

# **TP53 and Clonal Evolution in MDS: Biology of High-Risk Disease and Clinical Implications SINTOMA 2026**

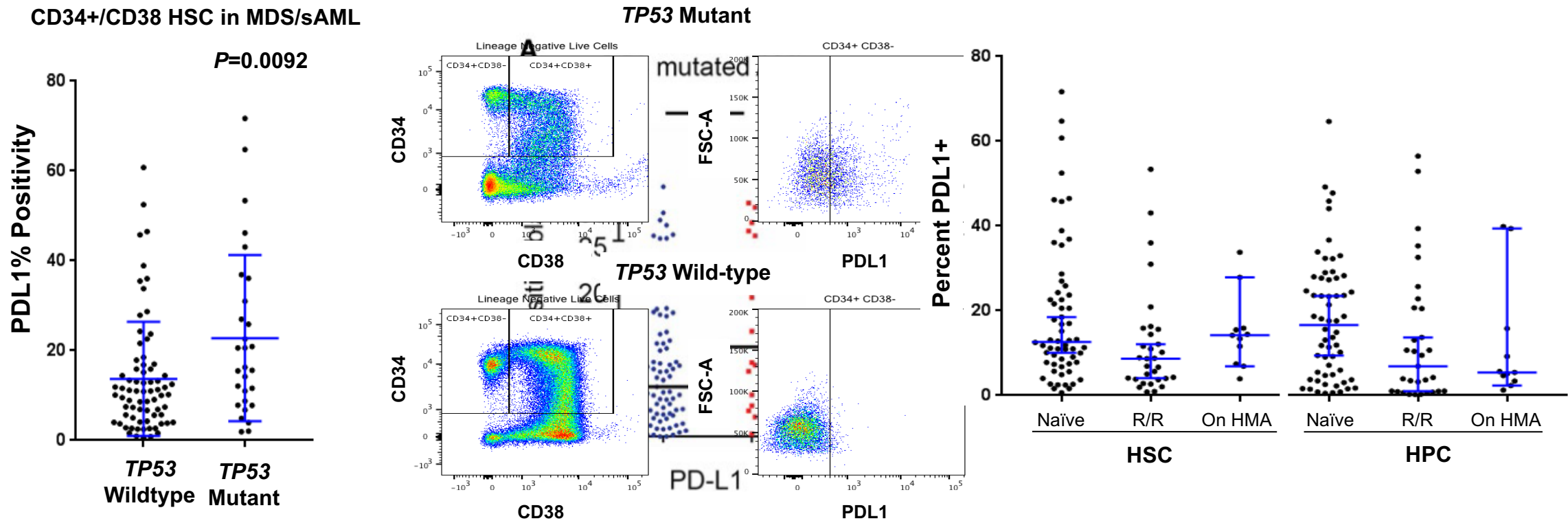
David A. Sallman, MD  
Associate Member  
Myeloid Section Head  
Department of Malignant Hematology  
Moffitt Cancer Center  
[david.sallman@moffitt.org](mailto:david.sallman@moffitt.org)

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# Disclosures

- Advisory Board: Abbvie, Agios, Astellas, AvenCell, Bristol-Myers Squibb, BlueBird Bio, Dark Blue Therapeutics, Geron, Janseen, Kura, Novartis, Shattuck Labs, Servier, Syndax, Syros, Taiho Oncology
- Research Support: Aprea, Jazz

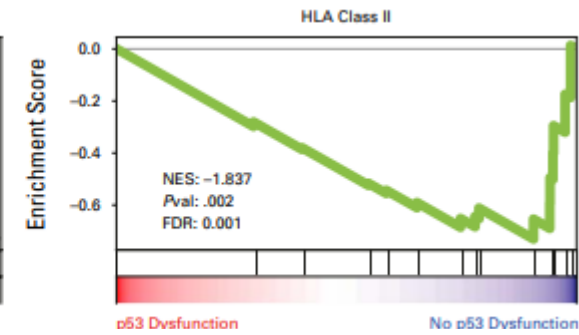
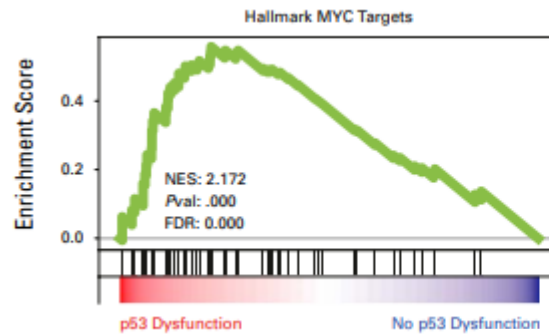
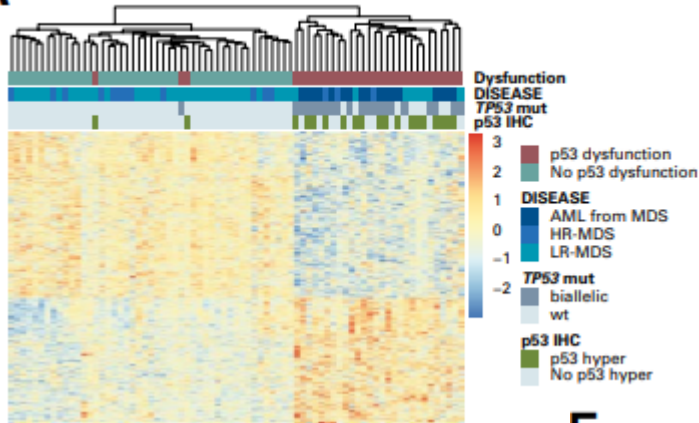
# Checkpoint Inhibitors: *TP53* MT HSC with Increased PDL1 Expression



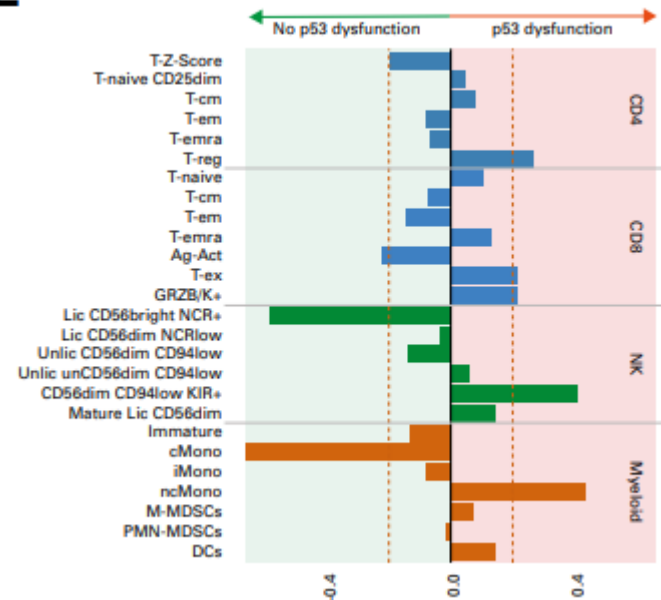
However, multiple negative trials with PD1/PDL1 in MDS/AML, including large *TP53* MT Subsets

# Immune Dysfunction in *TP53* mutant (or hyperexpression of abnl p53 protein) in MDS

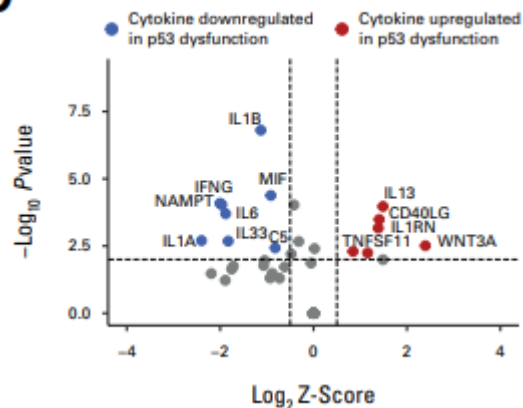
A



E



D

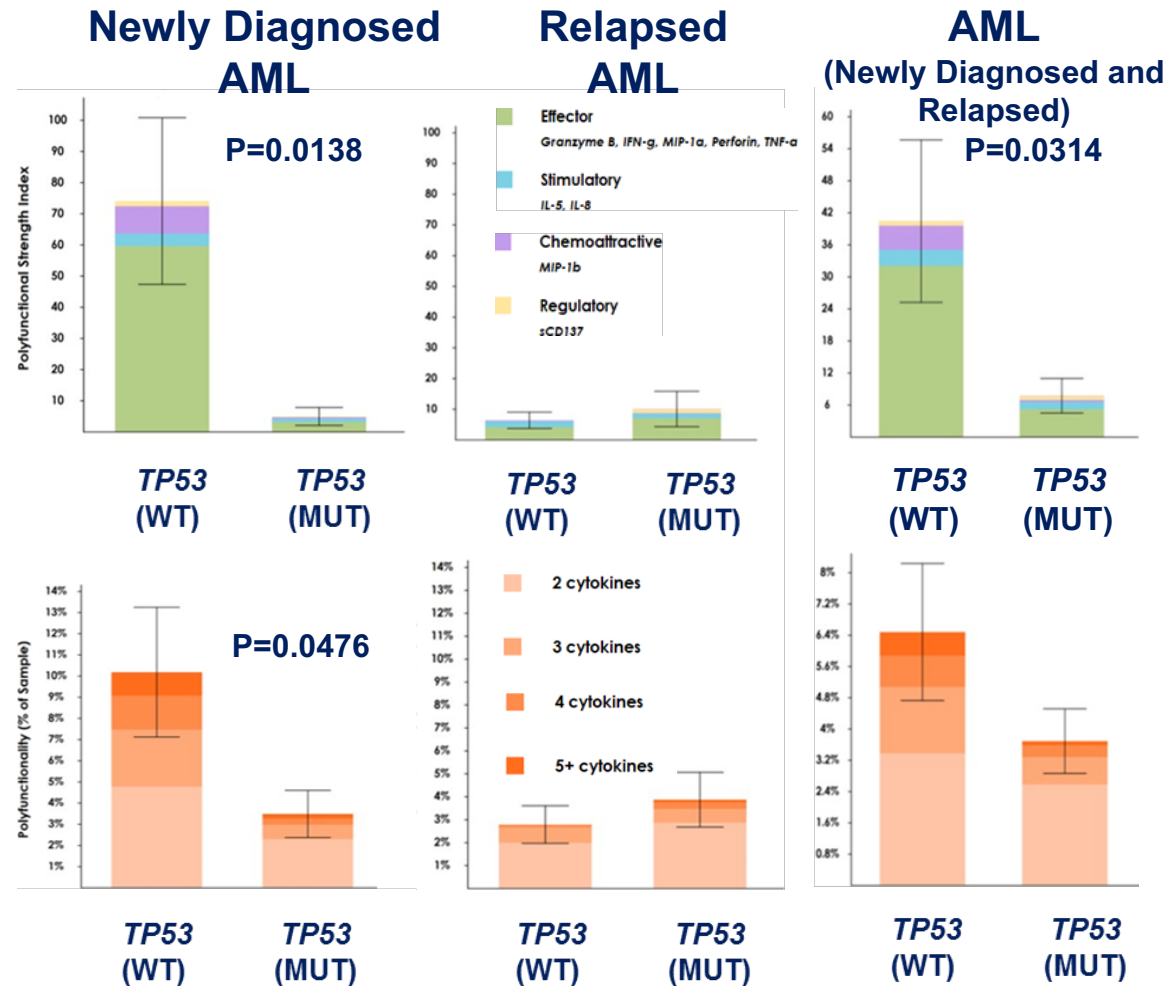


F

Cell Type	Frequency in MDS (With v Without p53 dysfunction)	Biological Meaning
Naive	↓	Maturation skewing towards advanced maturation stages. Reduced proliferative capacity and antigen response of T-cell compartment <sup>24</sup>
Tregs	↑	Immunosuppression, increased risk of disease progression, and poor prognosis in MDS and AML <sup>25</sup>
CD69+ CD8+ Antigen-activated	↓	Less early activated T cells. Less antitumor efficacy of T-cell compartment <sup>26</sup>
PD1+ TIM3+ Exhausted	↑	Loss of T-cell effector functions and impaired antitumor immune surveillance <sup>26-27</sup>
GRZB/K+	↑	Transitional stage from memory T cells to terminally differentiated effector T cells. Positive correlation with immune aging <sup>28-29</sup>
CD56bright NCR+	↓	Impaired NK-cell cytotoxic functions and antitumor activity <sup>30-31</sup>
Mature CD56dim KIR+	↑	Impaired NK-cell cytotoxic functions and target recognition <sup>32</sup>
Classical Monocytes	↓	Reduced antigen presentation <sup>33</sup>
Nonclassical Monocytes	↑	Proinflammatory phenotype in chronic inflammatory conditions (ie, inflammaging, autoimmune diseases) <sup>34</sup>

■ T cells ■ NK cells ■ myeloid cells

# TP53 mutant patients have significant defect in polyfunctionality vs wild-type patients at diagnosis



# MDS/AML with *TP53* mutation is a Unique Molecular Entity

WHO 2022

MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and <i>SF3B1</i> mutation <sup>a</sup> (MDS- <i>SF3B1</i> )		Absence of 5q deletion, monosomy 7, or complex karyotype	<i>SF3B1</i>
MDS with biallelic <i>TP53</i> inactivation (MDS-bi <i>TP53</i> )	<20% BM and PB	Usually complex	Two or more <i>TP53</i> mutations, or 1 mutation with evidence of <i>TP53</i> copy number loss or cnLOH

