II. Medical Clinic and Polyclinic
Oncology, Hematology and Bone Marrow Transplantation

4. Hamburger AML - Symposium

Neue Immunologische Ansätze in der Therapie der AML

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Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Universitätsklinikum
Hamburg-Eppendorf

Conflicts of interest

Travel grant: Daiichi Sankyo, Servier, Novartis

Advisory board: Servier, Daiichi Sankyo

Overview

I. T-Cell Based Immunotherapy for AML

Checkpoint Blockade

- Targeting TIM-3

Bispecific Antibodies

- BITEs
- DARTs (Dual affinity retargeting Antibodies)

Adoptive T Cell Therapies

- CAR-T cells

II. Targeting the Innate Immune System for AML

- Targeting CD47

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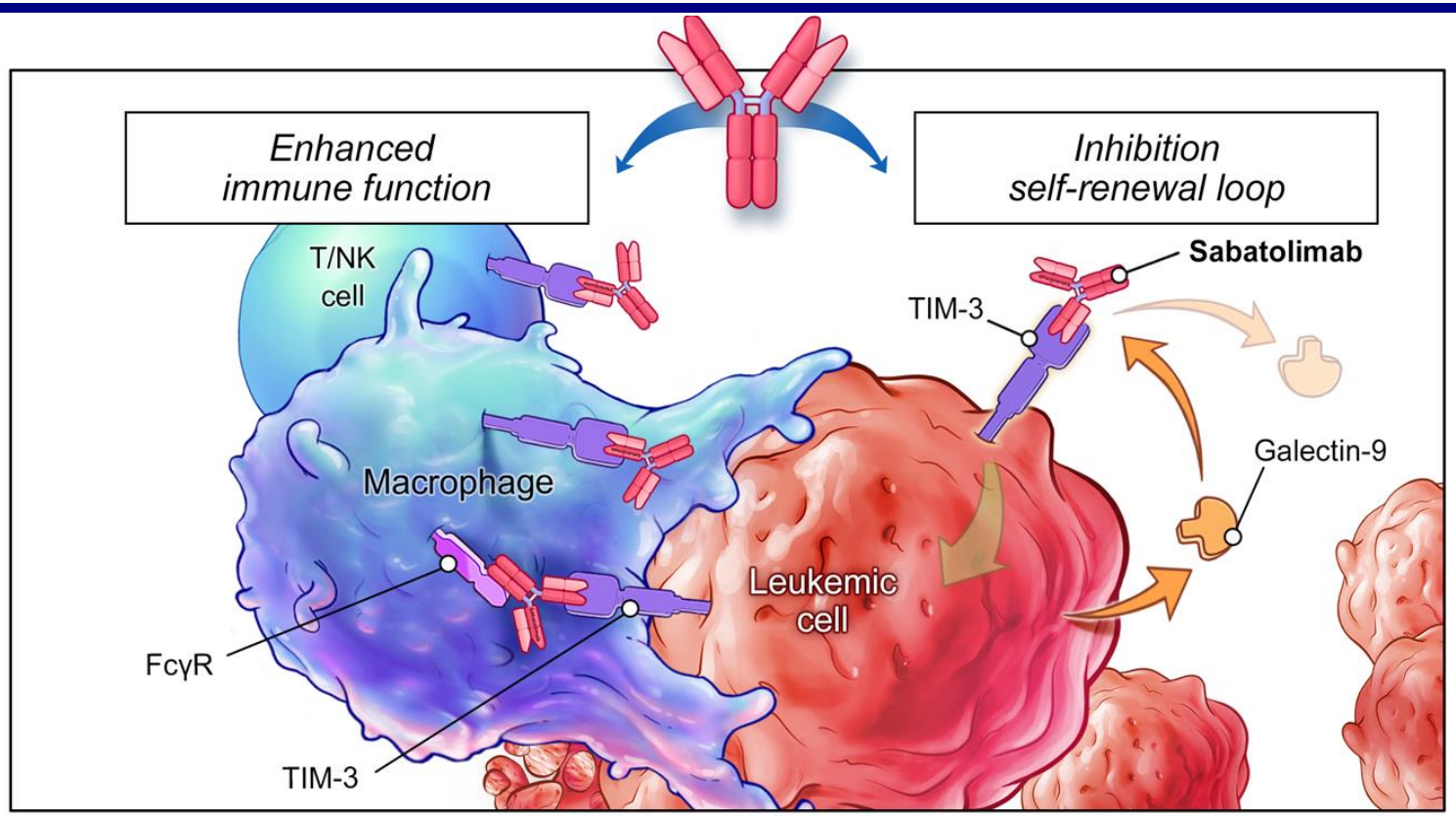
TIM-3 is a key regulator of innate and adaptive immune responses



- TIM-3 is aberrantly expressed on activated T cells, NK cells, regulatory T cells, Macrophages, DCs, LSCs and blasts, but not on normal HSCs,[1-5] which makes it a promising target in treatment for MDS and AML[2,4,6]
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop, which promotes LSC self-renewal[2,7]

1. Pardoll DM. *et al. 2012,* 2. Das M, et al. 2017, 3. Kikushige Y et al. 2013; 4. Kikushige Y, et al. 2010; 5. Ngiow SF. et al. 2011; 6. Sakuishi K, et al. 2011; 7. Sabatos-Peyton C. 2016.

Phase Ib trial:

Sabatolimab + HMA in MDS and AML

Brunner A.M. et al. *ASH 2021*

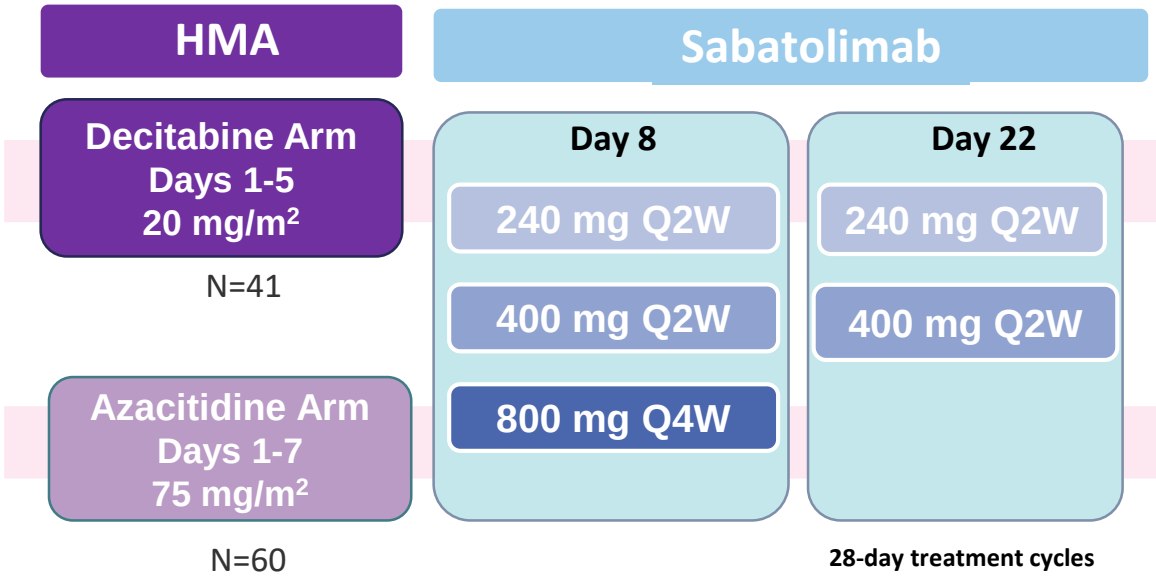
Treatment Schema

vHR/HR-MDS: IPSS-R high- or very high-risk MDS

ND-AML: Unfit, newly diagnosed AML, ineligible for standard chemotherapy

Patients with prior HMA treatment excluded

ClinicalTrials.gov Identifier: **NCT03066648**[a]



10 countries

11 trial centers

German sites: Dresden, Jena

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

Secondary Endpoints:
Preliminary efficacy: Response rates and duration of response

Baseline Characteristics: Cohort had high rates of adverse ELN risk

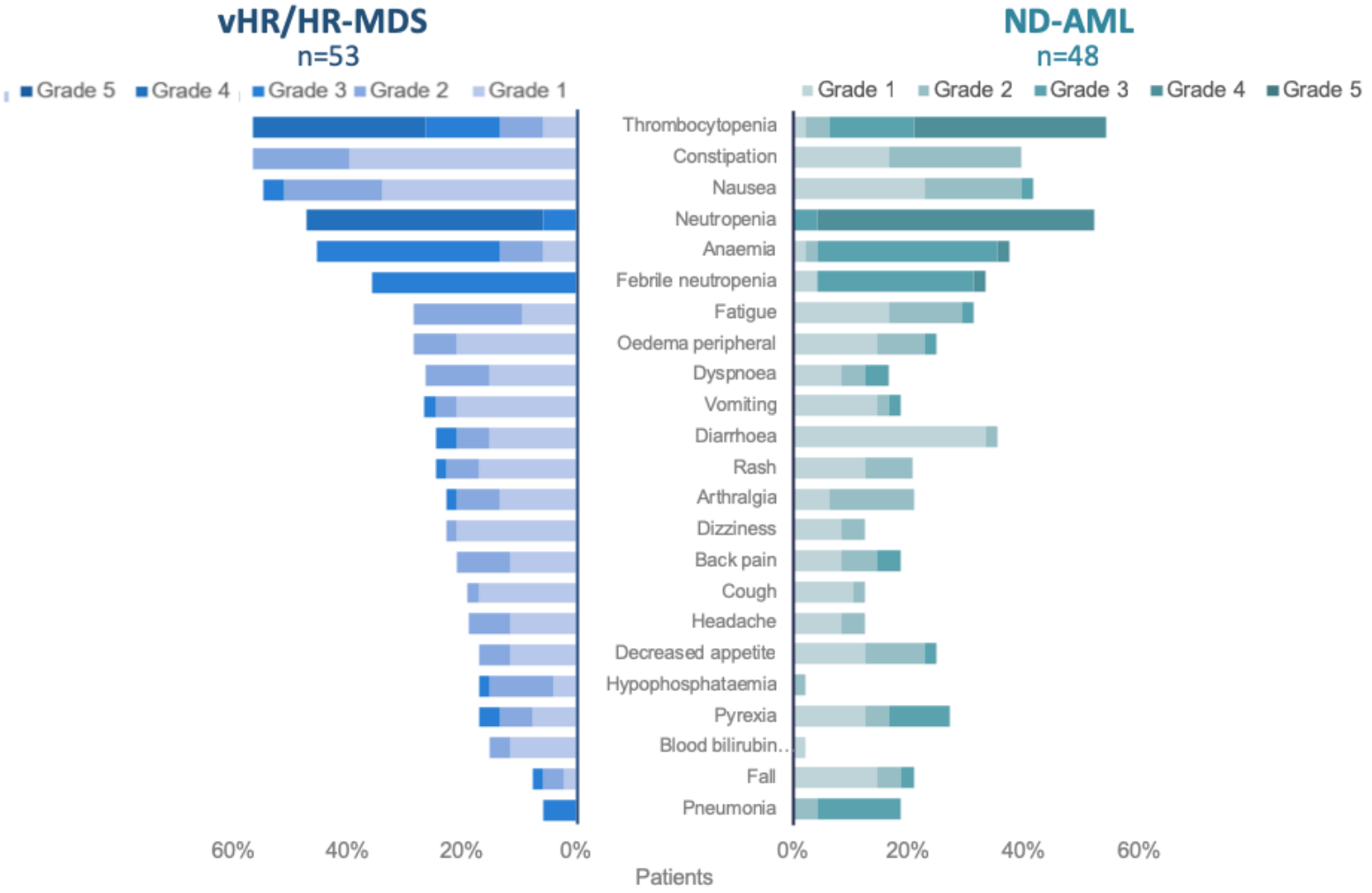
Parameter	vHR/HR-MDS n=53	ND-AML n=48
Sabatolimab + decitabine, n	**19**	**22**
Sabatolimab + azacitidine, n	**34**	**26**
Median age (range), years	70 (23-90)	75 (59-89)
Male, n (%)	29 (54.7)	26 (54.2)
ECOG performance status, n (%)		
0	18 (34.0)	14 (29.2)
1	30 (56.6)	29 (60.4)
2	5 (9.4)	5 (10.4)
Risk Category n (%)	IPSS-R[1]	2017 ELN risk[2]
	High: 32 (60.4)	Intermediate: 18 (37.5)
	Very high: 21 (39.6)	Adverse: 30 (62.5)

Select available mutation data:	TP53 (n)	≥1 ELN adverse risk mutation (n)[a]
vHR/HR-MDS (n=42[b])	15	33
ND-AML (n=33[b])	6	14

[a]ELN adverse risk mutations: TP53, ASXL1, and RUNX1; [b]Patients with any reported mutation, ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; IPSS-R, Revised International Prognostic Scoring System.

