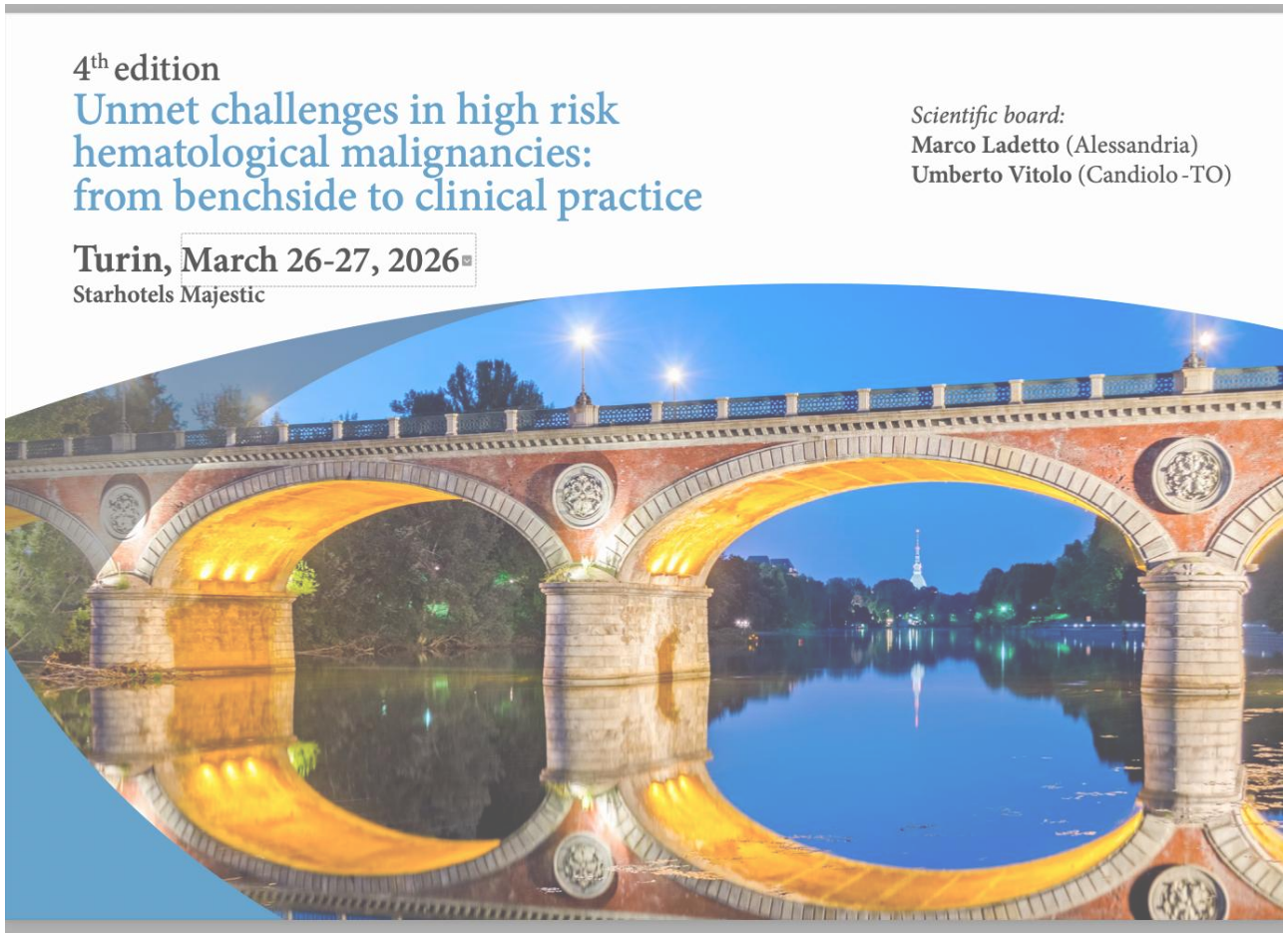
TP53-mutated MDS: is transplant the only way?



Daniela Cilloni
University of Turin
Mauriziano Hospital

TP53-mutated MDS: is transplant the only way?

Hematopoietic Stem cell Transplant is potentially curative

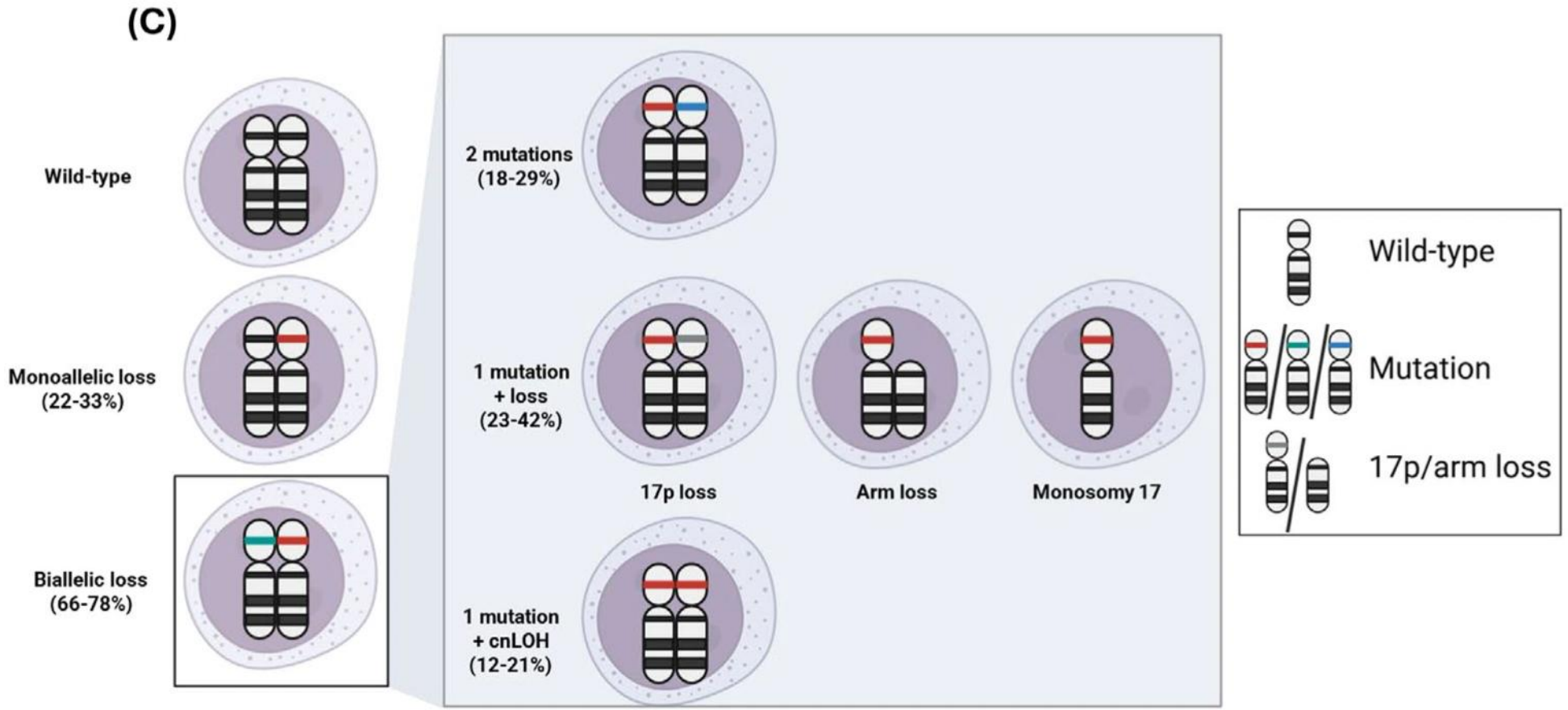
Potentially curative ≠ reliably effective

The question is not: ‘Do we have a better option than transplant?’

The question is: who truly has a realistic benefit from it?

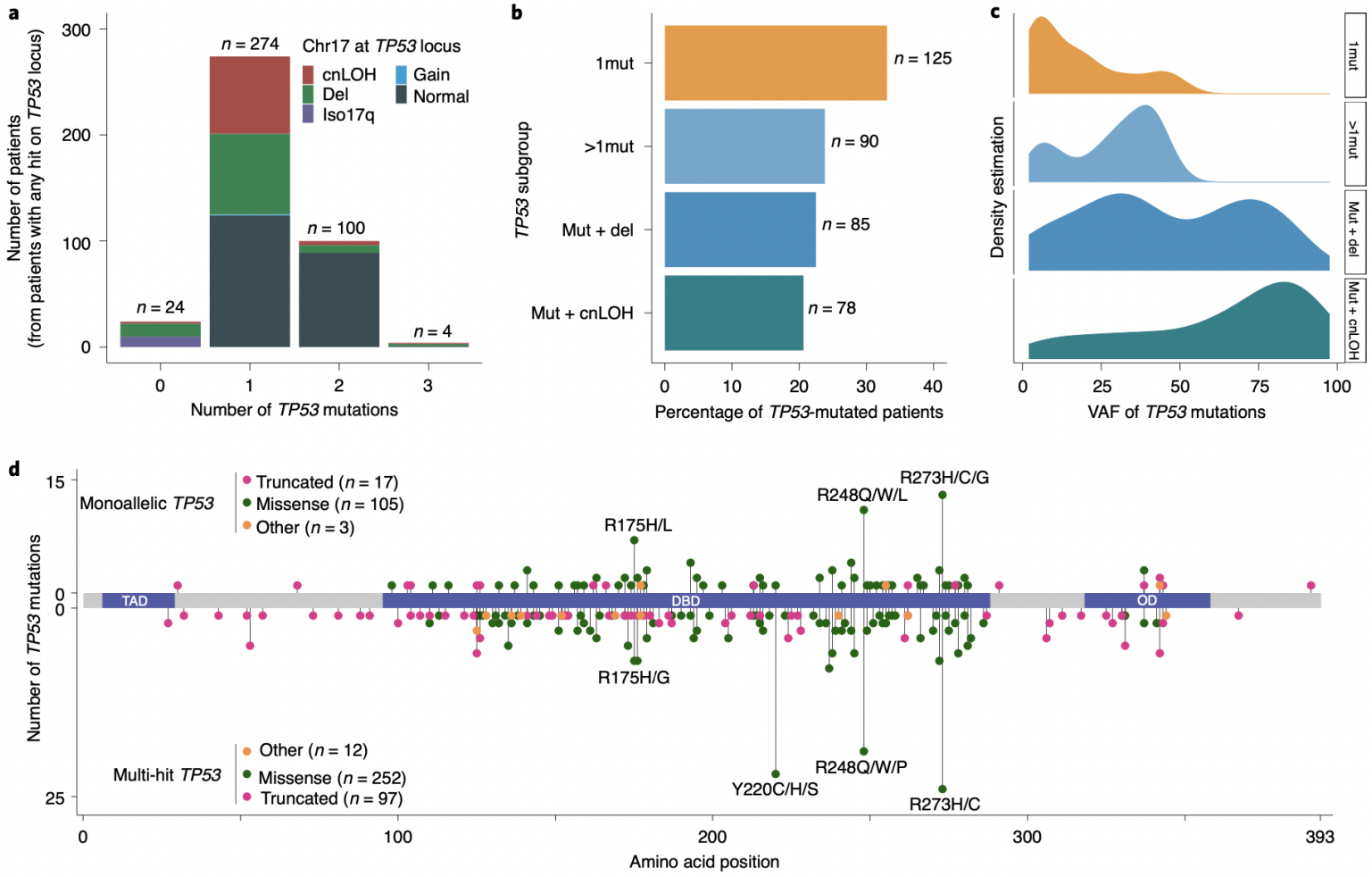
In TP53-mutated MDS, transplant is not ‘the only way.’
It is one option, and often an insufficient one

Are all TP53^{mut}MDS the same?