## Myeloid neoplasms with mutated *TP53*

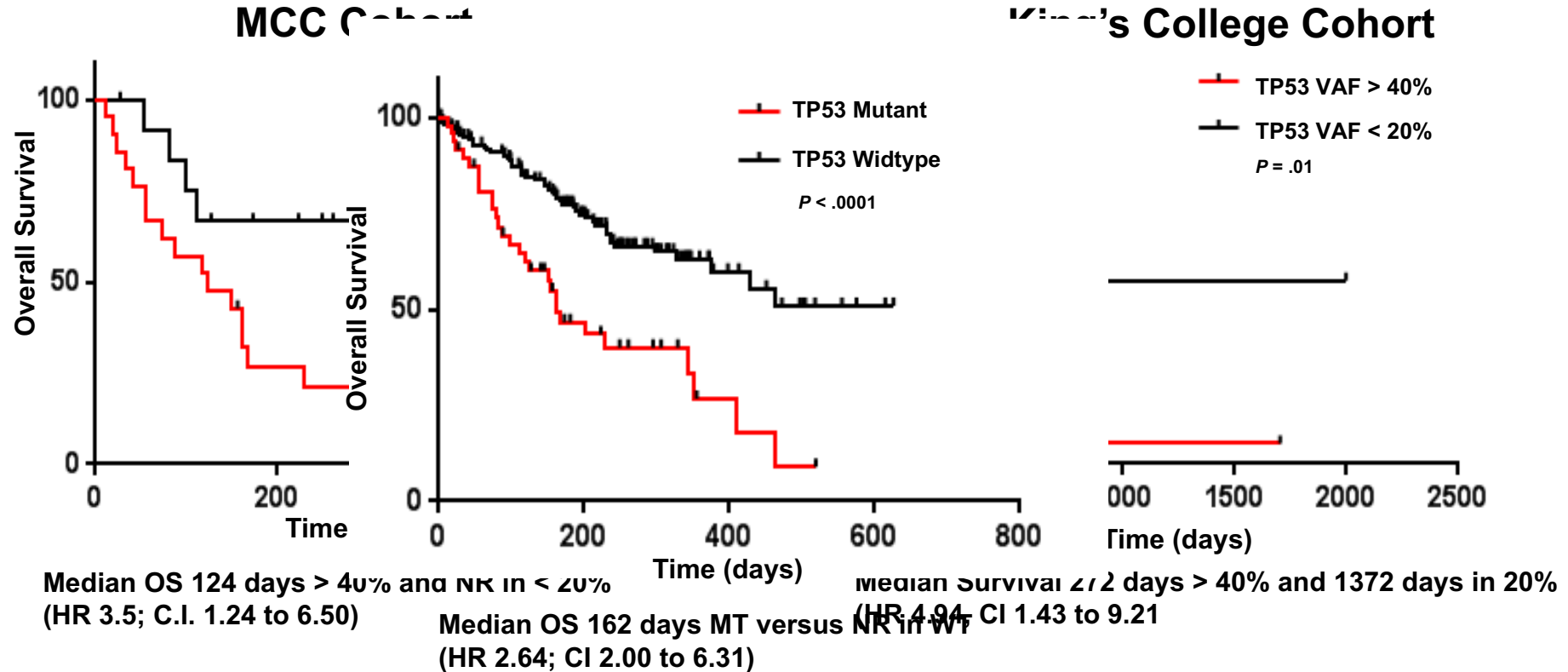
ICC 2022

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

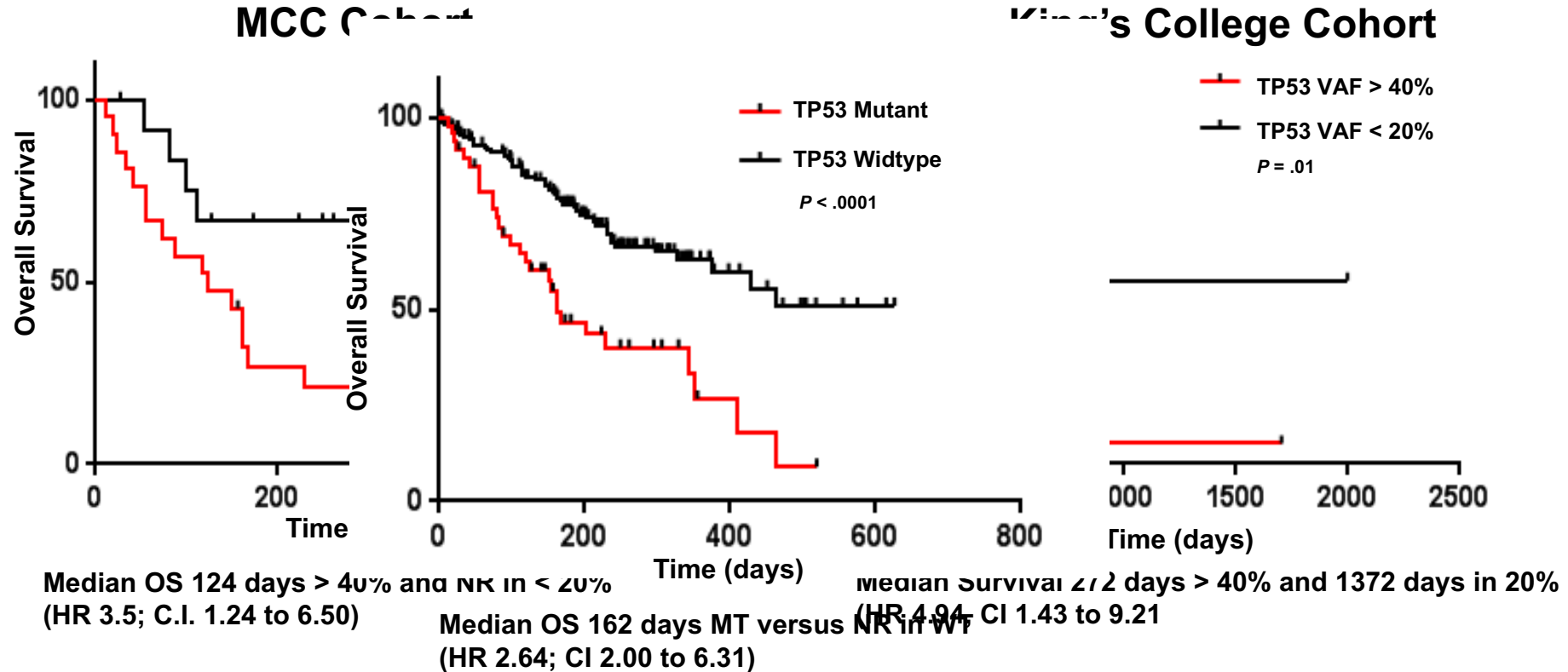
\* Defined as 2 distinct *TP53* mutations (each VAF > 10%) OR a single *TP53* mutation with (1) 17p deletion on cytogenetics; (2) VAF of >50%; or (3) Copy-neutral LOH at the 17p *TP53* locus.

† If *TP53* locus LOH information is not available.

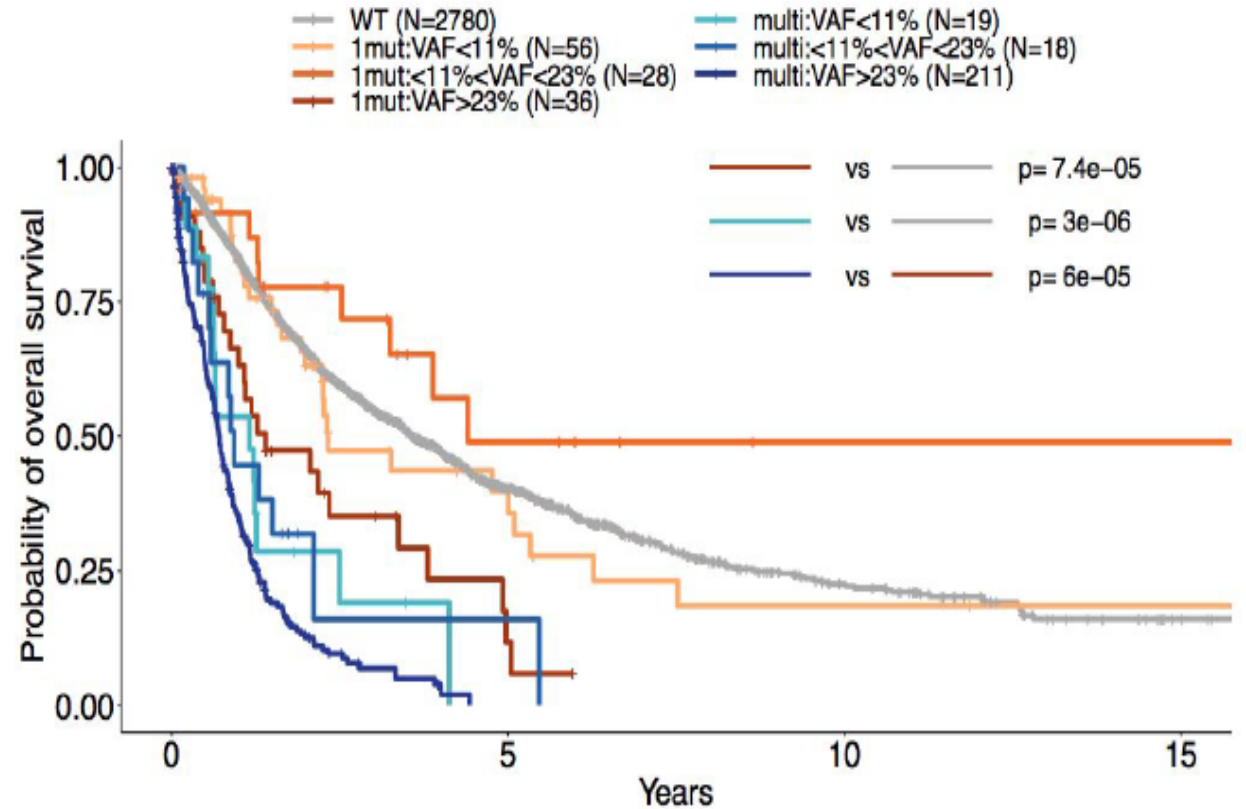
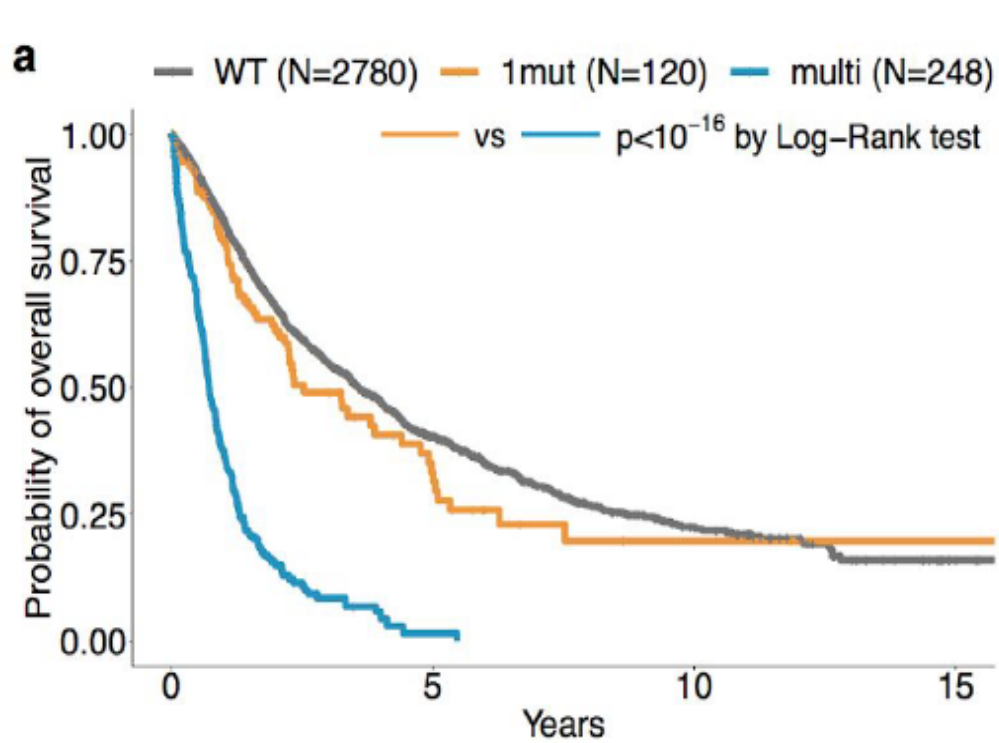
# TP53 Mutation Status and VAF Predicts Inferior Survival in MDS and sAML