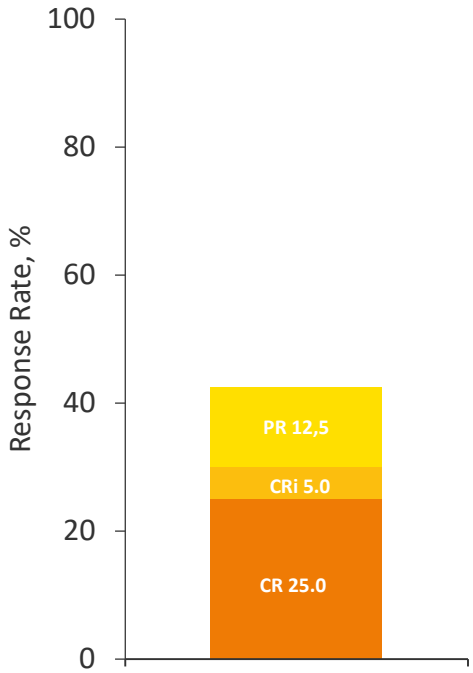
Results: Safety was comparable to HMA alone

Treatment related Adverse Events



Results: Durable Responses in ND-AML

Response Rate

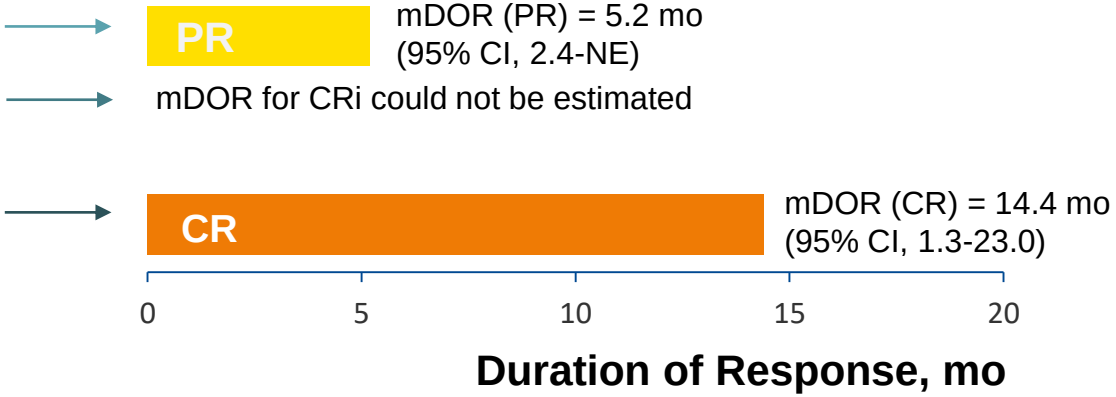


Durability Assessments

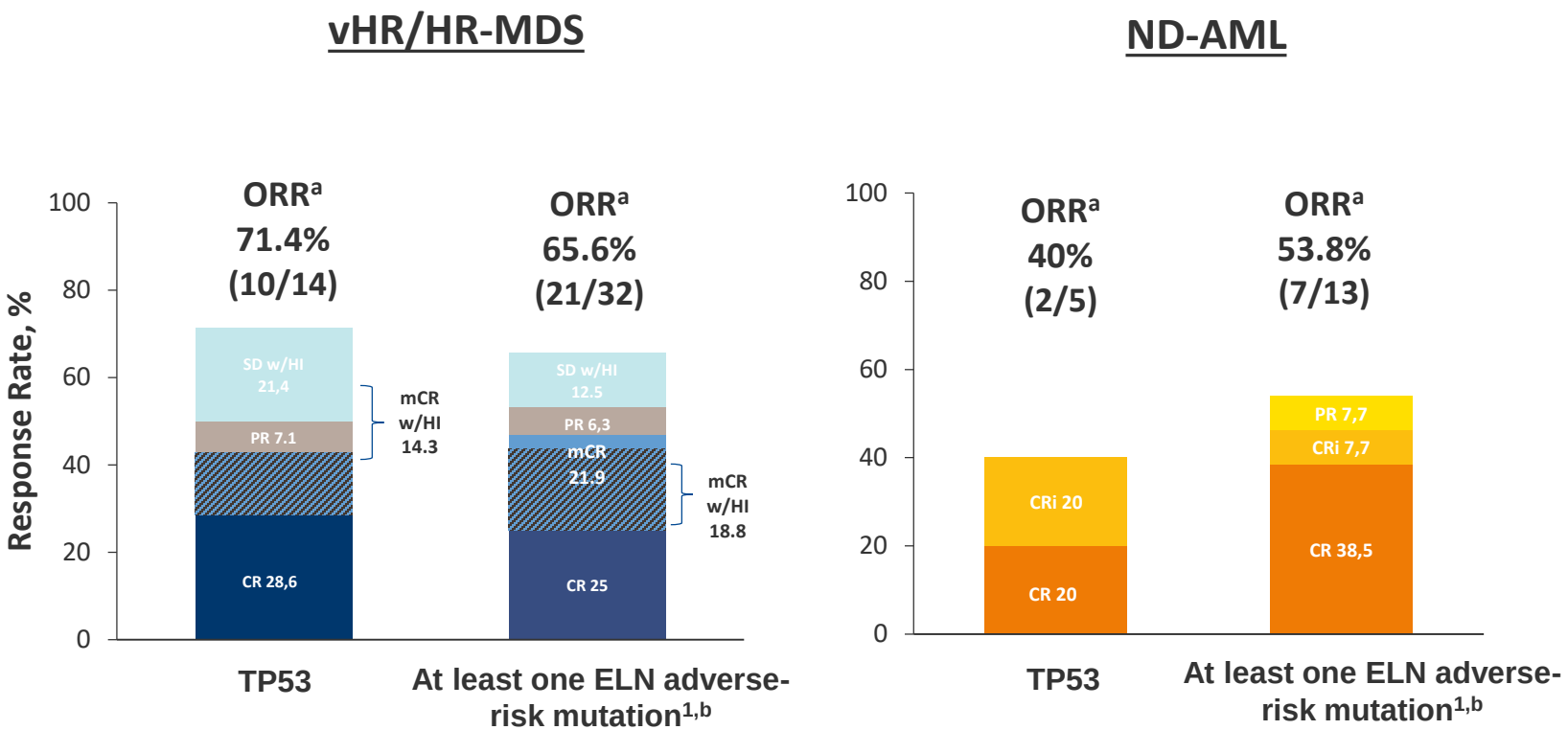
12.6 mo — **Median DOR [CR / CRi / PR] (95% CI, 5.2-18.0)**

26.8 % — **Estimated 12-mo PFS rate (95% CI, 14.2%-41.0%)**

Median Duration of Response (mDOR) by response category



Patients with adverse-risk disease were able to achieve durable responses



Median duration of response	21.5 mo	16.1 mo	6.4 mo	12.6 mo
	95% CI, 6.7-NE Events, 3/7[c]	95% CI, 6.7-NE Events, 7/17[c]	95% CI, 4.2-NE Events, 2/2[c]	95% CI, 1.3-NE Events, 5/7[c]

[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]ELN adverse-risk mutations: TP53, ASXL1, and RUNX1; [c]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

Conclusions

✓ **Sabatolimab + HMA is well tolerated in MDS/AML**

- **The most commonly observed AEs were similar to HMA alone**
- **Very few patients had clinically significant treatment-related possible imAEs**

✓ **Sabatolimab + HMA demonstrated durable clinical benefits in patients with vHR/HR-MDS and ND-AML**

- **vHR/HR-MDS, ORR: 56.9%; Median DOR: 17.1 months (95% CI, 6.7-NE)**
- **ND-AML, ORR: 42.5%; Median DOR: 12.6 months (95% CI, 5.2-18.0)**

✓ **Durable responses were seen in patients with mutations conferring adverse risk**

➢ **The STIMULUS clinical trial program is evaluating sabatolimab-based combination therapy in multiple Phase II and III studies in MDS and AML**

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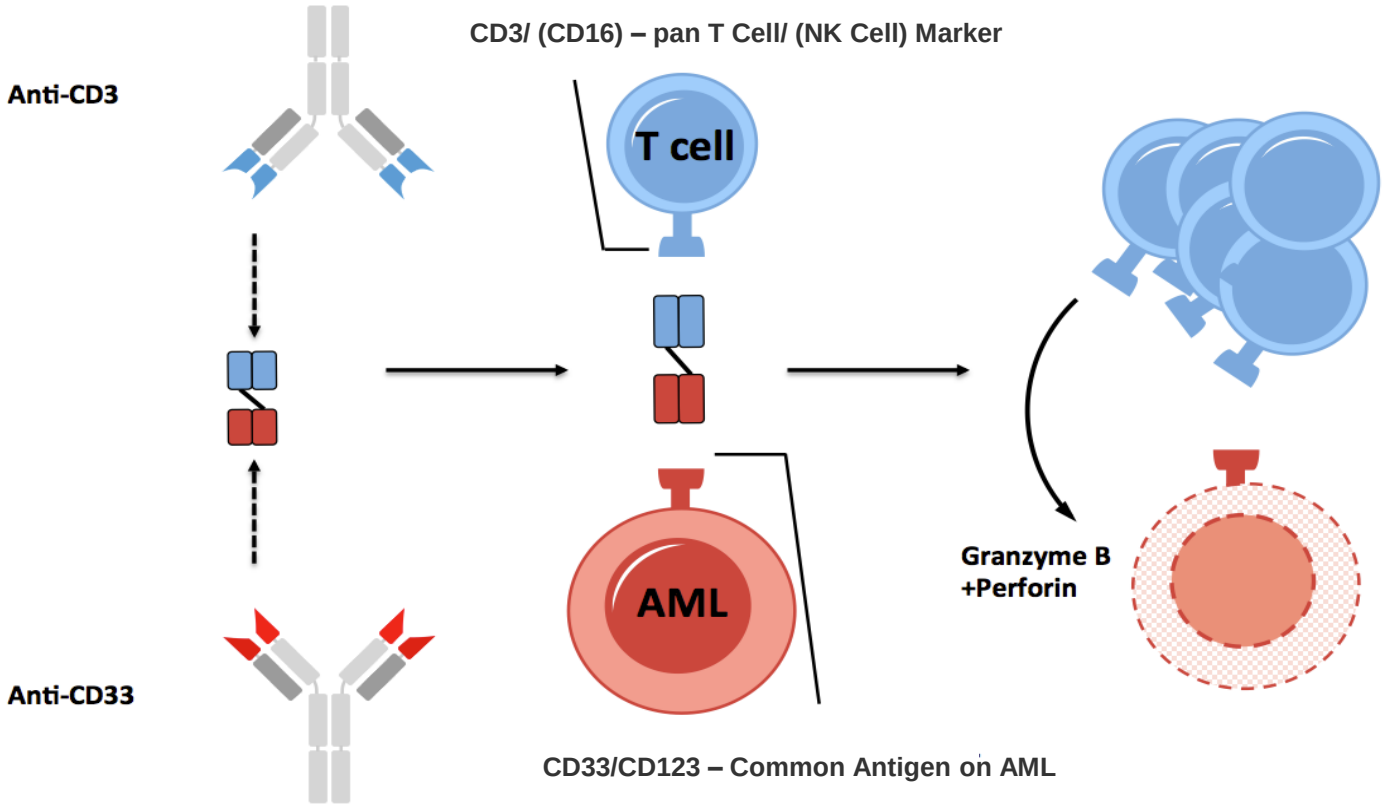
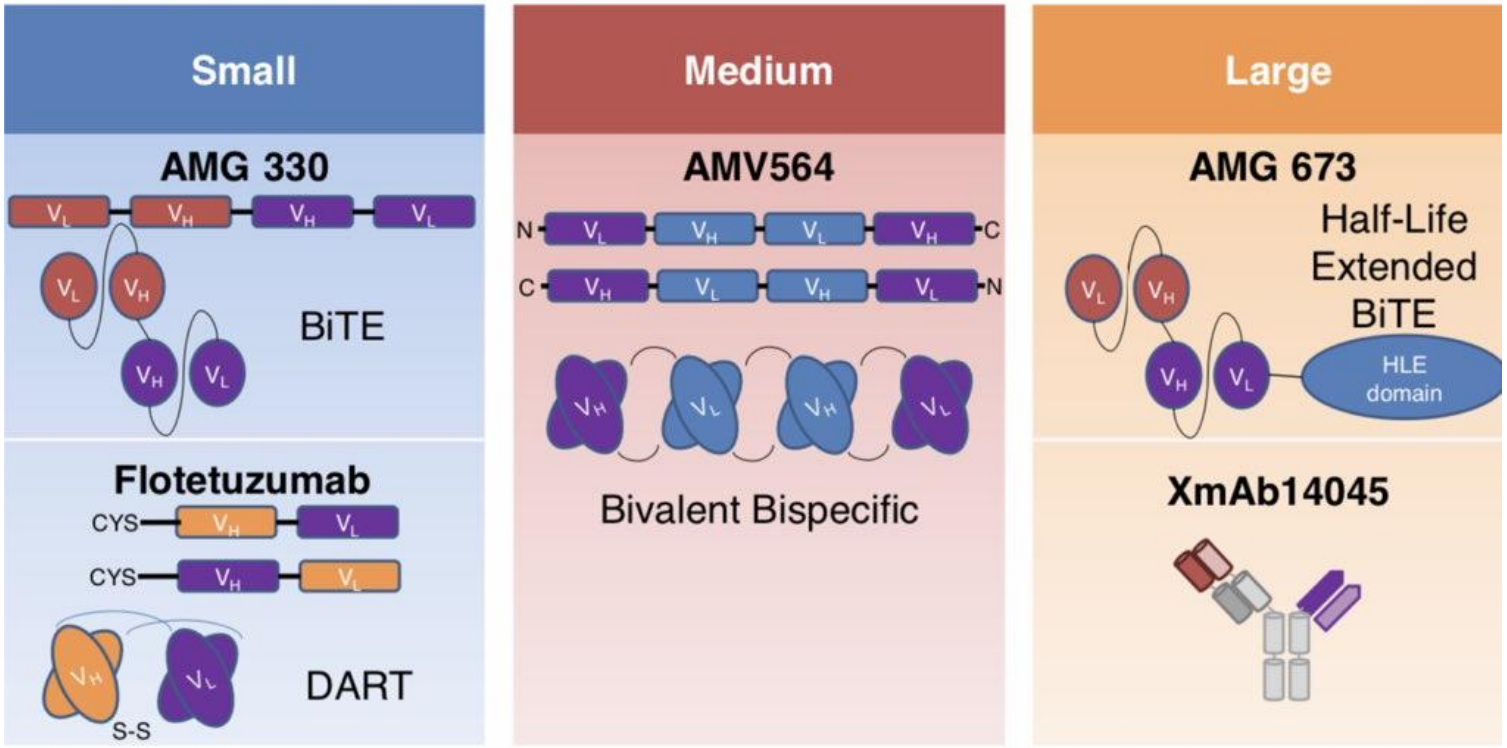
BiTEs, DARTS and TriKEs



