CD47 potential in AML/MDS

NOVEMBER 2021

Naval Daver, MD

Director, Leukemia Research Alliance Program,
Associate Professor
Department of Leukemia
MD Anderson Cancer Center

Disclosures | Naval Daver, MD

Research Funding

Pfizer, BMS, Novartis, Servier, Daiichi-Sankyo, Karyopharm, Incyte, Abbvie, Genentech, Astellas, Immunogen, Forty-Seven, Amgen, Trovagene, Novimmune

Advisory/Consulting

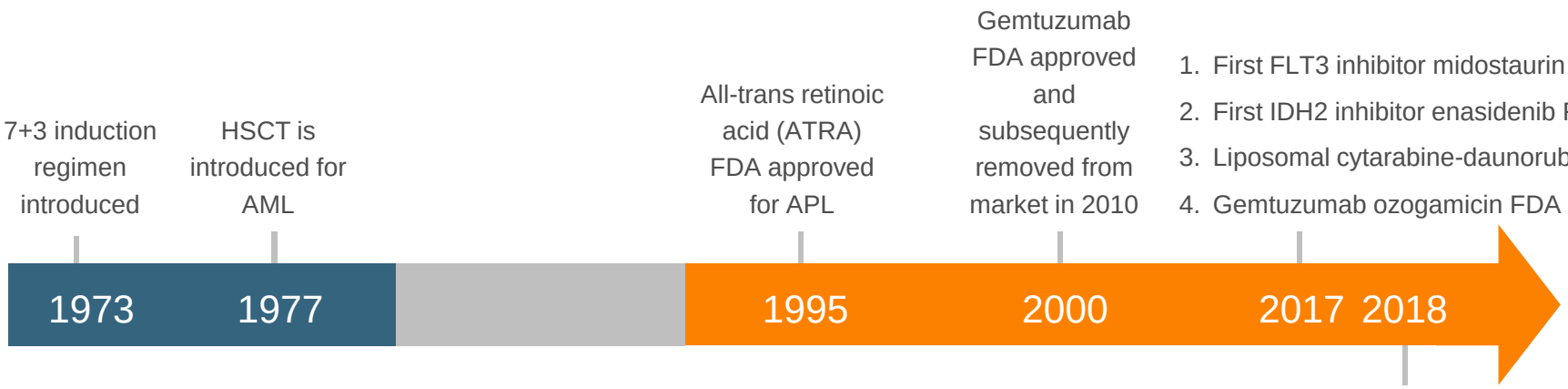
Pfizer, BMS, Daiichi-Sankyo, Novartis, Jazz, Astellas, Abbvie, Genentech, Agios, Servier, Immunogen, Forty-Seven, Gilead, Syndax, Trillium

Disclaimer

Data will include medications not yet approved or with indications still under clinical study

Treatment of AML (accelerated progress 2017–2019): History

Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML

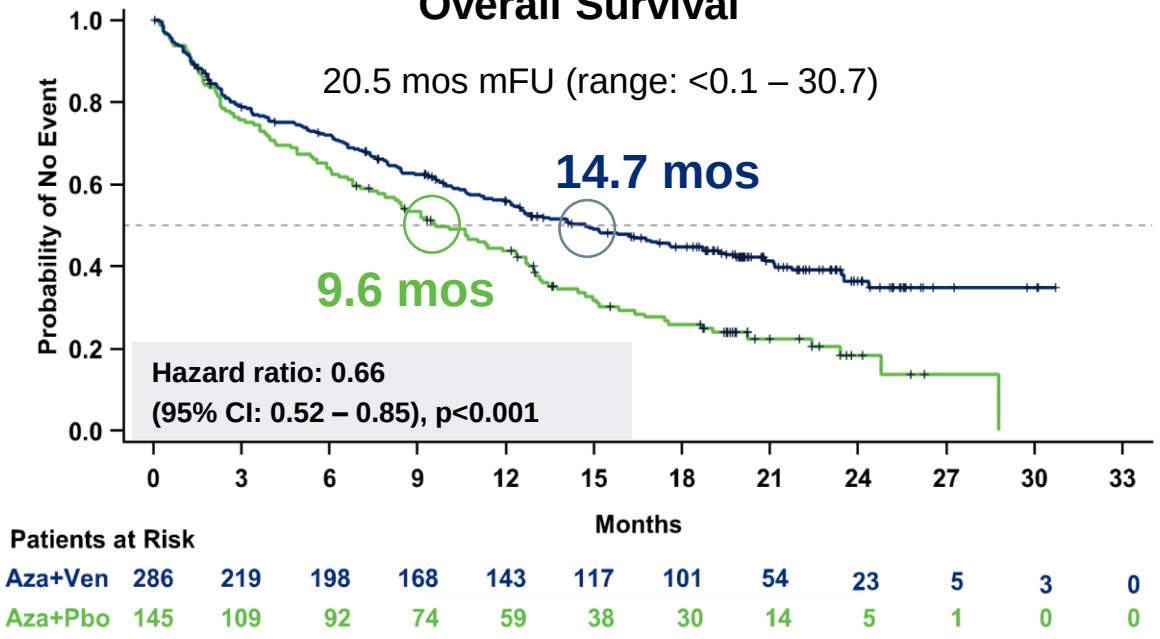


1. Ivosidenib is FDA approved in 2018 for r/r AML with a susceptible *IDH1m*
2. AZA + VEN and LDAC + Ven approved for older AML (Nov 21, 2018)
3. LDAC + glasdegib approved for older AML (Nov 21, 2018)
4. Gilteritinib for relapsed *FLT3* AML (Dec 2018)

Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

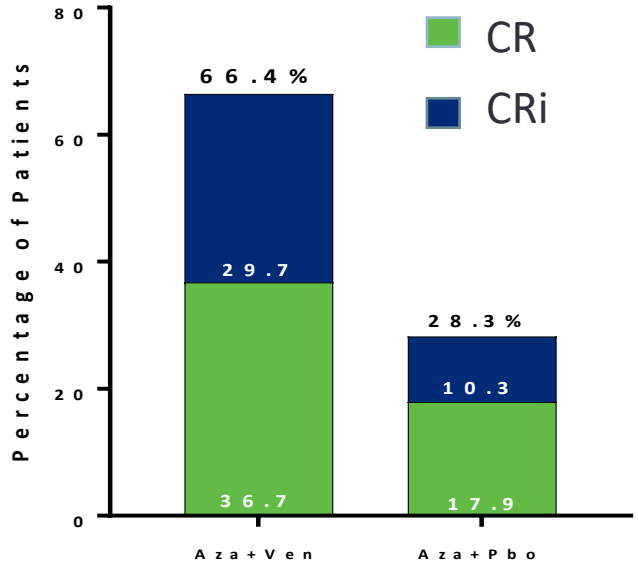
AZA+/- VEN in AML – Clinical Responses

Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

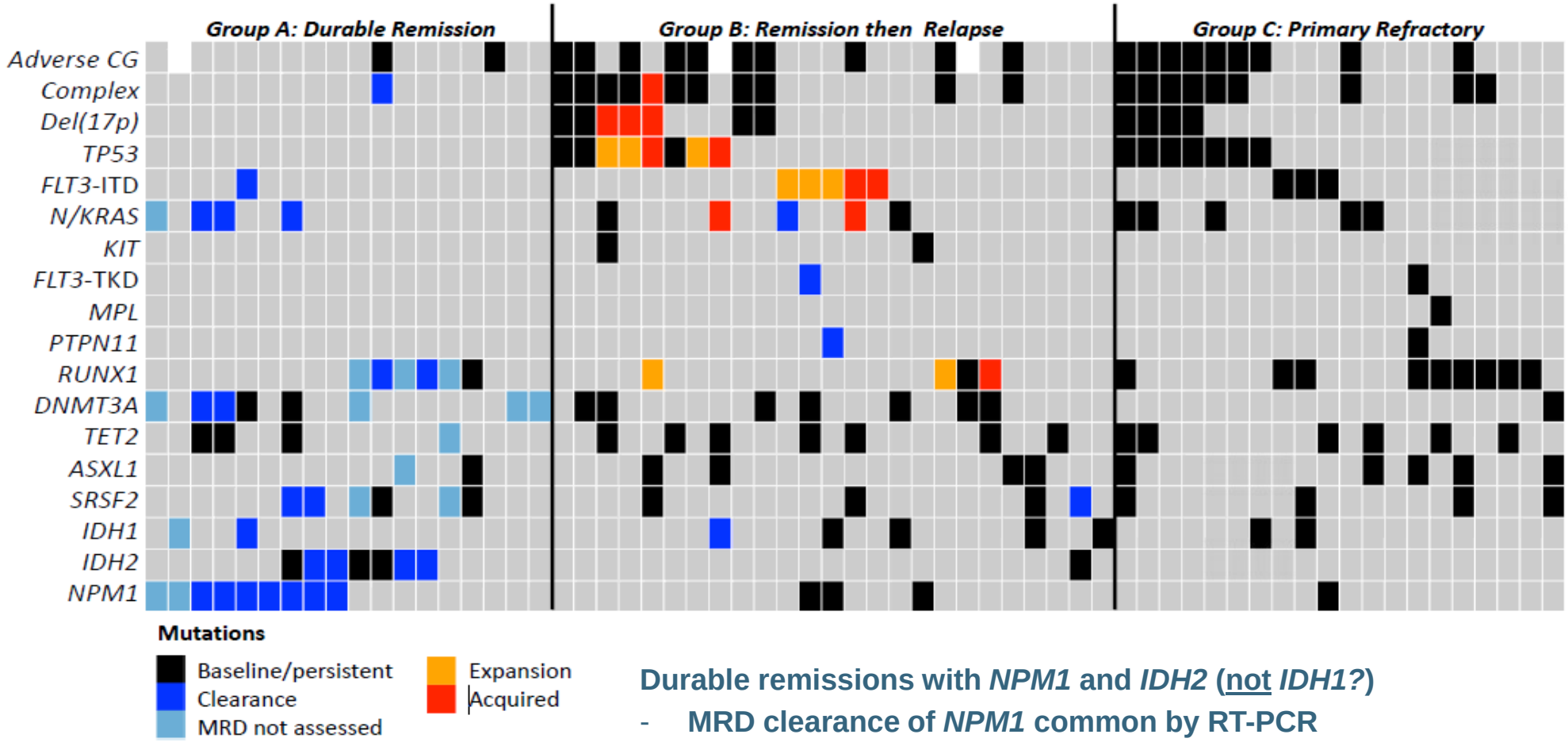
Composite Response Rate (CR+CRi)



	No. cycles, Median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

DiNardo EHA 2019 *CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Molecular Determinants of Outcome With Venetoclax Combos: Several Molecular subsets with sub-optimal benefit from HMA+VEN (TP53, RAS, CBL, KIT, FLT3, others…



Durable remissions with *NPM1* and *IDH2* (not *IDH1?*)

