XIX CONGRESSO NAZIONALE SIES 2026

TP53 nelle neoplasie mieloidi

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Palazzo degli Affari

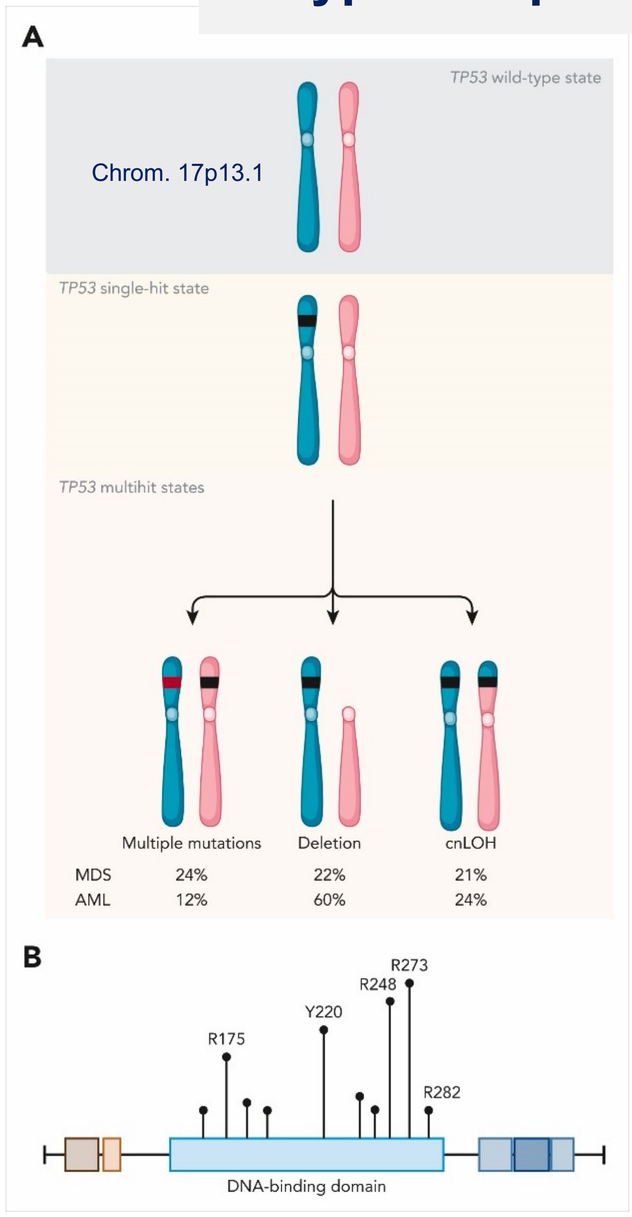
Disclosures of Maria Teresa Voso

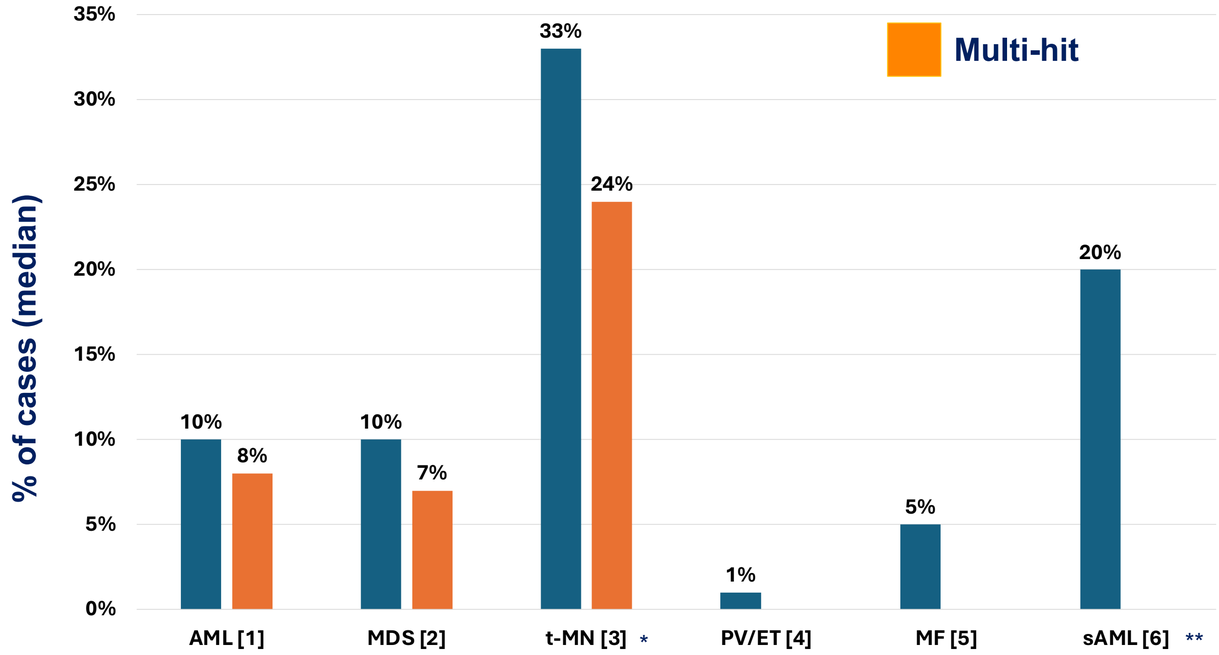
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Astellas					X	x	
Jazz					X	X	
Servier					X	x	
Abbvie					X		
Daychii-Sankyo					x	x	
SDK						x	

Outline

- ✓ Oncogenic activity of TP53 mutations
- ✓ TP53 CHIP and clonal progression
- ✓ *In-vitro* modeling of therapy-related myeloid neoplasms
- ✓ Impact of previous disease and type of cytotoxic drugs on TP53mut development
- ✓ Clinical impact of TP53 mutations and risk stratification

Type and prevalence of TP53 mutations in myeloid neoplasms





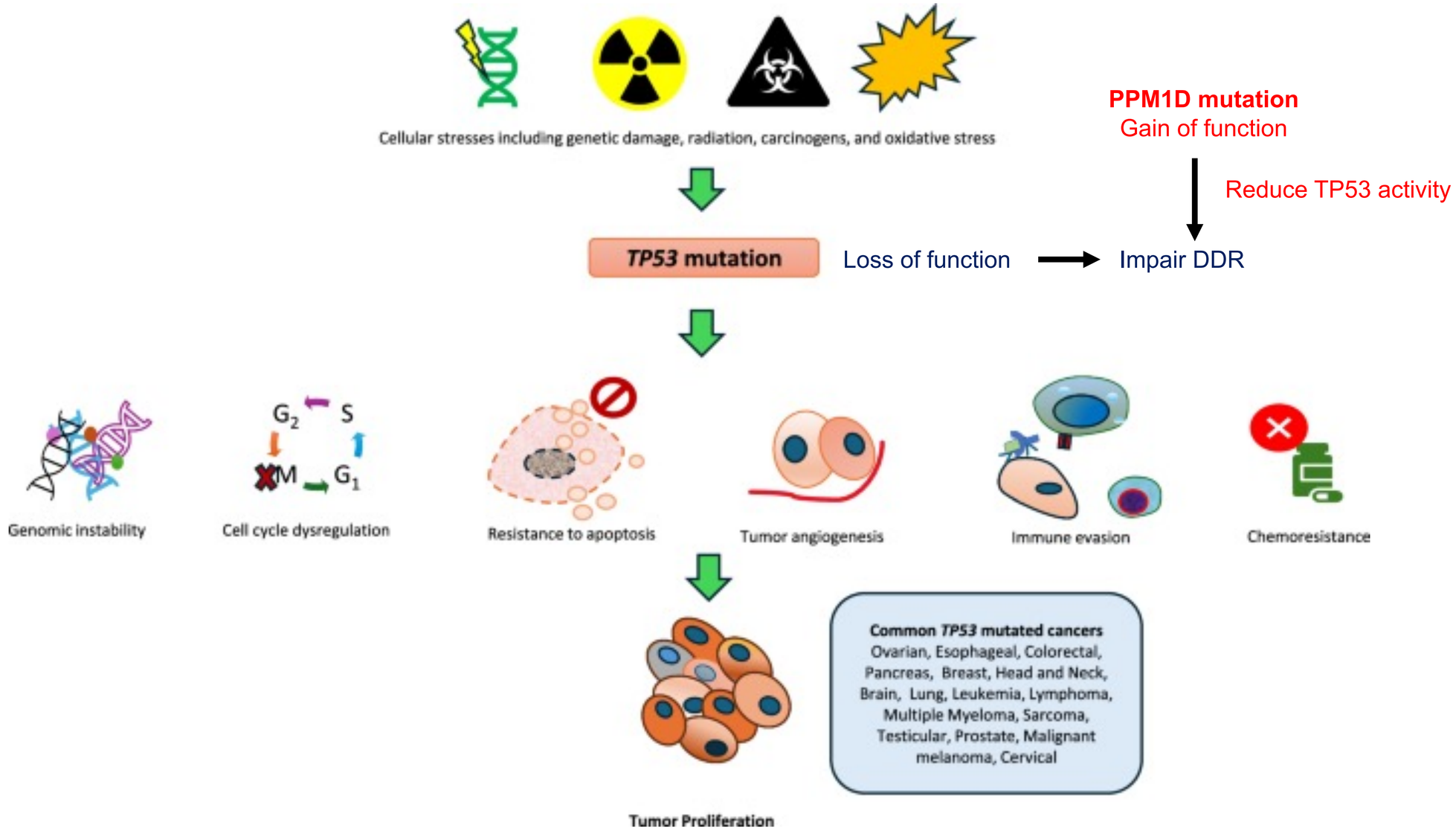
[1] PMID: 27276561, 23634996, 35108372 , 27288520, 39109820
[2] PMID: 40195329, 32747829
[3] PMID: 31413096, 40195329, 25952993, 40195329
[4] PMID: 31945802
[5] PMID: 37846894
[6] PMID: 31413096, 39109820

