Immunotherapies in AML & ALL

Marion Subklewe, M.D.

Department of Hematology / Oncology, LMU – University Hospital Munich
Head of the Cell & Gene Therapy Program at the LMU – University Hospital Munich
Head of the Lab for Translational Cancer Immunology at the LMU – Gene Center Munich

Disclosures

Research Support:

Amgen

Educational Grant:

BMS, Gilead/Kite,, Johnson & Johnson, Roche, Takeda

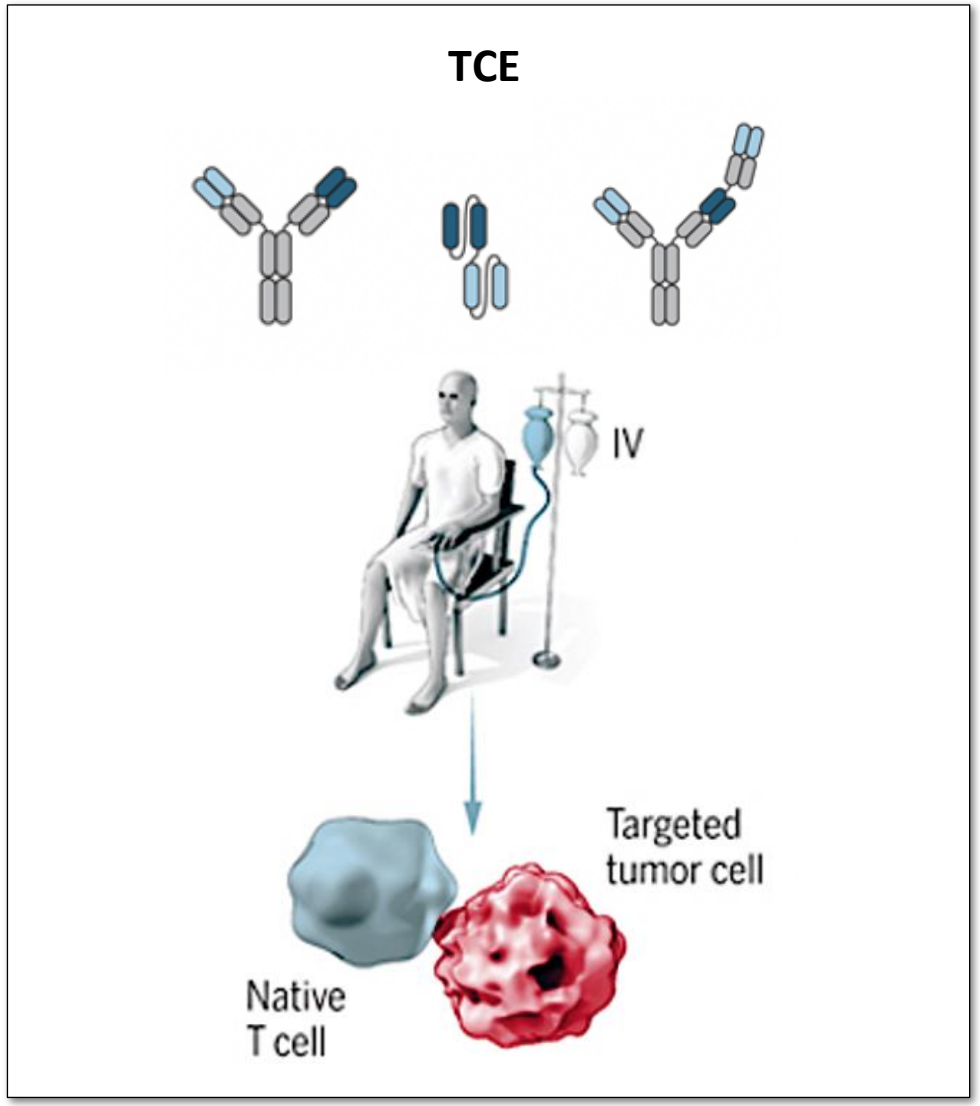
Consulting/ Scientific Advisory Board:

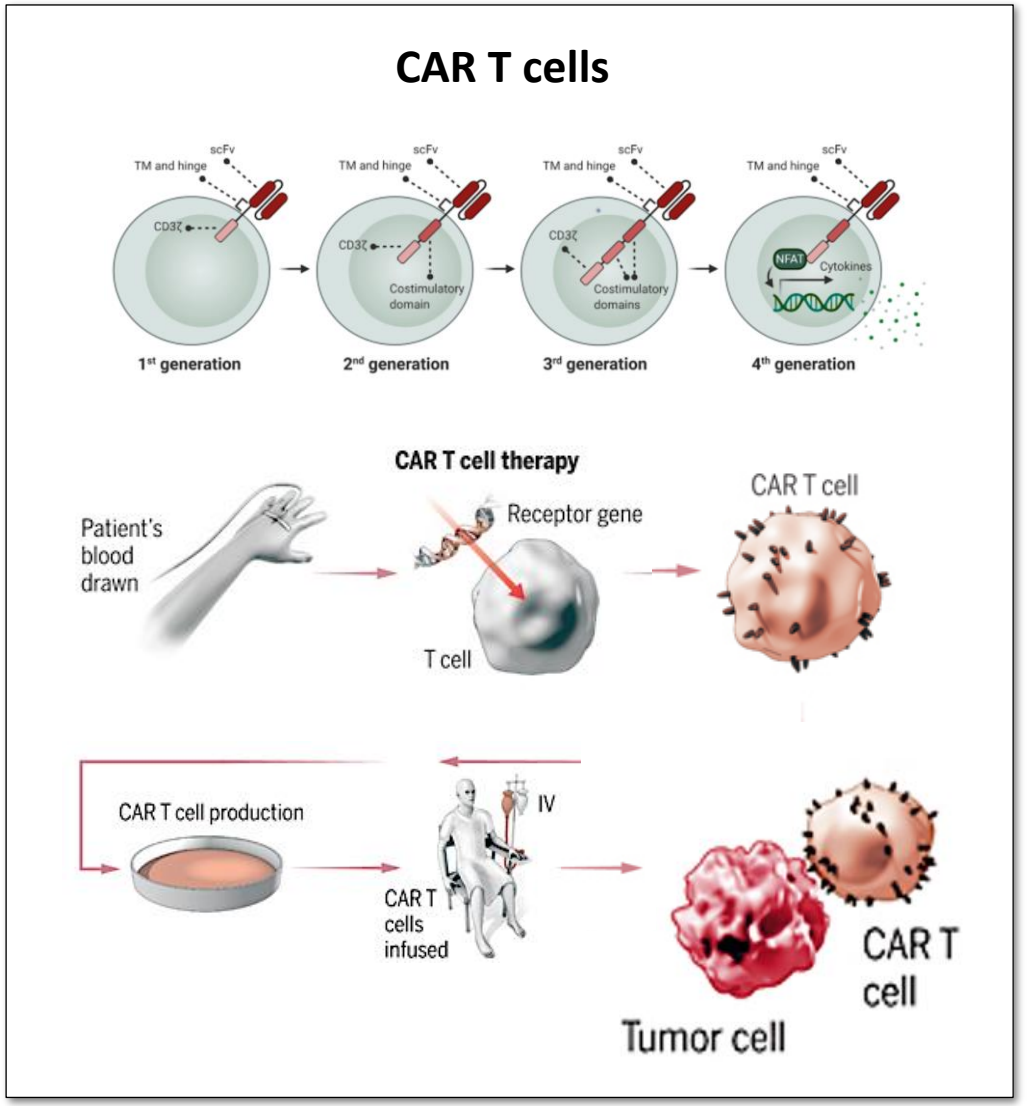
AbbVie, BMS, Gilead/Kite, Johnson & Johnson, Molecular Partners, Novartis

Travel Support:

Gilead/Kite, Pierre Fabre, Roche

Synthetic Immunity: Bispecific T-cell engagers (TCE) & CART cells





Kaiser et al, Science 2020

Agenda

1

BiTE in ALL

Blinatumomab: R/R → MRD → Frontline | TOWER · BLAST · E1910 | Combinatorial approaches ? with TKI ?

2

CAR-T in ALL

Pediatric & Adult | ELIANA · ZUMA-3 · FELIX | Consolidation with allogeneic Stem Cell Transplantation ?

3

T-cell Engagers in AML

CD33 BiTE · WT1 TCE | How to reduce toxicity and improve efficacy ? Multiple targeting ? Combi with VEN/AZA ?

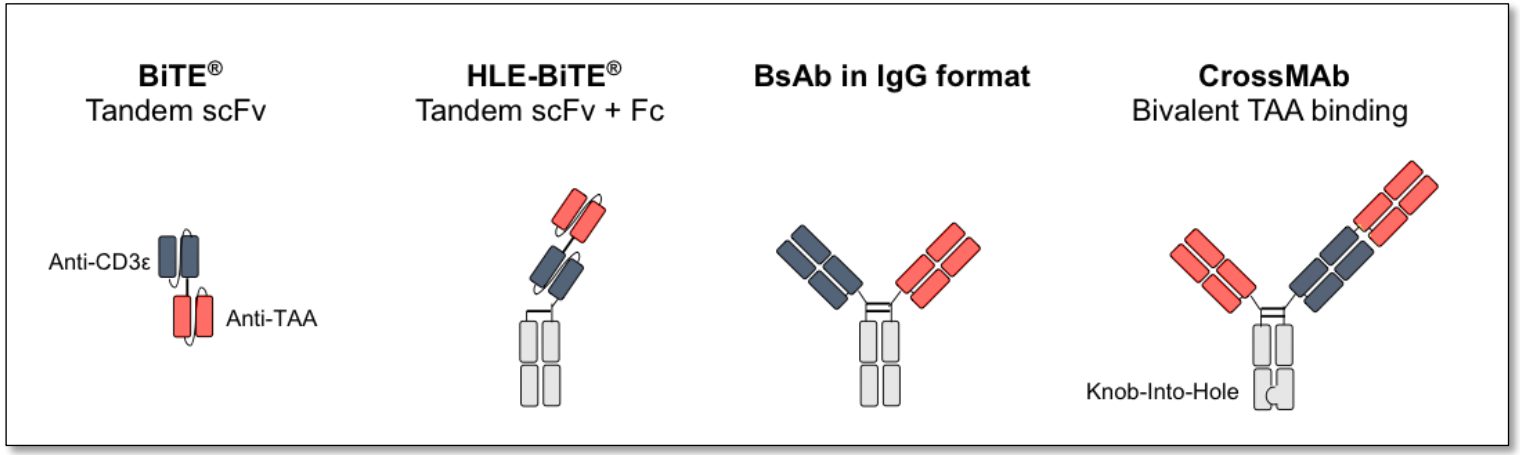
4

CAR-T in AML

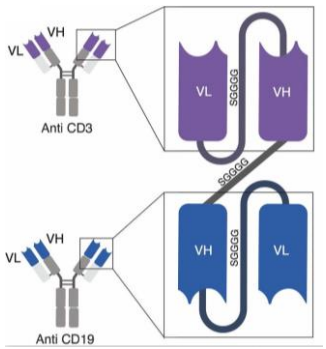
Targets · 2nd Generation CART | How to reduce toxicity and improve efficacy ? IL-18 ? Menin ? Edited SCTx ?

Bispecific T-cell engagers (BTCE): Format determines PK, scFv determines Affinity

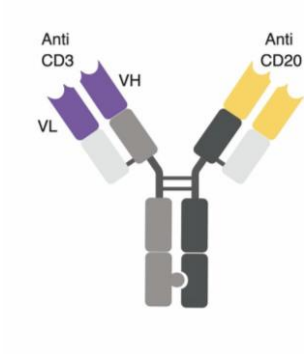
- Off-the-Shelf Product
- Flexible Targeting
- Titratable
- Intermittent Exposure
- Safety profile: CRS common, MAS/ HLA Syndrome occur, ICANS rare



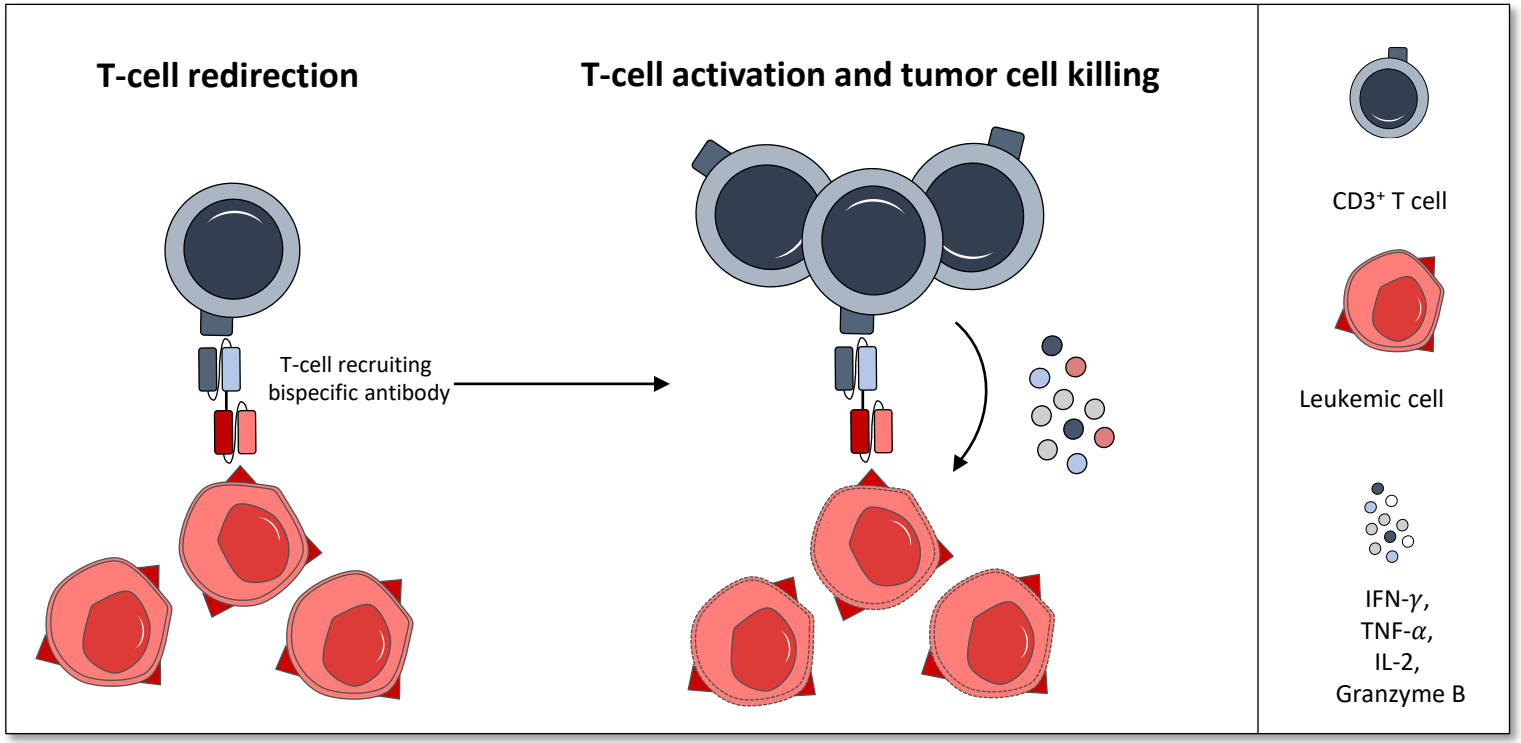
Fusion of scFvs – PK differ depending on TCE size



50 – 60 kDa



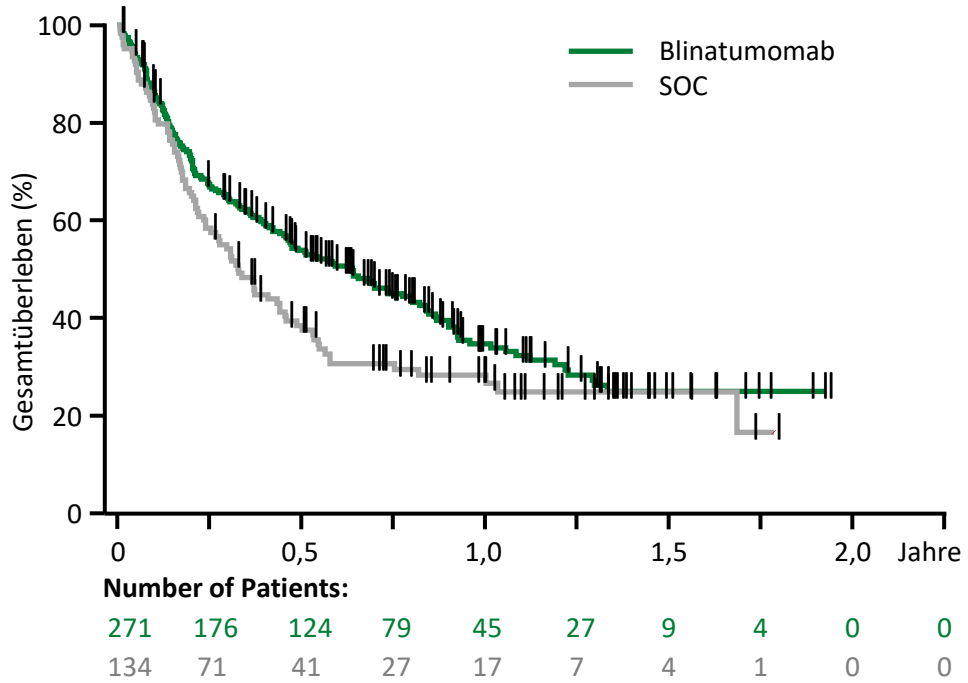
ca. 150 kDa



Tower Trial in R/R ALL (Blin vs SOC): OS 7.7 vs 4.0 Months; Salvage 1 > Salvage 2

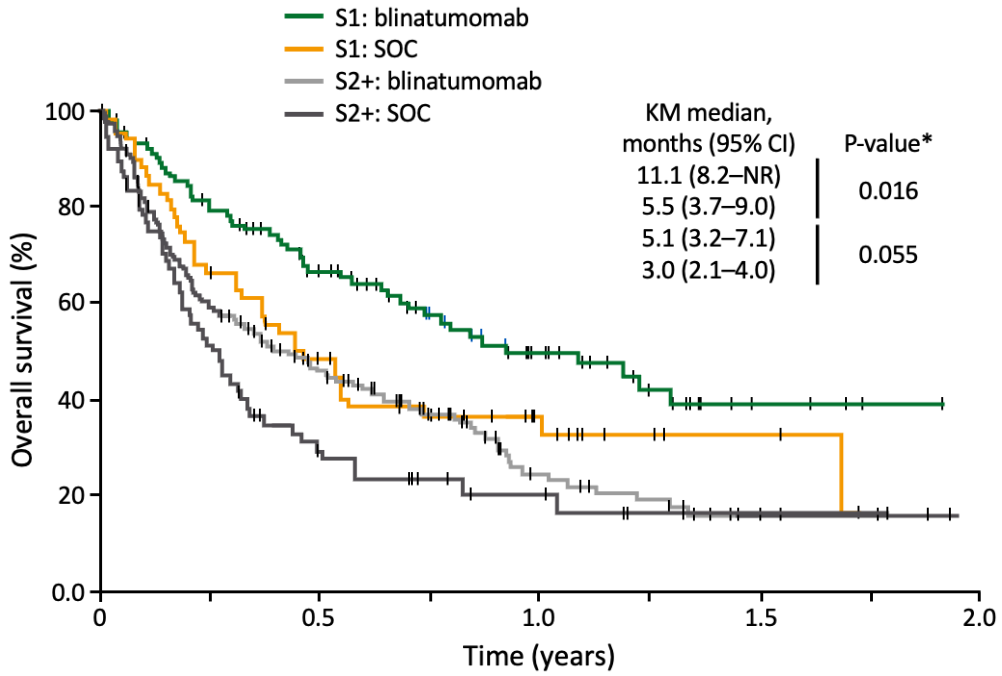
RCT: Median OS superior with Blinatumomab vs SOC

	Blinatumomab	SOC
Median OS, Months (95% CI)	**7,7 (5,6-9,6)**	**4,0 (2,9-5,3)**
Median Follow-Up, Months	11,7	11,8
HR for OS (95% CI)	0,71 (0,55–0,93); P=0,01*	



Adapted of Kantarjian H, et al. N Engl J Med 2017;376:836-47. Topp et al, Cancer 2021

Best OS in salvage 1 (S1), Median OS 11 months



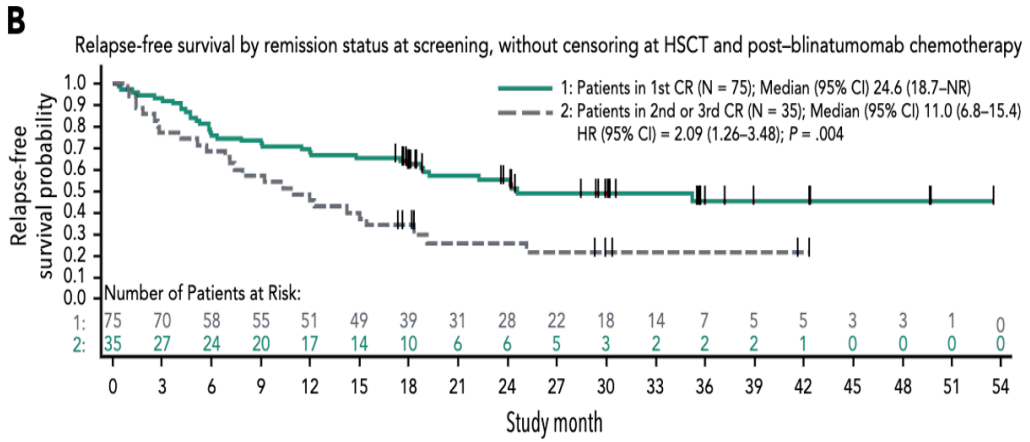
Patients at risk:

S1: blinatumomab	104	80	59	39	26	14	5	1	0
S1: SOC	63	39	26	18	11	5	3	0	
S2+: blinatumomab	167	96	65	40	19	13	4	3	0
S2+: SOC	71	32	15	9	6	2	1	1	0

Dombret H, et al. *Leuk Lymphoma*. 2019;60:2214-2222

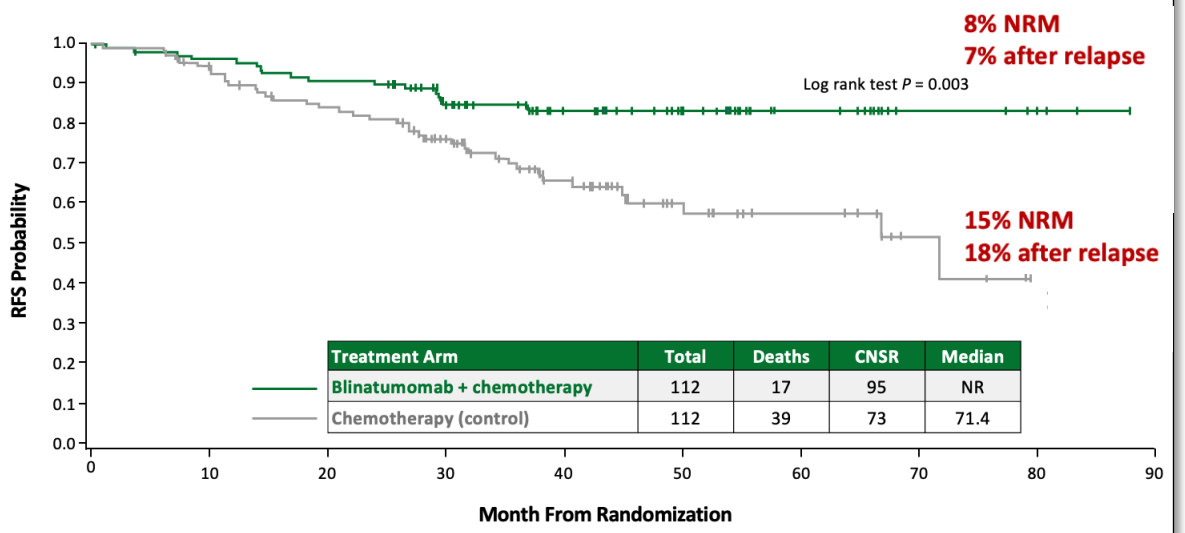
Blinatumomab with high Efficacy in MRD$^+$, but also MRD$^-$ Patients with *de novo* BCP-ALL

BLAST Trial: Blina in MRD$^+$ (> 0.1 %): MRD Conversion Rate after 1 Cycle of 78%,



Gökbuget et al., Blood 2018

ECOG-ACRIN (E1910): OS with Blina in MRD$^-$ (< 0.01%): not reached vs 71.4 months in the Control Arm



Treatment Arm	Total	Deaths	CNSR	Median
Blinatumomab + chemotherapy	112	17	95	NR
Chemotherapy (control)	112	39	73	71.4

Deaths on Blin+Chemo Arm = 17 (2° to ALL = 8, NRM = 9),
Deaths on Chemo Arm = 39 (2° to ALL = 20, NRM = 17, Unknown=2)

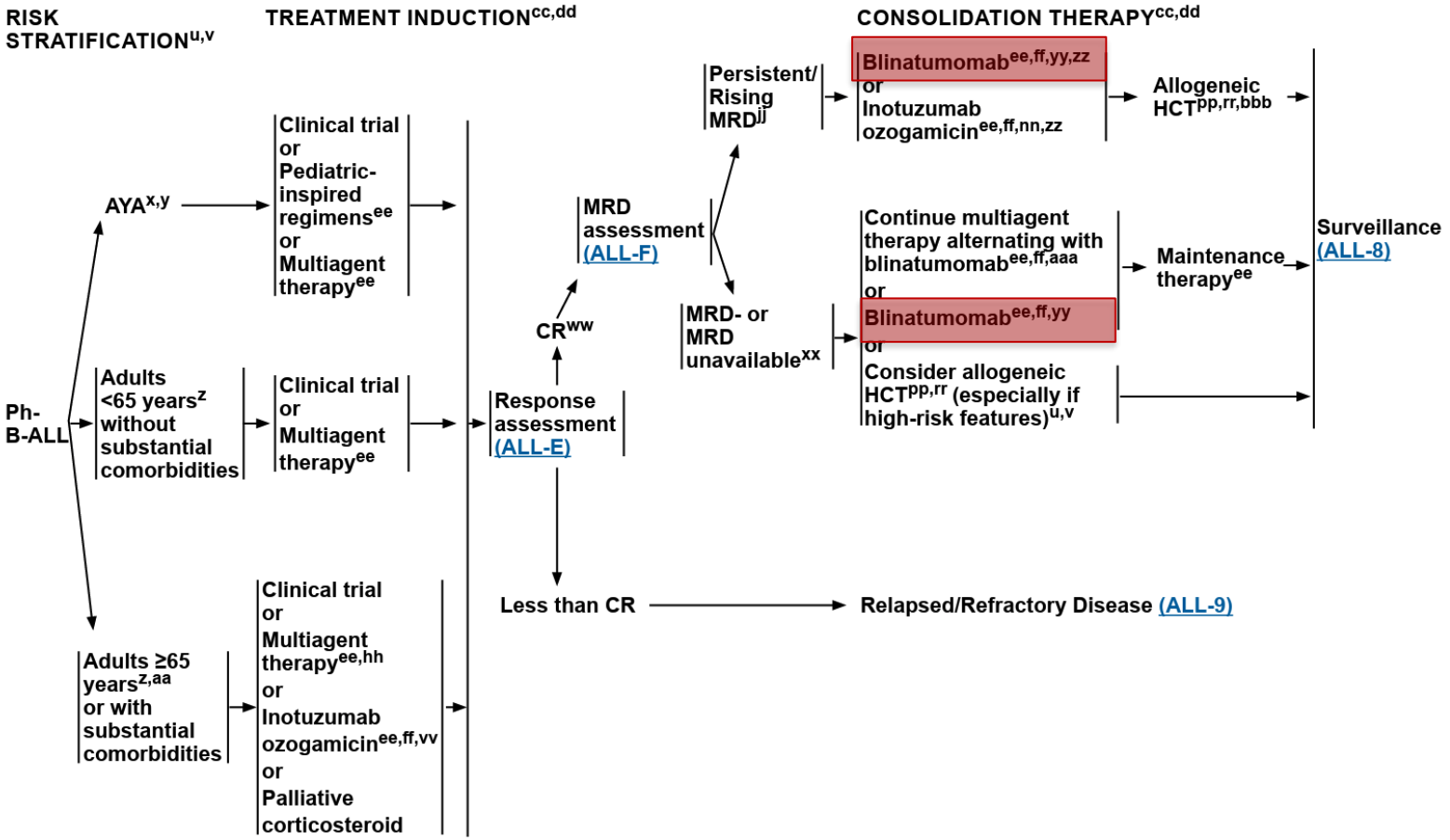
Litzow MR, et al, NEJM 2024

NCCN Treatment Algorithm of BCP-ALL: Blina in 1st Line independent of MRD Status

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Acute Lymphoblastic Leukemia

NCCN Guidelines Index
Table of Contents
Discussion



Note: All recommendations are category 2A unless otherwise indicated.

