3rd Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2023

CUNEO
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Rondò dei talenti, Cuneo

Update on antibody-based therapeutics and molecular targets in AML: preclinical development and clinical progresses

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Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo, Italy
and Centro Interdipartimentale di Ricerca in Biologia Molecolare (CIRBM), Torino, Italy

DICHIARAZIONE

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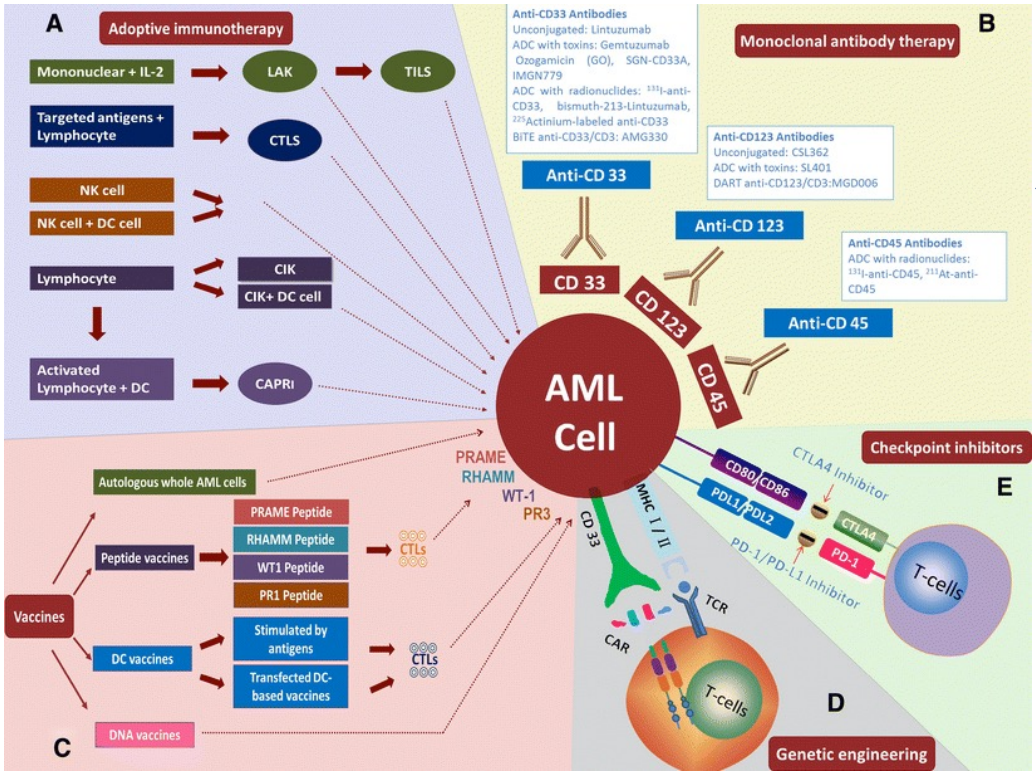
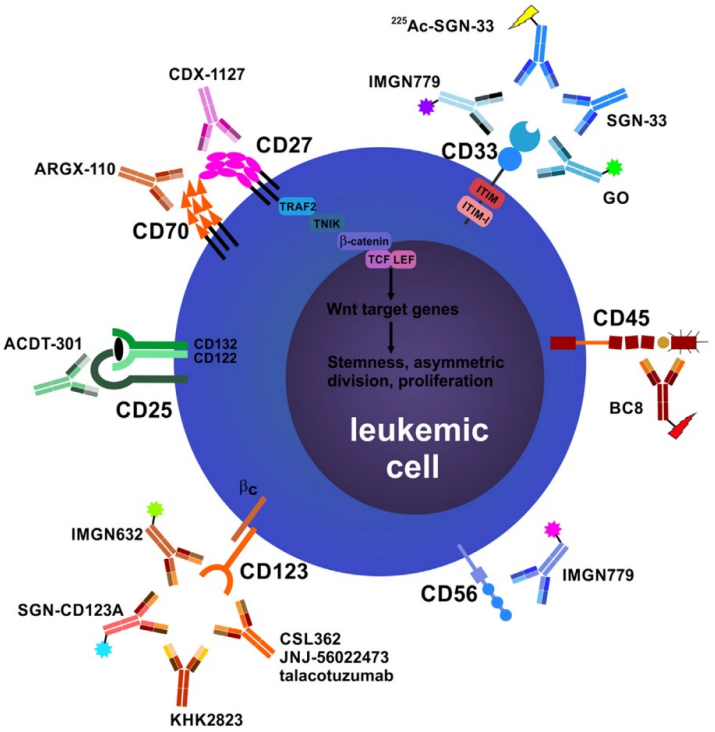
Immunotherapy in AML



ANTIBODY THERAPY

Yang D et al, Annals of Hematology 2017

Target antigens in AML

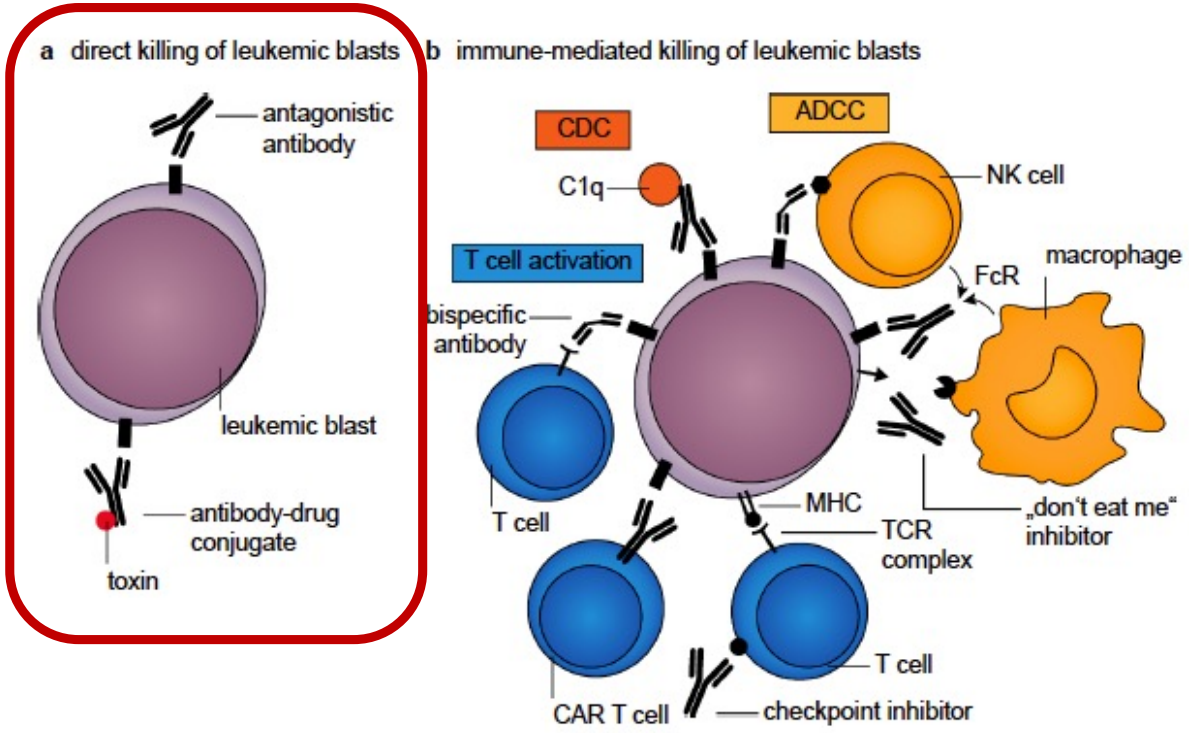


Schurch C.M. et al, Front Oncol 2018

THE «IDEAL» TARGET ANTIGEN

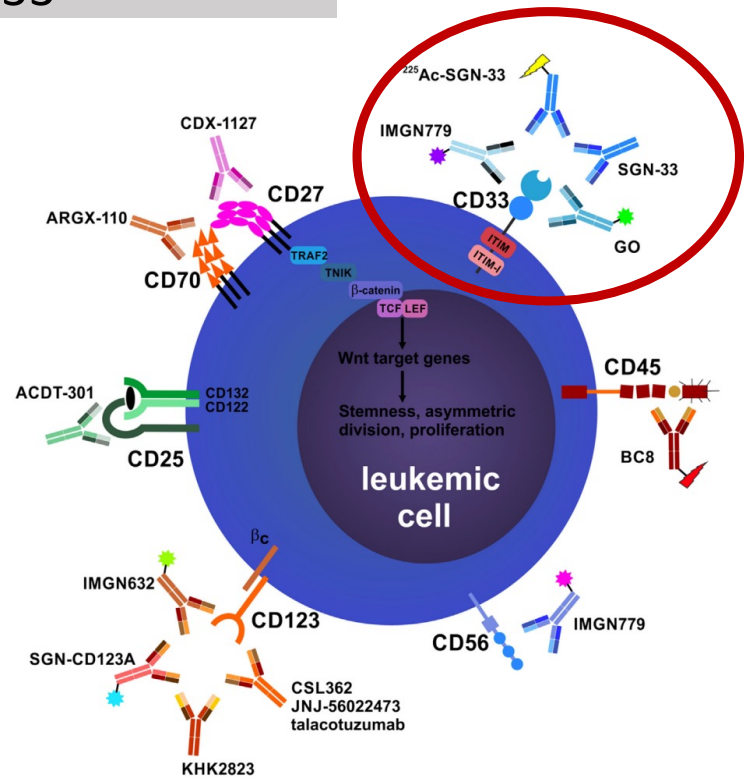
- High level of **expression** on all **AML** cells, including LSCs
- Minimal to **no expression in normal tissues**
- Important role in AML **pathogenesis**
- Not shed into the circulation
- Sufficiently immunogenic (in case of active immunization strategies)

