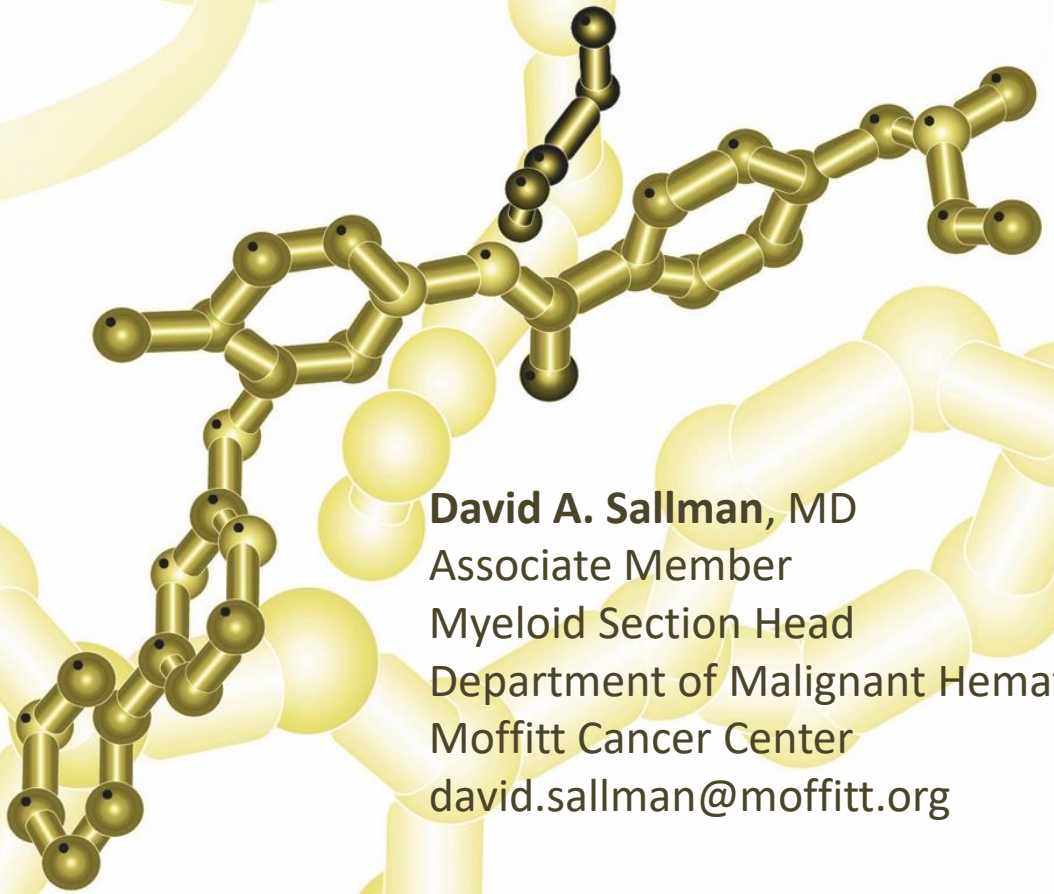
Anti-CD47 MoAbs in AML and MDS



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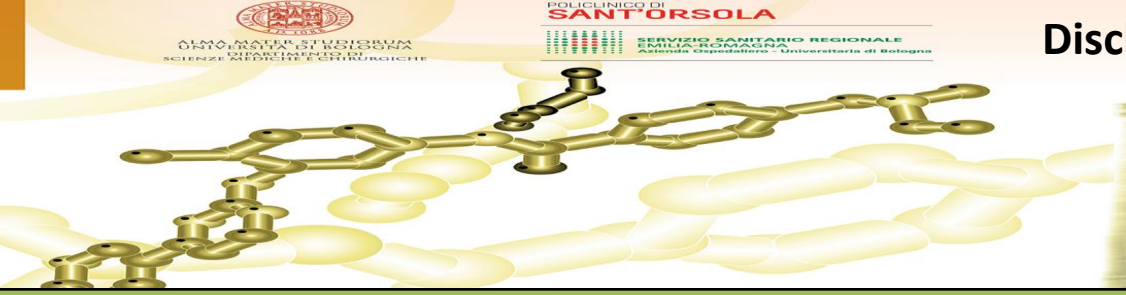
New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024



Disclosures of Dr. Sallman

New Drugs in Hematology

President: Pier Luigi Zinzani
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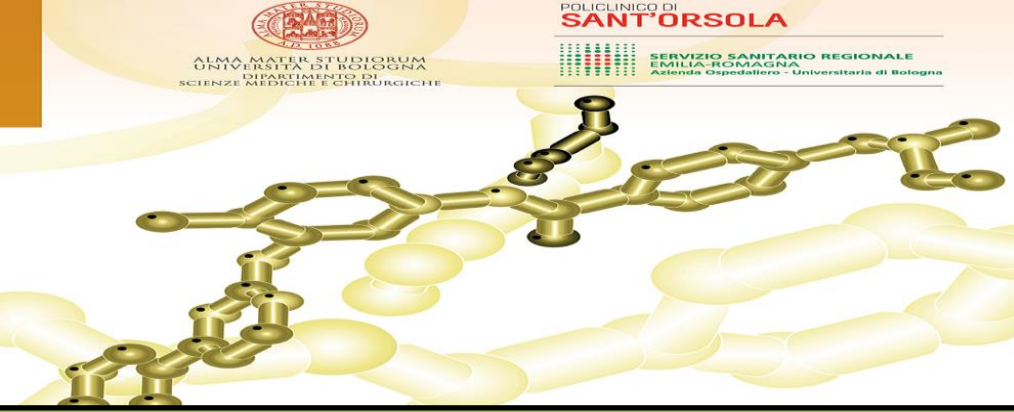
January 15-17, 2024

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X				
Affirmed Gmbh			X				
Froghorn			X				
Gilead			X				
Incyte			X				
Intellisphere, LLC			X				
Molecular Partners AG			X				
Takeda			X				
PGEN Therapeutics, Inc			X				
Zentalis			X				
Avencell						X	
Bluebird Bio						X	
BMS						X	
Dark Blue Therapeutics						X	
Itellia						X	
Kite						X	



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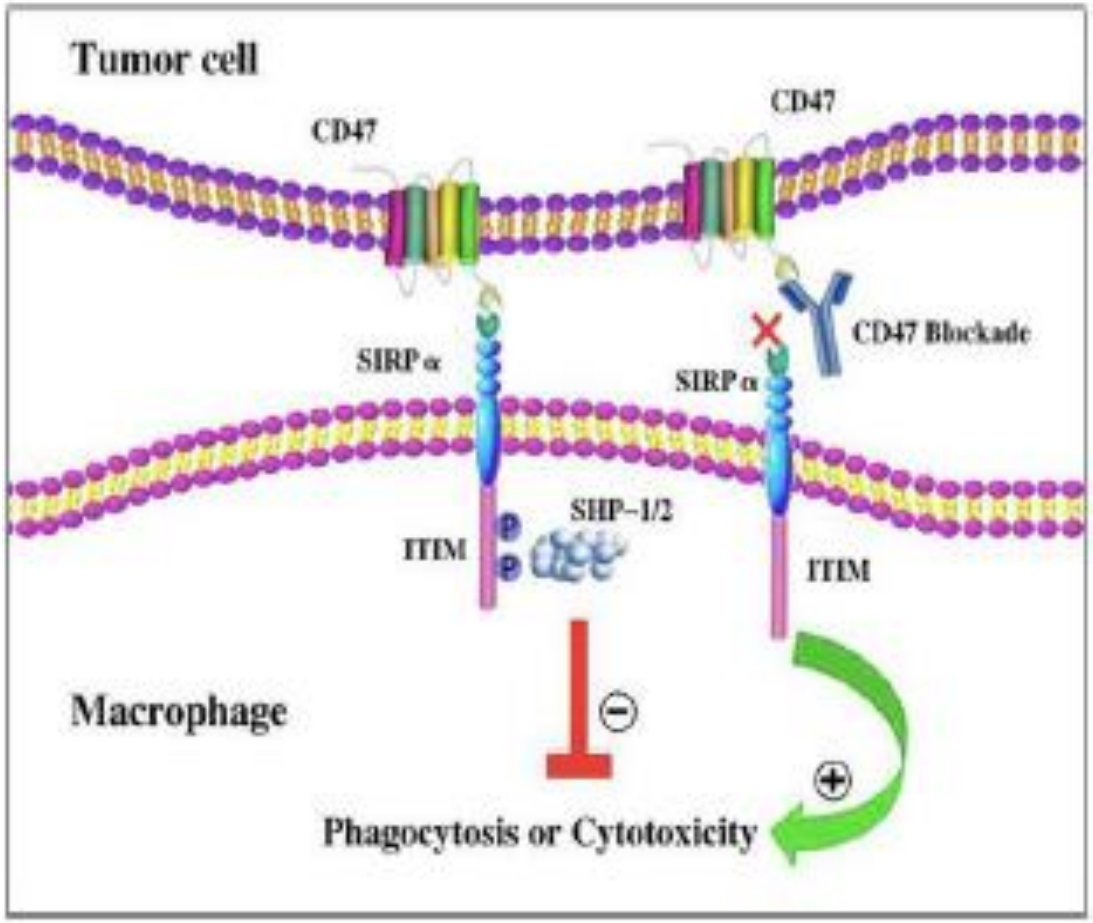
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Jasper Therapeutics						X	
Magenta Therapeutics						X	
NKARTA						X	
Novartis						X	
Orbital Therapeutics						X	
Shattuck Labs						X	
Servier						X	
Syndax						X	
Syros						X	
Aprea	X						
Jazz	X						

Structure and Function of CD47 and SIRPα

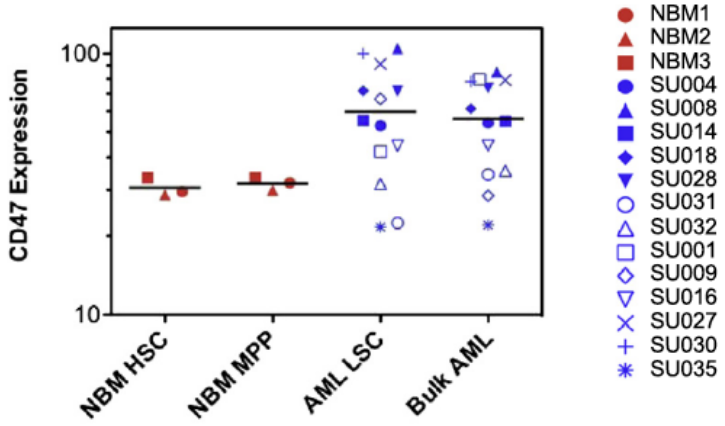
- CD47 is a widely expressed transmembrane protein and serves as the ligand for signal regulatory protein alpha (SIRPα)
- SIRPα is expressed on phagocytic cells including magrophages and dendritic cells
- CD47/SIRPα binding initiates a signal transduction cascade resulting in SHP 1/2 activation and consequent inhibition of phagocytosis
- CD47 helps maintain immunotolerance by non-malignant cells under physiological conditions
- CD47 Blockade can abrogate this suppression signal

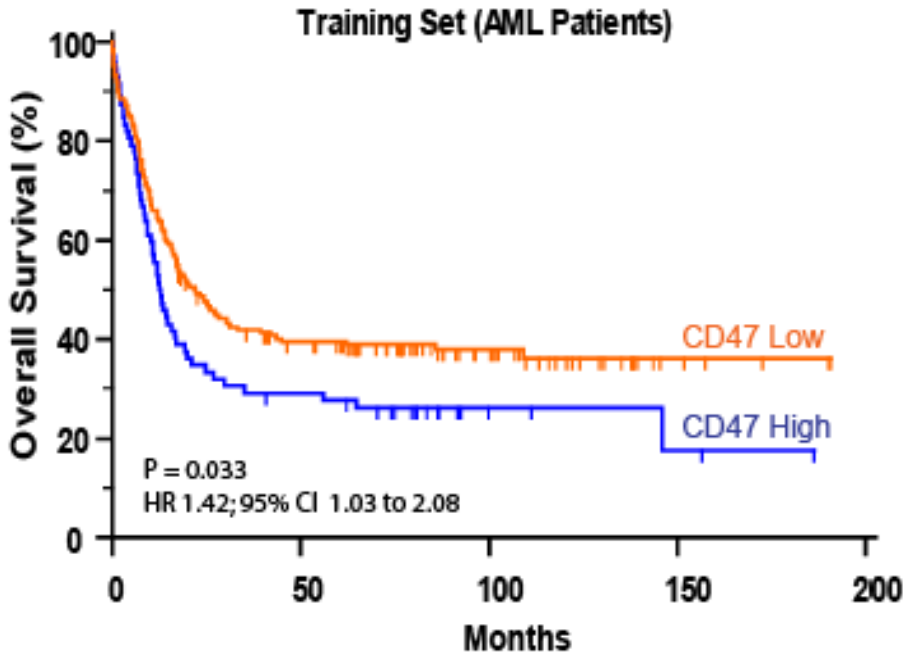


Brown et al., 2001; Blazer et a., J. Exp. Med. 2001
Barclay et al., Nat. Rev. Immunol 2006
Zhang W et al., *Frontiers in Immunology* 2020

