PD1, CD47, and Other Immune Based Approaches in AML

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Disclosures

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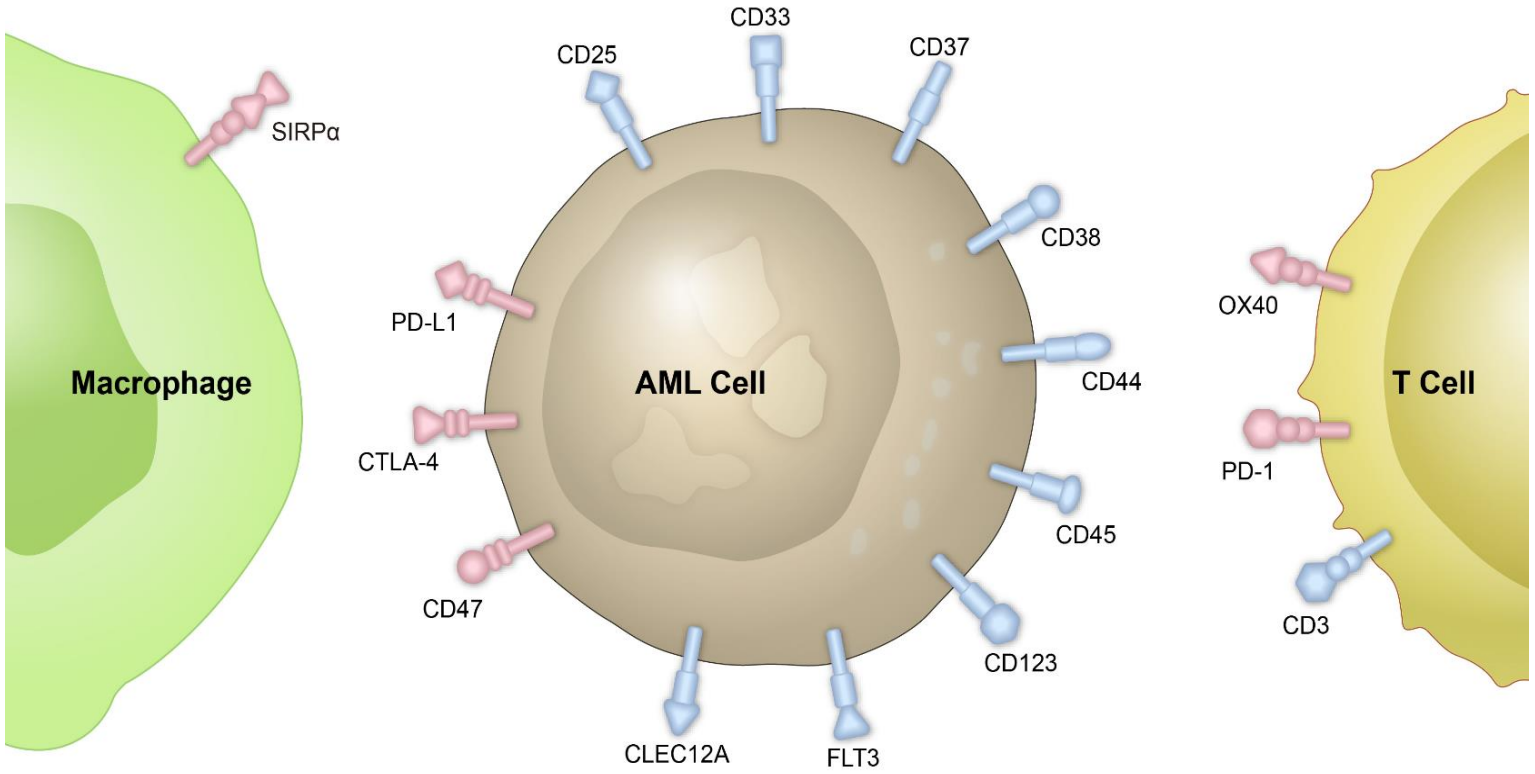
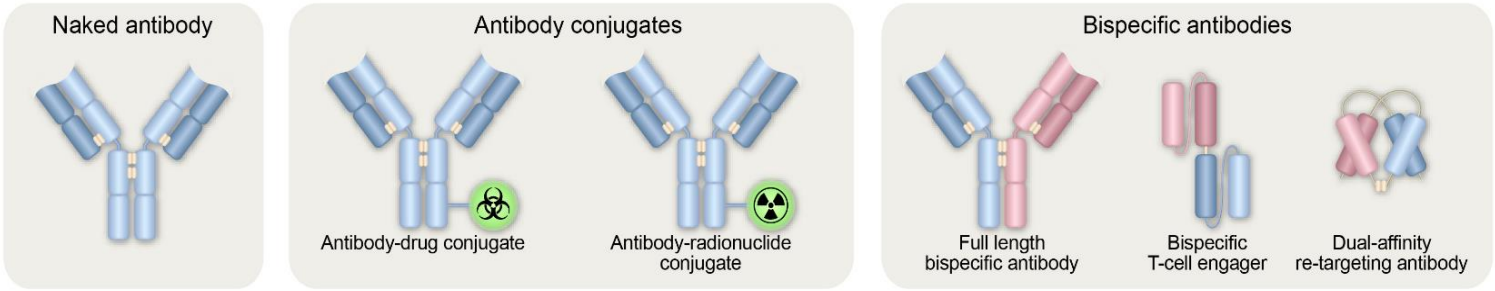
Disclaimer: Data will include medications not yet approved or with indications still under clinical study

Immune Based Approaches in AML





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

Two major approaches:

1. **<u>Antibody drug conjugates</u> (CD33, CD123, CLL1)**
2. **<u>Adaptive or Innate immune</u> system harnessing therapies:**

a. **Bi-specific antibodies (CD3 x AML antigen; CD47 x CD3, others)**

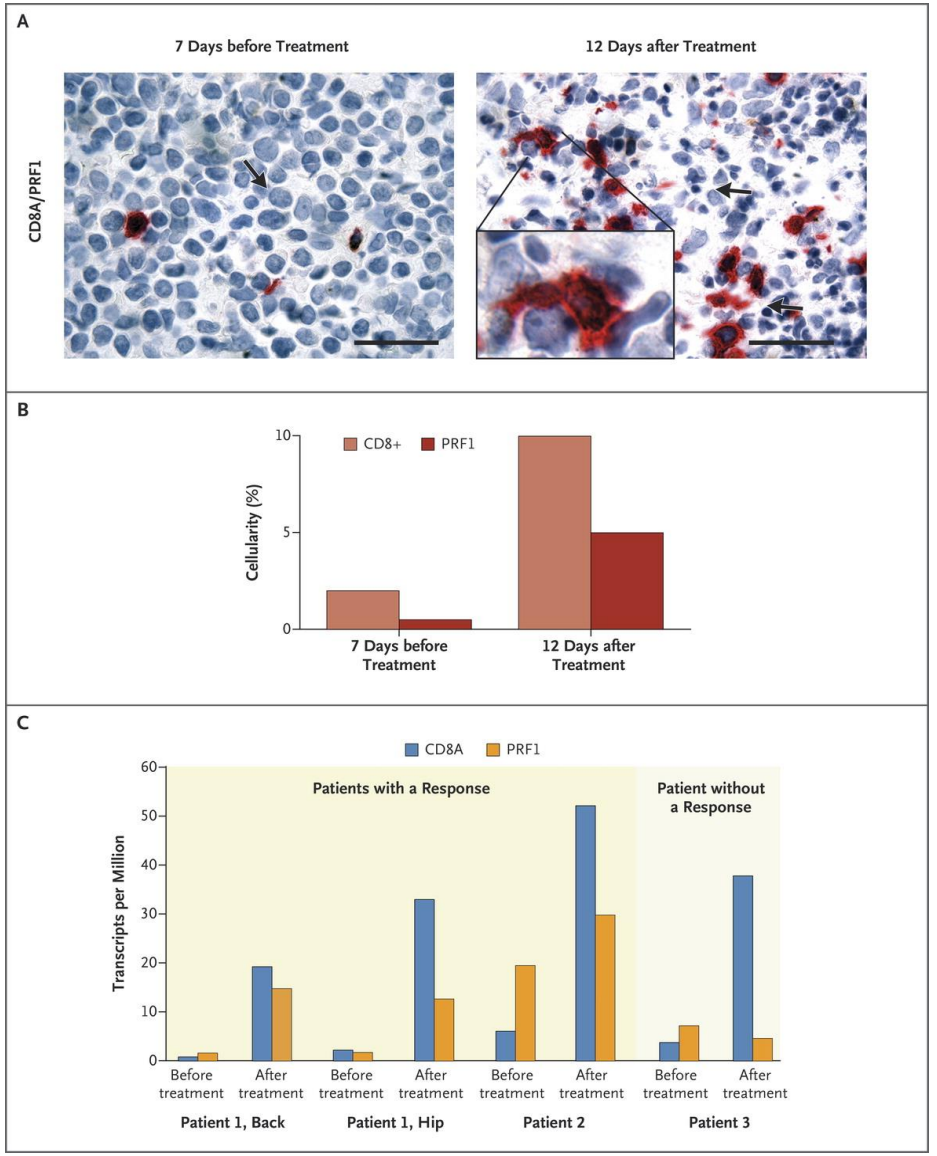
b. **Immune checkpoint based approaches: T-cell and macrophage checkpoints**

