8th POSTGRADUATE
Lymphoma
Conference

Novel agents/Tandem CARs

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Grand Hotel Santa Lucia

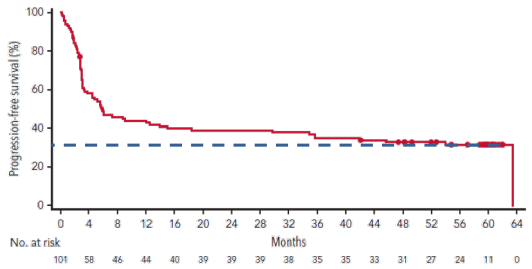
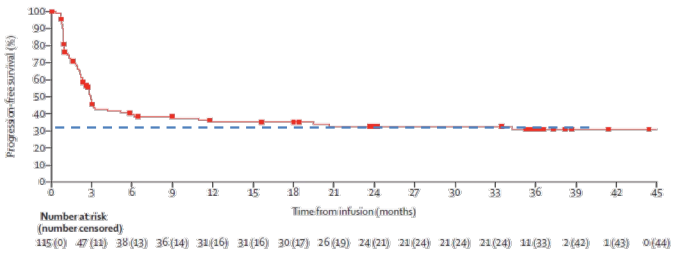
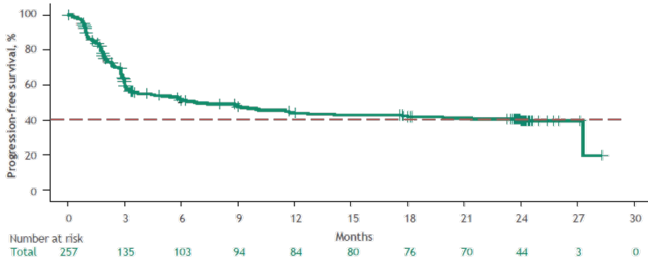
President:
P.L. Zinzani

Disclosures of Prof. Stephen J. Schuster

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie						X	
AstraZeneca						X	
BeiGene						X	
Caribou Biotech						X	Steering committee
Fate Therapeutics							Safety DSMB
Genentech/Roche	X					X	Steering committee
Genmab	X					X	Steering committee
Incyte/Morphosys						X	Honoraria for presentation
Kite Pharmaceuticals						X	
Legend Biotech						X	Steering committee
Novartis						X	Steering committee
Mustang Biotech						X	
Nordic Nanovector						X	Steering committee
Takeda							Honoraria for presentation

Approved CAR T products as ≥ 3rd-line therapy for large B-cell lymphomas

- **Roughly 1/3 of patients with relapsed or refractory large B-cell lymphomas achieve long-term remissions with commercially available CAR-T products as ≥ *3rd-line therapy***
- **About 2/3 of patients fail to achieve durable responses as ≥ *3rd-line therapy***

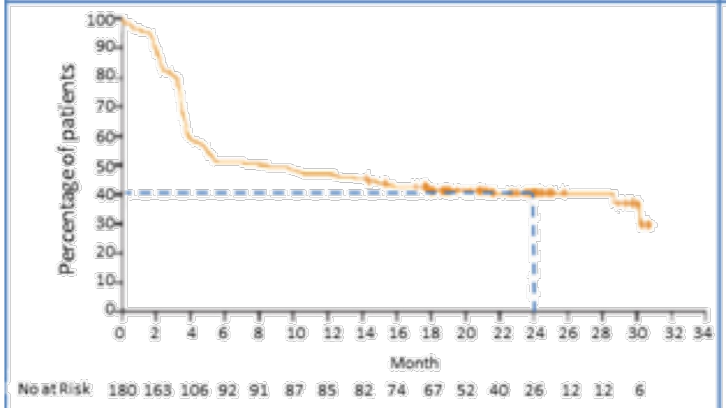
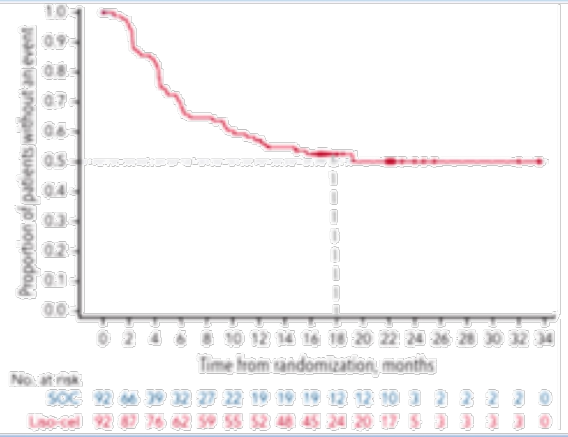
Axicabtagene ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene maraleucel[3]
ZUMA-1[1]: axi-cel as ≥ 3rd-line therapy for LBCL N = 101 Median follow-up: 63.1 months **Estimated 5-year EFS: 30.3% (95% CI, 21.5-39.6)**	**JULIET**[2]: tisa-cel as > 3rd-line therapy for LBCL N = 115 Median follow-up: 40·3 months **Estimated 40-month PFS: ~30%**	**TRANSCEND**[3]: liso-cel as ≥ 3rd-line therapy LBCL N = 257 Median follow-up: 23.9 months **Estimated 24-month PFS: 40.6% (95% CI, 34.0-47.2)**
		

*The studies summarized above differ in their designs, patient characteristics and follow-up; therefore, direct comparisons are precluded.

[1]Neelapu SS, et al. Blood 2023; 141(19):2307-2315; [2]Schuster SJ, et al. Lancet Oncol 2021;22(10):1403-1415; [3]Abramson J, et al. Blood 2024;143(5):404-416.

Approved CAR T products as 2nd-line therapy for large B-cell lymphomas

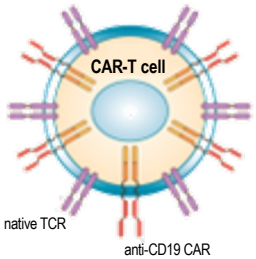
- **Earlier administration of CAR-T as *2nd-line of therapy* may provide an additional ~10% EFS benefit**

Axicabtagene ciloleucel[1]	Lisocabtagene maraleucel[2]
ZUMA-7[1]: axi-cel as ≥ 2nd-line therapy for r/r LBCL N = 180 Median follow-up: 24.9 months **Estimated 24-month EFS: 41% (95% CI, 33-48)**	**TRANSFORM**[2]: liso-cel as ≥ 2nd-line therapy for r/r LBCL N = 92 Median follow-up: 17.5 months **Estimated 18-month EFS: 52.6% (95% CI, 42.3-62.9)**
	

*The studies summarized above differ in their designs, patient characteristics and follow-up; therefore, direct comparisons are precluded.