*therapy-related AML or MDS
** AML secondary to MDS or MPN

Urrutia S.,et al, Blood, 2025

Slide courtesy of Luca Guarnera

Oncogenic activity of TP53 mutations

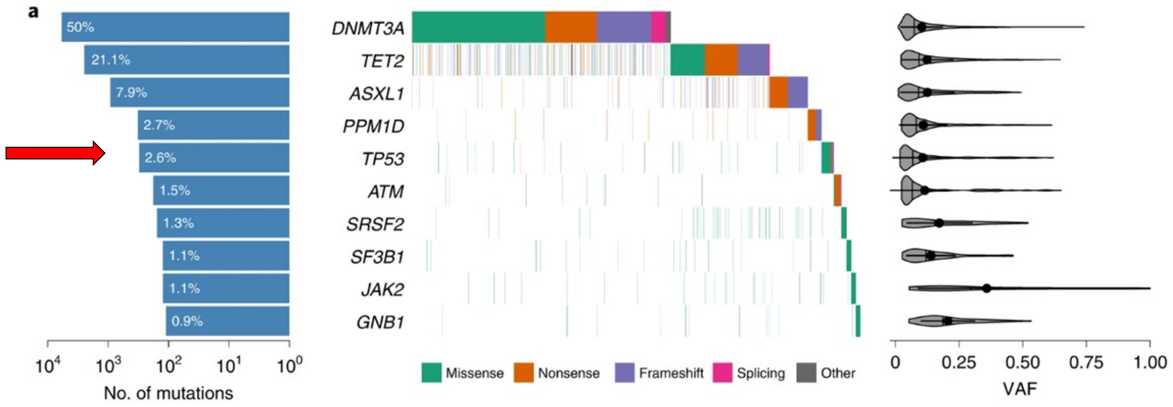


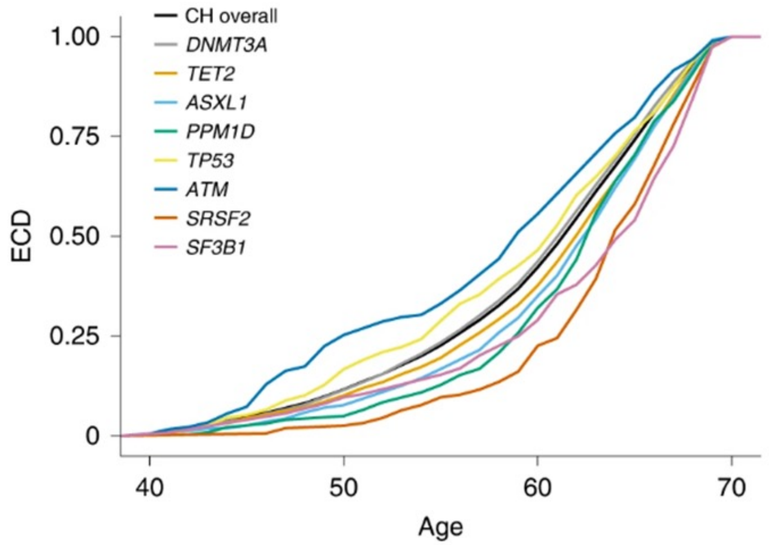
Modified from Shazad M. et al., BCJ 2024

Prevalence of TP53 CHIP

✓ 200,453 UK Biobank participants, WES

✓ 10 most common driver genes in 10,924 individuals



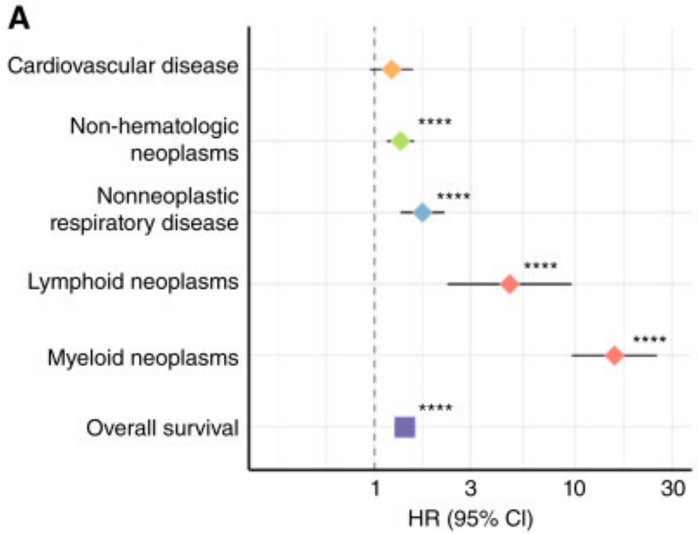


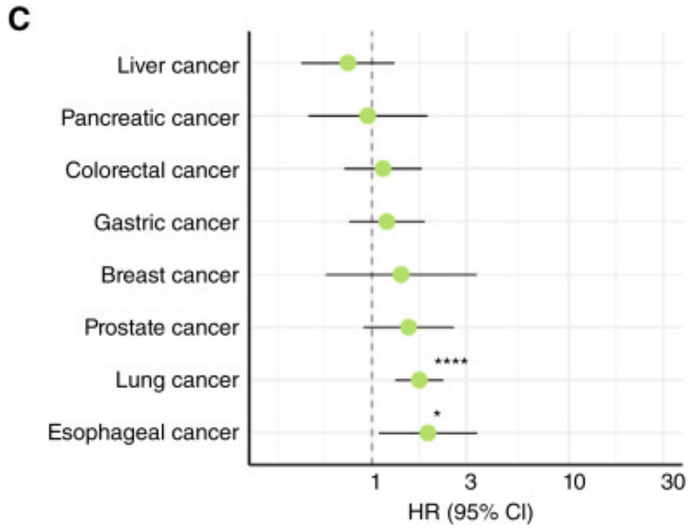
✓ TP53 CHIP is rare, but frequency increases early

Kar S. et al., Nature genetics 2022

✓ 140,597 individuals without hematologic neoplasms in BioBank Japan

✓ 1,157 individuals with *TP53*-CHIP (0.8%)





Usui Y. et al., Blood Cancer Discovery 2025

From CHIP to CCUS to MN: clonal hematopoiesis risk score (CHRS)

n= 470 960 participants in the UK Biobank

Table 2. CHRS Values.*

Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	Present	Absent			
High-risk mutation		Absent			Present
Mutation number		1		≥2	
Variant allele fraction		<0.2		≥0.2	
Red cell distribution width		<15			≥15
Mean corpuscular volume		<100			≥100
Cytopenia		CHIP	CCUS		
Age (yr)		<65	≥65		

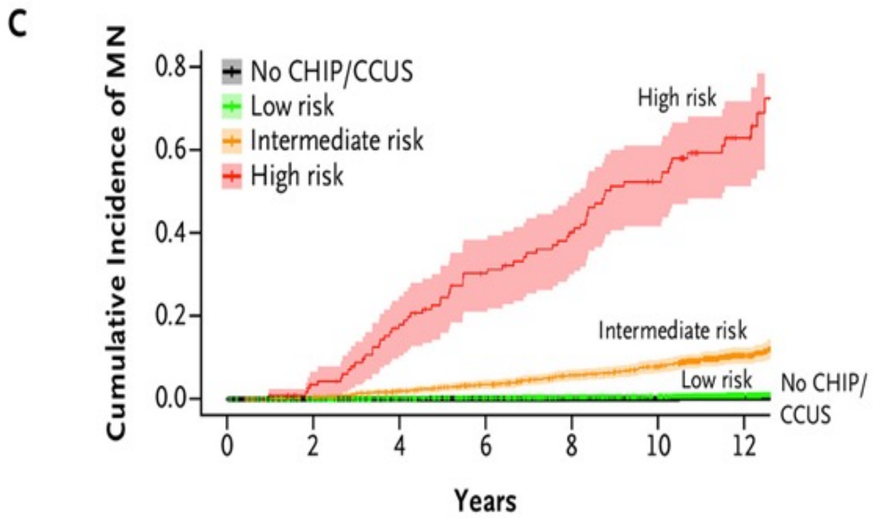
* CCUS denotes clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; and CHRS, clonal hematopoiesis risk score.

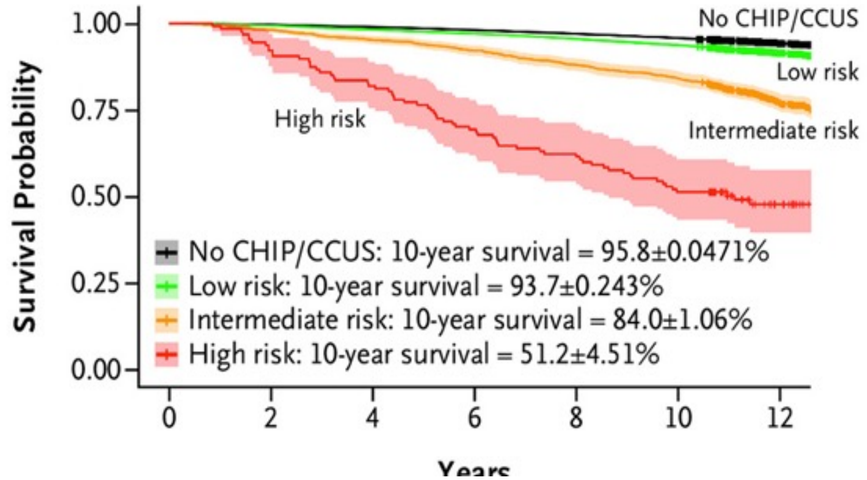
High-risk mutations

- ✓ *SRSF2*, *SF3B1*, and *ZRSR2*
- ✓ AML-like genes (*IDH1*, *IDH2*, *FLT3*, and *RUNX1*)
- ✓ ***TP53*-related genes (*TP53* and *PPM1D*)**