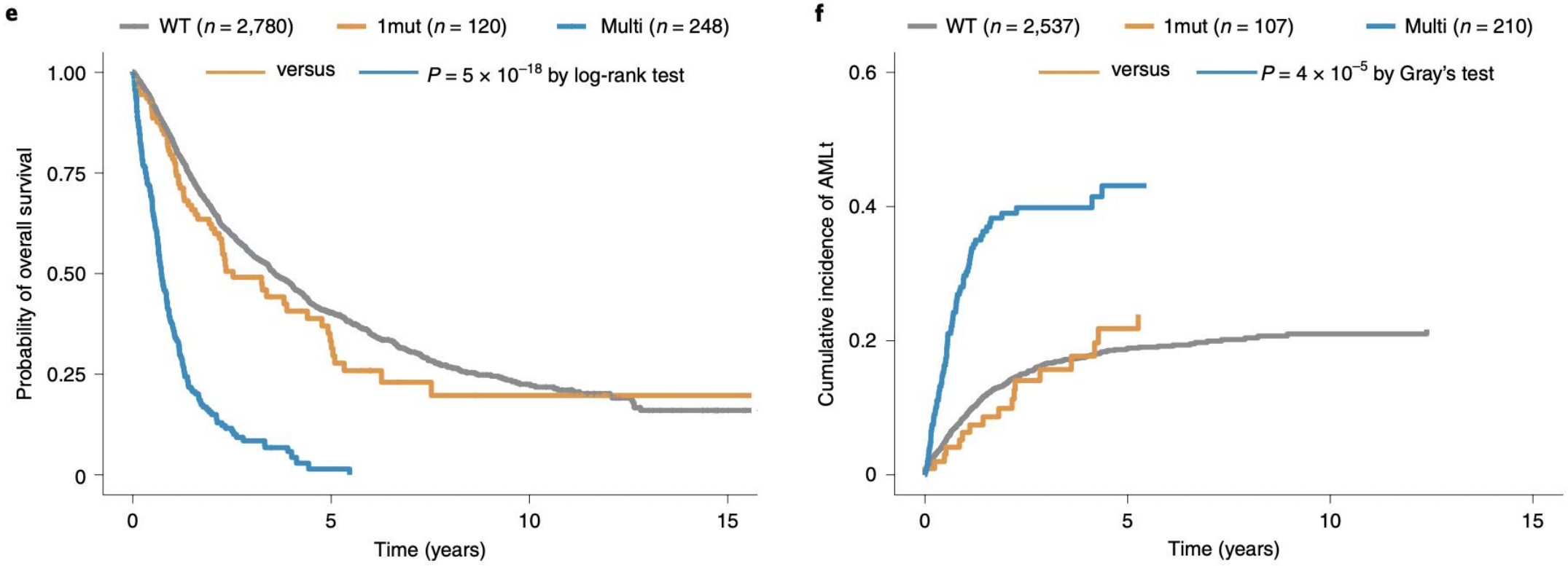
Adapted from Shah MV, American J of Hem, 2025

Monoallelic or biallelic TP53 mutation: does it matter?



Bernard E. et al. Nat Med, 26. 2020: 1549–1556

Monoallelic TP53 status does not appear to be associated with a different prognosis compared with TP53wt patients



Bernard E. et al. Nat Med, 26. 2020: 1549–1556

IPSS-M score

Blast
Hb
PLTs
Neutrophil
Age

Cytogenetic

*Presence of		
del(5q)	No	Yes
-7/del(7q)	No	Yes
-17/del(17p)	No	Yes
Complex Karyotype	No	Yes

Molecular abnormalities

N° of TP53 mutations: 0-1-2
TP53 Loss of heterozygosity Y/N
MLL PTD
FLT3 ITD or TKD

mutations

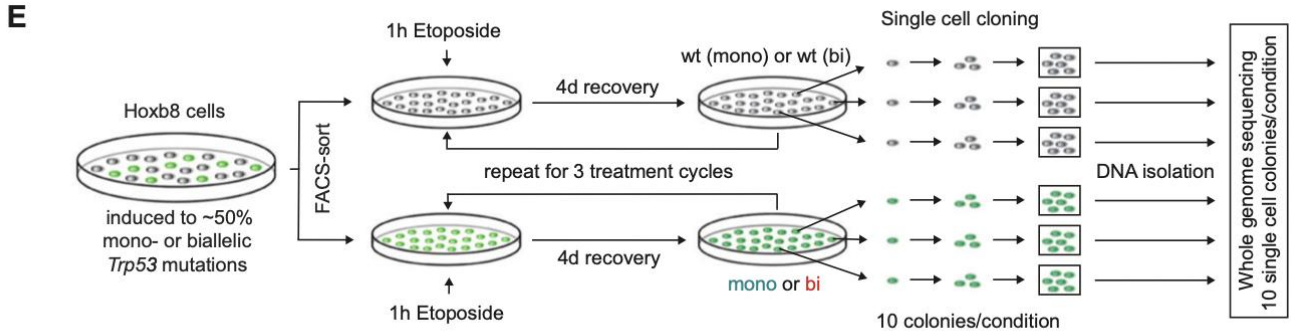
ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH2
KRAS
NPM1
NRAS
RUNX1
SF3B1
SRSF2
U2AF1
BCOR
BCORL1
CEBPA
ETNK1
GATA2
GNB1
IDH1
NF1
PHF6
PPM1D
PRPF8
PTPN11
SETBP1
STAG2
WT1

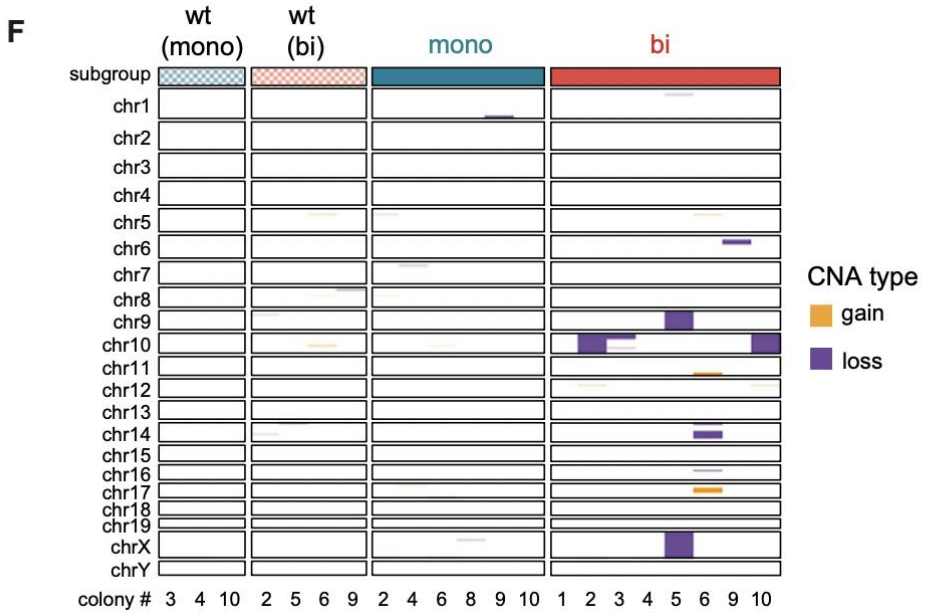
Risk category

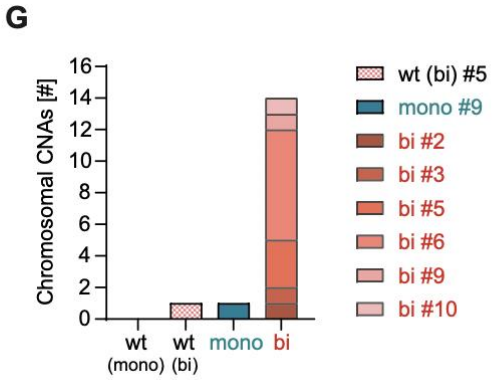
Very Good	-Y, del(11q).
Good	Normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones.
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities.
Very Poor	Complex: > 3 abnormalities.

Bernard E, et al. NEJM Evidence Aug 2022

Only biallelic TP53 mutations induce genomic instability

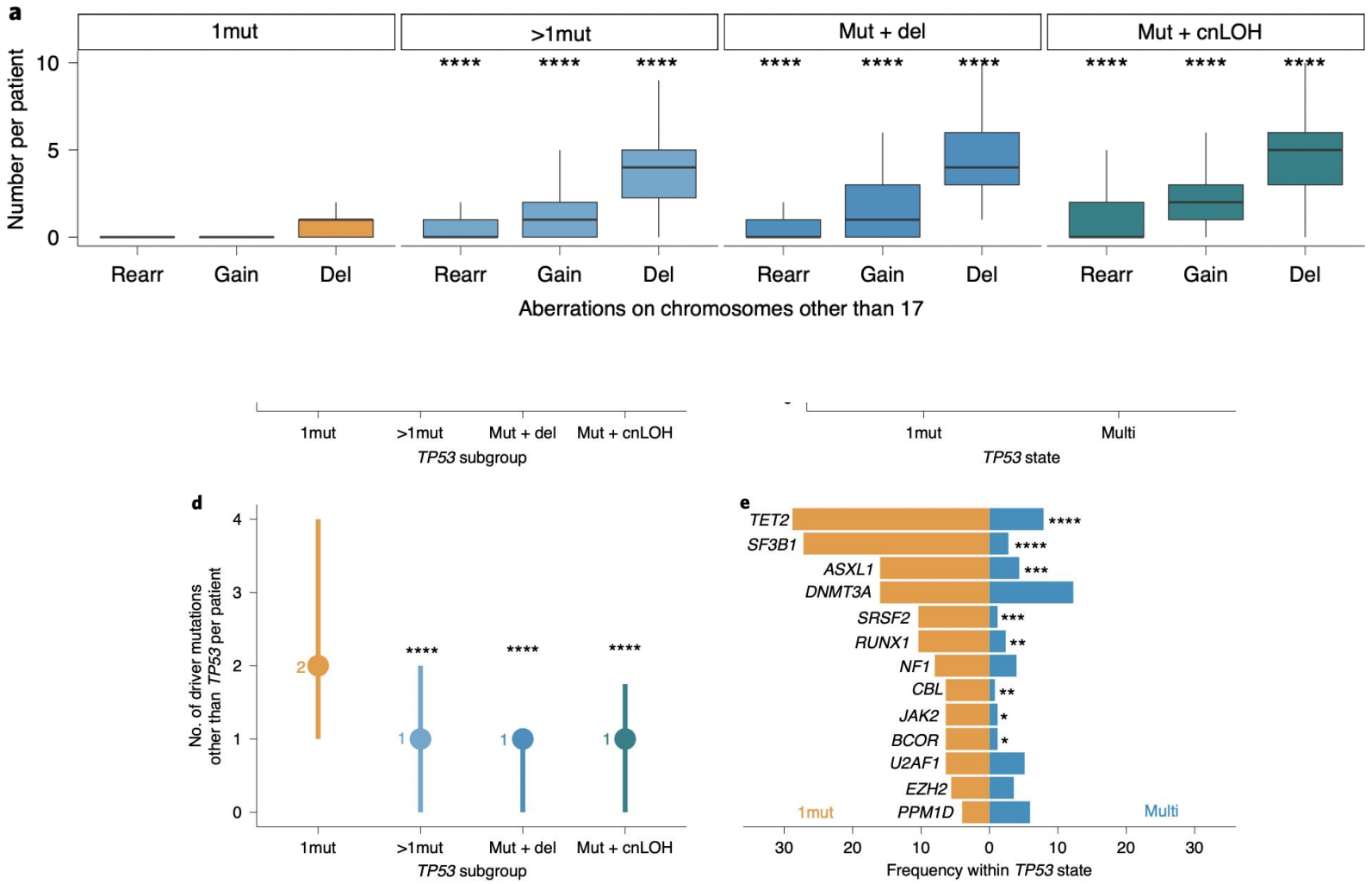






Fullin J. et al Leukemia (2026) 40:279–292

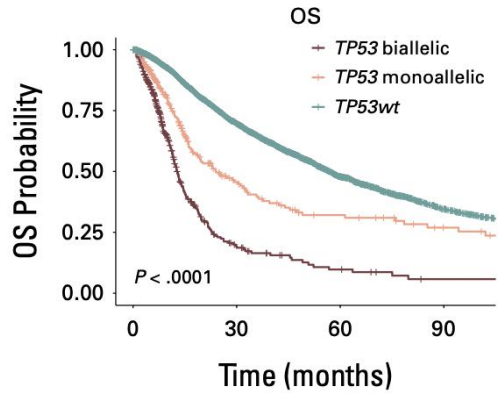
Association between TP53 status and additional genetic aberration