# TP53 Mutation Status and VAF Predicts Inferior Survival in MDS and sAML

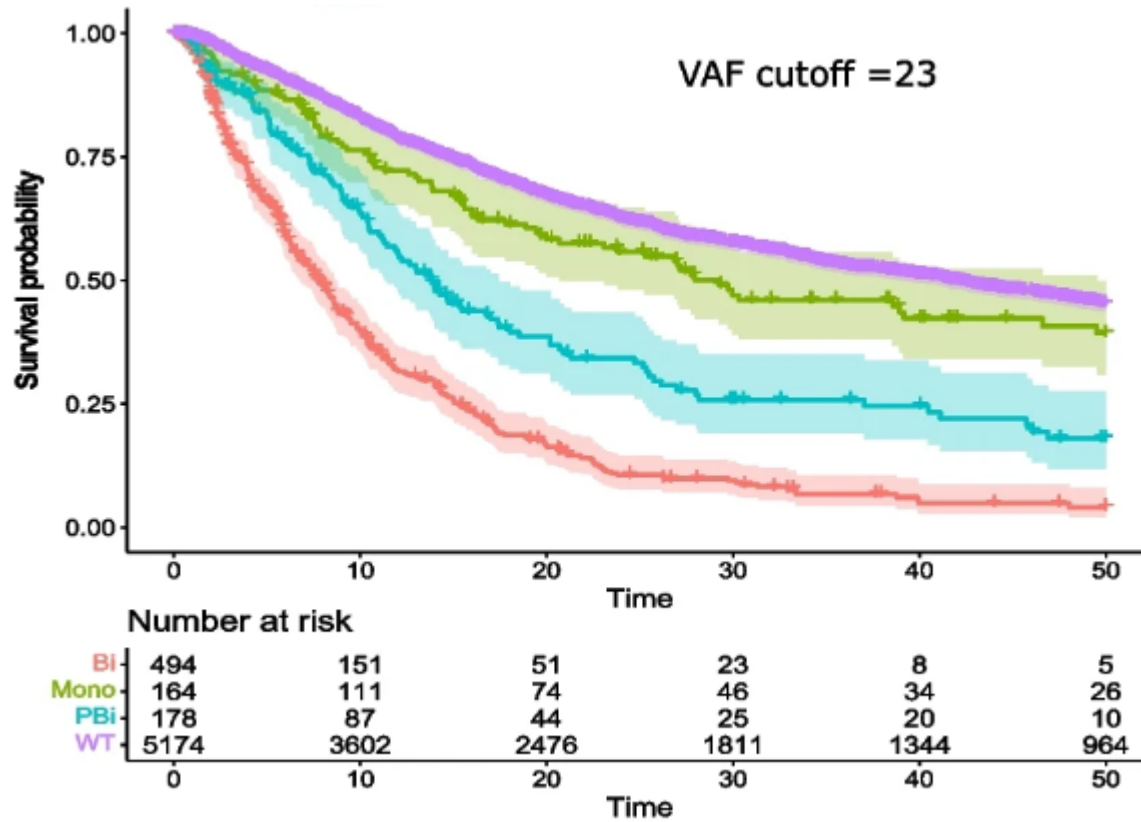


# Overall survival per *TP53* state and VAF stratification



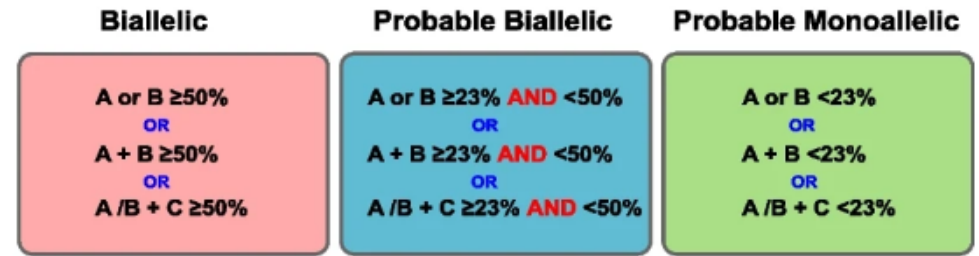
# TP53 VAF Correlates Strongly with Multi-Hit State

■ Biallelic   
 ■ Monoallelic   
 ■ Probable Biallelic   
 ■ Wild Type



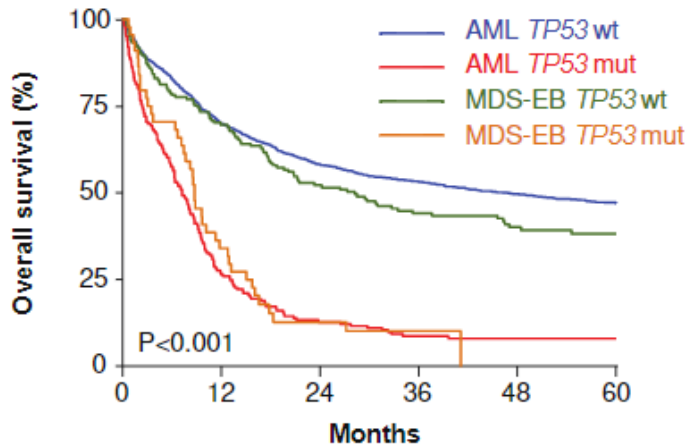
## E Diagnostic algorithm

A: VAF of TP53 MT #1  
 B: VAF of TP53 MT #2  
 C: Clonality of 17p del



# TP53 Mutant MDS and AML, One Disease ?

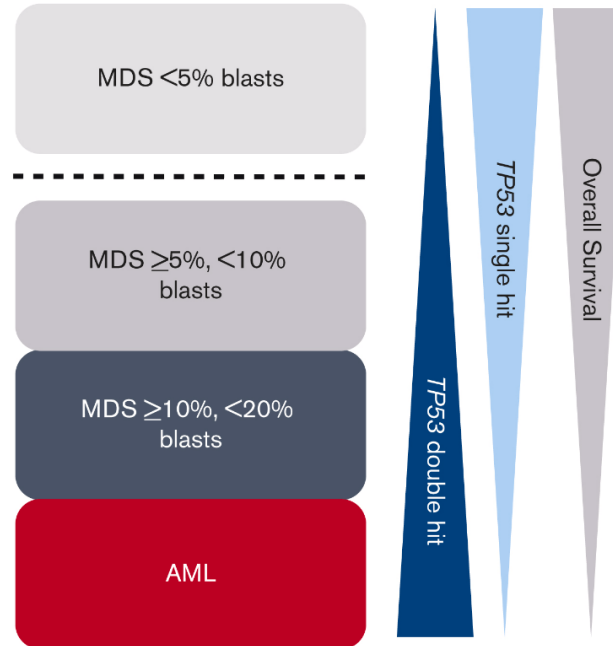
**B**



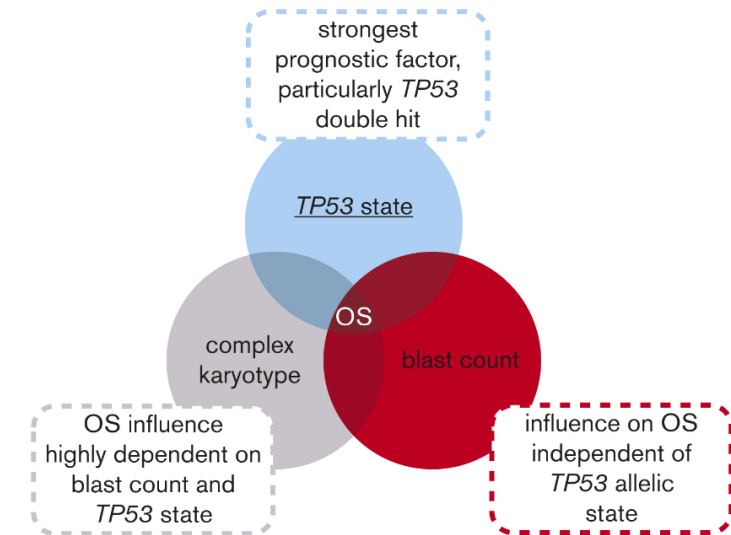
No. at risk:

	0	12	24	36	48	60
AML <i>TP53</i> wt	1805	1255	1014	807	572	397
AML <i>TP53</i> mut	186	50	23	14	9	5
MDS-EB <i>TP53</i> wt	165	114	81	62	45	35
MDS-EB <i>TP53</i> mut	44	15	5	1	0	0

**A**

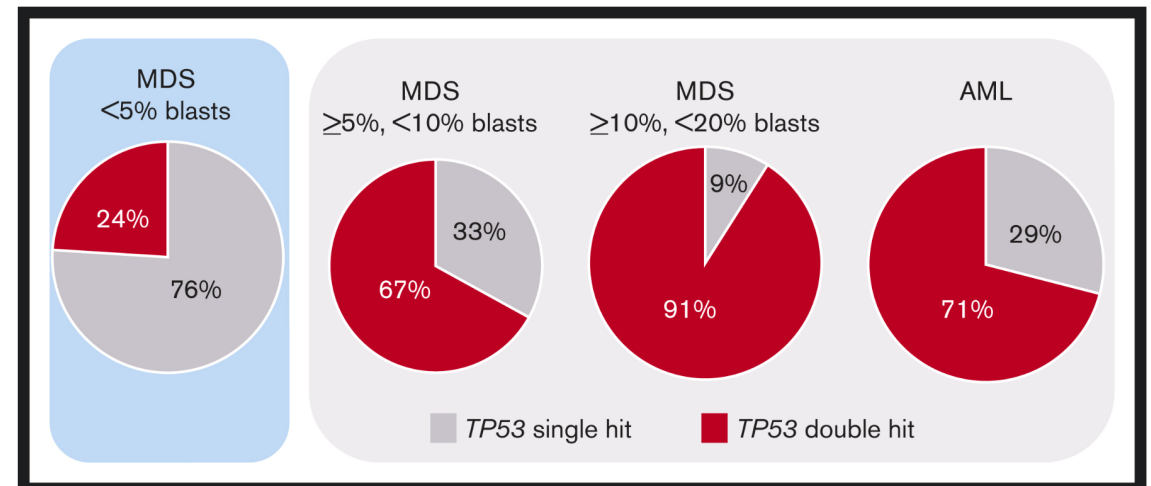
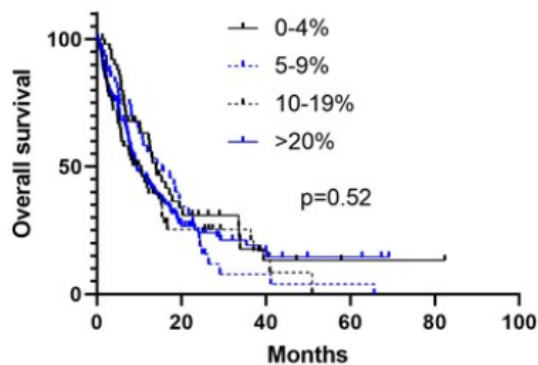


**B**

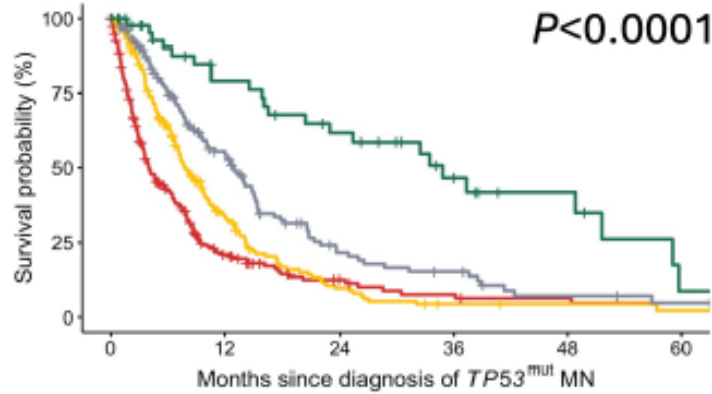


**C**

Overall survival based on bone marrow blast strata



# Harmonization of *TP53* MDS/AML Patients

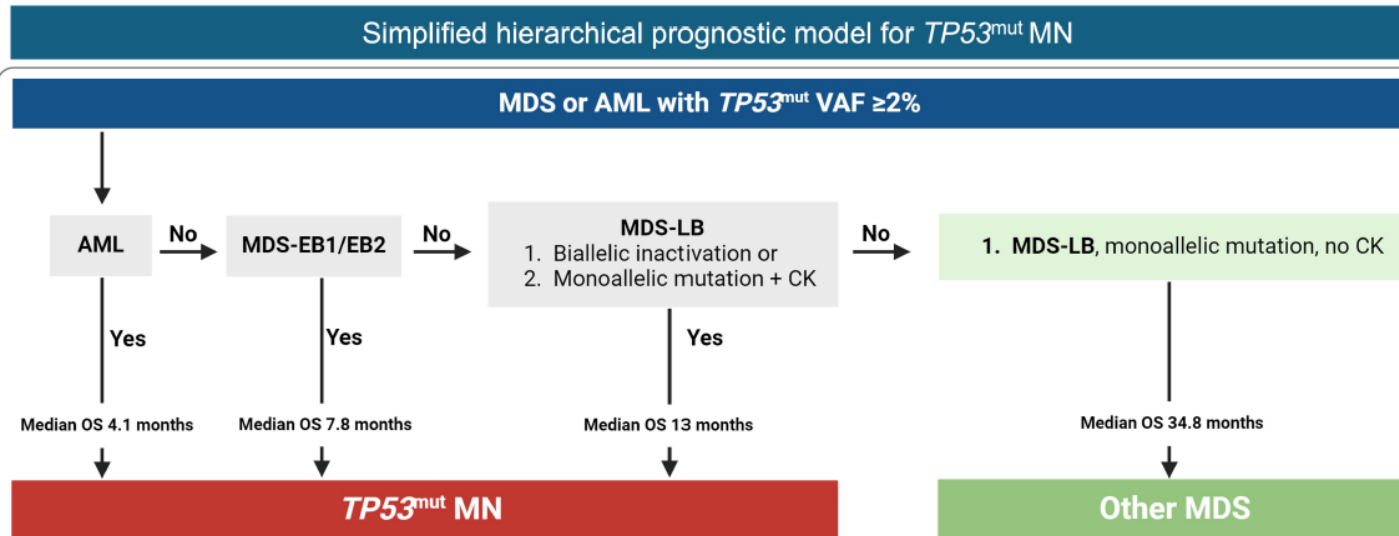


	Median OS (95% CI)	AML	MDS-EB1 and MDS-EB2	MDS-LB biallelic or monoallelic plus CK
AML (n=219)	4.1 (3.5-5.9)	-	<0.0001	<0.0001
MDS-EB1 and EB2 (n= 167)	7.8 (7.1-9.9)	<0.0001	-	0.00069
MDS-LB biallelic or monoallelic plus CK (n=145)	13.0 (10.2-15.3)	<0.0001	0.00069	-
MDS-LB monoallelic without CK (n=47)	34.8 (22.9-NA)	<0.0001	<0.0001	<0.0001