SCORE

- ✓ high : ≥12.5, 1.1% of pts
- ✓ intermediate risk: 10 to 12, 10.5%
- ✓ Low: ≤9.5, 88.4%

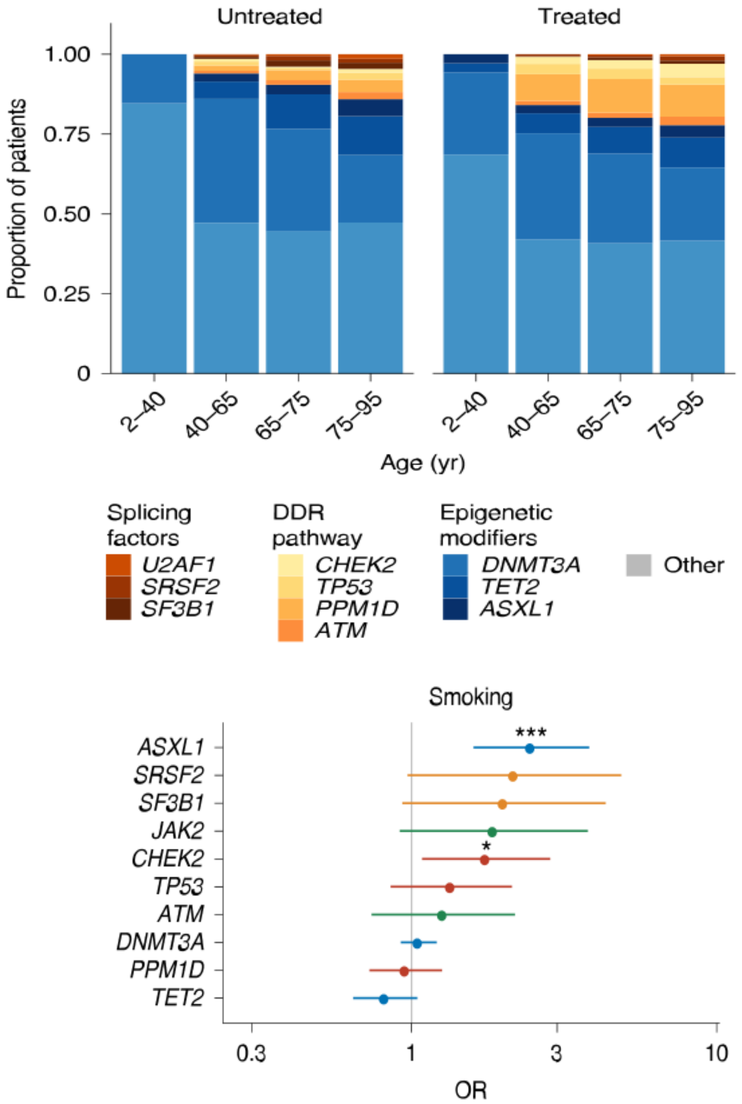


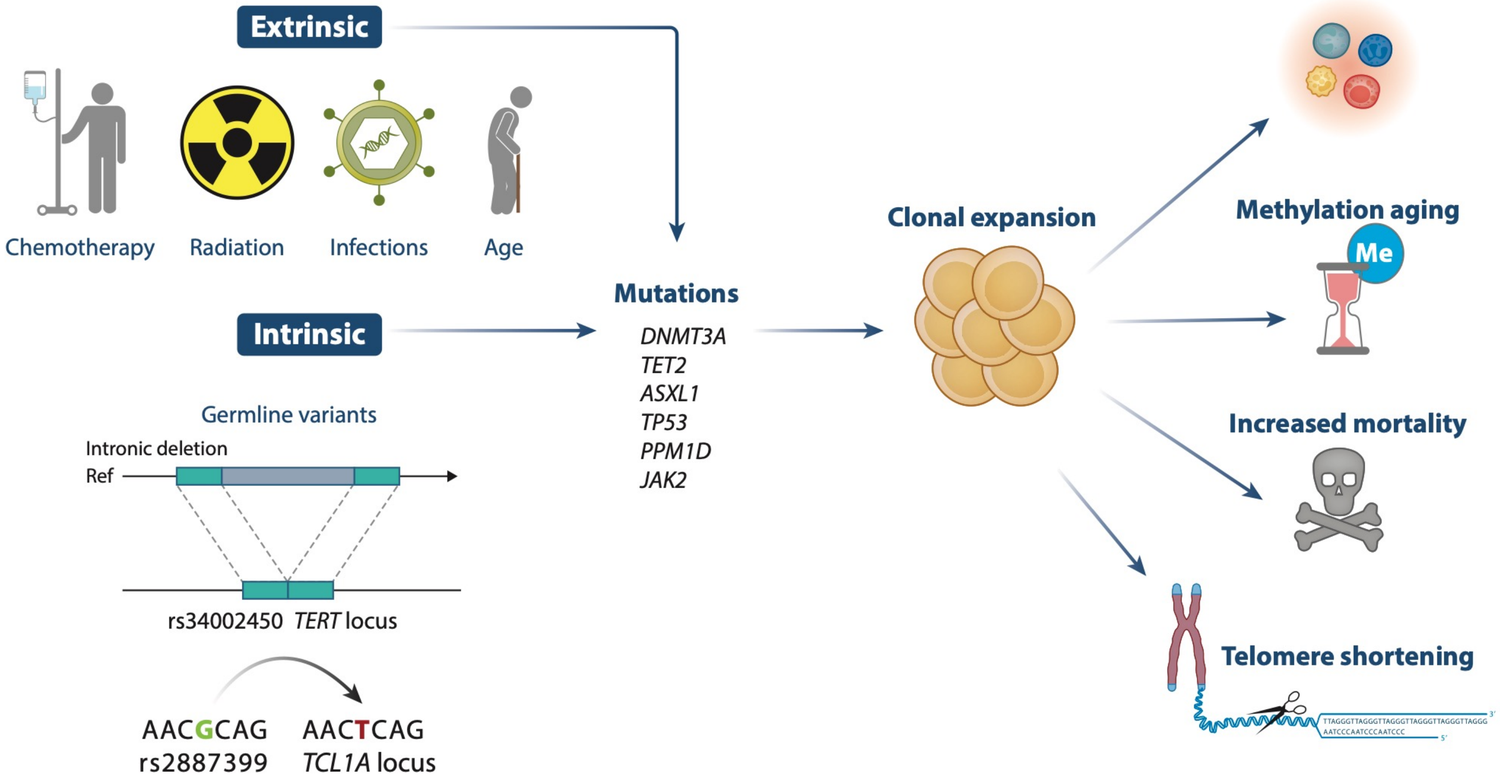


Weeks et al, NEJM Evidence 2023

Factors synergizing with CHIP leading to «pathological» aging

Cancer patients



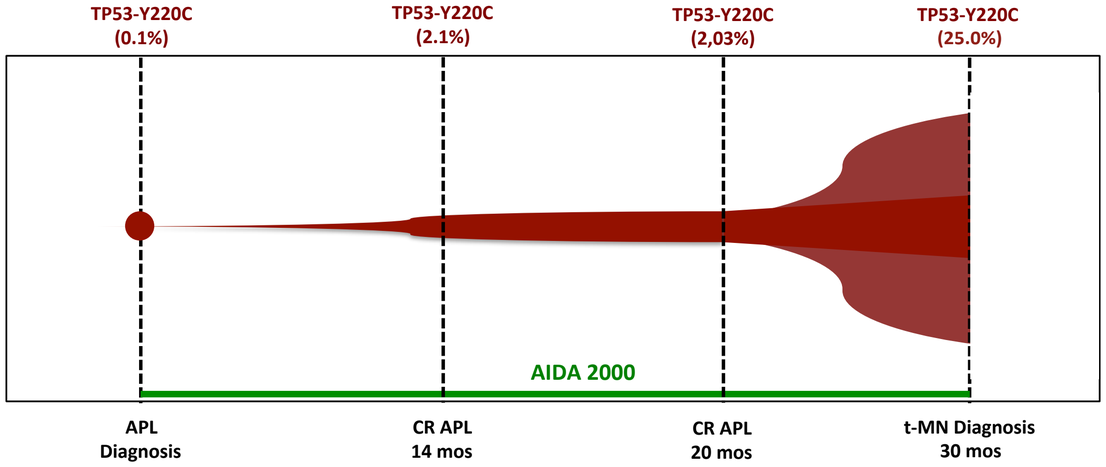


Bolton et al, Nature Genetics 2020

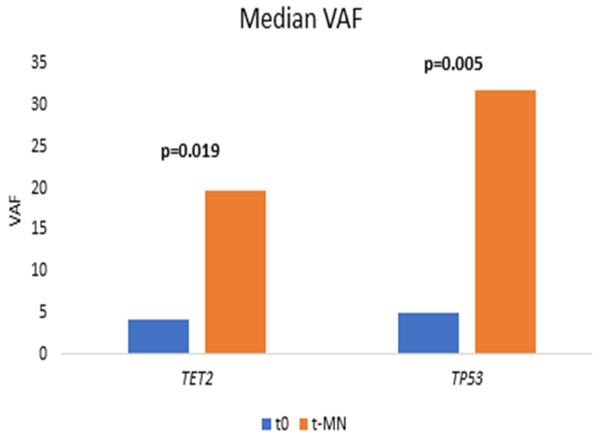
Jaiswal S. et al, Ann Reviews 2022

Clonal expansion in therapy-related MN

UPN 2



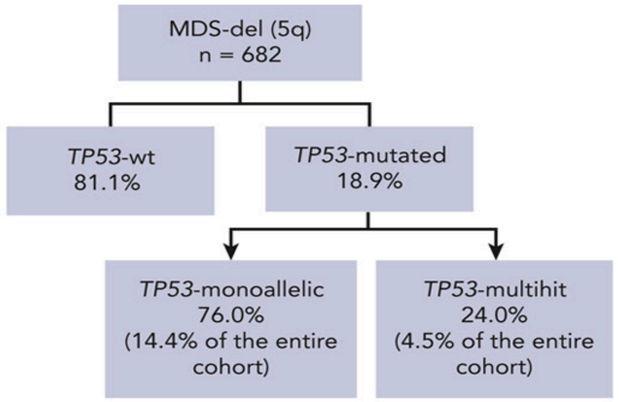
2A



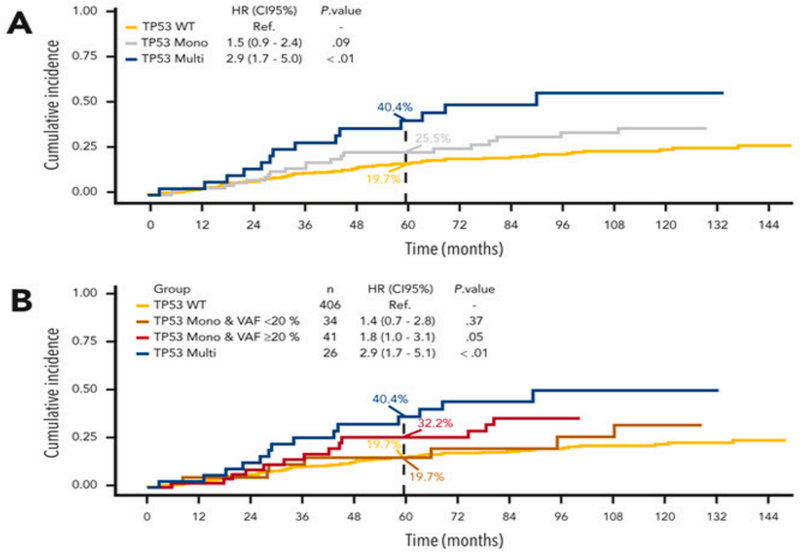
TP53 VAF and 5q- MDS

TP53 Gene Alterations in Myelodysplastic Syndromes With Isolated 5q Deletion (MDS-del (5q))

Classification of patients with MDS-del (5q) according to *TP53* gene alterations