The FDA has granted approval to blinatumomab (Blincyto®, Amgen Inc.) for adult and pediatric patients ≥1 month of age with CD19-positive, Philadelphia chromosome–negative B-cell precursor acute lymphoblastic leukemia (Ph-negative BCP ALL) in the consolidation phase of multiphase chemotherapy.

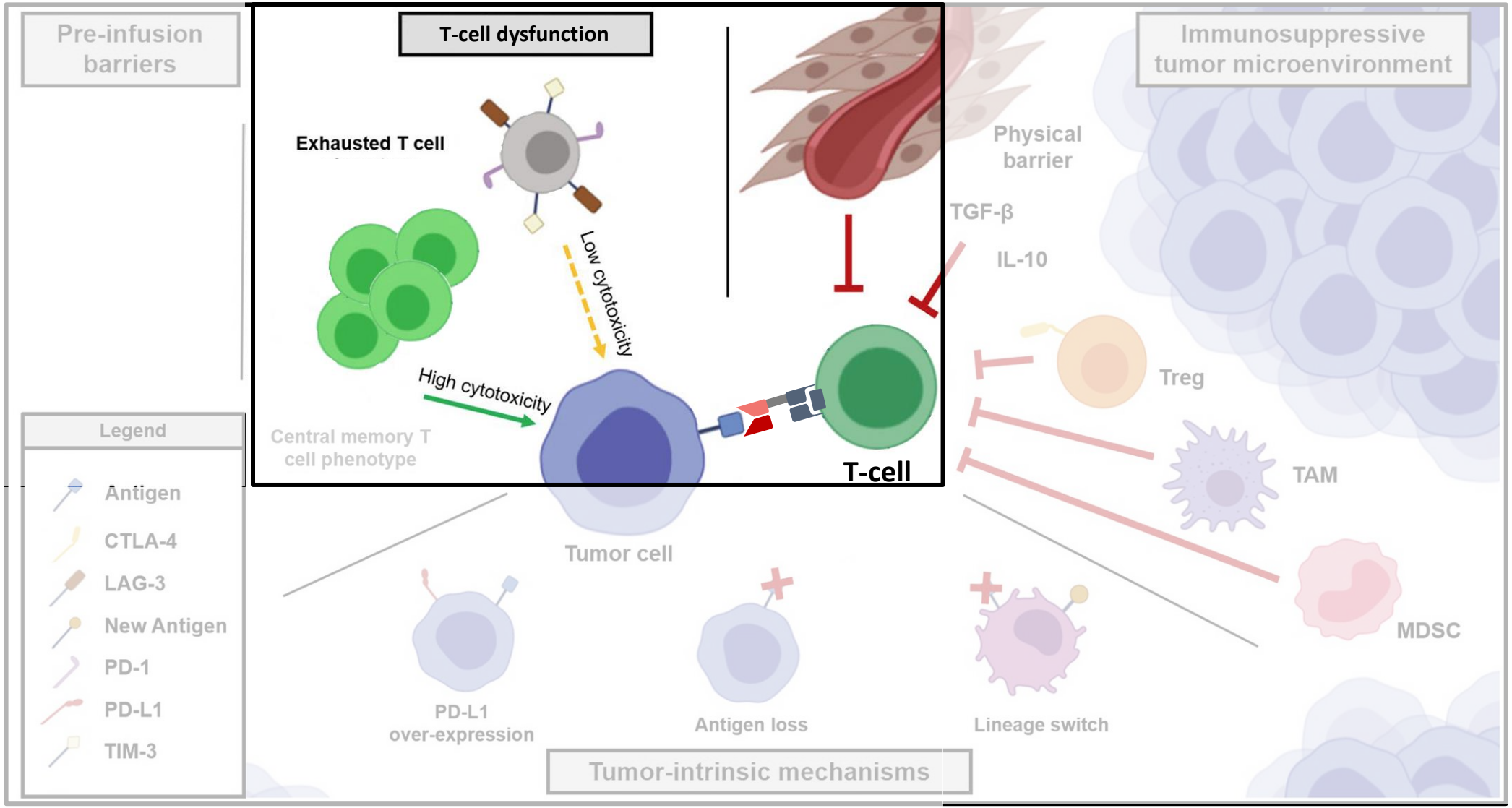
News | Article | January 30, 2025

European Commission Approves Blinatumomab Consolidation in Newly Diagnosed CD19+ B-ALL

Author(s): Ashley Chan
Fact checked by: Chris Ryan

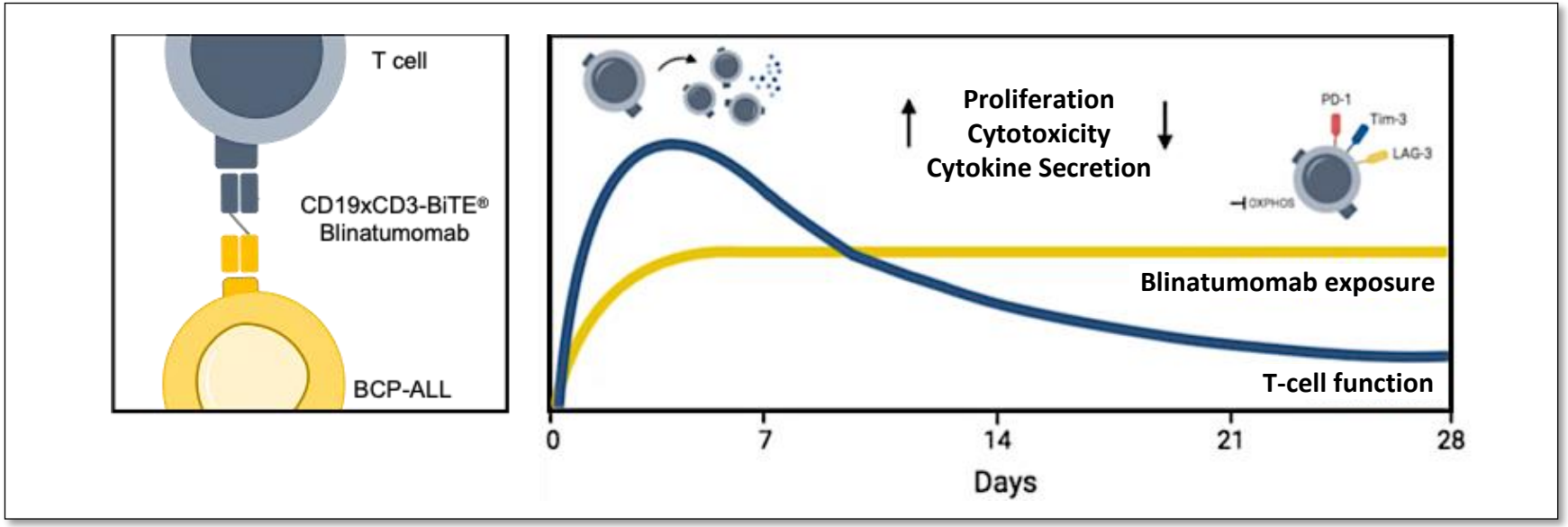
NCCN Guidelines, 2024, Onkopedia Guidelines 2025

Mechanisms of Resistance to bispecific T-cell engagers: T cell dysfunction

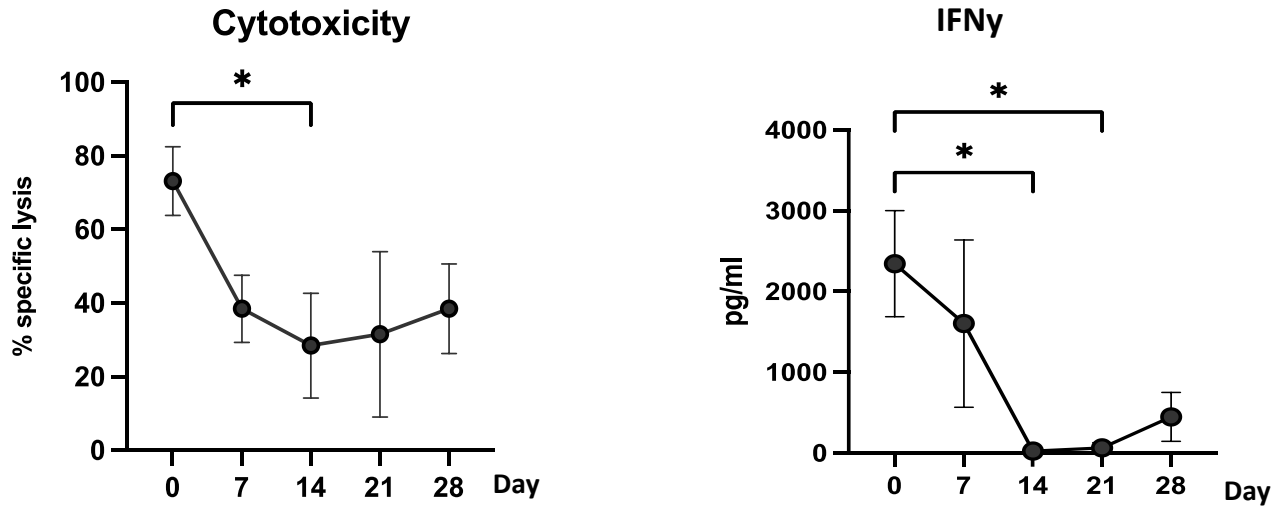


Adapted from Ghilardi G., BJM, 2020

Continous Exposure to bispecific T-cell engagers Induces T-cell Exhaustion



Immunmonitoring of ALL pt on Blin Tx (CD19 x CD3 BiTE)

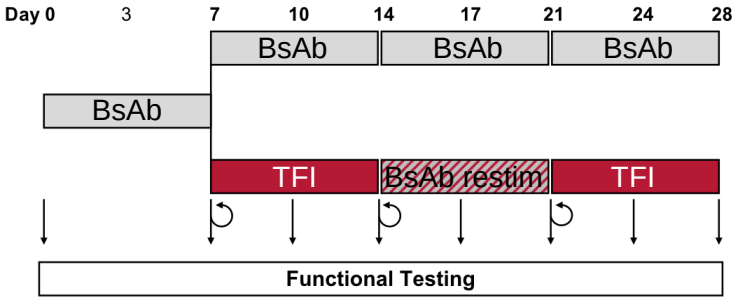


Philipp et al, Blood 2022

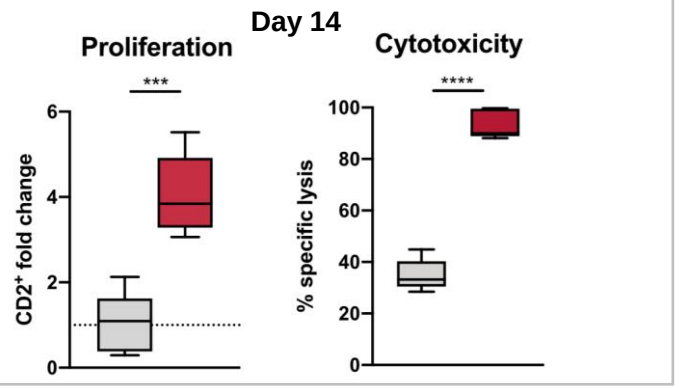
Continous Exposure to a T-cell engager leads to T-cell exhaustion – Treatment-Free Intervals counteract evolving T-cell dysfunction

Nora Philipp

Experimental Set-Up

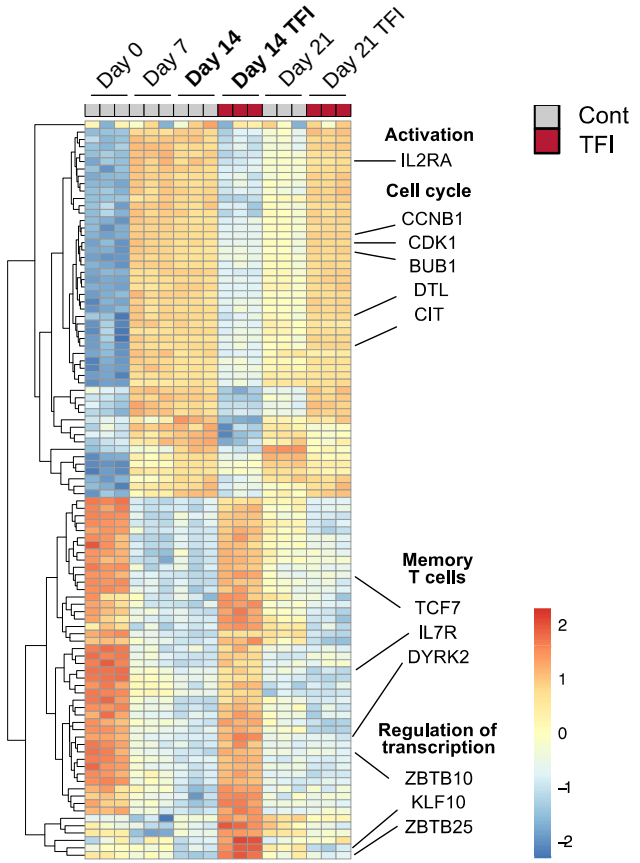


Proliferation & Cytotoxicity



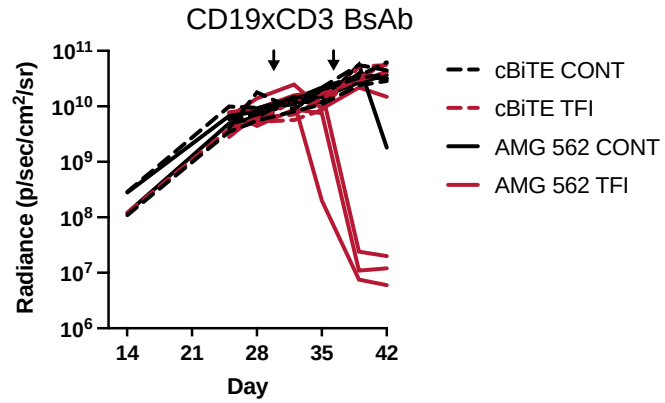
2-way ANOVA and Sidak´s multiple comparison test; n=3-9

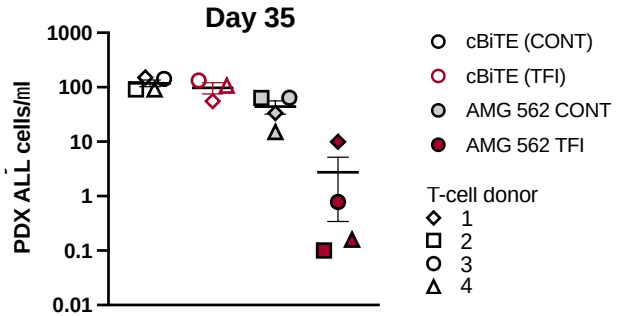
Differentially Expressed Genes



padj<.05, Log2foldchange >1 or <-1

in vivo Tumor Burden



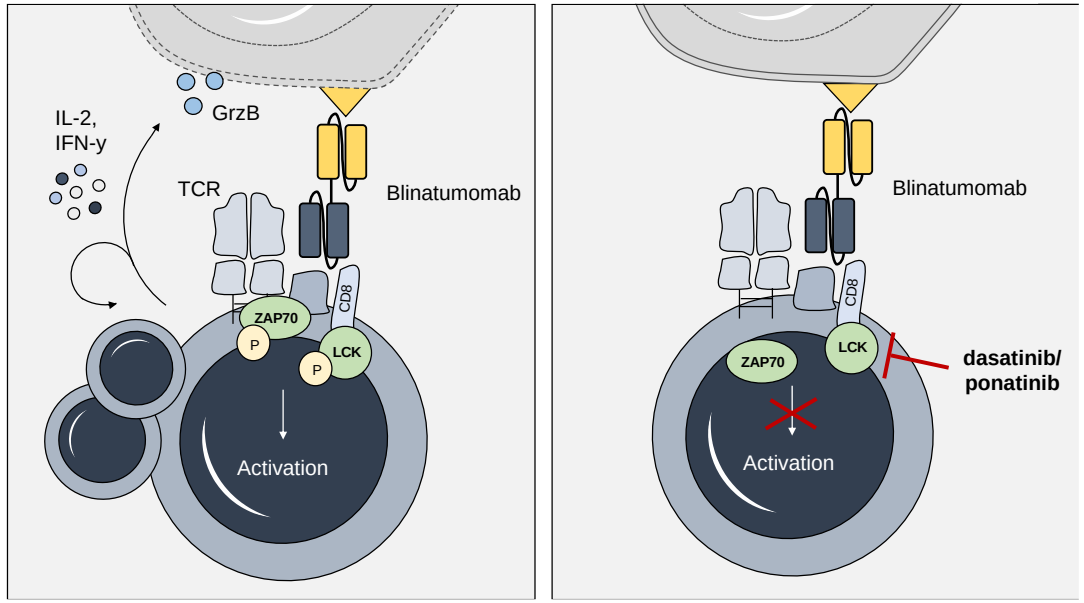


Continuous BsAb TFI BsAb re-exposure after TFI

Philipp et al. 2022 *Blood*

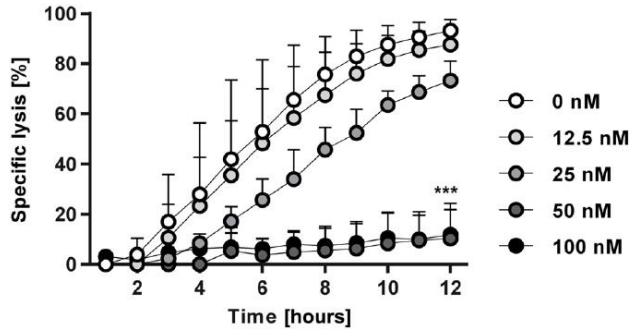
Dasatinib inhibits T-cell Effector Function, but appears to ameliorate Exhaustion

Mode of Action



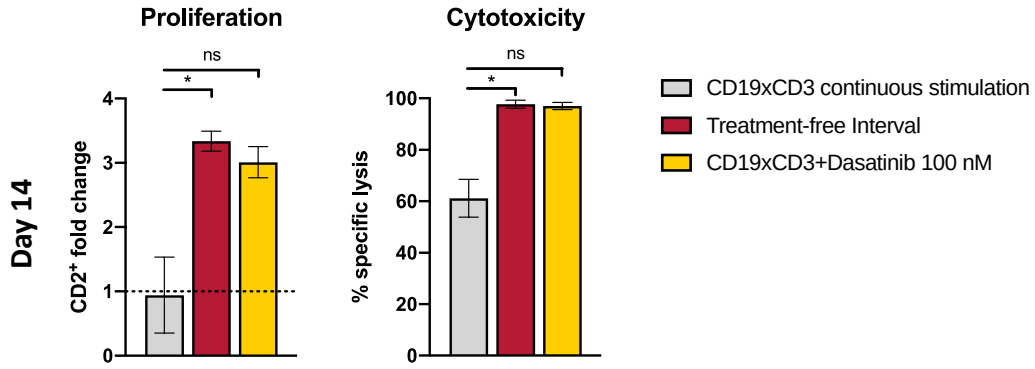
Adapted from Seggewiss, Price & Purbhoo, 2008, Cytotherapy

Dasatinib Inhibits CAR T-cell Function



Mestermann et al. 2019, Sci Transl Med

Rest by Dasatinib Ameliorates T-Cell Exhaustion

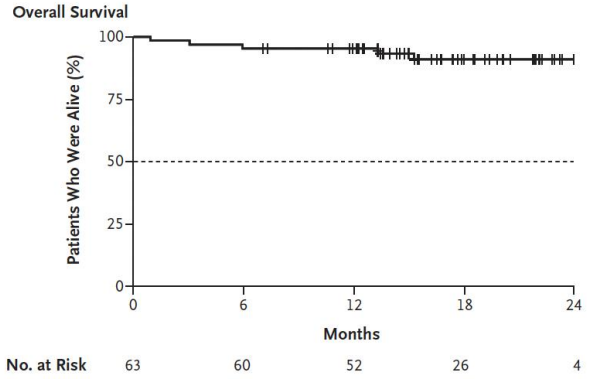


Philipp et al. 2022, Blood

Blinatumomab plus TKI in Ph$^+$ BCP-ALL Patients with excellent results

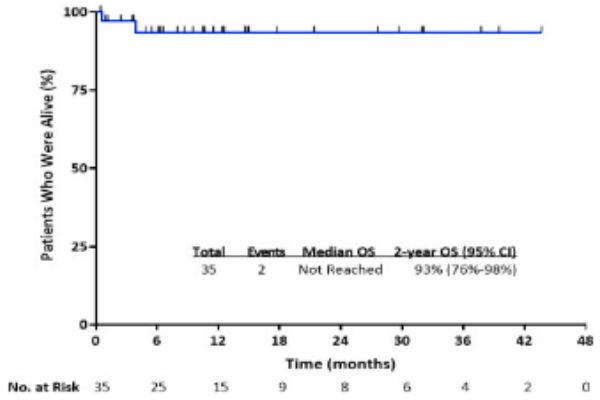
Blinatumomab + Dasatinib or Ponatinib

Blinatumomab + dasatinib



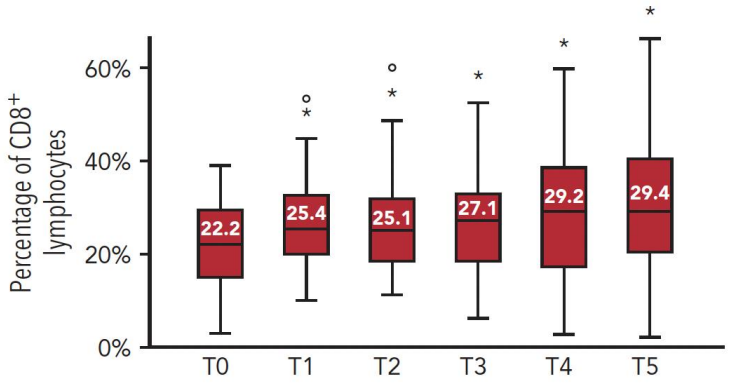
Foà et al. 2020, NEJM

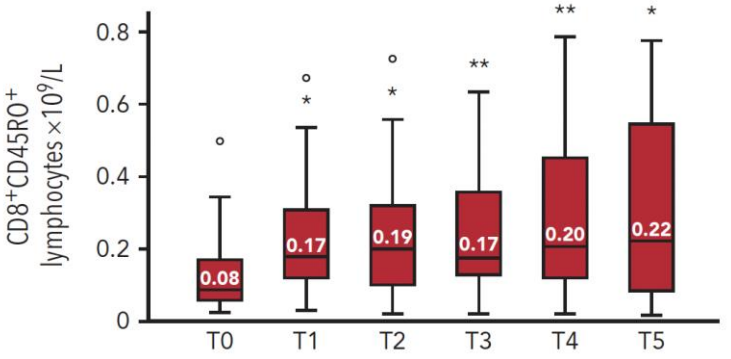
Blinatumomab + ponatinib



Jabbour et al. 2023, Lancet Hematol

CD8$^+$ Expansion during blina + dasatinib





Puzzolo et al. 2021, Blood

Agenda

1

BiTE in ALL

Blinatumomab: R/R → MRD → Frontline | TOWER · BLAST · E1910 | Combinatorial approaches ? with TKI ?

2

CAR-T in ALL

Pediatric & Adult | ELIANA · ZUMA-3 · FELIX | Consolidation with allogeneic Stem Cell Transplantation ?

3

T-cell Engagers in AML

CD33 BiTE · WT1 TCE | How to reduce toxicity and improve efficacy ? Multiple targeting ? Combi with VEN/AZA ?

