CD47 Macrophage Checkpoint-Based Immunotherapy (Lymphomas, MDS, AML)

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Disclosures

I disclose the following financial relationship(s):

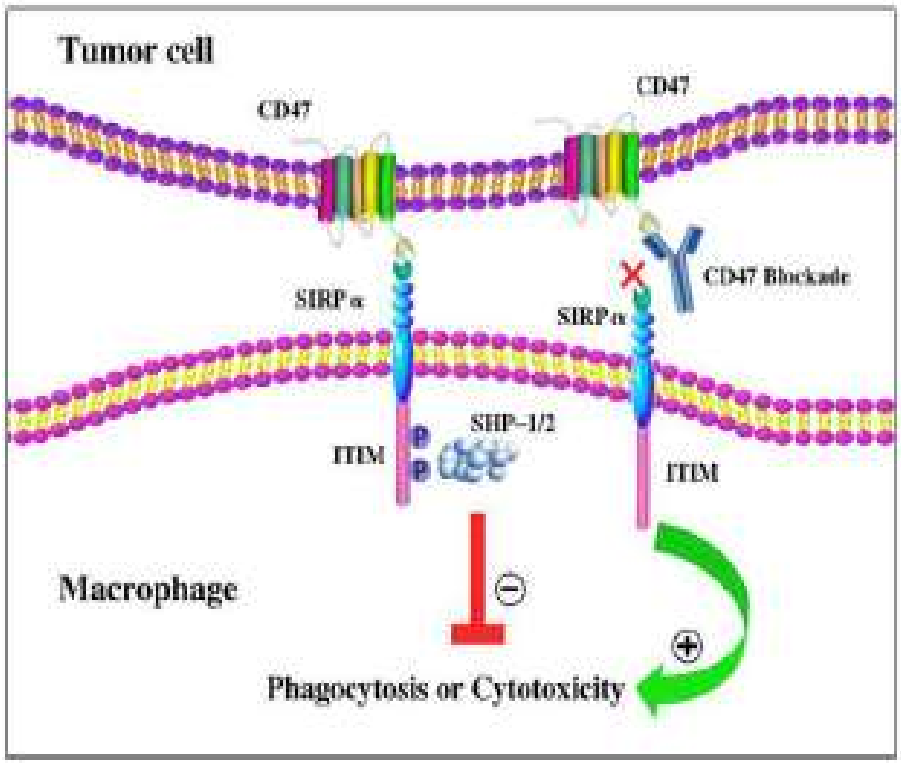
- Agios, Advisory Board or Panel, Speaker's Bureau
- Celyad, Advisory Board or Panel
- Celgene, Grants/Research Support
- Jazz, Grants/Research Support
- Incyte, Speaker's Bureau
- Novartis Advisory Board or Panel
- Abbvie Advisory Board or Panel
- Syndax – Advisory Board or Panel
- Intella – Advisory Board or Panel
- BMS – Advisory Board or Panel, Speaker's Bureau
- Gilead – Advisory Board or Panel
- Kite – Advisory Board or Panel
- Magenta – Consultant

Objectives

- Impact of CD47 Overexpression in Cancer
- Targeting CD47/SIRPα in Hematologic Malignancies
- Safety and Efficacy of Magrolimab + Azacitidine in MDS/AML patients
- Novel Therapeutic Strategies in Therapeutic Targeting of CD47/SIPRα in MDS/AML patients.

Structure and Function of CD47 and SIRPα

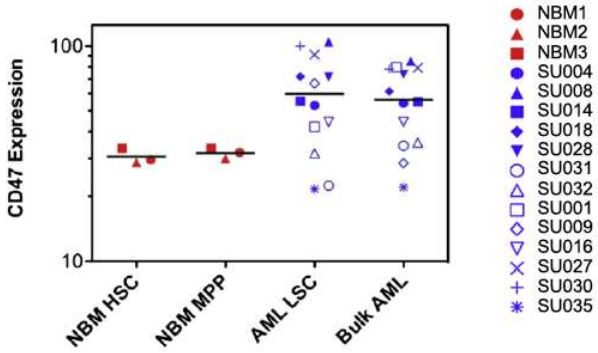
- CD47 is a widely expressed transmembrane protein and serves as the ligand for signal regulatory protein alpha (SIRPα)
- SIRPα is expressed on phagocytic cells including magrophages and dendritic cells
- CD47/SIRPα binding initiates a signal transduction cascade resulting in SHP 1/2 activation and consequent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

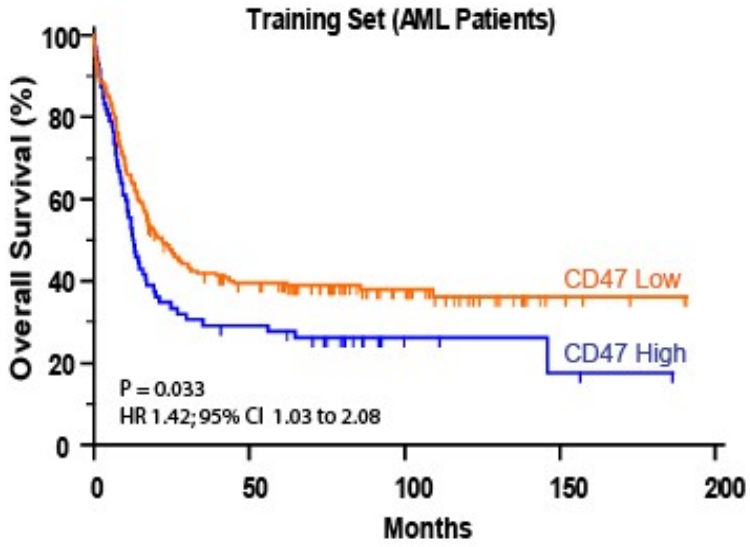


Brown et al., 2001; Blazer et a., J. Exp. Med. 2001
Barclay et al., Nat. Rev. Immunol 2006
Zhang W et al., *Frontiers in Immunology* 2020

Innate Immune System Evasion via CD47

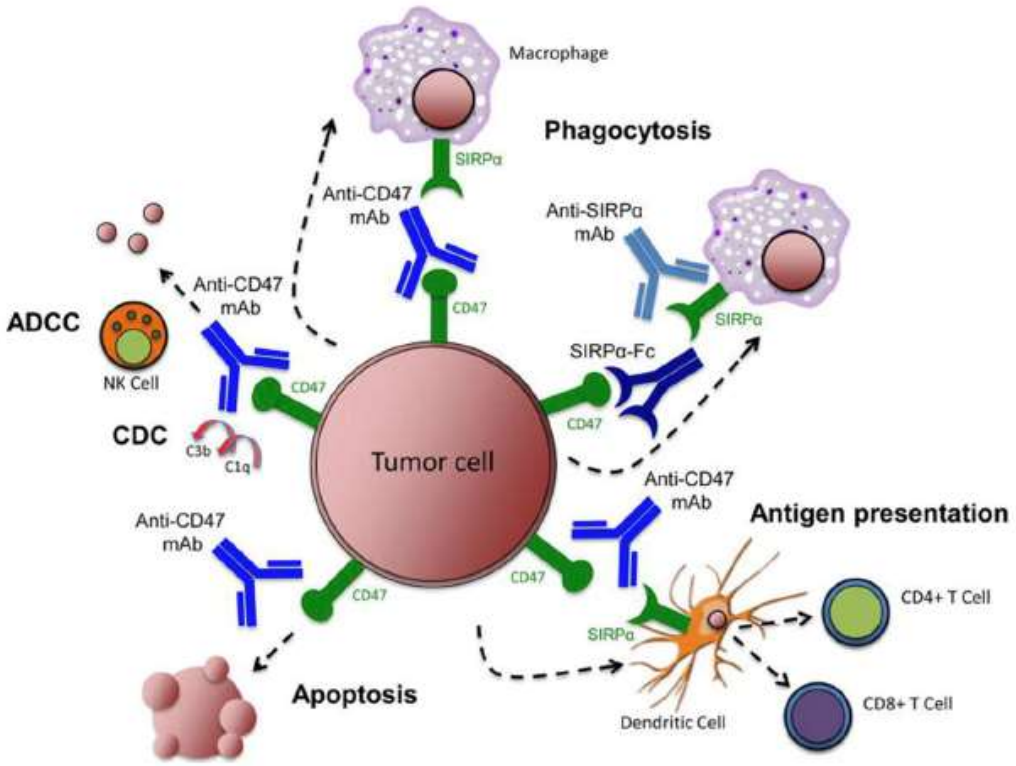
- CD47 is a “do not eat me” signal on cancers that enables macrophage immune evasion
- CD47 is the dominant macrophage checkpoint overexpressed on most cancers
- In AML, CD47 expression is overexpressed on LSC/bulk AML vs normal HSC/MPP
- CD47 leads to a strong fitness advantage in AML LSCs
- Increased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





