



10th POSTGRADUATE
**Lymphoma
Conference**

CAR-T for DLBCL: next generation

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Venice,
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Hotel Monaco & Grand Canal

President:
P.L. Zinzani

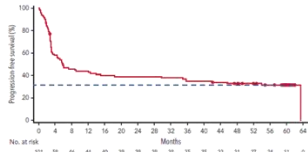
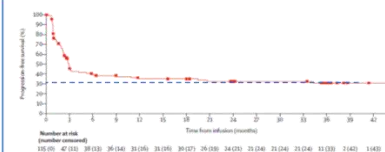
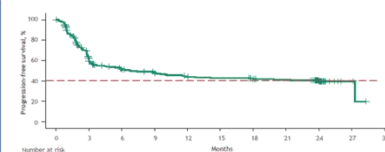
Disclosures for Stephen J. Schuster, M.D.

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie						X	
ADC Therapeutics						X	
AstraZeneca	X		X			X	
BeiGene						X	
BioNTech			X				
BMS	X					X	
Caribou Bio			X			X	
Genentech/Roche	X					X	
Genmab	X		X			X	
Incyte			X				
Janssen						X	
Novartis	X		X			X	
Vittoria Bio						X	

CD19-Directed CAR-T for Relapsed/Refractory Large B-Cell Lymphomas

as \geq 3rd-line therapy

~ 2/3 of patients ultimately fail

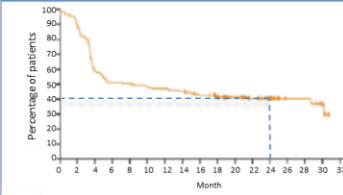
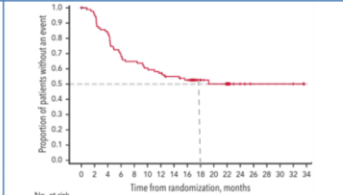
Axicabtagene ciloleucel ¹	Tisagenlecleucel ²	Lisocabtagene maraleucel ³
ZUMA-1 ¹ : axi-cel as \geq 3rd-line therapy for LBCL N = 101 Median follow-up: 63.1 months Estimated 5-year EFS: 30.3% (95% CI, 21.5-39.6)	JULIET ² : tisa-cel as $>$ 3rd-line therapy for LBCL N = 115 Median follow-up: 40.3 months Estimated 40-month PFS: ~30%	TRANSCEND ³ : liso-cel as \geq 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.

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

as 2nd-line therapy

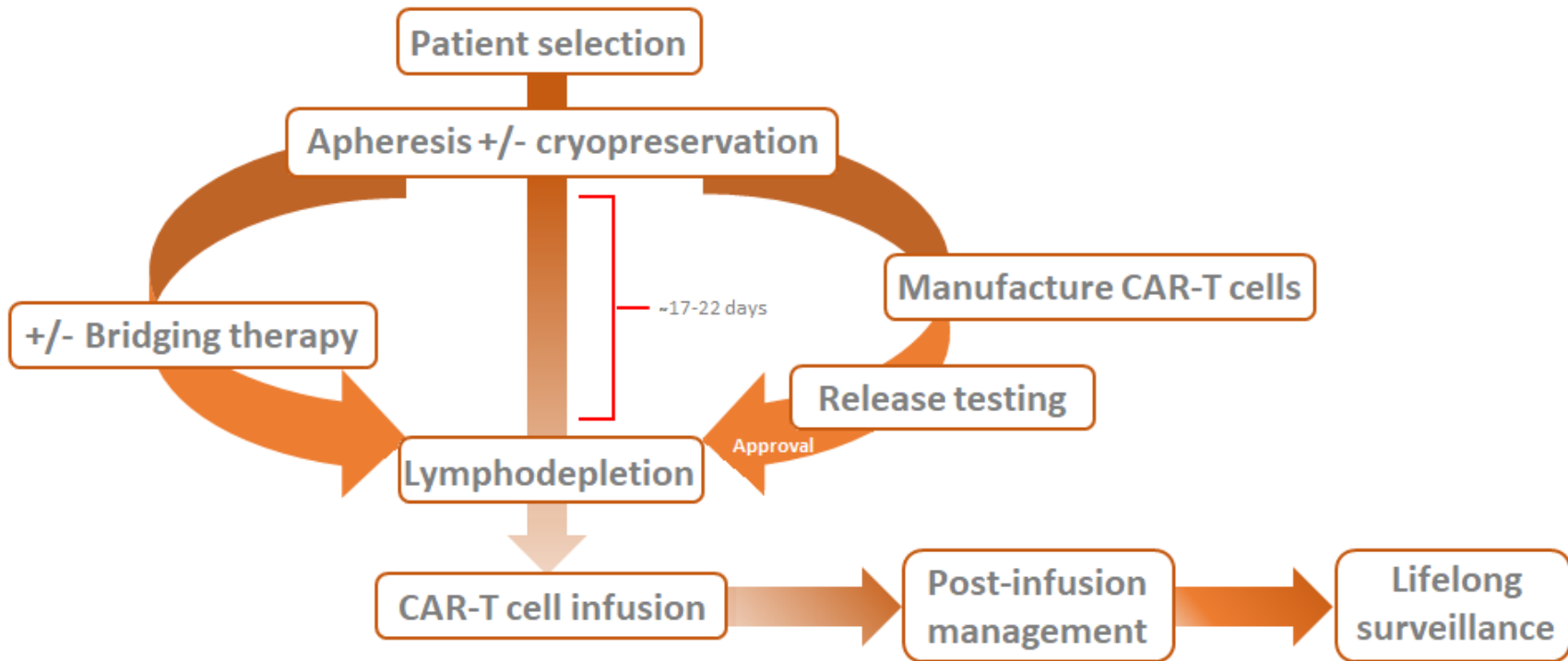
~ 1/2 of patients fail by 2 years

Axicabtagene ciloleucel ¹	Lisocabtagene maraleucel ²
ZUMA-7 ¹ : axi-cel as \geq 2 nd -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 \geq 2 nd -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)
	

