Targeting CD47 by Monoclonal Antibody

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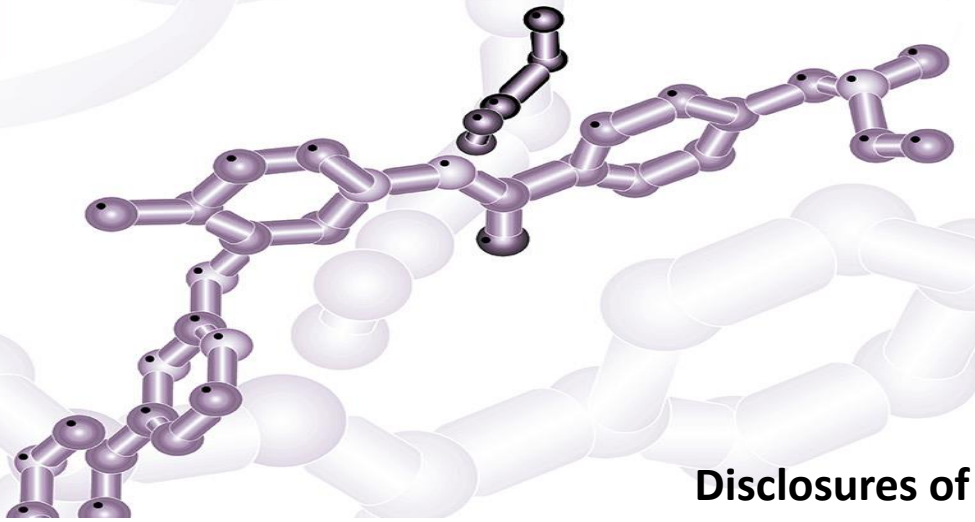

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

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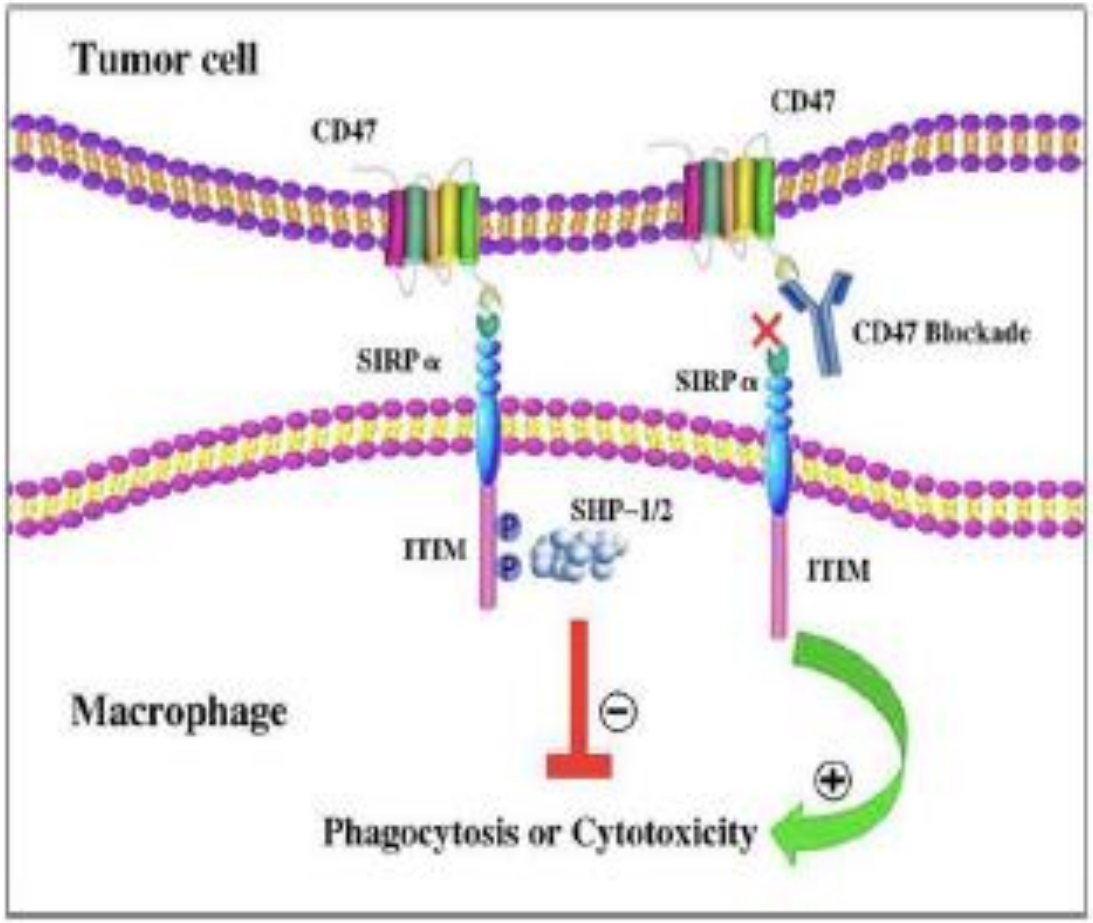
Royal Hotel Carlton
May 18-20, 2022

Disclosures of David Sallman

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie, AvenCell						X	
BlueBird Bio						X	
BMS, Gilead, Intellia						X	
Janssen, Kite, Novartis, Servier						X	
Shattuck Labs, Syndax, Syros						X	
Aprea, Jazz	X						
Magenta, Molecular Partners, Takeda			X				
Incyte, Servier					X		

Structure and Function of CD47 and SIRPα

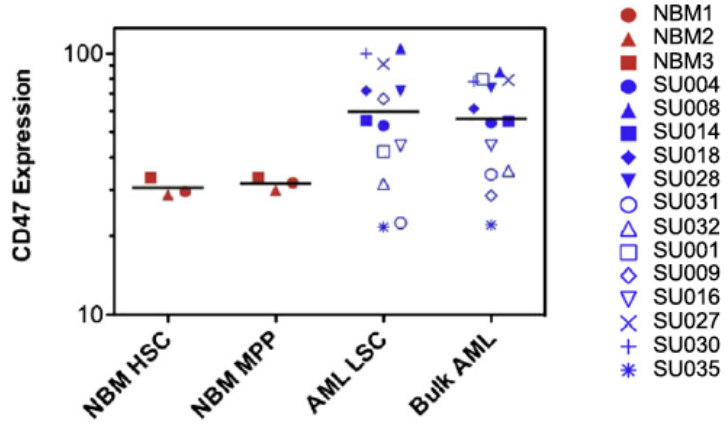
- CD47 is a widely expressed transmembrane protein and serves as the ligand for signal regulatory protein alpha (SIRPα)
- SIRPα is expressed on phagocytic cells including magrophages and dendritic cells
- CD47/SIRPα binding initiates a signal transduction cascade resulting in SHP 1/2 activation and consequent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

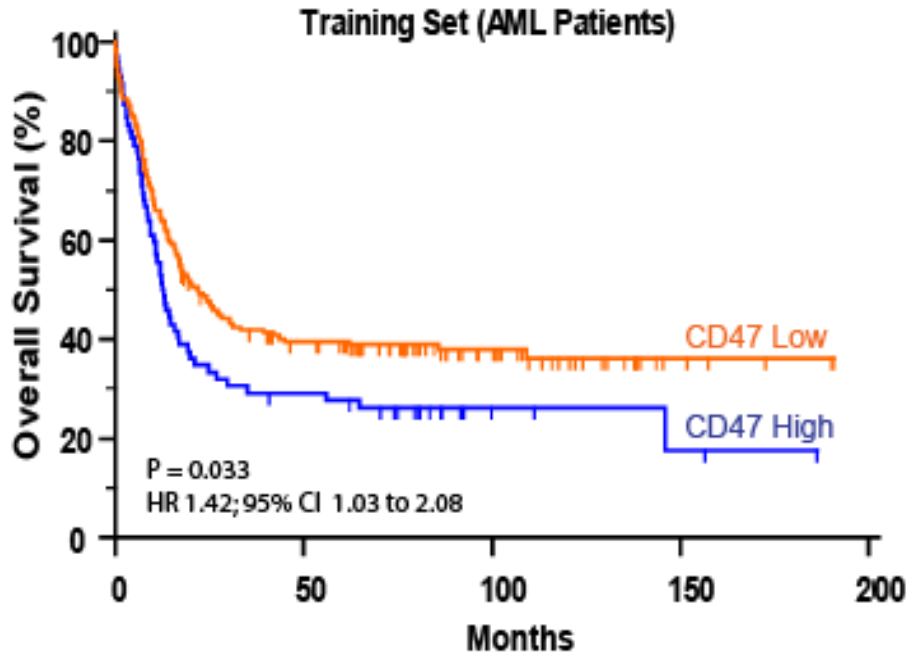


Brown et al., 2001; Blazer et a., J. Exp. Med. 2001
Barclay et al., Nat. Rev. Immunol 2006
Zhang W et al., *Frontiers in Immunology* 2020