Krupka C et al. 2014

Development for increased Half Life



6 hours **48 hours** **40-167 hours**

DiPersio J. et al. 2021

Three Open Trials in Germany

Drug	NCT	Patient Population	Targe	Phase	German Sites
AMG330	NCT02520427	Relapsed/Refractory AML, Minimal residual Disease+ AML, MDS	CD33 x CD3 BITE	1	Kiel, LMU München, Ulm
GEM333	NCT03516760	Relpased/ refractory AML	CD3 x CD33 BiTE	1	Mannheim, TU München, Würzburg, Frankfurt, Marburg, Dresden, Berlin
GTB-3550	NCT03214666	Relapsed/Refractory AML, MDS, Advanced Systemic Mastocytosis	CD16/IL-15 x CD33 TriKE	1/2	--
APVO 436	NVT03647800	Relapsed/Refractory AML,MDS	CD3 x CD123 BiTE		--
XmAb 14045	NCT05285813	AML MRD cohort only, MDS post-HMA failure	CD3 x CD123 BITE	2	--
MCLA-117	NCT03038230	ND R/R AML, MDS	CD3 + CLEC12A BITE	1	--
AMG427	NCT03541369	Replased/Refractory AML	CD3 x CD135 (FLT3) BITE	1	Dresden, LMU München

Published Results Show Improvable Response Rates

Drug	Construct	Population	Outcome	Author
AMG330 (anti-CD3 x CD33 BiTE)	2 single-chain fragments (scFv)	R/R-AML n=55 28d cycles (cIV14 to 18d)	**Efficacy:** 16% ORR (9% CR); Median DoR: 38.5 days (14-121) **Safety**: 67% CRS, skin disorders, elvated transaminases	Ravandi, *ASCO 2020*
AMV564 (anti CD3 x CD33 BiTE)	4 single-chain fragments (scFv)	R/R AML n=36 21d cycles (cIV/sc 14d)	**Efficacy**: BM Blast reduction in 49% with CR n=1, CRi n=1, **Safety**: no Grade 3 or higher CRS, 4 (11%) patients anemia	Westerveldt, *ASH,2019*
AMG673 (HLE anti-CD3 x CD33 BiTE)	2 single-chain fragments + IgG1 Fc region	R/R AML n=38 14d cycles, (admin. d1+5)	**Efficacy**: BM blast reduction in 44% with CRi n=1 **Safety:** 50% CRS (13% ≥ grade 3), elevated transaminases, anemia, febrile neutropenia	Subklewe, *ASCO 2020*
Flotetuzumab (anti CD3 x *CD123* DART)	2 single-chain fragments + 2 disulfide bridges	R/R AML n=92 28d cycles (C1: cIV 28d C2:4d/3d on/off/week)	Primary induction failure or early relapse cohort (n=30): **Efficacy**: 27% with CR/CRh; median OS 10.2 **Safety**: 100% CRS (3% ≥ grade 3)	Uy, *Blood 2021*
Vibecotamab (XmAb14045; anti CD3 x *CD123* BiTE)	full-length immunoglobulin	R/R-AML n=104 (B-ALLn=1, CMLn=1) 28d cycles (iv 2hs d1,3…22)	**Efficacy**: 14% ORR (4% CR), 71% SD **Safety:** 59% CRS (15% ≥ grade 3)	Ravandi, *ASH 2020*
APVO436 (anti CD3 x CD123 BiTE)	2 single-chain domians + IgG1 Fc region	R/R AML n=39 (R/R MDS n=7) 28d cycles (cIV)	**Efficacy**: CR 2/34, SD 6/34; median surviall$_{responders}$ = 338.5d **Safety:** infusion reaction 28%, CRS 22%, 11% transient neurotocity	Watts *ASH 2021*
GTB3550	tri-specific scFv recomb. protein (anti CD16, CD33, IL-15)	R/R AML n=5 (R/R AML) 21d cycles (cIV 1-4d)	**Efficacy**: 3/5 patients had a BM blast reduction (2/4 a significant blast reduction) **Safety**: 0% CRS	Warlick *Blood 2020*

Biomarkers predict BiTE Response Rates

- ✓ BiTE/DART response rates were more likely in patients with lower leukemic burden in PB and BM
- ✓ Biomarker of response: TME Immune Infiltration/IFN-related profiles predict Response
- ✓ Responses were seen at higher doses
- ✓ Higher leukemic burden and higher effector:target ratio were associated with higher grade CRS
- ✓ “Lead in phase”, steroid pretreatment and early use of tocilizumab may reduce CRS

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Ongoing Clinical trials for CAR T cells in AML

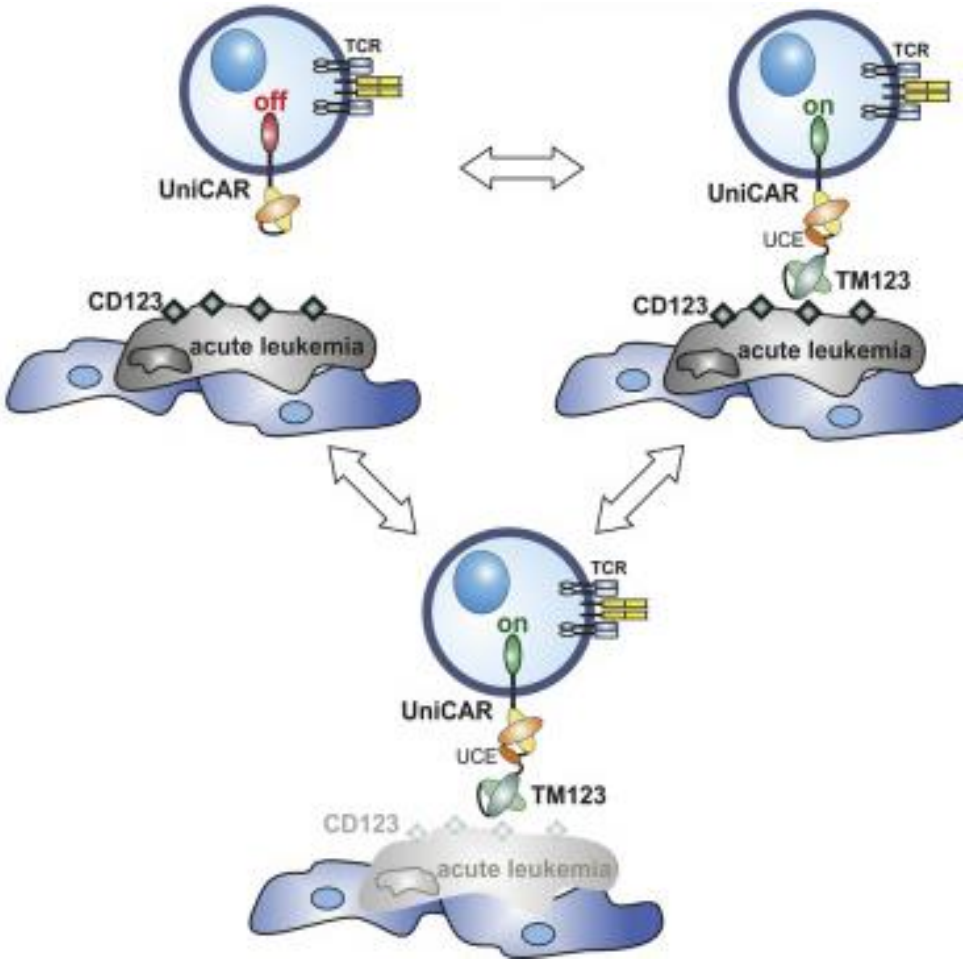
Target	Phase	Study population	Intervention	Status	NCT.gov identifier
CD33/CLL-1	Phase I	R/R high-risk hematologic malignancies	CD33/CLL-1 cCAR T cells	Recruiting	NCT03795779
CD123/CLL-1	Phase II/III	R/R AML	CD123/CLL-1 CAR-T cells	Recruiting	NCT03631576
CD123	Phase I	R/R AML	allogeneic anti-CD123 CAR-T cells (UCART123)	Recruiting	NCT03190278
CD123	Phase I	R/R AML after allo-HSCT	CD123CAR-41BB-CD3zeta-EGFRt-expressing T cells	Recruiting	NCT03114670
CD123	Phase I	CD123+ R/R AML and persistent/recurrent BPDCN	Autologous or allogeneic CD123CAR-CD28-CD3zeta-EGFRt-expressing T cells	Recruiting	NCT02159495
CD123	Phase I/II	R/R AML	CD123 CAR-T cells	Recruiting	NCT04272125
Muc1/CLL-1/CD33/CD38/CD56/ CD123	Phase I/II	R/R AML	Muc1/CLL-1/CD33/CD38/CD56/CD123-specific gene-engineered T cells	Recruiting	NCT03222674
NKG2D	Phase I/II	Seven refractory cancers including AML	NKG2D CAR-T cells	Recruiting	NCT03018405
CLL-1, CD33 and/or CD123	Phase I/II	R/R AML	CLL-1, CD33 and/or CD123-specific CAR gene-engineered T cells	Recruiting	NCT04010877
CD44v6	Phase I/II	R/R AML or MM expressing CD44v6	CD44v6 CAR-T cells	Recruiting	NCT04097301

Ongoing Clinical trials for CAR T cells in AML

Phase 1 trial: UniCAR02-T in Combination With CD123 Target Module for Patients With Hematologic and Lymphatic Malignancies Positive for CD123