4

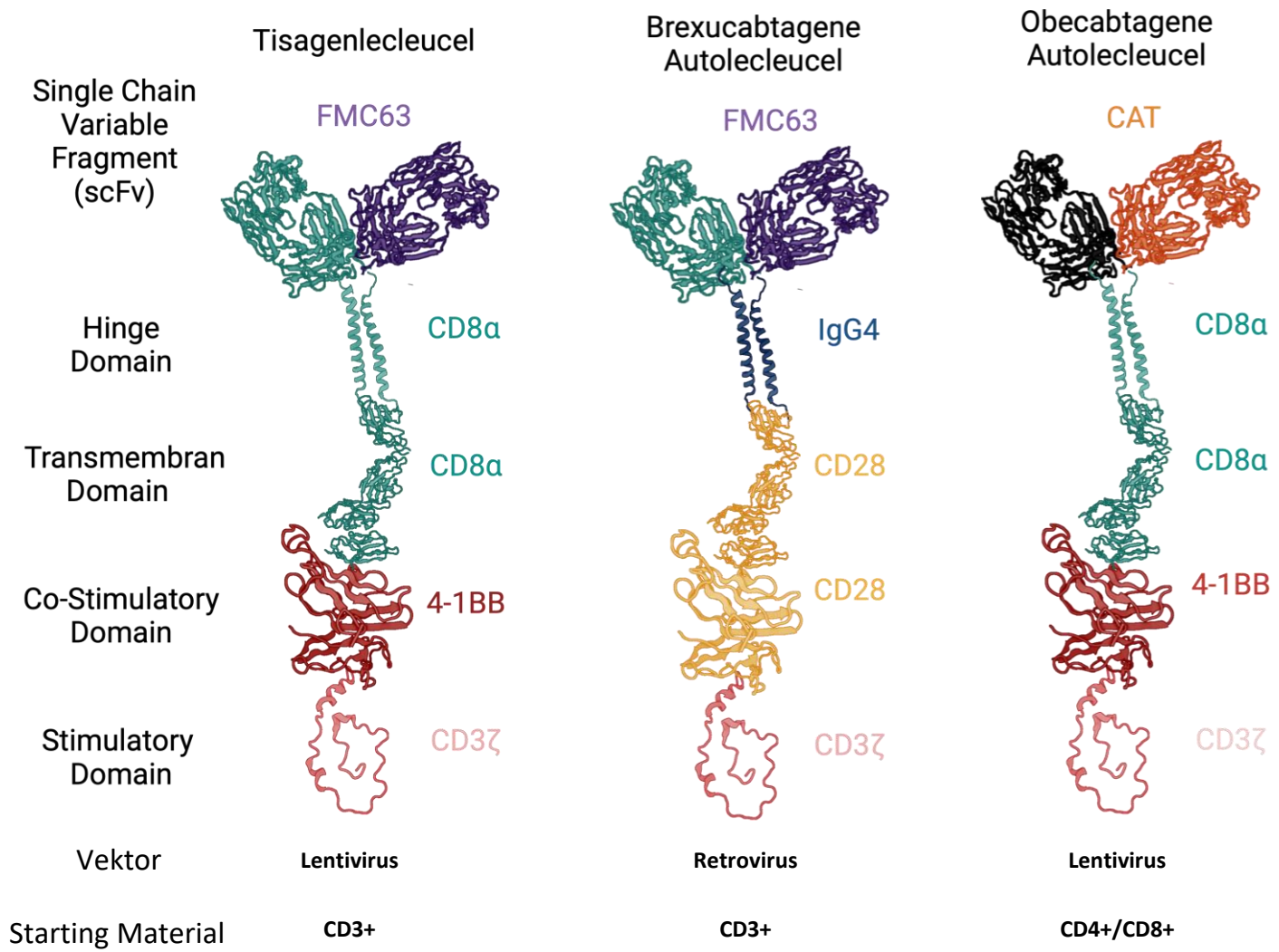
CAR-T in AML

Targets · 2nd Generation CART | How to reduce toxicity and improve efficacy ? IL-18 ? Menin ? Edited SCTx ?

Tisa-Cel vs Brexu-Cel vs Obe-Cel

Differences in

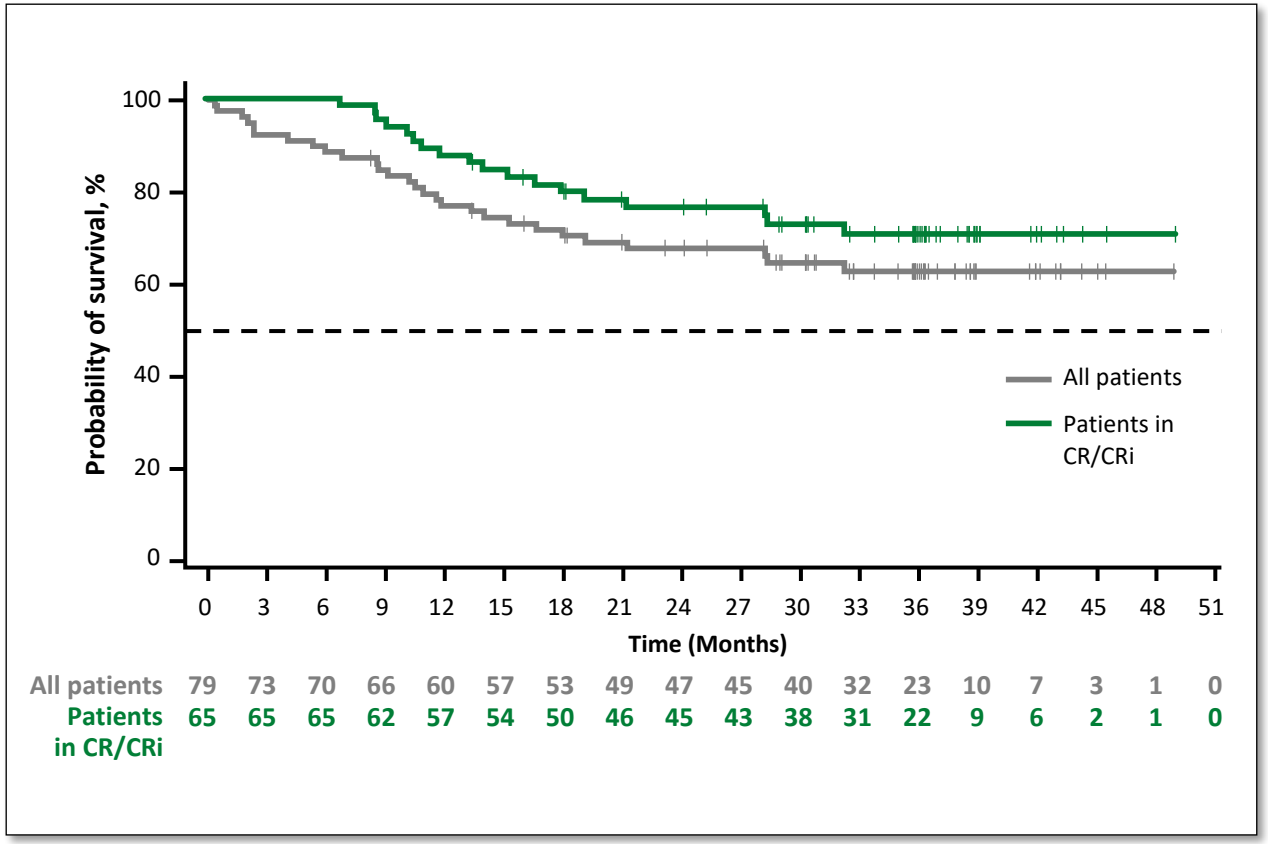
- Target Binding domain
- Hinge domain
- Transmembrane domain
- Costimulatory domain
- Vector type
- Lymphodepletion dose



Slide by M. Subklewe

ELIANA Trial in R/R BCP-ALL between age 3 to 26 years old: 3 year RFS of 52%

CR: 82%, 6 month EFS and OS: 73% and 90%, **36 months EFS** and OS: **44%** and 63%, censoring for allo HSCT

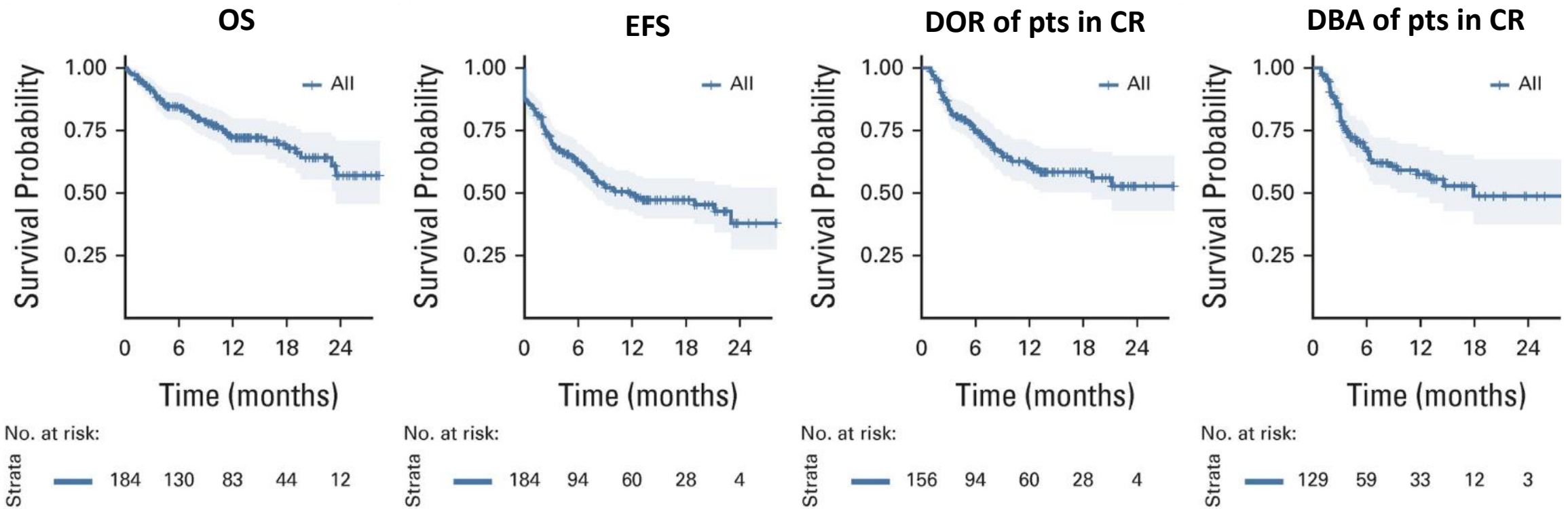


Survival Probability, % (95% CI)	All Patients (N = 79)	Patients in CR/CRi as BOR (n = 65)
Month 12	77.1 (66.1-84.9)	87.7 (76.9-93.6)
Month 24	67.7 (56.0-76.9)	76.5 (64.0-85.1)
Month 36	62.8 (50.7-72.7)	70.6 (57.3-80.5)
Month 48	**62.8 (50.7-72.7)**	**70.6 (57.3-80.5)**

Maude et al, NEJM 2018

USA Real World Data confirm ELIANA trial data

CR: 85%, 6 month EFS and OS: 73% and 90%



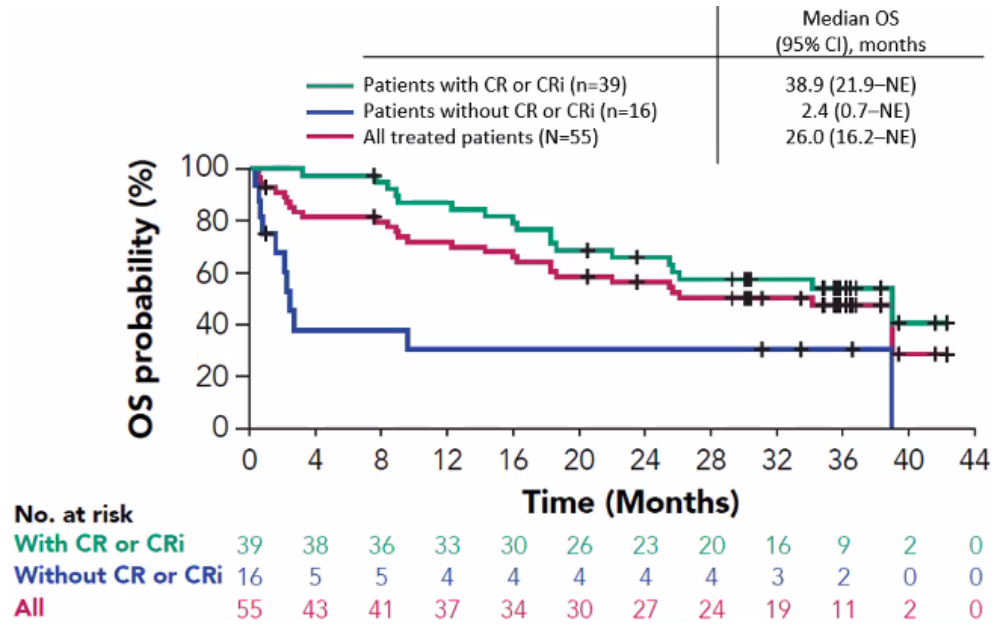
Outcome	6-Month OS	1-Year OS	6-Month EFS	1-Year EFS	6-Month DOR	1-Year DOR	6-Month DBA	1-Year DBA
All patients	0.85	0.72	0.62	0.5	0.75	0.62	0.68	0.57

Schultz et al, JCO 2022

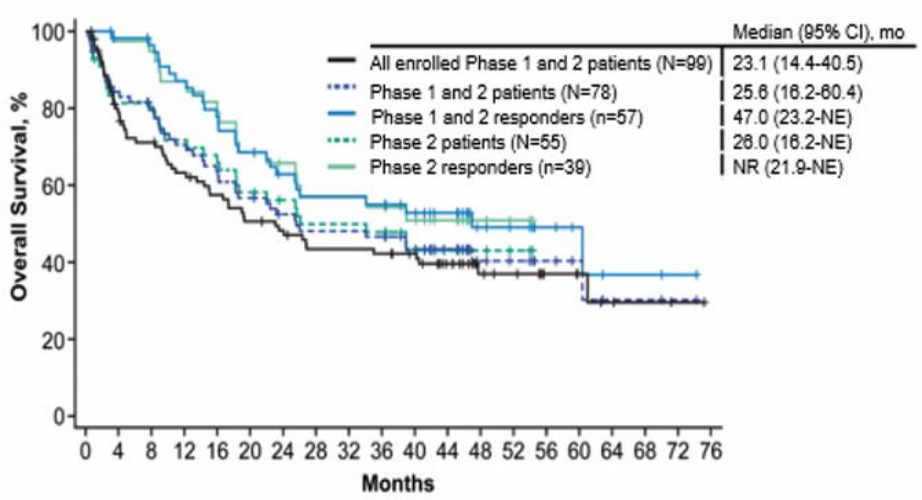
ZUMA-3 trial in R/R ALL: Overall Survival after 3 & 4 years was 47% & 40%

CR/CRi: 71%, Median PFS and OS: 11.6 and 18.2 months; Median duration of response: 14.6 months

OS[a] in Phase 2 Treated Patients



Median FU: 53.6mo, 4y OS 40%

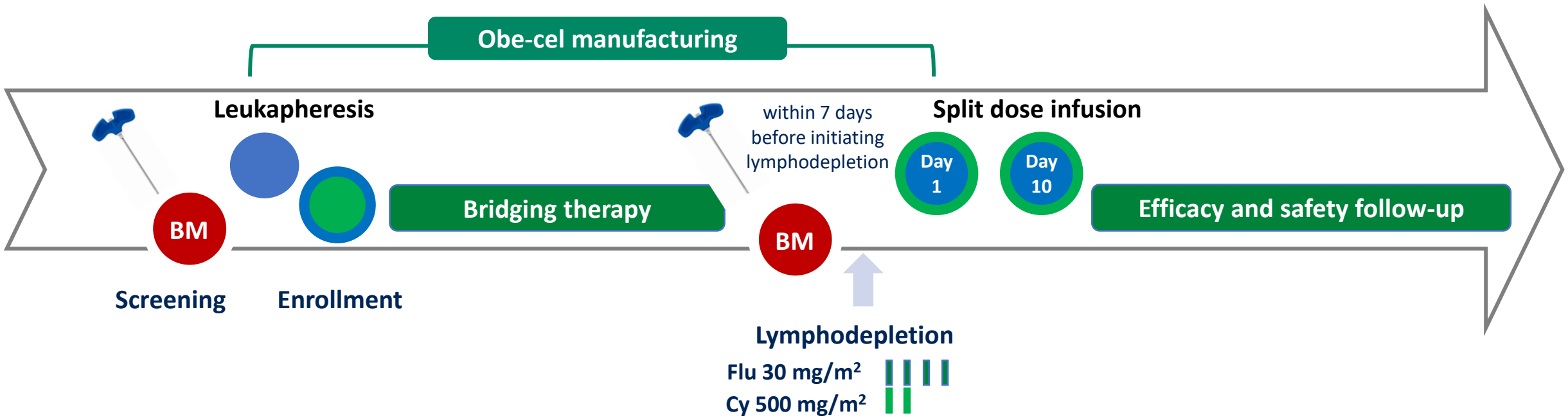


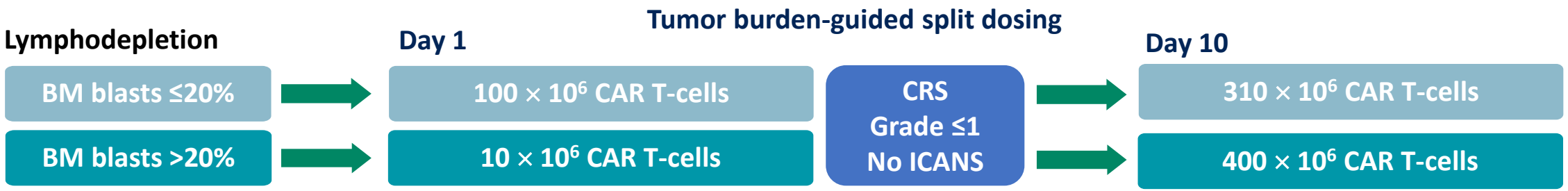
- **The median OS (95% CI) was 26.0 months** (16.2-NE) in all treated Phase 2 patients and was 38.9 months (21.9-NE) among Phase 2 patients with CR or CRi (n=39)
- The OS rate at 36.0 months was 47.1% (95% CI, 32.7-60.2) in Phase 2
- 11% EM disease: 6 month PFS and OS was 50%

Data cutoff date: 23 July 2022; median follow-up: 38.8 months (range, 32.7-44.6). "Median follow up for OS (calculated via reverse KM approach) was 35.6 months (95% CI, 31.0-36.4) for Phase 2 patients

Hadjivassileva T, et al. Presented at EBMT-EHA CAR T-Cell Meeting 2023; abstract 34
Oluwole et al., Presented at ASCO 2024; Abstract #6531,

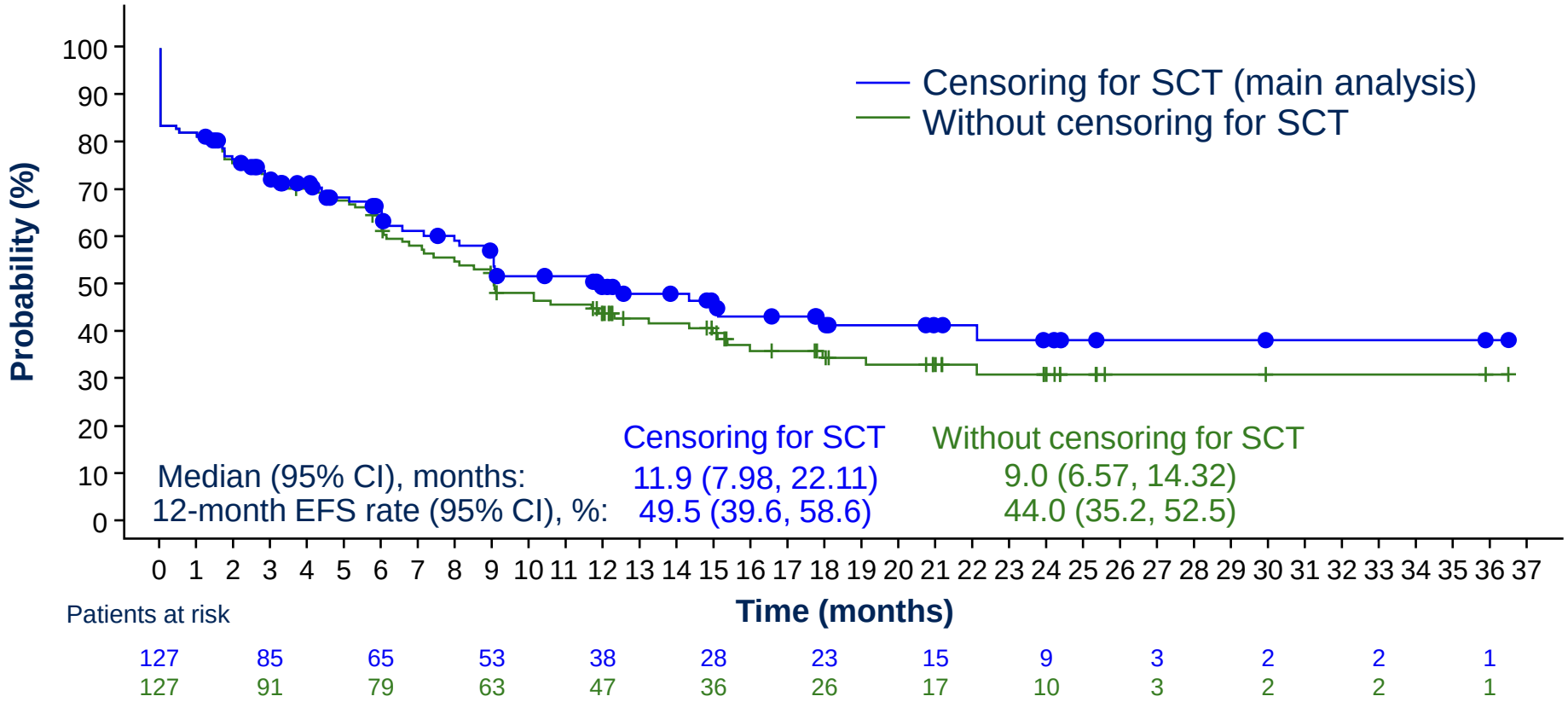
FELIX Trial in R/R B-ALL: Obe-cel used in a Tumor burden—guided split dosing





Roddie et al, NEJM 2024

Felix Trial: Event-free survival



Roddie et al, NEJM 2024

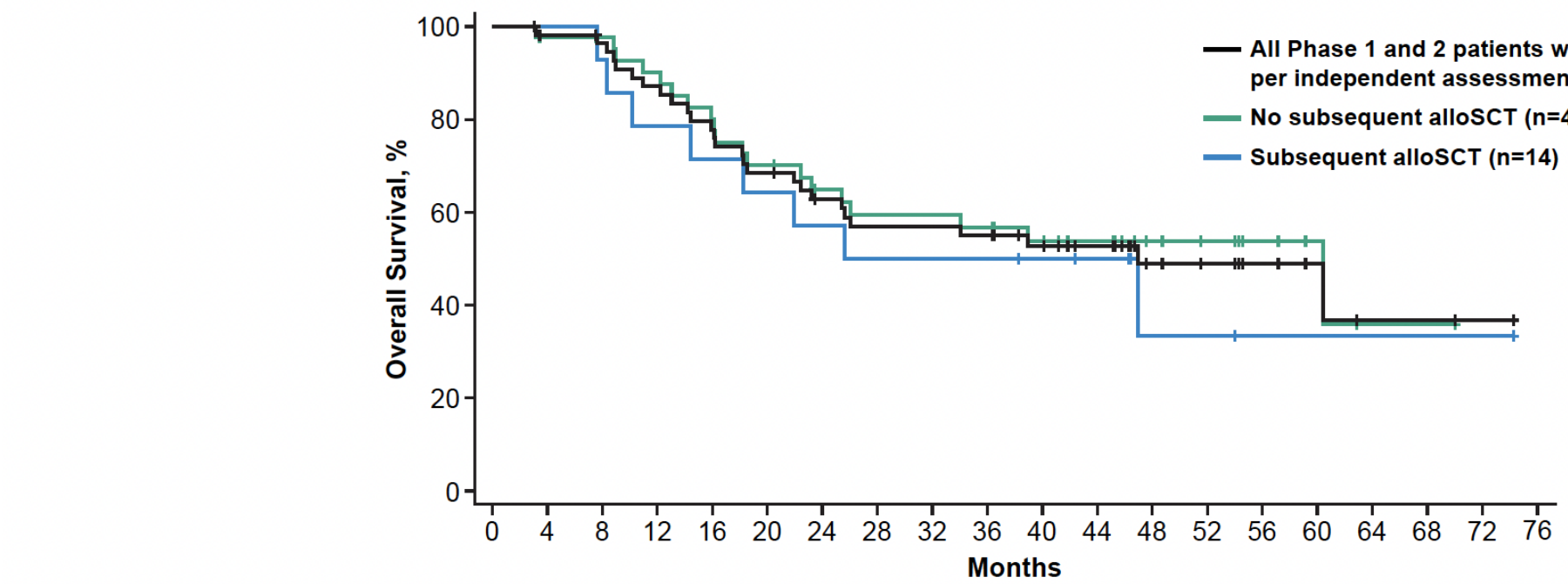
40 – 60% of patients will relapse in the 1st year post CART – how to define high risk and identify patients that might benefit from further consolidation with SCTx / or maintenance ?