Antibody therapy in AML



Angenendt L et al, Cancer Treatment Reviews 2022

Target antigens in AML: CD33

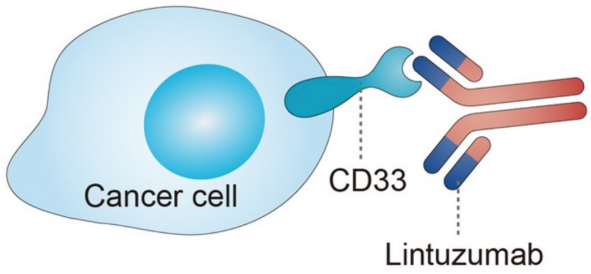


- **Frequently expressed** on AML blast cells (80-90%)
- Expressed also in human lungs, prostate and skin, which may lead to **toxicities to normal organs**
- **Absent on normal hematopoietic stem cells**--> ideal target for AML therapy

Schurch C.M. et al, Front Oncol 2018; Angenendt L et al, Cancer Treatment Reviews 2022

How can we target CD33?
Monoclonal Antibody: Lintuzumab

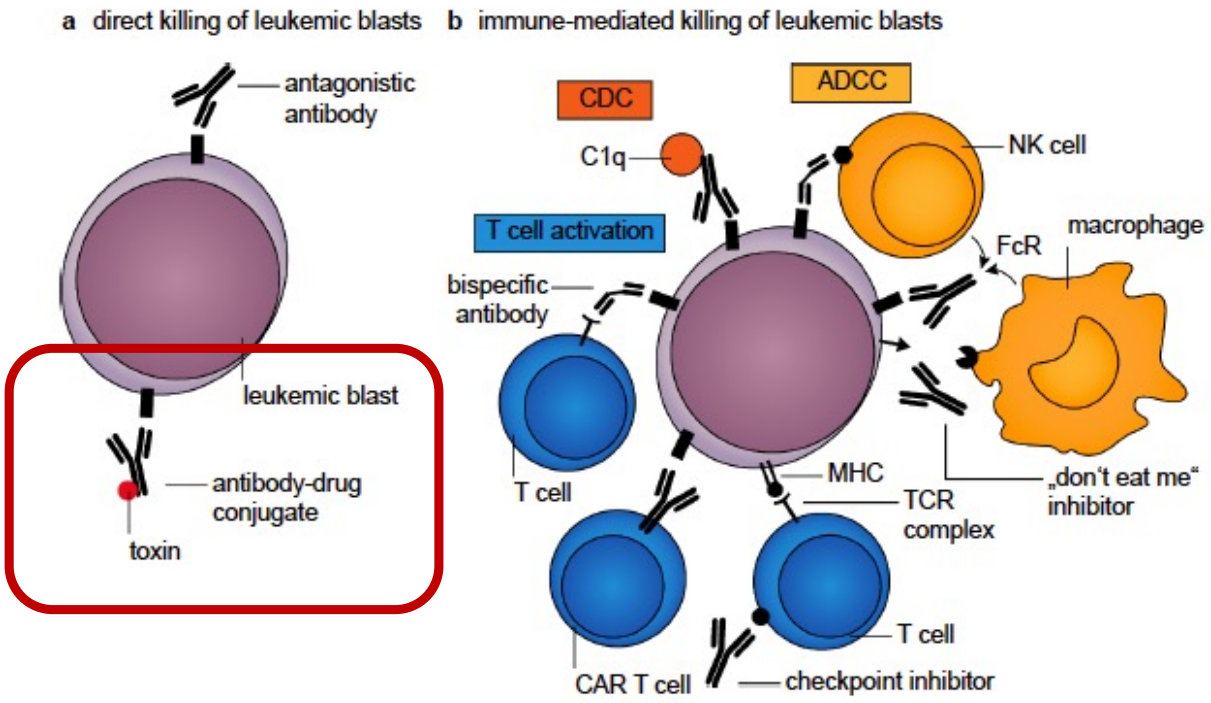
- It induces cell death by **complement and/or antibody-directed cellular cytotoxicity** or as a **direct effect of engaging the CD33 receptor**
- Mostly unsuccessful in the clinic, despite combination with chemotherapy



Antigen	Antibody	Main results
CD33	Lintuzumab (HuM195, SGN-CD33)	• Similar CR/CRp rate and OS with MEC ± Ab in R/R AML (n=191)[1] • Similar OS with low dose cytarabine ± Ab in ND AML (n=211)[2]

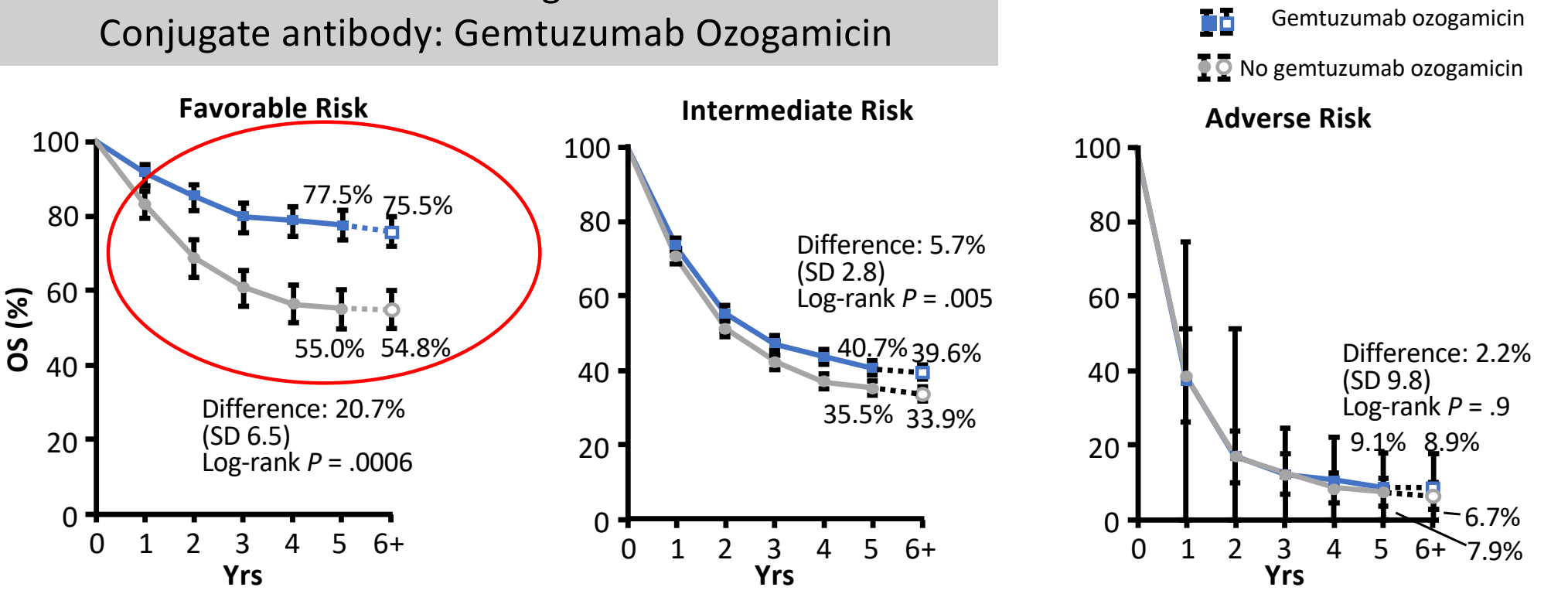
Feldman E. et al, JCO 2005; Sekeres MA et al, Haematologica 2013

Antibody therapy in AML



Angenendt L et al, Cancer Treatment Reviews 2022

How can we target CD33?
Conjugate antibody: Gemtuzumab Ozogamicin



Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No gemtuzumab ozogamicin	14.1% SD 1.9	0% SD 0

Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

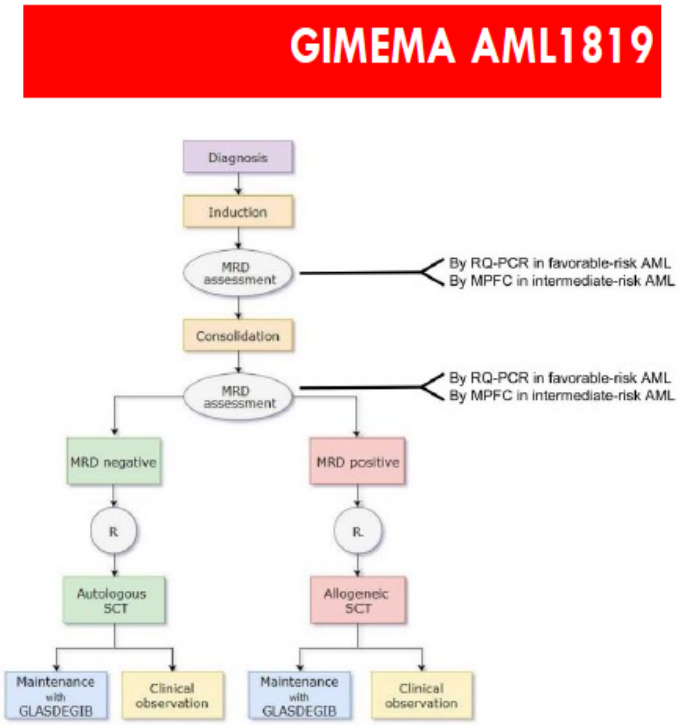
Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

Hills. Lancet Oncol. 2014;15:986.

