TP53-mutated MDS: is transplant the only way?

YES!!!!.....almost alwats

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MYMAR Myeloid Malignancies Research Group
Vall d'Hebron Institute of Oncology. Barcelona

Vall d'Hebron Barcelona Hospital Campus

VHIO Vall d'Hebron Institute of Oncology

HCTO Hematology Clinical Trials Office

ECI Comprehensive Cancer Centre

Conflict of Interest

Company Name	Honoraria/Expenses	Consulting/ Advisory Board	Funded Research	Meetings ,travel, accommodation
Abbvie	X	X		X
Agios	X		X	X
Amgen	X	X		X
Asofarma	X			
Astellas	X	X		
Celgene/BMS	X	X	X	X
Grifols	X			X
Jansen	X			
Jazz	X	X		X
MSD	X			
Novartis	X	X		
Pfizzer	X			
Sanofy	X	X		
Servier		X		
Sobi	X	X		
Syros		X		
Takeda	X	X		

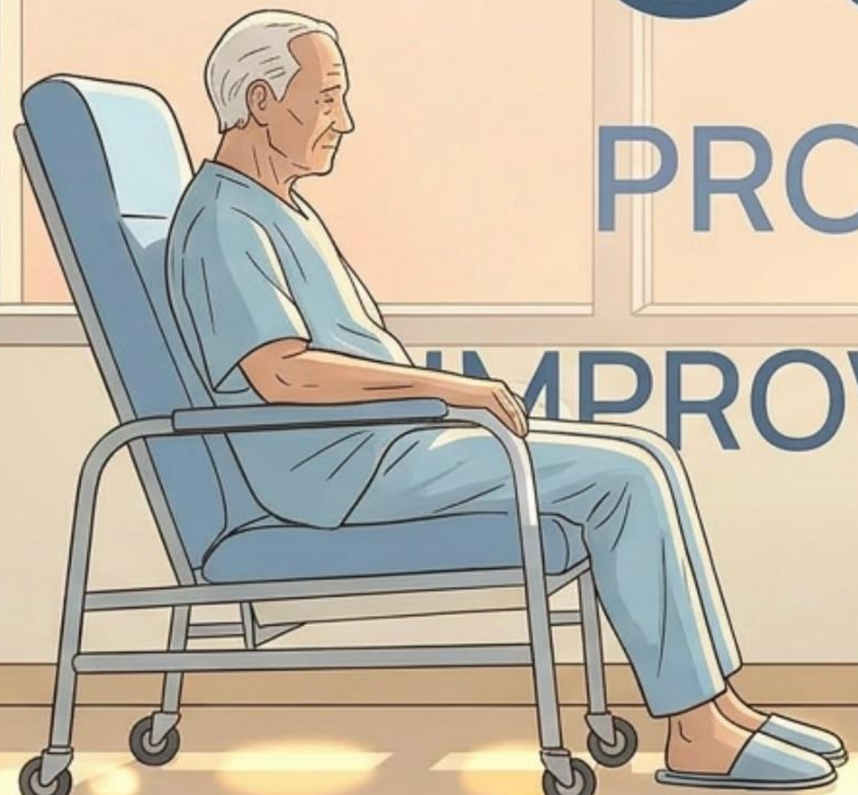
This presentation can include the use of **out of label use of drugs,** drugs in **investigational phase** or **not approved in some countries**

WHY DO WE TREAT PATIENTS WITH MDS?

CURE?

PROLONG SURVIVAL?

IMPROVE QUALITY OF LIFE?



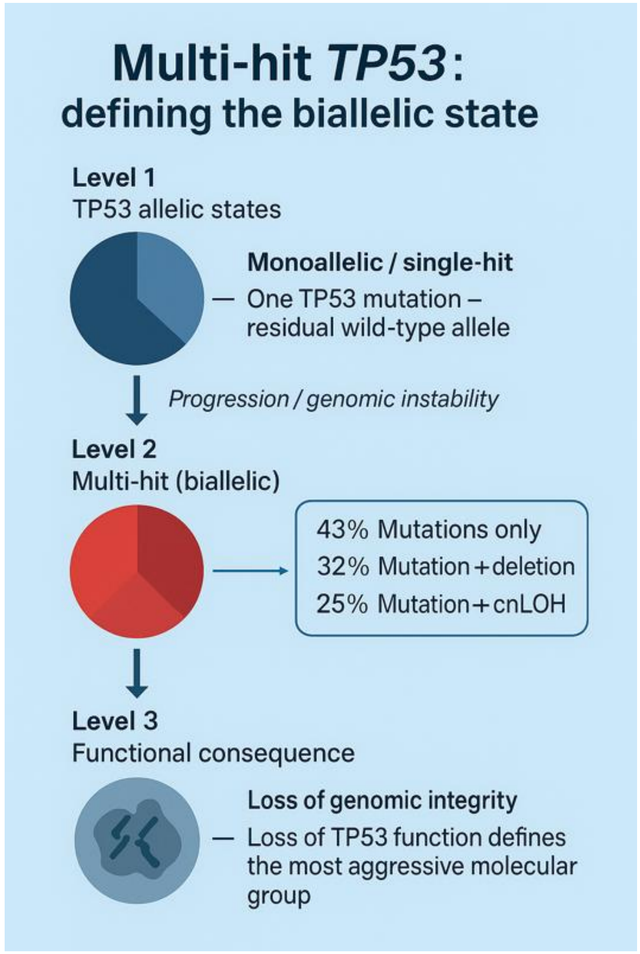
In *TP53*-mutated MDS...

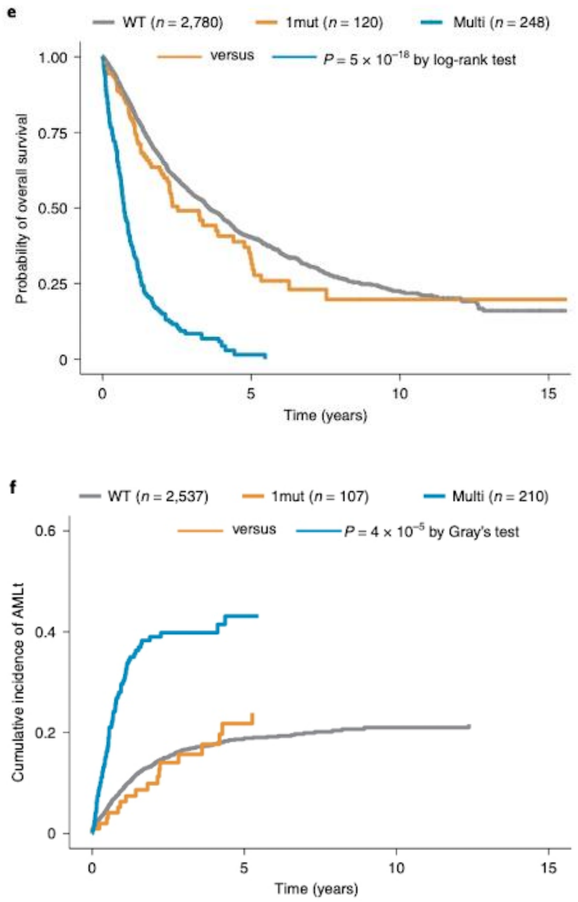
we fail in all three.

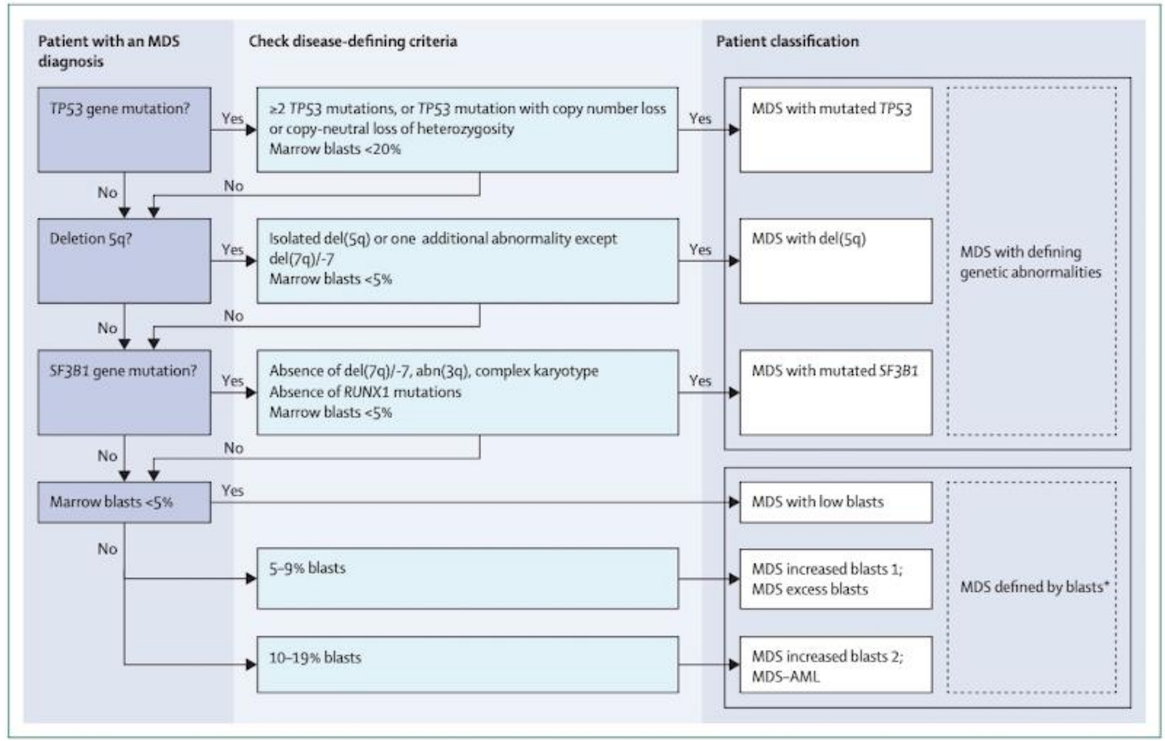
Except for one strategy that
can still make a difference.