[1]Locke FL, et al. N Engl J Med. 2022;386(7):640-654; [2]Abramson, et al. Blood. 2023; 141(14):1675-1684.

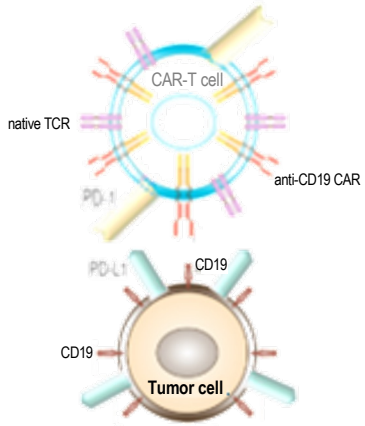
Putative mechanisms of resistance to CD19-directed CAR-T cells in large B-cell lymphomas



CD19 antigen loss

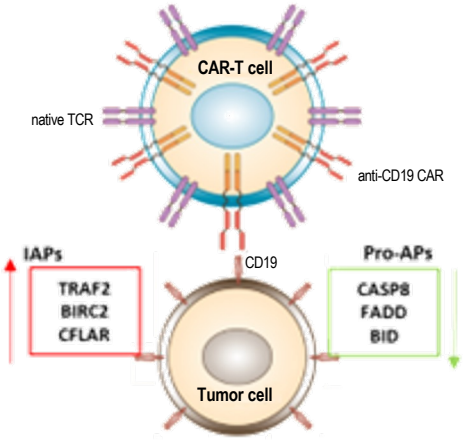
- acquired mutations and alternative splicing of CD19

(Sotillo...Thomas-Tikhonenko Cancer Disc. 2015)



T-cell exhaustion/hypofunction

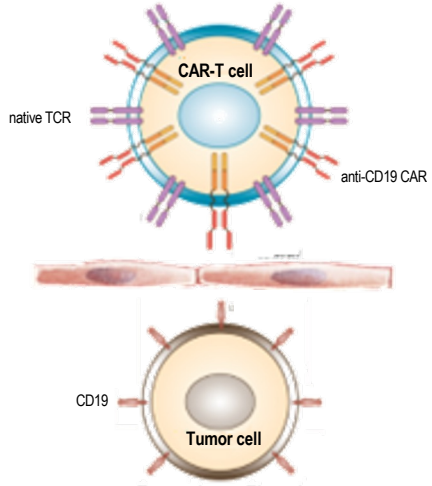
- mediated by inhibitory CAR T receptors and ligands in the tumor microenvironment
- peripheral self-tolerance (B cell recovery? late relapses?)
- TME-induced T cell hypofunction (reversible)



Intrinsic tumor resistance

- loss of death receptor signaling molecules causes resistance to CAR T in vitro + in vivo
- failed CAR T assoc./w lower death receptor-assoc. gene expression by tumor cells

(Singh, et al. Cancer Disc. 2020)



Insufficient T-cell infiltration

- T cells paralysis
- physiologic factors (high interstitial fluid pressure, hypoxia, pH)

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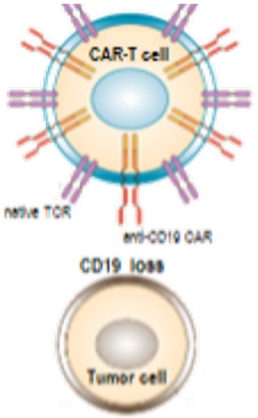
CD19 antigen loss-mediated resistance to CD19-directed CAR-T cells

Problem



CD19 antigen loss

- acquired mutations and alternative splicing of CD19

(Sotillo...Thomas-Tikhonenko Cancer Disc. 2015)

Potential Solutions

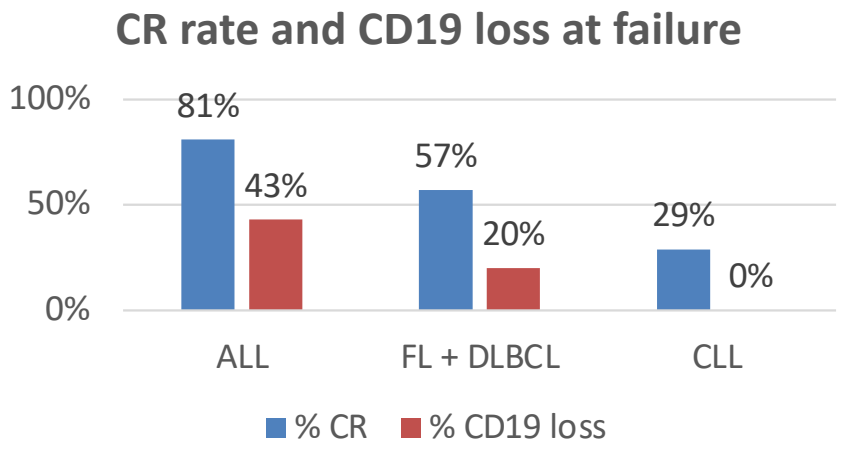
1. Manufacture <u>CAR-T cells with dual specificity</u> to target more than one tumor antigen (*i.e.*, "bispecific" CAR-T cell)
   - *a) bicistronic* CARs on a single cell's surface
   - *b) tandem* scFv as a single CAR on a single cell's surface
2. <u>Coadministration of monospecific CAR-T</u> cell products, each CAR-T with different tumor antigen specificities (so-called, "cocktail" approach)
   - *a) sequential* administration
   - *b) simultaneous* coadministration
3. <u>Combine T cell-engaging bispecific antibodies</u> (BsAb) and monospecific CAR-T cells, with each product, BsAb and CAR-T, having different tumor antigen specificities

CD19 antigen loss-mediated resistance to CD19-directed CAR-T cells

- **CD19 loss or downregulation: early CTL019 efficacy and CD19 expression data from Penn and CHOP**

Penn and CHOP Data

Disease	N	CD19 loss at PD
ALL[1]	30	3/7
FL + DLBCL[2]	28	1/5
CLL[3]	14	0/10



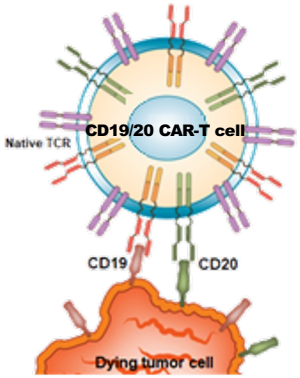
- **More responsive diseases seem more likely to fail due to CD19 loss**
- **Less responsive diseases, like CLL, require alternative explanations**

[1]Maude S, *et al*. NEJM. 2014; 371(16): 1507-1517; [2]Schuster SJ, *et al*. N Engl J Med. 2017;377(26):2545-2554; [3]Porter DL, *personal communication,* 2018 Mar 12.

