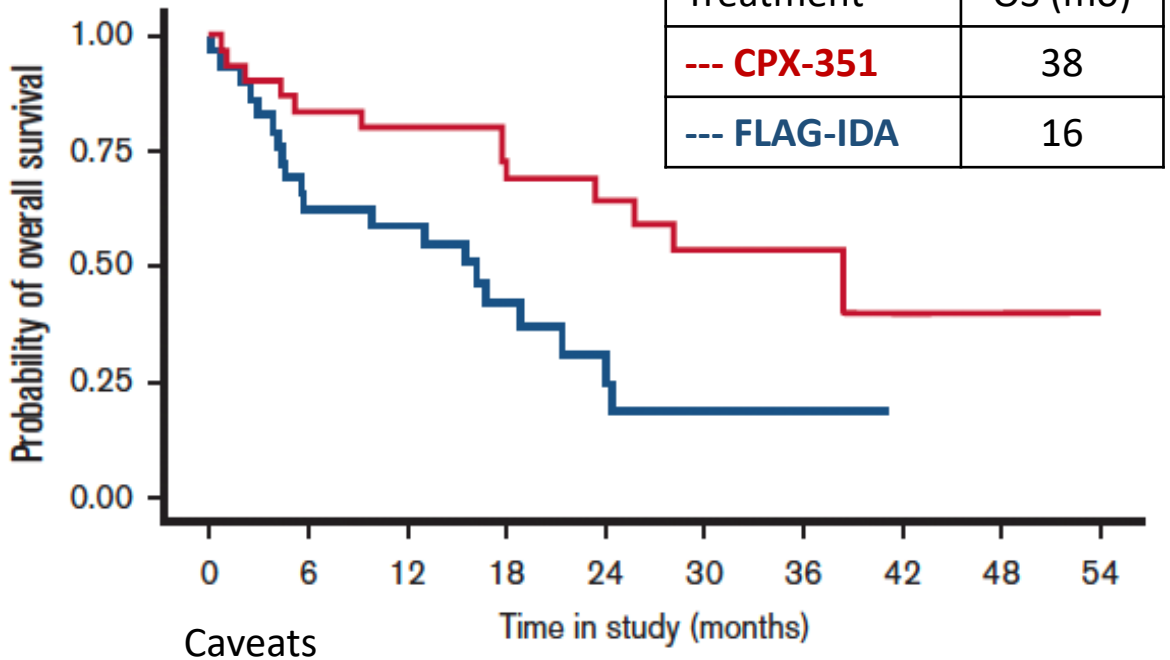
AZA-VEN



4-gene	OS (mo)
--- High/Int	20
--- High	23
--- Int	13

Döhner et al, Blood 2024

CPX-351 vs FLAG-IDA



Treatment	OS (mo)
--- CPX-351	38
--- FLAG-IDA	16

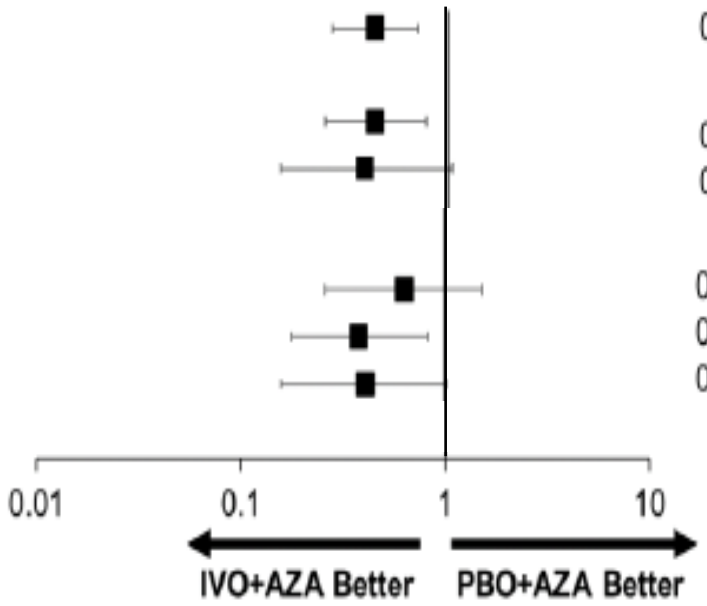
Caveats

- N=30 in CPX-351 arm, median age 56
- CPX-351 benefit in high risk MDS (32% pop)
- Increased remission deaths for FLAG-IDA
- Higher HCT rate for CPX-351 arm (64% vs 48%)

