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Gene Center Munich

T-cell engagers in ALL & AML

Marion Subklewe, M.D.
Head of the Cellular Immunotherapy Program at the LMU – University Hospital Munich
Head of the Lab for Translational Cancer Immunology at the LMU – Gene Center Munich

Head of the Early Clinical Trial Unit

Head of Flow within the Lab for Leukemia Diagnostics

Subklewe Lab for Translational Cancer Immunology

Disclosures

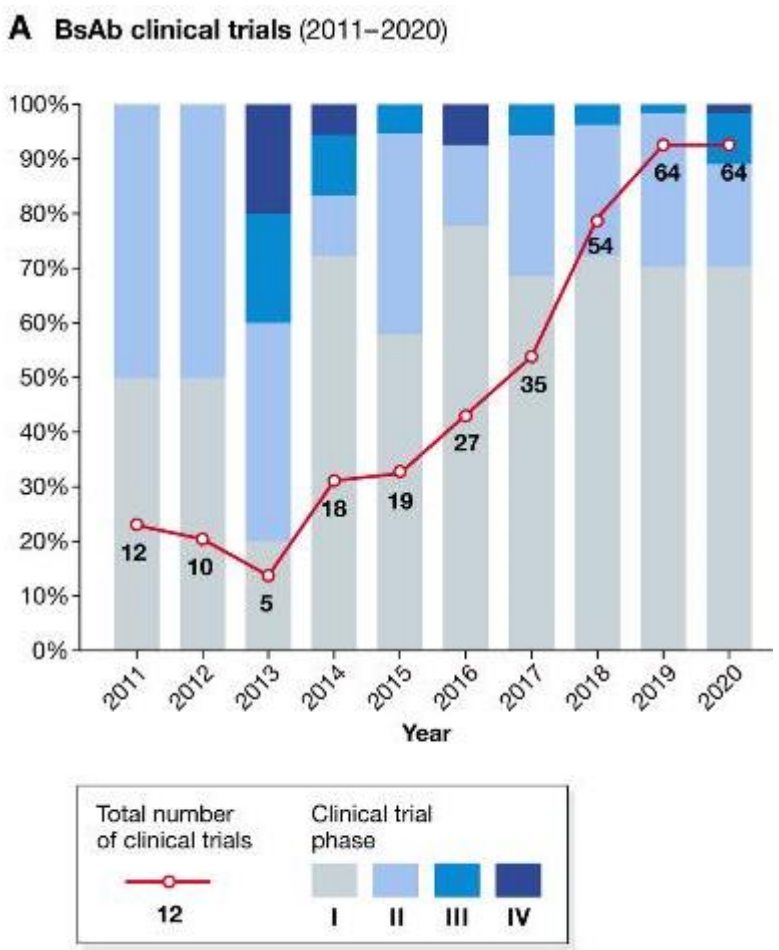
Educational Grant:	BMS/Celgene, Gilead/Kite, Janssen, Novartis,Takeda
Research Support:	Amgen, Miltenyi, Molecular Partners, Roche, Seattle Genetics
Advisory Board:	Avencell, Ichnos, Incyte, Janssen, Molecular Partners, Novartis, Pfizer, Takeda
Speaker’s Bureau:	Amgen, BMS/Celgene, Gilead/Kite, Novartis

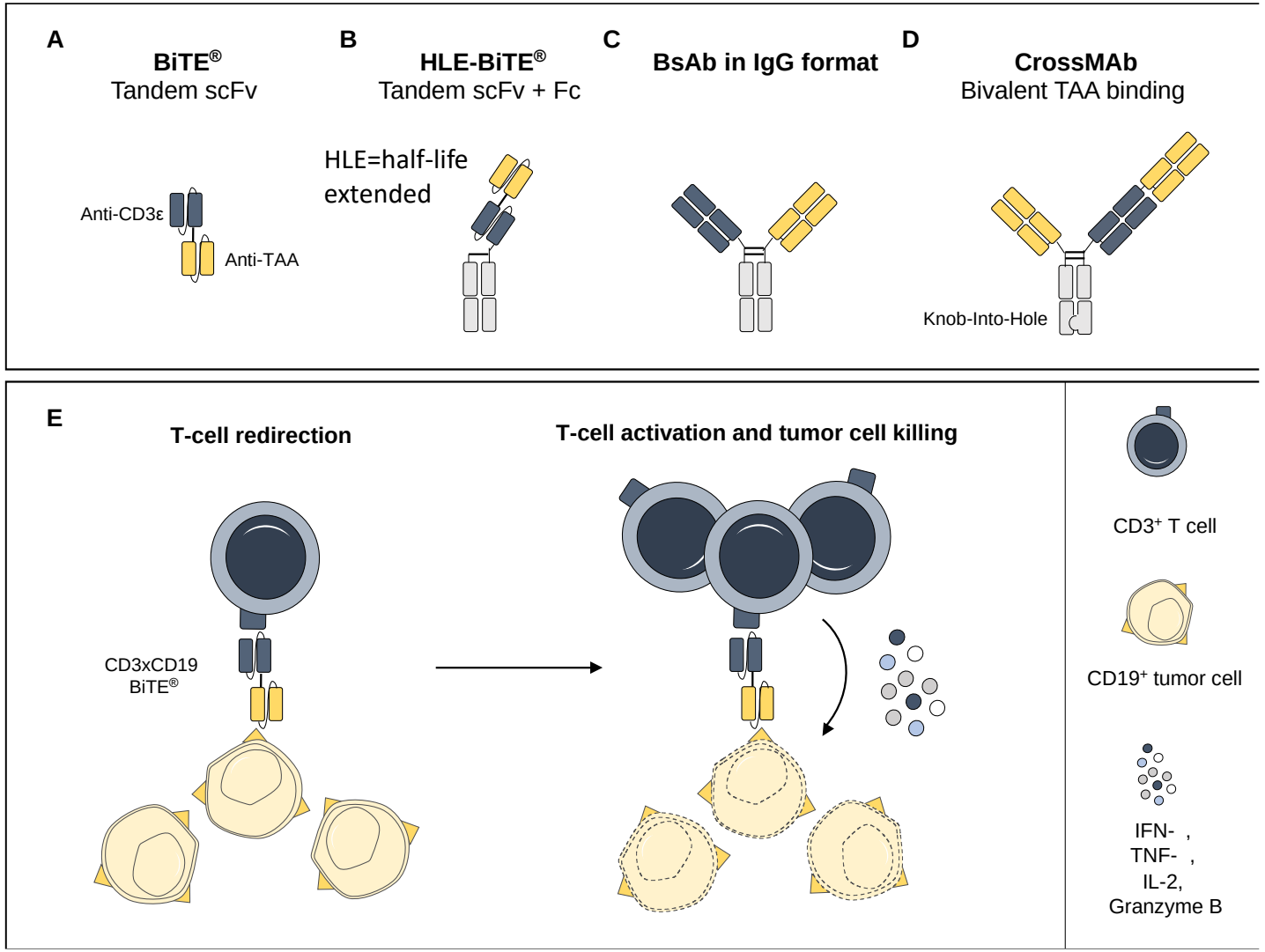
Agenda

Disease Entity	Drug	Clinical Scenario / Translational Question	Reference
ALL	Blinatumomab	R/R	Kantarjian et al; NEJM 2017
		MRD	Gökbuget et al; Blood 2018
		Resistance	Corrado et al; ASH 2023
			Philipp et al; Blood 2022
		Combination with TKI	Philipp et al; ASH 2023
AML	AMG 330, AMG 673, Flotetuzumab and others	Suitable Target Antigens	Haubner et al, Leukemia 2019 Daver et al, Leukemia 2021
		Clinical Trial Results	Subklewe, ASH 2019 Rezvani et al, ASH 2020 Hutschings et al, ASH 2023
		Combination with co-stim bispecifics, IMiDs, STING agonists, VEN/AZA,	Augsberger et al, Blood 2021 Neumann et al, DGHO 2023 Nixdorf et al, ASH 2023 Hänel et al, Leukemia 2024
ALL	Blinatumomab	MRD negative (<0.01 %)	Litzow MR, et al. ASH 2022

Redirection of T cells by Bispecific Antibody Constructs (BsAbs or TCE)

Format impacts Pharmacokinetics, but its impact on Efficacy & Toxicity is unclear





Adapted from Del Bano et al. *Antibodies* 2015; Voynov et al. Antibodies 2020; Daver et al. *Leukemia* 2021; You et al. *Vaccines* 2021; Wang et al. *EMBO Mol Med* 2021

Blinatumomab was the first, and still approved**, T-cell engaging bispecific antibody**

Milstein & Cuello. 1983. „Hybrid Hybridomas“

Staerz et al, 1985. First T cell redirection paper

Clark & Waldmann, 1987. First CD3-based T cell redirection

Nitta et al. 1990. First Bispecific T-cell redirection clinical trial

Haagen et al. 1992. CD19 x CD3 redirecting igG

Mack et al. 1995. First BITE-like Bispecific scFv (anti CD3K17-1A)

De Gast et al., 1995. First Clinical trial with a CD19 x CD3 redirecting IgG

Ridgeway et al., 1996. KIH asymmetric bispecific igG

Zeidler et al., 1999 First description of Trion rat/mouse bispecific Abs

Löffler et al., 2000. First description of CD19xCD3 BITE

2006 - First clinical trial of MT103 (now Blinatumomab; CD19 x CD3 BITE)

2009 - Catumaxomab: First bispecific Ab approved anti-CD3 x EpCAM

Blincyto approved for r/r BCP-ALL (CD19xCD3 BITE)

Emicizumab. approved for treatment of Hemophilia A: FIX/FX

1960 1964 1975 1983 1985 1987 1992 1995 1997 1999 1999 2000 2004 2007 2009 2012 2013 2014 2015 2017 2018 2019 2020 2021 2022 2023

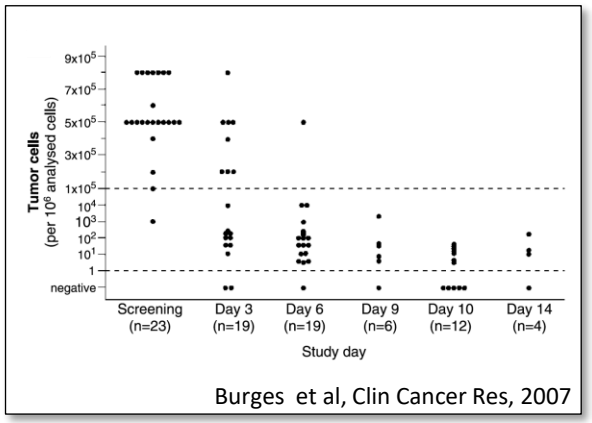
Catumaxomab (Removab®)
2009 by EMA
(2013 voluntarily withdrawn)

Blinatumomab (Blincyto®)
2014 by FDA
2015 by EMA

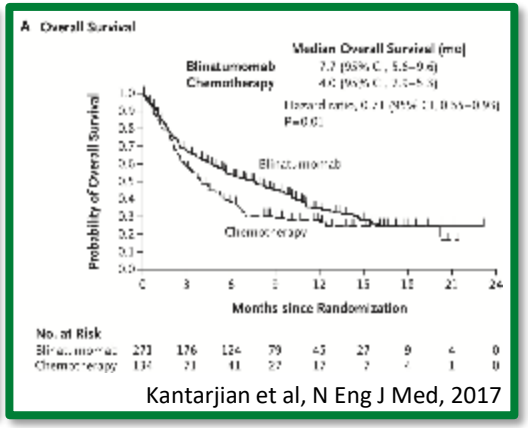
Emicizumab (Hemlibra®)
2017 by FDA
2018 by EMA

Mosunetuzumab (Lunsumio)
2022 by FDA
2022 by EMA

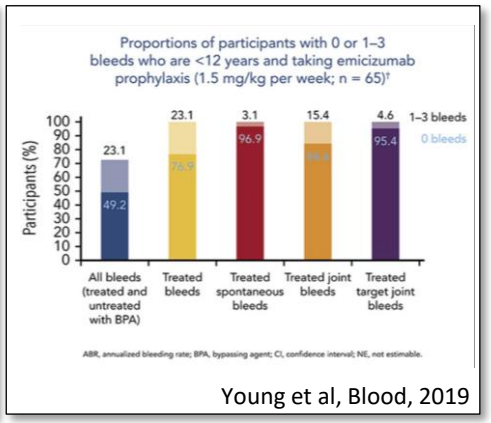
Teclistamab (Tecvayli)
2022 by FDA
2022 by EMA



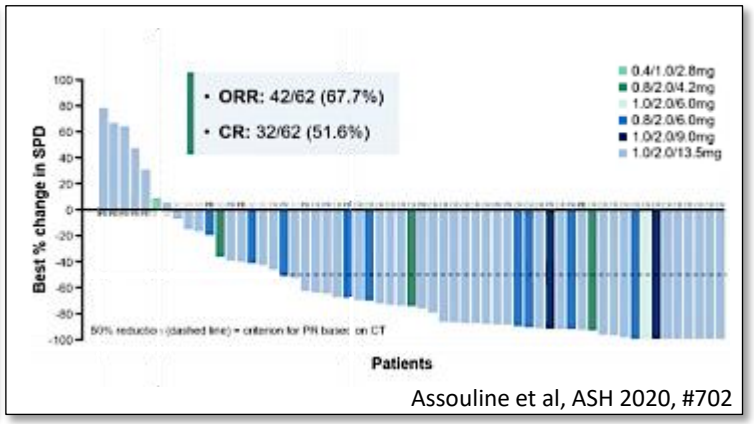
Burges et al, Clin Cancer Res, 2007



Kantarjian et al, N Eng J Med, 2017

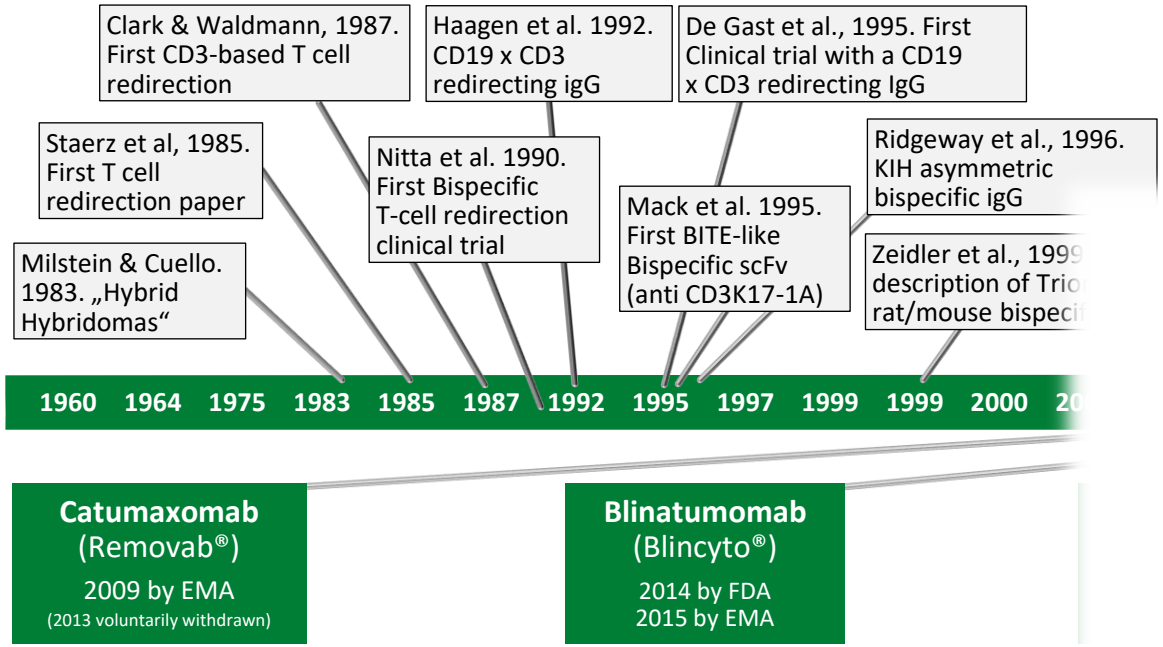


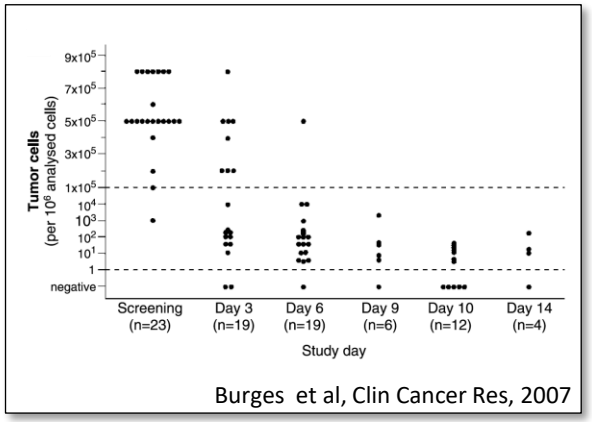
Young et al, Blood, 2019



Assouline et al, ASH 2020, #702

Approved in R/R Ph$^{+/-}$ BCP-ALL (in Ph^{+}after 2 TKIs) and MRD^{+} $^{(0.1\%)}$ BCP-ALL