c. **CART, CAR NK, High volume hn-NK cells**

d. **Vaccines**

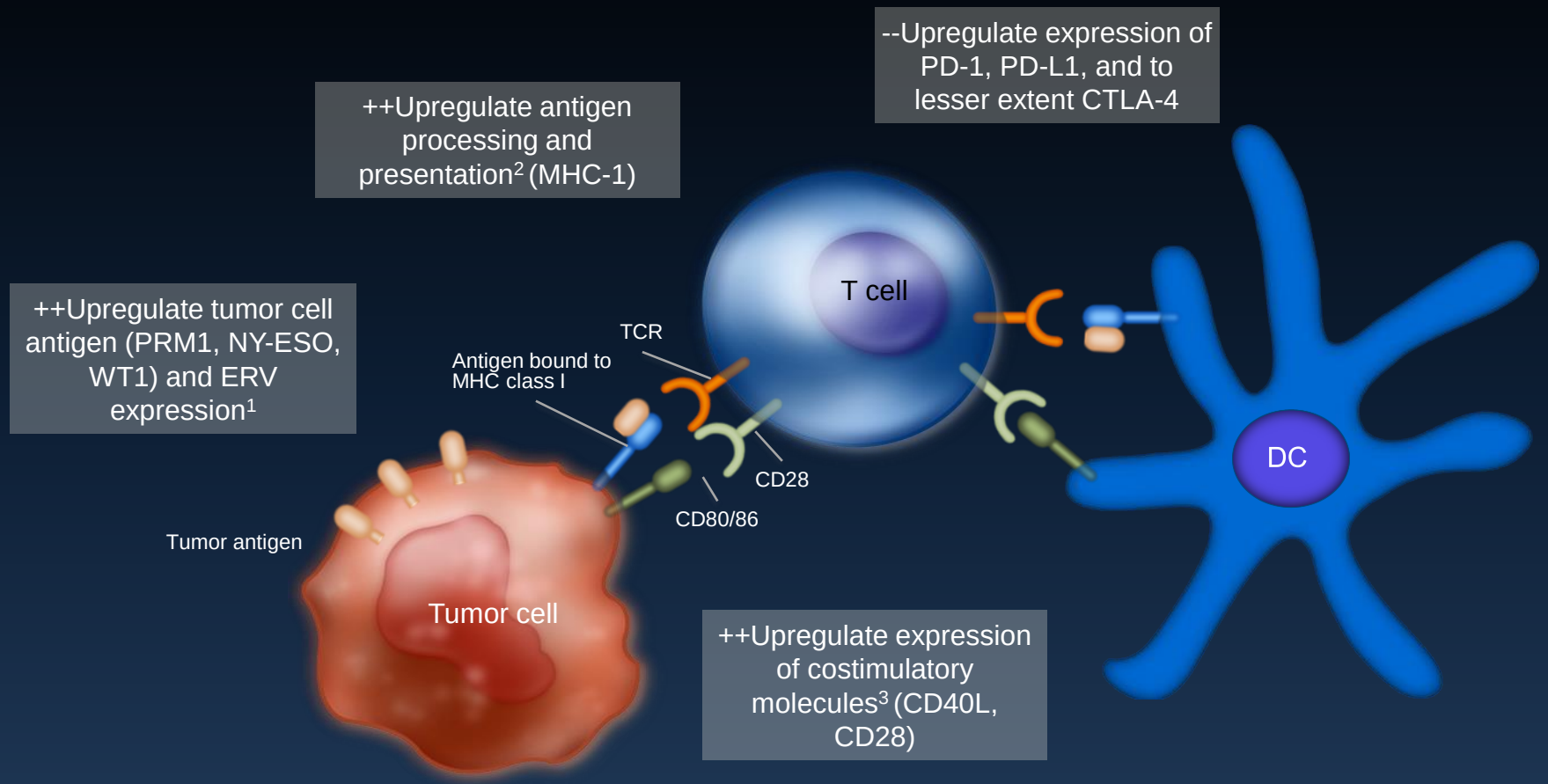
A Multicenter Phase I/Ib Study of Ipilimumab for Relapsed Hematologic Malignancies after Allogeneic Hematopoietic Stem Cell Transplantation

- 28 patients following allo-SCT; AML=12
- Ipilimumab at: 3 mg/Kg or 10 mg/Kg, every 3 weeks
- Median time from allo-SCT was 19.3 months (late postSCT)
- Efficacy in patients at the higher dose level (5/13 AML CR, median: 3 prior Rx)
- Extramedullary AML more sensitive?
- 6 (23%) cases of immune AE, 1 death



Davids M et al , NEJM July 2016

Hypomethylating Agents and Immune Regulation

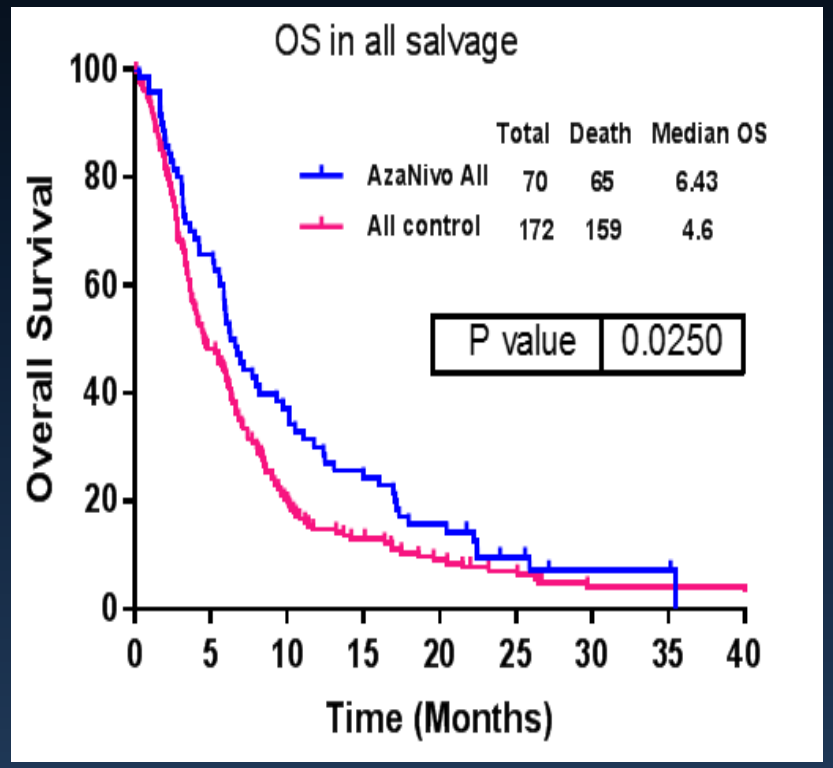


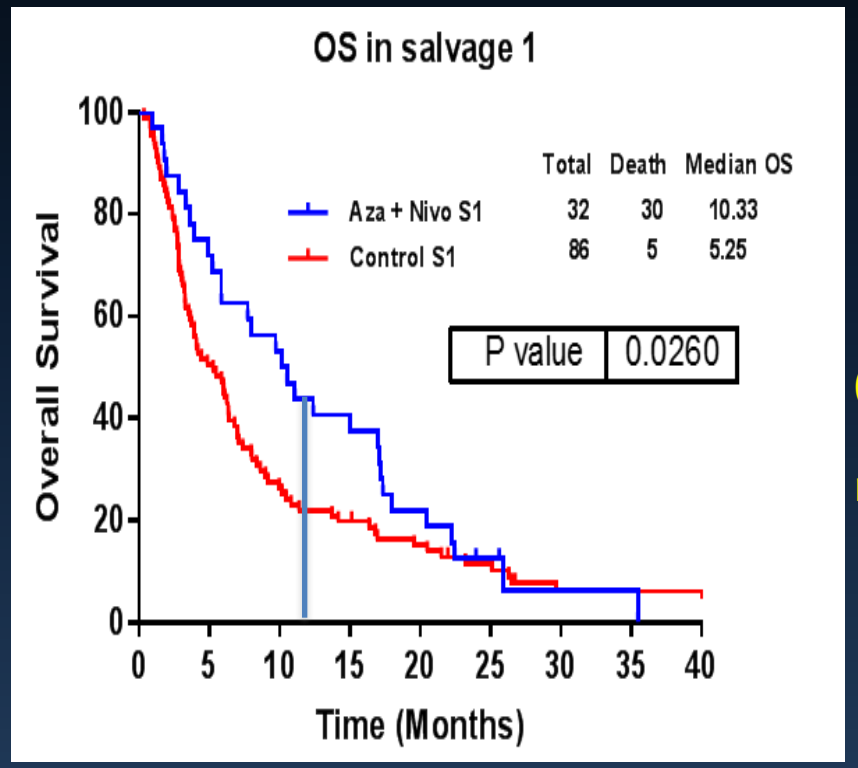
1. Sato T, et al. Cold Spring Harb Perspect Med. 2017;7(5); 2. Li H, et al. Oncotarget. 2014;5:587-598; 3. Wang LX, et al. PLoS One. 2013;8:e62924; 3. Alatrash G, Daver N et al. Pharmacol Rev. 2016; 4. Daver N, Kantarjian H, et al. Leukemia. 2018.