The *TP53* multihit/biallic issue

TP53 multihit is associated a worse and has been proposed as the main classifier in MDS







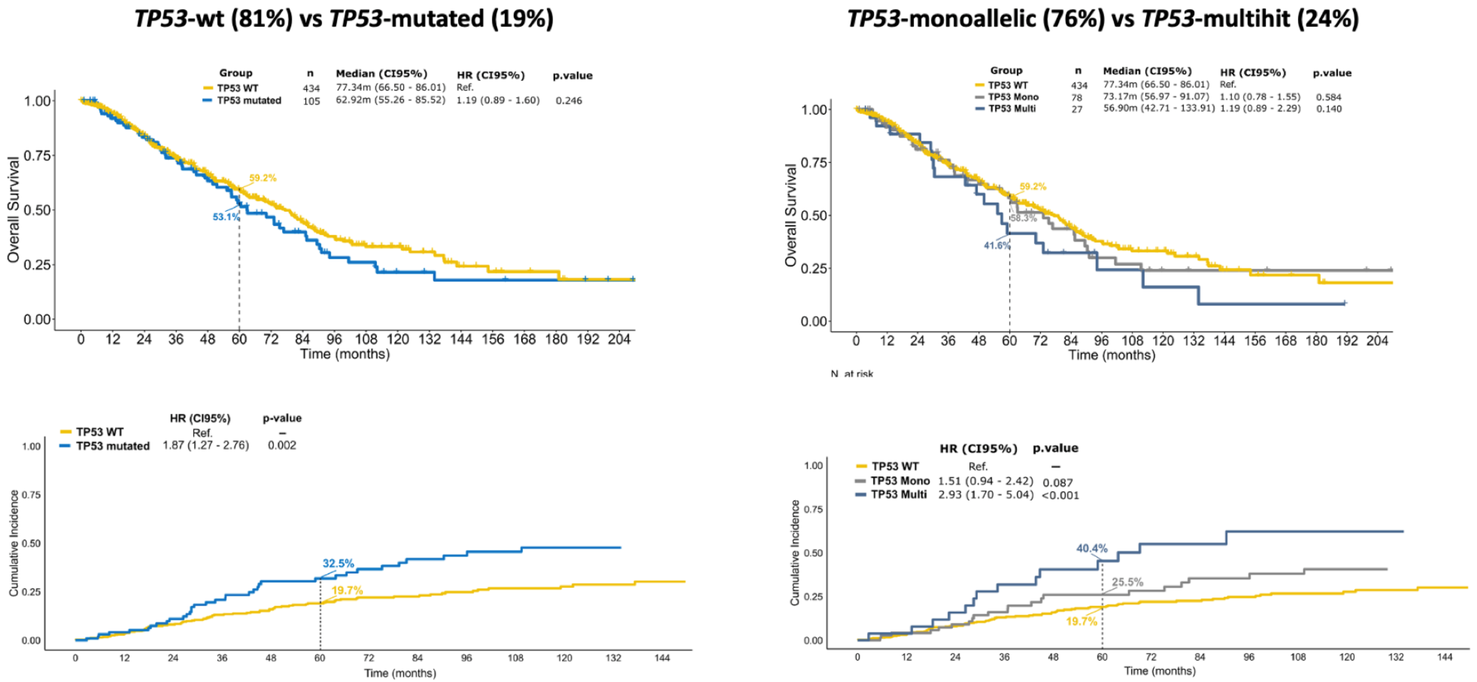
Bernard E et al. Nature Medicine 2020

Komrokji R, et al. Lancet Haematology 2024*

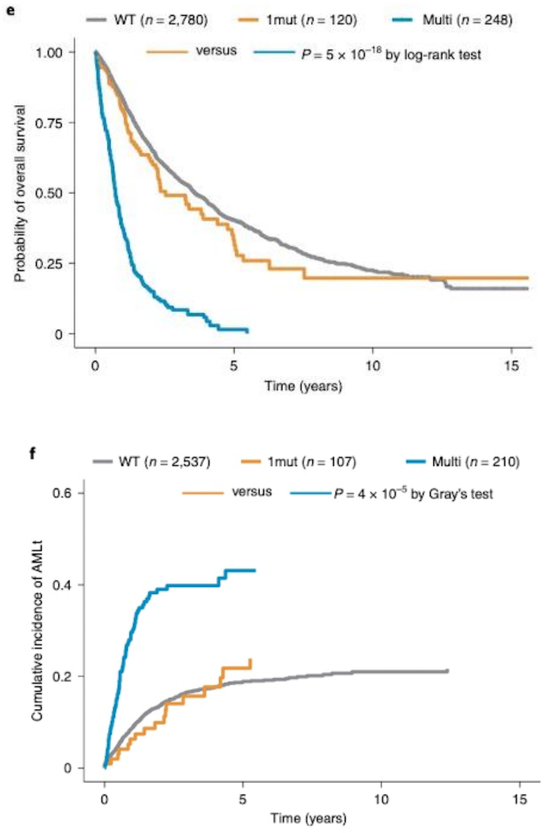
Is it the same for *TP53*^{mut} in del5q MDS

TP53 multihit remains adverse, though its impact is tempered in del(5q) MDS.

N= 682 MDS-del(5q)