Innate Immune System Evasion via CD47

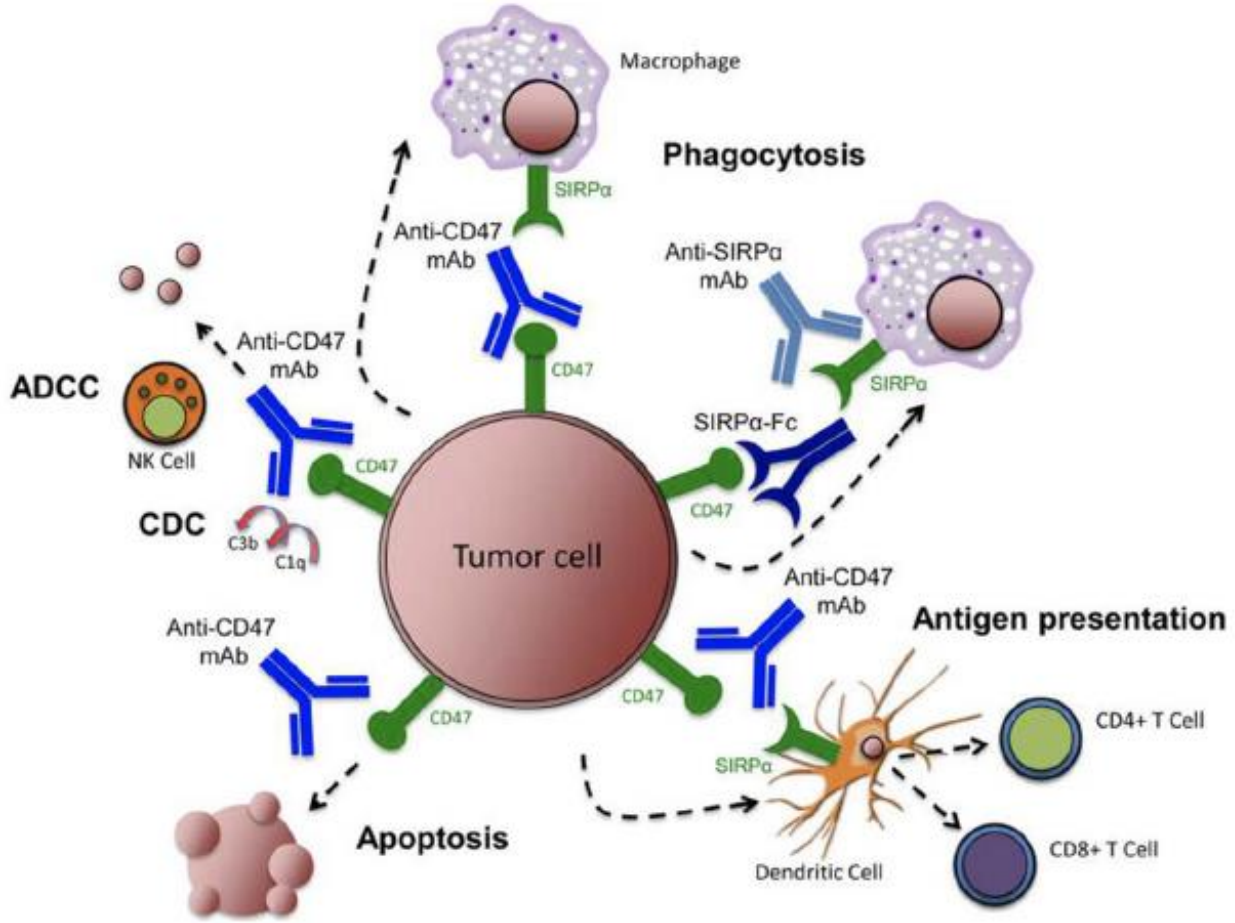
- CD47 is a “do not eat me” signal on cancers that enables macrophage immune evasion
- CD47 is the dominant macrophage checkpoint overexpressed on most cancers
- In AML, CD47 expression is overexpressed on LSC/bulk AML vs normal HSC/MPP
- CD47 leads to a strong fitness advantage in AML LSCs
- Increased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





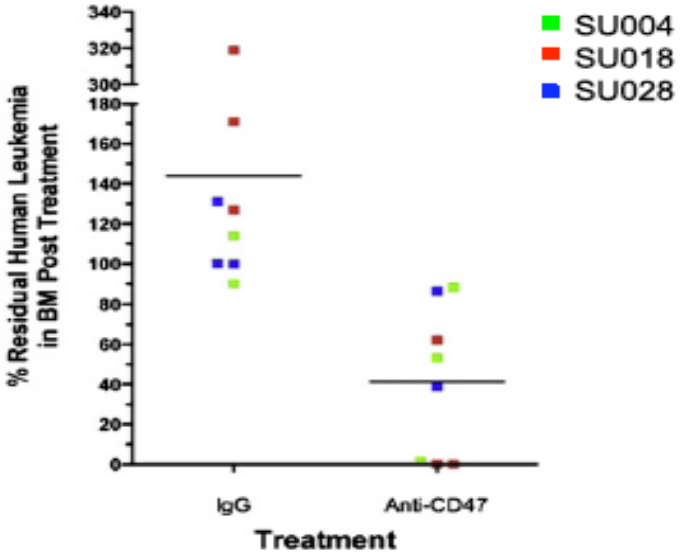
Majeti, Chao et al., Cell 2009;
Jaiswal et al., Cell 2009

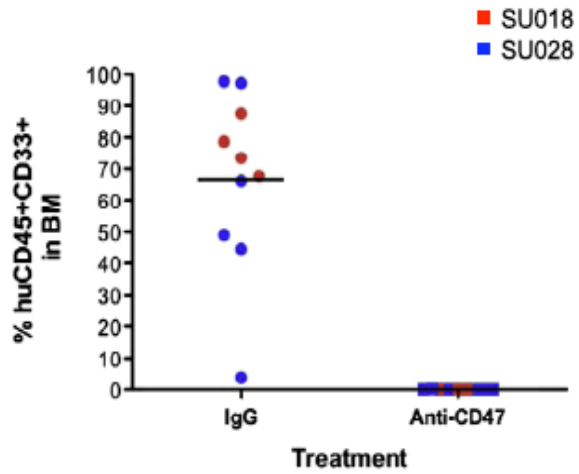
Therapeutic Impact of CD47/SIRPα Blockade in Cancer

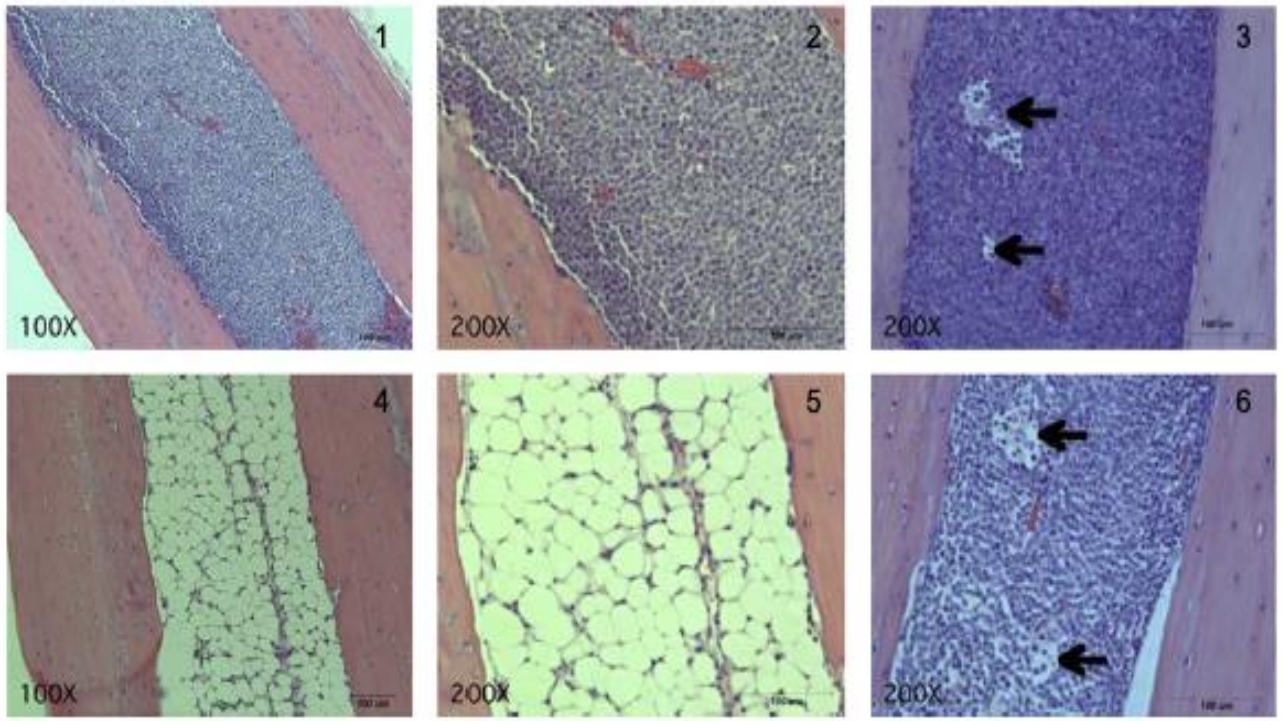


Zhang W et al., *Frontiers in Immunology* 2020; Chao M et al., *Curr Opin Immunol* 2012