OS AZA + NIVO vs Historical HMA Combo Protocols at MDACC R/R AML; Censored for ASCT

Improved OS predominantly in early salvage

- 70 pts with R/R AML (median age 70 years)
- [1]Median OS better in salvage 1 (10.5 months vs 5.4 months, P<0.011); 1 yr OS = 50%





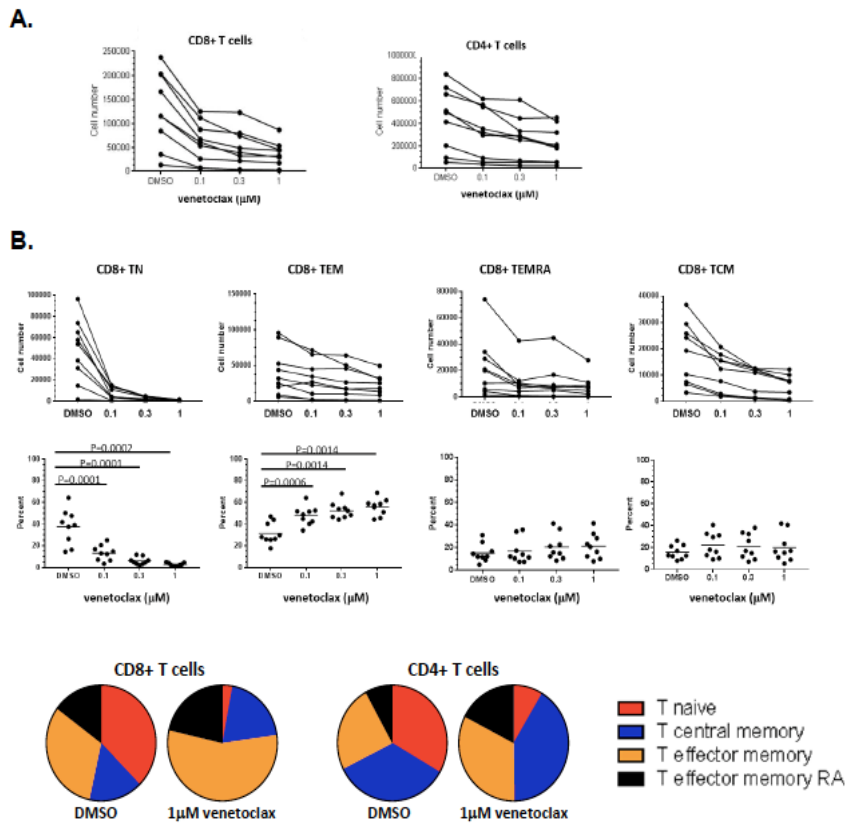
[2]Expected survival in salvage 1 with HMA (n=670): 6.0 mos median, 12-mo OS: 16%[2]

Improved efficacy in early salvage: Blina and CART in ALL, MGD006 in prim ref AML

1. Daver N, et al. Cancer Discovery 2019 Mar;(9)3 2. Stahl M, et al Blood Advances 2018 Apr 24;2(8):923-932

Venetoclax appears to spare activated T-cells (TEM) during anti-tumor immunity and may synergize with PD-1's

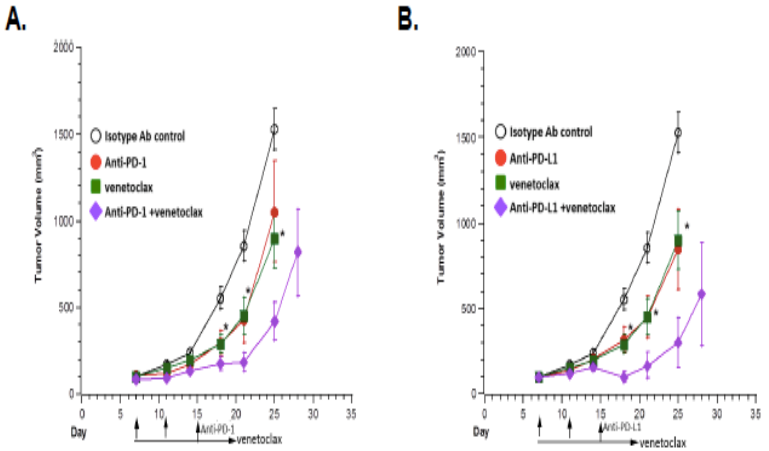
Figure 4. *In vitro* venetoclax treatment differentially affects T cell subsets in human PBMCs



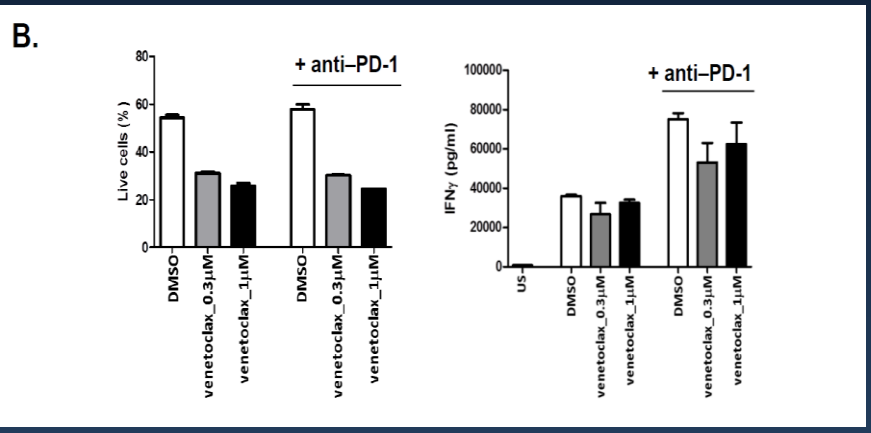
TEM: CD62L- CD45RA-
TEM RA: CD62L- CD45RA+
TCM: CD62L+ CD45RA-

Mali R et al, Cancer Discovery 2021

Figure 1. Venetoclax does not antagonize the anti-tumor activity of anti-PD-1 or anti-PD-L1 antibodies

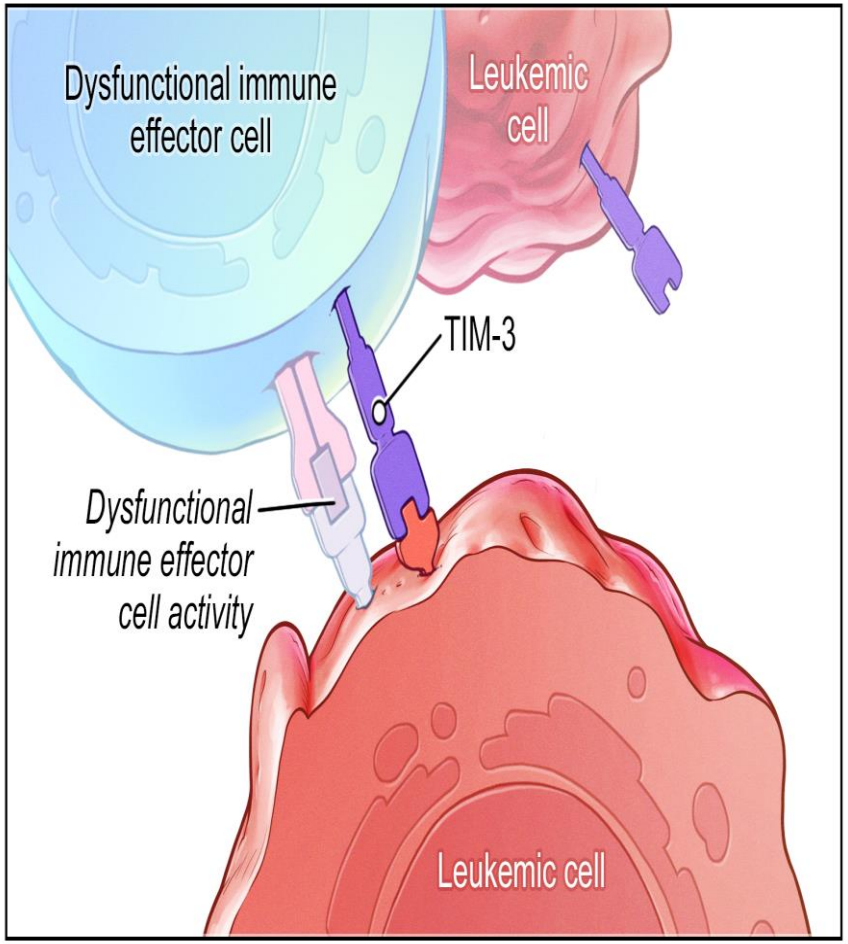


Tumor efficacy studies in immunocompetent C57BL/6 syngeneic mice bearing MC38 tumors.



CMV Recall Assay: *In vitro* venetoclax treatment in an antigen-specific cytomegalovirus (CMV) assays.

TIM-3: Cancer immunotherapy and leukemic stem cell target

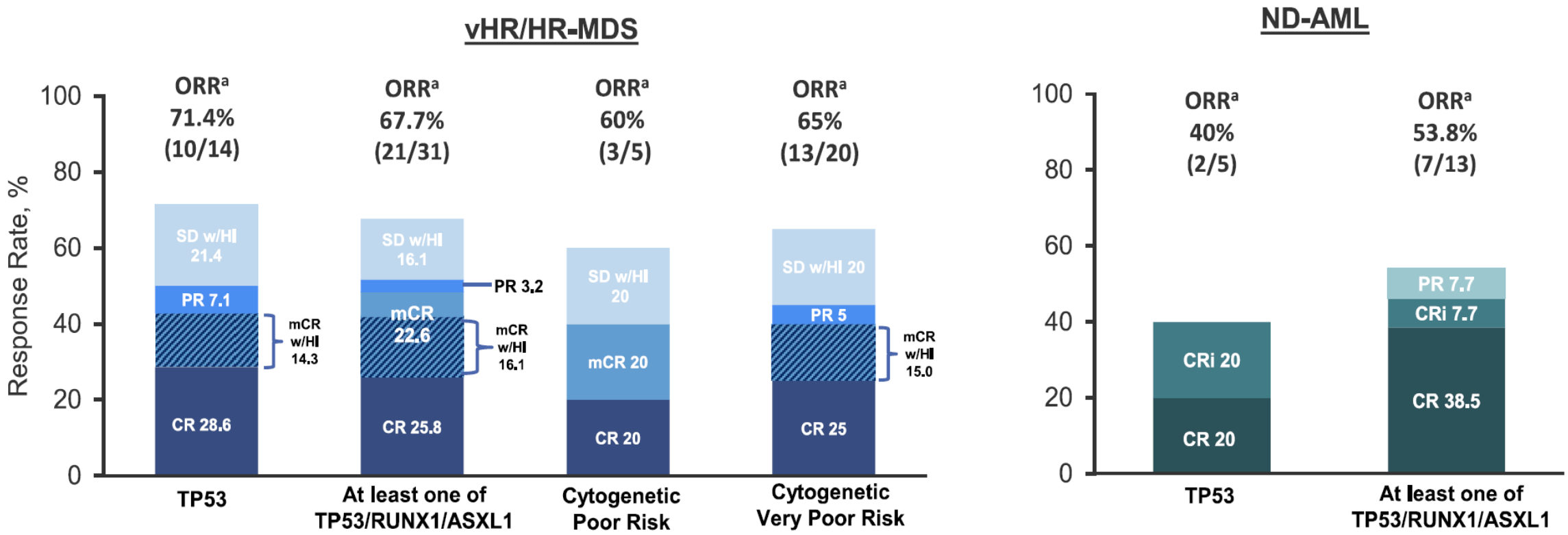


- TIM-3 is an i**nhibitory receptor on multiple immune cell** types, with a key role in regulating adaptive and innate immune responses[1,2]
- **TIM-3 is expressed on the majority of leukemic progenitors in AML**, but not on normal HSCs[3,4]
    - TIM-3 expression is seen to correlate with the severity of MDS and progression to AML[5]
    - TIM-3 activation is involved in LSC self-renewal and activation,[6] as well as immune escape in AML[7]
- TIM-3 is a promising therapeutic target, providing an opportunity to both target leukemic stem cells and restore immune function[4,8,9]