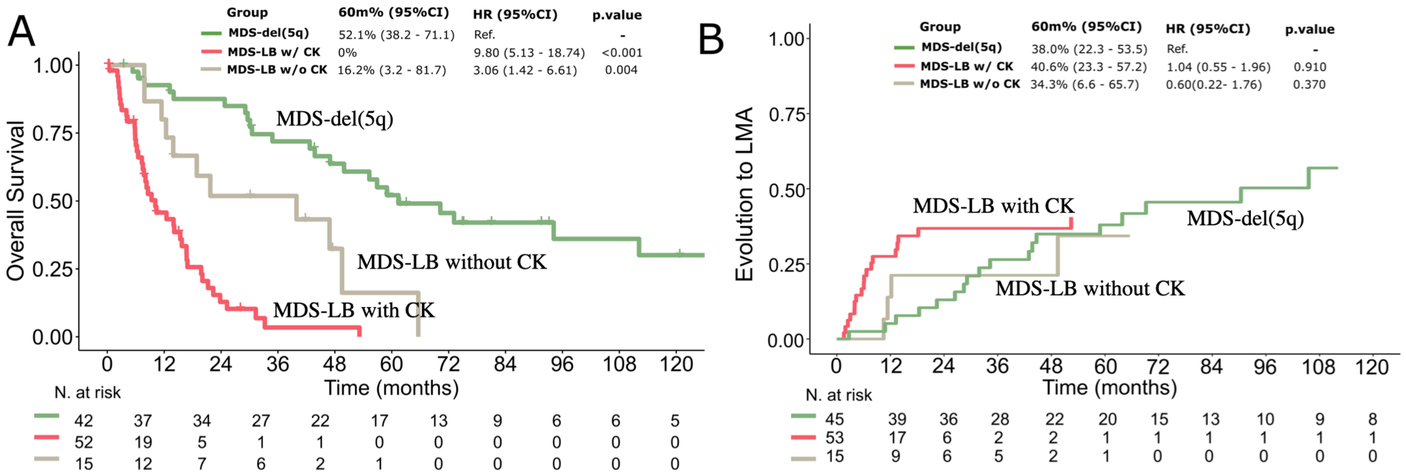
Montoro J et al, Blood 2024

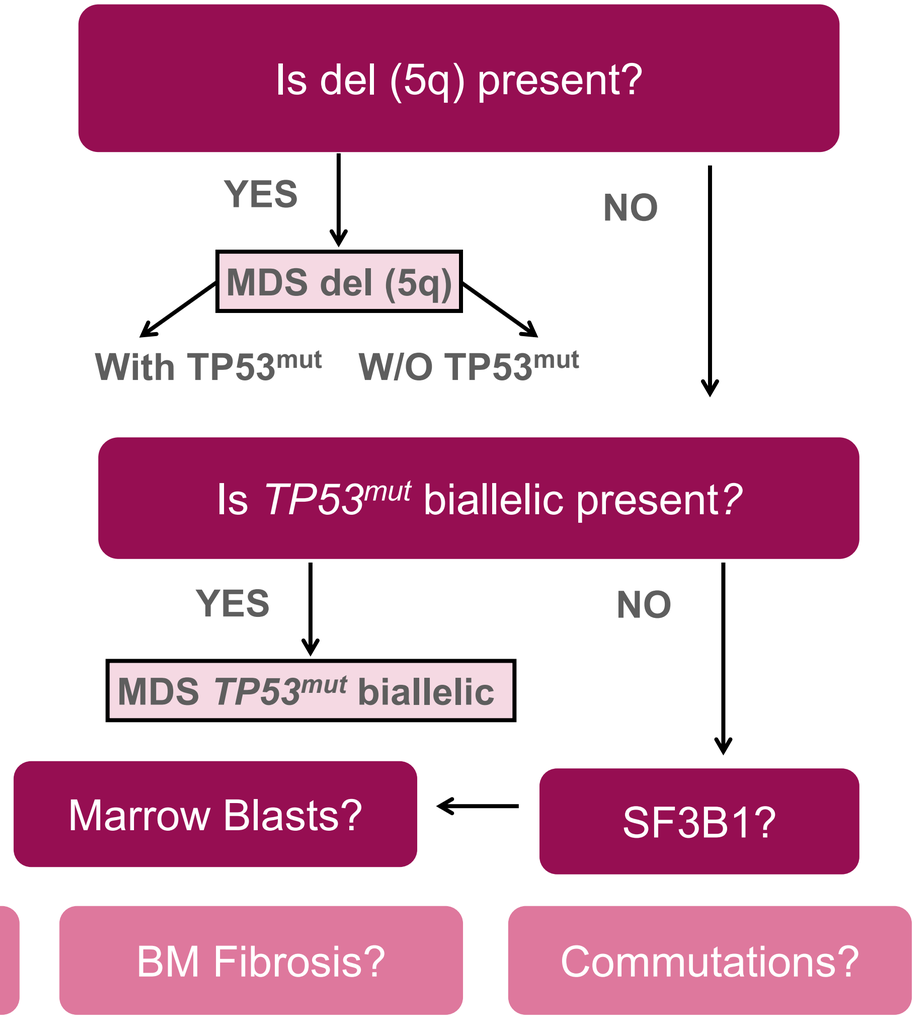


Bernard E et al. Nature Medicine 2020

Clinical impact of *TP53*^{mut} in del5q MDS

TP53-mutated del(5q) MDS a retain survival advantage compared with other low-blast TP53-mutated subtypes.



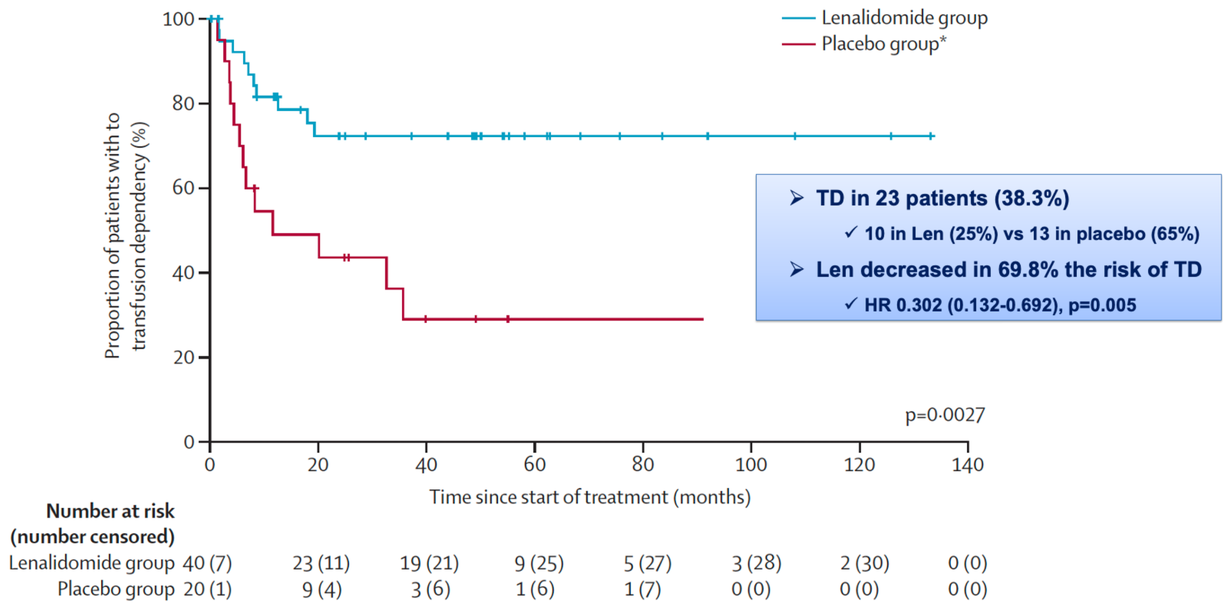


Montoro J et al, Leukemia 2026, in press

Treatment of Del5q with *TP53*^{mut}

Lenalidomide remains the standard of care, though caution is warranted in *TP53*-mutated cases

Results from SintraRev Study



- TD in 23 patients (38.3%)
  - ✓ 10 in Len (25%) vs 13 in placebo (65%)
- Len decreased in 69.8% the risk of TD
  - ✓ HR 0.302 (0.132-0.692), p=0.005

RESPONSES	*TP53*^{MUT}
Erythroid response	40%
Cytogenetic response	60%
Duration of response	Similar
Transfusion Dependence	80%Len & 60%PBO
Time to TD (median)	12.6mo Len & 6.6mo PBO
AML	20%Len & 20%PBO
Time to AML (median)	NR/NR

But….do not forget to start a donor search while starting lenalidomide!!!

Courtesy of Dr. Díez Campelo

Díez Campelo & López Cadenas, Lancet Haematology 2024

What about the all other drugs

We do not have a good option: Results are constantly worse for *TP53^{mut} thant TP^{wt}*

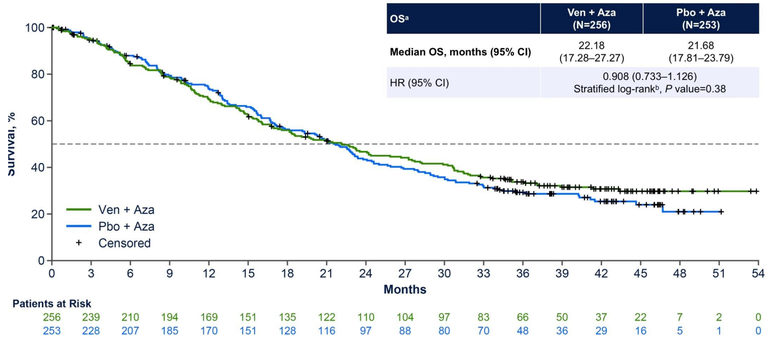
Study (phase)	CR (%)	OS (months)
CPX-351 (Phase 3)	37 (*TP53*^{mut} 29)	9.3 (*TP53*^{mut} 4.5)
Decitabine 10 days (Phase 2)	53–100	12.7 (WT 15.4)
Decitabine 5 days (Phase 2)	25	5.5 (*TP53*^{mut} 5.5)
ASCERTAIN (Oral decitabine/cedazuridine)	66 (*TP53*^{mut} 55)	14.7 (*TP53*^{mut} 5.2)
VIALE-A (AZA + venetoclax)	66–33	10.8 (*TP53*^{mut})
Magrolimab + AZA (Phase 1b)	44	10.8
Eprenetapopt + AZA (Phase 1b/2)	38	10.8
Eprenetapopt + venetoclax + AZA (Phase 1)	38	10.8 (*TP53*^{mut})
Sabatalimab + HMA (Phase 1b)	20–29	26.7
SL-172154 ± AZA (Phase 1/2)	23	1 CR in *TP53*^{mut}