Innate Immune System Evasion via CD47

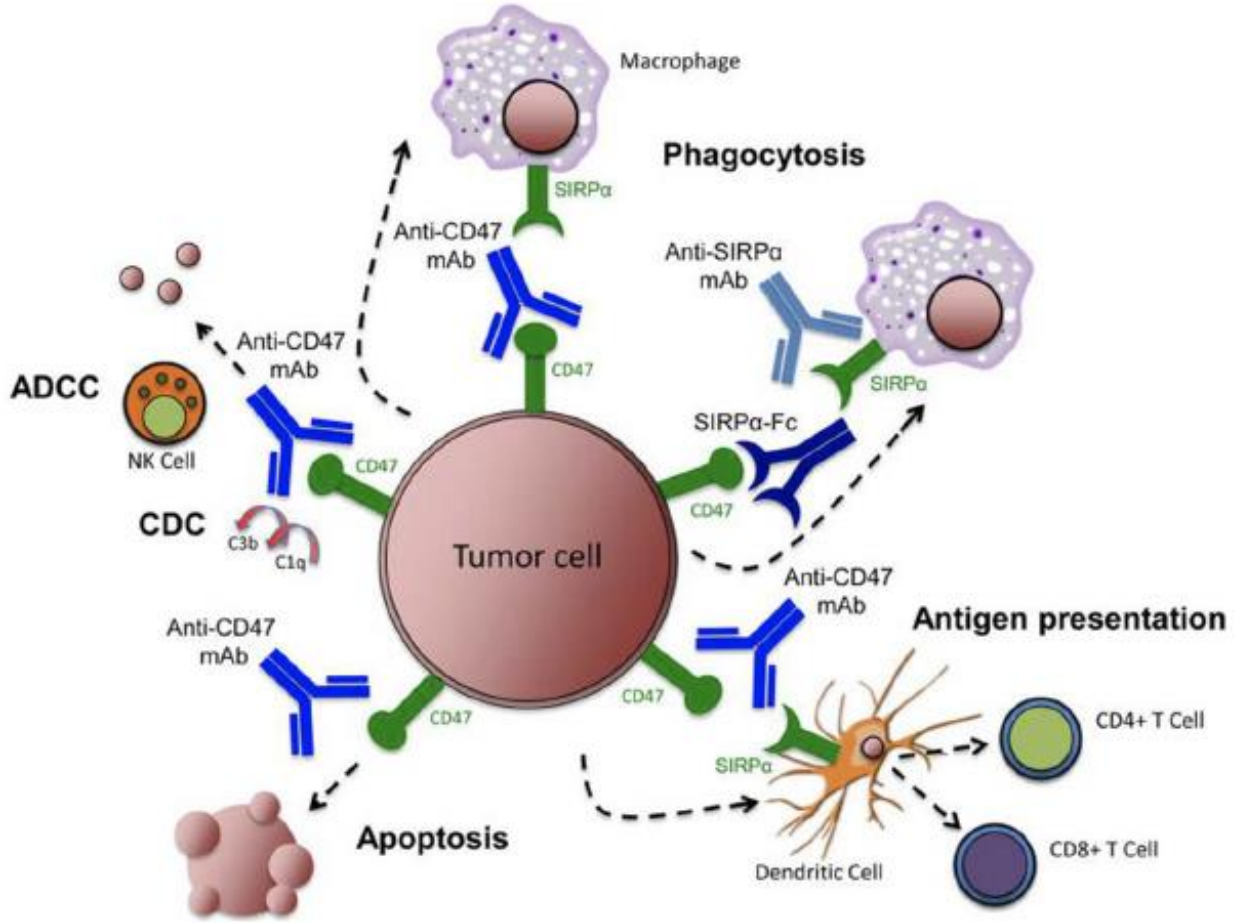
- CD47 is a “do not eat me” signal on cancers that enables macrophage immune evasion
- CD47 is the dominant macrophage checkpoint overexpressed on most cancers
- In AML, CD47 expression is overexpressed on LSC/bulk AML vs normal HSC/MPP
- CD47 leads to a strong fitness advantage in AML LSCs
- Increased CD47 expression predicts worse prognosis in AML patients
- In MDS, increased CD47 expression associated with RAEB disease and higher risk by IPSS





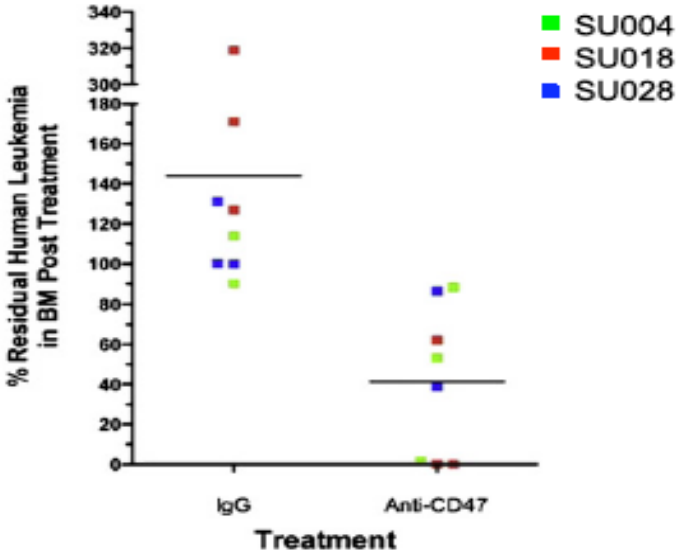
Majeti, Chao et al., Cell 2009;
Jaiswal et al., Cell 2009

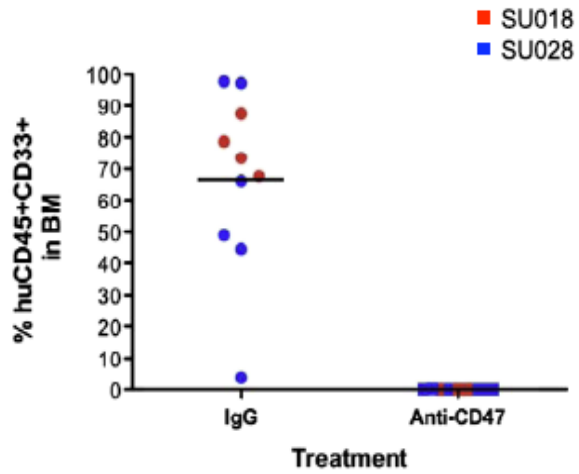
Therapeutic Impact of CD47/SIRPα Blockade in Cancer

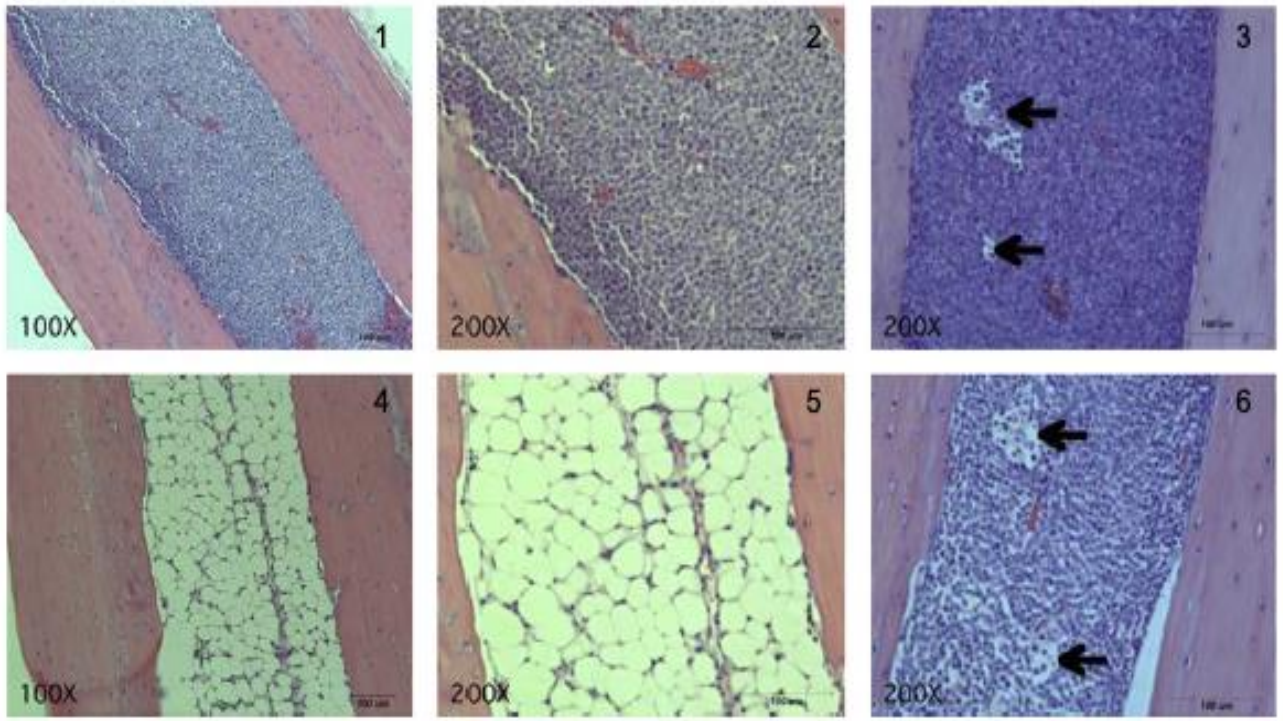


Zhang W et al., *Frontiers in Immunology* 2020; Chao M et al., *Curr Opin Immunol* 2012

Preclinical efficacy of CD47 and AML

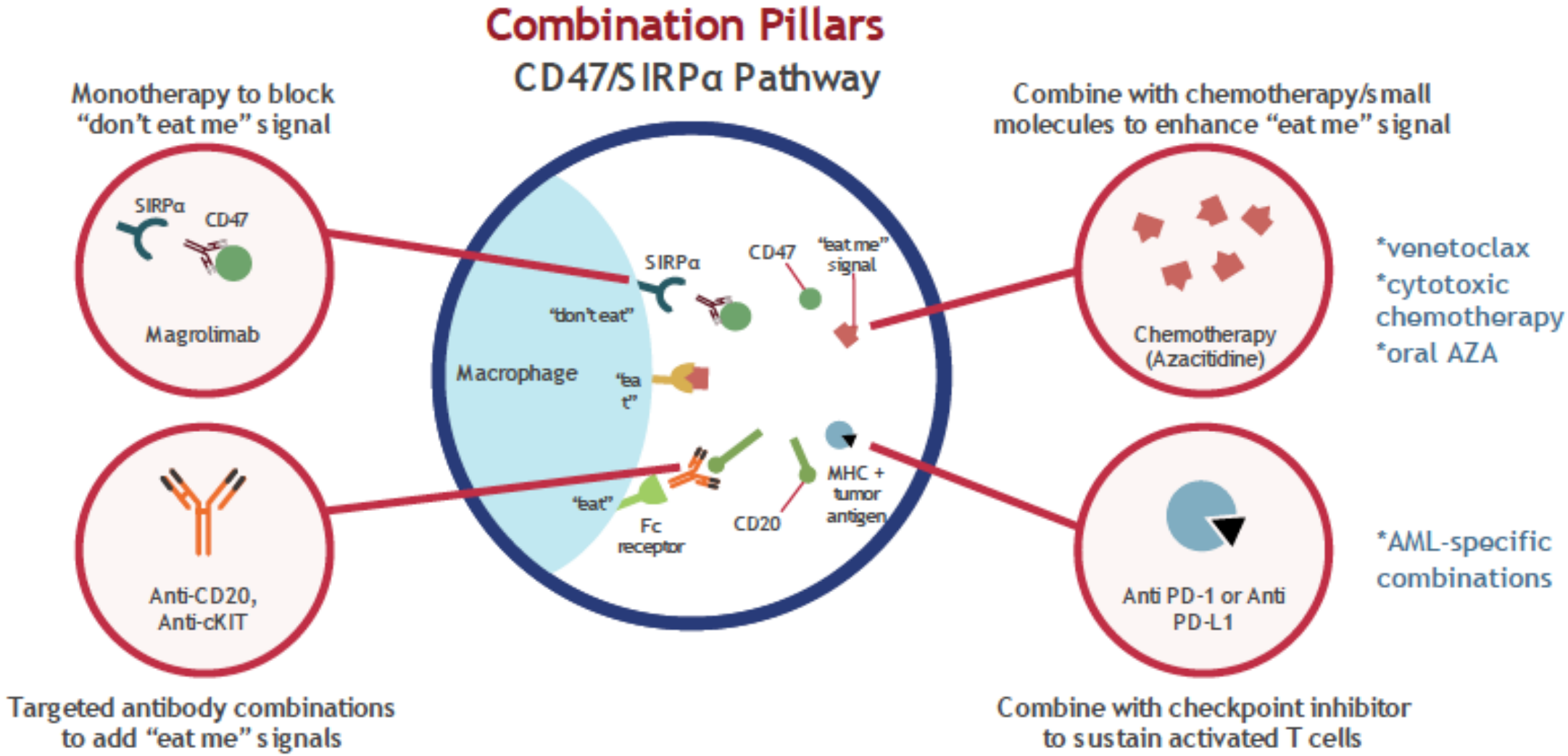






Majeti, Chao et al., *Cell* 2009;

