THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CAR T-cell therapy for lymphoma: Current and future trends

Sattva S. Neelapu, M.D.
Professor and Deputy Chair
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas, USA

3rd Cuneo City ImmunoTherapy Conference
Cuneo, Italy
May 18-20, 2023

Disclosures

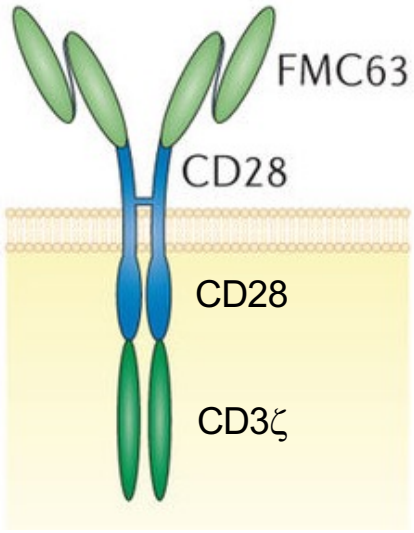
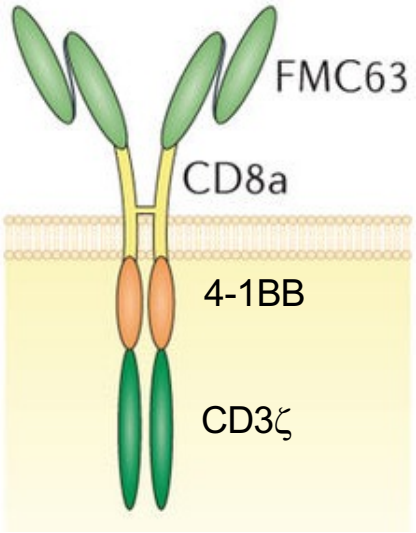
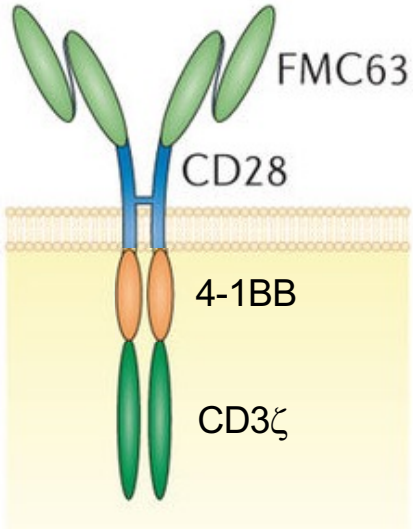
Disclosure	Company name
Research Support	Kite/Gilead, BMS, Allogene, Precision Biosciences, Adicet Bio
Advisory Board / Consultant	Kite/Gilead, Sellas Life Sciences, Athenex, Allogene, Incyte, Adicet Bio, BMS, Bluebird Bio, Fosun Kite, Sana Biotechnology, Caribou, Astellas Pharma, Morphosys, Janssen, Chimagen, ImmunoACT, Orna Therapeutics, Takeda
Honoraria	MJH Life Sciences, PeerView
Speaker's Bureau	None
Employment	None
Royalties	None
Stocks / Stock Options	Longbow Immunotherapy
Patents	Related to cell therapy

- I will discuss investigational use of CAR T-cell therapy

Outline

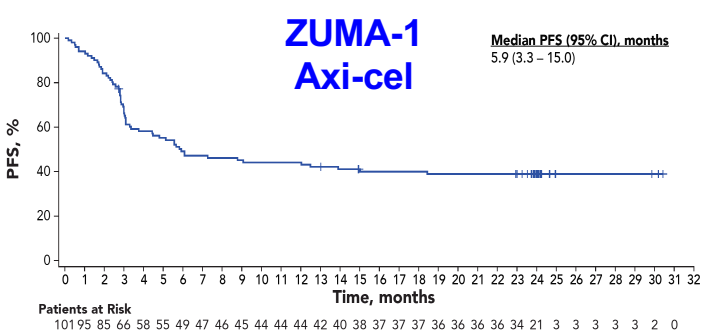
- Outcomes with autologous CD19 CAR-T in NHL
- Mechanisms of resistance to CAR T therapy
- Approaches to improve CAR-T efficacy

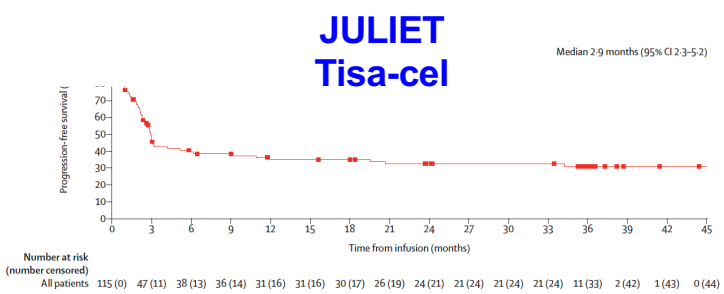
Autologous CD19 CAR T products approved in NHL

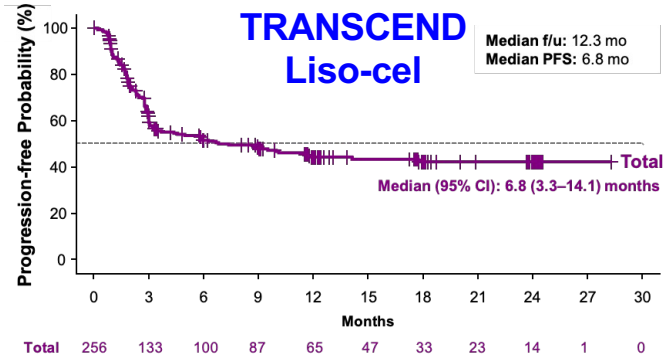
	Axicabtagene ciloleucel **Brexucabtagene autoleucel** **Axi-cel / Brexu-cel**	**Tisagenlecleucel** **Tisa-cel**	**Lisocabtagene maraleucel** **Liso-cel**
CD19 Ab			
Hinge Transmembrane			
Signal 2			
Signal 1			
Gene transfer	Retrovirus	Lentivirus	Lentivirus
FDA approvals	**LBCL** (2nd and 3rd line) **FL** (3rd line) **MCL** (2nd line)	**LBCL** (3rd line) **FL** (3rd line)	**LBCL** (2nd and 3rd line)

van der Stegen SJC et al. *Nat Rev Drug Discov*.2015;14(7):499-509.

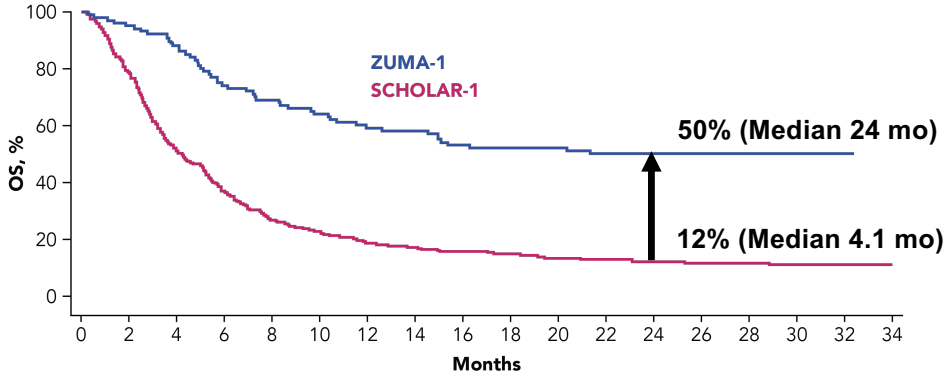
CD19 CART in ≥3rd line LBCL: PFS and OS







Standardized OS Comparison: ZUMA-1 vs. SCHOLAR-1 (historical)



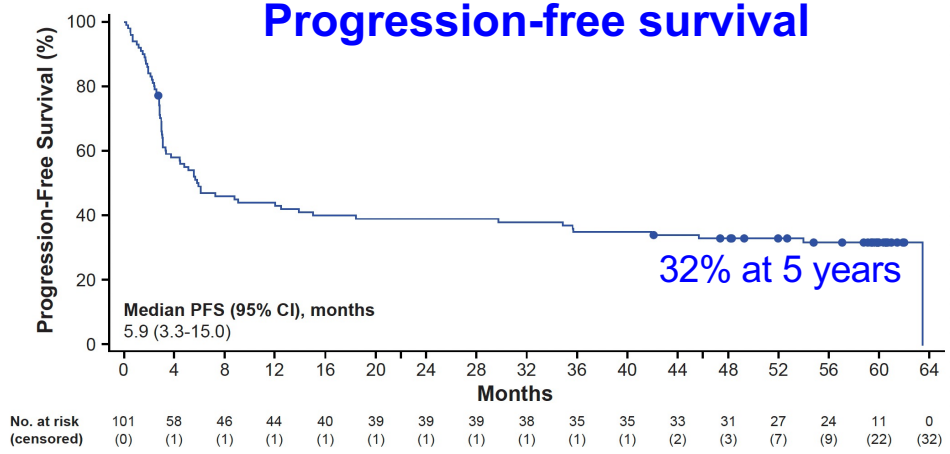
FDA Approval

Axi-cel, tisa-cel, and liso-cel for adult patients with r/r LBCL after 2 or more lines of systemic therapy

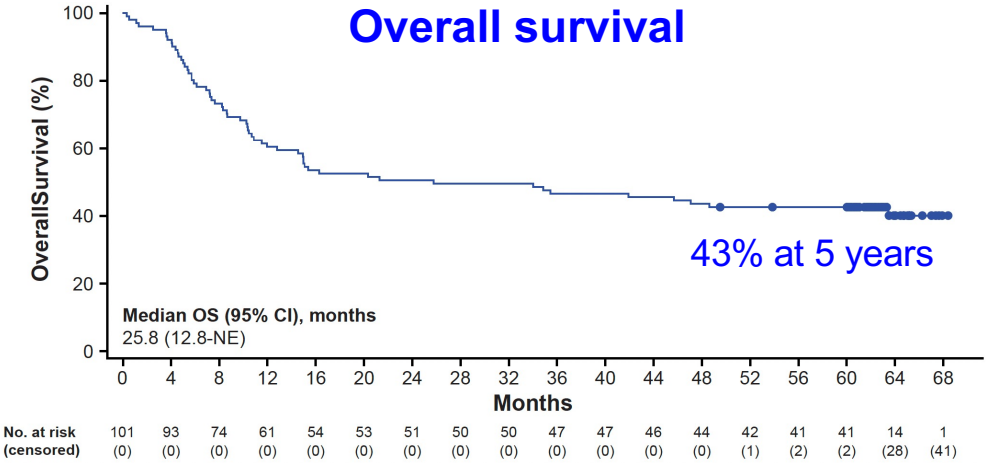
Neelapu SS et al. *N Engl J Med.* 2017;377:2531-2544. Locke FL et al. *Lancet Oncol.* 2019;20(1):31-42.
Schuster SJ et al. *N Engl J Med.* 2019;380:45-56. Schuster SJ et al. *Lancet Oncol.* 2021;22(10):1403-1415.
Abramson JS et al. *Lancet.* 2020;396(10254):839-852. Neelapu SS et al. *Blood Adv.* 2021;5(20):4149-4155.