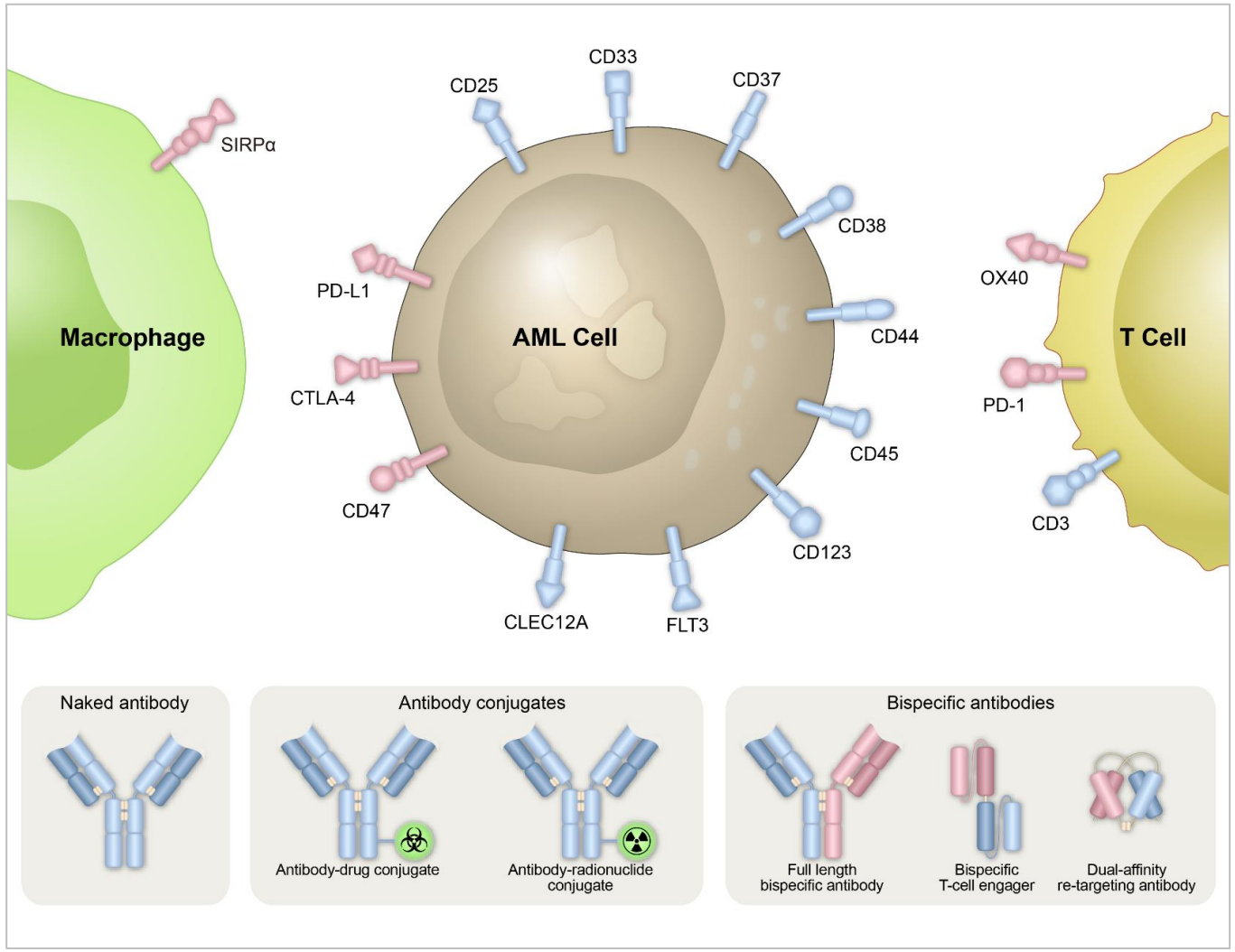
- **MRD clearance of *NPM1* common by RT-PCR**

Resistance commonly associated with expansion or acquisition of *TP53* or signaling mutations including *K/NRAS* and *FLT3*-ITD

Patients treated at MDACC and The Alfred (n = 81)

DiNardo CD, et al. *Blood.* 2020;135(11):791-803.

Heavy Shift in Focus to Developing Immune Based Approaches in AML



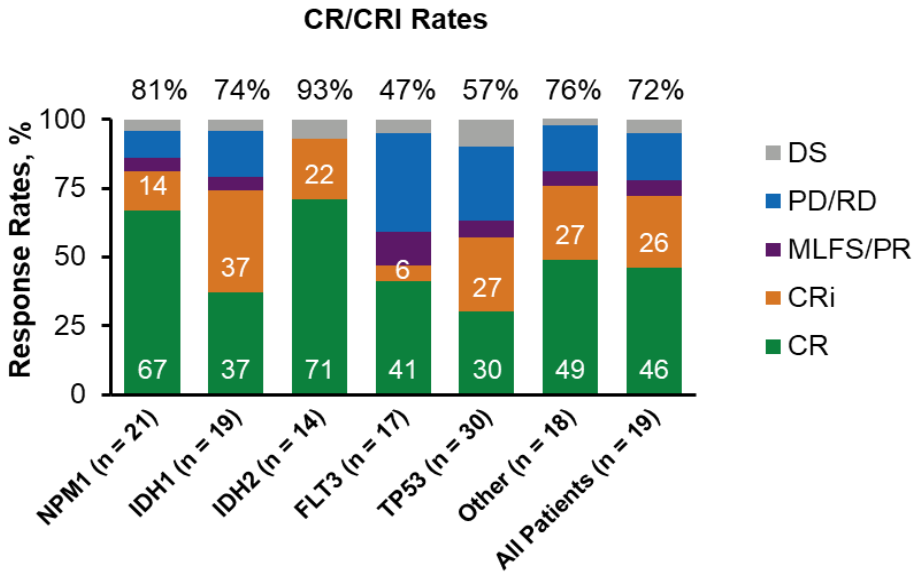
Short N….Daver N, et al, Cancer Discovery 2020

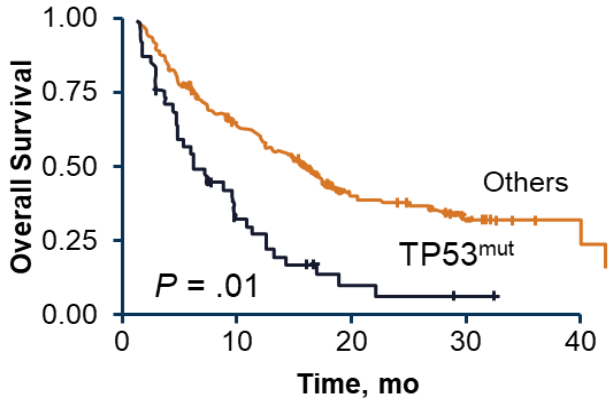
Two major approaches:

1. Antibody drug conjugates (CD33, CD123, CLL1)
2. Adaptive or Innate immune system harnessing therapies:
   a. Bi-specific antibodies (CD3 x AML antigen; CD47 x CD3, others)
   b. Immune checkpoint based approaches: T-cell and macrophage checkpoints
   c. CART, CAR NK, High volume hn-NK cells
   d. Vaccines