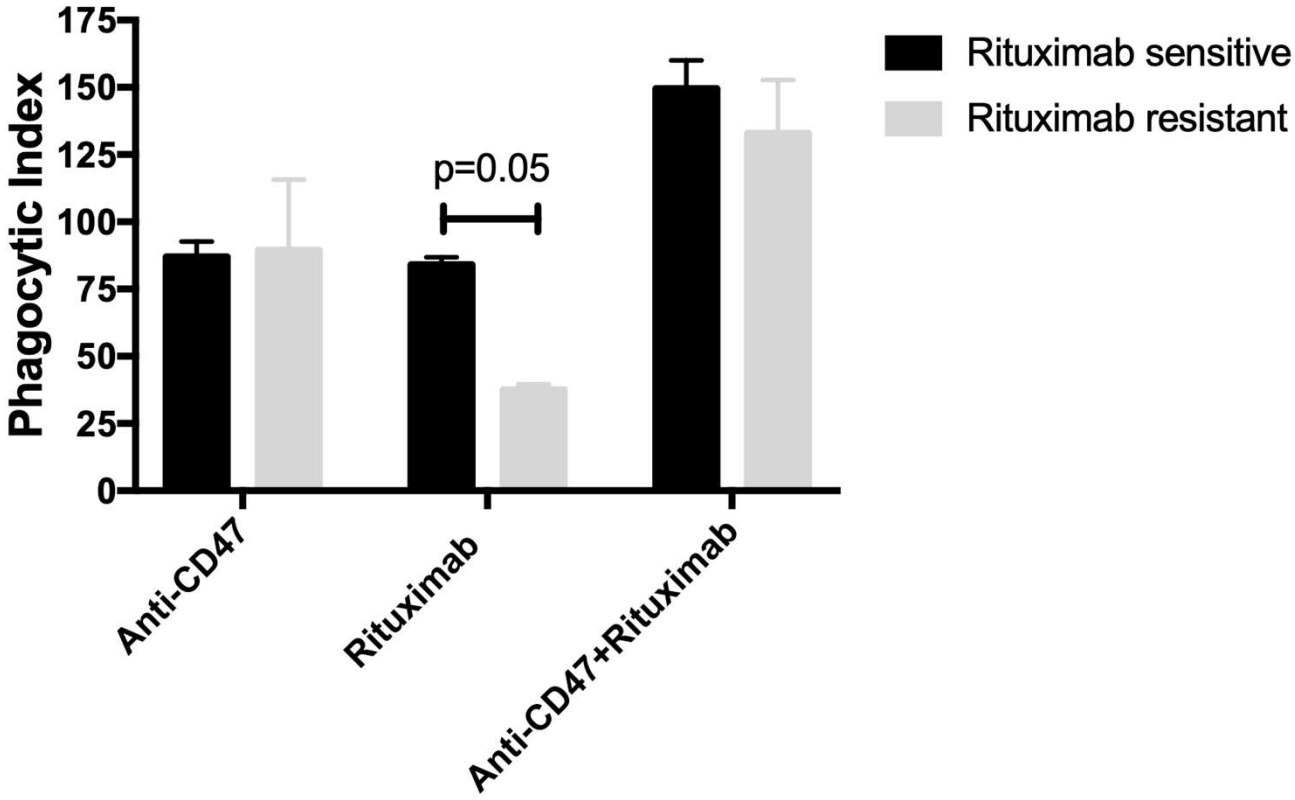
Majeti, Chao et al., Cell 2009;
Jaiswal et al., Cell 2009

Therapeutic Impact of CD47/SIRPα Blockade in Cancer



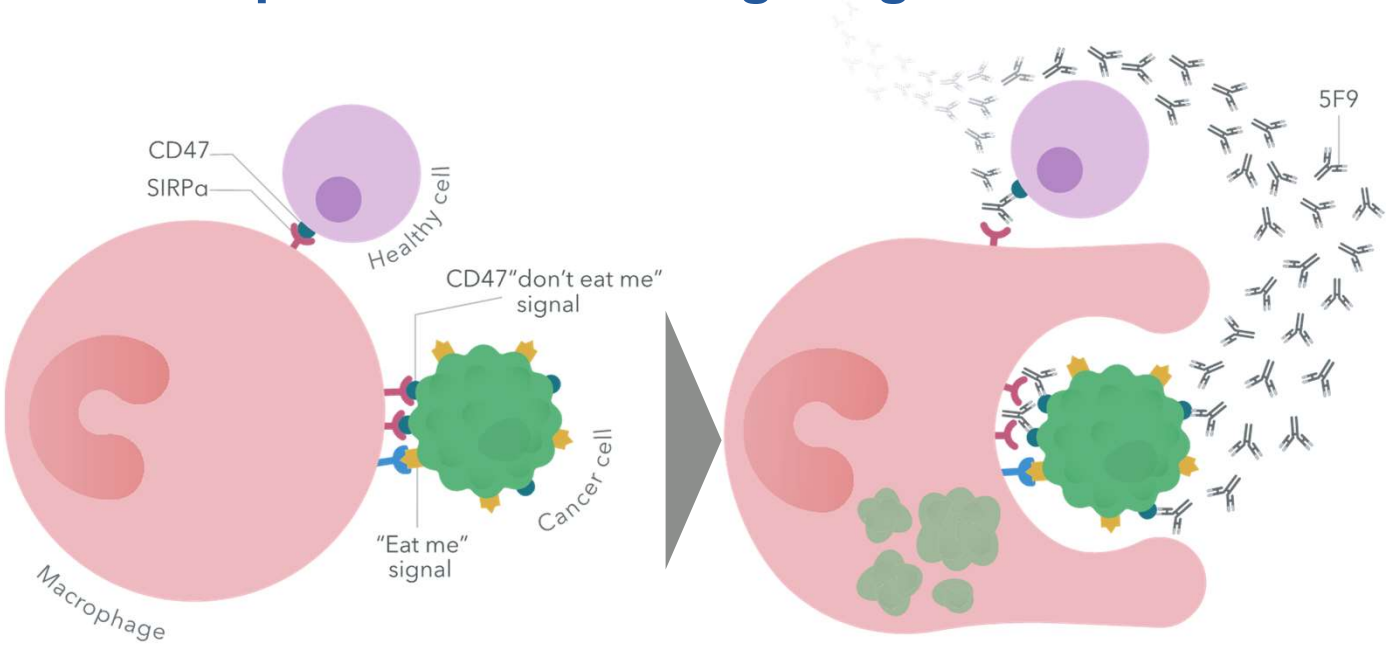
Zhang W et al., *Frontiers in Immunology* 2020; Chao M et al., *Curr Opin Immunol* 2012