Risk of AML evolution according to a) *TP53* allelic state and b) *TP53* VAF cutoff point of 20%

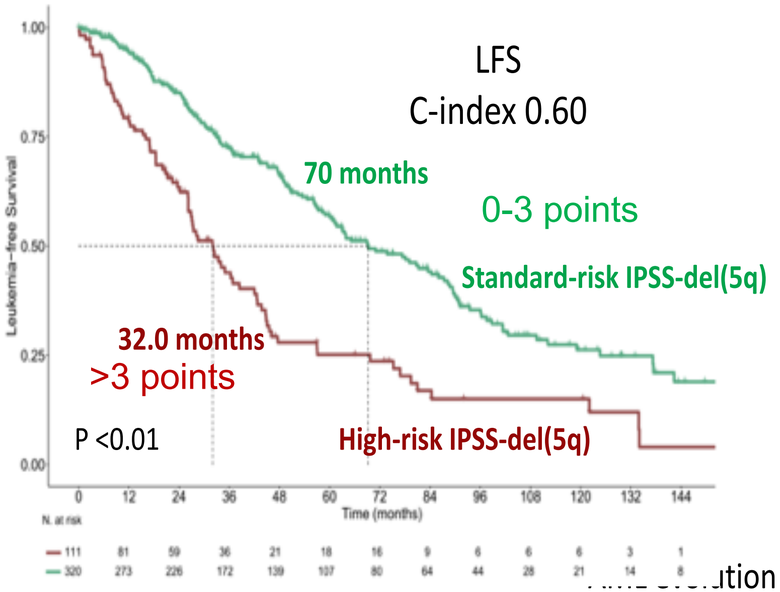


Conclusions: ***TP53*** **mutations are prevalent in MDS-del (5q) (18.9%), but the presence of a multihit state is rare (4.5% of the entire cohort).** ***TP53*****-multihit state and** ***TP53*** **VAF ≥20% are associated with poor outcomes.**

*Montoro et al. DOI: 10.1182/**blood**.2024023840*

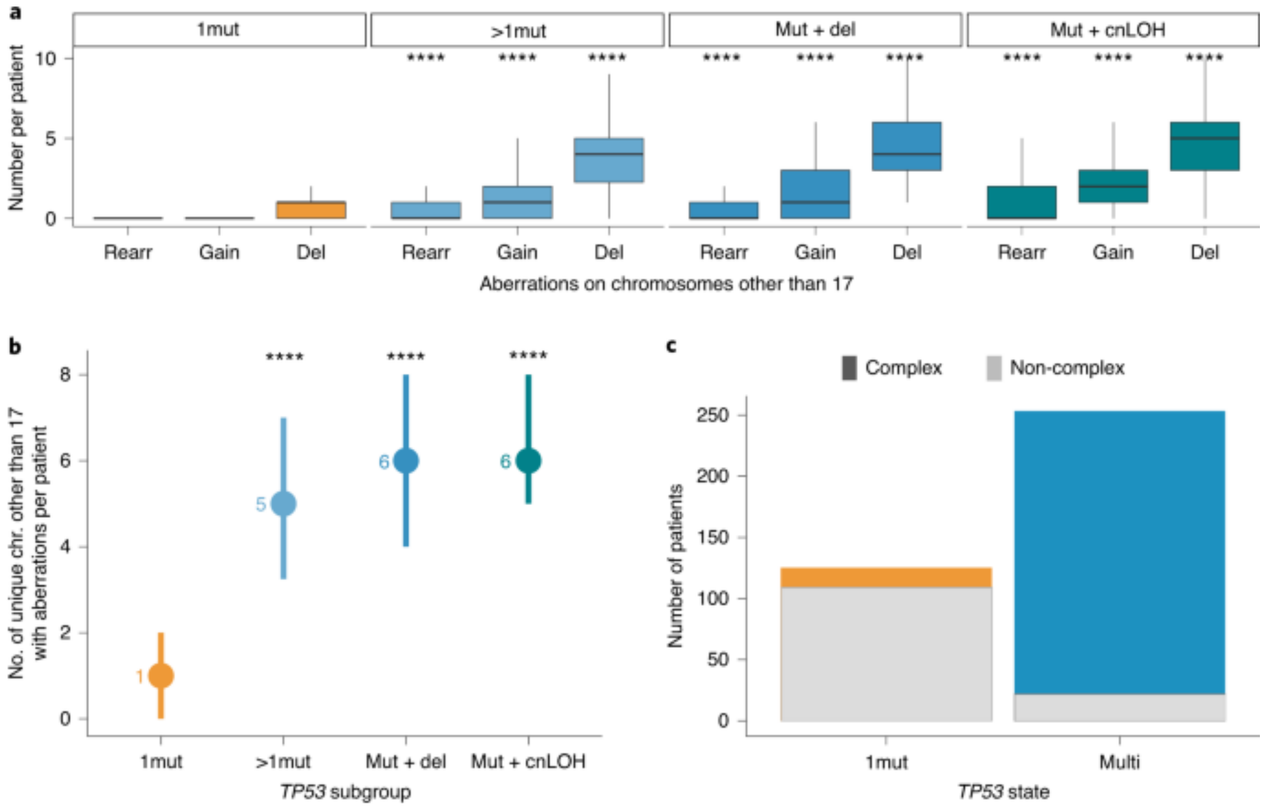
blood Visual Abstract

Variable	Points
Sex, male	1
Hemoglobin ≤ 10 g/dL	2
Platelet ≤ 100 x10^9/L	2
≥ 2 additional mutations	2
SF3B1 mutations	1
HR-*TP53 status*	1



M.J. Montoro et al, Blood 2024

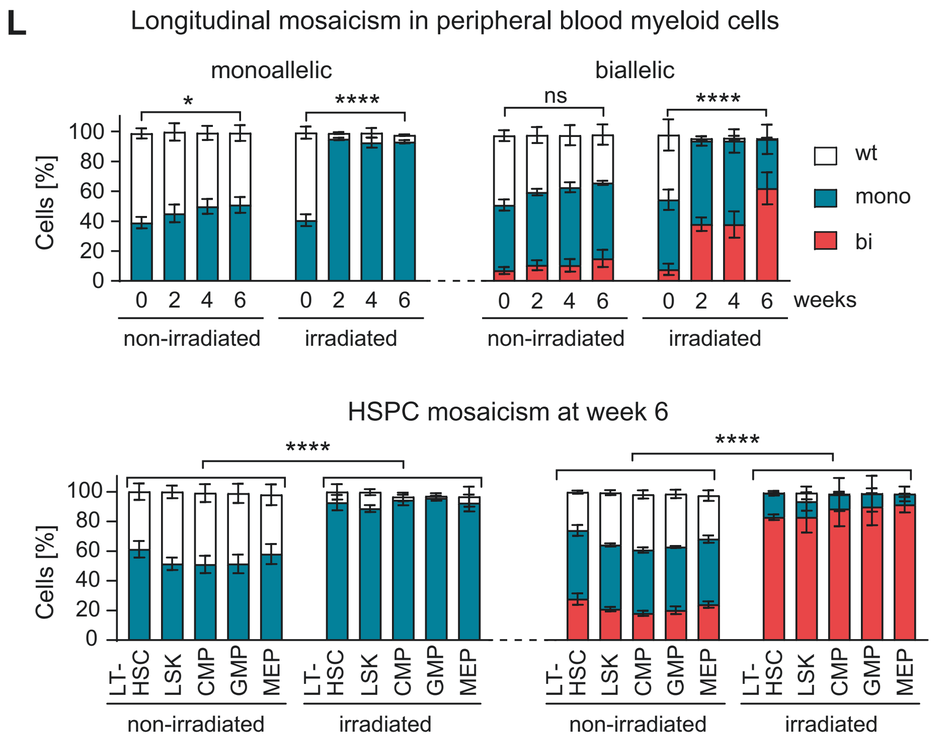
MDS: TP53 mutational burden and genomic instability



