LEUKEMIA2020-2021

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AIL President: S. Amadori

ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

Recent developments in immunotherapy

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fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

SIES Società Italiana Ematologia Sperimentale

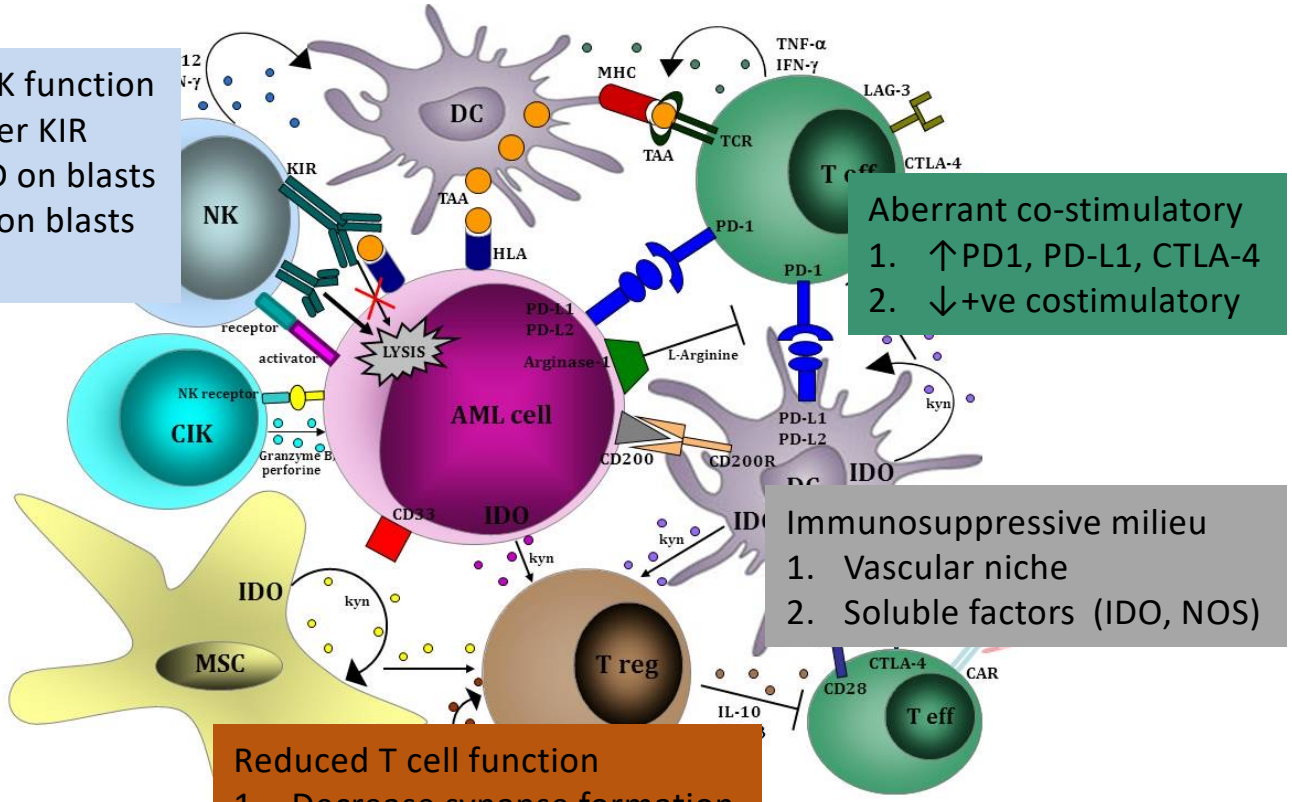
SIE - Società Italiana di Ematologia

Background

- Despite advancement in AML in recent years, survival has not significantly improved
- Therefore, novel therapeutics approaches are urgently needed
- Harnessing the immune system, against cancer, represent the new frontier of research

The mechanisms of immune escape in AML

Blocked NK function
1) stronger KIR
2) NKG2D on blasts
3) GITRL on blasts



Aberrant co-stimulatory
1. ↑PD1, PD-L1, CTLA-4
2. ↓+ve costimulatory

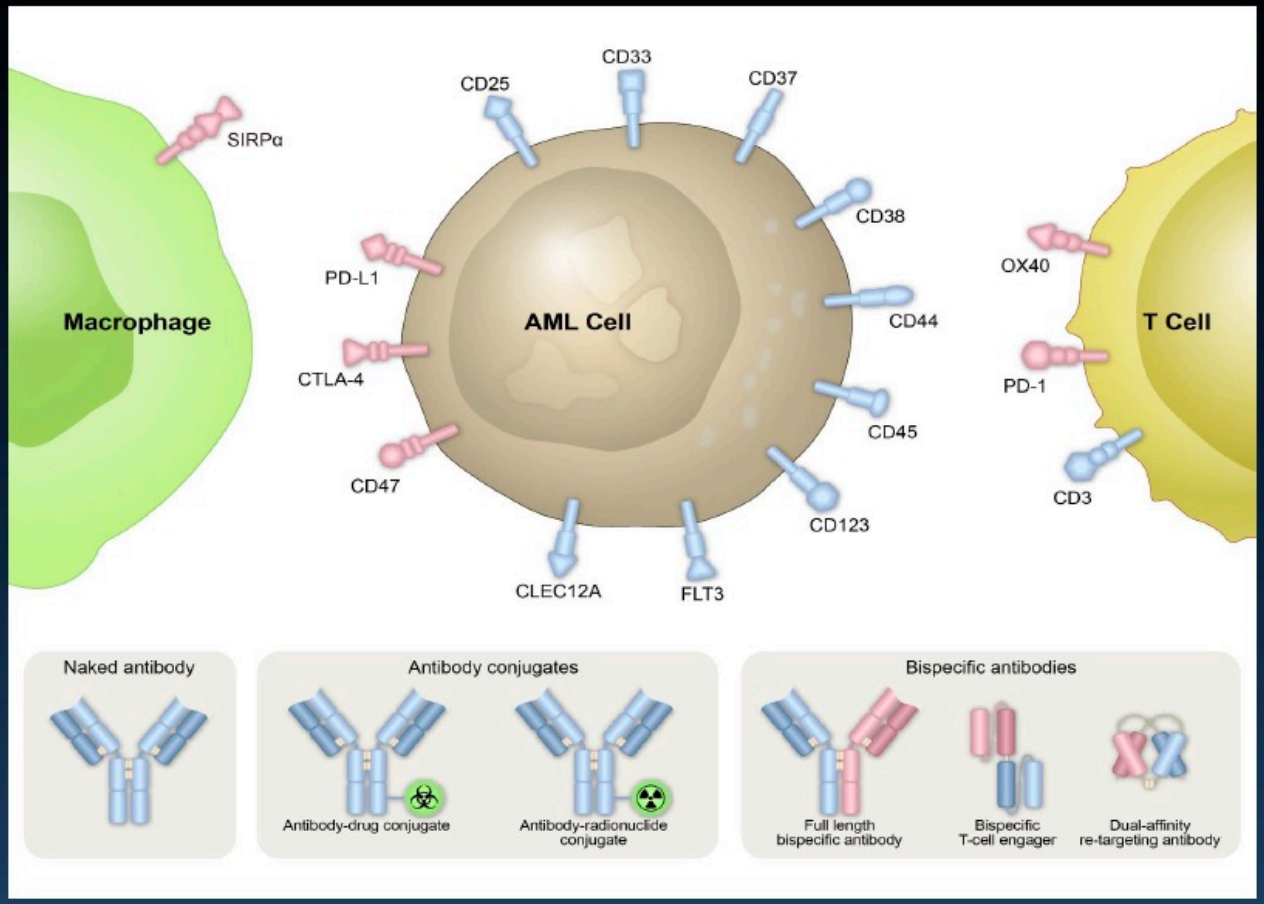
Immunosuppressive milieu
1. Vascular niche
2. Soluble factors (IDO, NOS)

Reduced T cell function
1. Decrease synapse formation
2. Blocked T mitogenesis

Isidori A & Curti A, Exp Rev Haematol, 2014

Isidori A & Curti A, Cancer Res Frontiers, 2016

Immune Based Approaches in AML/MDS



Two major approaches:

1. **Antibody drug conjugates (CD33, CD123, CLL1)**

2 **T-cell based therapies**

a. **Bi-specific antibodies (CD3 x AML antigen)**

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

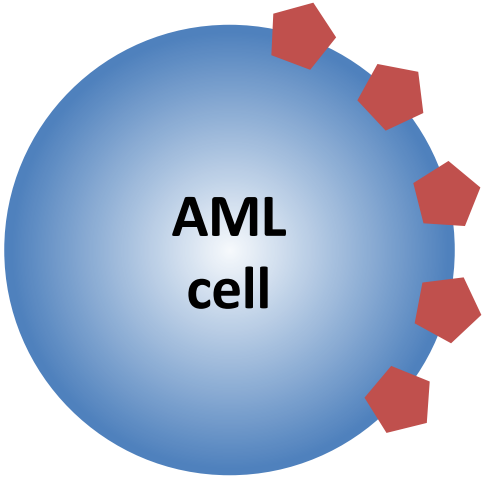
c. **CART (CAR NK)**

d. **Vaccines**

Short N…..[Daver N], Cancer Discovery 2020

Target Antigens and Novel Antibodies in AML

Multiple antigen targets and agents



CD33
- ^{225}Ac-Lintuzumab
- Gemtuzumab ozogamicin
- Vadastuximab talirine (SGN-CD33A)
- IMGN779
- AMG 330 (BiTE; CD33/CD3)

CD123
- SGN-CD123 (Halted)
- IMGN632
- XmAb 14045 (CD3/CD123)
- MGD006 (CD3/CD123)

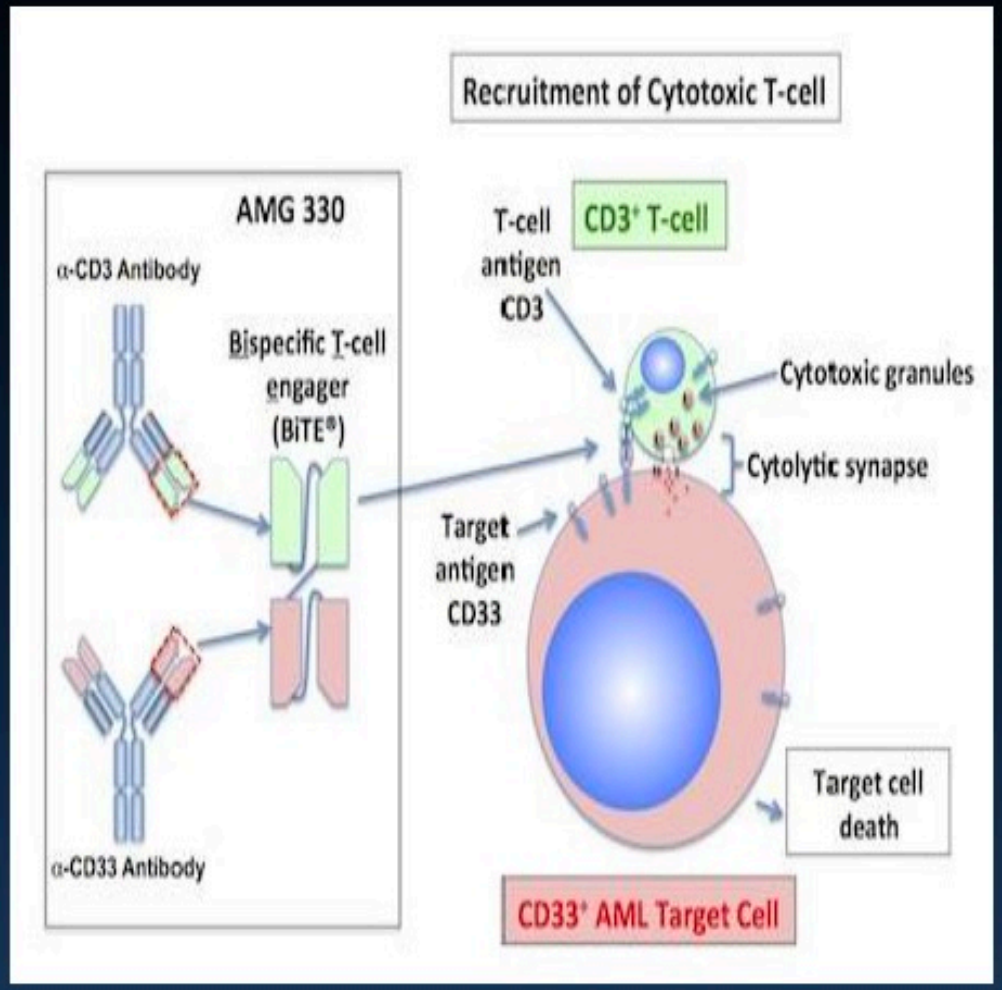
CD45 Iodine (^{131}I) Apamistamab (Iomab B)

CD47 Hu5F9-G4

CLL1 MCCLA-1117 (BiTE)

Bi-specific: Can we develop a blina for ALL?