AML, acute myeloid leukemia; HSC, hematopoietic stem cell; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer* 2012;12:252–264; 2. Das M, *et al. Immunol Rev* 2017;276:97–111; 3. Kikushige Y and Miyamoto T. *Int J Hematol* 2013;98:627–633; 4. Kikushige Y, *et al. Cell Stem Cell* 2010;7:708–717; 5. Asayama T, *et al. Oncotarget* 2017;8:88904–88917; 6. Kikushige Y, *et al. Cell Stem Cell* 2015;17:341–352; 7. Gonçalves Silva I, *et al. EBioMedicine* 2017;22:44–57; 8. Ngiow SF. *Cancer Res* 2011;71:3540–3551; 9. Sakuishi K, *et al. Trends Immunol* 2011;32:345–349.

AZA + TIM3 Ab Sabatolimab in frontline MDS/AML, encouraging activity in high-risk patients , especially for MDS



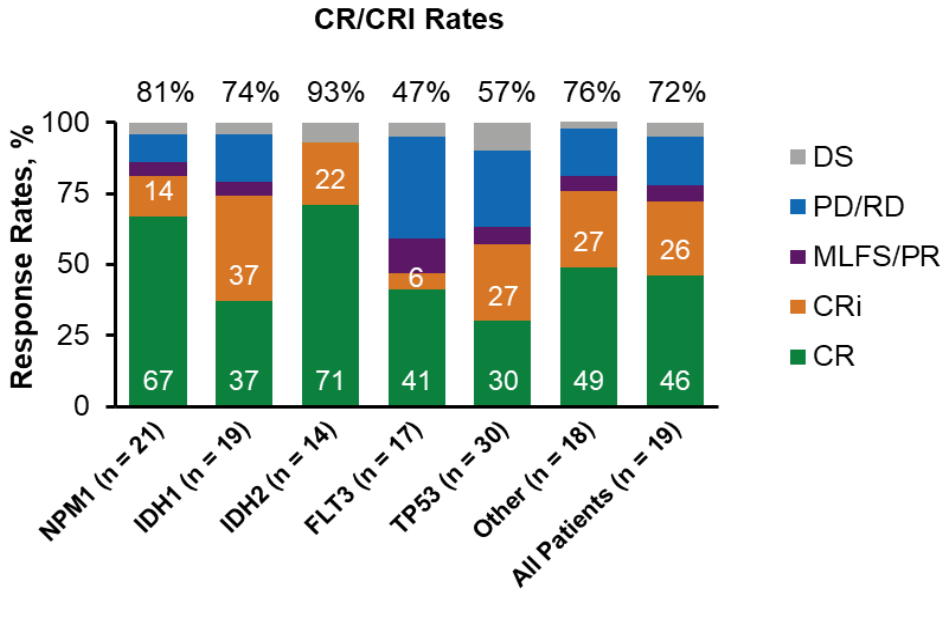
Median duration of response	14.7 mo	16.1 mo	12.1 mo	7.9 mo	4.2 mo	12.6 mo
	95% CI, 6.7-NE Events, 3/7[b]	95% CI, 3.0-NE Events, 7/16[b]	95% CI, NE-NE Events, 1/2[b]	95% CI, 3.0-NE Events, 4/9[b]	95% CI, NE-NE Events, 1/2[b]	95% CI, 1.3-NE Events, 4/7[b]

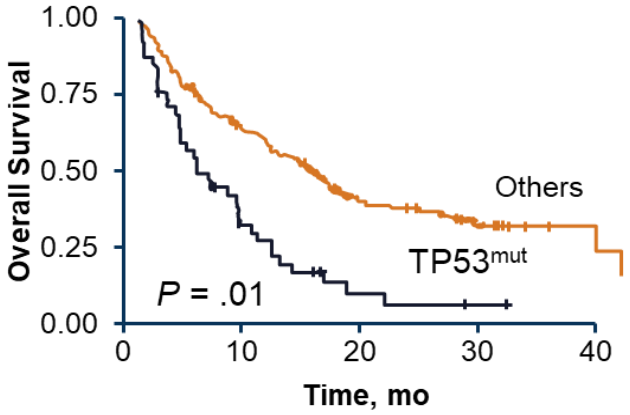
[a]ORR for patients with MDS was defined as CR + mCR + PR + SD with HI; ORR for patients with ND-AML was defined as CR + CRi + PR.
[b]DOR events (including progression/relapse and death) reported out of the number of patients with a BOR of CR, mCR, or PR (for MDS) or CR, CRi, or PR (for AML).

Wei A et al, EHA 2021

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

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

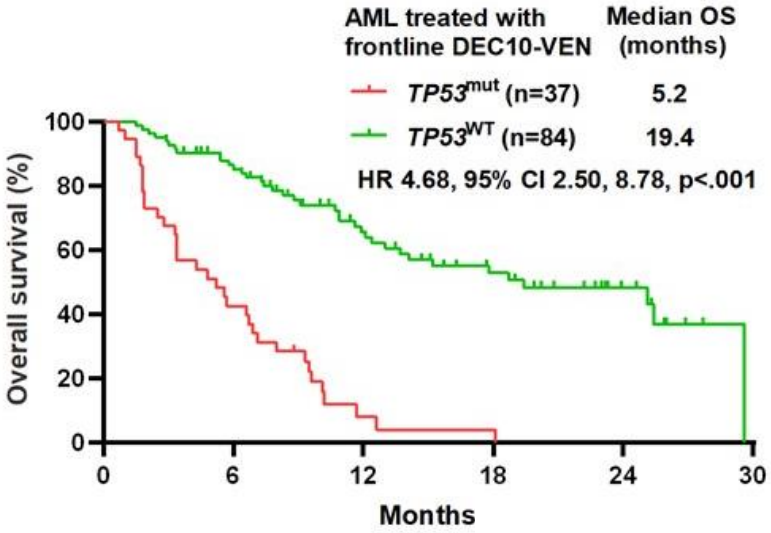




Median OS = 6.4 months

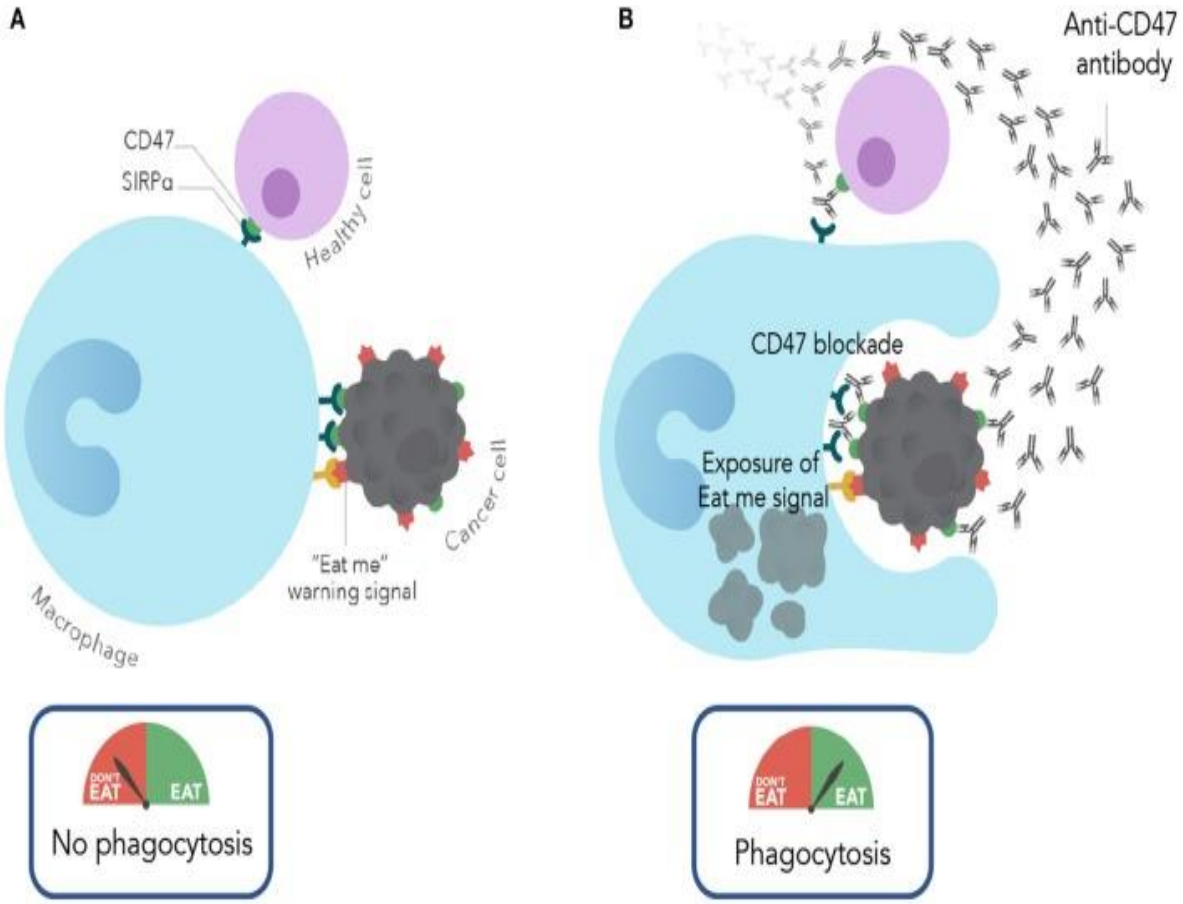
N = 121 patients with newly diagnosed AML receiving decitabine + venetoclax[2]

- **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.