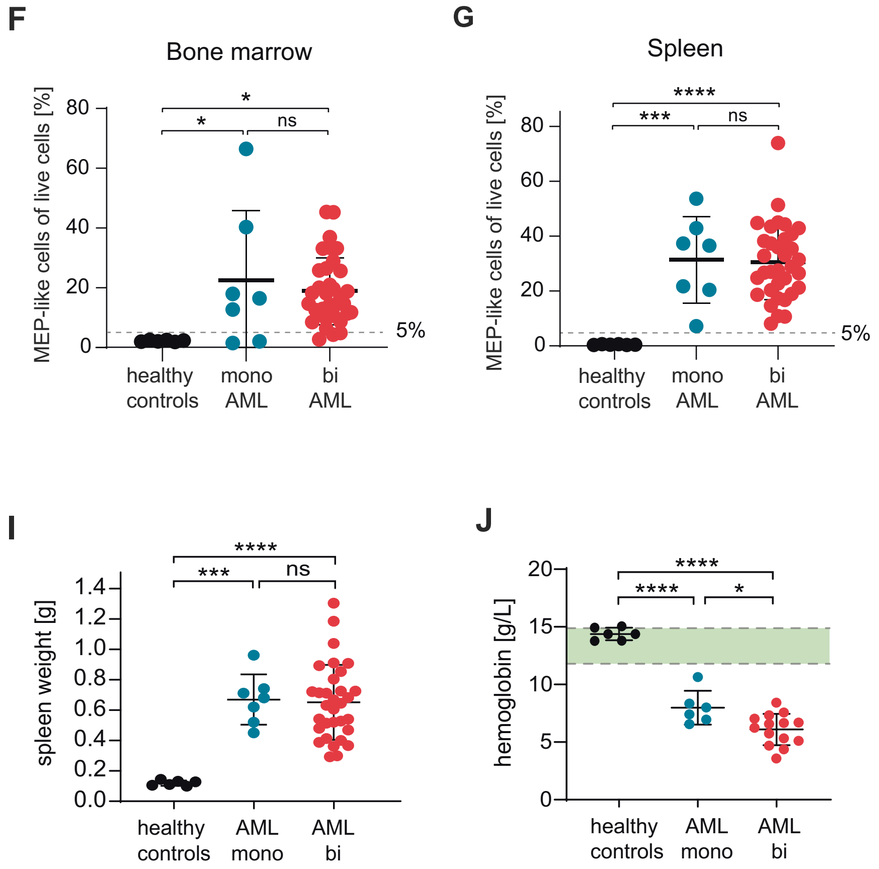
***TP53* multi-allelic state correlates with increasing levels of genome instability, but fewer co-mutations.**

Bernard E. et al., Nat Gen 2020

Modelling TP53^{mut} therapy-related myeloid neoplasms



Expansion of mosaicism in irradiated mice

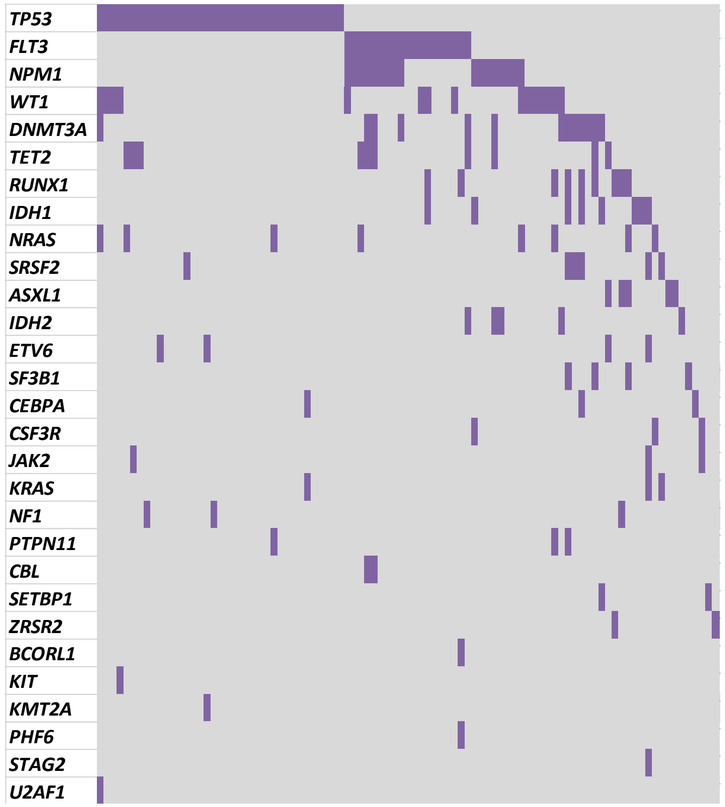


Fullin J. et al. Leukemia 2026

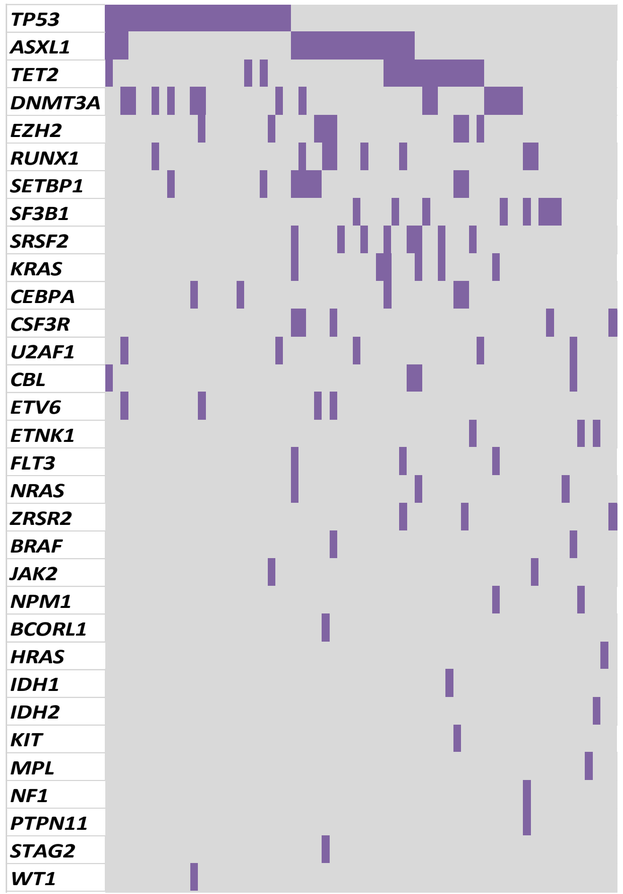
Therapy-related myeloid neoplasms and TP53 mutations