Anti-CD47 Therapy + Rituximab can Overcome Rituximab Resistance

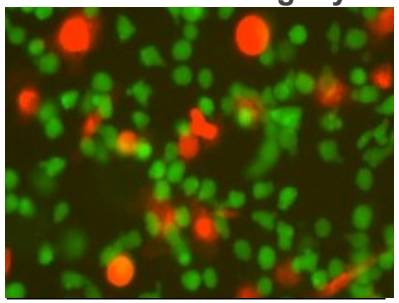


Advani R et al., *NEJM* 2018; Chao M et al., Cell 2010

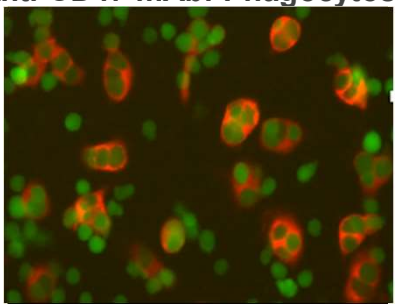
Magrolimab (Formerly 5F9) is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages Cancer cells

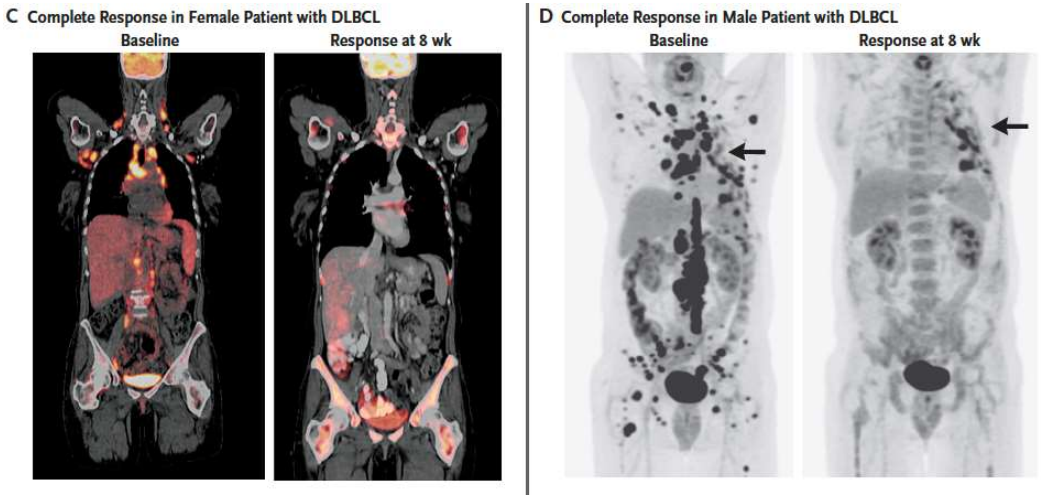
- Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers

Sallman D et al., 2020 ASCO

Efficacy of Magrolimab + Rituximab in NHL

Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

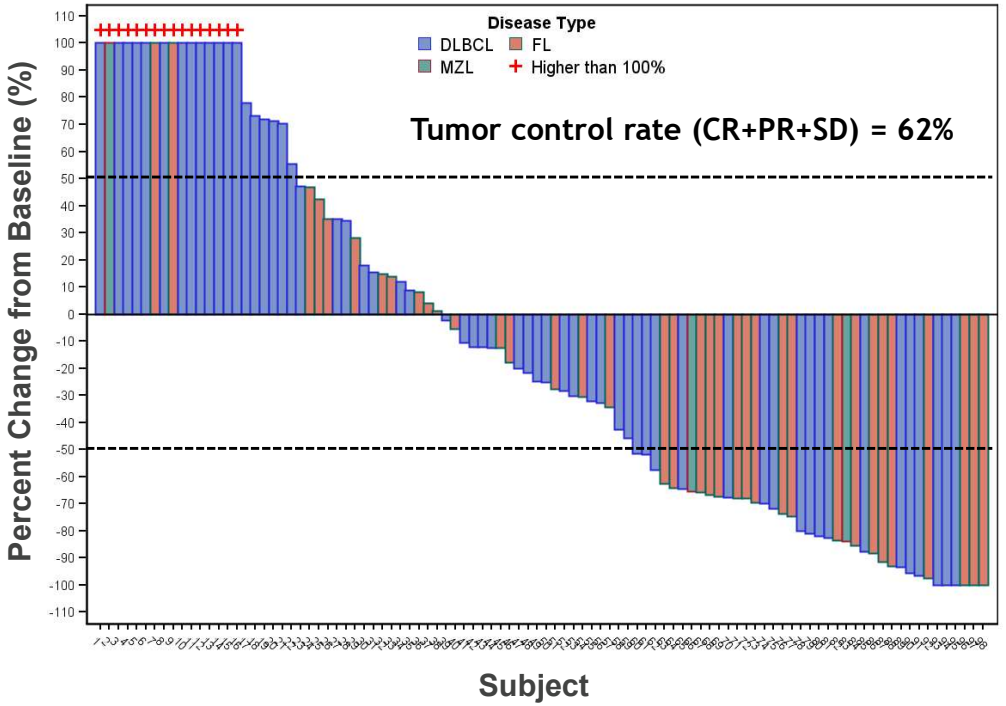
Response	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Objective response	11 (50)	6 (40)	5 (71)
Complete response	8 (36)	5 (33)	3 (43)
Partial response	3 (14)	1 (7)	2 (29)
Stable disease	3 (14)	3 (20)	0
Progressive disease	8 (36)	6 (40)	2 (29)
Disease control	14 (64)	9 (60)	5 (71)



Advani R et al., NEJM 2018

Phase 2 Data of Magrolimab and Rituximab in NHL

Best overall response	Total N=97	DLBCL N=59	Indolent lymphoma (FL N=35, MZL N=3)
ORR	44 (45%)	21 (36%)	23 (61%)
CR	18 (19%)	9 (15%)	9 (24%)
PR	26 (27%)	12 (20%)	14 (37%)
SD	16 (17%)	7 (12%)	9 (24%)
PD	37 (38%)	31 (53%)	6 (16%)



- The ORR across all patients is 45% (36% for DLBCL, 61% for indolent lymphoma) per Lugano criteria
- Median time to response is rapid at 1.8 months (range: 1.6 – 7.3 months)

Roschewski M et al., EHA 2019

SIRPα Fusion Proteins Active in NHL

- TTI-621 (IgG1) +/- rituximab – 18-29% ORR with monotherapy responses; thrombocytopenia AEsTTI-622 (IgG4) +/- rituximab – dose escalation ongoing in R/R NHL, 33% ORR (n=6; 1 durable CR) with monotherapy, 1 thrombocytopenia DLT
- ALX-148 + rituximab - 35% ORR in NHL, overall well tolerated
- Multiple other trials ongoing