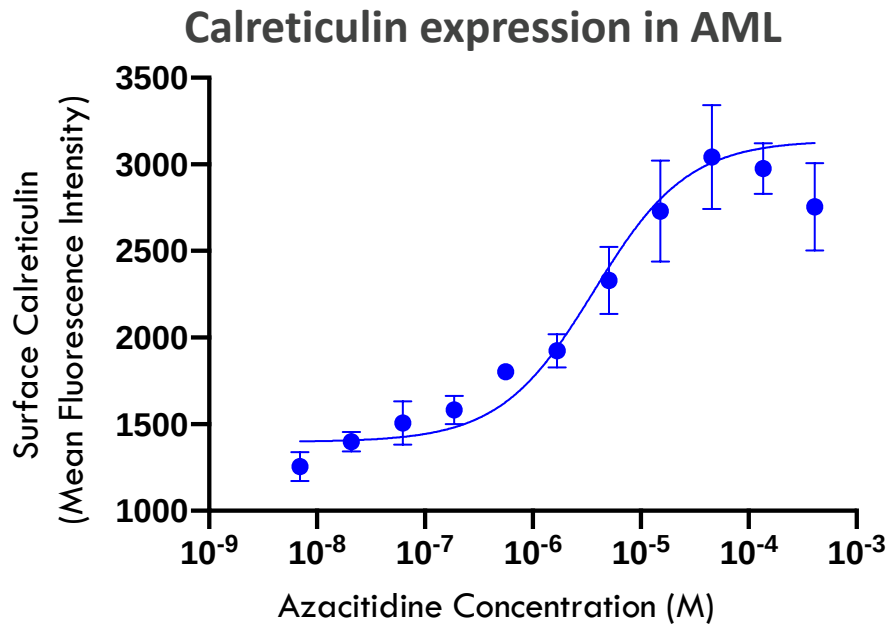
Combination Therapy with CD47 Targeted Therapy

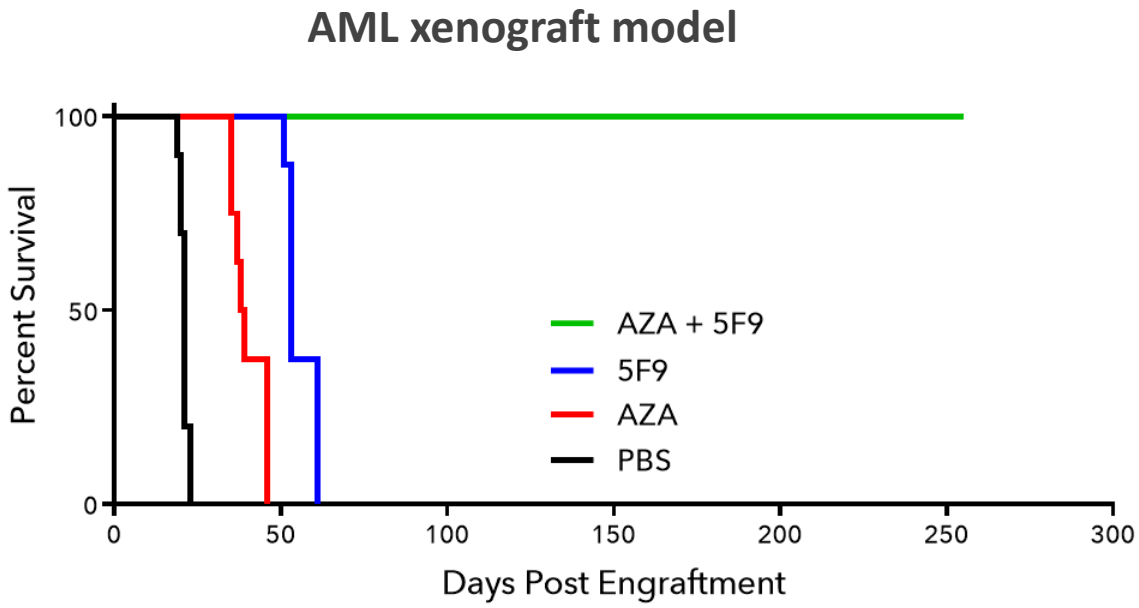


Chao et al., Cell 2010; Sikic et al., JCO 2019; Feng et al., ASH 2019

Magrolimab Synergizes with Azacitidine to Induce Remissions in AML Xenograft Models

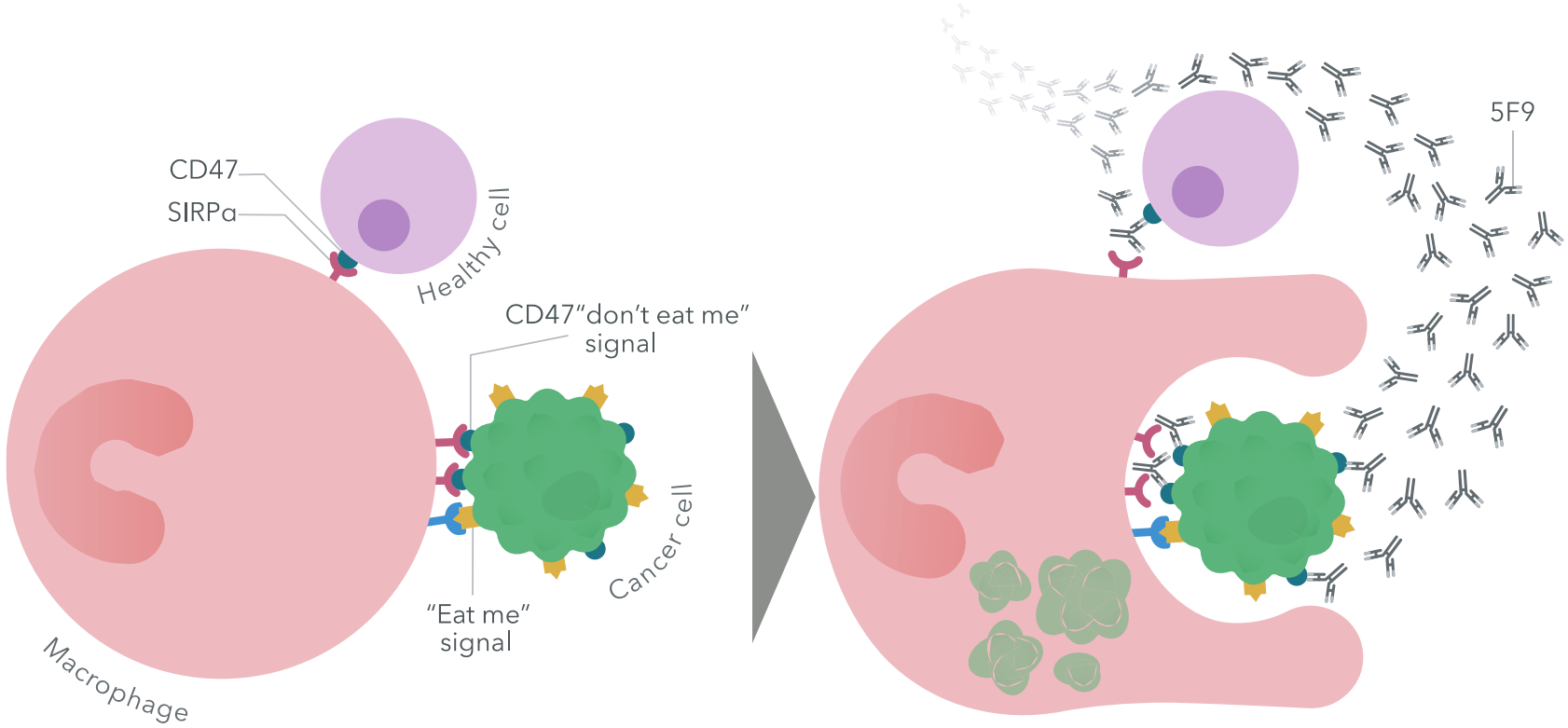
- Azacitidine (AZA) induces pro-phagocytic “eat me” signals like calreticulin on cancer cells
- Increased eat me signals induced by azacitidine synergizes with CD47 blockade of the “don’t eat me” signal leading to enhanced phagocytosis



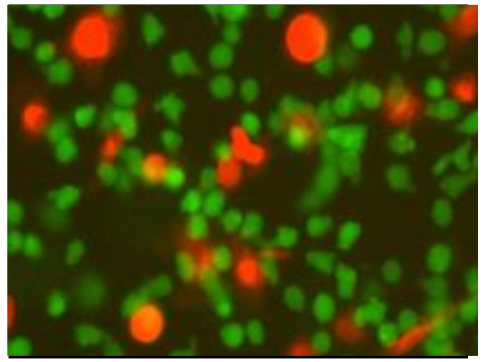


Feng D et al., ASH 2018

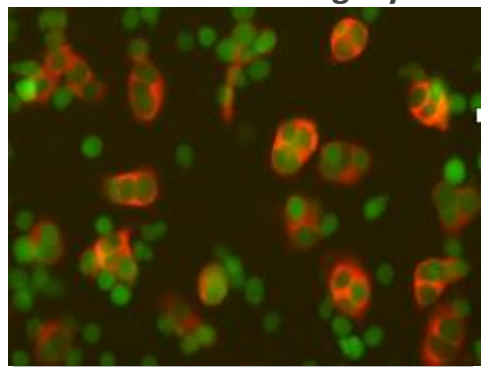
Magrolimab (Formerly 5F9) is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers
- Magrolimab was well tolerated in a UK Phase 1 trial in r/r AML with no MTD reached (Vyas et al., EHA abs 2018)

5F9005 Study Design: Magrolimab in Combination With AZA in MDS and AML

Untreated AML ineligible for induction chemotherapy or untreated MDS intermediate to very high risk by IPSS-R

Magrolimab + AZA Combo Safety Evaluation (N=6)

Magro: 1, 30 mg/kg* weekly
AZA: 75 mg/m^2 D1–7

Expansion

Magro: 1, 30 mg/kg* weekly or Q2W
AZA: 75 mg/m^2 D1–7

Primary objectives

1. Safety of magrolimab alone or with AZA
2. Efficacy of magrolimab + AZA in untreated AML/MDS

Secondary objectives

1. Pharmacokinetics, pharmacodynamics, and immunogenicity of 5F9
2. Additional measures of efficacy (DOR, PFS, OS)

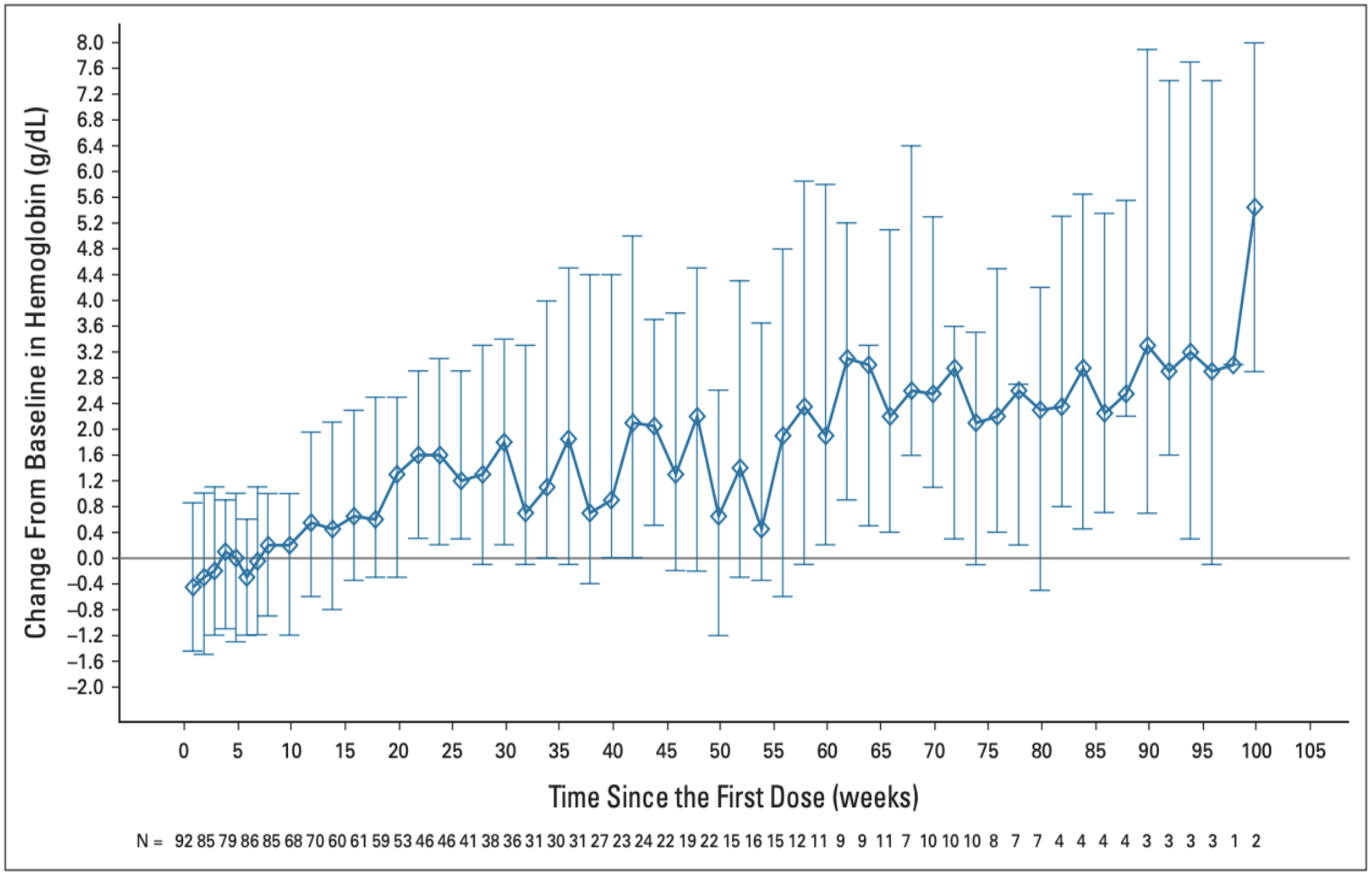
Exploratory objective

To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

- A magrolimab priming dose (1 mg/kg) and dose ramp-up was utilized to mitigate on-target anemia
- Data from the expansion cohort is presented

*Dose ramp-up from 1 mg/kg to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing or 30 mg/kg Q2W starting Cycle 3+.
IPSS-R: Revised International Prognostic Scoring System.