Bernard E. et al. Nat Med, 26. 2020: 1549–1556

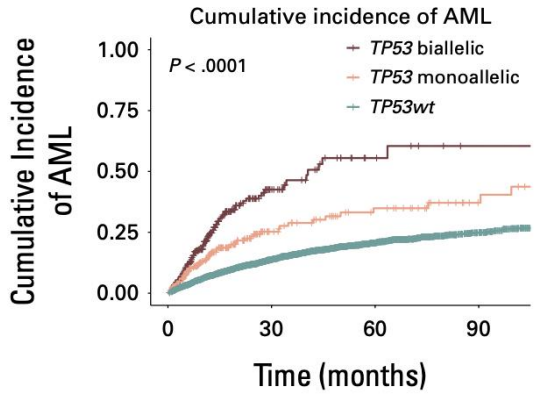
OS, incidence of AML and incidence of relapse according to TP53 status

A



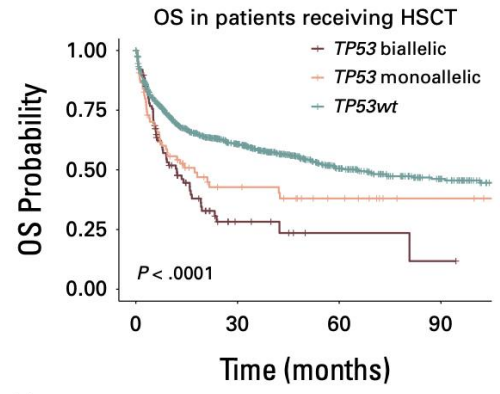
No. at risk:				
TP53 biallelic	356	29	10	3
TP53 monoallelic	270	55	29	17
TP53wt	5578	2132	850	332

B



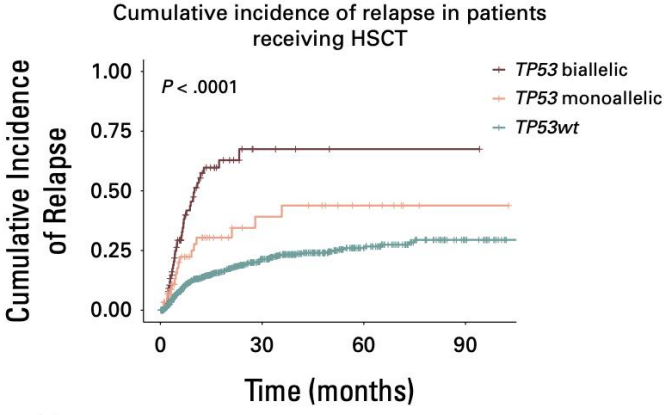
No. at risk:				
TP53 biallelic	356	37	10	4
TP53 monoallelic	270	65	38	19
TP53wt	5578	2426	1026	432

E



No. at risk:				
TP53 biallelic	87	8	2	1
TP53 monoallelic	81	19	10	3
TP53wt	998	392	152	72

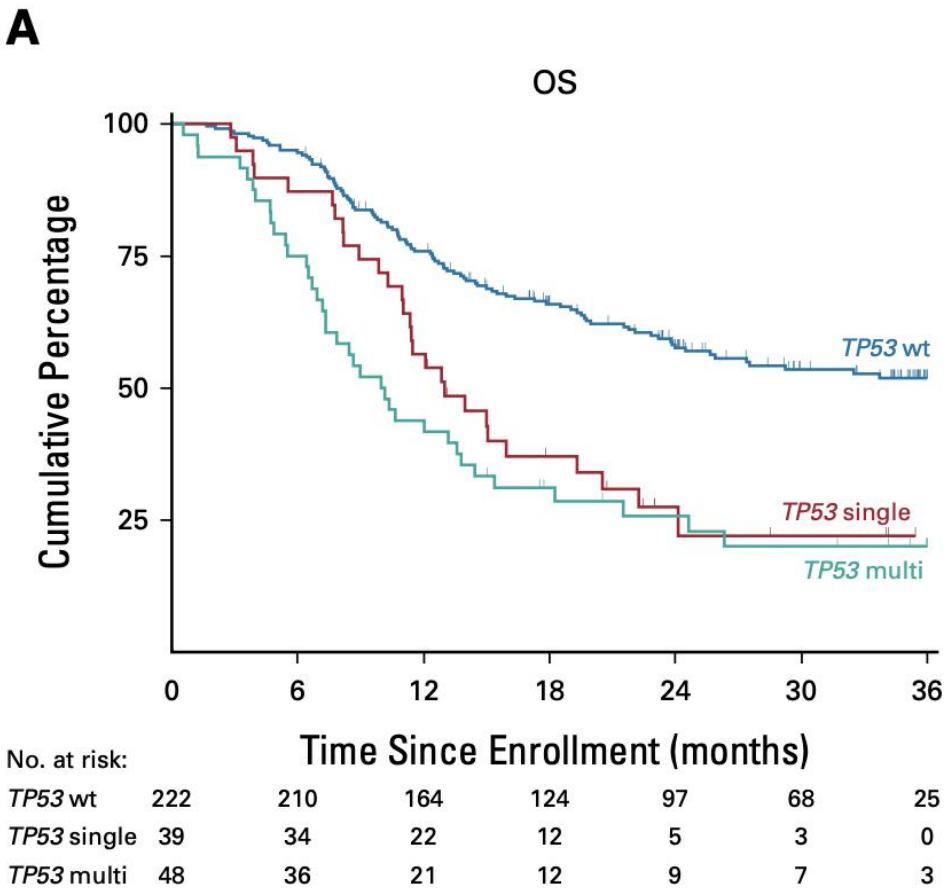
F

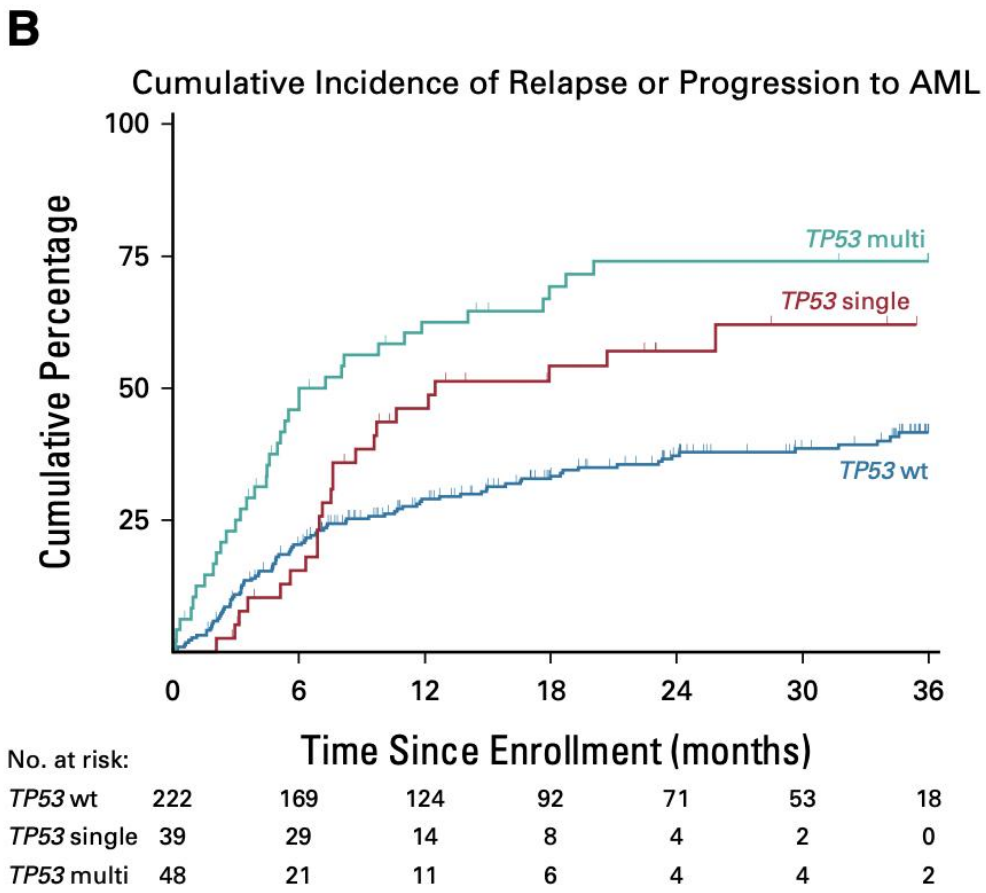


No. at risk:				
TP53 biallelic	85	4	1	1
TP53 monoallelic	75	13	7	1
TP53wt	951	316	111	44

Zampini M. et al JCO 2025

Monoallelic mutations impact on OS and progression to AML



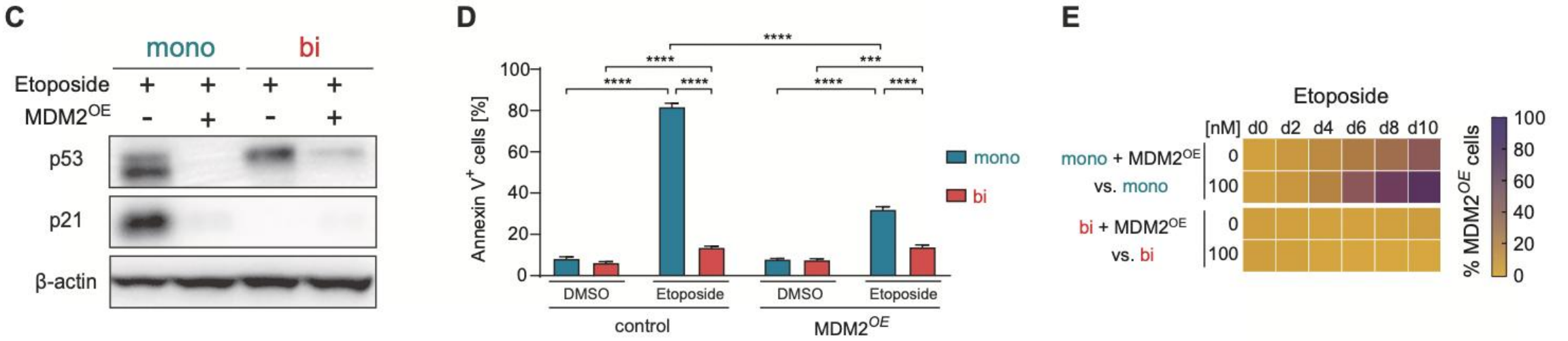


Versluis J. et al. JCO 2023

Biallelic TP53 inactivation clearly drives poor survival, higher leukemic progression, and unfavorable transplant outcomes