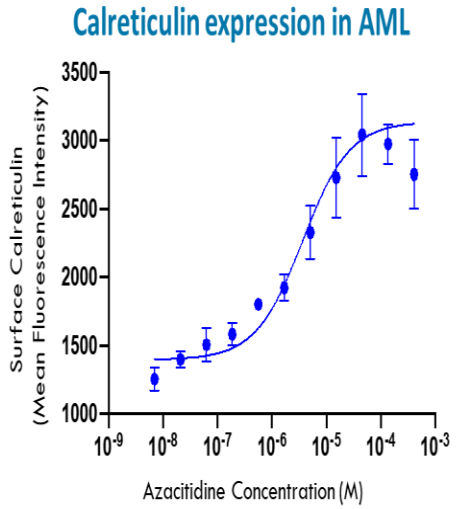
Mechanism of Action of CD47 Blocking Antibodies[1]

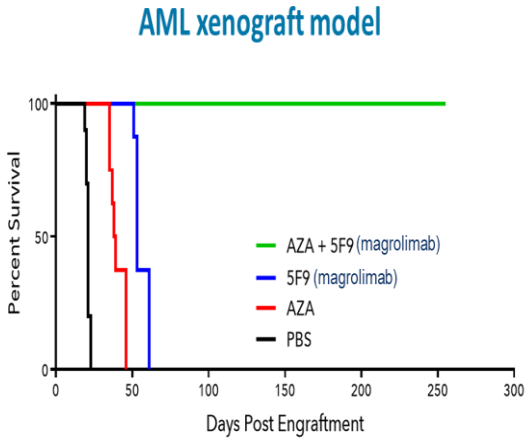


Chao MP et al. Front Oncol. 2019;9:1380.

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

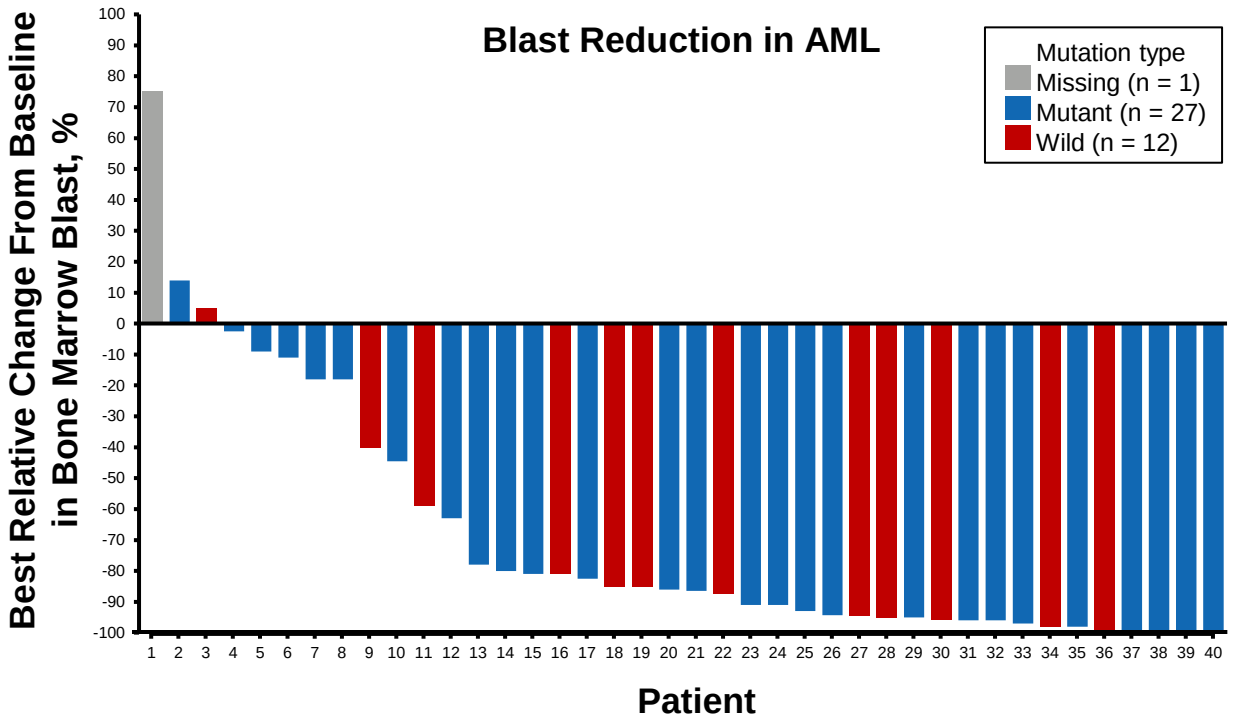




Feng D, et al. ASH 2018, Abstract #616 (with adaptations).

Magrolimab + AZA in Newly Diagnosed AML[1,2]

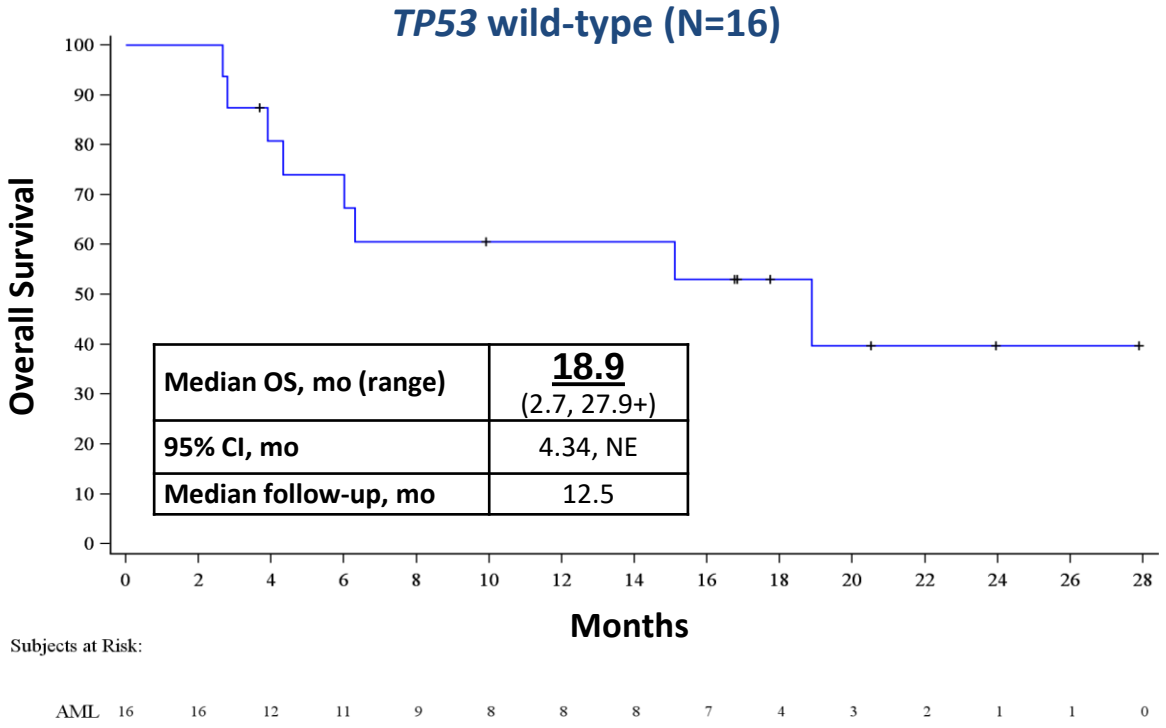
Best Overall Response	All AML (N = 43), n (%)	*TP53*-Mutant AML (n = 29), n (%)
ORR	27 (63)	20 (69)
CR	**18 (42)**	**13 (45)**
CRi	5 (12)	4 (14)
PR	1 (2)	1 (3)
MLFS	3 (7)	2 (7)
SD	14 (33)	8 (28)
PD	2 (5)	1 (3)

