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ZUMA-12 and beyond

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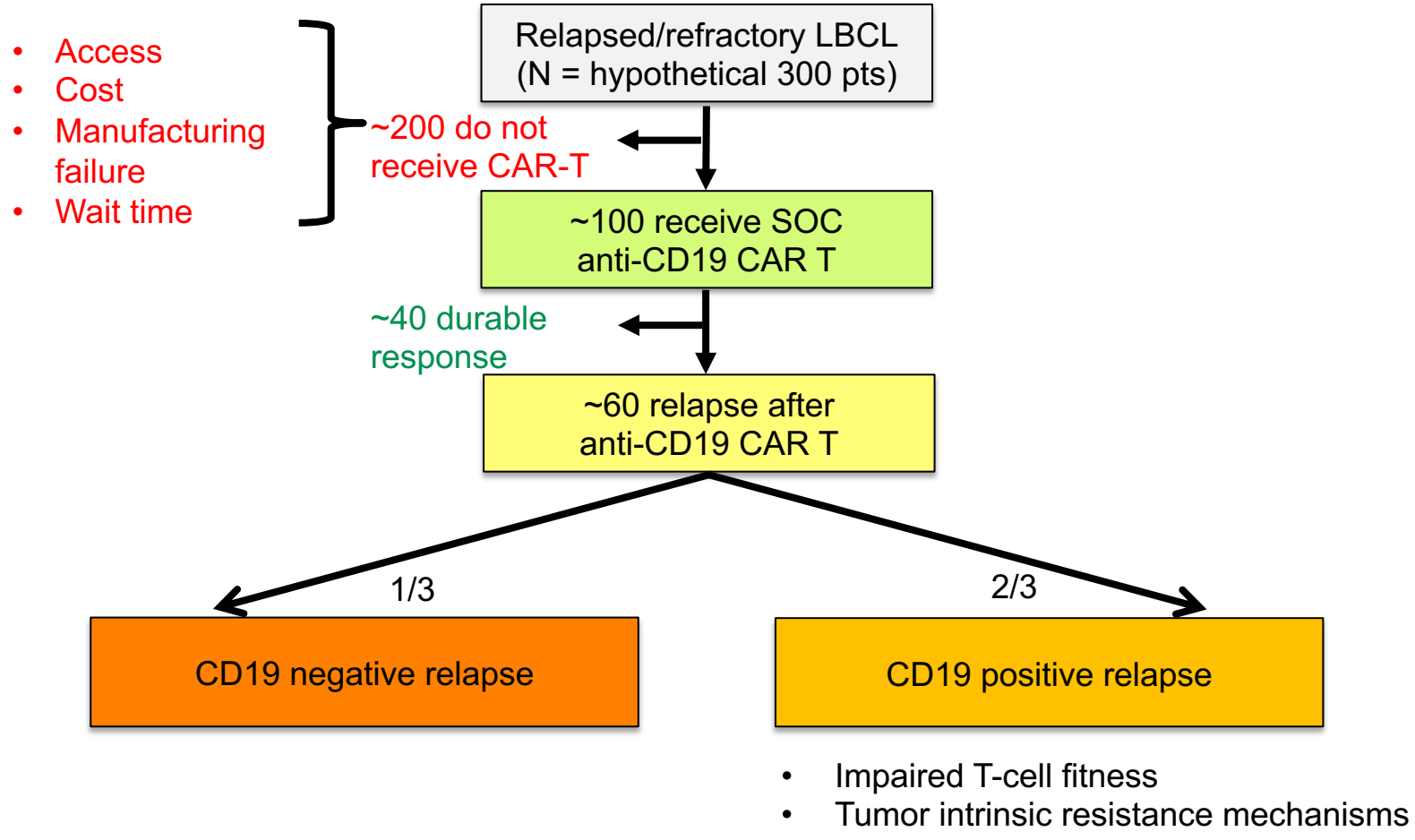
Disclosures