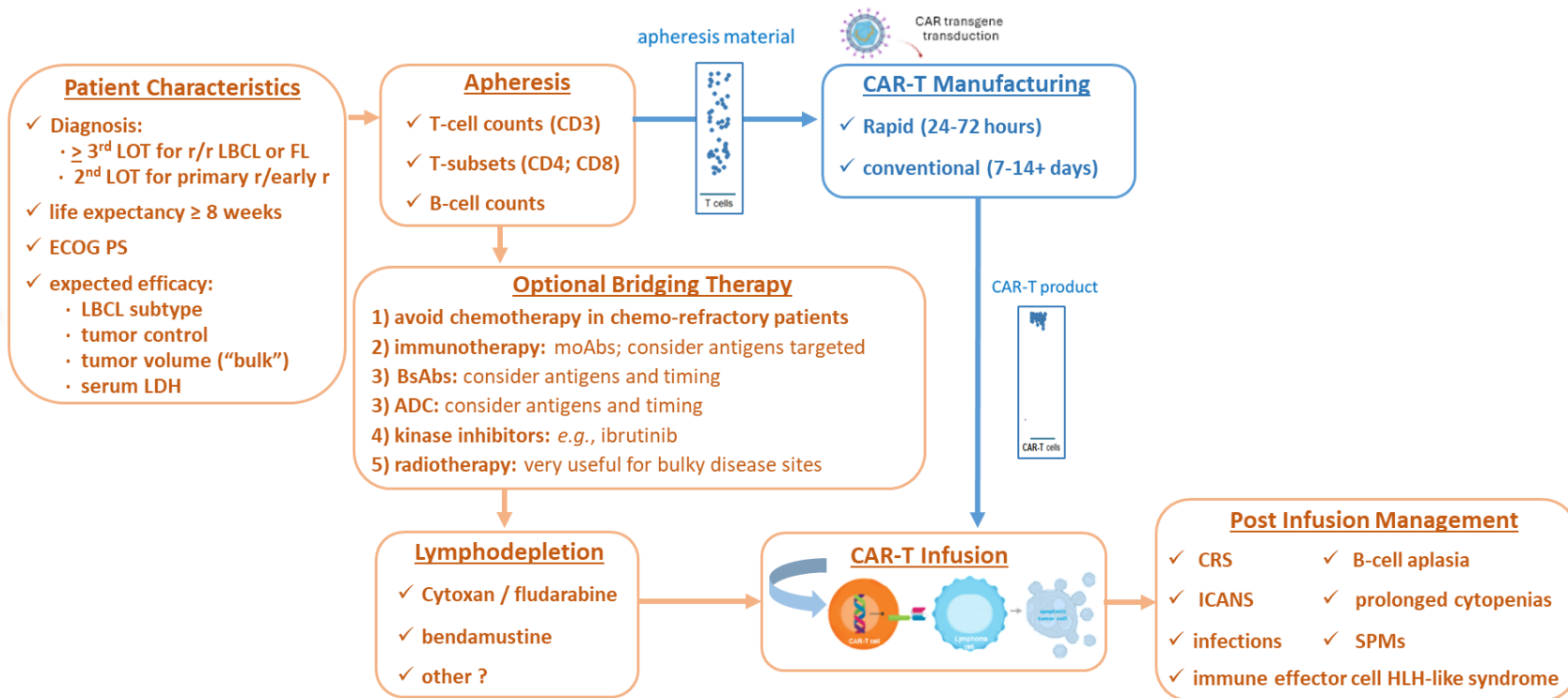
¹Locke FL, et al. N Engl J Med. 2022;386(7):640-654; ²Abramson, et al. Blood. 2023;141(14):1675-1684.

Opportunities to improve CD19-Directed CAR-T for B-Cell Lymphomas

- a complex, multistep process with many opportunities to improve outcomes



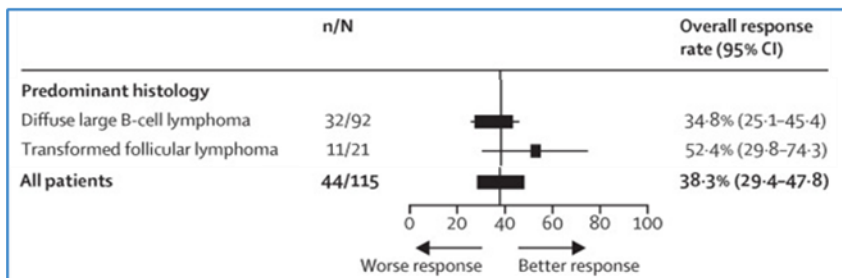
Opportunities to improve CD19-Directed CAR-T for B-Cell Lymphomas



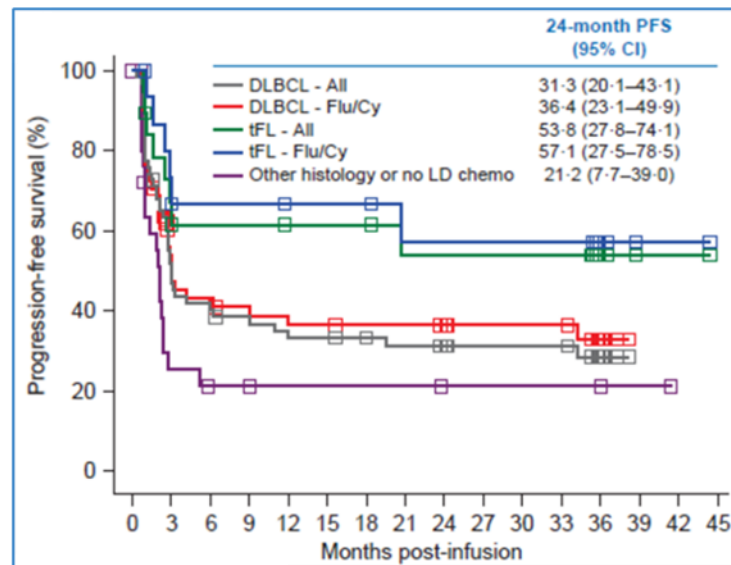
Patient characteristics impact outcome: LBCL Subtype