Preclinical efficacy of CD47 and AML

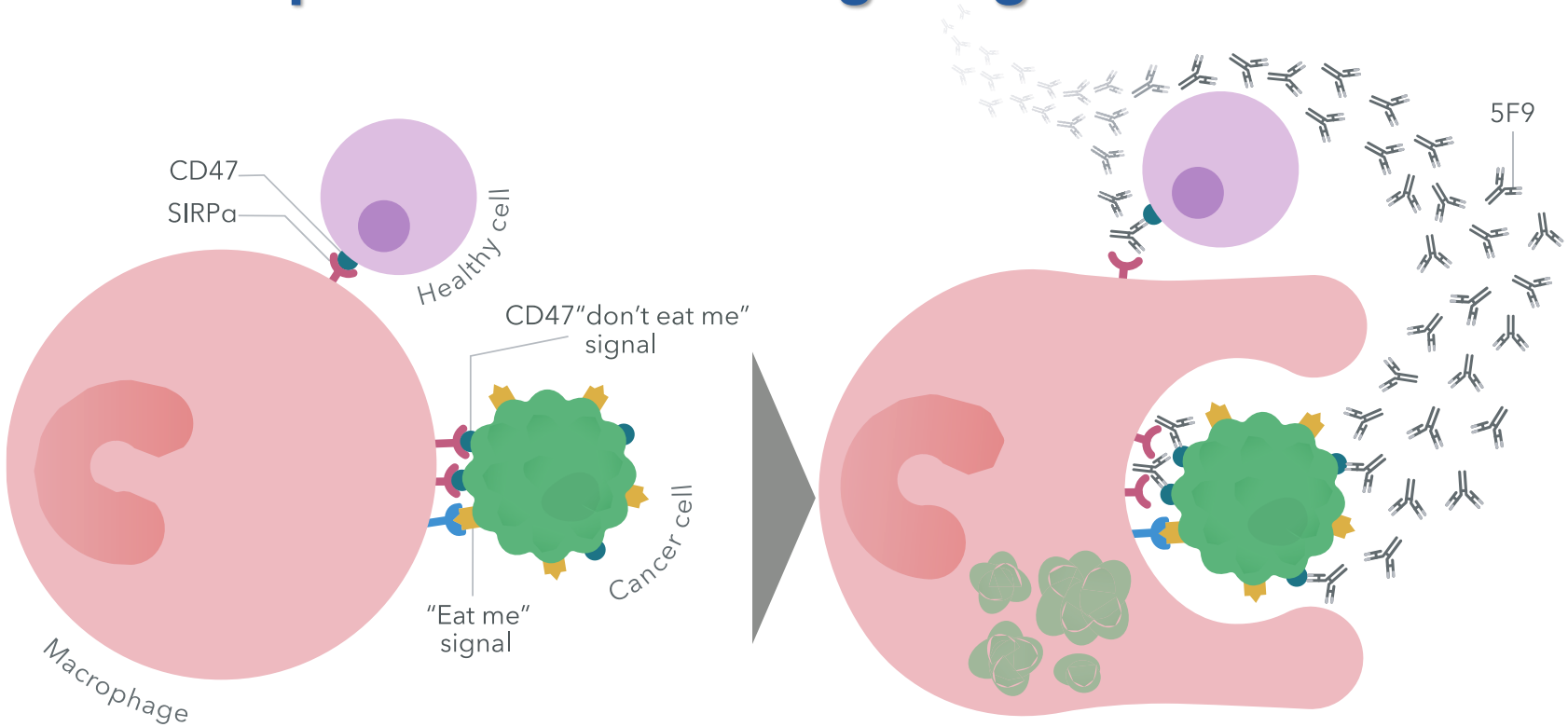




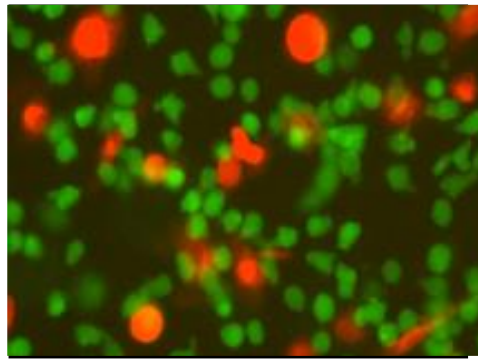


Majeti, Chao et al., *Cell* 2009;

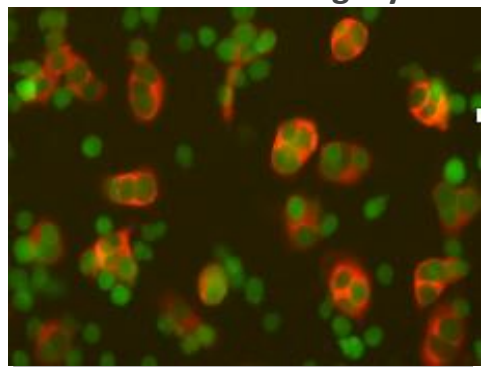
Magrolimab (Formerly 5F9) is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



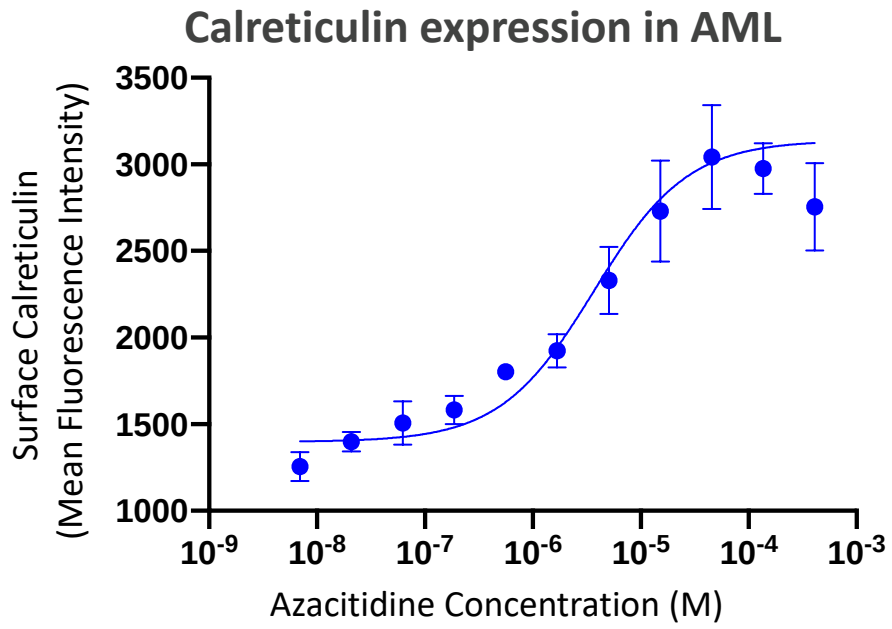
Macrophages Cancer cells

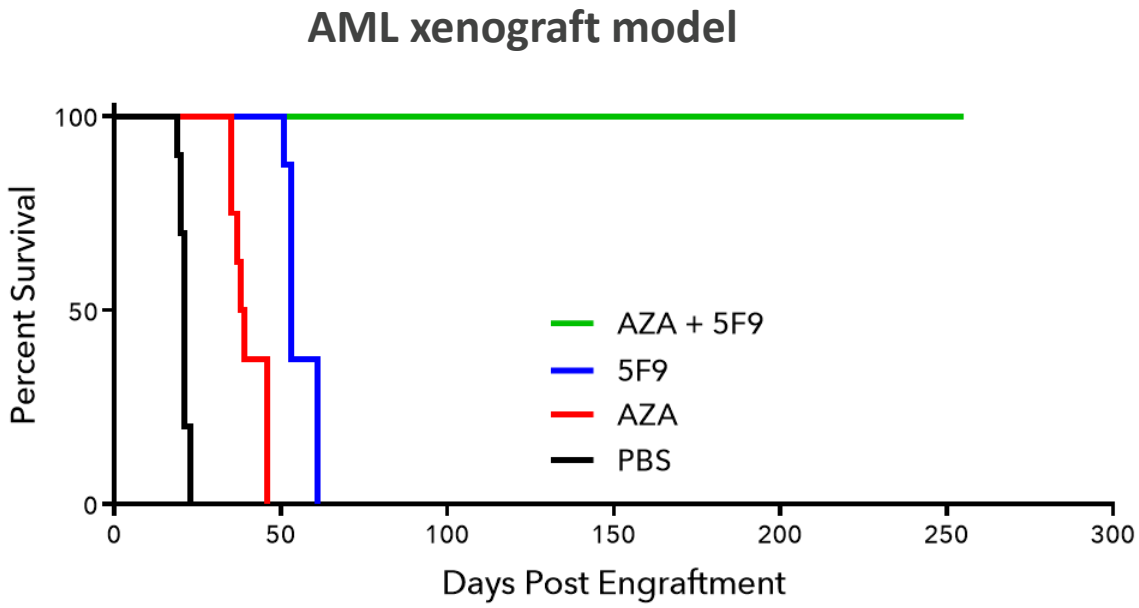
- Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers

Sallman D et al., 2020 ASCO

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

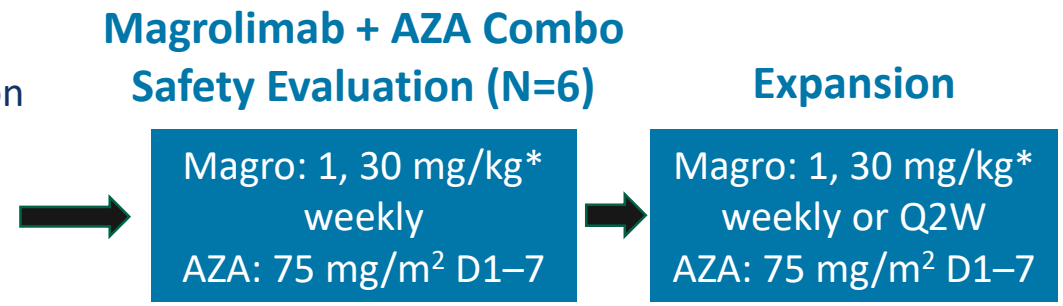




Feng D et al., ASH 2018

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



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)