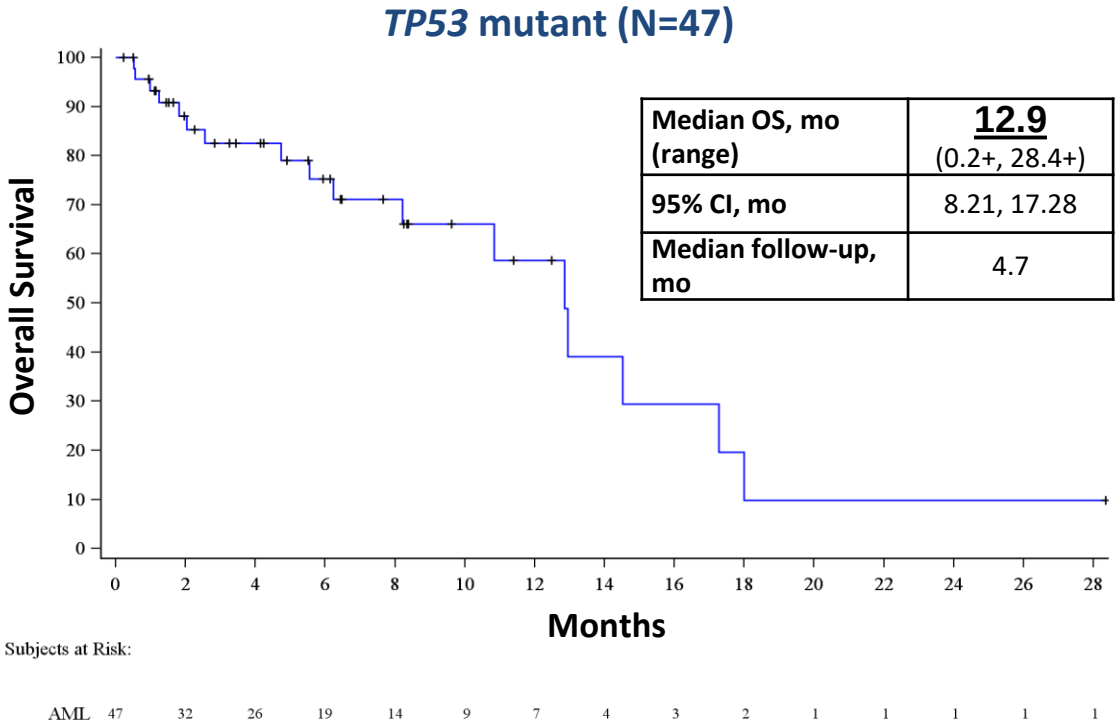


- Magrolimab + AZA with 63% ORR and **42% CR rate** in AML (similar responses in *TP53*-mutant disease)
- Median time to response is 1.95 months (range, 0.95-5.6 mo); more rapid than AZA monotherapy
- Magrolimab + AZA efficacy compares favorably with AZA monotherapy (CR rate: 18%-20%)
- No significant 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 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
- Med OS with venetoclax + hypomethylating agent combinations (**14.7-18.0 mo** in all-comers,[1,3] **5.2–7.2 mo** in *TP53* mutant[2,3])
- Additional patients and longer follow-up needed

NE, not evaluable.

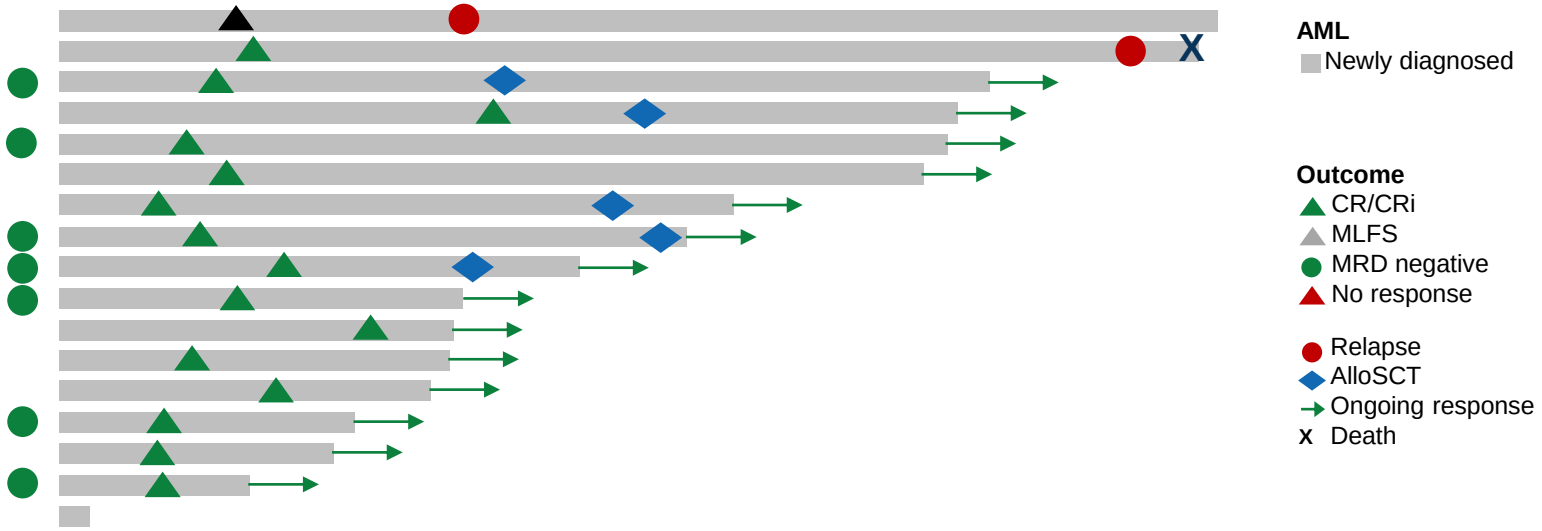
1. DiNardo CD, et al. *N Eng J Med*. 2020;383(7):617-629. 2. Kim K, et al. Poster presented at: 62nd ASH Annual Meeting; December 5-8, 2020 (virtual). 3. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

AZA/Magro/VEN Is a Highly Active Triplet in Newly Diagnosed Older/Unfit and R/R AML (*TP53* Mutant and WT)

- **ASH 2021: phase 1/2 study of AZA, magrolimab, and venetoclax was assessed in different frontline and R/R AML cohorts**
- Frontline cohort enrolled
  - Patients aged ≥75 y
  - Patients with documented comorbidities conferring ineligibility for intensive therapy
  - Patients with adverse risk karyotype and/or *TP53* mutation regardless of age/fitness
- **8 (47%) of patients in the frontline cohort had *TP53*-mutated AML**

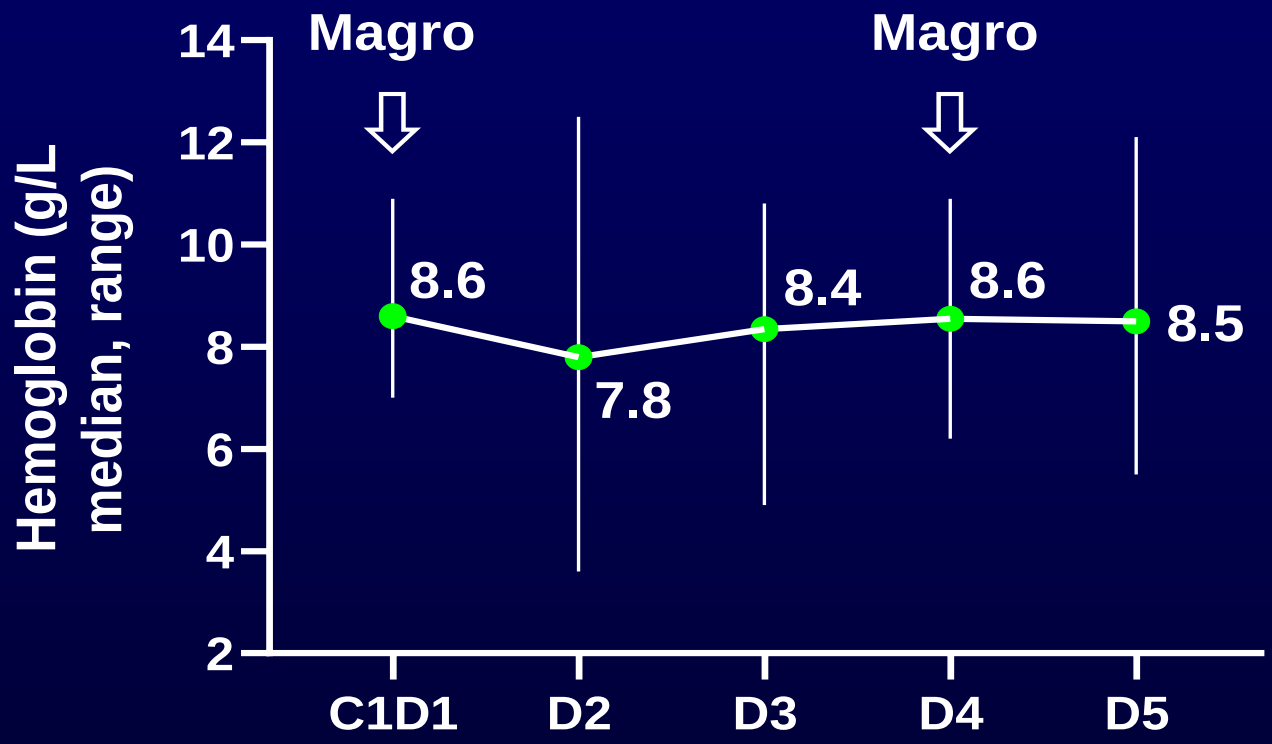
ASH 2021: Sunday, December 12: 9:30 AM

Outcomes, n (%)	Frontline AML (n = 16)	R/R AML	
		Venetoclax Naïve (n = 8)	Venetoclax Failure (n = 11)
ORR	16 (100)	6 (75)	3 (27)
CR/CRi	15 (94)	5 (63)	3 (27)
CR	13 (81)	3 (38)	0 (0)
CRi	2 (13)	2 (25)	3 (27)
MLFS	1 (6)	1 (13)	0 (0)
No response	0 (0)	2 (25)	8 (62)