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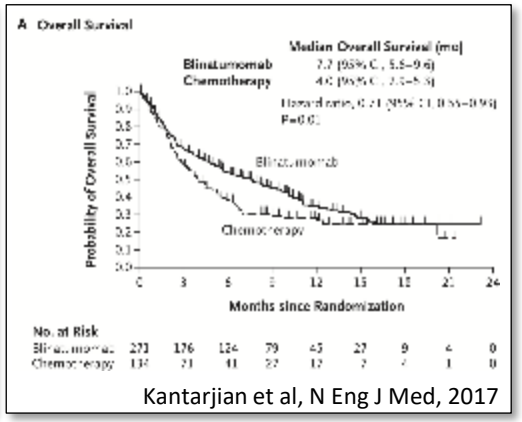
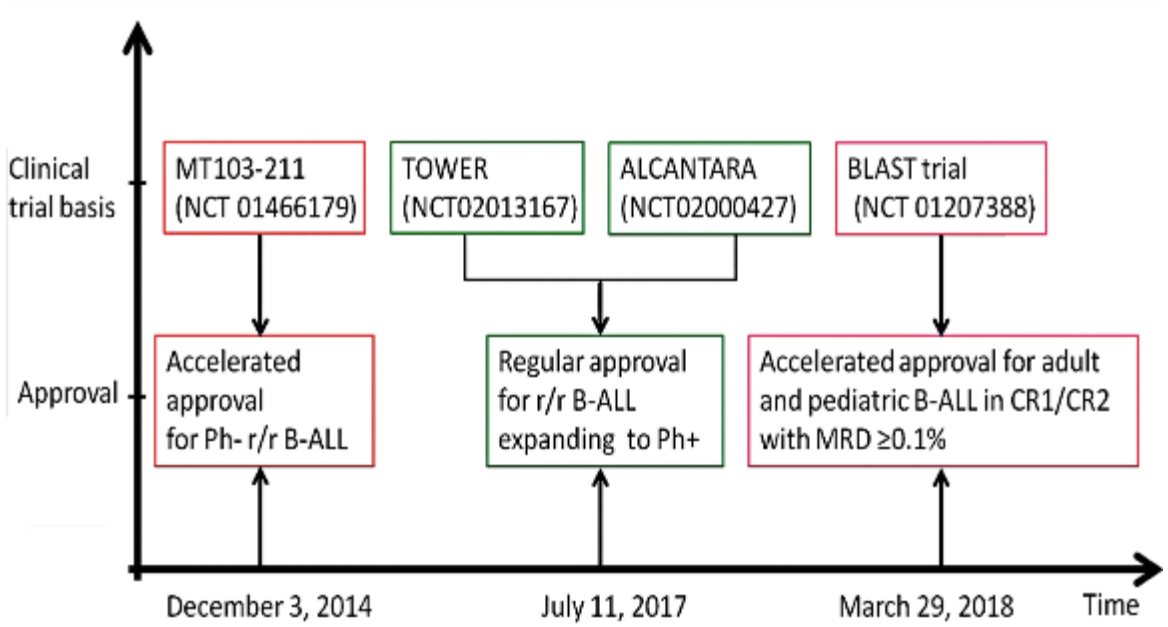


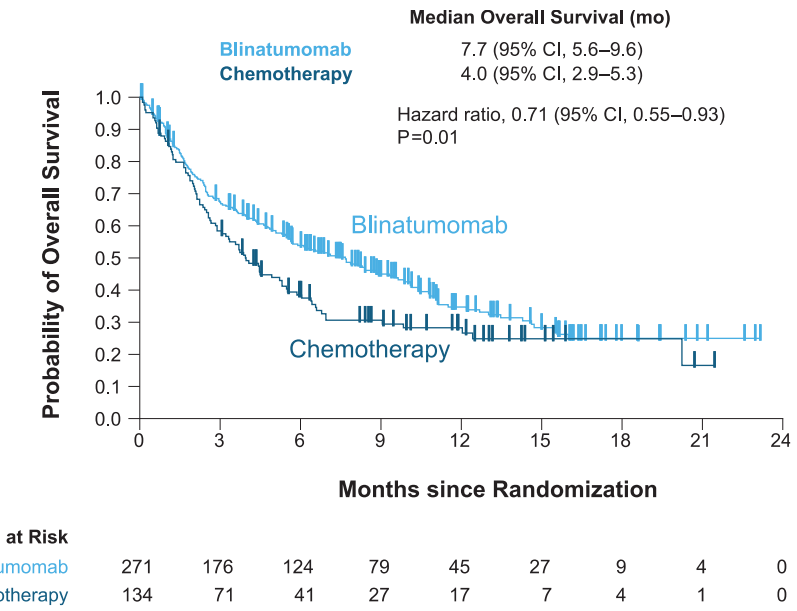
Kantarjian et al, N Eng J Med, 2017

2014: Approval in R/R BCP-ALL (MT103-211)
2017: Confirmed in a randomized trial (Tower)
2018: Approval in MRD^{+} (0.1%) BCP-ALL



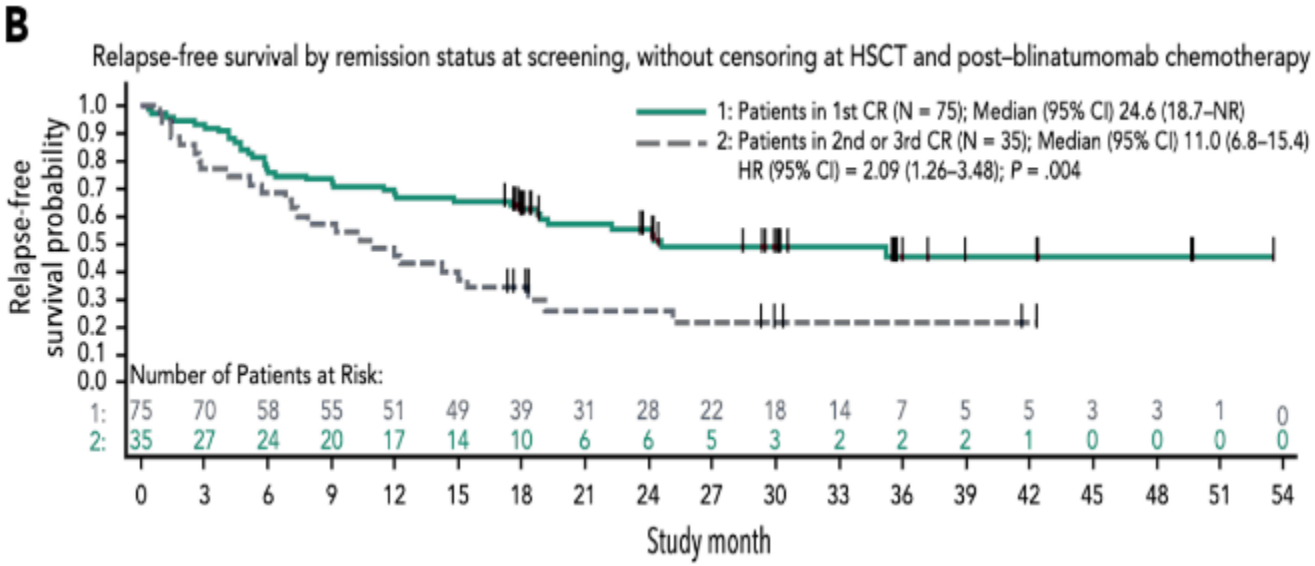
However, Relapse and Lack of Response to Blinatumomab remain a Challenge in BCP-ALL

r/r BCP-ALL patients



Kantarjian et al, *N Eng J Med*, 2017

MRD⁺ BCP-ALL patients

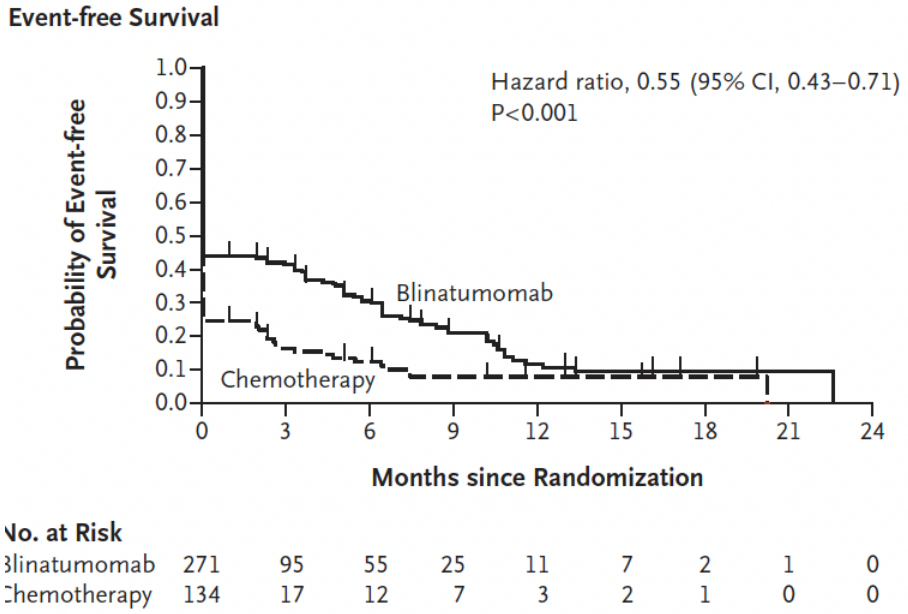


Gökbuget et al. *Blood* 2018

However, Relapse and Lack of Response to Blinatumomab remain a Challenge in BCP-ALL

Relapsed/Refractory Disease

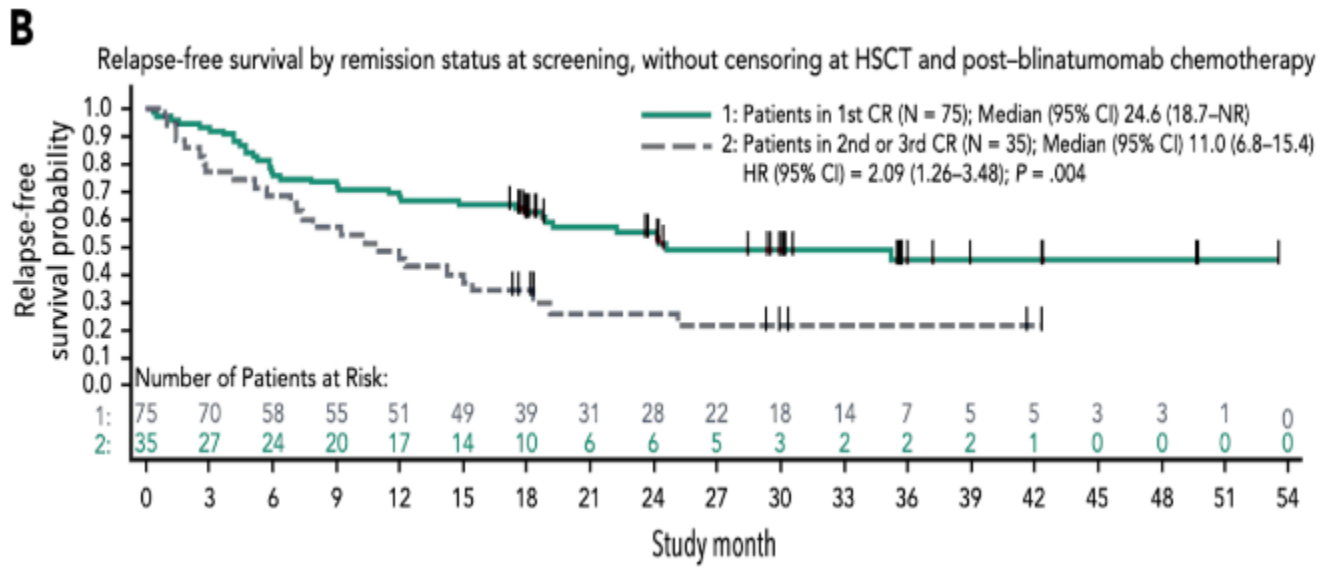
- **~50% do not respond to Blinatumomab[1]**
- The median DoR is **7.3 months**



Kantarjian et al, *N Eng J Med*, 2017

Measurable Residual Disease(MRD)

- **~20% of patients do not achieve MRD negativity[2]**
- The median RFS is **18 months**



Gökbuget et al. *Blood* 2018

Why do patients remain refractory or relapse after Blinatumomab ?

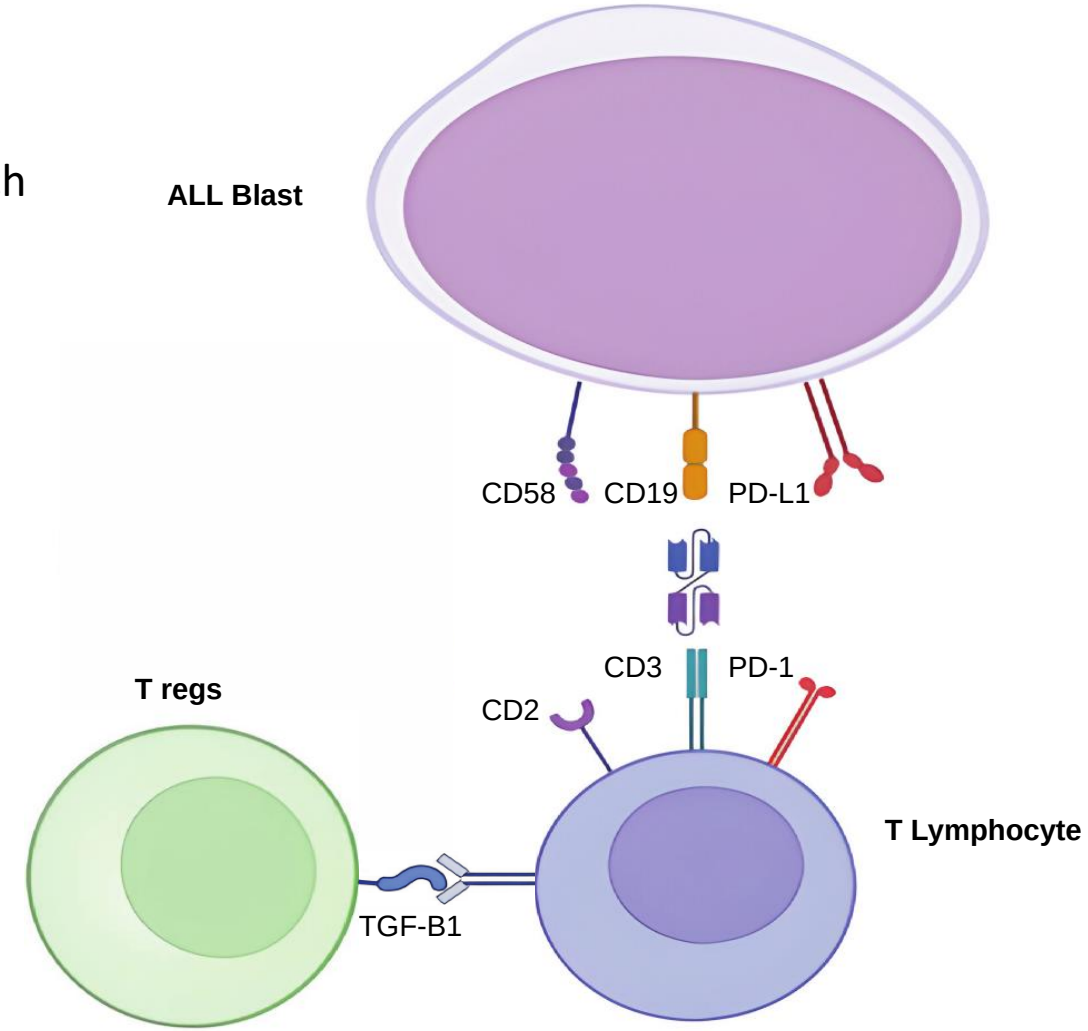
Resistance to Blinatumomab: Tumor Intrinsic & Tumor Extrinsic Factors

Tumor-intrinsic factors

- **8-35%** of relapses **are CD19 negative**[1]
- **2.2%** of BCP-ALL cases harbor **PAX5 mutations**[2], which impairs immune synapse formation
- PD-L1 upregulation has been described at relapse[3]

Tumor-extrinsic factors

- The percentage of circulating **CD4⁺ CD25⁺ FOXP3⁺** is **negatively associated** with response to Blina[4]



1. Zhao et al. Blood, 2021; 2. Li et al. Sci Adv, 2022; 3. Köhnke et al. J Hematol Oncol, 2015; 4. Duell et al. Leukemia, 2017

Resistance to Blinatumomab: Tumor Intrinsic & Tumor Extrinsic Factors

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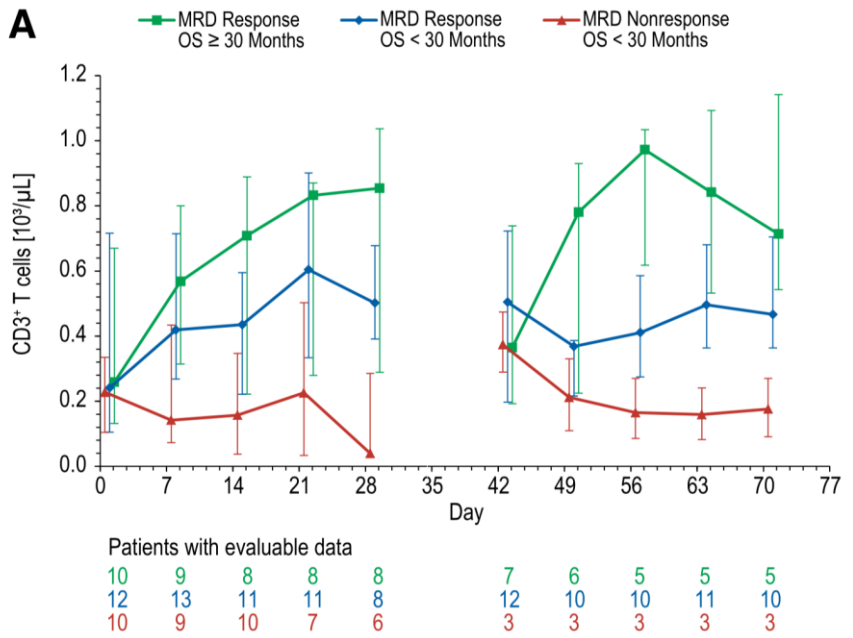
Study Aim

- **Characterize pretreatment peripheral blood T-cell features that are** associated with response to Blinatumomab