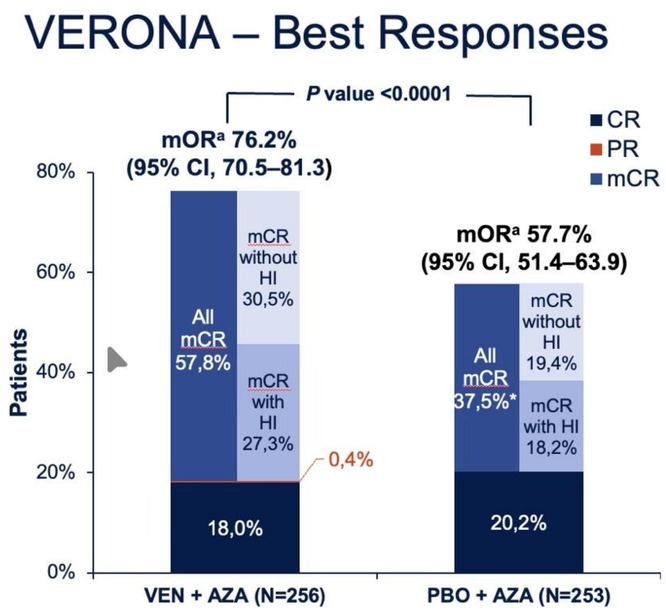
Mehta AK & Konopleva M. Hematology (ASH educational program) 2024

What about VERONA trial

Preliminary results

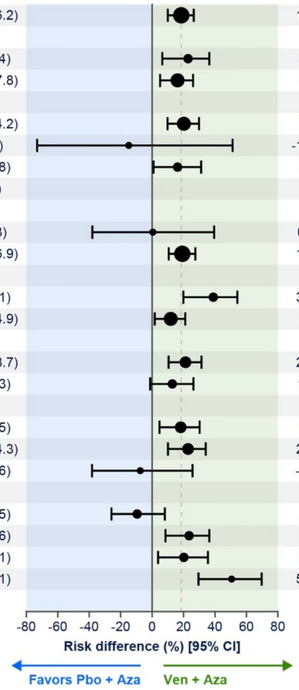
The combination of HMA-Ven is not approved for MDS



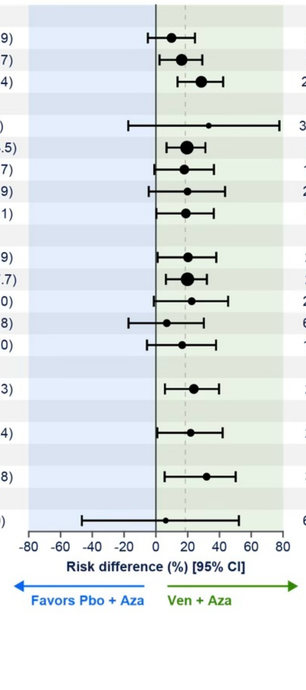


Subgroup analyses: Ven + Aza trended toward an mOR benefit vs Pbo + Aza for patients with >5% to <20% bone marrow blasts or *ASXL1*, *TP53*, and *RUNX1* mutations at baseline

	Pbo + Aza Responders/N (%)	Ven + Aza Responders/N (%)	Risk difference (%) [95% CI] Ven + Aza vs Pbo + Aza
Overall (n=341)	146/253 (57.7)	195/256 (76.2)	18.464 [10.048, 26.516]
Sex			
Female	44/87 (50.6)	69/94 (73.4)	22.830 [6.453, 36.357]
Male	102/166 (61.4)	126/162 (77.8)	16.332 [5.145, 26.130]
Race			
White	98/182 (53.8)	138/186 (74.2)	20.347 [9.790, 29.890]
Black or African American	3/4 (75.0)	3/5 (60.0)	-15.000 [-73.215, 51.227]
Asian	44/66 (66.7)	53/64 (82.8)	16.146 [0.904, 31.209]
Other	0/0	1/1 (100)	- [-, -]
Ethnicity			
Hispanic or Latino	7/11 (63.6)	9/14 (64.3)	0.649 [-38.012, 39.488]
Not Hispanic or Latino	138/240 (57.5)	186/242 (76.9)	19.360 [10.645, 27.525]
Age (years)			
18- <65	27/64 (42.2)	43/53 (81.1)	38.945 [19.925, 54.242]
≥65	119/189 (63.0)	152/203 (74.9)	11.914 [1.737, 21.103]
Age (years)			
18- <75	86/150 (57.3)	133/169 (78.7)	21.365 [10.529, 31.439]
≥75	60/103 (58.3)	62/87 (71.3)	13.012 [-1.235, 26.327]
Baseline ECOG PS			
0	66/101 (65.3)	81/97 (83.5)	18.159 [4.659, 30.215]
1	68/132 (51.5)	104/140 (74.3)	22.771 [10.118, 34.058]
2	12/20 (60.0)	10/19 (52.6)	-7.368 [-38.165, 25.737]
Baseline bone marrow blast (%)			
≤5	42/69 (60.9)	34/66 (51.5)	-9.354 [-25.938, 8.097]
>5- ≤10	52/91 (57.1)	75/93 (80.6)	23.502 [8.470, 36.416]
>10- ≤15	39/61 (63.9)	53/63 (84.1)	20.193 [3.848, 35.498]
>15- <20	13/28 (46.4)	33/34 (97.1)	50.630 [29.527, 69.655]
≥20	0/4	0/0	- [-, -]



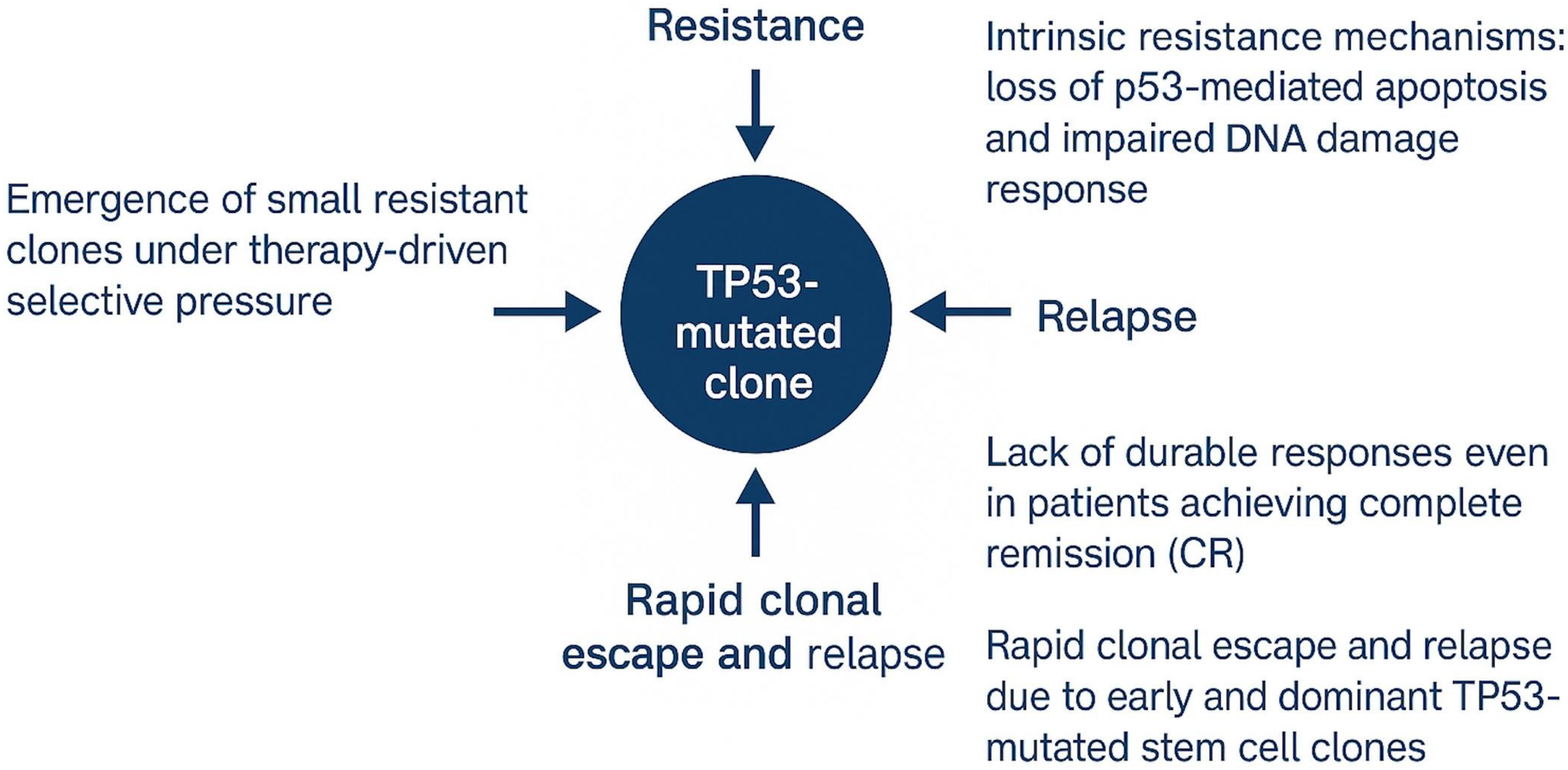
	Pbo + Aza Responders/N (%)	Ven + Aza Responders/N (%)	Risk difference (%) [95% CI] Ven + Aza vs Pbo + Aza
Baseline IPSS-R prognostic risk			
Intermediate	49/72 (68.1)	53/68 (77.9)	9.886 [-5.145, 24.577]
High	57/99 (57.6)	70/95 (73.7)	16.108 [2.309, 29.230]
Very high	40/82 (48.8)	72/93 (77.4)	28.639 [13.559, 42.294]
Baseline IPSS-R cytogenetic risk			
Very good	4/6 (66.7)	6/6 (100)	33.333 [-17.393, 77.722]
Good	74/116 (63.8)	86/103 (83.5)	19.702 [6.691, 31.144]
Intermediate	28/46 (60.9)	37/47 (78.7)	17.854 [-1.038, 36.472]
Poor	13/29 (44.8)	24/37 (64.9)	20.037 [-4.542, 43.540]
Very poor	26/55 (47.3)	41/62 (66.1)	18.856 [0.269, 36.389]
Region			
North America	25/56 (44.6)	37/57 (64.9)	20.269 [1.081, 37.961]
Europe	64/111 (57.7)	87/112 (77.7)	20.021 [6.306, 32.085]
Japan	16/23 (69.6)	23/25 (92.0)	22.435 [-1.262, 45.430]
China	20/27 (74.1)	21/26 (80.8)	6.695 [-17.182, 30.154]
Rest of World	21/36 (58.3)	27/36 (75.0)	16.667 [-5.622, 37.829]
***ASXL1* mutation**			
Detected	37/68 (54.4)	47/60 (78.3)	23.922 [5.722, 39.660]
***TP53* mutation**			
Detected	18/38 (47.4)	34/49 (69.4)	22.019 [0.899, 41.967]
***RUNX1* mutation**			
Detected	25/49 (51.0)	24/29 (82.8)	31.738 [5.498, 50.243]
***EZH2* mutation**			
Detected	7/13 (53.8)	3/5 (60.0)	6.154 [-46.594, 52.182]