Very Poor Outcomes in *TP53* Mutant AML, Even With Venetoclax-Based Treatment

Venetoclax + LDAC or HMA
(Phase IB study)[1]

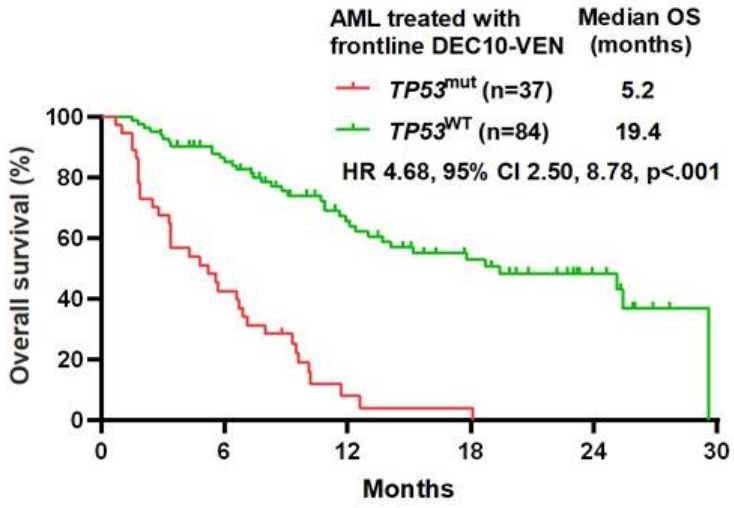




Median OS = 6.4 months

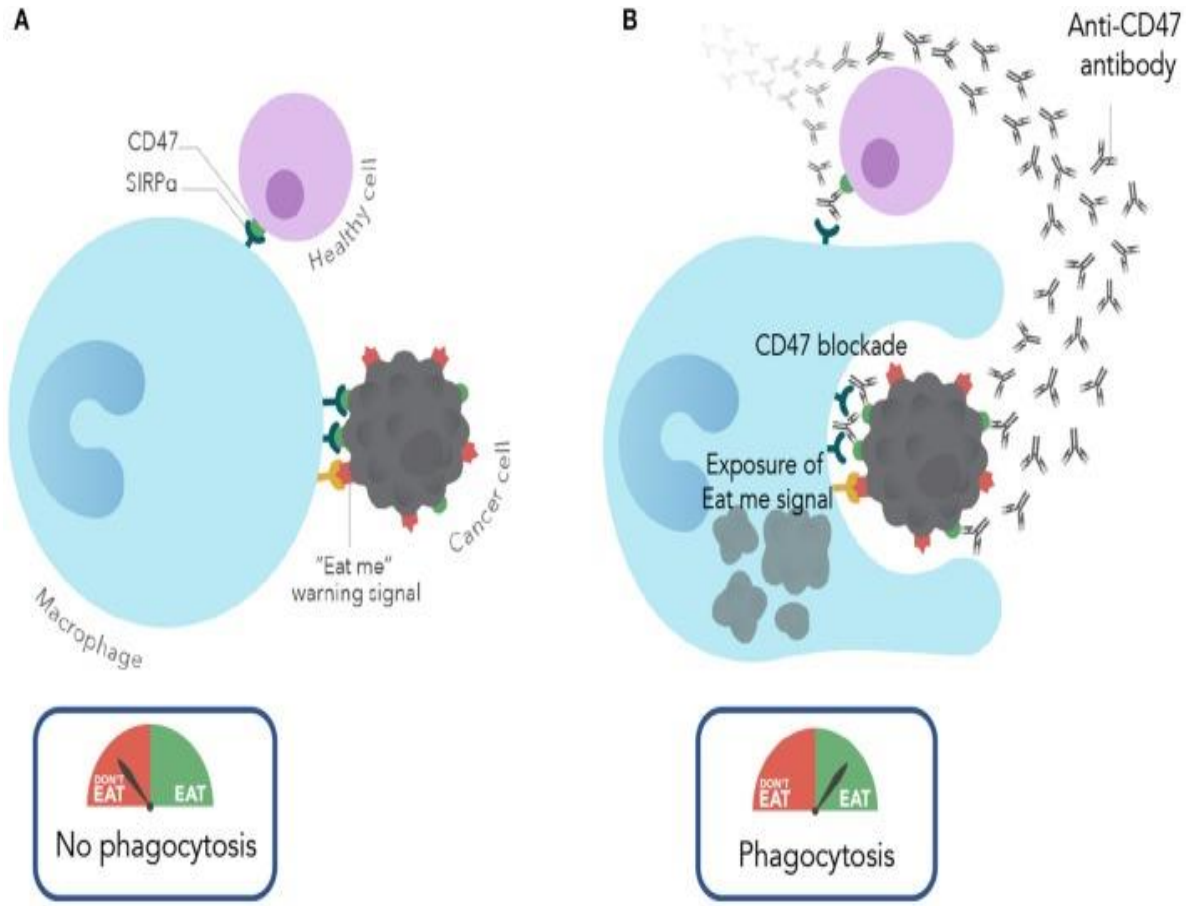
N = 121 patients with newly diagnosed AML receiving decitabine + venetoclax[2]

- Those with *TP53*^{mut} (N=35) had a lower rate of CR at 35% vs 57% in pts with *TP53*^{WT} (N=83) (P = 0.026)
- Lower rate of CR/CRi (54% vs. 76%; *P* .015),



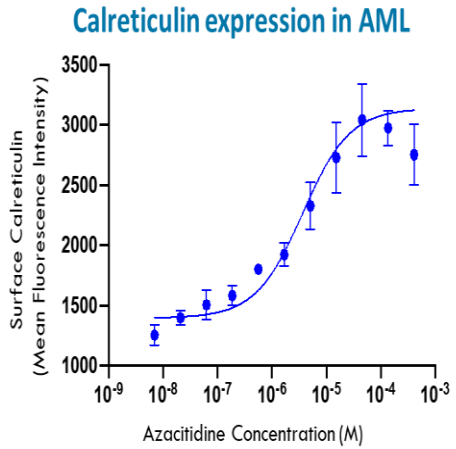
1. Chyla BJ et al. ASH 2019. Abstract 546. 2. Kim K, et al. ASH 2020. Abstract 693