Number at risk

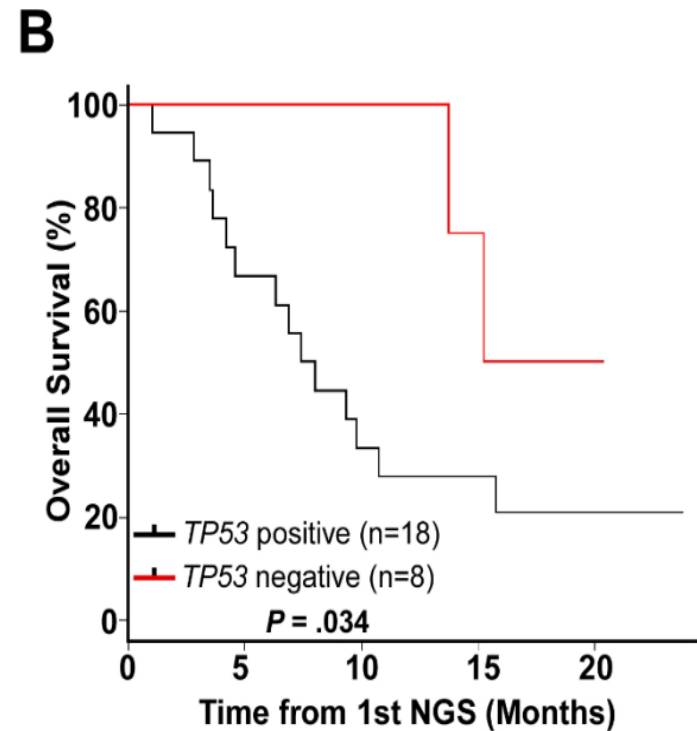
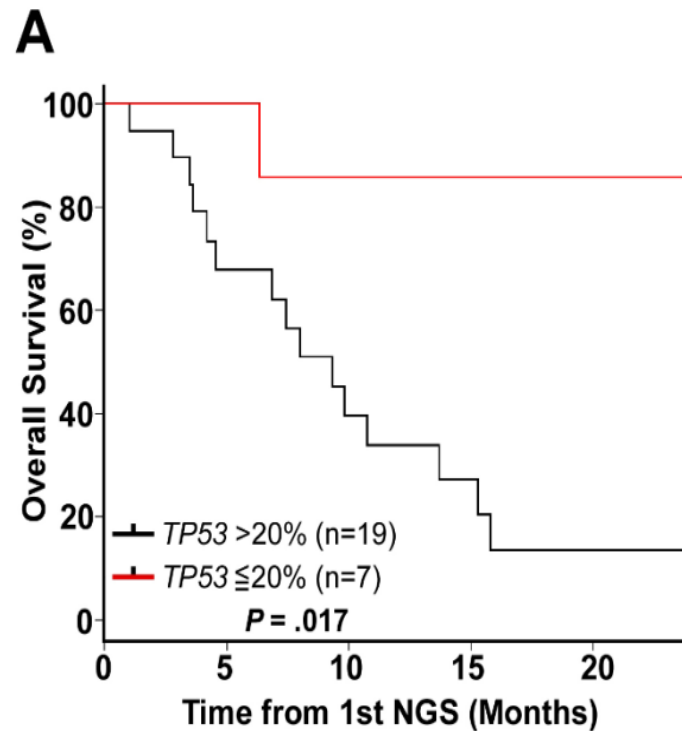
	0	12	24	36	48	60
219	219	31	11	6	4	3
167	167	42	11	3	2	1
145	145	60	17	11	4	2
47	47	28	20	10	6	1

91% of *TP53* MDS/AML with poor survival

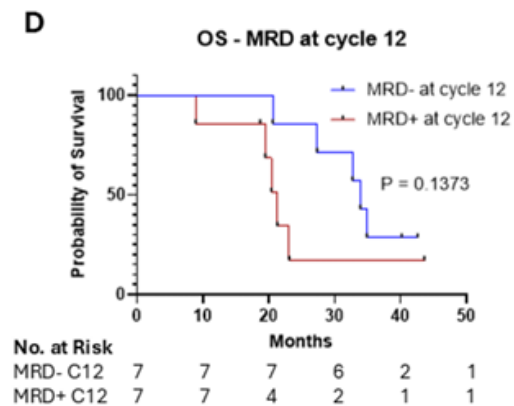
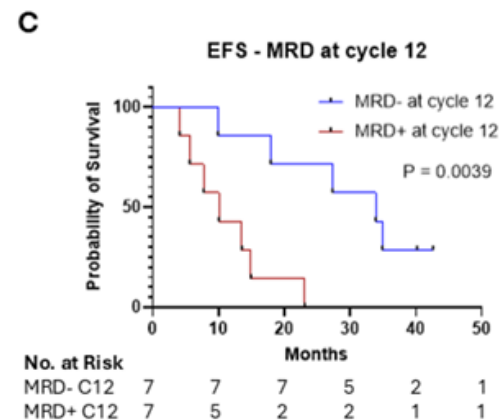
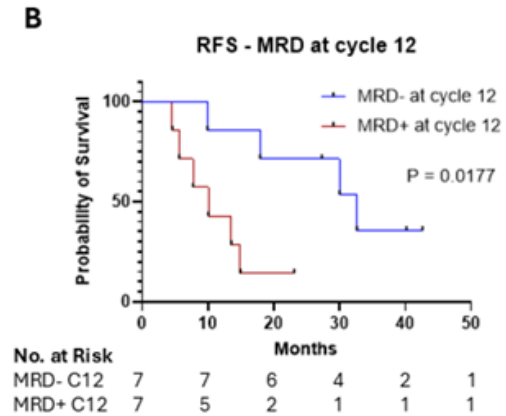
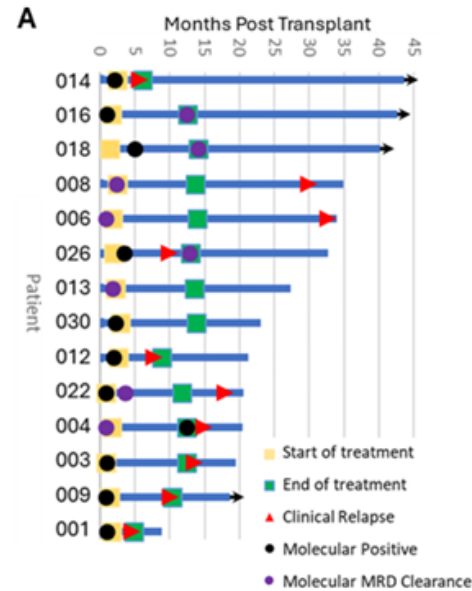


Pathology	WHO 2022	ICC 2022
<b>MDS biallelic <i>TP53</i> inactivation/Multi-hit <i>TP53</i></b>	<ul style="list-style-type: none"> <li>Two or more <i>TP53</i> mutations (No VAF Cutoff)</li> </ul> Or <ul style="list-style-type: none"> <li>One mutation with copy number loss (cnLOH)</li> <li><i>TP53</i> VAF &gt; 50%</li> </ul>	<ul style="list-style-type: none"> <li>Myeloblasts 0-9%</li> <li>2 distinct <i>TP53</i> mutations each with VAF &gt; 10%</li> </ul> or <ul style="list-style-type: none"> <li>single <i>TP53</i> mutation with either 17p deletion, VAF &gt;50%, cnLOH</li> </ul> or <ul style="list-style-type: none"> <li><i>TP53</i> mutation VAF &gt;10% and complex karyotype (often with loss of 17p).</li> </ul>
<b>MDS/AML with <i>TP53</i></b>		<ul style="list-style-type: none"> <li>Myeloblasts 10-19%</li> <li>any somatic <i>TP53</i> mutation VAF ≥10%</li> </ul>
<b>AML with <i>TP53</i></b>		<ul style="list-style-type: none"> <li>Myeloblasts ≥20%</li> <li>any somatic <i>TP53</i> mutation VAF ≥10%</li> </ul>
	<b>Harmonized classification</b>	
<ul style="list-style-type: none"> <li><b>Myeloid neoplasm with biallelic (multi-hit) <i>TP53</i></b></li> </ul>	<ul style="list-style-type: none"> <li>A definitive biallelic (multi-hit) <i>TP53</i> : two or more <i>TP53</i> distinct mutations in trans, single <i>TP53</i> mutation and del17 or CN-LOH at 17p13.1.</li> <li>A probable biallelic (multi-hit) would include <i>TP53</i> VAF ≥ 50% or ≥ 2 distinct mutations trans not confirmed or complex karyotype.</li> </ul>	
<b>Clinical</b>	<b>Proposed Clinical classification</b>	
<b>Favorable</b>	Myeloblasts < 5% Single <i>TP53</i> mutation/mono-allelic or single hit (consider also VAF < 20%) No complex karyotype	
<b>Unfavorable</b>	Biallelic/multi-hit <i>TP53</i> ( two different mutations, one mutation plus cnLOH/del17, single mutation VAF > 50% (probable if VAF > 20%) Single hit/monoallelic <i>TP53</i> with increased myeloblasts > 5% or complex karyotype	

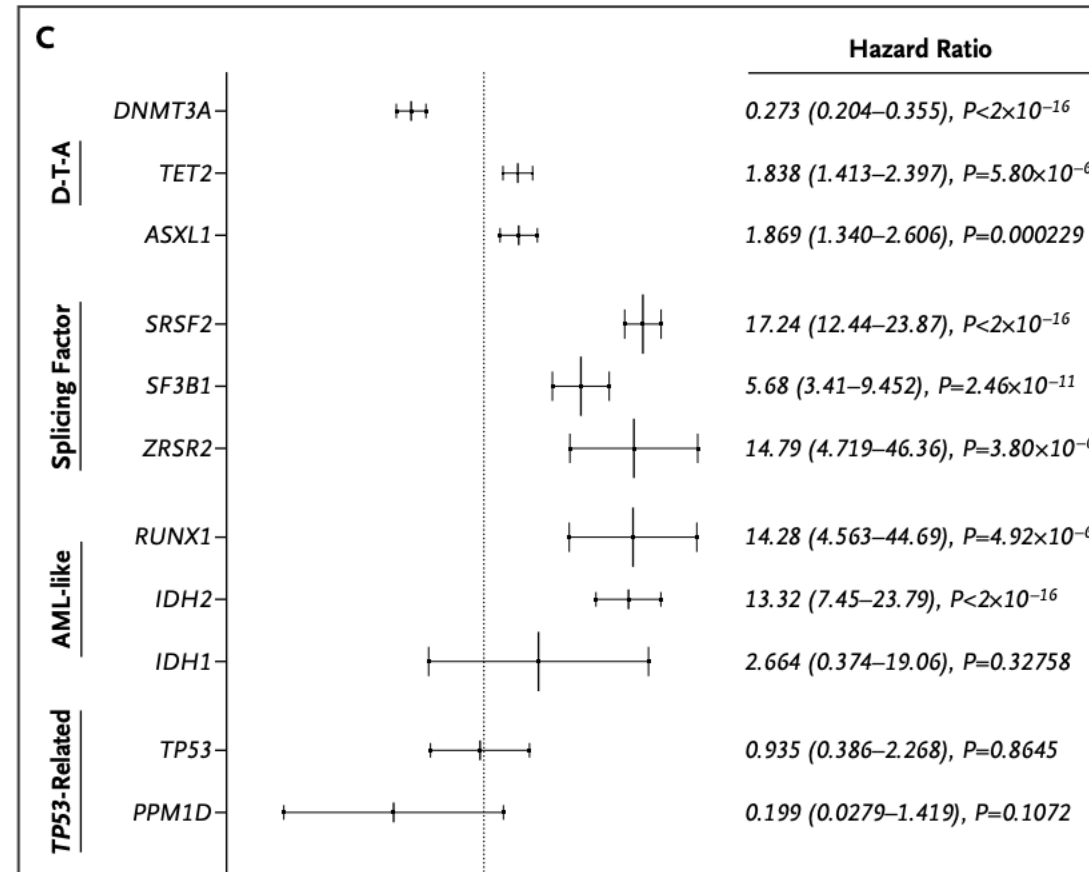
# Serial *TP53* VAF Predicts OS



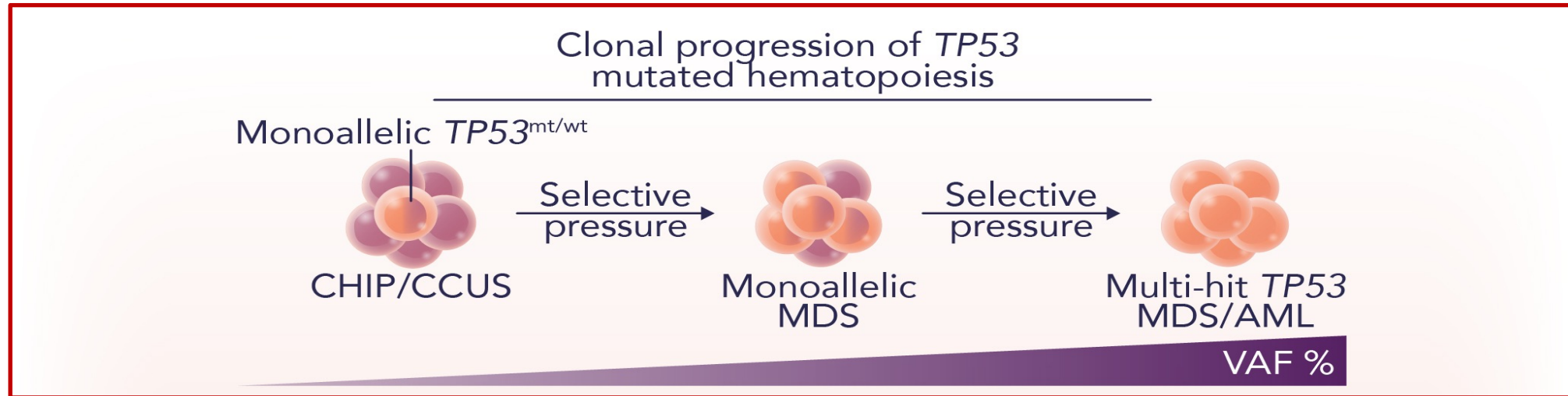
# Serial MRD Predicts Outcomes in *TP53* mutant MDS/AML Pts



