Penn Medicine
Center for Cellular Immunotherapies

CAR-T cells for adult ALL and AML

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Presenter disclosure information

- ***Inventor:*** CART technologies, Univ. of Pennsylvania, partly licensed to Novartis, Tmunity, and viTToria biotherapeutics

- ***Research Funding:*** AbClon, Beckman-Coulter, ONI, Lumicks, viTToria bio

- ***DSMB****:* PeproMene

- ***Consultancy/Honoraria:*** GLG, Guidepoint

- ***Advisory Board:*** viTToria bio, AbClon, BMS, Sana, GSK, Bayer

- ***Scientific Founder:*** viTToria biotherapeutics

FDA-approved CART in the US

August 2017: Ped./AYA B-ALL 3rd line >
May 2018: LBCL 3rd line >
May 2022: FL 3rd line >

October 2017: LBCL 2nd line >
March 2021: FL 3rd line >

July 2020: r/r MCL 3rd line >
Oct 2021: r/r adult B-ALL 3rd line >

February 2021: LBCL 2nd line >

March 2021: MM 5th line >

March 2022: MM 5th line >

Selected autologous CART19 trials in adult and pediatric ALL

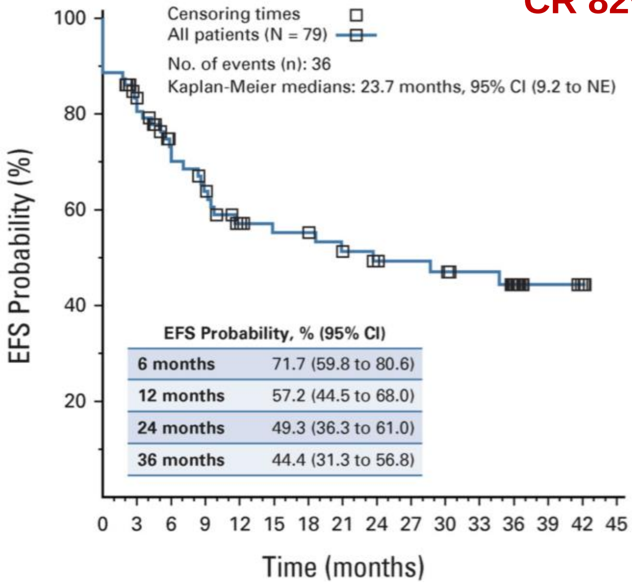
Reference	Co-stim Domain	N	Age	Prior Blina	Prior SCT	CR
ADULT PATIENTS						
Reuben B, Lancet Haematol, 2022	Allo 4-1BB UCART19	25	37 (16-70)	48%	72%	**48%**
Shah, J Hemat Oncol, 2022	CD28	55	40 (28-52)	45%	42%	**71%**
Roddie, JCO, 2021	4-1BB fast off rate	20	41.5 (18-62)	25%	65%	**85%**
Frey, JCO, 2020	41BB	35	34 (21-70)	31%	37%	**69%**
Hay, Blood, 2019	41BB	53	39 (20-76)	20%	43%	**85%**
Park, NEJM, 2018	CD28	53	44 (23-64)	25%	36%	**83%**
COMBINED PEDIATRIC AND ADULT PATIENTS						
Ortiz-, MolTher 2020	41BB	38	24 (3-67)	26%	87%	**85%**
Wang, BrJHem, 2020	41BB	23	42 (10-67)	NA	0%	**83%**
Jiang, AJH, 2019	41BB	58	28 (10-65)	NA	5%	**88%**
Maude, NEJM, 2014	41BB	30	14 (5-60)	10%	60%	**90%**
PEDIATRIC AND ADOLESCENT YOUNG ADULT PATIENTS						
Shah, JCO, 2021	CD28	50	13.5 (4.3-30.4)	10%	40%	**62%**
Maude, NEJM, 2018	41BB	75	11(3-23)	0	61%	**81%**
Gardner, Blood, 2017	41BB	45	12.2(1.3-25.3)	14%	62%	**93%**

- **High CR rates (62-93%)**
- Remissions:
  - Occur quickly (by 1 month)
  - Often MRD negative
- CARTs traffic into CNS & other extra- medullary sites
- Heavily pretreated pts
- Impact of prior CD19-specific immuno-therapy
- Impact of disease-assoc. mutations

4-1BB costimulated CART19 for B-ALL (CTL019, tisa-cel)

Ped. and AYA B-cell Acute Lymph. Leukemia (ELIANA)

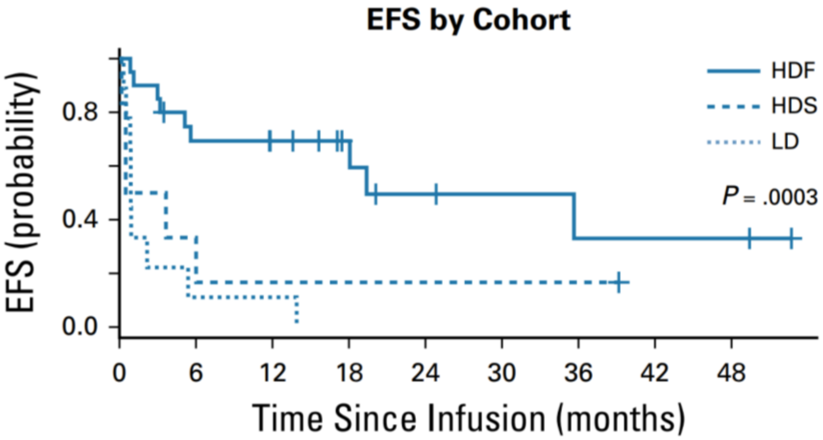
CR 82%



Laetsch TW, JCO, 2022

Adult B-cell Acute Lymph. Leukemia (no FDA approval)

CR 69%

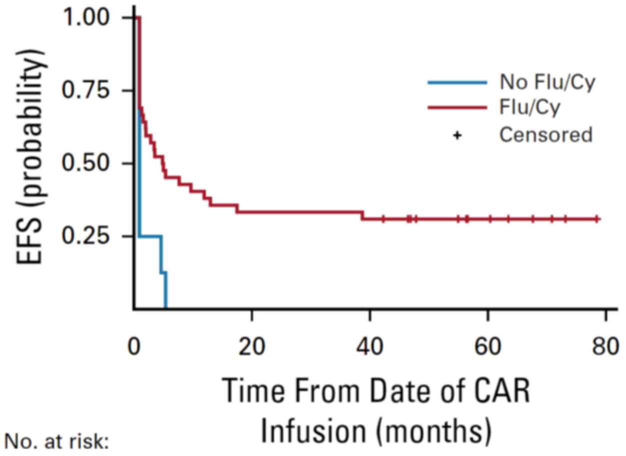


Frey N, JCO, 2020

CD28-costimulated CART19 for B-ALL (KTE-X19, brex-cel))