How can we target CD33?
Conjugate antibody: Gemtuzumab Ozogamicin

The only approved immunotherapy in AML

- Treatment of **newly-diagnosed CD33-positive AML** in adults
  - Combination therapy
    - Induction: 3 mg/m² (up to one 4.5 mg vial) on days 1, 4, and 7 in combination with daunorubicin and cytarabine
    - Consolidation: 3 mg/m² on day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine



How can we target CD33?
Conjugate antibody: Gemtuzumab Ozogamicin

GIMEMA AML1819 TRIAL: GEMTUZUMAB OZOGAMICIN PLUS INTENSIVE CHEMOTHERAPY IMPACTS ON THE LEVEL OF POST-CONSOLIDATION MEASURABLE RESIDUAL DISEASE (MRD) IN ACUTE MYELOID LEUKEMIA

A Venditti

Author(s): Adriano Venditti, Alfonso Piciocchi, Luca Maurillo, Maria Ilaria Del Principe, Raffaele Palmieri, Stefano Soddu, Federico Moretti, Prassede Salutari, Maurizio Martelli, Maria Paola Martelli, Mario Luppi, Alessandro Pulsoni, Francesco Zaja, Roberto Cairoli, Fabrizio Pane, Sergio Siragusa, Renato Bassan, Michela Rondoni, Milena Mirabile, Antonino Mulè, Germana Beltrami, Patrizia Zappasodi, Laura Cudillo, Andrea Mengarelli, Antonio Curti, Felicetto Ferrara, Giovanni Rossi, Ernesta Audisio, Giuseppina Spinosa, Alessia Tieghi, Monica Bocchia, Vincenza Martini, Catello Califano, Luigi Rigacci, Agostino Tafuri, Michele Gottardi, Paola Fazi, Marco Vignetti, Francesco Buccisano

(Abstract release date: 05/11/23) EHA Library. Venditti A. 06/08/2023; 386334; P505

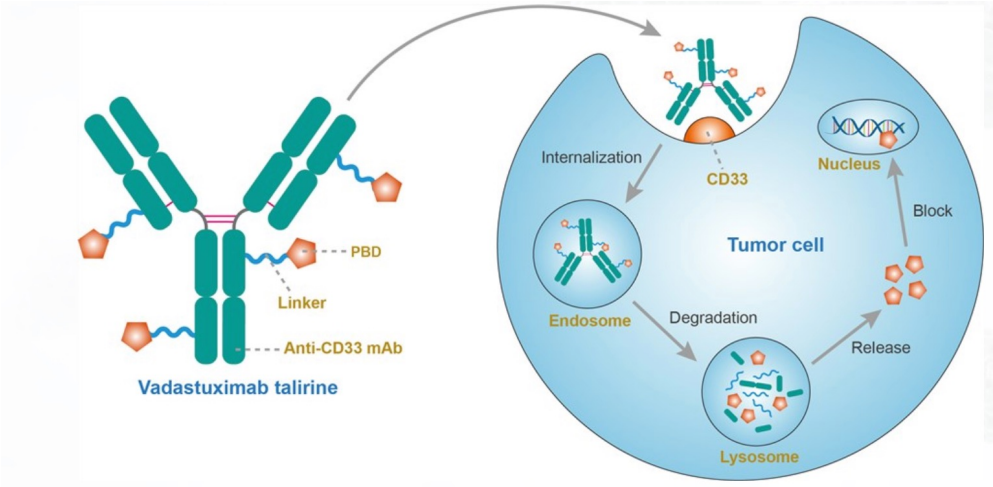
FLAG-IDA COMBINED WITH GEMTUZUMAB OZOGAMICIN (GO) REDUCED MRD LEVELS AND IMPROVED OVERALL SURVIVAL IN NPM1MUT AML INDEPENDENT OF FLT3 AND MRD STATUS, RESULTS FROM THE AML19 TRIAL

Prof. Nigel Russell

Author(s): Nigel Russell, Jad Othman, Richard Dillon, Nicola Potter, Charlotte Wilhelm-Benartzi, Steven Knapper, Leona Batten, Joanna Canham, Emily Laura Hinson, Ulrik Malthe Overgaard, Amanda Gilkes, Priyanka Mehta, Panagiotis Kottaridis, Jamie Cavenagh, Claire Hemmaway, Claire Arnold, Sylvie Freeman, Mike Dennis

(Abstract release date: 05/11/23) EHA Library. Russell N. 06/08/2023; 387834; S134

How can we target CD33?
Conjugate antibody: Vadastuximab talirine



Humanized anti-CD33 MoAb linked to a pyrrolbenzodiazepine dimer, which binds DNA with high intrinsic affinity[1]

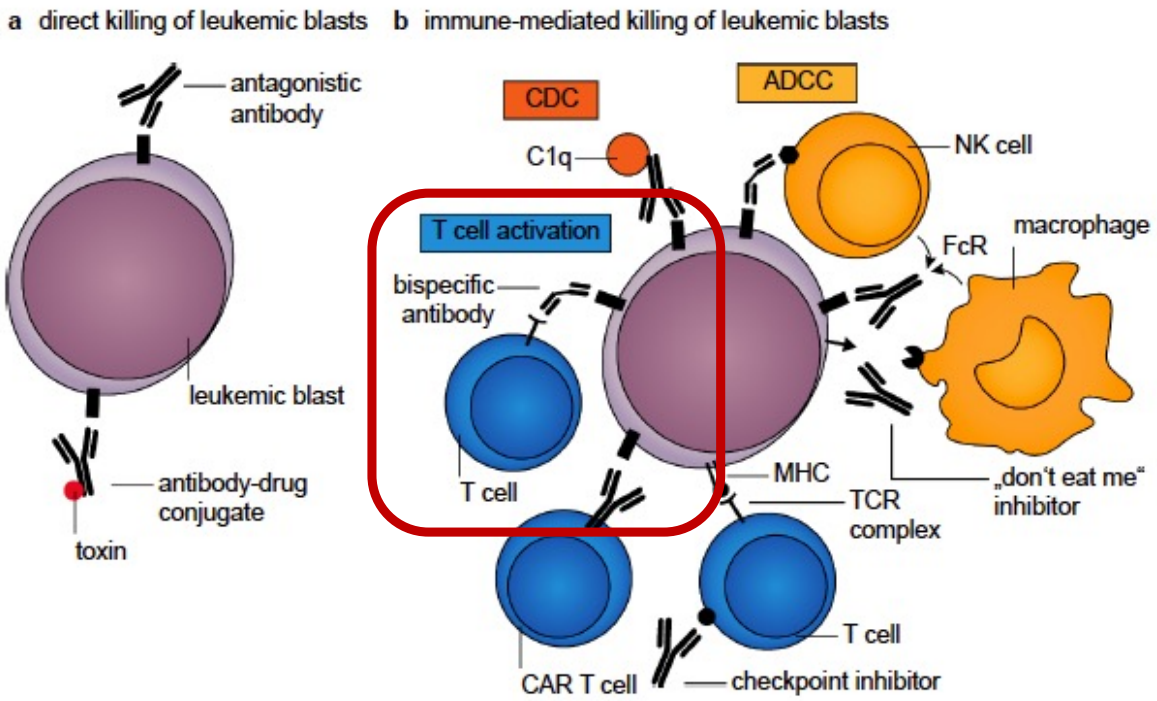
Synergy with HMAs to enhance antileukaemic activity[2]

CR rate 29% in a phase I study for R/R AML with no liver toxicity (VOD)[3]

Phase 3 trial CASCADE with HMAs discontinued due to infections→ drug suspended from clinical development in 2017