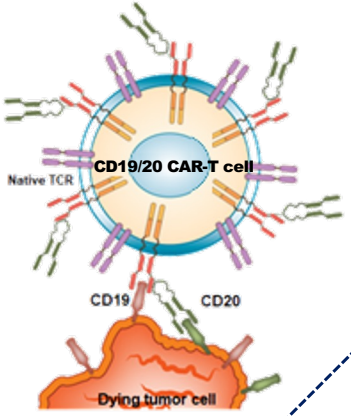
Dual antigen targeting CAR-T approaches

Bispecific CAR-T cell formats

Bicistronic receptors

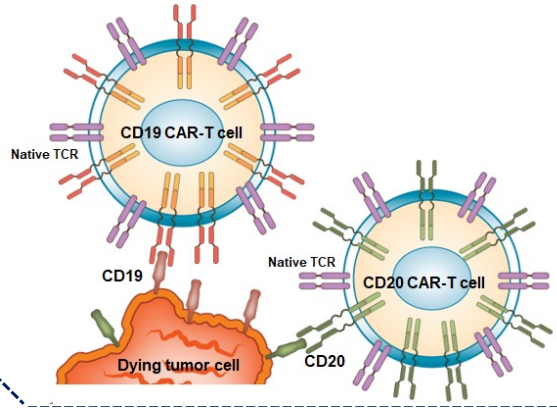


Bivalent tandem receptor

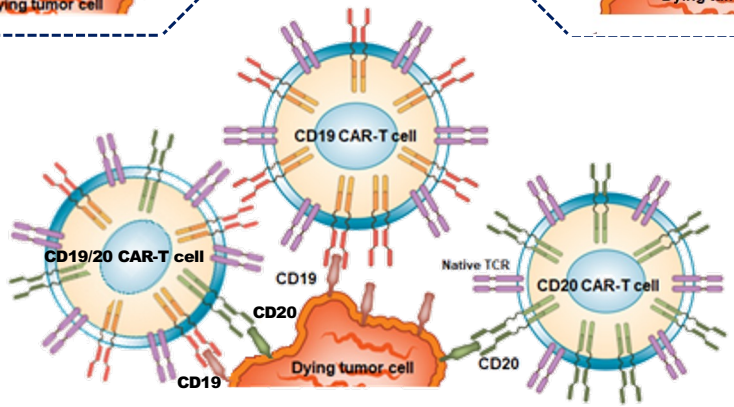


Coadministration of CAR-T cells

Sequential or simultaneous administration



Cotransduction



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Dual antigen targeting CAR-T approaches

- **8 Phase 1/2, single-arm, noncomparative, prospective, open-label clinical trials**

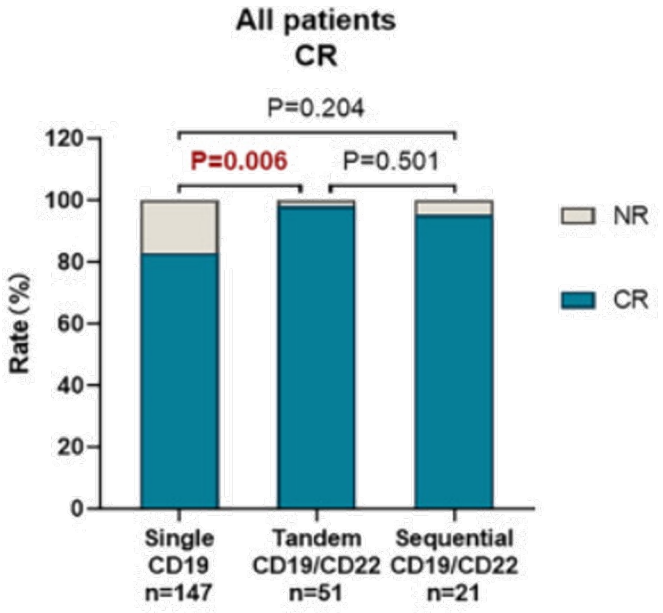
	Study	CAR targets	CAR design	N (% DLBCL)	Prior CAR-T	Prior transplant	LD chemo	CAR T cell dose	Response (OR/CR)	PFS - median - rate	Follow-up - median
CD19/CD22	Zhang, et al.[1]	CD19/CD22	bispecific	32 (84%)	No	Auto, 4 (12.5%)	FC	3.7-32.8 x 10^8 total	79%/**34%**	6.8 mo. **40%, 12-mo.**	8.7 mo.
	Wei, et al.[2]	CD19/CD22	bispecific, tandem	16 (81%)	No	Auto, 1 (5%)	FC	4.9-9.4 x 10^6/kg	87%/**62%**	8.1 mo. **40%, 24-mo.**	13 mo.
	Roddie, et al.[3]	CD19/CD22	bispecific, bicistronic	52 (69%)	No	Auto, 16 (31%)	FC	50-450 x 10^6 total	66%/**49%**	3.3 mo. **26%, 12-mo.**	21.6 mo.
	Spiegel, et al.[4]	CD19/CD22	bispecific, tandem	21 (64%)	No	Auto, 4 (19%)	FC	1.0-3.0 x 10^6/kg	62%/**29%**	3.2 mo. **~23%, 12-mo.**	10 mo.
	Wang, et al.[5]	CD19 + CD22	cocktail	38 (60%)	No	Auto, 6 (15.8%)	FC	CD19: 5.1 +/- 2.1 x 10^6/kg CD22: 5.3 +/- 2.4 x 10^6/kg	72%/**50%**	9.9 mo. **50%, 12-mo.**	14.4 mo.
CD19/CD20	Zhang, et al.[6]	CD19/CD20	bispecific, tandem	87 (66%)	9 (10%)	Auto, 12 (14%)	FC	0.5-8 x 10^6/kg	78%/**70%**	27.6 mo. **61%, 12-mo.**	27.7 mo.
	Shah, et al.[7]	CD19/CD20	bispecific, tandem	16 (56%)	1 (6%)	Auto, 5 (31%); Allo, 1 (6%)	FC	2.5 x 10^6/kg	82%/**64%**	**44%, 24-mo.**	31 mo.
	Sang, et al.[8]	CD19 + CD20	cocktail	21 (100%)	No	Auto, 1 (5%)	FC (n=19) or ifosfamide	CD19: 0.2-4.0 x 10^6/kg CD20: 0.1-4.0 x 10^6/kg	81%/**52%**	5.0 mos. **~24%, 12-mo.**	6.6 mo.
	Summary		**Total N = 283**		**CR rate, median (range) = 51% (29-70)**			**≥12-mo PFS rate, median (range) 40% = (23-61)**			