Garcia-Manero G et al, SOHO 2025

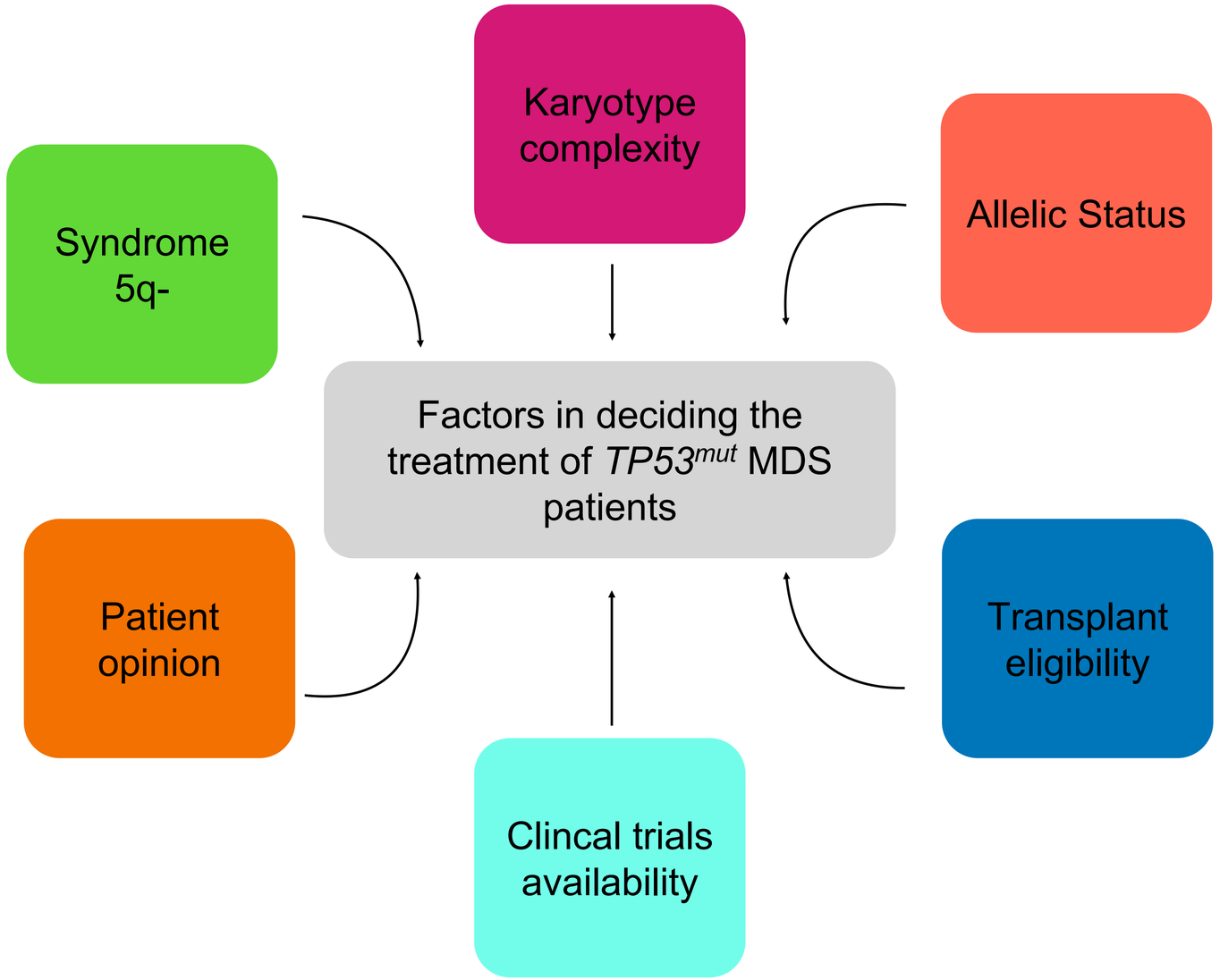
Courtesy of Garcia-Manero G

Why do conventional therapies fail in TP53-mutated MDS?



Treatment of *TP53^{mut} patients*

Factors guiding treatment decision



REVIEW ARTICLE

blood advances

Utility or futility? A contemporary approach to allogeneic hematopoietic cell transplantation for *TP53*-mutated MDS/AML

Mariam T. Nawas and Satyajit Kosuri

Hematopoietic Cellular Therapy Program, Department of Medicine, The University of Chicago Medicine, Chicago, IL

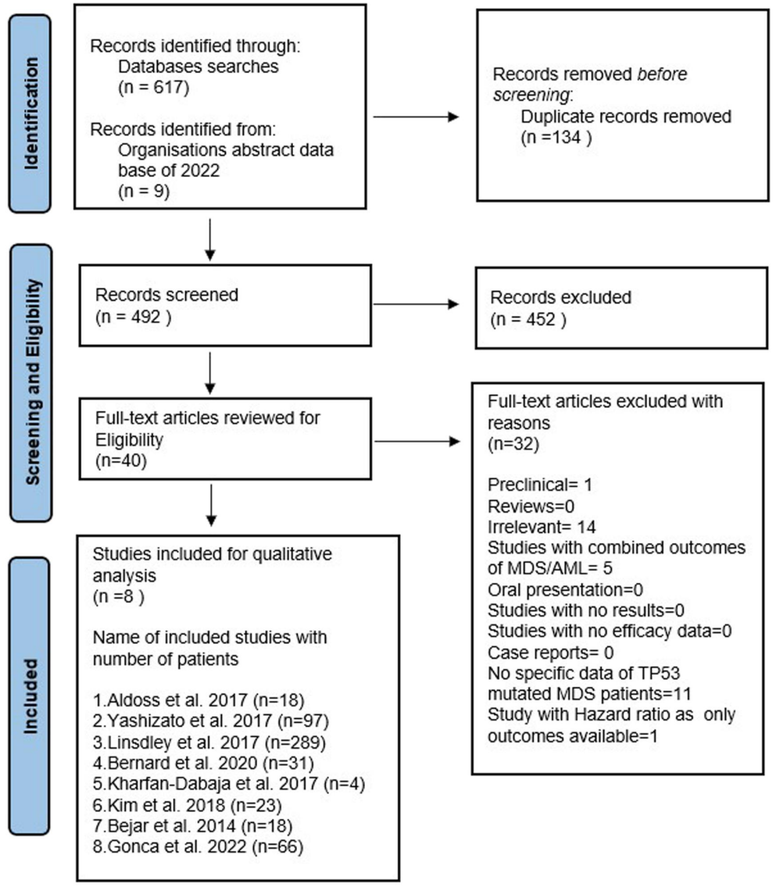
Author	Study type	Disease	Pts with *TP53* LOF receiving allo-HCT	Subset with high-risk cytogenetics	DFS from time of HCT	OS from time of HCT
MDS*						
Lindsley et al[25]	Registry	MDS	*TP53* mut: 289 pts	Not listed	Not listed	3-y OS: ~15% (complex)
Yoshizato et al[26]	Registry	MDS including subset with sAML	*TP53* mut: 98 pts	Complex: 86 pts	Not listed	Median OS: 4.3 mo 3-y OS: ~10% (complex)
AML						
Middeke et al[23]	Registry	AML	17p abnl: 201 pts	Monosomal: 77 pts Complex: 180 pts	3-y EFS: 9% (monosomal) 3-y EFS: 9% (complex)	3-y OS: 11% (monosomal) 3-y OS: 11% (complex)
Middeke et al[22]	3 multicenter clinical trials	AML	*TP53* mut: 40 pts	Adverse†: 40 pts	3-y PFS: 7.5% (adverse)	3-y OS: 10% (adverse)
Luskin et al[27]	Single center	AML	*TP53* mut: 9 pts	Adverse‡: 6 pts	All relapsed (adverse; range, 1.6-18.6 mo after HCT)	Not listed
Poire et al[24]	Registry	AML	17p abnl: 125 pts	Monosomal: 86 pts –5/5q-: 58 pts	2-y: 17% (monosomal) 2-y: 11% (–5/5q-)	2-y OS: 19% (monosomal) 2-y OS: 16% (–5/5q-)
Najima et al[28]	Single center	AML (nonremission)	*TP53* mut: 23 pts	Monosomal: 11 pts	Not listed	All died within 12 mo post allo-HCT (monosomal)
Grob et al[18]	4 multicenter clinical trials	MDS-EB AML	*TP53* mut: 59 pts	Complex: 48 pts	Not listed	3-y OS: ~10% (complex)
Loke et al[21]	Registry	AML	*TP53* mut: 179 pts	17p loss and/or complex: 126 pts	2-y PFS: 15.2% (17p loss and/or complex)	2-y OS: 24.6% (17p loss and/or complex)