High Risk Profile – cave differences between ped vs adult and CART products

1. **P53 mutation**
2. **High Tumor Volume (> 5% blasts in the BM pre-LD), EM disease**
3. **Loss of CART cell persistence* –** cave CART product dependent 4-1BBz > CD28z
4. **Loss of B cell aplasia in the first 6 months**,** cave CART product dependent 4-1BBz > CD28z
5. **MRD positivity** by MPFC or qPCR or NGS of PB or BM***, „*the deeper the longer the interval*"

In the ZUMA-3 trial CART cells did not persist beyond 24 months; ** Definition of B cell aplasia (BCA): no universal BCA definition, different thresholds; cave – risk of CD19-relapse is not predicted by BCA; *** Sensitivity varies between PB and BM, Flow or qPCR sensitivity between 1/10.000 to 1/100.000 by ClonoSEQ the sensitivity goes done to 1/1.000.000 events, cave: number of cells you put in determins sensitivity independent of method used

ZUMA 3: OS according to HSCT vs none: no difference

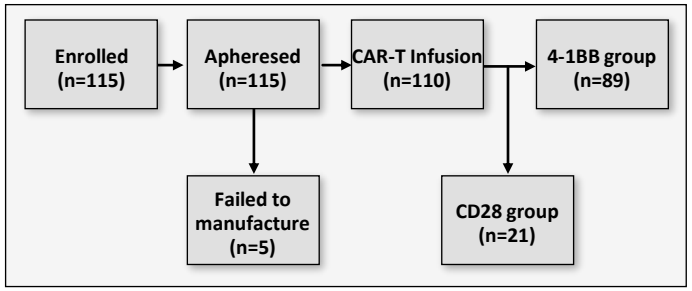


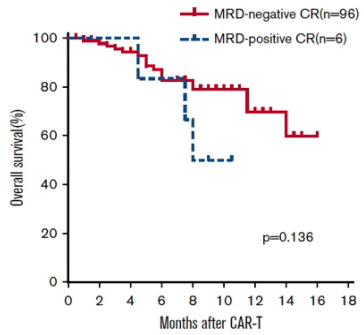
Oluwole O, et al. ASCO 2024 (Abstract 6531; poster)

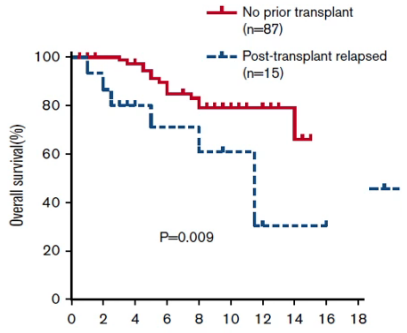
CD19 CART in ped+adult r/r ALL: High-Risk: > 20% BM blasts, TP53 mutation, CART only

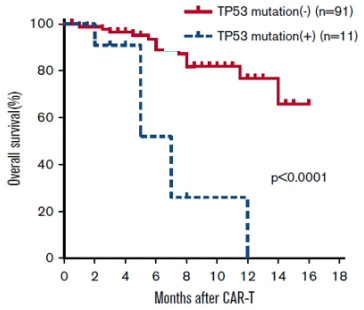
N=115
Age 2-75y
Follow up 233d
CR 86%
1y-OS 64%

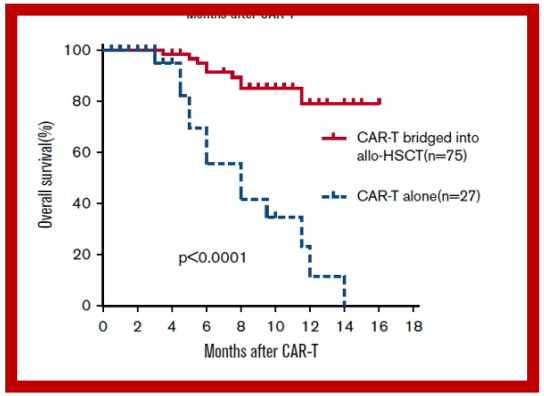
13% relapse in post CAR-T post allo
48% relapse in post CAR-T w/o allo











Multivariable analysis of OS and LFS for subgroups

Subgroup	HR	95% CI	P
OS			
CD28 vs 4-1BB	0.609	0.254-1.461	.267
With vs without EMD	0.455	0.196-1.056	.067
No previous transplant vs posttransplant relapse	2.184	0.830-5.744	.113
BM blasts ≤ 20% vs > 20%	2.968	1.270-6.901	.012
TP53^{+} mutation vs TP53^{-} mutation	**0.189**	**0.073-0.488**	**.001**
CAR T-cell bridged into allo-HSCT vs CAR T-cell therapy alone	12.250	4.774-31.438	<.001

Age without influence – BCR/ABL pos vs neg without influence

Zhang et al, Blood Advances 2020; 21 pts with CD28 costim, the rest with 4-1BB costim, age 2 to 75 years

Roadmap

1

BiTE in ALL

Blinatumomab: R/R → MRD → Frontline | TOWER · BLAST · E1910 | Combinatorial approaches ? with TKI ?

2

CAR-T in ALL

Pediatric & Adult | ELIANA · ZUMA-3 · FELIX | Consolidation with allogeneic Stem Cell Transplantation ?

3

T-cell Engagers in AML

Targets · CD33 BiTE · WT1 TCE | How to reduce toxicity and improve efficacy ? Multiple targeting ? Combi with VEN/AZA ?

4

CAR-T in AML

2nd Generation CART | How to reduce toxicity and improve efficacy ? IL-18 ? Menin ? Edited SCTx ?

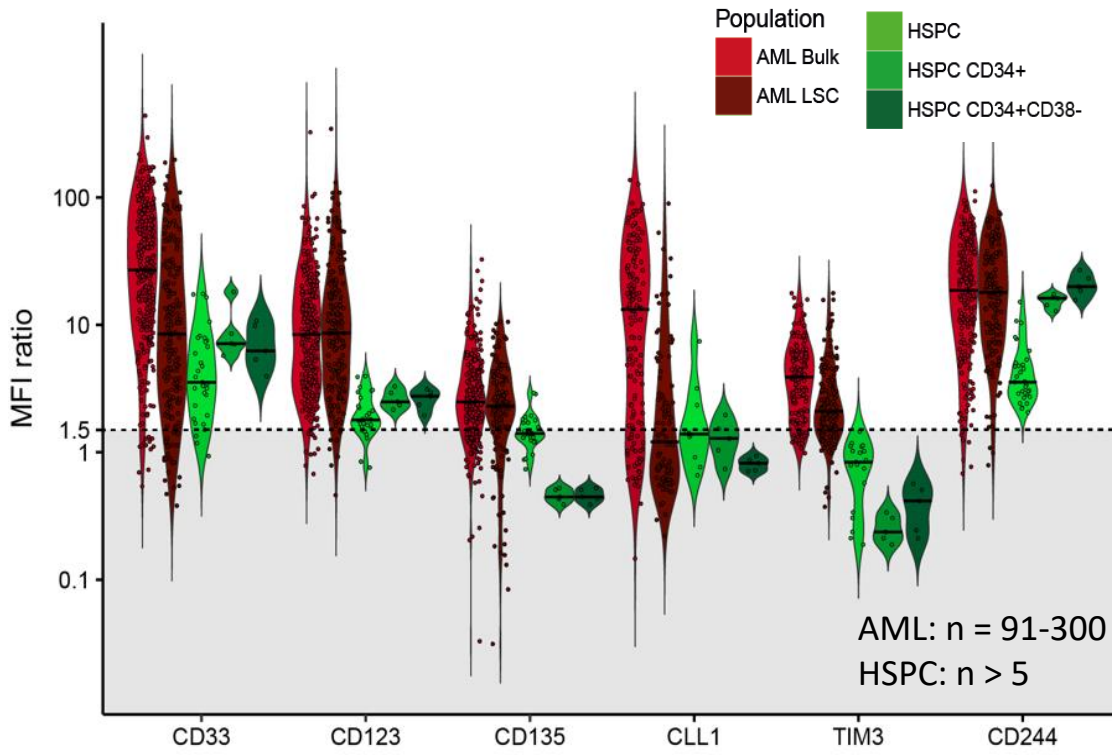
Challenge for TCE & CART in AML: Choice of Target Antigen

An ideal Target Antigen is expressed on most AML cells + LSCs, critical for AML biology and absent on vital healthy cells

- **Small Therapeutic Window**: On-Target-Off-Leukemia Toxicity; Possible Impact on CRS Occurence
- **Antigen Sink:** Ubiquitous Expression of Internalizing Target Antigens like CD33, CD123, CLL-1
- **Escape Variants:** Heterogeneous expression profile Inter- and Intraindividually
- **T-cell Dysfunction:** Chronic stimulation through continous antigen exposure within the (healthy) myeloid compartment

Daver…Subklewe, Leukemia 2021

Antigen Expression in AML and Normal Hematopoiesis

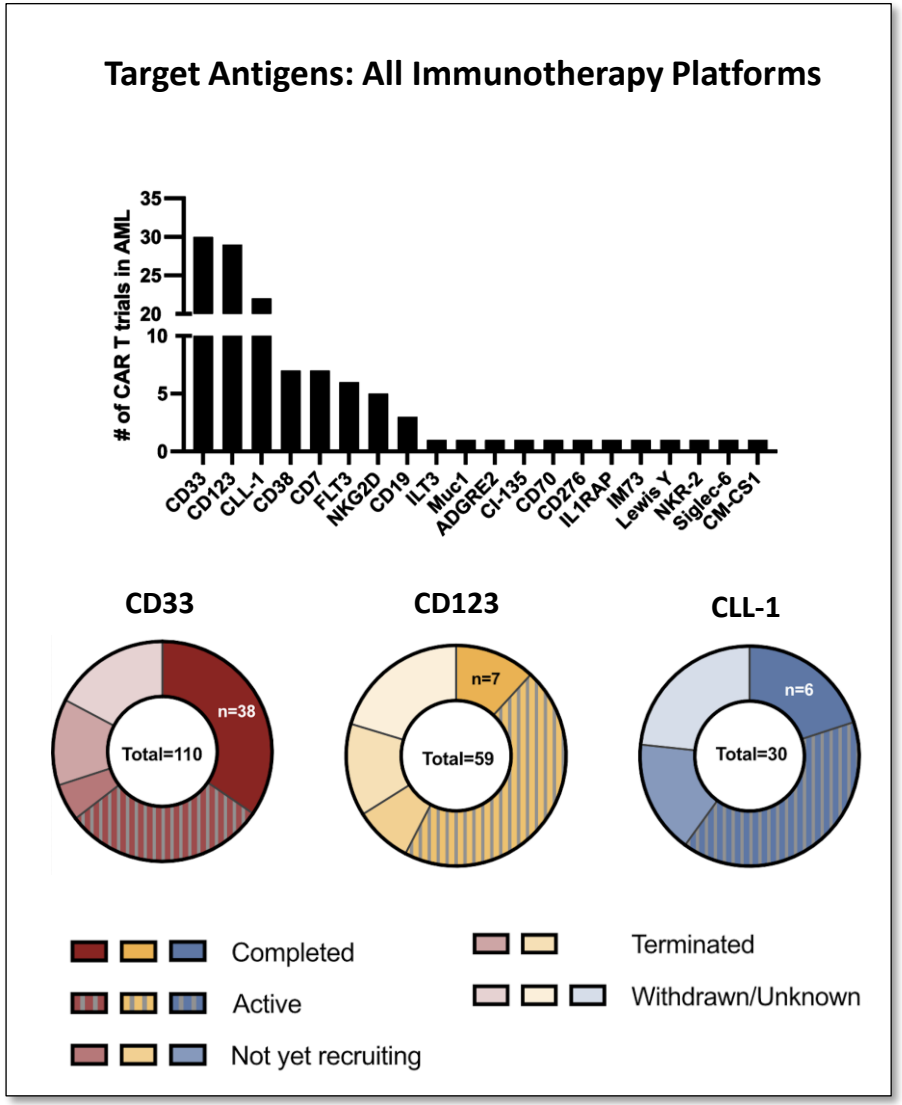


Haubner et al, Subklewe, Leukemia 2019

The Lineage restricted, Myeloid Antigens CD33, CD123, CLL-1 are most commonly targeted

Current target antigens are of myeloid lineage: On-Target-Off-Leukemia Toxicity

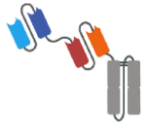
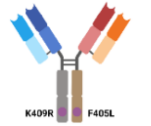
Antigen	Description	bulk %	LSC	Normal tissue expression
CD33 (Siglec-3)	Transmembrane receptor	90	Yes	HSCs; myeloid progenitors, monocytes, mast cells, Kupffer cells, microglial cells in the brain
CD123 (IL-3Rα)	IL-3 receptor-α	50-100	Yes	HSCs; myeloid progenitors, monocytes, basophils, dendritic cells, epithelial cells
CLL1 (CLEC12A)	Transmembrane receptor	77-100	Yes	HSCs, Monocytes, granulocytes, tissue-resident lung macrophages
FLT3 (CD135)	Type III receptor tyrosine kinase	70-100	Yes	HSCs; myeloid progenitors, neurons
ADGRE2	Promotes cell-cell adhesion, granulocyte chemotaxis	> 80	Yes	Monocytes, macrophages, kupffer cells, granulocytes
CD44v6	Transmembrane receptor/splice variant	64	Yes	Monocytes, keratinocytes; different epithelial tissues (respiratory gastrointestinal, genitourinary)
Lewis Y (CD174)	Blood group carbohydrate antigen	50	Likely	HSCs; intestinal epithelial cells
CD45	Pan-Leukocyte Antigen	100, dim	Yes	Myeloid and Lymphoid Cells
FOLR2 (folate receptor-β)	Folate-binding protein receptor	70	Possibly	Myeloid cells, macrophages
IL1RAP	Component of IL-1 R complex	> 80	yes	Hepatocytes, placenta, monocytes, PBMCS
CD7	Transmembrane protein; member of the Ig superfamily	30	Possibly	T cells
NKG2D-L	Activator of NK and T cells:	67 – 100		NK cells, gamma/delta T cells
CD38	Activation marker of T cells	Up to 55%		Myeloid progenitor cells, lymphocytes
CD81	entry coreceptor for HCV	80	Yes	Hepatocytes, stroma and epithelial cells, Immune cells



Adapted from Schorr & Perna, Front Immunol 2022

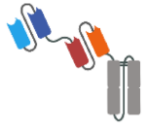
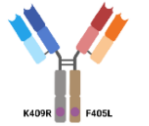
Subklewe et al, ASH Educational 2023

Selected Early Clinical Trials in AML using T-cell engaging bispecific Antibodies

Ab type	CD33			CD123			CD123	CLL-1
	AMG330[1]	AMG 673[2]	AMV-564[3]	Flotetuzumab[4]	JNJ-63709178[5]	Vibecotamab[6]	SAR443579[8-10]	MCLA-117[7]
Structure								
Manufacturer	Amgen	Amgen	Amphivena	Macrogenics	Janssen	Xencor	Innate/Sanofi	Merus
Phase	1	1	1	1, RP2D	1	1/2	I/II	1
N	55	30	36	88	62	106	I/II	58
Histology	r/r AML, MRD$^+$ AML	r/r AML	r/r AML	r/r AML	r/r AML	r/r AML, B-ALL, CML	43	r/r AML, ND elderly
Prior Therapies	≥1	≥4	≥1	≥2	1-10	1-8	r/rAML, B-ALL and MDS	0-≥4
CRS (grade ≥3)	67% (13%)	50% (13%)	n.a. (0%)	50% (7%)	44% (15%)	58% (15%)	1 – 10	36% (9%)

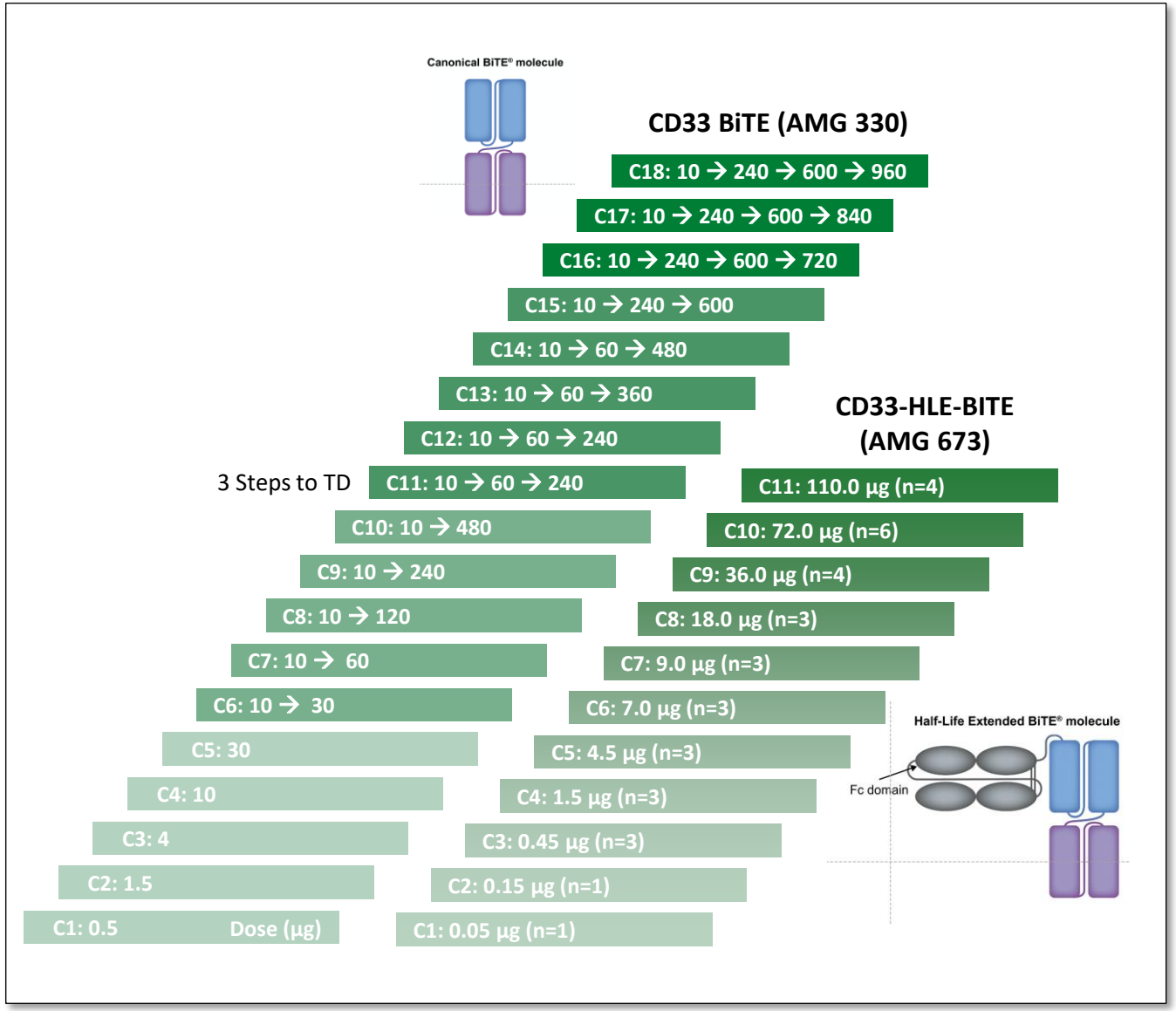
1. Ravandi F, et al. ASCO 2020. Abstract #7508. 2. Subklewe M, et al. ASH 2019. Abstract #833. 3. Westervelt P, et al. ASH 2019. Abstract #834. 4. Uy GL, et al. Blood 2021. 5. Boyiadzis M, et al. Clin Transl Sci. 2023
6. Ravandi F, et al. ASH 2020. Abstract #460. 7. Mascarenhas J, et al. EHA 2020. Abstract #538; 8. Labrijn et al, Nature Reviews Drug Discovery 2019; 9. Stein et al, ASH 2022; 10. Bajel et al, ASH 2023 #3474

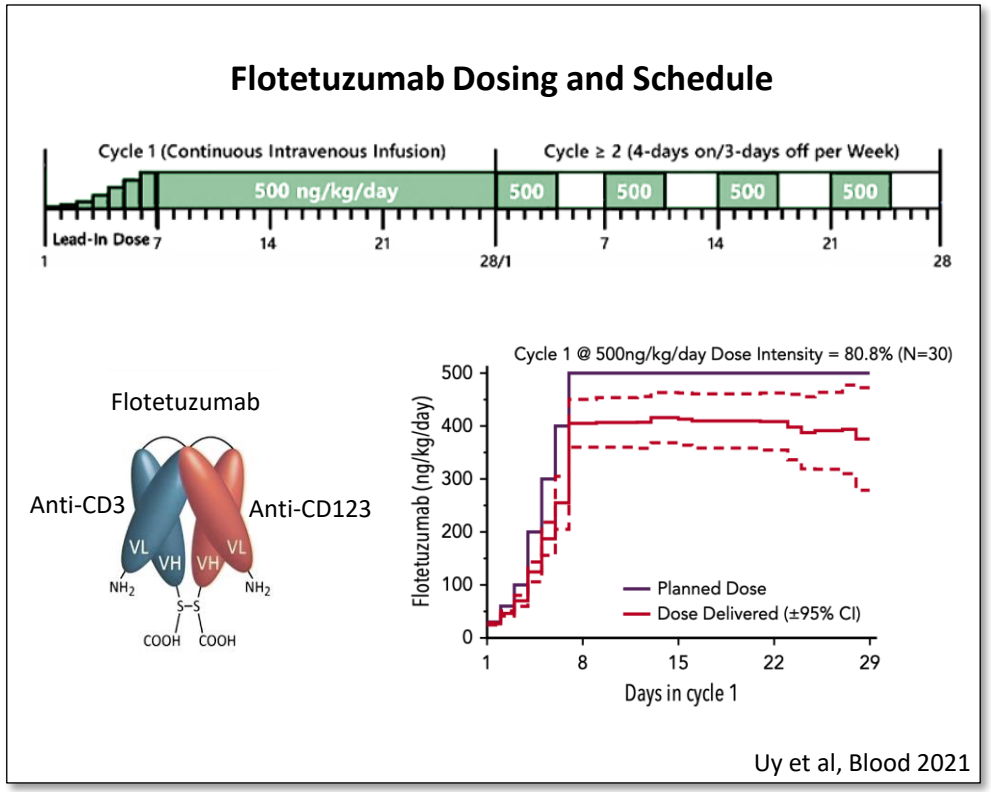
Selected Early Clinical Trials in AML using T-cell engaging bispecific Antibodies

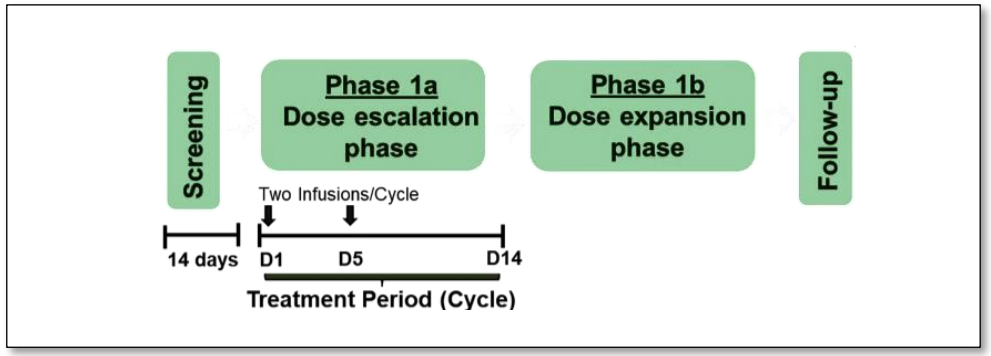
Ab type	CD33			CD123			CD123	CLL-1
	AMG330[1]	AMG 673[2]	AMV-564[3]	Flotetuzumab[4]	JNJ-63709178[5]	Vibecotamab[6]	SAR443579[8-10]	MCLA-117[7]
Structure								
Manufacturer	Amgen	Amgen	Amphivena	Macrogenics	Janssen	Xencor	Innate/Sanofi	Merus
Phase	1	1	1	1, RP2D	1	1/2	I/II	1
N	55	30	36	88	62	106	I/II	58
Histology	r/r AML, MRD$^+$ AML	r/r AML	r/r AML	r/r AML	r/r AML	r/r AML, B-ALL, CML	43	r/r AML, ND elderly
Prior Therapies	≥1	≥4	≥1	≥2	1-10	1-8	r/rAML, B-ALL and MDS	0-≥4
CRS (grade ≥3)	67% (13%)	50% (13%)	n.a. (0%)	50% (7%)	44% (15%)	58% (15%)	1 – 10	36% (9%)

1. Ravandi F, et al. ASCO 2020. Abstract #7508. 2. Subklewe M, et al. ASH 2019. Abstract #833. 3. Westervelt P, et al. ASH 2019. Abstract #834. 4. Uy GL, et al. Blood 2021. 5. Boyiadzis M, et al. Clin Transl Sci. 2023
6. Ravandi F, et al. ASH 2020. Abstract #460. 7. Mascarenhas J, et al. EHA 2020. Abstract #538; 8. Labrijn et al, Nature Reviews Drug Discovery 2019; 9. Stein et al, ASH 2022; 10. Bajel et al, ASH 2023 #3474

Step up Dosing needed to mitigate CRS & multiple Steps required to achieve active dose

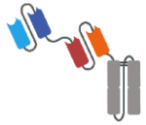
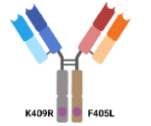






Ravandi et al, ASCO 2020, Subklewe et al ASH 2019

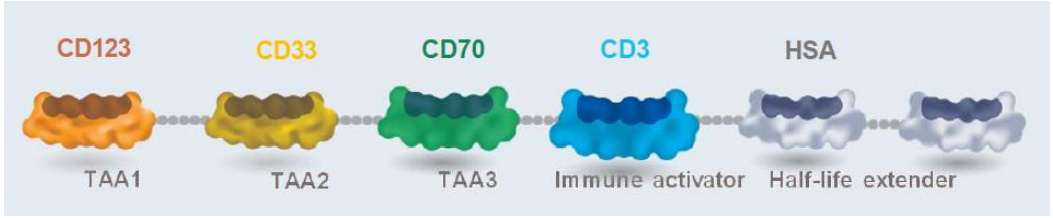
Early Trials showed safety, but low response rates in pts with > 3 prior Tx Lines

Ab type	CD33			CD123			CD123	CLL-1
	AMG330[1]	AMG 673[2]	AMV-564[3]	Flotetuzumab[4]	JNJ-63709178[5]	Vibecotamab[6]	SAR443579[8-10]	MCLA-117[7]
Structure								
Manufacturer	Amgen	Amgen	Amphivena	Macrogenics	Janssen	Xencor	Innate/Sanofi	Merus
Phase	1	1	1	1, RP2D	1	1/2	I/II	1
N	55	30	36	88	62	106	I/II	58
Histology	r/r AML, MRD$^+$ AML	r/r AML	r/r AML	r/r AML	r/r AML	r/r AML, B-ALL, CML	43	r/r AML, ND elderly
Prior Therapies	≥1	≥4	≥1	≥2	1-10	1-8	r/rAML, B-ALL and MDS	0-≥4
CRS (grade ≥3)	67% (13%)	50% (13%)	n.a. (0%)	50% (7%)	44% (15%)	58% (15%)	1 – 10	36% (9%)
ORR	**19%**	**44% (12/27)**	**49%**	**30%**	**n.a.**	**>0.75 µg/kg 14% (7/51)**	5% (0 %)	**n.a.**
CR/CR$_i$	**17% (7/42)**	**4% (1/27)**	**6% (2/35)**	**27% (8/30)**	**0%**	**10% (5/51)**	**12 %**	**0%**

1. Ravandi F, et al. ASCO 2020. Abstract #7508. 2. Subklewe M, et al. ASH 2019. Abstract #833. 3. Westervelt P, et al. ASH 2019. Abstract #834. 4. Uy GL, et al. Blood 2021. 5. Boyiadzis M, et al. Clin Transl Sci. 2023
6. Ravandi F, et al. ASH 2020. Abstract #460. 7. Mascarenhas J, et al. EHA 2020. Abstract #538; 8. Labrijn et al, Nature Reviews Drug Discovery 2019; 9. Stein et al, ASH 2022; 10. Bajel et al, ASH 2023 #3474

