3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

Scientific board:
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Potential opportunities to overcome resistance to CAR-T therapy in diffuse large B-cell lymphoma

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Disclosures of 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							Chair DSMB
Genentech/Roche	X					X	Steering committee
Genmab	X					X	Steering committee
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Kite Pharmaceuticals						X	
Legend Biotech						X	Steering committee
Novartis						X	Steering committee
Mustang Biotech						X	
Nordic Nanovector						X	Steering committee
Takeda							Honoraria for presentation

Outline

- Background: the unmet need
- Optimizing patient characteristics
- Optimizing lymphodepletion
- Optimizing CAR-T product characteristics
- Overcoming tumor-specific mechanisms of resistance

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Potential opportunities to overcome resistance to CAR-T

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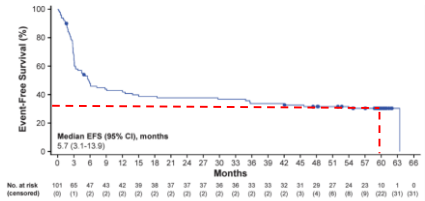
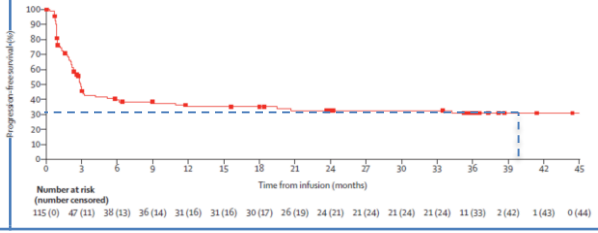
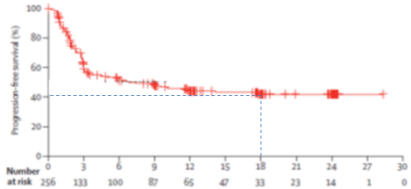
- **Roughly 1/3 of patients with relapsed or refractory large B-cell lymphomas achieve long-term remissions with commercially available CAR-T products as 3rd-line therapy**
- **2/3 of patients fail to achieve durable responses**

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%**	**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 = 256 Median follow-up: 12.3 months **Estimated 18-month PFS: 42.1%**
		

[1]Neelapu SS, et al. Blood. 2023;Epub ahead of print; [2]Schuster SJ, et al. Lancet Oncol 2021;22(10):1403-1415; [3]Abramson J, et al. Lancet. 2020;396(10254):839-852.

Potential opportunities to overcome resistance to CAR-T

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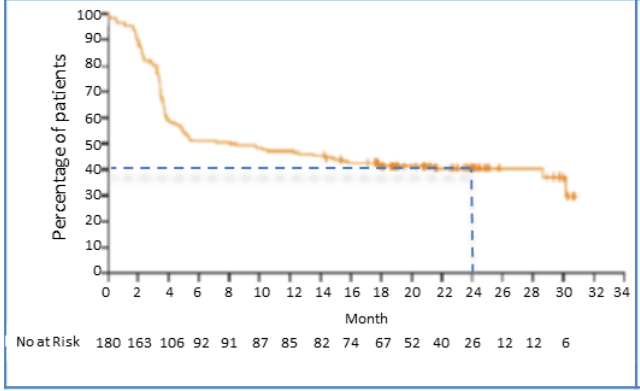
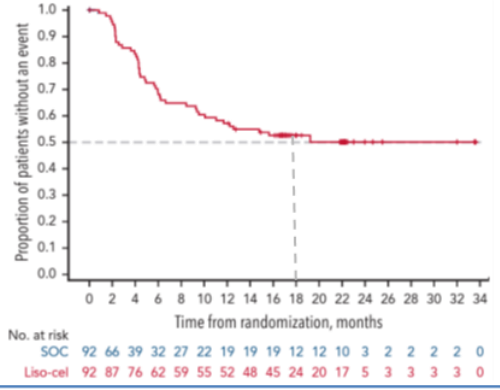
- **Earlier administration of CAR-T as 2nd-line of therapy may provide an additional 10% EFS benefit**

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)**
	

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

Outline

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Potential opportunities to overcome resistance to CAR-T

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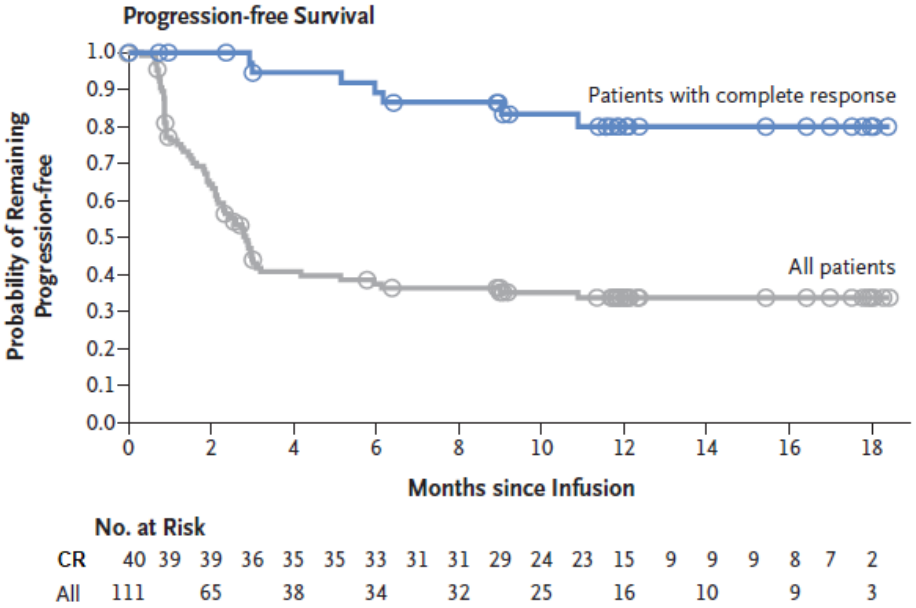
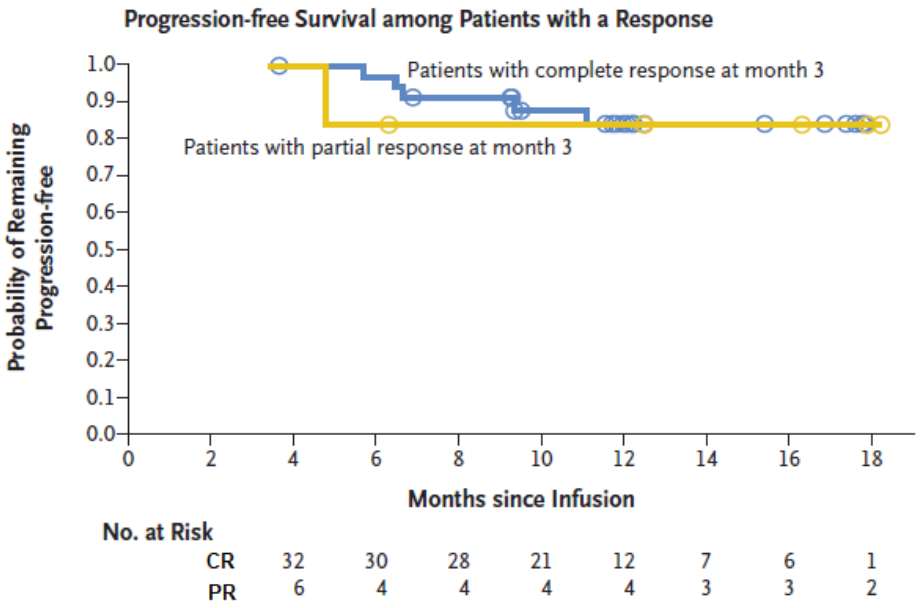
- **Best response and outcome**
  - **Data from the JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL**