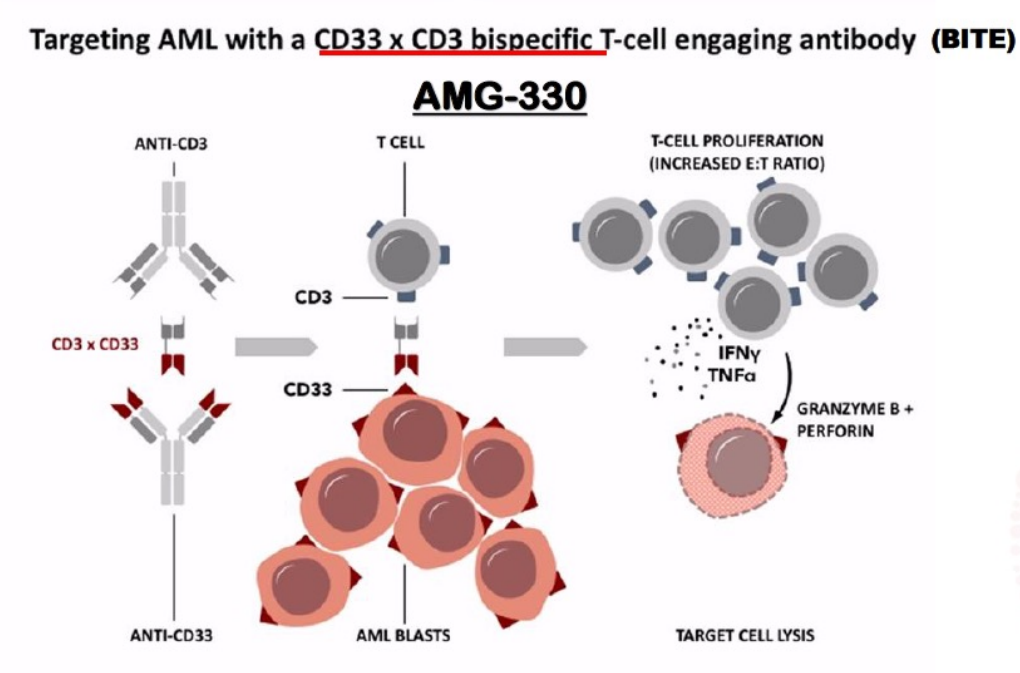
Stein EM et al, Blood J Am Soc Hema 2018

Antibody therapy in AML



Angenendt L et al, Cancer Treatment Reviews 2022

How can we target CD33?
Bispecific Antibody: AMG-330



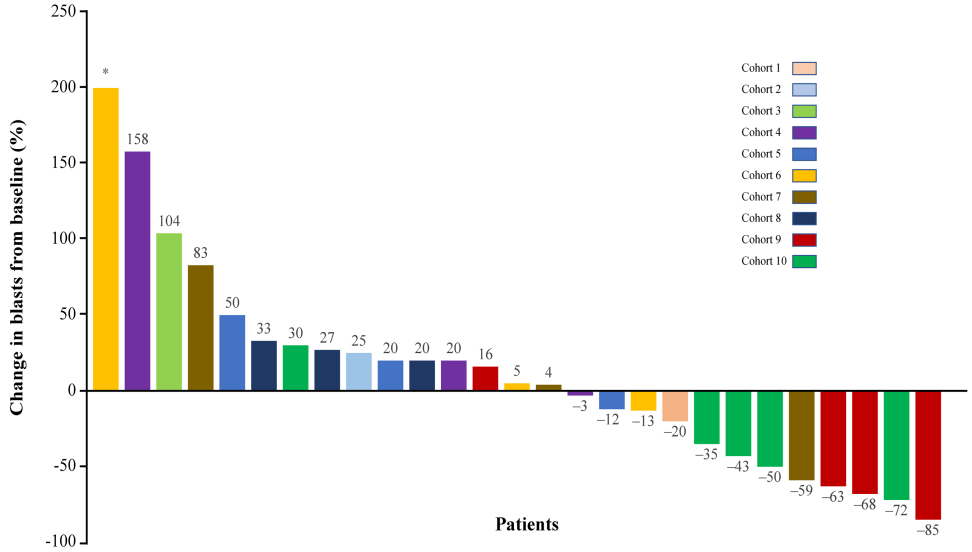
- Preliminary data showed **encouraging early evidence of tolerability and anti-leukemic activity** in R/R AML
- ORR 19% in updated cohort
- More responders observed among patients with a lower leukemic burden (<25%)

Friedrich M et al, Mol Cancer Ther 2014; Ravandi F et al, ASH 2018; Ravandi F et al, ASCO 2020

How can we target CD33?
Bispecific Antibody: AMG-673

- New anti-CD33 anti-CD3 BiTE antibody with **increased half-life** (7 days)
- Early evidence of acceptable safety profile and anti-leukemic activity
- Decreased BM blast cells in 44% of the patients

Figure 1. Waterfall plot showing percentage change in bone marrow blasts from baseline to best response in patients with R/R AML treated with AMG 673 (as defined by the revised IWG criteria)



AML, acute myeloid leukemia; IWG, International Working Group; R/R, relapsed/refractory
*The percentage change in blasts from baseline for this patient was 469

Subklewe M et al, ASH 2019

CD33-Targeted Therapies: Beating the Disease or Beaten to Death?

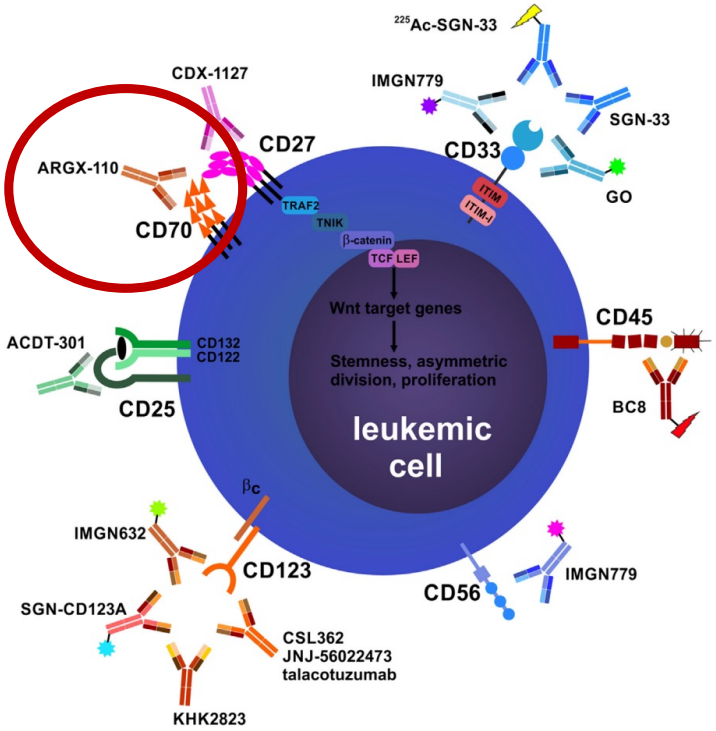
The Journal of Clinical Pharmacology
2021, 61(1) 7–17

DOI: 10.1002/jcph.1730

Joseph E. Maakaron, MD[1], John Rogosheske, PharmD[1], Meixiao Long, MD, PhD[2], Veronika Bachanova, MD, PhD[1], and Alice S. Mims, MD, MSCR[2]

- CD33 represents a **bona fide target** in AML therapy.
- **Gentuzumab ozogamicin was the first** developed targeted agent and produced overall survival benefit for a subset of patients.
- The **optimal strategy to take advantage of this target is yet to be determined**, as responses thus far have been lackluster.
- **ADCs could be promising in this case**, given the endocytic properties of CD33. ADCs are also **specific and short-lived**; thus, on-target/off -tumor toxicity would be temporary and manageable.

Target antigens in AML: CD70

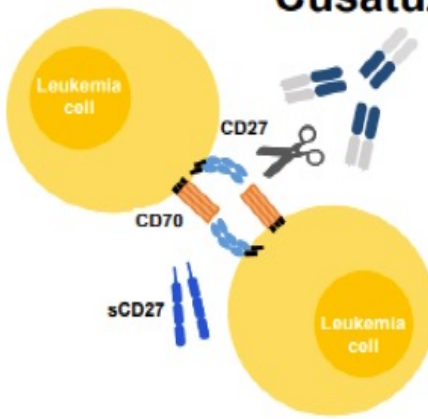


- It is mainly a **lymphoid lineage marker**, but **also expressed on myeloid leukemic blasts**
- Absent or **low level expression in normal BM cells**
- Interaction with its ligand CD27 induces the activation of molecular pathways including Wnt, JAK/STAT, Hh and promotes cell division

Schurch C.M. et al, Front Oncol 2018; Angenendt L et al, Cancer Treatment Reviews 2022

Targeting CD70: Cusatuzumab

1. **Blocking CD70-CD27 signaling,** which leads to myeloid differentiation and stops proliferation of LSCs