ZUMA-1 @ 5 years

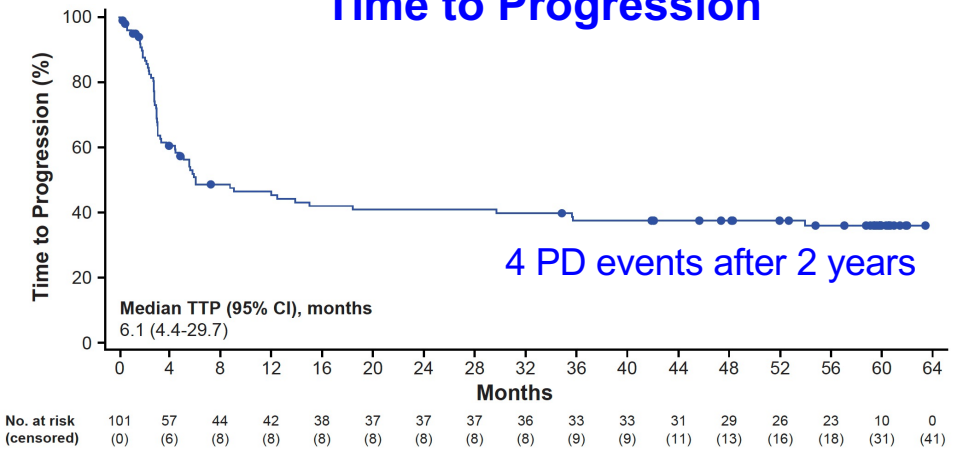
Progression-free survival



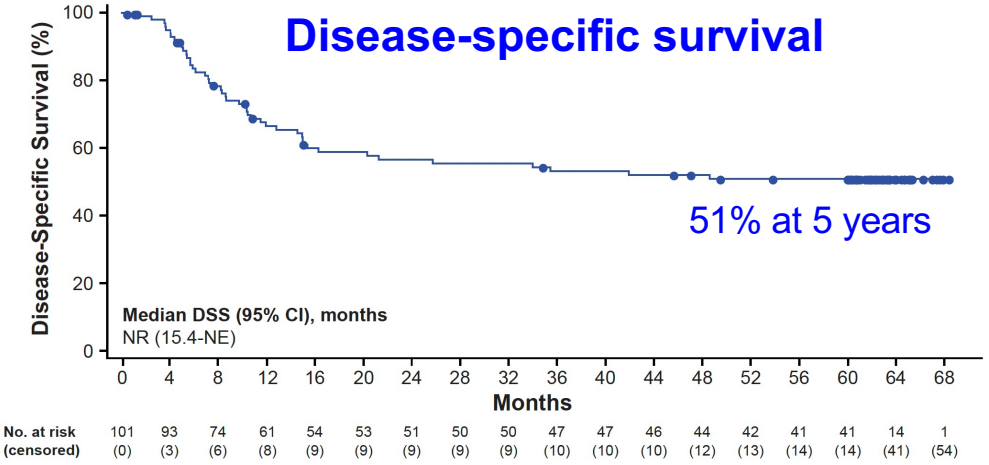
Overall survival



Time to Progression



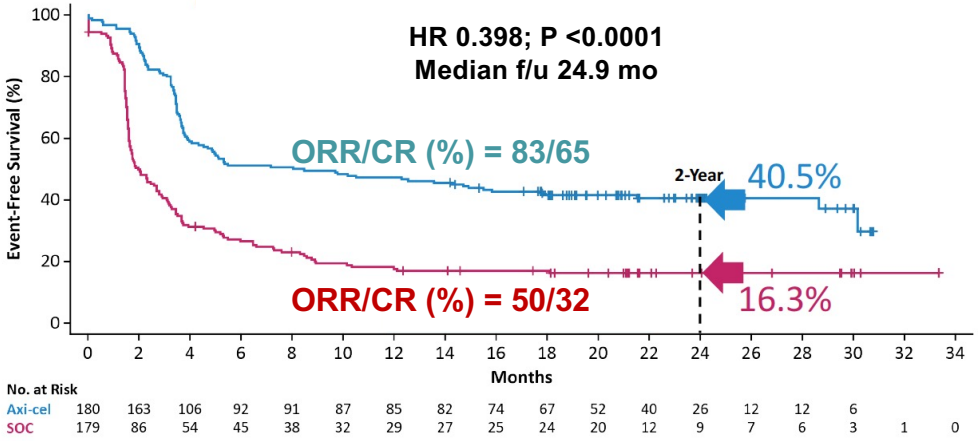
Disease-specific survival



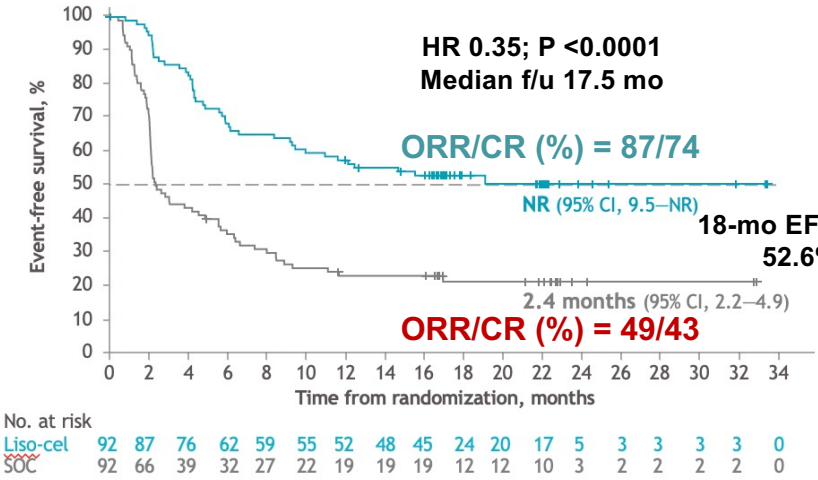
Neelapu et al. *Blood,* 2023 May 11;141(19):2307-2315

CD19 CAR T vs. SOC in 2nd line LBCL: EFS

ZUMA-7 / Axi-cel



TRANSFORM / Liso-cel



March 21, 2023 Kite Press Release:
Significant improvement in overall survival with axi-cel vs. SOC

Locke FL et al. *N Eng J Med.* 2022;386:640-654.
Locke FL et al. *Blood.* 2021;138(suppl 1):2.
Kamdar M et al. *Lancet.* 2022;399(10343):2294-2308.
Abramson et al. 2022 ASH Annual Meeting. Abstract 655.

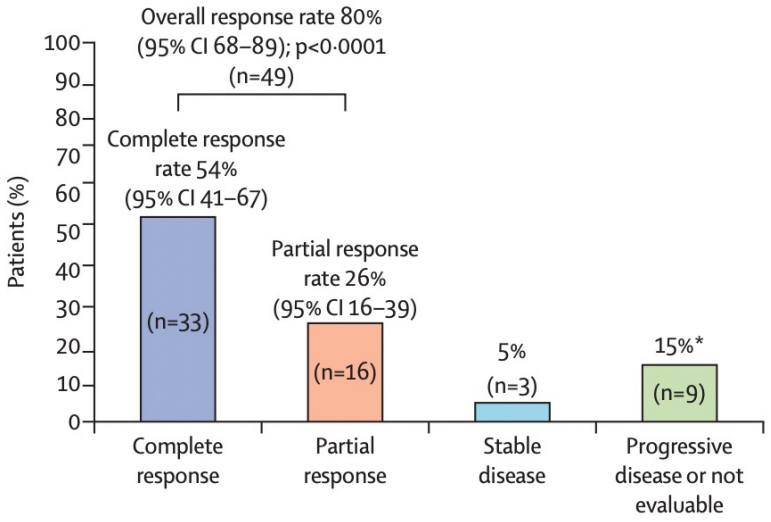
FDA Approval

Axi-cel and liso-cel for adult patients with LBCL that is refractory to 1st line chemoimmunotherapy or relapses within 12 mos of 1st line chemoimmunotherapy

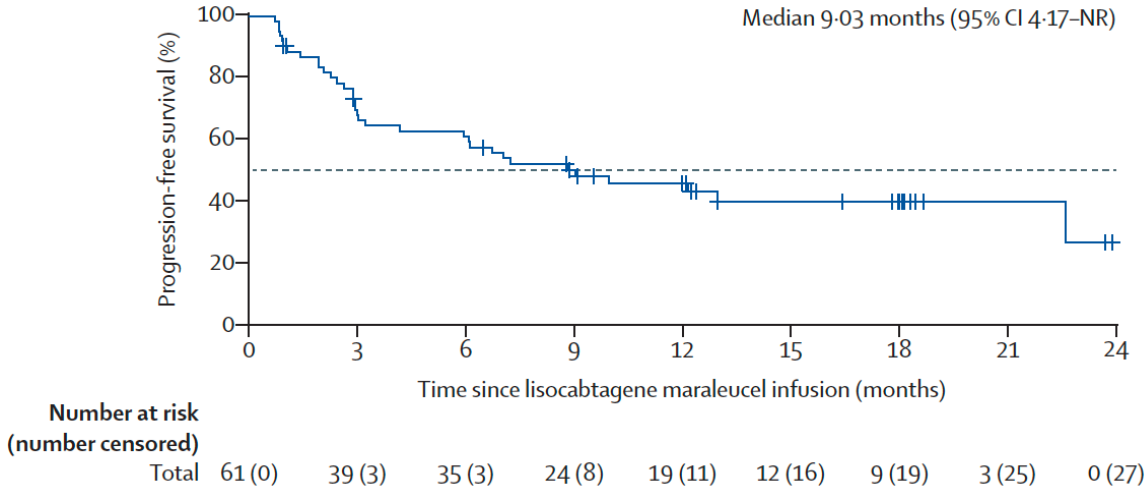
Liso-cel in 2nd line LBCL patients ineligible for HSCT: PILOT study

Phase 2 single-arm multicenter study
N = 61

Response rates



Progression-free survival



Sehgal A, et al. Lancet Oncol. 2022;23:1066-1077.

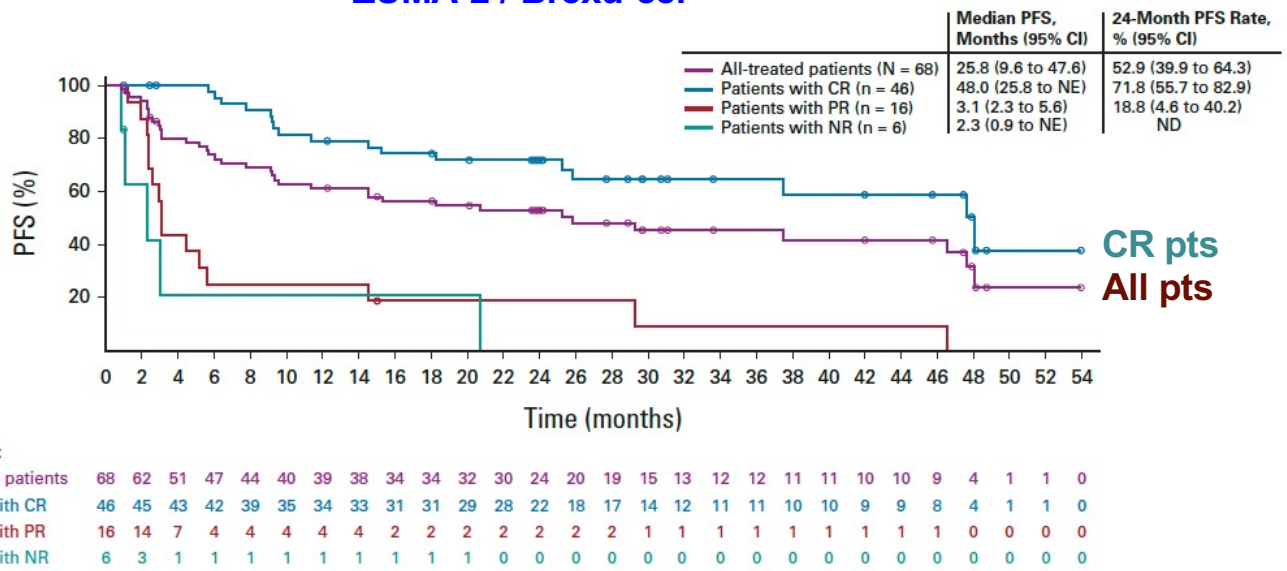
FDA Approval

Liso-cel for adult patients with r/r LBCL after 1st line chemoimmunotherapy who are ineligible for HSCT

ZUMA-2: Efficacy with brexu-cel in ≥2nd line MCL

N = 68
ORR = 91%
CR = 68%

ZUMA-2 / Brexu-cel



- Median follow-up = 35.6 mo
- Median DOR = 28.2 mo; Median PFS = 25.8 mo; Median OS = 46.6 mo
- At data cut-off, 37% of all efficacy-evaluable patients remain in response (all CRs)
- Three relapses beyond month 24

FDA Approval

Brexu-cel for adult patients with r/r MCL

Wang et al, *N Eng J Med*, 2020
Wang et al. *J Clin Oncol 2022 & ASCO 2022*

ZUMA-2 vs. SCHOLAR-2 comparison of outcomes in R/R MCL after prior BTKi Treatment

ZUMA-2 (brexu-cel)