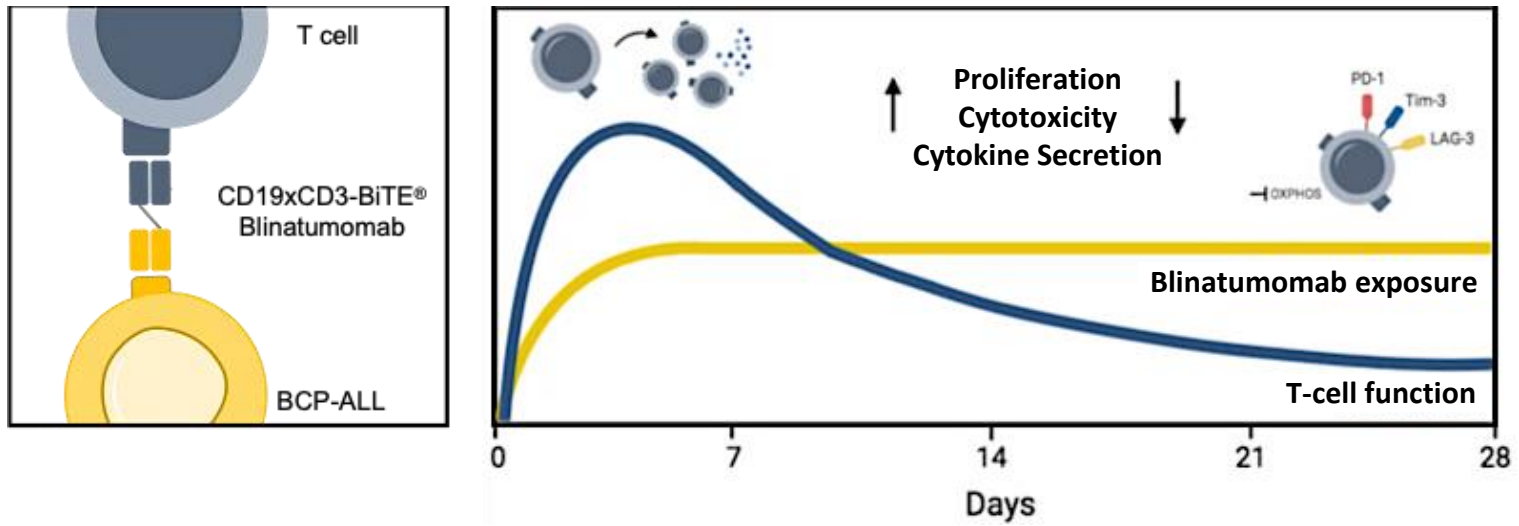
T-cell expansion correlates to response



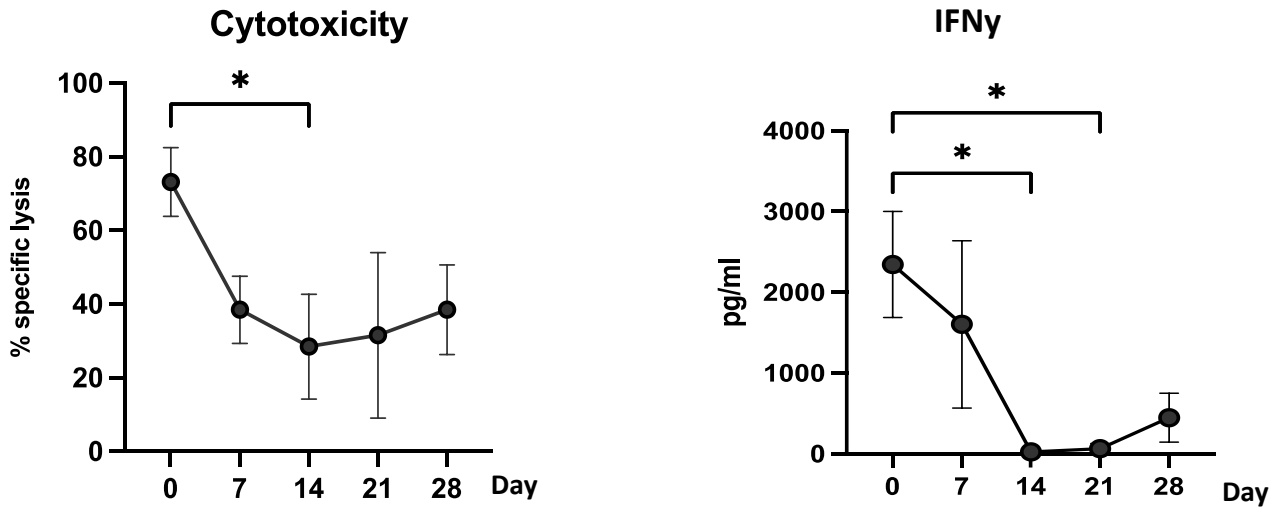
Zugmaier et al. *Blood* 2015

1. Zhao et al. Blood, 2021; 2. Li et al. Sci Adv, 2022; 3. Köhnke et al. J Hematol Oncol, 2015; 4. Duell et al. Leukemia, 2017

Hypothesis: Continous Exposure to Bispecifics Induces T-cell Exhaustion



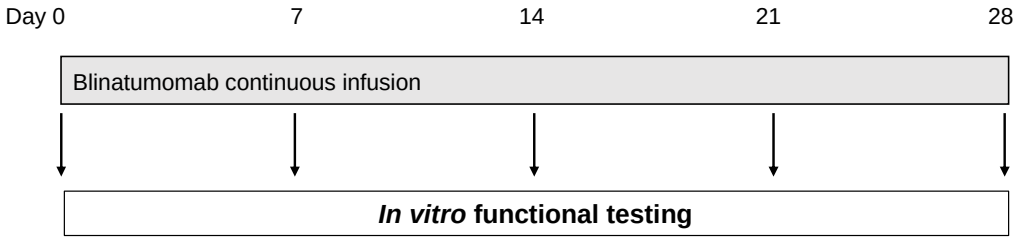
Immunmonitoring of ALL pt on Blin Tx (CD19 x CD3 BiTE) given for 28 days as c.i.v.

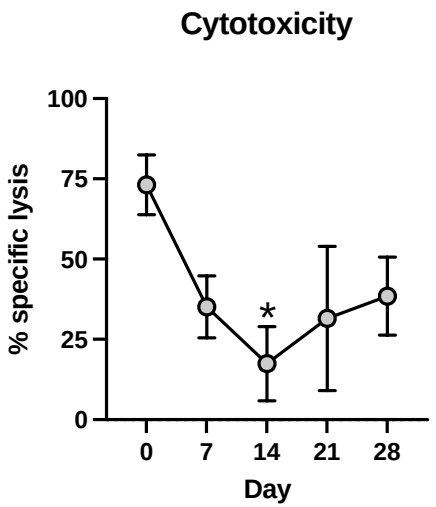


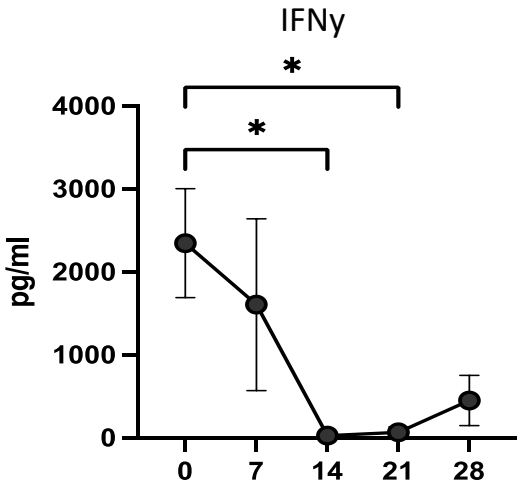
Philipp et al, Blood 2022

In Vitro Model System Mimics Continuous BsAb Exposure in Patients: loss of T-cell function

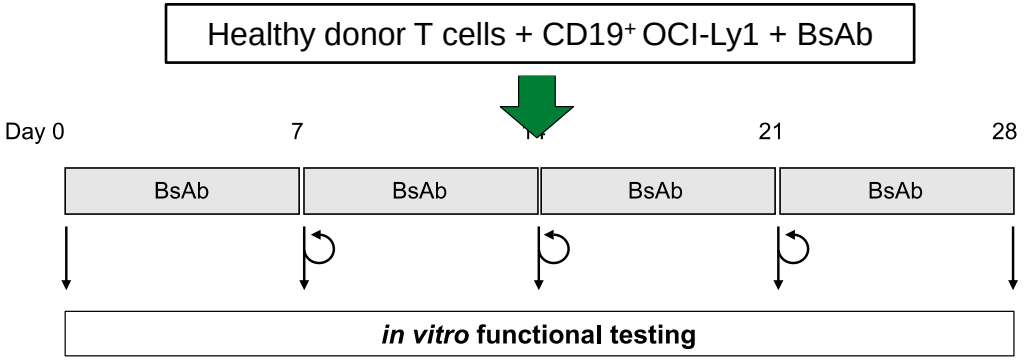
Patient data: Continuous Blinatumomab Infusion

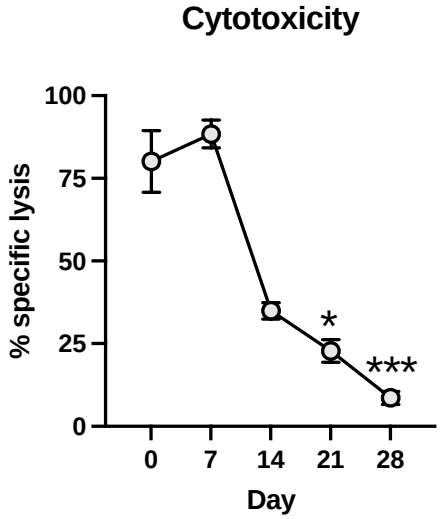




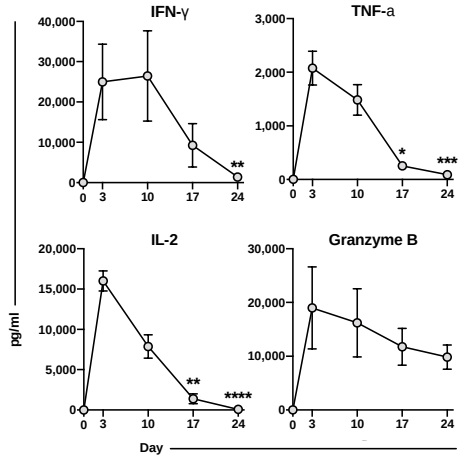


*In vitro M*odel System of Continuous BsAb Exposure





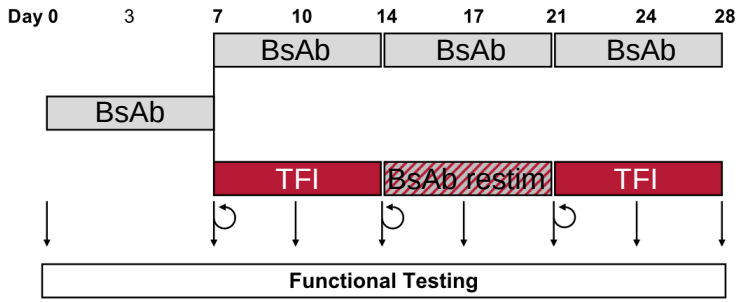
Cytokines: IFNy, IL-2 TNF, Granzyme B



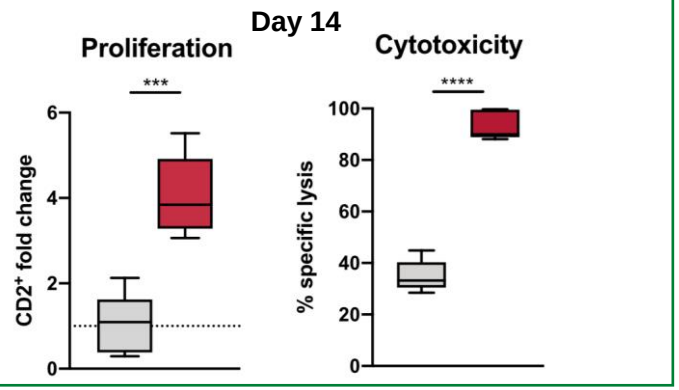
BsAb T-cell isolation T-cell restimulation

Treatment-Free Intervals Ameliorate T-Cell Exhaustion

Experimental Set-Up

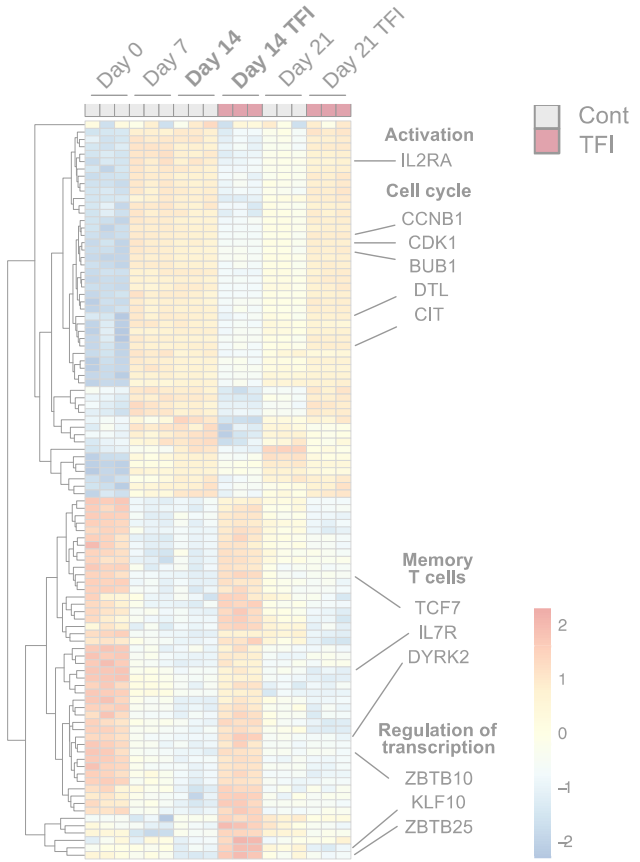


Proliferation & Cytotoxicity



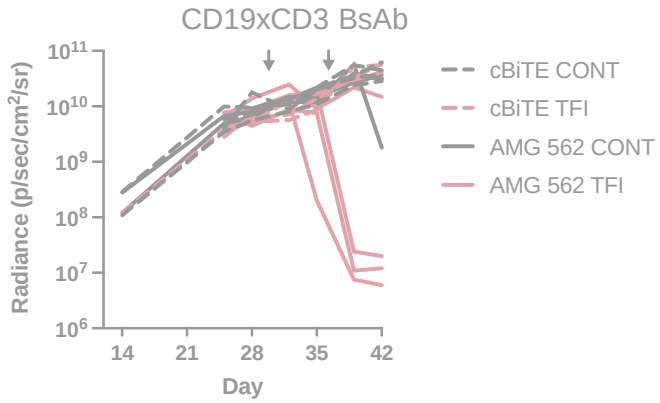
2-way ANOVA and Sidak´s multiple comparison test; n=3-9

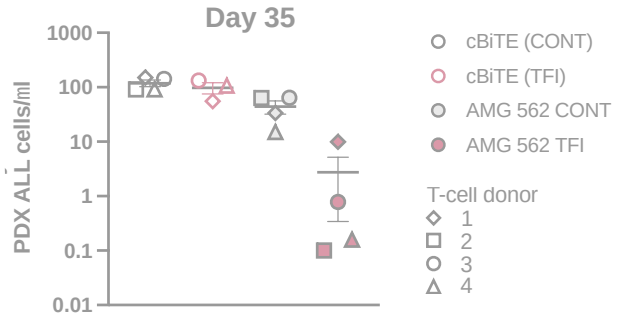
Differentially Expressed Genes



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

in vivo Tumor Burden



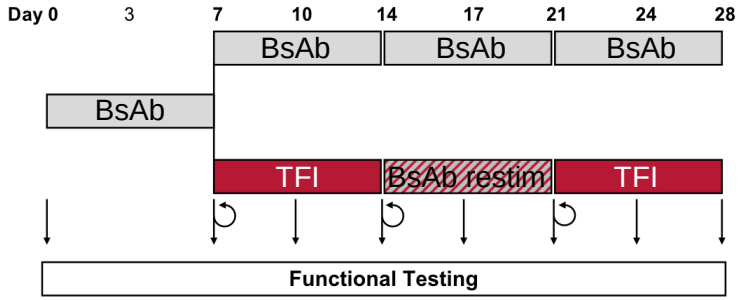


Continuous BsAb TFI BsAb re-exposure after TFI

Philipp et al. 2022 *Blood*

Treatment-Free Intervals Ameliorate T-Cell Exhaustion

Experimental Set-Up



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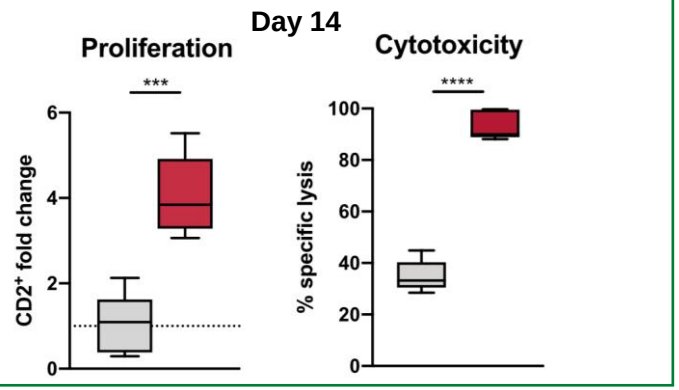

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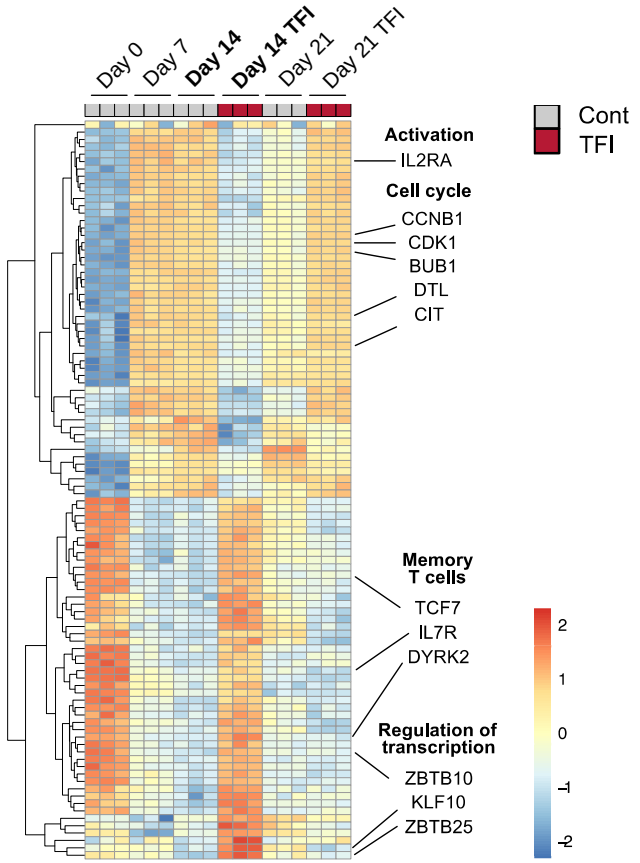

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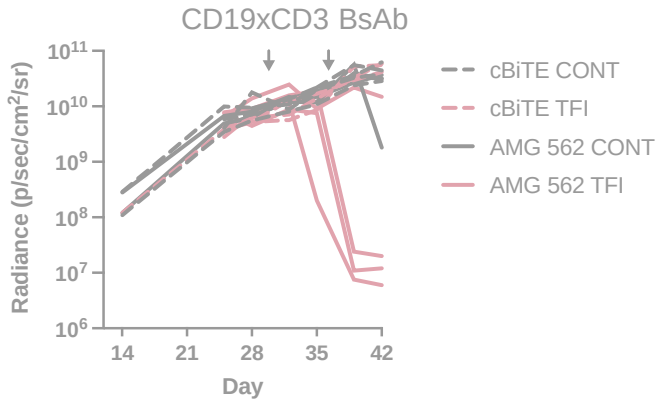