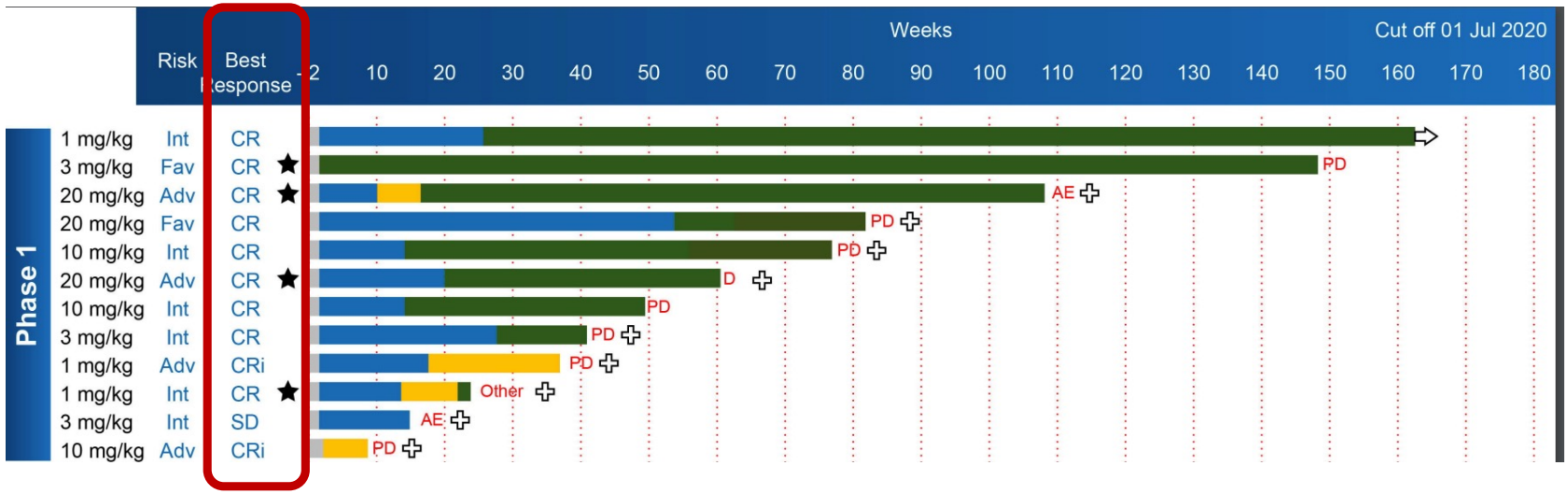


2. **Killing cells** via Fc-dependent, complement dependent cytotoxicity and enhanced antibody-dependent cellular cytotoxicity (ADCC)

Results from a phase I/II trial of cusatuzumab combined with azacitidine in patients with newly diagnosed acute myeloid leukemia who are ineligible for intensive chemotherapy

by Thomas Pabst, Norbert Vey, Lionel Adès, Ulrike Bacher, Mario Bargetzi, Samson Fung, Gianluca Gaidano, Domenica Gandini, Anna Hultberg, Amy Johnson, Xuewen Ma, Rouven Müller, Kerri Nottage, Cristina Papayannidis, Christian Recher, Carsten Riether, Priya Shah, Jeffrey Tryon, Liang Xiu, and Adrian F. Ochsenbein

Median follow-up 10.9 months
Median duration of first response 4.5 months
Median OS 11.5 months
Most common TEAE: infections (84.2%)



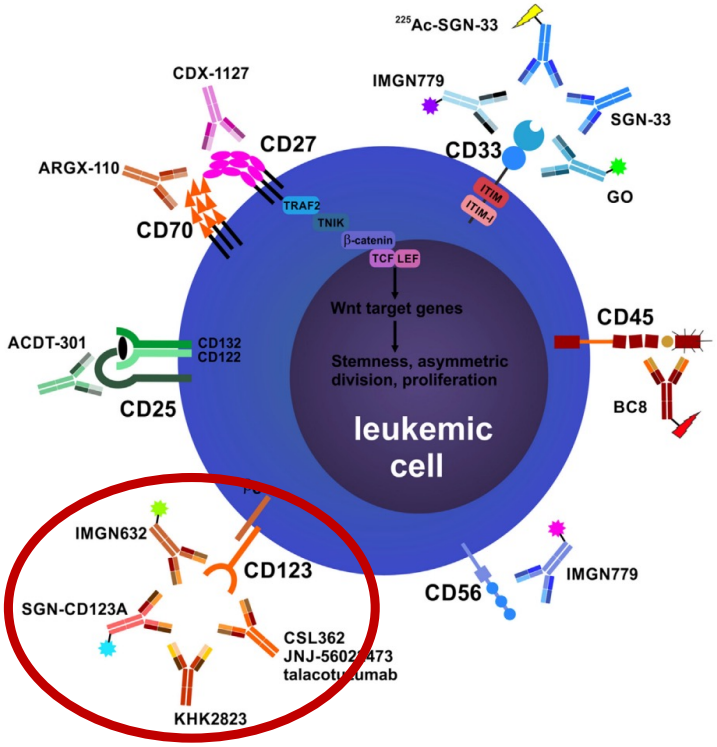
Haematologica 2022

Targeting CD70: Cusatuzumab+Aza+Ven

	Intention-to-treat, N (%)*	Response evaluable, N (%)*
Number of subjects	44	42
Best response		
Complete remission (CR)	20 (45.5)	20 (47.6)
CR with partial hematologic recovery (CRh)†	10 (22.7)	10 (23.8)
CR with incomplete hematologic recovery (CRi)	14 (31.8)	14 (33.3)
CR + CRh† + CRi	34 (77.3)	34 (81.0)
Morphologic leukemia-free state (MLFS)	5 (11.4)	5 (11.9)
Partial remission (PR)	0	0
Stable disease (SD)‡	3 (6.8)	3 (7.1)
Progressive disease (PD)	0	0
Not evaluable (NE)*	2 (4.5)	0

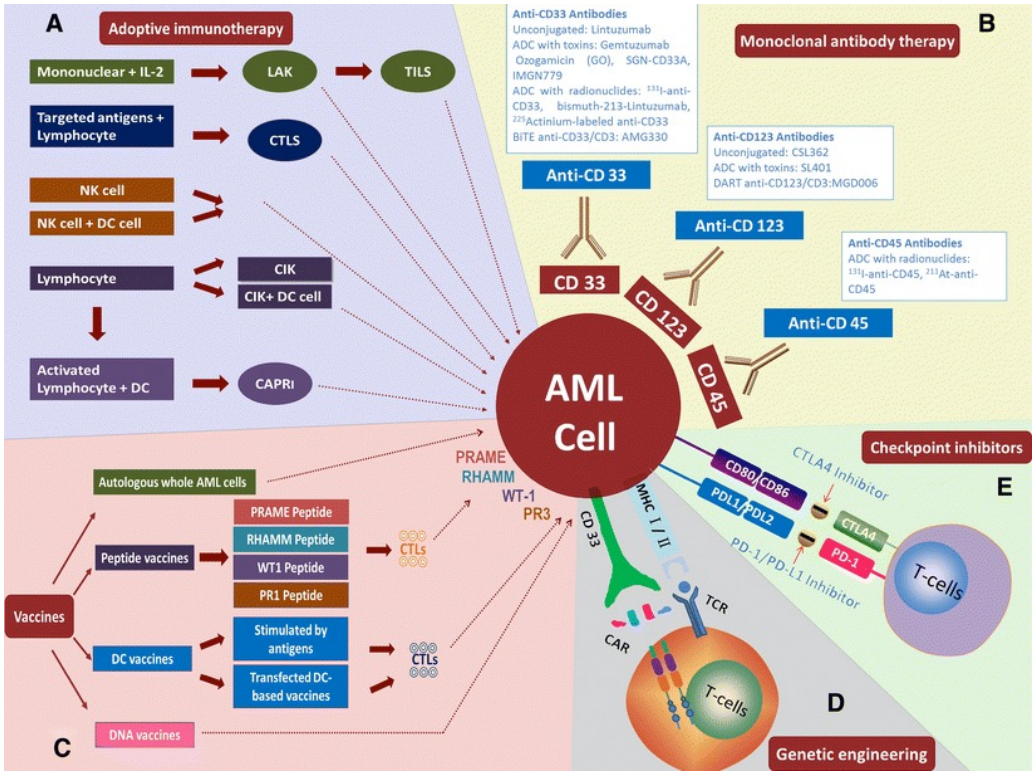
Roboz GJ et al, ASH 2021

Target antigens in AML: CD123



Schurch C.M. et al, Front Oncol 2018; Angenendt L et al, Cancer Treatment Reviews 2022