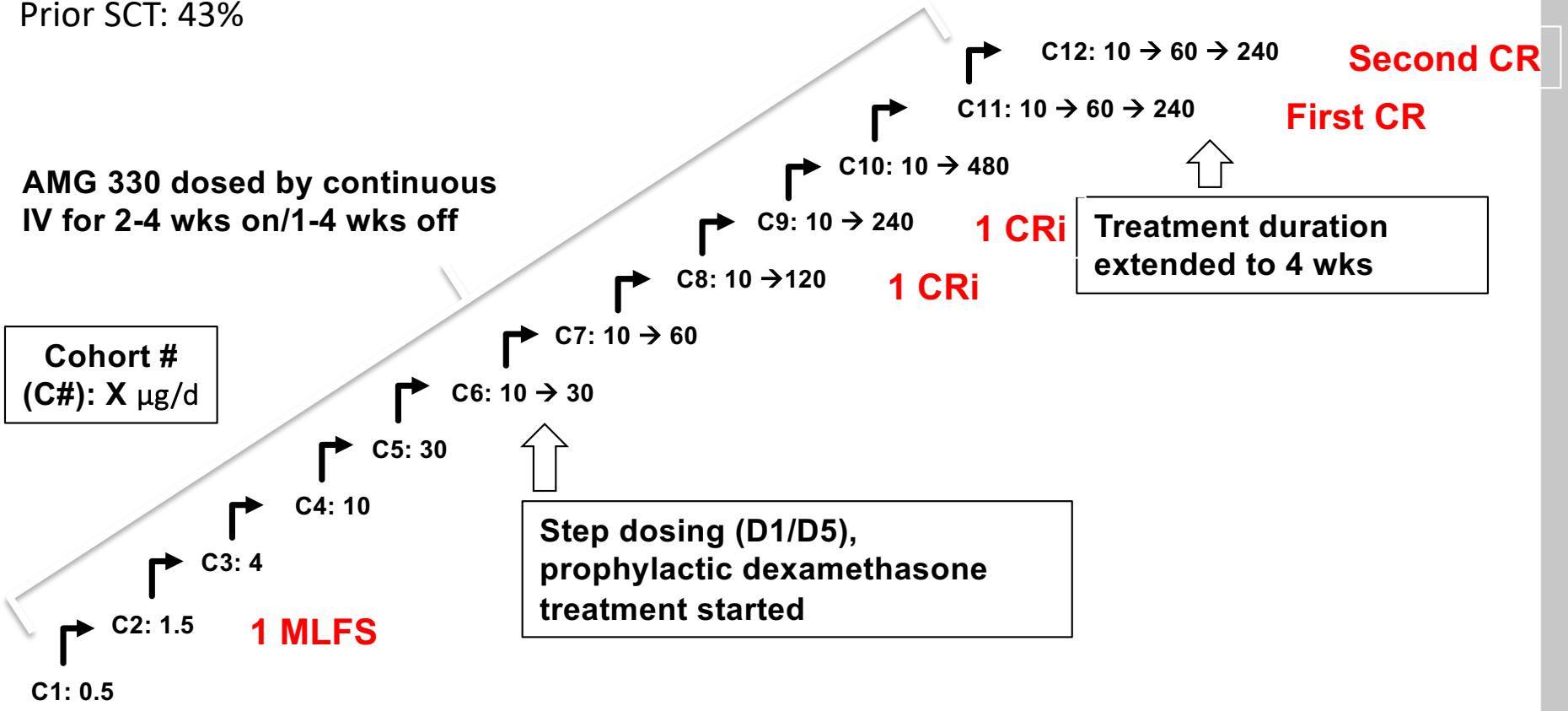
- **Bi-Specific antibodies targeting CD33 and T-cell antigens**
  - AMG330, CD33/CD3 bispecific T-cell engager (BITE)
  - Very promising in preclinical models
  - In phase 1 clinical trials
  - Showing activity at higher dose levels



1. Burke JM et al. *Bone Marrow Transplant*. 2003;32:549-556. 2. Hagenbeek A. *Leuk Lymphoma*. 200344(Suppl 4):S37-S47. 3. Jurcic GJ et al. 2015 American Society of Clinical Oncology Annual Meeting (ASCO 2015). Abstract 7050. 4. Laszlo GS et al. *Blood*. 2014;123:554-561. Image courtesy of Laszlo G (Fredhutch.org)

First-in-Human Phase I Trial of Anti-CD33 BiTE AMG 330 in R/R AML

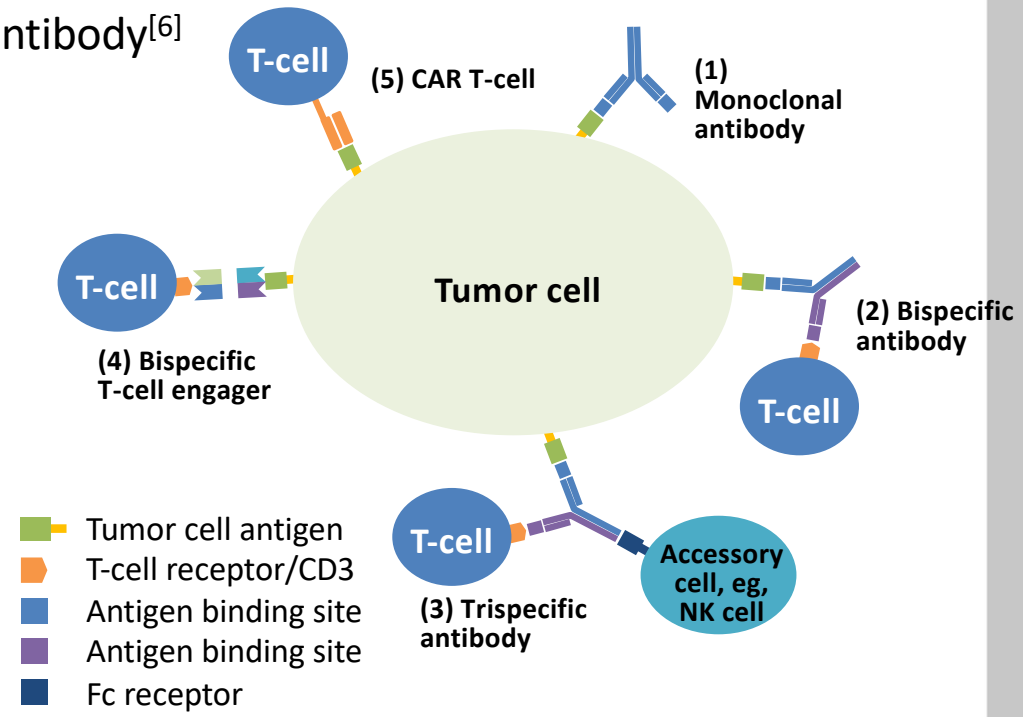
- Enrolled adults with R/R AML and > 5% BM blasts, no APL or AML from MDS (N = 40)
- Median age 58.5 years, median lines of prior therapy 4
- Prior SCT: 43%



Ravandi. ASH 2018. Abstr 25.

Other Antibody Targets in AML: CD123

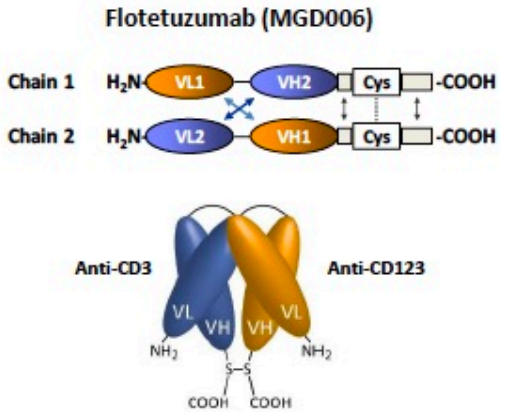
- CD123 (IL-3 receptor): expressed on most myeloid leukemic cells and targeted by multiple investigational agents[1,2]
  - **Flotetuzumab (MGD006):** CD123 x CD3 bispecific DART construct[3]
  - **IMGN632 (CD123 directed)** and **IMGN779 (CD33 directed):** antibodies conjugated to novel DNA alkylating agent[4,5]
  - **XmAb14045:** CD3 x CD123 bispecific antibody[6]



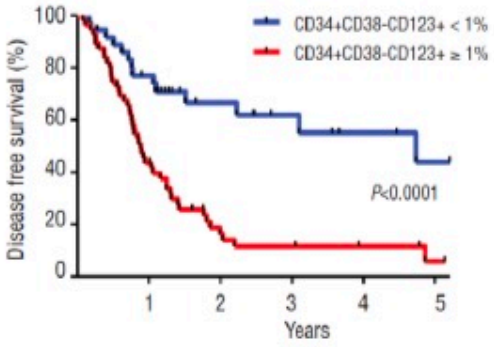
1. Jordan. Leukemia. 2000;14:1777. 2. Testa. Leukemia. 2004;18:219. 3. Uy. ASH 2017. Abstr 637.
4. Kovtun. ASH 2016. Abstr 768. 5. Cortes. ASH 2017. Abstr 1312. 6. Lichtenegger. J Hematol Oncol. 2017;10:142.

Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART® Protein

- Flotetuzumab:
  - An investigational bispecific molecule that co-engages T cells (anti-CD3) with a tumor associated antigen (CD123)
  - Designed to:
    - Redirect T cells to kill tumor cells
    - Recognize tumors independent of TCR & MHC
  - Currently being tested in a Phase 1/2 study in patients with AML



- CD123, the low-affinity IL-3 receptor (IL3Rα)
  - Normally expressed on hematopoietic progenitor cells (HPCs), plasmacytoid dendritic cells (pDCs), basophils, monocytes
  - Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies
  - Increased CD123 expression associated with increased risk of relapse[1]



1. Vergez F et al, Haematologica (2011) 96: 1792

Flotetuzumab Phase 1/2 Study Design

Expansion in primary induction failure & early relapsed AML patients

Key Entry Criteria (refractory AML population)

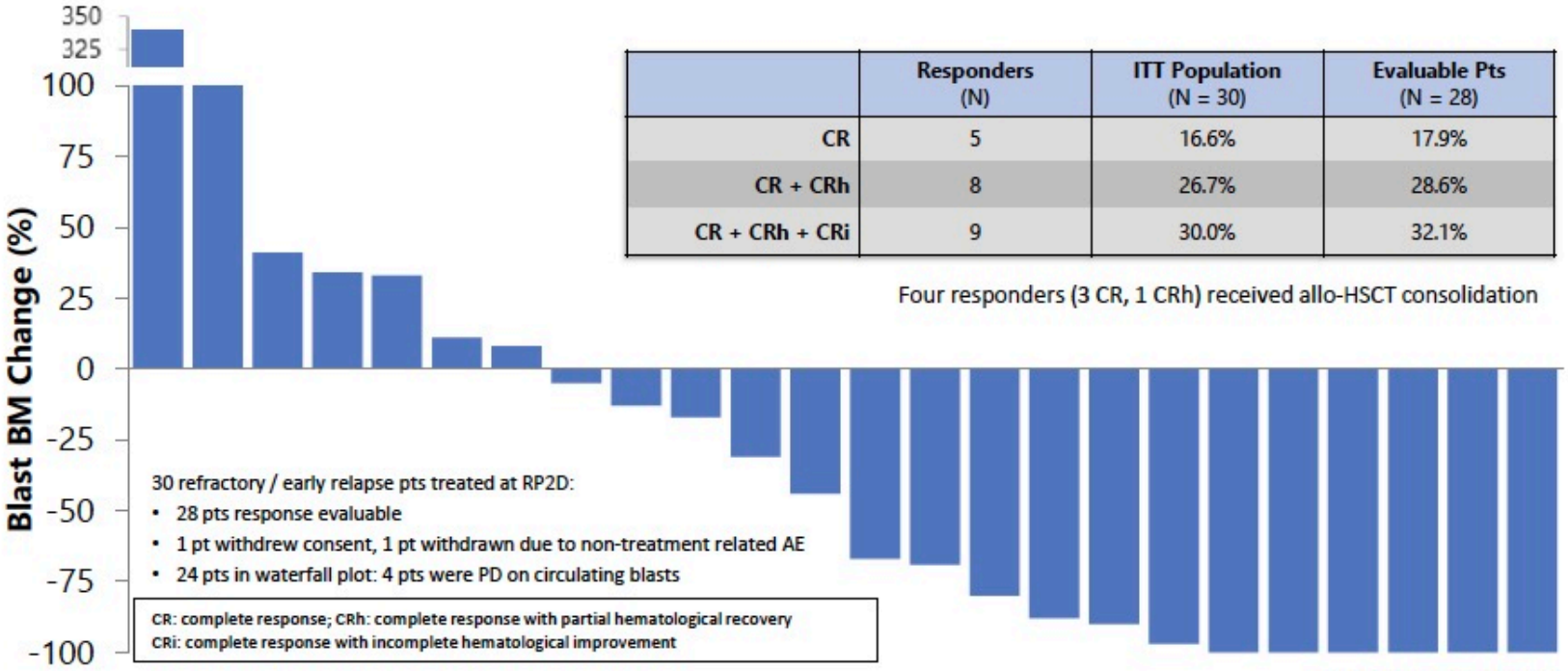
- Primary induction failure (PIF): refractory to ≥ 2 induction attempts
- Early relapse: First relapse with initial CR duration of < 6 months or any prior unsuccessful salvage
- No prior allogeneic hematopoietic cell transplant

Study Objectives

- Safety and preliminary clinical activity
- Optimize delivery and supportive care
- Define PK, PD and PK/PD relationships

Flotetuzumab is Active in Primary Induction Failure & Early Relapsed AML Patients

Benchmark analysis suggests historical CR+CRh rates in this setting of ~12.5% [1]



	Responders (N)	ITT Population (N = 30)	Evaluable Pts (N = 28)
CR	5	16.6%	17.9%
CR + CRh	8	26.7%	28.6%
CR + CRh + CRi	9	30.0%	32.1%

Four responders (3 CR, 1 CRh) received allo-HSCT consolidation

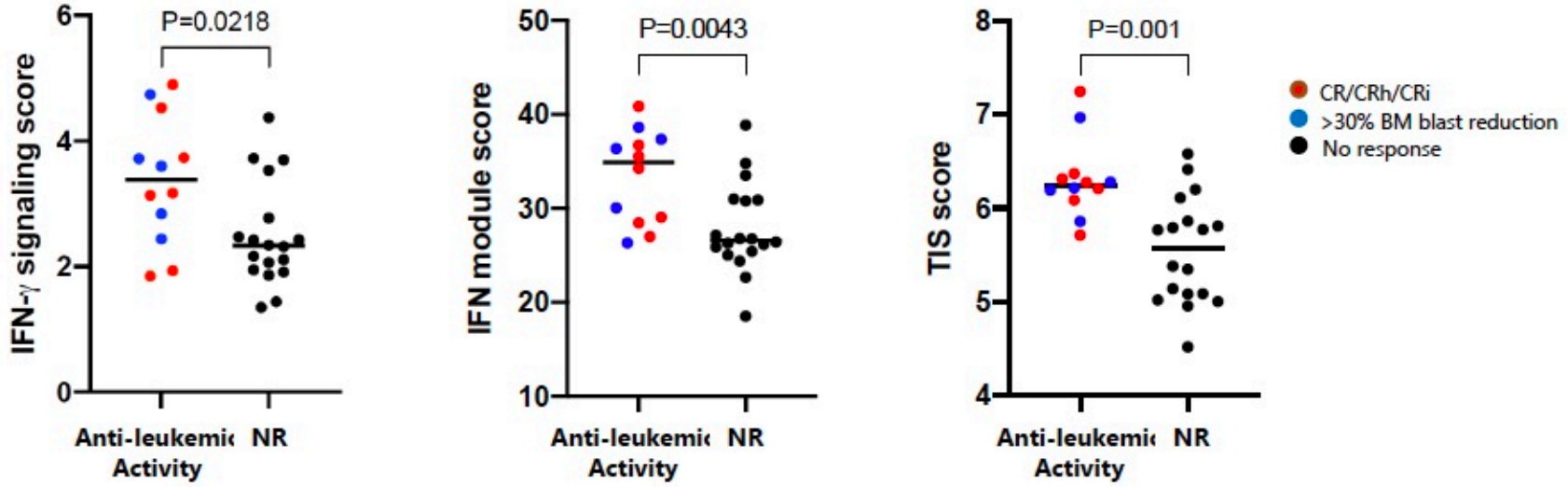
30 refractory / early relapse pts treated at RP2D:
- 28 pts response evaluable
- 1 pt withdrew consent, 1 pt withdrawn due to non-treatment related AE
- 24 pts in waterfall plot: 4 pts were PD on circulating blasts

CR: complete response; CRh: complete response with partial hematological recovery
CRi: complete response with incomplete hematological improvement

Data cut-off Nov 1, 2019

1. Unpublished analysis of the CLASSIC I, VALOR, ADMIRAL trials and additional trials that included venetoclax, gemtuzumab-ozogamicin, and IDH1/2 inhibitors; (n=1328): CR/CRh = 12.5% [95% CI = 7.7%, 19.6%]

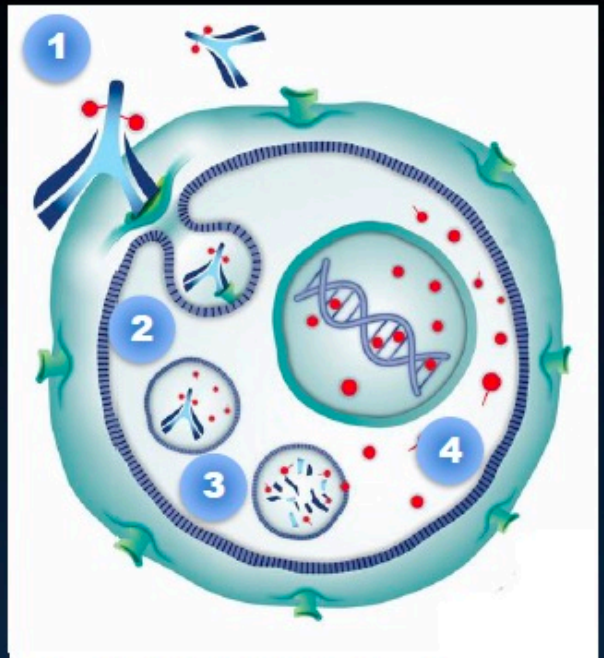
Baseline IFN-γ-related Gene Signatures Associate with Flotetuzumab Activity



IFN-γ-related gene signatures (NanoString PanCancer IO 360™ panel) in baseline BM samples
NR= no response); Data shown as mean, *p-value* calculated by Mann-Whitney *U* test for unpaired determinations
Samples n=30; subgroup of patients treated at the RP2D for whom BM samples were available
TIS: Tumor Inflammation Signature

Rutella et al. ASH 2019 Abstract # 460

IMGN632: A Novel CD123-Targeting ADC



1 - ADC binds target
2 - ADC internalized
3 - Payload released
4 - Payload alkylates DNA

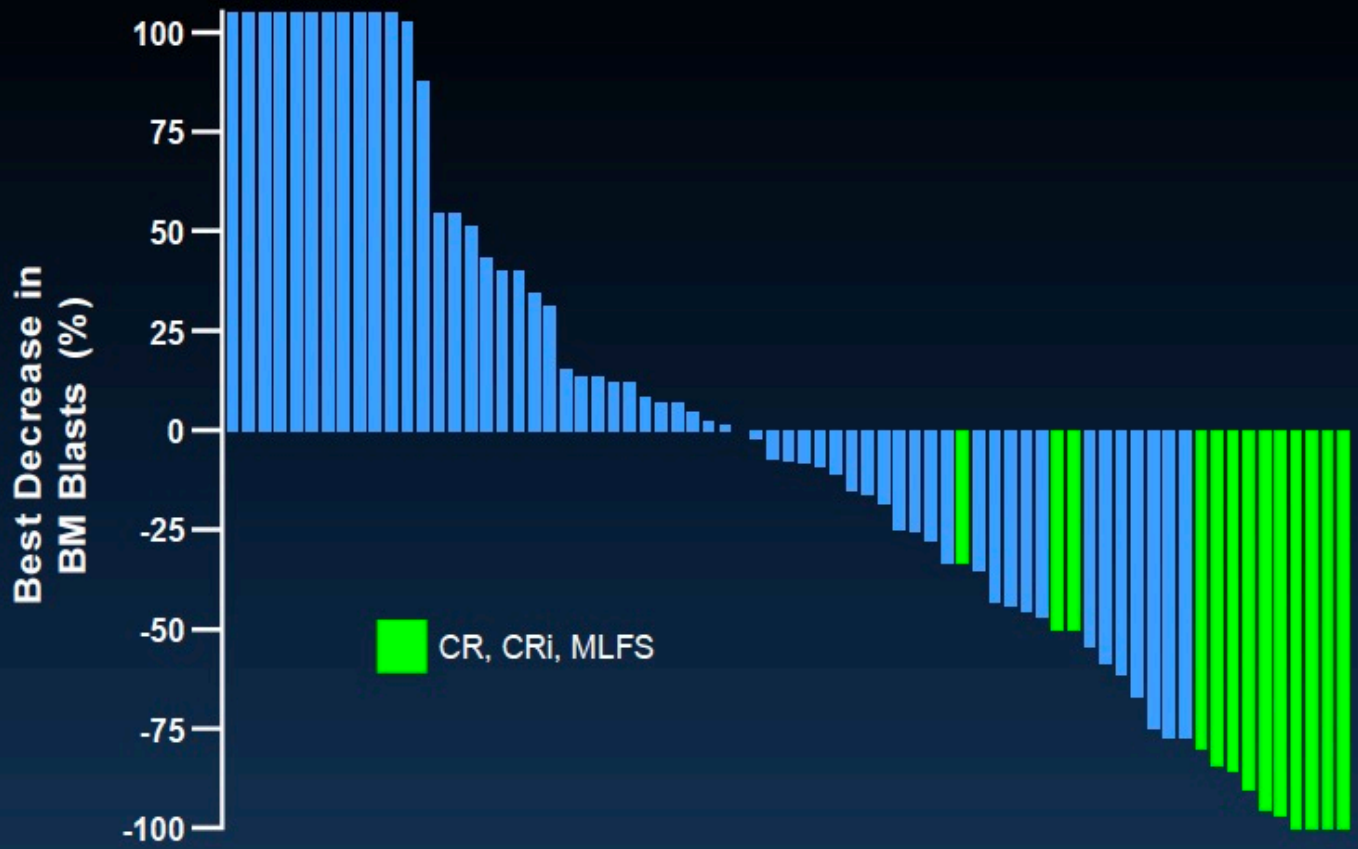
- Novel Anti-CD123 Antibody
  - Higher affinity binding to CD123
  - Unique epitope in extracellular domain
- Novel IGN Payload (DGN549)
  - DNA-alkylating activity, single strand DNA breaks (vs. double strand)
  - 10-20x more potent than the IGN in IMGN779
  - Uniform loading of 2 IGN molecules per antibody
- Stable Peptide Linker
  - Protease cleavable
  - Confers stability in circulation, and controlled intracellular payload release