Pediatric and AYA B-cell Acute Lymph. Leukemia (no FDA approval)

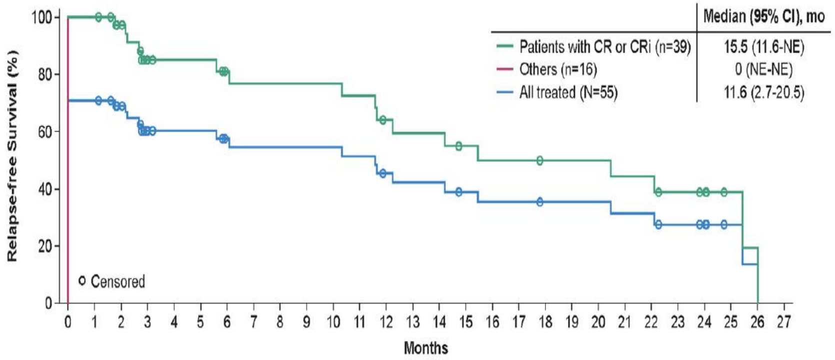
CR 62%



Shah N, JCO, 2021

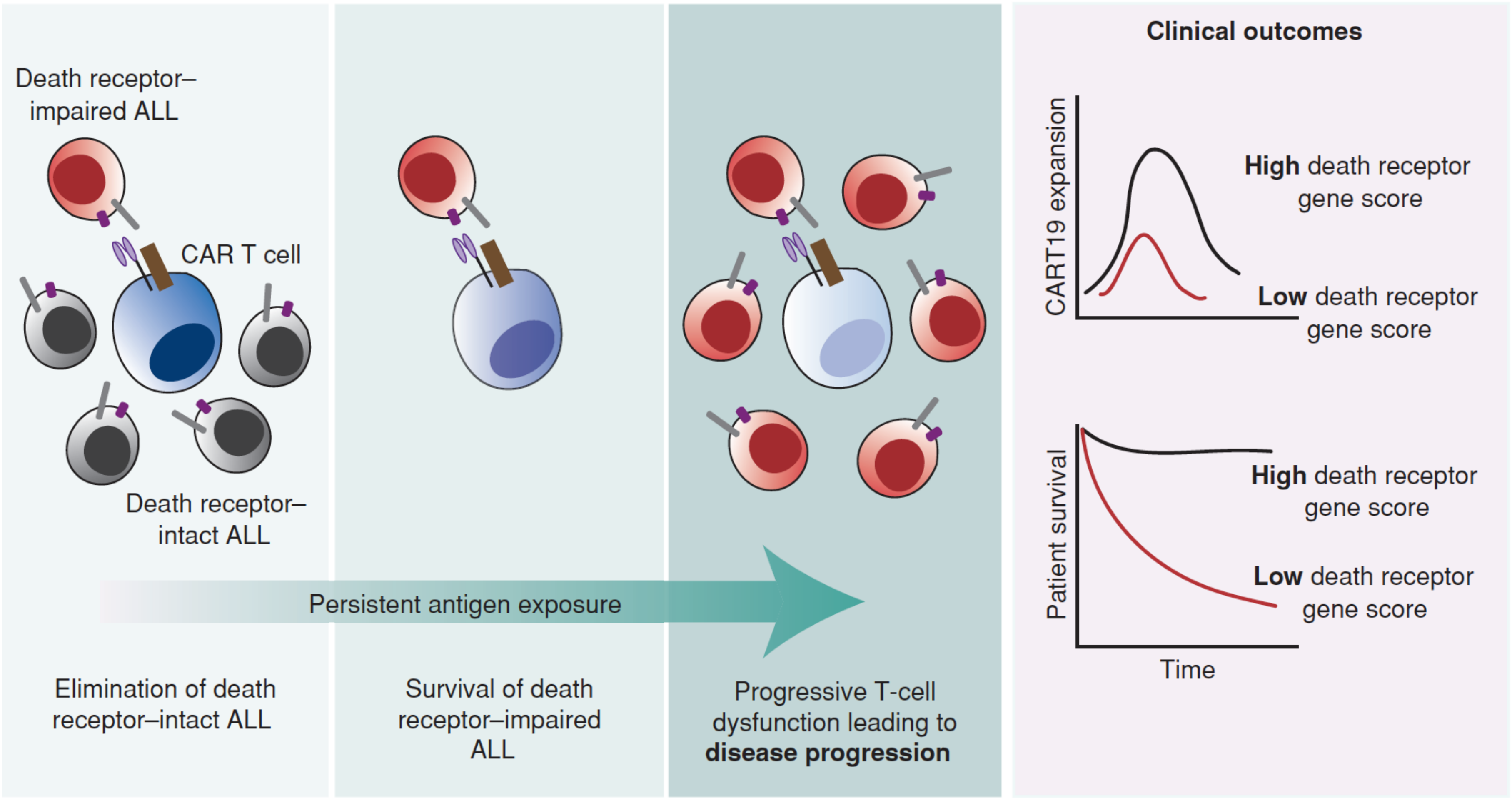
Adult B-cell Acute Lymph. Leukemia (ZUMA-3)