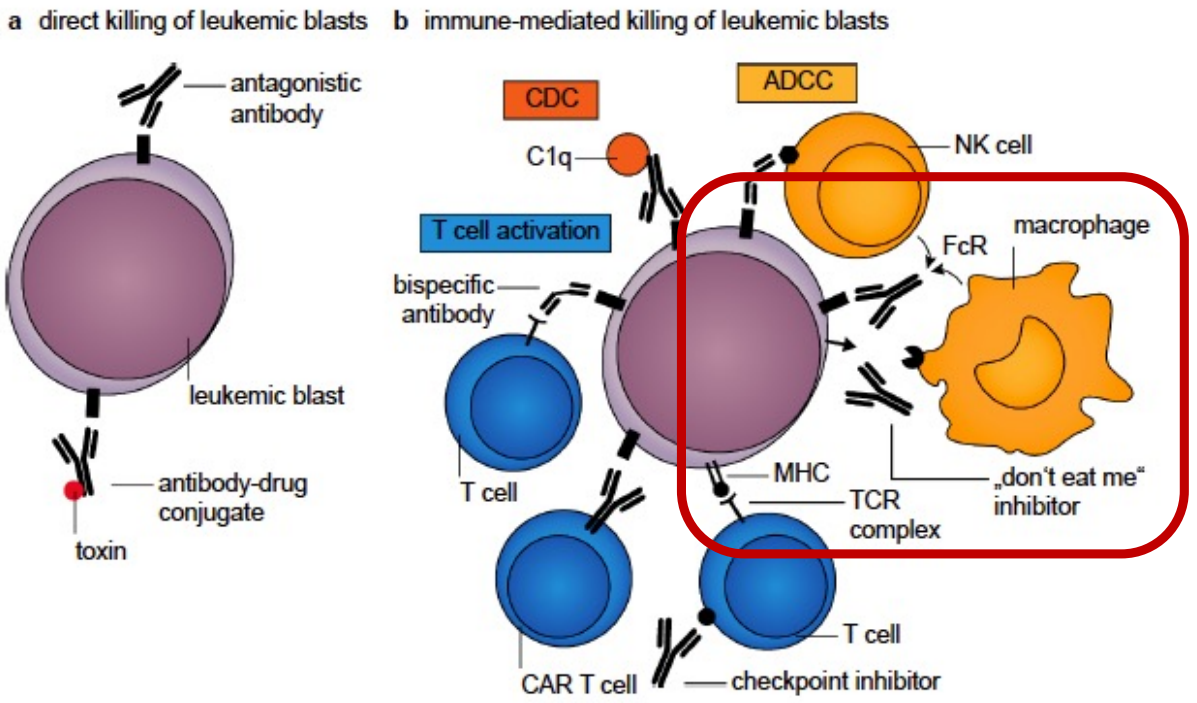
Immunotherapy in AML



CHECKPOINT INHIBITORS

Yang D et al, Annals of Hematology 2017

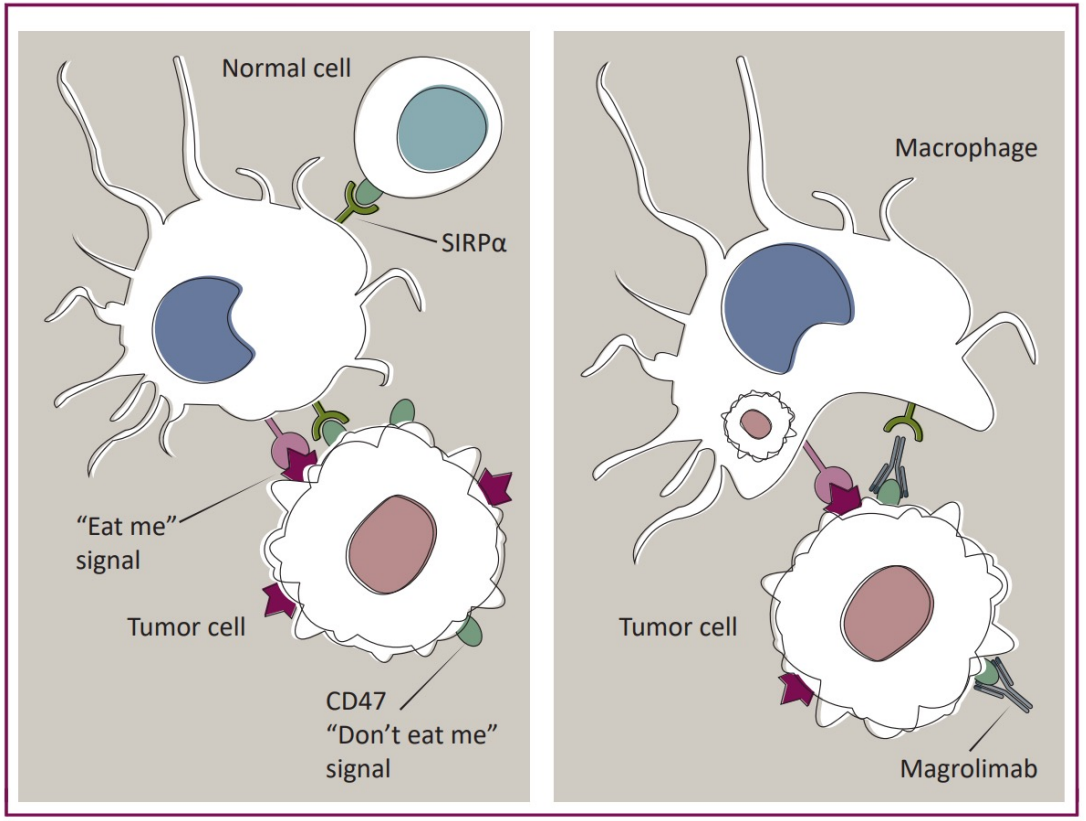
Antibody therapy in AML



Angenendt L et al, Cancer Treatment Reviews 2022

«Don't eat me» signal

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis



Maute R et al, ESMO 2022

Magrolimab+Azacitidine in TP53 mutated AML

Efficacy Outcome	*TP53*m AML (N = 72)
ORR, % (95% CI)	48.6 (36.7-60.7)
CR rate, % (n/N) ▪ MRD-negative CR	33.3 (24/72) 50.0 (12/24)
CRi/CRh, n (%)	6 (8.3)
PR, n (%)	4 (5.6)
MLFS, n (%)	1 (1.4)
SD, n (%)	12 (16.7)
Median DoR, mo (95% CI)	8.7 (6.5-10.4)
Median DoCR, mo (95% CI)	7.7 (4.7-10.9)
Median duration of CR/CRi, mo (95% CI)	8.7 (5.3-10.9)
Median EFS, mo (95% CI)	4.6 (3.7-9.2)
Median PFS, mo (95% CI)	7.3 (3.7-9.7)
Median OS, mo (95% CI)	10.8 (6.8-12.8)

- 29.7% of patients converted to RBC transfusion independence
- 45.8% of patients converted to platelet transfusion independence
- 9 patients (12.5%) received SCT

Daver. ASCO 2022. Abstr 7020.

#61 Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML

AZA-VEN-Magro in AML abs#616

Characteristics FRONTLINE (n=43): A very high risk cohort

Parameters		Full Frontline	De novo		Secondary AML*	
		N=43	*TP53*^{mut} (N=22)	*TP53*^{WT} (N=11)	*TP53*^{mut} (N=5)	*TP53*^{WT} (N=5)
			N (%), Median [range]			
Age (yrs)		70 [32-84]	65 [33-81]	76 [67-80]	75 [61-84]	72 [69-82]
Age >65 years		30 (70)	11 (50)	10 (100)	4 (80)	5 (100)
Gender	Females	16 (37)	10 (45)	4 (36)	1 (20)	1 (25)
ECOG PS	0	2 (5)	2 (10)	0 (0)	0 (0)	0 (0)
	1-2	40 (93)	20 (90)	11 (100)	5 (100)	4 (100)
Therapy (for non-hematological cancer) related AML		16 (37)	10 (45)	1 (9)	2 (40)	3 (75)
ELN 2017 risk stratification	Intermediate	4 (9)	0 (0)	4 (36)	0 (0)	0 (0)
	Adverse	39 (91)	22 (100)	7 (64)	5 (100)	4 (100)
CTG per ELN 2017	Intermediate	15 (35)	4 (18)	8 (73)	1 (20)	1 (25)
	- Diploid	10	3	6	1	0
	- Others	4	1	2	0	1
	Adverse	28 (65)	18 (82)	3 (27)	4 (80)	3 (75)
	- CK	23	17	1	4	1
	- Isolated -5/5q- or -7/7q-	4	1	2	0	1
	- Other adverse	1	0	0	0	1
Mutations	*IDH1/IDH2*	7 (16)	4 (18)	3 (27)	0 (0)	0 (0)
	FLT3 ITD/TKD	1 (2)	1 (5)	0 (0)	0 (0)	0 (0)
	NPM1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ASXL1	7 (16)	2 (9)	5 (45)	0 (0)	0 (0)
	RUNX1	5 (12)	2 (9)	3 (27)	0 (0)	0 (0)

**This includes treated and untreated sAML, except prior HMA treatment (such as targeted Rx, investigational agents, LDAC-based, growth factors, ImiDs, etc)*