Kovtun et al. 2018 Blood Adv 2:848-858

IMGN632 in R/R AML and BPDCN, abstract #734

AML Efficacy

BM-evaluable patients (n=71): BM blast reductions in >50% patients



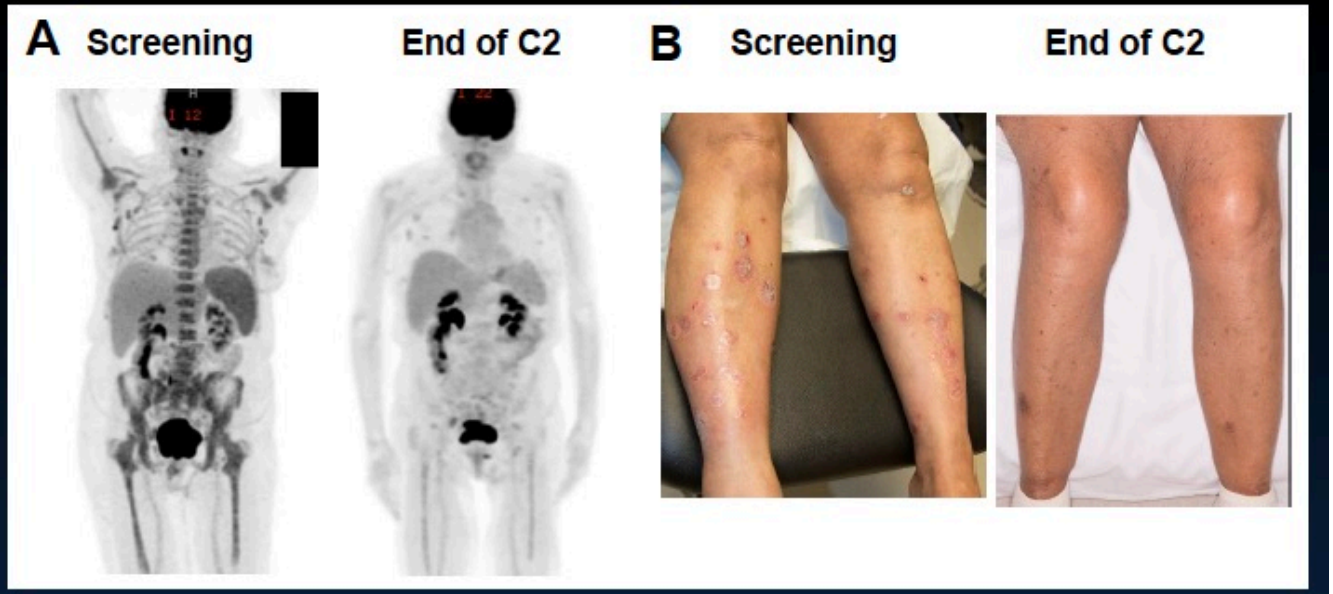
- 54% of BM-evaluable patients had a reduction in BM blasts
- 13 responses (2 CR, 10 CRi, 1 MLFS*) observed across both schedules and at multiple dose levels
- Fractionated Schedule B did not appear to provide increased efficacy

Daver N et al, IMGN632 in R/R AML and BPDCN, ASH 2019 abstract #734

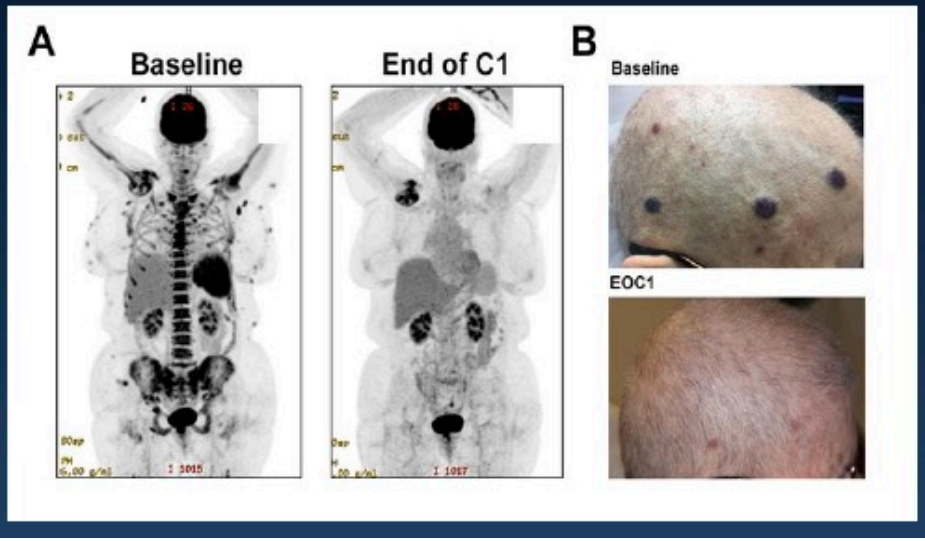
IMGN632 in R/R AML and BPDCN, abstract #734

Responses in refractory BPDCN

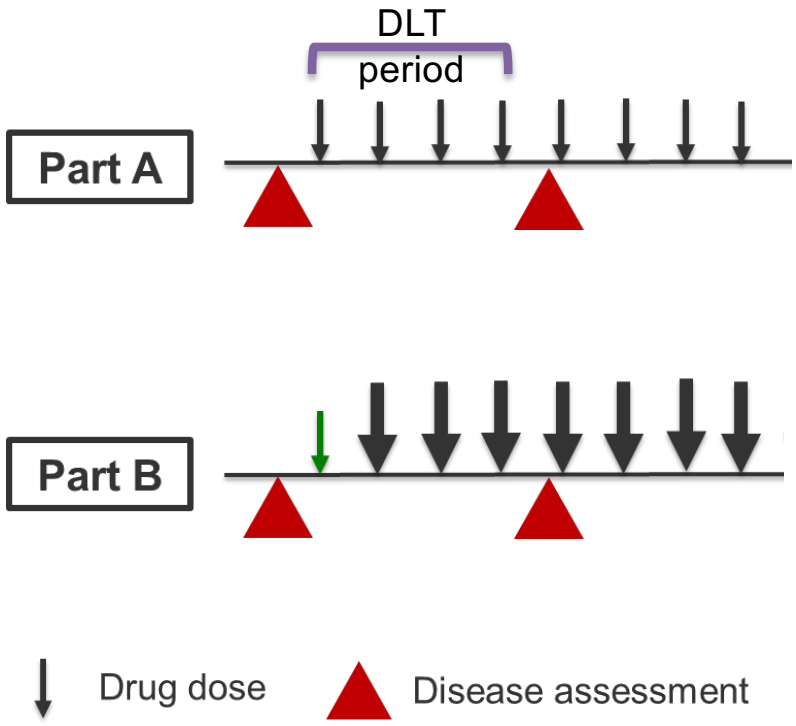
63yo female with BPDCN, refractory to SL-401 x2 presented with extensive marrow and skin involvement. After 1 dose, BM cleared from 84% to 0%. After 2 cycles, skin cleared active lesions and "Partial Remission" based on lymph nodes reduction.



69yo female with MDS/BPDCN, refractory to SL-401, CLAG-M, CLAG and presented with extensive skin/PET/BM involvement. After 1 cycle, in CRi, BM cleared from 37% to 0%.



Phase I Trial of XmAb14045 (CD123 x CD3 Bispecific Antibody) in R/R Hematologic Malignancies



- Enrolled patients with R/R AML (N = 66), median age 61 years
- Patients received weekly doses of XmAb®14045 infused over 2 h
  - Cycles were 28 d in length
  - Part A: 15 planned dose cohorts starting at 0.003 µg/kg
  - Intrapatient dose escalation allowed
- Disease assessments at end of odd-numbered cycles
- DLT period: D1-22
- More cycles permitted if deemed clinically beneficial by investigator

Ravandi. ASH 2018. Abstr 763.

XmAb14045 in R/R AML: Safety

Related TEAEs in ≥ 10% of Patients, n (%)	Patients (N = 66)	
	Any Gr	Gr ≥ 3
CRS*	36 (55)	4 (6)
Chills	26 (39)	
Fever	18 (27)	
Tachycardia	14 (21)	
Increased ALT	12 (18)	5 (8)
Anemia	11 (17)	9 (14)
Hypotension	11 (17)	1 (2)
Fatigue	10 (15)	1 (2)
Hypertension	9 (14)	3 (5)
Increased AST	8 (12)	2 (3)
Lymphopenia	7 (11)	5 (8)
Nausea	7 (11)	
Vomiting	7 (11)	

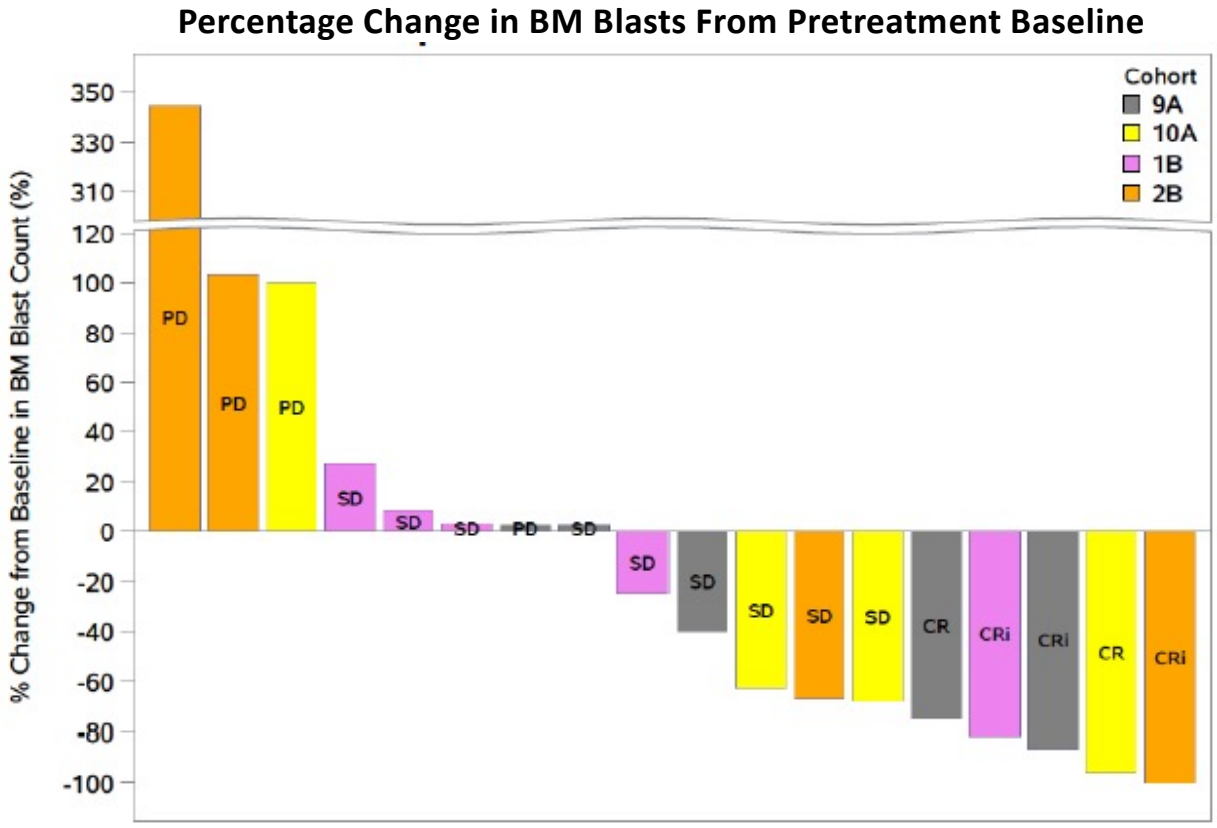
*Per Lee. Blood. 2014;124:188.