CR 71%



Shah B, Lancet, 2021
Shah B, J Hemat Onc, 2022

CD19+ relapses: primary resistance

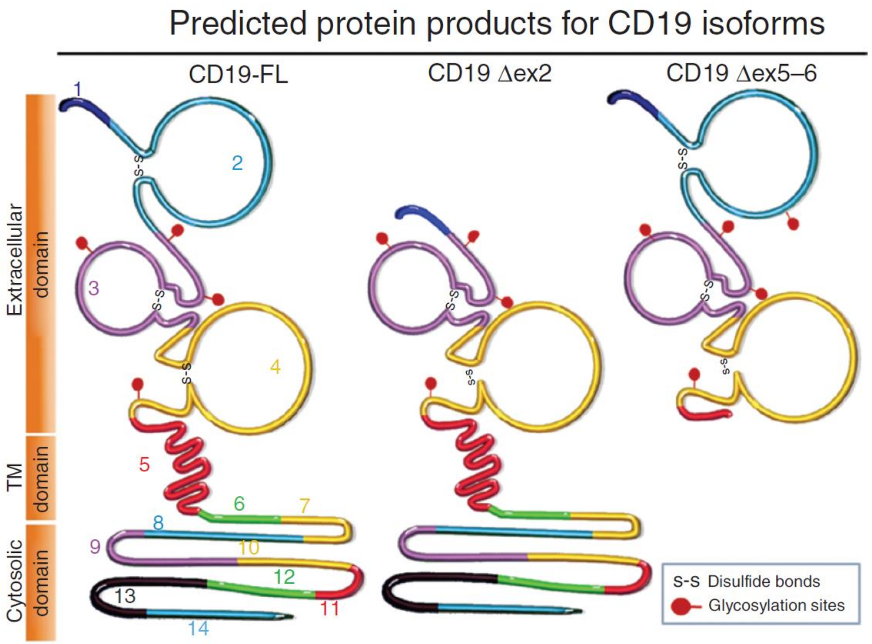


Singh et al, Cancer Discovery 2020;10:55

CD19-neg relapses

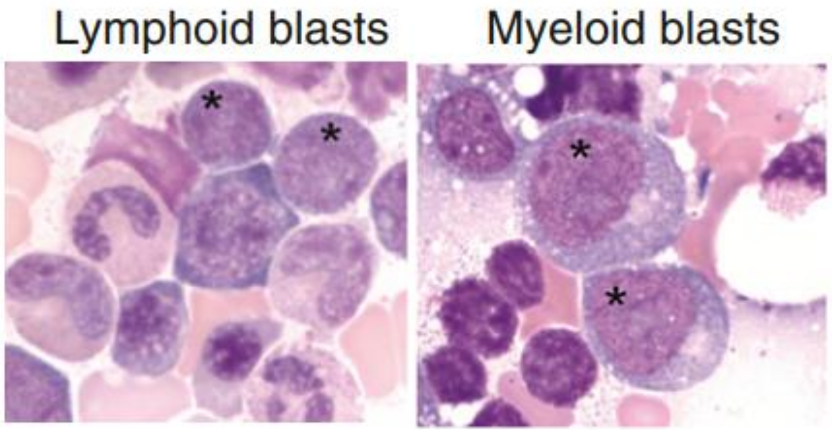
Convergence of acquired mutations and alternative splicing of CD19

(Sotillo, 2015; Orlando EJ, Nat Med, 2018)



Transdifferentiation

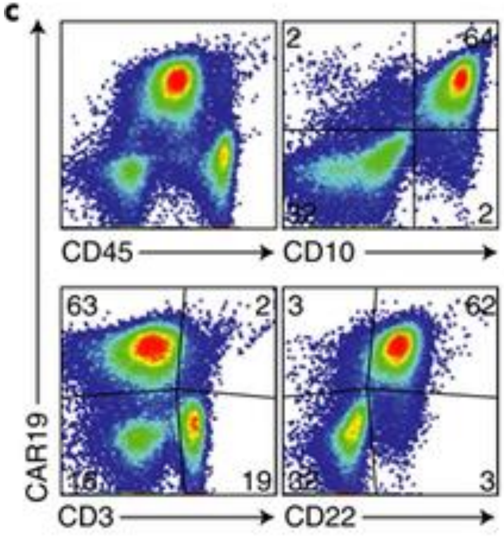
(Gardner, 2016, Oberley Mj, 2018)

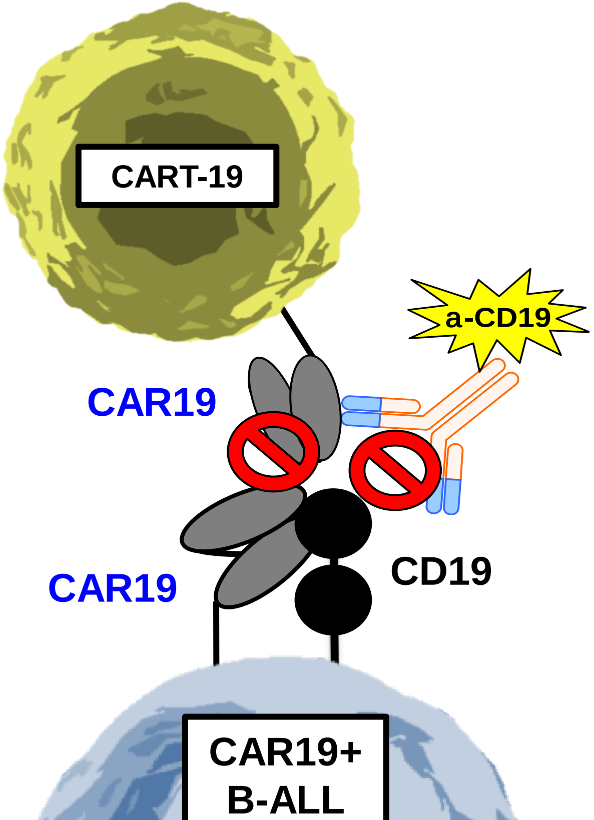


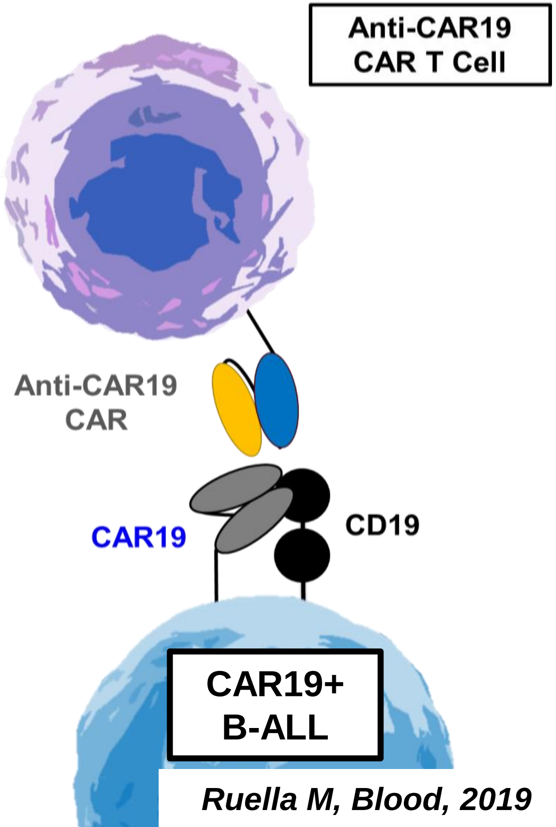
CAR19+ B-ALL: relapse by epitope-masking