2014-2024, n=514 pts

t- AML

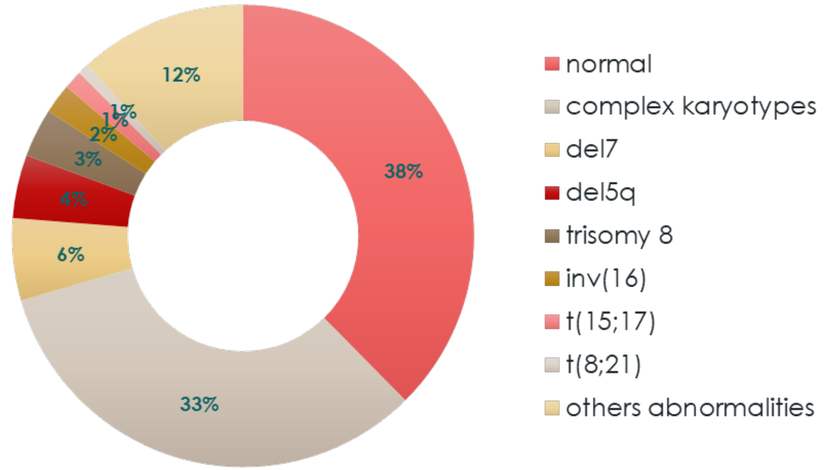


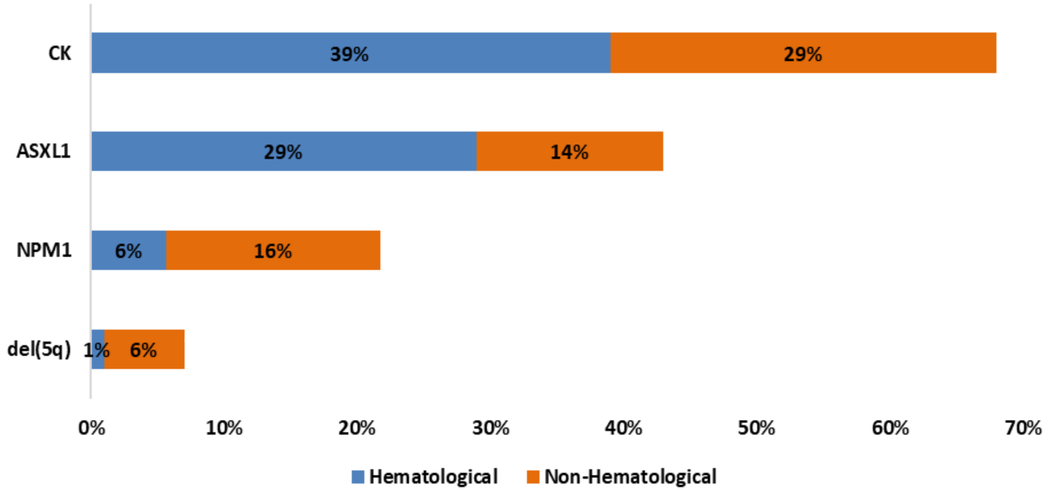
t- MDS



Karyotype

N= 483

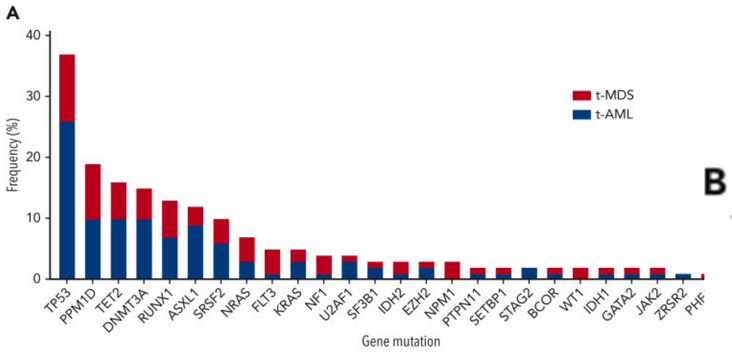


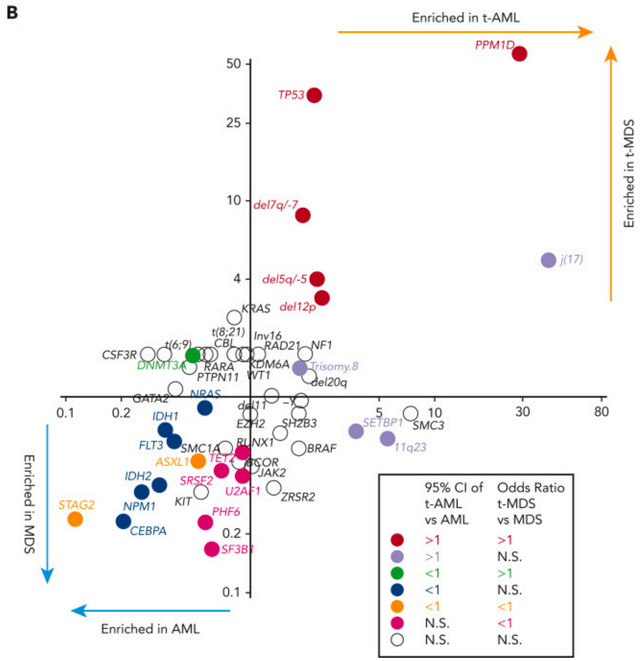


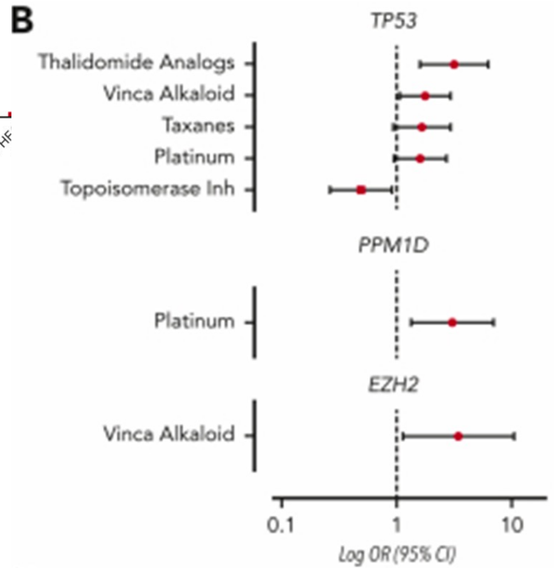
- Complex Karyotypes (33%) and *TP53* (44%) mutations co-occurred in 80% of cases

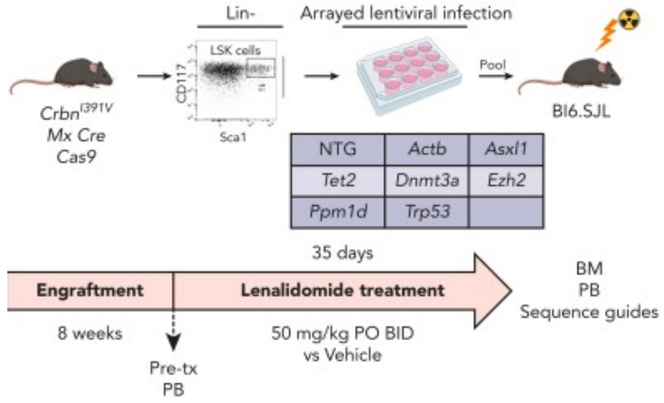
Voso MT, Gurnari C et al, in preparation