- CRS in 55%, with 29% having events within 24 h of infusion consistent with CRS (eg, chills, fever, hypotension, tachycardia)
- No drug-related myelosuppression
- Grade 3 transaminase elevation within 24 h of infusion in 5 patients, all resolved in 7 d
  - No relationship with dose, mostly seen with first dose of XmAb14045
  - 1 patient developed hyperbilirubinemia (Gr 1)
- 4 patients had recurrent infusion-related back or head pain, managed with analgesics
- 5 patients with neurologic events (transient infusion-related cognitive changes)

Ravandi. ASH 2018. Abstr 763.

XmAb14045 in R/R AML: Efficacy

- CR/CRi in 5 out of 18 patients (28%) dosed with ≥ 1.3 µg/kg
- SD lasting > 3 mos in 3 patients (17%)
- BM blast reduction in 56% of patients
- Blast reduction observed in first cycle
- Clinical hematologic recovery from CRi to CR sometimes took 1-2 more cycles



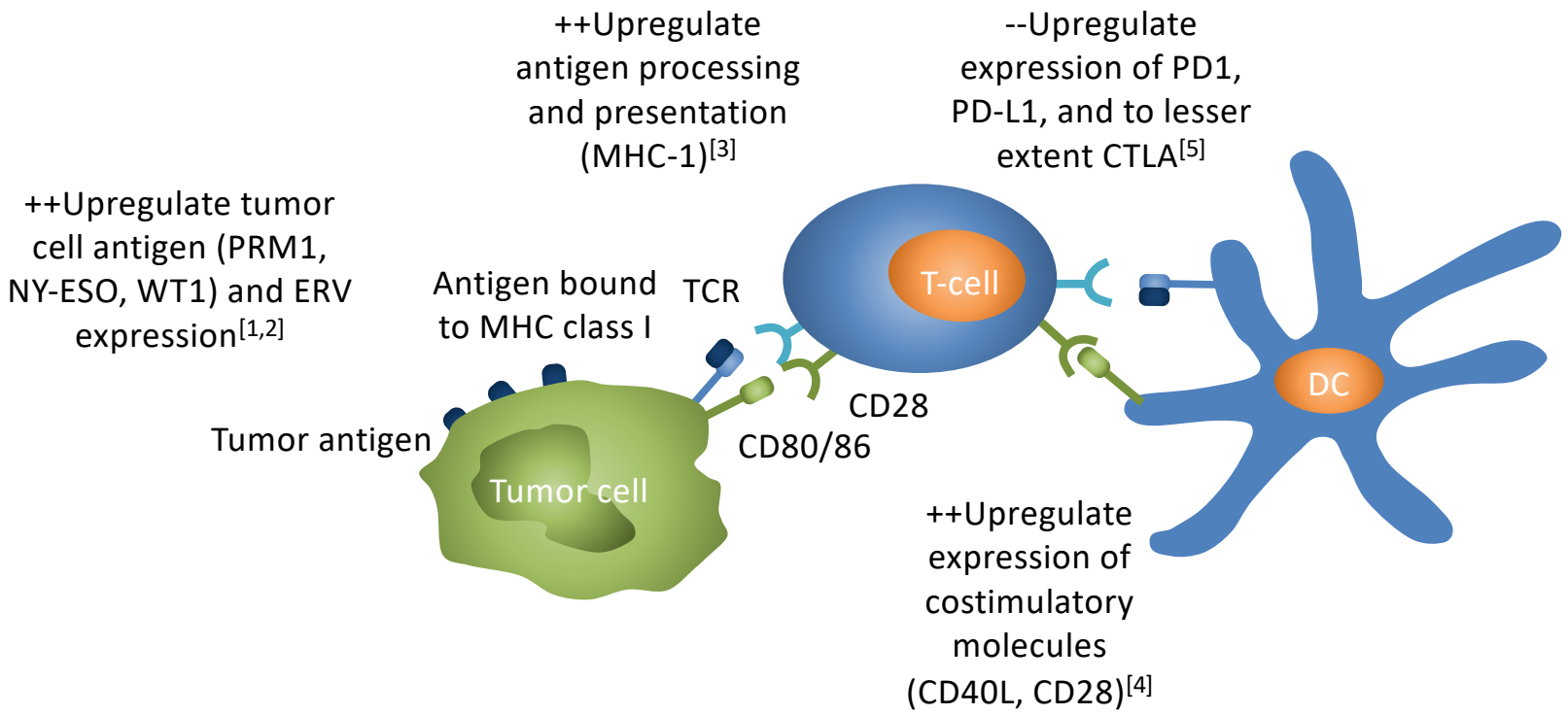
Ravandi. ASH 2018. Abstr 763.

Immune checkpoints in AML/MDS

- Increased PD1/PDL1 at AML progression independent negative factor, especially postSCT.
- Anti-PDL1 antibody decreases AML and improve murine survival.
- Post alloSCT CTLA4 blockade: 5/12 CR in relapsed AML with median 3 prior salvage, including 3 EMD
- Single agent PD1 inhibition with low response rate in relapsed AML and postHMA MDS. HMA+PD1 encouraging in frontline MDS.
- HMAs have dual impact on tumor immunity: favorably increase expression of MHC2, up-regulate tumor antigen and ERV expression, costim molecules; unfavorably increase PD1 and PDL1.

-Dieu L et al, Blood 2009
-Daver N, Sharma P et al, ASH 2016
-Chen et al. Cancer Biol Ther, 2008
-Zhang et al, Blood 2009
-Matthews D et al. NEJM 2016
-Tamura et al, CCR 2005
-Berger et al, Blood 2008
-Yang, Garcia-Manero et al. Leukemia, 2014
-Garcia-Manero et al, EHA 2017
-Boddu P, Daver N et al Leuk and Lymphoma 2016

Hypomethylating Agents and Immune Regulation



1. Sato. Cold Spring Harb Perspect Med. 2017;7. 2. Goodyear. Blood. 2010;116:1908.
3. Li. Oncotarget. 2014;5:587. 4. Wang. PLoS One. 2013;8:e62924. 5. Yang. Leukemia. 2014;28:1280.

Phase Ib/II Study of AZA + Nivo in Relapsed AML

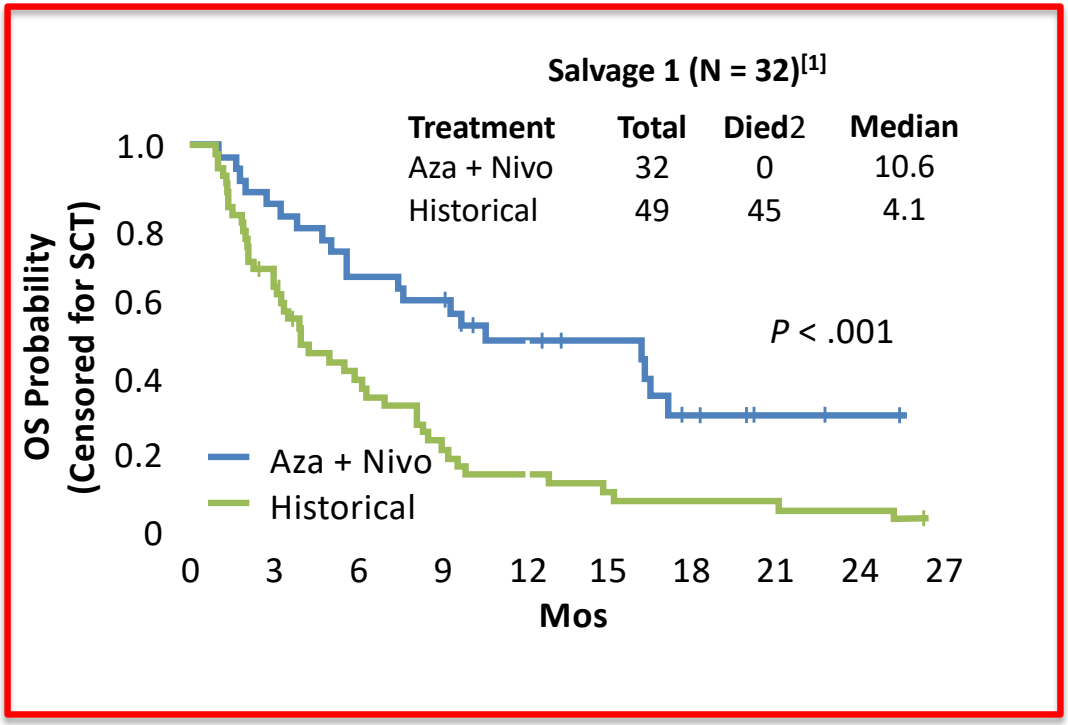
Best Response/Outcome[1]	Evaluable Patients (N = 70)
ORR, n (%)	23 (35)
▪ CR/CRi/PR	17 (25)
▪ HI + 50% blast reduction (> 6 mos)*	7 (10)
▪ SD > 6 mos	6 (9)
▪ PD	41 (56)
8-wk mortality, n (%)	8 (11)
Median no. cycles to response (range)	2 (1-13)
Median follow-up, mos (range)	13.3 (8.2-25.5)

*Response maintained > 6 mos.

- How does this compare?
  - Single-agent AZA/DAC (N = 655) with CR/CRi rate of 16%[2]
  - AZA/DAC + VEN with CR/CRi of 21%[3] to 27%[4]

1. Daver. Cancer Discov. 2018 Nov 8. [Epub ahead of print.] . 2. Stahl. Blood Adv. 2018;2:923.
3. DiNardo. Am J Hematol. 2018;93:401. 4. Goldberg M. ASH 2018. Abstr 1353.