1. Daver N et al. ASH 2021. Abstract 371.

Results: Important to monitor Hgb closely after dose 1 and dose 2 of Magro



Hb drop	g/L (median, range)	p
Day 1-2	1.5 (0-4.3)	.165
Day 4-5	0.5 (0-2.6)	.112

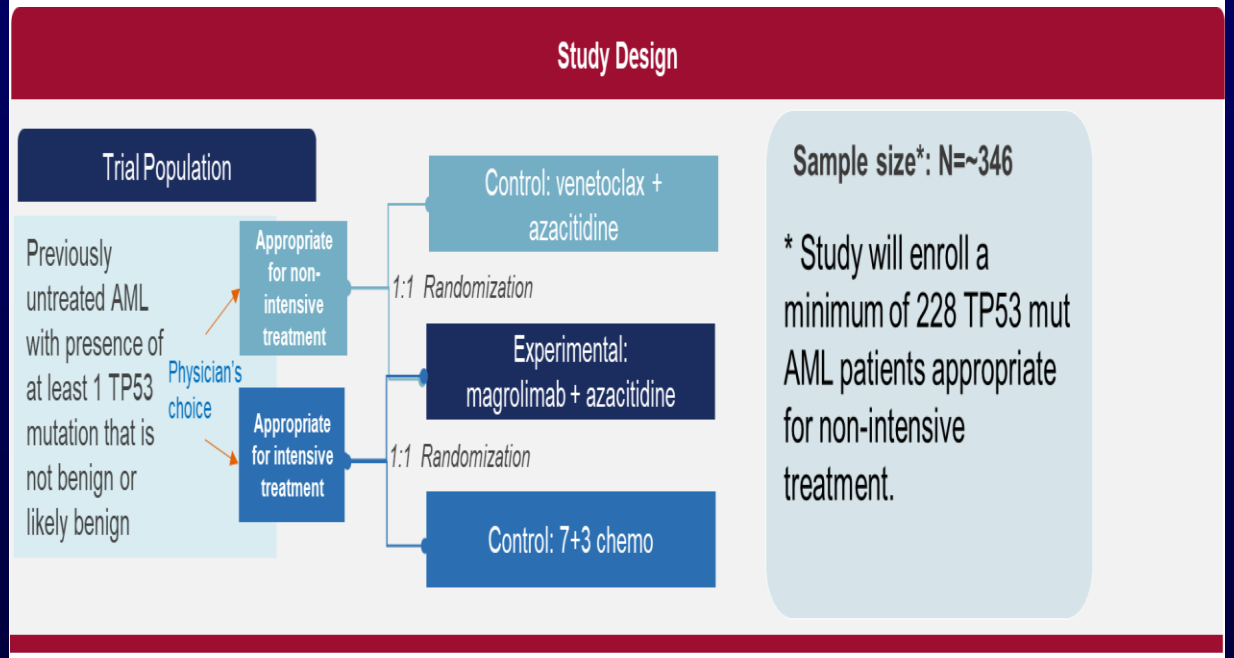
D1-2 drop
- > 2g drop – 19% (n=9)
- > 3g drop – 6% (n=3)

D4-5 drop
- > 2g drop – 6% (n=3)
- > 3g drop – 0

No patients had Hgb >2g after the second dose Magro

Ongoing Phase III Studies with Magro in Frontline AML

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



Stratification:

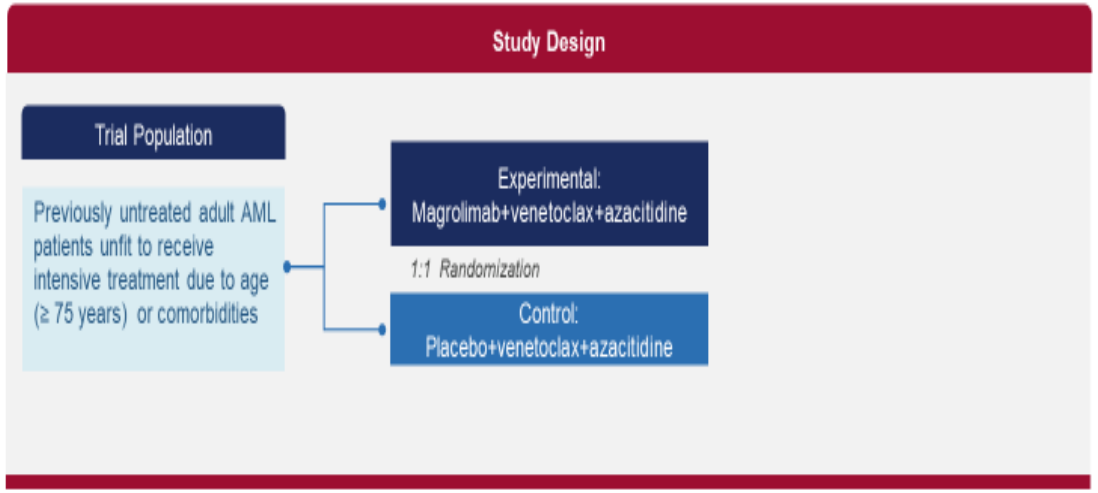
1) Appropriateness for non-intensive therapy vs. intensive therapy
2) Age <75 vs. ≥75
3) Geographic region: US vs. outside the US

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

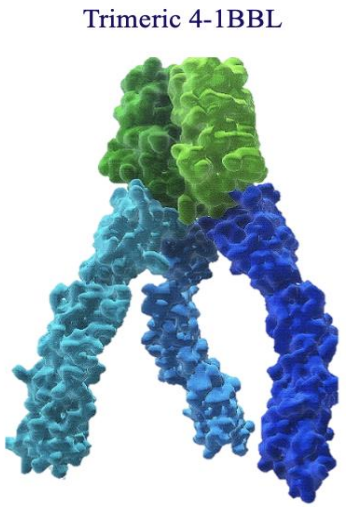
Multiple CD47-SiRPa targeting Ab and Bispecifics in or entering clinic for AML/MDS, lymphoma and solid tumors

Candidate	Magrolimab (AML, MDS)	TTI-621	TTI-622 (AML)	ALX148 (AML, MDS)	Lemzoparlimab (AML, MDS)	AO-176	SL-172154 (AML, MDS)
Molecule	CD47 mAb	**WT SIRPαFc fusion protein**	WT SIRPαFc fusion protein	**High aff. SIRPαFc fusion protein**	CD47 mAb	CD47 mAb	**WT SIRPα-Fc-CD40L fusion protein**
Fc isotype	IgG4	**IgG1**	IgG4	**Inert IgG1**	IgG4	IgG2	Inert IgG4
Proposed MoA	CD47	CD47 + NK	CD47	CD47	CD47	CD47 + direct killing	CD47 + CD40
Mol. weight (approx.)	150 kD	75kD	75kD	75kD	150 kD	150kD	>500kDa
RBC binding	Yes	No	No	Yes	No	No	No
Monotx/incl CR observed	Yes/ No	Yes/ Yes	Yes/ Yes	No/ No	Yes/No	No data	No data
Development stage	P3	P1b/2	P1b/2	P1/2	P1/2	P1/2	P1

Sources: Publications, presentations and filings; www.clinicaltrials.gov

Other companies with clinical stage CD47-targeting agents: ImmunOncia, Innovent Bio, Kahr Medical, TG Therapeutics, Zai Lab, Akeso

Bispecific CD47-SiRPa and T-cell (41BB) engaging approaches (DSP-107): Activating the innate and adaptive immune system

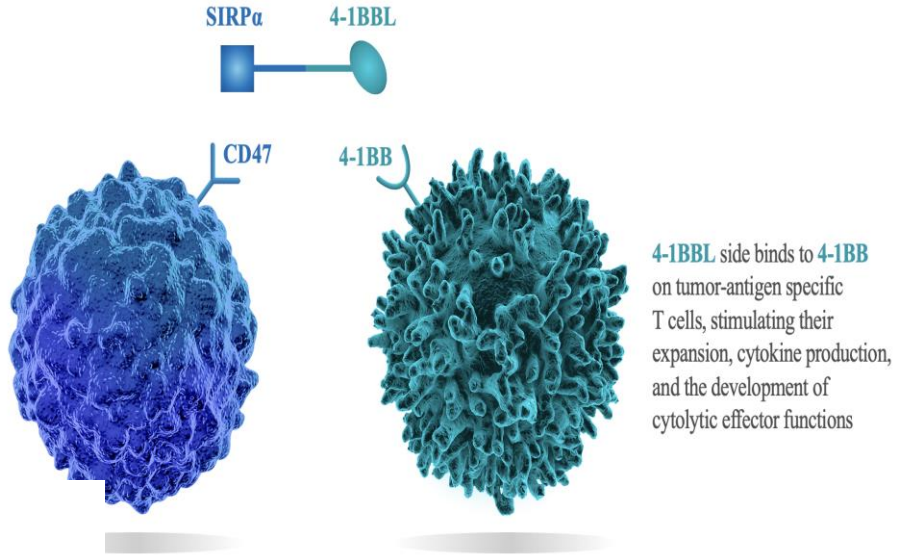


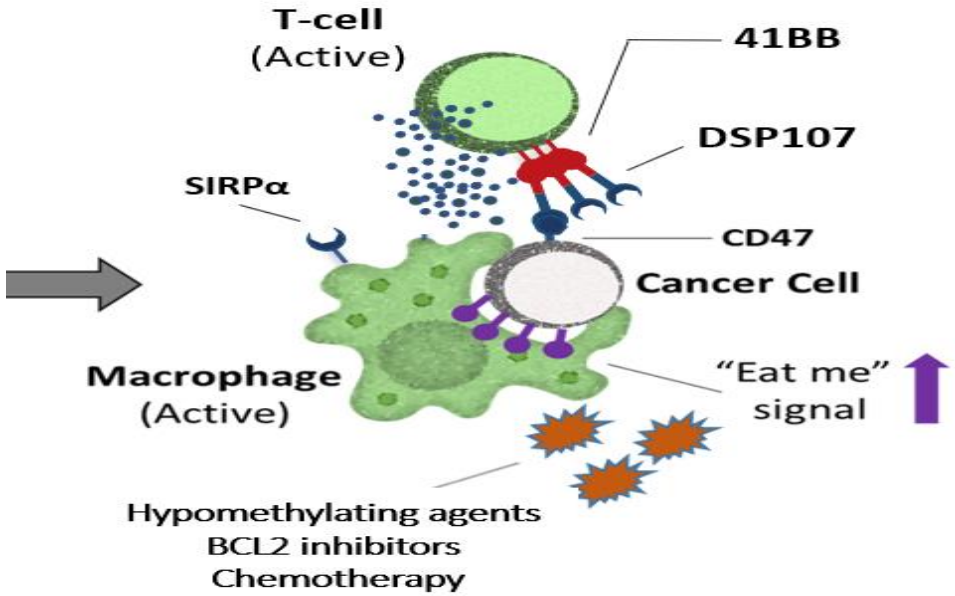
Immune cell stimulation

Proliferation

Checkpoint inhibition

Tumor microenvironment modulation





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) or SIRP alpha on macrophages (Trillium, CC95251, ALX148)
- Recruiting **NK** cells-- allo NK-CARTs; NK engineered cells (hn, CD38 ko, IL15) - repeated infusions