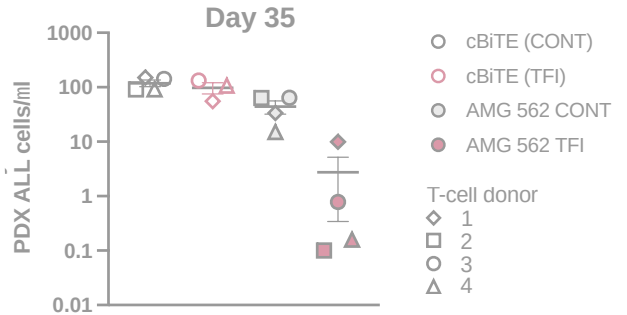

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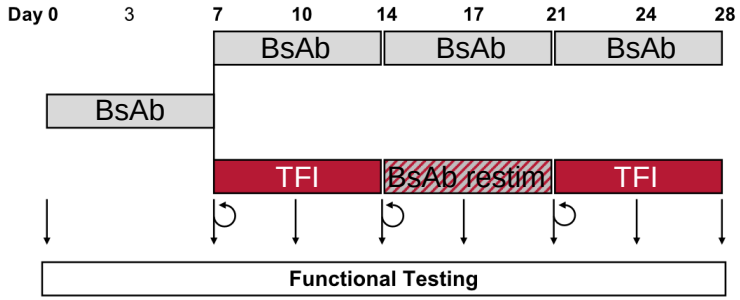

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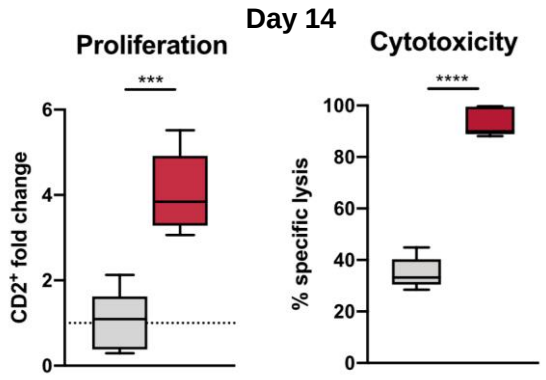

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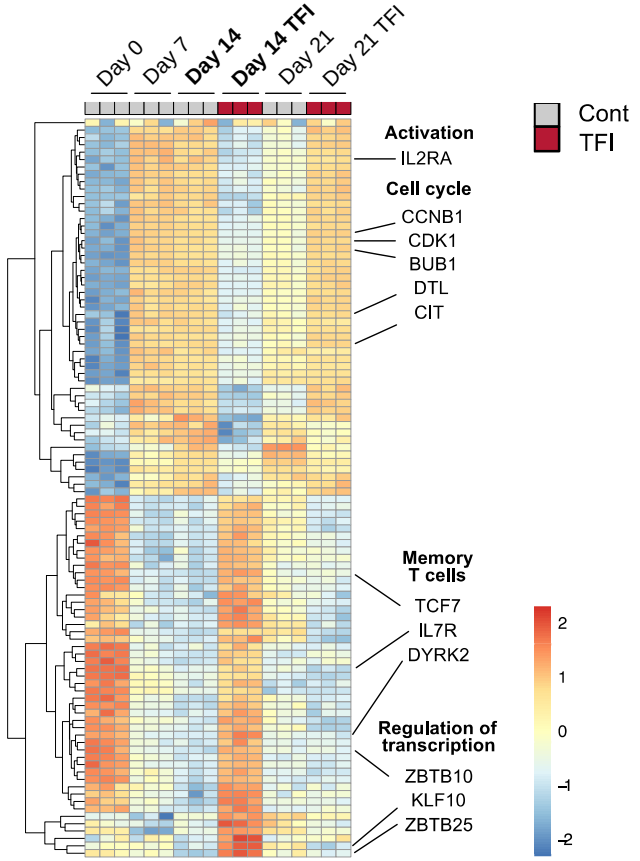

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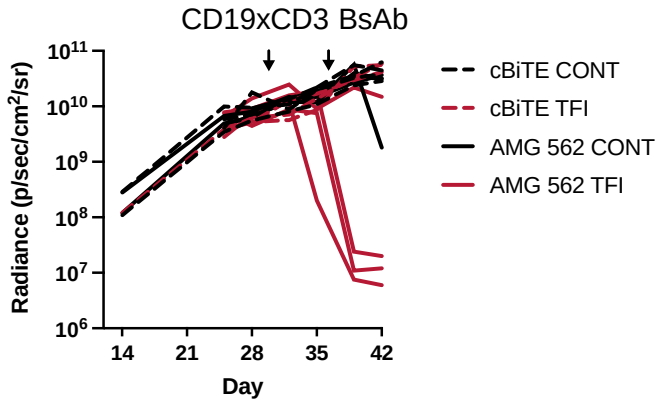
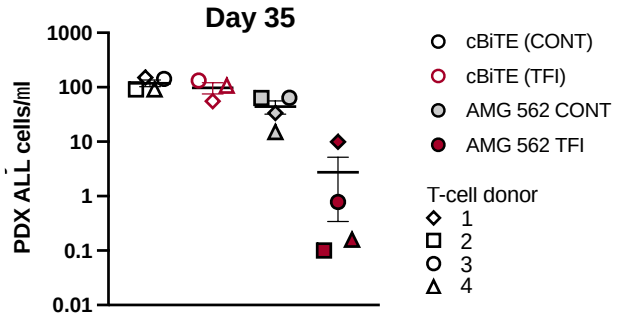
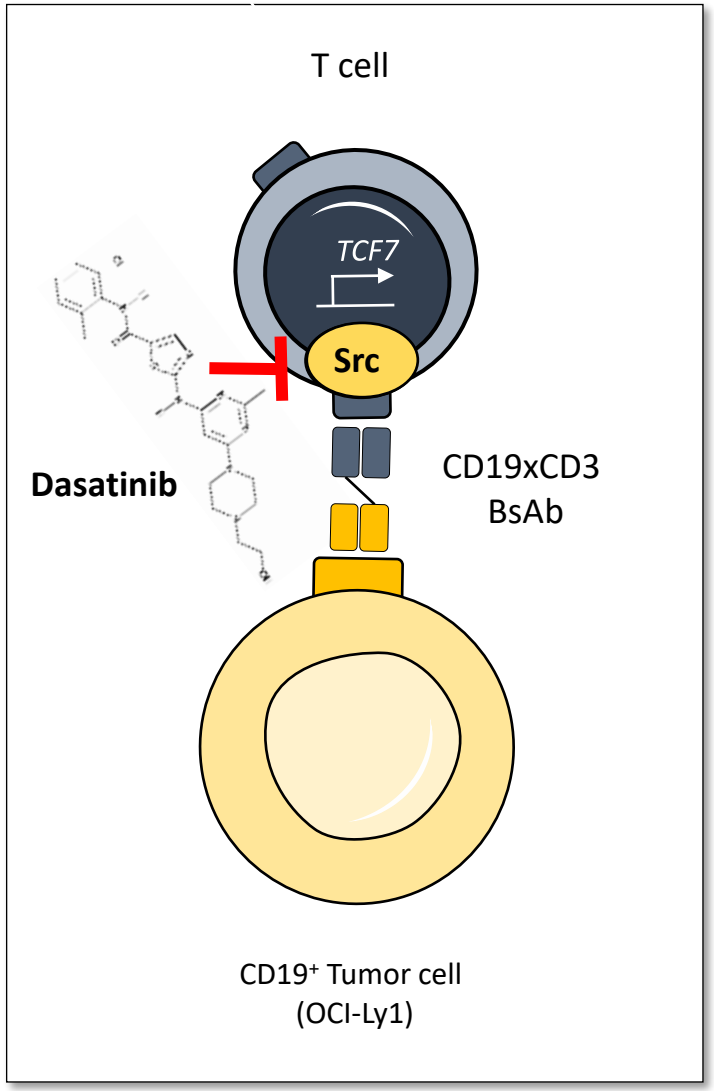


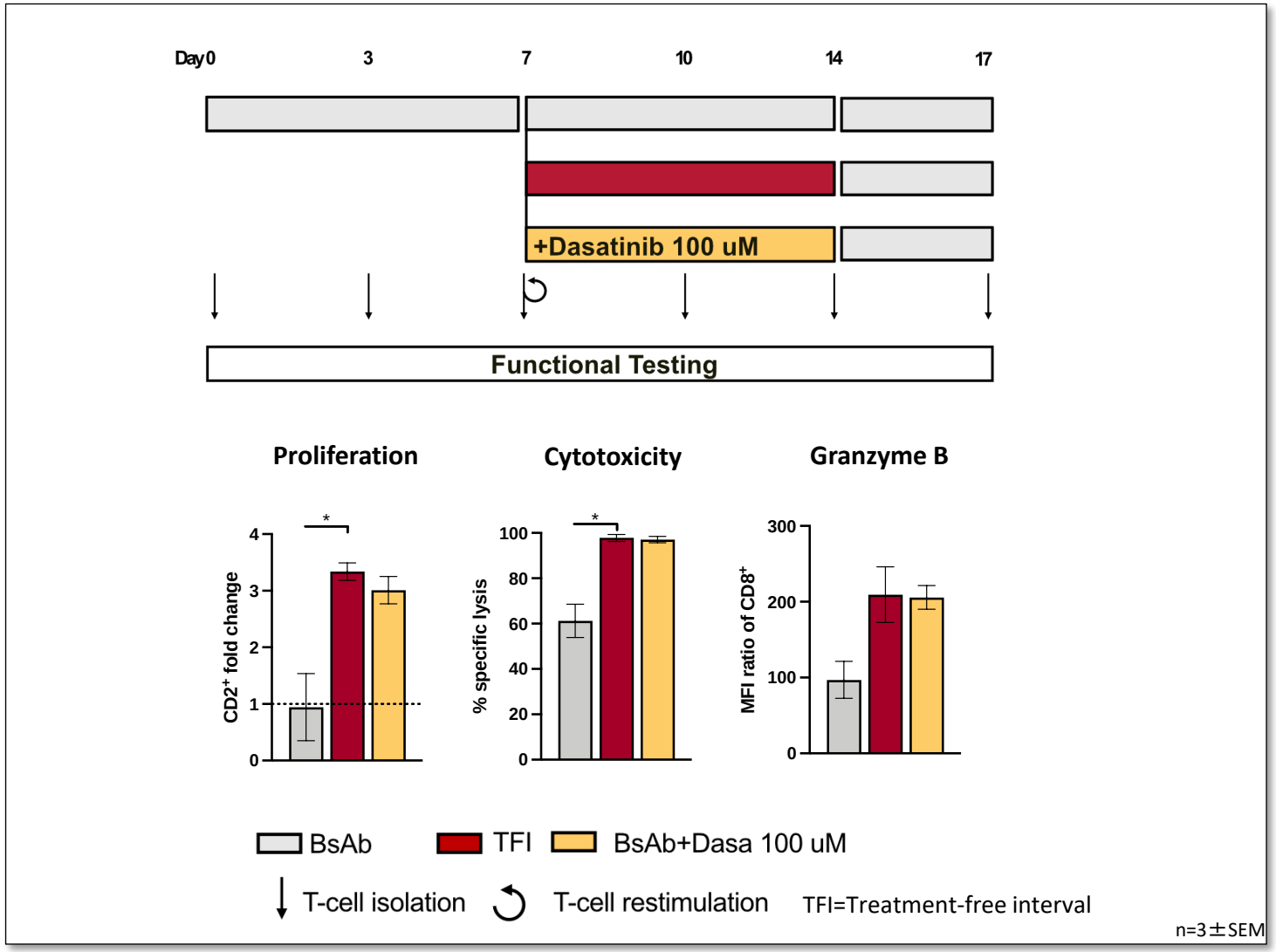


Continuous BsAb TFI BsAb re-exposure after TFI

Philipp et al. 2022 *Blood*

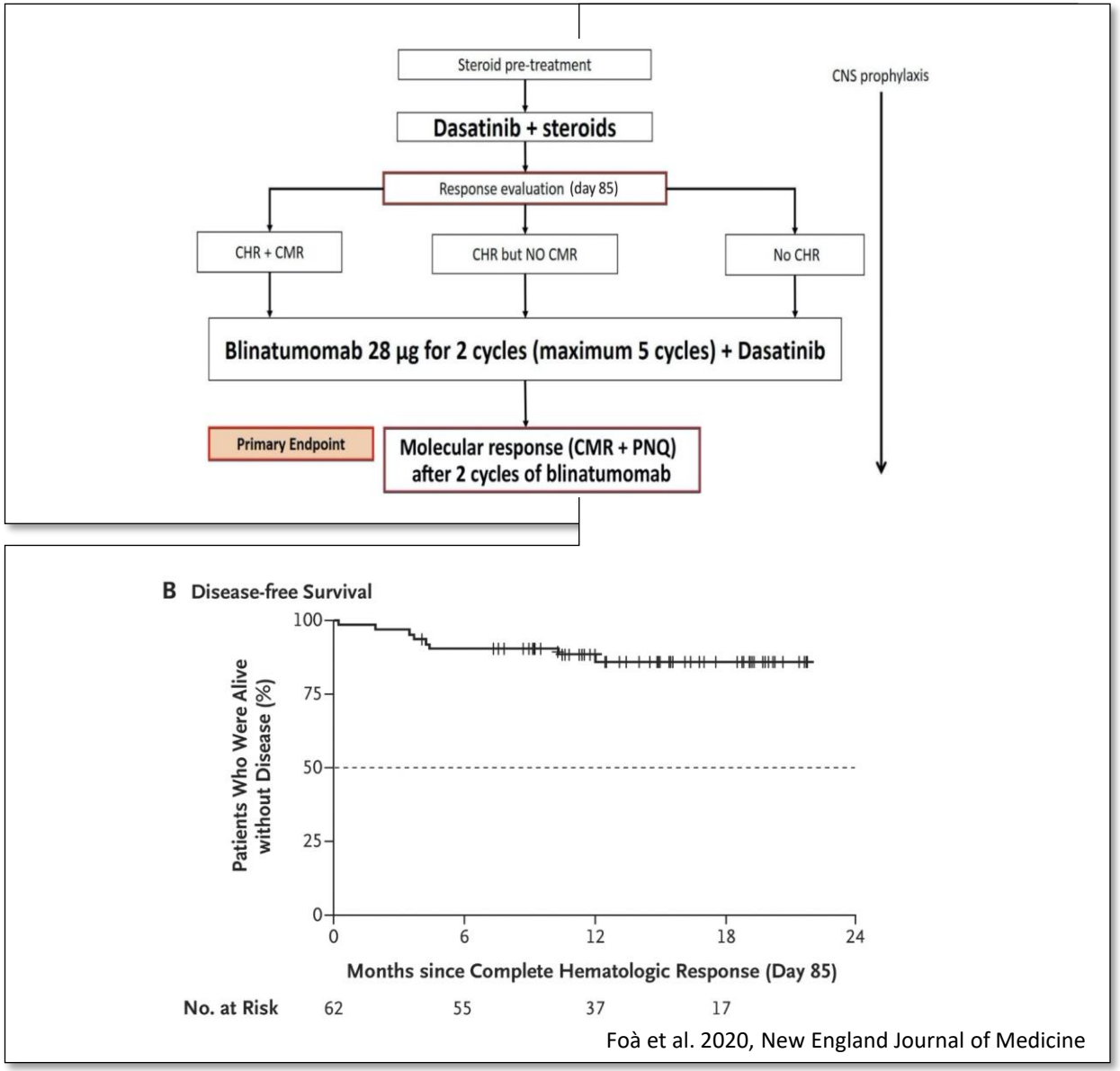
Treatment Free Intervals (TFI) + BsAb vs Dasatinib + BsAb: Similar Results





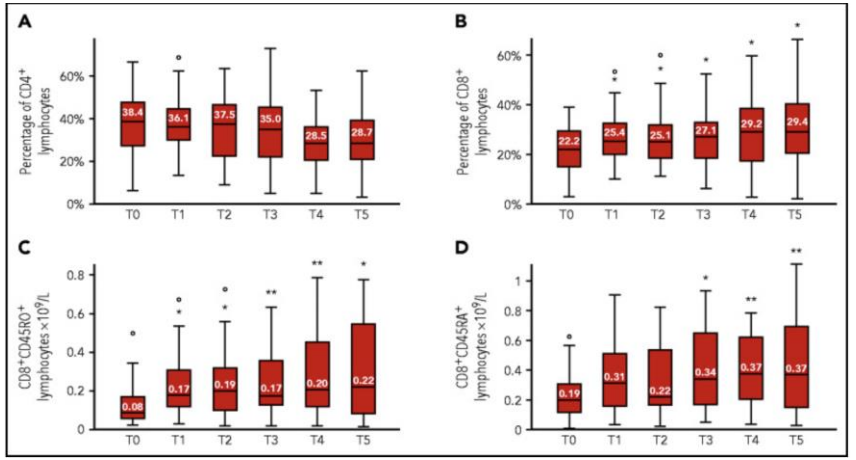
Philipp et al. 2022 Blood

D-ALBA Trial: Dasatinib followed by Dasatinib + Blinatumomab in de novo Ph+ BCP-ALL

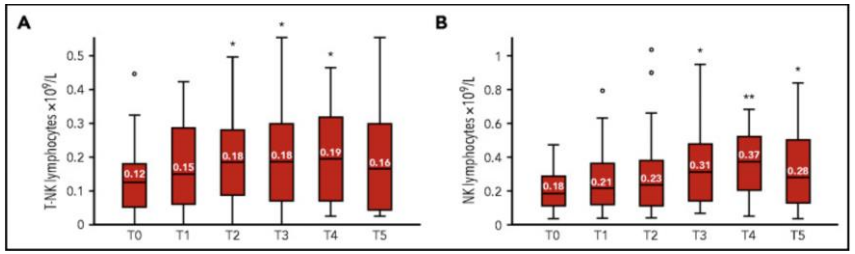


Foà et al. 2020, New England Journal of Medicine

T cells



NK cells



The Immunomodulatory effect of Blinatumomab likely contributes to the progressive increase in CMR rate during the consolidation phase

Puzzolo et al. 2021, Blood

Blinatumomab + dasatinib or ponatinib in Ph$^+$ ALL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2020 VOL. 383 NO. 17

Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, M.D., Paolo Di Bartolomeo, M.D., Alessandra Mancino, M.S., Maria-Stefania De Propris, Ph.D., Marco Vignetti, M.D., Anna Guarini, Ph.D., Alessandro Rambaldi, M.D., and Sabina Chiaretti, M.D., Ph.D., for the GIMEMA Investigators*