Schuster SJ, *et al*. N Engl J Med. 2019;380(1):45-56.

Potential opportunities to overcome resistance to CAR-T

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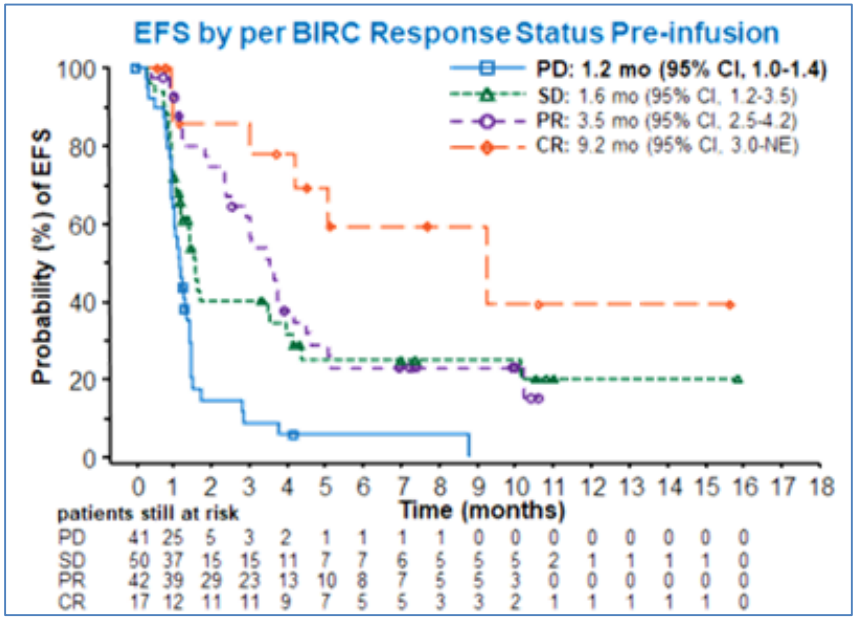
- **Disease status at the time of LD-CAR-T and its impact on outcome**
  - **Data from the BELINDA trial: tisagenlecleucel vs SOC**



Multivariate Logistic Regression Model for Post-Infusion Best Overall Response (CR/PR vs SD/PD/UNK) in Arm A (second-line CAR-T)

	Odds Ratio Estimates		
Variable	Point Estimate	95% Wald Confidence Limits	
CR/PR before infusion vs. SD/PD before infusion at mean cell dose	7.75	3.23	18.62

The odds ratio is the odds of having a best overall response of CR/PR vs. SD/PD/UNK; *i.e.*, an odds ratio >1 means patients are more likely to have a best overall response of CR/PR.

EFS time is relative to date of tisagenlecleucel infusion; median time from pre-infusion disease assessment to infusion was 10 days (range, 2-57; Q1-Q3, 8-15).
EFS events defined as PD/SD after day 71 from randomization or death at any time.

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

Potential opportunities to overcome resistance to CAR-T

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- **Lab studies independently prognostic of response to CAR-T**
  - **Data from the JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL**

Univariable Factors Analyzed

- LDH (≤1 × ULN vs >2 × ULN)
- LDH (>1–2 × ULN vs >2 × ULN)
- CRP (high vs low/normal)
- Platelets at baseline (grade 0–2 vs grade 3/4)
- Lymphocytes before LD chemo. (grade 3/4 vs grade 0)
- Lymphocytes before LD chemo. (grade 1/2 vs grade 0)
- Ferritin (high vs low/normal)
- ECOG PS (0 vs 1)
- Age group (<65 years ≥65 years)
- Metabolic tumor volume (<100 vs ≥100 mL)
- IPI risk (≥2 vs <2 risk factors)
- IFNγ
- IL10
- IL12
- P70
- IL6
- IL8
- IL13
- TNFα

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	
Thrombocytopenia		
CTCAE grades 0 - 2	43/99	7.23 (0.84-62.31)
CTCAE grades 3 - 4	1/16	

- Lab analytes are defined as the closest time before or on the day of infusion
  - 93% of values fell on the day of infusion
- Thrombocytopenia: grade 4, <25; grade 3, 25-50; grade 2, 50-75; grade 1, 75-LLN × 10^9/L

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

Potential opportunities to overcome resistance to CAR-T

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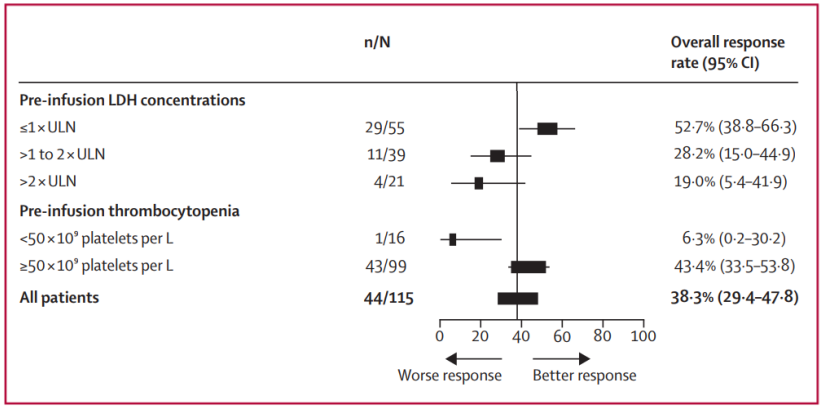
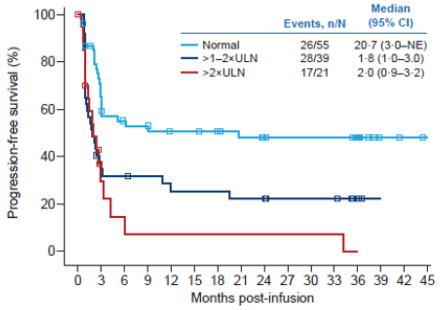
- **Lab studies independently prognostic of outcome to CAR-T**
  - **Data from the JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL**