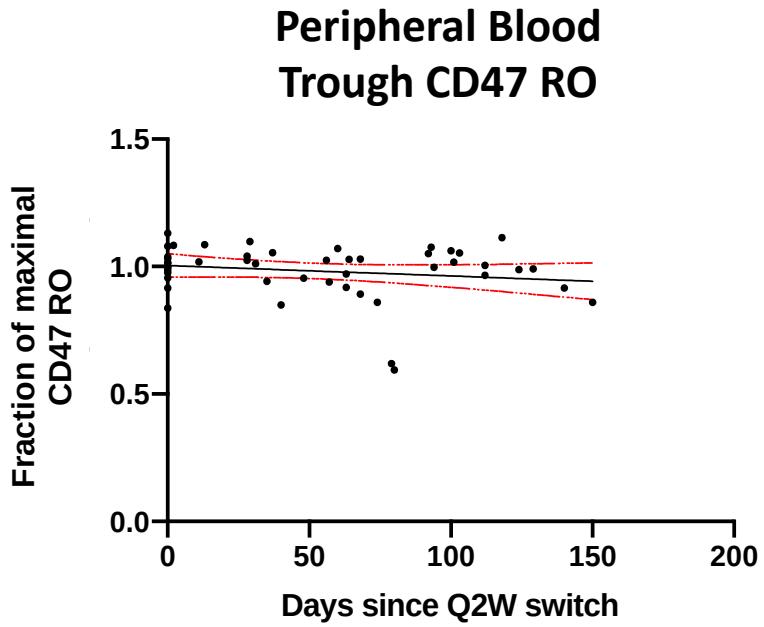
Exploratory objective

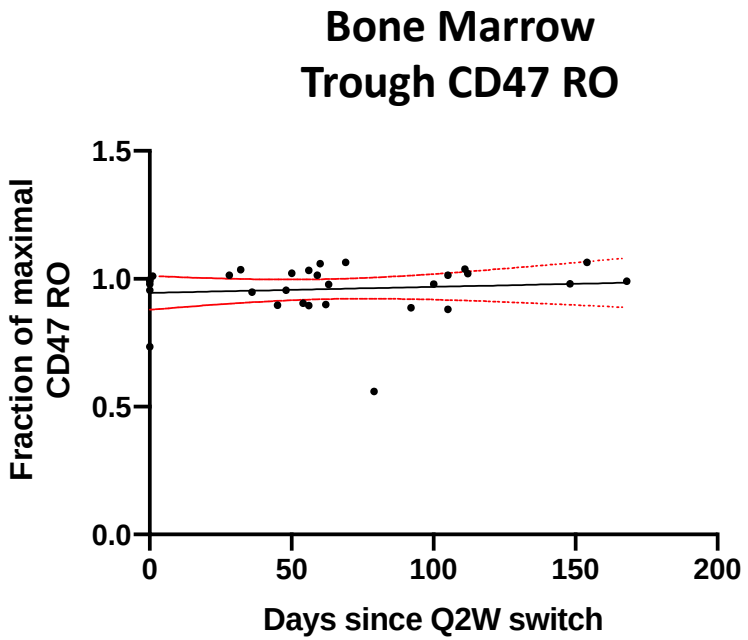
To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

- 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.

Magrolimab Q2W Dosing Results in Similar CD47 Receptor Occupancy as Q1W Dosing





RO: receptor occupancy.
Black line: linear regression best fit.
Red lines: 95% confidence intervals.

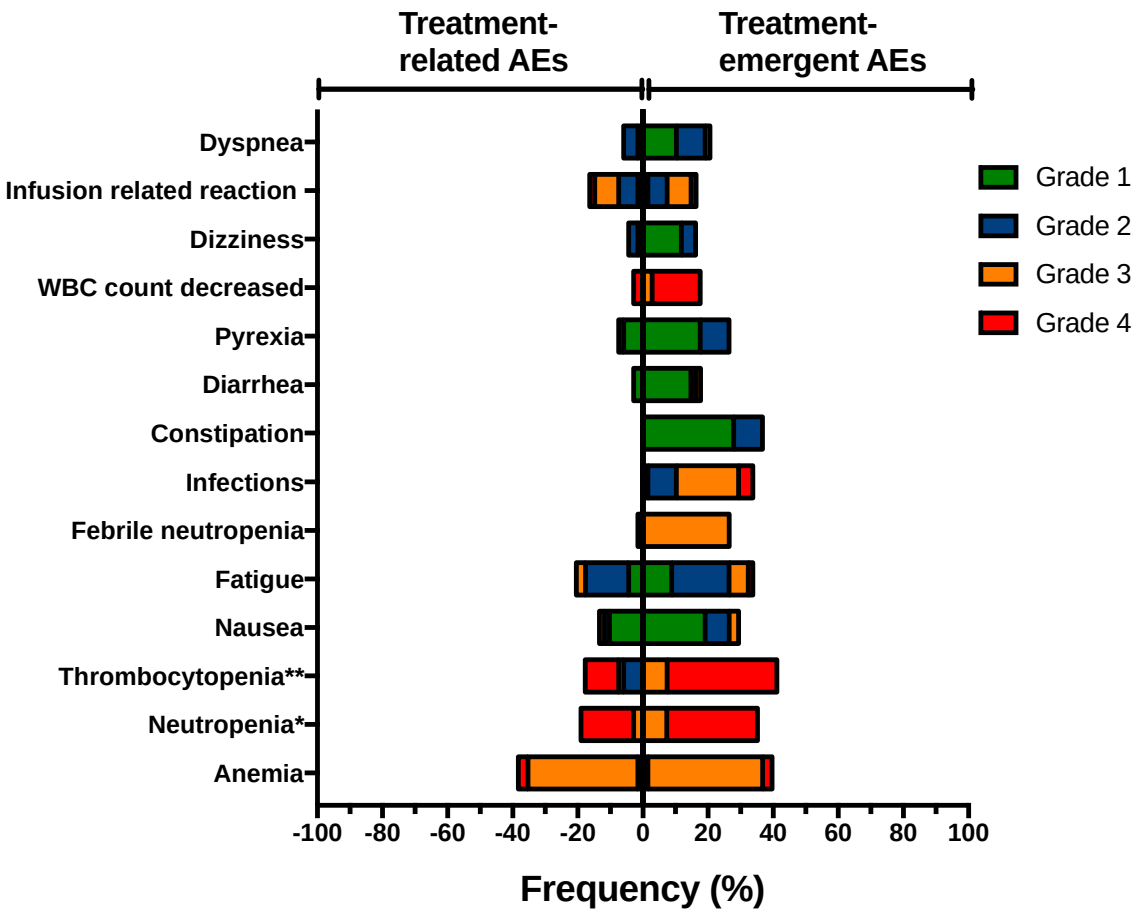
- Patients were dosed with magrolimab Q1W throughout or Q2W dosing starting Cycle 3 and beyond
- Similar CD47 RO was observed in the peripheral blood and bone marrow after Q2W dosing change in Cycle 3+
- **A magrolimab Q2W dose regimen has been selected based on PK/PD results and patient convenience**

*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.

Sallman D…... Daver N et al., 2020 ASCO

Magrolimab in Combination With AZA Is Well Tolerated

MDS and AML Patients (N=68)



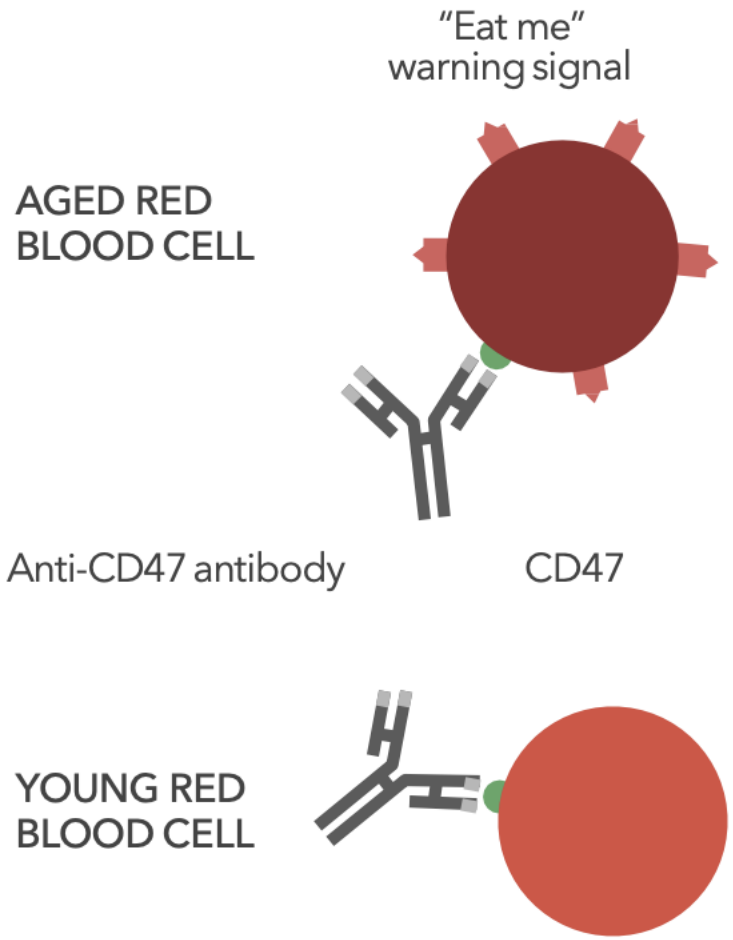
- No maximum tolerated dose was reached; magrolimab + AZA profile consistent with AZA monotherapy
- No significant cytopenias, infections, or immune-related AEs were observed (most patients were cytopenic at baseline)
- Anemia and transfusion frequency improved over time
- No deaths occurred during the first 60 days on study for either AML or MDS patients
- Treatment discontinuation due to drug-related AE occurred in only 1 of 68 (1.5%) of all patients treated with magrolimab + AZA

AEs ≥15% or AEs of interest are shown. All patients with at least 1 magrolimab dose are shown.
*Includes neutropenia and neutrophil count decreased. **Includes thrombocytopenia and platelet count decreased. AEs, adverse events.

Sallman D…... Daver N et al., 2020 ASCO

On Target Anemia and Mitigation Strategies

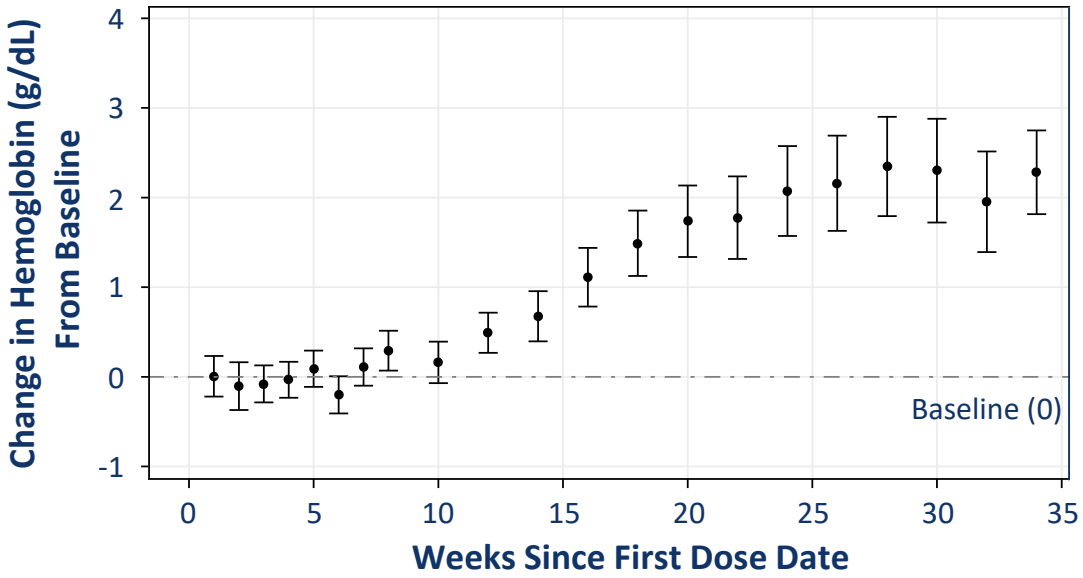
- Aged RBCs express pro-eat me signals whereas young RBCs do not leading to clearance of senescent RBCs
- Anemia Mitigation via:
  - Priming strategy (e.g. magrolimab)
  - RBC pruning process of CD47
  - Decrease/eliminate RBC affinity (e.g. TTI-621/622, ALX-147 and others)
  - Novel platforms (prodrug 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