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

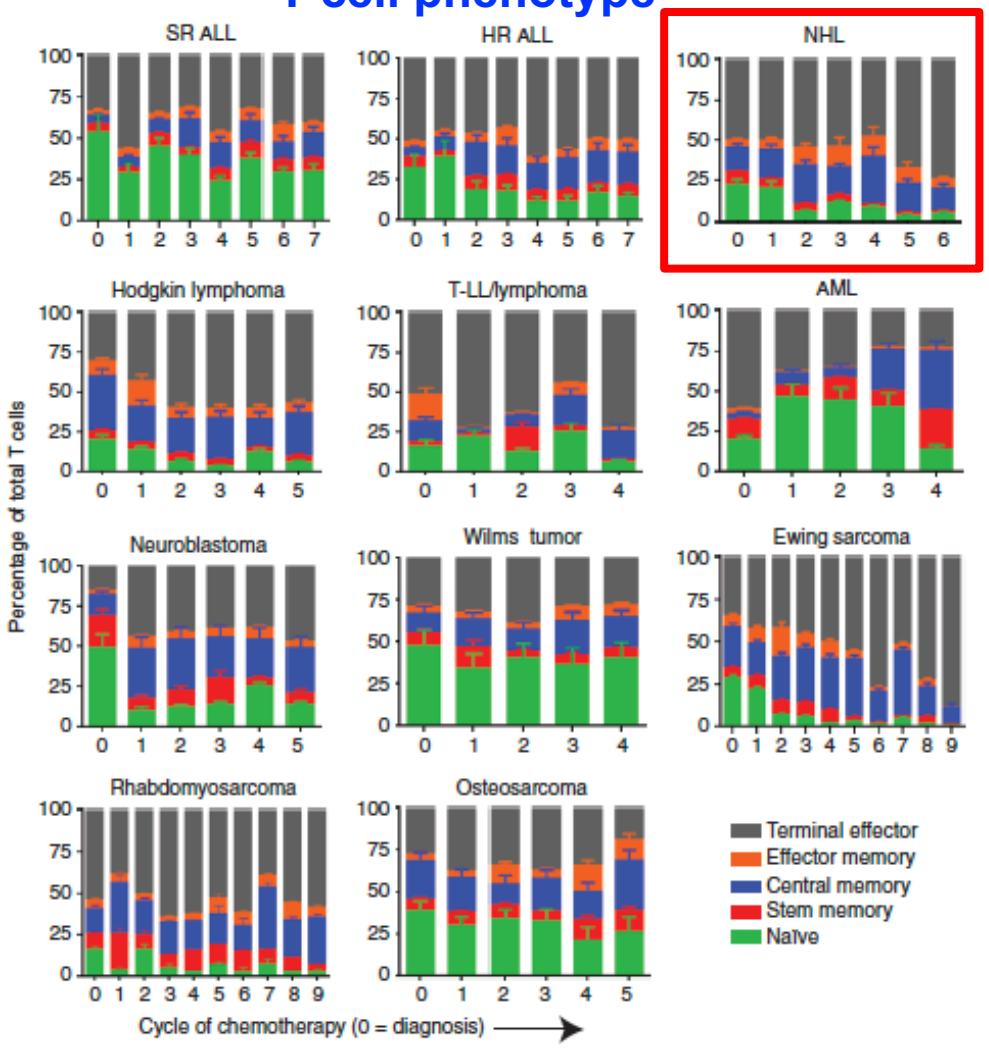
- I will discuss investigational use of CAR T-cell therapy