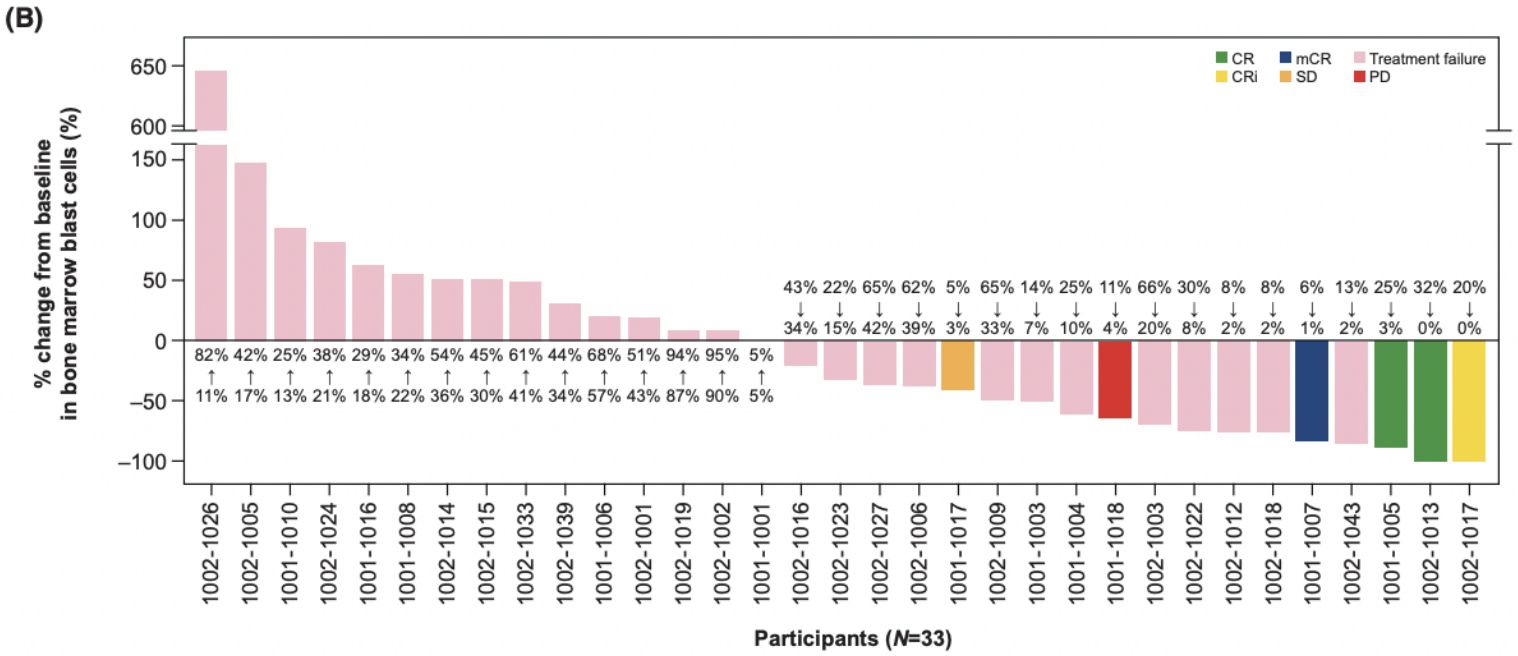
The role of monoallelic TP53 inactivation is less well defined, although available data suggest it may also carry adverse prognostic impact

MDM2 overexpression mimics biallelic inactivation



Fullin J. et al Leukemia (2026) 40:279–292

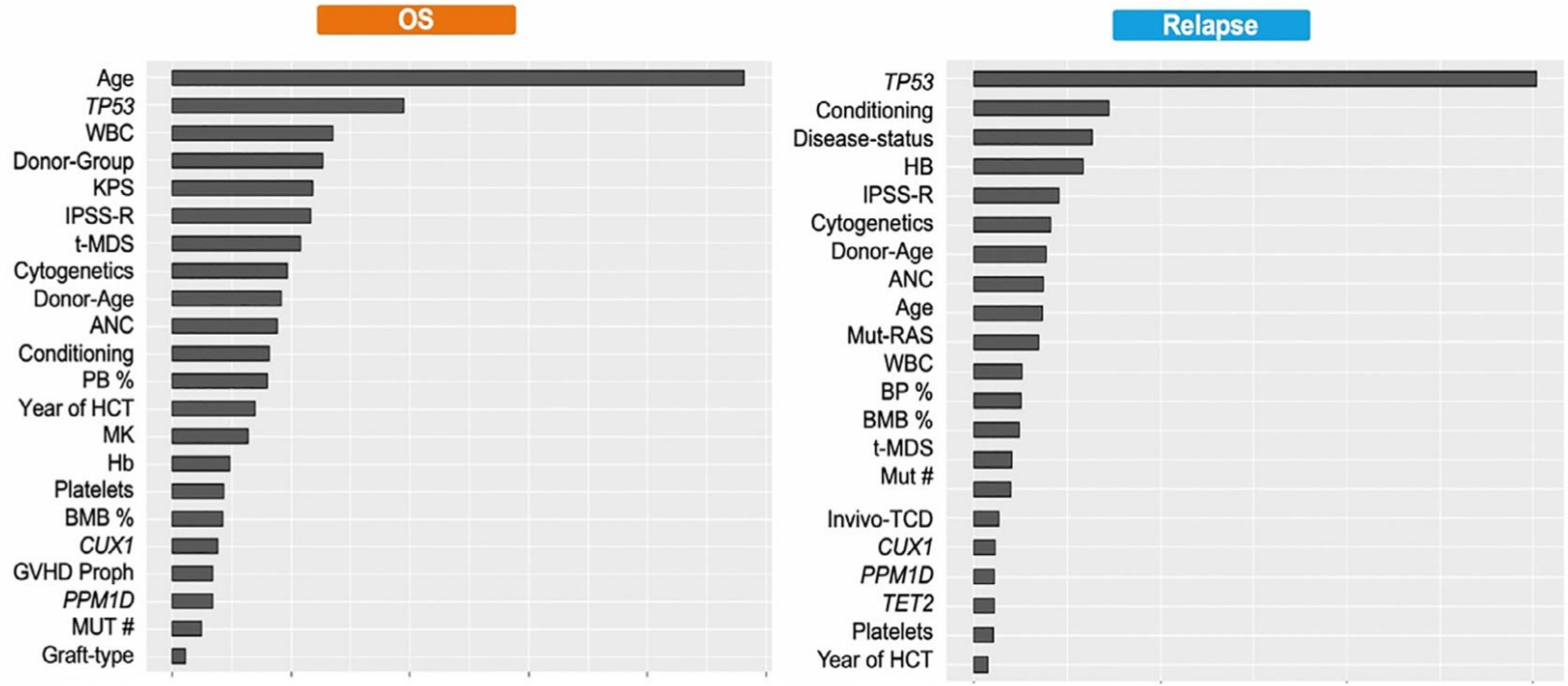
Phase 1 dose escalation study of the MDM2 inhibitor milademetan as monotherapy and in combination with azacitidine in patients with myeloid malignancies



Di Nardo C. et al. Cancer Med 2025

Initial question: Who truly has a realistic benefit from transplant ?

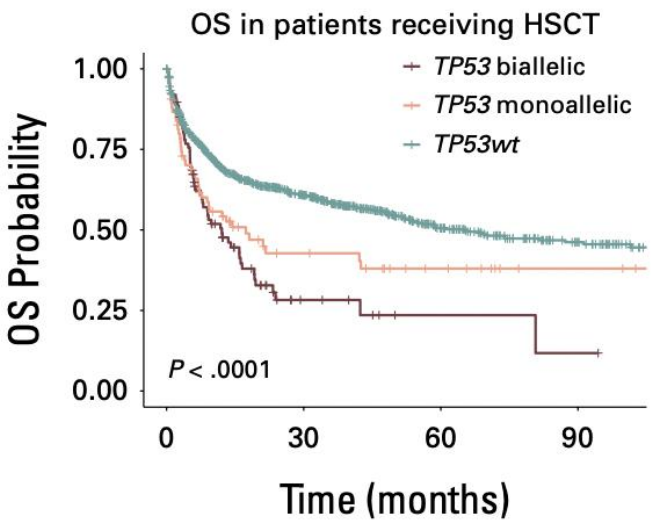
A Personalized Prediction Model for Outcomes after Allogeneic Hematopoietic Cell Transplant in Patients with Myelodysplastic Syndromes



Nazha A. et al. Biol Blood Marrow Transplant 2020

Considering the low OS and the high risk of relapse after HSCT in MDS with biallelic TP53 mutations, do we have alternative options?

E



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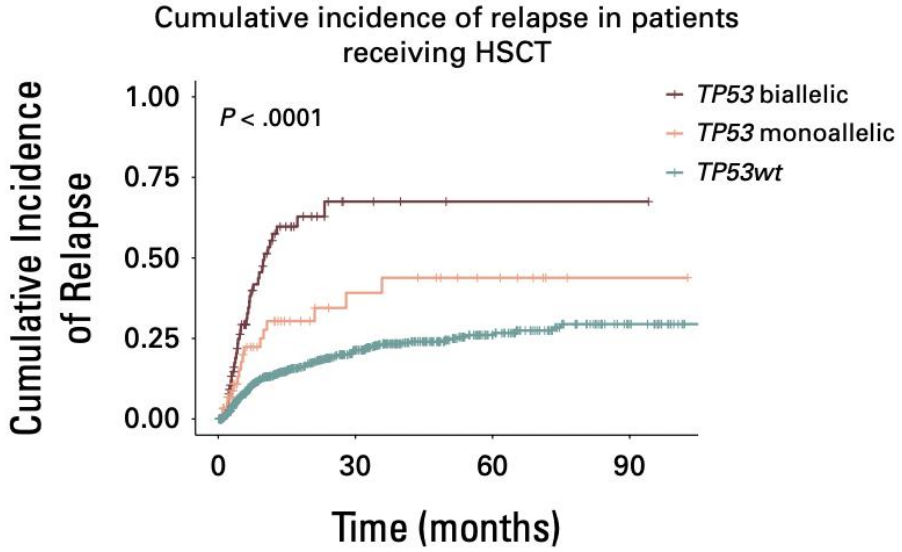
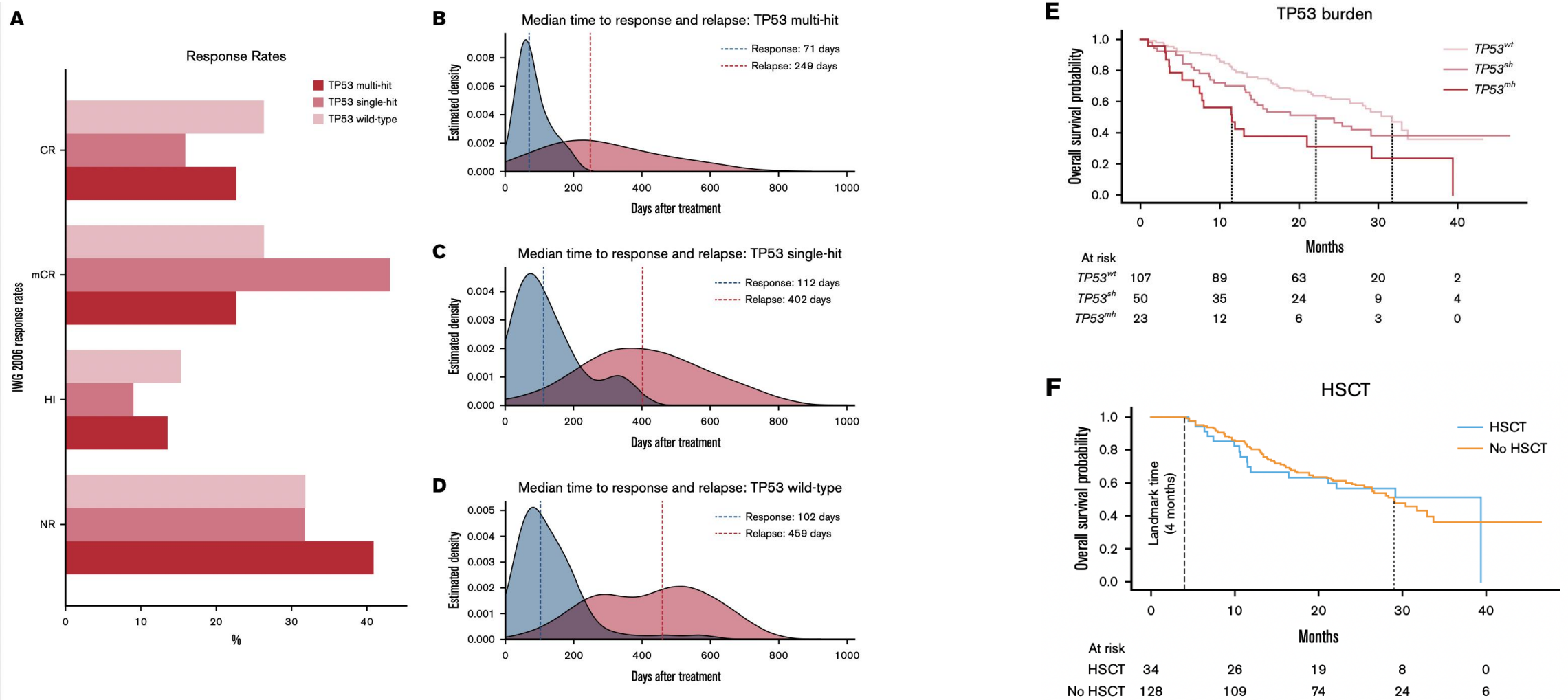
F