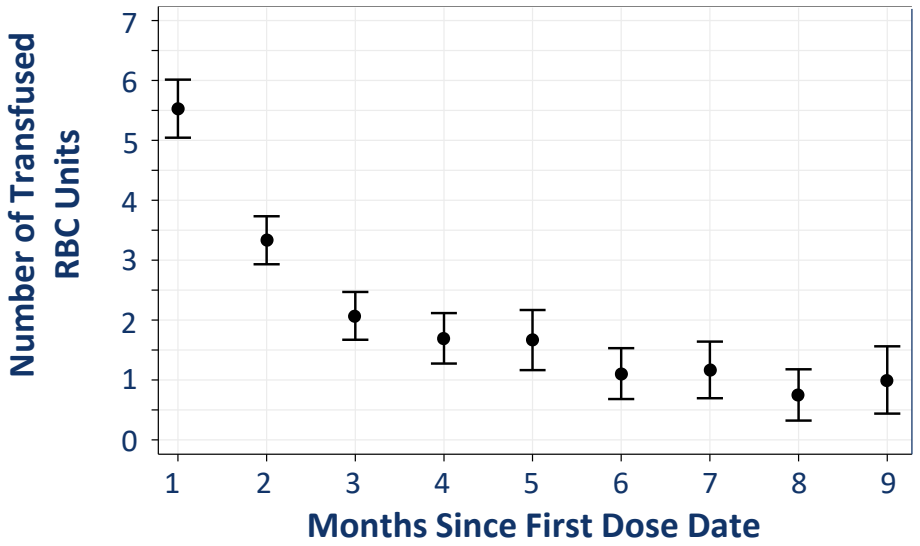
On-Target Anemia Is a Pharmacodynamic Effect and Is Mitigated With a Magrolimab Priming and Maintenance Dosing Regimen

Hemoglobin Changes on Therapy



Patients:	64	57	59	52	55	53	50	53	50	39	38	34	30	31	25	22	20	17	17	15	17

RBC Transfusion Frequency on Therapy

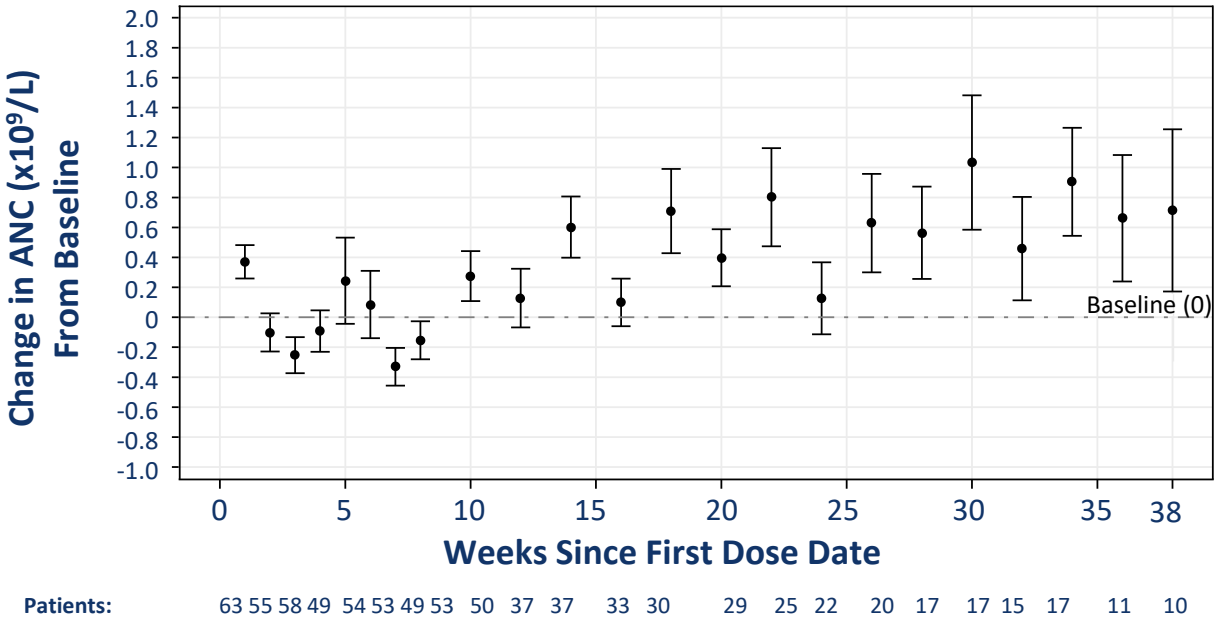


- An initial priming dose mitigates on-target anemia by CD47 blockade, resulting in a transient mild hemoglobin drop on the first dose (mean of 0.4 g/dL), which returns to baseline
- **The majority of patients had significant hemoglobin improvement and decrease in transfusion frequency over time**

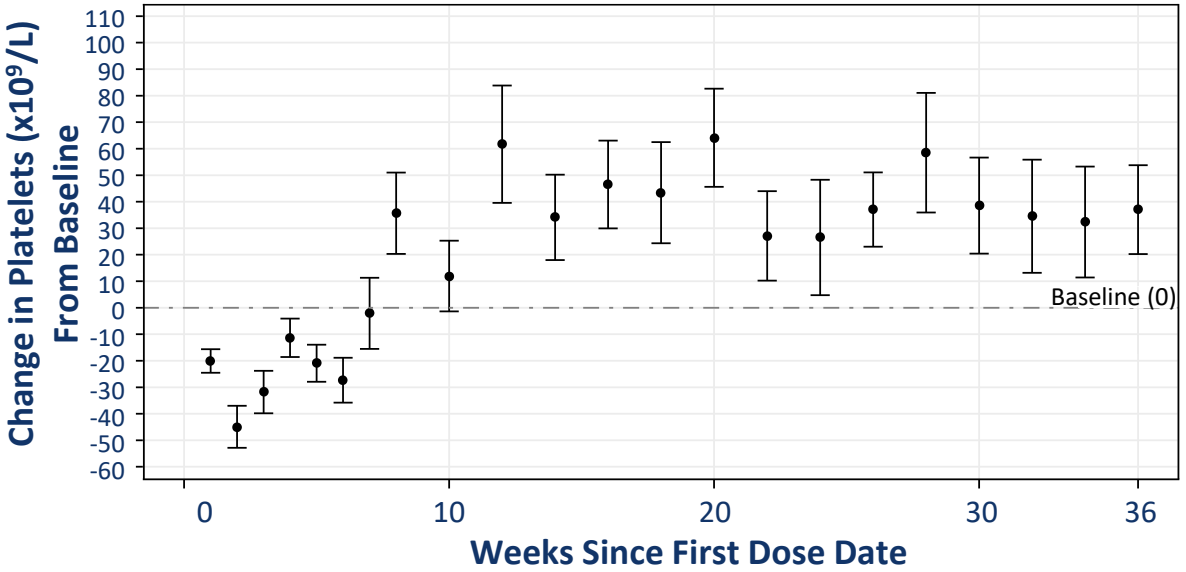
Sallman D…... Daver N et al., 2020 ASCO

Neutrophil and Platelet Improvement Is Seen on Magrolimab + AZA Therapy

Neutrophil Changes on Therapy



Platelet Changes on Therapy

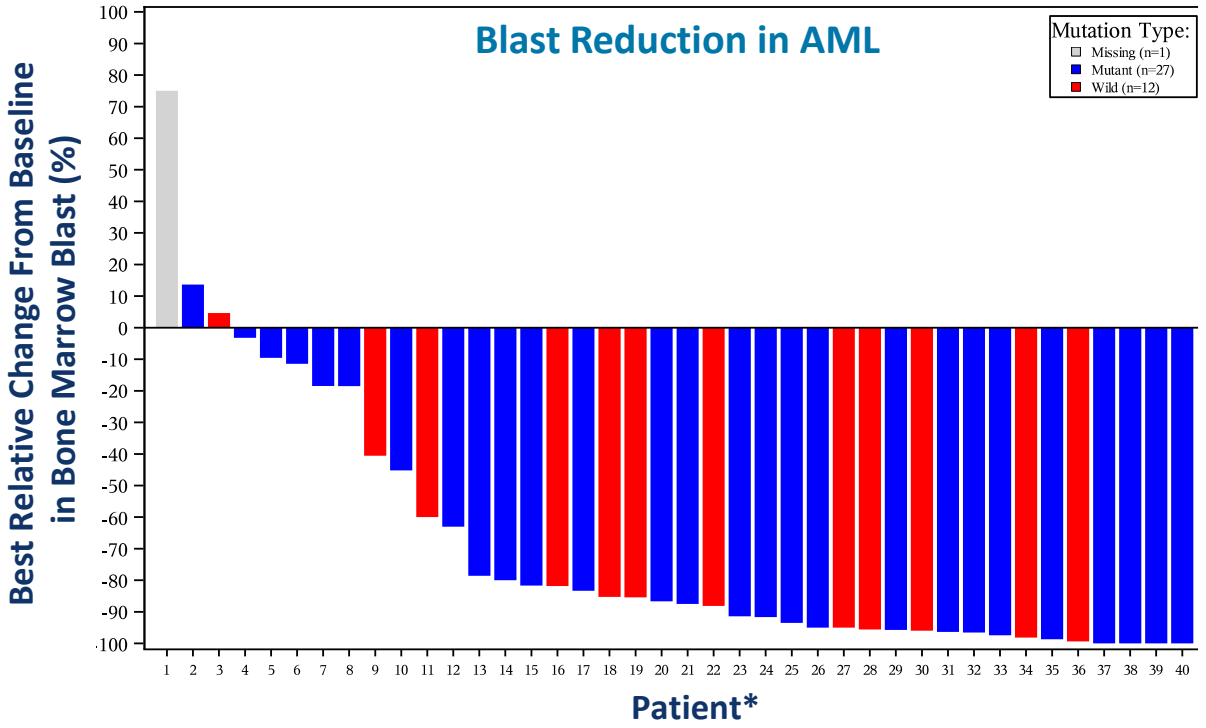


- Magrolimab + AZA does not induce significant neutropenia or thrombocytopenia
- The majority of patients improve their neutrophil and platelet count while on therapy

