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LIVE Symposium

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THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

CAR T-cell constructs: current and future options

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4-30-22

Disclosures

- Speaker bureaus: Astra Zeneca, BeiGene, Bristol Myers Squibb

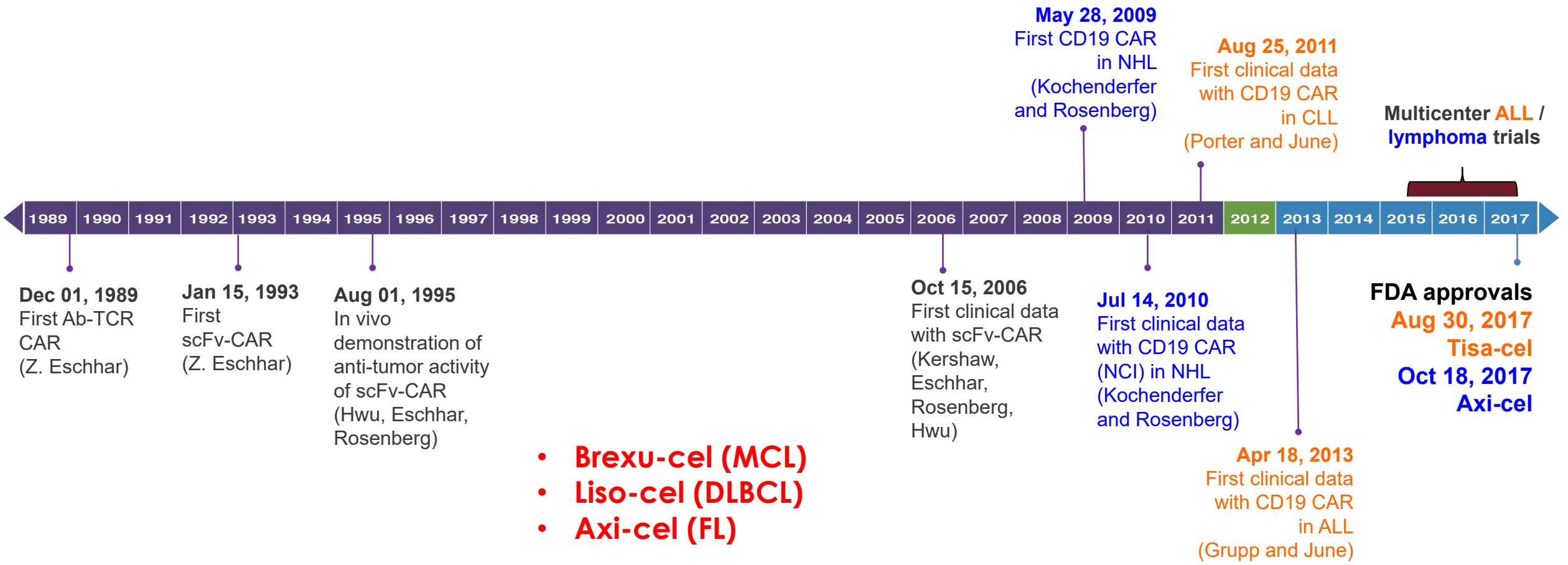
- Advisory boards: Astra Zeneca, BeiGene, Bristol Myers Squibb, Celgene, Pharmacyclics, Abbvie, Gilead

Agenda

- CD19CAR T cells
- Other targets:
  - BAFF-R
  - CD22
  - Dual antigen targeting
  - CD30
  - ROR1

CAR T cell therapy development: From discovery to FDA approval

Discovery to FDA approval ~25 years



- **Brexu-cel (MCL)**
- **Liso-cel (DLBCL)**
- **Axi-cel (FL)**

CD19CAR T cells in B-NHL

	NCI	U Penn	FHCRC / SCH
CD19 Ab	FMC63	FMC63	FMC63
Hinge Transmembrane	CD28	CD8a	CD28
Signal 2	CD28	4-1BB	4-1BB
Signal 1	CD3ζ	CD3ζ	CD3ζ
Gene transfer	Retrovirus	Lentivirus	Lentivirus
	KTE-C19 Axicabtagene ciloleucel Axi-cel	**CTL-019 Tisagenlecleucel**	**JCAR017 (CD4:CD8 = 1:1) Lisocabtagene maraleucel Liso-cel**

Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

CD19CAR T cells in MCL, FL, CLL/SLL

- Relapsed/refractory Mantle Cell Lymphoma
  - ORR 85%, CRR 59%
- Relapsed/refractory Follicular Lymphoma
  - ORR 73-80%, CRR 40-54%, encouraging durability
- Relapsed/refractory high-risk CLL/SLL
  - ORR 74%, CRR 21%, flow- marrow 88%
  - Ibrutinib may improve expansion and efficacy while reducing CRS

Wang M, et al. N Engl J Med 2020
Schuster, et al. Proc ASH 2015
Turtle, et al. Sci Trans Med 2016
Turtle, et al. Proc ASH 2016
Fraietta, et al. Blood 2016.