Number of prior LOT

- 2: (18%); 3: (44%); 4: (37%)

mDuration of BTKi therapy: 6.5 mo

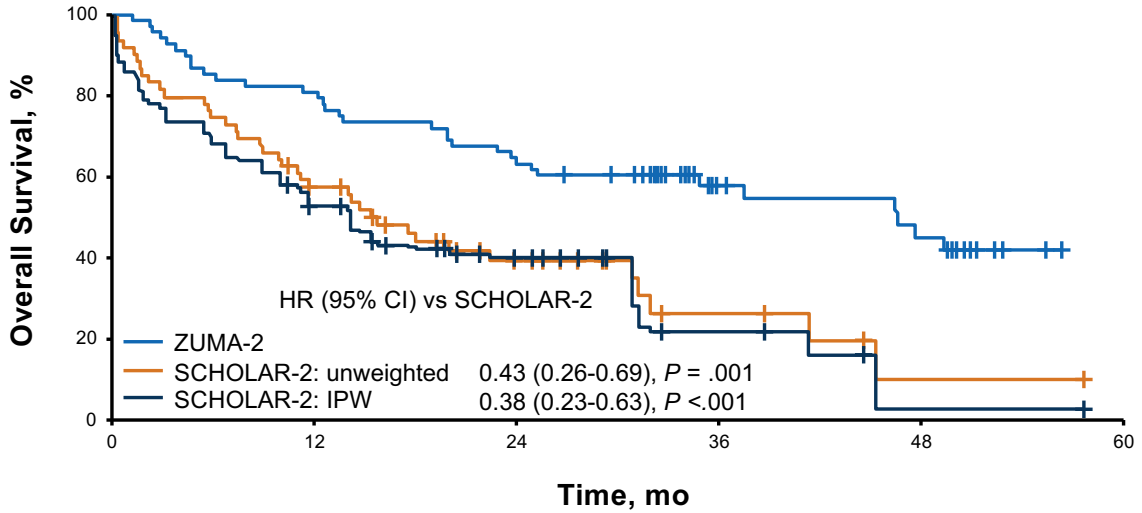
SCHOLAR (SOC)

Number of prior LOT

- 2: (36%); 3: (32%); 4: (27%)

mDuration of BTKi therapy: 7.3 mo

Results from ZUMA-2 suggest improved OS with brexu-cel versus SOC in patient with R/R MCL post-BTKi

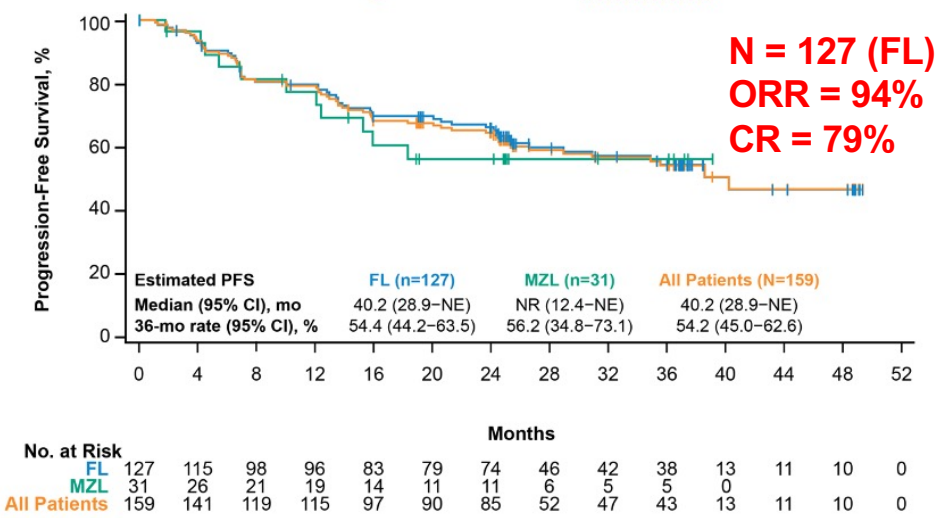


No. at Risk (Number Censored)						
ZUMA-2	66 (0)	55 (0)	43 (0)	19 (21)	14 (22)	0 (35)
SCHOLAR-2: unweighted	59 (0)	32 (0)	15 (10)	6 (17)	1 (19)	0 (20)
SCHOLAR-2: IPW	59 (0)	30 (1)	15 (9)	4 (16)	0 (18)	0 (19)

1. Hess G. et al. ASH 2022. Abstract 4627.

CD19 CAR-T in ≥3rd line iNHL: PFS

ZUMA-5 / Axi-cel

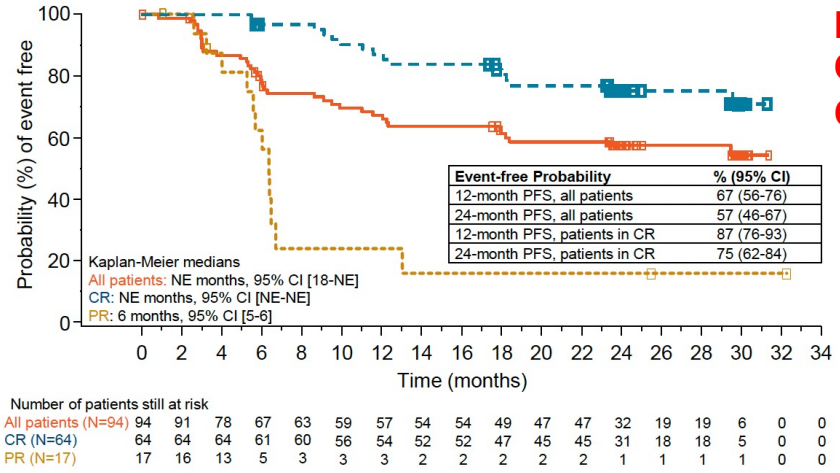


N = 127 (FL)
ORR = 94%
CR = 79%

- Median follow-up of 40.5 months
  - 24-month PFS rate for FL was 63%
  - 36-mo PFS rate for FL was 54%

Neelapu et al. ASH 2022; Abstract 4660
Jacobson et al, *Lancet Oncol*, 2022

ELARA / Tisa-cel



N = 97 (FL)
ORR = 86%
CR = 69%

- Median follow-up of 29 months
  - 24-month PFS rate for FL was 57%

Dreyling et al, *ASH*, 2022

FDA Approval

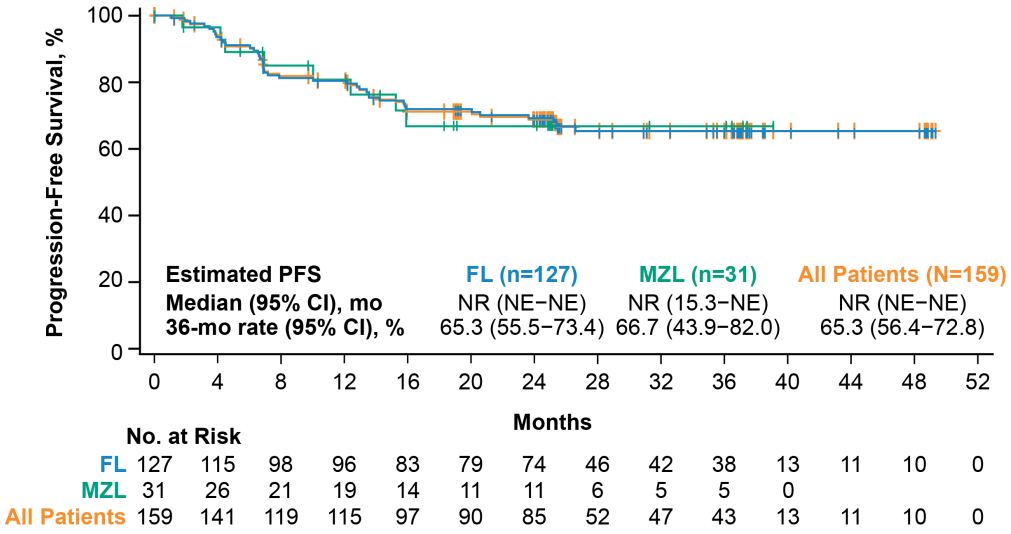
Axi-cel for adult patients with r/r FL after 2 or more lines of systemic therapy

FDA Approval

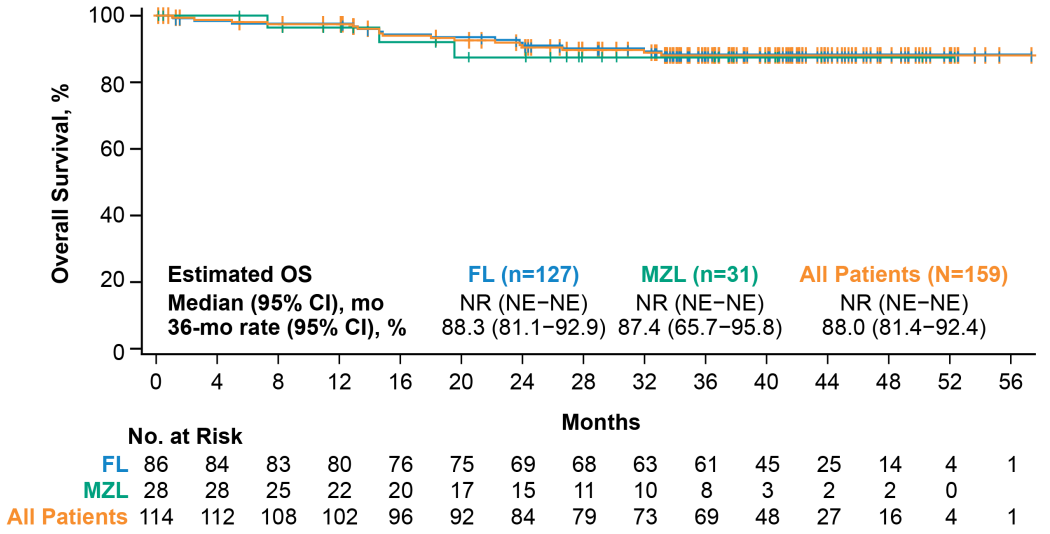
Tisa-cel for adult patients with r/r FL after 2 or more lines of systemic therapy

ZUMA-5: Lymphoma-specific PFS and Lymphoma-specific survival

Lymphoma-specific PFS



Lymphoma-specific survival



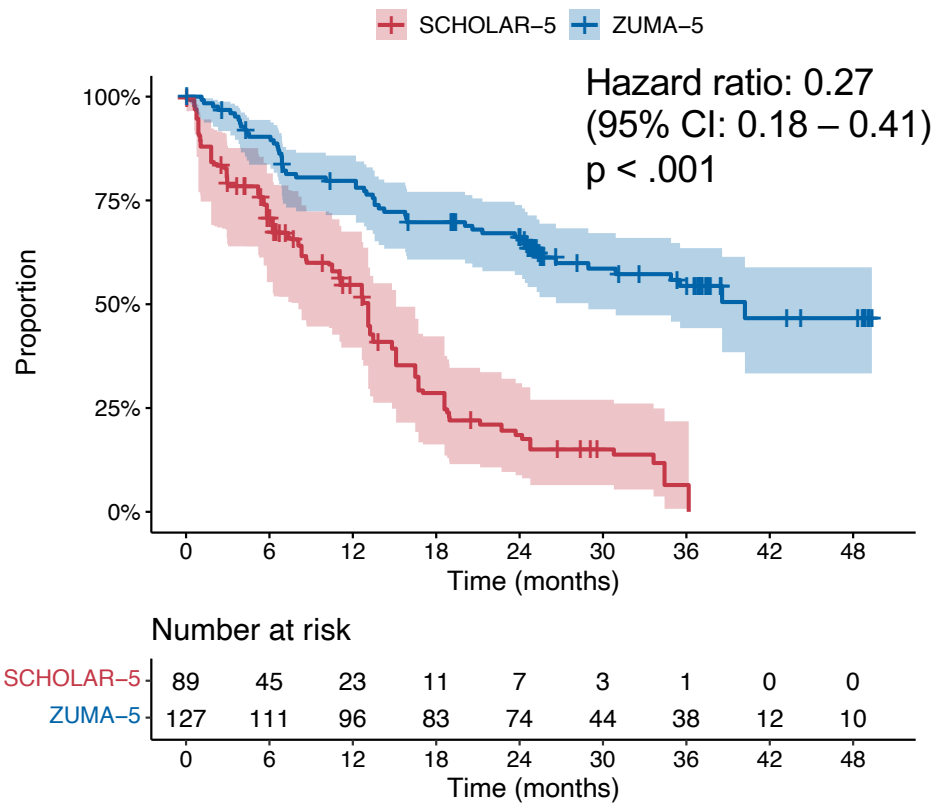
- Medians for lymphoma-specific survival endpoints were not yet reached
  - No PD events after month 24