Limitations of autologous CD19 CAR T-cell therapy in LBCL

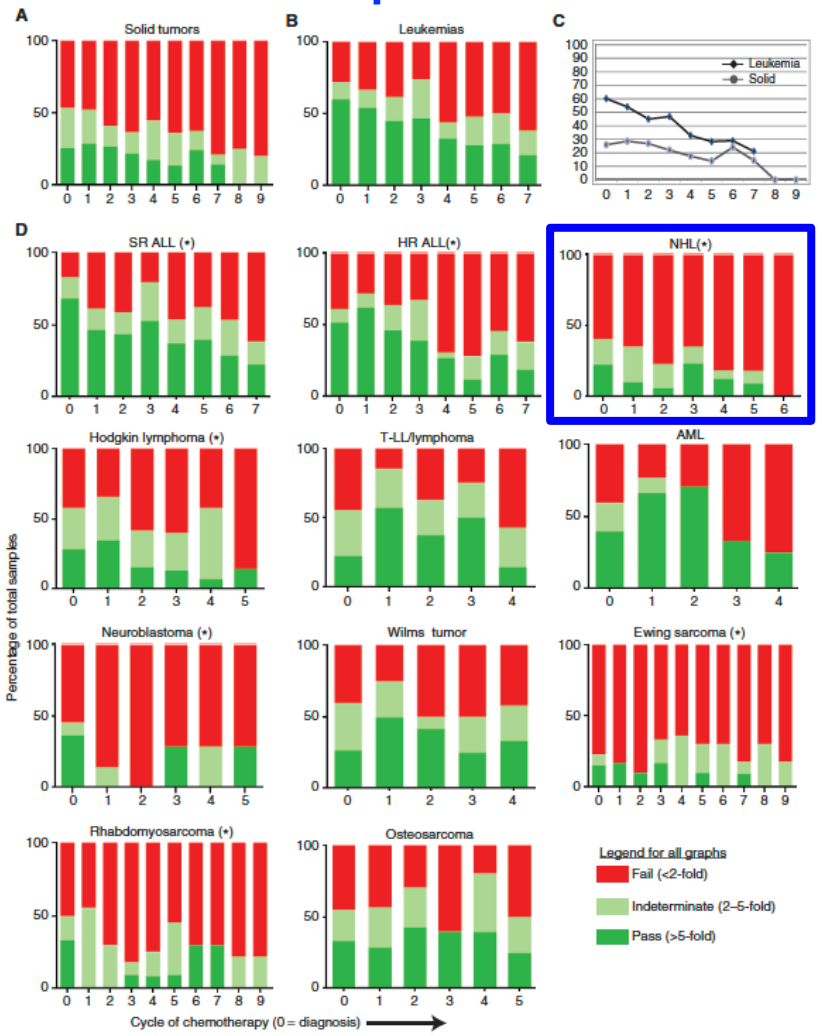


Chemotherapy impairs immune cell phenotype and fitness