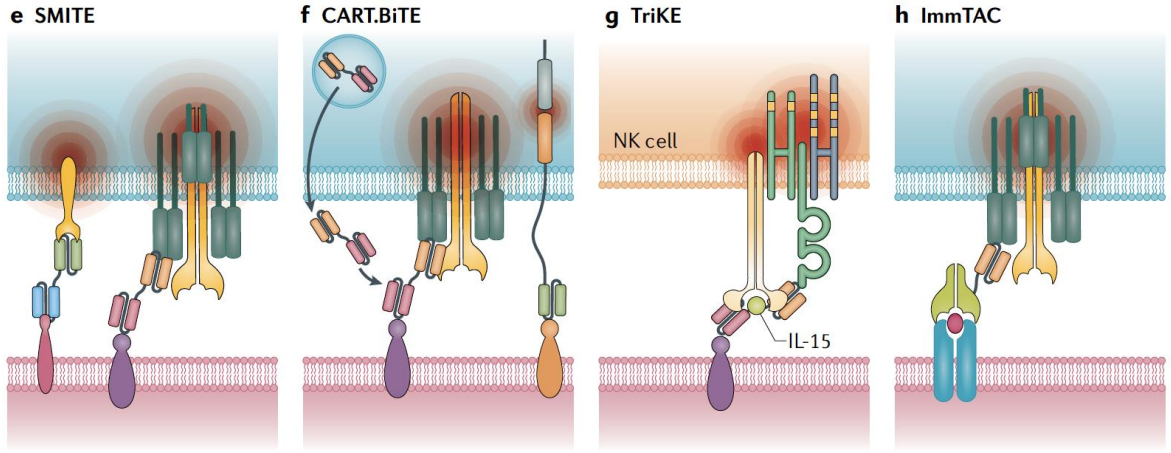
Overcome Resistance to T-cell engaging bispecific Antibodies: Novel Constructs

Multi-targeting



Pabst et al, ASH 2023 #2921 (triple targeting CD123, CD33, CD70);
Zeng et al, ASH 2023 #1418 (dual targeting CD33/CD123 nanobody)

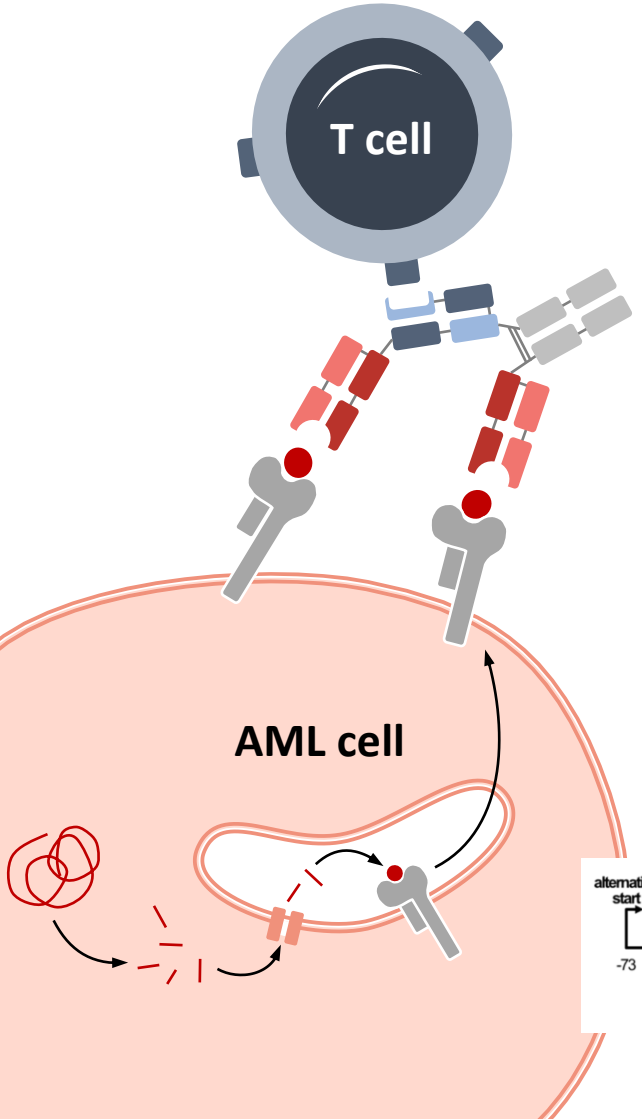
Intracellular Targets

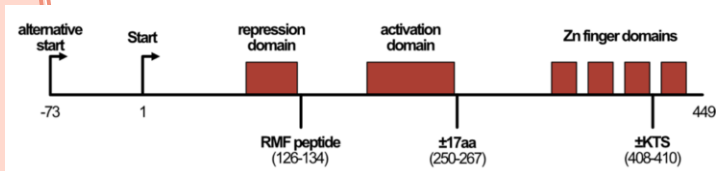


Goebeler et al, Nature Reviews Clinical Oncology 2020; Hsiue et al. "Targeting p53", Science 2021;
Dougless et al., "Targeting RAS", Science Immunology 2021;
Augsberger et al, Blood 2021 "Targeting WT1", Dao et al, Blood 2023

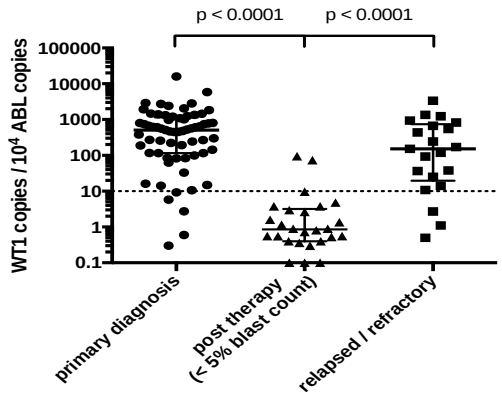
ASH 2023: Shi et al, #1415 (Tcrm-bispecific against a leader peptide of Cathepsin G);
Hutchings et al, #1537 (WT1/HLA-A2 bispecific)

Initiation of a Phase I Trial in HLA-A2$^+$ Patients with r/r AML & MRD$^+$ (> 0.1%)

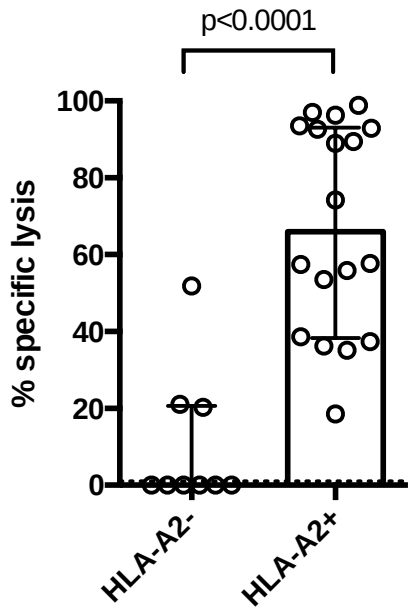




WT1 Expression

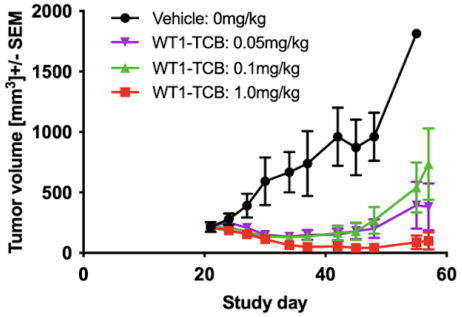


Specific lysis of primary AML cells

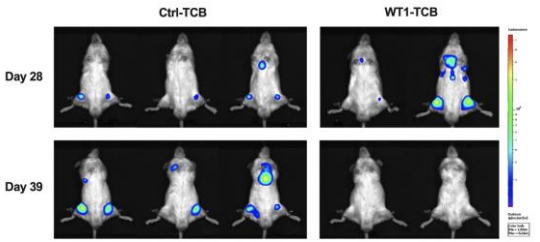


Anti-tumor Efficacy of WT1-TCB in a humanized mouse model

Tumor growth



Tumor Growth in AML PDX mice



Currently recruiting into a Phase I clinical Trial in r/r AML and also MRD$^+$ AML

Augsberger, Hänel et al, Subklewe, Blood 2021

Dose Escalation of HLA-A2-WT1 CD3 TCE in a phase I Trial in R/R AML

Table 1: Patient characteristics

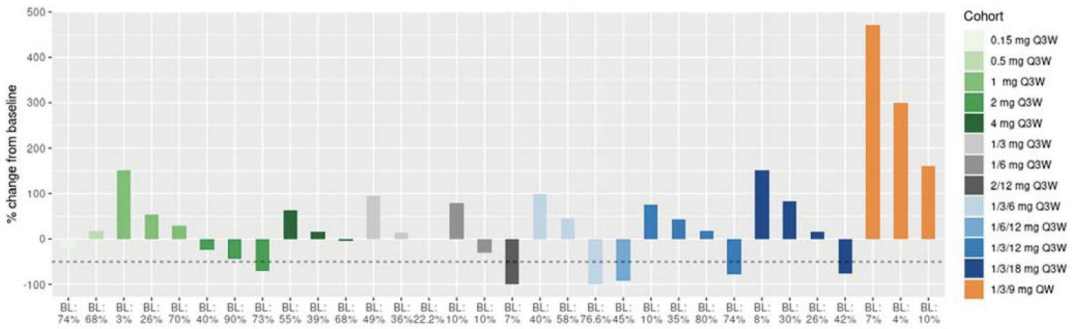
N (%) unless stated	N=50
Median age, years (range)	65 (35–84)
Male	29 (58)
ECOG PS score	
0	28 (56)
1	19 (38)
2	3 (6)
AML disease status at study entry	
Relapsed	21 (42)
Recurrent	29 (58)
ELN 2017 risk category	
Favorable	4 (8)
Intermediate	19 (38)
Adverse	24 (48)
Missing	3 (6)

N (%) unless stated	N=50
Prior lines of therapy	
1	6 (12)
2	23 (46)
>2	19 (38)
Missing	2 (4)
Bone Marrow Balst Count	
<30%	20 (40)
≥30% to <50%	13 (26)
≥50%	16 (32)
Missing	1 (2)
Genetic abnormalities (n=47)	10 (21)
RUNX1	8 (17)
ASXL1	5 (11)
TP53	3 (6)
FLT3-ITD	3 (6)
NPM1	

Table 2: Most common adverse events

	Fixed dose (n=13)	Single step-up (n=8)	Double step-up (n=29)	All patients (n=50)
All AEs (n,%)				
Cytokine release syndrome	8 (62)	6 (75)	20 (69)	**34 (68)**
Pneumonia	5 (39)	3 (38)	6 (21)	**14 (28)**
Febrile neutropenia	5 (39)	3 (38)	5 (17)	**13 (26)**
Pyrexia	3 (23)	1 (13)	9 (31)	**13 (26)**
Hyperglycaemia	2 (15)	2 (25)	8 (28)	**12 (24)**
Hypokalemia	0	1 (13)	10 (34)	**11 (22)**
Nausea	3 (23)	1 (13)	6 (21)	**10 (20)**
Related AEs				
Cytokine release syndrome	8 (62)	6 (75)	20 (69)	**34 (68)**

Max Blast Reduction from Baseline



Hutchings et al, Subklewe, Blood Neoplasia 2025

Dose Escalation of HLA-A2-WT1 CD3 TCE in a phase I Trial in R/R AML

Table 1: Patient characteristics

N (%) unless stated	N=50
Median age, years (range)	65 (35–84)
Male	29 (58)
ECOG PS score	
0	28 (56)
1	19 (38)
2	3 (6)
AML disease status at study entry	
Relapsed	21 (42)
Recurrent	29 (58)
ELN 2017 risk category	
Favorable	4 (8)
Intermediate	19 (38)
Adverse	24 (48)
Missing	3 (6)

N (%) unless stated	N=50
Prior lines of therapy	
1	6 (12)
2	23 (46)
>2	19 (38)
Missing	2 (4)
Bone Marrow Balst Count	
<30%	20 (40)
≥30% to <50%	13 (26)
≥50%	16 (32)
Missing	1 (2)
Genetic abnormalities (n=47)	10 (21)
RUNX1	8 (17)
ASXL1	5 (11)
TP53	3 (6)
FLT3-ITD	3 (6)
NPM1	

Table 2: Most common adverse events

	Fixed dose (n=13)	Single step-up (n=8)	Double step-up (n=29)	All patients (n=50)
All AEs (n,%)				
Cytokine release syndrome	8 (62)	6 (75)	20 (69)	**34 (68)**
Pneumonia	5 (39)	3 (38)	6 (21)	**14 (28)**
Febrile neutropenia	5 (39)	3 (38)	5 (17)	**13 (26)**
Pyrexia	3 (23)	1 (13)	9 (31)	**13 (26)**
Hyperglycaemia	2 (15)	2 (25)	8 (28)	**12 (24)**
Hypokalemia	0	1 (13)	10 (34)	**11 (22)**
Nausea	3 (23)	1 (13)	6 (21)	**10 (20)**
Related AEs				
Cytokine release syndrome	8 (62)	6 (75)	20 (69)	**34 (68)**

Tissue	Cluster	Cluster composition	Immunophenotype	Baseline cluster frequency in patients with blast reduction
BM	CD4_C4	Treg, CM	↑ **TIGIT**, ↑ **PD-1**, ↑ CD95	low
	CD8_C1	Naive	↑ CD197, ↓ CD95, ↓ **TIGIT**, ↑ CD45RA, ↓ **CD57**	high
PB	CD8_C1	EM, CM	↑ HLA-DR, ↑ Ki-67, ↑ CD95, ↓ CD45RA, ↓ **CD127**	low
	CD8_C6	EM, TEMRA	↑ **TIGIT**, ↓ CD28, ↑ **CD57**, ↑ CD45RA, ↑ HLA-DR	low
	CD8_C16	TEMRA	↑ CD16, ↑ CD45RA, ↑ **CD57**, ↑ **TIGIT**, ↓ CD95	low

Pre-treatment biomarkers associated with lack of response

- **Bone marrow Tregs** ▲
- **Exhausted CD8 T-cells** ▲
- **Naive CD8 T-cells** ▼

Hutchings et al, Subklewe, Blood Neoplasia 2025

Dose Escalation of HLA-A2-WT1 CD3 TCE in a phase I Trial in R/R AML: Trial terminated

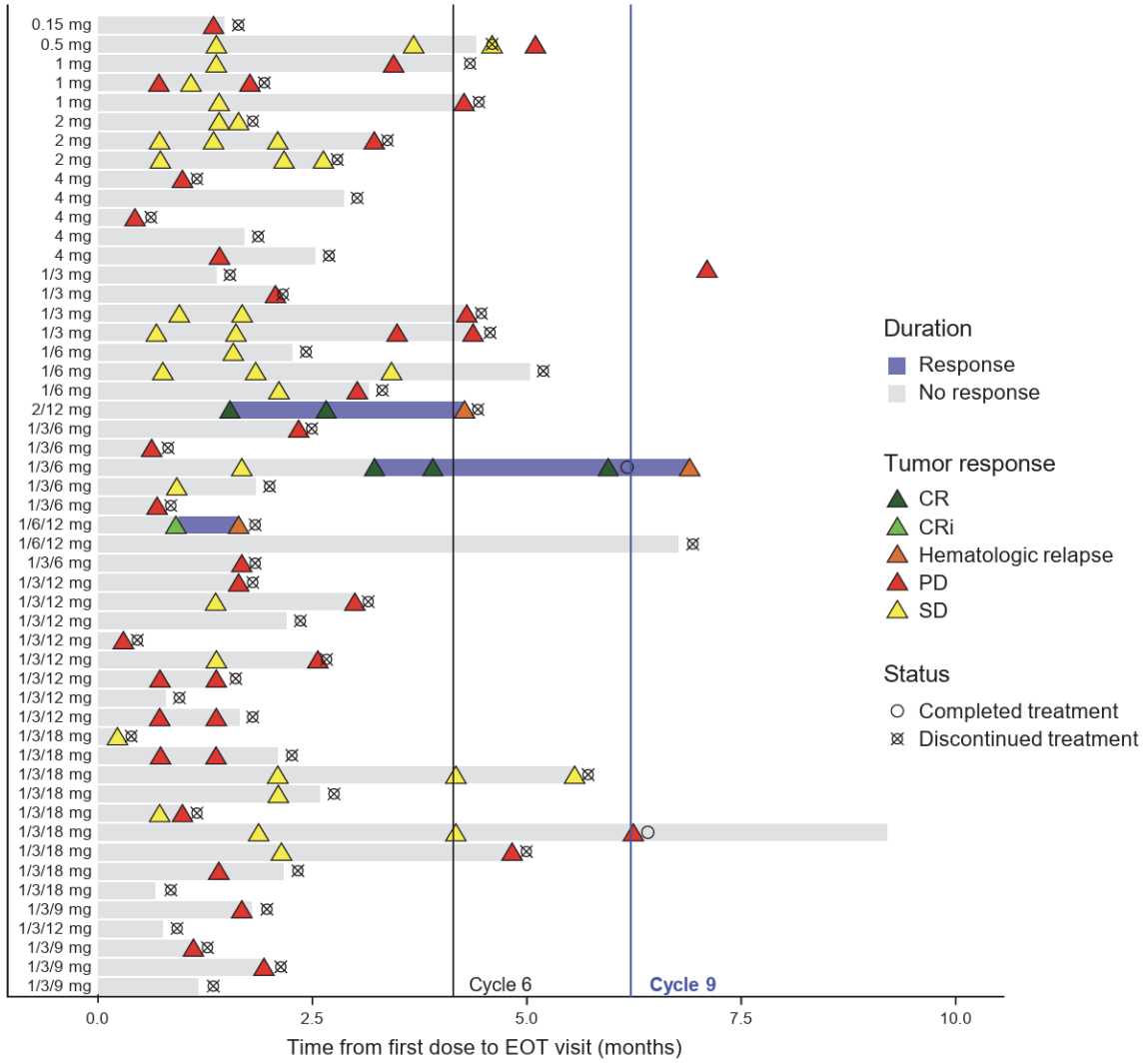
Table 1: Patient characteristics

N (%) unless stated	N=50
Median age, years (range)	65 (35–84)
Male	29 (58)
ECOG PS score	
0	28 (56)
1	19 (38)
2	3 (6)
AML disease status at study entry	21 (42)
Relapsed	29 (58)
Recurrent	
ELN 2017 risk category	
Favorable	4 (8)
Intermediate	19 (38)
Adverse	24 (48)
Missing	3 (6)

N (%) unless stated	N=50
Prior lines of therapy	
1	6 (12)
2	23 (46)
>2	19 (38)
Missing	2 (4)
Bone Marrow Balst Count	
<30%	20 (40)
≥30% to <50%	13 (26)
≥50%	16 (32)
Missing	1 (2)
Genetic abnormalities (n=47)	10 (21)
RUNX1	8 (17)
ASXL1	5 (11)
TP53	3 (6)
FLT3-ITD	3 (6)
NPM1	

Table 2: Most common adverse events

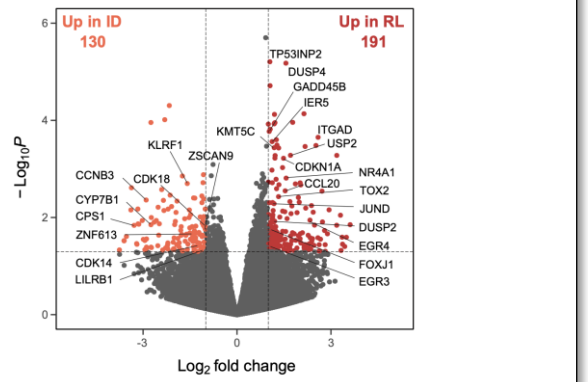
	Fixed dose (n=13)	Single step-up (n=8)	Double step-up (n=29)	All patients (n=50)
All AEs (n,%)				
Cytokine release syndrome	8 (62)	6 (75)	20 (69)	**34 (68)**
Pneumonia	5 (39)	3 (38)	6 (21)	**14 (28)**
Febrile neutropenia	5 (39)	3 (38)	5 (17)	**13 (26)**
Pyrexia	3 (23)	1 (13)	9 (31)	**13 (26)**
Hyperglycaemia	2 (15)	2 (25)	8 (28)	**12 (24)**
Hypokalemia	0	1 (13)	10 (34)	**11 (22)**
Nausea	3 (23)	1 (13)	6 (21)	**10 (20)**
Related AEs				
Cytokine release syndrome	8 (62)	6 (75)	20 (69)	**34 (68)**

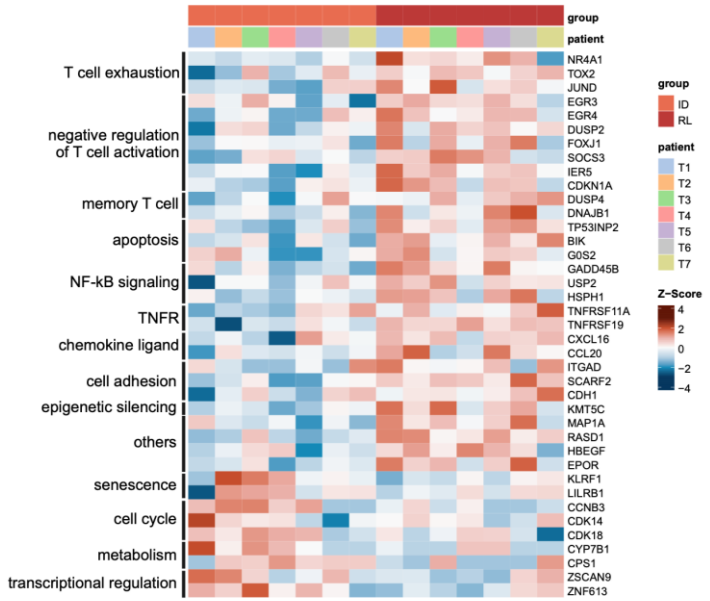


Hutchings et al, ASH 2023

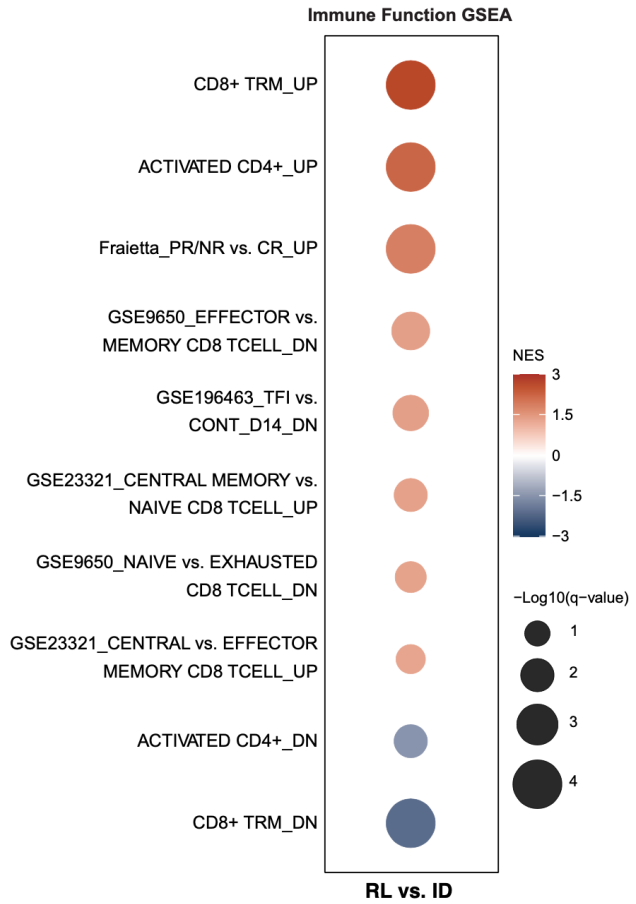
Further Resistance due to T-cell dysfunction at time of R/R: T cells at RL exhibit memory and exhaustion-associated transcriptional and epigenetic profiles compared to ID

Differentially Expressed Genes

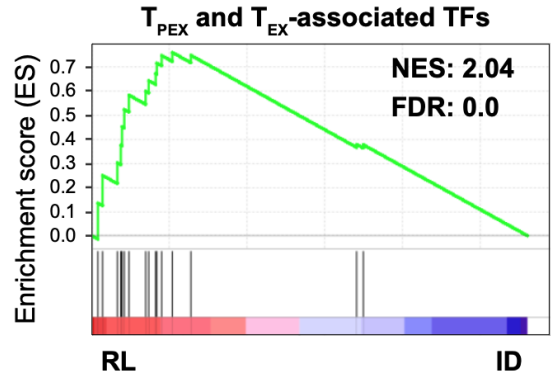




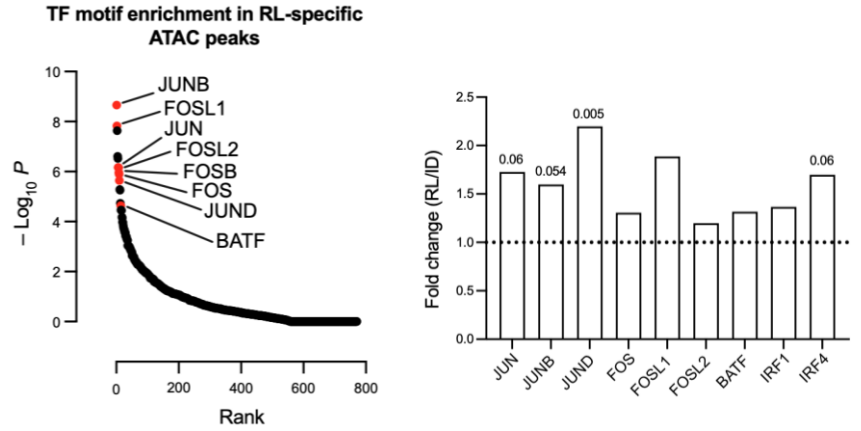
Pathway Analysis



Enrichment of Exhaustion-Associated TFs



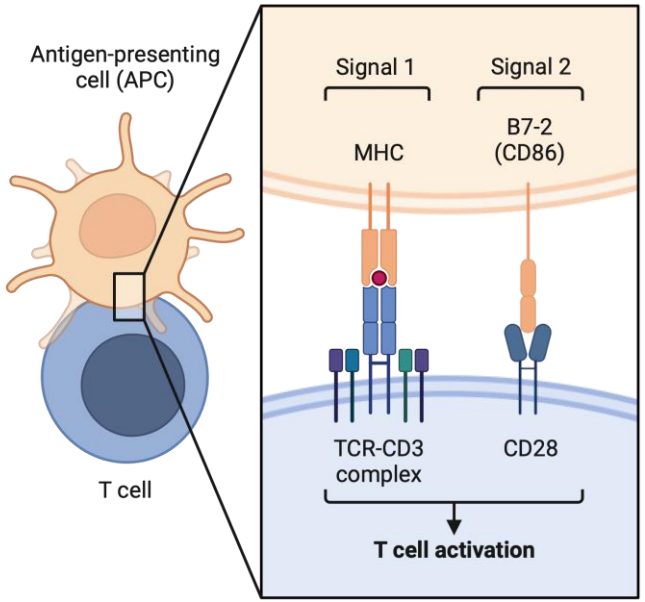
Enrichment of Exhaustion-Associated TF Binding Motifs in Accessible Regions