# CHRS performance was not significantly altered by the empiric inclusion of *TP53* as a high-risk mutation.



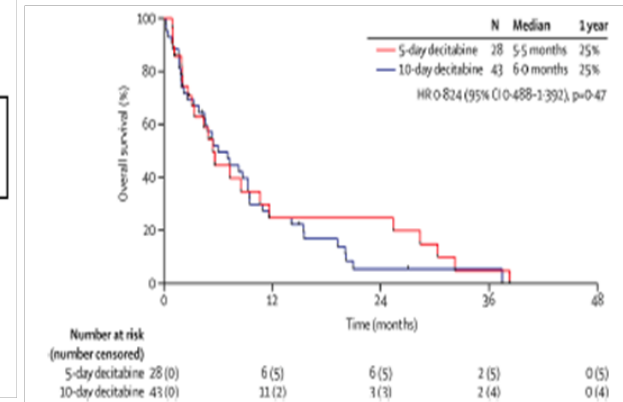
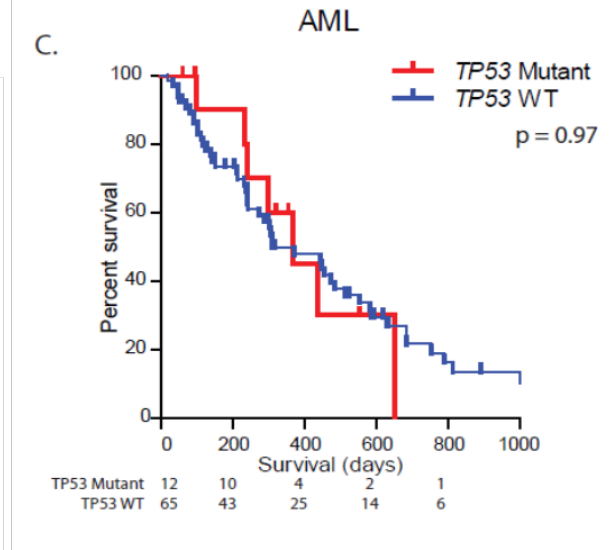
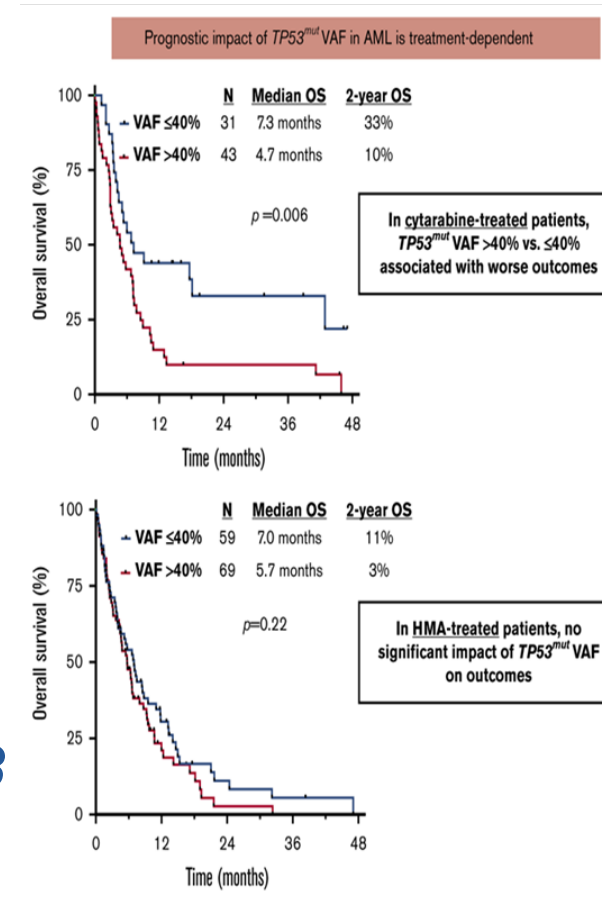
# Interplay of *TP53* Mutant State and Clinical Presentation



? To Intervene or not to intervene early on?

# Outcomes to Therapy in *TP53* MDS/AML

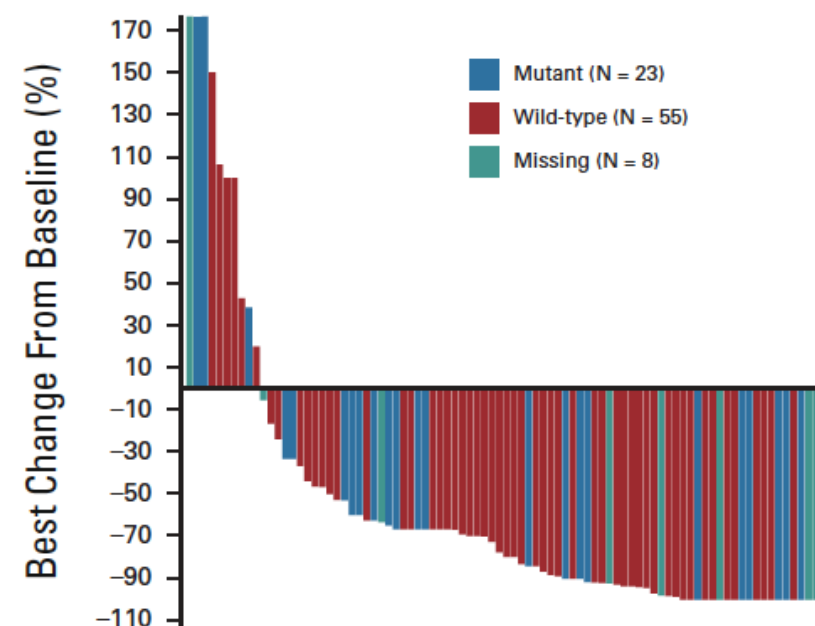
- Current therapies in *TP53* mutant MDS/AML
  - Hypomethylating agents (HMA) result in 15-20% CR and 40-45% ORR, similar to *TP53* wildtype patients
  - Despite HMA responses, significantly inferior OS in *TP53* mutant patients (6-12 months)
    - OS < 6 months
  - IC maybe an option for patients with *TP53* subclone



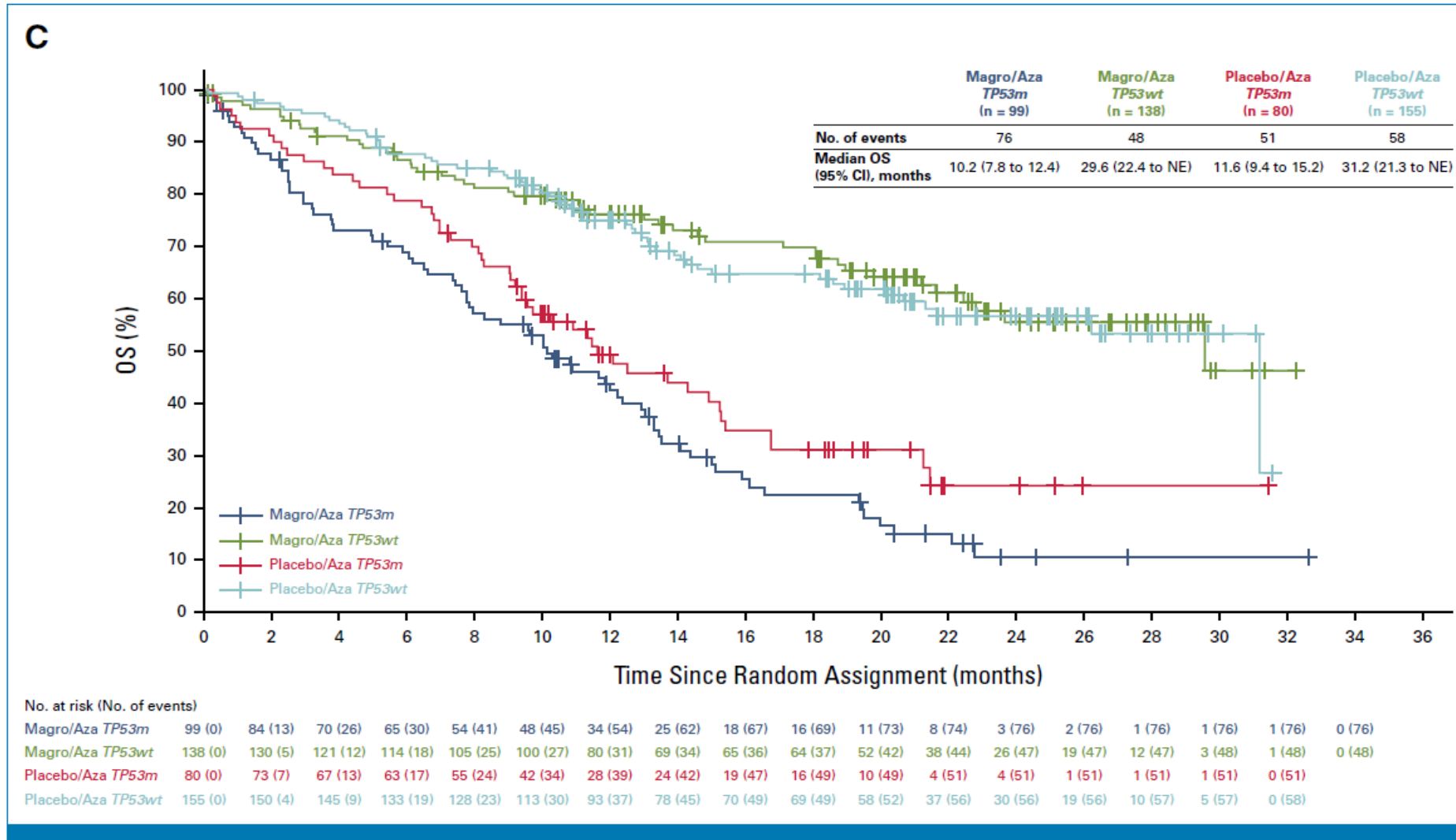
# Magrolimab + AZA Induces High Response Rates in HR-MDS

**TABLE 3.** Efficacy Outcomes

Outcome	All (N = 95 <sup>a</sup> )	TP53-wt MDS (N = 61)	TP53-mut MDS (N = 25)
OR rate, % <sup>b</sup>	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4 to 43.0)	31.1 (19.9 to 44.3)	40.0 (21.1 to 61.3)
mCR, %	31.6	37.7	20.0
PR, %	0	0	0
SD with HI, %	10.5	9.8	8.0
Duration of CR, months, median (95% CI)	11.1 (7.6 to 13.4)	12.9 (8.0 to NR)	7.6 (3.1 to 13.4)
Time to CR, months, median (range)	3.7 (1.7-7.2)	4.6 (1.7-7.2)	3.1 (1.9-4.0)
Duration of OR, months, median (95% CI)	9.8 (8.8 to 12.9)	9.8 (8.5 to 18.5)	9.2 (5.0 to 12.2)
Time to OR, months, median (range)	1.9 (0.7-10.9)	1.9 (0.7-5.5)	1.9 (1.8-10.3)
mCR with HI/Any HI, %	16.8/58.9	19.7/60.7	12.0/56.0
Converted to RBC transfusion independence, % <sup>c</sup>	35.1	26.1	46.2
PFS, months, median (95% CI)	11.6 (9.0 to 14.0)	11.8 (8.8 to 16.6)	11.0 (6.3 to 12.8)
OS, months, median (95% CI)	NR (16.3 to NR)	NR (21.3 to NR)	16.3 (10.8 to NR)



# ENHANCE and OS across *TP53* mutant and Wildtype



38% *TP53* mutant in Trial; 41% *TP53* mutant Combo; 34% *TP53* mutant placebo

# ENHANCE-2 (First *TP53* AML Specific P3 Trial)

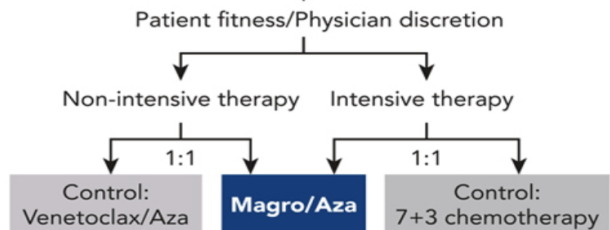
## Magrolimab Plus Azacitidine in Untreated *TP53*-Mutated Acute Myeloid Leukemia (AML): The ENHANCE-2 Study

### Context of Research

- Patients with *TP53*-mutated AML have an extremely poor prognosis
- Magrolimab (Magro) is a humanized IgG4 monoclonal antibody that blocks CD47
- The randomized, phase 3 ENHANCE-2 trial evaluated Magro plus azacitidine (Magro/Aza) in patients with previously untreated *TP53*-mutated AML