UniCAR-T Cells for Treatment of CD123+ Leukemia

Rapid switch on/off CAR-T

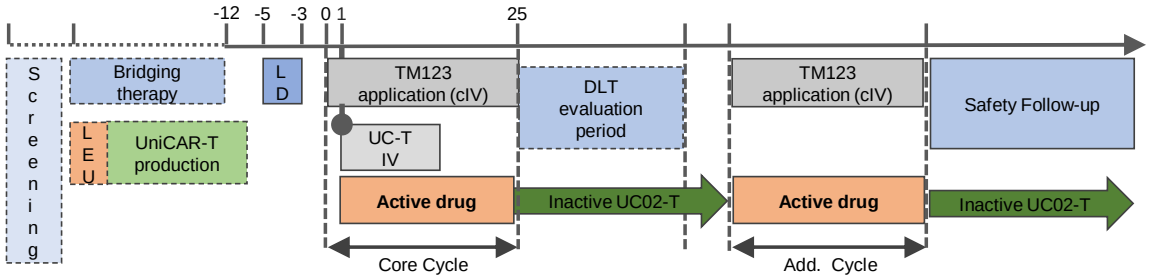


- UniCAR-T → alternative to CD123-directed CAR-T cells
- Systhemic switch-off activity within less than 4h (plasma half-life of <1h)
- Reduction of AEs → treatment of patients with bulky leukemic burdens

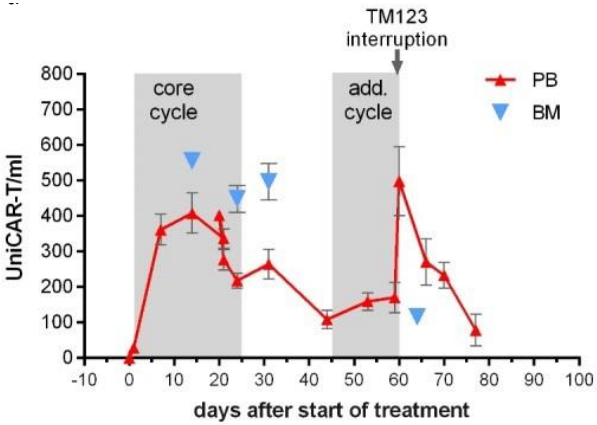
Loff S. et al.,2021.

Re-activation of UniCAR-T-cells with 2nd cycle of TM123 in R/R AML patient

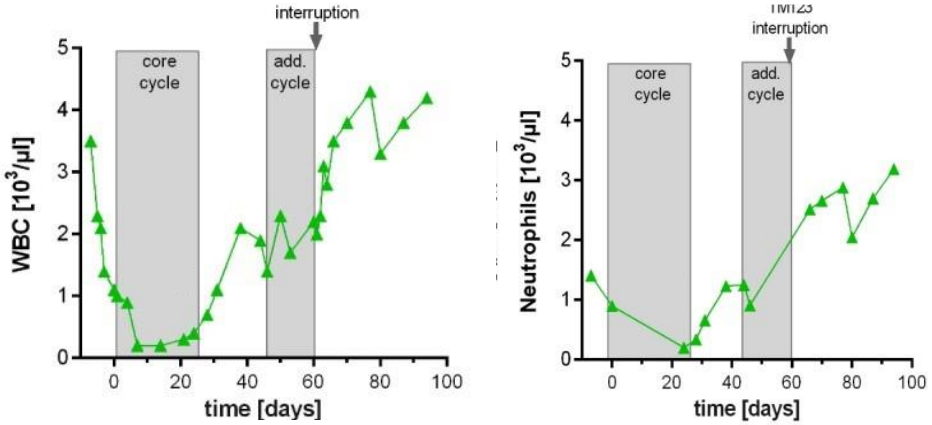
Treatment Schema



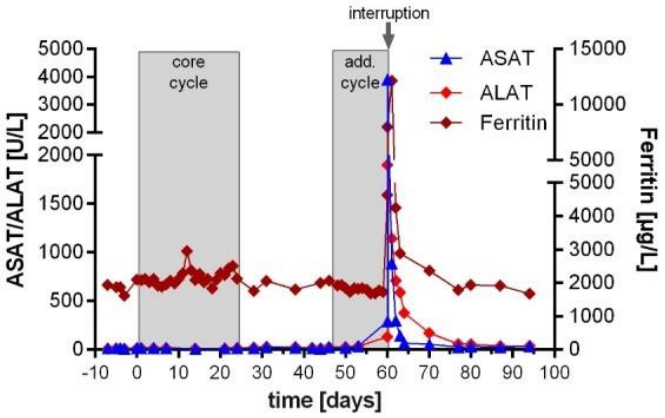
UniCAR T Expansion



Hematologic Recovery



Cours of transaminases

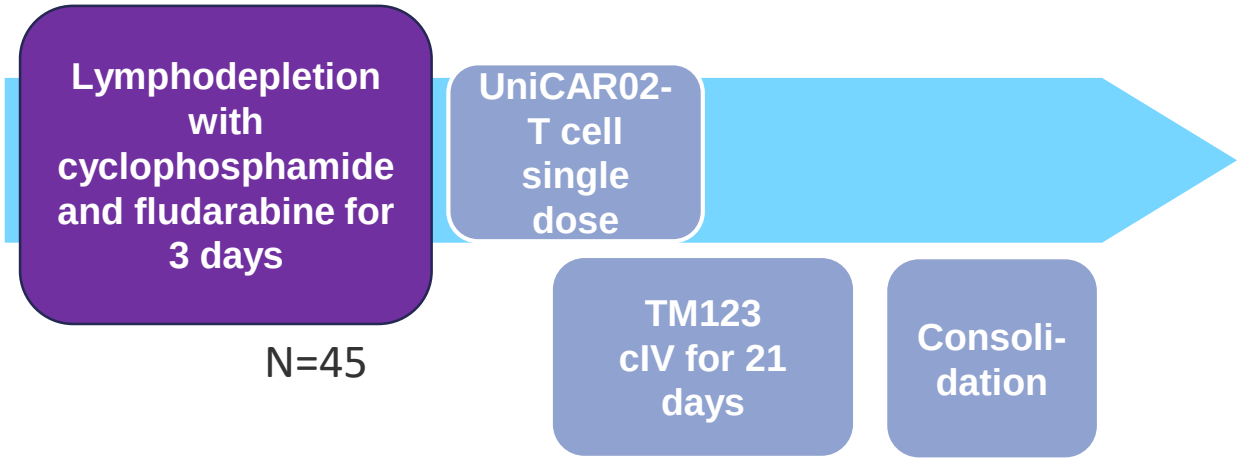


Kraus et al. EHA 2021

Treatment Schema

R/R-AML, R/R B-ALL or BPDCN: >20% CD123^{+} blasts, ≥18 y, without access to approved CAR-T cell product, ECOG 0-1, life expectancy of at least 2 months

ClinicalTrials.gov Identifier: NCT04230265



N=45

Primary Endpoints:
safety and tolerability, Incidence of dose limiting toxicity, Maximum tolerated dose/recommended dose,
Secondary Endpoints:
RP2D, Complete and partial remission disease stabilization, Best response rate, PFS, OS, Toxicity

1 country

6 trial centers

Ulm, Würzburg, Marburg, Dresden, Leipzig, Hamburg

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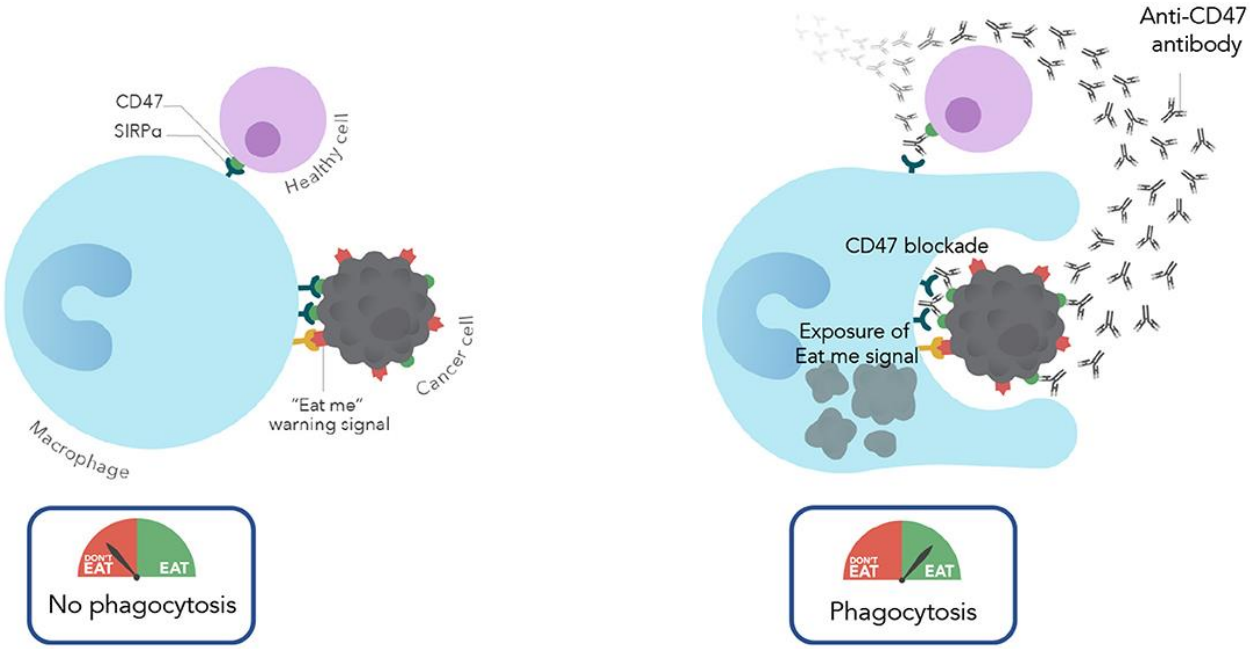
CD47 - The New Kid on the Block



- Magrolimab (anti-CD47 mAb):
  - Triggers anti-tumoral phagocytosis[1-3]
  - synergize with azacitidine → induction of pro-phagocytic signals[1-3]

- HMA + CD47 blockade has shown encouraging safety and activity in single-arm studies in frontline *TP53*m and *TP53*wt AML[4-6]

[1]DiNardo et al; N Engl J Med (2020). [2]Short N et al; Blood Adv (2021). [3]DiNardo et al Lancet Haematol (2020). [4]Stahl M et al; Blood Adv (2021).
[5]Daver N et al; EHA abst #S144 (2020). [6]Sallman D et al; ASH abst #330 (2020).

Phase I/II Trial

Azacitidine, Venetoclax and Magrolimab for Newly Diagnosed and Relapsed/Refractory AML

Daver N. et al., ASH 2021

Study Design

Phase 1 (Dose finding)

- **ND and R/R AML**
- **≥ 18 yrs**
- **ECOG PS ≤ 2**
- **Adequate organ function**
- **WBC ≤ 15x10^9/L**

Phase 2 cohorts

1. Frontline

- ≥ 75 yrs or
- <75 yrs, ineligible for intensive therapy
- ≥ 18 yrs with *TP53*^{mut} or adverse risk genetics, regardless of 'fitness'

2. R/R venetoclax-naïve
(Salvage 1 and 2)

3. R/R prior venetoclax
(Salvage 1 and 2)

Objectives

Primary objectives

- Determine MTD and RP2D
- CR/CRi rate

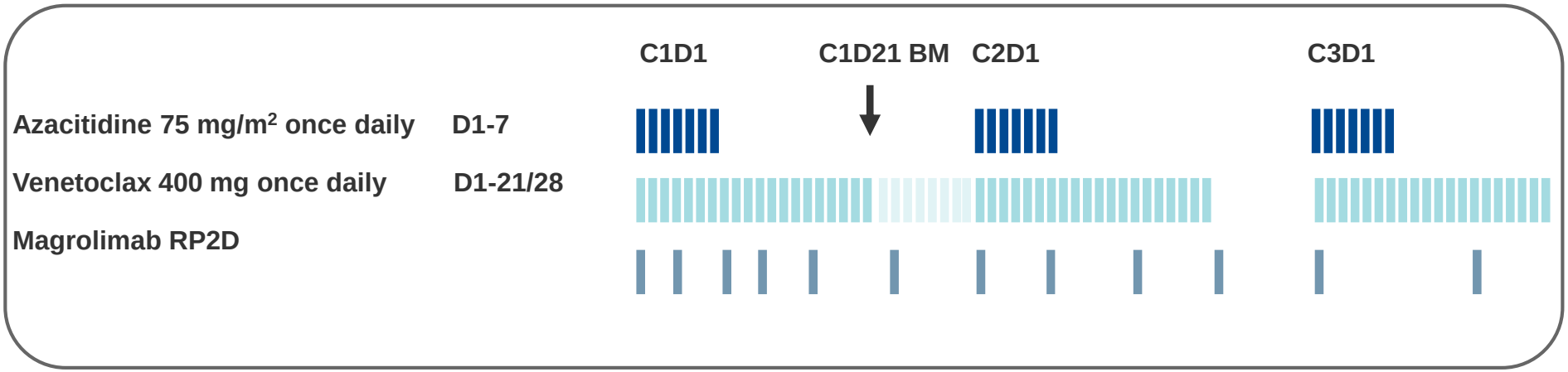
Secondary objectives

- ORR: CR/CRi + PR + MLFS
- Duration of response
- Event-free survival
- Overall survival
- MRD negative rate
- 4- and 8-wk mortality
- No. of pts transitioning to SCT