Neelapu et al. ASH 2022; Abstract 4660

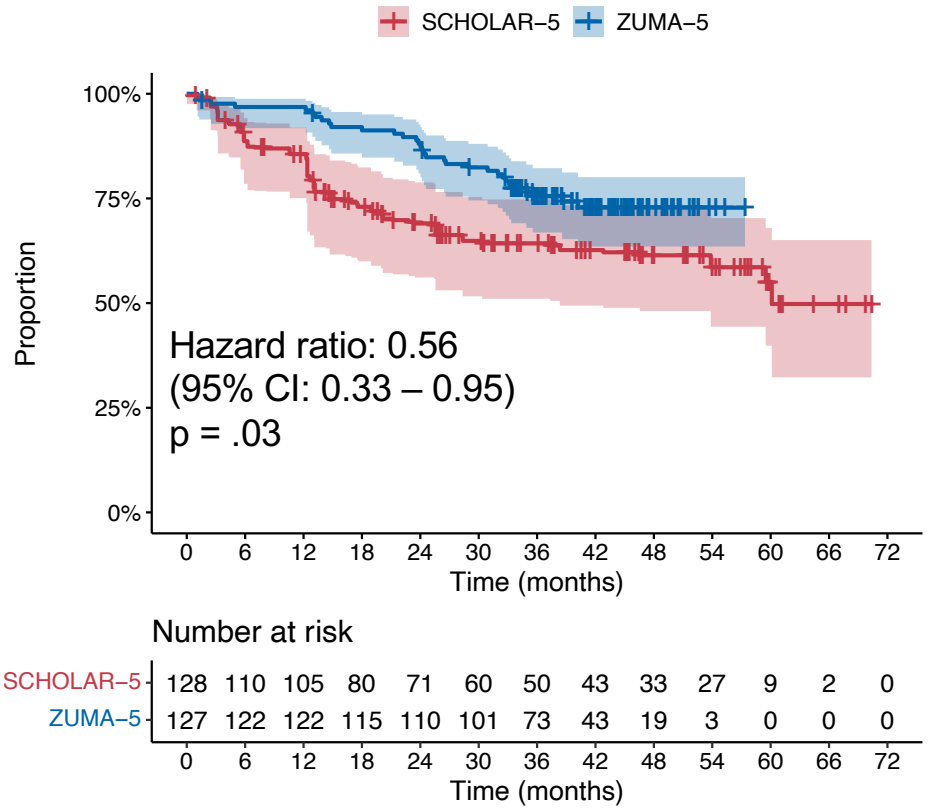
[a] Death related to lymphoma-specific reasons including complications of underlying lymphoma, axi-cel or lymphodepleting chemotherapy were per investigator assessment.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; FL, follicular lymphoma; mo, month; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached, OS, overall survival; PFS, progression-free survival; PML, progressive multifocal leukoencephalopathy.

ZUMA-5 vs. SCHOLAR-5 comparison of outcomes in R/R FL after ≥2 lines of therapy

Progression-free survival



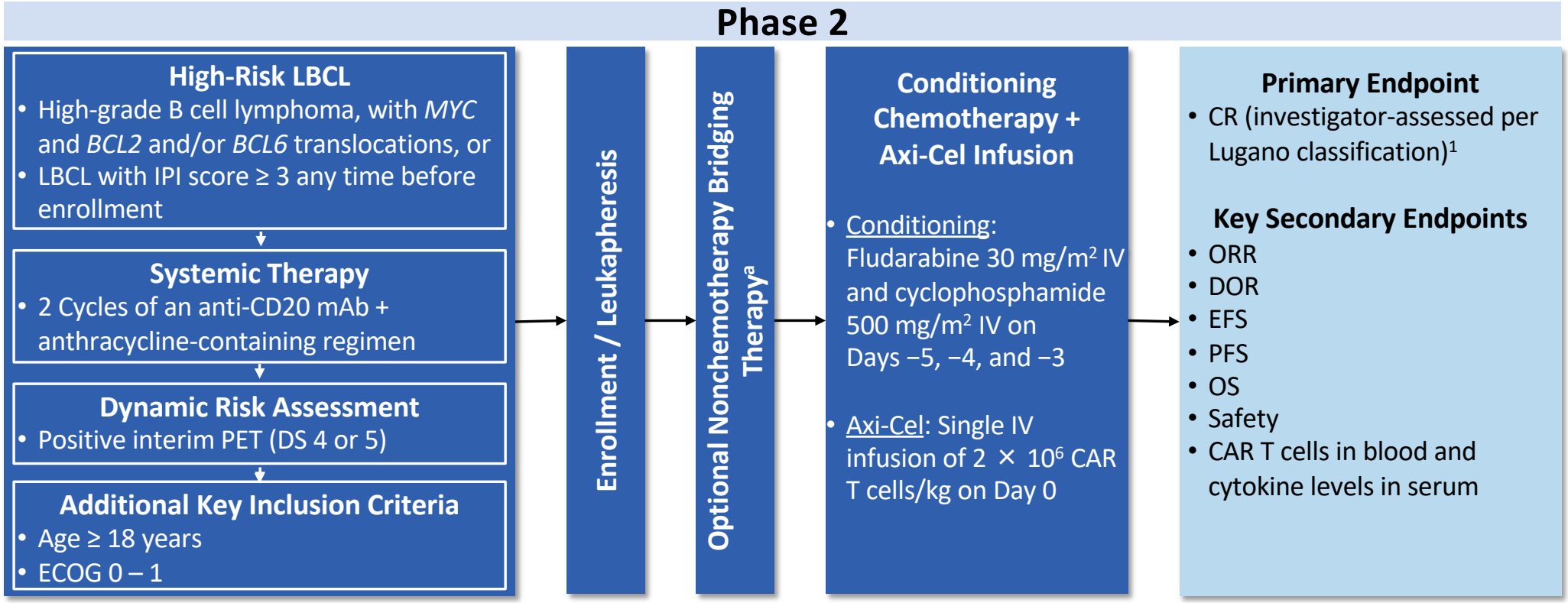
Overall survival



Ghione P. et al. ASH 2022. Abstract 2038

Where do we go from here?

ZUMA-12: Multicenter phase 2 study of axi-cel as part of first-line therapy in patients with high-risk LBCL



Neelapu SS et al. 2021 ASH Annual Meeting. Abstract 739.
Neelapu SS et al. *Nat Med.* 2022;28(4):735-742.

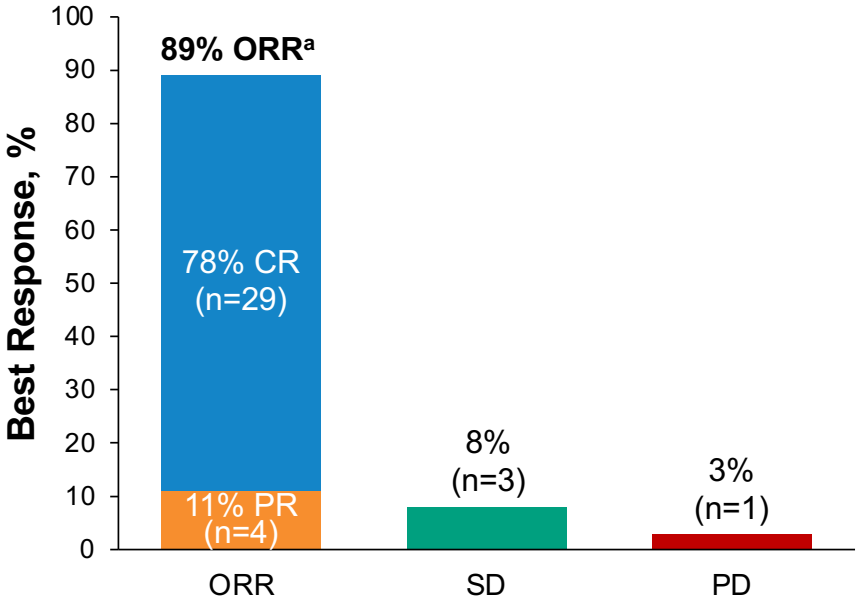
ZUMA-12: Baseline characteristics

Characteristic	All Treated (N=40)
Median age (range), years	61 (23–86)
≥65 years, n (%)	15 (38)
Male, n (%)	27 (68)
Disease stage III/IV, n (%)	38 (95)
ECOG 1, n (%)	25 (63)
1 Prior line of systemic therapy (2 cycles), n (%)	40 (100)
Best response of PR/SD to prior therapy	23 (58)
Best response of PD to prior therapy	16 (40)
Double- or triple-hit as determined by FISH per investigator, n (%)	16 (40)
Double- or triple-hit as determined by FISH per central laboratory, n (%)	10 (25)
IPI score ≥3, n (%)	31 (78)
Deauville score 4, n (%)	19 (48)
Deauville score 5, n (%)	21 (53)

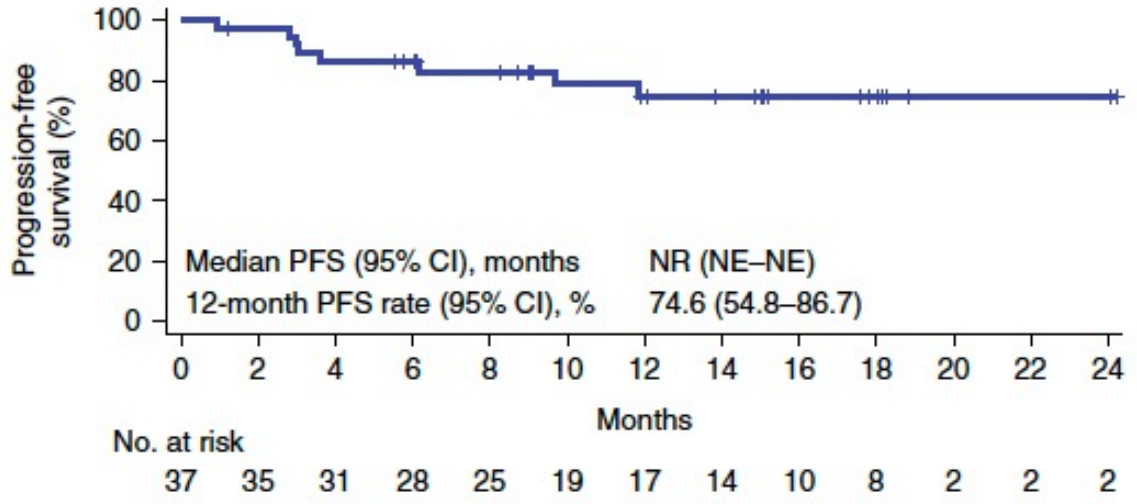
Neelapu SS et al. 2021 ASH Annual Meeting. Abstract 739.
Neelapu SS et al. *Nat Med.* 2022;28(4):735-742.

ZUMA-12 primary analysis: Efficacy

Response rates



Progression-free survival



- Among all treated patients (N=40), ORR was 90% (95% CI, 76–97); CR rate was 80% (95% CI, 64–91)
- After median follow-up of 15.9 mo, 73% of patients in ongoing response

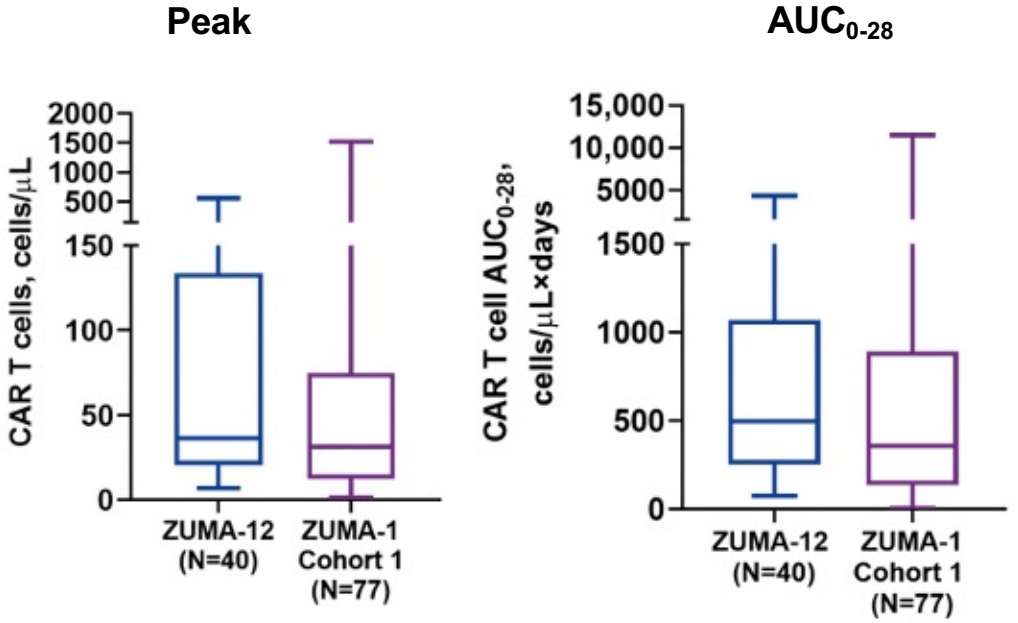
Neelapu SS et al. 2021 ASH Annual Meeting. Abstract 739.
Neelapu SS et al. *Nat Med.* 2022;28(4):735-742.