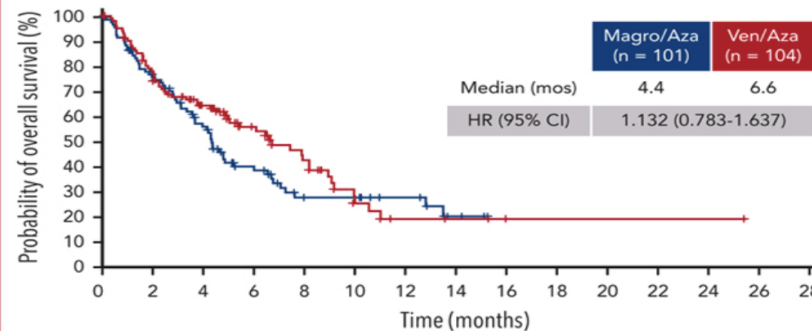
### Patients and Methods (NCT04778397)

**Key eligibility criteria:**  
Adults with previously untreated AML and  $\geq 1$  *TP53* mutation that was not benign or likely benign, or with biallelic 17p deletion

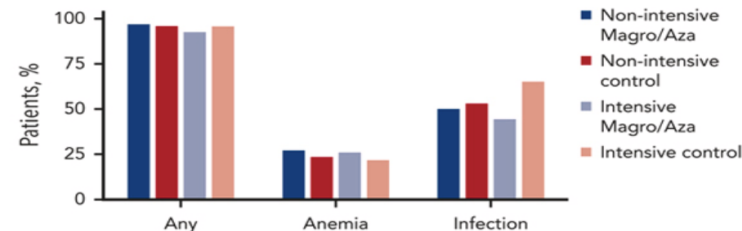


### Main Findings

- In the non-intensive arm, Magro/Aza did not improve overall survival vs Venetoclax (Ven)/Aza



- Rates of grade  $\geq 3$  adverse events with Magro/Aza were comparable with those in control groups

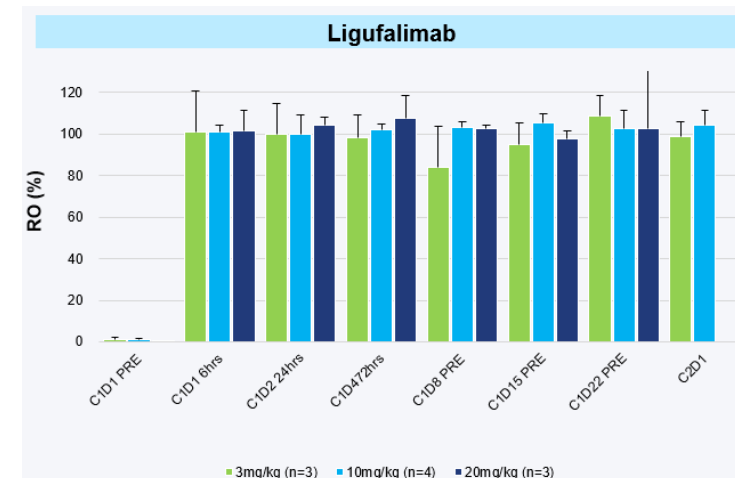
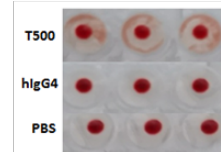
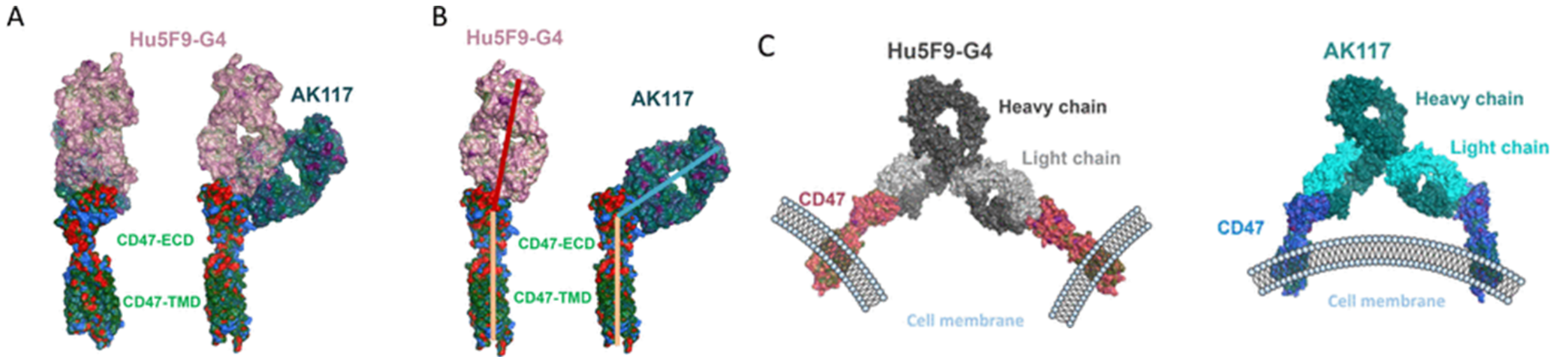


**Conclusions:** In patients with *TP53*-mutated AML determined inappropriate for intensive therapy, the administration of Magro/Aza did not improve overall survival compared to Ven/Aza.

Zeidner et al. DOI: 10.1182/*blood*.2024027408

 **blood**  
Visual  
Abstract

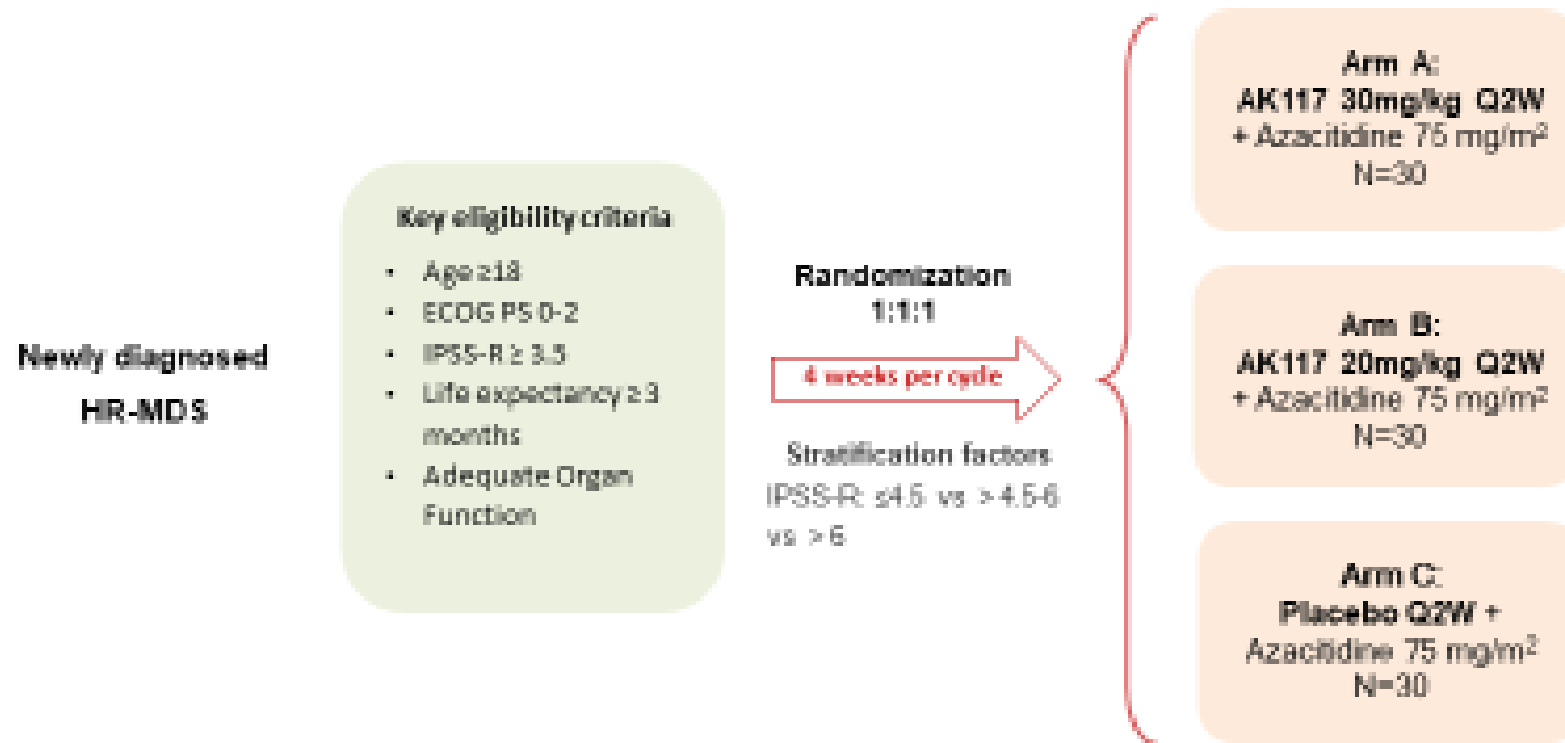
# AK117 (Ligafulimab) does not induce Hemagglutination



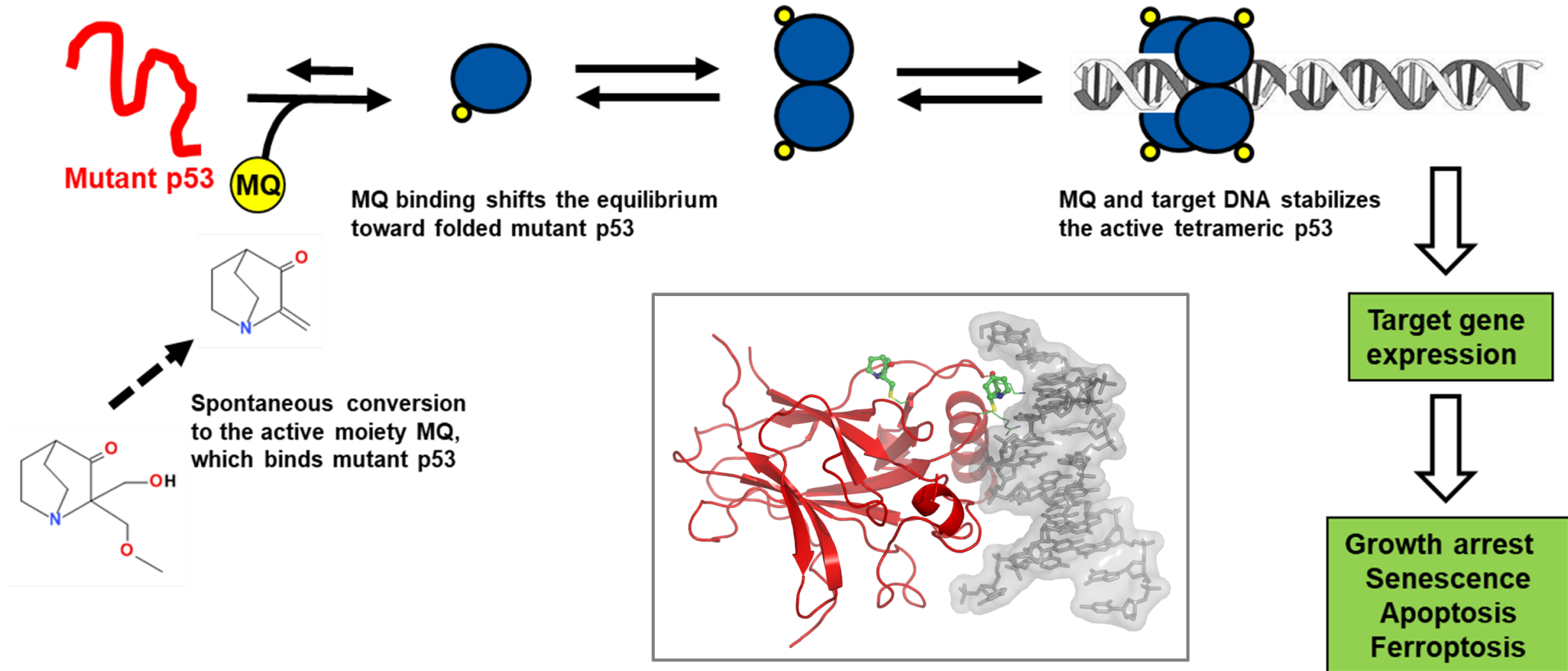
Less anemia in early clinical trials (29% in MDS pts, no large drops) with no priming dose; CR ~50%

# Randomized P2 AK117 Study

A randomized, double-blind, placebo-controlled, multicenter phase 2 study of AK117/placebo in combination with azacitidine in patients with newly diagnosed higher-risk myelodysplastic syndromes