No. at risk:				
TP53 biallelic	85	4	1	1
TP53 monoallelic	75	13	7	1
TP53wt	951	316	111	44

Zampini M. et al JCO 2025

Decitabine-cedazuridine in patients with MDS and *TP53* mutations



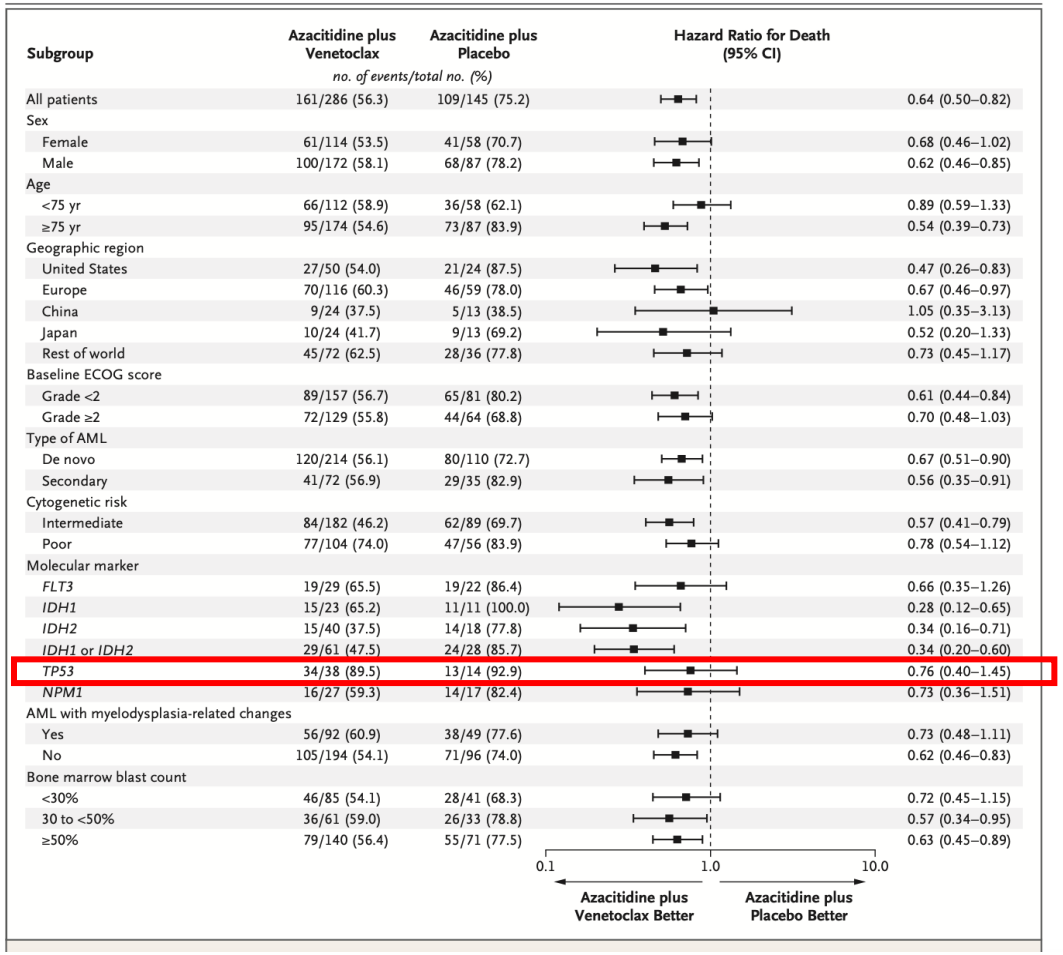
Urrutia S. et al. Blood Advances 2026

Azacitidine or decitabine plus something?

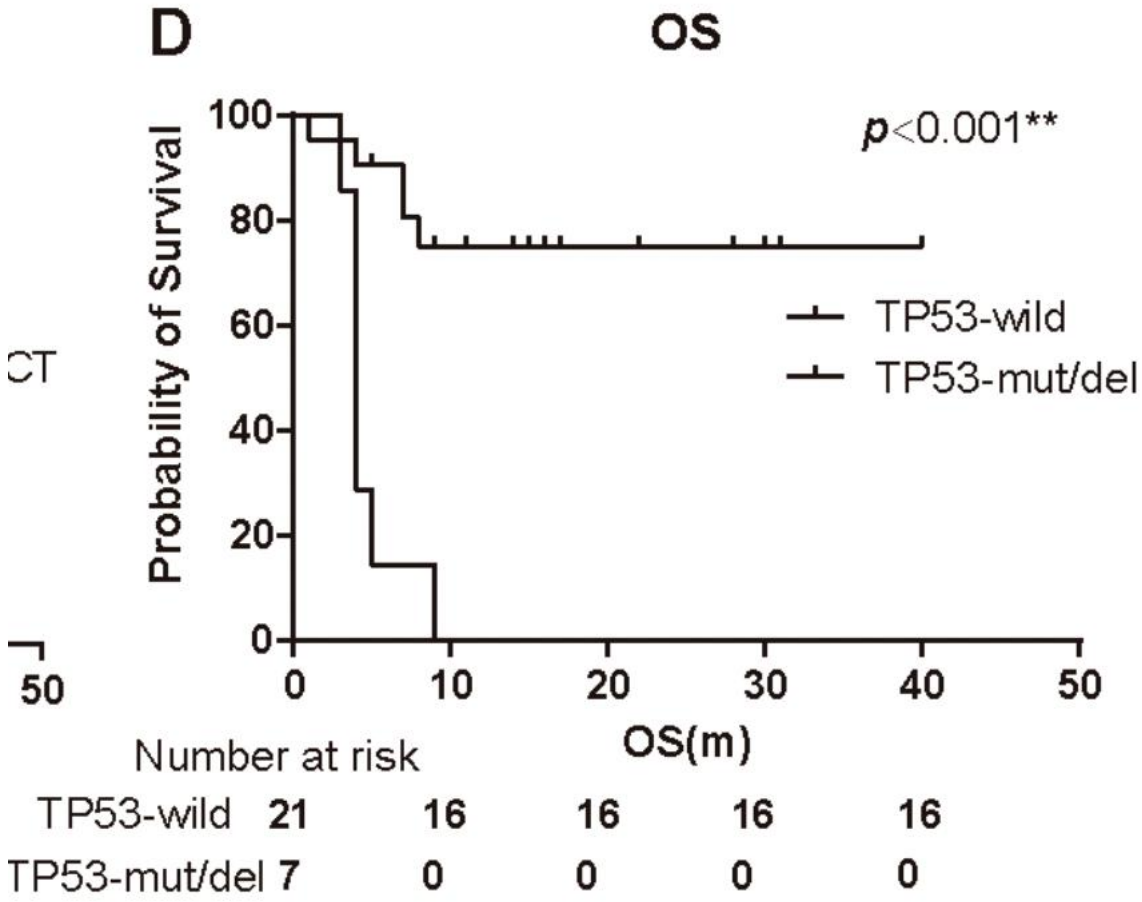
Azacitidine + venetoclax is better than azacitidine in **AML** with TP53 mutation (results from VIALE-A trial)

The NEW ENGLAND JOURNAL of MEDICINE

Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Female	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Male	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)



15-Day Duration of Venetoclax Combined with Azacitidine in Treatment-Naive Higher-Risk Myelodysplastic Syndromes: A Prospective Multicenter Study



Lai B et al. Cancers 2026, 18, 159

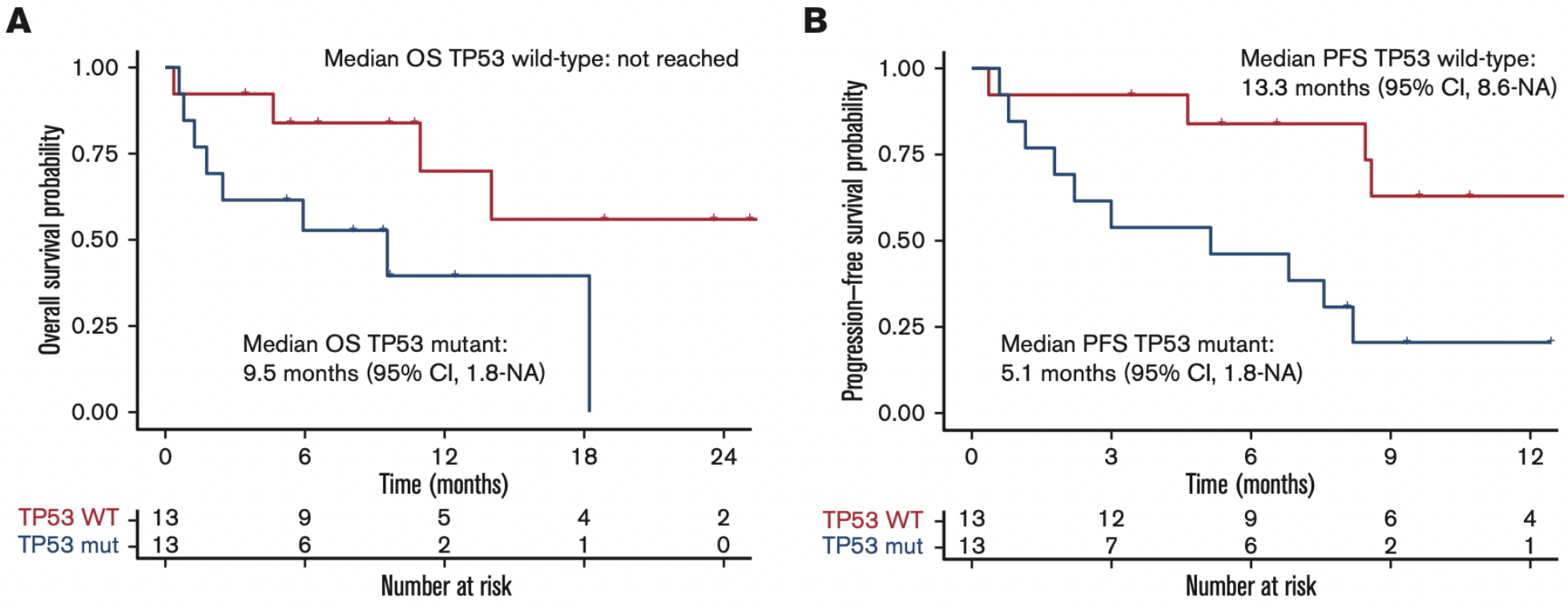
Many promising drugs failed to meet the primary endpoint

	PANTHER		STIMULUS	ENHANCE	SELECT-MDS-1	VERONA
	Pevonedistat	**Eprenetapopt**	**Sabatolimab**	**Magrolimab**	**Tamibarotene**	**Venetoclax**
Target	NEDD8 inhibitor	TP53 reactivator	TIM3 inhibitor	CD47 mAb	Selective RARa agonist	BCL2 inhibitor
Population	Intermed High Very high	TP53 mutant	Intermed High Very high CMML-2	Intermed High Very high	RARa positive 5% blasts Intermed High Very high	Intermed High Very high
Number recruited	454	154	127	520	190	509
Randomization	2:1	1:1	1:1	1:1	2:1	1:1
Endpoint	EFS	CR	CR and PFS	CR and OS	CR	OS
Result	Did not meet primary endpoint	Did not meet primary endpoint	Did not meet primary endpoint	Futility	Did not meet primary endpoint	Did not meet primary endpoint

Azacitidine or decitabine plus something?