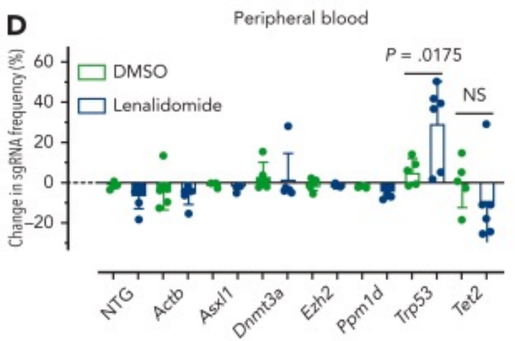
t-MN after multiple myeloma

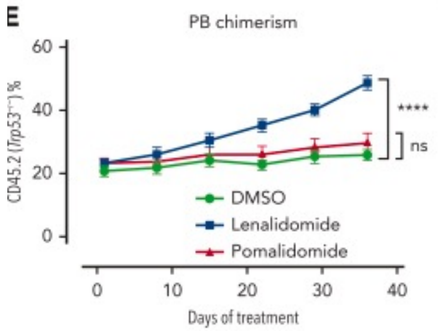


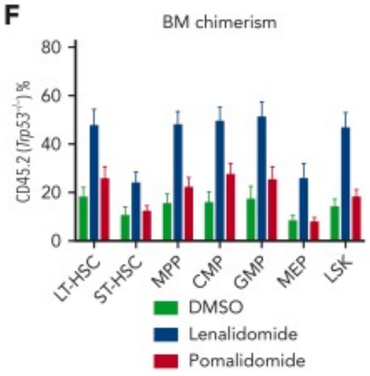


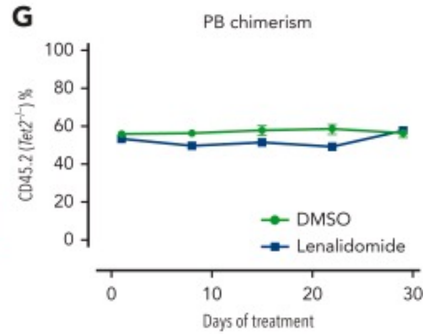








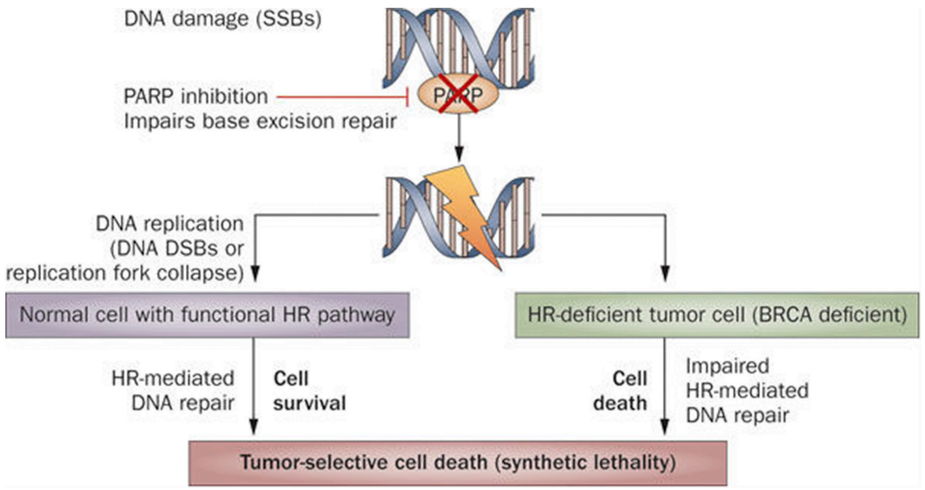




Lenalidomide (but not Pomalidomide) select Tp53-mutant HSPCs

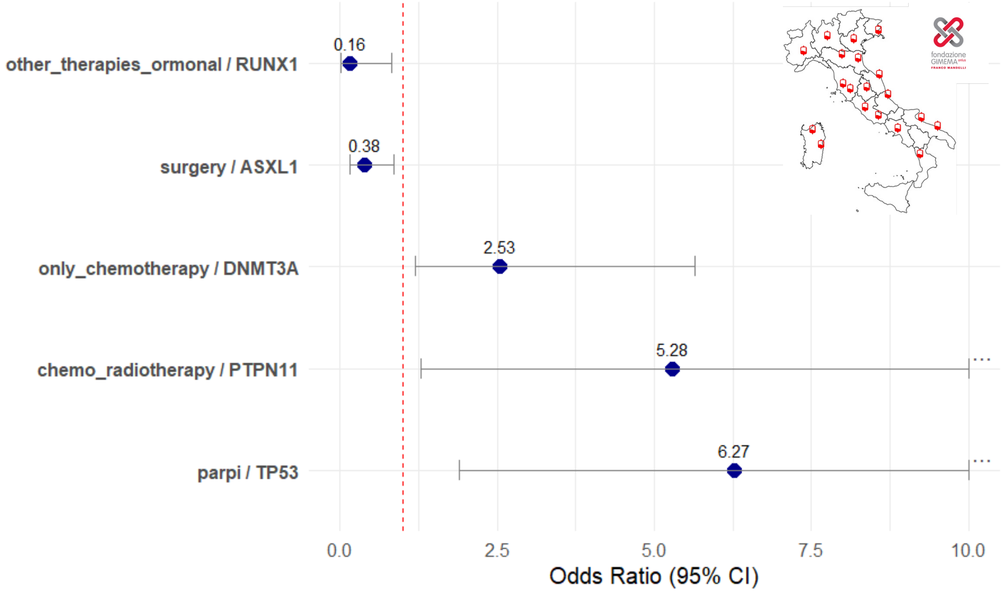
Sperling A et al. Blood 2022

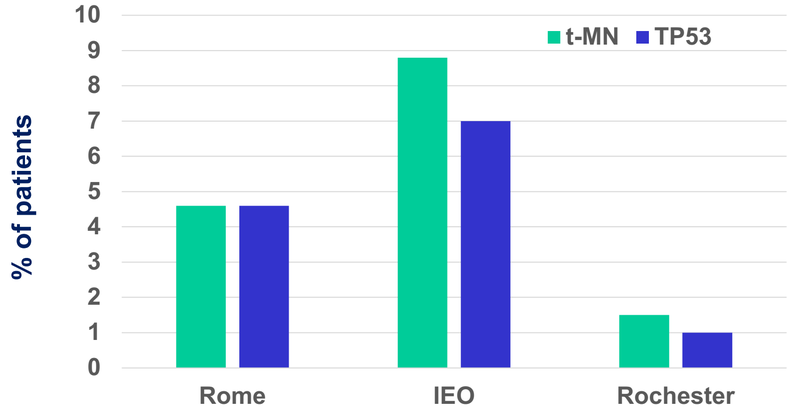
t-MN after *PARPi*



The Italian MITO-MaNGO experience: multicentric survey

- ✓ 2320 patients (1254 BRCA-mutated), 56 (2.55%) developed MN: 35 MDS and 21 AML
- ✓ 31 had BRCA mutations (2.5%).
- ✓ Incidence by drug: olaparib 2.5%, niraparib 2%, and rucaparib 3.4%.
- ✓ Unclear correlation between treatment duration and t-MN risk, with a median onset of 18.9 months.
- ✓ Risk increased with additional therapy lines: 0.52% (first) to 12.2% (>4. line).





TP53 mutations included in the DNA binding domain (DBD) (exons 5-8), at six major mutational hot spots including codons 175, 245, 248, 249, 273, and 282, showing a propensity for arginine residues.

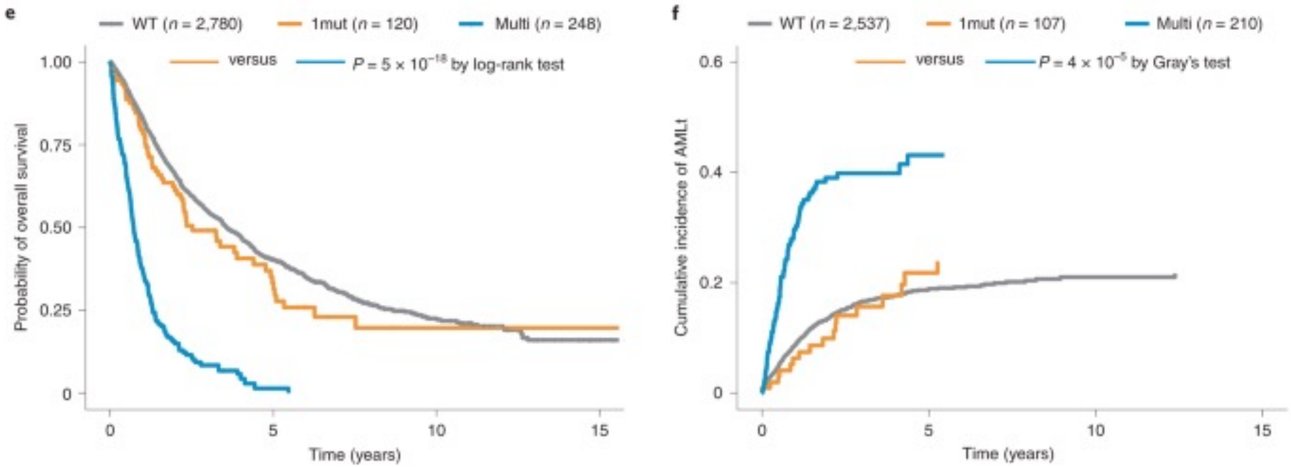
Mutations at p.(Arg175) are in common in all the considered studies.

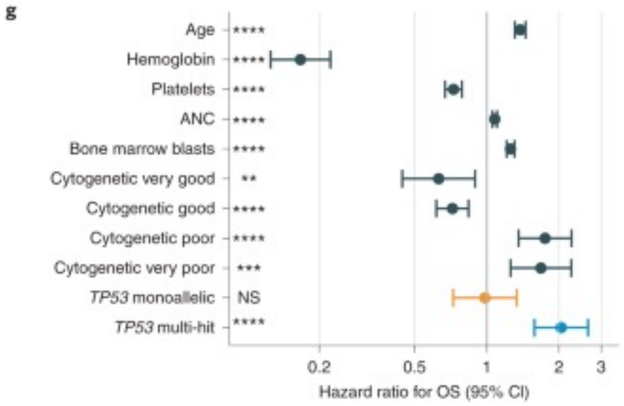
Voso MT, Gurnari C et al, in preparation

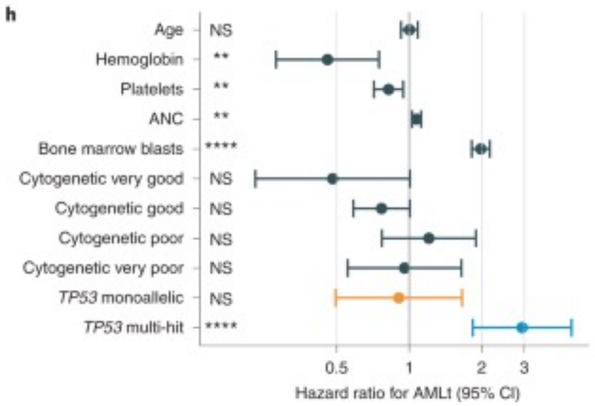
Turinetto M et al, ESMOopen 2025; Chiusolo P. et al, Am J Hematol 2022, Todisco E. et al, Int J cancer 2022; Oliveira JL et al, Blood Cancer J, 2022

Clinical impact of multi-hit mutations

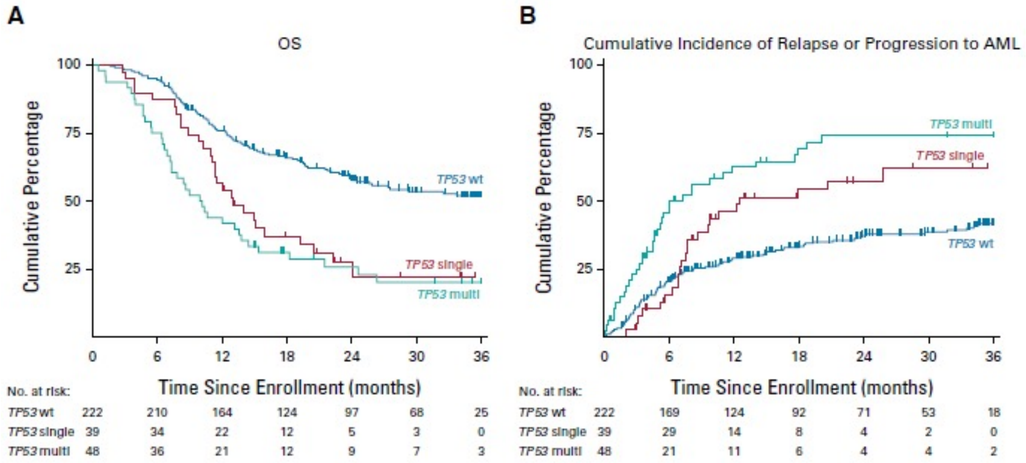
MDS





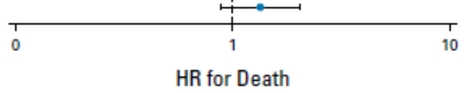


AML



B Multivariable Analysis—OS (HCT as time-dependent covariate)

Variable		HR	95% CI
HCT	No *v* yes	2.31	1.53 to 3.49
TP53 mutation	Single *v* absent	1.43	0.80 to 2.55
	Multi *v* absent	2.47	1.45 to 4.20
DDX41 mutation	Present *v* absent	0.36	0.13 to 1.00
KMT2A-PTD	Present *v* absent	2.14	1.05 to 4.34
Karyotype	Complex *v* noncomplex	1.53	0.97 to 2.42
Sex	Male *v* female	1.57	1.07 to 2.31
MDS duration	≥3 *v* <3 months	1.45	1.01 to 2.09
MDS IPSS	High *v* intermediate-2	1.50	1.04 to 2.17
Age	>65 *v* ≤65 years	1.00	0.69 to 1.44
ECOG	1 *v* 0	1.22	0.56 to 2.68
Karnofsky	<90 *v* 90-100	1.34	0.88 to 2.03



Multi-hit Tp53-mutations are unfavourable independent of de novo or therapy-related

Bernard E. et al. Nat Gen 2020

Versluis J. et al. JCO 2023

TP53-mutated MN are a nosologic entity by ICC

ICC classification

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation[a], or *TP53* mutation (VAF >10%) and complex karyotype often with loss of 17p[b]
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF >10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF >10%)