ZUMA-12: CAR T-cell expansion was greater in ZUMA-12 (1st line LBCL) vs. ZUMA-1 study (r/r LBCL)

Higher frequency of CCR7+CD45RA+ T cells in ZUMA-12 vs. ZUMA-1 CAR-T products

Parameter Median (Range)	ZUMA-12 (N = 40)	ZUMA-1 (N = 77)
Total no. of CAR T cells infused × 10^6, n	165 (95 – 200)	160 (96 – 200)
Total no. of CCR7+CD45RA+ T cells infused × 10^6, n	105 (33 – 254)	40 (2 – 215)
CCR7+CD45RA+ T cells, %	35 (7 – 80)	14 (1 – 76)

CAR T-cell expansion in ZUMA-12 vs. ZUMA-1

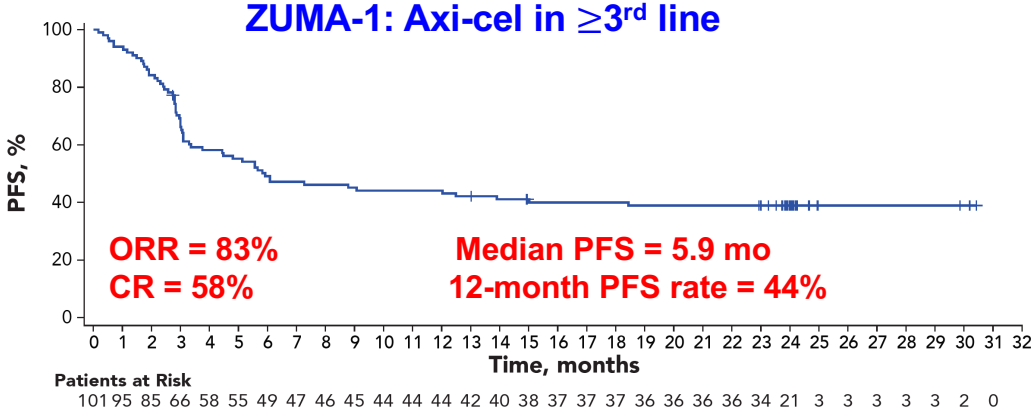


- Suggests T-cell fitness may be better in earlier lines of therapy
- ZUMA-23: Phase 3 randomized study in 1L high-risk LBCL launched

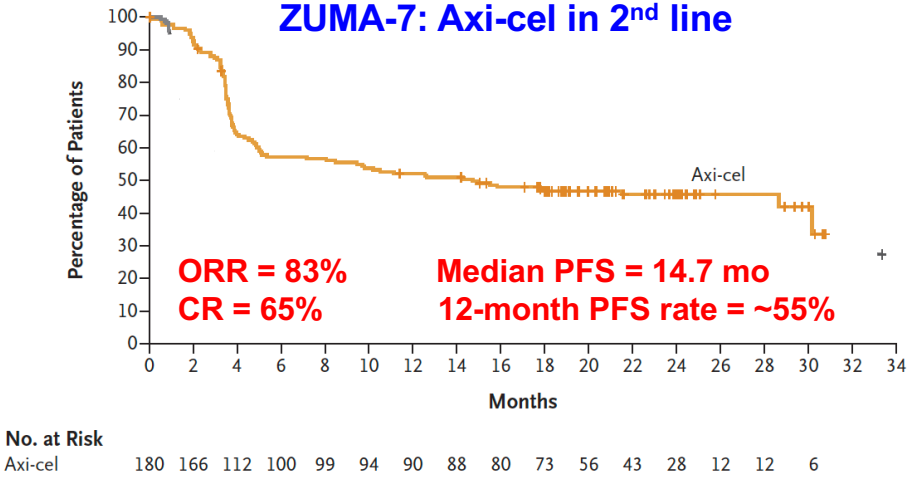
Neelapu SS et al. 2021 ASH Annual Meeting. Abstract 739.
Neelapu SS et al. *Nat Med.* 2022;28(4):735-742.

Axi-cel in LBCL: 3rd line vs. 2nd line vs. 1st line

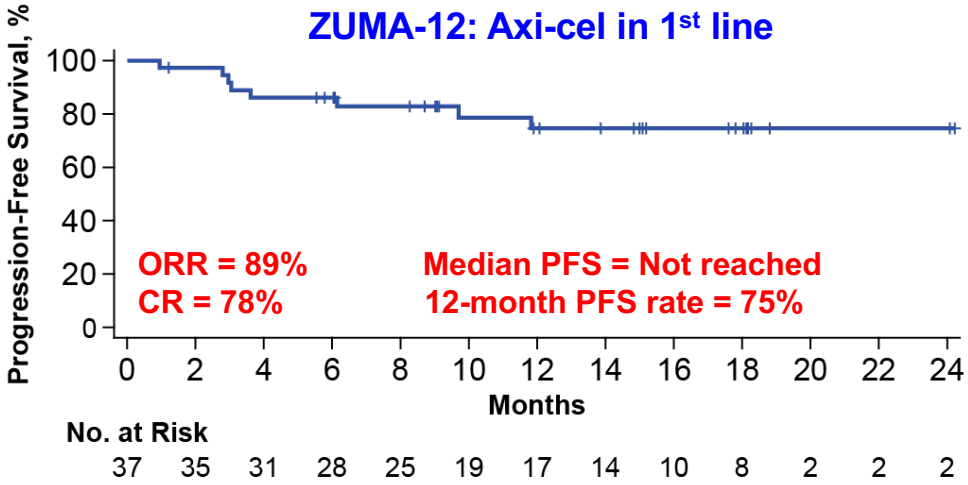
ZUMA-1: Axi-cel in ≥3rd line



ZUMA-7: Axi-cel in 2nd line



ZUMA-12: Axi-cel in 1st line



Neelapu et al, *N Eng J Med* 2017
Locke et al, *Lancet Oncol* 2019
Locke et al, *N Eng J Med* 2021
Neelapu et al, *Nat Med* 2022

CD19 CAR-T in r/r primary and secondary CNS lymphoma

Pilot study with axi-cel

- R/R PCNSL or SCNSL after 1 prior CNS-directed systemic therapy
- Cohort 1 = 9 pts with CNS only disease
- Cohort 2 = 9 pts with CNS and systemic disease
- Endpoints: Safety and efficacy

Interim analysis

- 9 leukapheresed
- 9 infused
- 6 PCNSL; 3 SCNSL
- 9 had parenchymal lesions; 2 CSF
- Bridging therapy was not allowed
- Stable steroid doses were allowed but tapered dexamethasone 2 mg by day 0

Safety and Efficacy

- CRS Gr 1-2 vs. ≥3 = 89% vs. 0%
- ICANS Gr 1-2/ vs. 3 = 44% vs.33% (No gr 4 ICANS)
- ORR = 78%
- CR rate = 67%
- Axi-cel PK profile was similar to ZUMA-1
- Longer f/u is needed to assess durability
- Enrollment is ongoing

Jacobson CA et al. 2022 ASH Annual Meeting. Abstract 440.

Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial

Matthew J. Frigault,[1,2,*] Jorg Dietrich,[3,*] Kathleen Gallagher,[2] Mark Roschewski,[4] Justin T. Jordan,[3] Deborah Forst,[3] Scott R. Plotkin,[3] Daniella Cook,[1,2] Keagan S. Casey,[1,2] Kevin A. Lindell,[1,2] Gabriel D. Depinho,[1,2] Katelin Katsis,[2] Eva Lynn Elder,[2] Mark B. Leick,[1,2] Bryan Choi,[2,5] Nora Horick,[2] Frederic Preffer,[6] Meredith Saylor,[1] Steven McAfee,[1] Paul V. O'Donnell,[1] Thomas R. Spitzer,[1] Bimalangshu Dey,[1] Zachariah DeFilipp,[1] Areej El-Jawahri,[1] Tracy T. Batchelor,[7] Marcela V. Maus,[1,2,*] and Yi-Bin Chen[1,*]

Blood. 2022 Apr 14;139(15):2306-2315.

Limitations of autologous CD19 CAR T-cell therapy in LBCL

- Access
- Cost
- Manufacturing failure
- Wait time

~200 do not receive CAR-T

Relapsed/refractory LBCL (N = hypothetical 300 pts)

~100 receive SOC anti-CD19 CAR T

~40 durable response

~60 relapse after anti-CD19 CAR T

1/3

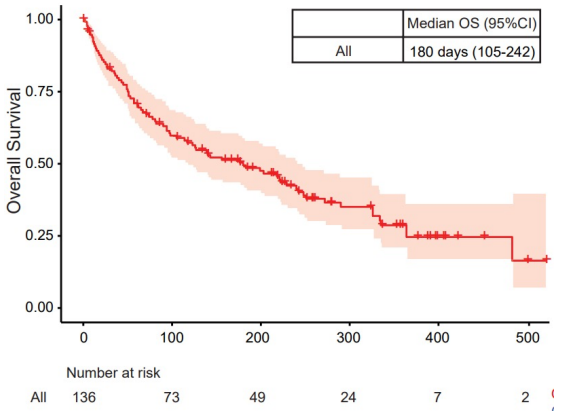
2/3

CD19 negative relapse

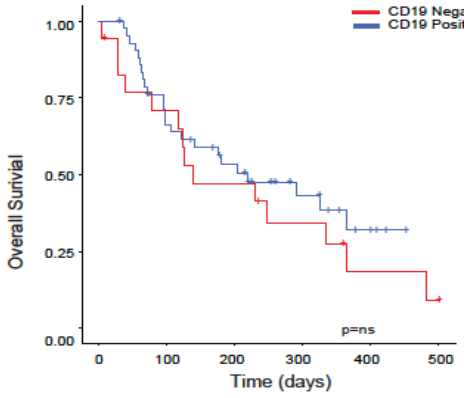
CD19 positive relapse

- Impaired T-cell fitness
- Tumor intrinsic resistance mechanisms

OS after CAR-T failure in LBCL



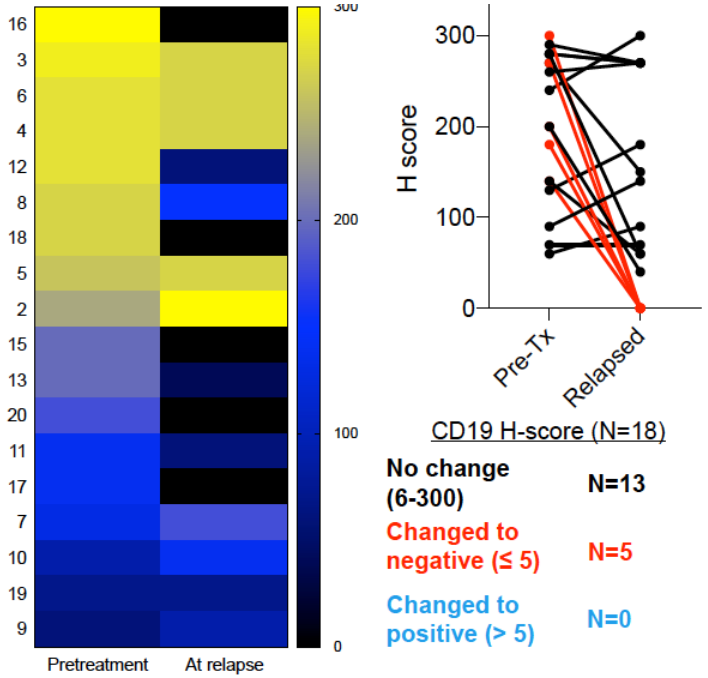
OS CD19+ vs. CD19- relapse after CAR-T failure in LBCL



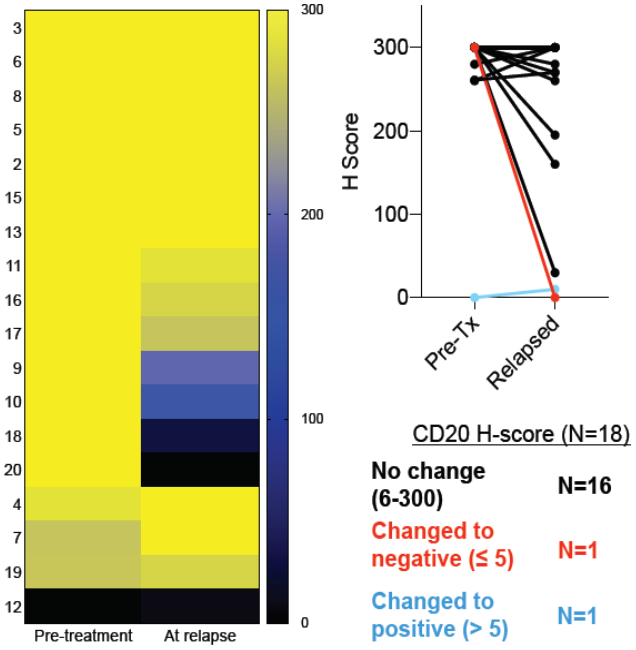
Spiegel et al. Blood. 2021 Apr 1;137(13):1832-1835.