Daver N et al, ASH 2022

#61 Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML

AZA-VEN-Magro in AML abs#616

Responses per ITT FRONTLINE (n=43): CR/CRi rates similar in TP53m and TP53wt

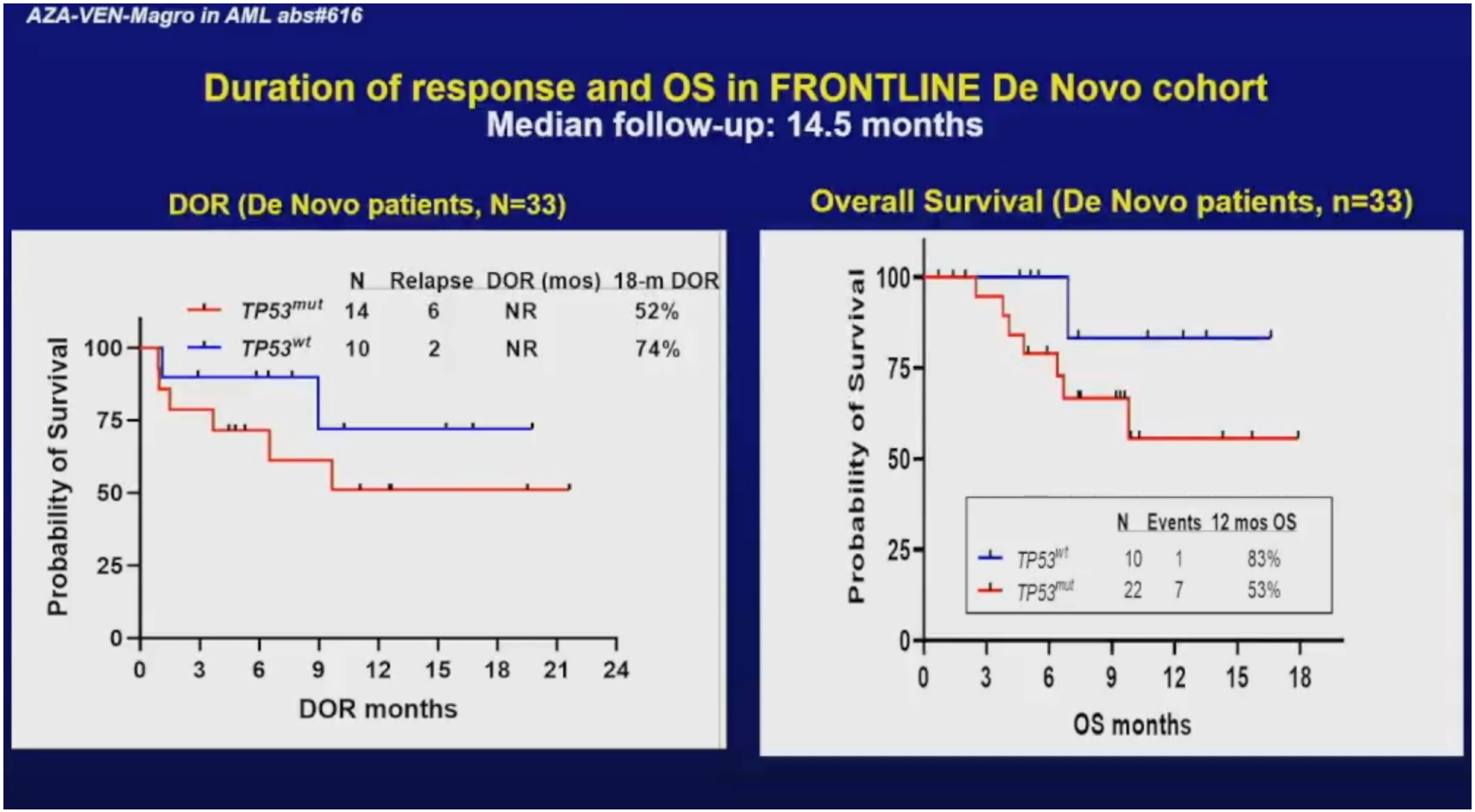
Parameters		Full Frontline	De novo		Secondary AML	
		N=43	$TP53^{mut}$ (N=22)	$TP53^{WT}$ (N=11)	$TP53^{mut}$ (N=5)	$TP53^{WT}$ (N=5)
			N (%), Median [range]			
Overall response	CR	21 (49)	10 (46)	6 (55)	2 (40)	3 (60)
	CRi	10 (23)	4 (18)	4 (36)	1 (20)	1 (20)
	CR + CRi	31 (72)	14 (64)	10 (91)	3 (60)	4 (80)
	MLFS	4 (9)	1 (5)	1 (9)	2 (40)	0 (0)
MRD-ve best responses#	FCM-CR/CRi	16/28 (67)#	8/14 (64)	6/10 (60)	0 (0)	2/4 (50)
Cytogenetic responses*	CCyR	11/21 (52)*	5/10 (50)	4/6 (67)	2/5 (40)	
Time to response (days)	First response	23 [19-105]	24 [20-81]	20 [20-29]	20 [19-105]	27 [20-73]
	Best response	51 [20-130]	49 [20-130]	33 [20-63]	48 [20-105]	62 [20-88]
Counts recovery (days)	ANC ≥ 500/cu mm	36 [16-88]	36 [16- 88]	34 [26-62]	34 [31-36]	39 [23-59]
	Platelet ≥ 100 x 10^9/L	32 [0-74]	31 [15-55]	33 [19-74]	28 [22-49]	33 [0-46]
Cycles on therapy		3 [1-17]	3 [2-6]	3 [1-17]	1 [1-3]	2 [1-3]
Mortality:						
- 4 week		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- 8 week		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Amongst CR/CRi patients with longitudinally MRD evaluable samples