T-cell phenotype



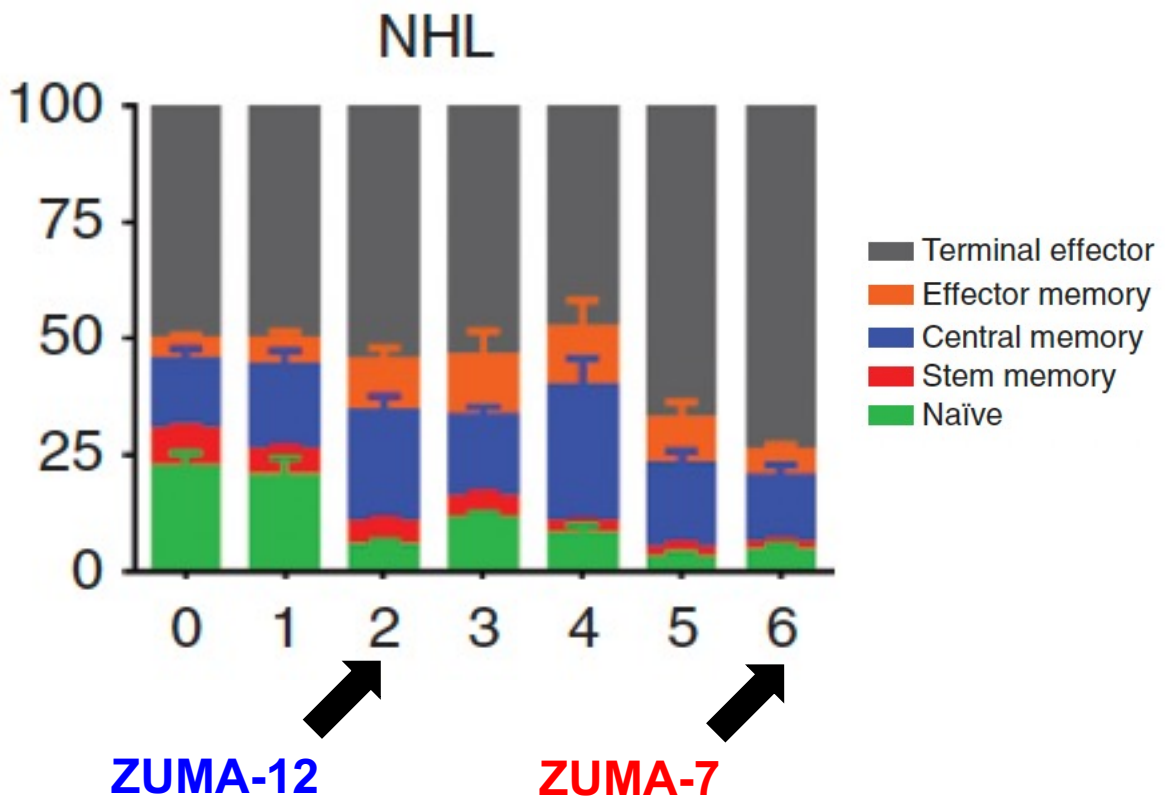
T-cell proliferation



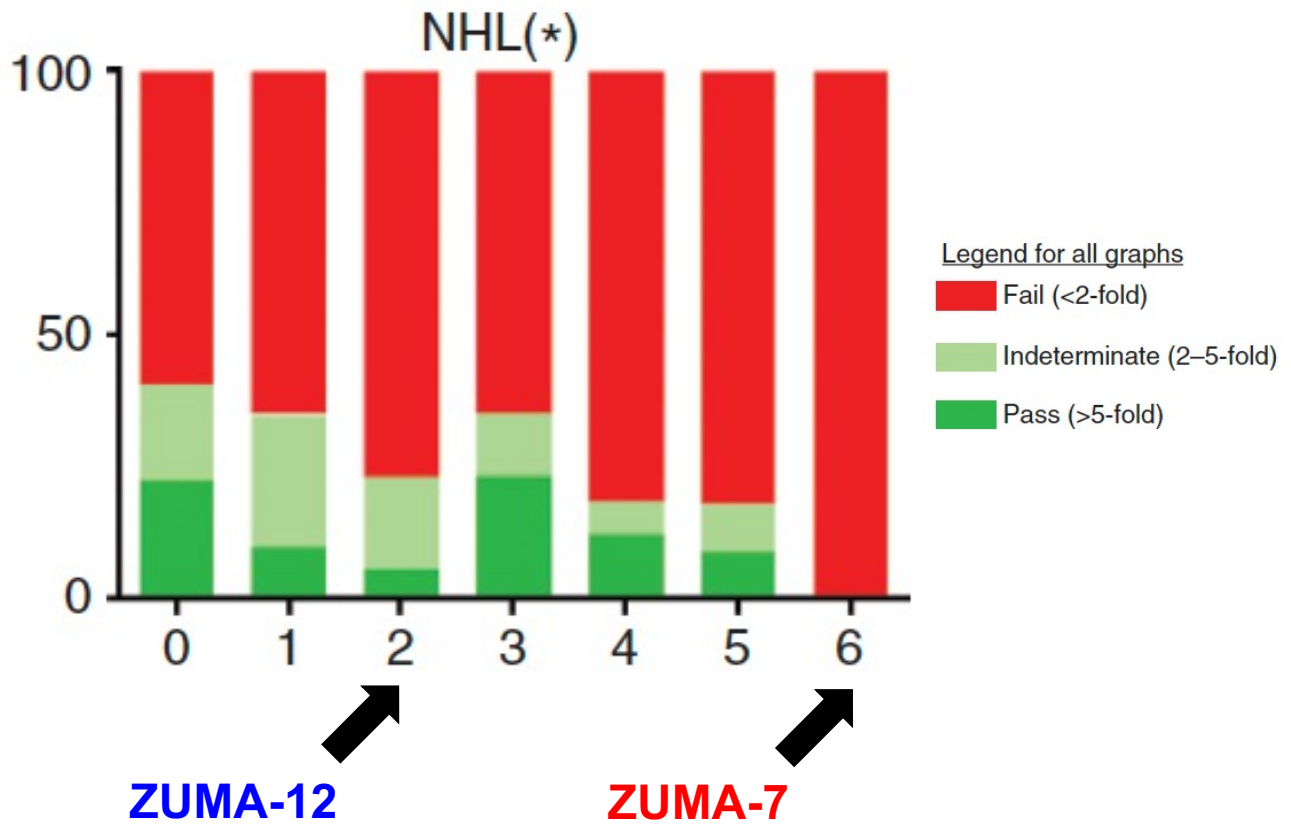
Das et al. *Cancer Discov* 2019; 9(4): 492-499