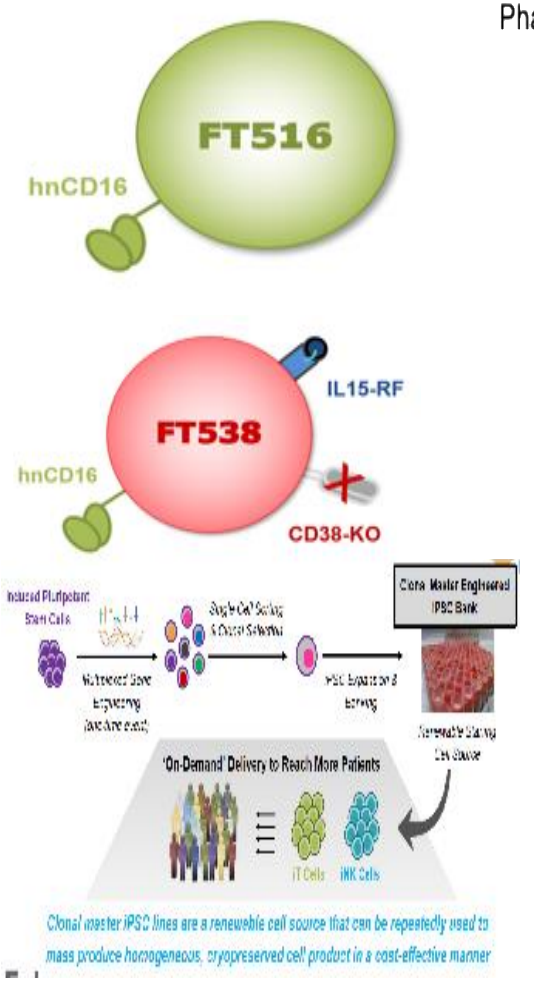
Emerging Novel, potentially mutation agnostic approaches: may be especially important in high risk AML like TP53m

Anti-CLL1 CARTs in Children with R-R AML

- 2nd generation CLL1 CARTs 0.3-1 million/kg single dose post lymphodepletion with Flu-CTX
- 11 children with R-R AML treated
- **9 responses = 82%** : 5 CR MRD-, 3 CR MRD+, 1PR

Zhang. JCO 39 (suppl). May 2021. ASCO 2021

FT516 / FT538: Monotherapy in Relapsed / Refractory AML



Phase 1 studies (n=12 treated)

- 3 doses per cycle (D1, D8, D15) x 2 cycles; each cycle 28 days
- Lympho-conditioning: Cyclophosphamide 500 mg/m2 IV x Fludarabine 30 mg/m2 IV x 3 days
- FT516 -- IL-2 6MU SC with each dose FT516; FT538 endogenous IL2 (no external IL2 needed)
- Median 3 (1 - 6) prior Rx lines, 9/11 adverse ELN risk
- 5 of 12 (42%) responses (4 CRi + 1 MLFS)

FT516 (n=9): 3 CRi + 1 MLFS (90M and 300M cells); FT538 (n=3): 1 CRi (100M cells)

- No observed DLTs, No CRS, ICANS, or GVHD of any grade
- Ongoing remission >6 months in 2 FT516 patients without additional intervention, FT538 CRi ongoing

FATE. Public presentation April 2021

New ADCs and Bispecifics in AML

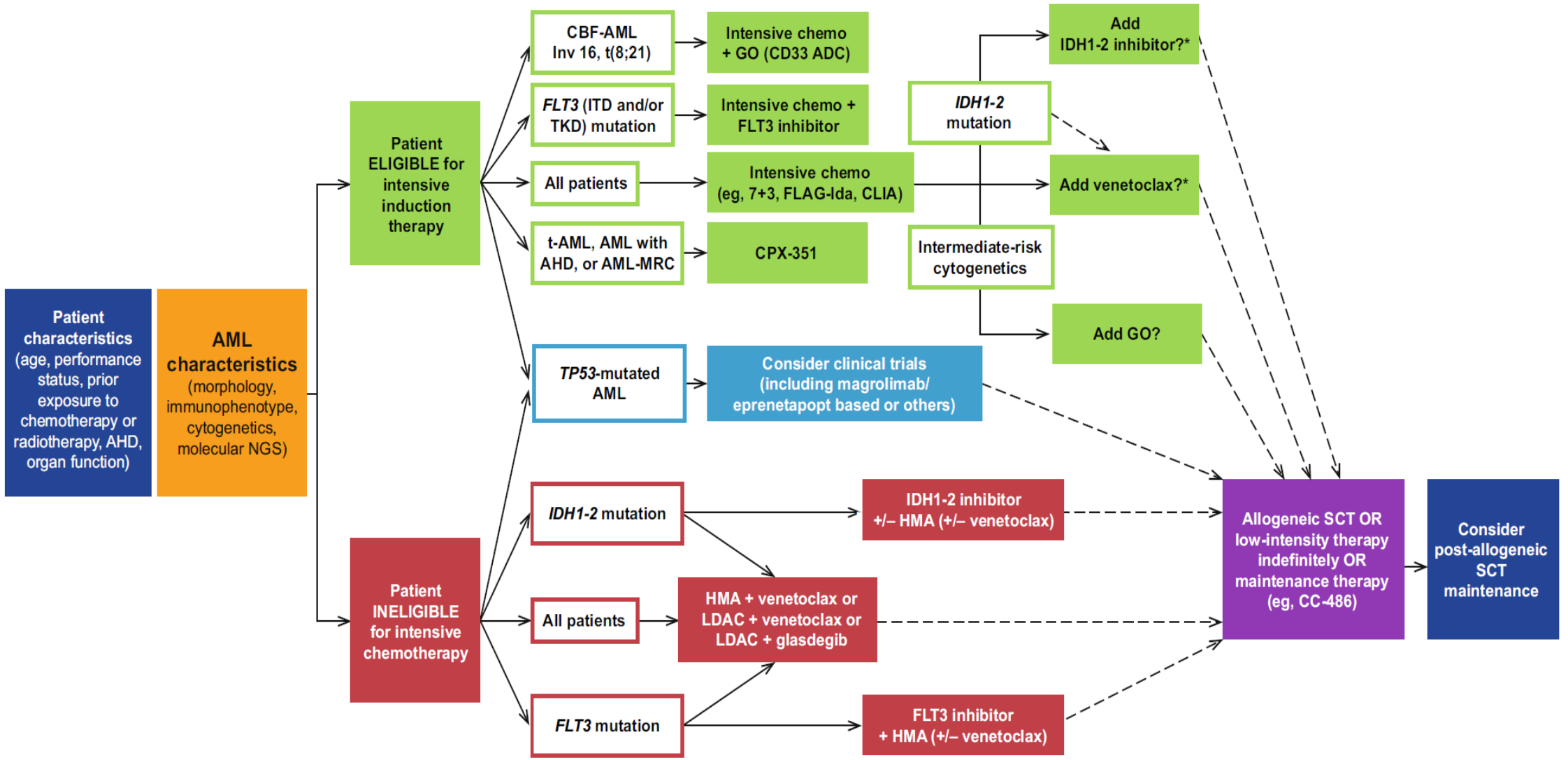
CD33 and CD123 various novel agents:

- **IMGN632 (CD123) :** ADC with novel single strand alkylating payload
  - CR/CRi rate 17%, ORR 20% in n=66 evaluable AML pts *(Daver et al, ASH #734)*
- **Flotetuzumab (MGD006):** CD123xCD3 dual-affinity re-targeting (DART) molecule
  - CR/CRi 32% in n=30 primary refractory AML cohort *(Uy et al, ASH #733)*
- **XmAb 14045** CD3xCD123 bispecific
  - CR/CRi rate 23% in Part A (Ravandi ASH 2018)
- **AMG330 and AMG673** CD3xCD33
  - CR/CRi rate 15% in n=27 evaluable pts (AMG330)
  - *Subklewe et al, ASH #833 (AMG673)*
- **AMV564** CD3xCD33 bispecific
  - *Westervelt et al, ASH #834*

Other promising targets:

- **Cusatuzumab (ARGX-110): CD70 + AZA for Newly Dx Older AML**
  - CR/CRi 83% and ORR 92% in n=12 (Ochsenbein ASH 2018)
- **Magrolimab (5F9): CD47 + AZA**
  - CR/CRi 50% and ORR 69% in n=16 evaluable AML *(Sallman et al, ASH #569)*
- **MCLA-117: CD3 x CLL1**

Evolving Diagnostic and Treatment Paradigm for Newly Dx AML (TP53 should all be enrolled on clinical trials irrespective of age/fitness)



Questions: Feel free to contact ndaver@mdanderson.org

Daver N et al, Blood Cancer J. 2020 Oct 30;10(10):107.