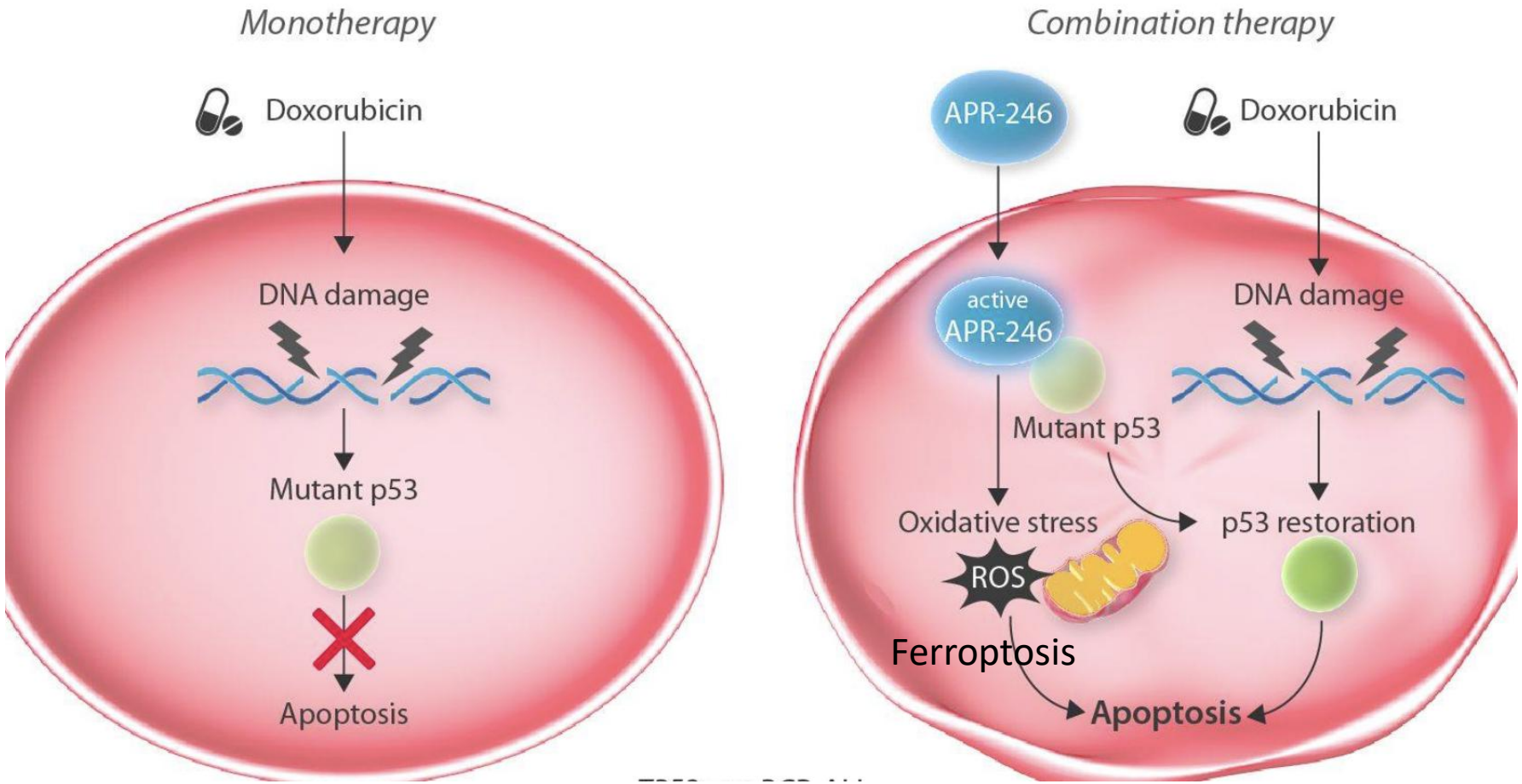
NCT#	Year	Phase	Patients	Interventions	N (TP53m)	No. of mono- vs bi-allelic mutation	Responses (TP53m vs WT)	Median OS, mon (TP53m vs WT)
NCT01687400 (75)	2016	II	MDS or AML	Decitabine	116 (21)	20;1	ORR: 100% vs. 41%	12.7 vs. 15.4
NCT02397720 (76)	2019	II	AML	Azacitidine + Nivolumab	70 (16)	NR	ORR: 19% vs. 33%	5.98 vs. 6.60
NCT03404193 (77)	2020	II	AML	Decitabine + Venetoclax	168 (31)	30;1	CR/CRi: 69% vs. 81%	6.9 vs. 18.1
NCT02152956 (78)	2021	I/II	AML	Flotetuzumab	88 (1)	NR	ORR: 30.0 vs NR	4.0 vs. 11.2
NCT03588078 (79)	2021	II	MDS or AML	Eprenetapopt + Azacitidine	52 (52)	31;21	ORR 52%, CR 37%	12.1 (MDS); 10.4 (AML)
NCT03072043 (80)	2021	II	MDS or AML	Eprenetapopt (APR-246) + Azacitidine	55 (55)	6;49	ORR: 71.0% vs. NR	10.8 vs. NR
ISRCTN78449203 (81)	2023	III	MDS or AML	CPX-351 vs FLAG-Ida	189 (81)	NR	NR	7.0 vs. 28.0
NCT03248479 (82)	2023	Ib	MDS	Magrolimab+ Azacitidine	95 (25)	NR	ORR: 68.0% vs. 78.7%	16.3 vs. not reached
NCT04214860 (83)	2023	I	AML	eprenetapopt + venetoclax + azacitidine	49 (49)	9;40	ORR: 64% vs. NR	NR
NCT03113643 (84)	2024	Ib/II	AML	Tagraxofusp + Azacitidine + Venetoclax	26 (13)	4;9	ORR: 54% vs. 85%	9.5 vs. not reached
NCT03946670 (85)	2024	II	MDS	Sabatolimab + HMA vs Placebo + HMA	127 (47)	NR	ORR 68% (Sabatolimab + HMA) vs. 61% (Placebo + HMA)	19.0 (Sabatolimab + HMA) vs. 18.0 (Placebo + HMA)
NCT03214562 (86)	2025	II	AML	FLAG-Ida + Ven	138 (6)	5;1	ORR 97% vs. 100% (ND); 52% vs. 79% (R/R)	13 vs. not reached (ND); 9 vs. not reached (R/R)
NCT03588078 (87)	2025	II	MDS or AML	Eprenetapopt (APR-246) + Azacitidine	100(100)	12:88	ORR 69%; CR 41%	11.8

Phase 1b trial of tagraxofusp in combination with azacitidine with or without venetoclax in acute myeloid leukemia



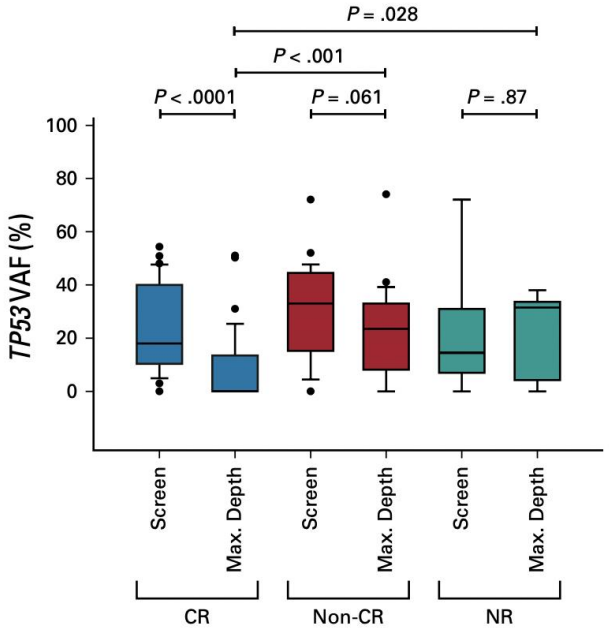
Lane A. et al. Blood Adv.2024

Mechanism of action of Eprenetapopt



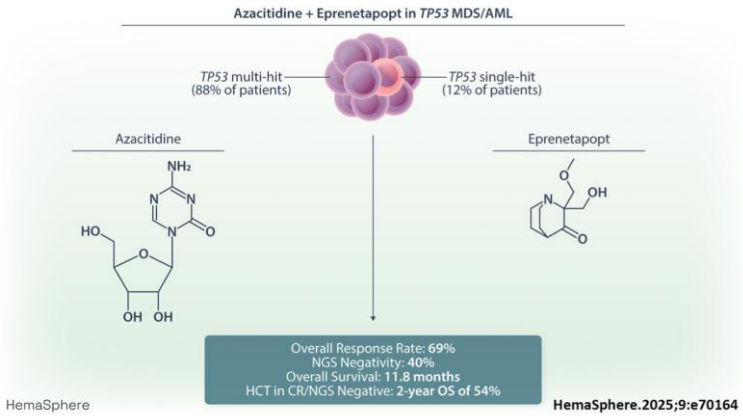
Eprenetapopt (APR-246) and Azacitidine in *TP53*-Mutant Myelodysplastic Syndromes