Othman *et al*, Blood Adv, 2023

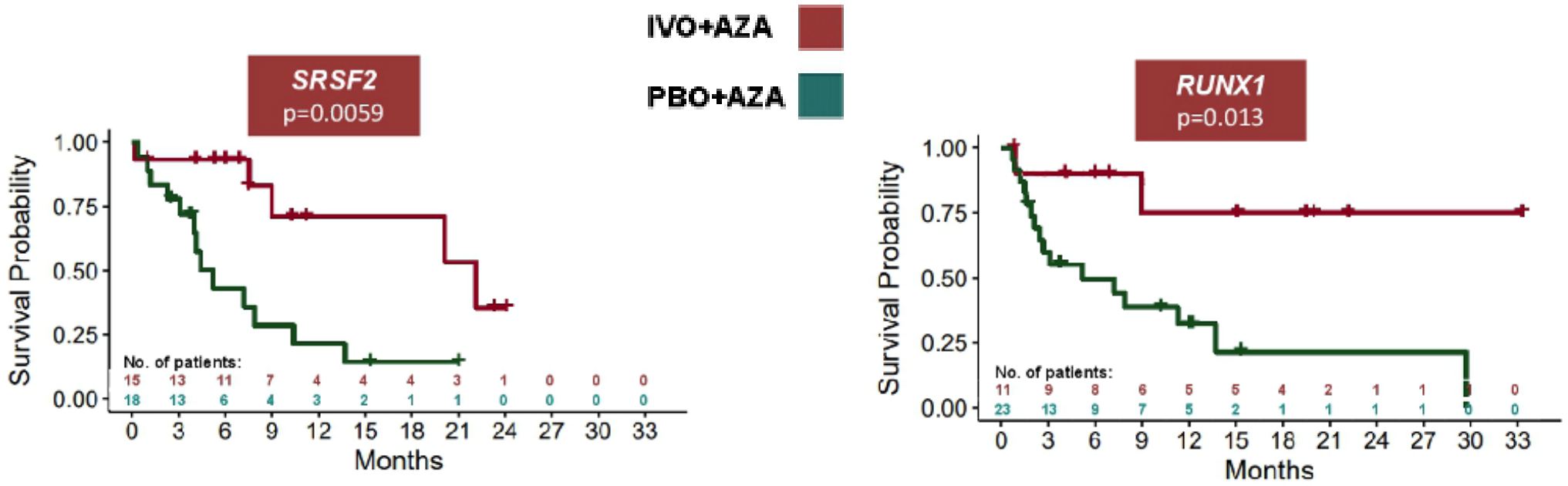
AZA + IVO for *IDH1* mut AML with MDS-related mutations

	IVO+AZA Events/N*	PBO+AZA Events/N*	HR	Lower 95% CI	Upper 95% CI
Overall	28/72	46/74	0.44	0.27	0.71
Primary AML on basis of IRT					
Yes	21/56	33/55	0.44	0.25	0.78
No	7/16	13/19	0.39	0.15	1.05
WHO classification of AML					
AML with recurrent genetic abnormalities	8/16	15/24	0.64	0.26	1.53
AML with myelodysplasia-related changes	12/28	18/26	0.38	0.18	0.83
Therapy-related myeloid neoplasms or AML not otherwise specified‡	8/28	13/24	0.41	0.16	1.03