Sallman D…... Daver N et al., 2020 ASCO

Magrolimab + AZA Induces High Response Rates in AML

Best Overall Response	All AML (N=43)	*TP53*-mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)



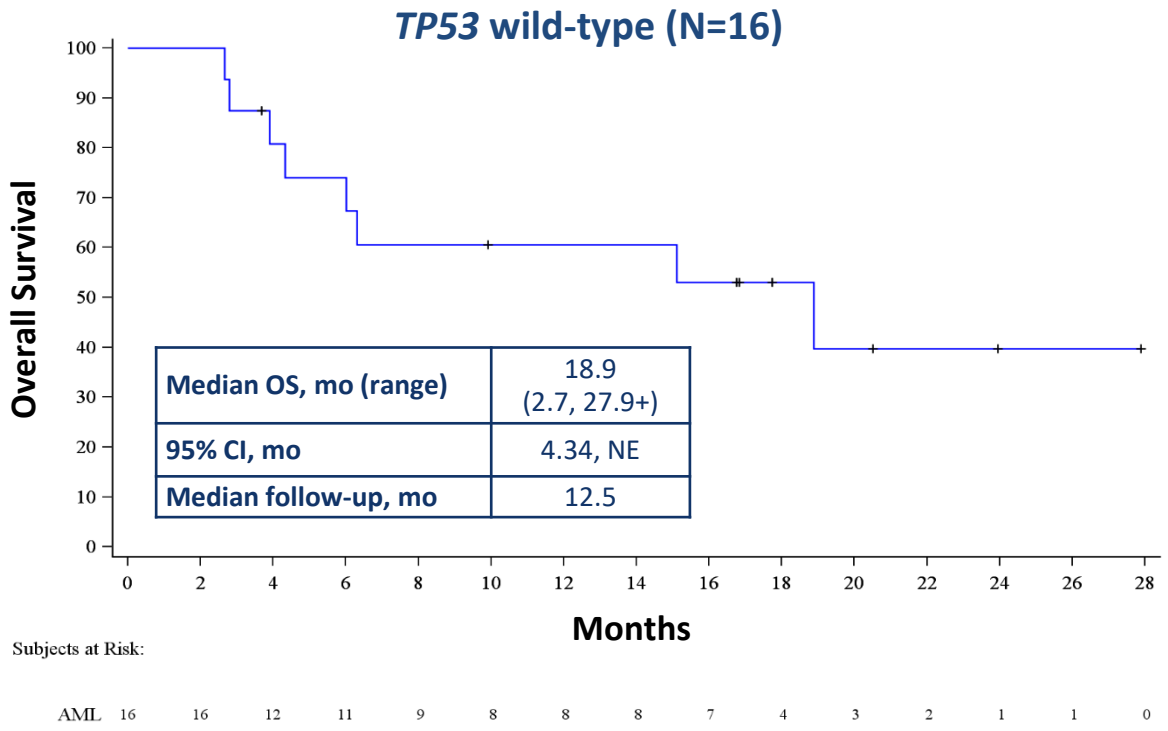
- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%–20%)[1,2]

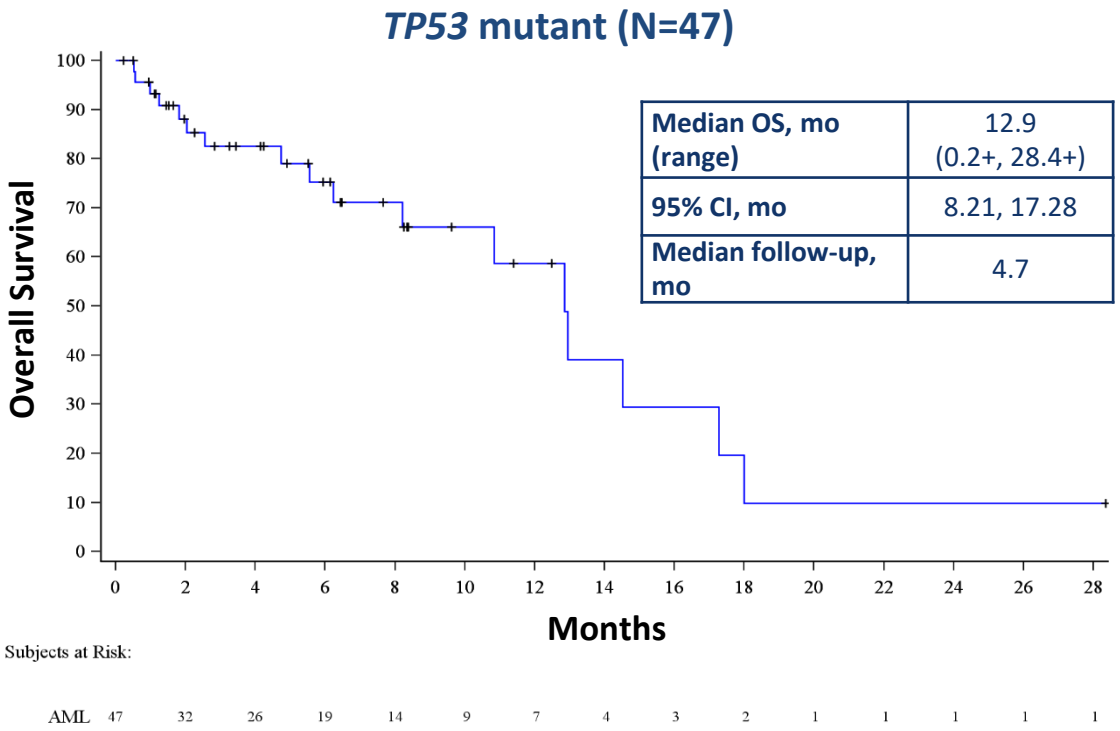
Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569. 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Sallman D …. Daver N et al., ASH 2020

Preliminary Median Overall Survival Is Encouraging in Both *TP53* Wild-Type and Mutant Patients



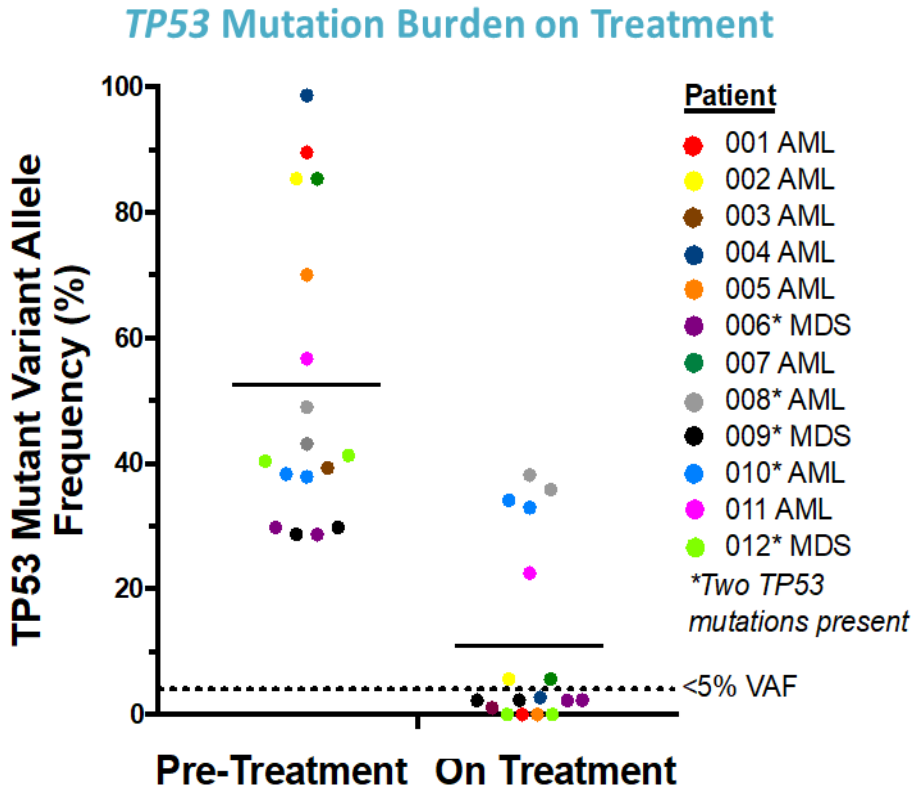


- The median OS is 18.9 months in *TP53* wild-type patients and 12.9 months in *TP53*-mutant patients
- This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (14.7-17.5 mo in all-comers,[1,3] 5.2–7.2 mo in patients who are *TP53* mutant[2,3])
- Additional patients and longer follow-up are needed to further characterize the survival benefit

NE, not evaluable.