On-Target Anemia Is a Pharmacodynamic Effect and Mitigated with a Magrolimab Priming and Maintenance Dosing Regimen



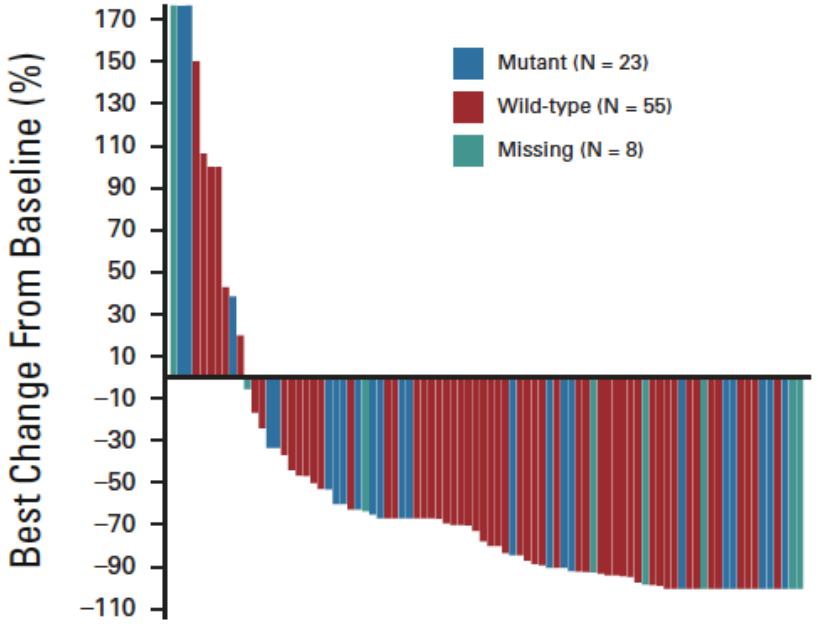
- An initial priming dose mitigated on-target anemia by CD47 blockade, resulting in a transient hemoglobin drop.
- Median hemoglobin change from baseline was –0.7 g/dL (range –3.1 to +2.4) at first post-treatment visit.
- 37 (38.9%) patients were transfusion dependent at baseline; 13 (35.1%) of these converted to RBC transfusion independence.

Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

Magrolimab + AZA Induces High Response Rates in HR-MDS

TABLE 3. Efficacy Outcomes

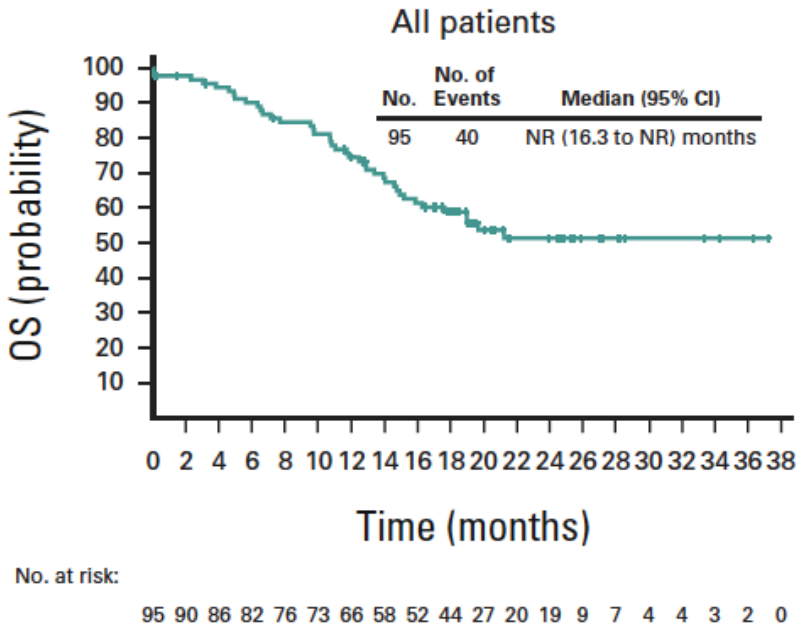
Outcome	All (N = 95[a])	*TP53*-wt MDS (N = 61)	*TP53*-mut MDS (N = 25)
OR rate, %[b]	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4 to 43.0)	31.1 (19.9 to 44.3)	40.0 (21.1 to 61.3)
mCR, %	31.6	37.7	20.0
PR, %	0	0	0
SD with HI, %	10.5	9.8	8.0
Duration of CR, months, median (95% CI)	11.1 (7.6 to 13.4)	12.9 (8.0 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, %[c]	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)

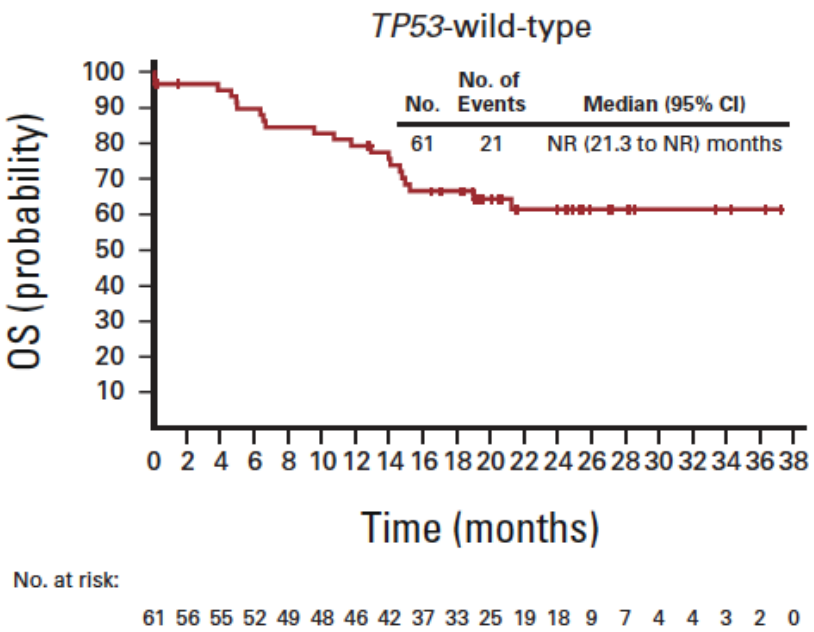


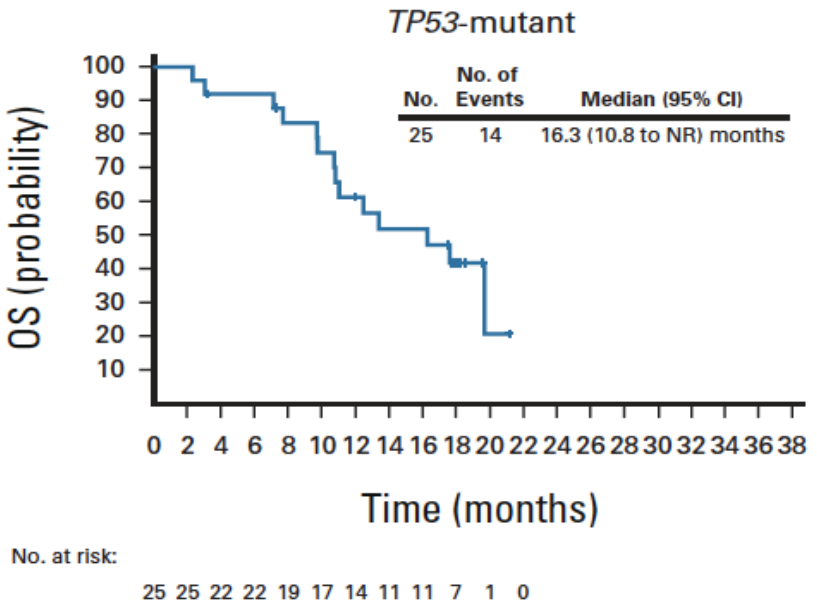
Sallman D et al., JCO. 2023

Median OS in *TP53*-Wild Type and Mutant HR-MDS Patients

– With a median follow-up of 17.1 months, median OS was not reached and was 16.3 months in *TP53*-mut MDS.

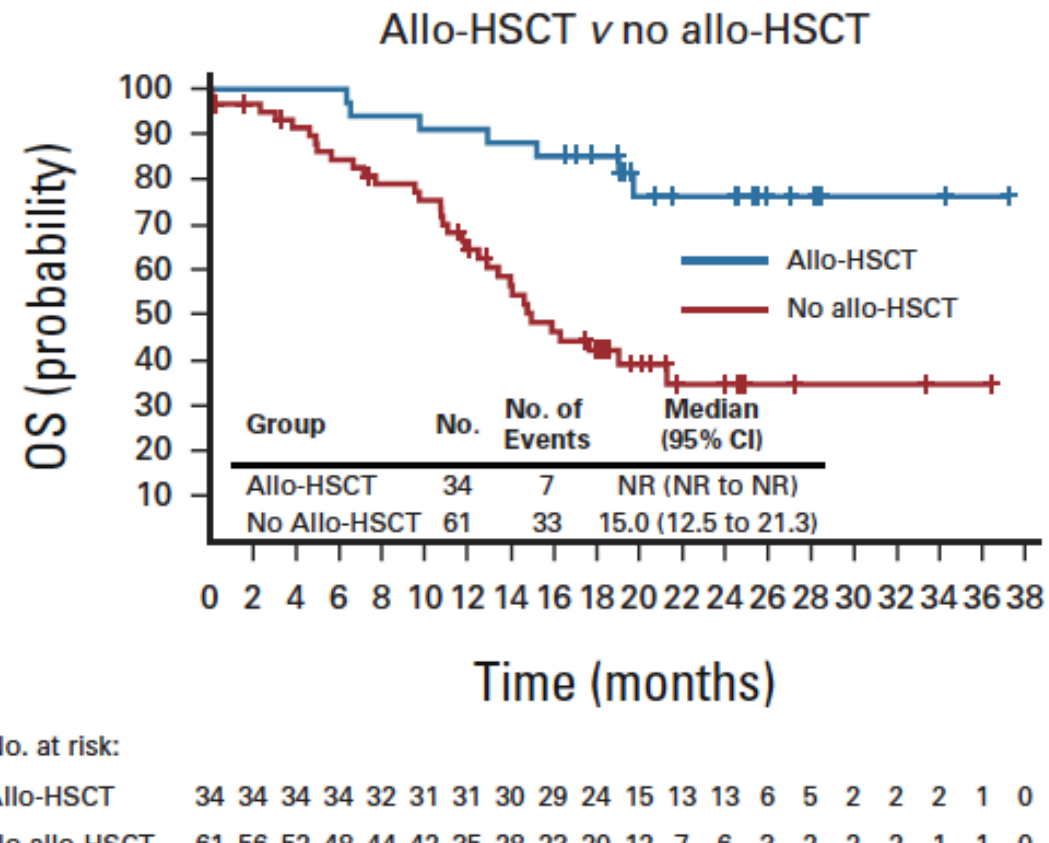






Sallman D et al., JCO. 2023

Stem Cell Transplant Outcomes Are Encouraging in HR-MDS Patients Treated with Magrolimab + AZA