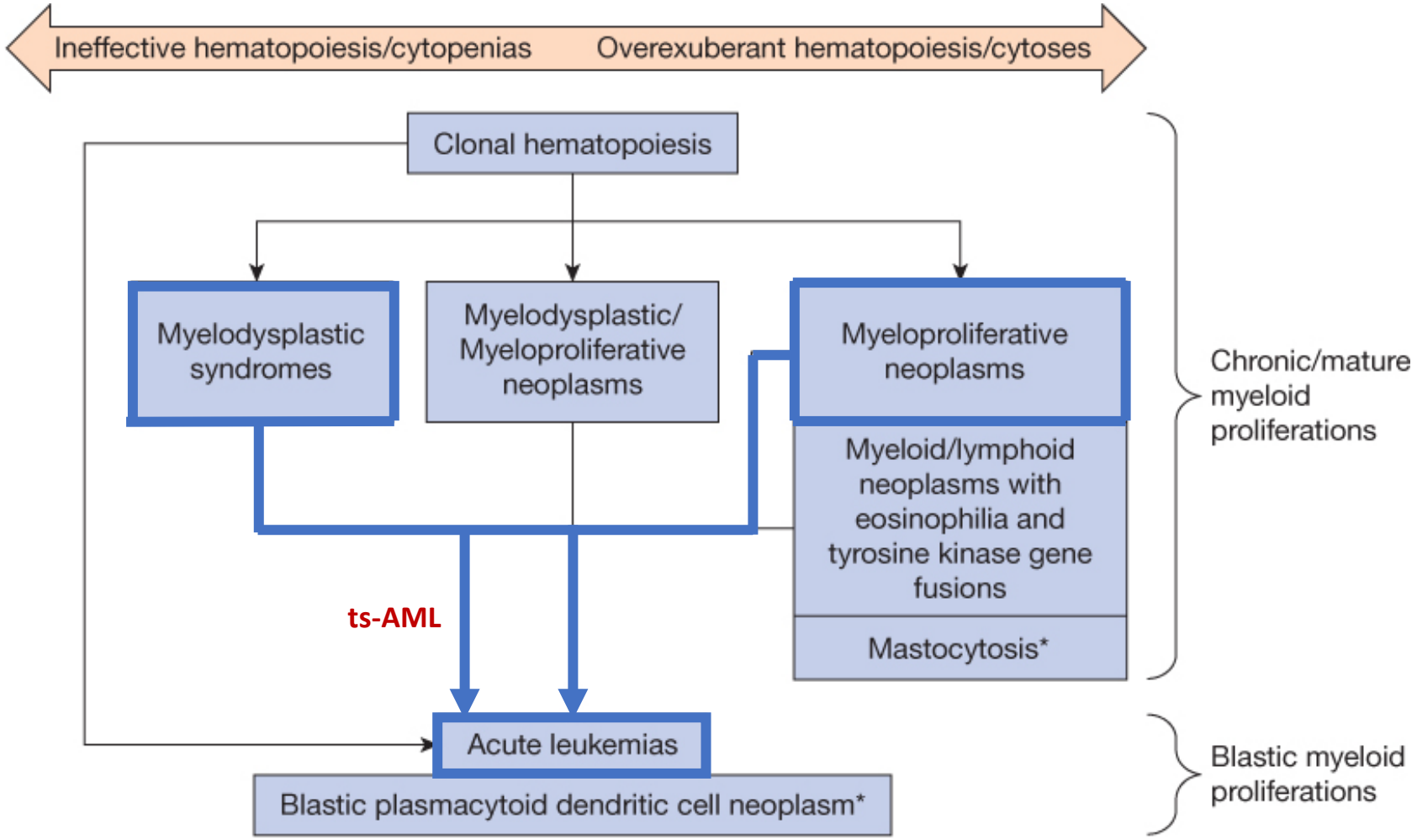
Montesinos et al, NEJM 2022

AZA + IVO for *IDH1* mut AML with MDS-related mutations



De Botton *et al*, ASCO 2022

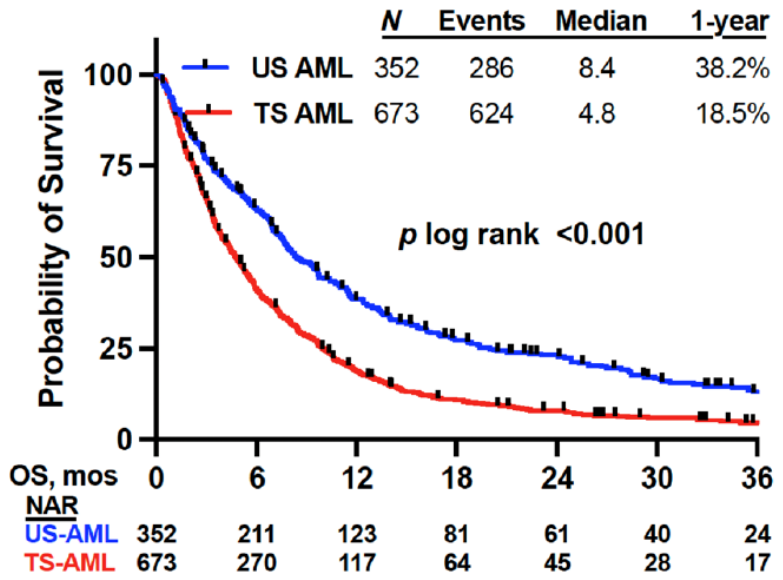
AML with antecedent hematologic disease

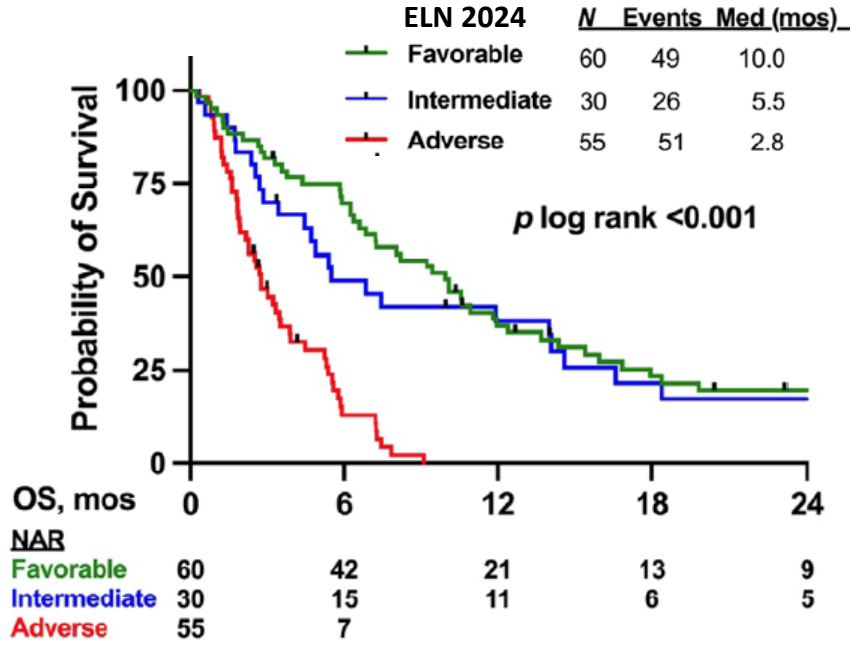


Arber, Daniel, A. et al. The International Consensus Classification of Myeloid and Lymphoid Neoplasms. Available from: Wolters Kluwer, Wolters Kluwer Health, 2024

Treated secondary AML

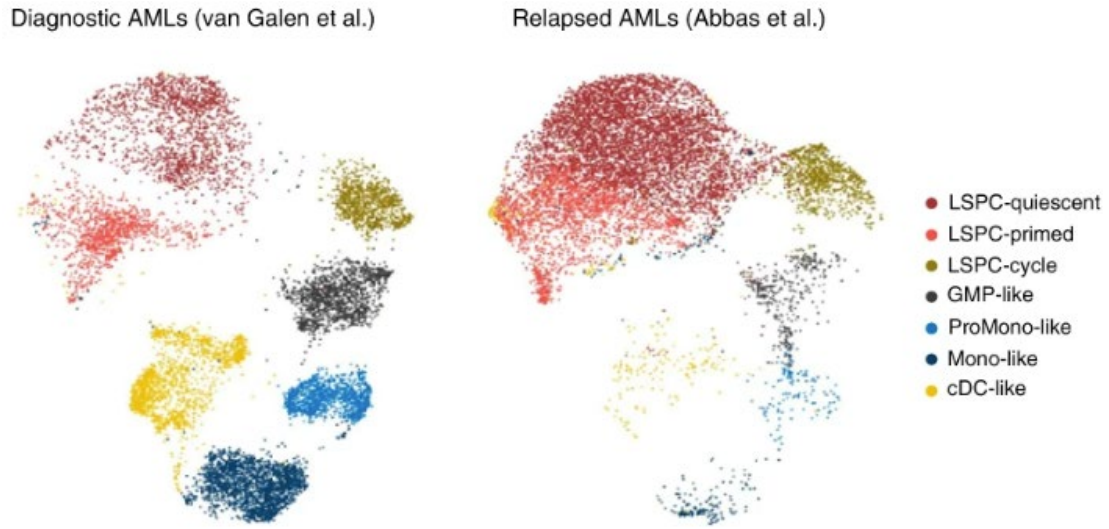
ts-AML (n=673)	Parameter
Age	70.1 (19-91)
Prior MDS	80%
CMML	17%
MDS/MPN	3%
Prior therapy	
HMA	98%
VEN	10%
HCT	13%
Adverse karyotype	58%
Complex karyotype	41%
Molecular	
TP53	34%
RAS	29%
ASXL1	26%
RUNX1	18%
FLT3-ITD	7%
IDH1	8%
IDH2	6%
NPM1	5%