- Subtype of lymphoma impacts CAR-T response rates and progression-free survival
 - Data from the JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL

Overall response rates by lymphoma subtype



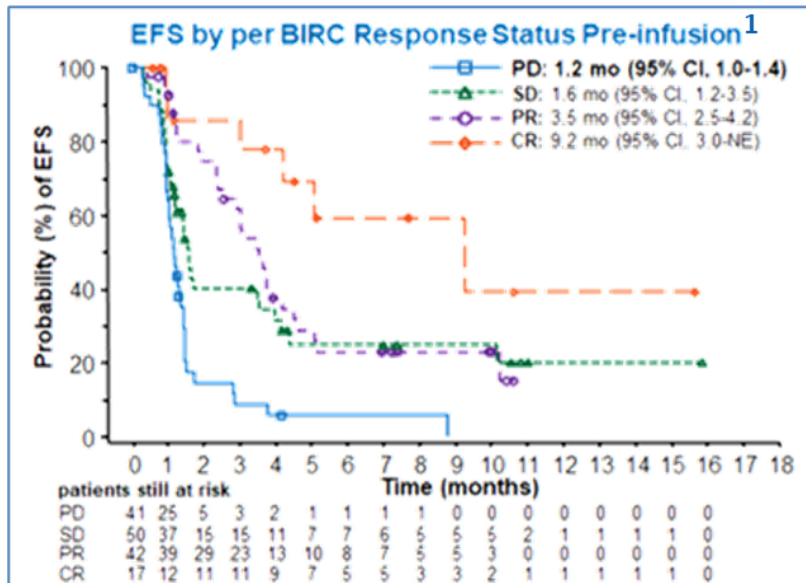
Progression-free survival by lymphoma subtype



Patient characteristics impact outcome: Tumor Control

- Disease status at the time of CAR-T infusion impacts best response and EFS

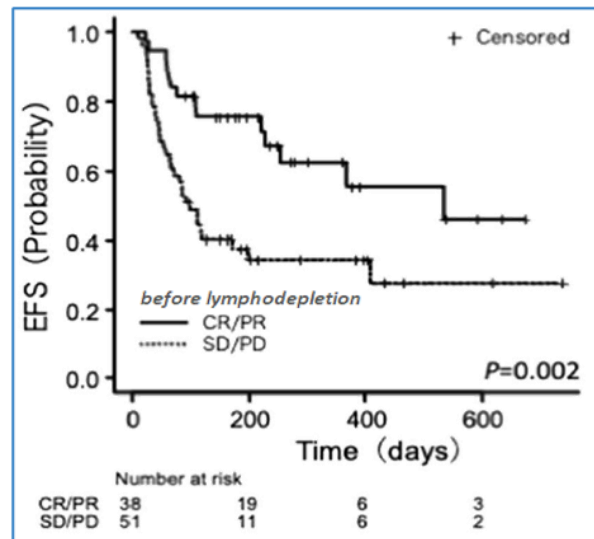
- Belinda trial: tisagenlecleucel vs SOC as 2nd LOT in r/r LBCL



EFS time is relative to date of tisagenlecleucel infusion
EFS events defined as PD/SD after day 71 from randomization or death at any time.
PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response

¹Bishop *et al.* N Engl J Med. 2021 Dec 14. Epub

- Real-world data from Japan for tisagenlecleucel in r/r LBCL²
EFS after tisa-cel by disease status *after* bridging therapy and *before* LD

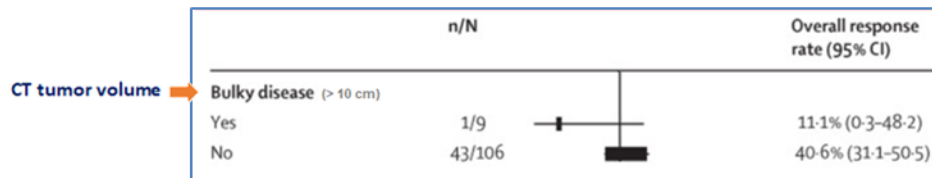


*EFS defined as the period from infusion to either progression or death

²Goto H, et al. Int J Clin Oncol. 2023;28:816–826.

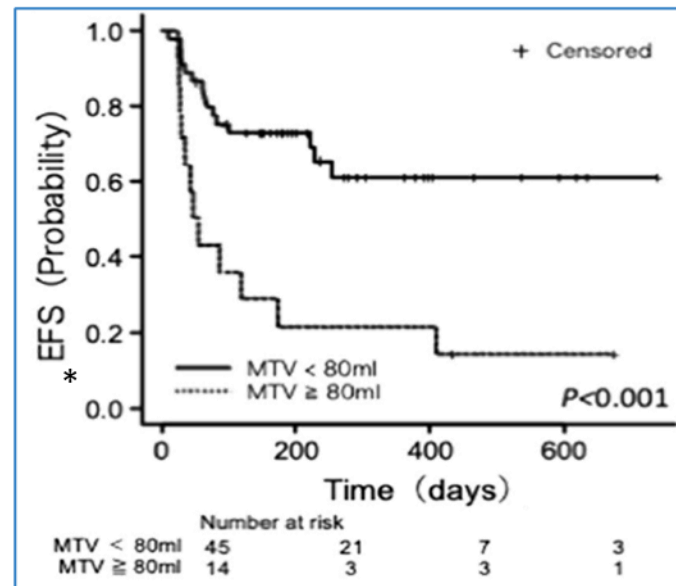
Patient characteristics impact outcome: Tumor Volume

- Tumor bulk and its impact on response (“size matters”)¹
 - Data from JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL



¹Schuster SJ, et al. Lancet Oncol. 2021;22(10):1403-1415.