Foà et al. 2020 NEJM

THE LANCET Haematology

Volume 10, Issue 1, January 2023, Pages e24-e34

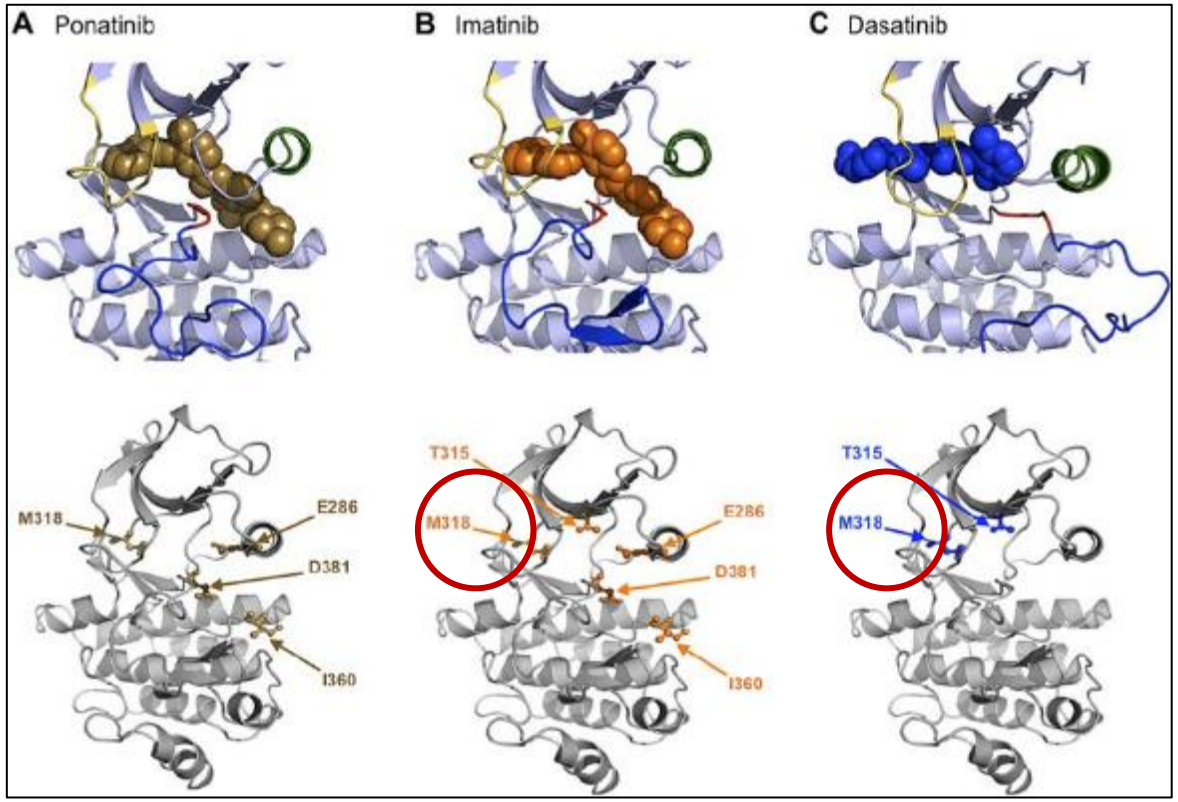
Articles

Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial

Prof Elias Jabbour MD [a †], Nicholas J Short MD [a †], Nitin Jain MD [a], Prof Xuelin Huang PhD [b], Guillermo Montalban-Bravo MD [a], Pinaki Banerjee PhD [c], Prof Katayoun Rezvani MD [c], Xianli Jiang PhD [d], Kun Hee Kim [d], Rashmi Kanagal-Shamanna MD [e], Joseph D Khoury MD [e], Prof Keyur Patel MD [e], Prof Tapan M Kadia MD [a], Naval Daver MD [a], Kelly Chien MD [a], Yesid Alvarado MD [a], Prof Guillermo Garcia-Manero MD [a], Ghayas C Issa MD [a], Fadi G Haddad MD [a], Monica Kwari RN [a]...Prof Hagop Kantarjian MD [a]

Jabbour et al. 2023 The Lancet Haematology

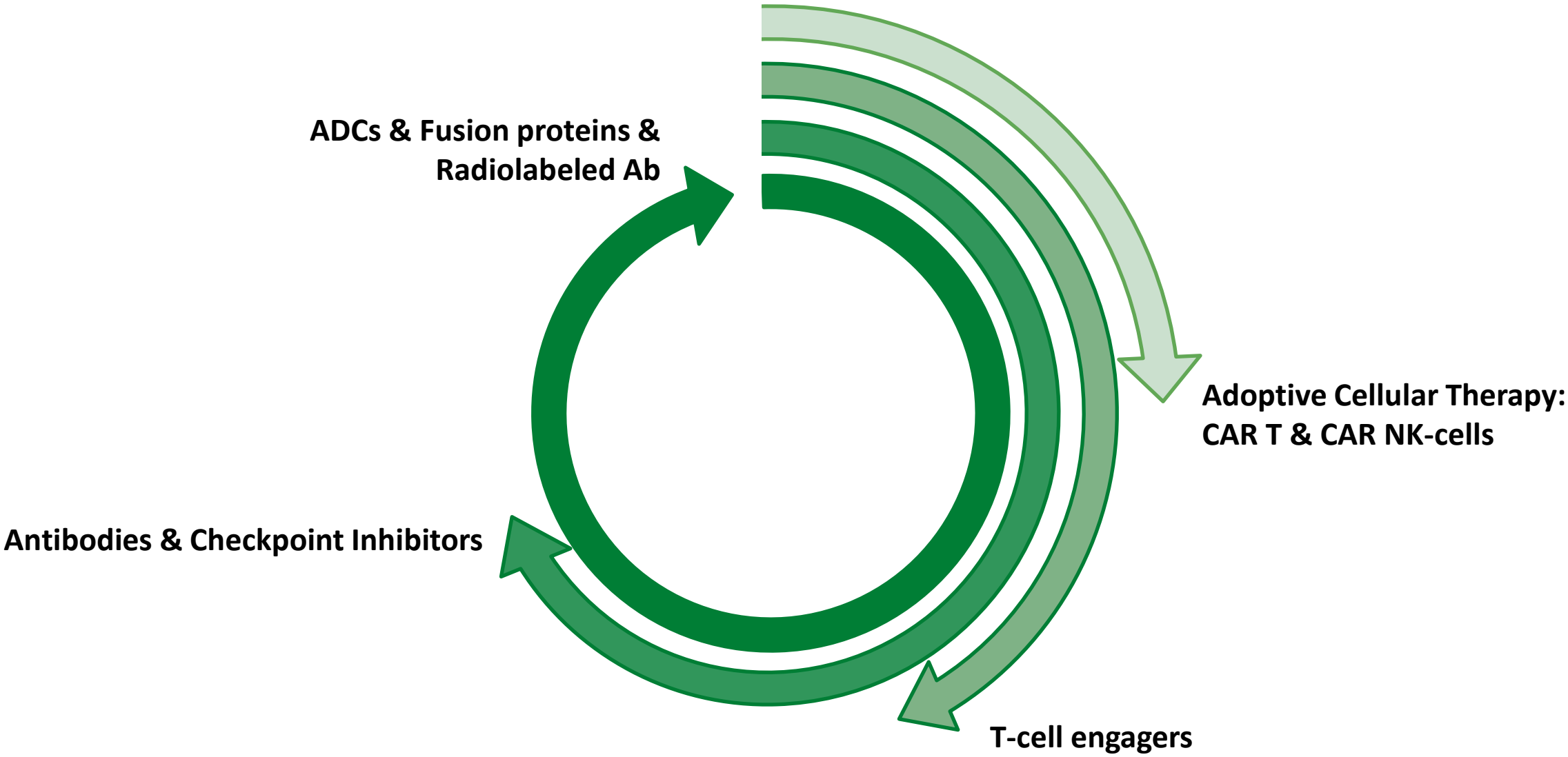
Ponatinib can bind T315-mutated BCR-ABL



Buffa et al. 2014 The FASEB Journal

So far, only ADCs have received Approval in AML

Immunotherapy Platforms are at different stages of clinical development



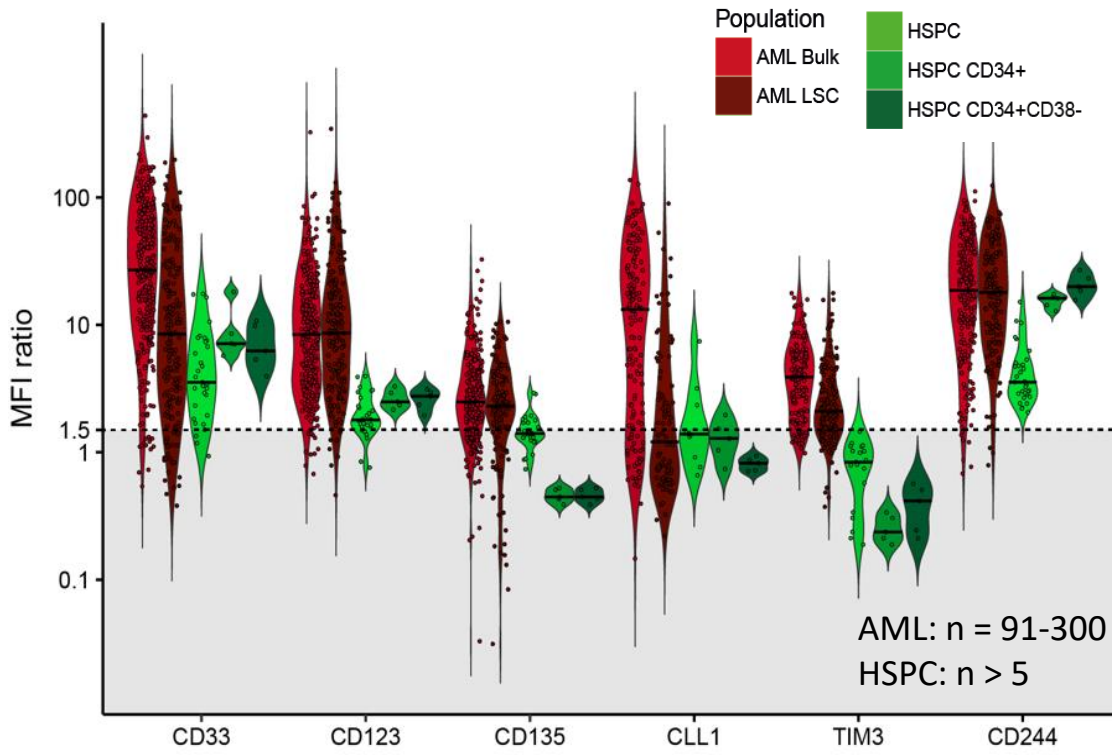
Challenge in AML: Choice of Target Antigen

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
- **T-cell Dysfunction:** Chronic stimulation through continous antigen exposure within the (healthy) myeloid compartment
- **Escape Variants:** Heterogeneous expression profile Inter- and Intraindividually

Daver…Subklewe, Leukemia 2021

Antigen Expression in AML and Normal Hematopoiesis



Haubner et al, Subklewe, Leukemia 2019

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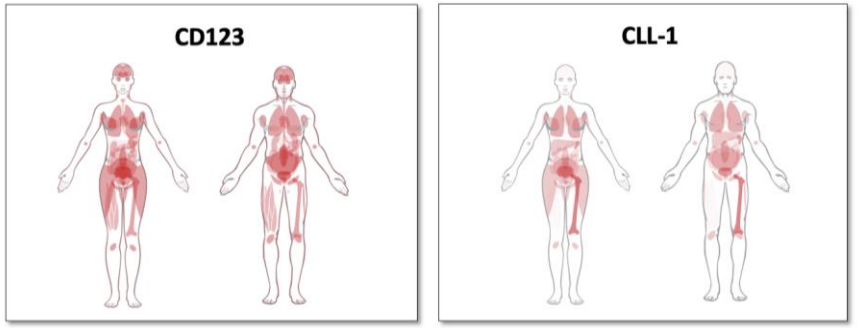
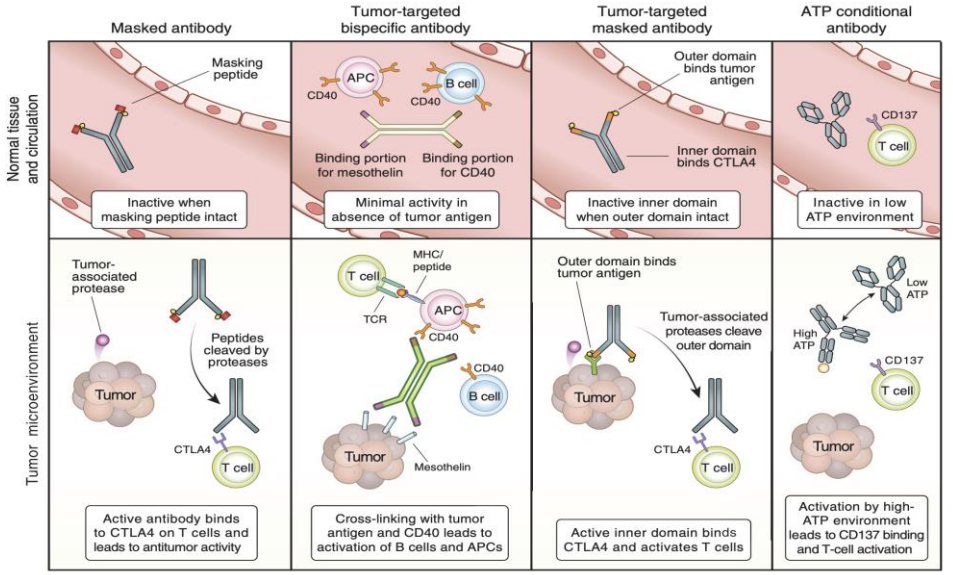


Inactive Antibodies in Circulation and normal Tissue and Enhanced Activity within Tumors



Cattaruzza et al. Nat. Cancer 2023; Kamata-Sakurai et al, Cancer Discovery 2021

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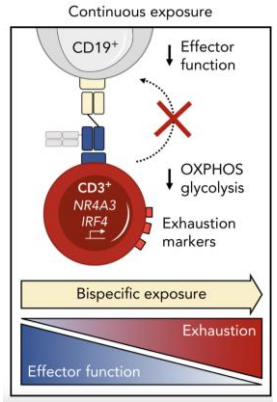
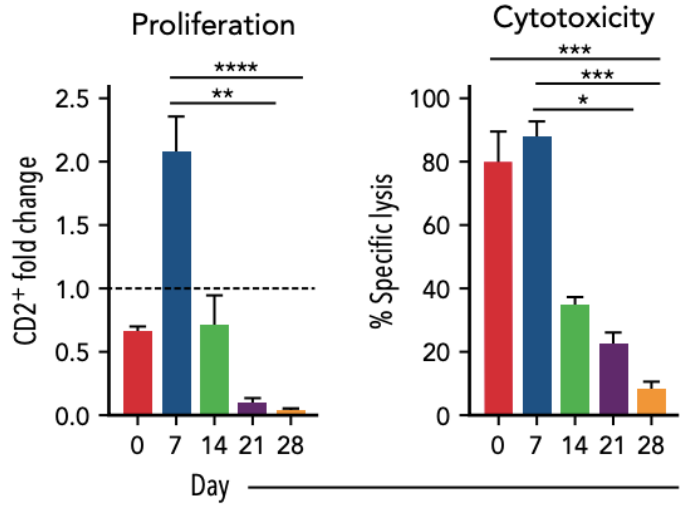
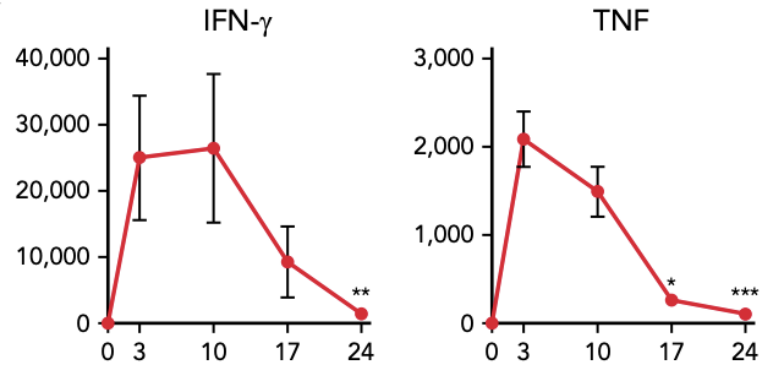
Daver…Subklewe, Leukemia 2021

Continous Antigen Exposure leads to T-cell Exhaustion



T cell engager





Phillip et al, Subklewe, Blood 2022

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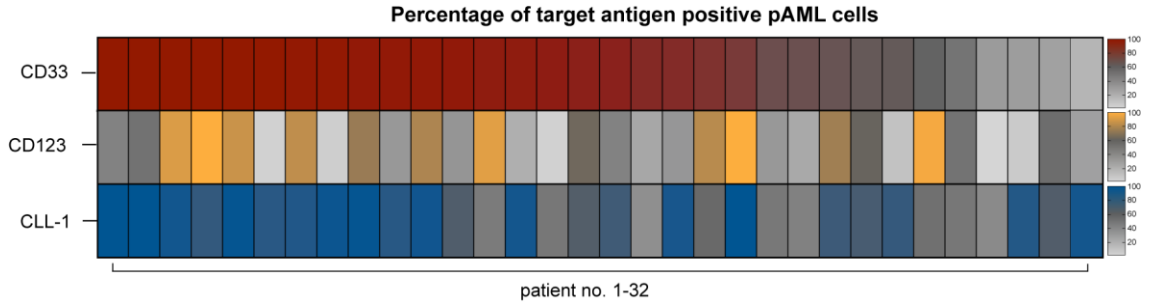
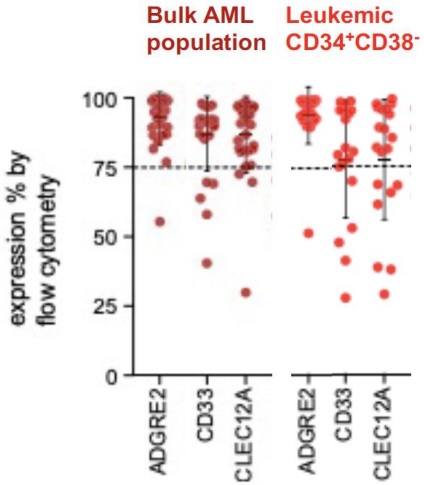
Daver…Subklewe, Leukemia 2021