CD19 antigen loss after CD19 CAR-T in r/r LBCL but expression of other B-cell antigens is preserved

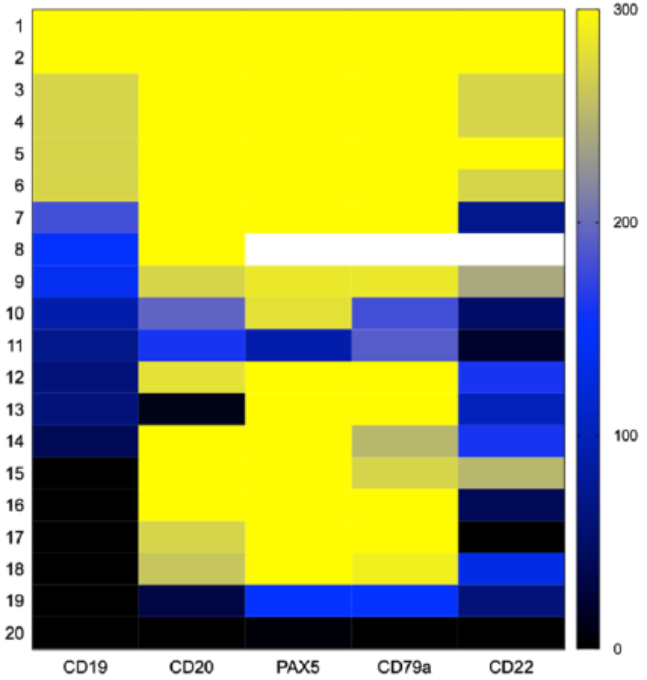
CD19 loss in paired LBCL



CD20 in paired LBCL



Relapsed LBCL after CD19 CAR-T

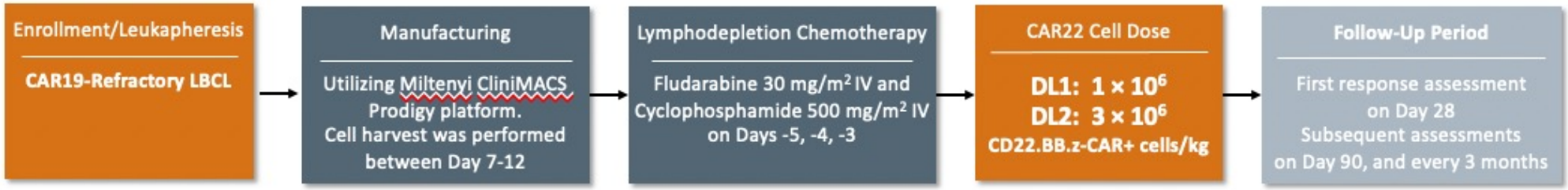


- CD19 loss is due to genomic alterations
- Provides a rationale to target multiple B-cell antigens to minimize antigen escape and improve efficacy

Plaks et al. Blood. 2021 Sep 23;138(12):1081-1085.

CD22 CAR-T: Study design

Phase 1



Primary Endpoints

- Manufacturing feasibility
- RP2D
- Safety and toxicity (*TEAEs*)

Key Secondary Endpoints

- ORR* (*Investigator-assessed*)
- DOR
- PFS
- OS
- CAR-T associated toxicity**
- CD22 antigen expression
- CAR+ cell levels in blood
- Serum cytokine profiling

Median vein to vein time: 18 days

Frank MJ et al. 2023 TCT

CD22 CAR-T: Baseline characteristics

LBCL	DL1 (N = 29)	DL2 (N = 9)	Total (N = 38)
Median age, years [range]	65 [25-84]	68 [36-76]	65 [25-84]
Male sex, n (%)	15 (52%)	6 (67%)	21 (55%)
ECOG PS ≤ 1, n (%)	29 (100%)	9 (100%)	38 (100%)
Disease classification, n (%)			
DLBCL	21 (73%)	7 (78%)	28 (74%)
TFL	6 (20%)	2 (22%)	8 (21%)
PMBCL	1 (3%)	0 (0%)	1 (3%)
Follicular 3B	1 (3%)	0 (0%)	1 (3%)
Double-hit status	6 (21%)	0 (0%)	6 (18%)
non-GCB cell of origin status	11 (38%)	4 (44%)	15 (39%)
Pre-LD chemo LDH > ULN, n (%)	22 (76%)	8 (89%)	30 (79%)
Prior therapies, n (%)			
Median number of lines [range]	4 [3-8]	4 [4-7]	4 [3-8]
No prior CR to any line of therapy	8 (28%)	3 (33%)	11 (29%)
Prior autologous HSCT	3 (10%)	4 (44%)	7 (18%)
Prior CAR19 therapy	28 (97%)	9 (100%)	37 (97%)

Frank MJ et al. 2023 TCT

CD22 CAR-T: Safety

Parameter	DLBCL DL1 (N = 29)	DLBCL DL2 (N = 9)	Total N=38
Cytokine Release Syndrome*, n (%)			
None	2 (7%)	0 (0%)	2 (5%)
Grade 1	13 (45%)	1 (11%)	14 (37%)
Grade 2	14 (48%)	7 (78%)	21 (55%)
Grade 3	0 (0%)	1 (11%)	1 (3%)
Neurologic events / ICANS*, n (%)			
Grade 1	2 (7%)	1 (11%)	3 (8%)
Grade 2	1 (3%)	1 (11%)	2 (5%)
carHLH toxicity, n (%)			
Yes	2 (7%)	3 (33%)	5 (18%)

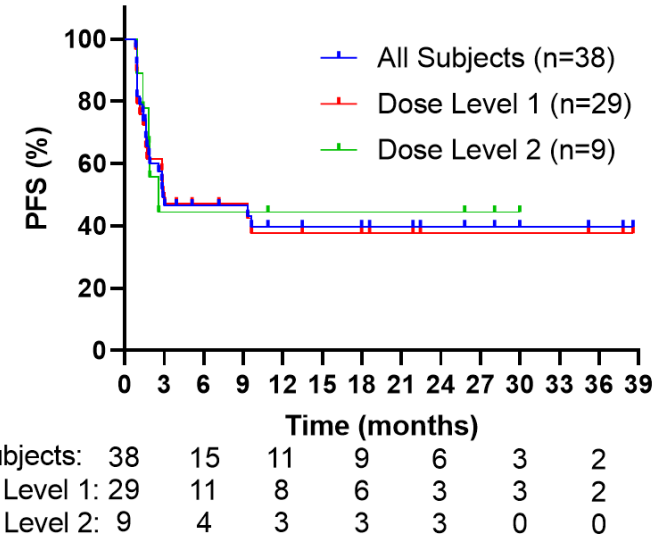
- 1 Grade 5 event from sepsis leading to multi-organ failure at day 40
- 1 patient develop MDS without evidence of LBCL relapse 11 months after CAR22 infusion
- HLH was associated with higher expansion of CAR-22 cells

Frank MJ et al. 2023 TCT

CD22 CAR-T: Efficacy

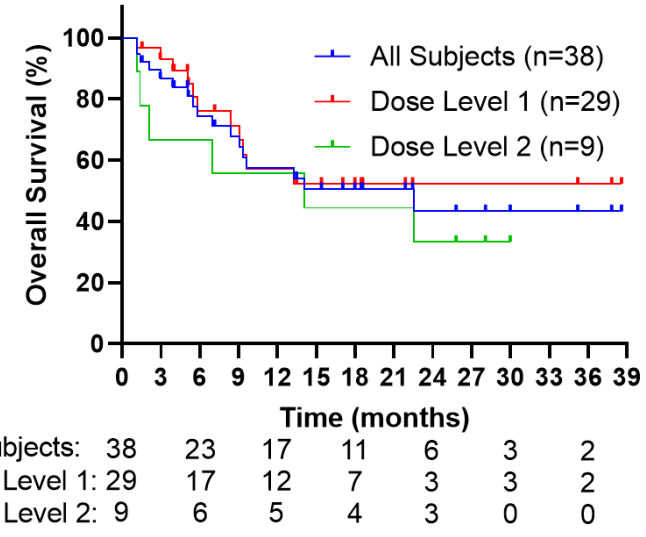
LBCL	DL1 (N = 29)	DL2 (N = 9)	Tot (N = 38)
Median follow up, months [range]	14.1 [1.5-38.6]	27.1 [24.7-33.5]	18.4 [1.5-38.6]
Overall Response Rate (ORR)*, n (%)	19 (66%)	7 (78%)	26 (68%)
CR Rate	15 (52%)	5 (56%)	20 (53%)

PFS



All Subjects:	38	15	11	9	6	3	2
Dose Level 1:	29	11	8	6	3	3	2
Dose Level 2:	9	4	3	3	3	0	0

OS



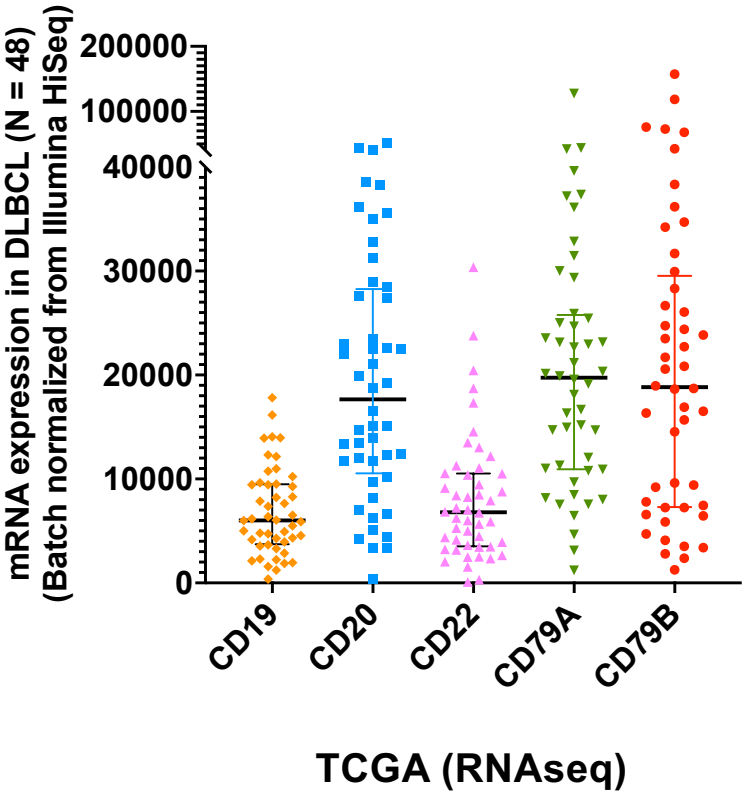
All Subjects:	38	23	17	11	6	3	2
Dose Level 1:	29	17	12	7	3	3	2
Dose Level 2:	9	6	5	4	3	0	0

- Median f/u 18.4 mo
- CRs appear to be durable
  - Only 1 of 20 CR patients has relapsed
- Dose Level 1 is the RP2D
  - 1×10^6 CAR22+ cells/kg
- Phase 2 registration study planned