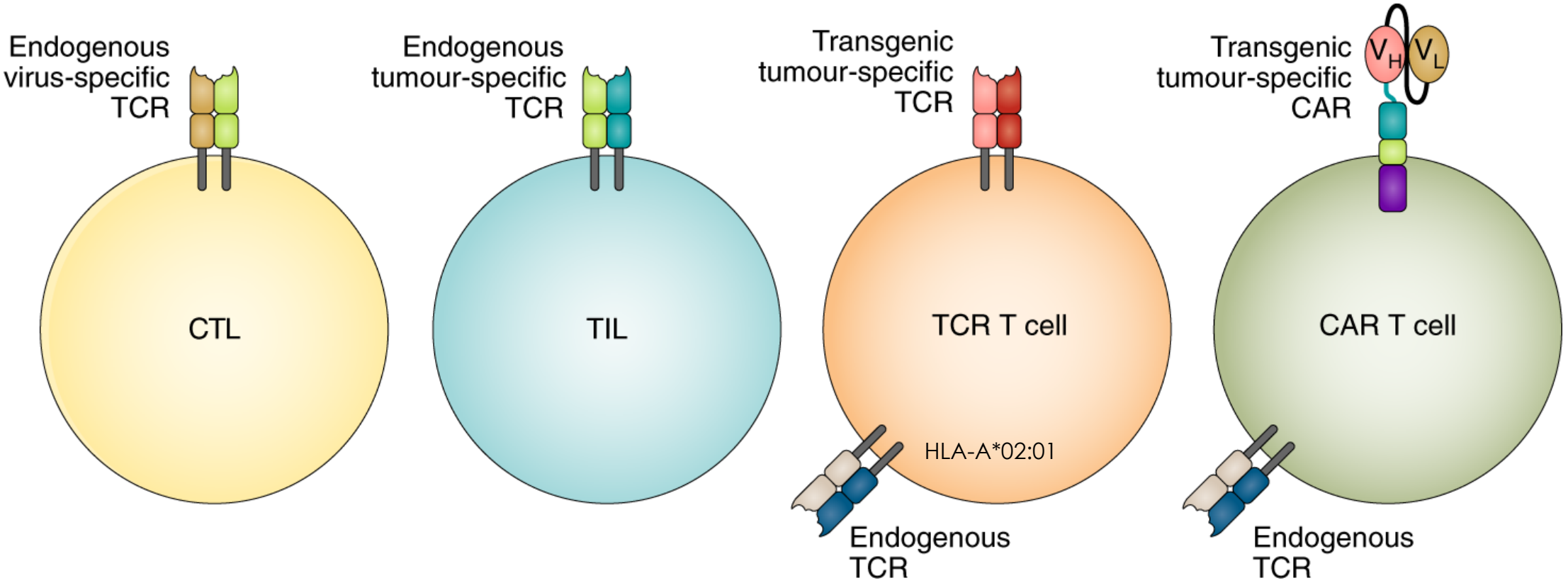
CD19CAR T cells for R/R CLL: high rates of deep responses in ibru-refractory, BCL2i-refractory patients

Author	Publication	N	Product	ORR	CR/CRi	Flow MRD-negative marrow response
CD19 CAR T cells monotherapy						
Porter	Science Translational Medicine, 2015	14	CTL019	57%	28%	Not reported
Turtle	JCO, 2017	24	JCAR014	71% **Ibru-R: 69%**	21% **Ibru-R: 25%**	88% **Ibru-R: 86%**
Geyer	JCI Insight, 2019	16	19-28z	25%[#]	25%[#]	12%
Frey	JCO, 2020	32	CART-19	44%	28%	Not reported
Siddiqi	ASH Abstract 2020	23	JCAR017	82% **BTKi/BCLi-R: 80%**	45% **BTKi/BCLi-R: 60%**	75% (blood) **BTKi/BCLi-R: 78% (67% NGS-negative marrow)**
CD19 CAR T cells with concurrent ibrutinib						
Gill	ASH Abstract 2018	19 (all ibru-E)	CTL119	71%	43%	83%
Gauthier	Blood, 2020	19 **(all ibru-R)**	JCAR014	83%	22%	72%
Wierda	ASH Abstract 2020	19	JCAR017	95%	47%	89% (blood)

Unmet need

- PFS in NHL with various CAR T products appears to be 40% or better
- Salvage after CAR T cell therapy rarely works
- CD19 target is lost in 30-50% of relapses post-CAR T cell therapy

Modalities for T cell-based Cancer Therapy



- Tabelecleucel (EBV+ PTLD)
- CMV-directed CTLs (Post-HCT)

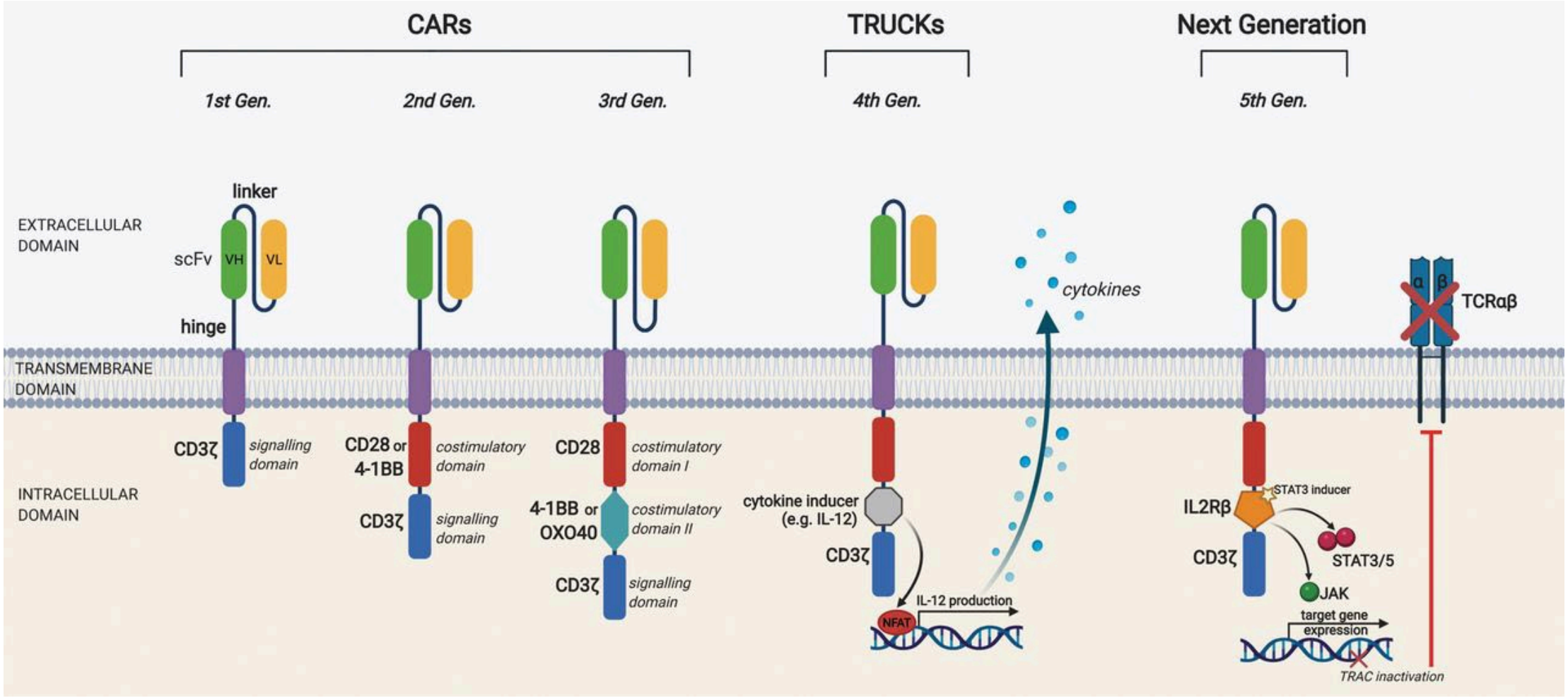
- Lifileucel (Melanoma)
- LN-145 (HNSCC, Cervical, NSCLC)
- Investigational: 25+ trials ongoing