CORRELATIVE STUDIES | MECHANISM | POSSIBLE THERAPY

Ped. B-ALL Relapse
9 month after CART19



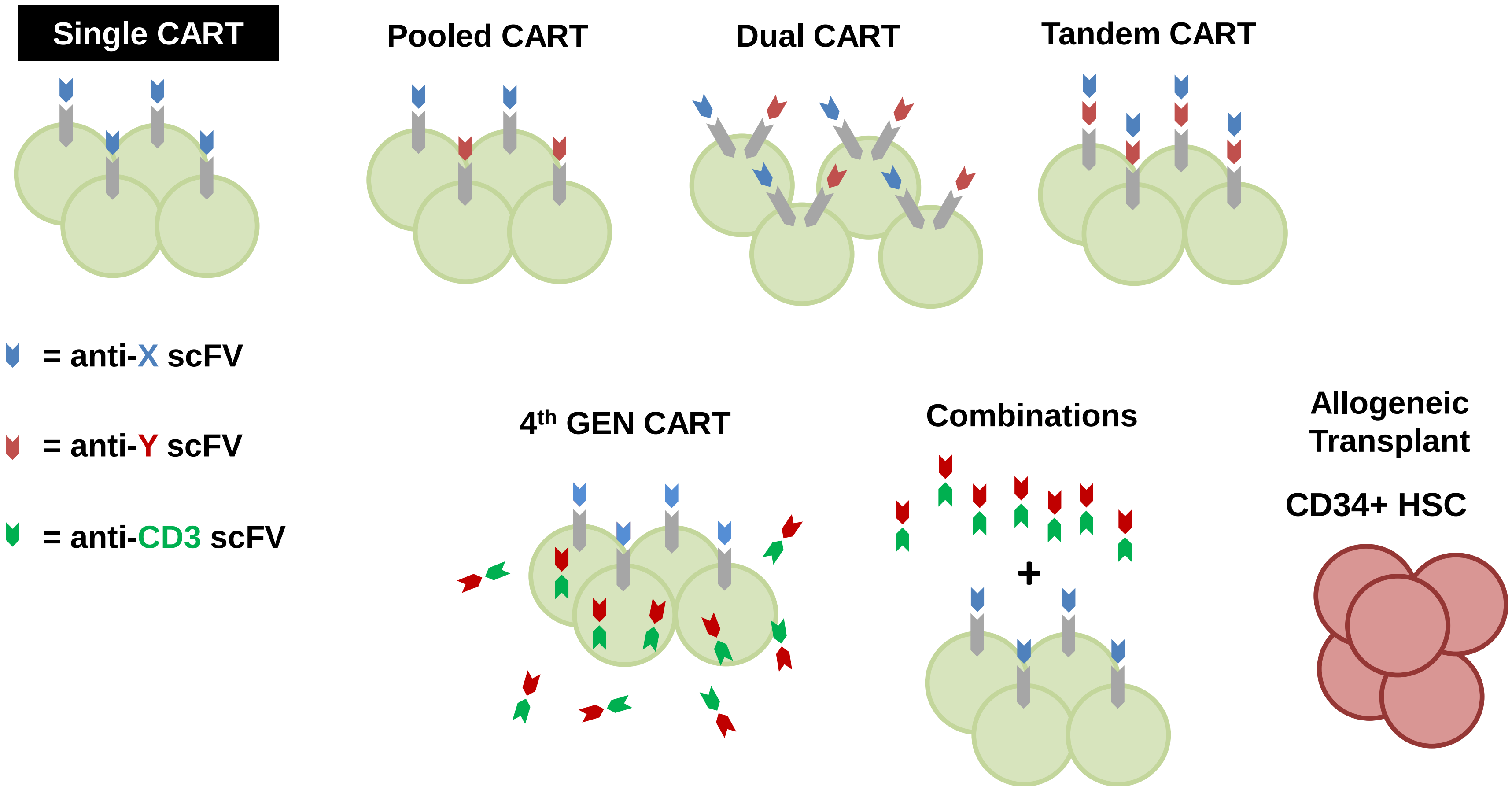




Ruella M, Nat Med, 2018

Ruella M, Blood, 2019

Strategies to overcome CD19-neg antigen-escape



Adapted from Ruella M. Comput Struct Biotechnol J 2016

CART-22 (Penn & CHOP)

nature medicine

ARTICLES

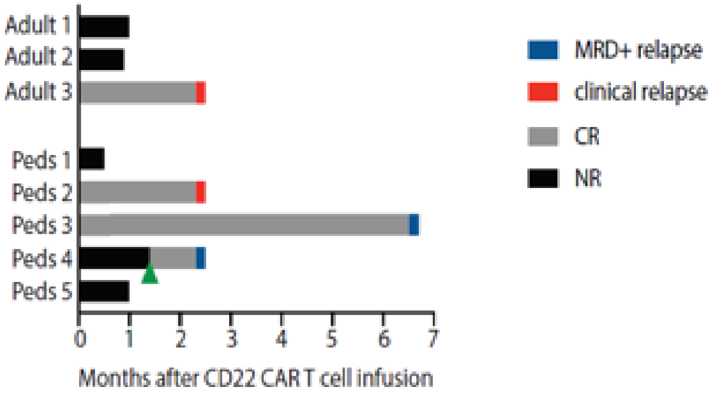
https://doi.org/10.1038/s41591-021-01326-5

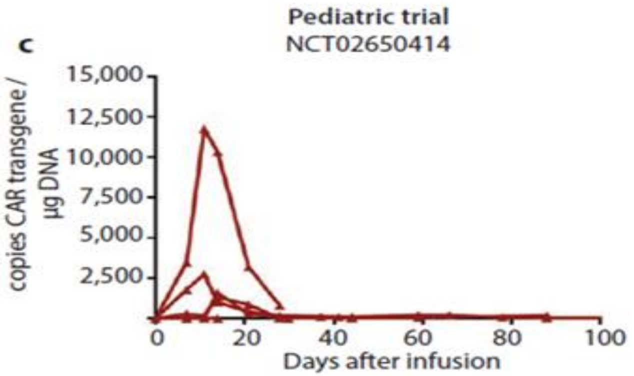
Check for updates

Antigen-independent activation enhances the efficacy of 4-1BB-costimulated CD22 CAR T cells

Nathan Singh[1,2,15,16] ✉, Noelle V. Frey[1,16], Boris Engels[3,16], David M. Barrett[4,5], Olga Shestova[2], Pranali Ravikumar[2], Katherine D. Cummins[2], Yong Gu Lee[2], Raymone Pajarillo[2], Inkook Chun[2], Amy Shyu[3], Steven L. Highfill[3], Andrew Price[3], Linlin Zhao[3], Liaomin Peng[3], Brian Granda[3], Melissa Ramones[3], Xueqing Maggie Lu[6], David A. Christian[7], Jessica Perazzelli[4], Simon F. Lacey[2,8,9], Nathan H. Roy[9,10], Janis K. Burkhardt[9,10], Florent Colomb[11], Mohammad Damra[11], Mohamed Abdel-Mohsen[11], Ting Liu[12], Dongfang Liu[12,13], Daron M. Standley[14], Regina M. Young[2], Jennifer L. Brogdon[3], Stephan A. Grupp[4], Carl H. June[1,2,9], Shannon L. Maude[4,16], Saar Gill[1,2,16] and Marco Ruella[1,2,16] ✉