Frank MJ et al. 2023 TCT

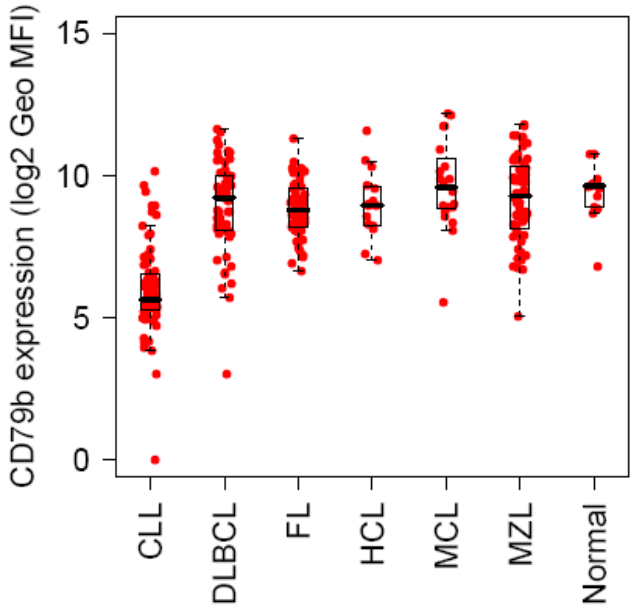
CD79b is a pan-B-cell Ag expressed across most B-cell NHL

LBCL (N = 48)



TCGA (RNAseq)

Lymphoma subtypes

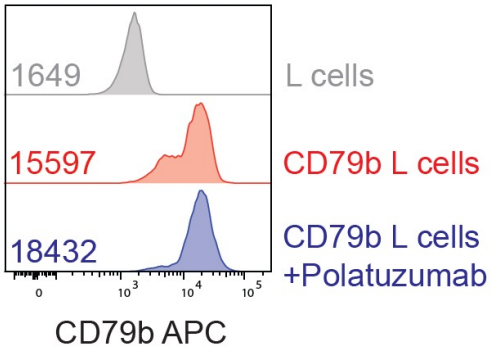


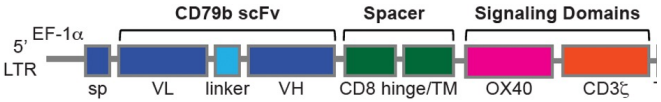
Flow cytometry (protein)

Dornan et al. *Blood* 2009

CD79b CAR-T: Antitumor efficacy in xenograft models

CD79b mAb binding not inhibited by polatuzumab

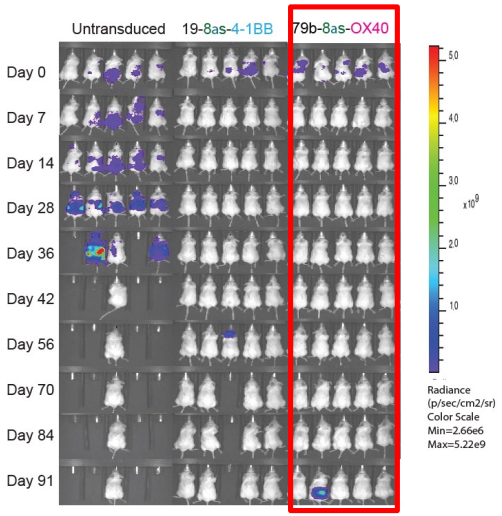


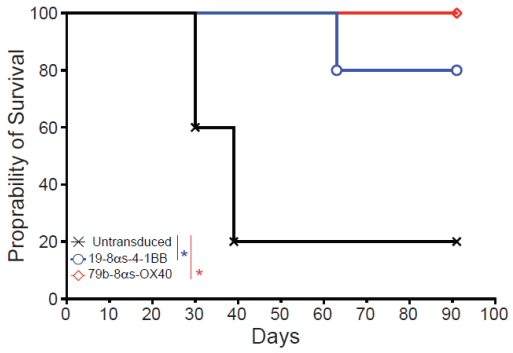


- Phase 1 clinical trial initiated

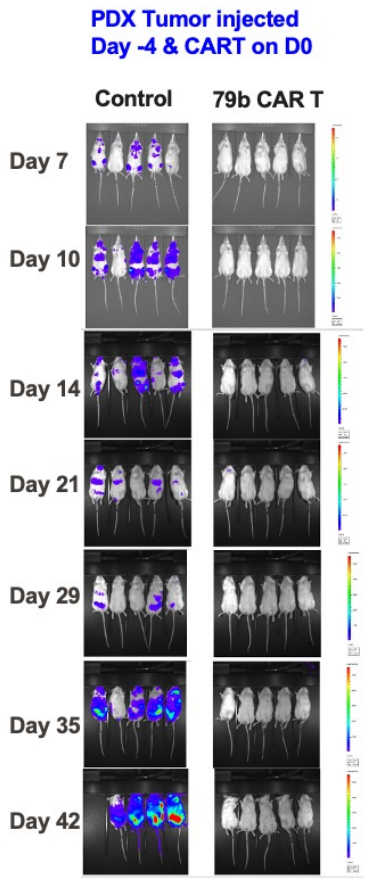
Daudi Burkitt lymphoma

Daudi Tumor injected Day -11 & CART on D0





HGBCL PDX

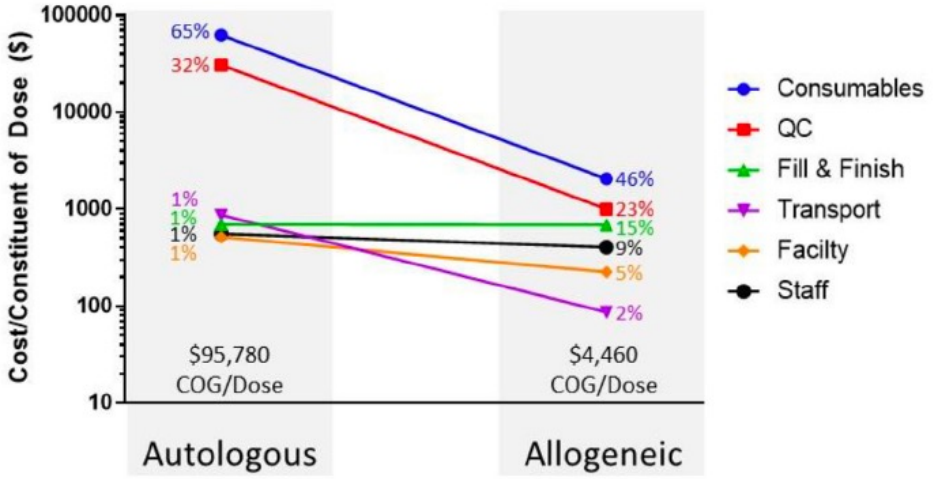


- Similar effects seen in Jeko-1 MCL xenograft model

Rationale for allogeneic CAR T-cell therapy

- Potential to improve efficacy as the T-cell fitness is expected to be better than autologous products
- Consistent product quality
- No wait period as they are off-the-shelf
- Improve access at non-transplant centers
- Potential to lower the cost of CAR T-cell therapy
- Long-term B-cell aplasia and hypogammaglobulinemia less likely
- Long-term risk of insertional mutagenesis less likely

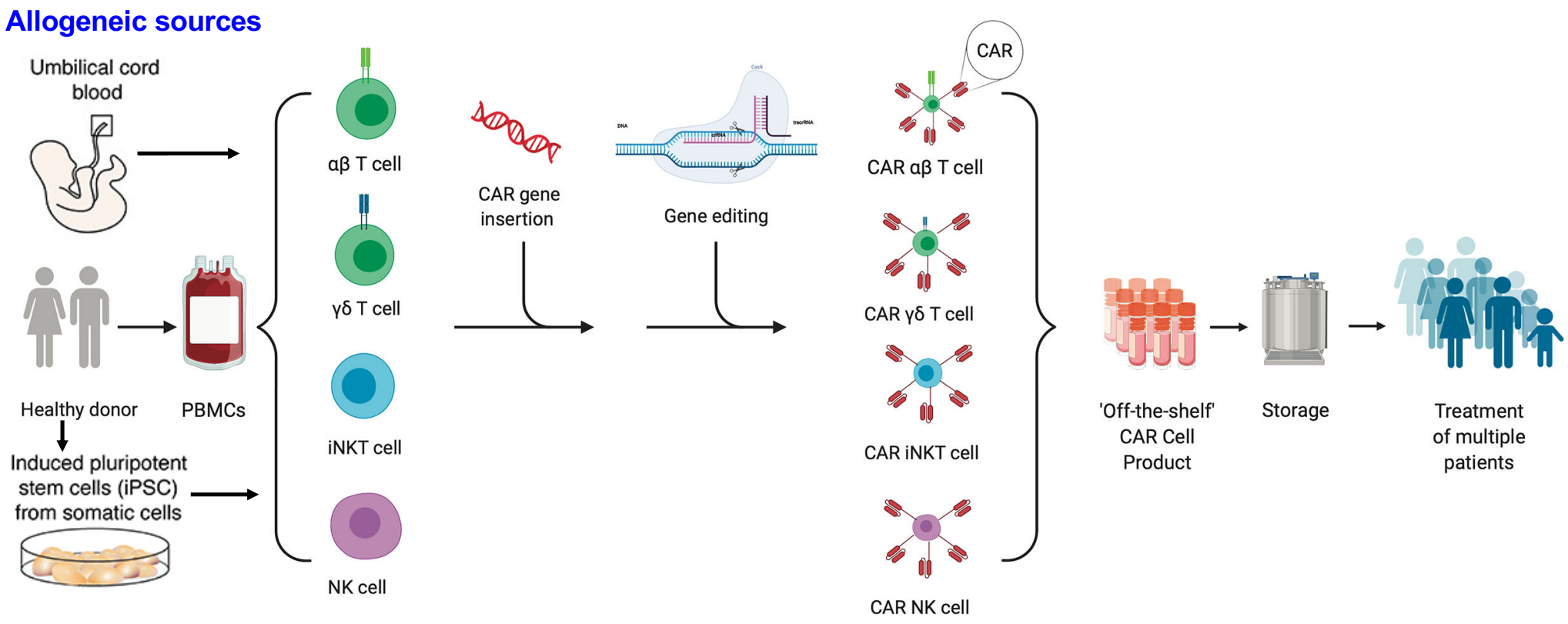
Cost of goods/dose: Auto vs. Allo



~100 doses/manufacturing run

Harrison et al. *Cytotherapy*, 2019; 21:224-233

Allogeneic CAR cell therapy

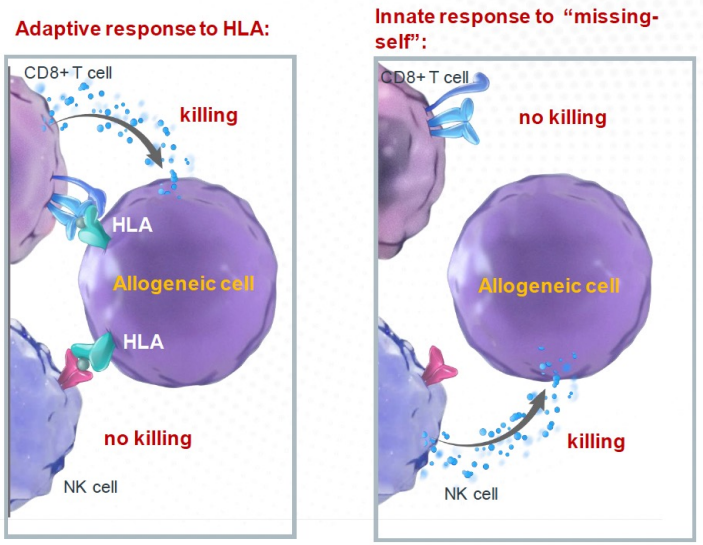


Bedoya DM et al. *Front Immunol.* 2021;12:640082.
Caldwell KJ et al. *Front Immunol.* 2021;11:618427.