Patel K et al., ASCO 2020; Kim T et al., ASH 2019

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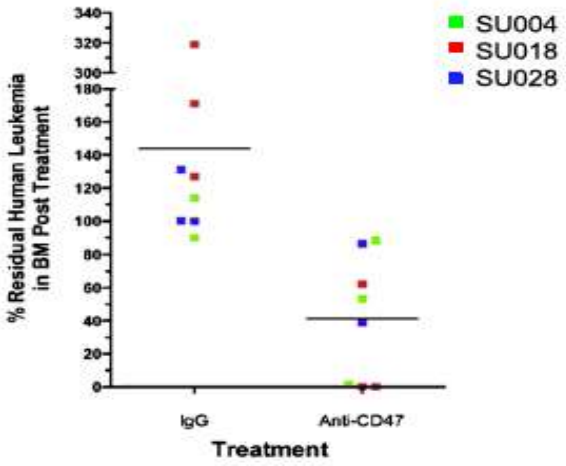
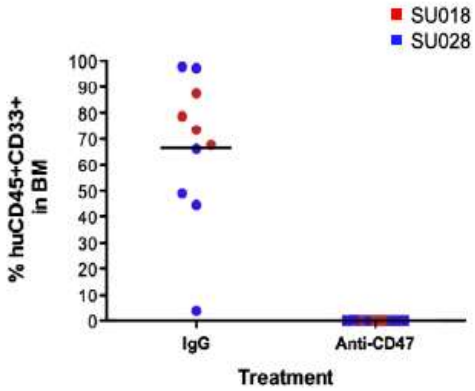
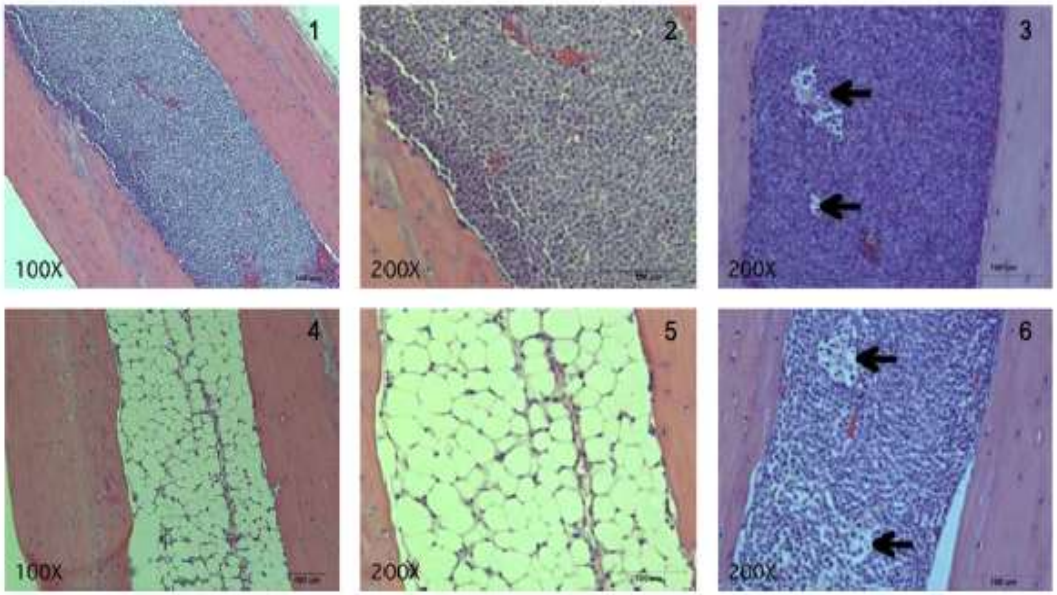
Preclinical efficacy of CD47 and AML

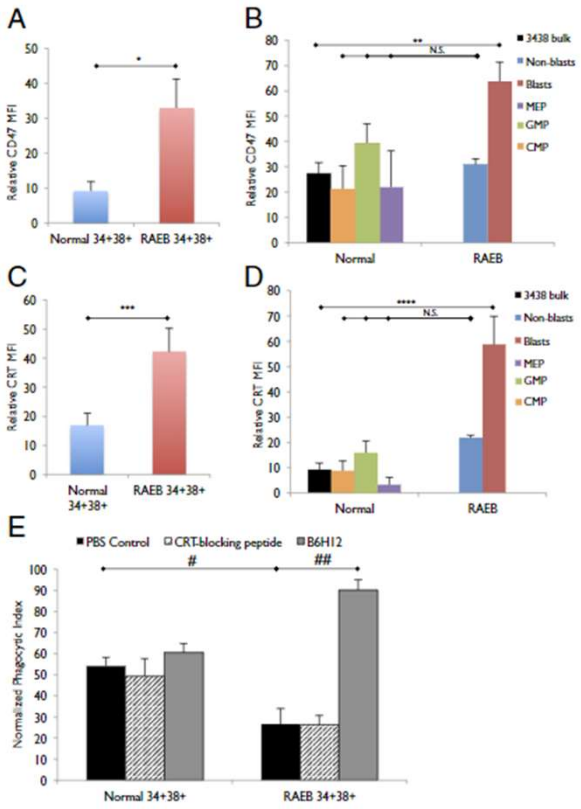


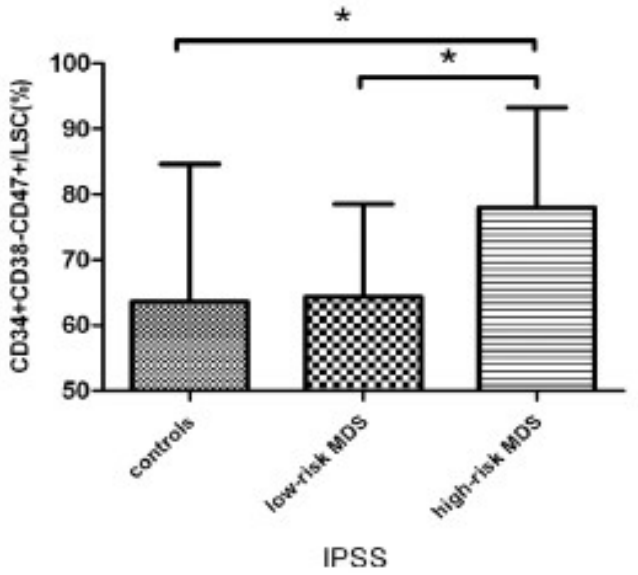




Majeti, Chao et al., *Cell* 2009;

Calreticulin and CD47 in MDS Patients

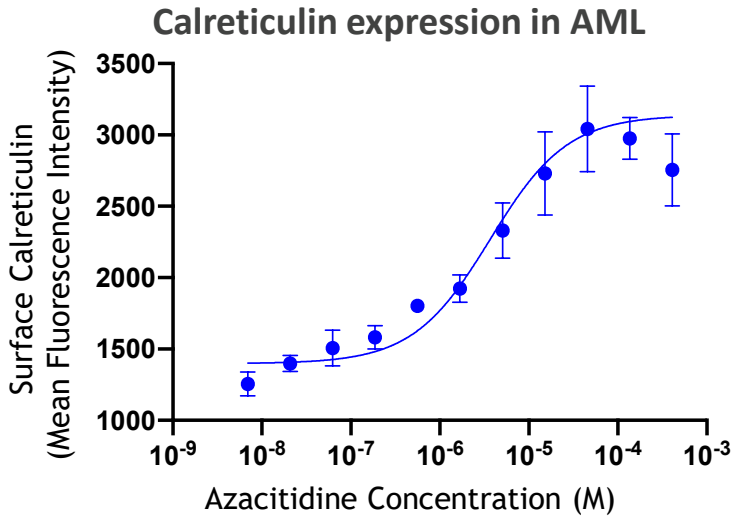


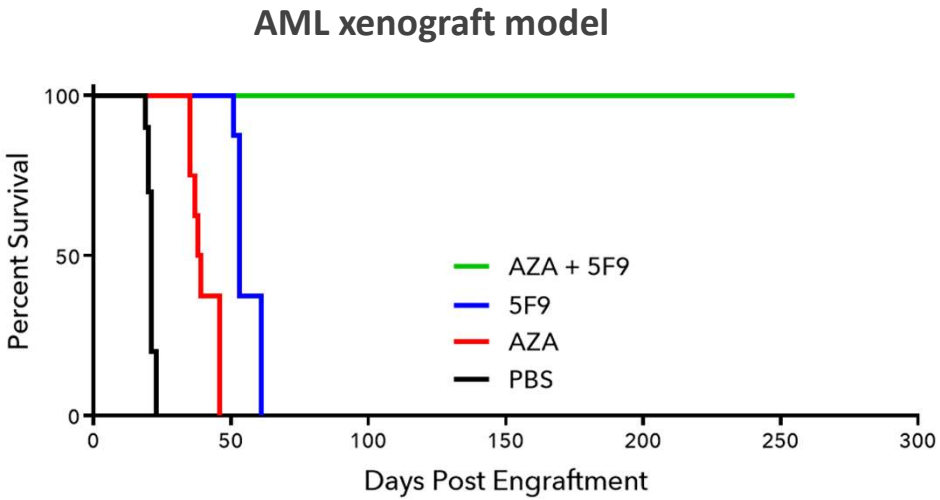


Pang W et al., *PNAS* 2013; Jiang H et al., *Leukemia Research* 2013

Magrolimab Synergizes with Azacitidine to Induce Remissions in AML Xenograft Models