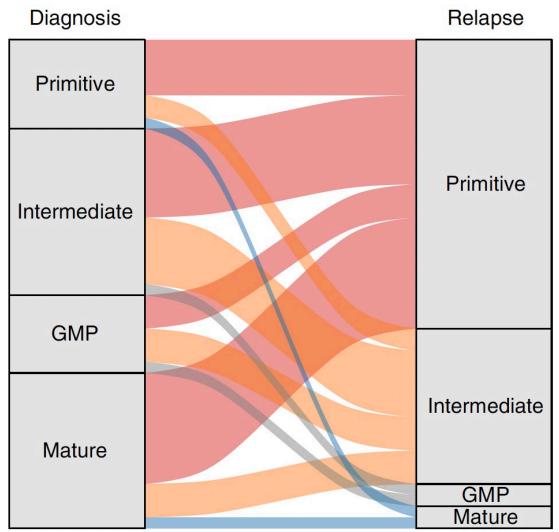
Senapati et al, AJH 2025

At relapse, primitive LSPCs enriched in MDS related and *TP53* mut



12 cases

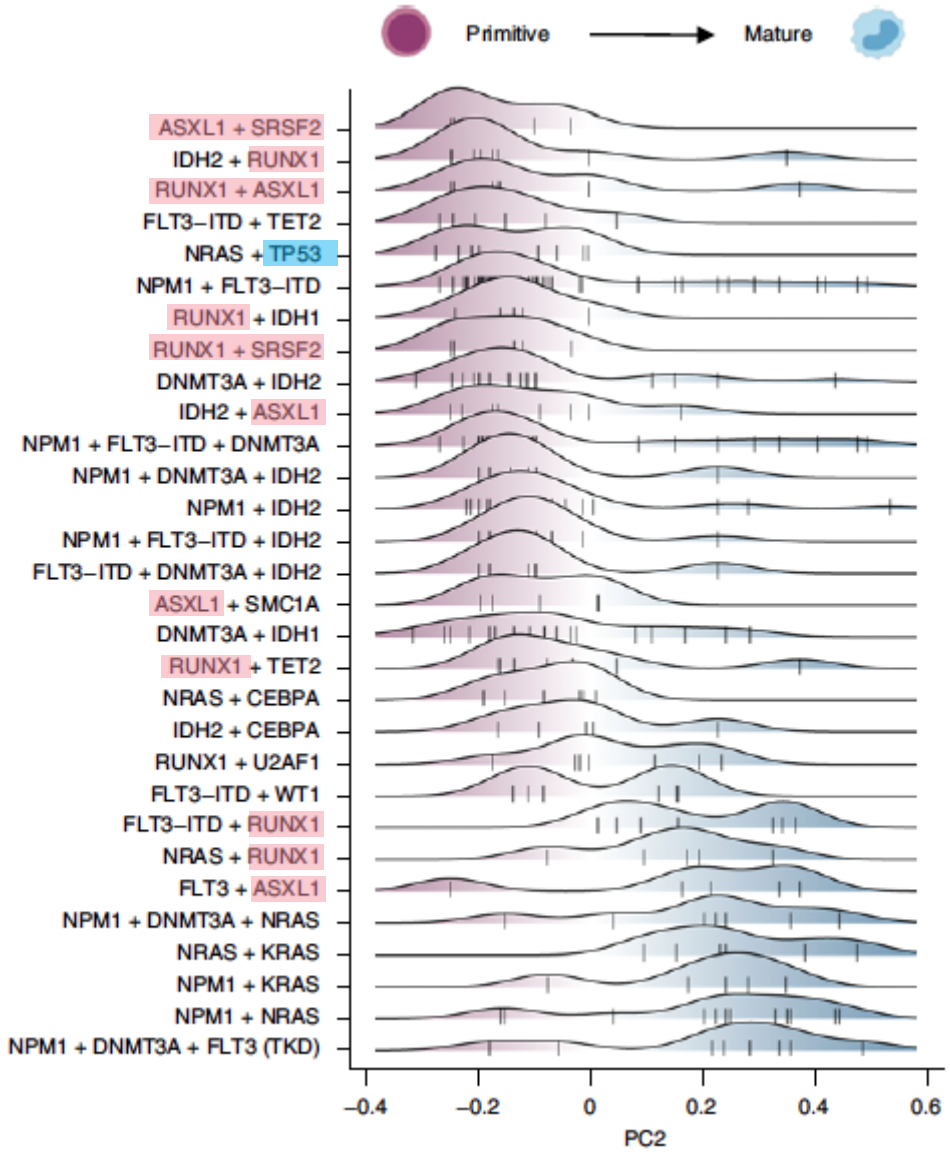
8 cases



44 pairs

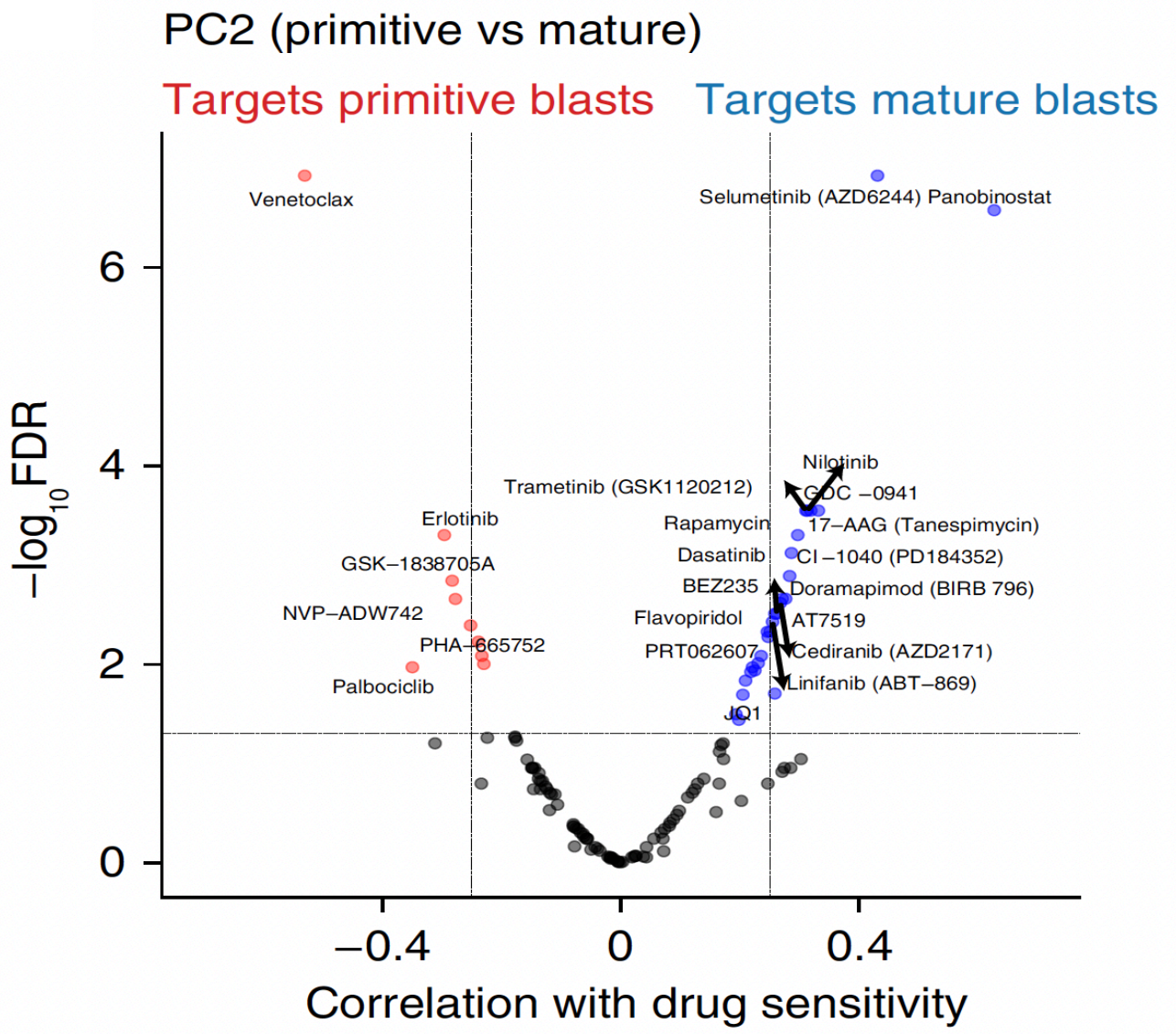
Zeng…Dick, Nature Med, 2022

At relapse, primitive LSPCs enriched in MDS related and *TP53* mut