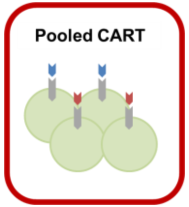
- **Response rates and persistence with PENN product lower than anticipated**
- **The NCI product appeared more promising in the clinic; PENNs construct very similar except for a longer linker length**
- **Preclinical studies showed linker length impacted CAR structure which impacted effector function: shorter linker better**
- **PENN developed CART22 with shorter linker for further clinical testing- now enrolling at CHOP: Steve Grupp PI**





Singh et al, Nature Medicine 2021

Pooled huCART19 + CART22-65s for Adults with r/r BALL



Lympho depletion → **Day-1 (BM BX)** → **Day 0:** 10% CART19 + 10% CART22 * → **Day 1:** 30% CART19 + 30% CART22 * → **Day 2:** 60% CART19 + 60% CART22 → **Day 28 Response Assessment**

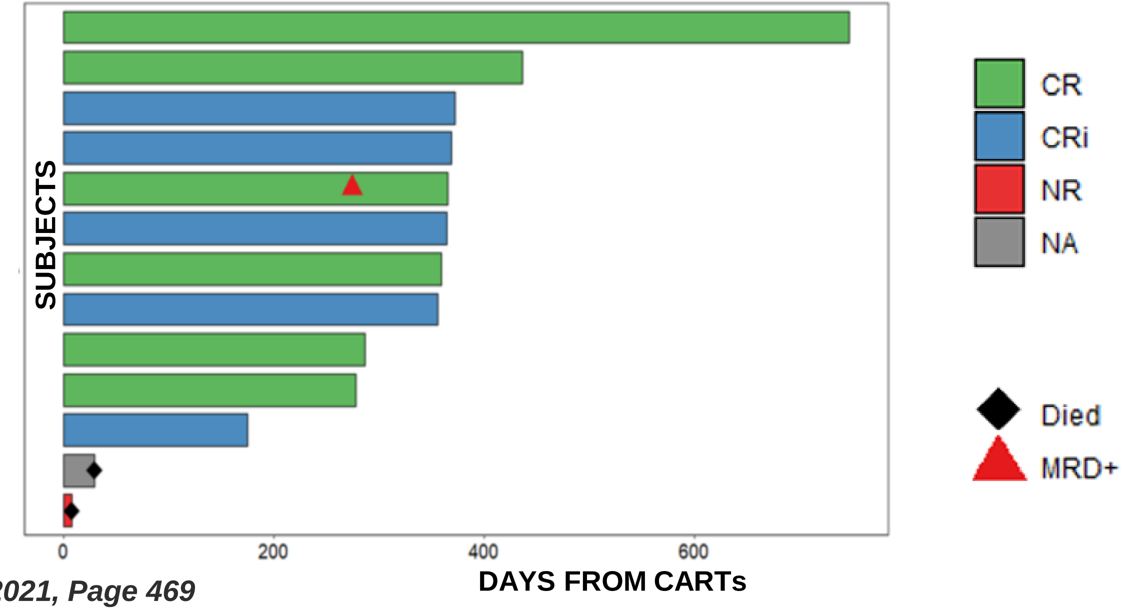
Fractionated Dosing:
Doses held for Early CRS

CART19 and CART22: (N=13)

- 13 pts infused
- 11 pts evaluable D28
- 11 CR/CRi (MRD -) **85%**

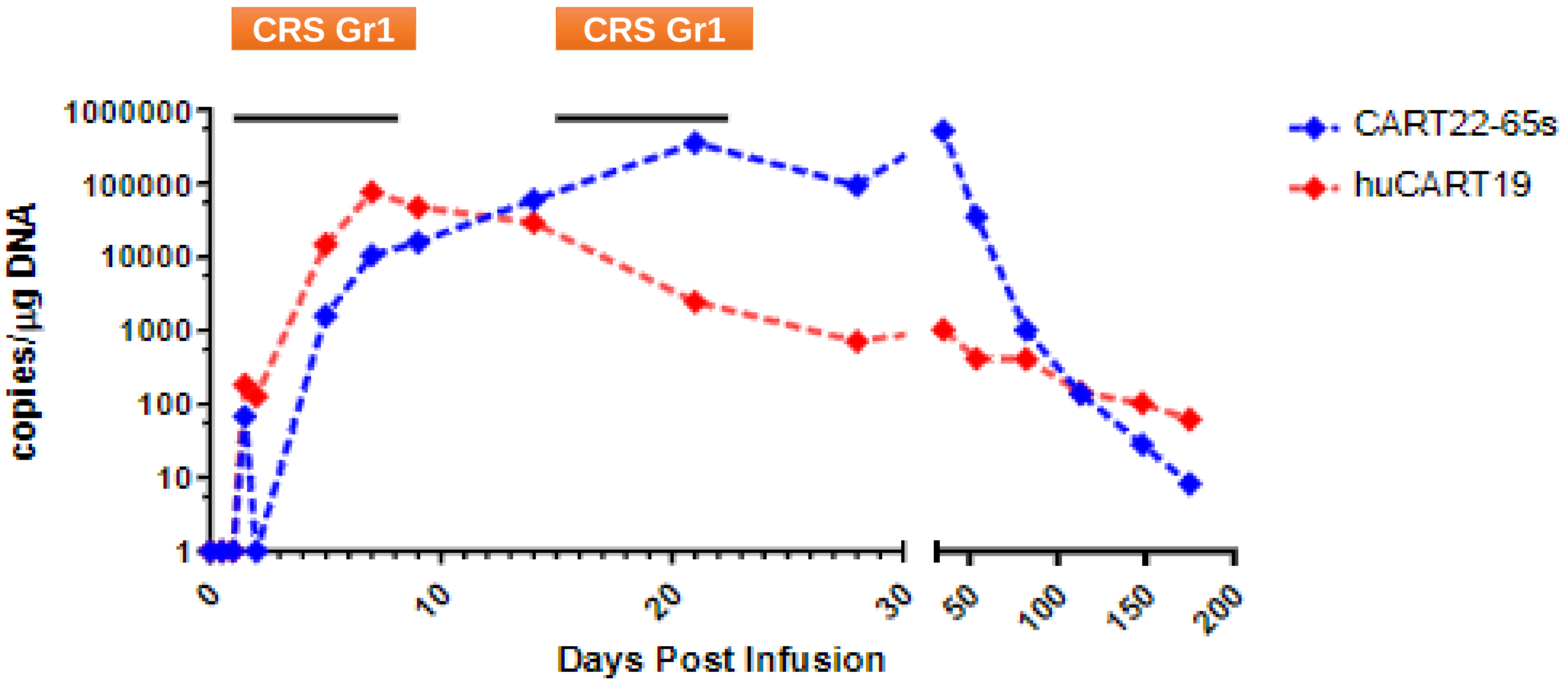
Med follow up 11.8 mo:

- One pt with molecular recurrence
- 10 with ongoing CR/CRi



Frey N. Volume 138, Supplement 1, 23 November 2021, Page 469

Different peak expansions correlate with distinct CRS events



Frey N. ***Volume 138, Supplement 1**, 23 November 2021, Page 469*

AML clinical results – published & abstracts

Agent	Patients treated	Responses	Toxicity	Comments	Reference
			CD123		
Donor CART-123	1	PR (?)	CRS gr. 4		Yao 2019
UniCART-123	3	1 PR, 2 CRi	CRS gr. 1 (n=2) Myelosuppression	Expansion, persistence seen. IL-6, TNF, IFNγ detected.	Wermke 2021
CART-123	7 (18 enrolled)	2 MLFS, 1 CRi	CRS gr. 1-2	Peak expansion at day 14. No CD123 loss.	Budde 2019
UCART-123	16	1 MLFS, 1 CR (uMRD)	CRS in 15/16 including 2 gr.4 and 1 gr.5 CRS.		Sallman 2022
			CD33		
UltraCART-33	24 (10 without and 14 with lymphodepletion)	Objective responses in 30%	Gr. 1 CRS (n=10), gr. 2 CRS (n=6), gr. 3 CRS (n=1). No bone marrow aplasia	Dose-dependent expansion in blood and marrow. Persistence up to 7 months.	Sallman 2022
CART-33	1	PR	CRS, pancytopenia	IL-6, IL-8,TNF, IFNγ detected.	Wang 2015
CART-33	3	None	CRS (n=2). ICANS (n=1)	IL-6, TNF, IFNγ detected.	Tambaro 2021
			CLL-1 (CLEC12A)		
CART-CLL1	7 (pediatric)	CR in 5 / 7	Gr. 1-2 CRS (n=7)		Pei 2023
CART-CLL1	10 (adult)	CR or CRi in 7/10	Low grade CRS (n=4). High grade CRS (n=6). Severe pancytopenia (n=10)		Jin 2022
CART-CLL1	8 (pediatric)	MLFS in 5/8, CRi in 1/8, 1 PR	CRS (n=8)	Loss of CLL1+ subset in 1 patient	Zhang 2022
			Other		
CART-Lewis Y	4	Cytogenetic response 1 / 4	None	Trafficking to marrow demonstrated using radiolabeling	Ritchie 2013
NKG2D ligands	12	Objective response in 3 / 12	Gr. 3-4 CRS (n=5)		Sallman 2023

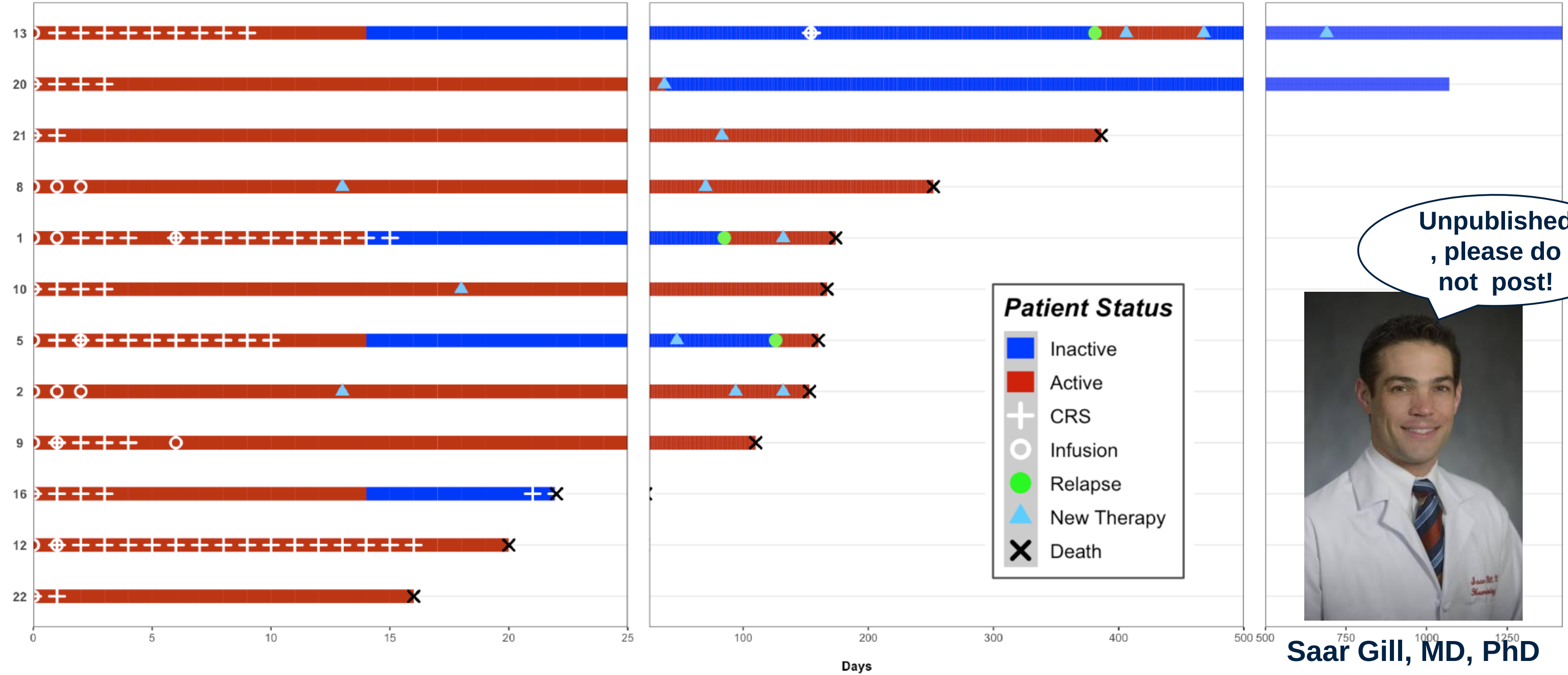
~30% response rate

CART-123 in AML: clinical trial at UPenn

Sex		Age		Race		Prior lines of therapy		Prior alloHCT		Cytogenetics *		Molecular ^		Marrow blasts		Infused	
Male	9	Median	59.5	Caucasian	17	Median	5	Yes	11	Favorable	0	Favorable	0	Median	40%	Yes	12
Female	11	Range	22 - 69	Black	2	Range	1 -9	No	9	Intermediate	5	Intermediate	13	Range	4 - 85%	No	8
				Asian	1					Adverse **	15	Adverse ^^	7				