- MTV Data for tisagenlecleucel in r/r LBCL²
 - Real-world evidence from Japan



* EFS defined as the period from infusion to either progression or death

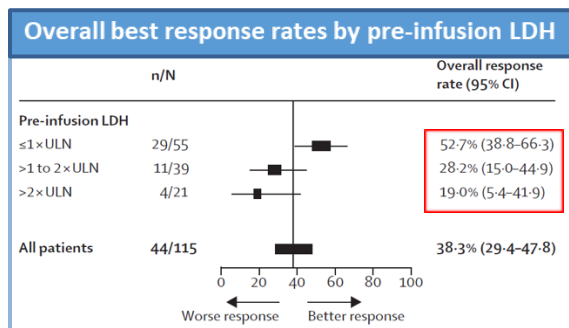
MTV, metabolic tumor volume, EFS, event-free survival

²Goto H, et al. Int J Clin Oncol. 2023;28:816–826.

Patient characteristics impact outcome: Serum LDH

- Pre-infusion serum LDH impacts response to CAR-T and survival outcome
 - Data from the JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL

Response

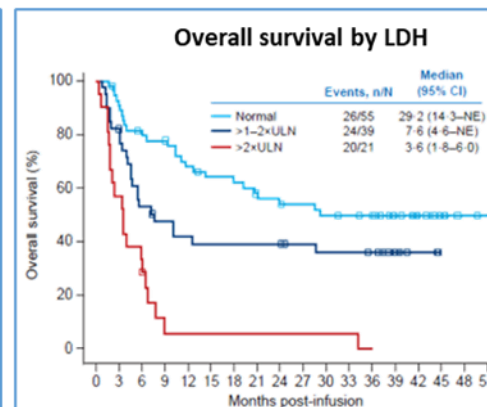
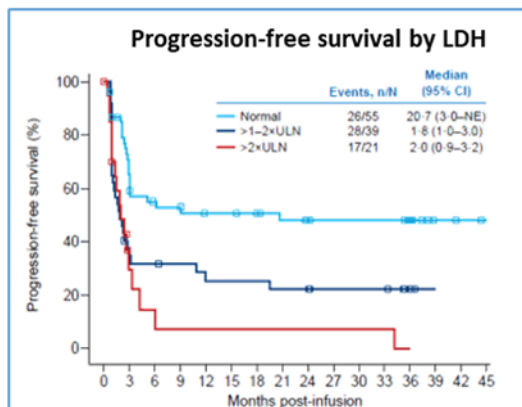


Multivariable analysis *

Predictive Factors from Univariable Analysis	Responders/Patients	Odds Ratio (95% CI)
LDH		
≤ x ULN	29/55	2.74 (0.71-10.56)
> 2 x ULN	4/21	
>1 - 2 x ULN	11/39	0.97 (0.23-4.06)
>2 x ULN	4/21	

*Lab analytes are defined as the closest time before or on the day of infusion (93% of values were obtained on the day of infusion)

Survival



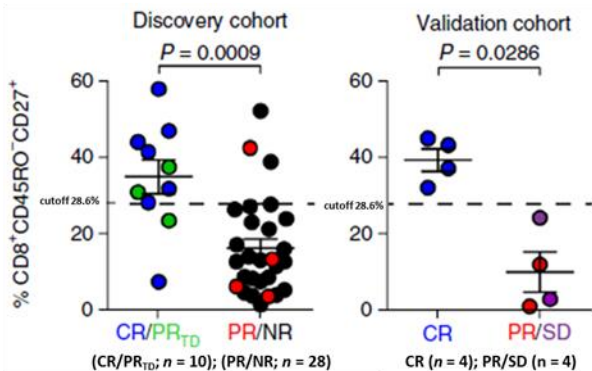
Patient characteristics impact outcome: T-cell fitness

T-cell fitness refers to the functional capacity and metabolic vigor of T cells, reflected by their ability to effectively *recognize antigens, respond to co-stimulation, proliferate, produce cytokines, differentiate into effector cells, resist exhaustion, and provide immunologic memory.*

Patient characteristics impacting T cell fitness: Considerations

- Age-related immunosenescence
- Lymphoma-related immunosuppression
- Therapy-related (iatrogenic) immunosuppression

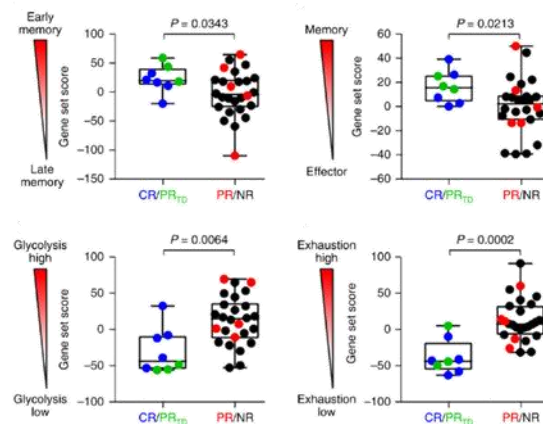
Naïve and memory CD8⁺ T cell content (CD45RO⁻CD27⁺ cells) in leukapheresis material contribute to response to CAR-T in CLL



Genomic evaluation of CLL patient-derived CAR-T cell products and response to CAR-T cells