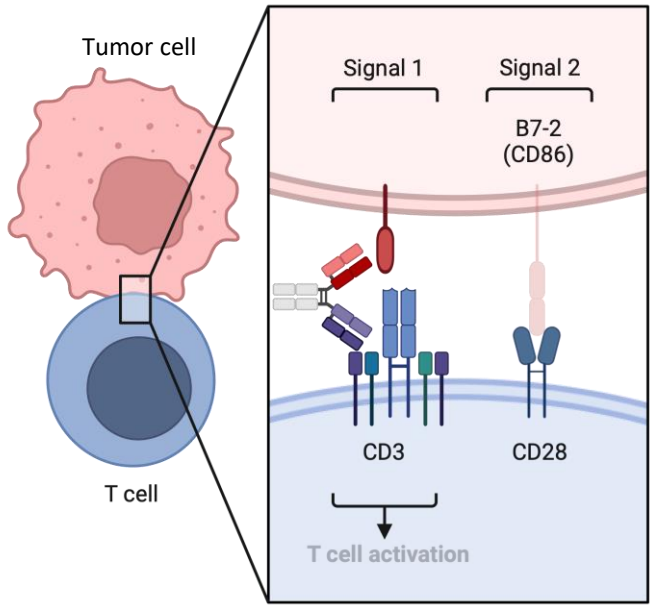
Kazerani M., Subklewe. Leukemia 2025

Several positive Costimulatory Molecules are able to enhance T-cell Activation (Signal 2)

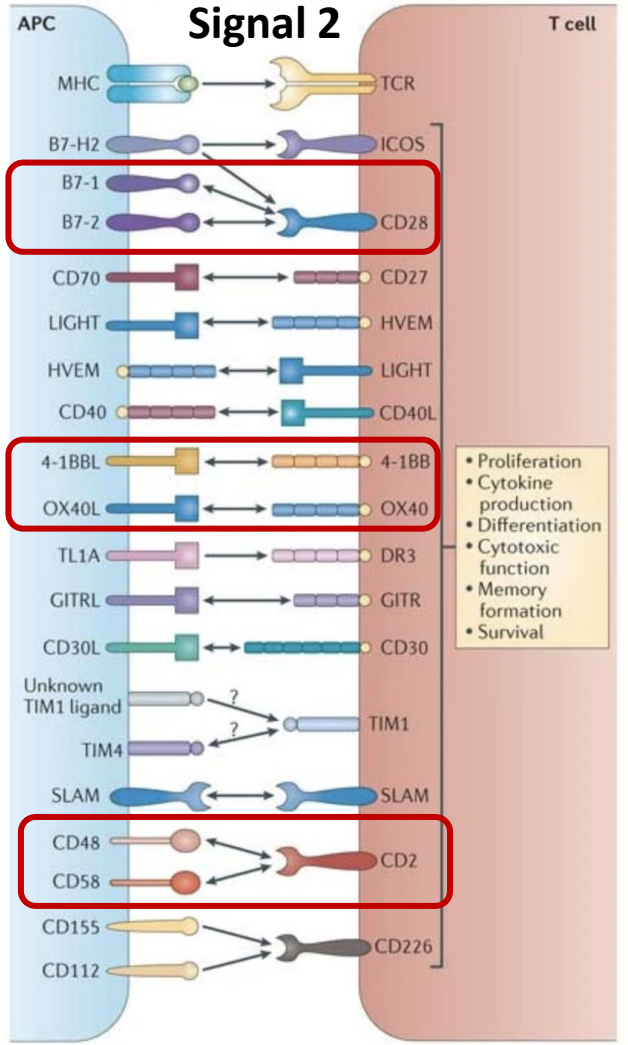
Physiological T cell Activation: Signal 1 + 2



T cell engagermediated Activation: Signal 1



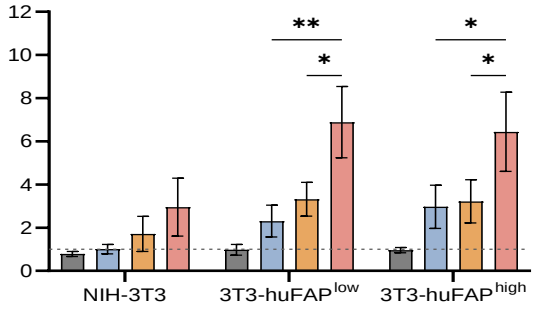
Signal 2



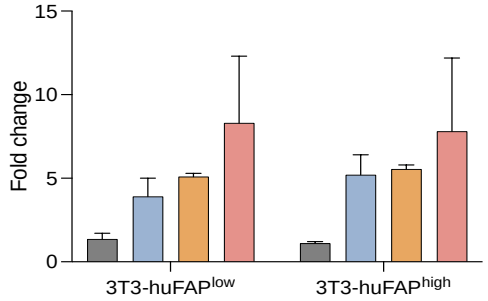
Chen L., Flies D., Nat Rev Immunol 2013

Combination of WT1-bispecific + FAP-4-1BBL enhances Cytotoxicity against AML Cells

Improved AML cell killing



Increased T-cell proliferation

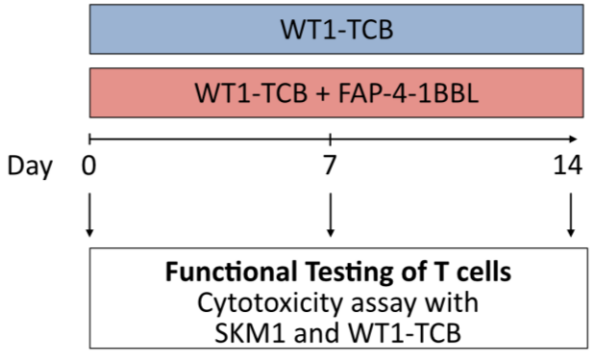


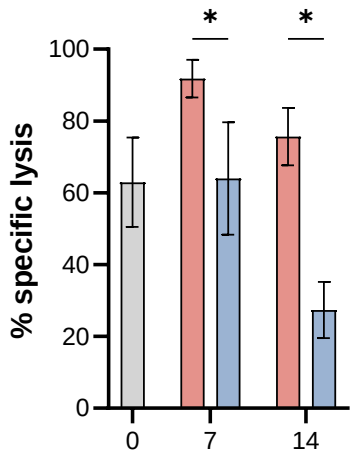
FAP-4-1BBL + WT1-TCB
Ctrl-4-1BBL + WT1-TCB
WT1-TCB only
FAP-4-1BBL only

Data represent mean ± SEM; n=5

Long-term culture system: Increased Cytotoxicity

Continuous stimulation
of HD T cells in coculture with SKM1:



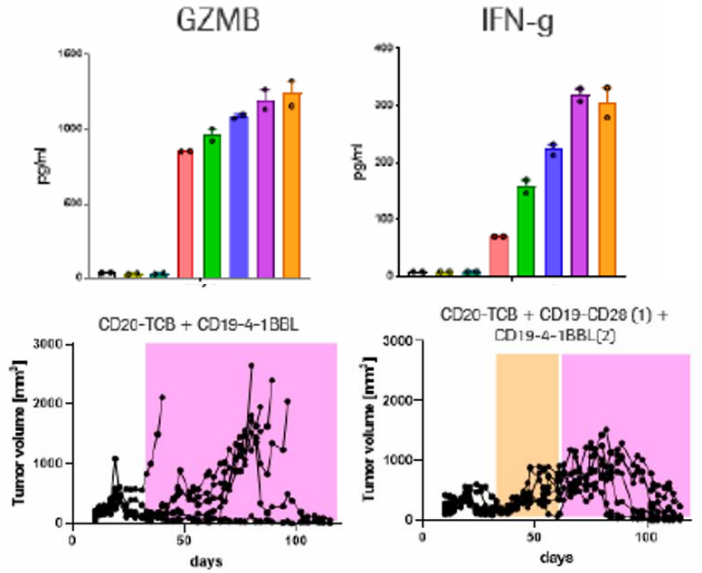


FAP-4-1BBL + WT1-TCB
WT1-TCB only

Neumann et al, Subklewe. in revision

Preclinical: Triple combination in LBCL superior *in vivo* mouse model:

- CD19-CD28 +
- CD20-TCB +
- CD19-4-1BBL



Phase I Clinical Trials in R/R NHL:

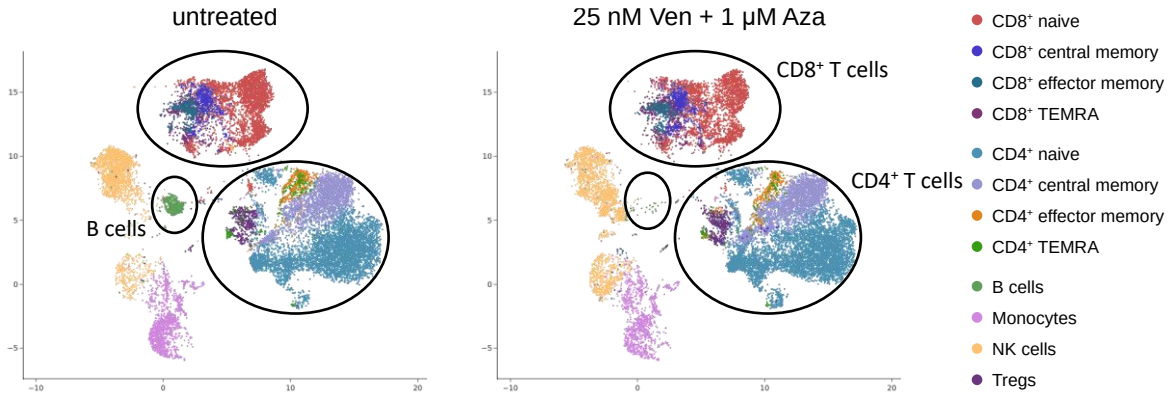
CD19-CD28 BsAb + Glofitamab:
NCT NCT05219513

CD19-4-1BB BsAb + Obinutuzumab +/- Glofitamab:
NCT04077723

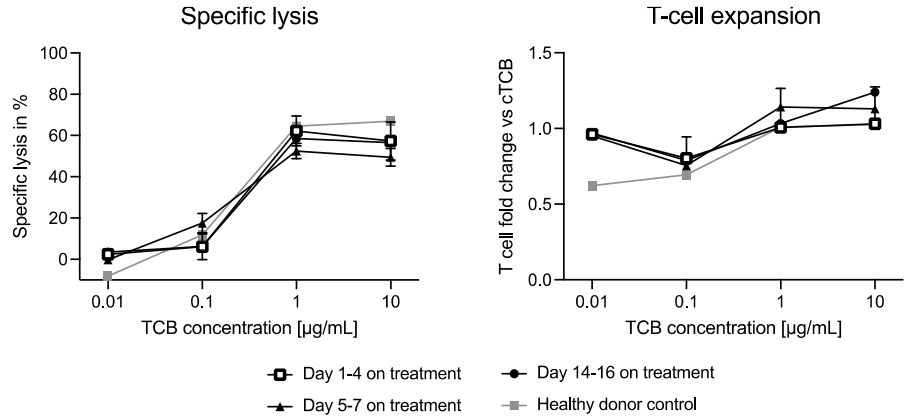
Sam et al, ASH 2022

TCE + VEN/AZA: Increased Cytotoxicity against AML cell lines + pAML cells *in vitro + in vivo*

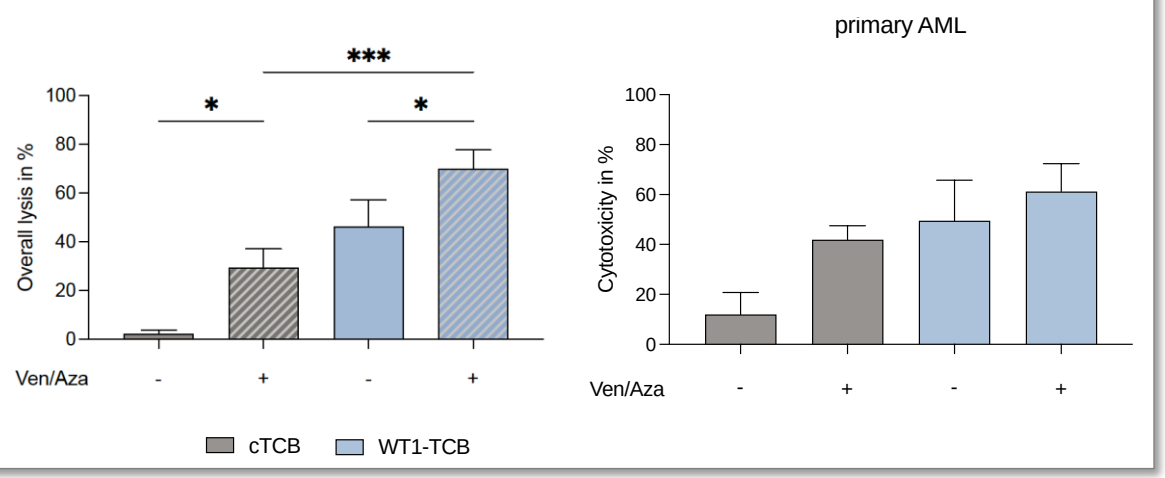
Ven/Aza has limited impact in the T-cell compartment



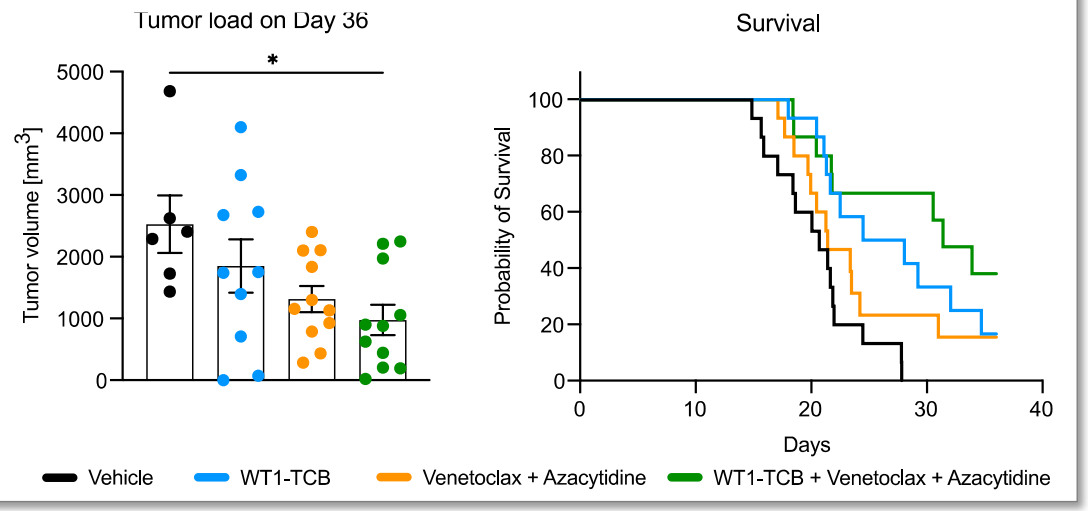
T-cell function is not impaired by Ven/Aza in AML patients



Increased lysis of OCI-AML3 and primary AML cells *in vitro*



Ven/Aza + WT1-TCB significantly enhance survival *in vivo*



Haenel et al. Subklewe, Leukemia 2024

Roadmap

1

BiTE in ALL

Blinatumomab: R/R → MRD → Frontline | TOWER · BLAST · E1910 | Combinatorial approaches ? with TKI ?

2

CAR-T in ALL

Pediatric & Adult | ELIANA · ZUMA-3 · FELIX | Consolidation with allogeneic Stem Cell Transplantation ?

3

T-cell Engagers in AML

Targets · CD33 BiTE · WT1 TCE | How to reduce toxicity and improve efficacy ? Multiple targeting ? Combi with VEN/AZA ?

4

CAR-T in AML

2nd Generation CART | How to reduce toxicity and improve efficacy ? IL-18 ? Menin ? Edited SCTx ?

Three different Concepts of CAR Application in AML

Concept	CAR as Bridge to SCTx	Edited SCTx followed by CAR	Selectivity-Enhancd CAR Approaches
Sequence	CAR T/NK => allo SCT (alternatively TCE, moAb)	Target-KO or Epitope edited SCT => CAR T (TCE, moAb)	CAR T/NK
Target Antigen	Myeloid antigens, e.g. CD33, CD123, CLL1, CD117	Engineered stem cell graft, e.g. CD45, CD123, FLT-3, KIT	Restricted expression, e.g. ADGRE2, TCR based, e.g. FLT3-TKD^{mut}, NPM1^{mut}
Hematopoeitic Toxicity	Yes CART depletion, Stem Cell Salvage	No normal hematopoiesis invisible	Yes / No, depends
CAR	2nd/3rd generation CART, Compound CART	2nd/3rd generation CART, Dual CART	2nd CART, Split CART, „if better“, adapter CART, TCR transgenic T cells
Cell Source	auto or allo T & NK cells, no persistence	donor derived, possibly autologous	patient derived, allo CAR T/NK donor derived post allo SCT
Potential	Improve outcome post SCT; decrease conditioning and thereby increase number of pts eligible for allo SCT	Increase safety by decreasing on-target-off-leukemia toxicity; multiple-targeting possible to overcome antigen escape	Replace allo SCT, applicable to the majority of AML pts
References	Driouk et al, Front Immunol 2020; Zhang et al, Leukemia 2022, Budde et al, Blood 2017; 130, Tambaro et al, Leukemia 2021; Zhang et al, Clin Cancer Res 2021; Liu et al, Blood 2018; 132. Sallman et al, ASH 2022, ASGCT 2023; ASH 2023: Shah et al, #771, Zhang et al, #2106	Kim et al, Cell 2018; Borot F. et al, PNAS 2019; Wellhausen et al, STM 2023; Humbert et al, Leukemia 2019, Chiesa et al, NEJM 2023; Casirati et al, Nature 2023; Marone et al, J Exp Med 2023; Reviews: Kim. Trends in Cancer 2023; Saniei et al, Cell Stem Cell 2023, Volta et al, J Exp Med 2023	Haubner et al, Cancer Cell 2023; Sallman et al, Blood 2019; 134:3826 and Blood 2020;136:(Suppl1); Biernracki etal, JCI 2020, Giannakopoulou et al, Nature Cancer2023 Wermke et al, Blood 2021; Nixdorf et al, Leukemia 2023; Wermke et al, ASH 2023 #3465

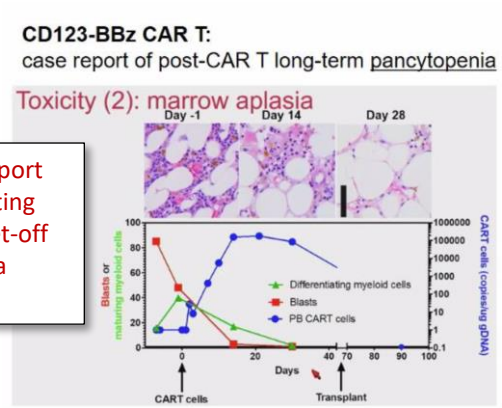
Bridge to SCTx

Concept	CAR as Bridge to SCTx	Edited SCTx followed by CAR	Selectivity-Enhancd CAR Approaches
Sequence	CAR T/NK => allo SCT (alternatively TCE, moAb)	Target-KO or Epitope edited SCT => CAR T (TCE, moAb)	CAR T/NK
Target Antigen	Myeloid antigens, e.g. CD33, CD123, CLL1, CD117	Engineered stem cell graft, e.g. CD45, CD123, FLT-3, KIT	Restricted expression, e.g. ADGRE2, TCR based, e.g. FLT3-TKD^{mut}, NPM1^{mut}
Hemato-poeitic Toxicity	Yes CART depletion, Stem Cell Salvage	No normal hematopoiesis invisible	Yes / No, depends
CAR	2nd/3rd generation CART, Compound CART	2nd/3rd generation CART, Dual CART	2nd CART, Split CART, „if better“, adapter CART, TCR transgenic T cells
Cell Source	auto or allo T & NK cells, no persistence	donor derived, possibly autologous	patient derived, allo CAR T/NK donor derived post allo SCT
Potential	Improve outcome post SCT; decrease conditioning and thereby increase number of pts eligible for allo SCT	Increase safety by decreasing on-target-off-leukemia toxicity; multiple-targeting possible to overcome antigen escape	Replace allo SCT, applicable to the majority of AML pts
References	Driouk et al, Front Immunol 2020; Zhang et al, Leukemia 2022, Budde et al, Blood 2017; 130, Tambaro et al, Leukemia 2021; Zhang et al, Clin Cancer Res 2021; Liu et al, Blood 2018; 132. Sallman et al, ASH 2022, ASGCT 2023; ASH 2023: Shah et al, #771, Zhang et al, #2106	Kim et al, Cell 2018; Borot F. et al, PNAS 2019; Wellhausen et al, STM 2023; Humbert et al, Leukemia 2019, Chiesa et al, NEJM 2023; Casirati et al, Nature 2023; Marone et al, J Exp Med 2023; Reviews: Kim. Trends in Cancer 2023; Saniei et al, Cell Stem Cell 2023, Volta et al, J Exp Med 2023	Haubner et al, Cancer Cell 2023; Sallman et al, Blood 2019; 134:3826 and Blood 2020;136:(Suppl1); Biernracki etal, JCI 2020, Giannakopoulou et al, Nature Cancer2023 Wermke et al, Blood 2021; Nixdorf et al, Leukemia 2023; Wermke et al, ASH 2023 #3465

Severe Hematoxicity, but „bridge“ to Transplant Strategy demonstrates Proof-of-Concept

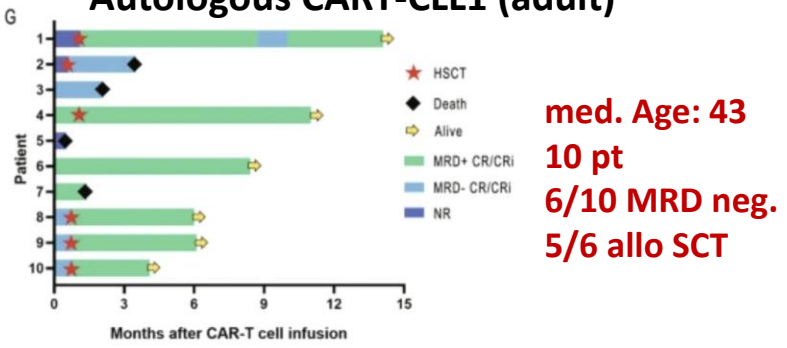
Integration of CART into conditioning Regimen: Myeloid Targets, Reduce Toxicity (GI !) & Improve RFS

CASE Report highlighting on-target-off leukemia toxicity



Gill et al., ASH 2022, update ASH 2023 #217

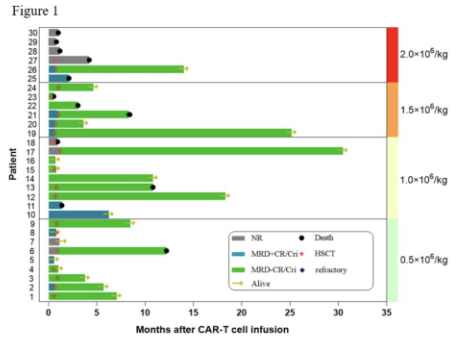
Autologous CART-CLL1 (adult)



med. Age: 43
10 pt
6/10 MRD neg.
5/6 allo SCT

Jin et al, JHO 2022

ASH 2023: Autologous CART-CLL1*

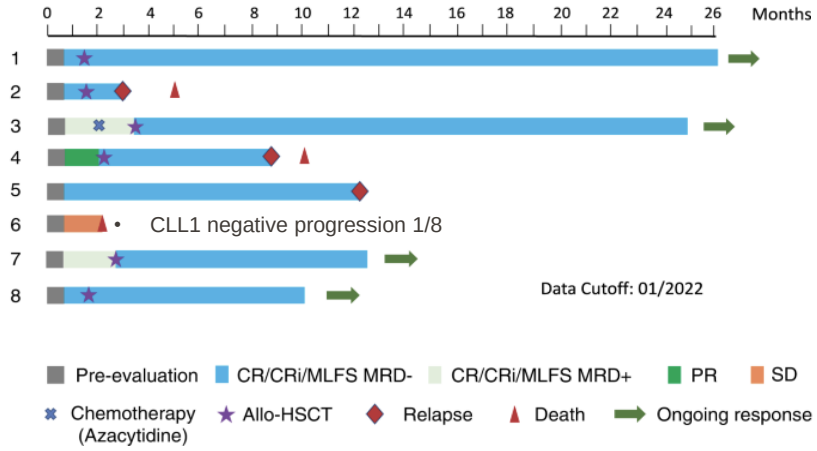


N=30
Med Age 38
100 % CRS
96% hematotoxicity
12/30 MRD- CR/Cri
10/30 MRD+ CR/CRi

ASH 2023: *Zhang et al, # 2106, Shah et al, #771 (Trial Results CD33 CART)

Prior Treatment	AML blasts in % prior to pre-conditioning
Relapse after HSCT	62
Relapse after HSCT	92
5 Chemo	21
4 Chemo	28
2 Chemo	14
2 Chemo + Venetoclax	91
2 Chemo	30
4 Chemo	69

Autologous CART-CLL1 (Ped)



CART Construct: CLL1-CD8.BB.z

Population: median age 12y (8-16)

Blasts: 46% (14-92), **Prior Rx:** 4 (2-5)

CLL1 expression: median 89% (65-96)