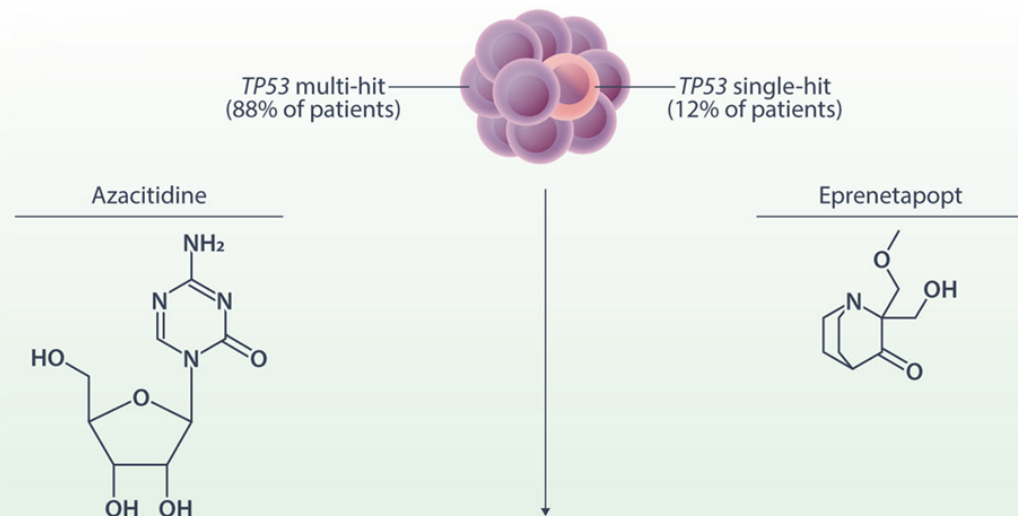
# Eprenetapopt (APR-246) Mechanism of Action



# Long-term Results of APR-246 (eprenetapopt) in *TP53* mutant MDS/AML

## Graphical Abstract

Azacitidine + Eprenetapopt in *TP53* MDS/AML

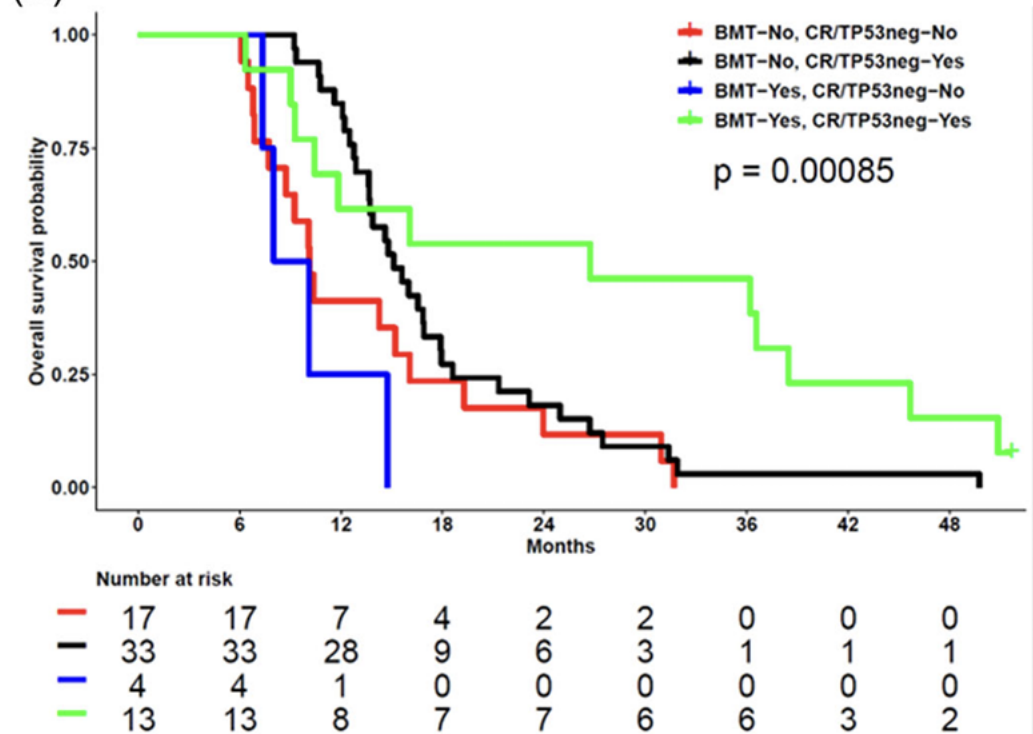


Overall Response Rate: 69%  
 NGS Negativity: 40%  
 Overall Survival: 11.8 months  
 HCT in CR/NGS Negative: 2-year OS of 54%

HemaSphere

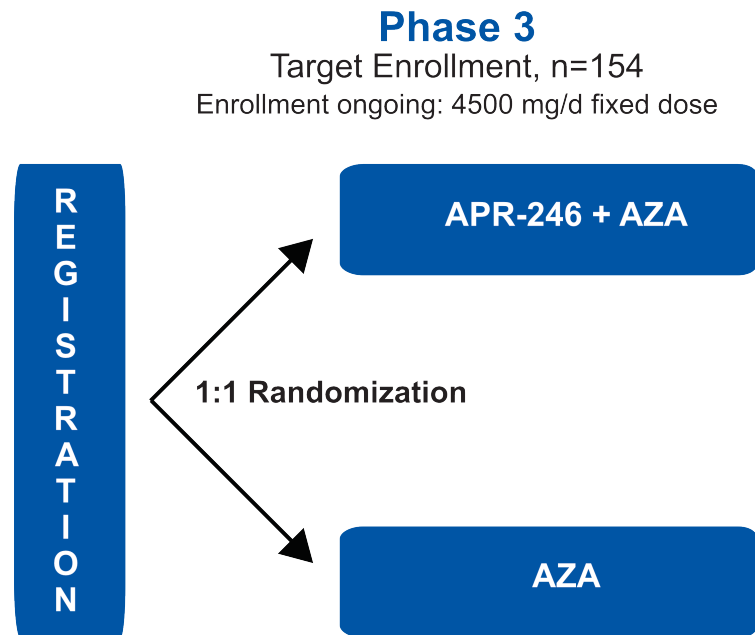
HemaSphere.2025;9:e70164

(B)



# Pivotal Phase 3 MDS Trial in *TP53* Mutant MDS

- Randomized study of frontline azacitidine ± APR-246 in *TP53* mutant MDS



- Intermediate/High/Very High Risk *TP53* mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

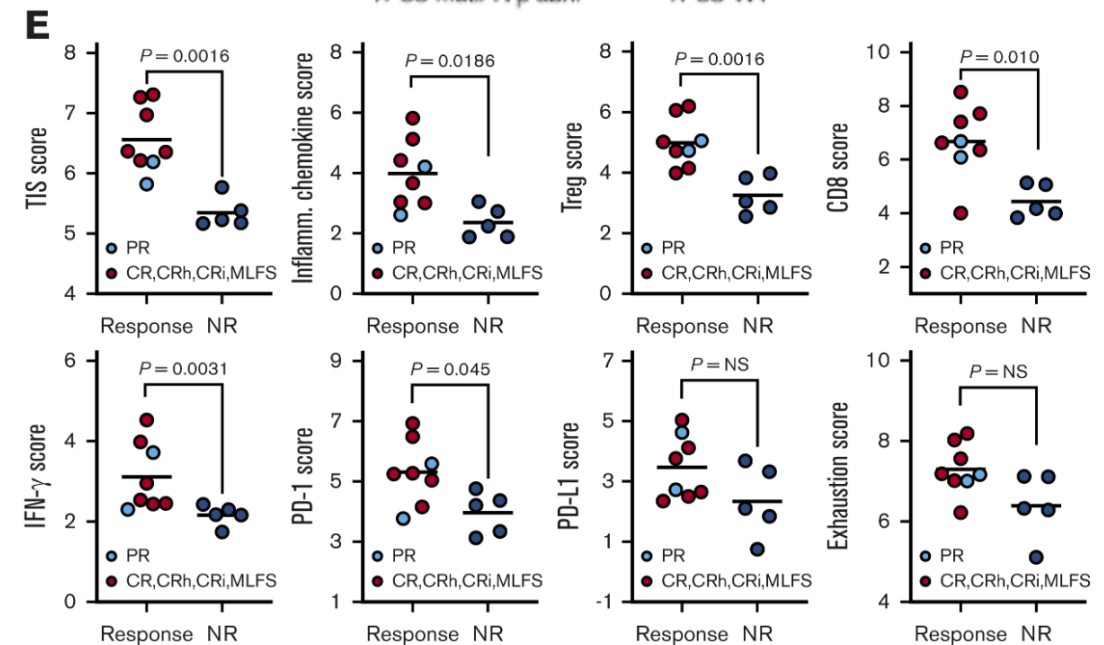
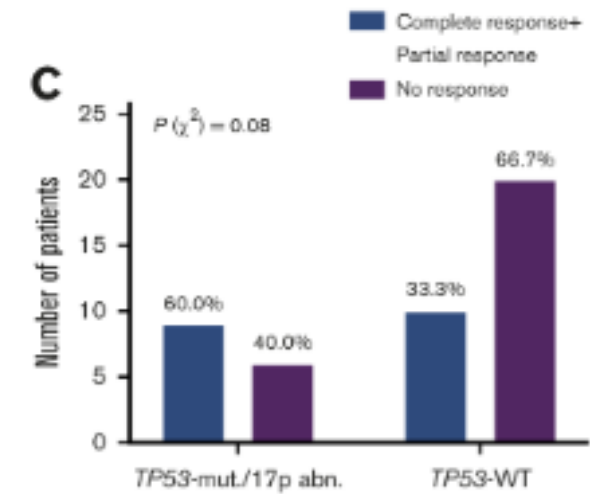
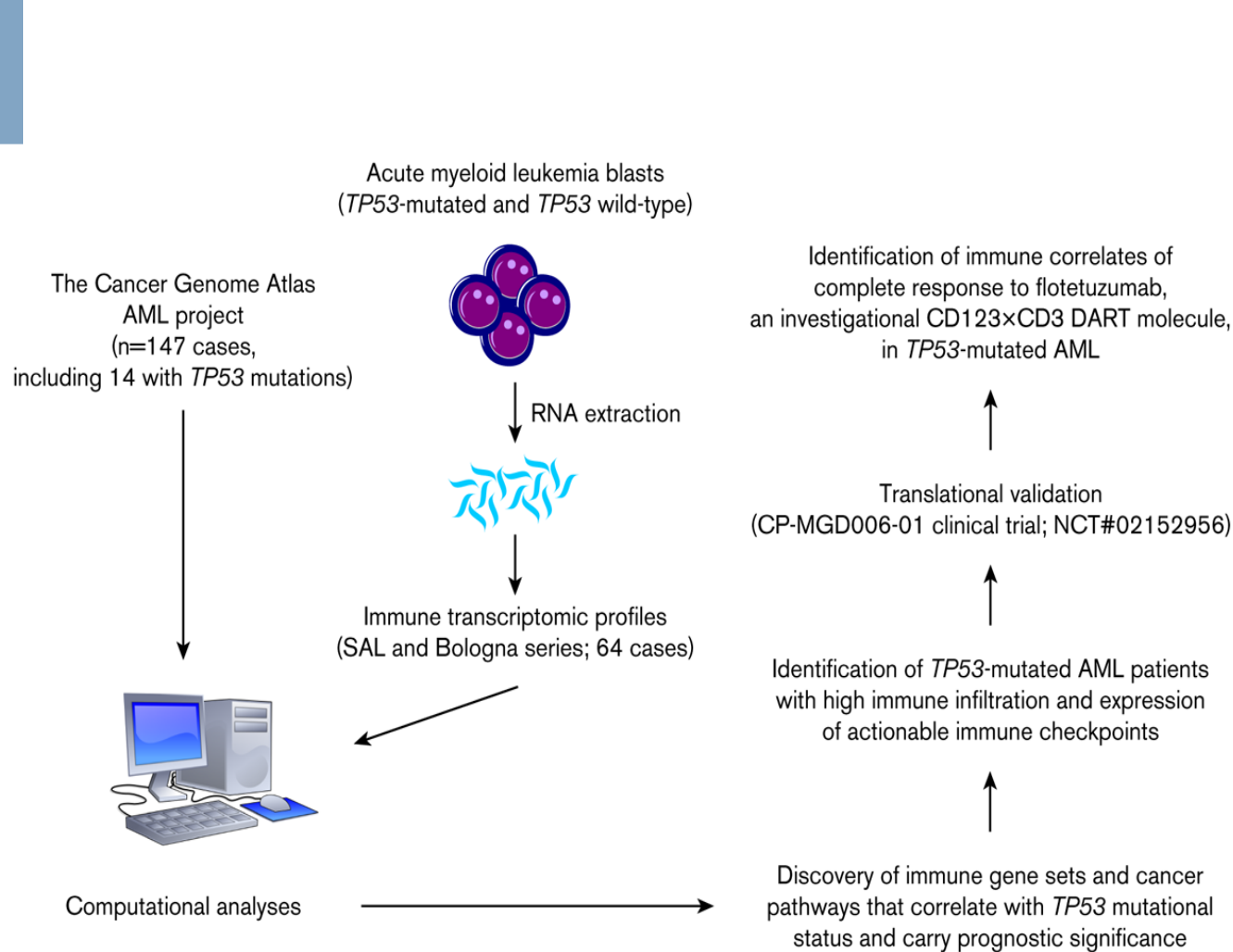
- Status

- The trial failed to meet its primary endpoint of complete remission (CR) rate
- CR rate was 53% higher in eprenetapopt with AZA arm compared to AZA alone, but did not reach statistical significance
  - 33.3% (95% CI: 23.1% - 44.9%) compared to 22.4% (95% CI: 13.6% - 33.4%) in the AZA alone arm (P = 0.13).