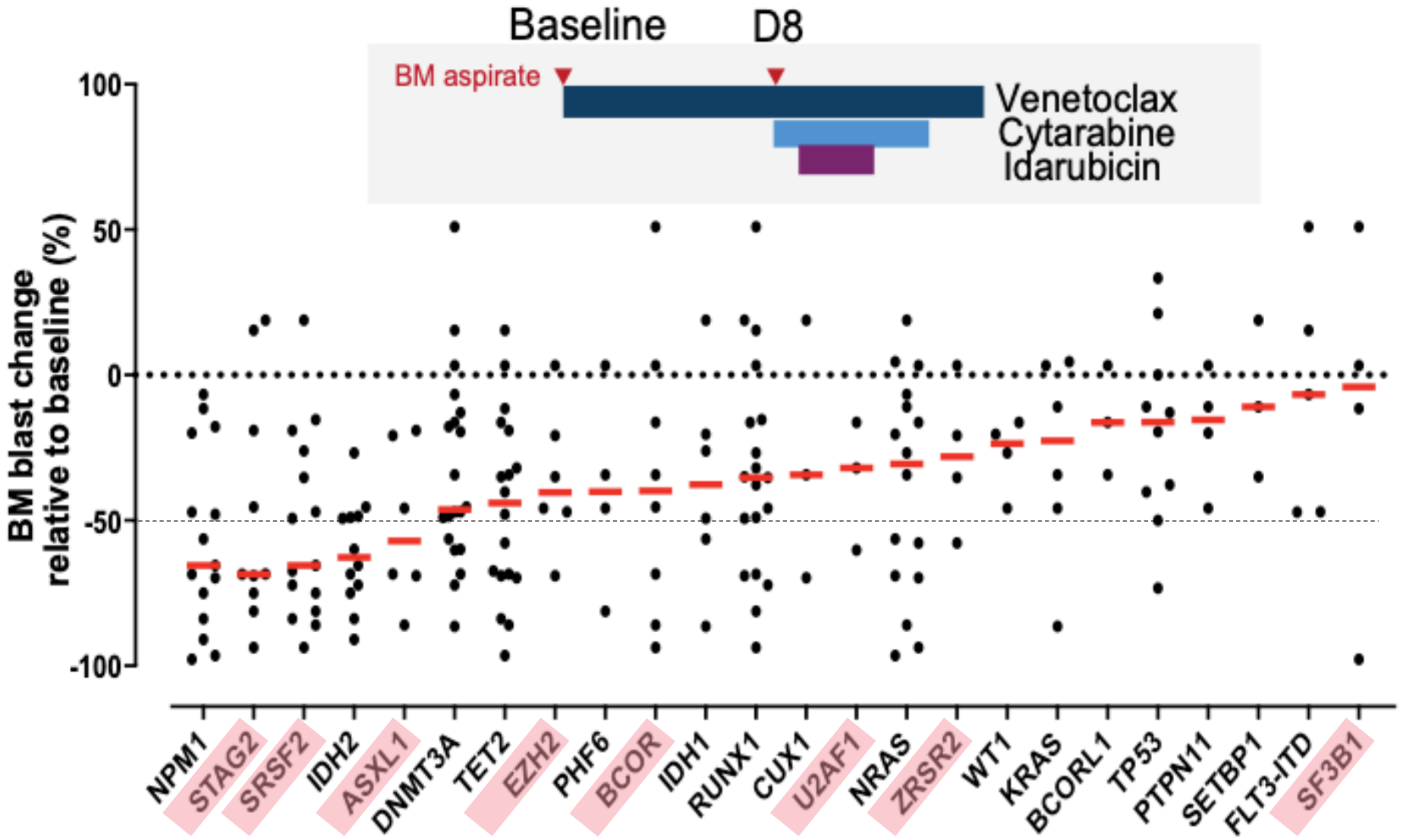
Zeng…Dick, Nature Med, 2022

At relapse, primitive LSPCs enriched in MDS related and *TP53* mut



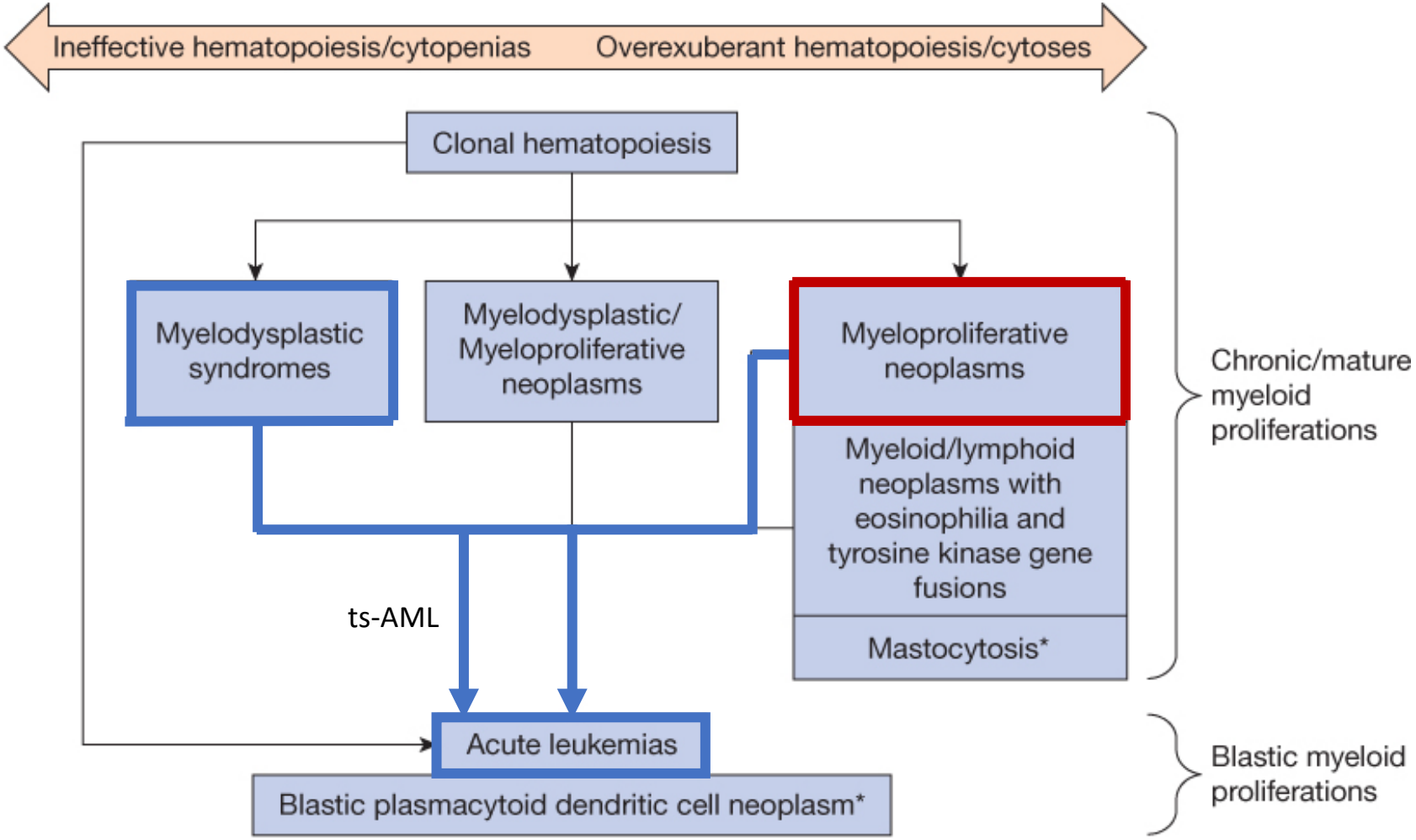
Zeng…Dick, Nature Med, 2022

Genotype-associated reductions in marrow blasts after 7 days of VEN



Chua et al, ASH 2023

AML with prior MPN



MPN	Post-MPN AML
ET	0.7% to 3.8%
PV	2.3% to 6.8%