- NY-ESO-directed TCR-T (MM, Melanoma, Sarcoma, Ovarian, NSCLC)
- MAGE-directed TCR-T (Melanoma, Sarcoma)

- SOC CD19-directed CAR-T (NHL, B-ALL)
- SOC BCMA-directed CAR-T (MM)
- Investigational: **500+ trials registered**

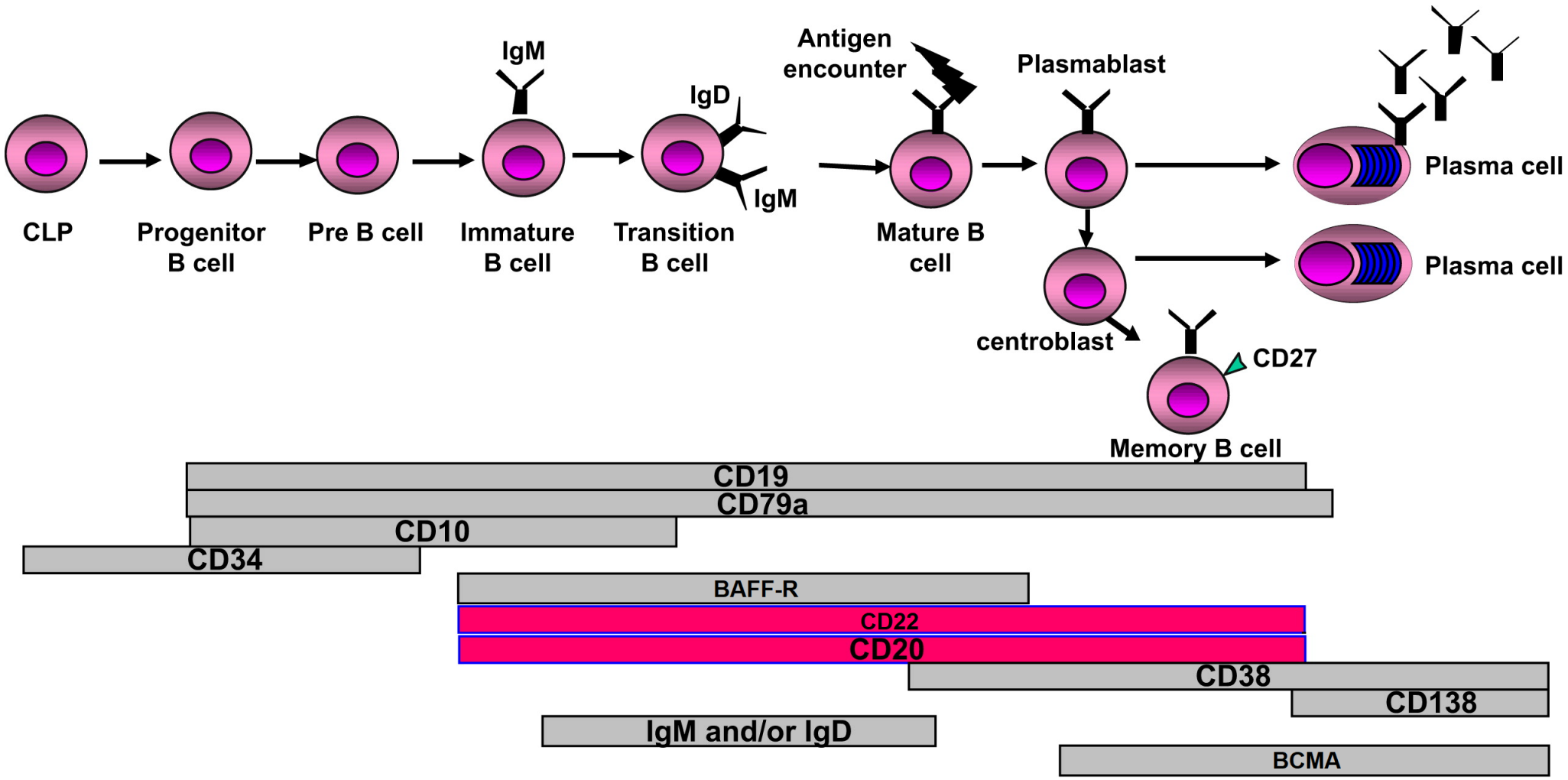
Slide credit: *Modified from* Gong N et al. Nat Nanotechnol 2021. doi: 10.1038/s41565-020-00822-y.

Evolution in CAR Design



Slide credit: Rallis KS et al. Anticancer Res 2021. doi: 10.21873/anticanres.14871.

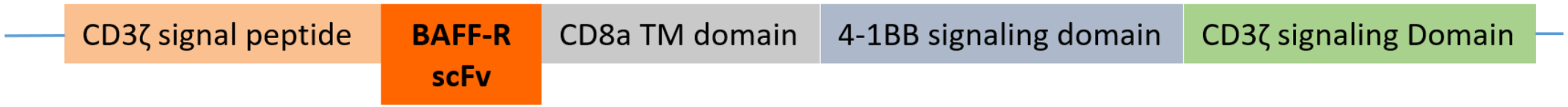
B-cell Development



Slide credit: *Modified from* Small TN et al. BBMT 2009. doi: 10.1016/j.bbmt.2008.10.016.