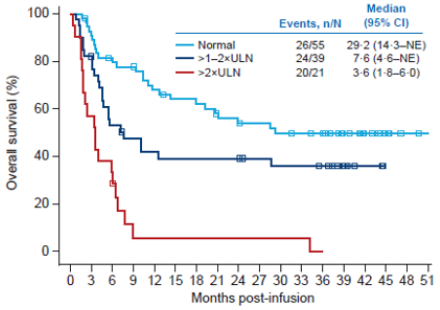
Overall response rates by LDH and platelet count



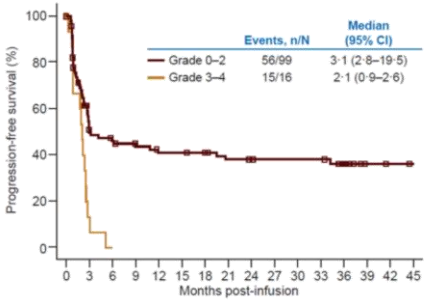
Progression-free survival by LDH



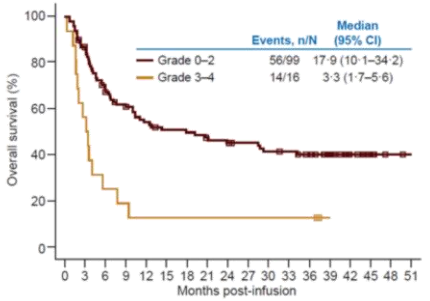
Overall survival by LDH



Progression-free survival by platelets



Overall survival by platelets



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

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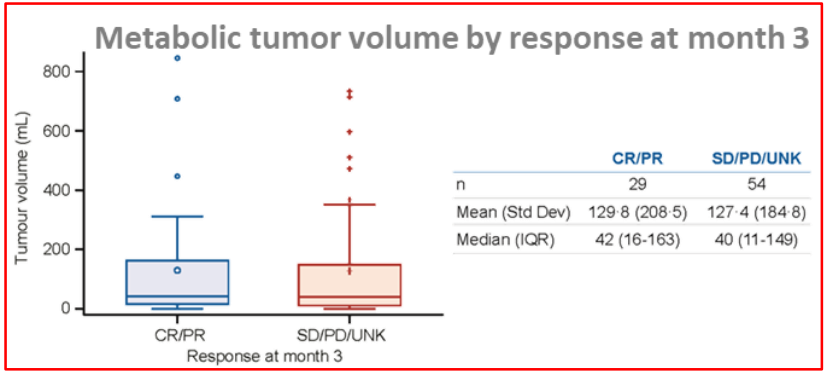
- **Tumor bulk and its impact on response ("size matters")**
  - **Data from the JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL**

	n/N	Overall response rate (95% CI)
Baseline tumour volume		
<100 mL	23/64	35·9% (24·3–48·9)
≥100 mL	11/36	30·6% (16·3–48·1)
Unknown	10/15	66·7% (38·4–88·2)
Bulky disease (> 10 cm)		
Yes	1/9	11·1% (0·3–48·2)
No	43/106	40·6% (31·1–50·5)



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

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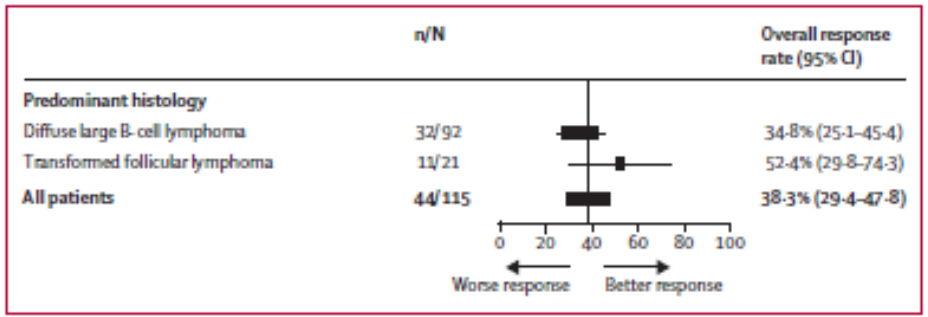
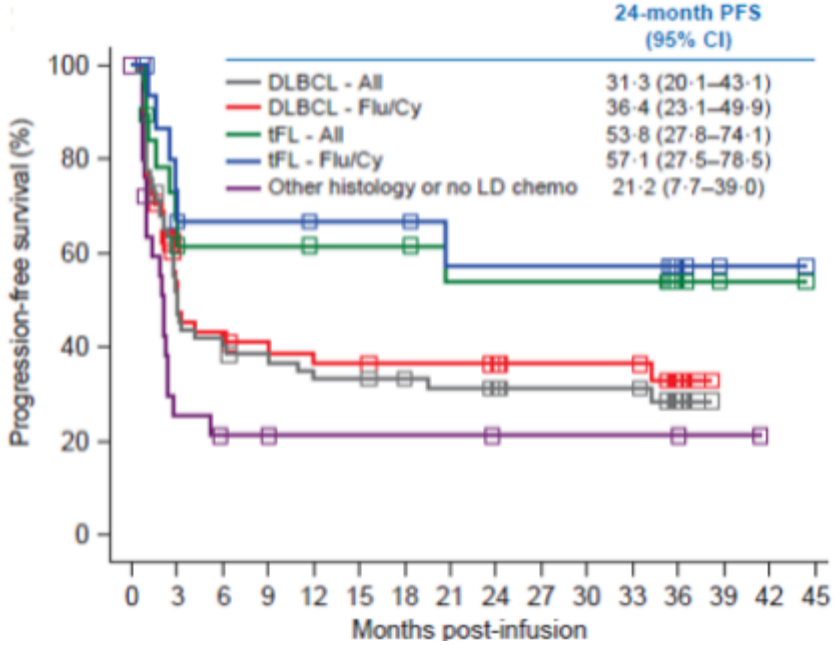
- **Lymphoma subtype and its impact on outcome**
  - **Data from the JULIET trial: Phase 2 trial of tisagenlecleucel in r/r LBCL**

Overall response rates by lymphoma subtype





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- **Is cyclophosphamide/fludarabine required for lymphodepletion?**