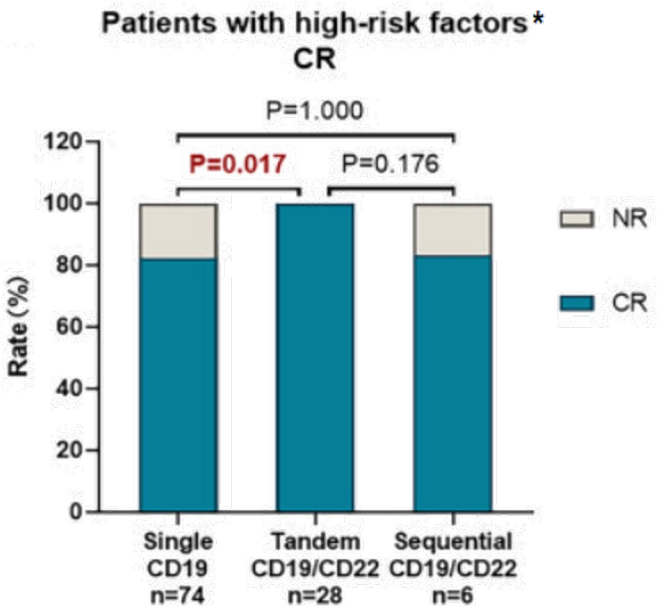
[1]Zhang, *et al*. Front Oncol 2021;11:664421; [2]Wei, *et al*. Cancer Immunol Res 2021;9(9):1061–1070; [3]Roddie, *et al*. Blood 2023; 141(20):2470-2482; [4]Spiegel, *et al*. Nat Med 2021;27(8):1419–1431; [5]Wang, *et al*. Blood 2020;135(1):17–27; [6]Zhang, *et al*. Leukemia 2022;36(1):189–196; [7]Shah, *et al*. Am J Hematol 2022;97(12):1580–1588; [8]Sang, *et al*. Cancer Med 2020;9(16):5827–5838.

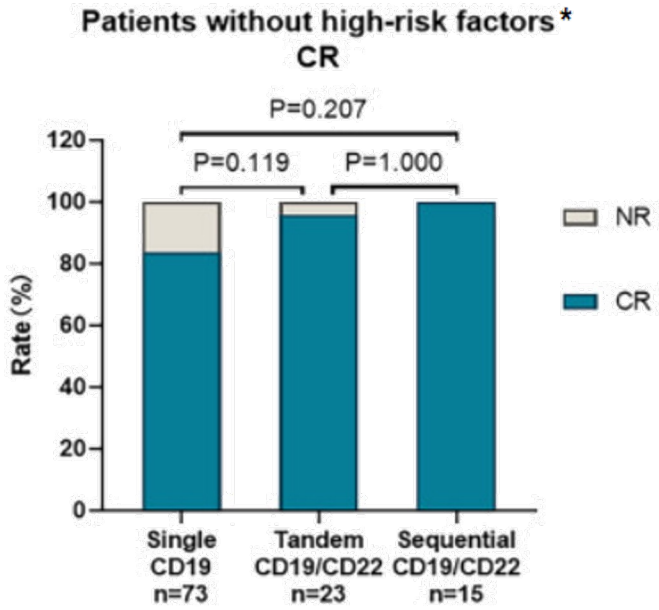
Dual antigen targeting CAR-T approaches in B-cell ALL

- **Outcomes for dual antigen targeting in acute B-cell lymphoblastic leukemia (ALL) may be different from B-cell NHL**

219 patients with relapsed/refractory ALL enrolled in clinical trials of *single CD19*, *tandem CD19/CD22*, or *sequential CD19/CD22* CAR-T







*High-risk defined as complex karyotype, *KMT2A* rearranged, *BCR-ABL1*, Ph-like ALL, mutated *TP53* or *IKZF1*

Liu S, *et al.* Blood Cancer J. 2023;13(1):60.

Dual antigen targeting by combining CAR-T + BsAb approaches

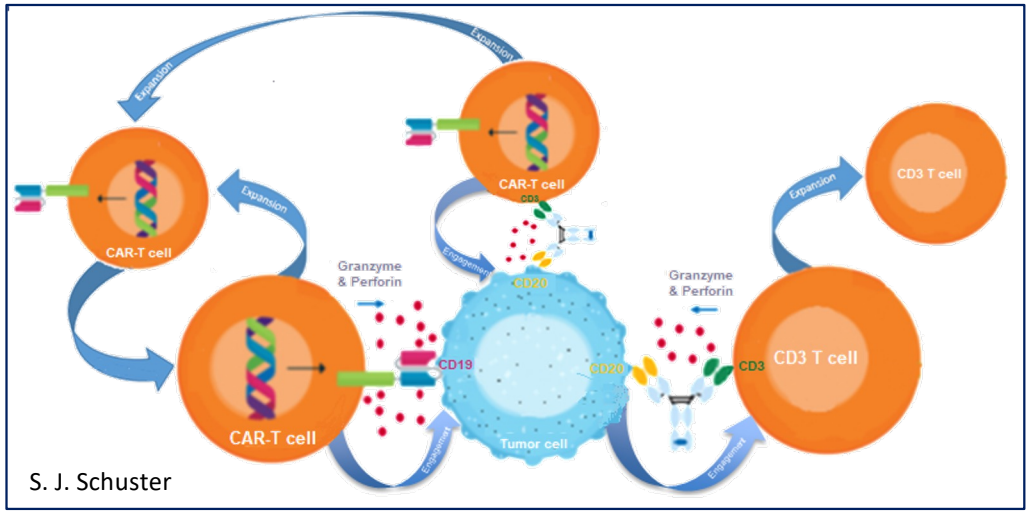
- **Active UPenn clinical trial addressing CD19 antigen loss or downregulation**