Challenges for allogeneic CAR T-cell therapy

- GVHD
  - Mediated by αβ T cells
  - May be overcome by TCR knock-out or by using alternative cell types such as NK cells, NKT, γδ T cells
- Graft rejection
  - Mediated by αβ T cells and NK cells

Graft rejection by T and NK cells



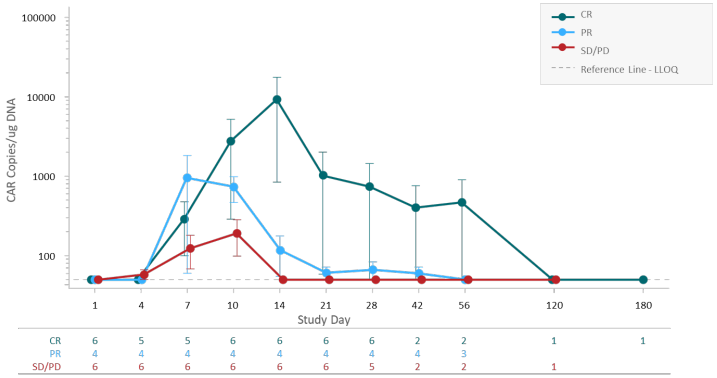
Depil et al. *Nat Rev Drug Discov*, 2020; 19(3) 185-199
Schrepfer et al, 2022 ASH Annual Meeting, Abstract 1690

Allogeneic CAR cell therapy approaches in NHL

Product / Sponsor	Cell type	CAR Target	GVHD prevention	Allorejection strategy	Additional comments
ALLO-501/A Allogene	αβ T cells	CD19	TCR KO (TALEN)	CD52 KO	Anti-CD52 Ab + Standard Cy/Flu
PBCAR0191 Precision Bio	αβ T cells	CD19	TCR KO (ARCUS)	Enhanced Cy/Flu	
CTX110 CRISPR Therapeutics	αβ T cells	CD19	TCR KO (CRISPR)	B2M KO + Standard Cy/Flu	
CAR-NK MDACC	NK cells (Cord blood)	CD19	Cell type	Standard Cy/Flu	IL-15 transgene
FT596 Fate Therapeutics	NK cells (iPSC)	CD19	Cell type	Standard Cy/Flu	Non-cleavable CD16 IL-15 transgene
KUR-502 Athenex	iNKT cells	CD19	Cell type	B2M & CD74 down regulation	IL-15 transgene Standard Cy/Flu
ADI-001 Adicet Bio	γδ T cells	CD20	Cell type	Enhanced Cy/Flu	

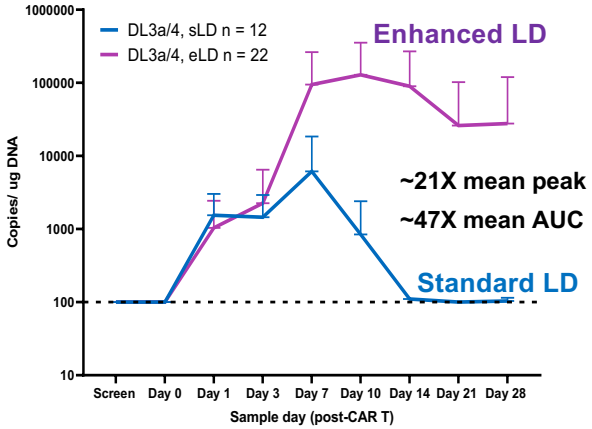
CAR-T expansion and persistence in phase 1 allogeneic CAR-T trials in r/r B-cell lymphomas

ALLO-501 (CD19 αβ CAR)



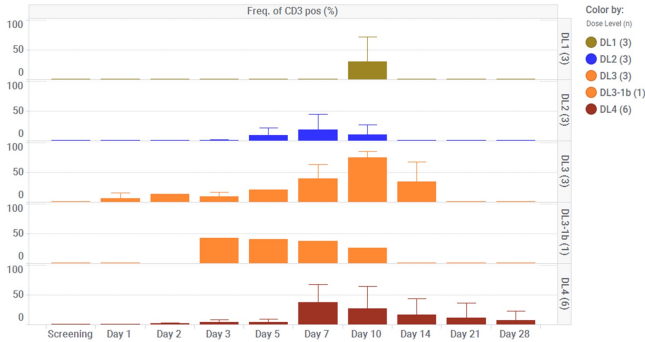
Neelapu et al. 2020 ASCO Annual Meeting, Abstract 8002

PBCAR0191 (CD19 αβ CAR)



Shah et al. 2021 ASH Annual Meeting, Abstract 302

ADI-001 (CD20 γδ CAR)



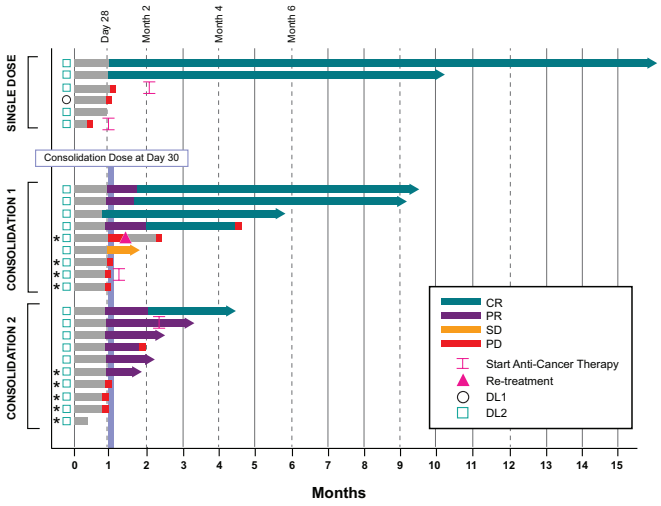
Neelapu et al. 2022 ASH Annual Meeting, Abstract 2018

- No GvHD, Grade ≥3 NE or CRS in any of the trials
- Higher rate of grade ≥3 infections with enhanced LD

Efficacy in phase 1 allogeneic CAR-T trials in r/r LBCL

ALLO-501 (CD19 αβ CAR)

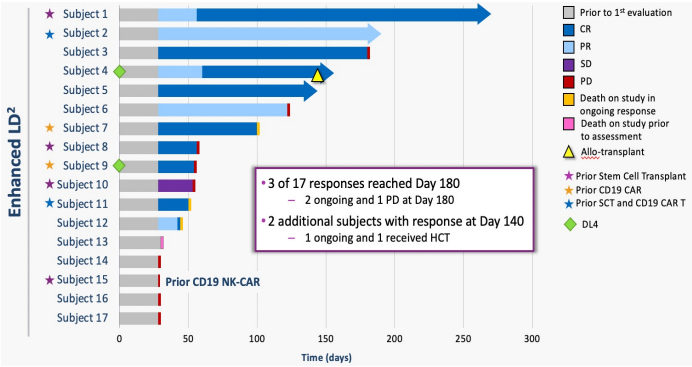
ORR/CR rate % = 48/28



Lekakis et al. 2021 ASH Annual Meeting, Abstract 649

PBCAR0191 (CD19 αβ CAR)

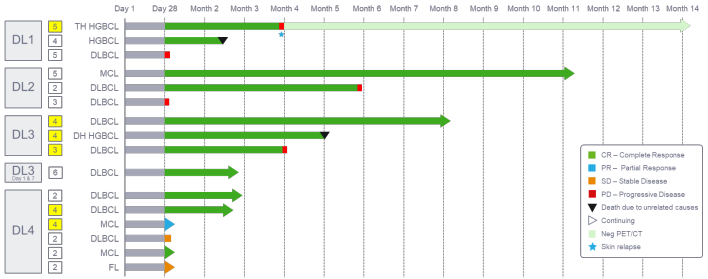
ORR/CR rate % = 69/56



Shah et al. 2021 ASH Annual Meeting, Abstract 302

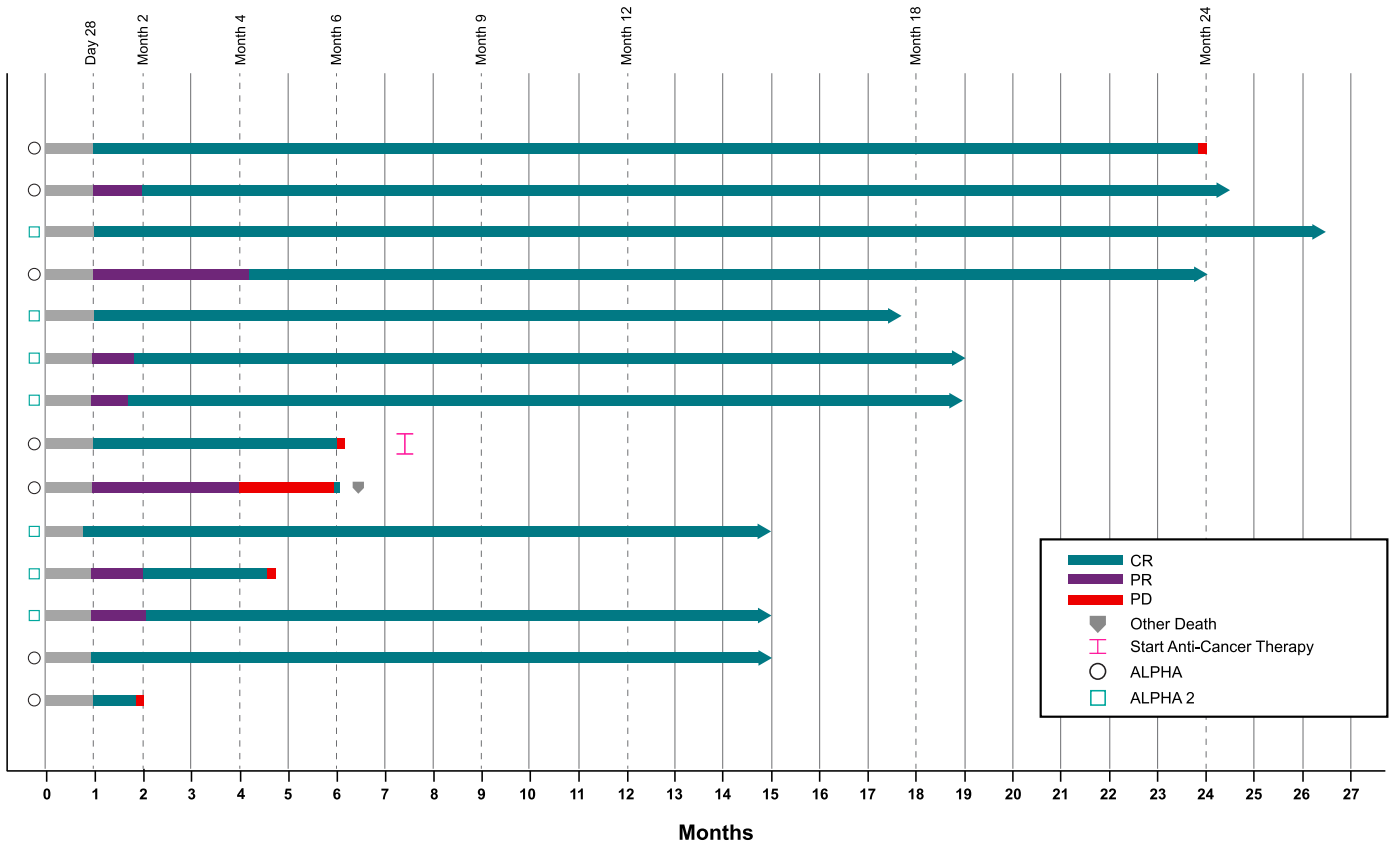
ADI-001 (CD20 γδ CAR)

ORR/CR rate % = 75/69



Neelapu et al. 2022 ASH Annual Meeting, Abstract 2018

Durable remissions after allogeneic CD19 CAR-T in LBCL



Data Cutoff Date: October 25, 2022

ALLO-501/A Phase 1 study:

9 of 14 (64%) patients in ongoing CR despite short persistence of allo-CAR-T

Allogene press release, Dec 2022

Summary

- Autologous CD19 CAR-T products have shown unprecedented efficacy and are approved for r/r LBCL, r/r MCL, and r/r FL and now being tested in 1st line
- Multiple strategies are likely needed to further improve efficacy of CAR T-cell therapy
- CD22 appears to be a promising target for CAR-T therapy in LBCL and future strategies may employ multispecific CARs
- The fitness of the T cells could potentially be improved by altering the manufacturing process or moving CAR T-cell therapy to earlier lines
- Early data suggests that allogeneic CAR cell therapies are safe and response rates in NHL appear to be comparable to autologous CAR T
  - However, follow-up is short and durability of responses is not known
- More effective approaches to prevent immune rejection are likely needed to achieve consistent *in vivo* expansion and persistence of allogeneic CAR products

Thank you for your attention!

Email: sneelapu@mdanderson.org