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas

G. Ghilardi[1,2,3†], E. A. Chong[1,2,3†], J. Svoboda[1,2,3], P. Wohlfarth[4], S. D. Nasta[1,3], S. Williamson[5], J. D. Landsburg[1,3], J. N. Gerson[1,3], S. K. Barta[1,2,3], R. Pajarillo[1,2,3], J. Myers[5], A. I. Chen[5], L. Schachter[5], R. Yelton[1,2], H. J. Ballard[1,3], A. Hodges Dwinal[5], S. Gier[2,3], D. Victoriano[2,3], E. Weber[1,3], E. Napier[1,3], A. Garfall[2,3], D. L. Porter[1,3], U. Jäger[4], R. T. Maziarz[5], M. Ruella[1,2,3†] & S. J. Schuster[1,2,3*†]

[1]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia; [2]Center for Cellular Immunotherapies and Cellular Therapy and Transplant, University of Pennsylvania, Philadelphia; [3]Division of Hematology-Oncology, Hospital of the University of Pennsylvania, Philadelphia, USA; [4]Medical University of Vienna, Division of Hematology and Hemostaseology, Department of Medicine I Wien, Comprehensive Cancer Center, Vienna, Austria; [5]Oregon Health & Science University Knight Cancer Institute, Adult Blood and Marrow Stem Cell Transplant & Cell Therapy Program, Portland, USA

Potential opportunities to overcome resistance to CAR-T

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ORIGINAL ARTICLE

Bendamustine is safe and effective for lymphodepletion

- Retrospective comparison of fludarabine/cyclophosphamide and bendamustine as lymphodepletion prior to tisagenlecleucel
- University of Pennsylvania; Oregon Health & Science University; University of Vienna
- **Bendamustine, n = 90; Fludarabine/Cyclophosphamide, n = 42; patient characteristics balanced between LD as shown below**

Characteristics	Total population N = 132 (100%)	Flu/Cy n = 42 (31.8%)	Benda n = 90 (68.2%)	p
Sex				
Female	50 (37.9%)	16 (38.1%)	34 (37.8%)	0.972
Male	82 (62.1%)	26 (61.9%)	56 (62.2%)	
Age at infusion (median – [IQR])	65 [56-70]	67 [56-73]	65 [56-70]	0.222
Diagnosis				
DLBCL NOS	66 (50.0%)	27 (64.3%)	39 (43.3%)	0.128
HGBCL NOS	5 (3.8%)	1 (2.4%)	4 (4.4%)	
tFL	47 (35.6%)	12 (28.6%)	35 (38.9%)	
HGBCL with MYC + BCL2 and/or BCL6 rearrangements	14 (10.6%)	2 (4.8%)	12 (13.3%)	
ECOG PS				
0-1	124 (93.9%)	39 (92.9%)	85 (94.4%)	0.722
≥2	8 (6.1%)	3 (7.1%)	5 (5.6%)	
Renal function				
Normal	108 (81.8%)	32 (76.2%)	76 (84.4%)	0.252
Reduced	24 (18.2%)	10 (23.8%)	14 (15.6%)	
Previous ASCT				
No	104 (78.8%)	31 (63.8%)	73 (81.1%)	0.339
Yes	28 (21.2%)	11 (26.2%)	17 (18.9%)	

Characteristics	Total population N = 132 (100%)	Flu/Cy n = 42 (31.8%)	Benda n = 90 (68.2%)	p
No. of previous lines of therapy (median [IQR])	3 [3-4]	3 [2-4]	3 [3-4]	0.569
Serum LDH (N=131)				
Normal	68 (51.9%)	20 (47.6%)	48 (53.9%)	0.500
Elevated	63 (48.1%)	22 (52.4%)	41 (46.1%)	
Pre-LD CRP (N=54)				
Normal	34 (63.0)	13 (65.0)	21 (61.8)	0.812
Elevated	20 (37.0)	7 (35.0)	13 (38.2)	
Pre-LD Ferritin (N=52)				
Normal	28 (53.8)	11 (55.0)	17 (53.1)	0.895
Elevated	24 (46.2)	9 (45.0)	15 (46.9)	
Bulky disease (>10cm)				
No	119 (90.2%)	36 (85.7%)	84 (92.2%)	0.242
Yes	13 (9.8%)	6 (14.3%)	7 (7.8%)	
Bridging therapy				
No	27 (20.5%)	11 (26.2%)	16 (17.8%)	0.264
Yes	105 (79.5%)	31 (73.4%)	74 (82.2%)	

Ghilardi G, *et al*. Ann Oncol. 2022;S0923-7534(22)01722-7.

Potential opportunities to overcome resistance to CAR-T

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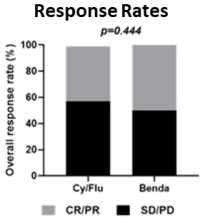
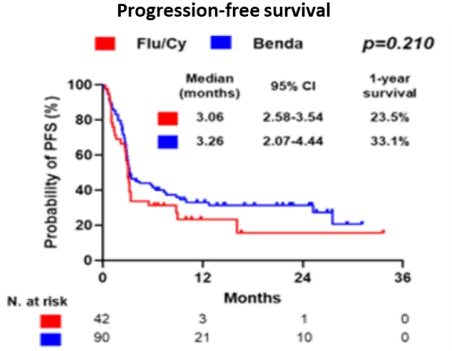
ORIGINAL ARTICLE

Bendamustine is safe and effective for lymphodepletion

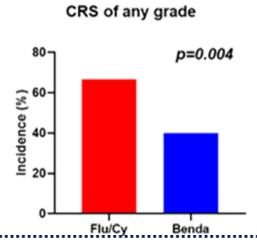
Bendamustine, n = 90
Fludarabine/Cyclophosphamide n = 42

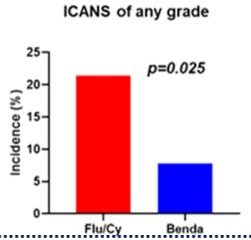
Clinical Outcomes

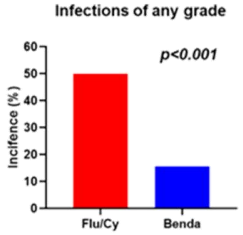


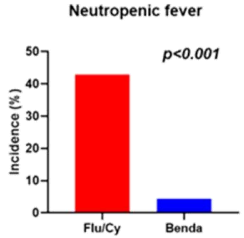


Toxicities









Ghilardi G, *et al*. Ann Oncol. 2022;S0923-7534(22)01722-7.