Phase II Study of Dual Targeting of CD19 and CD20 Antigens Using Sequential CD19-directed 4-1BB-CD3ζ CAR-T Cells Followed by Mosunetuzumab or Glofitamab in Relapsed or Refractory DLBCL or Transformed FL

Rationale:

Early administration of CD20:CD3 bispecific antibodies (mosunetuzumab or glofitamab) after CD19-directed CAR-T cell therapy may enhance tumor cytotoxicity by:

- synergistic or additive B cell cytotoxicity via simultaneously targeting two different B cell (tumor) antigens, *i.e.*, CD19 and CD20
- reducing CD19-negative tumor cell escape by targeting a second B cell antigen
- enhancing *in vivo* expansion of CAR T cells, as observed for T cells in general, after bispecific T cell engaging antibody exposure



S. J. Schuster

ClinicalTrials.gov Identifier: NCT04889716

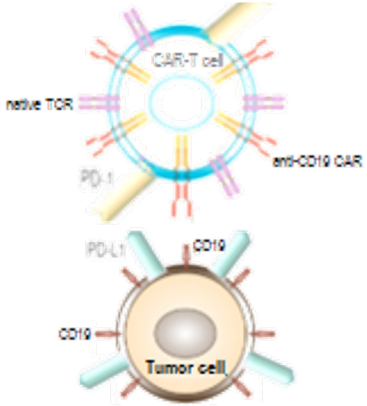
Recruitment Status : Recruiting
First Posted : May 17, 2021

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	42 participants
Allocation:	Non-Randomized
Intervention Model:	Sequential Assignment
Actual Study Start Date :	November 5, 2021
Estimated Primary Completion Date :	December 31, 2023
Estimated Study Completion Date :	December 31, 2025

PI: Elise Chong

T cell exhaustion and hypofunction as mechanisms of resistance to CD19-directed CAR-T cells

Problem	Potential Solutions



T-cell exhaustion/hypofunction

- mediated by inhibitory CAR T receptors and ligands in the tumor microenvironment
- peripheral self-tolerance (B cell recovery? late relapses?)
- TME-induced T cell hypofunction (reversible)

1. **Combining immunomodulatory drugs with CAR-T cells**
   a) ***e.g.*, ibrutinib**
2. **Shorted *ex vivo* manufacturing time**
   a) ***e.g.*, rapcabtagene autoleucel (YTB323)**
3. **Autologous armored CAR T cells**
   a) ***e.g.*, IL-18 armored CAR-T cells**
4. **Autologous CAR T cells with alternative receptor costimulatory domains**
   a) ***e.g.*, KIR-CAR/Dap12 CAR-T cells**
5. **Restimulation of CAR-T cells with CD19 peptide mimotopes (*peptides that mimic epitopes of an antigen*)**
6. **Allogeneic CAR-T cells**

Immunomodulatory drugs to address CAR-T cell exhaustion/hypofunction

- **Ibrutinib before apheresis and throughout therapy may improve CAR-T product characteristics and outcomes in relapsed/refractory large B-cell lymphomas: a Phase 1b study**

Rationale: ibrutinib is a clinically viable, irreversible inhibitor of ITK that drives a Th1-selective pressure in T cells. Ibrutinib treatment of CLL enhances the generation of CAR-T cells and may improve CAR-T outcomes in CLL.

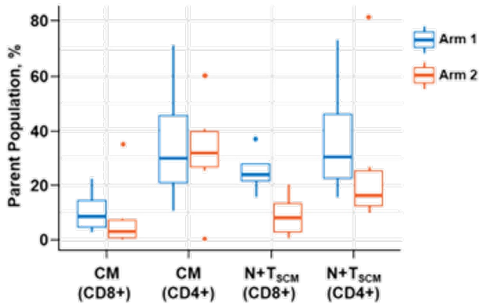
- **Study of ibrutinib + tisagenlecleucel in relapsed/refractory large B-cell lymphomas**
- **2 Arms: patients initiated ibrutinib *prior to* (arm 1) or *post* apheresis (arm 2)**

Patient characteristics

	Arm 1 (N=4)	Arm 2 (N=6)
Age, median, (range)	59 (32-67)	64 (58-76)
Sex		
Male/female	4 (100)/0	4 (67)/2 (33)
ECOG performance status		
0/1	3 (75)/1 (25)	1 (17)/5 (83)
Lines of prior therapy		
2	2 (50)	4 (67)
3	0	2 (33)
4-6	2 (50)	0
Cells of origin of cancer		
Germinal center B-cell type	2 (50)	4 (67)
Activated B-cell type	1 (25)	2 (33)
T-cell/histiocyte-rich	1 (25)	0
Disease stage at study entry		
Stage I	0	0
Stage II	2 (50)	0
Stage III	2 (50)	0
Stage IV	0	6 (100)
Previous autologous HSCT	1 (25)	2 (33)
LDH at screening (U/L), median (range)	198 (146-234)	217 (178-303)

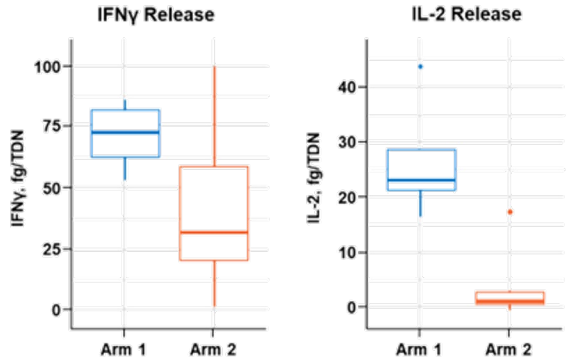
Impact of Ibrutinib on T-cell phenotype in apheresis material and final CAR-T product

T cell phenotype in leukapheresis starting material



- Arm 1 was associated with an increased percentage of naïve/T_{SCM} cells

CAR-T cell product



- Arm 1 final product characterized by preserved production of IFNγ (effector cytokine) and increased production of IL-2 (proliferative cytokine) upon antigen-specific stimulation