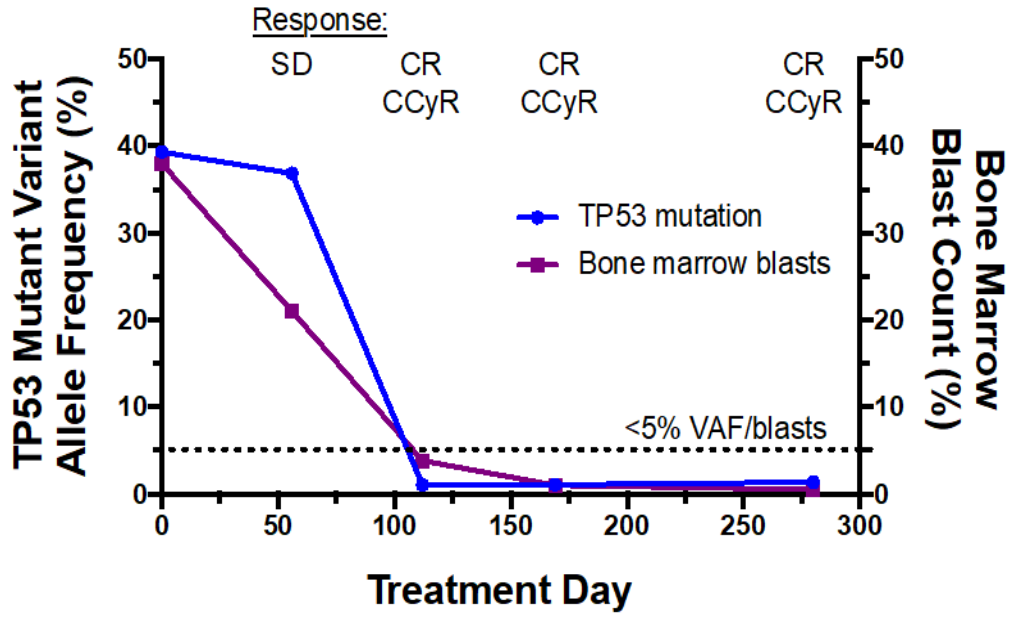
1. DiNardo CD, et al. *N Eng J Med*. 2020;383(7):617-629. 2. Kim K, et al. Poster presented at: 62nd ASH Annual Meeting; December 5-8, 2020 (virtual). 3. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

Magrolimab + AZA Eliminates *TP53* Mutational Burden



Patient data available for analysis. Best overall reduction is shown. NGS data shown.

65F therapy-related, complex karyotype, and *TP53* mutant AML: Achieved CR, CyCR, clearance of *TP53* mutations at Cycle 5 and ongoing



CyCr: complete cytogenetic response

Daver N ….. Sallman D et al., EHA 2020

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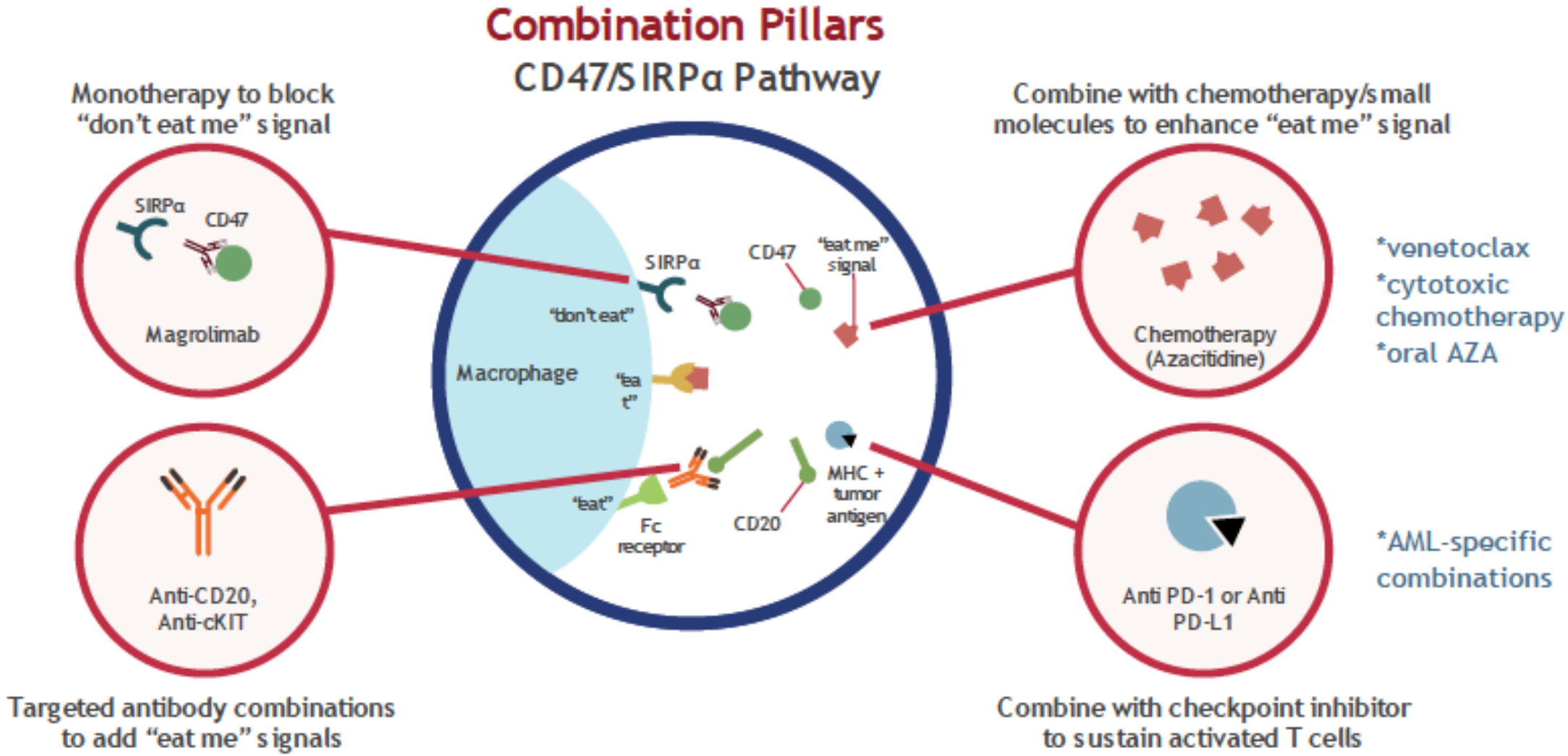
Combination Therapy with CD47 Targeted Therapy



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

AZA-VEN-Magro in AML abst #371

Results: Response Rates per ITT (n=48)

Outcomes	Frontline Cohort (n=25)		R/R Cohort (n=23)	
	TP53 mutated (n=14)	*TP53* wild type (n=11)	VEN-naïve (n=8)	Prior VEN (n=15)
ORR	12 (86)	11 (100)	6 (75)	3 (20)
CR/CRi	9 (64)	10 (91)	5 (63)	3 (20)
CR	9 (64)	7 (64)	3 (38)	0
CRi	0	3 (27)	2 (25)	3 (20)
MLFS / PR[1]	3 (21)	1 (9)	1 (13)	0
MRD neg FCM	5/9* (55)	4/9 (45)	2/6 (33)	0
CCyR	4/9‡ (44)	5/6 (83)	3/5 (60)	1/2 (50)
No response	2 (14)	0	2 (25)	12 (80)
TT 1st response	0.7 [0.6-1.9]	0.7 [0.7-1.5]	0.7 [0.6-4.1]	2.2 [1.8-2.6]
TT Best response	1.5 [0.7-3.2]	1.1 [0.7-2.9]	1.5 [1.0-4.1]	2.0 [1.2-3.9]
Med TT ANC>500	28 (20 – 41) days			
Med TT Plt>50K	24 (18 – 41) days			
8-wk mortality	0	0	1 (13)	3 (20)

Results expressed as n (%), n/N (%) or median [range]. FCM = multiparametric FCM, sensitivity 0.1-0.01%, *Only among pts with evaluable longitudinal samples; ‡Only among patients with baseline cytogenetic aberrations and longitudinal cytogenetic samples; [1]Two with PR per ELN2017

Daver N et al., ASH 2021

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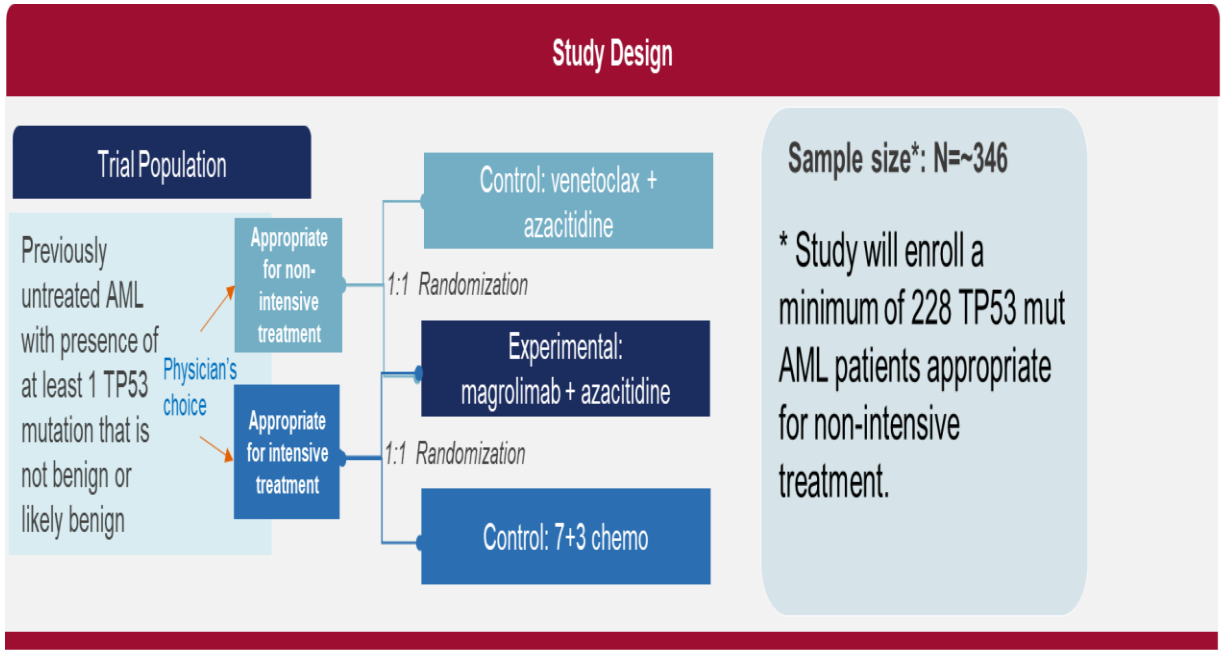
Ongoing Phase 3 Studies with Magro in FL AML