Genes Significantly Up- or Down-regulated

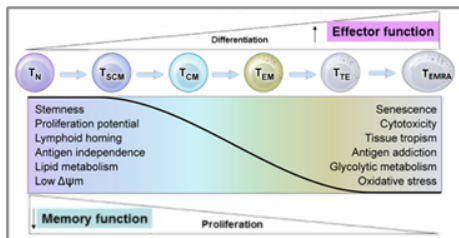
Early memory T cell
Nonexhausted T cell
Naive vs. activated T_H2 Cd4⁺ T cell
Unstimulated vs. stimulated memory T cell
Resting vs. bystander activated CD4⁺ T cell
Conventional vs. effector memory T cell
Multipotent vs. progenitor CD4⁺ T cell
Memory vs. effector CD8⁺ T cell
Exhausted vs. effector T cell
Exhausted T cell
Activated T_H2 vs. naive CD4⁺ T cell
Stimulated vs. unstimulated memory T cell
Glycolysis
Hypoxia
Effector vs. memory CD8⁺ T cell
Apoptosis



CR, complete remission; PR_{TD}, partial remission with late relapse of transformed disease; PR, partial response; NR, no response

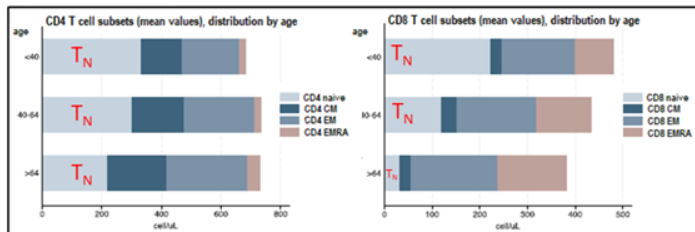
Impact of *age-related* immunosenescence on naïve and memory T cells

- Study of healthy adults (n = 363) established *age-specific, immune cell reference ranges*;
A systematic review and meta-analysis validated these findings (n = 7,425)¹



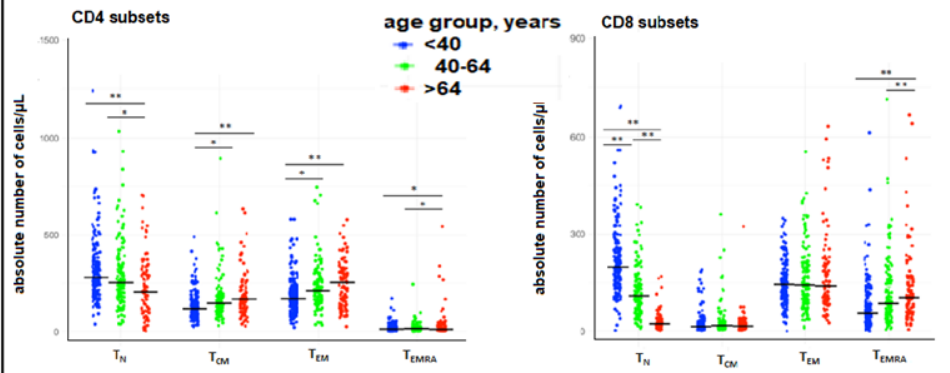
CD4 naïve
CD4 CM
CD4 EM
CD4 EMRA

CD8 naïve
CD8 CM
CD8 EM
CD8 EMRA



Demographics and immune cell subsets distribution of study population (n = 363) by three age groups

	< 40 years old (n = 158)	40–64 years old (n = 127)	> 64 years old (n = 78)
Age, median (Q1, Q3)	29 (27, 34)	47 (43, 55)	70.5 (67, 76)
Gender; Male, n (%)	72 (45.6%)	56 (44.1%)	29 (37.2%)

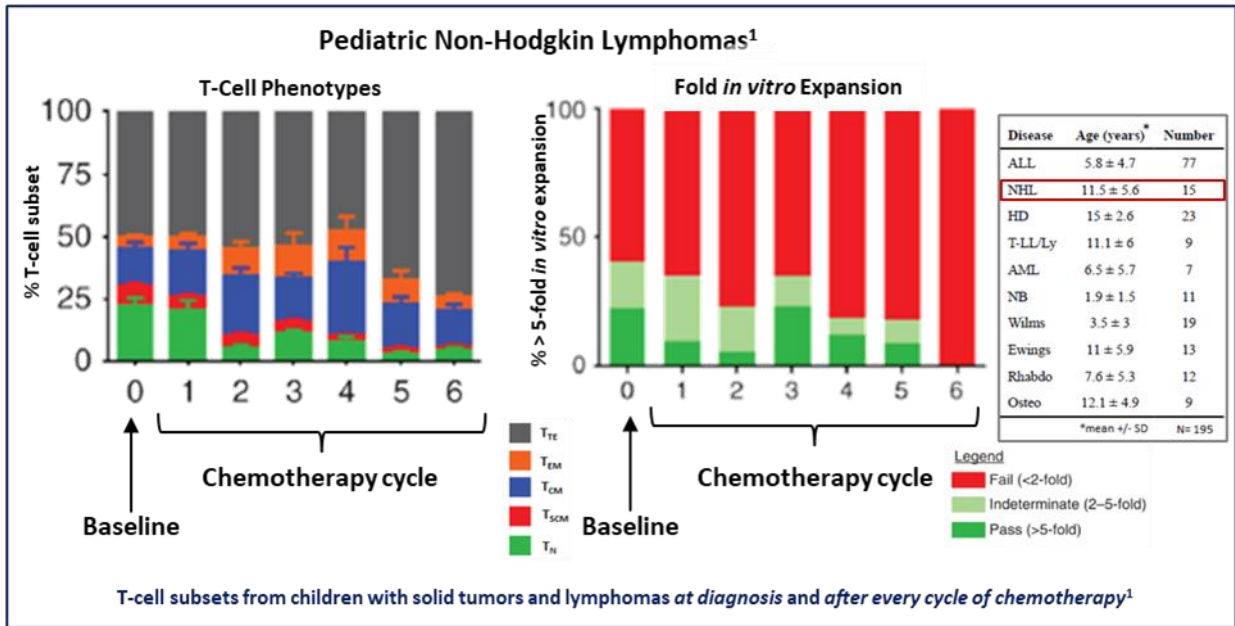


T_N, naïve T cells; T_{SCM}, T stem cell memory cells; T_{CM}, T central memory cells; T_{EM}, T effector memory cells; T_{TE}, T effector cells; T_{EMRA}, CD45RA⁺ terminal effector memory T cells