Kaplan–Meier Survival Estimates

All Patients	SCT (N = 35)	No SCT (N = 60)
Median follow-up, months	19.6	12.9
Median OS (95% CI)	NR (NR, NR)	14.8 (11.9, 21.3)
1-year OS, % (95% CI)	91.4 (75.7, 97.2)	64.0 (49.9, 75.1)
2-year OS, % (95% CI)	77.3 (57.3, 88.8)	33.9 (20.0, 48.3)

Sallman D et al., EHA 2022; Sallman D et al., JCO. 2023

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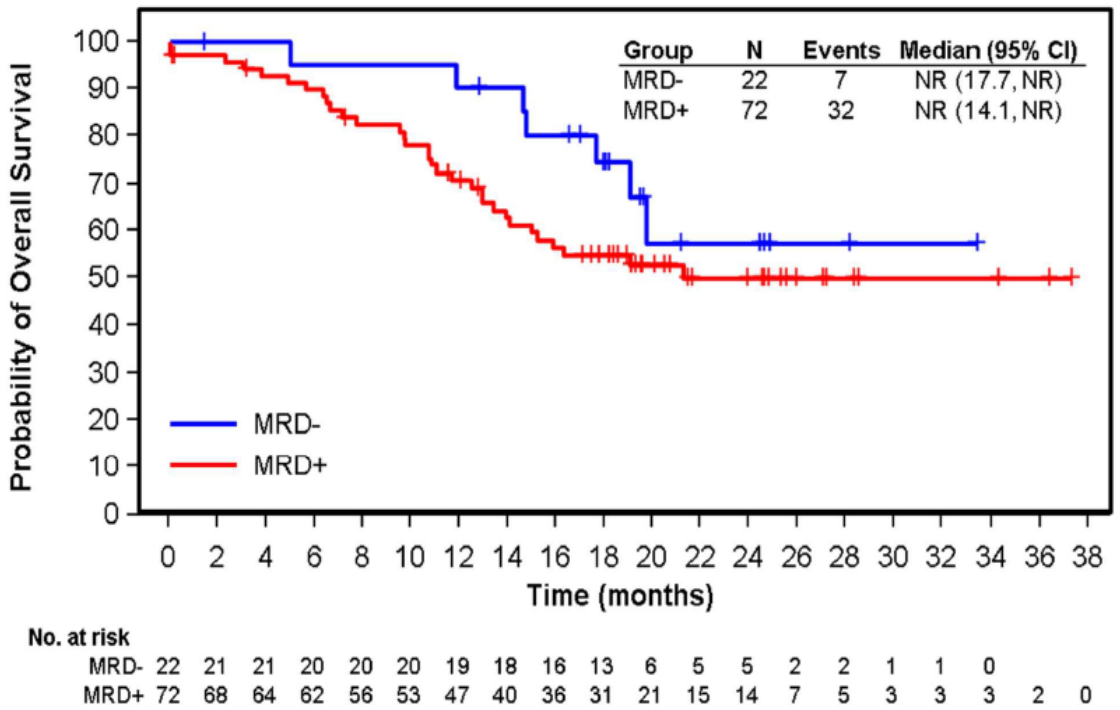
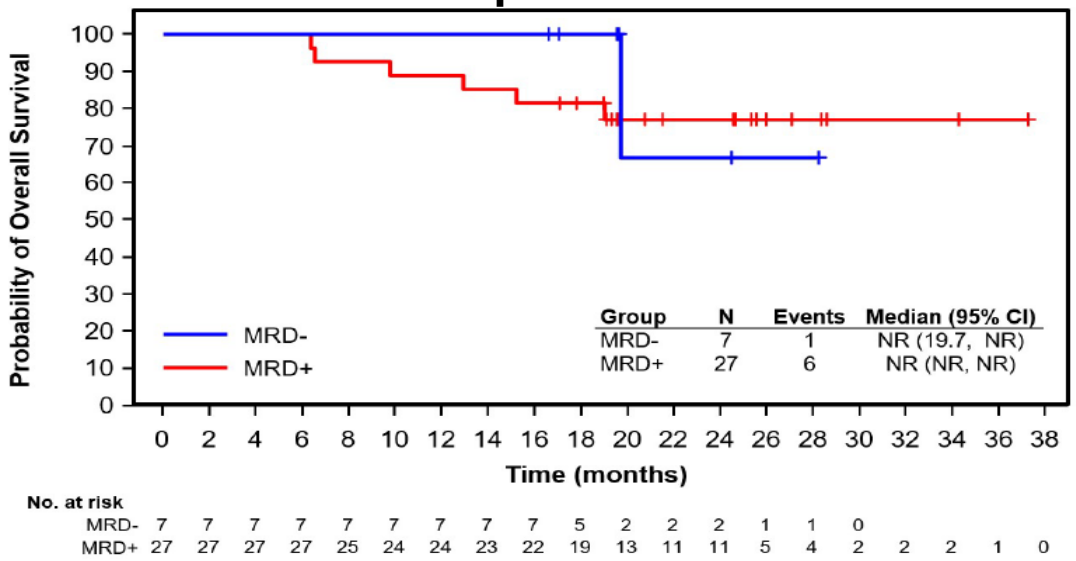
Prognostic Value of MRD in MDS

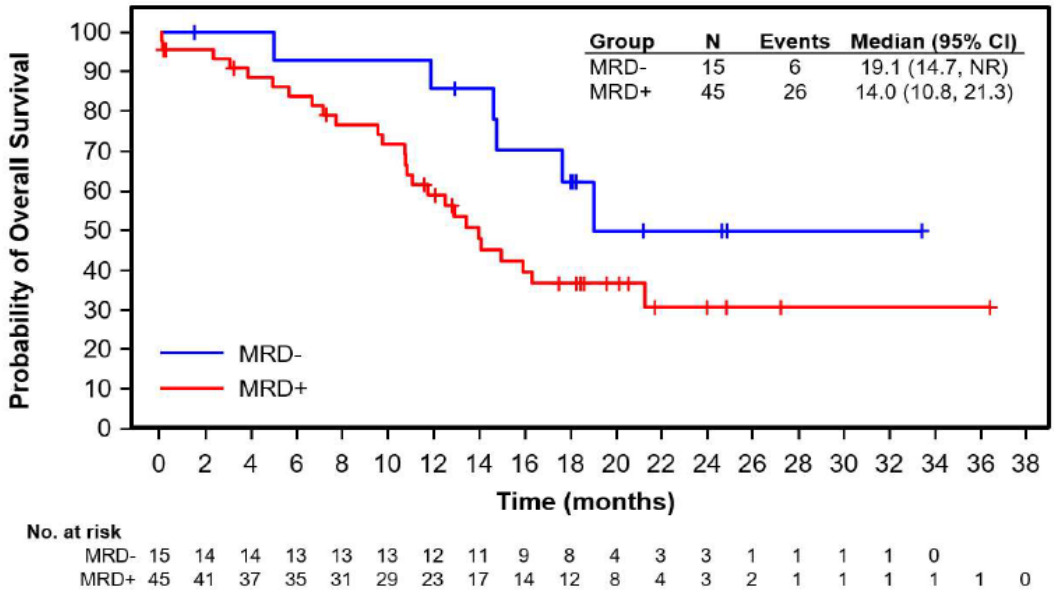
Total Cohort



Transplanted Cohort



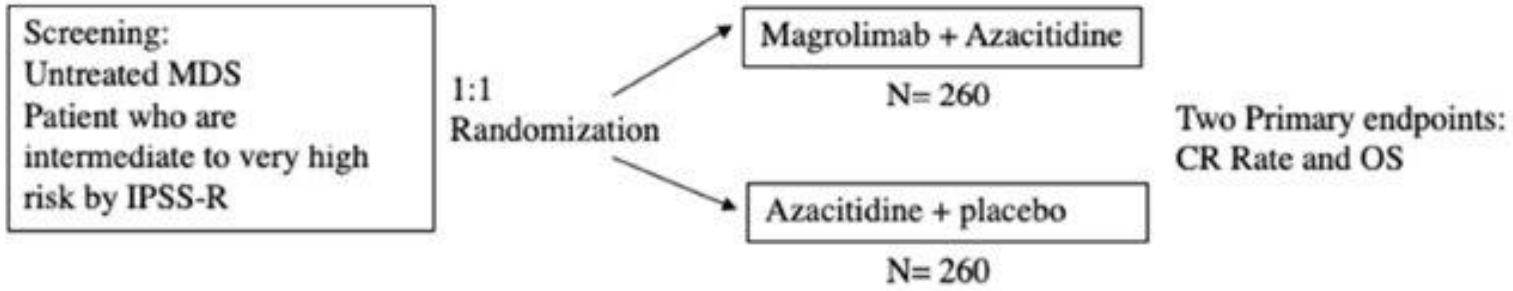
Non-Transplanted Cohort



Sallman D et al., JCO. 2023

ENHANCE Randomized Phase 3 MDS Study

Figure 4. Study 5F9009 Schematic



Magrolimab (or saline placebo) dosing:
Cycle 1:
- Priming (1 mg/kg) on Days 1 and 4
- 15 mg/kg on Day 8
- 30 mg/kg Days 11, 15, 22

Cycle 2: 30 mg/kg Days 1, 8, 15, 22
Cycle 3 and onward: 30 mg/kg Q2W

Azacitidine dosing:
75 mg/m^2 IV or SC Days 1-7 (or Days 1-5 and 8-9) every cycle

Cycles are 28 days long

ENHANCE Closed for Futility; Data to be presented at an upcoming meeting

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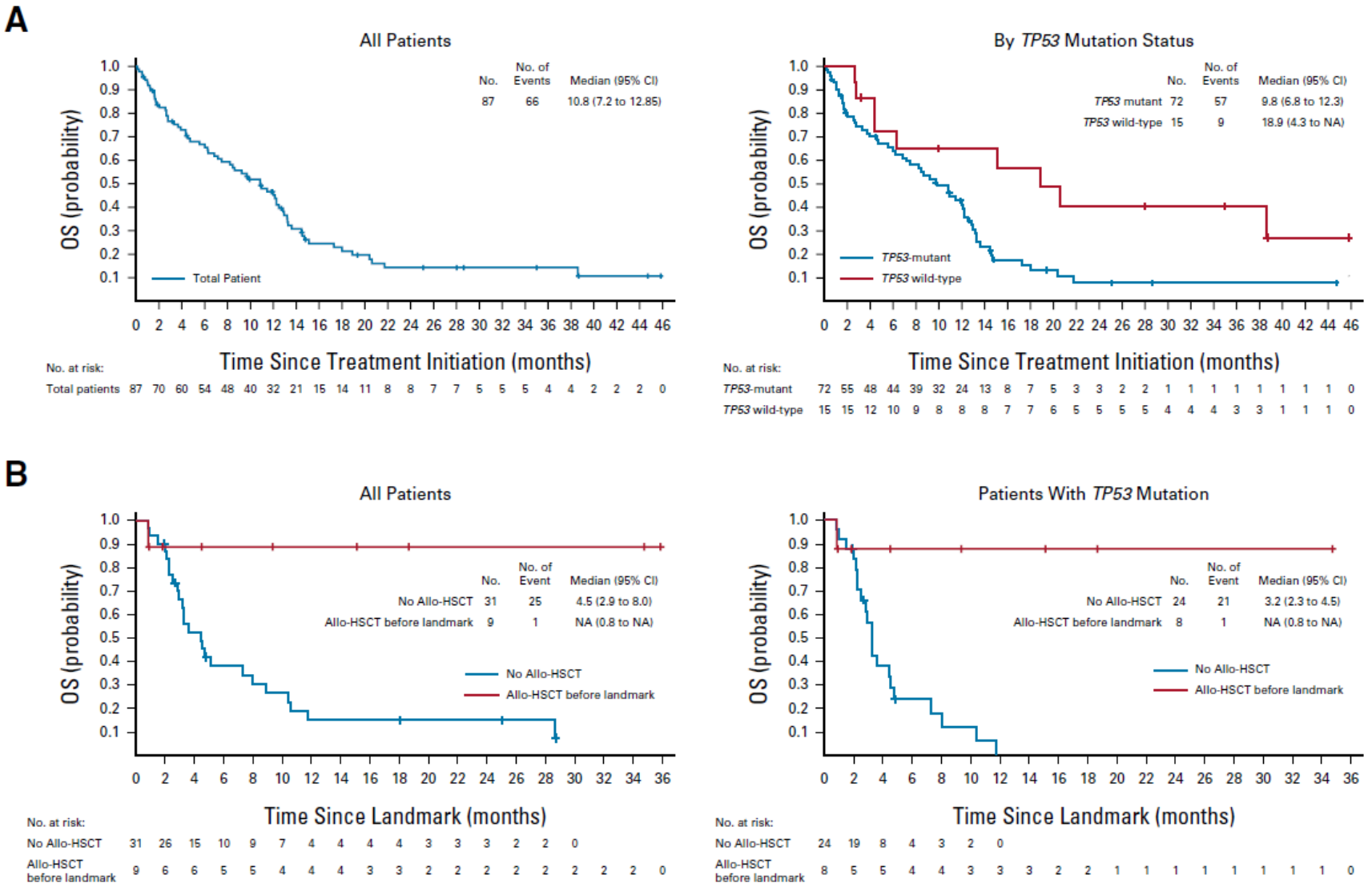
Magrolimab in Combination with AZA Demonstrated Encouraging Response Rates in *TP53*-mut AML