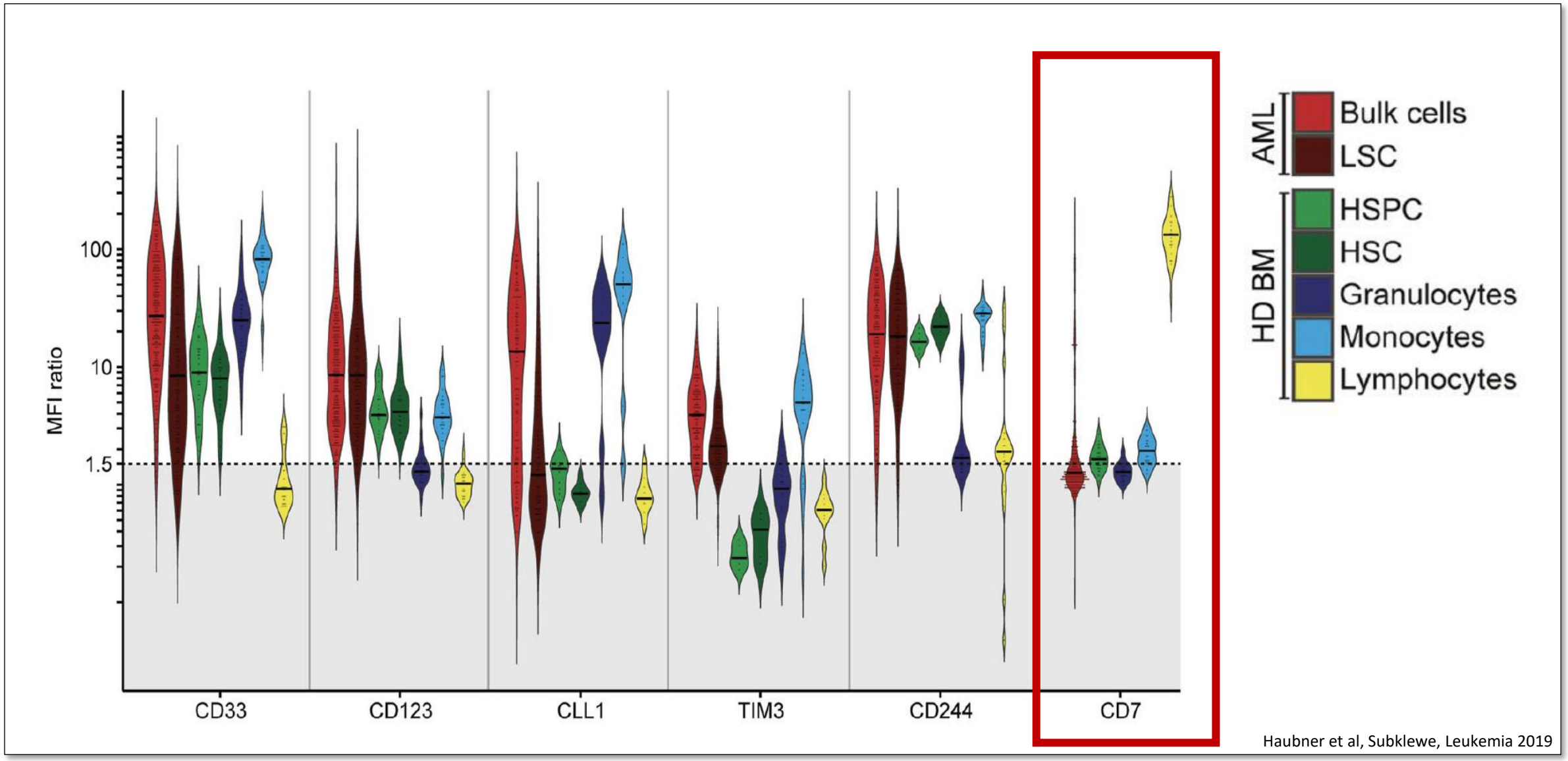
4/8 MRD-, 2/8 MRD+

6/8 allo SCT

4/8 CR/Cri/MLFS MRD-

Zhang et al, Leukemia 2022

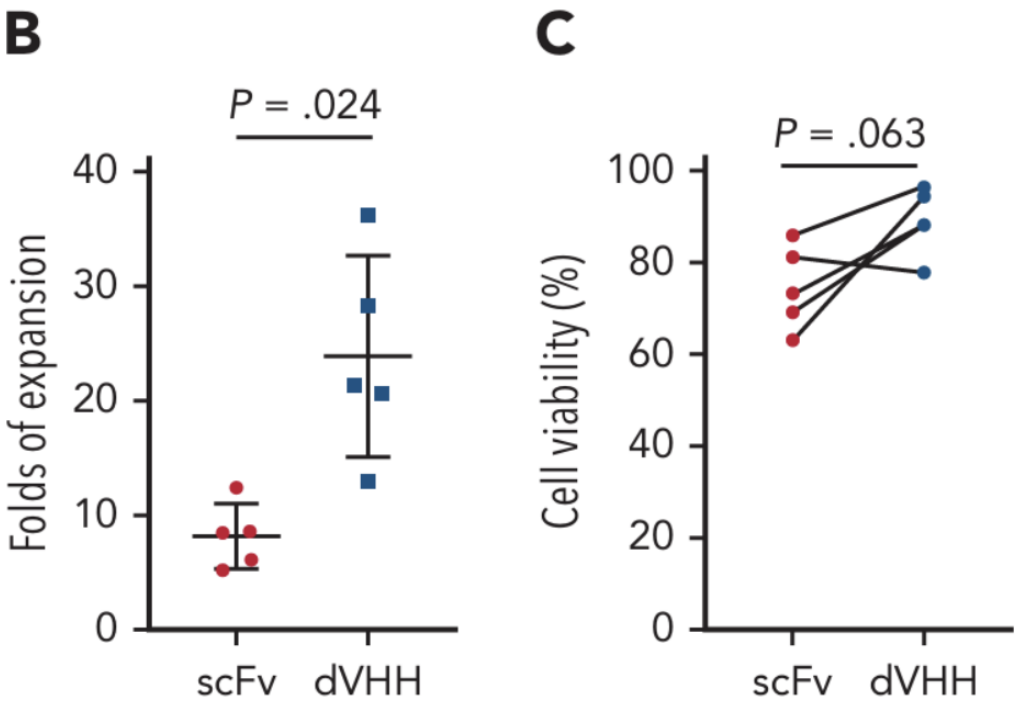
Antigen Expression in AML (Bulk + LSC) and normal Hematopoiesis

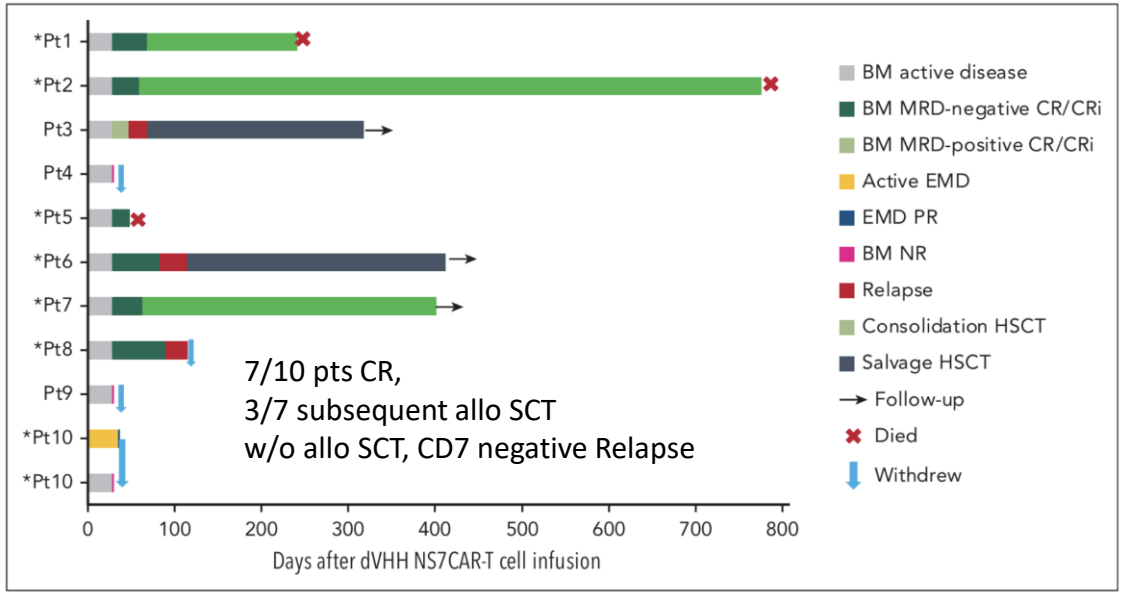


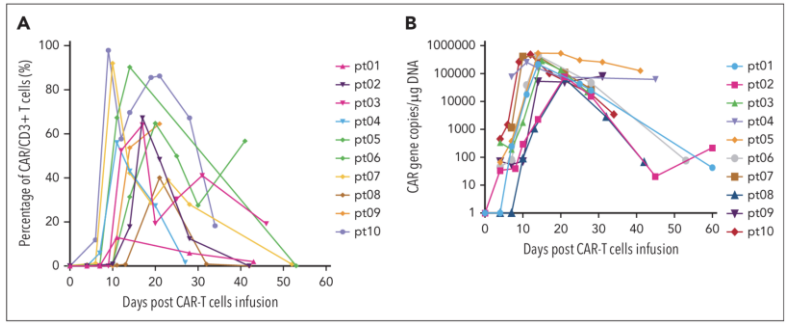
Haubner et al, Subklewe, Leukemia 2019

Nanobody-based CD7-targeted CAR-T therapy for AML

Nanobodies (single domain binders, no mispairing) better than scFv in binding affinity and induction of T-cell proliferation

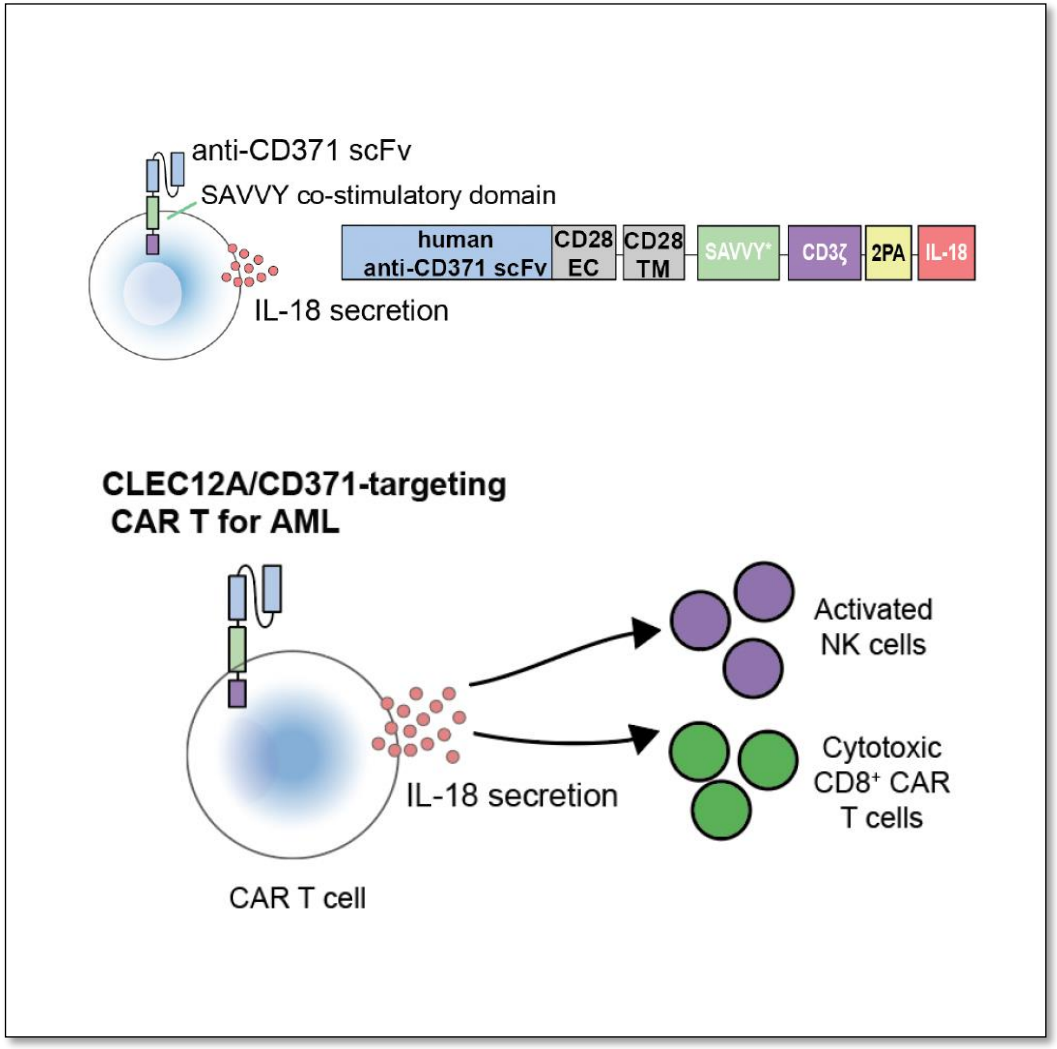


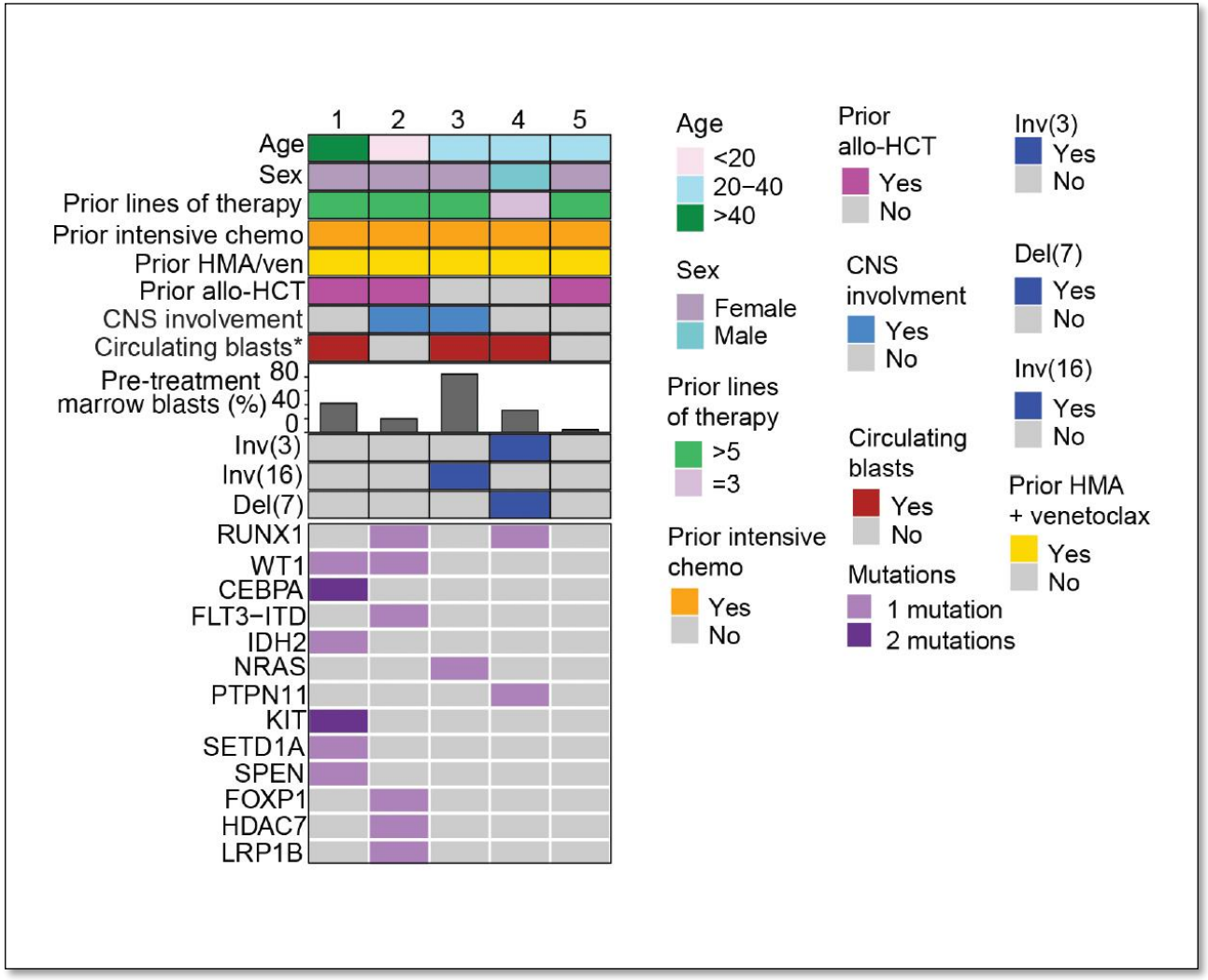




Lu et al, Blood 2025

Phase I Trial (CLEAR): CLL-1 CART Cells secreting IL-18





Geyer et al, Blood 2025

CLEAR: 5 patients treated, 2/5 CRS G III/IV, 1/5 ICANS G3, 3/5 MRD negative by FLOW

Pt Characteristics:

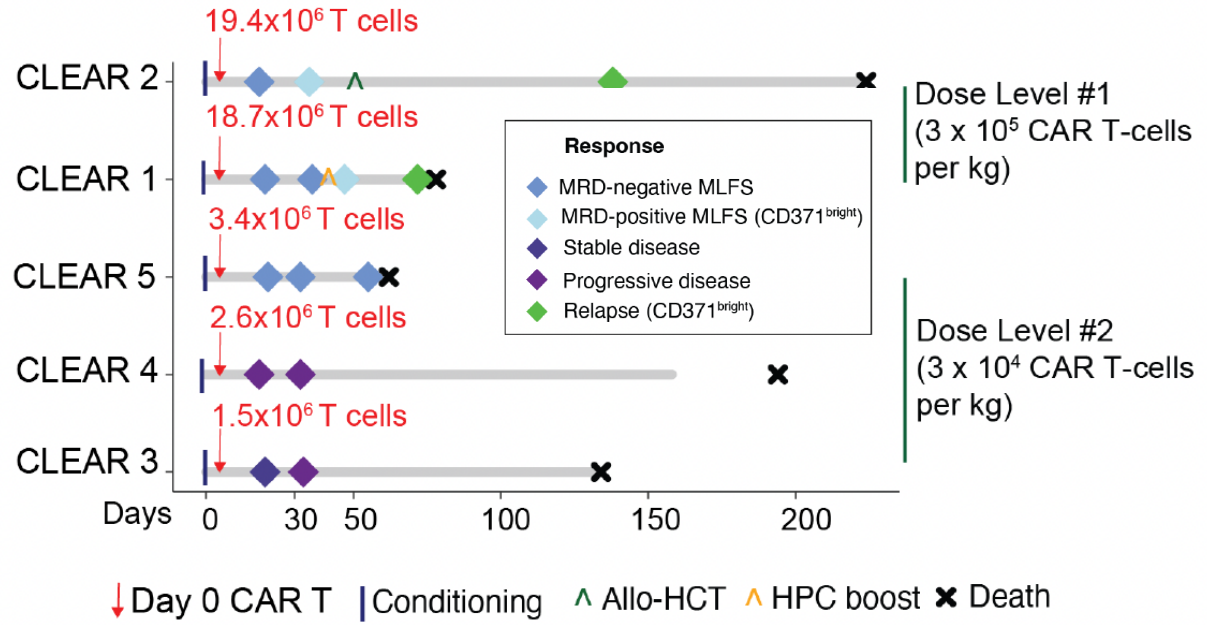
- Dose escalation
- 5 patients screened and infused
- median age 32 years (range, 16-45 years)
- Prior therapy: ven / cytarabine, 3 prior HSCT

Toxicities:

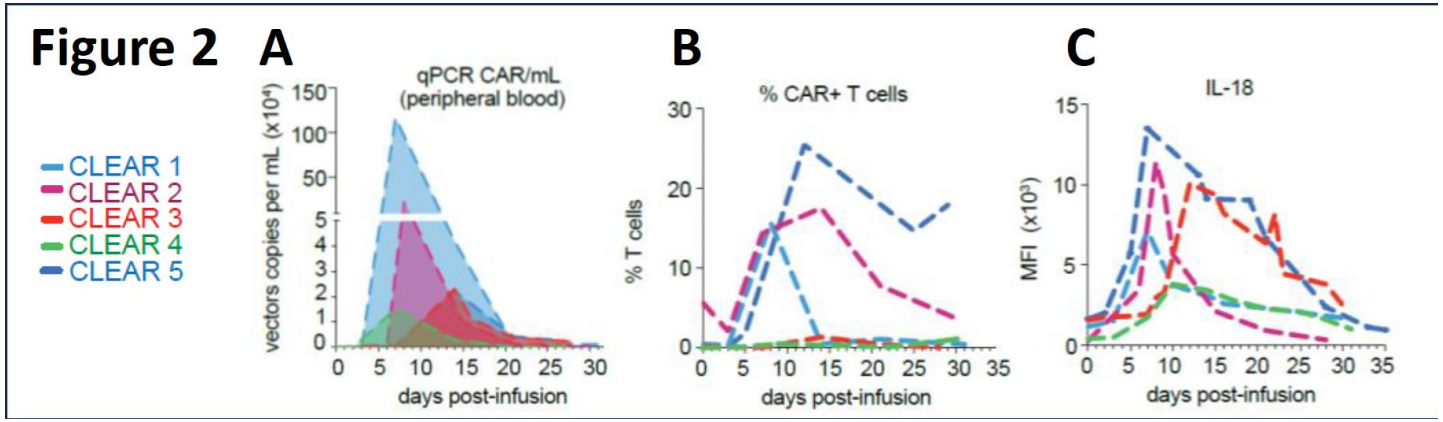
- 5/5 CRS, 2/5 G3-4
- 1/5 ICANS G3
- DLT x 2 with dose level 1, 1DLT at step down dose ($3x10^{-4}$)

Responses:

- 3/5 flow MRD neg MLFS (CAVE)
- 2/5 bridged to HSCT



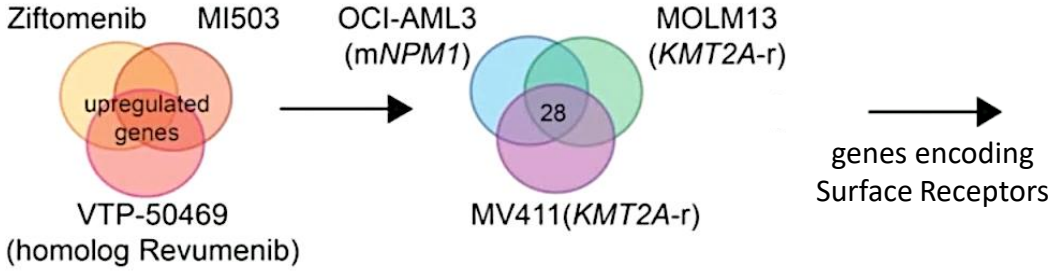
Peak CAR T expansion co-incided with peak IL-18 levels (d7-14)



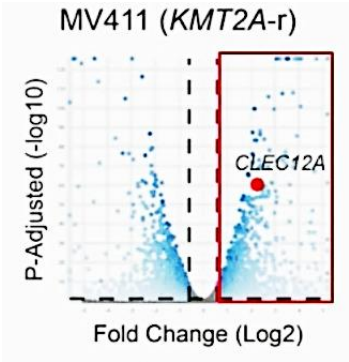
Geyer et al., MSKCC, ASH 2024

Menin-Inhibition leads to Differentiation of AML Cells and Induction of Immune Target Antigens like CLL1 (CLEC12a)

Genes commonly upregulated by Menin-inhibition



C-type lectin domain family 12 member A (CLEC12A) - transcriptionally induced in AML upon menin-inhibition



expressed on AML
& low on HSCS

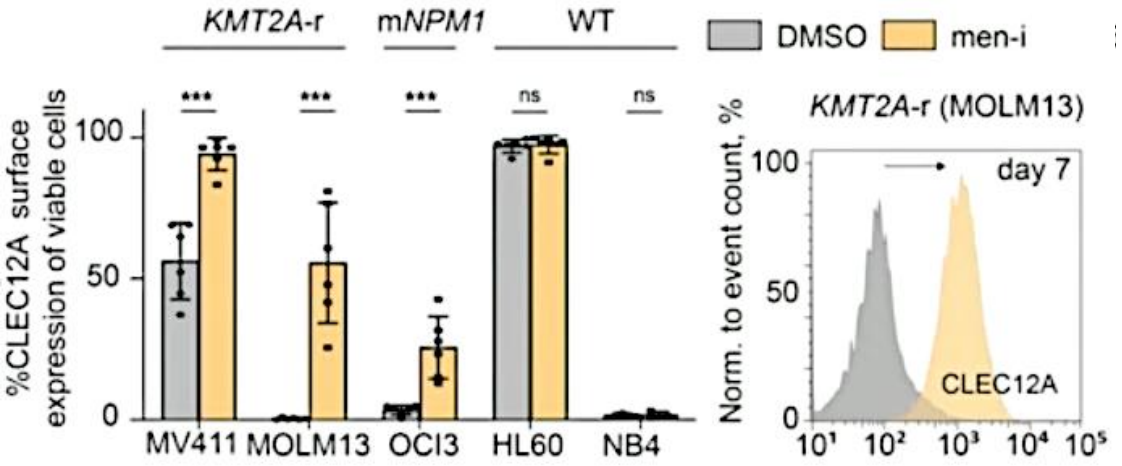
CLEC12A

not expressed by
other tissues

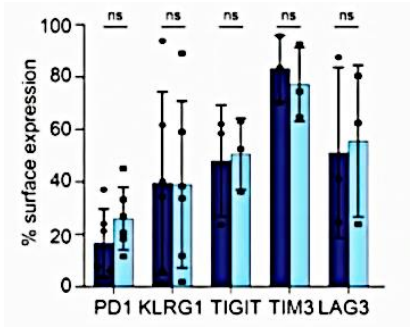
→ **Putative CAR-T Cell Target in AML[1-6]**

Johanna Rausch et al, ASH 2025, # 866, also presented at the „Best of ASH“ session, Fetsch et al, Blood 2026

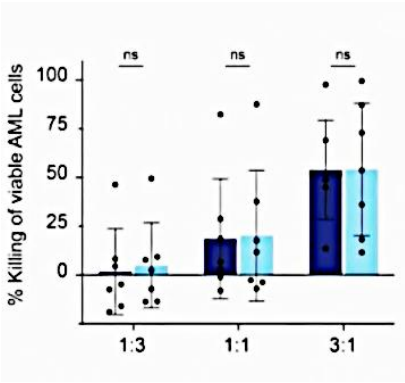
Menin-inhibition leads to Upregulation of CLL1 w/o impacting T cell Fitness