Response	All Patients (N = 55)	MDS (n = 40)	AML (n = 11)	MDS/MPN (n = 4)
ORR (95% CI)[a]	39 (71) [57 to 82]	29 (73) [56 to 85]	7 (64) [31 to 89]	3 (75)[b]
Time to first response, months, median (range)	2.1 (0.1-5.4)	1.9 (0.1-5.4)	2.3 (1.2-3.0)	2.7 (2.0-2.9)
Duration of response, months, median [95% CI][c]	8.0 [6.5 to 11.2]	8.4 [6.5 to 13.2]	7.5 [4.2 to NE]	7.4 [NE to NE]
Best response by IWG, n (%)				
CR	24 (44)	20 (50)	4 (36)	0 (0)
PR	0 (0)	0 (0)	0 (0)	0 (0)
mCR + HI	8 (15)	7 (18)	0 (0)	1 (25)
mCR	4 (7)	1 (3)	2 (18)	1 (25)
HI	3 (5)	1 (3)	1 (9)	1 (25)
SD	4 (7)	2 (6)	1 (9)	1 (25)
NE	10 (18)	7 (18)	3 (27)	0 (0)
PD	2 (4)	2 (4)	0 (0)	0 (0)
CR (95% CI)	24 (44) [30 to 58]	20 (50) [34 to 66]	4 (36) [11 to 69]	0 (0)
Time to CR, months, median (range)	3.1 (2.5-6.1)	3.1 (2.5-6.1)	3.2 (2.8-3.5)	NA
Duration of CR, months, median (95% CI)	7.3 [5.8 to NE]	7.3 [5.8 to NE]	7.0 [3.3 to NE]	NA
Cytogenetic response (95% CI)	26 (47) [34 to 61]	23 (58) [41 to 73]	3 (27) [6 to 61]	0[d]
Partial	8 (15) [7 to 27]	8 (20) [9 to 36]	0 (0) [NE]	
Complete	18 (33) [21 to 47]	15 (38) [23 to 54]	3 (27) [6 to 61]	
TP53				
NGS-negative	21 (38)	17 (43)	4 (36)	0
Serial IHC ≤ 5%	26 (47)	19 (48)	6 (55)	NA

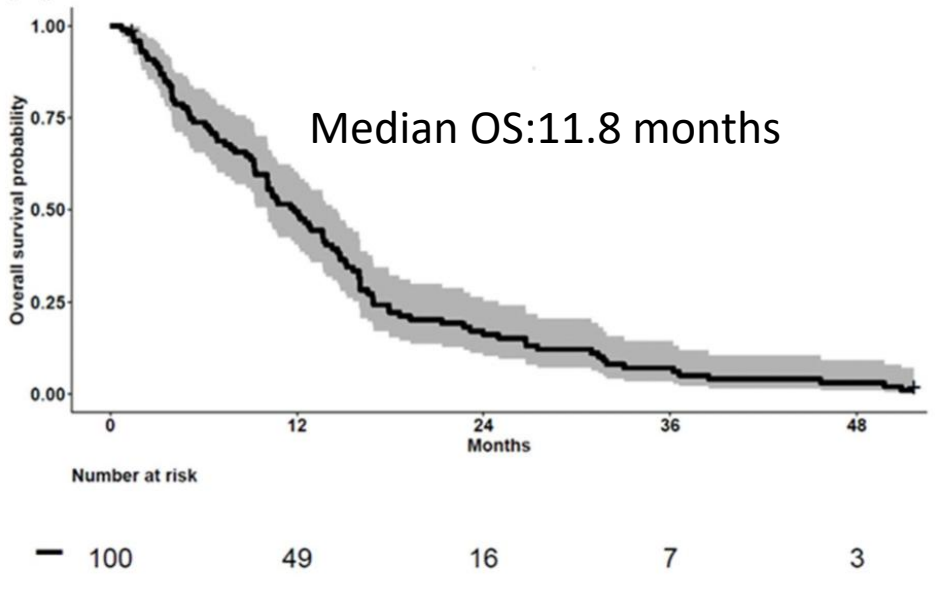


Sallman D.et al. JCO 2021

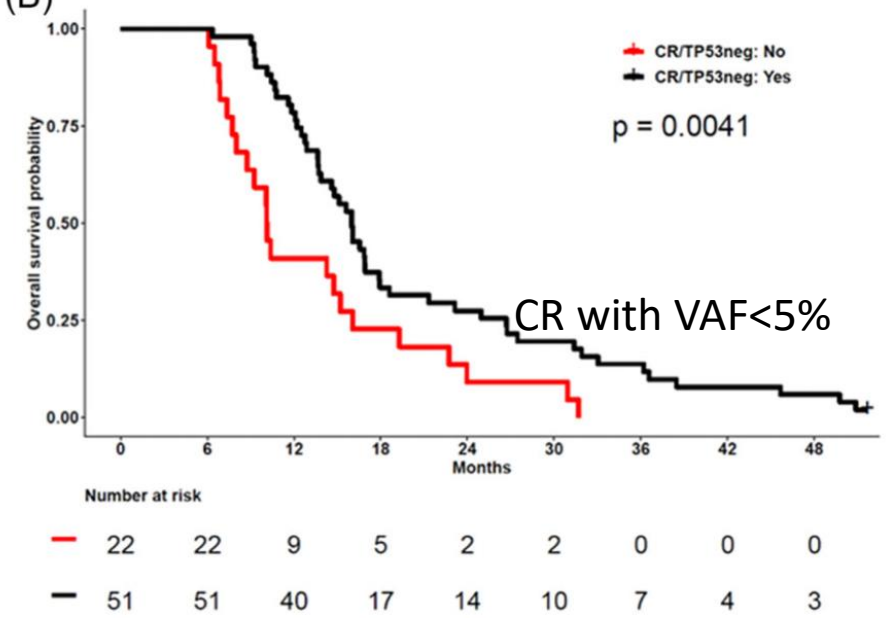
Long-term follow-up and combined Phase 2 results of eprenetapopt and azacitidine in patients with *TP53* mutant MDS/AML



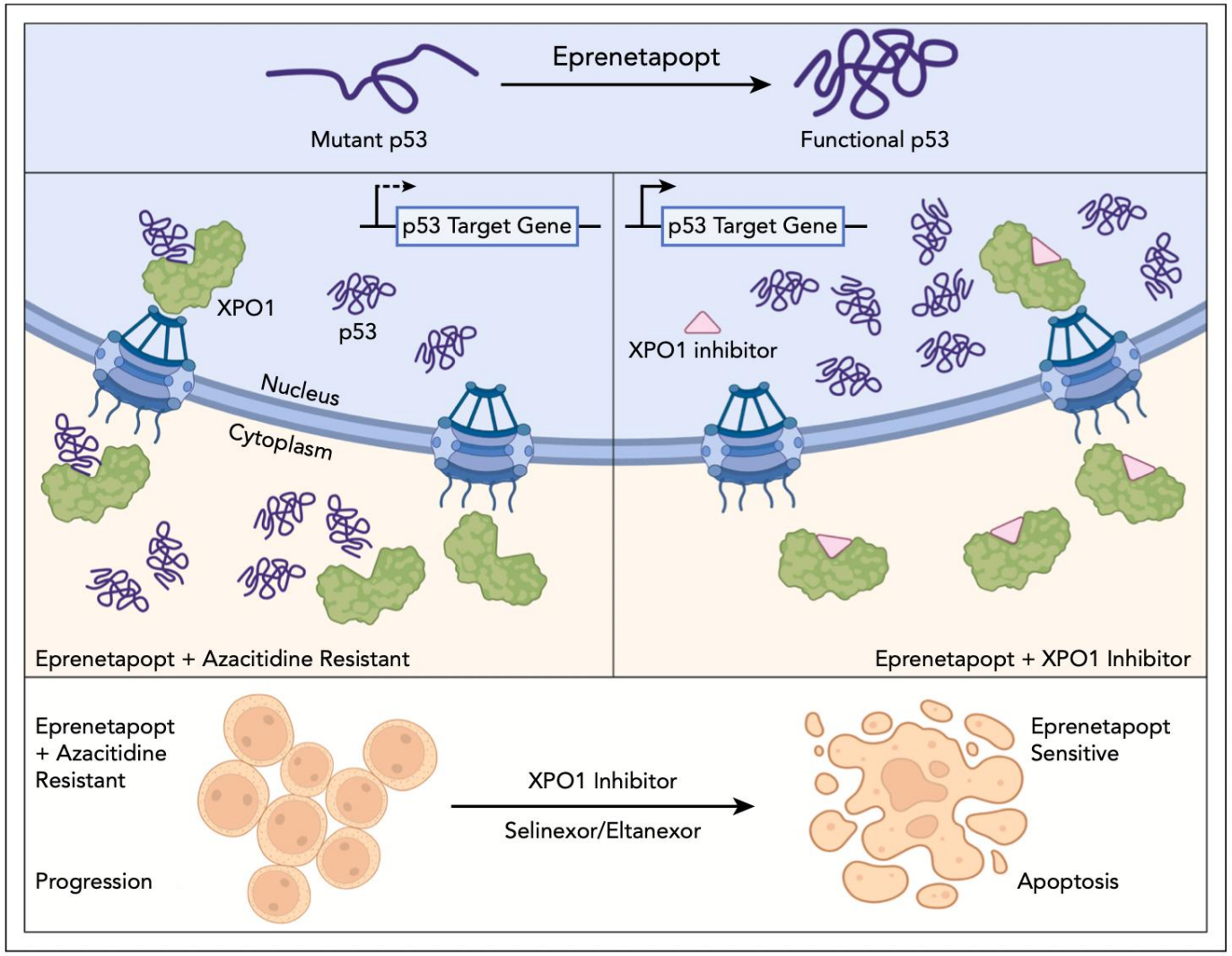
(A)



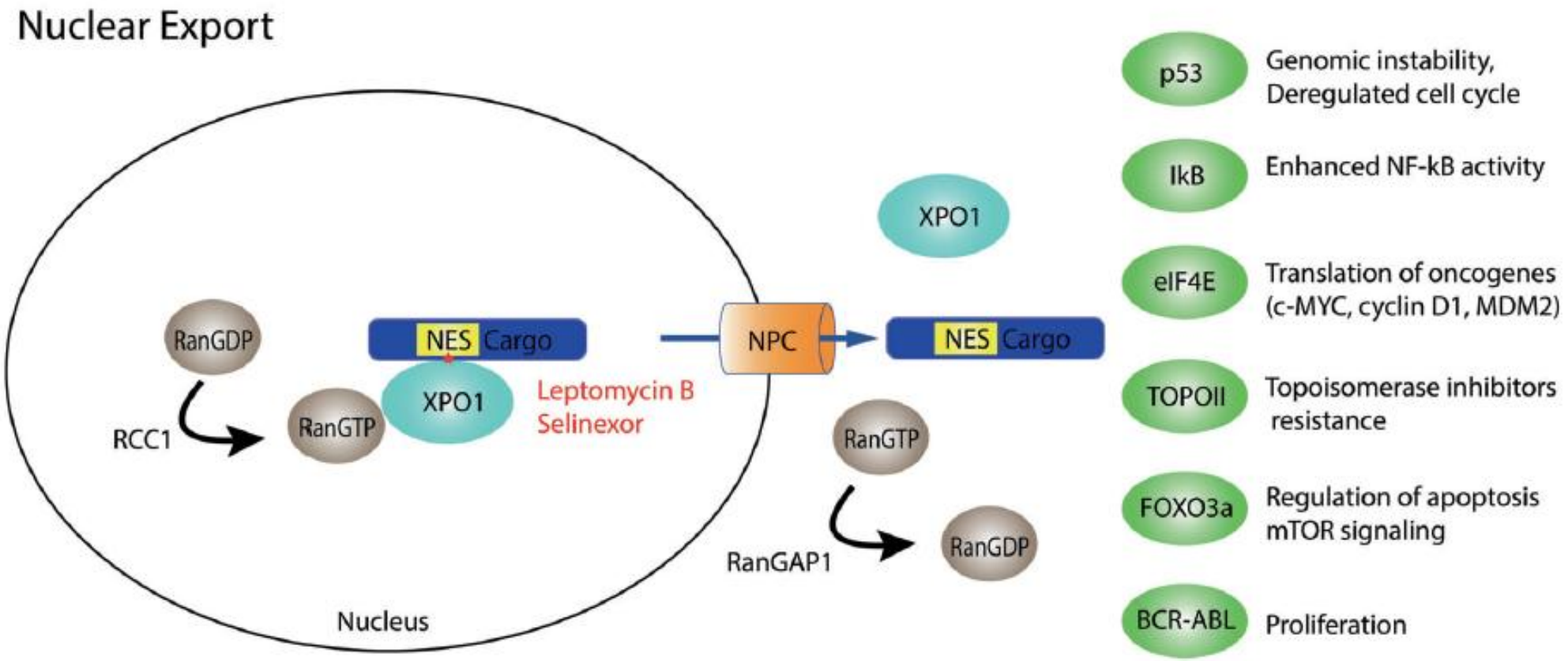
(B)



Why patients relapse after aza+eprenetapopt?