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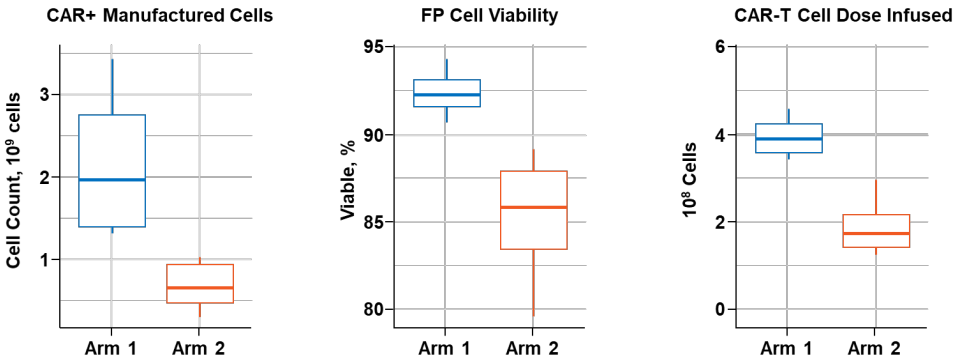
Immunomodulatory drugs to address CAR-T cell exhaustion/hypofunction

- **Ibrutinib before apheresis and throughout therapy may improve CAR-T product characteristics and outcomes in relapsed/refractory large B-cell lymphomas: a Phase 1b study**

Impact of ibrutinib on CAR-T cell manufacturing



- Arm 1 had higher total CAR+ manufactured cells and higher viability of the final product compared with Arm 2
- The median dose of tisagenlecleucel infused was higher in Arm 1 compared with Arm 2: 3.9 (range, 3.4-4.6) vs 1.7 (range, 1.2-3.0) × 10^8 CAR+ T cells, respectively

Response rates: Three of 4 patients (75%) in Arm 1 and 2 of 6 patients (33%) in Arm 2 achieved CR

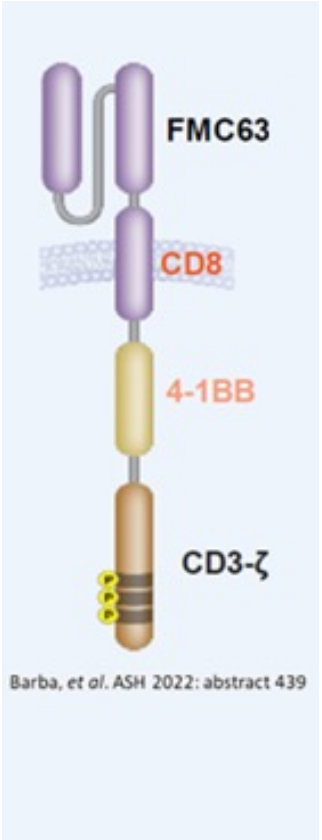
	Patient No.	CAR-T Cell Dose (×10⁸)	CRS, Grade[a]	ICANS, Grade[a]	BOR (Assessment)[b]	PFS, Median (95% CI)
Arm 1	1	3.4	1	0	**CR (Month 6)**	NE (NE-NE)
	2	3.6	0	0	**CR (Month 6)**	
	3	4.1	0	0	PR (Day 28)	
	4	4.6	0	0	**CR* (Month 3)**	
Arm 2	5	2.2	1	0	**CR (Month 12)**	2.5 months (1.0-NE)
	6	1.6	0	0	PD (Day 28)	
	7	1.2	1	0	PD (Day 28)	
	8	1.4	1	1	PD (Day 28)	
	9	1.9	1	0	PD (Month 2)	
	10	3.0	1	0	**CR* (Month 6)**	

*Two patients responded to ibrutinib alone: Patient No. 4 in Arm 1 and patient No. 10 in Arm 2

Chavez … Schuster: Poster Presentation: ASH 2020

Rapid CAR-T cell manufacturing to address CAR-T cell exhaustion/hypofunction

- **Rapcabtagene autoleucel (YTB323)** is an autologous CD19-directed CAR-T cell therapy that is **rapidly manufactured (<2 days)** using a next-generation manufacturing platform that preserves T-cell stemness



Barba, *et al*. ASH 2022: abstract 439

LD chemo: cyclophosphamide (500 mg/m2/d for 3 days) and fludarabine (30 mg/m2/d for 3 days)

Dose level 1: 2.5x10^6 CAR-T cells (N=4)
Dose level 2: 12.5x10^6 CAR-T cells (N=30), RP2D
Dose level 3: 25x10^6 CAR-T cells (N=7)
Dose level 4: 40x10^6 CAR-T cells (N=6)

Dose response

Rapcabtagene Autoleucel Dose Levels				
Best response rates	DL1 2.5×10^6 (N=4)	**DL2 12.5×10^6 (N=30)**	DL3 25×10^6 (N=7)	DL4 40×10^6 (N=6)
CR, patients infused ≥ 28 days before cutoff excluding patients in CR before infusion, n/N (%)	1/2 (50)	**19/27 (70)**	5/7 (71)	4/6 (67)
Overall response rate, n (%) [95% CI]	3 (75) [19.4-99.4]	**25 (83) [65.3-94.4]**	5 (71) [29.0-96.3]	4 (67) [22.3-95.7]

Median follow-up (infusion to cutoff date) across the 4 dose levels was 13 months (4.4-34.3)

Adverse events of special interest

DL2 12.5×10^6	(N=30)
CRS, n (%)	11 (37)
Grade 1/2	9 (30)
Grade 3/4	**2 (7)**
Median time to onset, days (range)	8 (1-17)
Median time to resolution, days (range)	6 (2-25)

DL2 12.5×10^6	(N=30)
ICANS, n (%)	3 (10)
Grade 1/2	1 (3)
Grade 3/4	**2 (7)**
Median time to onset, days (range)	16 (10-28)
Median time to resolution, days (range)	16 (11-24)

Duration of response

DL2 12.5×10^6	(N=30)
Median follow-up (range)	16 mo (4.4-27.5)
BOR of CR	22/30 (73%)
CR at ≥ 3 mo	18/30 (60%)
CR at ≥ 6 mo	16/26 (62%)
CR at ≥ 9 mo	8/19 (42%)
CR at ≥ 12 mo	8/16 (50%)
Median DOR (95% CI)	16 mo (10.4-NE)

Cytokine-armored CARs to address CAR-T cell exhaustion/hypofunction

- **Active UPenn clinical trial**

Phase I trial of huCART19-IL18 cells in patients with relapsed or refractory CD19+ cancers