* Amongst responders with baseline clonal CTG abnormality

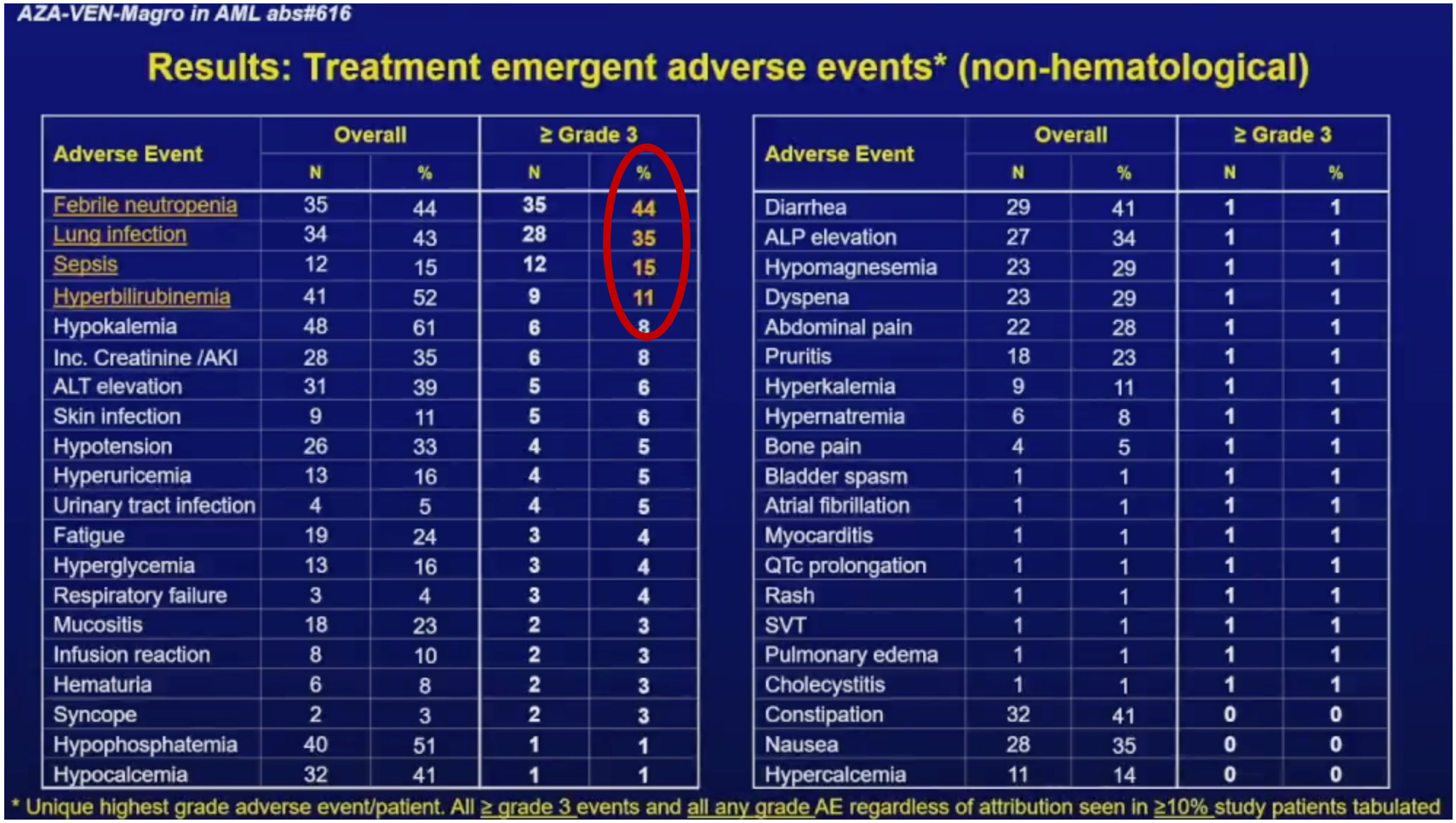
Daver N et al, ASH 2022

#61 Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML



Daver N et al, ASH 2022

#61 Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML



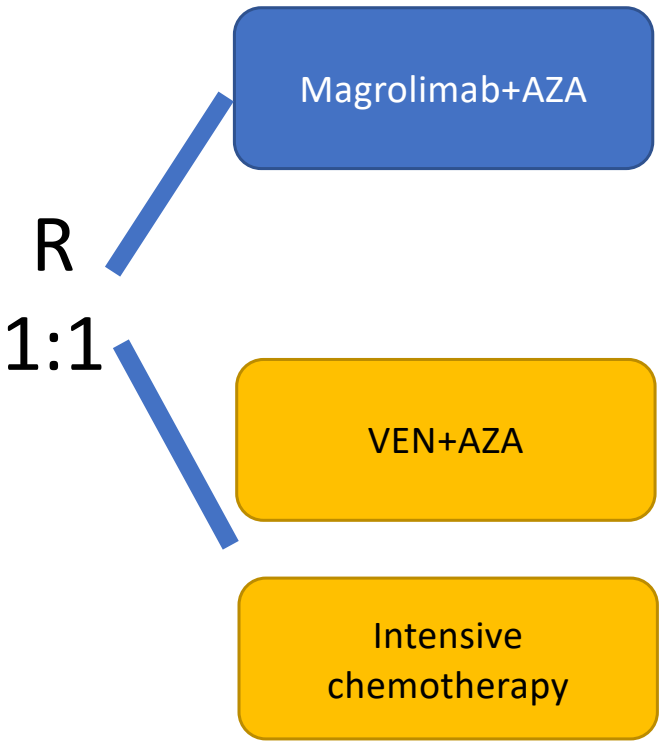
Adverse Event	Overall		≥ Grade 3	
	N	%	N	%
Febrile neutropenia	35	44	35	44
Lung infection	34	43	28	35
Sepsis	12	15	12	15
Hyperbilirubinemia	41	52	9	11
Hypokalemia	48	61	6	8
Inc. Creatinine /AKI	28	35	6	8
ALT elevation	31	39	5	6
Skin infection	9	11	5	6
Hypotension	26	33	4	5
Hyperuricemia	13	16	4	5
Urinary tract infection	4	5	4	5
Fatigue	19	24	3	4
Hyperglycemia	13	16	3	4
Respiratory failure	3	4	3	4
Mucositis	18	23	2	3
Infusion reaction	8	10	2	3
Hematuria	6	8	2	3
Syncope	2	3	2	3
Hypophosphatemia	40	51	1	1
Hypocalcemia	32	41	1	1

Adverse Event	Overall		≥ Grade 3	
	N	%	N	%
Diarrhea	29	41	1	1
ALP elevation	27	34	1	1
Hypomagnesemia	23	29	1	1
Dyspena	23	29	1	1
Abdominal pain	22	28	1	1
Pruritis	18	23	1	1
Hyperkalemia	9	11	1	1
Hypernatremia	6	8	1	1
Bone pain	4	5	1	1
Bladder spasm	1	1	1	1
Atrial fibrillation	1	1	1	1
Myocarditis	1	1	1	1
QTc prolongation	1	1	1	1
Rash	1	1	1	1
SVT	1	1	1	1
Pulmonary edema	1	1	1	1
Cholecystitis	1	1	1	1
Constipation	32	41	0	0
Nausea	28	35	0	0
Hypercalcemia	11	14	0	0

* Unique highest grade adverse event/patient. All ≥ grade 3 events and all any grade AE regardless of attribution seen in ≥10% study patients tabulated

Daver N et al, ASH 2022

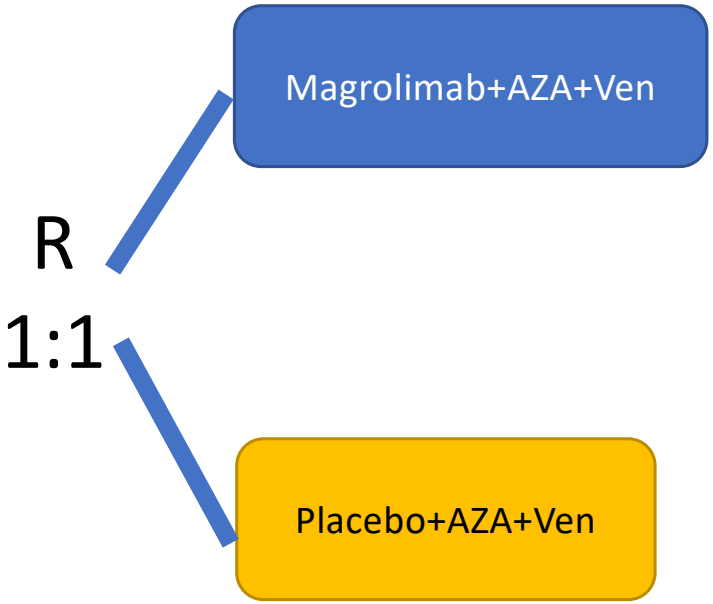
Ongoing clinical trial: newly diagnosed TP53 AML patients



Study to Evaluate the Safety and Efficacy of **Magrolimab in Combination With Azacitidine Versus Physician's Choice of Venetoclax in Combination With Azacitidine or Intensive Chemotherapy** in Previously Untreated Adults With TP53 Mutant Acute Myeloid Leukemia **(ENHANCE-2)**

NCT04778397

Ongoing clinical trial:
newly diagnosed older/unfit AML patients



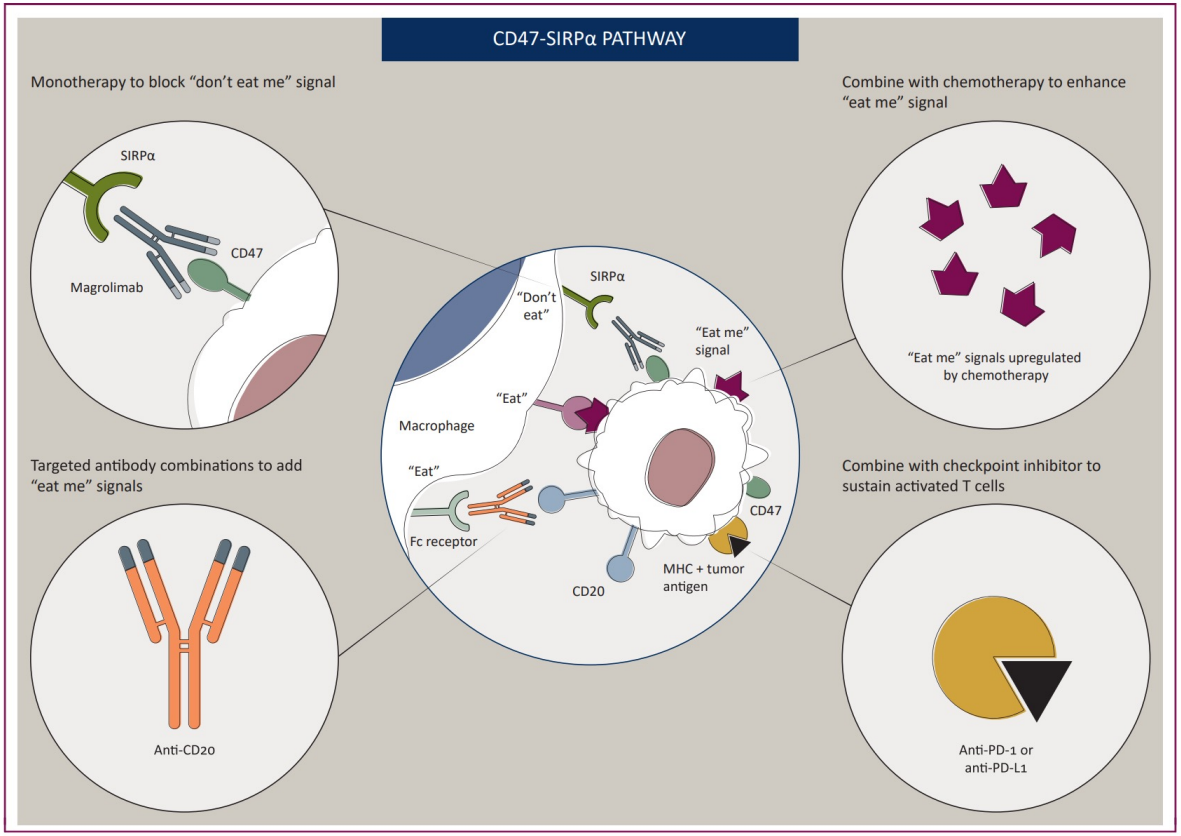
Study to Evaluate the Safety and Efficacy of **Magrolimab/placebo in Combination With Azacitidine Venetoclax** in Previously Untreated older/unfit Adults with newly diagnosed Acute Myeloid Leukemia **(ENHANCE-3)**

NCT05079230

How to increase Magrolimab activity?

EHA2023 JUNE 8 - 15 / FRANKFURT & VIRTUAL

TRIAL IN PROGRESS: PHASE 1B/2 STUDY OF PIVEKIMAB SUNIRINE (PVEK, IMGN632) IN COMBINATION WITH VENETOCLAX/AZACITIDINE OR MAGROLIMAB FOR PATIENTS WITH CD123-POSITIVE ACUTE MYELOID LEUKEMIA (AML)
Dr. Naval Daver



Maute R et al, ESMO 2022

Take home messages

- Immunotherapy is an **emerging, promising strategy in AML**, that needs to be further investigated in clinical trials
- **Unconjugated monoclonal antibodies** have shown **limited activity**
- Adverse events include **on-target-off leukemia toxicities**
- Currently, it remains to **decide its ideal setting and the biomarkers predictive** for response
- This will allow for a **biologically rational choice of a specific immunotherapy** strategy for the individual patient with AML

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Review

Immunotherapy in acute myeloid leukemia and myelodysplastic syndromes: The dawn of a new era?

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Thank you!

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