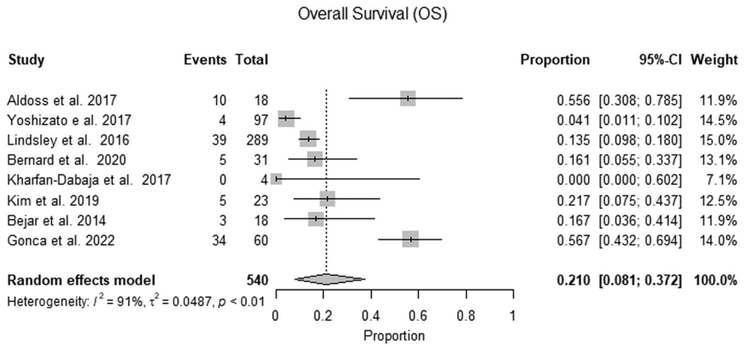
Nawas, M. T. & Kosuri, S. Blood Adv. 8, 553–561 (2024)

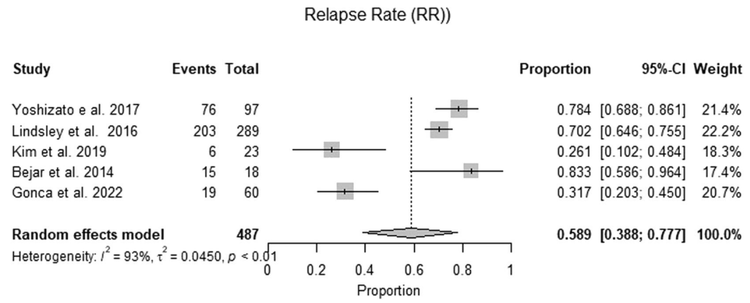
The role of Allo-Transplant in the setting of *TP53^{mut}* patients

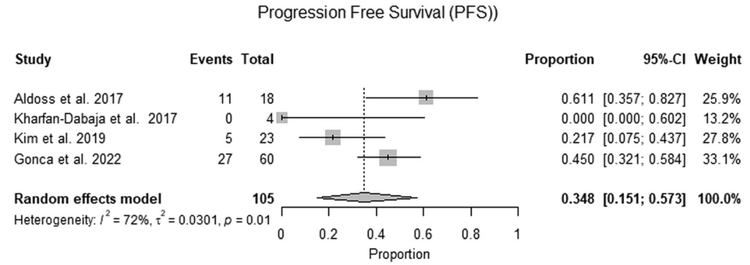
Results from a meta-analysis

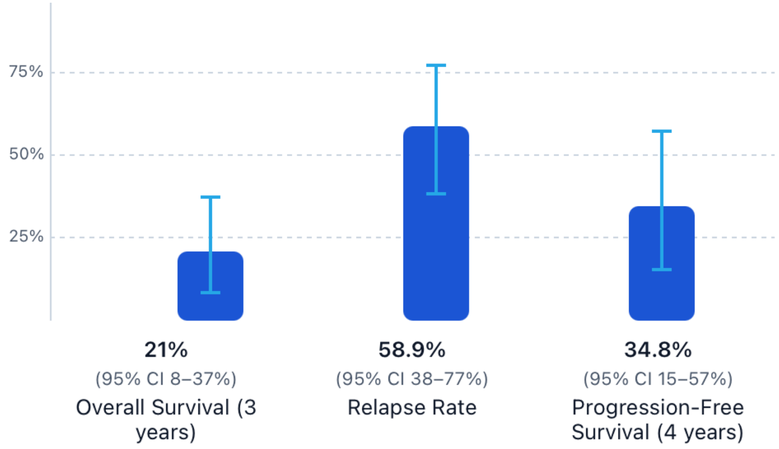
PRISMA diagram









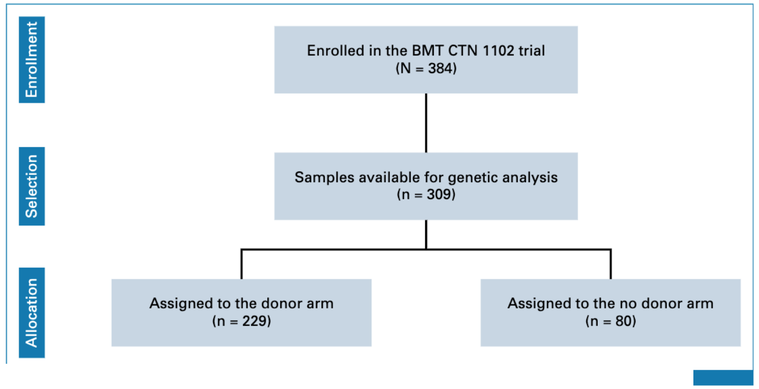


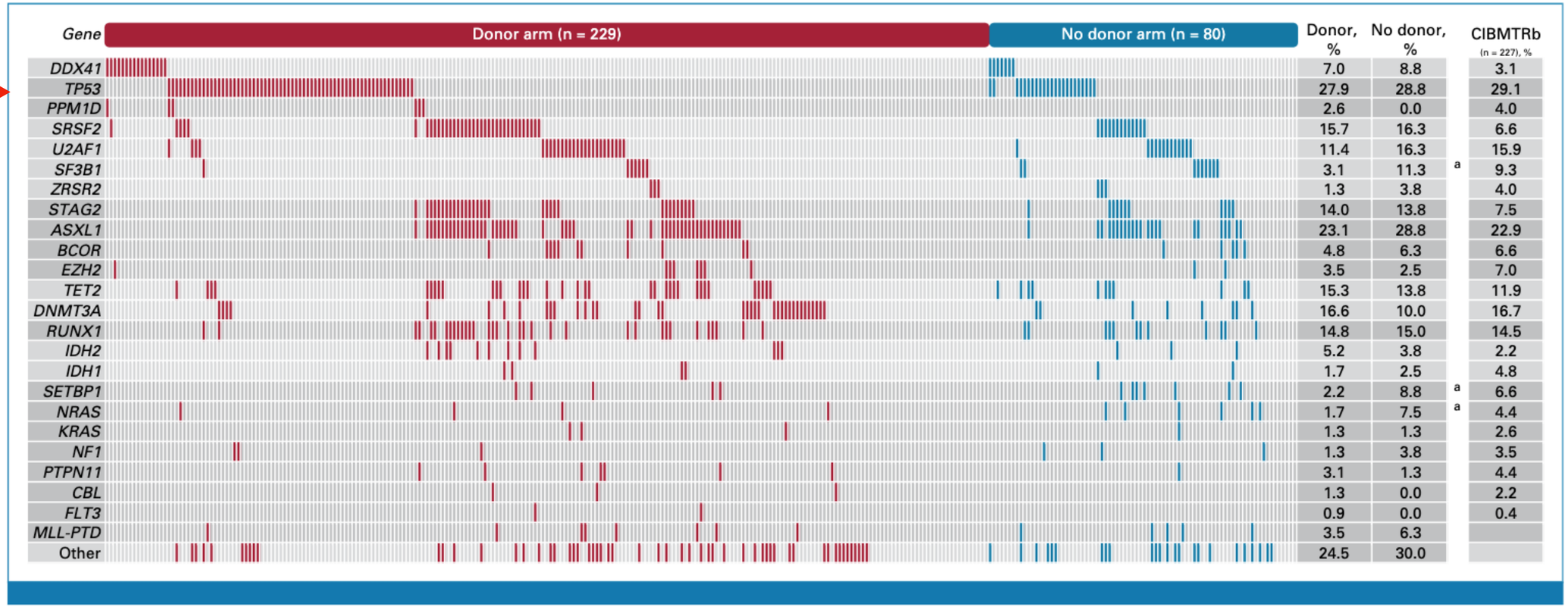
Shahzad M, et al Critical Reviews in Oncology/Hematology (2024)

The role of Allo-Transplant in the setting of *TP53^{mut}* patients

Results from donor vs donor study BMT CTN 1102 study

Multicenter trial **comparing reduced intensity conditioning (RIC) HCT with hypomethylating therapy or best supportive care** in patients age **50-75 years** with **IPSS int-2 or high**-risk de novo MDS.