Received: 1 May 2023 | Revised: 28 July 2023 | Accepted: 14 August 2023
DOI: 10.1002/ajh.27069

RESEARCH ARTICLE

AJH WILEY

Bendamustine lymphodepletion is a well-tolerated alternative to fludarabine and cyclophosphamide lymphodepletion for axicabtagene ciloleucel therapy for aggressive B-cell lymphoma

Shin Yeu Ong[1,2] | Stacy Pak[3] | Matthew Mei[1] | Yan Wang[4] | Leslie Popplewell[1] | John H. Baird[1] | Alex F. Herrera[1] | Geoffrey Shouse[1] | Liana Nikolaenko[1] | Jasmine Zain[1] | James Godfrey[1] | Myo Htut[1] | Ahmed Aribi[1] | Ricardo Spielberger[1,5] | Joshua Mansour[1,5] | Stephen J. Forman[1] | Joycelynne Palmer[4] | Lihua E. Budde[1]

Potential opportunities to overcome resistance to CAR-T

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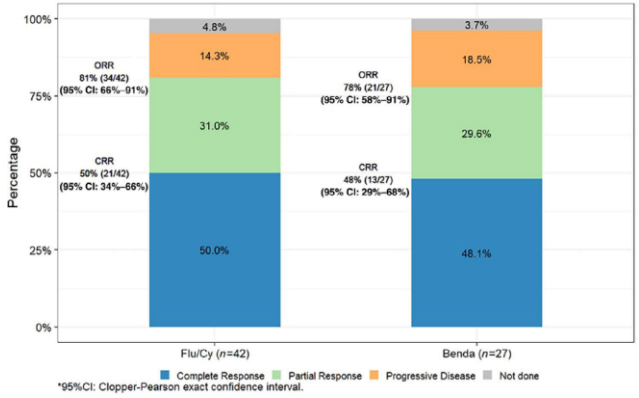
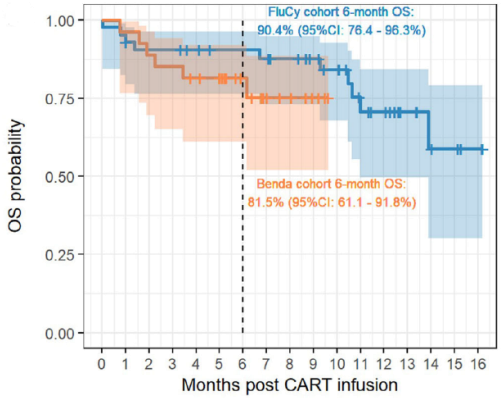
- **Patients receiving bendamustine relative to Flu/Cy followed by axi-cel had comparable efficacy and lower any grade ICANS**

Toxicity	bendamustine	Flu/Cy
any grade / grade ≥3 CRS	89% / 3.7%	86% / 4.8%
any grade ICANS / grade ≥3 ICANS	30% / 19%	55% / 31%
grade ≥3 neutropenia	68%	100%

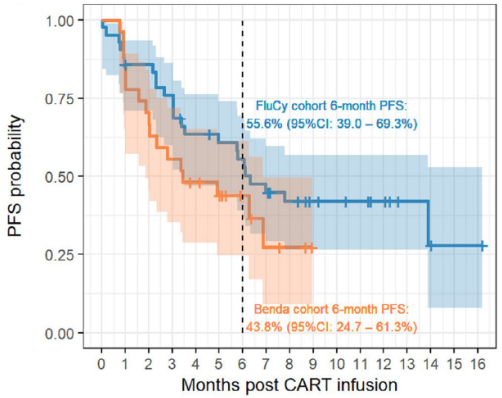
Response rates



Progression-free survival



Overall survival



Ong SY, et al. Am J Hematol. 2023;1-11.

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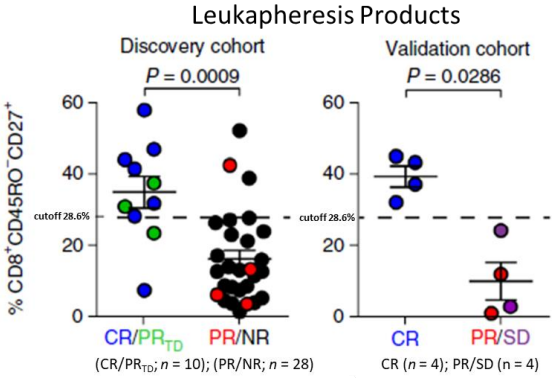
- **Functional T Cell Subsets Determine CAR T Cell Responses**

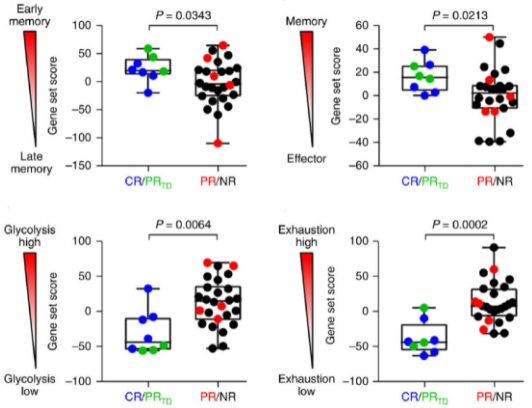
CD27$^+$ CD45RO$^-$ (memory phenotype) CD8$^+$ T cell content in CLL *patients' leukapheresis products* and response



Leukapheresis biomarker ($CD8^+CD45RO^-CD27^+$)

	Specificity	Sensitivity
Discovery	89%	80%
Validation	100%	100%

Genomic evaluation of CLL *patient-derived CAR T cells*



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

Fraietta, *et al*. Nat Med 2018; 24:563–571.

Outline

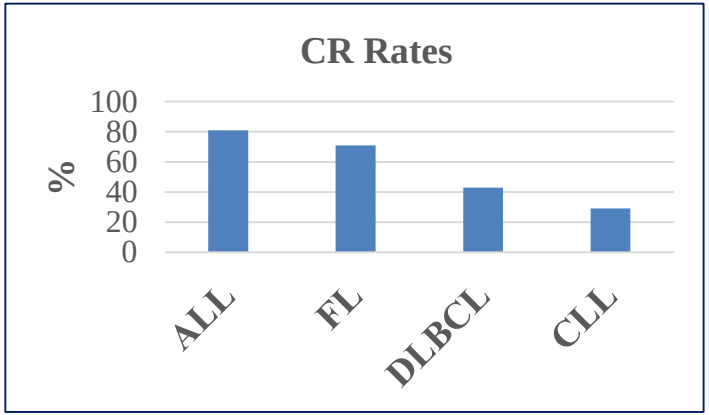
- Background: the unmet need
- Optimizing patient characteristics
- Optimizing lymphodepletion
- Optimizing CAR-T product characteristics
- Overcoming tumor-specific mechanisms of resistance