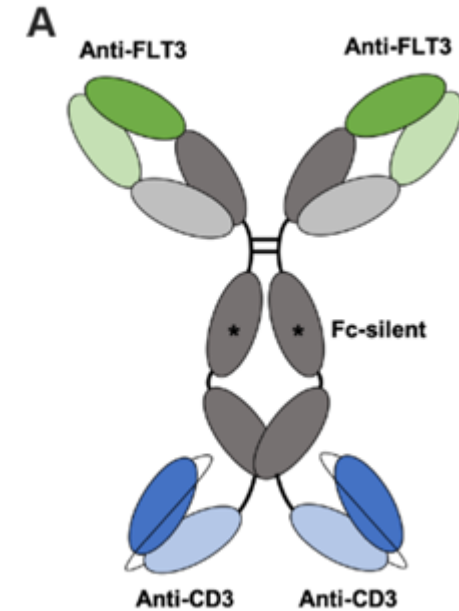
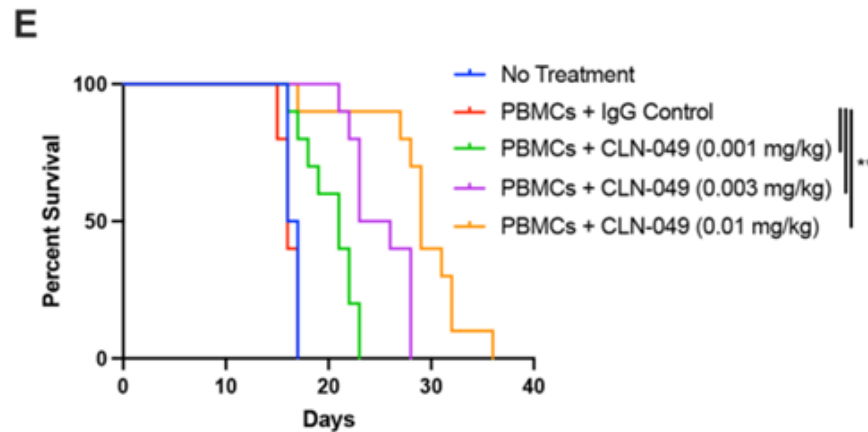
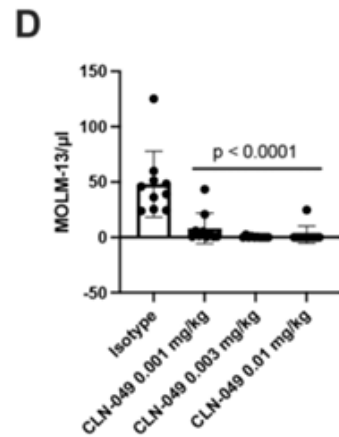
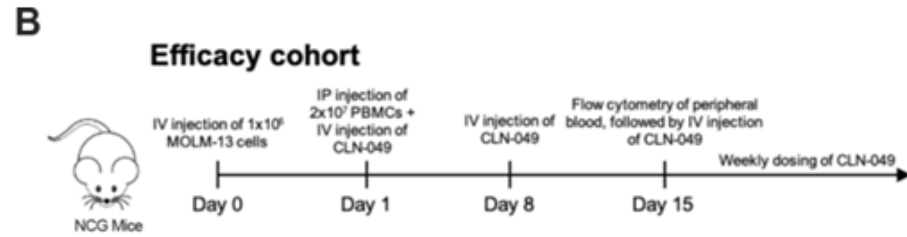
# Rezatapopt (PC14586) for *TP53* mutant MDS/AML?

- p53 reactivator for Y220C, one of 6 most common hotspot mutations
- Only evaluated in solid tumors to date, 2000mg PO daily was RP2D
- Overall safe with nausea/vomiting/Cr increase as most common TRAEs
- In heavily treated solid tumor patients (median lines 4), ORR was 20% and 30% in patients with RAS wildtype tumors (? Specific tumor vs resistant clone) while 0% if co-mutant RAS.
- Ideally will be tested in MDS/AML patients in near future.
- Synergy has been observed with BCL-2 inhibitors.
- Heme US study opened at MDACC (Dinardo C and colleagues, opening at MCC) in combination with azacitidine and ? parallel study in GFM

# TP53 Immune Infiltration has Correlated with Response to Flotetuzumab (CD123 DART)

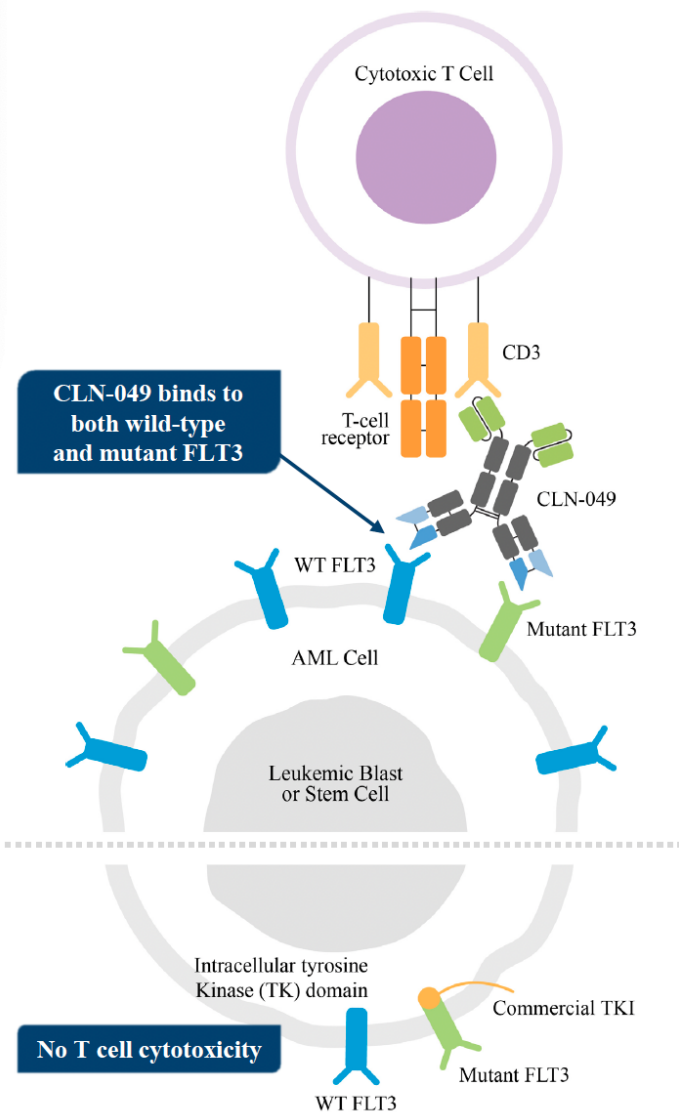


# Novel Targets: T-cell Engager for FLT3

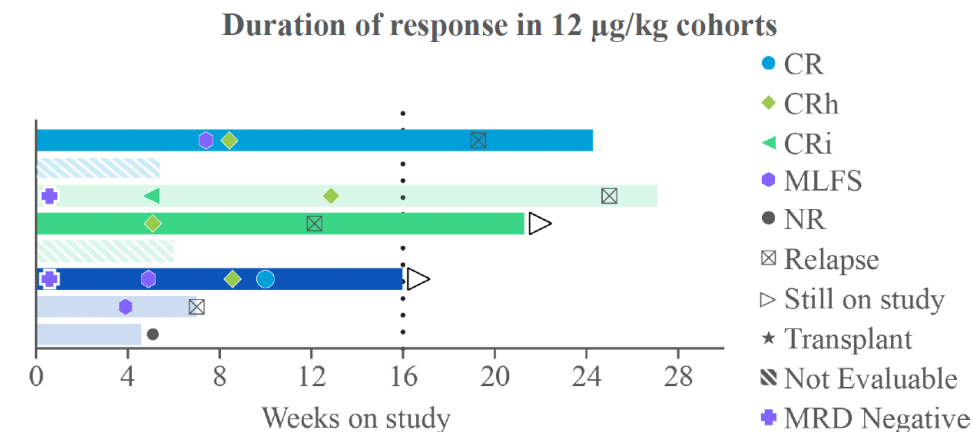


Phase 1 Clinical Trial in R/R AML is Ongoing (Abdul-Hay EHA 2023)

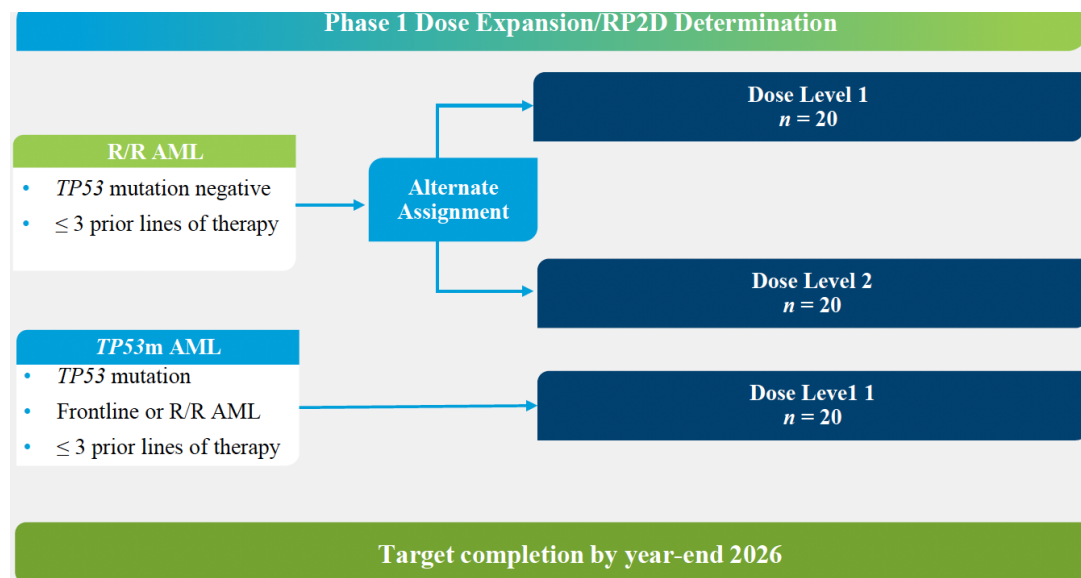
# CLN-049 in R/R AML, significant activity in *TP53* MT disease



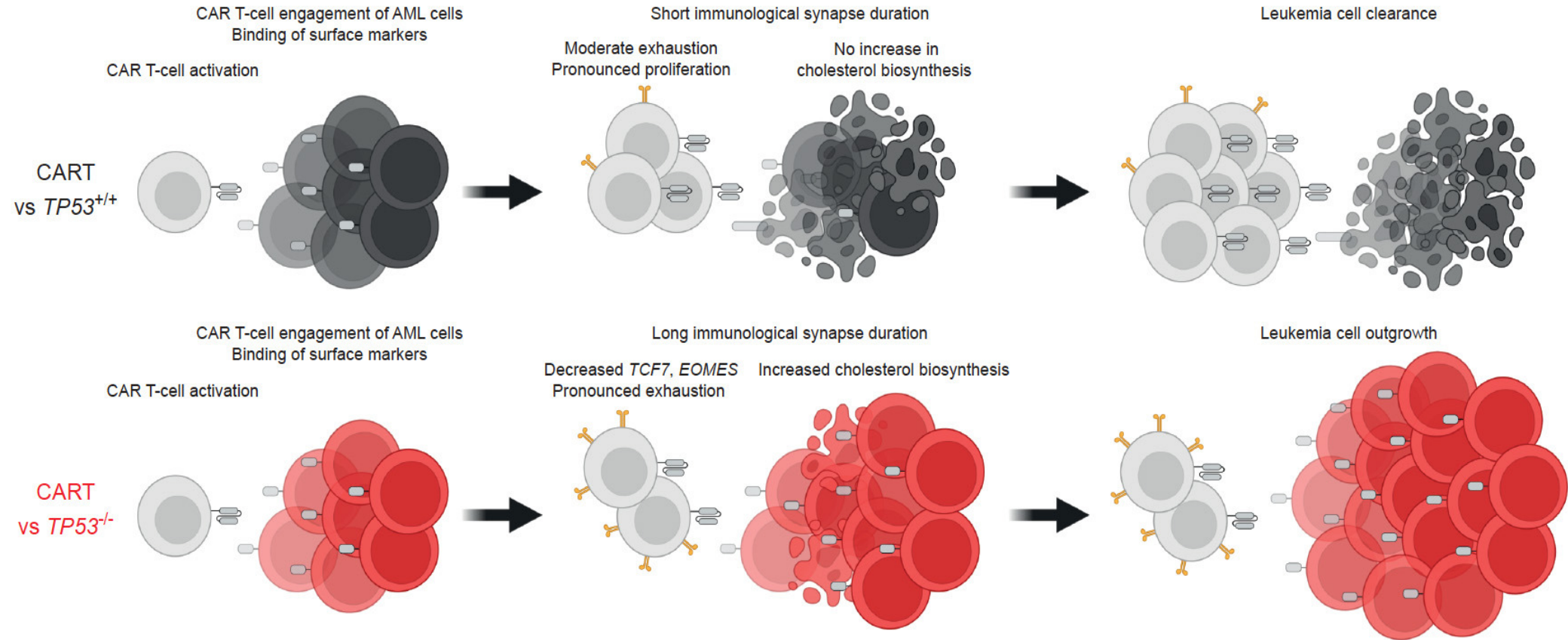
<i>TP53</i> -mutated AML response rate (best response), n (%)	All cohorts N=13	12 µg/kg cohorts N=8
<b>CR</b>	2 (15)	1 (13)
<b>CR+CRh</b>	5 (38)	4 (50)
<b>CRC</b>	5 (38)	4 (50)
<b>ORR</b>	6 (46)	5 (63)



- 4/8 patients with *TP53*-mutated AML treated at the highest TD of 12 µg/kg achieved CR or CRh
- CR+CRh responses were durable beyond 16 weeks in 3 of these patients



# TP53 Deficiency in AML Confers Resistance to CAR T-Cells



Cholesterol pathway identified as a potential therapeutic vulnerability of *TP53*-deficient AML

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## Collaborators across VALIDATE