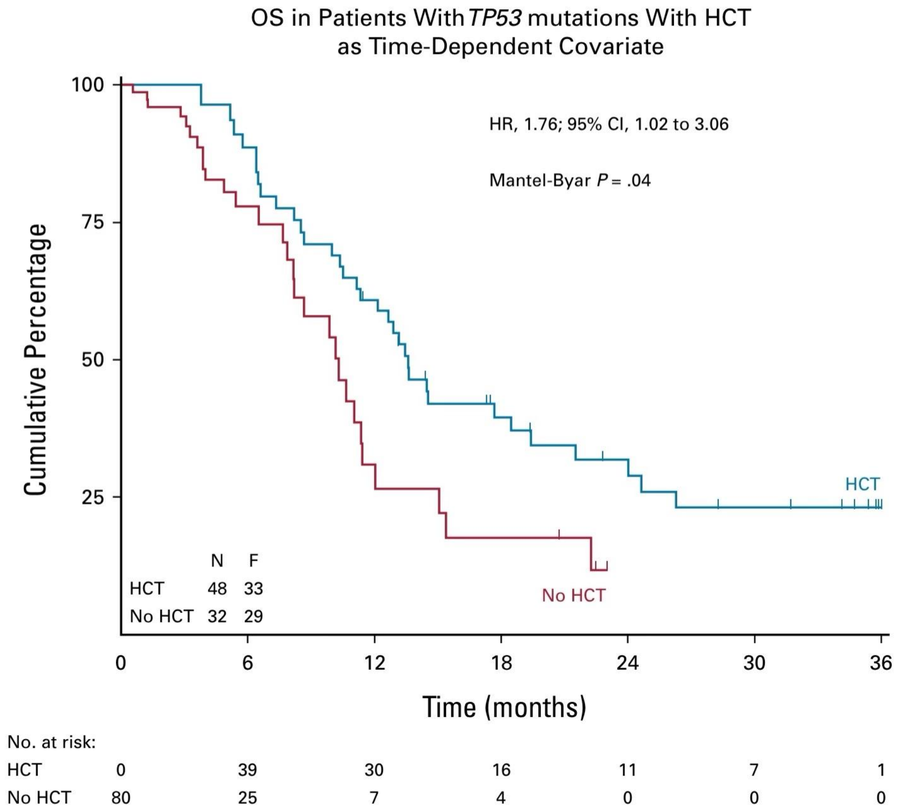


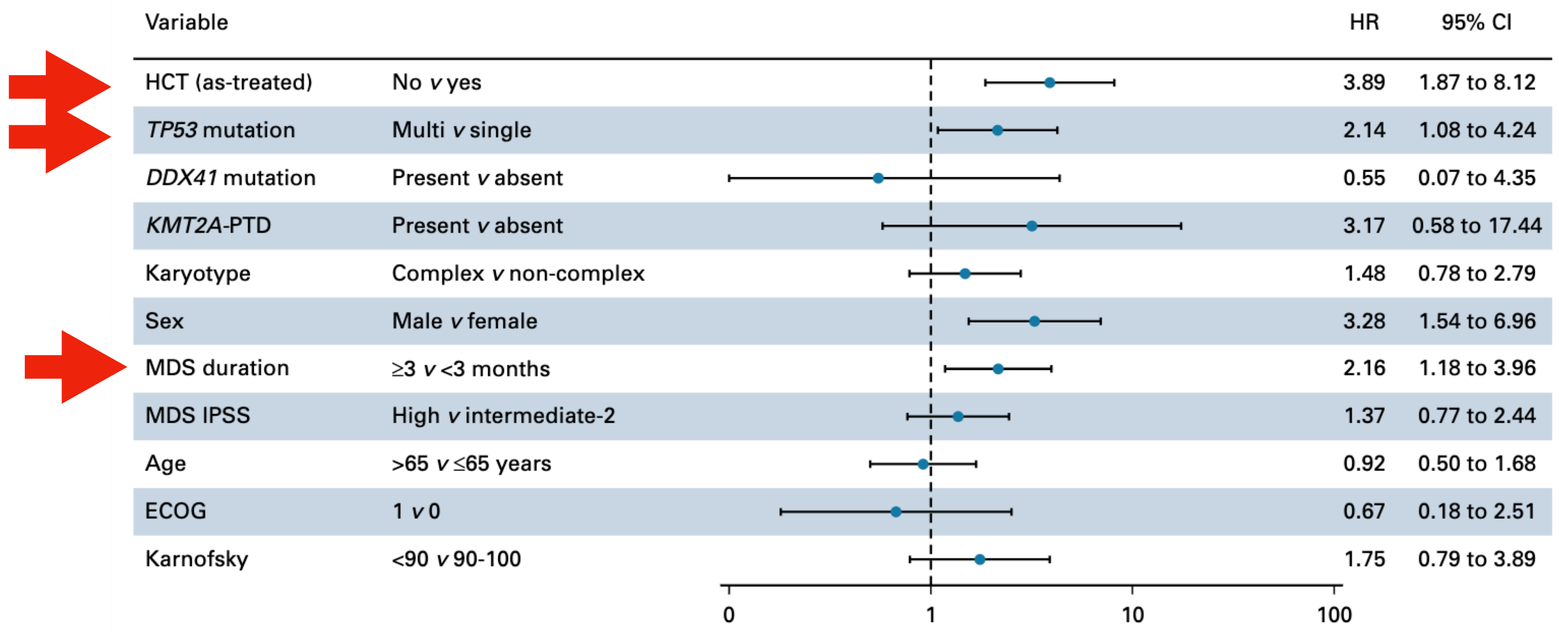
Gene	Donor arm (n = 229)	No donor arm (n = 80)	Donor, %	No donor, %		CIBMTRb (n = 227), %
DDX41			7.0	8.8		3.1
TP53			27.9	28.8		29.1
PPM1D			2.6	0.0		4.0
SRSF2			15.7	16.3		6.6
U2AF1			11.4	16.3		15.9
SF3B1			3.1	11.3	a	9.3
ZRSR2			1.3	3.8		4.0
STAG2			14.0	13.8		7.5
ASXL1			23.1	28.8		22.9
BCOR			4.8	6.3		6.6
EZH2			3.5	2.5		7.0
TET2			15.3	13.8		11.9
DNMT3A			16.6	10.0		16.7
RUNX1			14.8	15.0		14.5
IDH2			5.2	3.8		2.2
IDH1			1.7	2.5		4.8
SETBP1			2.2	8.8	a	6.6
NRAS			1.7	7.5	a	4.4
KRAS			1.3	1.3		2.6
NF1			1.3	3.8		3.5
PTPN11			3.1	1.3		4.4
CBL			1.3	0.0		2.2
FLT3			0.9	0.0		0.4
MLL-PTD			3.5	6.3		
Other			24.5	30.0		

Versluis J et al JCO 2023

The role of Allo-Transplant in the setting of *TP53*^{mut} patients

Although outcomes are worse than in *TP53*^{wt}, allo-HSCT still improves survival





Versluis J et al JCO 2023

Key-message

In TP53-mutated MDS, **transplantation is not futile**

It remains the **only intervention with true curative potential**

for **patients fit and willing to proceed**.

Next questions

To bridge or not to bridge?