Exploratory objectives

NCT04435691

Treatment Schema



- Phase Ib (n=6) → no DLTs
- Magrolimab RP2D was established at
  - 1 mg/kg → C1D1, C1D4;
  - 15 mg/kg → C1D8
  - 30 mg/kg → C1D11 and subsequent doses

Baseline Characteristics: Cohort had high rates of adverse ELN risk

	Frontline Cohort (n=25)		R/R Cohort (n=23)	
Characteristics	*TP53* mutated (n=14)	*TP53* wild type (n=11)	VEN-naïve (n=8)	Prior VEN (n=15)
Age, yrs	67 [46-77]	71 [32-82]	51 [28-74]	70 [35-79]
ECOG PS ≥2	7 (50)	7 (64)	1 (25)	3 (20)
BM blasts, %	37 (9-96)	33 (16-92)	29 (11-87)	57 (6-85)
Diagnosis				
De novo AML	4 (29)	6 (55)	4 (50)	5 (33)
Secondary AML	10 (71)	5 (45)	4 (50)	10 (67)
ELN 2017 CG				
Intermediate	2 (14)	6 (55)	2 (25)	4 (27)
Adverse	**11 (86)**	**5 (45)**	**6 (75)**	**11 (73)**
Mutations				
TP53	14 (100)	0	0	1 (7)
IDH1/2	4 (29)	2 (18)	1 (13)	1 (7)
RUNX1	1 (7)	2 (18)	1 (13)	1 (7)
ASXL1	1 (7)	3 (27)	4 (50)	8 (53)
K / NRAS	0	3 (27)	3 (28)	3 (20)
NPM1	0	0	2 (25)	7 (47)
FLT3	0	0	1 (13)	2 (13)
Prior therapies	0	0	2 (1-3)	2 (1-5)

Results expressed as no. (%) or median [range], unless specified.

AML, acute myeloid leukemia; BM, bone marrow; CG, classification group; ECOG, Eastern Cooperative Oncology Group, ELN, European LeukemiaNet; PS, performance status; R/R, relapsed/refractory

Results: Safety Profile comparable to Azacitidine alone

Adverse event	Grade 1/2		Grade 3/4	
	n	%	n	%
Febrile neutropenia			18	38
Lung infection	3	6	15	31
Bilirubin increased	20	42	5	10
Hypokalemia	22	46	4	8
Hypotension	14	29	4	8
Skin infection	2	4	4	8
ALT increased	16	33	3	6
Infections and infestations	4	8	3	6
Sepsis			3	6
Fatigue	17	35	2	4
Back pain	12	25	2	4
Hyperglycemia	5	10	2	4
Hematuria	1	2	2	4
Spinal cord compression			2	4
Medical procedure			2	4
Hypophosphatemia	24	50	1	2
Hyponatremia	23	48	1	2
Diarrhea	19	40	1	2
Constipation	18	38	1	2
Hypocalcemia	15	31	1	2
Anorexia	13	27	1	2
Dyspnea	13	27	1	2
Generalized muscle weakness	12	25	1	2
Respiratory disorder	9	19	1	2
Pruritus	9	19	1	2

Adverse event	Grade 1/2		Grade 3/4	
	n	%	n	%
Erythema multiforme	6	13	1	2
Gait disturbance	5	10	1	2
Renal and urinary disorders	5	10	1	2
AST increased	4	8	1	2
Gastrointestinal disorders	4	8	1	2
Vascular disorders	3	6	1	2
Hyperuricemia	3	6	1	2
Nausea	21	44		
Fever	19	40		
Alk phosphatase increased	18	38		
Headache	18	38		
Hypoalbuminemia	18	38		
Sinus tachycardia	18	38		
Edema limbs	17	35		
Insomnia	17	35		
Arthralgia	15	31		
Creatinine increased	14	29		
Dizziness	14	29		
Hypomagnesemia	14	29		
Vomiting	14	29		
Bruising	11	23		
Cough	11	23		
Abdominal pain	10	21		
Chills	10	21		
Mucositis oral	10	21		
Pain	10	21		

Results: CR rates similar in patient cohort with TP53 mutation and those with TP53wt

Outcomes	Frontline Cohort (n=25)		R/R Cohort (n=23)	
	TP53 mutated (n=14)	*TP53* wild type (n=11)	VEN-naïve (n=8)	Prior VEN (n=15)
ORR	12 (86)	11 (100)	6 (75)	3 (20)
CR/CRi	**9 (64)**	10 (91)	5 (63)	3 (20)
CR	**9 (64)**	7 (64)	3 (38)	0
CRi	0	3 (27)	2 (25)	3 (20)
MLFS / PR[1]	3 (21)	1 (9)	1 (13)	0
MRD neg FCM	5/9* (55)	4/9 (45)	2/6 (33)	0
CCyR	4/9‡ (44)	5/6 (83)	3/5 (60)	1/2 (50)
No response	2 (14)	0	2 (25)	12 (80)
TT 1st response	0.7 [0.6-1.9]	0.7 [0.7-1.5]	0.7 [0.6-4.1]	2.2 [1.8-2.6]
TT Best response	1.5 [0.7-3.2]	1.1 [0.7-2.9]	1.5 [1.0-4.1]	2.0 [1.2-3.9]
Med TT ANC>500	28 (20 – 41) days			
Med TT Plt>50K	24 (18 – 41) days			
8-wk mortality	0	0	1 (13)	3 (20)

Results expressed as n (%), n/N (%) or median [range]. FCM = multiparametric FCM, sensitivity 0.1-0.01%,
*Only among pts with evaluable longitudinal samples; ‡Only among patients with baseline cytogenetic aberrations and longitudinal cytogenetic samples;
[1]Two with PR per ELN2017

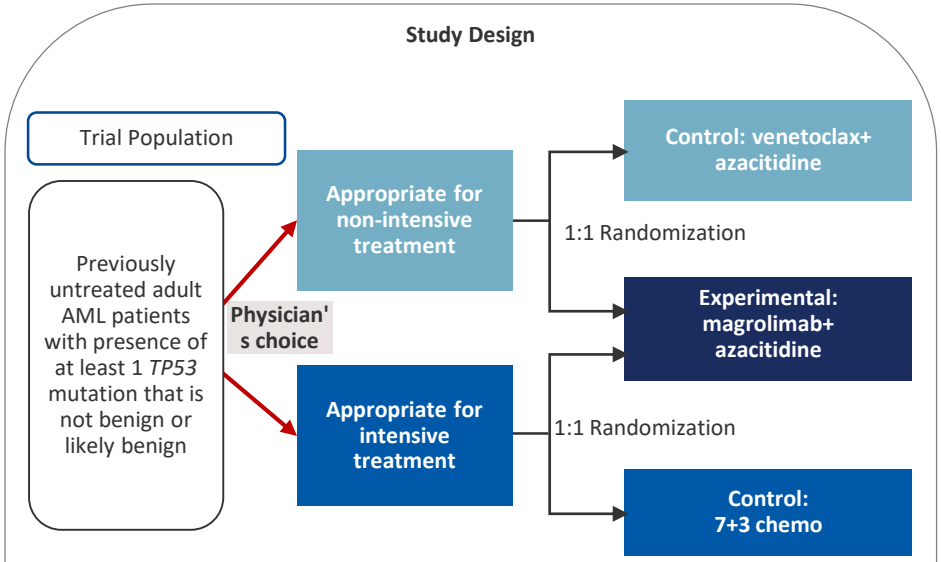
ANC, absolute neutrophil count; CCyR, complete cytogenetic response; CR, complete response; CRi, complete response with incomplete hematologic recovery; ELN, European LeukemiaNet; FCM, flow cytometry; ITT, intention-to-treat; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; ORR, overall response rate; Plt, platelet; PR, partial response; R/R, relapsed/refractory; TT, time to.

Conclusions

- ✓ CR rates were encouraging compared with HMA + VEN or AZA + Magro in frontline pts:
  - Frontline *TP53m* AML CR rate = 64%, ORR = 86%
  - Frontline *TP53wt* AML CR rate = 64%, ORR = 100%
  - 8 week mortality = 0
- ✓ R/R VEN-naïve AML CR/CRi = 63%, prior-VEN exposed AML CR/CRi = 20%
- ✓ TRAEs noted in >5% of patients included increased bilirubin and IRRs
- ✓ ANC and platelet recovery were robust (<28 days) in ND pts likely due to the lack of cumulative neutropenia or thrombocytopenia with Magro
- ▪ Hgb should be monitored closely after dose 1 and dose 2

Ongoing Phase III Studies with Magro in Frontline AML

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

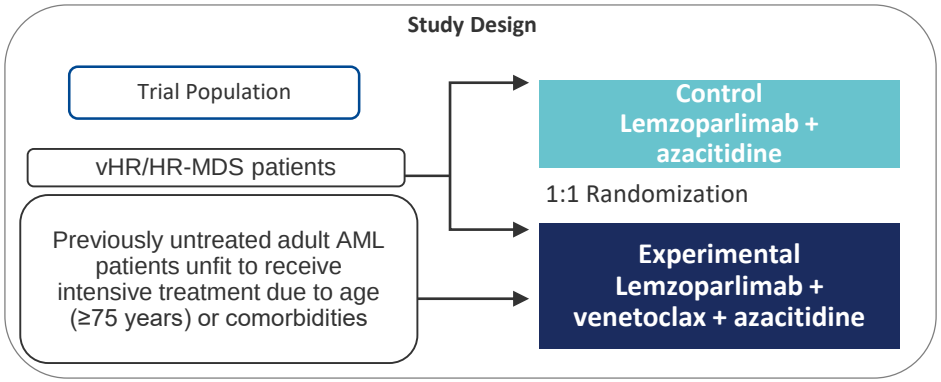


Sample size*: N=346
*Study will enroll a minimum of 228 TP53 mutAML patients appropriate for non-intensive treatment.