¹Chang, *et al.* Immunity & Ageing.2024; 21:75

Pre-existing *lymphoma-* and *therapy-related* immunodeficiency

- Naïve T-cell deficits at *diagnosis* and *after chemotherapy* may impair cell therapy potential



% T_N in blood of healthy children: Distribution by age
CD4, n = 805; CD8, n = 807 ²

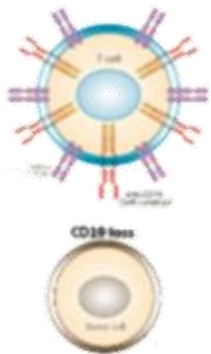
Subset	0-3 mo	2-6 y
CD 4+ /45RA + /62L+	89 (61-94)	70 (50-85)
CD 8+ /45RA + /62L+	79 (56-88)	64 (42-81)
	3-6 mo	6-12 y
CD 4+ /45RA + /62L+	88 (64-92)	58 (42-74)
CD 8+ /45RA + /62L+	77 (53-88)	58 (39-73)
	6-12 mo	12-18 y
CD 4+ /45RA + /62L+	83 (58-91)	51 (31-65)
CD 8+ /45RA + /62L+	72 (47-87)	56 (42-73)
	1-2 y	
CD 4+ /45RA + /62L+	79 (62-90)	
CD 8+ /45RA + /62L+	71 (46-85)	

T_N, naïve T cells; T_{SCM}, T stem cell memory cells; T_{CM}, T central memory cells; T_{EM}, T effector memory cells; T_{TE}, T effector cells; T_{EMRA}, CD45RA⁺ terminal effector memory T cells

¹Das, *et al.* Cancer Discov. 2019; 9(4):492-499.

²Shearer, *et al.* J Allergy Clin Immunol. 2003; 112(5):973-980.

CAR-T- and/or disease-specific mechanisms of CAR-T failure



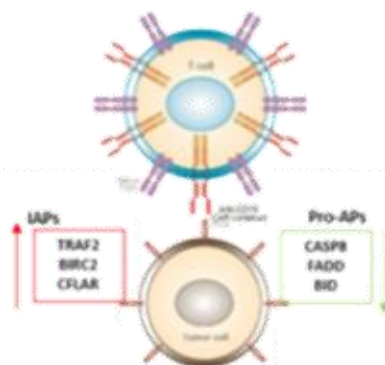
CD19 antigen loss

- acquired mutations and alternative splicing of CD19
(Sotillo et al. Cancer Disc. 2015)



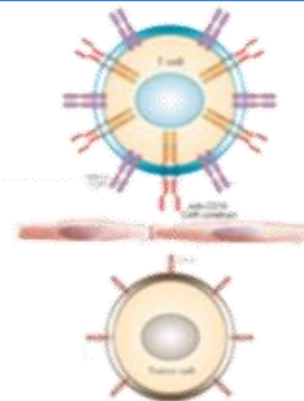
T-cell exhaustion/hypofunction

- mediated by inhibitory ligands on tumor cells and cells in the TME
- 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)

Investigator-initiated trials at UPenn addressing potential causes of CAR-T failure

CD19 ANTIGEN LOSS	T-CELL EXHAUSTION/HYPOFUNCTION	INTRINSIC TUMOR RESISTANCE	MISCELLANEOUS
<p>Phase II study of dual targeting of CD19 and CD20 antigens using CD19-CAR T cells and CD20-BsAb</p> <p>PI: E. Chong NCT04889716 • active • recruiting</p> <hr/> <p>Epcoritamab-CAR T Cells for Large B-cell Lymphomas</p> <p>PI: E. Chong NCT06458439 • active • recruiting</p>	<p>Interleukin-18 secreting anti-CD19 CAR T cells [huCART19-IL18 cells]</p> <p>PI: J. Svoboda NCT04684563 • fully accrued • Svoboda, et al. N Engl J Med 2025;392:1824</p> <hr/> <p>KIR-CAR/Dap12-modified T cells</p> <p>Pre-clinical completed*</p> <p>• Wang, et al. Cancer Imm Res 2015;3:815</p> <p>PI: S. Schuster NCT06544265 • active • recruiting</p> <hr/> <p>CD5 knockout CAR-T cells</p> <p>Pre-clinical completed*</p> <p>• Patel, et al. Sci Imm Res 2024;19(9)72</p> <p>PI: S. Barta NCT06420089 • active • recruiting</p>	<p>Venetoclax-resistant CAR T overexpressing mutated BCL-2(F104L) [BCL-2(F104L)-CART19]</p> <p>Pre-clinical completed*</p> <p>• Lee, et al. Cancer Disc 2022;12:2372</p> <p>PI: M. Ruela • clinical trial planned</p>	<p>BHB & CAR-T for Lymphomas</p> <p>Pre-clinical completed*</p> <p>• Liu, et al. Cell 2026; Epub ahead of print</p> <p>PI: E. Chong NCT06610344 • active • recruiting</p>
LYMPHODEPLETION and CAR-T IMAGING			
<p>Phase 1 Study of huCART19-IL18-eDHFR Cells in R/R Follicular Lymphoma</p> <p>PI: S. Schuster</p> <ul style="list-style-type: none"> • [¹⁸F]FP-TMP PET/CT imaging to track eDHFR labeled CAR-T cells • huCART19-IL18 without and with LD chemotherapy <p><small>*FLF funded; single center; IND submitted</small></p>		<p>Phase 3 Trial of Flu/Cy vs Bendamustine LD before Axi-Cel for R/R LBCL</p> <p>PI: S. Schuster</p> <p><small>*Kite funded; multicenter clinical trial</small></p>	