Conditioning regimen: MAC vs. RIC

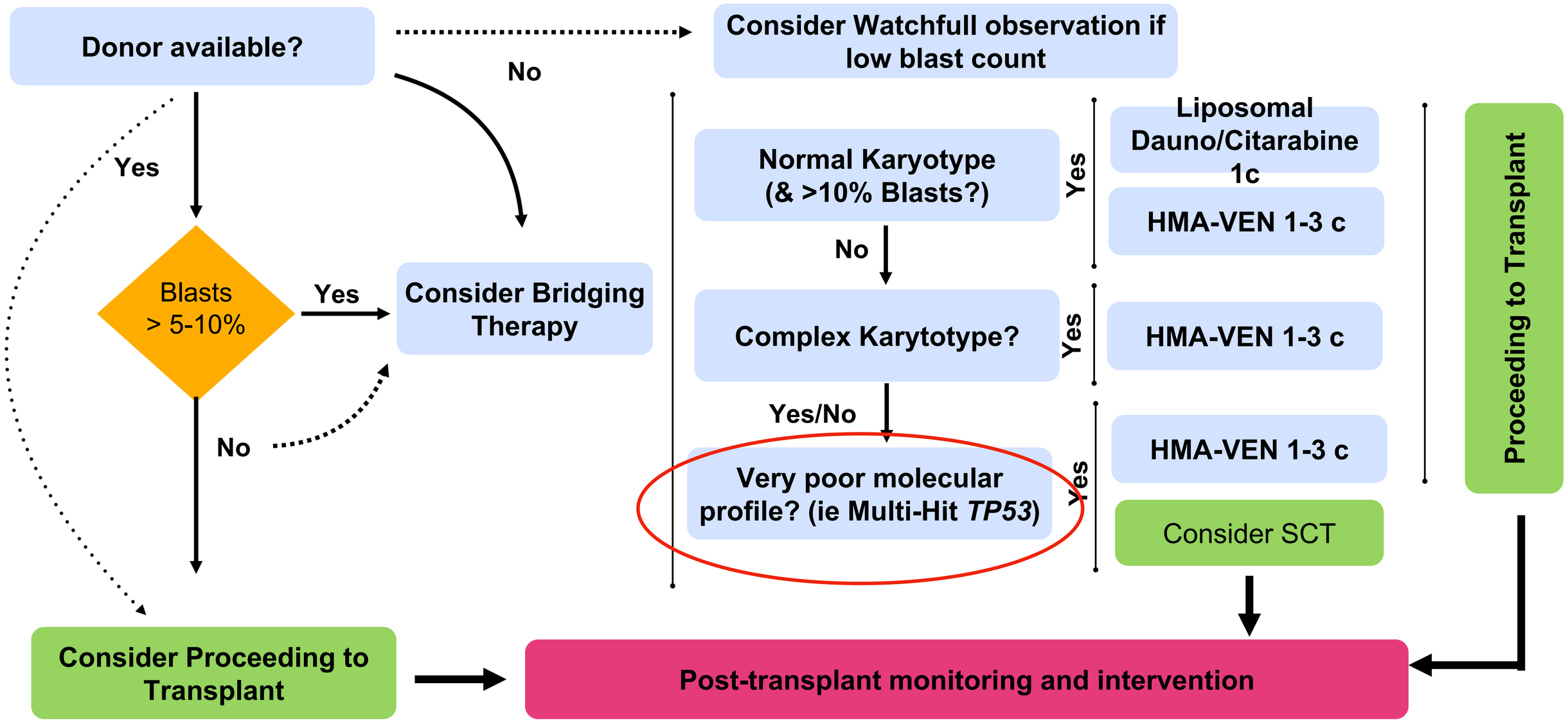
Some words about bridging in TP53^{mut} patients

This patients are different to “conventional” MDS

- *TP53* mutations **usually confer refractoriness** to conventional therapies
- Resposes are commonly short, so **in the case of response, proceed to transplant as soon as possible** is mandatory
- There is not a better option to bridge this patients. My personal reccomendation is to **avoid toxic therapies** as no data suggest they offer higher responses
- Though not optimal, HMA-VEN can be used, with close follow-up

*** Hypomethylating agents combined with venetoclax is not an approved indication for patients with MDS**

Personal approach



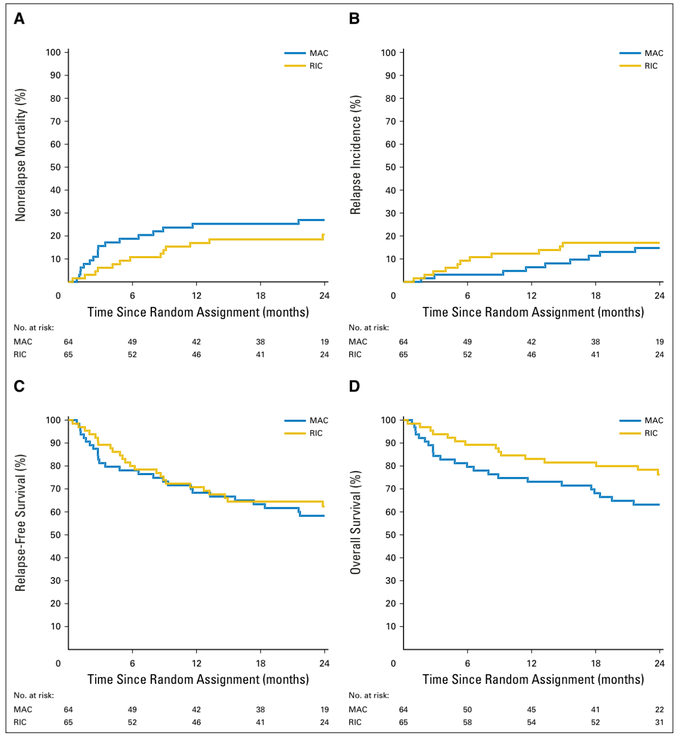
* Neither hypomethylating agents combined with venetoclax nor Liposomal Dauno/Citarabine are approved for patients with MDS

What about conditioning regimen?

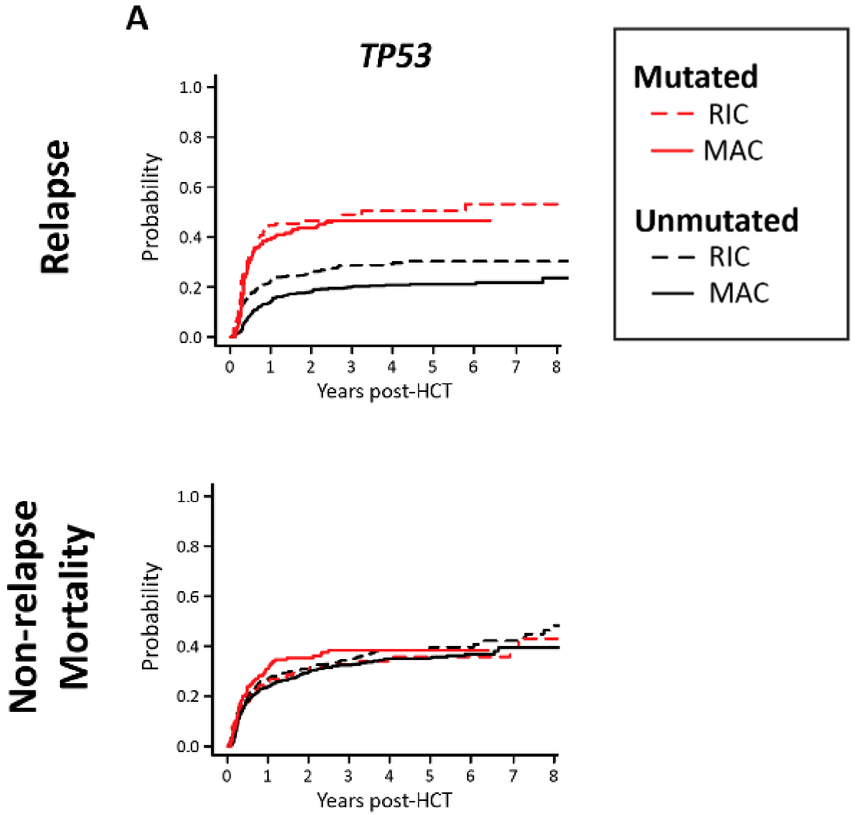
RIC seems a good option,

EBMT PROSPECTIVE RIC-MAC Study in MDS

	MAC	RIC
Ac GVHD (%) II-IV III-IV	 37.8 14	 32 15
Chr GVHD (%)	64.7	61.6
1 y NRM, %(CI 95%)	25.3 % (14.6-36)	16.9% (7.8-26)
2 y **Rel,** %(CI 95%)	14.8% (5.8-23.7)	17% (7.9-26)
2 y RFS, %(CI 95%)	58.3% (46-70.6)	62.4% (50.4-74.4)
2 y OS, %(CI 95%)	63.2% (51.1-73.2)	76.3% (65.8-86.9



Kroger N, et al. JCO, 2017



Lindsley RC, et al. NEJM, 2017

Final remarks

- ***TP53* mutations** are frequent in MDS and now define a **distinct molecular entity** in current classifications.
- **Genetic context matters:**
  Both **allelic state** and **cytogenetic complexity** determine prognosis and therapeutic response
  (e.g., *mono- vs multi-hit*, *complex karyotype*, *del(5q)*).
- **Standard therapies remain suboptimal** — responses are limited and survival is poor.
- **Allo-HCT is the only curative option**:
  - Despite inferior outcomes, **it should be offered to fit patients** as it provides the best chance of durable remission.
  - Optimizing **transplant timing and post-transplant interventions will be crucial** to improve outcomes in this high-risk population.

Gracias!

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VHIO Vall d'Hebron Institute of Oncology

HCTO Hematology Clinical Trials Office

ECI Comprehensive Cancer Centre