OS of Azacitidine + Nivolumab vs Historical HMA Combinations at MDACC; Censored for SCT



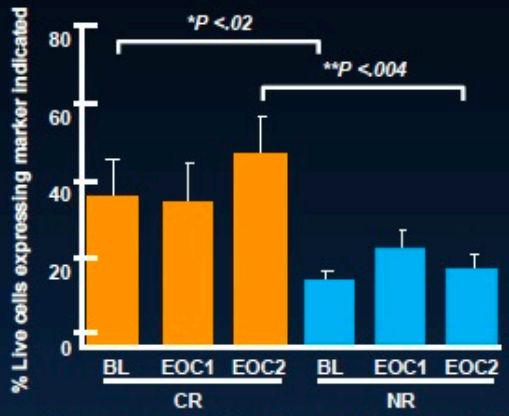
- Salvage 1[1]
  - Median age: 72 yrs
  - Secondary AML: 42%
  - Adverse cytogenetics: 35%
- Expected survival in salvage 1/2: 5-7 mos, 12-mo OS (N = 655): 16%[2]
- Survival with HMA + VEN in salvage (off protocol): 3-4 mos[3]

1. Daver. EHA 2017. Abstr S474. 2. Stahl. Blood Adv. 2018;2:923. 3. DiNardo. Am J Hematol. 2018;93:401.

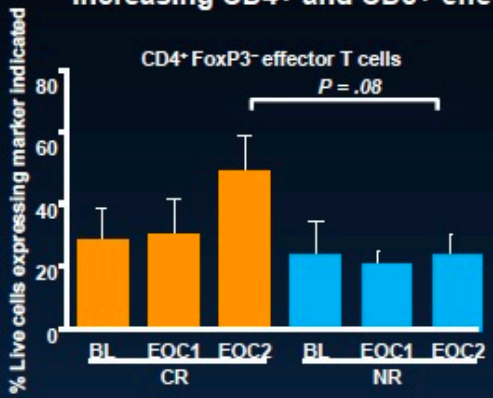
Azacitidine + Nivolumab in R/R AML: Biomarkers of Response and Effects on T Cells

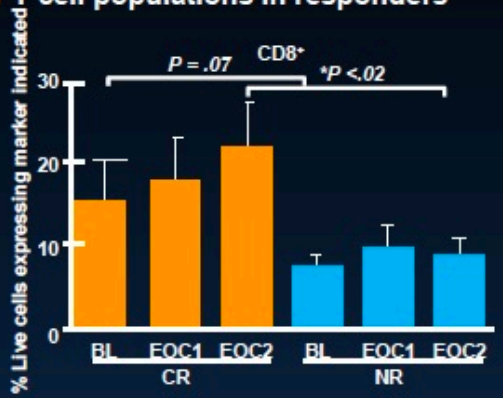
BM optimal cutoff CD3 >13.2%
25/48 (55%) of all patients were above optimal cutoff
ORR was 56% versus 23% (P=0.03), based on cutoff

Early increased CD3+ infiltrate in responders

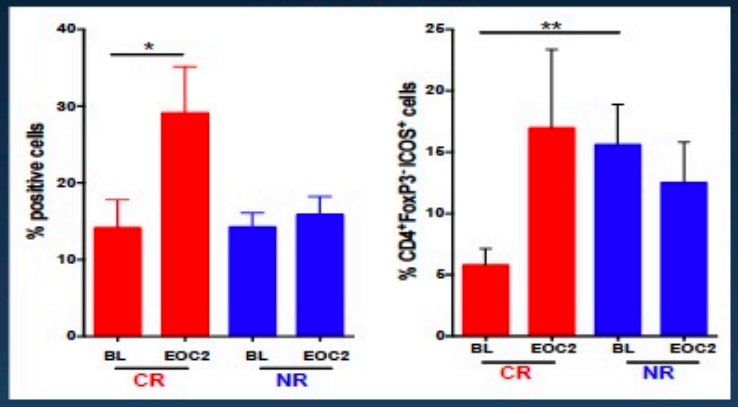


Increasing CD4+ and CD8+ effector T cell populations in responders

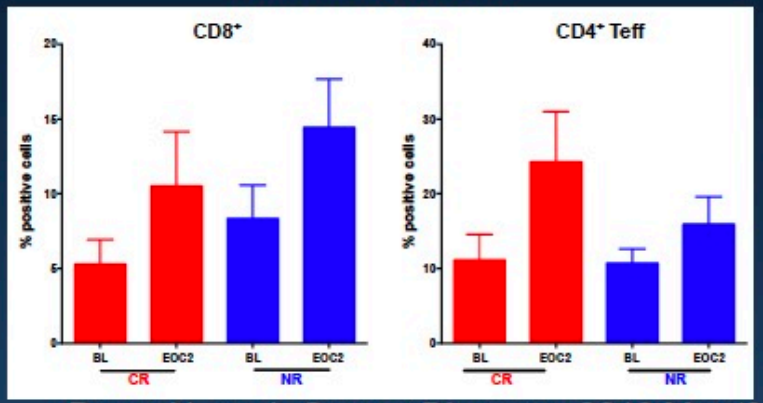




Increased activation markers on T cells (ICOS+) in responders



Baseline and dynamic increase in CD8+/CTLA4+ cells in responders



Daver N, et al. *Cancer Discovery* 2019 Mar;(9)3

Multi-center phase II study of pembroluzimab and azacitidine in patients with relapsed and refractory acute myeloid leukemia (AML) and in newly diagnosed (≥65 years old) AML patients

Ivana Gojo, Robert K. Stuart, Jonathan Webster, Amanda Blackford, Juan C. Varela, Jillian Morrow, Amy E. DeZern, Matthew Foster, Mark J. Levis, Catherine C. Coombs, Gabrielle T. Prince, B. Douglas Smith, Hendrick Van Deventer, Katarzyna Jamieson, Ravi Varadhan, Benjamin G. Vincent, Jonathan S. Serody, Leo Luznik, Joshua F. Zeidner

Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
Medical University of South Carolina, Hollins Cancer Center, Charleston, SC

Outcomes

Patients	Cohort 1 (n = 37)	Cohort 2 (n = 22)
Median follow up	19.3 months	20.2 months
Median time/cys on the study	4.4 mos / 4 cy (range, <1-20[+])	6.8 mos / 6 cy (range, <1-24)
Evaluable for response (≥ 2 cy)	29	17
ORR, evaluable: # (%)	9 (31%)	12 (70.6%)
CR/CRi/PR/HI: # (%), evaluable	2(7%)/ 2(7%)/ 1(3%)/ 4(14%)	8(47%)/ 1(6%)/ 2(12%)/ 1(6%)
SD ≥ 6 mos: # (%), evaluable	9 (31%)	4 (24%)
ORR whole cohort (ITT):	24%	55%
CR+ CRi whole cohort	11%	41%
Stable disease ≥ 6 mos	24%	18%
Median time to response, cys	4 (range, 2-6)	2 (range, 2-15)
8-week mortality	5 (13%) (PD**)	2 (9%) (PD*, sepsis)

- Not evaluable (Cohort 1): rapidly PD (5/2*), pt wishes (1), death due to co-morbidities (1), mucositis/oral GVHD (withdrawn) (1)
- Not evaluable (Cohort 2): sepsis/death (2), rapidly PD (1)*, MOF AML/infection + pembro tox (1), pembro-related fevers (withdrawn) (1)

* Did not receive pembro

ORR: CR/CRi + PR + HI

Efficacy and Safety of Azacitidine (AZA) in Combination with the Anti-PD-L1 Durvalumab (durva) for the Front-line Treatment of Older Patients (pts) with Acute Myeloid Leukemia (AML) Who Are Unfit for Intensive Chemotherapy (IC) and Pts with Higher-Risk Myelodysplastic Syndromes (HR-MDS): Results from a Large, International, Randomized Phase 2 Study

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CL Beach[6]; Lewis R. Silverman[7]

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TREATMENT RESPONSE, AML COHORT (ITT POPULATION*)

Response, n (%) [95% CI]	AZA + Durvalumab	AZA
	n=64	n=65
ORR (CR + CRi)	20 (31.3) [19.9, 42.6]	23 (35.4) [23.8, 47.0]
	P=0.6180	
CR	11 (17.2) [7.9, 26.4]	14 (21.5) [11.5, 31.5]
CRi	9 (14.1) [5.6, 22.6]	9 (13.8) [5.5, 22.2]
PR	4 (6.3) [0.3, 12.2]	2 (3.1) [0, 7.3]
SD	23 (35.9)	21 (32.3)
PD	3 (4.7)	3 (4.6)
NE/Missing,† n (%)	12 (18.8)	15 (23.1)

- Median number of treatment cycles: AZA + durvalumab, 6.5 cycles; AZA, 6.7 cycles
- Median duration of response: AZA + durvalumab, 24.6 weeks (95% CI, 16.4, 48.0); AZA, 51.7 weeks (15.1, 68.9); 40% and 43.5% of patients, respectively, were censored

*Defined as all randomized patients. †Includes patients without adequate data for response assessment at baseline and/or postbaseline prior to use of nonprotocol AML therapy.
Data cutoff: October 31, 2018.
NE, not evaluable; PD, progressive disease; SD, stable disease.

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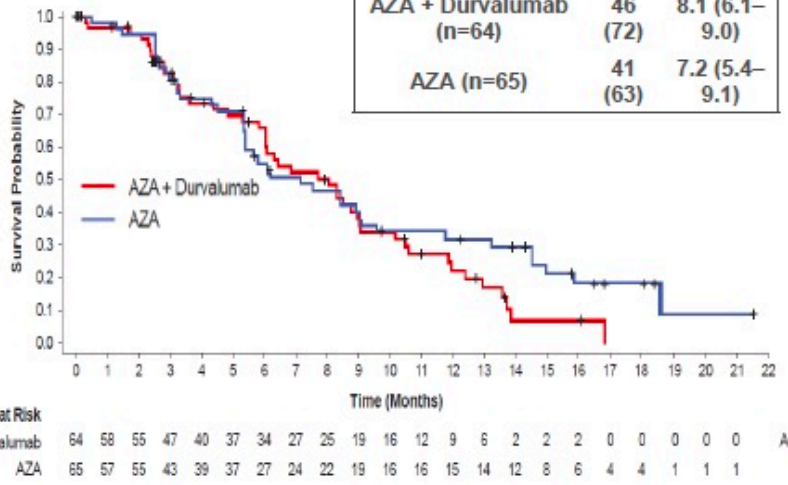
PFS AND OS IN PATIENTS WITH AML (ITT POPULATION)

Progression-Free Survival*†

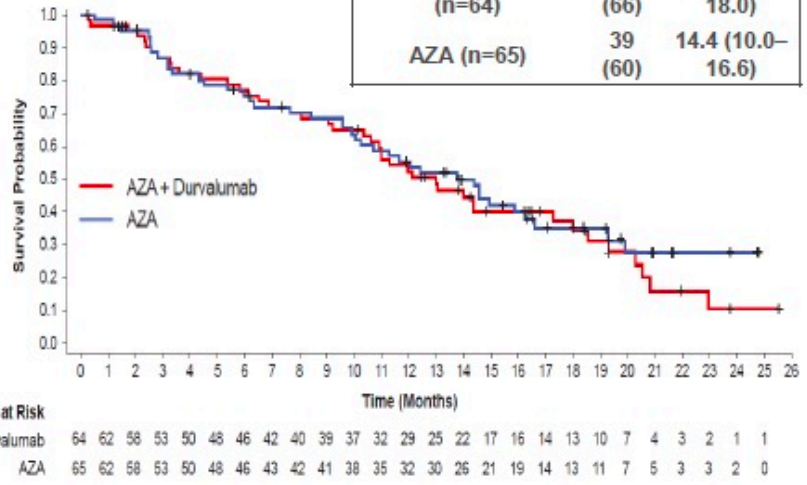
Treatment	Events, n (%)	Median PFS, mo (95% CI)
AZA + Durvalumab (n=64)	46 (72)	8.1 (6.1–9.0)
AZA (n=65)	41 (63)	7.2 (5.4–9.1)



No. at Risk																						
AZA + Durvalumab	64	58	55	47	40	37	34	27	25	19	16	12	9	6	2	2	2	0	0	0	0	0
AZA	65	57	55	43	39	37	27	24	22	19	16	16	15	14	12	8	6	4	4	1	1	1

Overall Survival‡

Treatment	Events, n (%)	Median OS, mo (95% CI)
AZA + Durvalumab (n=64)	42 (66)	13.0 (10.4–18.0)
AZA (n=65)	39 (60)	14.4 (10.0–16.6)



No. at Risk																									
AZA + Durvalumab	64	62	58	53	50	48	46	42	40	39	37	32	29	25	22	17	16	14	13	10	7	4	3	2	1	1
AZA	65	62	58	53	50	48	46	43	42	41	38	35	32	30	26	21	19	14	13	11	7	5	3	3	2	0

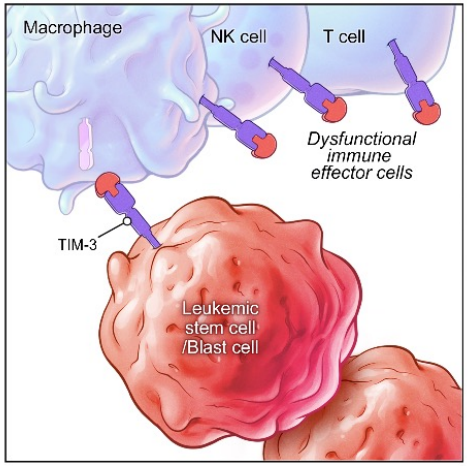
*Approximately 35% of patients censored.
†Time from randomization to the first documented PD or death due to any cause, whichever comes first.
‡Approximately 37% of patients censored.
Data cutoff: October 31, 2018.