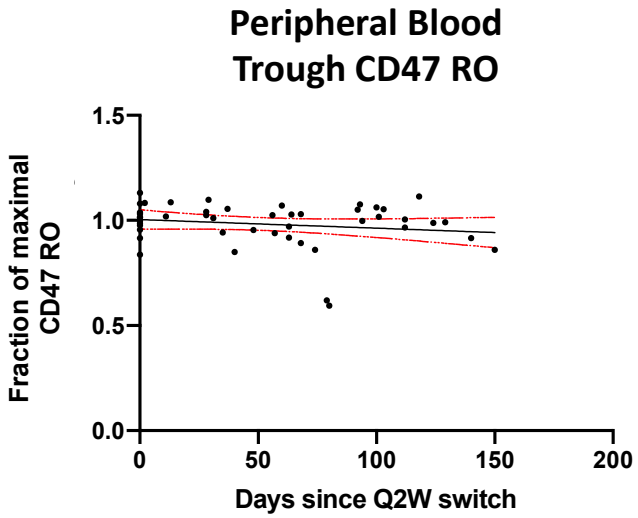
- Azacitidine (AZA) induces pro-phagocytic “eat me” signals like calreticulin on cancer cells
- Increased eat me signals induced by azacitidine synergizes with CD47 blockade of the “don’t eat me” signal leading to enhanced phagocytosis

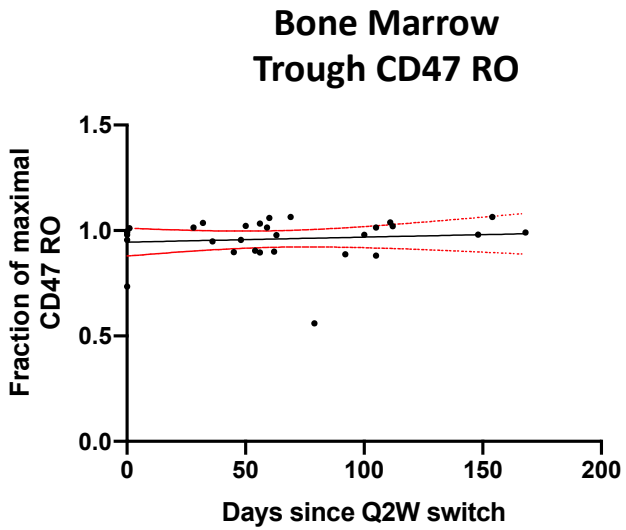




Feng D et al., ASH 2018

Magrolimab 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 et al., 2020 ASCO

Patient Characteristics (N=68): Magrolimab + AZA in Untreated (1L) MDS and AML

Characteristic	1L MDS 5F9+AZA (N=39)	1L AML 5F9+AZA (N=29)
Median age (range)	70 (47–80)	74 (60–89)
ECOG Performance Status: 0	11 (28%)	7 (24%)
1	26 (67%)	20 (69%)
2	2 (5%)	2 (7%)
Cytogenetic Risk: Favorable	0	0
Intermediate	11 (28%)	2 (7%)
Poor	25 (64%)	21 (72%)
Unknown/missing	3 (8%)	6 (21%)
WHO AML classification: MRC		19 (66%)
Recurrent genetic abnormalities	NA	2 (7%)
Therapy related		3 (10%)
Not otherwise specified		5 (17%)
WHO MDS classification:		
RS and single/multilineage dysplasia	1 (3%)	NA
Multilineage dysplasia	7 (18%)	
RS with multilineage dysplasia	3 (8%)	
Excess blasts	22 (56%)	
Unclassifiable/unknown/missing	6 (15%)	
IPSS-R (MDS): Intermediate	13 (33%)	NA
High	19 (49%)	
Very High	6 (15%)	
Unknown/missing	1 (3%)	
Therapy related MDS	12 (31%)	
Unknown/missing	1 (3%)	
Harboring a TP53 mutation	5 (13%)	13 (45%)

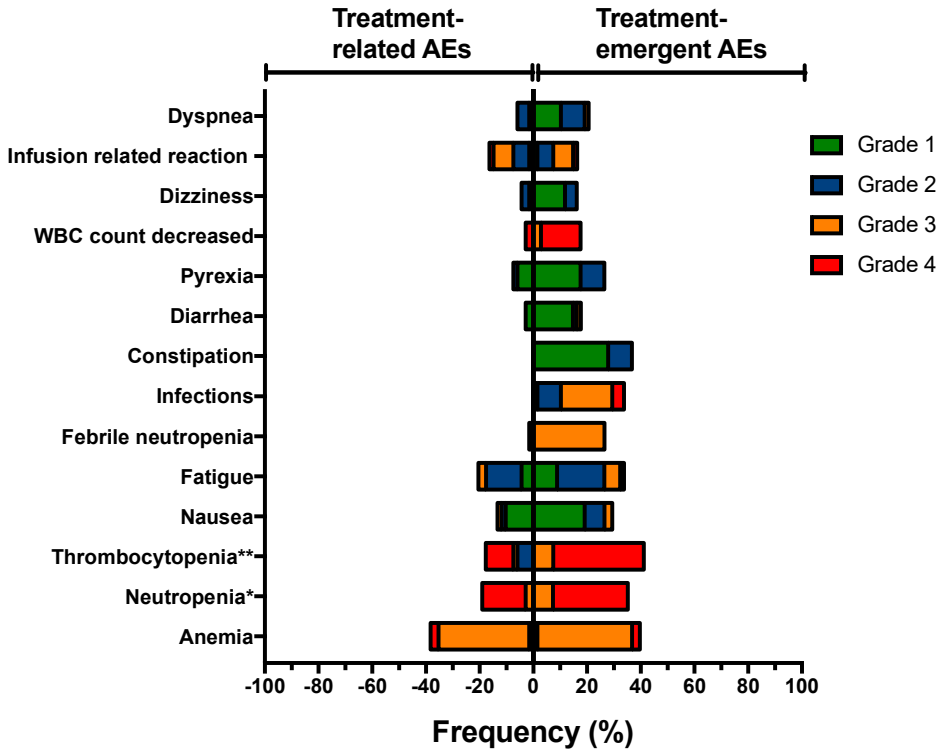
MRC, myelodysplasia-related changes; NA, not applicable; all patients enrolled on study are shown; WHO, World Health Organization.