MF	3.9% to 20.6%

Chim C-S, et al. Arch Intern Med. 2005
Barbui T, et al. J Clin Oncol. 2011
Tefferi A, et al. Blood. 2014
Passamonti F, et al. Cancer. 2005
Cervantes F, et al. Acta Haematol. 1991
Tam CS, et al. Blood 2008
Mesa RA, et al. Blood 2005

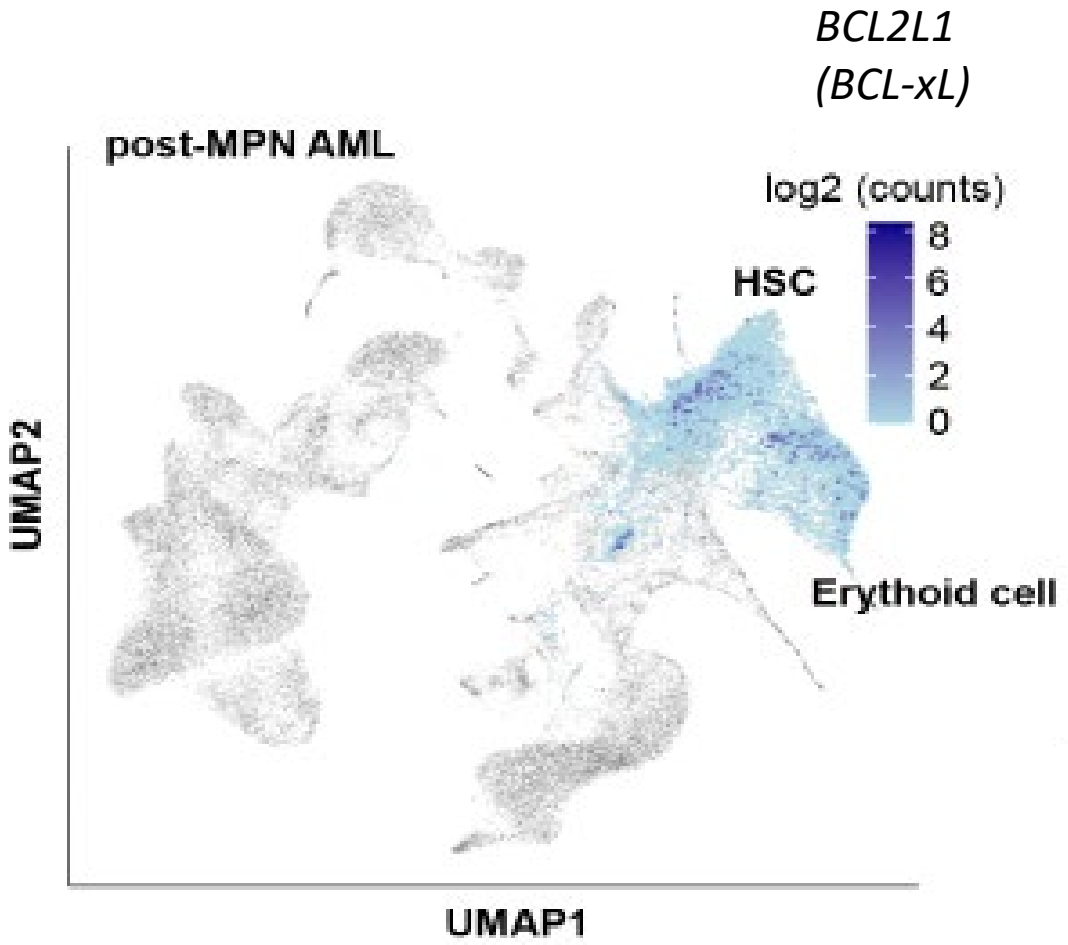
Arber, Daniel, A. et al. The International Consensus Classification of Myeloid and Lymphoid Neoplasms. Available from: Wolters Kluwer, Wolters Kluwer Health, 2024

Therapeutic strategies for Post-MPN AML

	AZA-VEN	AZA-VEN-RUXO*
N	32	5
Age	69 (47–81)	76 (72–84)
PV	12	2
ET	11	1
MF	9	2
Prior Rux	19%	80%
ORR	44%	80%
CR	31%	40%
Allo HCT	14%	-
Median OS	8 mo	10 mo
Median follow-up	7 mo	13.4 mo
	Gangat et al, Am J H 2021	Systchenko et al, BJH 2023