Zeidan AM et al., ASH 2019; Abstract #829 @Dr_AmerZeidan

TIM-3 is an inhibitory receptor expressed on immune and leukemic cells

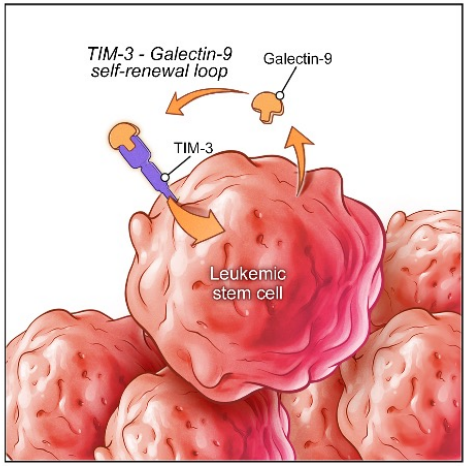
Immune Effectors

- An inhibitory receptor expressed on macrophages, monocytes, NK cells, dendritic cells, and T cells[1,2]
- Involved in regulating innate and adaptive immune responses[1,2]



Leukemic Cells

- Expressed on LSCs and blasts, but not on normal HSCs,[3,4] making it a promising target in MDS/AML[4-6]
- TIM-3/Galectin-9 interaction promotes an autocrine stimulatory loop promoting LSC self-renewal



AML, acute myeloid leukemia; HSC, hematopoietic stem cell; IgG4, immunoglobulin G4; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; NK, natural killer; 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. Ngiow SF. *Cancer Res.* 2011;71:3540–3551; 6. Sakuishi K, et al. *Trends Immunol.* 2011;32:345–349; 7. Sabatos-Peyton C. AACR 2016. Oral presentation; 8. Borate U, et al. ASH 2019. Oral presentation.

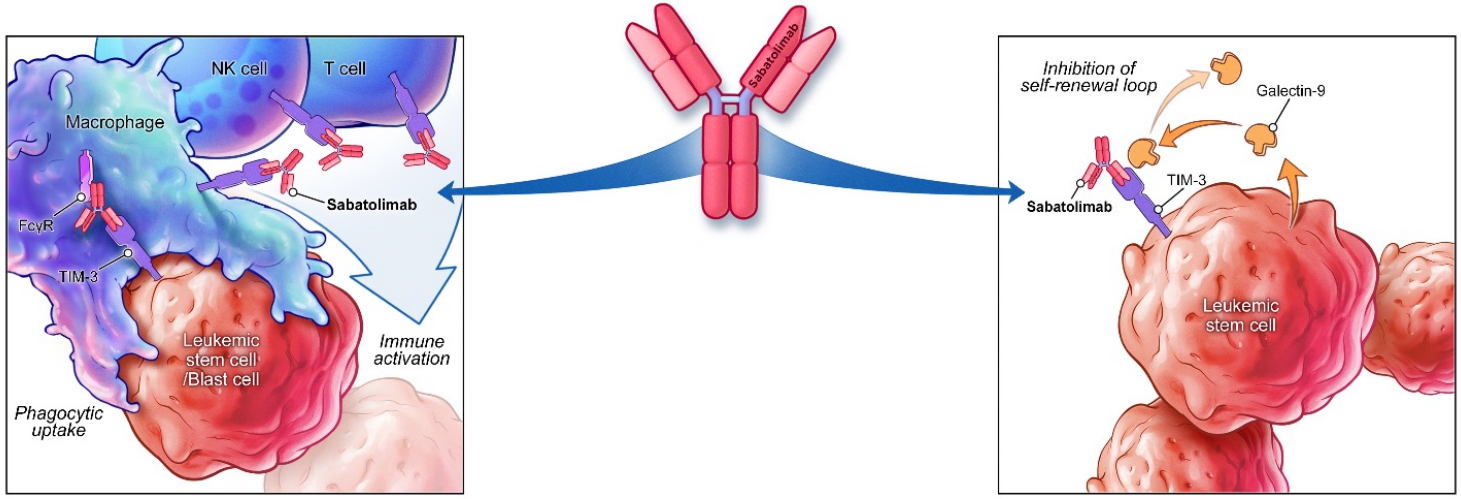
Dual Targeting of TIM-3 on Immune and Leukemic Cells by Sabatolimab

Targeting Immune Effectors

- Binds TIM-3 on immune cells, enhancing anti-leukemia immune activation
- Enhances phagocytic uptake, facilitating cell-mediated killing of LSCs and blasts

Targeting Leukemic Cells

- Directly targets LSCs through high-affinity binding of TIM-3
- Blockade of TIM-3 on LSCs may inhibit TIM-3/Galectin 9 driven self-renewal



AML, acute myeloid leukemia; HSC, hematopoietic stem cell; IgG4, immunoglobulin G4; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

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Trial design: Phase 1b study of Sabatolimab + HMA in MDS/AML[1,2]

Up to 207 Adult Patients

- IPSS-R high- or very high-risk MDS (HR-MDS)
- Unfit, newly diagnosed AML, ineligible for standard chemotherapy
- R/R AML, ineligible for standard chemotherapy

Patients with prior HMA treatment for MDS/AML were excluded

Decitabine Arm
Days 1-5
20 mg/m²
Started Aug 2017

Azacitidine Arm
Days 1-7
75 mg/m²
Started Feb 2019

Sabatolimab Day 8
- 240 mg Q2W
- 400 mg Q2W
- 800 mg Q4W

Sabatolimab Day 22
- 240 mg Q2W
- 400 mg Q2W

28-day treatment cycles

Additional study arms
- Sabatolimab ± spartalizumab (anti-PD-1)
- Spartalizumab + decitabine
- Spartalizumab + decitabine + sabatolimab

ClinicalTrials.gov identifier: NCT03066648[a]

8 countries

11 trial centers

Primary Endpoints:
Maximum tolerated dose/recommended dose, safety and tolerability

Secondary Endpoints:
Preliminary efficacy, pharmacokinetics

[a]Multi-arm, open-label, phase Ib dose-escalation and -expansion study of Sabatolimab as a single-agent or in combination with HMAs or spartalizumab.
HMA, hypomethylating agents; IPSS-R, Revised International Prognostic Scoring System; R/R, relapsed or refractory.
1. Borate U, et al. *Blood*. 2019;134(suppl 1):570; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03066648.

Patient characteristics

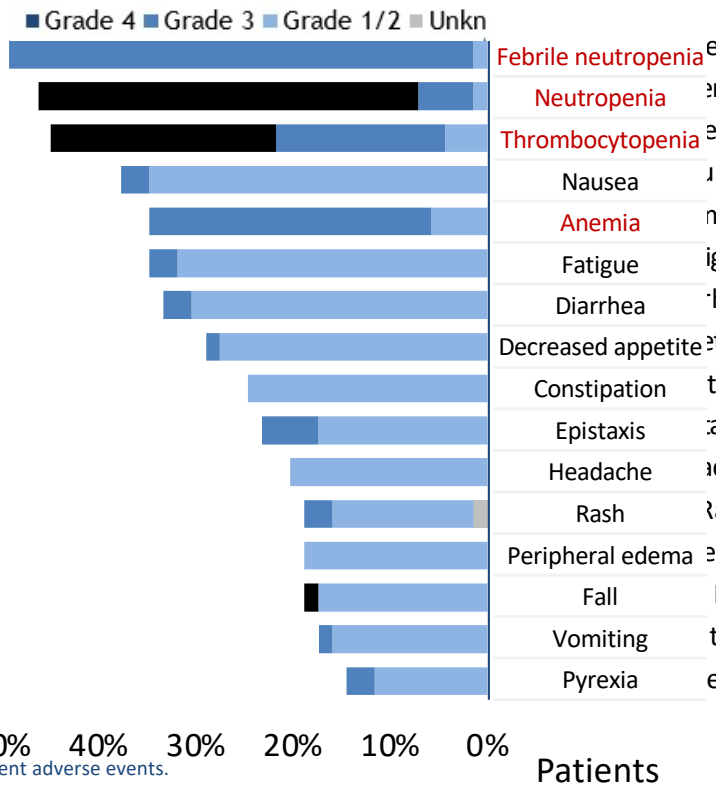
Parameter	Sabatolimab + Decitabine (N=69)			Sabatolimab + Azacitidine (N=37)	
	HR-MDS n=18	ND-AML n=22	R/R AML n=29	HR-MDS n=16	ND-AML n=21
Median age (range), years	69.5 (23–87)	72.0 (66–89)	68.0 (35–80)	70.5 (47–82)	75.0 (59–87)
ECOG performance status,[a] n (%)					
0	5 (28)	7 (32)	11 (38)	6 (38)	6 (29)
1	13 (72)	11 (50)	17 (59)	8 (50)	13 (62)
2	0	4 (18)	1 (3)	2 (13)	1 (5)
IPSS-R category (MDS), n (%)					
High	14 (78)	—	—	9 (56)	—
Very high	4 (22)	—	—	7 (44)	—
2017 ELN risk classification[1] (AML),[b] n (%)					
Favorable	—	0	3 (10)	—	0
Intermediate	—	11 (50)	15 (52)	—	9 (43)
Adverse	—	11 (50)	10 (34)	—	12 (57)

[a]ECOG performance status was unknown for 1 patient (ND-AML) in the Sabatolimab + azacitidine arm.
[b]For 1 patient with R/R AML, cytogenetic data were missing and the ELN risk classification is unknown.
ECOG, Eastern Cooperative Oncology Group; ND-AML, newly diagnosed AML.
1. Döhner H, et al. *Blood.* 2017;129:424–447.

Sabatolimab + HMA is safe and well tolerated
TEAEs occurring in ≥15% of patients overall

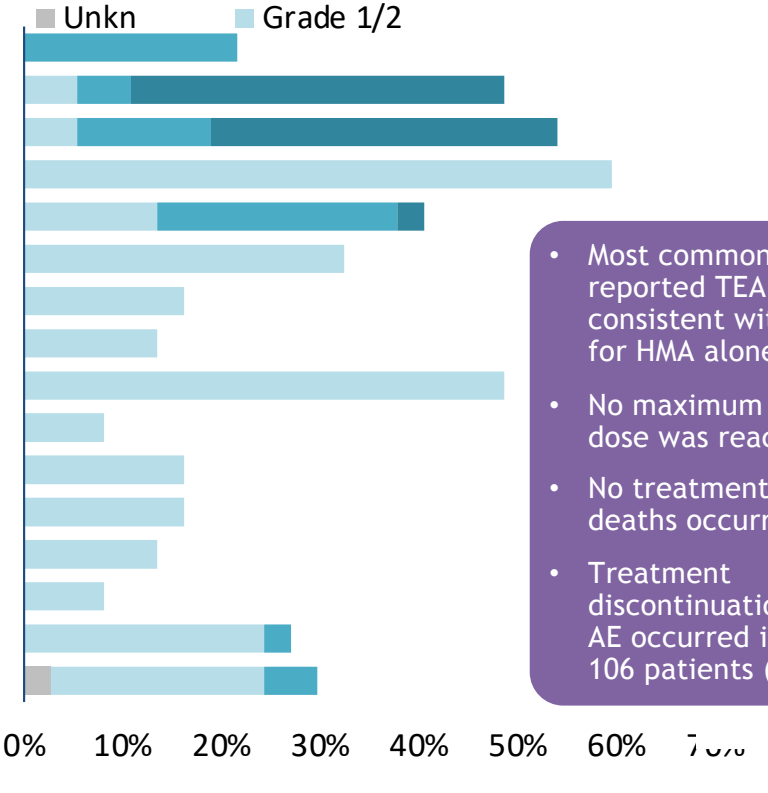
Sabatolimab + Decitabine (N=69)