* by 2017 ELN risk classification
** complex, inversion 3, del(5q), -7, KMT2A rearrangements,

^ by 2017 ELN risk classification and Papaemmanuil NEJM 2016
^^ TP53, RUNX1, GATA2, ASXL1



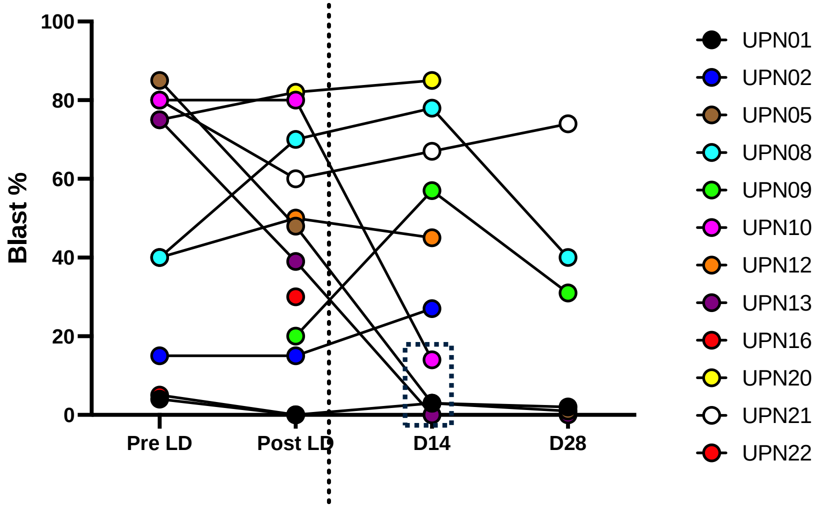
Unpublished, please do not post!

Saar Gill, MD, PhD

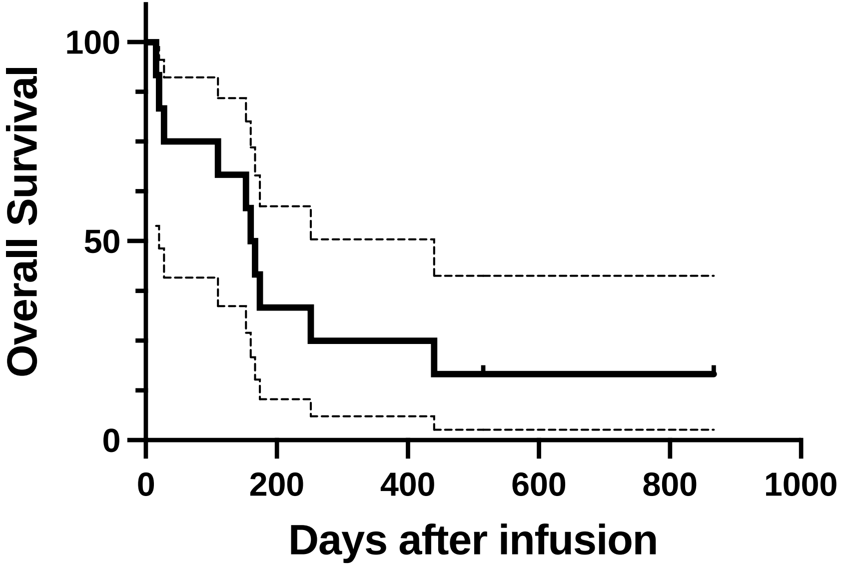
CART-123 in AML: Efficacy

Unpublished, please do not post!

Response



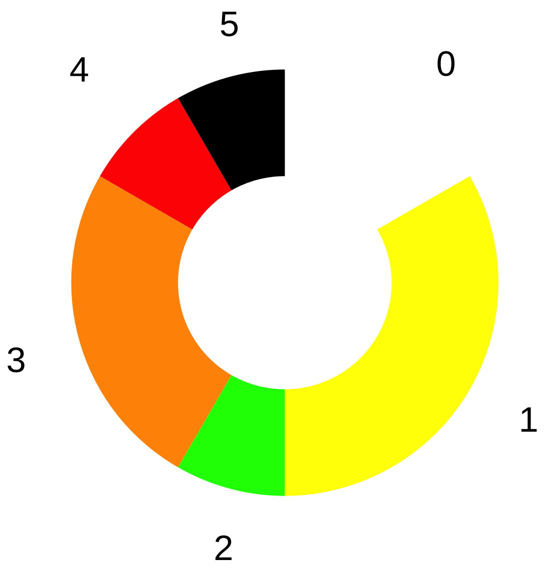
Overall Survival



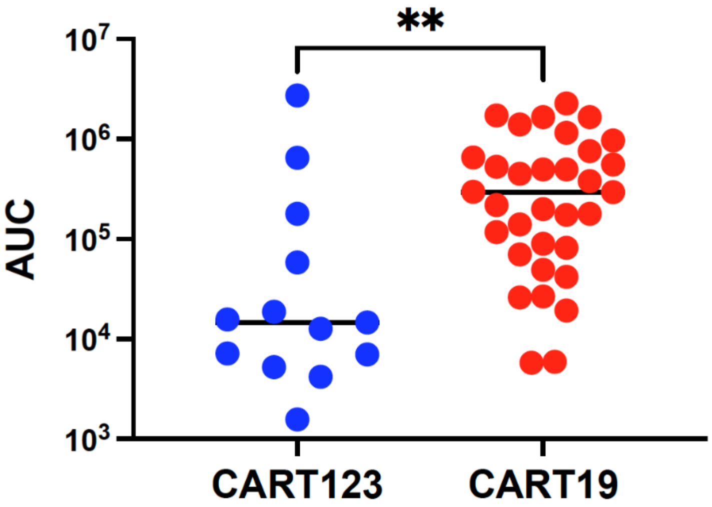
Saar Gill, MD, PhD

CART123: Cytokine release syndrome and CART expansion

CRS



CART expansion



Unpublished, please do not post!