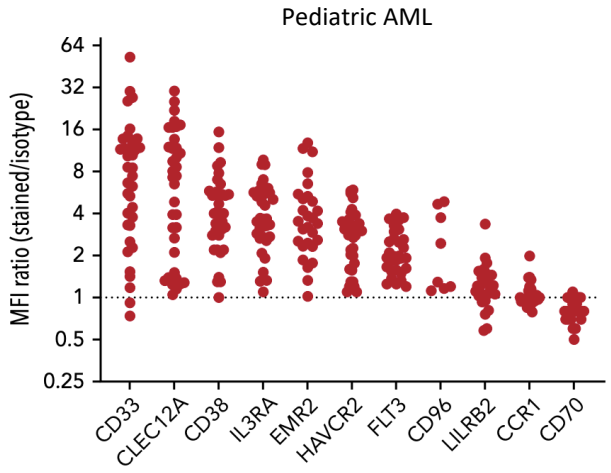
Heterogeneity of Antigen Expression on Bulk AML cells



Nixdorf et al, Subklewe, Leukemia 2023



Perna et al, Cancer Cell 2017



Willier et al, Blood 2021

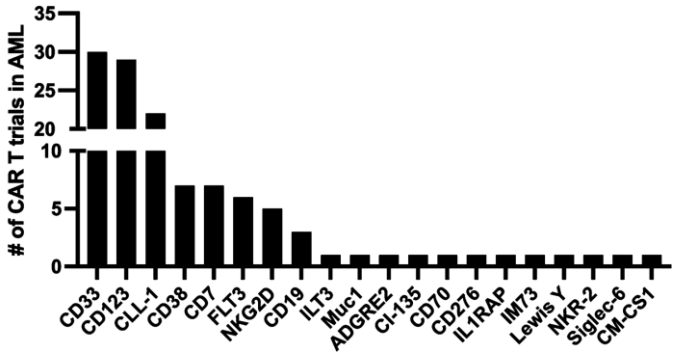
The Lineage restricted, Myeloid Antigens CD33, CD123, CLL-1 are most commonly targeted

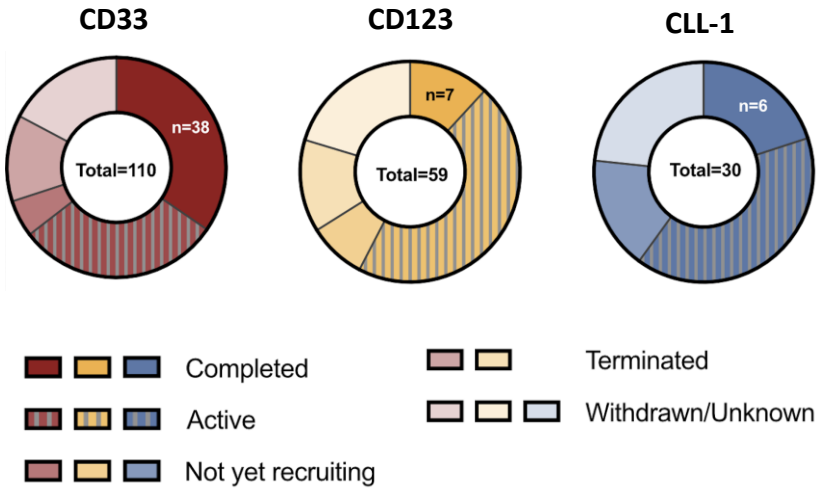
Current target antigens are of myeloid lineage: On-Target-Off-Leukemia Toxicity

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

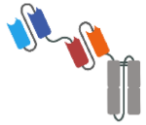
Target Antigens: All Immunotherapy Platforms
Search in Clinicaltrial.gov, December 4th, 2023





ASH2023: Abstracts on Antigen Discovery:
Halfond et al, #164; Lisi et al, #163; Gonzales et al, #168

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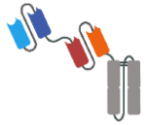
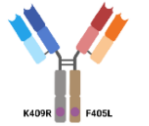
Structure								
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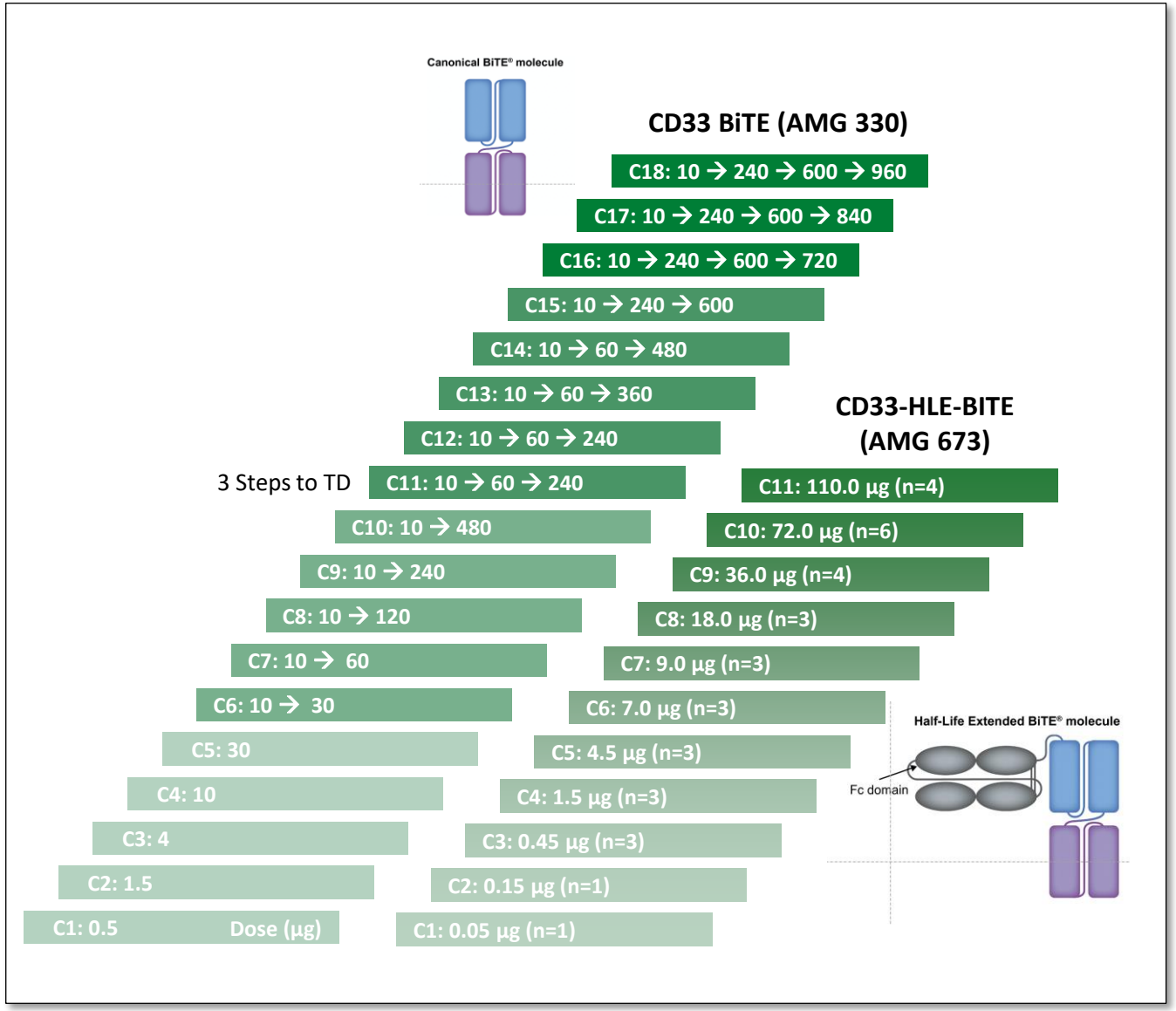
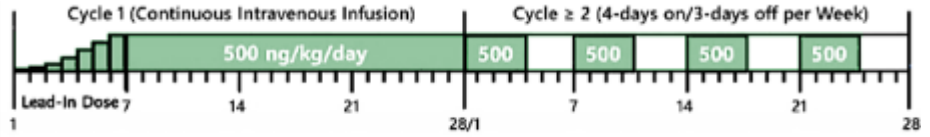
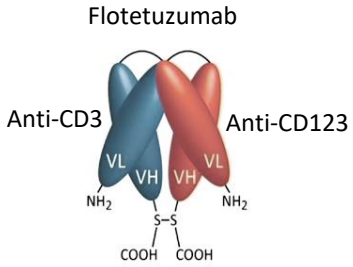
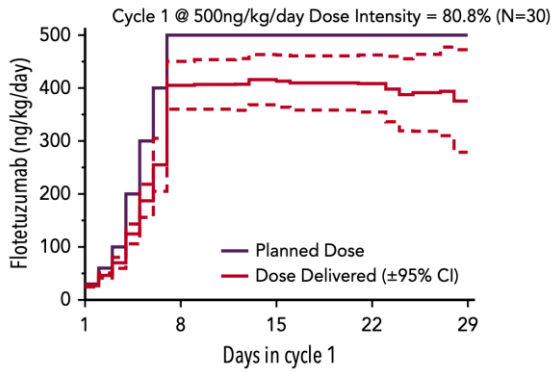
Step up Dosing needed to mitigate CRS & multiple Steps required to achieve active dose



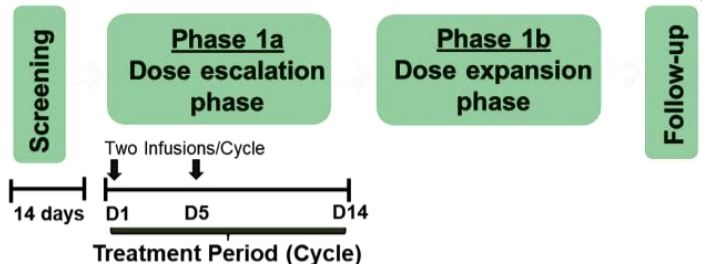
Flotetuzumab Dosing and Schedule







Uy et al, Blood 2021



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

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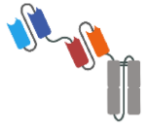
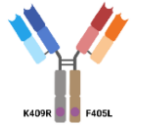
Structure								
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ORR	**19%**	**44% (12/27)**	**49%**	**30%**	**n.a.**	**>0.75 µg/kg 14% (7/51)**	5% (0 %)	**n.a.**
CR/CR$_i$	**17% (7/42)**	**4% (1/27)**	**6% (2/35)**	**27% (8/30)**	**0%**	**10% (5/51)**	**12 %**	**0%**

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
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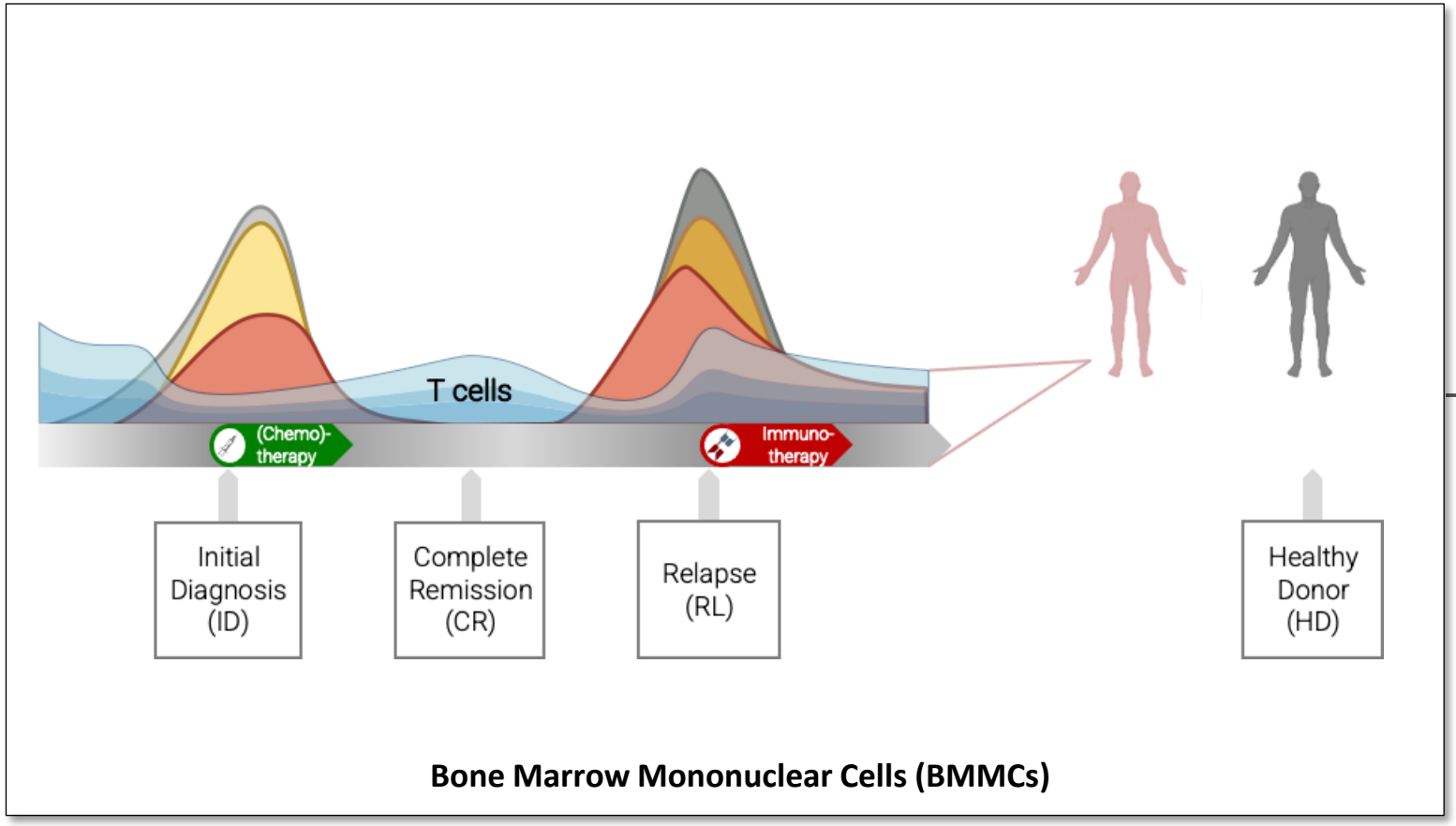
Characterization of T cells during AML Progression



Bone Marrow Mononuclear Cells (BMMCs)

Immunophenotyping:
- Expression of exhaustion markers
- T-cell subset distribution

T-cell function after stimulation with:
- CD3/CD28 beads
- AMG 330 + OCI-AML3 target cells
- AMG 330 + primary AML cells (pAML)

Bulk RNA-sequencing:
- 5000 sorted T cells
- 7 matched ID-RL pAML samples

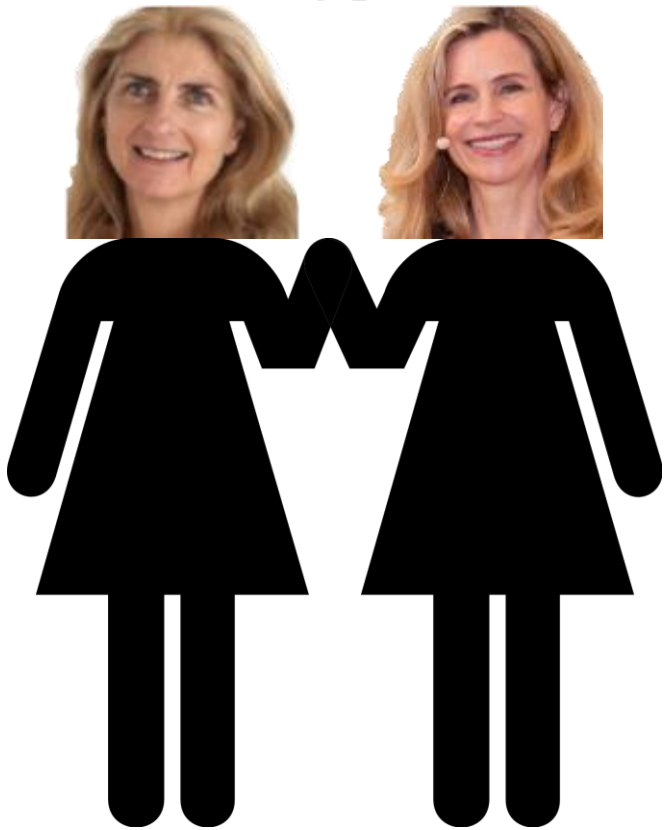
Kazerani et al, ASH 2023

A Perfect Match

Hope

Measurable Residual Disease

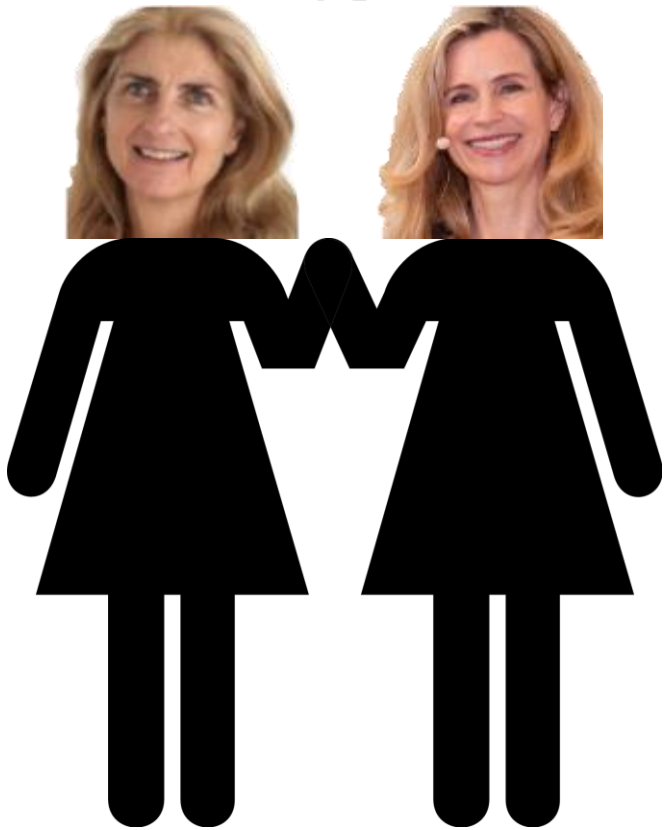
Novel Immunotherapy



Suggestions

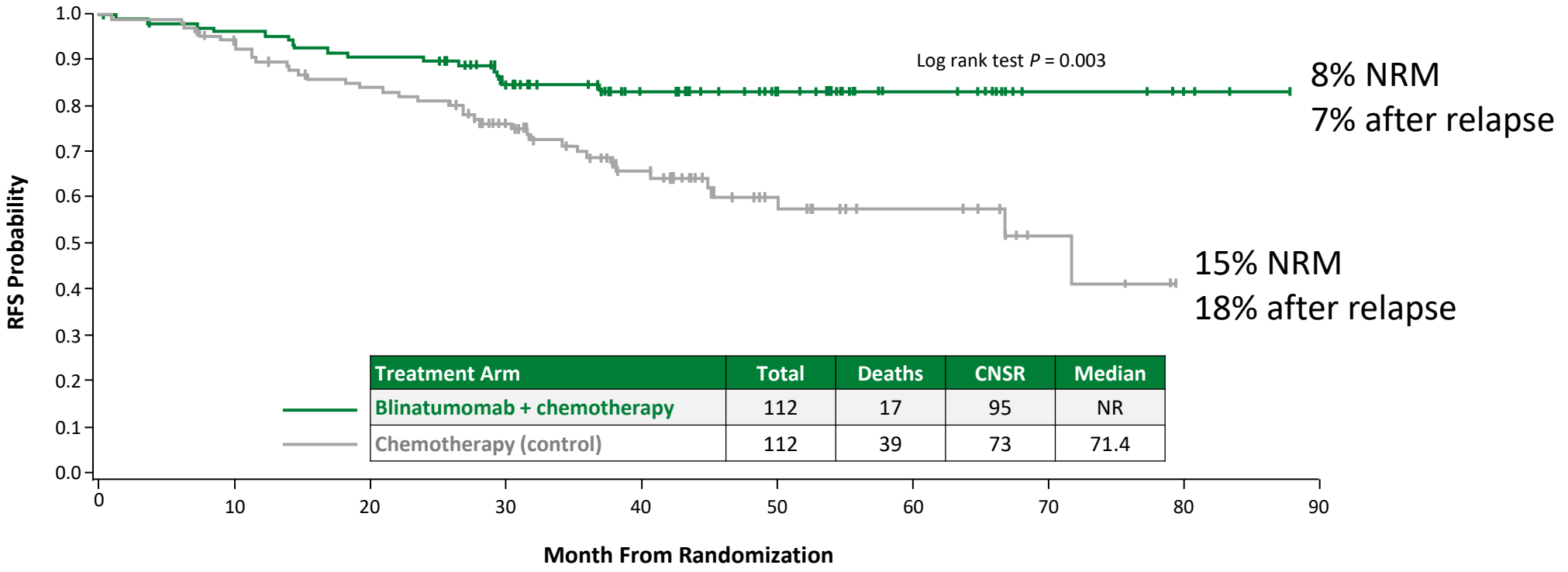
Measurable Residual Disease

Novel Immunotherapy



1. Move into first CR, ideally low or no MRD levels.

Example from ALL: ECOG-ACRIN (E1910): Randomized Trial with Blinatumomab Consolidation in de-novo, MRD negative (< 0.01%) BCP-ALL demonstrated improvement in RFS vs Chemo alone