BAFF-R CAR T cells

- MCL is a rare aggressive B-NHL
- Unmet need for novel, effective and well tolerated therapies for patients with MCL (elder patient population, troubling relapse pattern with small molecule targeted therapy, high toxicities associated with Brexu-cel).
- The Kwak group at City of Hope has developed BAFF-R CAR T cell therapy



BAFF-R CAR T cells

- BAFF-R antigen vs CD19 antigen

- BAFF-R is expressed on all subtypes of B-cell non-Hodgkin's lymphomas; not expressed by early-stage B-cells

- CD19 antigen loss is a common phenomenon post-CD19CAR T treatment.

- BAFF-R loss by tumor cells is unlikely because BAFF-R signaling appears to be required for survival

- BAFF-R CAR outperformed CD19 CAR T cells in preclinical models

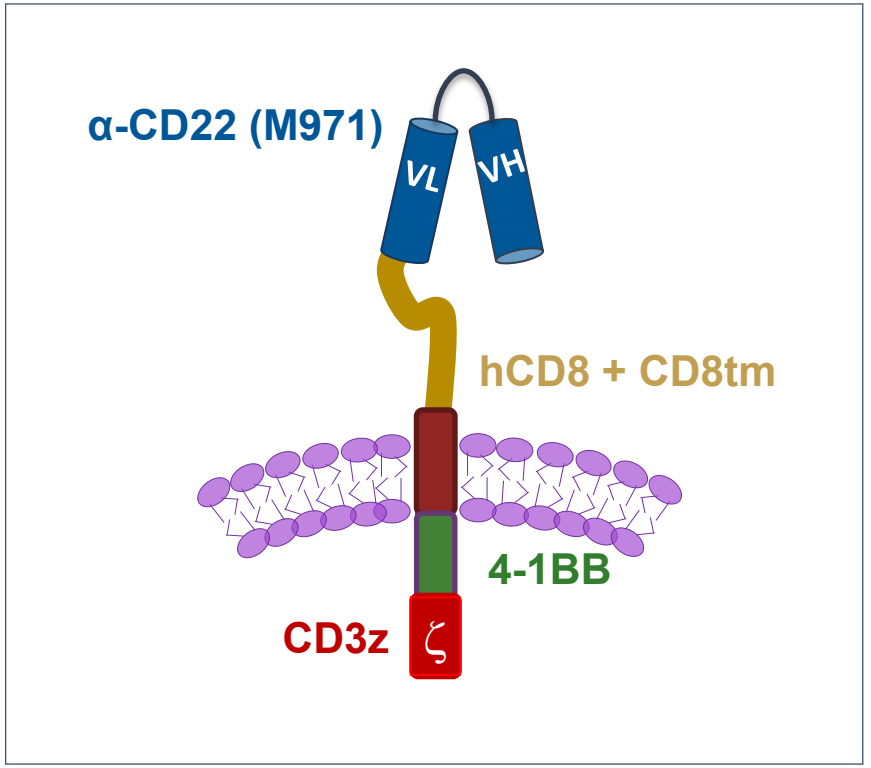
Phase I Dose Escalation Study of CAR22 in Adults with Relapsed/Refractory LBCL or B-ALL

Primary Objectives

- Determine feasibility of production
- Assess safety

LBCL (N = 20)

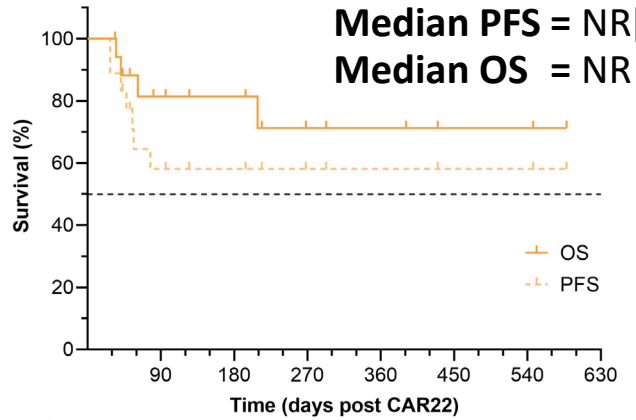
- 55.6% DEL, 25% DHL, and 35% primary refractory
- 22% had high tumor burden (SPD >50 cm2), 84% had elevated LDH at enrollment
- Median prior lines of therapy 5 [range 3-8], 30% relapsed after autoHCT
- 95% relapsed after CAR19



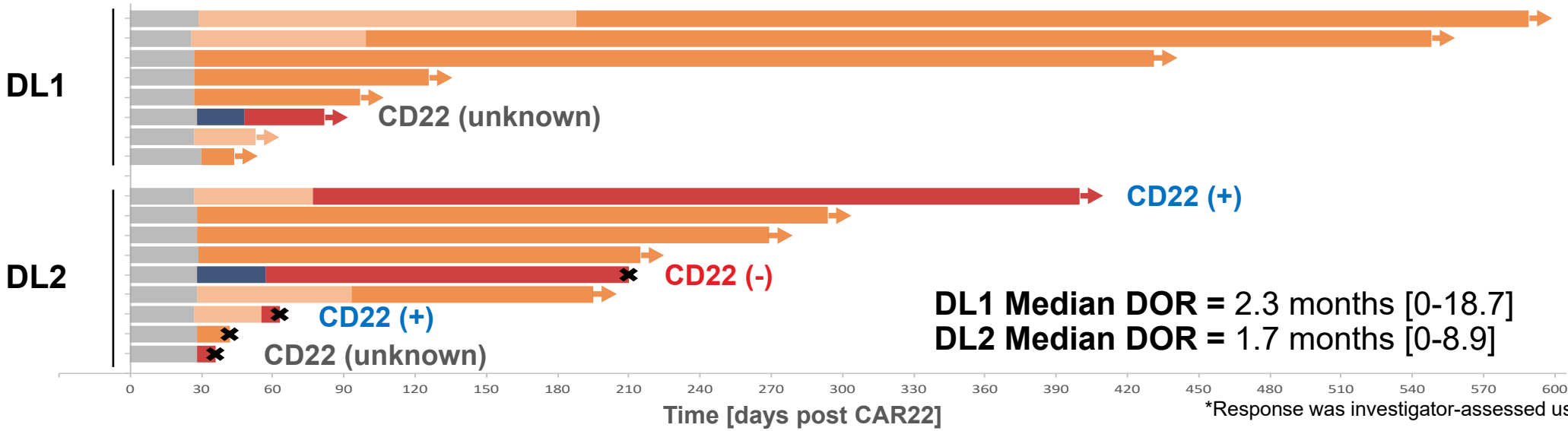
ClinicalTrials.gov NCT04088890

Frank MJ, Baird JH et al. *TCT 2021*, Abstract #79; Baird JH, Frank MJ et al. *ASH 2020*, Abstract #736
Baird JH, Frank MJ, Craig J et al. *Blood.* 2021