- 64%–72% of MDS and AML patients were poor cytogenetic risk
- 66% of AML patients had underlying myelodysplasia (MRC)
- 31% of MDS patients were therapy related
- 45% of AML patients were *TP53* mutant

Sallman D et al., 2020 ASCO

Magrolimab in Combination With AZA Is Well Tolerated

MDS and AML Patients (N=68)



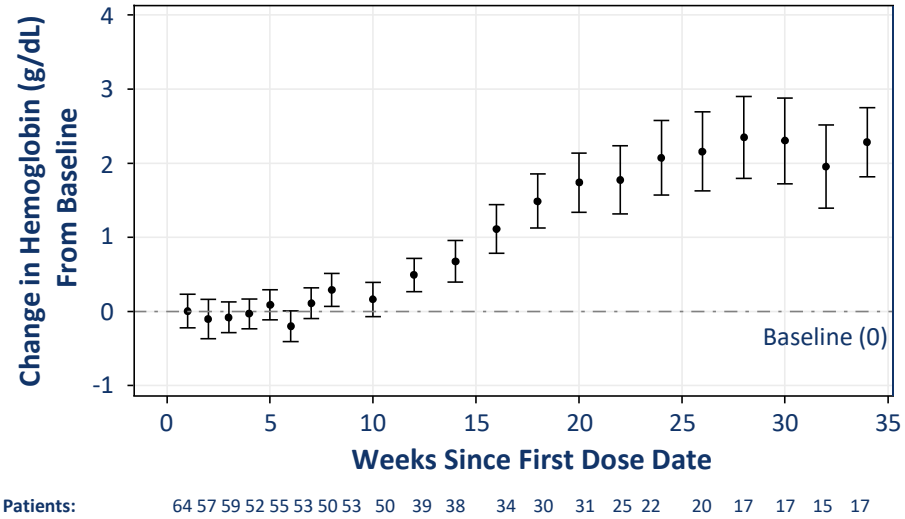
- No maximum tolerated dose was reached; magrolimab + AZA profile consistent with AZA monotherapy
- No significant cytopenias, infections, or immune-related AEs were observed (most patients were cytopenic at baseline)
- Anemia and transfusion frequency improved over time
- No deaths occurred during the 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.

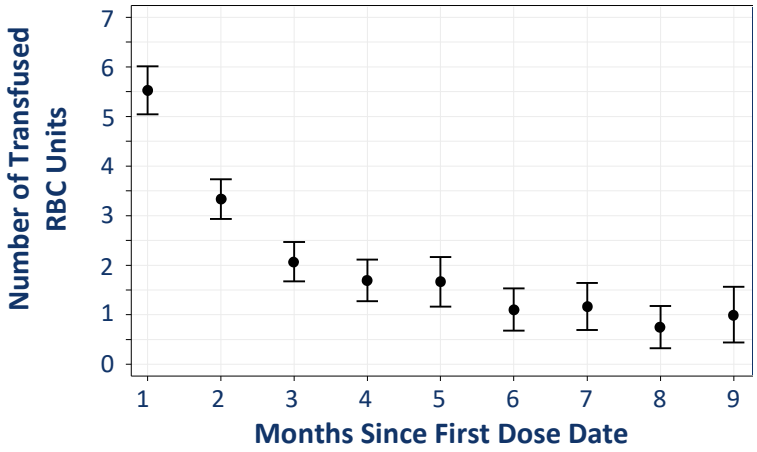
Sallman D et al., 2020 ASCO

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

Hemoglobin Changes on Therapy



RBC Transfusion Frequency on Therapy

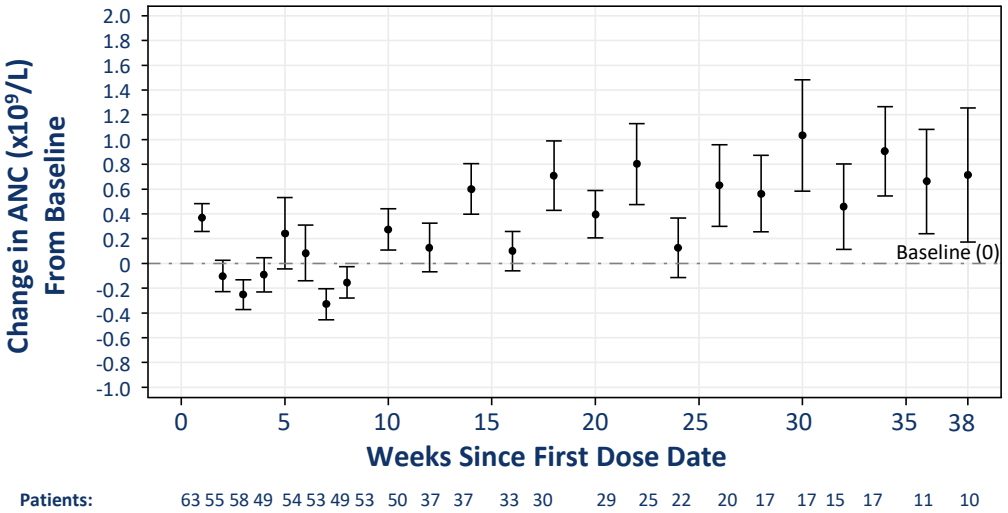


- An initial priming dose mitigates on-target anemia by CD47 blockade, resulting in a transient mild hemoglobin drop on the first dose (mean of 0.4 g/dL), which returns to baseline
- **The majority of patients had significant hemoglobin improvement and decrease in transfusion frequency over time**