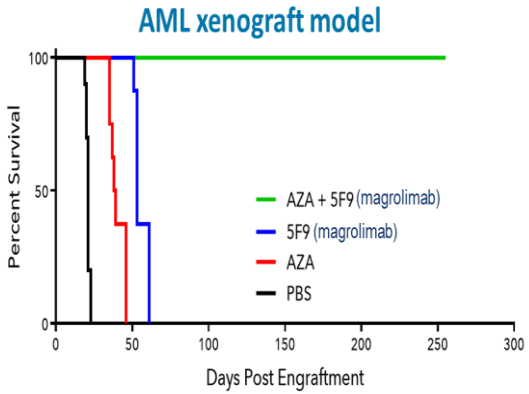
Mechanism of Action of CD47 Blocking Antibodies



Magrolimab Synergizes With Azacitidine to Induce Remissions in AML Xenograft Models

- Azacitidine (AZA) induces prophagocytic "eat me" signals, like calreticulin on cancer cells
- Increased "eat me" signals induced by AZA synergize with CD47 blockade of the "don't eat me" signal, leading to enhanced phagocytosis

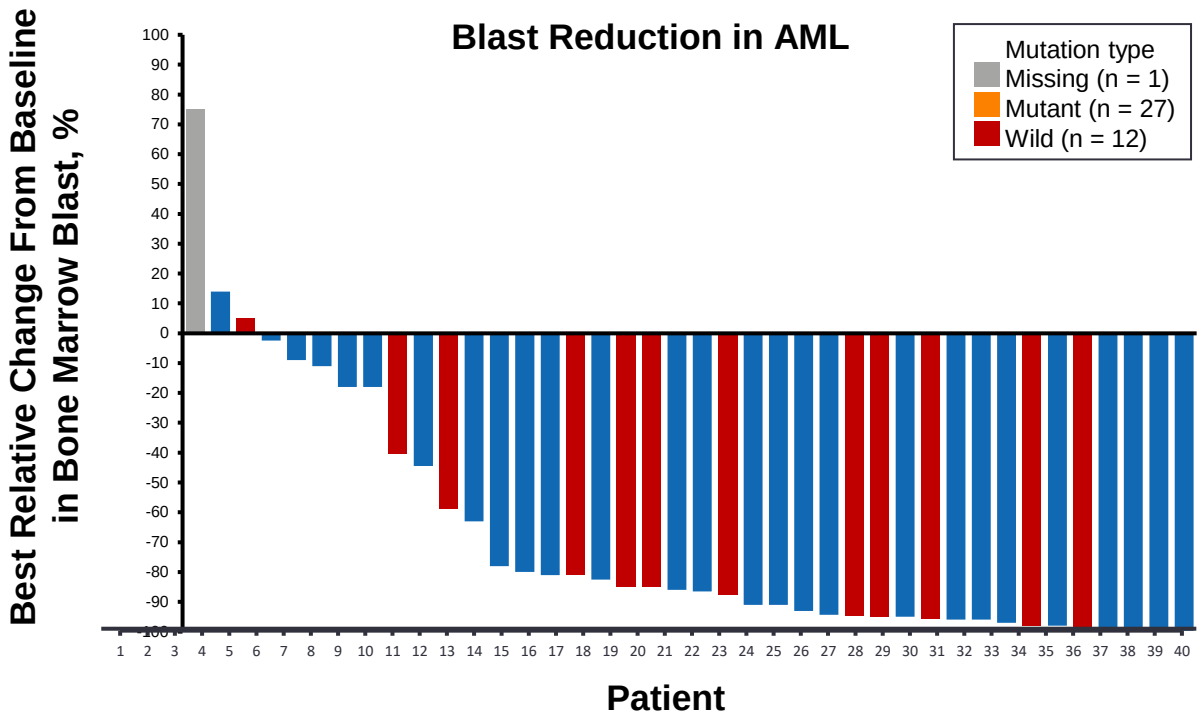




Feng D, et al. ASH 2018, Abstract #616 (with adaptations).

Magrolimab + AZA in Newly Diagnosed AML

Best Overall Response	All AML (N = 43), n (%)	*TP53*-Mutant AML (n = 29), n (%)
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)