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **Early CTL019 efficacy data: Penn and CHOP**
  - **Determinants of success or failure are probably *disease-specific***

Disease	N	CR rate	Median DOR	Median Follow-Up
r/r ALL[1]	75	81%	Not Reached	13.1 mo (2.1-23.5)
r/r FL[2]	14	71%	Not Reached	28.6 mo (3.5-37.9)
r/r DLBCL[2]	14	43%	Not Reached	46.8 mo (6.0-54.6)*
r/r CLL[3]	14	29%	40.0 mo (21.0-53.0)	19.0 mo (6.0-53.0)



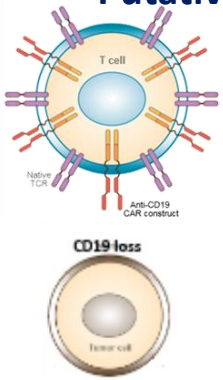
*Data updated December 2018

[1]Maude S, *et al*. NEJM. 2018;378(5): 439-448; [2]Schuster SJ, *et al*. N Engl J Med. 2017;377(26):2545-2554; [3]Porter DL, *et al.* Sci Transl Med. 2015; 7(303): 1-12.

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

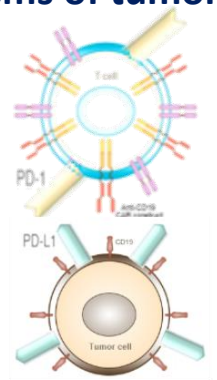
- **Putative mechanisms of tumor resistance to CAR T cells in DLBCL**



CD19 antigen loss

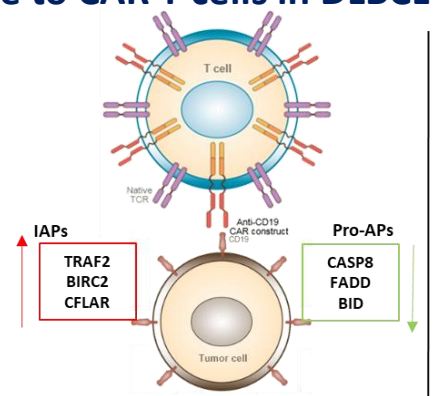
- acquired mutations and alternative splicing of CD19

(Sotillo…Thomas-Tikhonenko Cancer Disc. 2015)



T-cell exhaustion/hypofunction

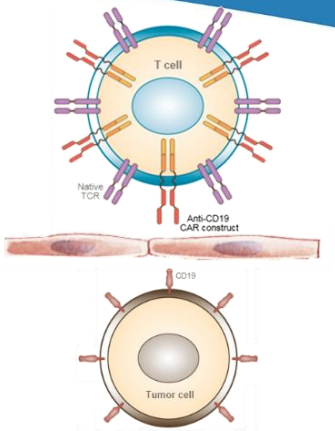
- mediated by inhibitory CAR T receptors and ligands on in tumor microenvironment
- peripheral self-tolerance (B cell recovery? late relapses?)
- TME-induced T cell hypofunction (reversible)



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)

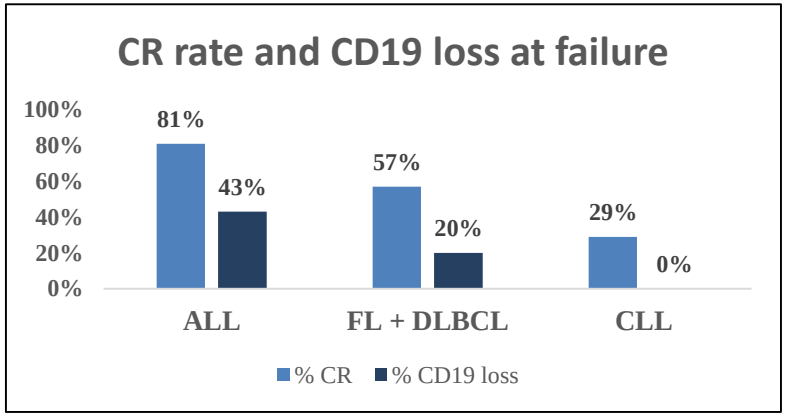
Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **Mechanisms of CAR-T failure: CD19 loss or downregulation**

- **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 as a result of 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.*

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **JULIET: Response rates vs tumor CD19 expression by IHC**

- **No Difference**

Table S12. Best Overall Response and Relative Expression Levels of CD19

Response Rate	Patients (N = 72)	
	CD19 Positive (N=49)	CD19 Negative/Low Expression (N=24)
CR, n	20	7
PR, n	4	5
Best ORR, % (95% CI)	49% (34-64)	50% (29-71)

Patients were classified as CD19 positive if they had an AQUA score ≥10,000. Patients with an AQUA score <10,000 were considered CD19 low/negative.

Schuster SJ, *et al*. N Engl J Med 2019;380(1):45-56.

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **Inhibitory protein expression vs response to CAR-T (DLBCL)**

Penn 13413 Trial: - Increase in checkpoint expression at baseline in non-responders (~ 2/10)
- Increase in checkpoint expression at disease progression (~ 2/5)