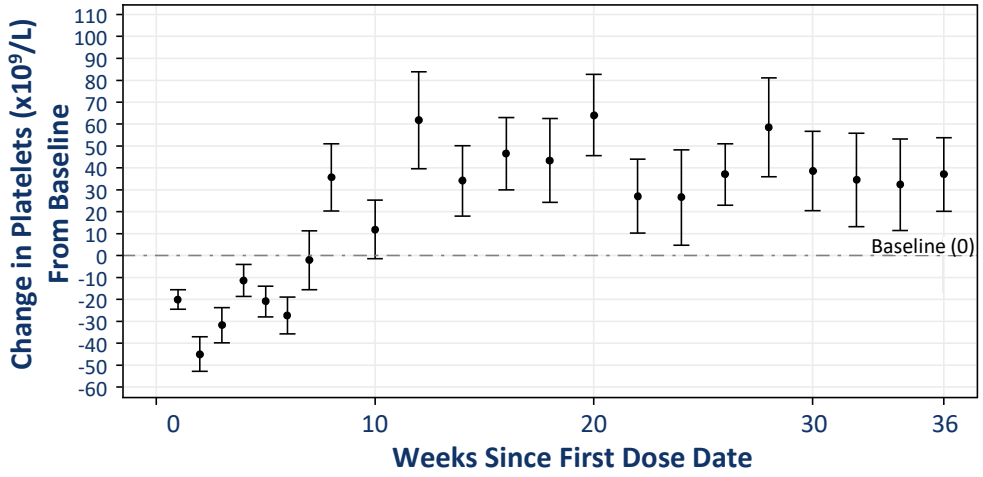
Sallman D et al., 2020 ASCO

Neutrophil and Platelet Improvement Is Seen on Magrolimab + AZA Therapy

Neutrophil Changes on Therapy



Platelet Changes on Therapy



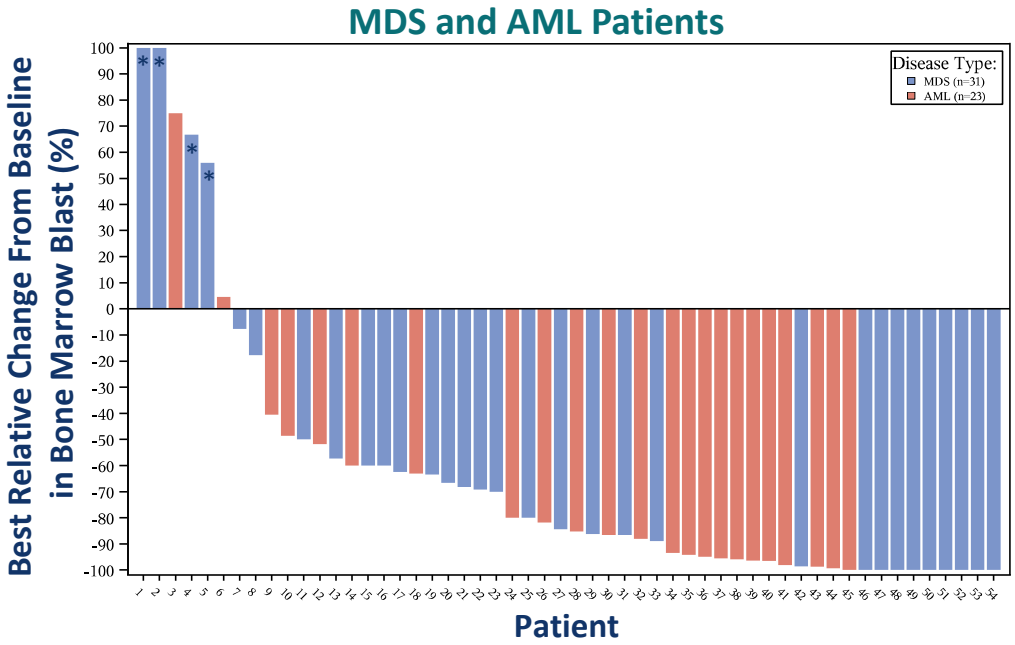
- Magrolimab + AZA does not induce significant neutropenia or thrombocytopenia
- The majority of patients improve their neutrophil and platelet count while on therapy

Sallman D et al., 2020 ASCO

Magrolimab + AZA Induces High Response Rates in MDS and AML

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

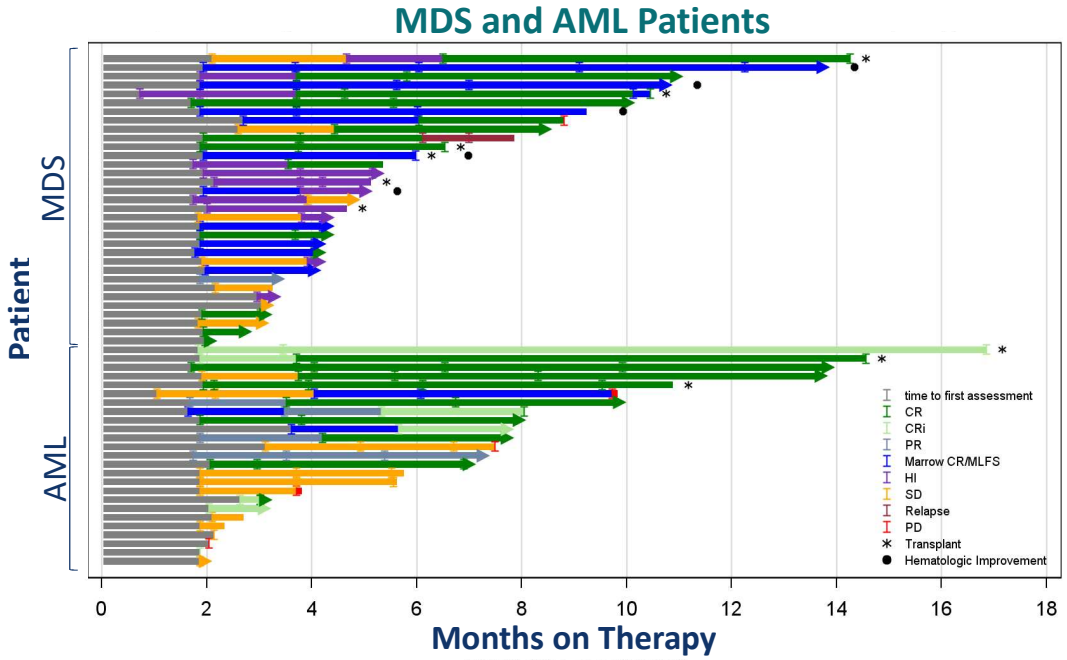
1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Sallman D et al., 2020 ASCO

Deep and Durable Responses Are Seen in Magrolimab + AZA Treated Patients

Parameter	1L MDS N=33	1L AML N=25
RBC transfusion independence*	11/19 (58%)	9/14 (64%)
Complete cytogenetic response†	9/26 (35%)	6/12 (50%)
MRD negativity in responders	6/30 (20%)	8/16 (50%)
Median duration of response (months)	Not reached (0.03+ – 10.4+)	Not reached (0.03+ – 15.1+)
Median follow-up (range) (months)	5.8 (2.0–15.0)	9.4 (1.9–16.9)

MRD was evaluated by multiparameter flow cytometry; cytogenetic response defined per 2003 and 2006 IWG criteria.
*Patients shown for those who were RBC transfusion dependent at baseline and achieved RBC transfusion independence at any time on study.
†Responses shown for all responding patients with abnormal cytogenetics at baseline.



- Complete cytogenetic responses and MRD negativity is observed in MDS and AML patients
- No median duration of response has been reached for MDS or AML
- 16% of patients (9/58) received an allogeneic stem cell transplant
- Median OS has not been reached in either MDS or AML patients

Sallman D et al., 2020 ASCO

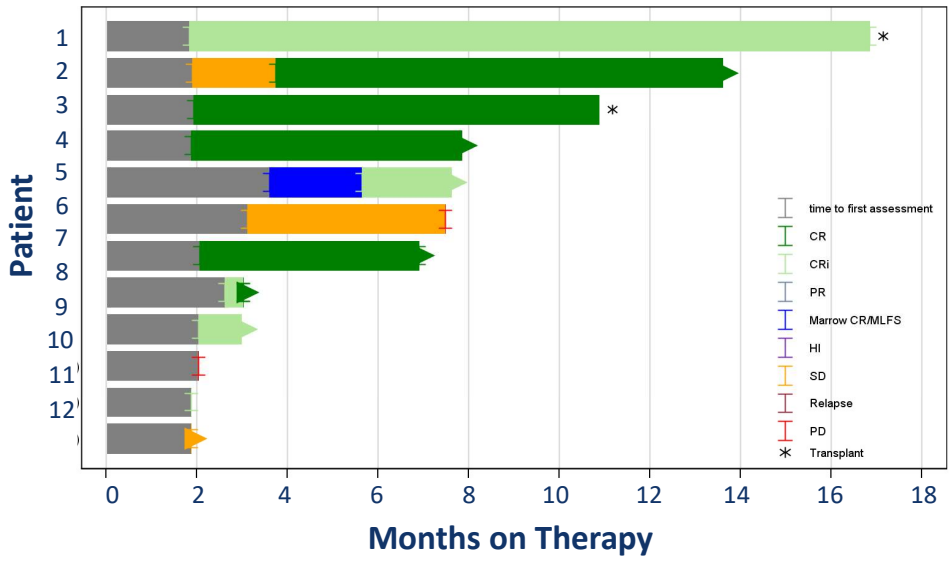
Magrolimab + AZA Eliminates Disease in AML and MDS Patients With *TP53* Mutation

Efficacy in *TP53*-Mutant Patients

Best Overall Response	AML *TP53* Mutant (N=12)	MDS *TP53* Mutant (N=4)
ORR	9 (75%)	3 (75%)
CR	5 (42%)	2 (50%)
CRi/marrow CR	4 (33%)	1 (25%)
Complete cytogenetic response *	4/8 (50%)	3/3 (100%)
MRD negative of responders	4/9 (44%)	0
Median duration of response (months)	Not reached (0.03+ – 15.1+)	Not reached (0.03+ – 5.2+)
Survival probability at 6 months	91%	100%
Median follow-up (range) (months)	8.8 (1.9 – 16.9)	7 (4.2 - 12.2)

*Based on 12 patients with abnormal cytogenetics at baseline.