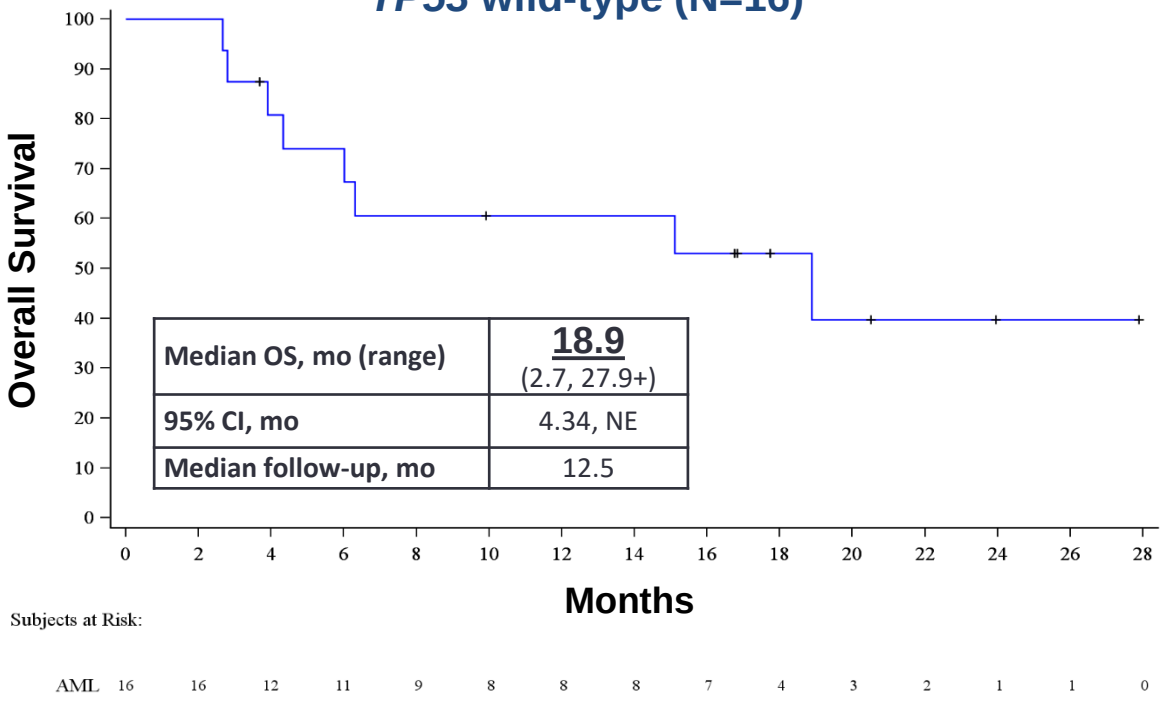


- Magrolimab + AZA with 63% ORR and **42% CR rate** in AML (similar responses in *TP53*-mutant disease)
- Median time to response is 1.95 months (range, 0.95-5.6 mo); more rapid than AZA monotherapy
- Magrolimab + AZA efficacy compares favorably with AZA monotherapy (CR rate: 18%-20%)
- No significant cytopenias, infections, or immune-related AEs were observed; on-target anemia
- Median TP53 VAF burden at baseline: **73.3% (range 23.1% - 98.1%)**

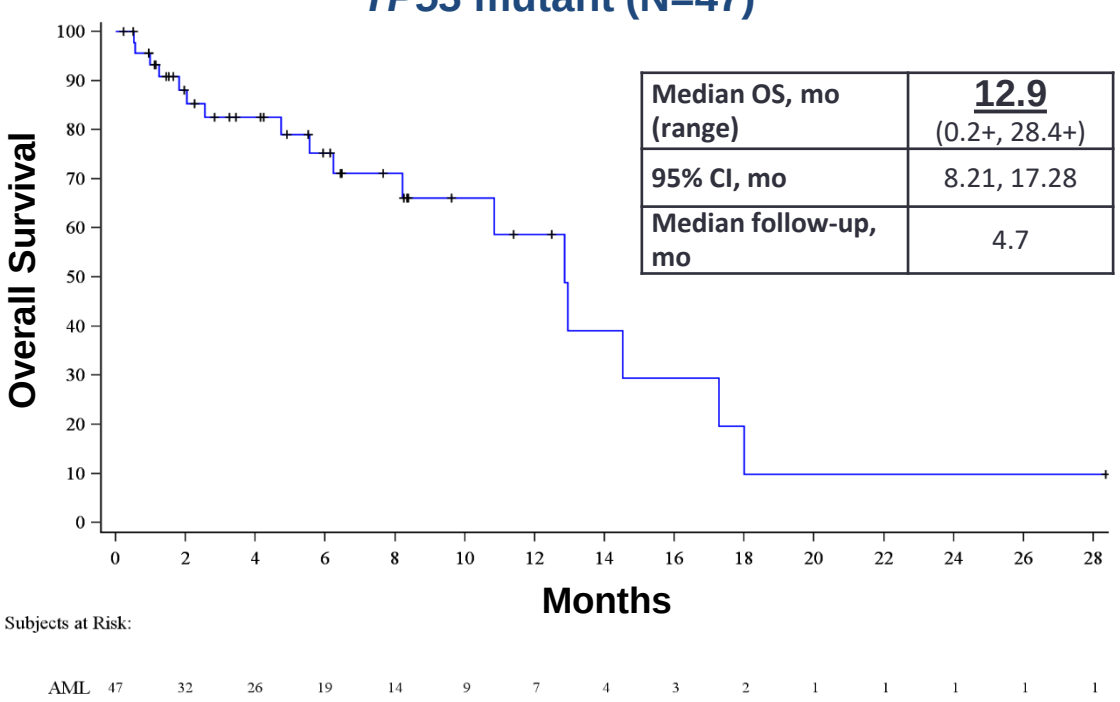
1. Daver N et al. EHA 2020. Abstract 2. Sallman D et al. ASH 2020. Abstract 330.

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

TP53 wild-type (N=16)



TP53 mutant (N=47)



- 18.9 mos mOS in *TP53* wild-type patients vs 12.9 mos in *TP53*-mutant patients
- mOS with venetoclax + hypomethylating agent combinations (**14.7-18.0 mos** in all-comers,[1,3] **5.2–7.2 mos** in *TP53m*[2,3])
- Additional patients and longer follow-up needed

NE, not evaluable. Sallman D et al, ASH 2020, abst #330

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.

Novel Immune Strategies to Kill AML, Potentially Mutation Agnostic

ADAPTIVE

Recruiting **CD3** T cell -- **BiTEs** linking to CD3 and targeting CD33/123; **CARTs** with modified CD3 killer cells (success in ALL, lymphoma, MM)