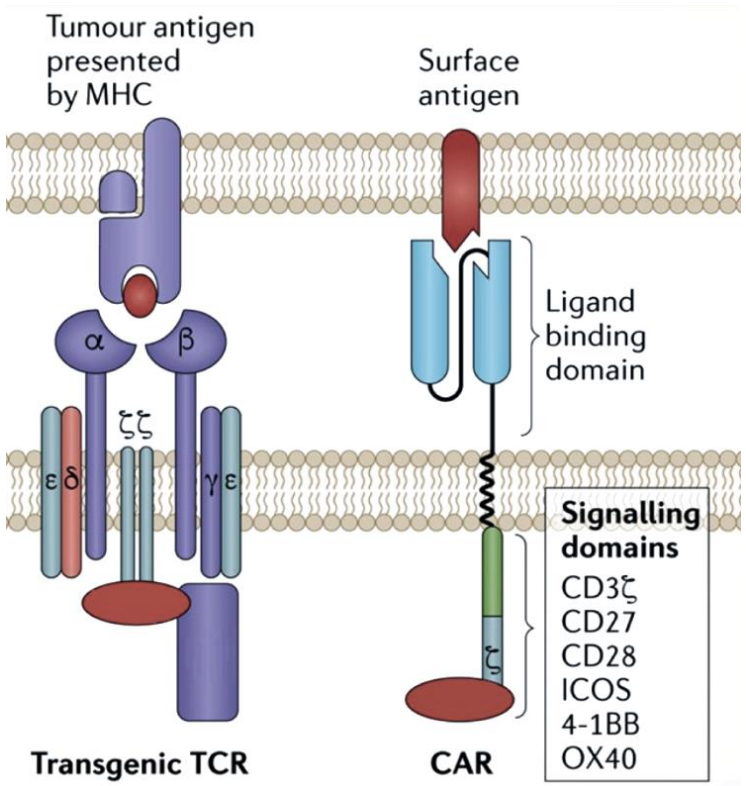


Treatment Arm	Total	Deaths	CNSR	Median
Blinatumomab + chemotherapy	112	17	95	NR
Chemotherapy (control)	112	39	73	71.4

With a median follow-up of 43 months, median OS in MRD– patients was NR in the Blinatumomab arm vs 71.4 months in the control arm (HR, 0.42; 95% CI, 0.24–0.75; log rank P = 0.003)

Litzow MR, et al. ASH 2022

2. Move to more restricted Target Antigens: Intracellular Antigens

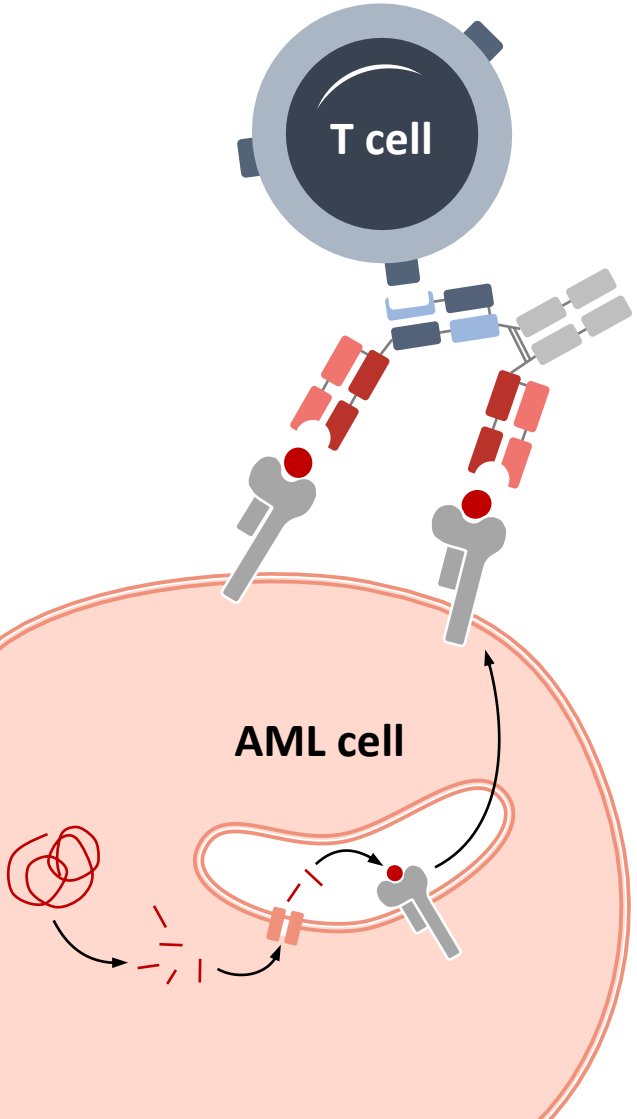


Garber K, Nature Biotechnology 2018

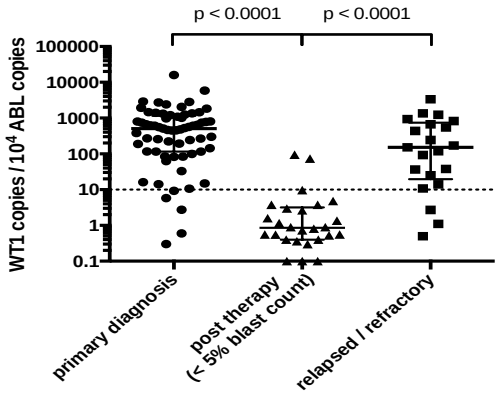
Identifier		Leukemia	Phase	Outcome measures	Status	Locations
NCT02550535	**Autologous WT1 TCR-T cells**	■ Myelodysplastic syndromes; ■ Acute myeloid leukaemia	Phase 1 Phase 2	■ Safety following gene-modified WT1 TCR T-cell therapy as measured by suspected unexpected serious adverse reactions (SUSARS); ■ Proportion of subjects achieving 1 or more IWG response criteria following gene-modified WT1 TCR T-cell therapy; ■ Safety and tolerability of gene-modified WT1 TCR therapy as measured by clinical laboratory parameters and adverse events. ■ Among 10 patients (6 AML, 3 MDS, and 1 TKI-resistant CML) enrolled in the study, All 6 AML patients survived, at last, follow-up (median 12 months) and median 3 months in the 3 patients with MDS. 3 deaths: 2 from disease progression and 1 from other causes.	Completed	■ AZ St. Jan Brugge-Oostende AV Brugge, Belgium ■ UZ Leuven Leuven, Belgium ■ Uniklinikum Dresden, Germany
UMIN00001159	**Autologous WT1 siTCR-T cells**	■ Acute myeloid leukemia; ■ Myelodysplastic syndromes	Unknown	■ No adverse events of normal tissue were seen. ■ 2 patients showed transient decreases in blast counts in bone marrow, which was associated with recovery of hematopoiesis.	Completed	■ Mie University Hospital, Japan ■ Ehime University Hospital, Japan ■ Fujita Health University Hospital, Japan ■ Nagoya University Hospital, Japan
NCT01621724	**Autologous WT1 TCR-T cells**	■ Acute myeloid leukemia; ■ Chronic myeloid leukemia	Phase 1 Phase 2	■ Identify organ toxicities and other side effects ■ Transduction efficiency and TCR expression on TCR-transduced cells ■ WT1-specific immune responses of TCR-transduced T cells	Completed	■ University Hospitals Bristol NHS Foundation Trust Bristol, UK ■ University College London Hospitals NHS Trust London, UK, NW1 2PG
NCT01640301	**Allogeneic WT1 TCR-T cells**	■ Recurrent adult acute myeloid leukemia; ■ Recurrent childhood acute myeloid leukemia; ■ Secondary acute myeloid leukemia	Phase 1 Phase 2	■ Antileukemic potential efficacy, in terms of duration of response (Arm II). ■ Efficacy, in terms of relapse rate (Arm I). ■ Incidence of chronic graft versus host disease (GVHD) (Arm I).	Active, not recruiting	■ Fred Hutch University of Washington Cancer Consortium Seattle, Washington, USA
NCT04284228	**Allogeneic WT1/PRAME/Cyclin A1-antigen-specific CD8* T cells (NEXI-001 T-cell product)**	■ Acute myeloid leukemia; ■ Myelodysplastic syndrome	Phase 1 Phase 2	■ Adverse events of special interest (AESIs) events of dose-limiting toxicities (DLTs) ■ AESI events of infusion-related reactions and cytokine release syndrome (CRS) ■ Survival, including median progressive-free survival (PFS), overall response rate (ORR), overall survival (OS).	Recruiting	■ City of Hope Comprehensive Cancer Center Duarte, California, USA ■ Advent Health Medical Group Blood & Marrow Transplant Orlando, Florida, USA ■ Karmanos Cancer Institute Detroit, Michigan, United States
NCT03503968	**Autologous PRAME TCR-T cells (MDG1011 cell product)**	■ High-risk myeloid; ■ Lymphoid neoplasms (including relapse AML after allo-HSCT)	Phase 1 Phase 2	■ Adverse events and dose limiting toxicities (safety and tolerability). ■ Maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of MDG101. ■ For feasibility: percent of all subjects who receive the planned target dose of MDG1011.	Recruiting	■ University Hospital Dresden, Dresden, Germany ■ University Hospital Erlangen, Erlangen, Germany ■ University Hospital Frankfurt, Frankfurt, Germany
NCT03326921	**Allogeneic HA-1 TCR-T cells**	■ Juvenile myelomonocytic leukemia ■ Recurrent acute biphenotypic leukemia ■ Recurrent acute undifferentiated leukemia	Phase 1	■ Feasibility of manufacturing minor H antigen (HA-1) T-cell receptor (TCR) CD8+ and CD4+ T cells. ■ Feasibility of administering minor H antigen (HA-1) T-cell receptor (TCR) CD8+ and CD4+ T cells. ■ Incidence of dose-limiting toxicities of HA-1 T-cell receptor (TCR) T cells.	Recruiting	■ Fred Hutch University of Washington Cancer Consortium Seattle, Washington, United States
NCT04464889	**Autologous HA-1 H TCR-T cells**	■ Acute myeloid leukemia ■ Myelodysplastic syndromes	Phase 1	■ Safety and tolerability of HA-1H TCR-transduced T cells: incidence and severity of adverse events. ■ Maximum tolerated dose (MTD) of HA-1H TCR-transduced T cells. ■ Recommended phase 2 doses (RP2D) of HA-1H TCR-transduced T cells.	Active, not recruiting	■ Leiden University Medical Centre Leiden, Zuid Holland, Netherlands

Kang et al, Front Oncol 2022

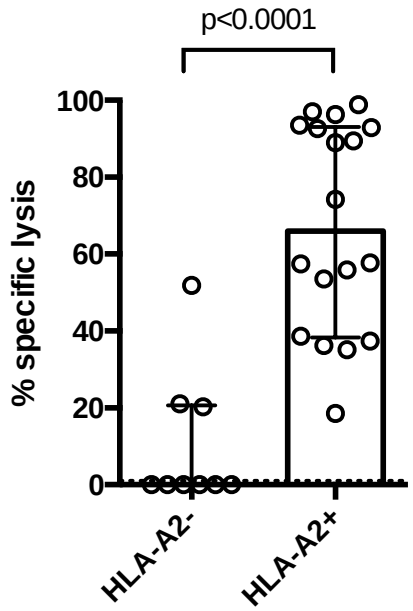
Increase Specificity by targeting intracellular LAA: $WT1_{RMF}$ (HLA-$A2^+$) with TCR mimicky Ab



WT1 Expression

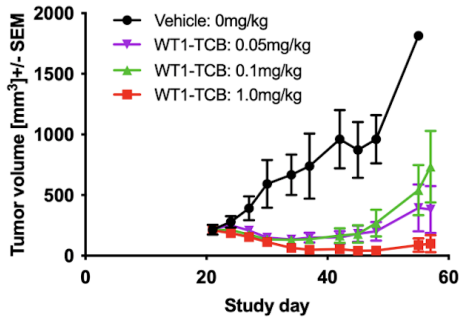


Specific lysis of primary AML cells

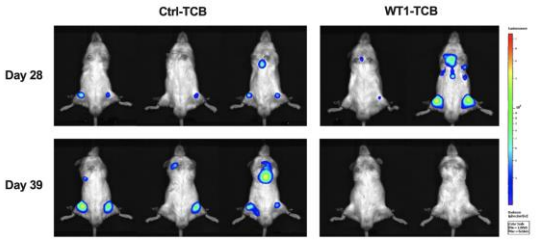


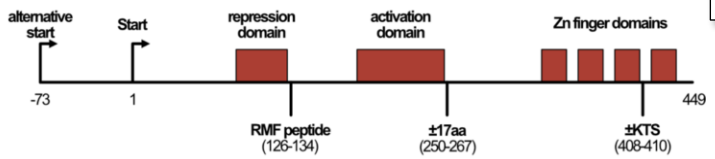
Anti-tumor Efficacy of WT1-TCB in a humanized mouse model

Tumor growth



Tumor Growth in AML PDX mice



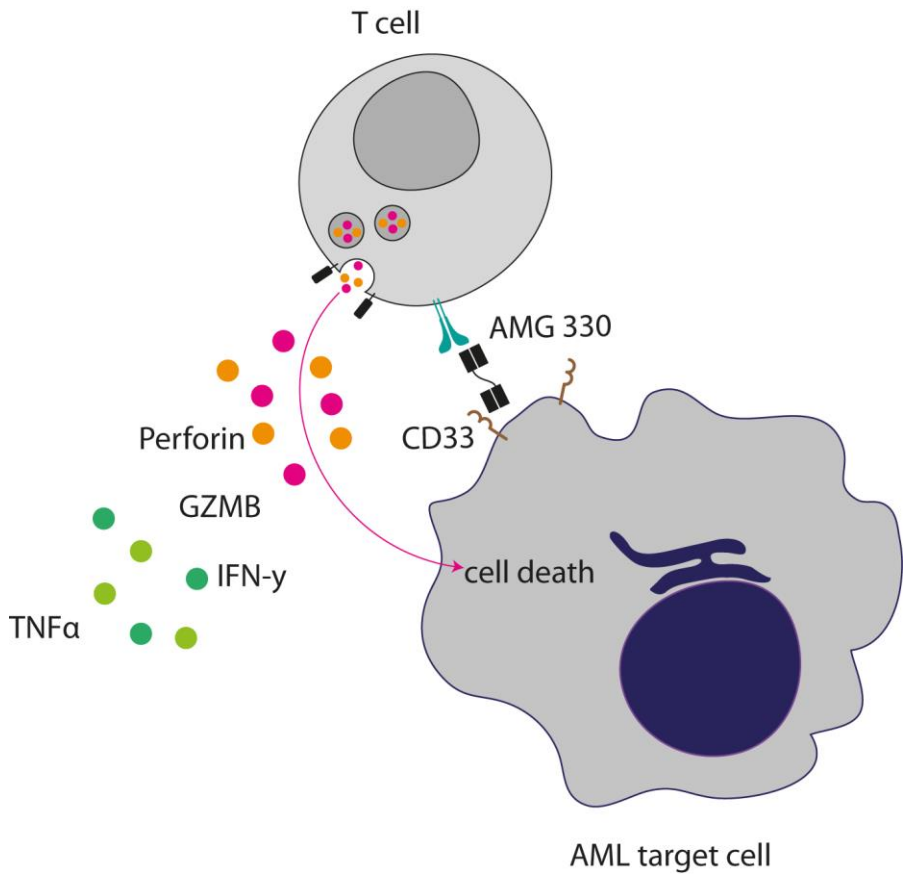


Phase I clinical Trial
in r/r AML and also MRD^+ AML

Augsberger, Hänel et al, Subklewe, Blood 2021, Hutschings et al, ASH 2023, first approval of this kind in uveal melanoma (Tebentafusp)

3 b. Use Combinatorial Strategies: Address Innate Immunity

CD33 targeting BiTE® construct (AMG 330)



- Limited sustained responses in AML
- Immunosuppressive tumor microenvironment
- Secretion of immune dampening metabolites by AML