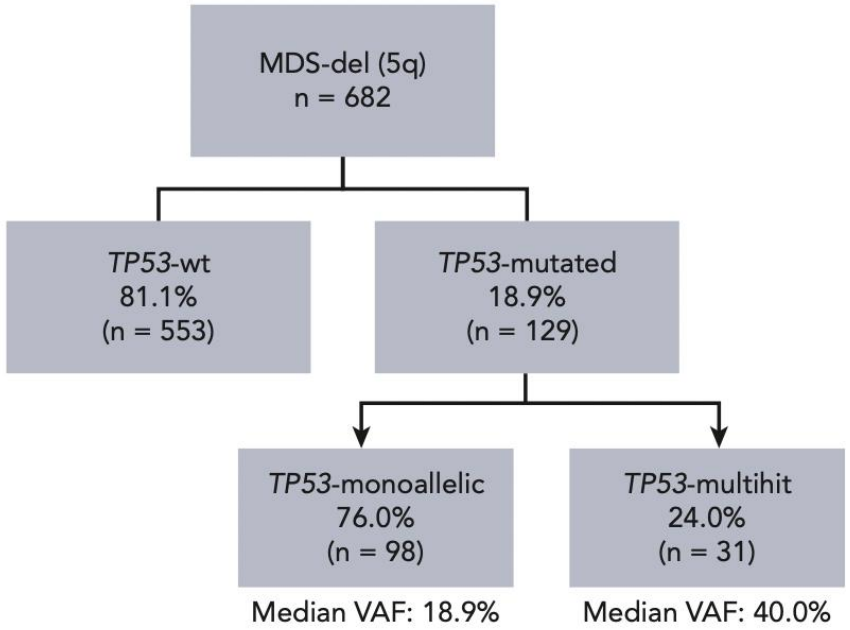


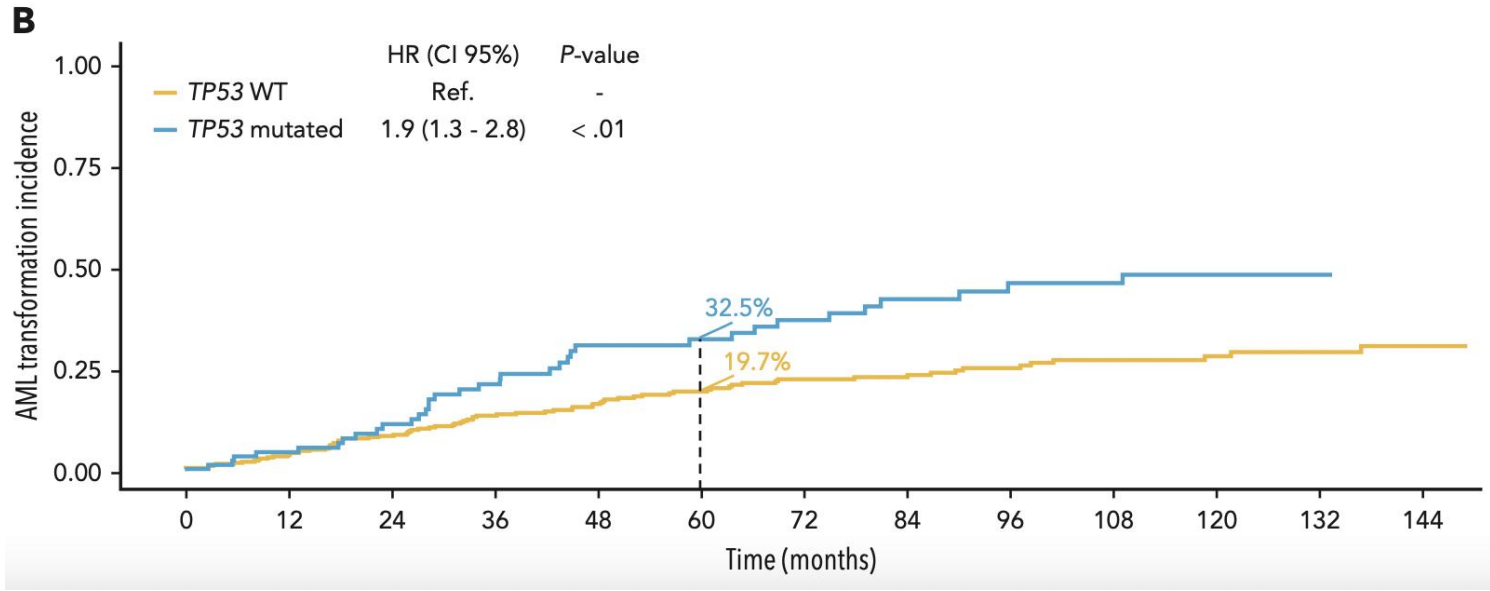
Targeting nuclear export (Exportin 1) enhances p53 activity



Nachmias B. et al. Leukemia 2020

Influence of *TP53* gene mutations and their allelic status in myelodysplastic syndromes with isolated 5q deletion





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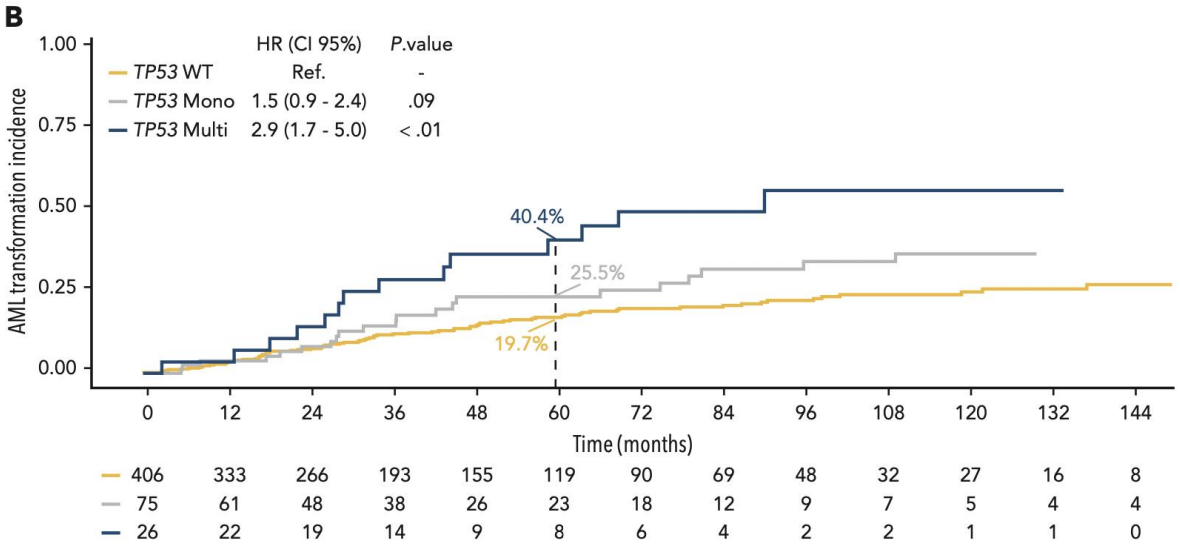
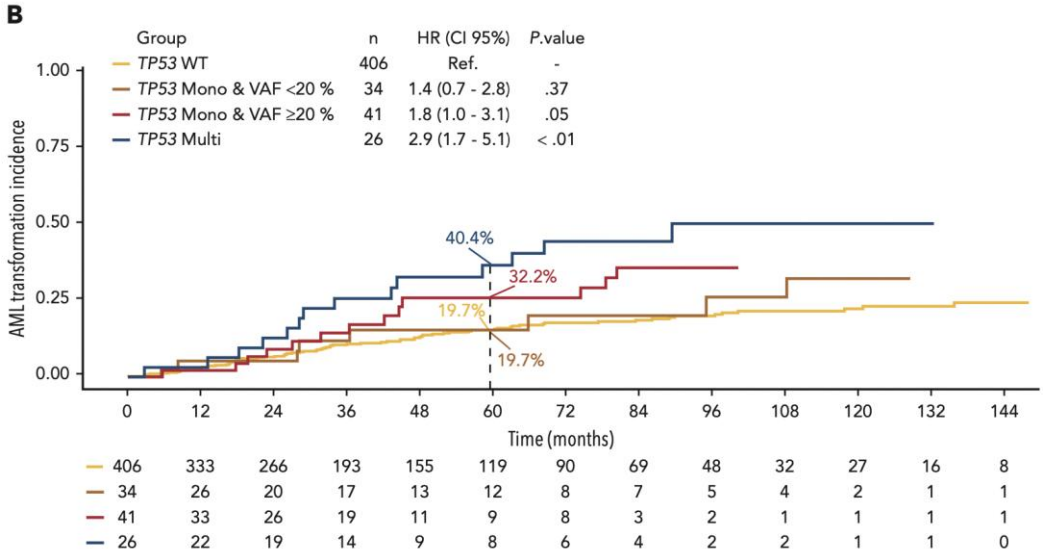
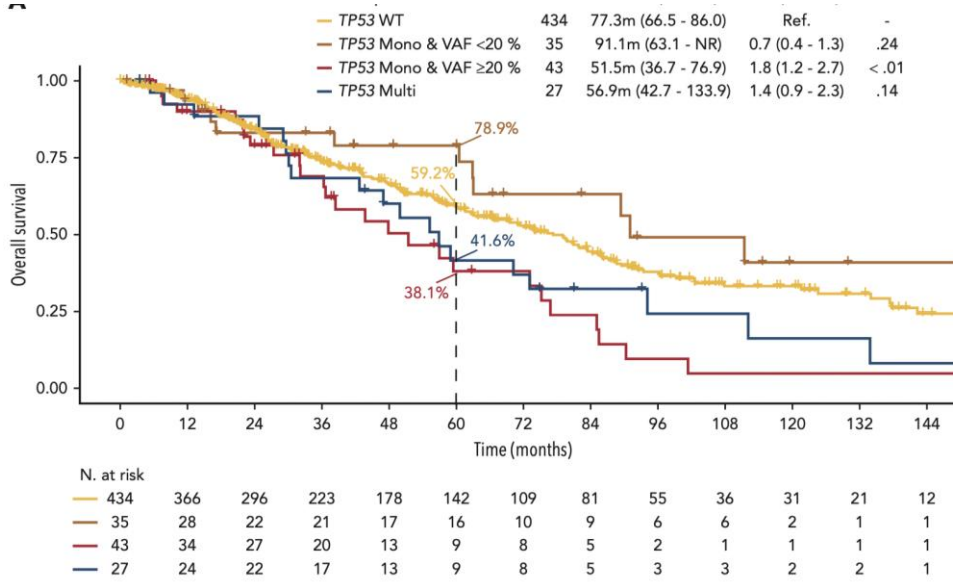
TP53 mutations have an impact on leukemic transformation in MDS 5q-





Patients with TP53 monoallelic mutations and VAF <20% exhibited behavior similar to TP53 wild type

TP53-monoallelic mutations and VAF ≥20% presented outcomes equivalent to TP53-multihit patients



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Conclusions

- TP53 remains the most difficult genetic alteration to treat
- TP53-mutated patients should be enrolled in dedicated clinical trials
- Current MDS trials often include too few TP53 cases → need for specific studies
- Allogeneic transplant is a valid option but rarely curative
- We lack more effective therapies, but can identify patients unlikely to benefit from transplant
- The treatment decision must be shared with the patient

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