TP53-Mutant AML Patients

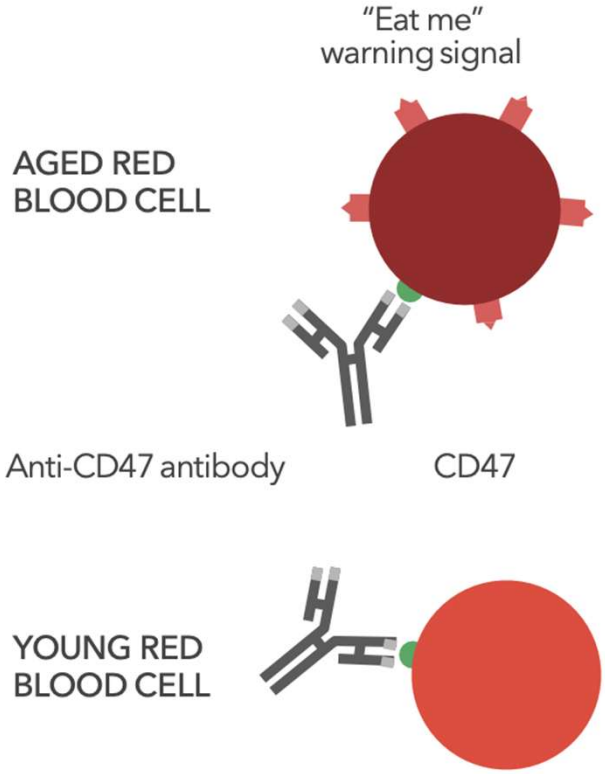


- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax + AZA in AML: ORR 47%, DOR 5.6 mo, OS 7.2 mo[1]

1. DiNardo CD. et al. *Blood*. 2019:133(1):7-17.

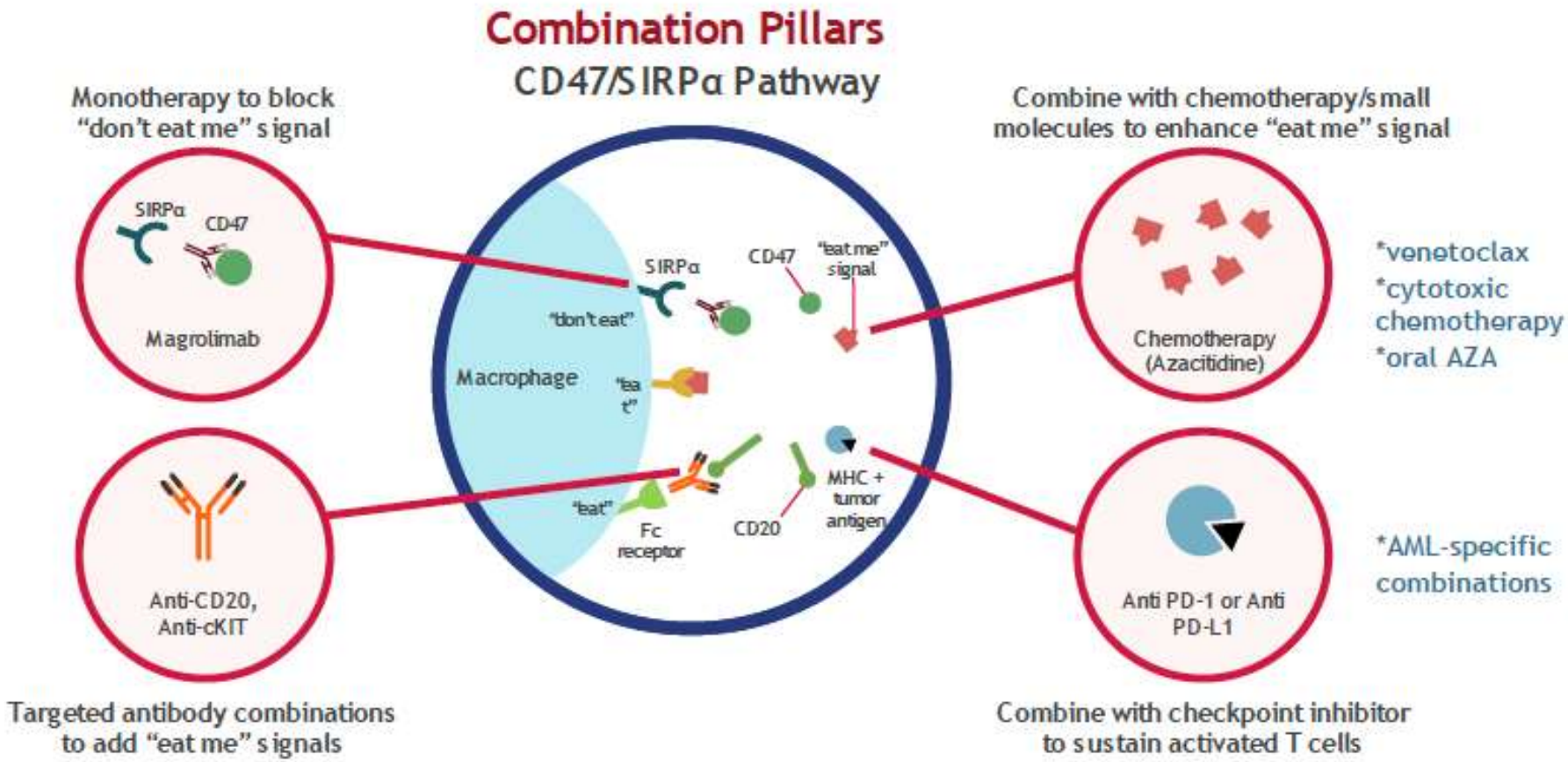
On Target Anemia and Mitigation Strategies

- 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

Combination Therapy with CD47 Targeted Therapy



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

Macrophage Directed Therapies in Myeloid malignancy

Therapy	Mechanism of action	Fc isotype	Eligibility	Phase (status)	NCT identifier	Reference
Magrolimab + Azacitidine	CD47 antibody	IgG4	Phase Ib (R/R and Treatment Naïve higher risk MDS and AML) Phase III (Treatment Naïve higher risk MDS)	Phase Ib (Recruiting) Phase III- ENHANCE (Not Yet Recruiting)	NCT02678338 NCT03248479 NCT04313881	[18, 19]
CC-90002	CD47 antibody	IgG4	R/R High risk MDS and AML	Phase I (Terminated)	NCT02641002	[17]
TTI-621	SIRPα fusion protein	IgG1	R/R hematologic malignancies including MDS, MPN and AML	Phase Ia/Ib (Recruiting)	NCT02663518	[26]
ALX148 + Azacitidine	High affinity SIRPα fusion protein + hypomethylating agent	Inert IgG1	Treatment Naïve or R/R Higher risk MDS	Phase I/II (Not Yet Recruiting)	NCT04417517	
Magrolimab and Venetoclax +Azacitidine	CD47 antibody + BCL-2 inhibitor + hypomethylating agent	IgG4	Phase Ib dose finding (R/R AML) Phase II (newly diagnosed AML not candidate for IC)	Phase Ib/II (Recruiting)	NCT04435691	
Magrolimab and Atezolizumab	CD47 antibody + PD-L1 antibody	IgG4	R/R AML	Phase Ib (Recruiting)	NCT03922477	

Current as of September 9th, 2020 on clinical trials.gov.

Swoboda D and Sallman D, manuscript under review

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 or pevonedistat)
- 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

Future Directions

- Further evaluation of mechanisms of synergy and resistance for HMA combination therapies and other novel strategies
- Biomarkers of response including other molecular cohorts
- Clinical investigation of novel triplet vs sequential strategies with incorporation of MRD by serial NGS and multiparameter flow cytometry.

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