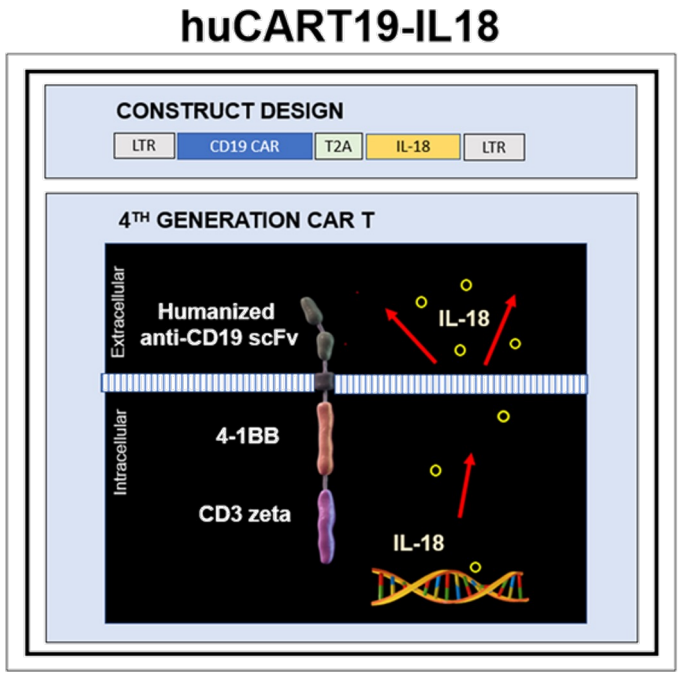
Rationale: to utilize IL-18 as a pro-inflammatory cytokine to:

- enhance CAR T cell proliferation
- recruit additional immune cells into the TME to mediate antitumor effects toward tumor cells resistant to CAR T cells
- mitigate the potential impact of CAR T cell exhaustion

ClinicalTrials.gov ID NCT04684563 **Sponsor** University of Pennsylvania

Brief Summary		The purpose of this study is to find the maximum dose of huCART19-IL18 cells that is safe for use in humans with CD19+ cancers.
Detailed Description		• Cohort A: Non-Hodgkin Lymphoma (NHL) • Cohort B: Chronic Lymphocytic Leukemia (CLL) • Cohort C: Acute Lymphoblastic Leukemia (ALL)
Study Type	ICMJE	Interventional
Study Phase	ICMJE	Phase 1
Study Design	ICMJE	Allocation: Non-Randomized Interventional Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment
Condition	ICMJE	• Chronic Lymphocytic Leukemia • Non-hodgkin Lymphoma • Acute Lymphoblastic Leukemia
Recruitment Status	ICMJE	Recruiting
Enrollment (Estimated) (Submitted: 2023-03-30)	ICMJE	72
Original Enrollment (Estimated) (Submitted: 2020-12-21)	ICMJE	30
Study Start Date (Actual)	ICMJE	2021-05-06

Treated, so far*:
NHL, n = 21
CLL, n = 2
ALL, n = 2
***January 2024**



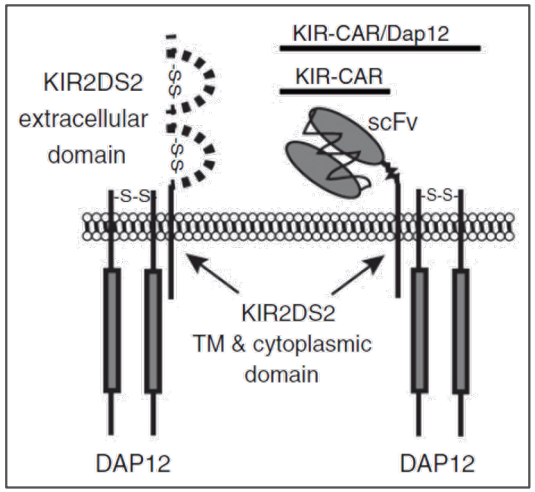
PI: Jakub Svoboda

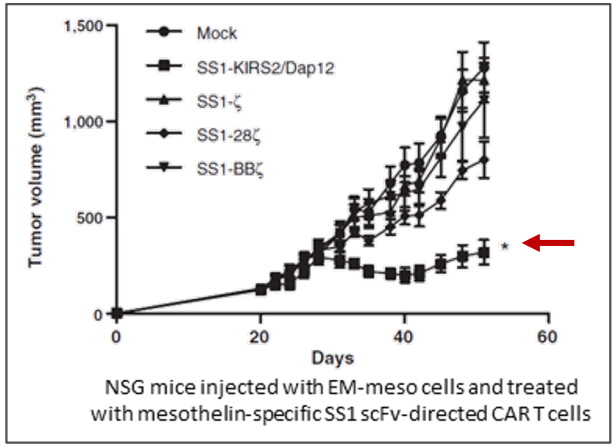
Alternative CAR costimulatory domains to address CAR-T cell exhaustion/hypofunction

- **UPenn clinical trial planned (IND filed)**

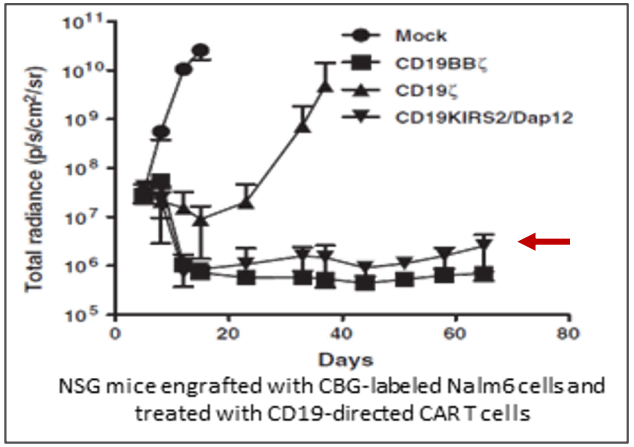
CD19-directed KIR-CAR/DAP12-modified cells for CD19+ lymphomas

Rationale: KIR-CAR/Dap12 expressing CAR T cells have potent *in vivo* antitumor activity that is resistant to the tumor- and/or TME-induced T-cell hypofunction observed with CD3ζ-based CAR T cells[1]. This potent activity *may* be of benefit in large B-cell lymphomas with bulky disease.