CAR22 Clinical Outcomes: LBCL



LBCL	DL1 (N = 8)	DL2 (N = 9)	Tot (N = 18)
Median follow up, months [range]	3.7 [1.5-19.6]	7.0 [1.2-13.1]	5.4 [1.2-19.6]
Overall Response Rate (ORR)*, n (%)	7 (87.5)	7 (77.8)	14 (77.8)
CR Rate	6 (75)	5 (55.6)	11 (61.1)



*Response was investigator-assessed using Lugano criteria for LBCL.

Frank MJ, Baird JH et al. *TCT 2021*, Abstract #79; Baird JH, Frank MJ et al. *ASH 2020*, Abstract #736

Summary

- CAR22 was successfully manufactured in 100% of LBCL and B-ALL patients using closed CliniMACS Prodigy system

- Single infusion of CAR22 produced high response rates in all patients
  - LBCL: Best ORR and CR rate of 78% and 61%, respectively

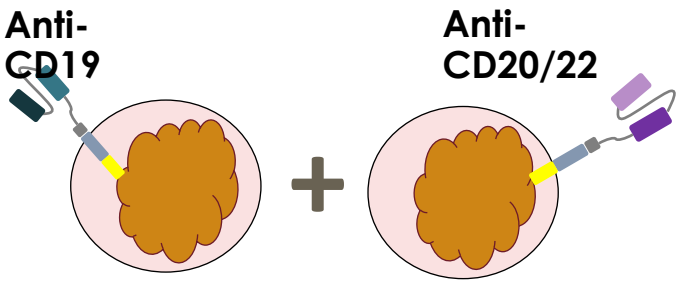
- CAR22 safety appears comparable with CAR19 and NCI pediatric reports

- 1 case of Grade 3 CRS, and 1 case of Grade 4 ICANS
- 63% of patients have a Grade ≥ 3 cytopenia beyond D+28; nearly all have self-resolved to Grade ≤ 2 at an average of 60 days post-infusion.

- CD22 loss represents putative mechanism of failure in ~50% of B-ALL, appears less frequent in LBCL

Strategies for Dual Antigen Targeting

Co-administration



Pros:

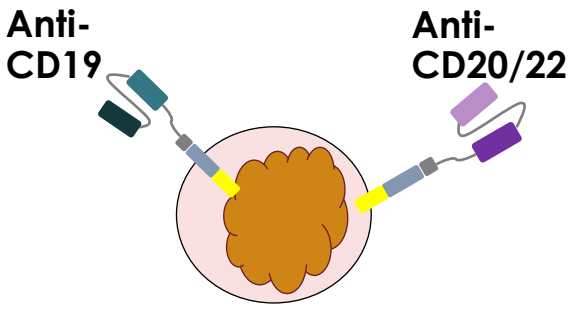
- Defined dose for each CAR

Cons:

- Multiple production runs
- Potential competition
- Timing for 2nd infusion

Co-expression

(co-transfection or bicistronic)



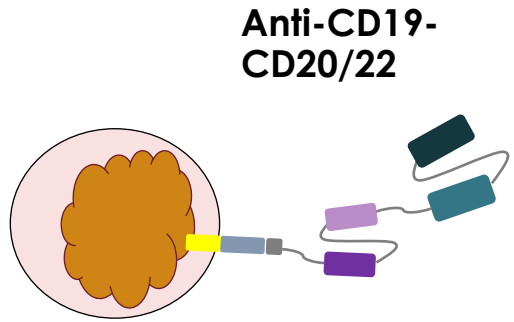
Pros:

- Each CAR molecule signals independently
- Reduces steric concerns

Cons:

- Can generate multiple CAR populations

Bivalent-bispecific receptor (tandem or loop)



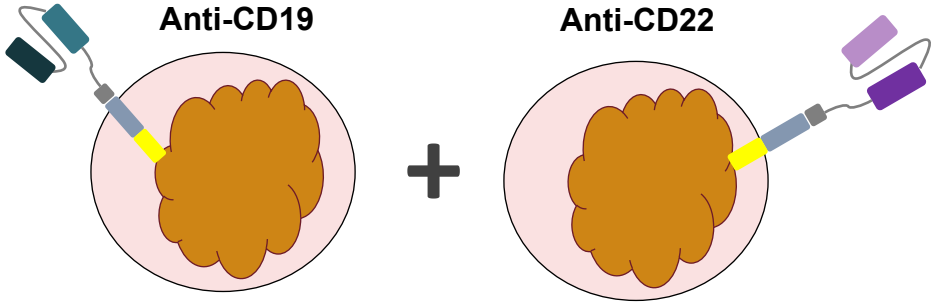
Pros:

- Each cell expresses both scFvs

Cons:

- Distal scFv may have signalling deficiencies

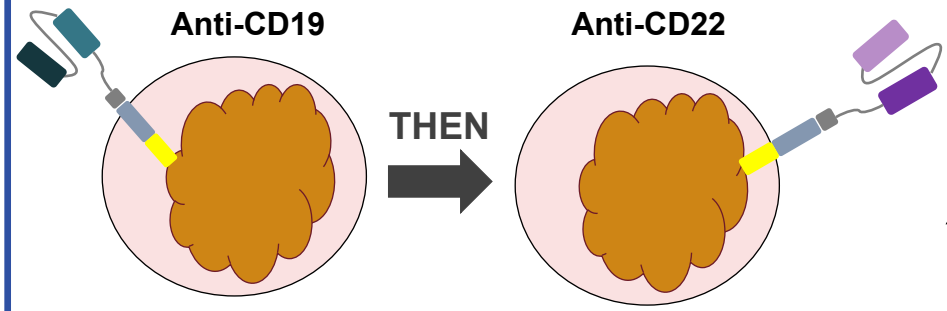
Options for CAR-T Targeting of CD19 and CD22



Co-administration

Pros:
- Defined dose for each CAR

Cons:
- Multiple production runs
- Potential competition
- When to infuse 2nd dose



Sequential Administration

Pros:
- Defined dose for each CAR
- Avoids steric/signaling concerns
- Combined DOR > single bispecific CAR?