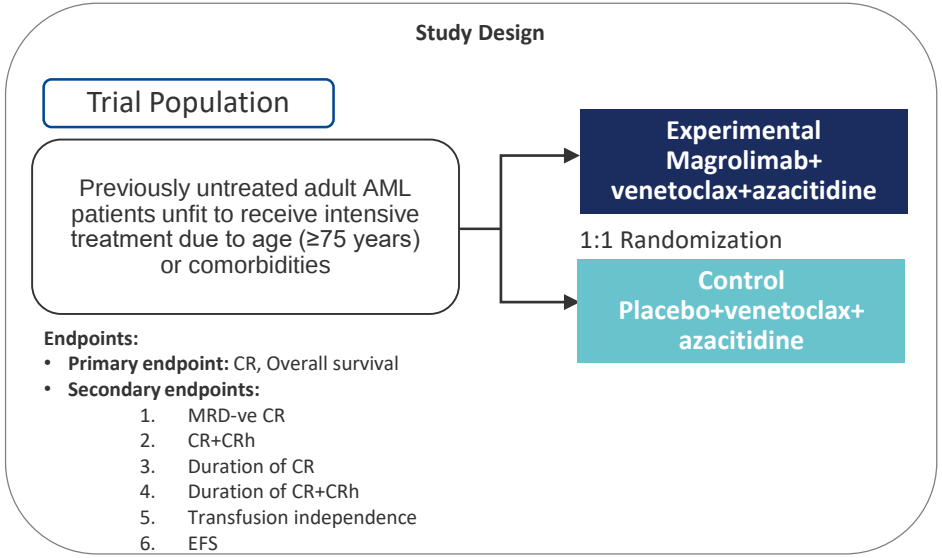
Stratification:
1. Appropriateness for non-intensive therapy vs. intensive therapy
2. Age <75 vs. ≥75
3. Geographic region: US vs outside the US

Endpoints:
- **Primary endpoint:** OS in *TP53* mutAML population appropriate for non-intensive treatment
- **First secondary endpoint (alpha Controlled):** OS in all *TP53* mutAML population
- **Other key secondary endpoints (alpha controlled):** EFS, Transfusion independence, CR/CR_{MRD-1} PRO in all *TP53* mutAML population

Phase 1b Dose Escalation of Lemzoparlimab in Combination With Venetoclax and Azacitidine



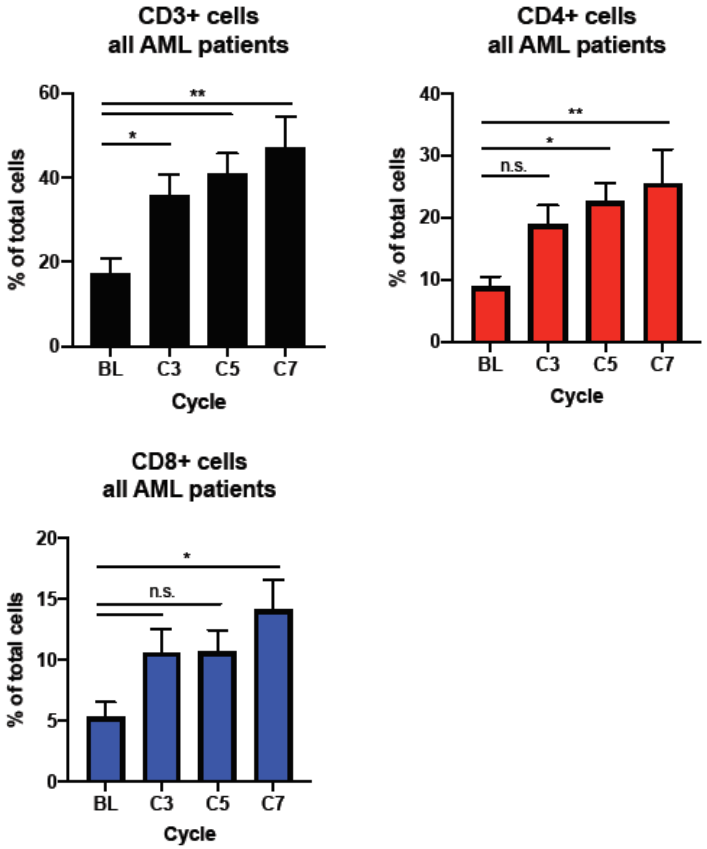
Phase III AZA+VEN+Magro vs AZA+VEN in older/unfit AML (ENHANCE-3)



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

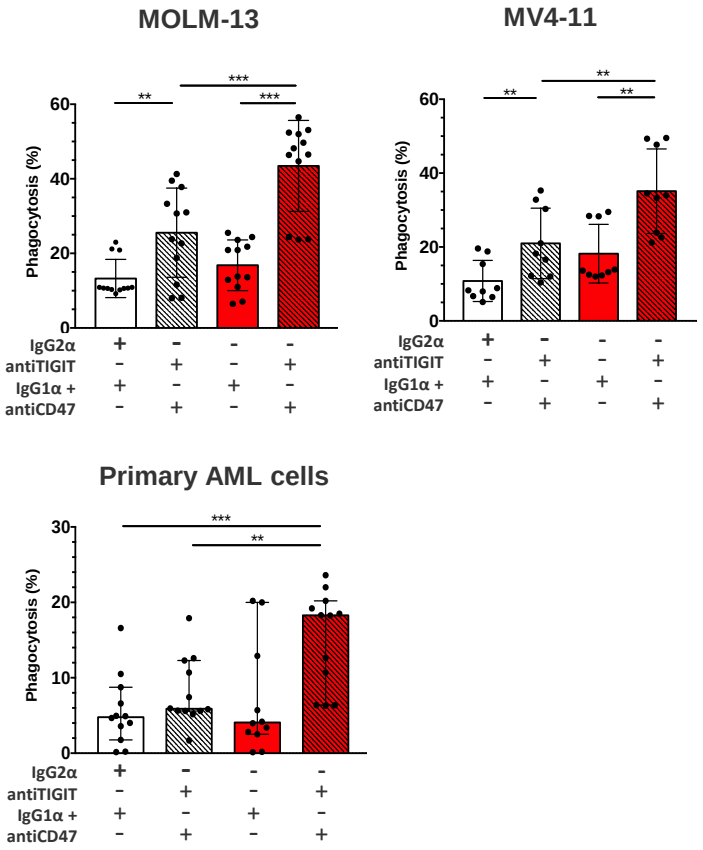
Opportunity for Combination of Co-Inhibitory Receptor Blockade with Magrolimab Treatment

Increased T Cell Infiltration in AML Patients Treated with Magrolimab-Azacitidine Combination



Daver N. et al. ASH 2020

Blockade of TIGIT increases CD47-dependent phagocytosis of AML cell lines and primary AML cells *in vitro*



Manuscript under revision

Summary

I. T-Cell Based Immunotherapy for AML

Checkpoint Blockade

✓ Targeting TIM-3

II. Targeting the Innate Immune System for AML

Checkpoint Blockade

✓ Targeting CD47

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Phase Ib trial:

Sabatolimab + HMA in MDS and AML

Brunner A.M. et al. *ASH 2021*

Patient disposition

		vHR/HR-MDS n=53	ND-AML n=48
Median exposure (range), mo	**Sabatolimab + decitabine[a]**	**8.02 (0.9-33.5)**	**6.8 (0.8-33.9)**
	Sabatolimab + azacitidine[b]	**4.45 (0.8-18.1)**	**5.98 (1.1-21.6)**
Ongoing,[c] n (%)		**9 (17)**	**2 (4.2)**
Discontinued, n (%)		**44 (83)**	**46 (95.8)**
Reason for discontinuation			
SCT		13 (24.5)	0
Disease progression		16 (30.2)	29 (60.4)
AE:	Unrelated to study treatment	0	2 (4.2)
	Related to study treatment	0	1 (2.1)
Death:	Unrelated to study treatment	2 (3.8)	4 (8.3)
	Related to study treatment	1[d] (1.9)	0
Patient decision		5 (9.4)	2 (4.2)
Physician decision		8 (15)	8 (16.7)
DLT		0	1 (2.1)[e]

[a]Enrollment started August 2017; [b]Enrollment started February 2019; [c]As of the cutoff date of September 6, 2021;
[d]1 patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock; [e]Single DLT was a grade 3 event of elevated ALT/hepatitis
AE, adverse event; ALT, alanine aminotransferase; DLT, dose-limiting toxicity; SCT, stem cell transplant.

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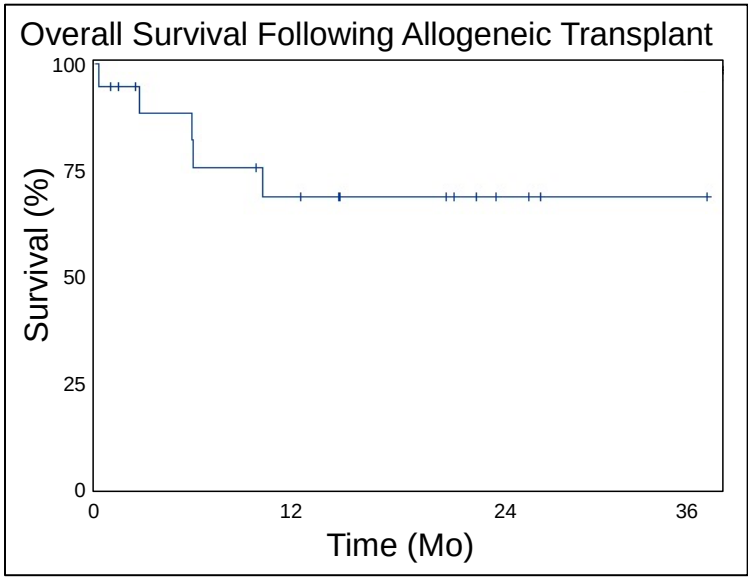
Independent exploratory analyses suggest that patients with MDS may successfully proceed to HSCT following sabatolimab + HMA

- **The outcomes of 19 patients[a] with MDS who received HSCT after study participation were assessed independent of the study by the investigators**
- **IPSS-R median score of 5.5 (range, 3.5-9)**
- **12 azacitidine + sabatolimab; 7 decitabine + sabatolimab**

- Post-transplant outcomes for patients treated with sabatolimab in combination with HMA for higher-risk MDS were generally favorable
  - Median follow-up of 21.2 months
  - 2 patients had grade 4 aGvHD
  - Overall survival was 69% 2 years after transplant
  - Relapse free survival 2 years after transplant was 59%



[a]Includes patients who discontinued study treatment for any reason and subsequently underwent HSCT. Patients who potentially received other treatments after stopping sabatolimab + HMA and prior to HSCT are included.

aGVHD, acute graft-versus-host disease; HCT, hematopoietic cell transplantation; HMA, hypomethylating agent; HR, high-risk; HSCT, hematopoietic stem cell transplant; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; vHR, very high-risk.

Updated Results From a Phase 1 First-in-Human Dose Escalation Study of AMG 673, a Novel Anti-CD33/CD3 BiTE® (Bispecific T-cell Engager) Molecule in Patients With Relapsed/Refractory Acute Myeloid Leukemia

M. SUBKLEWE[1], A. STEIN[2], R. WALTER[3], R. BHATIA[4], A. WEI[5], D. RITCHIE[6], V. BUECKLEIN[1], P. VACHHANI[4], T. DAI[7], A. HINDOYAN[7], S. AGARWAL[8], A. ANDERSON[7], S. KHALDOYANIDI[7], F. RAVANDI[9]

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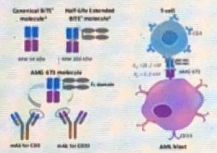
EUROPEAN HEMATOLOGY ASSOCIATION

EP548

INTRODUCTION

- BiTE® (Bispecific T-cell Engager) technology is a targeted immuno-oncology platform engineered to engage T cells to malignant cells
- CD33 is expressed on approximately 99% of acute myeloid leukemia (AML) blasts and is a validated therapeutic target in AML[1-4]
- AMG 673 is a half-life extended (HLE) BiTE® molecule that binds CD3 on T cells and CD33 on AML blasts. The molecular weight of AMG 673 is greater than canonical BiTE® molecules (Fig 1)
- In this study, we report updated results from the ongoing phase 1 study of AMG 673 (NCT03224819) in patients with relapsed/refractory (R/R) AML

Fig 1. AMG 673 – Mechanism of action



OBJECTIVES

- Assessment of safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of AMG 673 administered
- Identification of the recommended phase 2 dose of AMG 673

METHODS

Study Design and Interventions

- This is an ongoing, first-in-human, nonrandomized, open-label, multicenter, phase 1, dose escalation study in patients with R/R AML
- AMG 673 was administered as two, short, intravenous infusions on days 1 and 5 within each 14 day cycle (Fig 2)
- Dose escalation was initiated at 0.05 µg of AMG 673 in cohort 1 (Fig 3)
- Patients were treated with AMG 673 until disease progression or occurrence of unacceptable toxicities

Fig 2. Study design

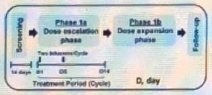
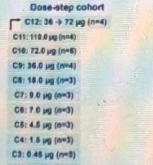


Fig 3. Dose escalation cohorts



Patients

- Key inclusion criteria
  - Male or female (≥ 18 years old) R/R AML patients with confirmed AML diagnosis
  - > 5% myeloblasts in bone marrow
  - Eastern Cooperative Oncology Group performance status score ≤ 2

Statistics

- Descriptive statistics were used for demographics, safety, PK, and PD data
- Validated assays were used to evaluate T-cell activation, and serum concentrations of cytokines and AMG 673

RESULTS

Demographics and baseline characteristics summarized

Characteristics	N = 38
Median age, years	67.5 (25–84)
Male, n (%)	20 (53)
AML type, n (%)	
AML with recurrent genetic abnormalities	15 (39)
AML, NOS	12 (32)
AML with myelodysplasia-related changes	8 (21)
Therapy-related myeloid neoplasms	3 (8)
Prior HSCT, n (%)	7 (18)

Characteristics	N = 38
Prior anti-AML therapies, n (%)	
1	4 (10)
2	3 (8)
3	6 (16)
≥ 4	25 (66)
Baseline myelosuppression (grade ≥ 3), n (%)	
Thrombocytopenia	32 (84)
Neutropenia	26 (68)
Leukopenia	17 (45)

AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; N, total numbers of patients enrolled; NOS, not otherwise specified; n, number of patients with observed data

- As of March 23, 2020, 38 patients have been treated with AMG 673 at 12 dosing levels

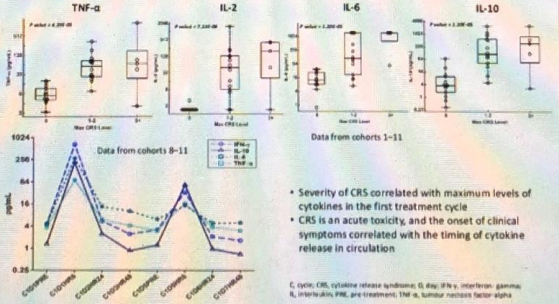
Safety Profile

Treatment-Related AEs*	All Grades; N = 38; n (%)	≥ Gr 3; n (%)
Patients with treatment-related AEs	34 (90)	20 (53)
Immune disorders		
Cytokine Release Syndrome (CRS)	24 (63)	7 (18)
Elevated liver tests (including ALT, AST, blood ALP, blood bilirubin, GGT, hepatic enzyme abnormal, transaminases)	12 (32)	7 (18)
Blood and lymphatic system disorders	8 (21)	
Anemia	3 (8)	3 (8)
Febrile neutropenia	3 (8)	3 (8)
Procedural complications		
Infusion-related reaction	7 (18)	0 (0)

*As per investigators; AE, adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; Gr, grade; N, total numbers of patients enrolled; n, number of patients with observed data

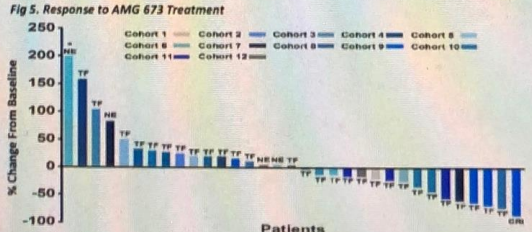
- Treatment-related adverse events (AEs) were reported in 34 (90%) patients; cytokine release syndrome (CRS) was the most common AE observed in 24 (63%) patients
- Treatment-emergent serious AEs (SAEs) were reported in 26 (68%) patients; 13 (34%) patients reported infections and infestations as the most common SAE
- Dose-limiting toxicities (DLTs) were reported in 2 of 4 patients in cohort 11, and the maximum tolerated dose (MTD) was identified as 72 µg (cohort 10)
- A dose step was initiated in cohort 12 to mitigate the severity of CRS and allow further dose escalation (Fig 3)

Fig 4. Correlation Between CRS and Cytokine Levels



- Severity of CRS correlated with maximum levels of cytokines in the first treatment cycle
- CRS is an acute toxicity, and the onset of clinical symptoms correlated with the timing of cytokine release in circulation

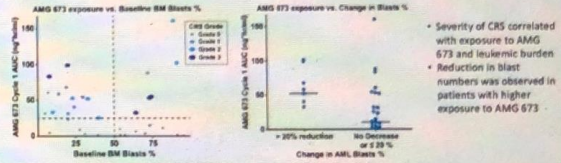
Fig 5. Response to AMG 673 Treatment



*The % change from baseline for this patient was > 400. CRi, complete remission with incomplete hematologic recovery; NE, not evaluable; TF, treatment failure

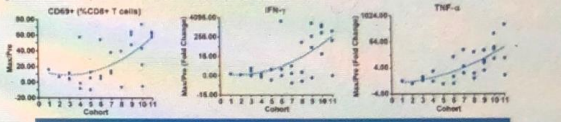
- Reduction in blasts was observed in 16 of 38 (42%) patients
  - ≥ 50% reduction in blasts was seen in six patients
  - One patient from cohort 9 achieved complete remission with incomplete hematologic recovery (CRi), with 85% reduction in bone marrow blasts and was bridged to allogeneic hematopoietic stem cell transplantation (HSCT)

Fig 6. Relationships Between CRS, Exposure, and Anti-AML Activity



- Severity of CRS correlated with exposure to AMG 673 and leukemic burden
- Reduction in blast numbers was observed in patients with higher exposure to AMG 673

Fig 7. Relationships Between AMG 673 Exposures and CD8+ T-cell Activation



Cohort	1	2	3	4	5	6	7	8	9	10	11
Dose (µg)	0.05	0.15	0.45	1.50	4.50	7.0	9.0	18.0	36.0	72.0	110.0
Mean C_{max} (ng/ml)	0.01	0.03	0.04	0.06	0.26	0.73	1.39	1.23	2.01	3.21	5.07
Mean AUC (ng*h/ml)	0.62	1.67	2.23	2.37	7.21	34.9	9.10	33.7	43.8	61.1	104.0

Data up to cohort 11; AML, acute myeloid leukemia; AUC, area under the curve; BM, bone marrow; CRS, cytokine release syndrome; IFN-γ, interferon-gamma; TNF-α, tumour necrosis factor-alpha

- Dose-related increase in AMG 673 exposure was observed across the tested dose range
- T-cell activation measured by CD69 expression in CD8+ T cells was observed at higher exposures
- Increased levels of cytokines in serum were observed at higher exposures

CONCLUSIONS

- AMG 673 was safe and tolerable at doses tested up to 72 µg, with 2 DLTs reported at 110 µg target dose
- CRS was a frequent mechanism of action–mediated toxicity with no unexpected toxicities reported to date
- CRS severity correlated with baseline tumor burden and AMG 673 exposures
- Dose-related increase in AMG 673 exposures was observed across the tested dose range of 0.05–110 µg, including the dose-step (36 → 72 µg) in cohort 12
- Decrease in AML blasts in bone marrow, and increased T-cell activation and cytokine levels were observed at higher AMG 673 exposures
- Continuation of AMG 673 dose escalation is in progress

ACKNOWLEDGMENTS

The authors thank the patients and their families, clinical staff, and the collaborators contributing to this study. Amgen Inc. funded this study and medical writing (Indira Venkatasubramanian of Amgen Inc. and Advait Joshi of Cactus Life Sciences – part of Cactus Communications); graphics support was provided by Robert Dawson (Cactus Life Sciences – part of Cactus Communications).

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CONTACT INFORMATION

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AMV564

Abstract #1455

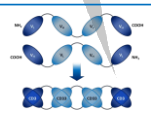
Phase 1 First-In-Human Trial of AMV564, a Bivalent Bispecific (2:2) CD33/CD3 T-Cell Engager, in Patients with Relapsed/Refractory Acute Myeloid Leukemia (AML)

Peter Westervelt[1], Gail J. Roboz[2], Jorge E. Cortes[3], Hagop M. Kantarjian[3], Sangmin Lee[2], Vivian G. Oehler[4], Michael P. Rettig[1], Tae H. Han[5], Jeanmarie Guenot[5], Eric J. Feldman[5] and John F. DiPersio[1]
[1]Washington University, St Louis, MO; [2]Weill-Cornell Medical College, New York, NY; [3]MD Anderson Cancer Center, Houston, TX; [4] Fred Hutchinson Cancer Research Center, Seattle, WA; [5]Amphivena Therapeutics Inc., South San Francisco, CA

BACKGROUND

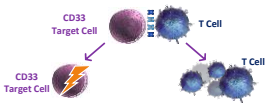
AMV564 is a novel bivalent, bispecific (2:2) CD33/CD3 T cell engager that binds CD33 on leukemic blasts and other CD33-expressing cells and the invariant CD3ε on the T-cell receptor creating an immune synapse that results in T-cell directed lysis of CD33-expressing cells and T cell activation and proliferation. AMV564 is broadly active with picomolar potency and activity is independent of cytogenetic or molecular abnormalities, CD33 expression level and disease stage, based on preclinical studies with AML patient samples (Reusch et al. 2016). AMV564 is well-tolerated in AML patients and demonstrates single agent anti-leukemic activity through T-cell engagement.

AMV564



- Homodimer that forms 4 scFvs
- Two binding sites for CD33 and CD3
- >100 kD, larger than the renal clearance threshold and not rapidly cleared

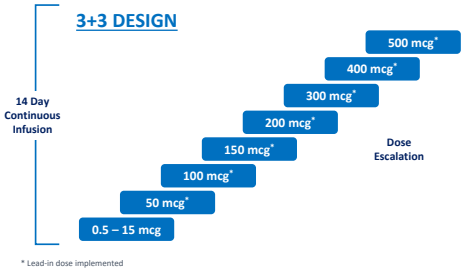
MECHANISM OF ACTION



Highly specific CD33 target cell killing

- Activation
- Cytokine release
- Proliferation
- Differentiation

3+3 DESIGN



* Lead-in dose implemented

KEY ELIGIBILTY

- Age ≥ 18 years
- High-risk R/R AML
  - 1-4 prior induction regimens
  - Post AlloHSCT relapse allowed
  - 2nd AML allowed
- Normal renal/hepatic function
- CD33 expression not required

KEY OBJECTIVES

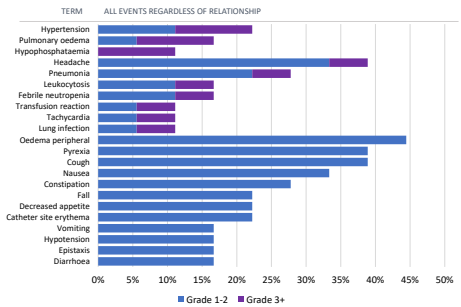
- Define MTD/RP2D
- Evaluate preliminary efficacy
- Assess PK
- Assess biomarkers

Poor prognosis population

	0.5 – 150 mcg x 14 d (N = 26)
Median age (range), y	73 (24, 84)
Sex, male, n (%)	13 (50)
ECOG score, n (%)	
0	5 (19)
1	17 (65)
2	4 (15)
Secondary AML, n (%)	17 (65)
≥ Second salvage, n (%)	18 (69)
Prior intensive chemotherapy, n (%)	16 (62)
Prior allogeneic transplant, n (%)	1 (4)
MRC cytogenetic risk group*, n (%)	
Favorable	0 (0)
Intermediate	13 (50)
Adverse	13 (50)
Enrollment BM, median (range)	28% (5%, 95%)
Baseline WBC, median (range), × 10^9/L	1.7 (0.4, 31.8)

No Dose Limiting Toxicities through 150 mcg

- No related Grade 3+ adverse events including cytokine release syndrome (CRS)
- 0% 30-day mortality
- Repeat cycles also well tolerated

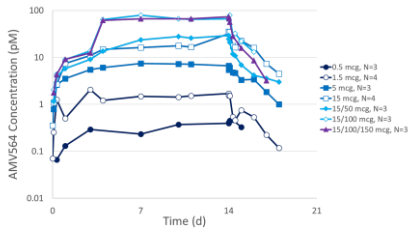


Cytokine Release Syndrome

- **No Grade 3+ CRS**
- **No Grade 2+ CRS with Lead-in Dose Strategy**

Lead-in Dose	Target Dose	# of Cycles	Grade 1	Grade 2	≥ Grade 3
N/A	15 mcg	20	3	0	0
15 mcg	100 mcg	13	4	0	0
15 → 100 mcg	150 mcg	4	2	0	0

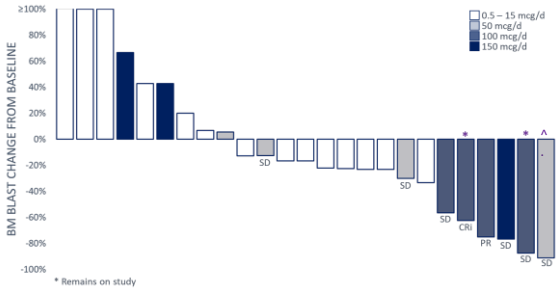
Terminal half-life of 2 days



Lead-in dosing of 15 mcg for patients at the 50 and 100 mcg dose levels
Lead-in dosing of 15 mcg and 100 mcg for patients at 150 mcg dose levels

- Gradual concentration increase to steady-state with continuous intravenous infusion
- Concentrations decline with a multi-phasic profile

Complete and partial responses observed



^. Spleen size reduced from 18 cm to 11 cm (patient with 1° myelofibrosis evolved to AML)
Response as per ELN AML criteria 2017

Summary through 150 mcg cohort

- **Safe and Well Tolerated**
- **Novel Pharmacokinetic Profile**
- **Single Agent Activity in Relapsed/Refractory AML**
  - Blast reductions in 16/26 poor prognosis AML patients, with PR and CRi at 100 mcg
  - Response in extramedullary disease in the spleen
  - T cell activation and proliferation in bone marrow and blood