CART19 = adults with B-ALL, Frey et al, JCO 2020;38(5):415-422

Target: How to achieve tumor specificity in AML

1. TCR-based therapies [1-4] (including TCR-like CARs [5]) that target *intracellular* neoantigens or cancer-testis antigens

2. Discover a cell surface marker that is specific to neoplastic myeloid cells [6,7]

3. Logic-gated CARs [8]

4. Create a cancer-specific antigen [9-11]

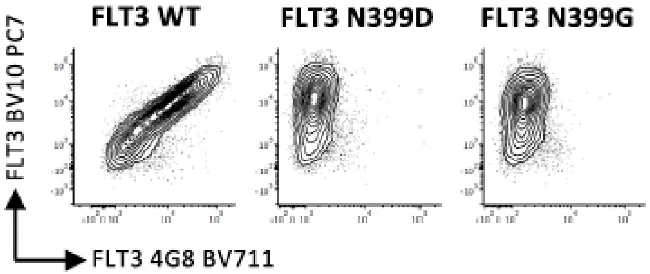
[1] Chapuis Nat Med 2019 [2] Biernacki J Clin Invest 2020 [3] Raskin Mol Ther 2021 [4] Lulla Blood 2021 [5] Xie Nat Biomed Eng 2021 [6] Reis ASH 2022 #6. [7] Mandal ASH 2022 #357 [8] Haubner Cancer Cell 2023 [9] Kim Cell 2018 [10]

Courtesy of Saar Gill, MD, PhD

4. Create a cancer-specific antigen

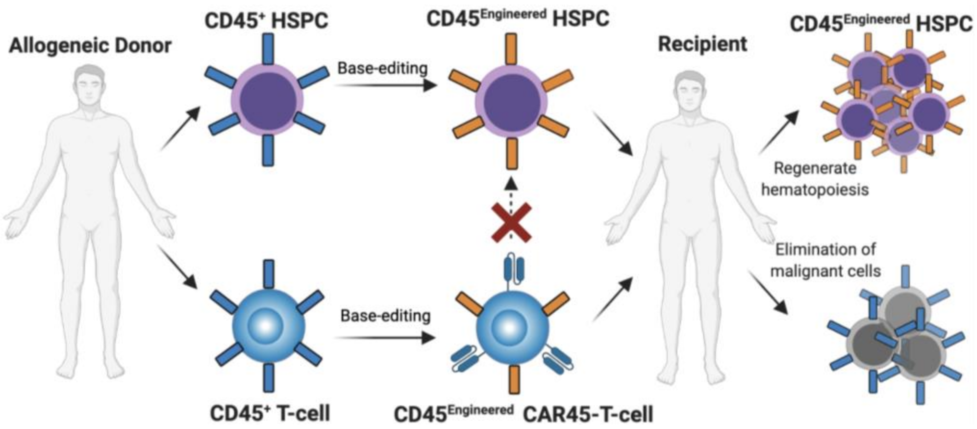
Epitope editing enables targeted immunotherapy of acute myeloid leukaemia

Epitope base editing CD45 in hematopoietic cells enables universal blood cancer immune therapy



Casirati… Genovese, Nature 2023

Marone… Jeker, JEM 2023



Wellhausen… Gill, Sci Transl Med, 2023

Conclusions and perspectives

CART for B-ALL:

- different effect in pediatric vs. adult patients
- CD19-neg escape an issues → ***DUAL TARGETING APPROACHES***
- CD19+ relapses → ***ENHANCE CART FUNCTION, ENHANCE TUMOR APOPTOSIS***
- Role of post-CART transplant TBD (adult, CD28, B-cell aplasia, MRD+, previous SCT)
- Effect post-blinatumomab
- Role of allogeneic CART and immunogenicity

CART for AML:

- limited responses and short lasting
- no pronounced myelosuppression
- absence of ideal targets → ***gated strategies, gene-editing of HSC***
- major toxicity: CRS

CART for T-ALL:

- initial results promising with CART7
- use as bridging therapy
- allogeneic
- CD7-neg escapes
- infections

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Leukemia & Lymphoma Society
Gabrielle's Angel Foundation for Cancer Research
AbClon
Parker Institute for Cancer Immunotherapy
Lymphoma Research • Foundation
Emerson Collective
National Cancer Institute
American Society of Hematology
Gilead Sciences International Research Scholars Program in Hematology/Oncology
The Mark Foundation for Cancer Research

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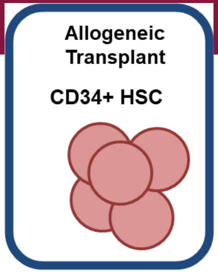
https://www.med.upenn.edu/ruella-lab/

Selected Bispecific Approaches with CARTs

Antigen target	CAR design		Disease	CR (*n* = treated patients)	References
CD19 + CD22	Tandem	19.22.4-1BBζ	B-ALL	87% (*n* = 15)	Wang Y et al., 2020
			B-ALL	100% (*n* = 6)	Dai H et al., 2020
			B-ALL	88% (*n* = 17)	Spiegel J et al., 2021
			DLBCL	29% (*n* = 21)	Spiegel J et al., 2021
			DLBCL	63% (*n* = 16)	Wei G et al., 2021
			B-ALL	83% (*n* = 7)	Hu Y et al., 2021
			DLBCL	64% (*n* = 33)	Qu C et al., 2022
			B-ALL	60% (*n* = 20)	Shalabi H et al., 2022
	Dual	19.OX40ζ and 22.4-1BBζ	B-ALL	86% (*n* = 15)	Cordoba S et al., 2021
	Sequential	CD19 CD22	B-ALL	98% (n=79)	Pan, Lancet Oncol. 2023
	Pooled	CD19 CD22	B-ALL	99% (n=192)	Wang, JCO 2023

Hamieh et al, Cancer Discovery 2023

The role allogeneic transplant after CART19 in B-ALL



No randomized data to make a strong statement on the role of SCT after CART19. However:

- CART19 lead to long-term remissions in a subset of B-ALL patients, however relapse (CD19-/+) common
- Toxicity for CART less impactful than SCT
- In retrospective, non-randomized comparisons SCT seems to be beneficial for: patients with short B-cell aplasia, adult B-ALL, ped B-ALL with CD28 CARTs, no prior SCT

Randomized trials needed

Until then, selection of patients that would benefit from SCT:

4-1BB vs CD28 and duration of B cell aplasia
Peds vs. adults
Prior SCT
Likelihood of antigen-escape (prior blinatumomab or inotuzumab; MLL-1, BCR-ABL)
Poor prognostic factors for CART (LDH, plts…)
Donor availability and donor type
Clinical fitness (PS and comorbidities)
Minimal residual disease after CART19

Early use of CART19, Dual CART19/22 will soon change the treatment paradigm for B-ALL and the use of SCT