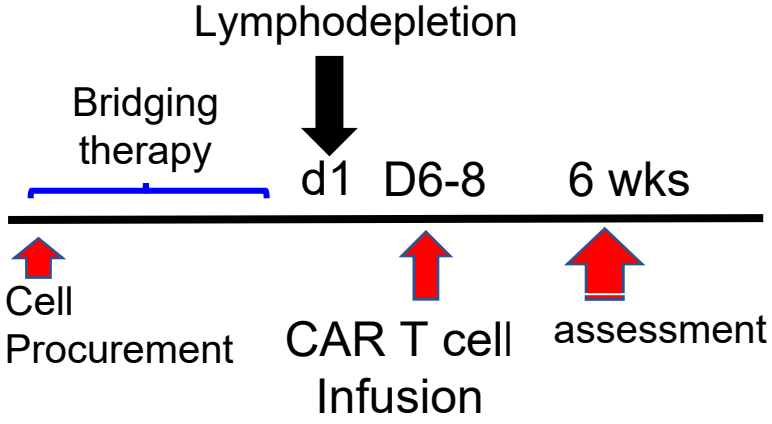
Cons:
- Multiple production runs, LD chemotherapy
- Narrow antigen selection pressure
- Compounding therapeutic toxicities

Stanford CD22.BB.z-CAR, NCT04088890

	Phase/trial	Sponsor	Name	Patient population	Target	Response	Toxicity
Bivalent-bispecific receptor	Phase 1	Medical College of Wisconsin	LV20.19 CAR T	Adult R/R NHL	CD19/CD20	82% ORR, 64% CR 18% PR	No DLTs, 64% CRS, 32% NTX
	Phase 1/2a	Chinese PLA General Hospital	TanCART19/20	Adult R/R NHL	CD19/CD20	84% ORR, 74% CR	71% CRS, 2% CRES
	Phase 1	CBMG	C-CAR039	Adult R/R LBCL	CD19/CD20	92% ORR, 72% CR	95% CRS, 5% ICANS
	Phase 1	Miltenyi Biotec	MB-CART2019.1	Adult R/R B-NHL	CD19/CD20	75% ORR, 42% CR	67% CRS, 8% ICANS
	Phase 1	Stanford University	CAR19.22	Parallel paediatric and adult R/R B-ALL	CD19/CD22	92% CR, 92% OS	75% CRS, 17% ICANS
	Phase 1	Chinese PLA General Hospital	TanCART-19/22	Adult R/R B-ALL	CD19/CD22	100% CR	100% CRS, no NTX
Co-expression	Phase 1 Alexander	Autolus Therapeutics	AUTO3	Adult R/R DLBCL or transformed DLBCL	CD19/CD22	69% ORR, 52% CR	No DLTs, no sCRS, 9% sNTX
	Phase 1 Amelia	Autolus Therapeutics	AUTO3	Paediatric R/R B-ALL	CD19/CD22	100% CR/CRi 100% MRD–	No DLTs, 90% CRS, 10% NTX
	Phase 1	Hebei Yanda Lu Daopei Hospital and Gracell Biotechnology Ltd	GC022	Paediatric and adult R/R B-ALL	CD19/CD22	25% CR (MRD+) (2.5–5 × 105/kg) 100% CR (1–2.5 × 106/kg)	100% CRS, no NTX
	Phase 1 PLAT-05	Seattle Children's Hospital	SCRI-CAR19x22v1	Paediatric and young adult R/R B-ALL	CD19 and CD22	71% CR	No DLTs, 71% CRS, 29% NTX
Co-administration	Phase 1	Beijing Boren Hospital	-	Paediatric R/R B-ALL	CD19 followed by CD22	100% CR (MRD–)	15% NTX in both CD19 CAR: 90% CRS CD22 CAR: 75% CRS
(Sequential admin.)	Phase 1	Stanford University	CAR22	Adult R/R B-ALL and CAR-refractory LBCL	CD19 followed by CD22	LBCL 86% ORR, 67% CR	CD22 CAR: 100% CRS, 19% NTX, 24% MAS