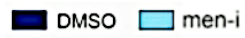


Similar exhaustion phenotype on day 21



Comparable cytotoxicity on day 7





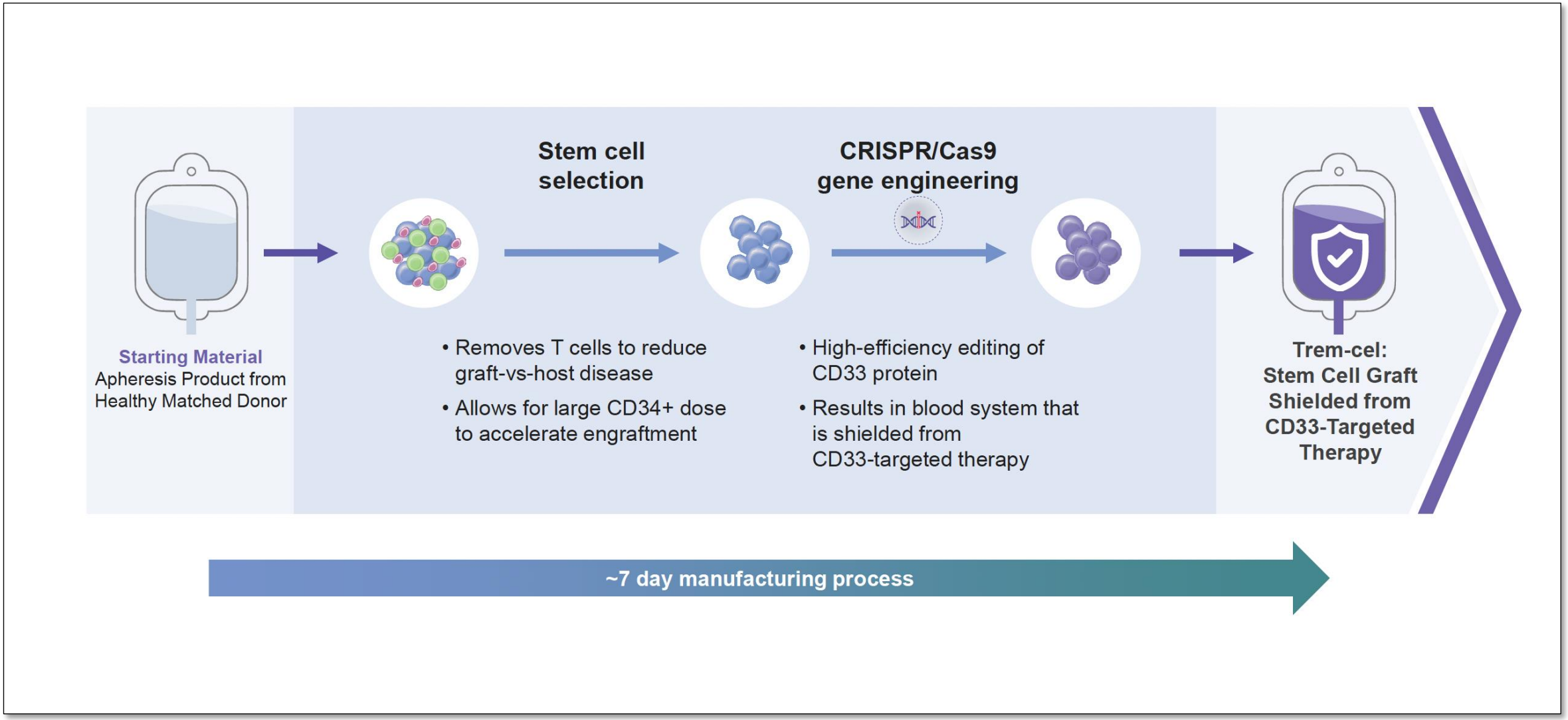
Johanna Rausch et al, ASH 2025, # 866, Fetsch et al, Blood 2026

Reverse the Sequence: Edited SCTx first, followed by Immunotherapy agent

Concept	CAR as Bridge to SCTx	Edited SCTx followed by CAR	Selectivity-Enhancd CAR Approaches
Sequence	CAR T/NK => allo SCT (alternatively TCE, moAb)	Target-KO or Epitope edited SCT => CAR T (TCE, moAb)	CAR T/NK
Target Antigen	Myeloid antigens, e.g. CD33, CD123, CLL1, CD117	Engineered stem cell graft, e.g. CD45, CD123, FLT-3, KIT	Restricted expression, e.g. ADGRE2, TCR based, e.g. FLT3-TKD^{mut}, NPM1^{mut}
Hemato-poeitic Toxicity	Yes CART depletion, Stem Cell Salvage	No normal hematopoiesis invisible	Yes / No, depends
CAR	2nd/3rd generation CART, Compound CART	2nd/3rd generation CART, Dual CART	2nd CART, Split CART, „if better“, adapter CART, TCR transgenic T cells
Cell Source	auto or allo T & NK cells, no persistence	donor derived, possibly autologous	patient derived, allo CAR T/NK donor derived post allo SCT
Potential	Improve outcome post SCT; decrease conditioning and thereby increase number of pts eligible for allo SCT	Increase safety by decreasing on-target-off-leukemia toxicity; multiple-targeting possible to overcome antigen escape	Replace allo SCT, applicable to the majority of AML pts
References	Driouk et al, Front Immunol 2020; Zhang et al, Leukemia 2022, Budde et al, Blood 2017; 130, Tambaro et al, Leukemia 2021; Zhang et al, Clin Cancer Res 2021; Liu et al, Blood 2018; 132. Sallman et al, ASH 2022, ASGCT 2023; ASH 2023: Shah et al, #771, Zhang et al, #2106	Kim et al, Cell 2018; Borot F. et al, PNAS 2019; Wellhausen et al, STM 2023; Humbert et al, Leukemia 2019, Chiesa et al, NEJM 2023; Casirati et al, Nature 2023; Marone et al, J Exp Med 2023; Reviews: Kim. Trends in Cancer 2023; Saniei et al, Cell Stem Cell 2023, Volta et al, J Exp Med 2023	Haubner et al, Cancer Cell 2023; Sallman et al, Blood 2019; 134:3826 and Blood 2020;136:(Suppl1); Biernracki etal, JCI 2020, Giannakopoulou et al, Nature Cancer2023 Wermke et al, Blood 2021; Nixdorf et al, Leukemia 2023; Wermke et al, ASH 2023 #3465

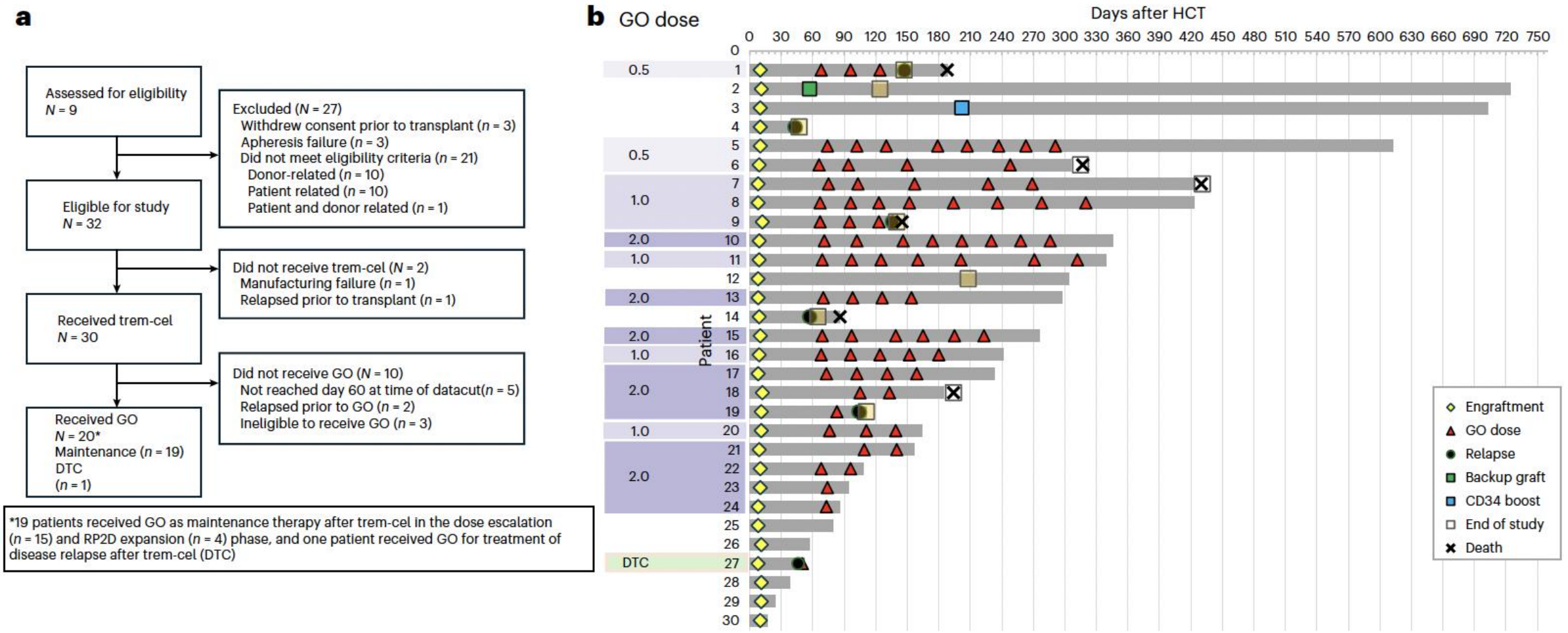
Generation of biallelic CRISPR/Cas9 edited Stem Cells for CD33-targeted Therapy

Phase I trial: G-CSF/Plerixafor-mobilized peripheral SCT; Myeloablative Conditioning with Busulfan or TBI with ATG



Slide provided by VOR, DiPersio et al, Nature Medicine 2026

Patient Disposition and Patient Status

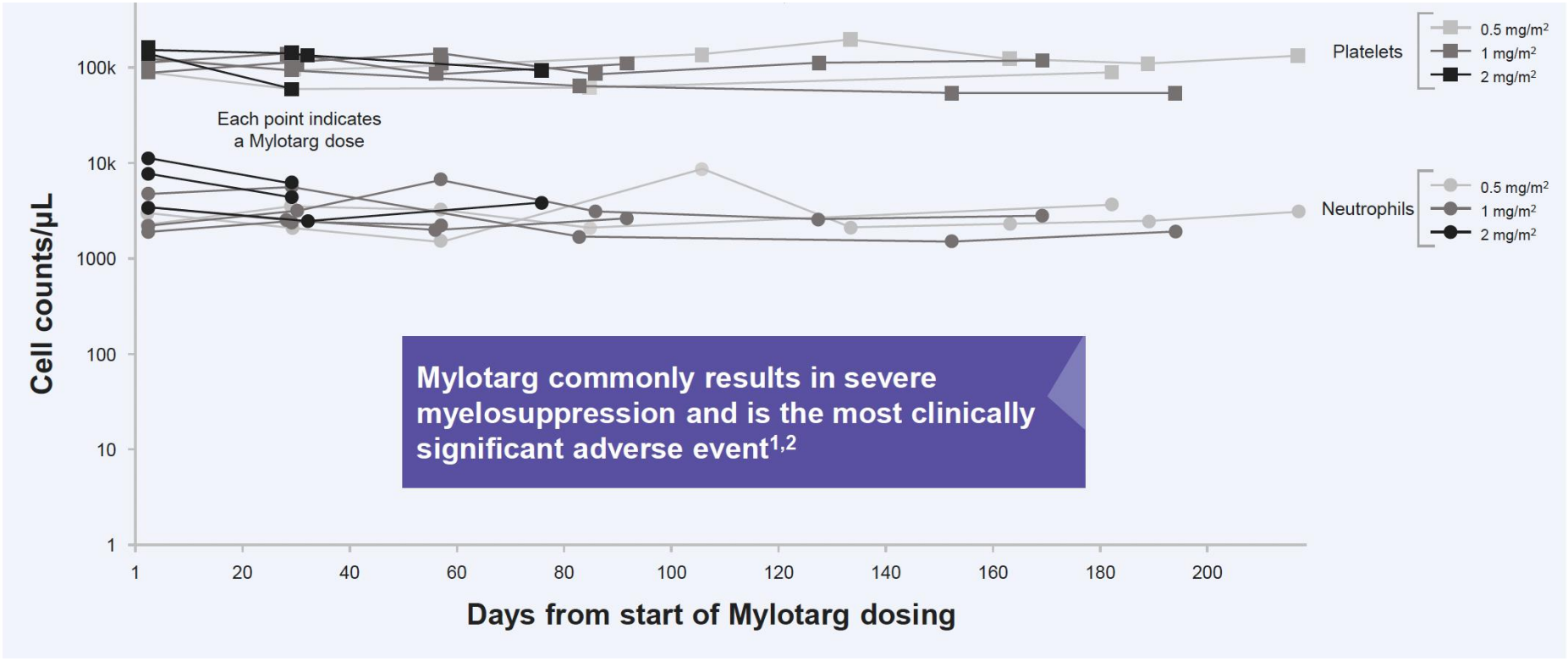


DiPersio et al, Nature Medicine 2026

Neutrophil and Platelet Peripheral Blood Counts after multiple GO Applications

Engraftment with the first 12 (n) and 16 (plt) days; Initiation of GO at day 60 post HCT; schedule: every 28 days for 4-8 cycles

30 pts treated



PROOF-of-CONCEPT

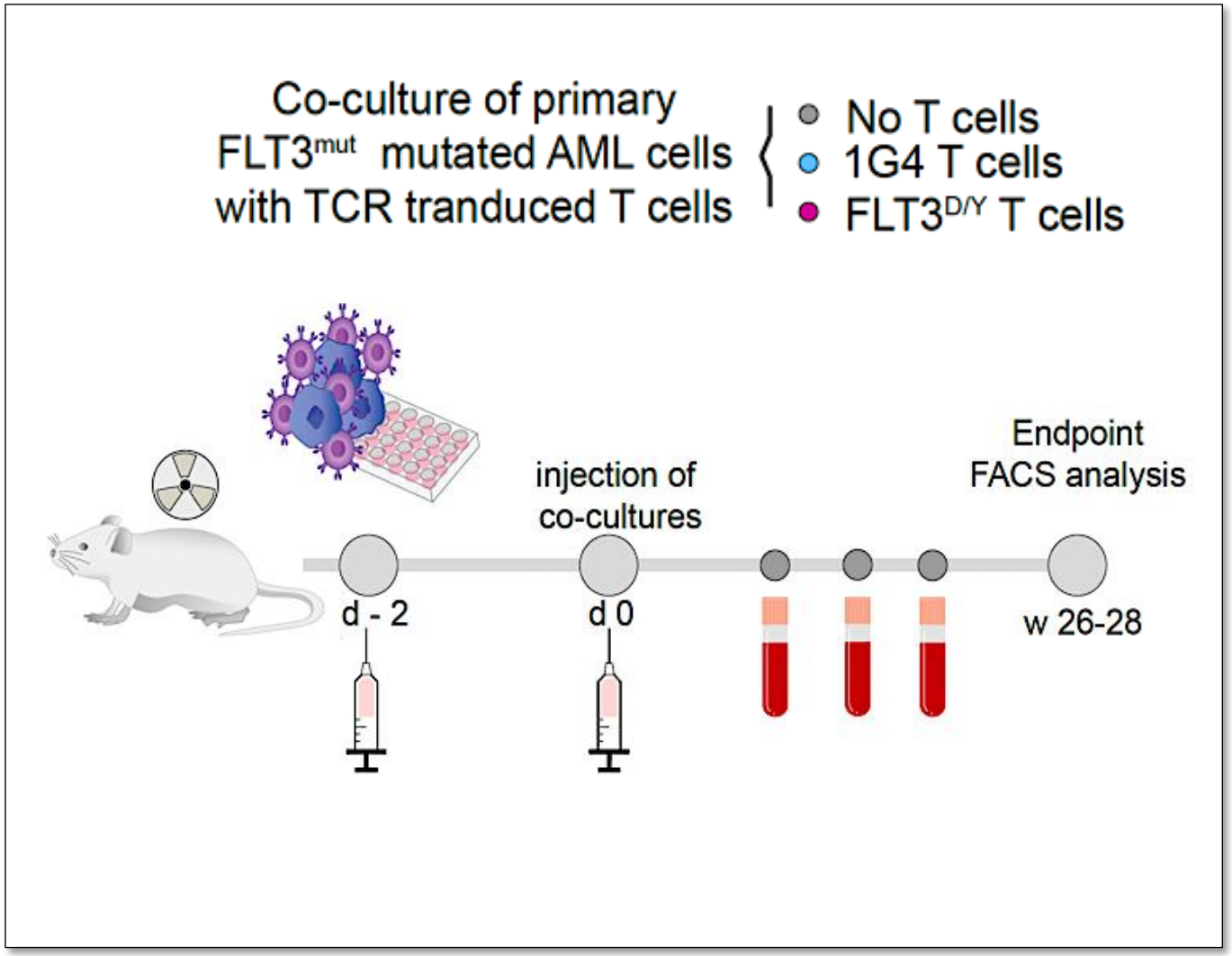
Koehne et al: EHA 2023 #P1396, (NCT04849910), Petty et al, Blood Advances 2025; DiPersio et al, ASH 2024; DiPersio et al, ASCTC 2025, DiPersio et al, Nature Medicine 2026

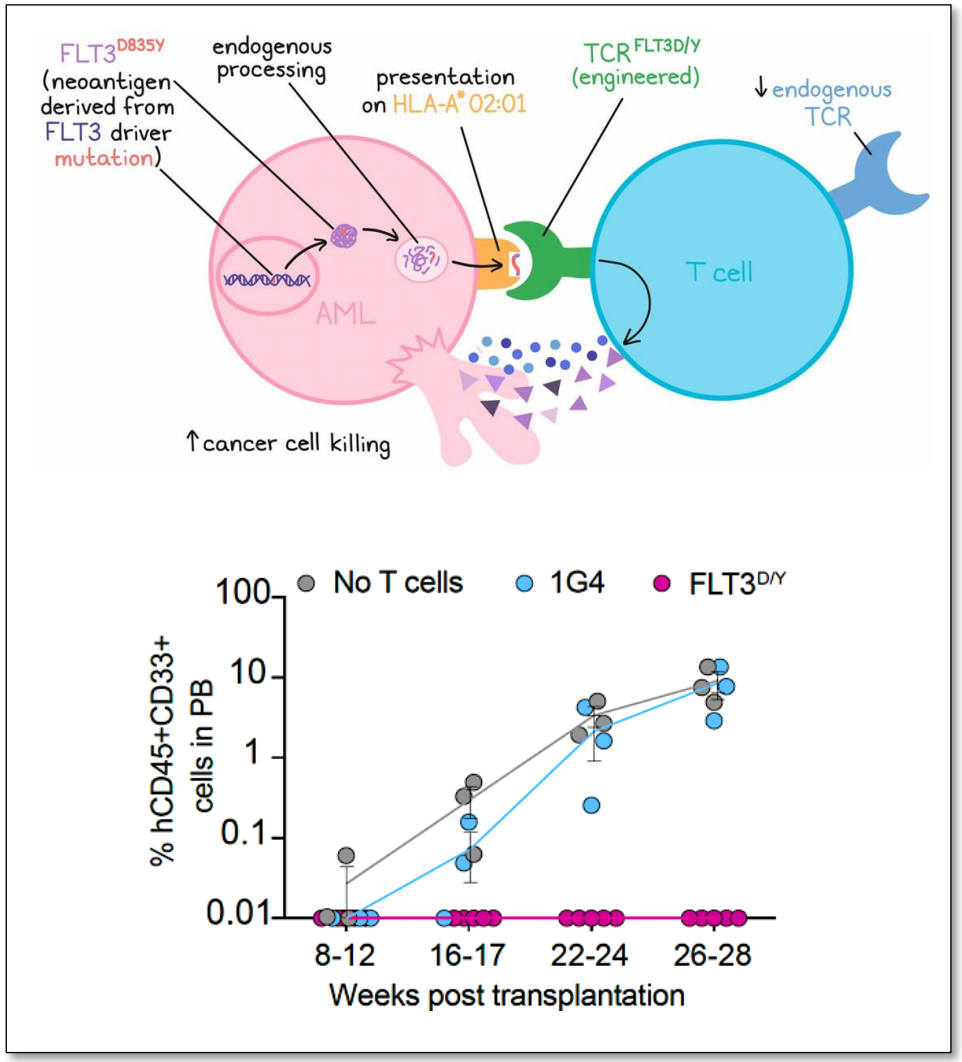
CART w/o allo SCTx (more pts eligible): Selectivity Enhanced CART approaches

Concept	CAR as Bridge to SCTx	Edited SCTx followed by CAR	Selectivity-Enhancd CAR Approaches
Sequence	CAR T/NK => allo SCT (alternatively TCE, moAb)	Target-KO or Epitope edited SCT => CAR T (TCE, moAb)	CAR T/NK
Target Antigen	Myeloid antigens, e.g. CD33, CD123, CLL1, CD117	Engineered stem cell graft, e.g. CD45, CD123, FLT-3, KIT	Restricted expression, e.g. ADGRE2, TCR based, e.g. FLT3-TKD^{mut}, NPM1^{mut}
Hemato-poeitic Toxicity	Yes CART depletion, Stem Cell Salvage	No normal hematopoiesis invisible	Yes / No, depends
CAR	2nd/3rd generation CART, Compound CART	2nd/3rd generation CART, Dual CART	2nd CART, Split CART, „if better“, adapter CART, TCR transgenic T cells
Cell Source	auto or allo T & NK cells, no persistence	donor derived, possibly autologous	patient derived, allo CAR T/NK donor derived post allo SCT
Potential	Improve outcome post SCT; decrease conditioning and thereby increase number of pts eligible for allo SCT	Increase safety by decreasing on-target-off-leukemia toxicity; multiple-targeting possible to overcome antigen escape	Replace allo SCT, applicable to the majority of AML pts
References	Driouk et al, Front Immunol 2020; Zhang et al, Leukemia 2022, Budde et al, Blood 2017; 130, Tambaro et al, Leukemia 2021; Zhang et al, Clin Cancer Res 2021; Liu et al, Blood 2018; 132. Sallman et al, ASH 2022, ASGCT 2023; ASH 2023: Shah et al, #771, Zhang et al, #2106	Kim et al, Cell 2018; Borot F. et al, PNAS 2019; Wellhausen et al, STM 2023; Humbert et al, Leukemia 2019, Chiesa et al, NEJM 2023; Casirati et al, Nature 2023; Marone et al, J Exp Med 2023; Reviews: Kim. Trends in Cancer 2023; Saniei et al, Cell Stem Cell 2023, Volta et al, J Exp Med 2023	Haubner et al, Cancer Cell 2023; Sallman et al, Blood 2019; 134:3826 and Blood 2020;136:(Suppl1); Biernracki etal, JCI 2020, Giannakopoulou et al, Nature Cancer2023 Wermke et al, Blood 2021; Nixdorf et al, Leukemia 2023; Wermke et al, ASH 2023 #3465

Targeting of Intracellular Proteins to increase Specificity against AML utilizing TCRtg T cells

FLT3^{D835Y} TCR T cells eliminate primary leukemia-propagating AML cells





Giannakopoulou et al, Nature Cancer, 2023

Summary

ALL – BiTE	Blinatumomab: approved in R/R (TOWER, HR 0.71) → MRD eradication (BLAST, 78% conversion) → frontline OS benefit (E1910, HR 0.41), Combinations with TKI in current clinical trials
ALL – CAR-T	tisa-cel (ELIANA, ORR 81%), brexu-cel (ZUMA-3, ORR 71%), obe-cel (FELIX, ORR 77%) in the R/R ALL setting; whom to consolidate with allo-SCT role remains exploratory, role of NGS-MRD & B-cell recovery still open
AML – TCE	T cell engagers: activity signals but CRS and on-target/off-tumor myelosuppression limiting; no approvals yet, novel concept of multiple targeting of combinatorial treatment in clinical trials
AML – CAR-T	Multiple targets (CD33, CD123, CLL-1, NKG2D): efficacy signals in Phase I but antigen escape, LSC resistance, CART pharmacy attractive, Stem cell editing looks super attractive, but safety needs to be shown
Bottom line	AML needs combinatorial strategies, better antigen selection, and immune microenvironment solutions — NOT a simple extrapolation from ALL

Acknowledgements

Contact: marion.subklewe@med.uni-muenchen.de

@MSubklewe
@LMU_Immutherapy

Laboratory for Translational Cancer Immunology

Pierluigi Carulli
Paulina Ernst
Saksham Garg
Gerulf Hänel
Rosella Labella
Giulia Magno
Amelie Muth
Anne-Sofie Neumann
Daniel Nixdorf
Nora Phillip
Giulia Rappa
Lisa Rohrbacher
Sabine Sandner
Lis Winter

Department of Medicine III – Oncology and Hematology

Michael v. Bergwelt
Veit Bücklein
Martin Dreyling
Adrian Gottschlich
Frederike Hildebrand
Alessandra Holzem
Florentine Kolbig
Linus Kruk
Giulia Magno
Michael Ruzika
Christian Rausch
Kai Rejeski
Christian Schmidt
Kayleen Shi
Sophia Stock
Oliver Weigert

Laboratory of Leukemia Diagnostics

Veit Bücklein
Elke Habben
Bianca Kirschbaum
Bianca Kostrau
Stephanie Schneider
Karsten Spiekermann
Ewelina Zientara

LMU – Department of ATMZH, Neurology, Klin Pharm, Neurosurgery, Radiology, Nuclear Medicine, IZB

Natalie Albert
Louisa von Baumgarten
Andreas Humpe
Florian Schöberl
Michael Winkelmann
Sebastian Kobold

Karl-Peter Hopfner
Veit Hornung
Tobias Straube
Andreas Linder

USA

Moffitt Cancer Center
Michael Jain
Frederick Locke

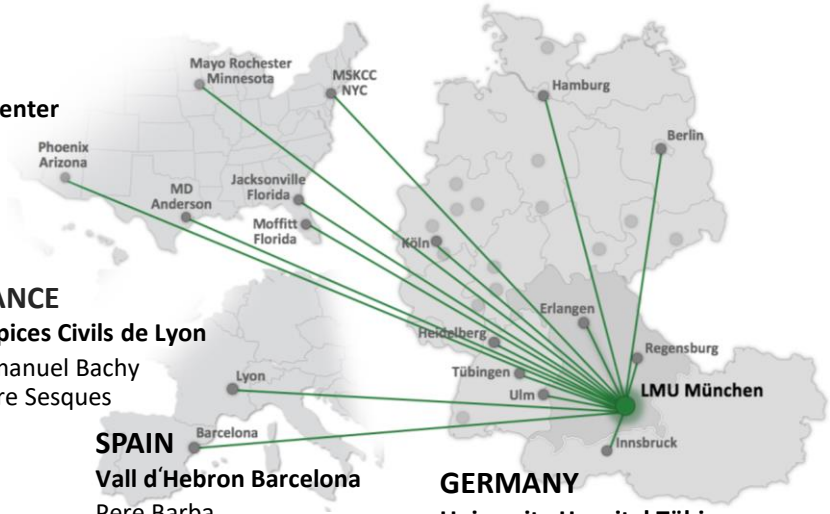
MSK
Roni Shouval

FRANCE

Hospices Civils de Lyon
Emmanuel Bachy
Pierre Sesques

SPAIN

Vall d´Hebron Barcelona
Pere Barba
Cecilia Carpio
Gloria Iacoboni



GERMANY

University Hospital Tübingen
Wolfgang Bethge
Christoph Faul
Christoph Stein-Thöringer

University Hospital Erlangen
Andreas Mackensen
Fabian Müller
Sam Völkl

Berlin Charité
Lars Bullinger
Olaf Penack

Heidelberg
Michael Schmidt

MetaboTargetAML