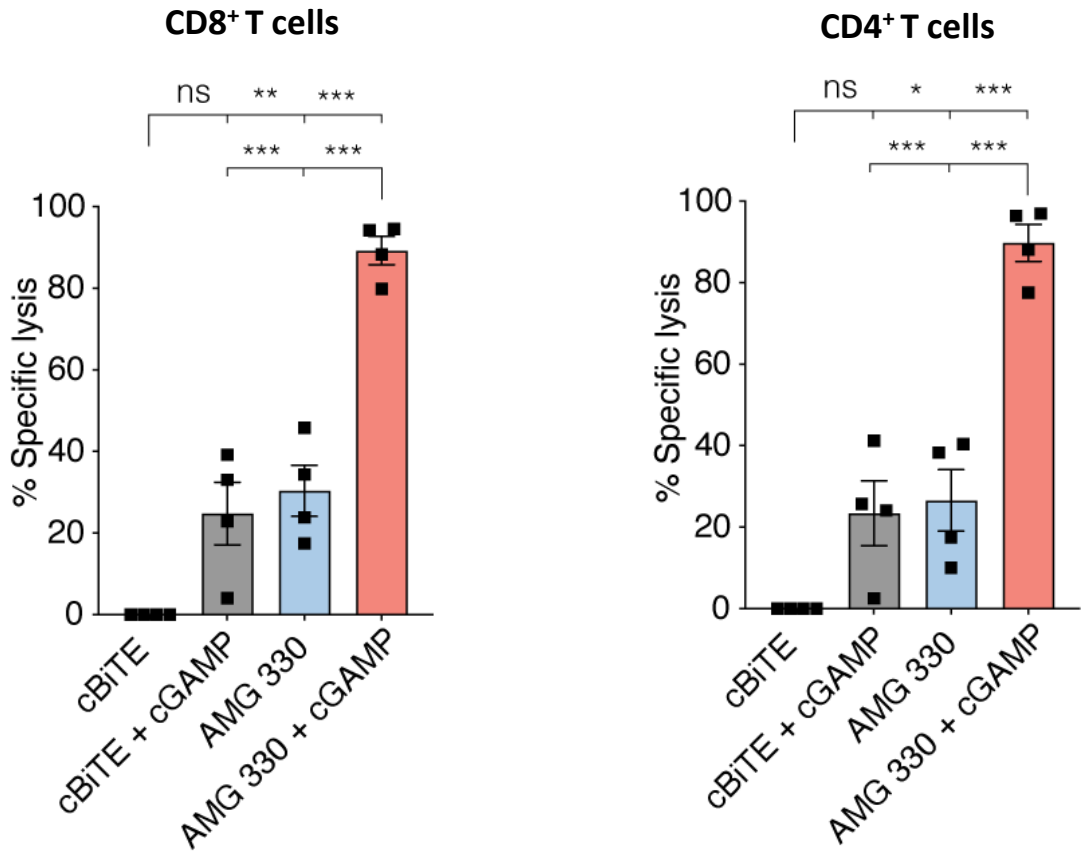
Hypothesis:

The combination with a STING agonist has the potential to augment anti-leukemic activity

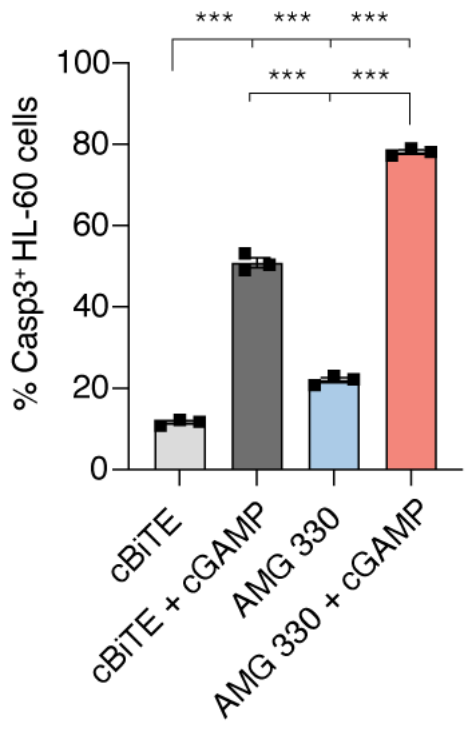
Knaus et al., 2019 and Le Dieu et al., 2009

STING activation improves CD33 BiTE (AMG 330)-mediated cytotoxicity

AMG 330-mediated cytotoxicity +/- cGAMP



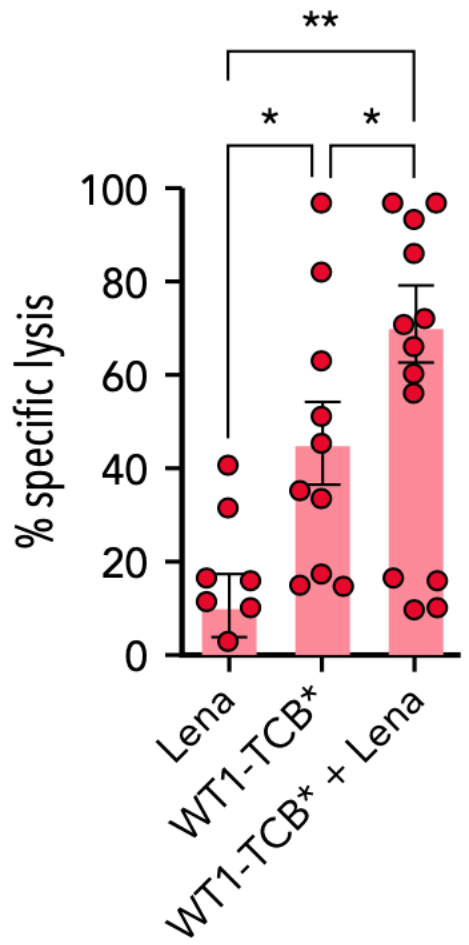
Caspase 3 activity in HL-60 cells



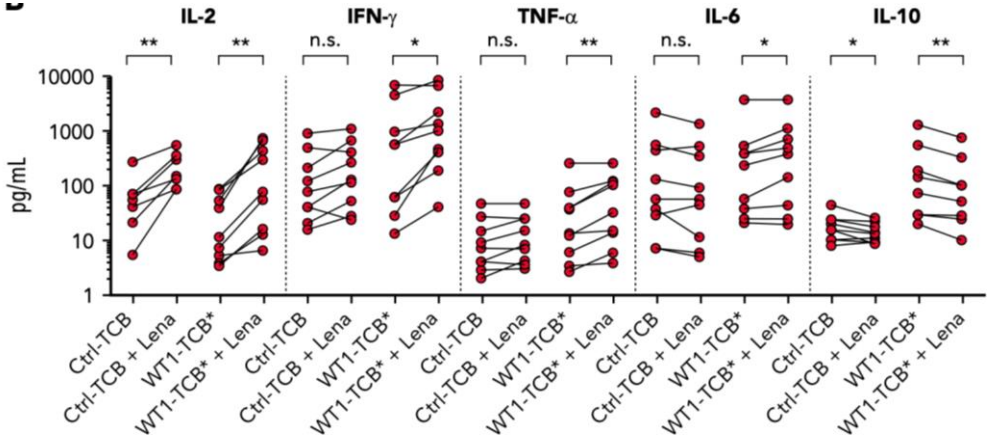
Linder & Nixdorf et al, Hornung, Subklewe. SITC 2022, ASH 2023

3c. Combinatorial: Lenalidomide enhances WT1-TCB-mediated cytotoxicity

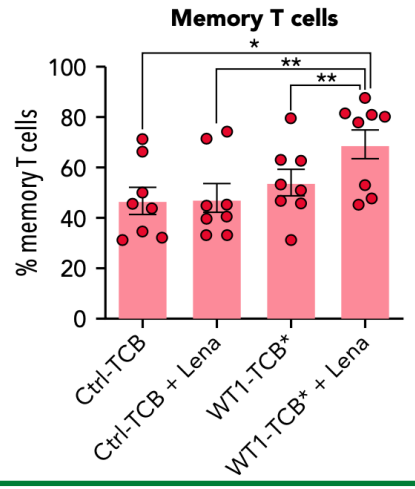
Increase in AML cell lysis

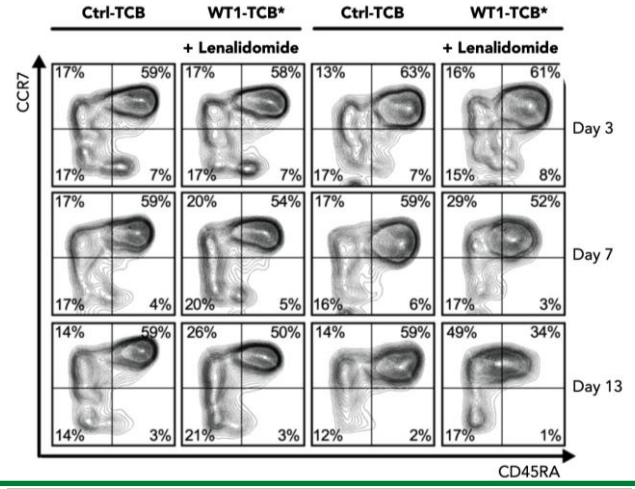


Len increases proinflammatory cytokine signaling



Len promotes formation of memory T cells



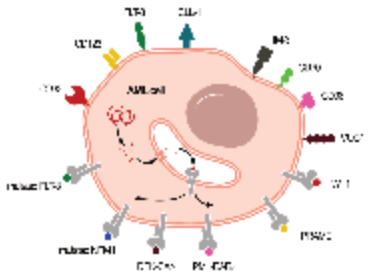


Augsberger et al. *Blood* 2021

TCE / BsAb: Use early (CR1) & in low disease burden (MRD$^+$/MRD$^-$)

Patient & Disease Characteristics:

- Fitness, ECOG, Patient Wish
- Phenotype (target antigen, PD-L1, CD47, TIM-3, TIGIT)
- Genotype (ELN, defined molecular lesions, LSC17 score)
- Inflammatory signature (IFN-gamma dominant, immune-enriched TME vs cold, immune-depleted profile)
- IFNg response



Stem Cell Infusion, possibly target antigen ablated, possibly epitope edited for imunotherapy post SCT

in high risk, consider post-allo bispecific Ab, possibly in conjunction with DLI

Allogeneic Stem Cell Transplantation

Conditioning | **GvHD prophylaxis** | **Maintenance**

in high risk: Bispecific Ab

Induction → CR, if MRD$^+$ → **Consolidation** → CR, if MRD$^+$ → **Maintenance**

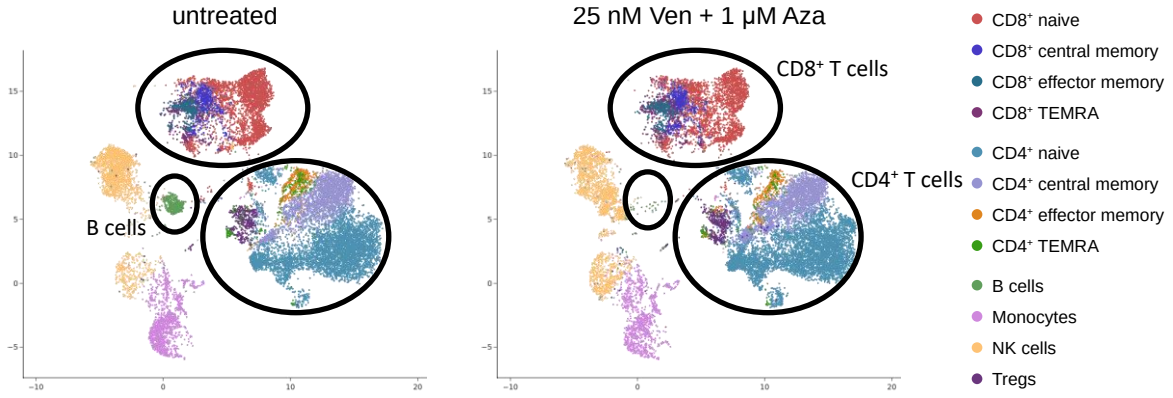
Diagnosis | **Post-Induction** | **Post-Consolidation** | **Year 1** | **Year 2** | **Year 3**

Bispecific Ab

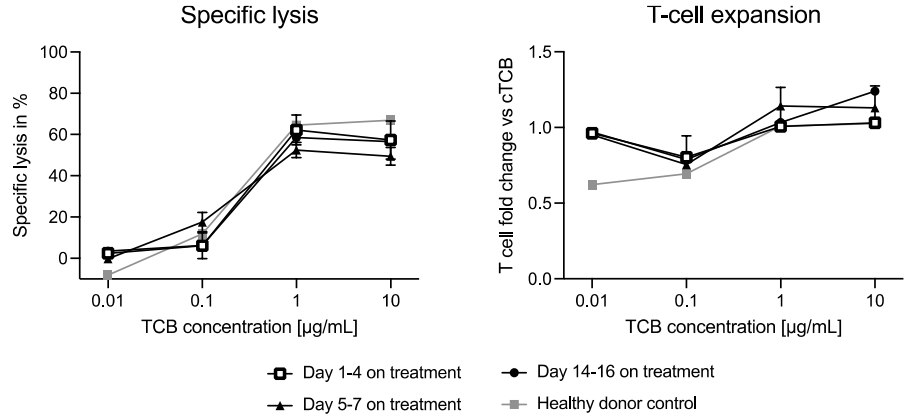
Bispecific Ab

3 d. Use Combinatorial Strategies: Combine with VEN/AZA

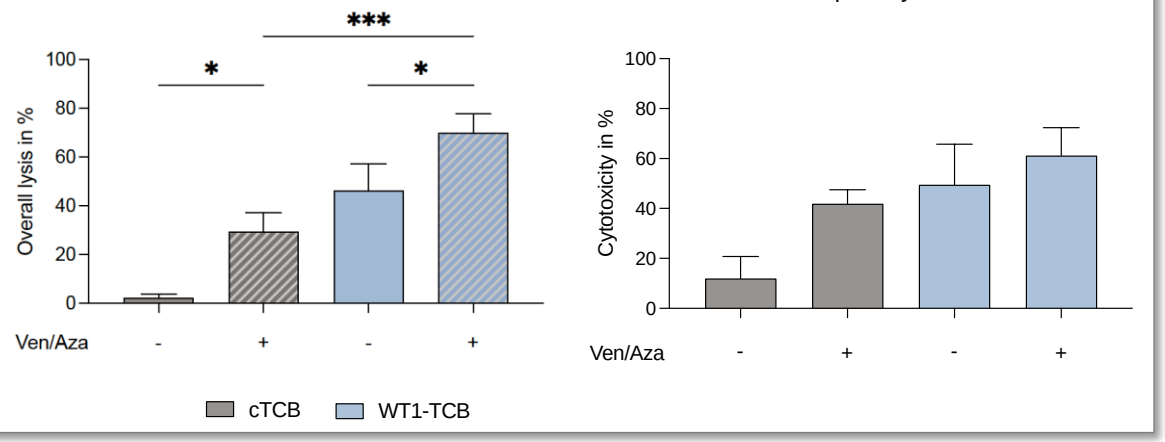
Ven/Aza has limited impact in the T-cell compartment



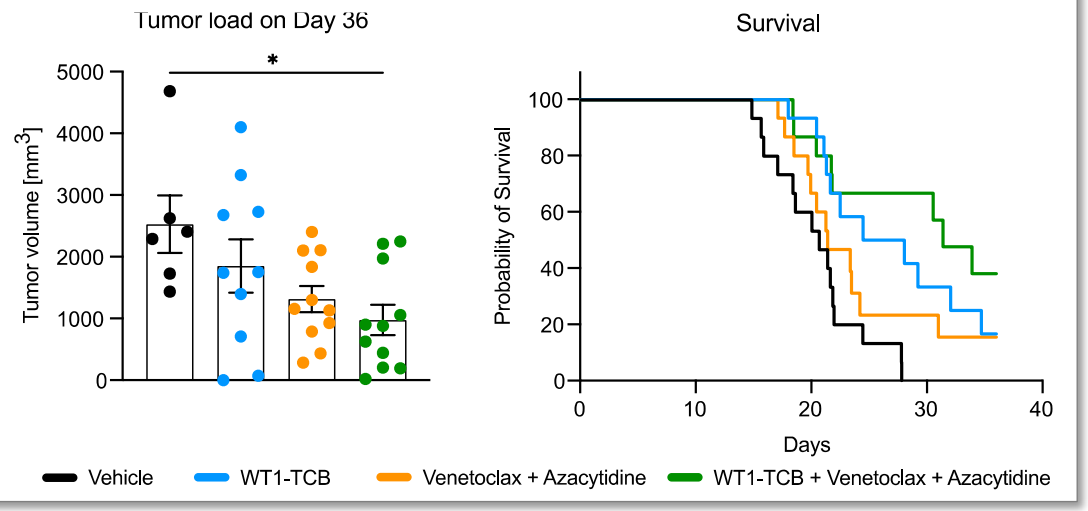
T-cell function is not impaired in by Ven/Aza in AML patients



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

Acknowledgements

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

@MSubklewe
@LMU_Immutherapy

LMU Gene Center Munich

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Department of Medicine III – Oncology and Hematology

Louisa Adolph
Michael v. Bergwelt
Veit Bücklein
Martin Dreyling
Alicia Emhardt
Lisa Frölich
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Laboratory of Leukemia Diagnostics

Veit Bücklein
Elke Habben
Tobias Herold
Bianca Kirschbaum
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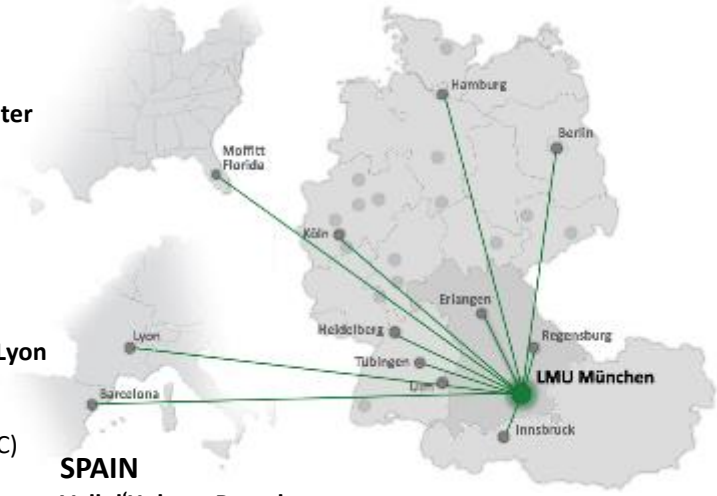

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