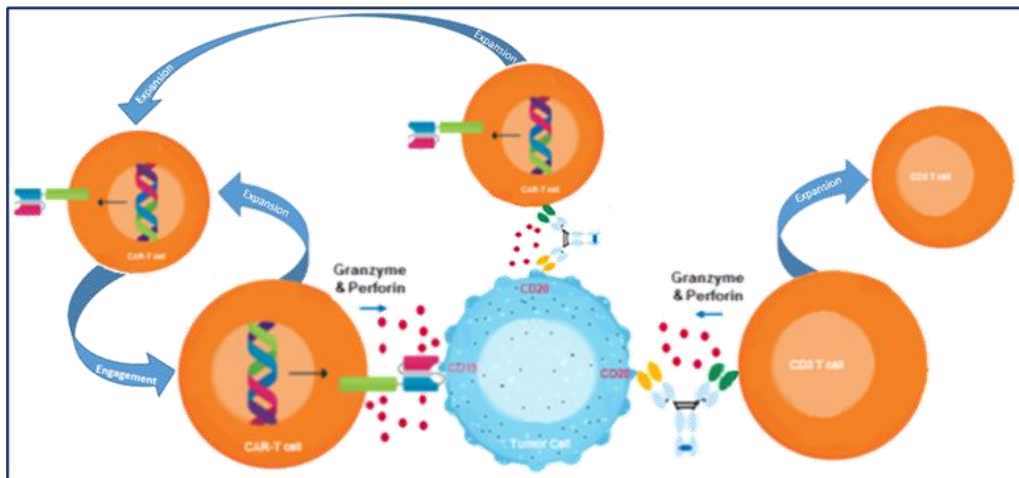
Disease-specific determinants of CAR-T success or failure: antigen loss

- Recruiting UPenn clinical trial addressing CD19 antigen loss or downregulation

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



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: E. Chong

CAR-T-specific determinants of CAR-T failure: T-cell exhaustion

• UPenn clinical trial addressing T cell exhaustion

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

Results

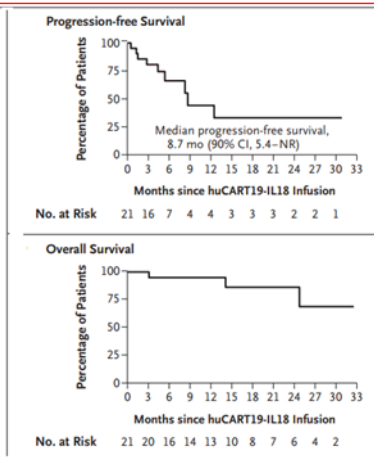
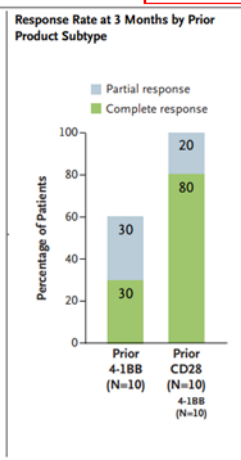
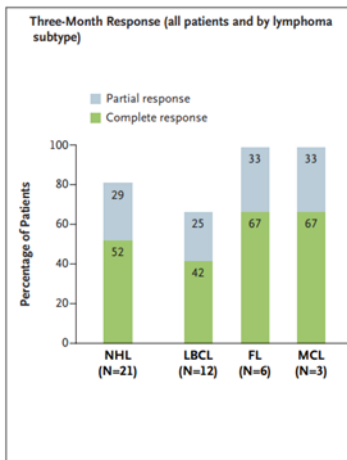
N = 21 received huCART19-IL18

Median follow-up: 17.5 months (range 3 - 34)

- 3-months ORR: 81% (90%CI, 62-93)
- 3-months CRR: 52% (90% CI, 33-71)
- Median DOR: 9.6 months (90% CI, 5.5-NR)

Characteristic	Patients (N = 21)
Median age (range) — yr	64 (47–74)
Male sex — no. (%)	16 (76)
ECOG performance-status score — no. (%) [†]	
0	2 (10)
1	19 (90)
Lymphoma subtype — no. (%)	
Large B-cell lymphoma	12 (57)
Diffuse large B-cell lymphoma, not otherwise specified	8 (38)
Transformed follicular lymphoma	2 (10)
High-grade B-cell lymphoma	1 (5)
T-cell histiocyte-rich large B-cell lymphoma	1 (5)
Follicular lymphoma	6 (29)
Mantle-cell lymphoma	3 (14)

Previous CAR therapy — no./total no. (%)	
CD28-based product	10/20 (50)
Axicabtagene ciloleucel	8/20 (40)
Brexucabtagene autoleucel	2/20 (10)
4-1BB-based product	10/20 (50)
Tisagenlecleucel	8/20 (40)
Lisocabtagene maraleucel	2/20 (10)
Response to previous therapy	
Progressive disease — no./total no. (%)	7/20 (35)
Median progression-free survival — mo (90% CI)	6.7 (3.1–10.2)