Phase 1 trial of CD30 CAR-T co-expressing CCR4 in r/r HL and CTCL

Study Design



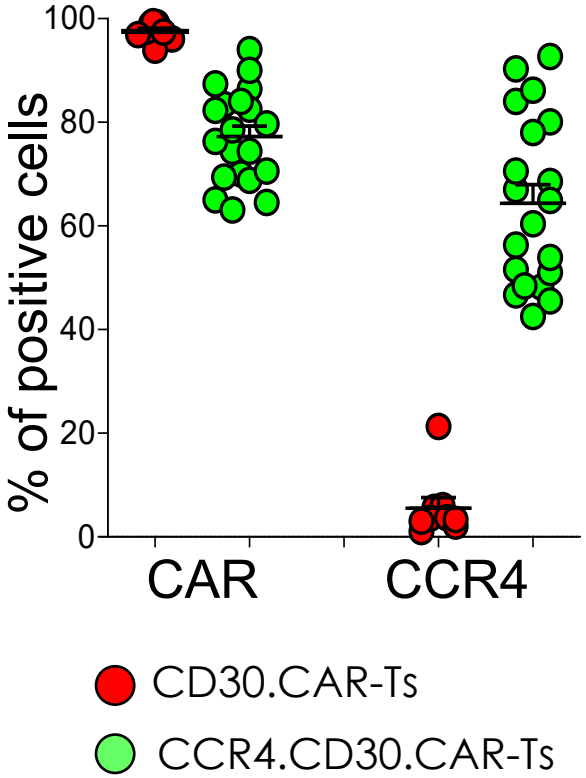
Lymphodepletion

Bendamustine (70 mg/m^2/day) x 3 days Fludarabine (30 mg/m^2/day) x 3 days

Patients

13 evaluable patients
11 HL, 2 CTCL
Median 5 prior lines of therapy

CCR4 expression on CAR-T products



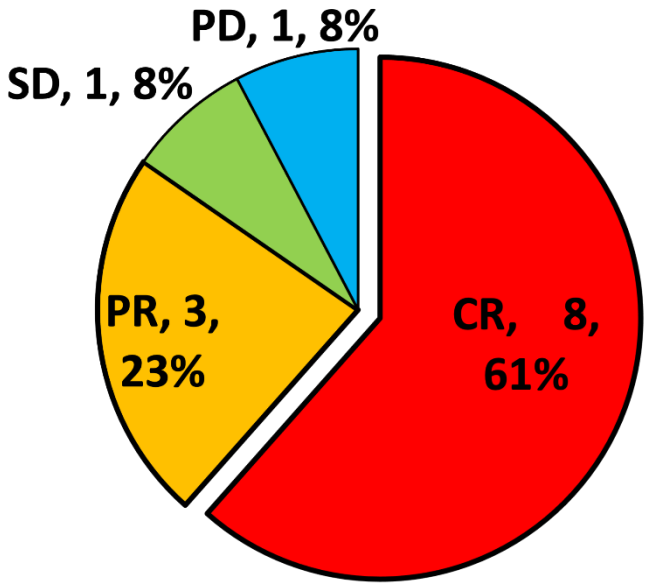
Safety

- 4 dose levels tested to date up to 5 x 10^7 CCR4.CD30 CAR-T cells/m2
- No DLT
- No ICANS
- 3 patients with CRS
  - 2 grade 2 which resolved with tocilizumab
  - 1 self-limiting grade 1 CRS
  - Onset day 13-19

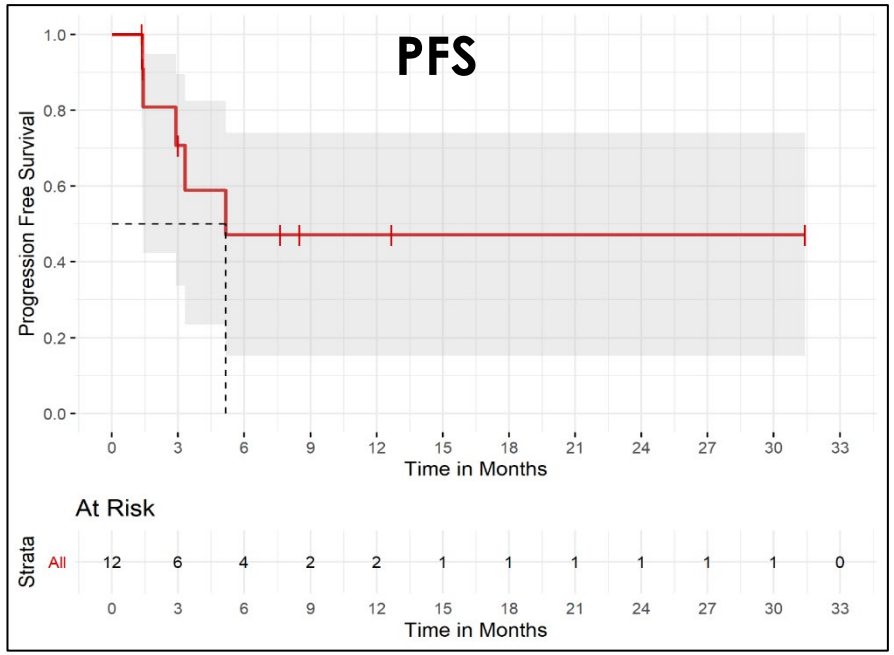
Grover et al, *ASH 2021*, Abstract 742

CCR4.CD30 CAR T cells: Efficacy

- N = 13
- All HL patients responded
  - 8 CRs; 3 PRs
- 2 CTCL patients
  - 1 SD; 1 PD



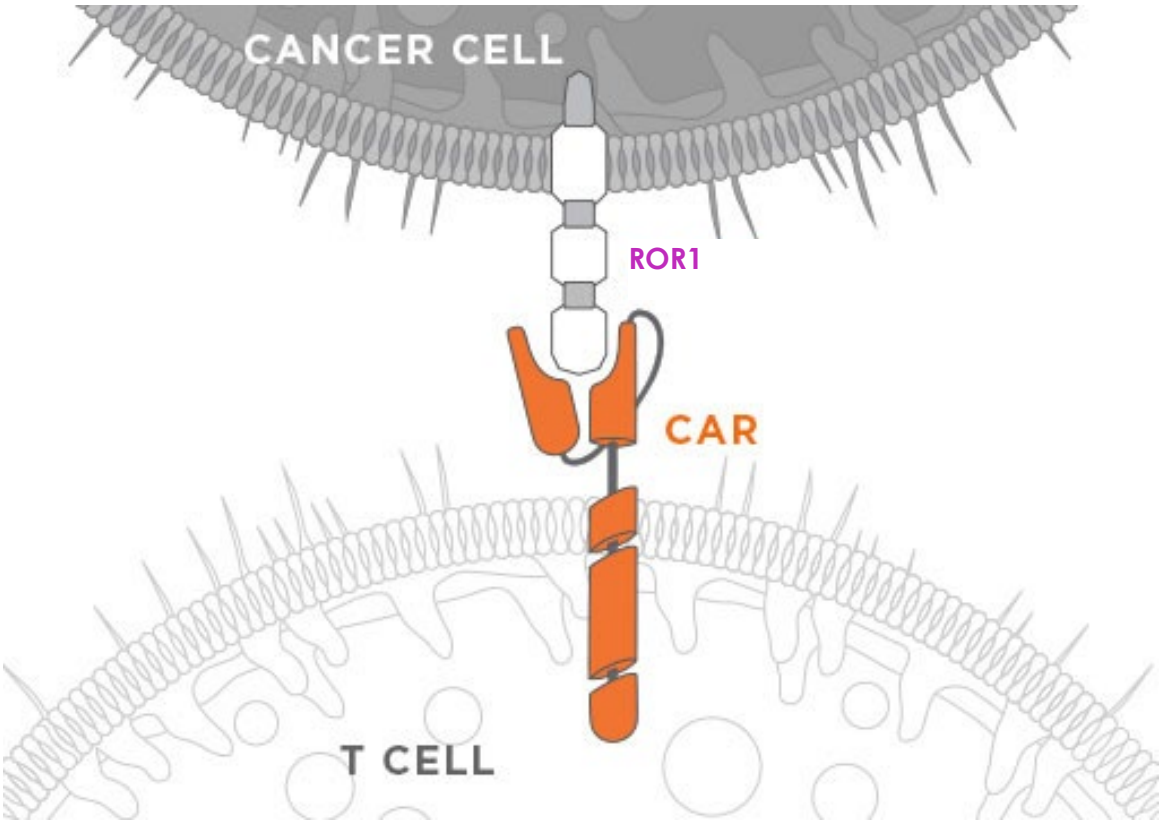
- Median f/u 8.5 mo
- Median PFS for all patients – 5.2 months
- Median PFS for HL patients – not reached
- 1 patient in CR at almost 3 years