Targets beyond CD33/123 e.g. **CLL1,** IL1RAP, TIM3, CD70, others

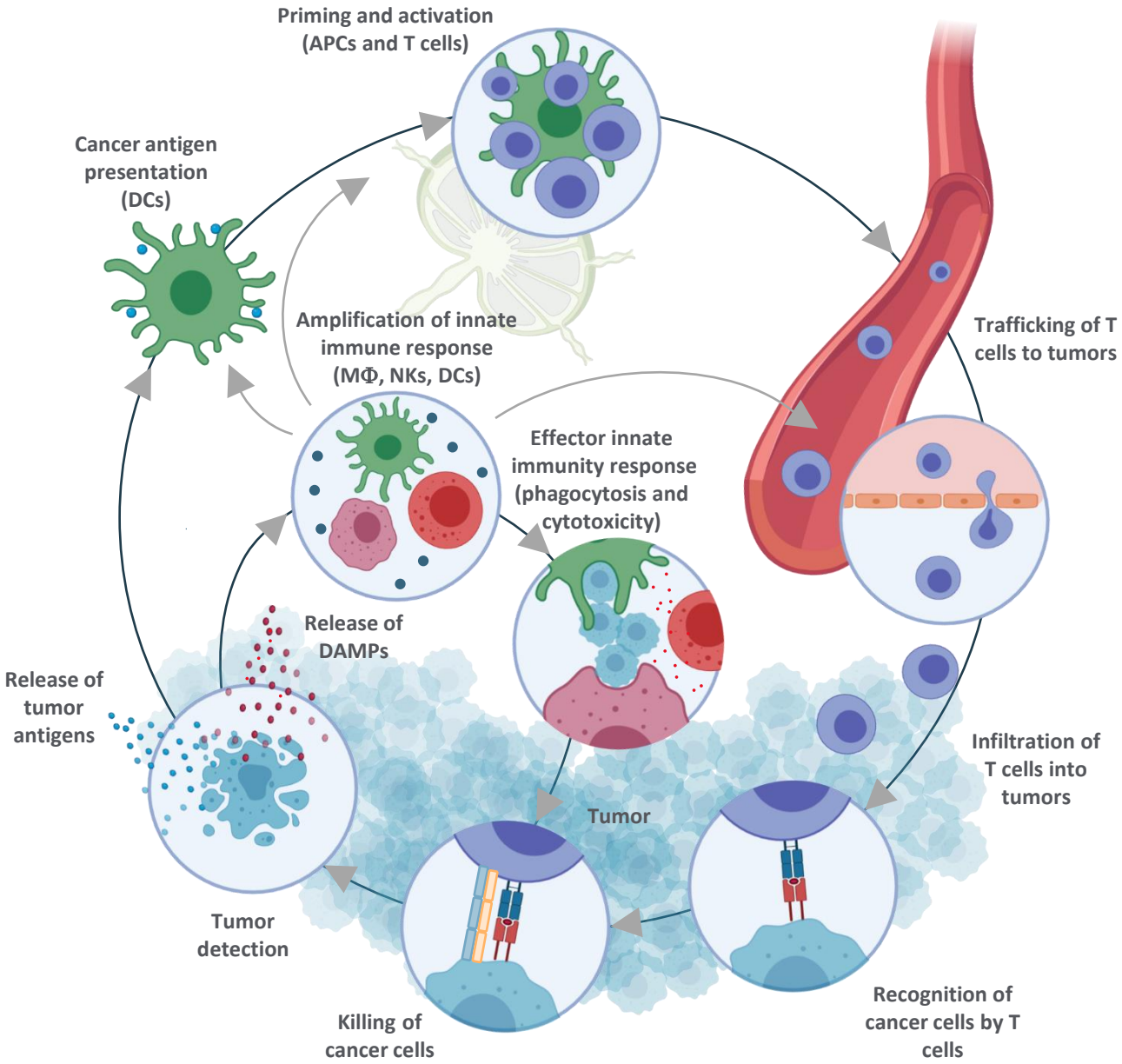
INNATE
(Appears to be more resilient and preserved in AML)

Recruiting **macrophages** -- targeting CD47 on AML (Magrolimab, Lemzo, TTI-622, Evorpacept, DSP107)

Recruiting **NK cells** -- allo NK-CARTs; NK engineered cells (hn, CD38 ko, IL15)

Innate Anti-Tumor Immune Responses

- The adaptive T-cell immune response to tumors does not progress in isolation
- The innate immune response supports and is inter-connected with the adaptive immune response
- Innate immune cells exert effector functions such as phagocytosis (macrophages, polymorphonuclear cells) and natural cytotoxicity (NK cells)



APCs, antigen-presenting cells; DAMPS, damage-associated molecular patterns; DCs, dendritic cells; MΦ, macrophage; NK, natural killer

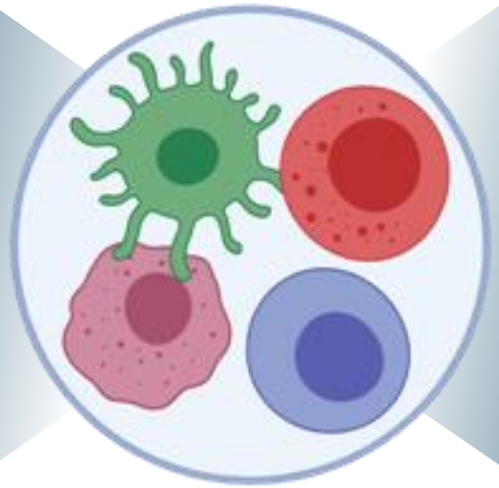
1. Demaria O, et al. *Nature* 2019;574:45-56.

Selected Innate Immune Checkpoint Targets

Investigational agents in development targeting innate immune cell effector functions

Phagocytosis Checkpoint Targets

Target	Cell Expression
CD47	Tumor cells, normal cells
SIRPa	MF, DCs, mast cells, neutrophils



Broad-spectrum Checkpoint Targets

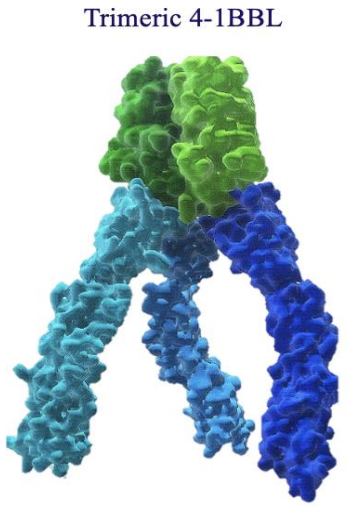
Target	Cell Expression
NKG2A	NK cells, T cells
TIGIT	NK cells, T cells
TIM-3	T cells, NK cells, NKT cells, DCs, and MFs
LAG-3	T_{reg} cells, CD8+ TILS, NK cells

DCs, dendritic cells; LAG-3, lymphocyte activation gene-3; MΦ, macrophage; NK, natural killer; NKG2A, NK group 2 member A; NKT cells, natural killer T cells; SIRPα, signal-regulatory protein α; TIGIT, T-cell immunoglobulin and ITIM domain; TILS, tumor infiltrating lymphocytes; TIM-3, T-cell immunoglobulin and mucin-domain containing 3; T_{reg} cells, regulatory T cells