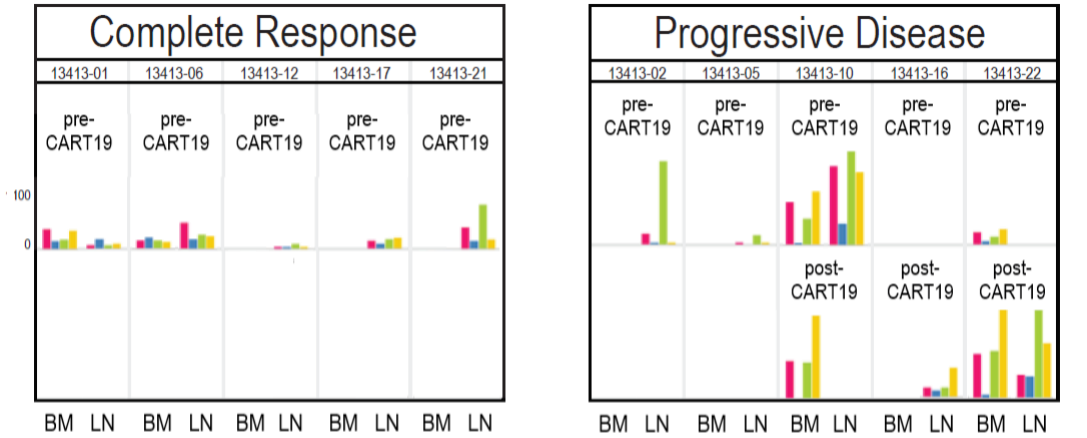


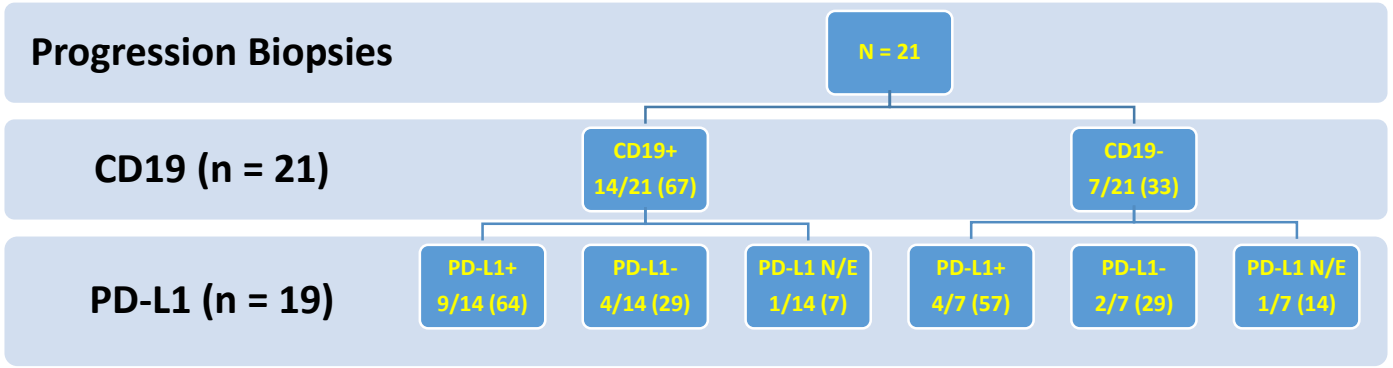
Figure 3 : Immune-checkpoint analysis in serial lymph node and bone marrow samples from patients with DLBCL. LAG3, PD1, PD-L1, TIM3 immunohistochemical (IHC) expression and quantitative analysis based on biomarker expression in both non-tumor (immune cells) and lymphoma cells by patient and clinical response.

Schuster SJ, *et al*. N Engl J Med. 2017;377(26):2545-2554.

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **ZUMA-1: Tumor CD19 and PDL-1 expression at progression by IHC (DLBCL)**



- **Post-progression tumor biopsies (21 evaluable patients)**
  - **33% were CD19- by IHC at progression by central review (7/21)**
  - **62% were PD-L1+ at progression by central review (13/21)**

- CD19 H-score of 0 was determined negativity. H-scores ≥ 1 were considered positive. H-score was calculated as a product of IHC intensity (scale 1-3) multiplied by the percentage of tumor cells at a given intensity (0-100%).
- PD-L1 status was determined by the percentage of tumor cells with any membrane staining above background or by the percentage of tumor-associated immune cells with staining at any intensity above background.

IHC, immunohistochemistry; N/E, not evaluable; PD-L1, programmed cell death-ligand 1.

Neelapu et al. ASH 2017. Abstract 578.

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **Active and upcoming clinical trials at UPenn addressing tumor-specific mechanisms of resistance to CAR-T**

CD19 antigen loss

Phase II study of dual targeting of CD19 and CD20 antigens using CD19-directed CAR-T cells followed by CD20-BsAb

NCT04889716

- **Recruiting**

PI: E. Chong

T-cell exhaustion and hypofunction

Phase I trial of interleukin-18 secreting anti-CD19 CAR-T cells for r/r CD19+ lymphomas and CLL [huCART19-IL18 cells]

NCT04684563

- **Recruiting**

PI: J. Svoboda

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

- **Pre-clinical studies completed***

****Wang, et al. Cancer Imm Res 2015; 3:815***

- **Clinical trial planned**

PI: S. Schuster

Intrinsic tumor resistance

Venetoclax-resistant CAR T cells engineered to express mutated BCL-2(F104L) for combination therapy of lymphomas

- **Pre-clinical studies completed***

****Lee, et al. Cancer Discov 2022; 12:2372***

- **Clinical trial planned**

PI: M. Ruella

Insufficient T-cell infiltration

Under non-disclosure agreement

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

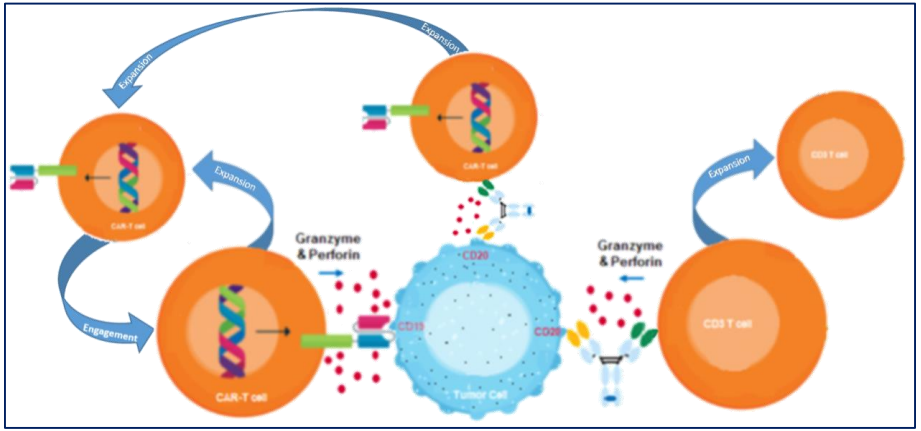
- **Active UPenn clinical trial addressing CD19 antigen loss or downregulation**

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**



Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **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 Diffuse Large B-cell or Transformed Follicular Lymphomas: NCT04889716

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
Intervention Model Description:	Cohort 1 subjects will receive mosunetuzumab. Pending demonstrated safety of cohort 1, the trial will progress to cohort 2, in which subjects will receive glofitamab with obinutuzumab.
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	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 Diffuse Large B-cell or Transformed Follicular Lymphomas
Actual Study Start Date :	November 5, 2021
Estimated Primary Completion Date :	December 31, 2023
Estimated Study Completion Date :	December 31, 2025

Potential opportunities to overcome resistance to CAR-T

S. J. Schuster

- **Active UPenn clinical trial addressing T cell exhaustion**

Phase I Trial of huCART19-IL18 Cells in Patients With Relapsed or Refractory CD19+ Cancers