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



Stratification:

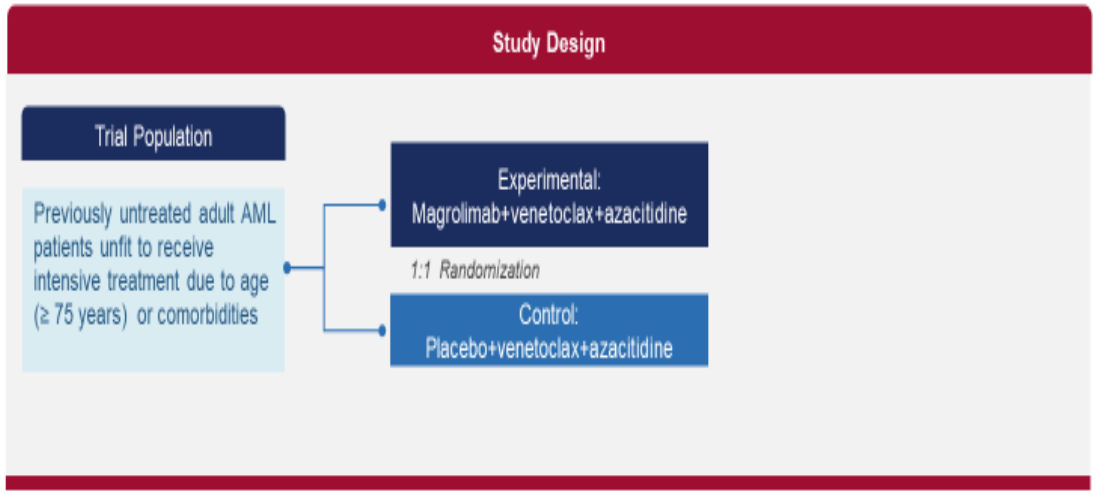
1) Appropriateness for non-intensive therapy vs. intensive therapy
2) Age <75 vs. ≥75
3) Geographic region: US vs. outside the US

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

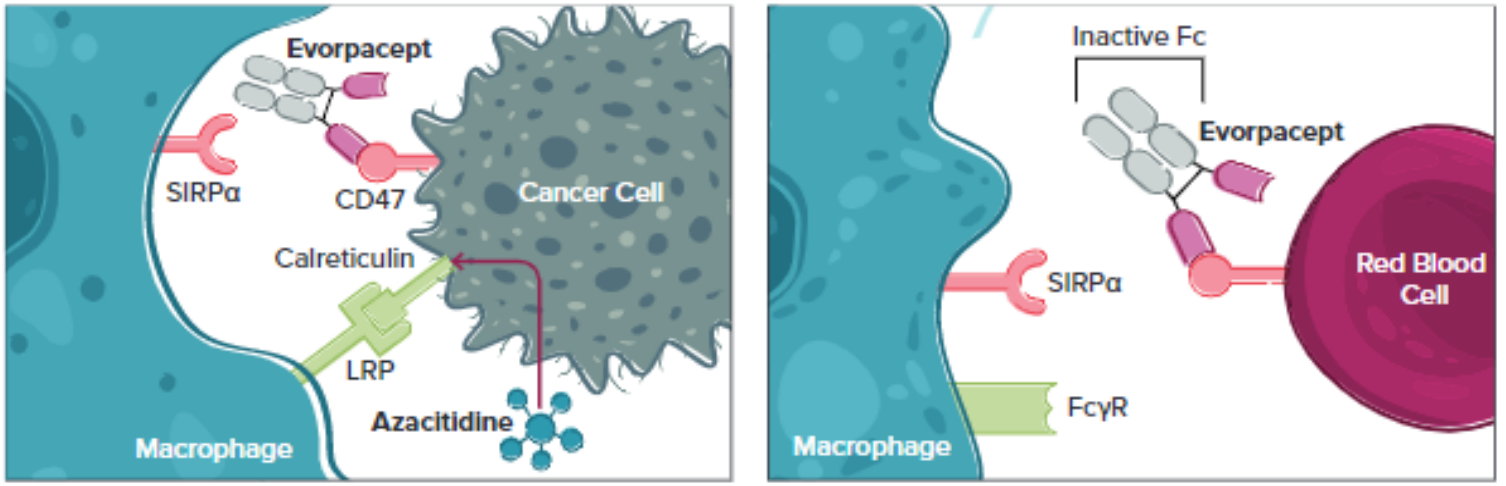


Endpoints:

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

Evorpacept (ALX148) – ASPEN-02 Study



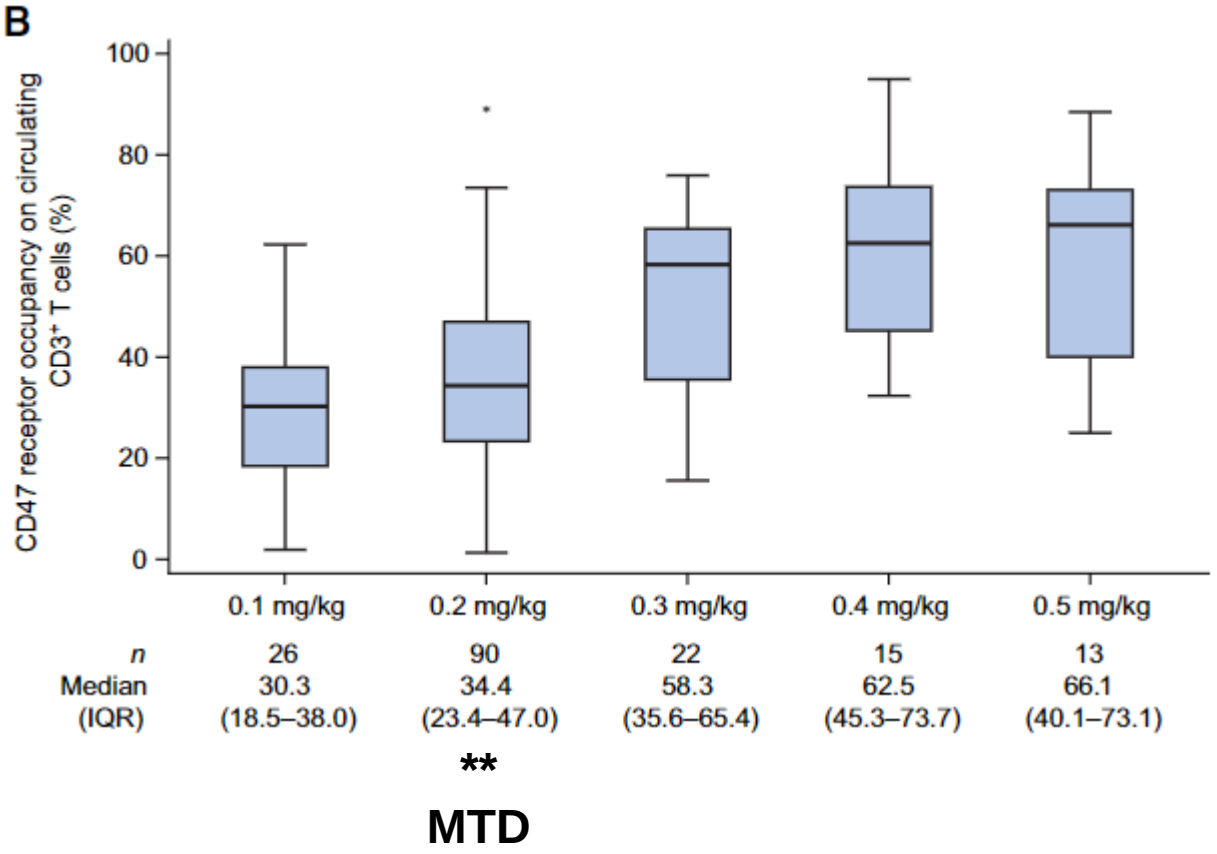
	Previously Untreated HR-MDS (N=6)	Previously Untreated HR-MDS with TP53 Mutation (N=5)	Relapsed/Refractory MDS (N=9)[#]
ORR	3 (50%)	3 (60%)	5 (56%)*
CR	2 (33%)	2 (40%)	0
PR	0	0	0
Marrow CR	1 (17%) with HI	1 (20%) with HI	5 (56%)*
HI	0	0	0
SD	2 (33%)	1 (20%)	2 (22%)
PD	1 (17%)	1 (20%)	1 (11%)

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 is recruiting

Garcia-Manero et al., ASH 2021

TTI-621 and TTI-622



- TTI-622 *TP53* AML study with azacitidine or *TP53* wildtype triplet with azacitidine + venetoclax has started accrual late 2021

Ansell S et al., CCR 2021

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Novel CD47 Modalities and Combination Possibilities in Myeloid Neoplasms

- Synergy with Fc receptor of mabs targeting myeloid antigens (e.g. CD33/CD123/TIM3/CLL1/CD70)
- Ongoing/possible Triplet strategies which could include:
  - Azacitidine + magrolimab + venetoclax in AML (NCT04435691)
  - Combination with traditional PD1/PDL1 adaptive immune checkpoints (NCT03922477)
  - Combination of azacitidine + magrolimab + APR-246 for *TP53* mutant patients
  - Combination with synergistic combinations in MDS/AML (such as HMA + MBG-453; planned phase 1 in 2022)
- HMBD004 is a bispecific anti-CD47xCD33 antibody which has shown decrease tumor burden and increased progression free survival in CD47+CD33+ AML mouse models
- CD47 directed CART cells
- Currently at least 13 CD47/SIRPα agents in clinical trial with ~50 agents in preclinical development

Zhang W et al., *Frontiers in Immunology* 2020; Swoboda D and Sallman D, manuscript under review

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