Arber et al, Leukemia 2022

TP53 mutations and prognosis in AML

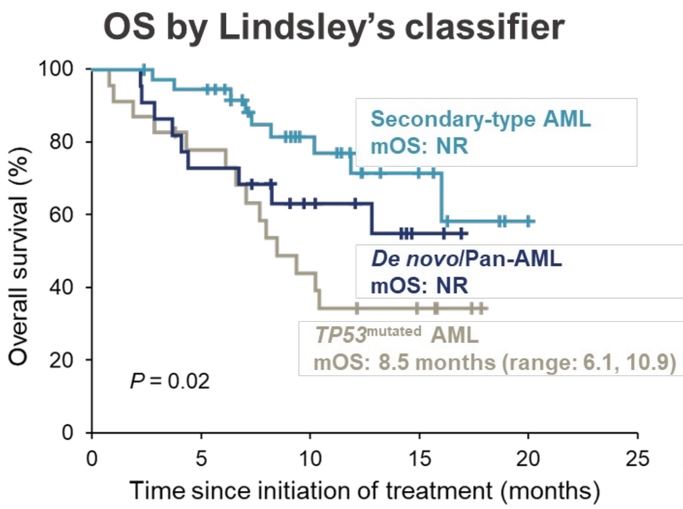
Intensive chemotherapy

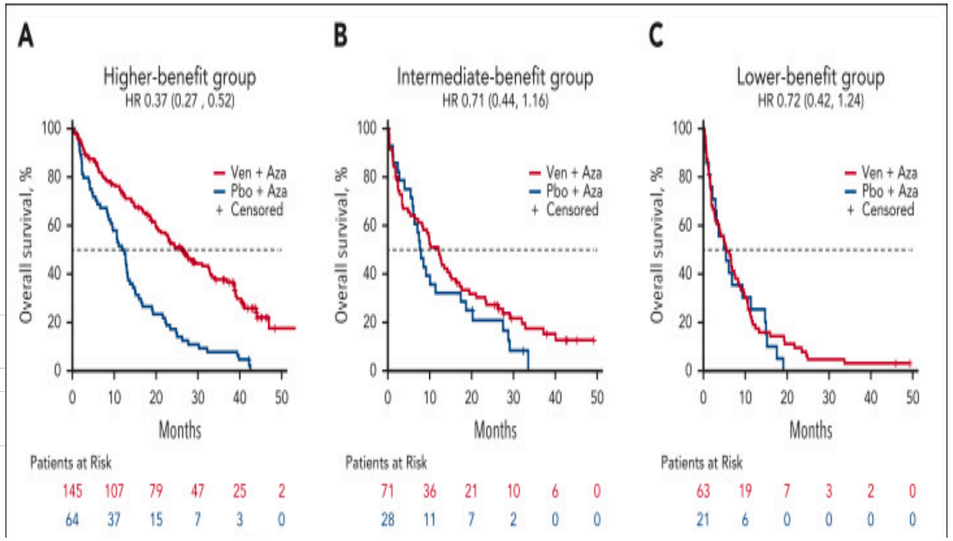
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• 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]

Semi-intensive treatment

Risk category	Genetic abnormality
Favorable	• Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH1*[b] (*TP53*^{wt}) • Mutated *DDX41*[c] • Other cytogenetic and/or molecular abnormalities[d] (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	• Other cytogenetic and molecular abnormalities[d] (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	• Mutated *TP53*

CPX-351





Dohner H. eL.al, Blood 2022 and 2024

Response to current/investigational drugs in AML

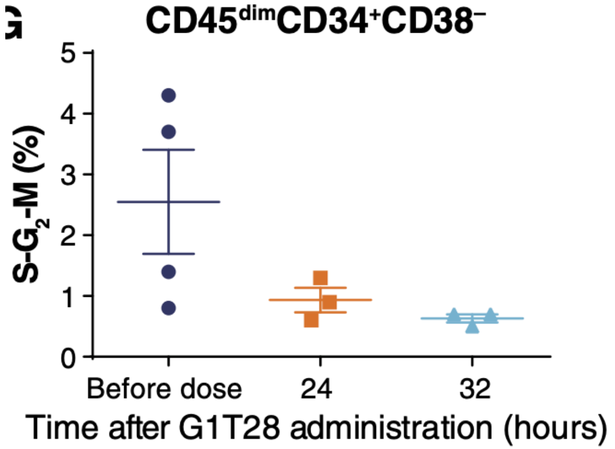
Treatment	Type of study	Population	TP53-mutated pts	Response	CR rate	Median OS (months)
Azacitidine or decitabine	II; retrospective	ND AML	22	CR/CRi 22%-38%	13%-22%	2.1–7.3
Venetoclax + azacitidine or 5-day decitabine	Ib/II, III	ND AML	36, 54	CR/CRi 41%-47%	NR–20%	4.9–7.2
Venetoclax + 10-day decitabine	II; post hoc	ND AML	26	ORR 77%	48%	5.4
Magrolimab + azacitidine	Ib	ND AML	72	CR/CRi 49%	33%	10.8
Magrolimab + venetoclax + azacitidine	Ib/II	ND AML	14	ORR 86%	64%	NR
Eprenetapopt + azacitidine	Ib/II	ND AML	18	ORR 33%	17%	10.4
Sabatolimab + HMA	Ib	ND AML	5	CR/CRi 40%	20%	DOR 6.4
SGN-CD33A + HMA	I/II	ND AML	7	CR/CRi 86%	NR	NA
Nivolumab + intensive chemotherapy	Post hoc	ND AML	4	ORR 50%	NA	NA
Intensive chemotherapy	Retrospective	ND AML	various	ORR 47%-55%	45%-55%	6.8–8.8
Low-intensity chemotherapy	Retrospective	ND AML	various	ORR 14%-50%	36%	6.7–9.0

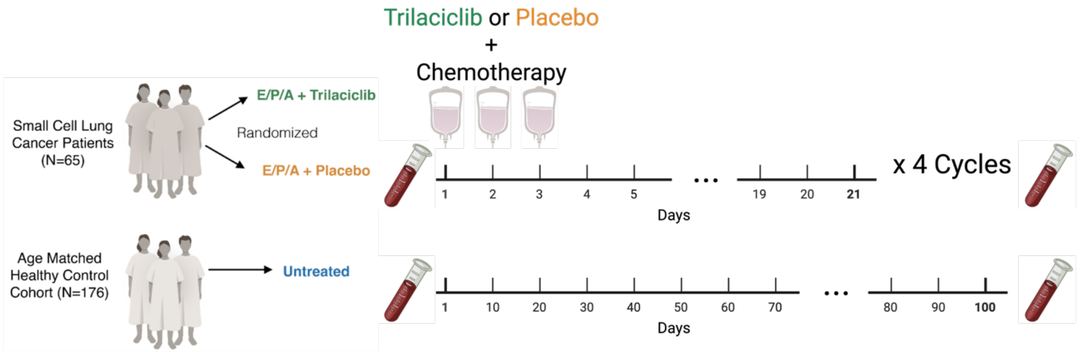
Adapted from Daver et al. Cancer Discov. 2022

How to reduce genotoxic stress during chemotherapy in patients with TP53^{mut} CHIP

CDK4/6 inhibition with Trilaciclib reduces hematopoietic stem cell (HSCs) cycling

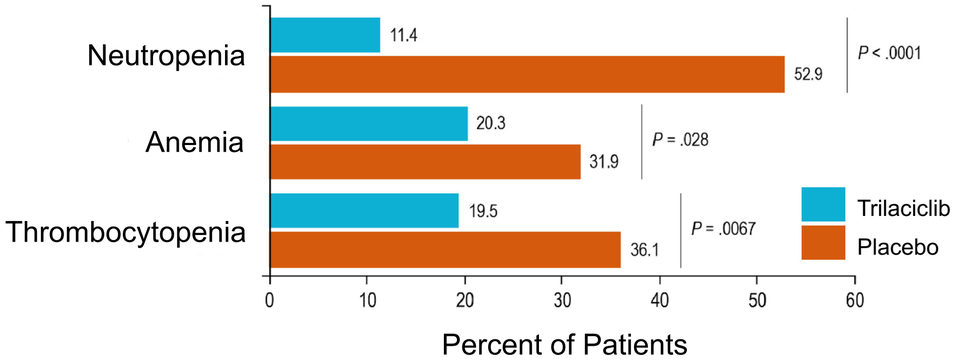
Human Bone Marrow HSCs

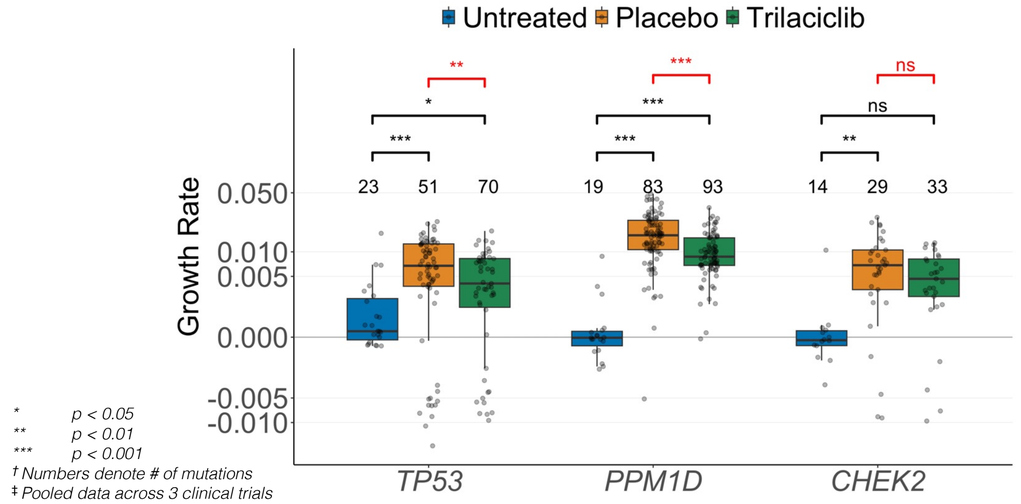




Deep, UMI-based sequencing (20,000x) using ArcherDX

Trilaciclib reduces CHT-related myelosuppression in SCLC patients





* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
† Numbers denote # of mutations
‡ Pooled data across 3 clinical trials

He et al., Sci Trans Med, 2017, Weiss et al., Clin. Lung Cancer, 2021

Irenaeus Chan, et al, Plenary ASH presentation 2025, by courtesy of K. Bolton

Take-home messages

- TP53 mutations are present at variable rates in MN, and are associated with multiple carcinogenic mechanisms
- TP53 CHIP is rare, but clones may expand under chemotherapy exposure, and lead to PB and BM mosaicism
- The clonal burden is associated with unfavourable outcome
- Therapy-related MN are an in-vivo model of TP53-driven leukemogenesis, due to different drugs
- TP53 mutations identify adverse prognostic disease-subgroups
- The genotoxic effect of CHT may be reduced by CDK4/6 inhibition

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