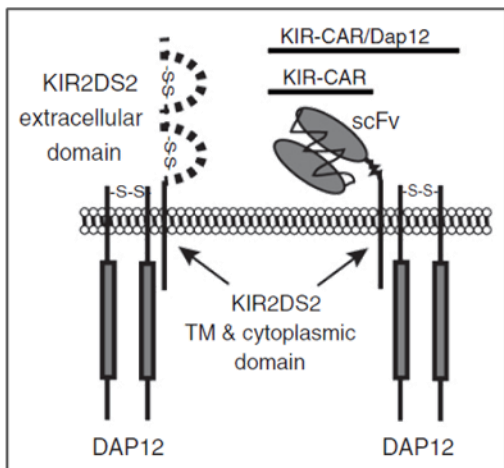


CAR-T-specific determinants of CAR-T failure: T-cell exhaustion

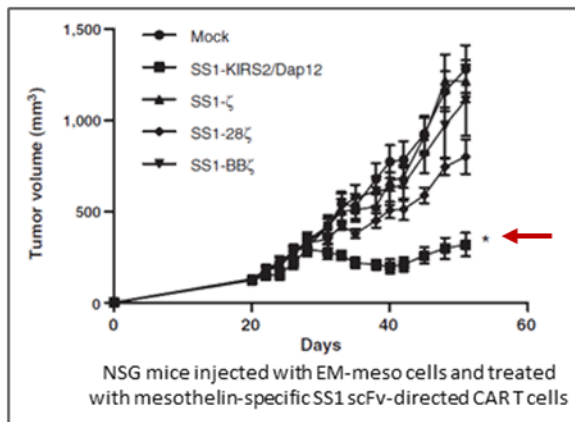
- Recruiting UPenn clinical trial addressing T cell exhaustion or hypofunction

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

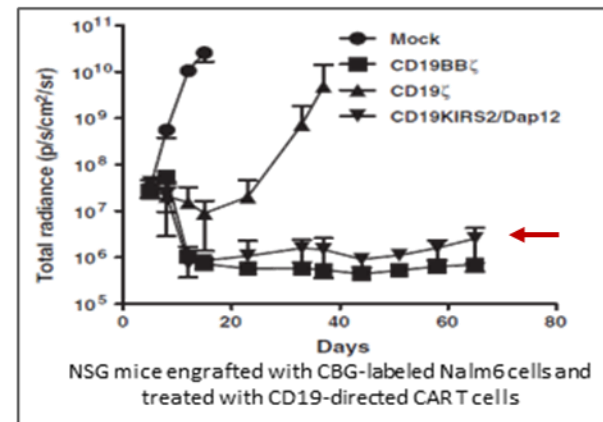
Rationale: KIR-CAR/Dap12 expressing CAR T cells have potent *in vivo* antitumor activity that is resistant to the tumor- and/or TME-induced T-cell hypofunction observed with CD3 ζ -based CAR T cells. This potent activity *may* be of benefit in LBCLs with bulky disease.



Solid tumor model



B-cell tumor model



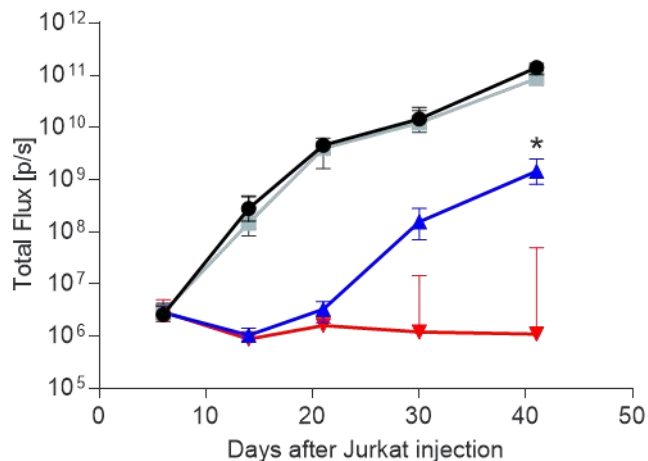
¹Moon, et al. Clin Cancer Res 2014;20:4262-73.

²Wang, et al. Cancer Imm Res 2015;3:815-826. (data show on the right)

CAR-T-specific determinants of CAR-T failure: T-cell exhaustion

CD5 KO CAR T cells can enhance efficacy in multiple liquid + solid tumor models

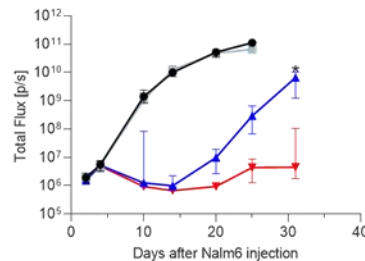
T-cell leukemia or lymphoma
CD5 KO vs Traditional CD5 CAR-T



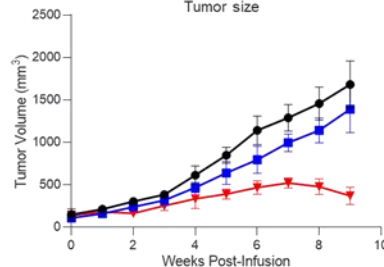
Ruella lab data

Patel RP, ASH, 2022 #662

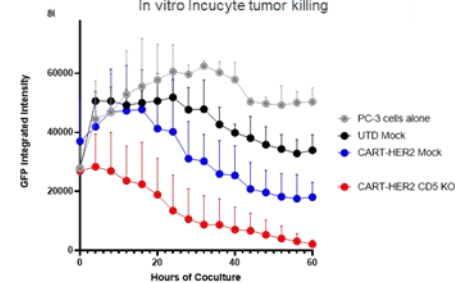
B-CELL LEUKEMIA AND LYMPHOMA
CD5 KO vs Traditional CD19 CAR-T
Tumor burden



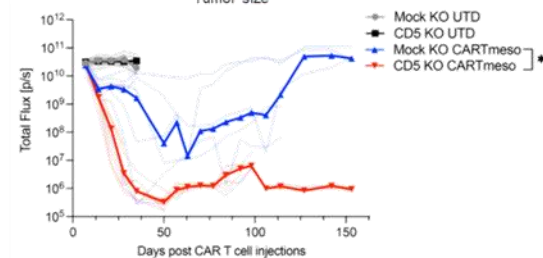
HODGKIN LYMPHOMA
CD5 KO vs Traditional CD30 CAR-T
Tumor size



OVARIAN CANCER
CD5 KO vs Traditional HER2 CAR-T
In vitro Incubate tumor killing



PANCREATIC CANCER
CD5 KO vs Traditional Mesothelin CAR-T
Tumor size



Grazie / Thank You!