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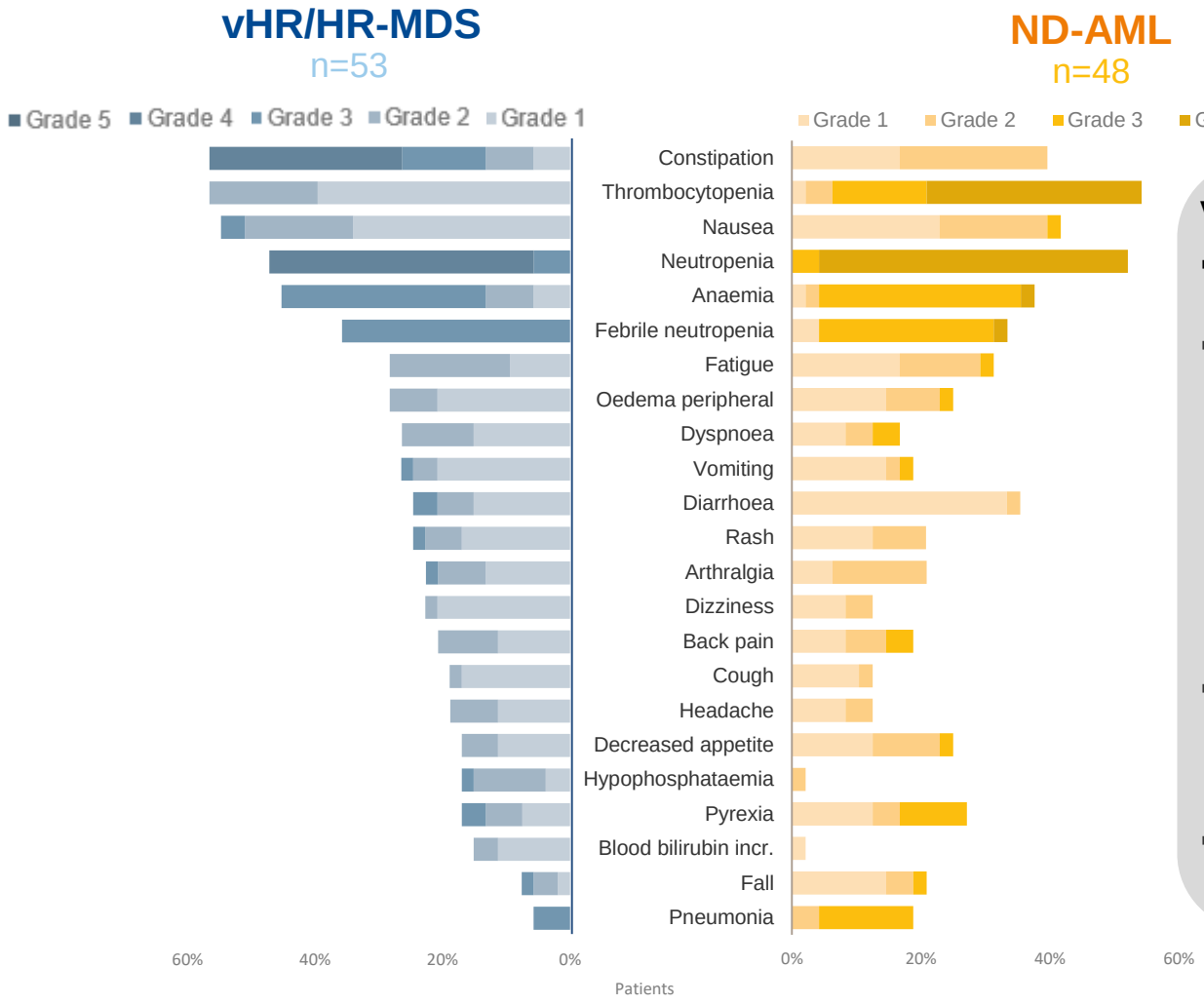
- Reusch U et al. Characterization of CD33/CD3 Tetravalent Bispecific Tandem Diabodies (TandAbs) for the Treatment of Acute Myeloid Leukemia. Clin Cancer Res. 2016 Dec 1;22(23):5829-5838. Epub 2016 May 17.

Results: Treatment related Adverse Events



vHR/HR-MDS and ND-AML Aes

- Most common reported AEs were consistent with HMA alone
- Low rate of sabatolimab dose modification:
  - 1/101 (1%) patients had dose reduction
  - 38/101 (38%) patients had dose interruption[a] due to AE
  - No patient with vHR/HR-MDS and only 3 with ND-AML discontinued treatment due to an AE
- 1 patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock. No other treatment-related deaths were reported
- No DLTs in vHR/HR-MDS and only 1 in ND-AML

Re-activation of UniCAR-T-cells with 2nd cycle of Targeting module TM123 in R/R AML patient

Re-activation of UniCAR-T-cells with 2nd cycle of Targeting Module TM123 in patient with Relapsed/Refractory AML

brina Kraus[1], Armin Ehninger[2], Ralf C. Bargou[3], Maria-Elisabeth Goebeler[3], Carla Kreissig[4], Jan Koedam[2], Michael Pehl[2], Hermann Einsele[1], Gerhard Ehninger[2], Marc Cartellieri[2]

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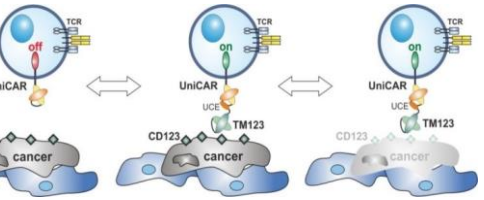


n

nt therapeutic advances, the outcome of patients with relapsed/refractory acute myeloid ML) remains poor.

ttractive target for immunotherapy of AML and other hematologic malignancies, as it is leukemia cells in 80% of AML patients, including leukemic stem cells (1).

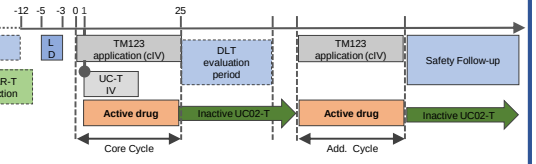
ventional CAR-T technology to AML has been hampered by the fact that all potential ns including CD123 being overexpressed on leukemic blast are also found on healthy enitor cells generating a risk for long-lasting aplasia (2, 3).

apidly switchable, two component CAR-T platform using a CD28 co-stimulatory domain

mponent is a universal CAR-T cell with a CAR that by itself does not recognize any human tigen but a peptide motif (UCE) included in the second component.

omponent is a soluble adaptor called targeting module (TM), which confers specificity he cancer antigen of choice; due to the high flexibility of the tumor binding domain ntigens in solid tumors and hematologic malignancies can be targeted (4).

combination with a CD123-specific targeting module (TM123) is currently explored in a in rrAML (NCT04230265) for safety and efficacy.



l Design

ase 1A study is depicted in Figure 2.

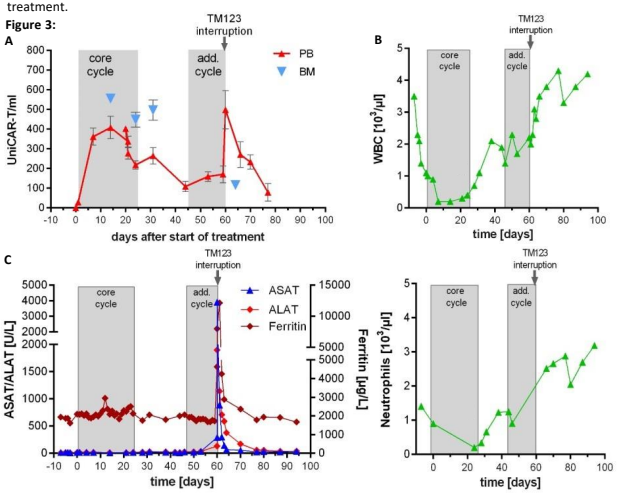
s are manufactured from autologous starting material (LEU), patients are allowed to g therapy if required; lymphodepletion (LD) with standard dose Flu/Cy is performed prior atment; TM123 is administered as continuous i.v. infusion over 25 days starting at day 0 niCAR-T administration at day 1 (core cycle).

allowed to receive a 2nd cycle (add. cycle) of TM123 based upon initial safety and efficacy e core cycle.

Patient Characteristics and Course of Treatment

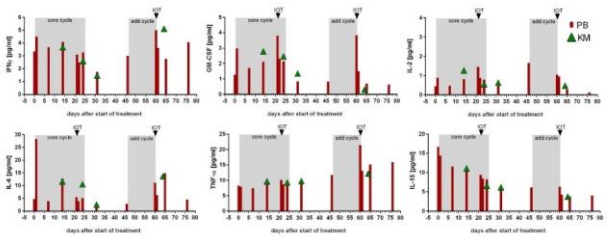
- 65 year old Caucasian male with rrAML after multiple lines of treatment including unrelated hematopoietic cell transplantation, donor lymphocyte infusion, and Azacitidine.
- Patient received 250 million UniCAR-T and a TM123 dose of 0.5 mg/day over 25 days in the core cycle. TM123 was interrupted for 24h on day 21 due to technical reasons (IOT, Figure 4).
- UniCAR-T showed a robust engraftment both in peripheral blood (PB) and bone marrow (BM) according to vector copy number determined by droplet digital PCR (Figure 3, core cycle).*
- White blood cells (WCB) and neutrophil counts returned to baseline or even better shortly after stop of TM123 infusion (Figure 3B).
- Patient achieved a complete remission with incomplete hematologic recovery (CRi) after core cycle treatment.

Figure 3:



- An increase in bone marrow CD123+ blasts was detected one week after end of treatment and patient underwent a second treatment cycle of TM123 administration at 0.5 mg/day without prior LD; a second dose of UniCAR-T was not given as UniCAR-T cells were still present in PB.
- A robust increase of UniCAR-T was detected upon re-activation by TM123 administration with a sharp increase by day 14 (Figure 3A).
- On day 14 of the second cycle (day 60 since start of core cycle) a grade 4 transaminitis (grade 2 CRS) developed, as determined by rapid increase of liver-specific biomarkers (Figure 3C)
- Immediate termination of TM123 infusion led to a rapid resolution of the CRS and complete normalization of liver values (Figure 3C) without the need for admission to intensive care unit (ICU); subsequently it was decided to not re-start/continue TM123 administration.
- Despite short course of re-treatment, patient presented with a CRi and normalization of neutrophil counts (Figure 3B).

Figure 4:



- Figure 4 shows the cytokine profiles during core and second cycle in peripheral blood and bone marrow.
- After UniCAR-T administration on day 1, infusion of TM123 lead to a mild transient increase of T cell specific cytokines like interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin (IL)-2 and more general inflammatory cytokines like IL-6 and tumor necrosis factor α (TNF-α). An exception was IL-15, which decreased from day 0 continuously, in line with literature describing IL-15 levels post LD chemotherapy (5). Cytokine levels decreased after stopping TM123 infusion. The rather rapid drop of cytokine levels after stop of TM123 administration was determined with cytokine measurements performed within 24h before and after interruption of infusion (IOT, arrows) in the core cycle and at the end of the additional cycle.

Summary and Conclusion

- Presented data provide, to our best knowledge, a first-time clinical evidence for safety and efficacy of rapidly switchable CAR-T in rrAML.
- UniCAR-T in combination with TM123 can induce durable CR in rrAML already after a single cycle.
- UniCAR-T cells can be re-activated after pausing TM123 administration by restarting TM infusion.
- Re-activated UniCAR-T mediate anti-leukemic activity and are able to deepen responses.
- Stop of TM123 infusion immediately abrogates UniCAR-T activity and allows to mitigate acute toxicities.
- Prompt recovery of neutrophils and WBC demonstrates capability of rapid switch-off mechanism of UniCAR to prevent long-term toxicities.
- Recruitment of the study is ongoing, updated results are presented by M. Wermke during the Flash Talks II session.

References

1. Ehninger et al. 2014, PMID 24927407
2. Cummins and Gill 2019, PMID 31221785
3. Loff et al. 2020, PMID 32462078
4. Cartellieri et al. 2016, PMID 27518241
5. Kochenderfer et al. 2017, PMID 28291388

presented in Figure 3A differ from those shown in Figure 1B in the abstract. Internal QA control revealed a calculation error after submission of the abstract, values were corrected accordingly.