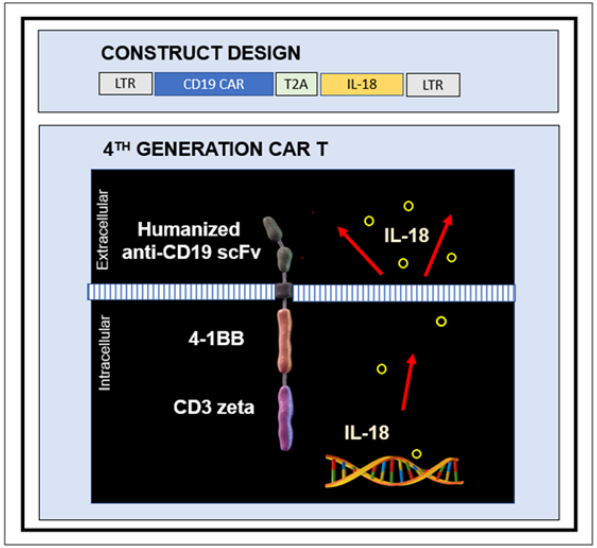
Rationale: to utilize IL-18 as a pro-inflammatory cytokine to:

- **enhance 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

huCART19-IL18



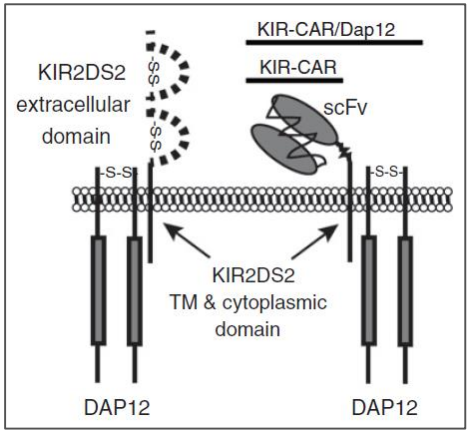
Potential opportunities to overcome resistance to CAR-T

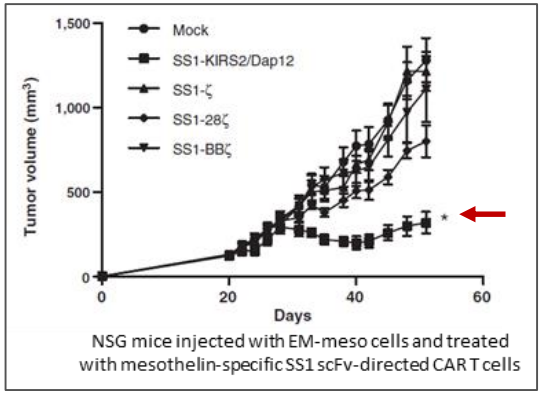
S. J. Schuster

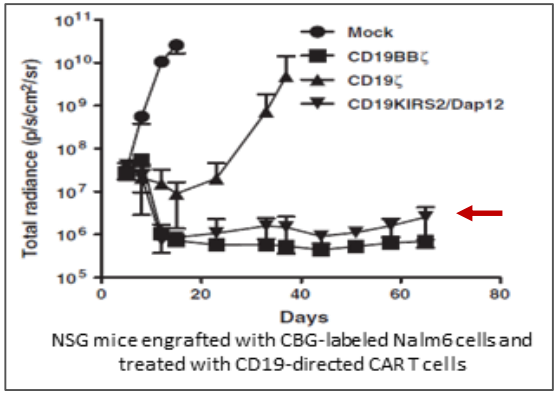
- **Planned UPenn clinical trial addressing T cell exhaustion or hypofunction**

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 CD3ζ-based CAR T cells[1]. This potent activity *may* be of benefit in large B-cell lymphomas with bulky disease.







[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*)

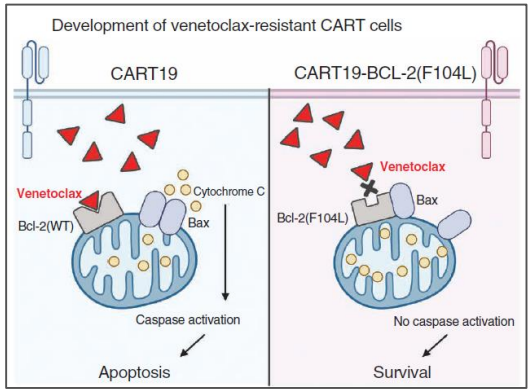
Potential opportunities to overcome resistance to CAR-T

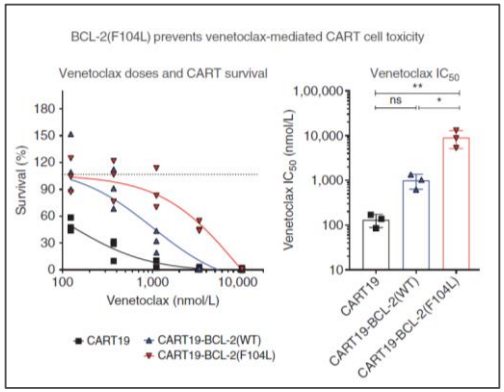
S. J. Schuster

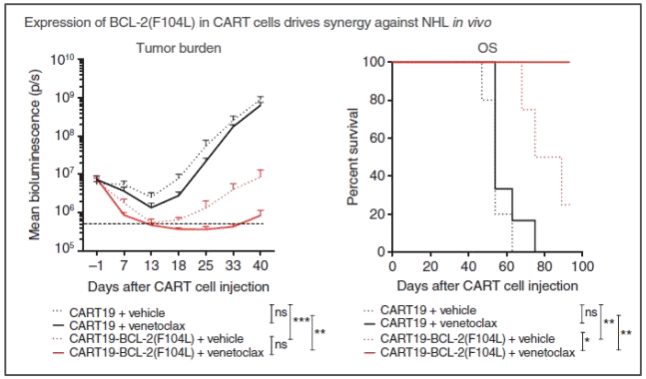
- **Planned UPenn clinical trial addressing intrinsic tumor resistance to CAR-T**

Venetoclax-resistant CAR T cells engineered to express mutated BCL-2(F104L) for combination therapy of lymphomas

Rationale: BCL-2 *overexpression in CAR T cells* and *inhibition in tumor cells* enhances CAR T cell efficacy in pre-clinical models by reducing apoptosis in CAR T cells and enhancing apoptosis in cancer cells. Thus, combination venetoclax and CAR T cell therapy is a compelling approach for B-cell lymphomas failing standard CAR T therapy.







MINO xenografted mice treated with CART19 or CART19-BCL-2(F104L)

[1]Lee, et al. Cancer Disc 2022;12:2372–91.

Grazie / Thanks!

Domande / Questions?