Outcome	*TP53*-Mutant (n = 72)	*TP53* Wild-Type (n = 15)	All Patients (ITT; N = 87)
ORR,[a] % (95% CI)	47.2 (35.3 to 59.3)	46.7 (21.3 to 73.4)	47.1 (36.3 to 58.1)
CR, % (95% CI)	31.9 (21.4 to 44.0)	33.3 (11.8 to 61.6)	32.2 (22.6 to 43.1)
MRD−CR[b]	n = 12/23	n = 4/5	n = 16/28
% (95% CI)	52.2 (30.6 to 73.2)	80.0 (28.4 to 99.5)	57.1 (37.2 to 75.5)
CRh, No. (%)	1 (1.4)	0	1 (1.1)
CRi, No. (%)	5 (6.9)	0	5 (5.7)
CR or CRh, No. (%)	24 (33.3)	5 (33.3)	29 (33.3)
CR or CRi or CRh, No. (%)	29 (40.3)	5 (33.3)	34 (39.1)
PR, No. (%)	4 (5.6)	1 (6.7)	5 (5.7)
MLFS, No. (%)	1 (1.4)	1 (6.7)	2 (2.3)
SD, No. (%)	13 (18.1)	5 (33.3)	18 (20.7)
DOR, months, median (95% CI)	7.7 (6.5 to 10.1)	18.7 (5.7 to NR)	8.7 (7.4 to 10.9)
DCR, months, median (95% CI)	7.6 (4.7 to 9.7)	31.3 (18.7 to 31.3)	9.6 (5.1 to 10.9)
Duration of CR/CRi, months, median (95% CI)	7.7 (5.3 to 10.4)	31.3 (18.7 to 31.3)	9.6 (7.5 to 11.5)
EFS, months, median (95% CI)	3.7 (2.0 to 9.2)	2.9 (0.0 to 20.4)	3.7 (2.1 to 7.3)
OS, months, median (95% CI)	9.8 (6.8 to 12.3)	18.9 (4.3 to NR)	10.8 (7.2 to 12.8)
Received allo-HSCT, No. (%)	8 (11.1)	2 (13.3)	10 (11.5)

Daver N ….. Sallman D et al., EHA 2022; *JCO In Press* 2023

Overall Survival in AML



Daver N ….. Sallman D et al., EHA 2022; *JCO* 2023

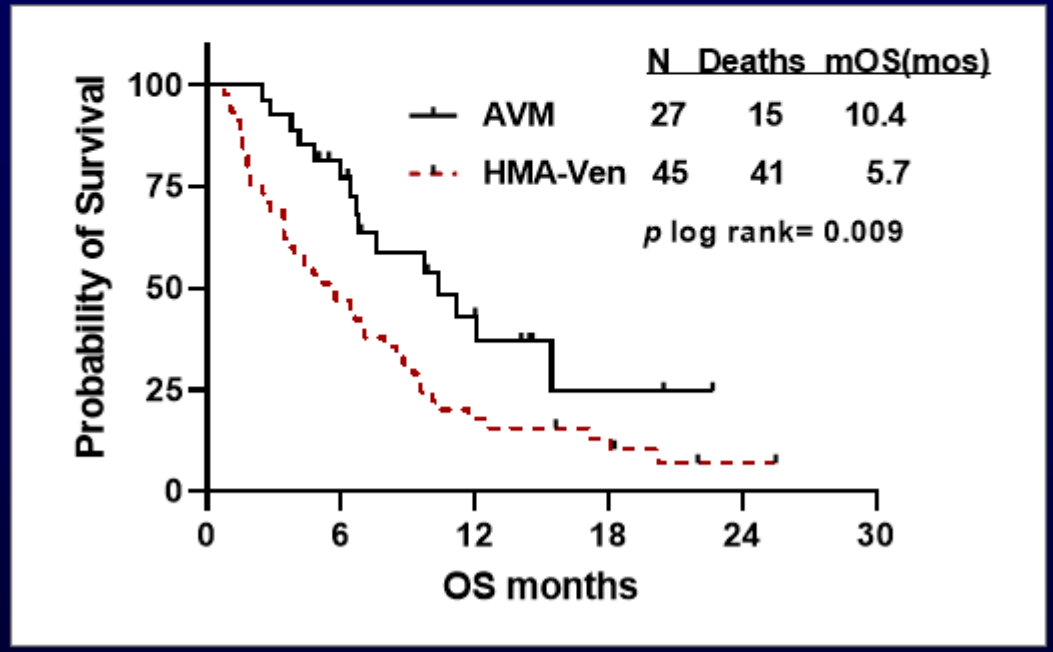
Triplet Azacitidine + Venetoclax + Magrolimab

Parameters		Full Frontline
		N=43
Overall response	CR CRi CR + CRi	21 (49) 10 (23) 31 (72)
	MLFS	4 (9)
MRD-ve best responses#	FCM-CR/CRi	16/28 (67)#
Cytogenetic responses*	CCyR	11/21 (52)*
Time to response (days)	First response Best response	23 [19-105] 51 [20-130]
Counts recovery (days)	ANC ≥ 500/cu mm Platelet ≥ 100 x 10^9/L	36 [16-88] 32 [0-74]
Cycles on therapy		3 [1-17]
Mortality: - 4 week - 8 week		0 (0) 0 (0)

Amongst CR/CRi patients with longitudinally MRD evaluable samples * Amo

Adjusted HR for AVM arm for death= 0.41, 95% CI=0.18-0.88

Comparison of overall survival (unmatched groups)



Daver N et al., ASH 2022

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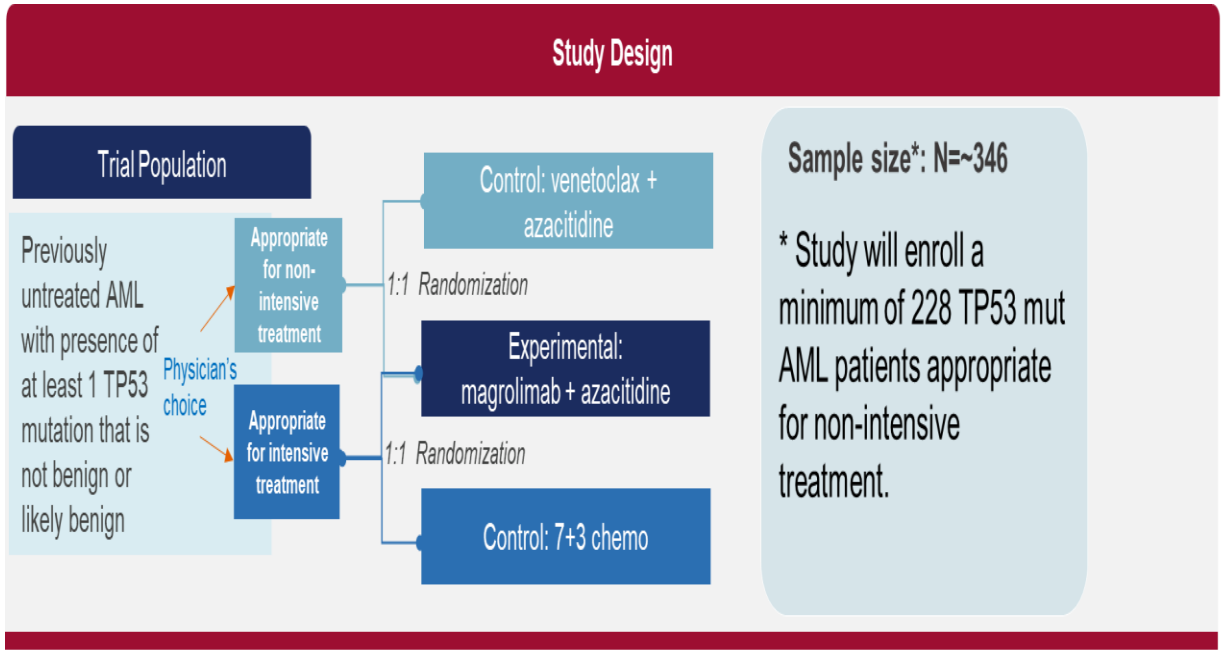
Ongoing Phase 3 Studies with Magro in FL AML

Phase III AZA+Magro vs Investigator Choice in TP53 AML (ENHANCE-2)



Stratification:

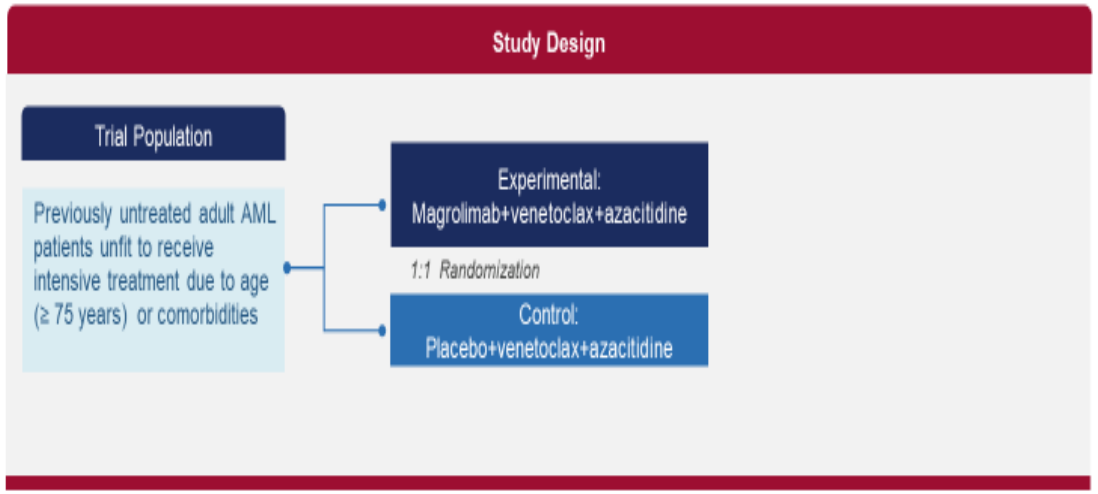
1) Appropriateness for non-intensive therapy vs. intensive therapy
2) Age <75 vs. ≥75
3) Geographic region: US vs. outside the US

Endpoints:

- **Primary endpoint:** OS in TP53 mut AML population appropriate for non-intensive treatment
- **First secondary endpoint (alpha controlled):** OS in all TP53 mut AML population
- **Other key secondary endpoints (alpha controlled):** EFS, Transfusion independence, CR/CR_{MRD-}, PRO in all TP53 mut AML population

Phase III AZA+VEN+Magro vs AZA+VEN in older/unfit AML (ENHANCE-3)

ENHANCE-3: Phase 3 study of 1L unfit All Comer AML with magrolimab +venetoclax+ azacitidine



Endpoints:

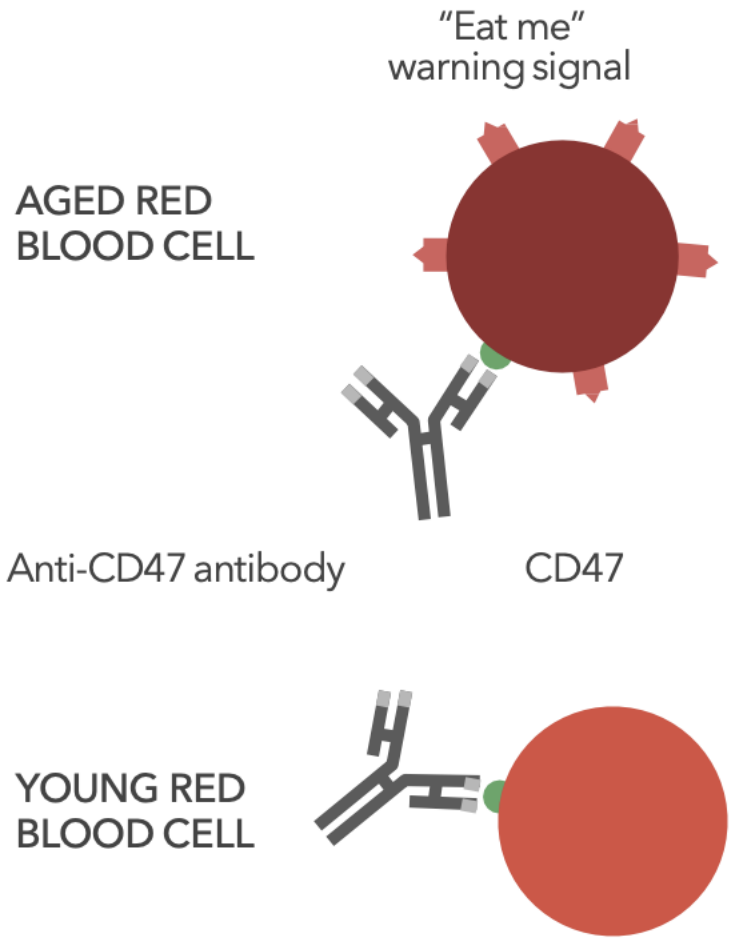
Primary endpoint: CR, Overall survival

Secondary endpoints: 1. MRD-ve CR 2.CR+CRh, 3. Duration of CR, 4. Duration of CR+CRh 5. Transfusion independence 6. EFS 6. QOL/PRO