Grover et al, *ASH 2021*, Abstract 742

ROR1 CAR T in CLL/SLL

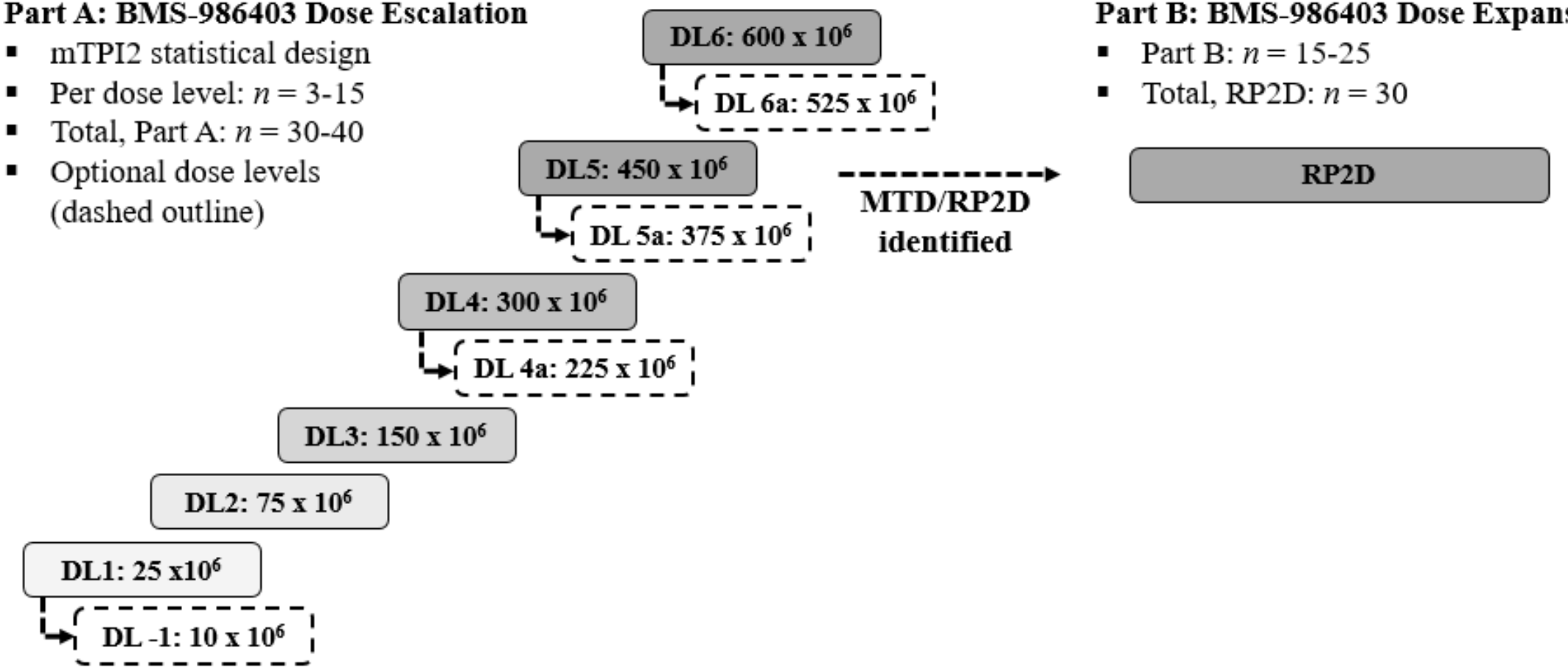
- BMS-986403 is an investigational ROR1-targeted CAR T cell product.
- ROR1 CAR T cell generation and initial preclinical testing of BMS-986403 reveals comparable cytotoxicity, proliferation and cytokine production to CD19 CAR T cells in primary CLL PBMCs
- BMS-986403 shows enhanced anti-tumor activity and survival in ROR1 expressing MCL cell line in vivo (JeKo-1)
- Autologous T cells are collected from subjects by leukapheresis, engineered to express the anti-ROR1 CAR via viral vector transduction, and administered to the subject by intravenous infusion to therapeutically target the tumor-specific antigen ROR1



Study Design/Schematic

Part A: BMS-986403 Dose Escalation

- mTPI2 statistical design
- Per dose level: n = 3-15
- Total, Part A: n = 30-40
- Optional dose levels (dashed outline)



Part B: BMS-986403 Dose Expansion

- Part B: n = 15-25
- Total, RP2D: n = 30

DL = dose level; mTPI-2 = the modified toxicity probability interval method 2; n = number of subjects; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose. For Part B, total n=30 results from total number treated at the RP2D in Part A (n=5-15) plus those treated in Part B (15-25)

Questions?

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