NSG mice injected with EM-meso cells and treated with mesothelin-specific SS1 scFv-directed CAR T cells



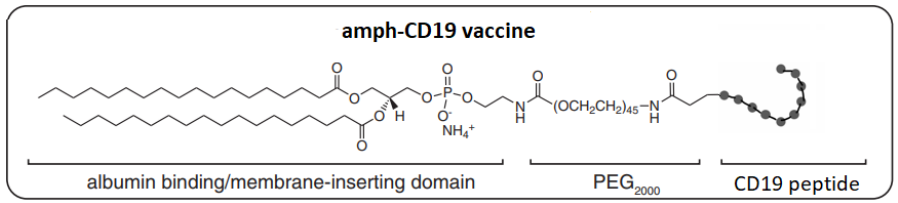
NSG mice engrafted with CBG-labeled Nalm6 cells and treated with CD19-directed CAR T cells

[1]Moon, et al. Clin Cancer Res 2014;20:4262–73.
[2]Wang, et al. Cancer Imm Res 2015;3:815-826. (*data show on the right*)

CD19 mimotope vaccination to address CAR-T cell exhaustion/hypofunction

(*and possibly even antigen negative escape*)

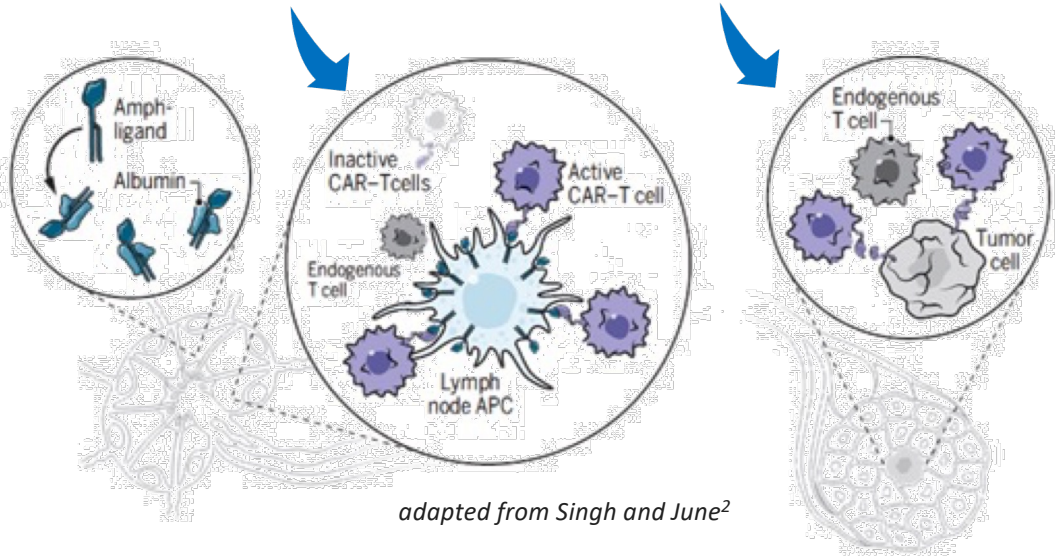
- **Preclinical work for CD19 completed *(manuscript submitted)*; clinical trial planned**



1) Amph-CD19 peptide vaccine is injected, binds to serum albumin, and migrates to lymph nodes.

2) In lymph nodes, CAR-T cells are stimulated by vaccine expressing antigen-presenting cells, resulting in CAR-T cell activation, proliferation and differentiation, as well as activation of endogenous T cells (epitope spreading).

3) CAR-T and endogenous T cells traffic from nodes to tumor sites, resulting in antitumor activity, as well as activation of endogenous T cell antitumor immunity.

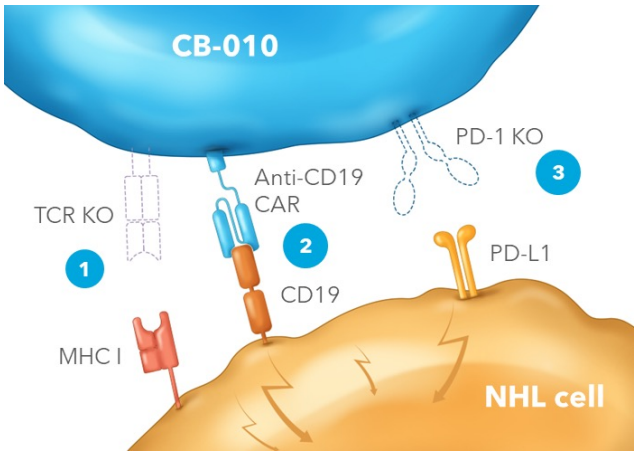


adapted from Singh and June[2]

[1]Ma L, *et al.* Science 2019;365(6449):162-168.
[2]Singh N and June C. 2019;365(6449):119-120.
[3]Ma L, *et al* Cell; 2023;186(15):3148-3165.

Allogeneic CAR-T cells to address CAR-T cell exhaustion/hypofunction

- **CB-010:** allogeneic anti-CD19 CAR-T cells with PD-1 and TRAC gene knockouts



1. ***TRAC* gene knockout (KO)**
   - Eliminates TCR, reduces GvHD risk
2. **CAR site-specific insertion into *TRAC* locus**
   - Eliminates random integration
3. **PD-1 KO for enhanced antitumor activity**
   - Reduces CAR-T cell exhaustion

Phase 1 data, February 2024

LD: cyclophosphamide (60 mg/kg/d for 2 days) followed by fludarabine (25 mg/m2/d for 5 days)

Dose level 1: 40x10^6 CAR-T cells (N=8)

Dose level 2: 80x10^6 CAR-T cells (N=5)

Dose level 3: 120x10^6 CAR-T cells (N=3)

Characteristics	Total (N=16)
Median age, years (range)	66 (55-82)
Male, n (%)	14 (88)
ECOG performance status, n (%)	
0	6 (38)
1	10 (62)
Non-Hodgkin lymphoma subtype, n (%)	
LBCL	10 (63)
DLBCL	7 (44)
HGBL	2 (13)
PMBCL	1 (6)
Other B-NHL	6 (38)
MCL	3 (19)
FL	2 (13)
MZL	1 (6)
CD19$^+$ disease, n (%)	16 (100)
Prior systemic therapies, median number (range)	2 (1-8)

CB-101	r/r B-NHL
Endpoints N, (%)	**All patients** (N=16)
Overall response rate (ORR)	15 (94%)
Complete response (CR) rate	11 (69%)
≥6-month CR rate	7 (44%)
CR at longest duration to date	24 months

AEs of special interest	ANTLER dose escalation (N=16)	
	CRS	ICANS
Any grade, N (%)	7 (44%)	4 (25%)
Grade 1	4 (25%)	2 (13%)
Grade 2	3 (19%)	-
Grade 3	-	1 (6%)
Grade 4	-	1 (6%)
Median time to onset, days (range)	3.5 (1,7)	7.5 (5,10)
Median duration, days (range)	3.0 (1,9)	2.0 (1,34)


Grazie molto!
Many thanks!