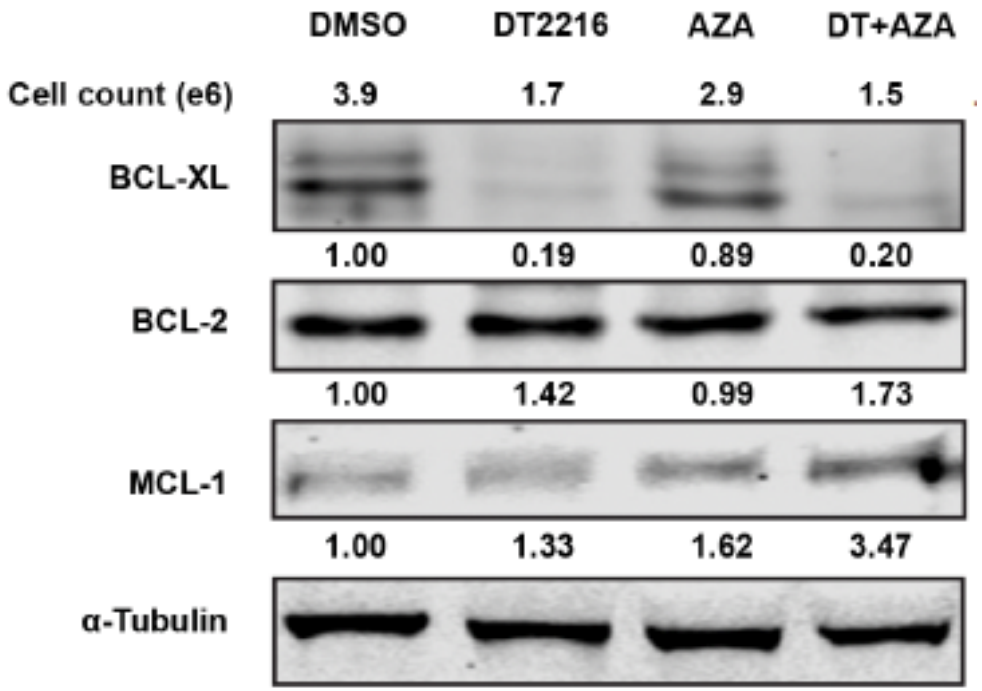
* Rux 10mg BD

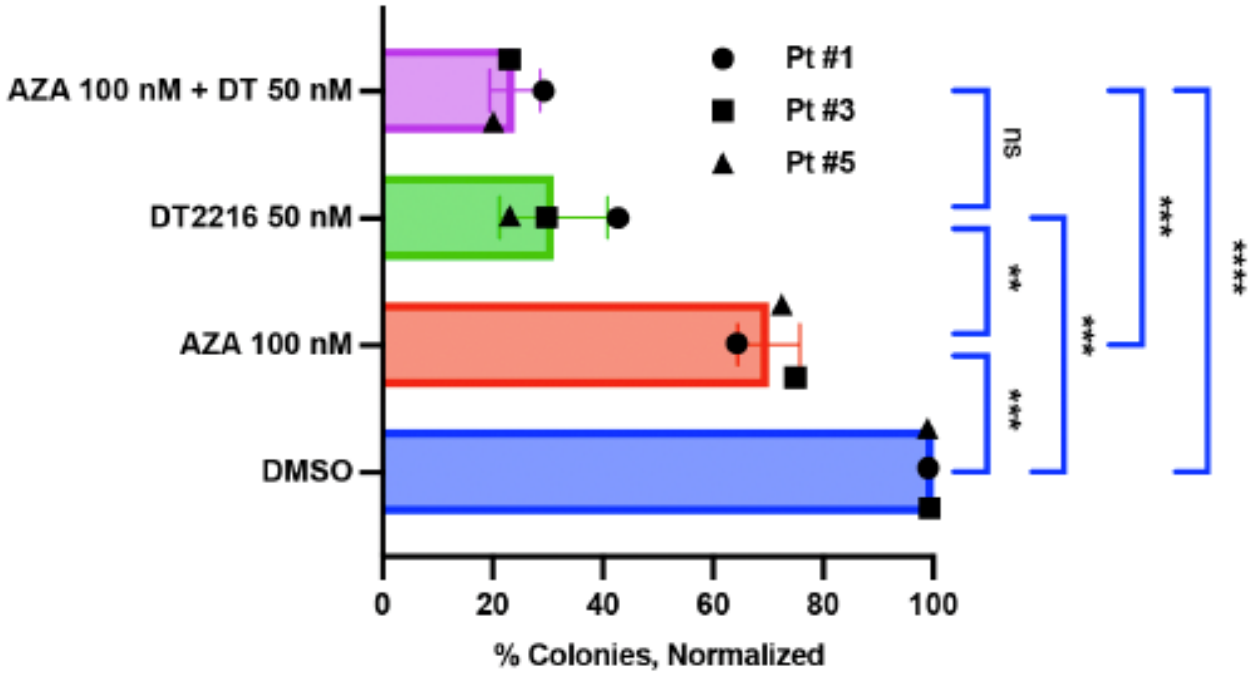
Post-MPN AML



Wang et al, Blood 2024

BCL-xL Degrader DT2216 in JAK2 mut Post-MPN AML





Wang et al, Blood 2024

Conclusions

- Secondary (treated) AML should be categorized molecularly
- Elderly pts with MDS related molecular abnormalities incurable without HCT
- New therapeutic strategies needed to target
  - Primitive LSPCs
  - BCL-XL overexpression
  - *TP53* abnormalities