Unfortunately ENHANCE 2 Trial Closed for Futility 9/2023

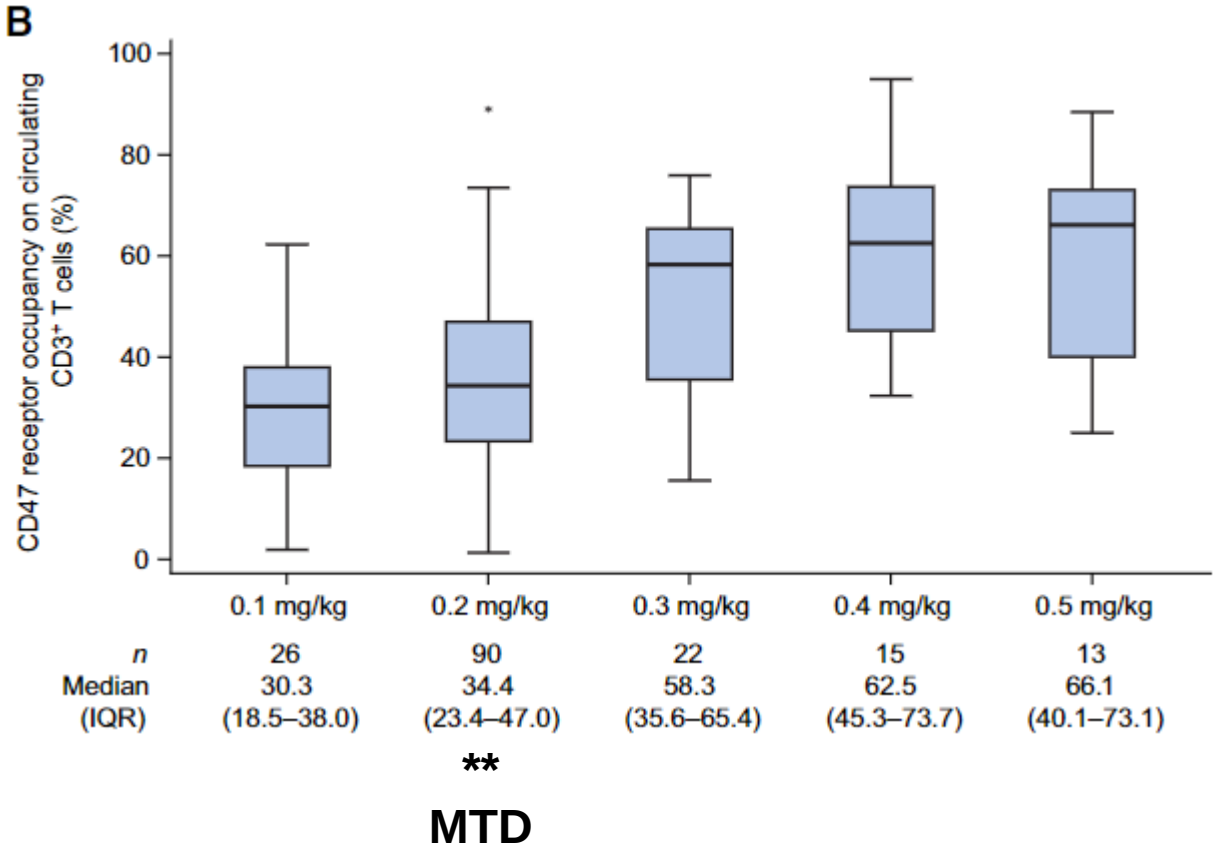
On Target Anemia and Mitigation Strategies

- Aged RBCs express pro-eat me signals whereas young RBCs do not leading to clearance of senescent RBCs
- Anemia Mitigation via:
  - Priming strategy (e.g. magrolimab)
  - RBC pruning process of CD47
  - Decrease/eliminate RBC affinity (majority of agents other than magrolimab)
  - Novel platforms (prodrug or tumor targeted nanoparticles)



Advani R et al., *NEJM* 2018; Chao M et al., *Curr Opin Immunol* 2012; Ishikawa-Sekigami T, *Biochem Biophys Res Commun* 2006

TTI-621 and TTI-622



- TTI-622 (maplirpacept) is a SIRPα-IgG4 Fc and has several concepts evaluating in hematologic malignancies (unclear if ongoing development in MDS/AML)

Ansell S et al., CCR 2021

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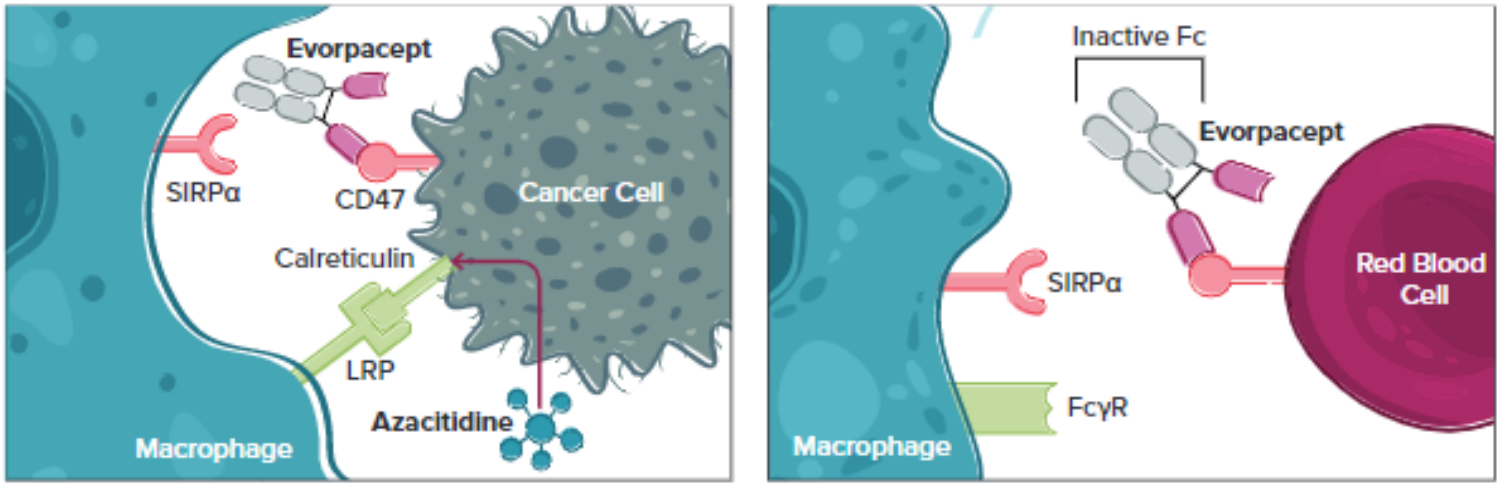
Evorpacept (ALX148) – ASPEN-02 Study



	Previously Untreated HR-MDS (N=6)	Previously Untreated HR-MDS with TP53 Mutation (N=5)	Relapsed/Refractory MDS (N=9)[#]
ORR	3 (50%)	3 (60%)	5 (56%)*
CR	2 (33%)	2 (40%)	0
PR	0	0	0
Marrow CR	1 (17%) with HI	1 (20%) with HI	5 (56%)*
HI	0	0	0
SD	2 (33%)	1 (20%)	2 (22%)
PD	1 (17%)	1 (20%)	1 (11%)

Data Cutoff 25Oct2021; Response evaluable population (n=15); *Includes 3 unconfirmed responses; [#]1 subject had G5 event unrelated to treatment prior to first disease assessment; **ORR** – Objective response rate; **CR** – Complete response;

ASPEN-05 Triplet Study with ven + aza without data reported to date; no current MDS/AML trials accruing

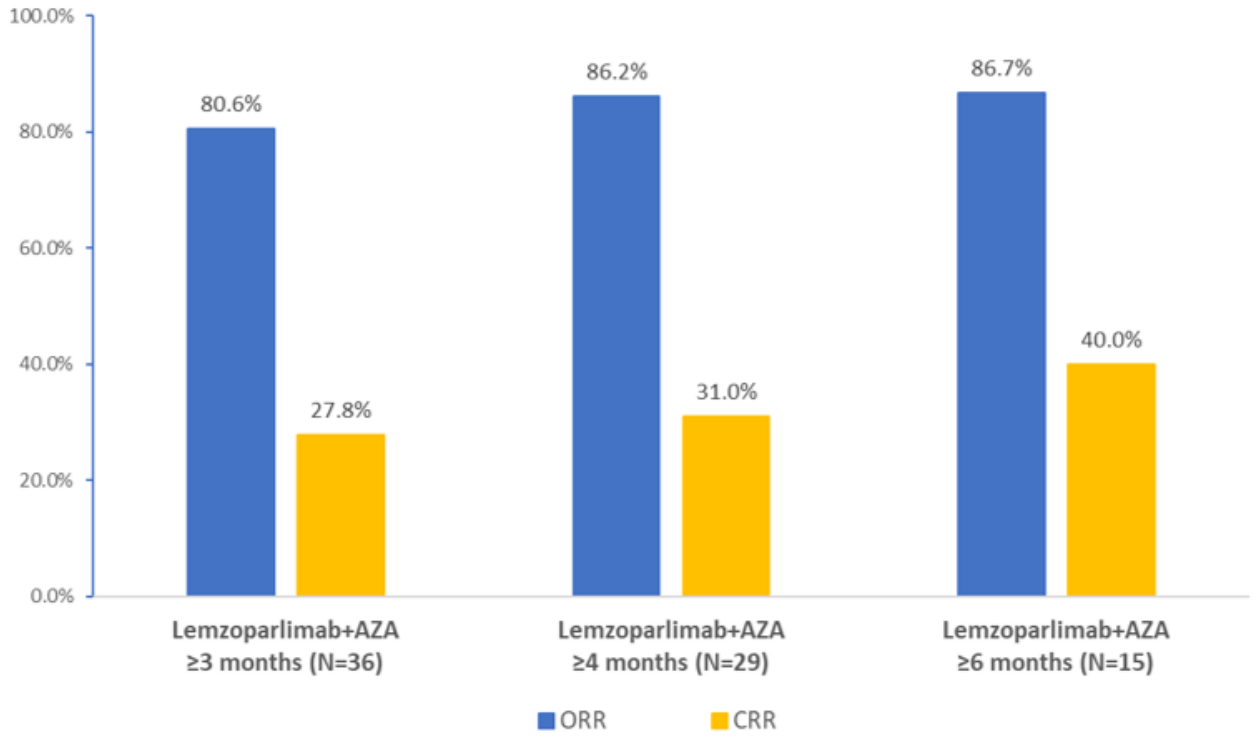
Garcia-Manero et al., ASH 2021

Lemzoparlimab in MDS (IgG4 mab against CD47)

BOR (%)	Time Since First Dose (ES N=47)		
	≥ 3m (N=36)	≥ 4m (N=29)	≥ 6m (N=15)
ORR	80.6	86.2	86.7
CR (95% CI)	27.8 (14.2, 45.2)	31.0 (15.3, 50.8)	40.0 (16.3, 67.7)
mCR with HI	13.9	17.2	13.3
mCR	30.6	27.6	20.0
HI	8.3	10.3	13.3
SD	16.7	10.3	13.3
PD	2.8	3.4	0

BOR: Best of response; ORR: overall response rate; mCR: marrow complete remission; HI: hematologic improvement; SD: stable disease; PD: disease progression
ES (Evaluable analysis set): Defined as subjects with at least one post-baseline tumor assessment

Data cutoff: date: March 31st, 2022



- CRR increased over time on therapy
- 31% and 40% CR rates achieved in subjects with time since first dose ≥ 4 months and ≥ 6 months, respectively