Median exposure: 4.3 (0.7–30.3) months



Sabatolimab + Azacitidine (N=37)

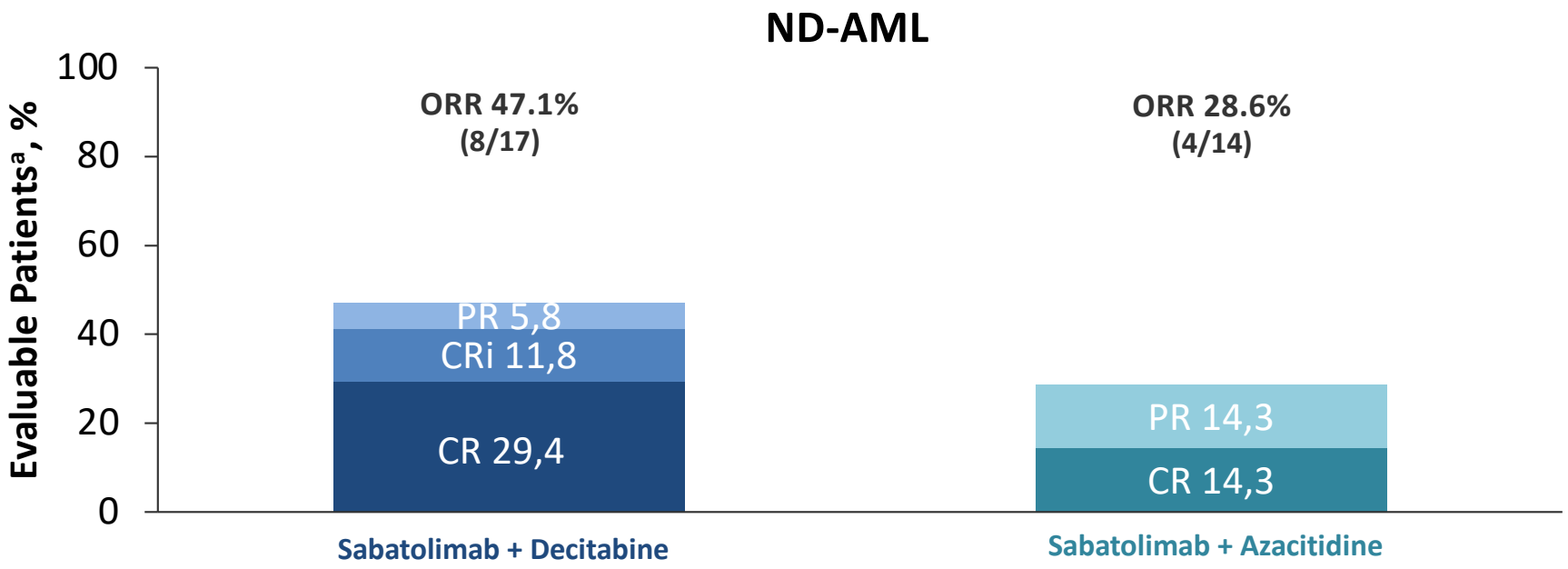
Median exposure: 3.1 (0.3–12.3) months



- Most commonly reported TEAEs were consistent with those for HMA alone
- No maximum tolerated dose was reached
- No treatment-related deaths occurred
- Treatment discontinuation due to AE occurred in only 4 of 106 patients (2.3%)

TEAE, treatment-emergent adverse events.

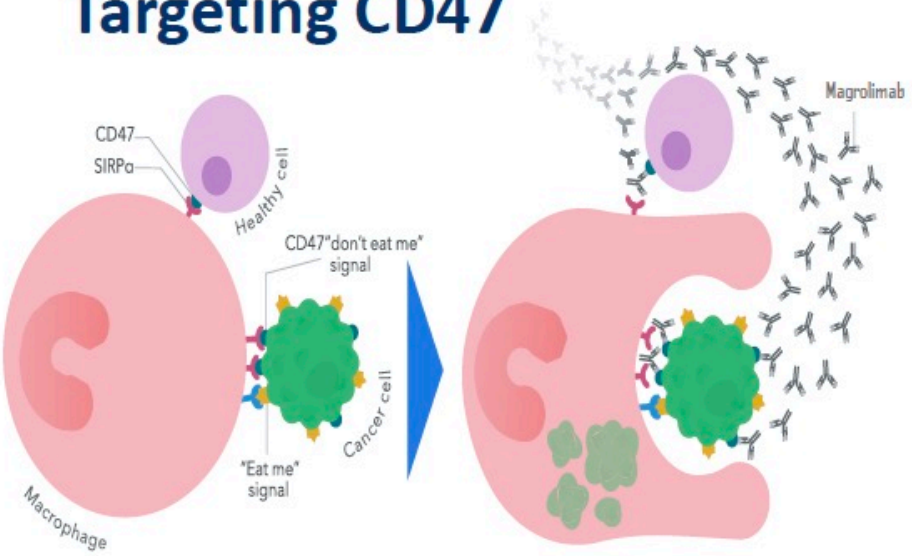
Responses observed with sabatolimab + HMA in AML



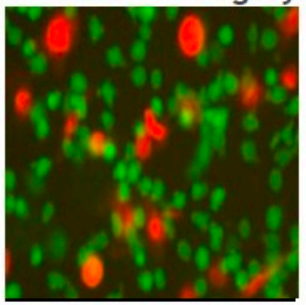
ORR with sabatolimab + decitabine in patients with R/R AML (26 evaluable[a]) was 23% (all CRi)

[a]Patients were evaluable if they had a valid baseline and at least one post-baseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.
CR, complete remission; CRi, complete remission with incomplete hematologic recovery; ORR, overall response rate; PR, partial remission; SD, stable disease.

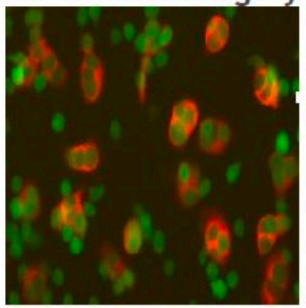
Magrolimab (Formerly 5F9) Is a First-in-Class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages
Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

EUROPEAN HEMATOLOGY ASSOCIATION

EHA25 VIRTUAL

Magrolimab Combined with Azacitidine is Effective in Untreated AML Patients Unfit for Intensive Chemotherapy Including TP53 Mutant

Patient Characteristics

Characteristic	1L AML Magro + AZA (N=29)
Median age in years (range)	74 (60–89)
ECOG Performance Status: 0 1 2	7 (24%) 20 (69%) 2 (7%)
Cytogenetic Risk: Favorable Intermediate Poor Unknown/missing	0 2 (7%) 21 (72%) 6 (21%)
WHO AML classification: MRC Therapy related	 19 (66%) 3 (10%)
Harboring a *TP53* mutation	13 (45%)

Efficacy: Response

Best Overall Response	1L AML N=25	TP53 Mutant N=12
ORR	16 (64%)	9 (75%)
CR	10 (40%)	5 (42%)
CRi	4 (16%)	4 (33%)
PR	1 (4%)	0
MLFS	1 (4%)	0
SD	8 (32%)	2 (17%)
PD	1 (4%)	1 (8%)
MRD negativity[1]	8/16 (50%)	4/9 (44%)

[1] responders

Efficacy: Durability

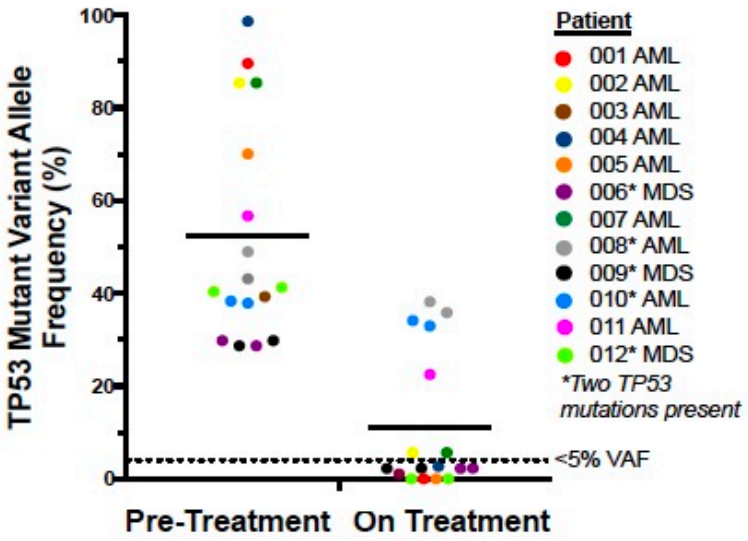
Median DOR in mos (range)	Not reached (0.03+ – 15.1+)
Median follow-up in mos (range)	9.4 (1.9–16.9)

- Magrolimab is a first-in-class anti-CD47 antibody, targeting a macrophage immune checkpoint
- Magrolimab + azacitidine was well-tolerated, achieving a 64% response rate in unfit AML with no median response duration reached
- A 75% CR/CRi rate was observed in TP53 mutant AML with clearance of TP53 mutational burden in the majority of patients

Daver N et al, EHA 2020, S144

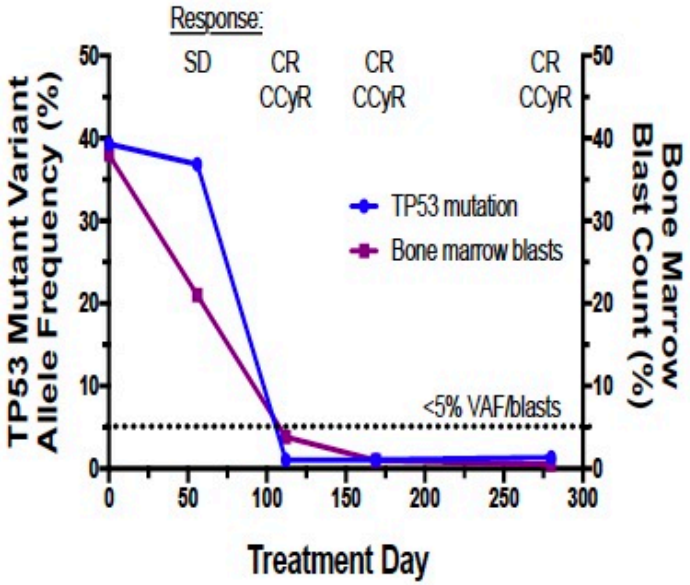
Magrolimab + AZA Eliminates *TP53* Mutational Burden

TP53 Mutation Burden on Treatment



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

- ***TP53* mutational burden is reduced in patients on therapy**

Date: June 13, 2020; Program Section: 04. Acute myeloid leukemia - Clinical

Daver N et al, EHA 2020, S144

Concluding remarks

- Immunotherapy: a new modality in AML
- Bispecific antibodies in early clinical trials showing activity
- Immune and macrophage checkpoint inhibitors in trials
- Next steps:
  - Potential role for these agents in MRD clearance
  - Ven + Aza + ICI
  - Novel combinations (AZA+TIM-3+/-VEN, Aza+ LAG-3, TIGIT, B7H3)

frontiers

Immunotherapy in Acute Myeloid Leukemia: where we stand.

Alessandro Isidori[1]*, Claudio Cerchione[2]*, Naval Daver[3]*, Courtney DiNardo[3], Guillermo Garcia-Manero[3], Marina Konopleva[3], Elias Jabbour[3], Farhad Ravandi[3], Tapan Kadia[3], Adolfo de la Fuente Burguera[4], Alessandra Romano[5], Federica Loscocco[1], Giuseppe Visani[1], Giovanni Martinelli[2], Hagop Kantarjian[2]**, Antonio Curti[6]**

Frontiers in Oncology 2021, accepted, in press

Thank you!

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