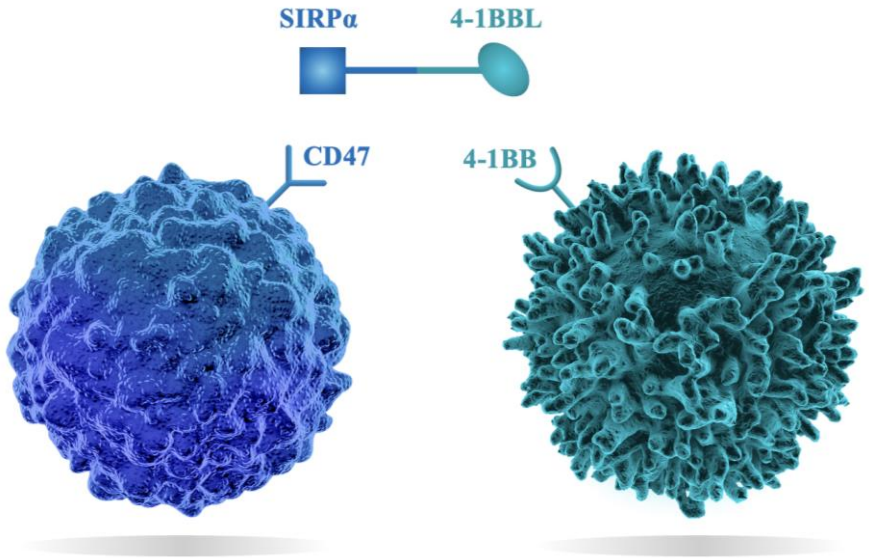
1. Demaria O, et al. *Nature* 2019;574:45-56.

Bispecific CD47-SiRPα and T-cell (4-1BB) engaging approaches (DSP107)

Activating the innate and adaptive immune systems

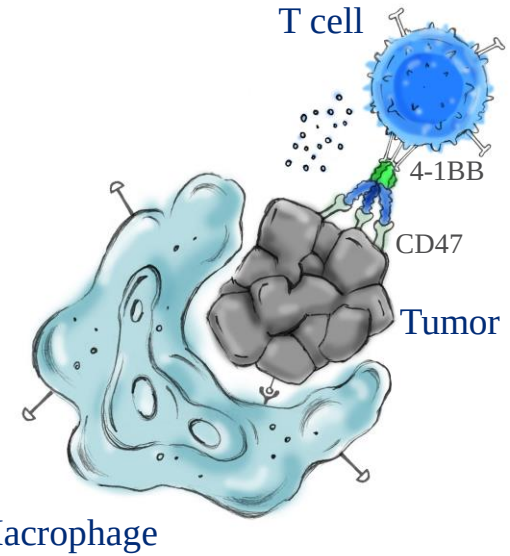


3 SIRPα for
CD47 Checkpoint Targeting



SIRPα binds to **CD47** overexpressed on cancer cells, disabling their 'don't eat me' signal

4-1BBL binds to **4-1BB** on tumor-antigen specific T cells, stimulating their expansion, cytokine production and development of cytolytic effector functions



Next-generation CD47 Programs Will Be Differentiated By Improved Safety

Clinical safety profile of CD47 mAbs

Company	Gilead/ Forty Seven	Surface Oncology	Trillium Therapeutics	Trillium Therapeutics	Celgene	ALX Oncology
Candidate	Magrolimab (n = 48)	SRF231 (n = 46)	TTI-621 (n = 89)	TTI-622 (n = 19)	CC-90002 (n = 28)	Evorpacept (n = 28)
Indication	r/r solid tumors and lymphomas	r/r solid tumors and lymphomas	r/r lymphoma	r/r heme malignancies and select solid tumors	r/r AML or MDS	r/r solid tumors and lymphoma
Dose Levels	0.1 - 45 mg/kg	0.1 - 12 mg/kg	0.1 - 0.2 mg/kg	0.1 - 8 mg/kg	0.1 – 4 mg/kg	0.3 – 30 mg/kg
Anemia (Grade All, ≥3)	56%, 10%	24%, 17%	11%, 9%	<10%, 0%	7%, 7%	≤4%, 0%
Thrombocytopenia (Grade All, ≥3)	13%, 0%	<10%, --	24%, 19%	5%, 0%	7%, 7%	11%, 7%
Neutropenia (Grade All, ≥3)	4%, 0%	22%, 20%	<10%, --	11%, 11%	0%, 0%	4%, 4%

Hematological toxicity safety advantage including lack of on target anemia and transfusion requirements can differentiate next generation CD47 programs vs competitors

Source: LifeSci report August 2020

CD47 Monotherapy Lacks Clinical Activity In AML/MDS

- Clinical experience to date with the majority of CD47 mAbs suggests lack of monotherapy activity in solid and hematological malignancies
- In patients with AML/MDS, responses were mostly observed when CD47 mAbs were combined with azacytidine
- Next generation CD47 programs with activity as a monotherapy will be differentiated in AML/MDS
- Effective treatments in R/R AML and R/R MDS remains an unmet need, with majority of responses to date occurring in the frontline setting

Source: LifeSci report August 2020

Summary and Unmet Needs in AML/MDS

- Entrance of venetoclax and other targeted therapies into the market has improved survival rates
- TP53-mutant patients with high-risk MDS and AML have dismal outcomes with standard therapy
- Long-term efficacy and efficacy in patients with high-risk molecular features remains an unmet need
- Targeting CD47 is an immune based approach that has demonstrated clinical responses in combination with azacitidine in both the frontline setting and in patients with high-risk features
- Current majority of CD47 mAbs lack therapeutic activity as a monotherapy and have hematological safety issues
- Novel strategies targeting both the adaptive and innate immune systems may help achieve mutation agnostic clinical responses with durable benefits
- Next-generation CD47-targeted therapeutic in development, including SIRPα/CD47 bi-specific inhibitors, with potential for more robust activity and improved safety