Xiao Z et al., ESMO 2022

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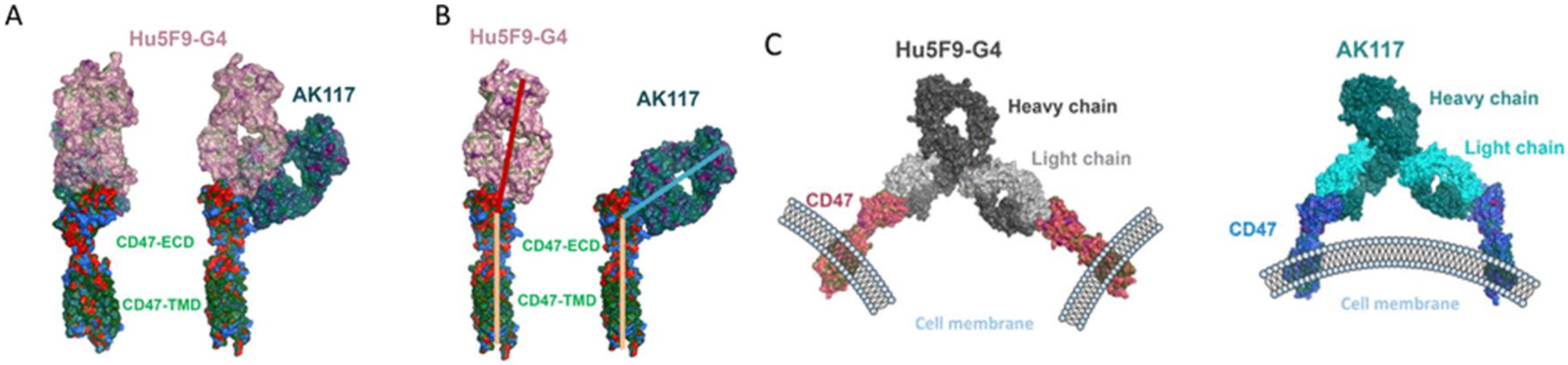
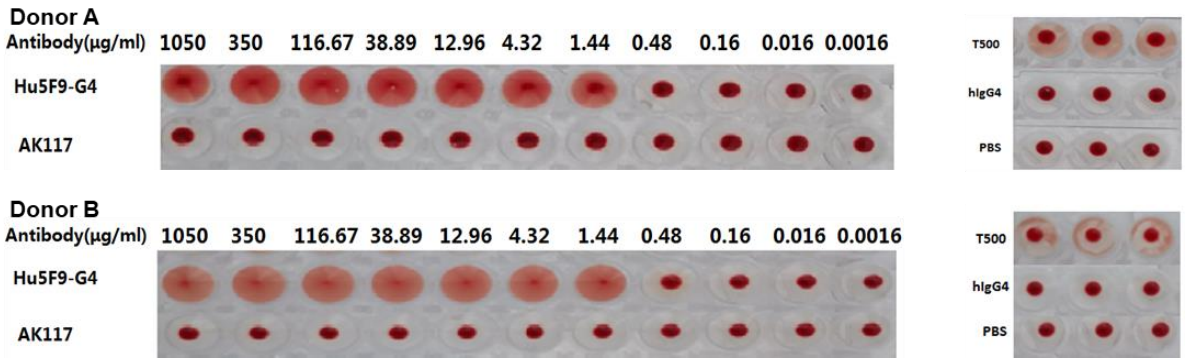
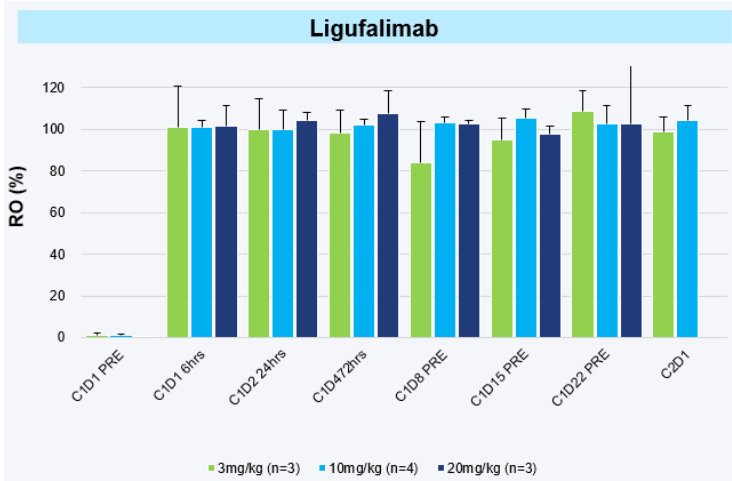
AK117 (Ligafulimab) does not induce Hemaglutination







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

Journal for ImmunoTherapy of Cancer 2022;**10:**e005517.

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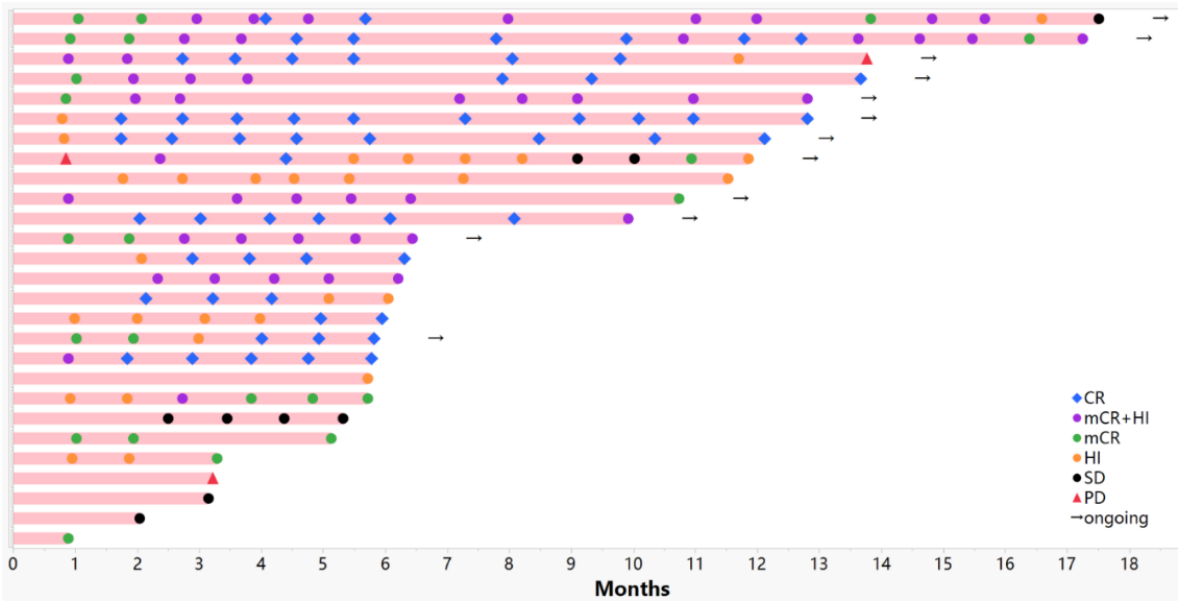
AK117 Efficacy in MDS (data cutoff 25-Aug-2023)



Evaluated Patients

	Magro +AZA[1] (N=95)	Lemzo +AZA[2] (N=53)	AK117 +AZA (N=27)	IBI188 +AZA[3] (N=45)	AZA
ORR	74.7%	70.2%	**85.2%**	/	~50%
CRR	**32.6%**	**21.3%**	**48.1%**	/	**10-20%**
CRR (Treatment ≥3 cycles)	/	27.8%	**52.0%**	/	/
CRR (Treatment ≥6 cycles)	/	40.0%	**68.4%**	31.1%	/

Similar data in AML (50% CR, 5% CRi)

[1] Poster # 7017. ASCO. 2022.
[2] Abstract # 6170. ESMO. 2022.
[3] Abstract # 1759. ASH. 2022.

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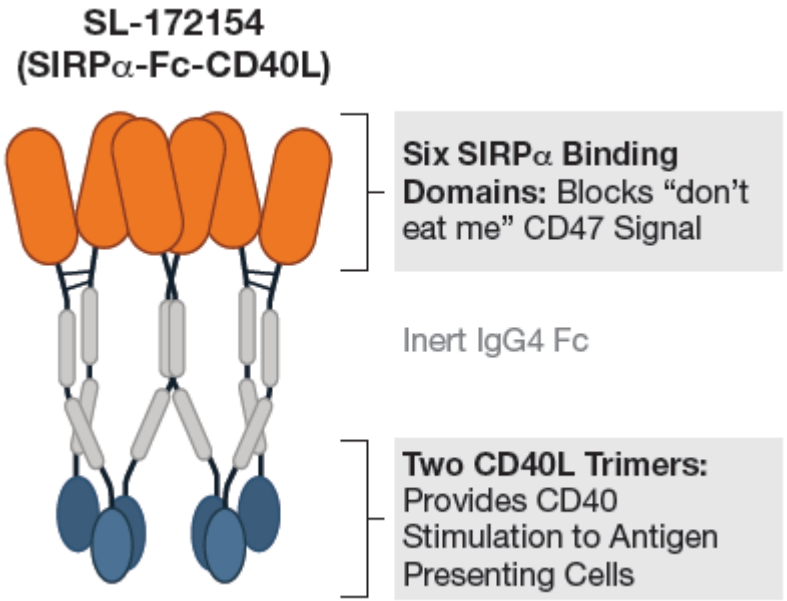
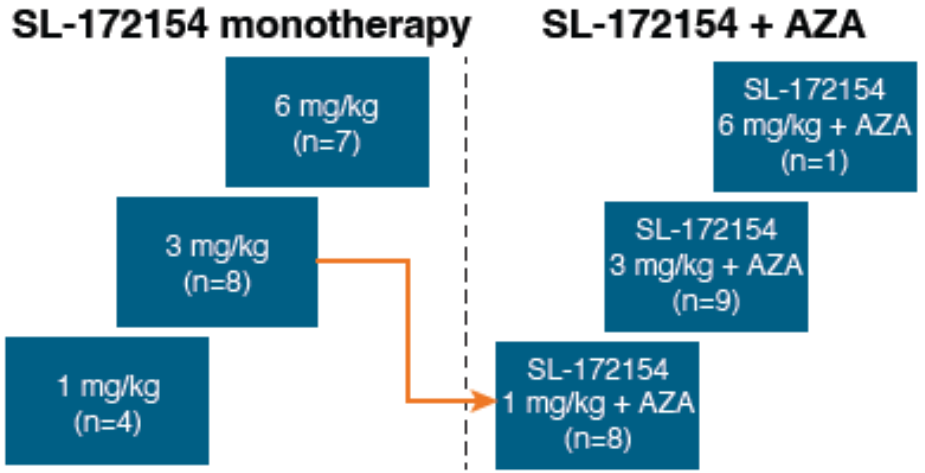
Phase 1 Study of SL-172154 in MDS and TP53 Mutant AML

- SL-172154 (SIRPα-Fc-CD40L), a hexameric, bi-functional fusion protein, consists of SIRPα domains linked to CD40L domains through an inert Fc linker
- CD40 Activation can increase antigen processing and cross-presentation by antigen presenting cells (APCs) to CD8 T cells, thus bridging innate and adaptive immunity

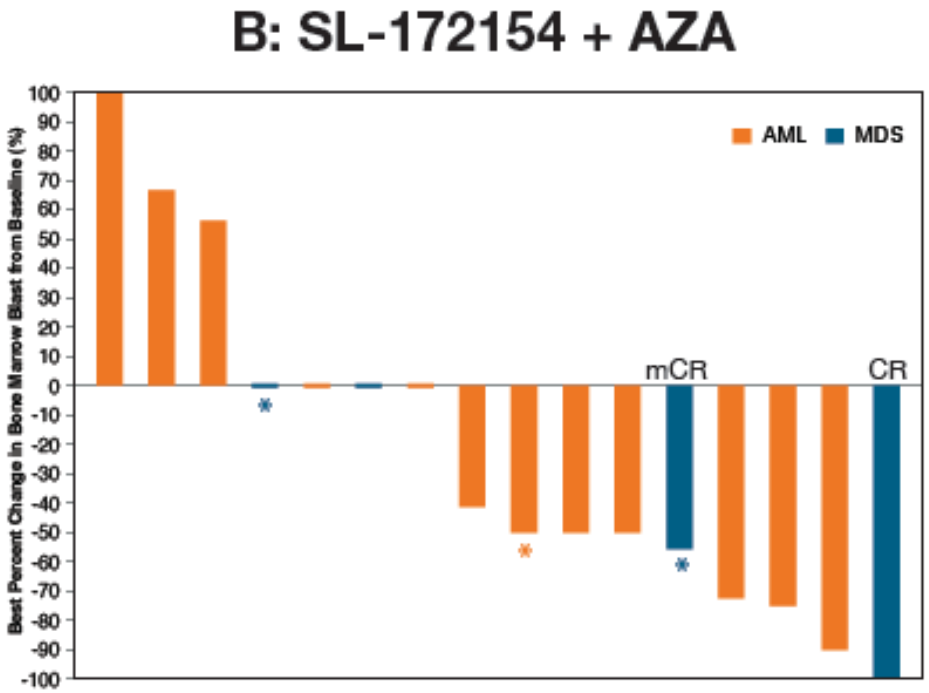




Daver N et al., ASH 2023

Phase 1 Study of SL-172154 in MDS and TP53 Mutant AML

- 2/4 evaluate TP53 mutant HR-MDS responded (CR and mCR)
- No objective response was reported in pts with R/R AML.
- BM Blast reduction 5/7 pts at 3 mg/kg cohort (ranging from -35% to -90%).
- SL-172154 increased on-target innate and adaptive serum cytokine levels of IL-12p40, IP-10, IL-8, IL-10, MIP3α and MCP1 at 3.0 mg/kg
- SL172154 monotherapy was associated with increase of the frequencies of phagocytic cells (such as CD45highCD34-CD11b+HLA-DR+ and CD45highCD34-CD36+CD64+) in bone marrow of patients with reduction in leukemic blasts.
- The magnitude of increase was higher in SL-172154 plus AZA cohort compared to SL-172154 monotherapy cohort.



Daver N et al., ASH 2023

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