Chemotherapy impairs immune cell phenotype and fitness

T-cell phenotype



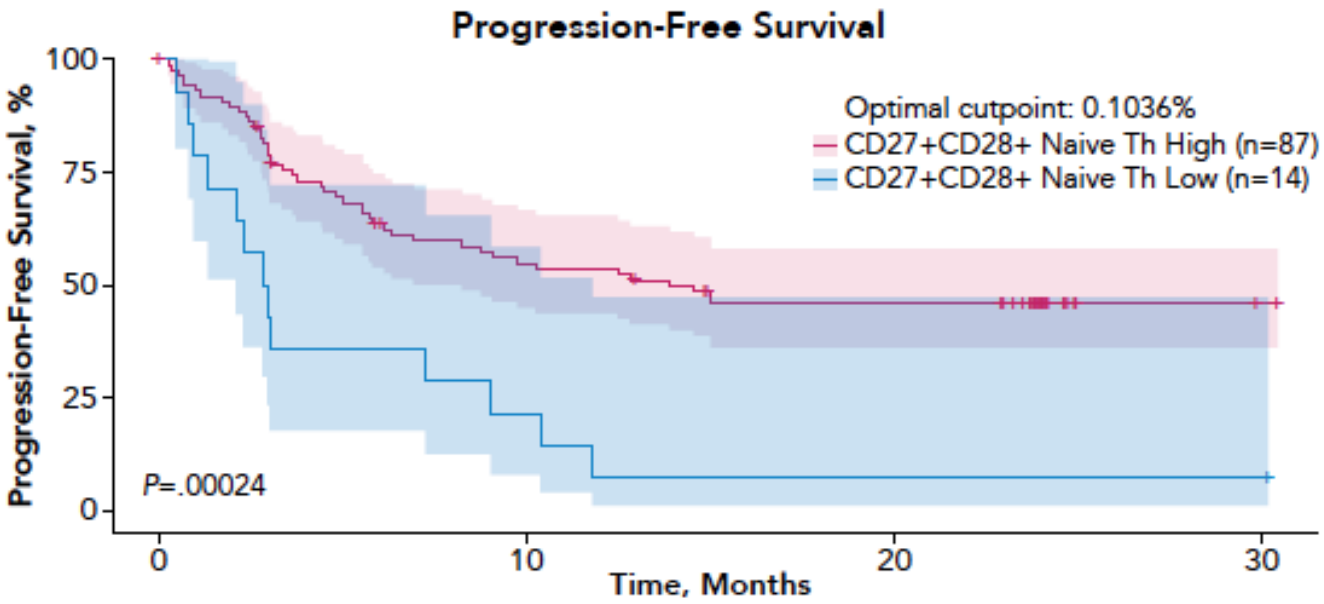
T-cell proliferation



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

$CD27^{+}CD28^{+}$ naïve T cells in apheresis associated with better efficacy

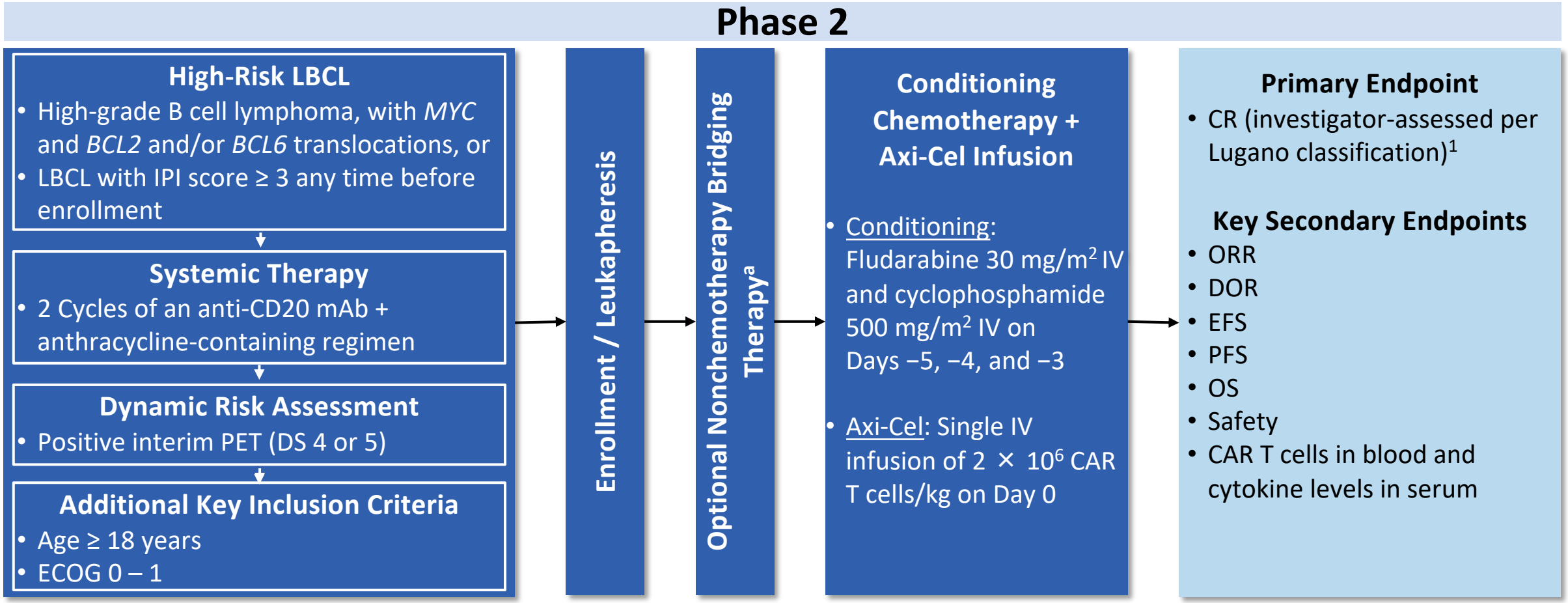
ZUMA-1



	High (n=87)	Low (n=14)
ORR, n (%)	74 (85)	10 (71)
CR rate, n (%)	52 (60)	7 (50)
Ongoing response, n (%)	36 (41)	2 (14)
Grade ≥3 NEs, n (%)	28 (32)	3 (21)
Grade ≥3 CRS, n (%)	9 (10)	2 (14)
Median CAR peak, cells/μL	42.588	19.836
Median CAR peak/tumor burden, cells/mm^2	0.01105	0.00872

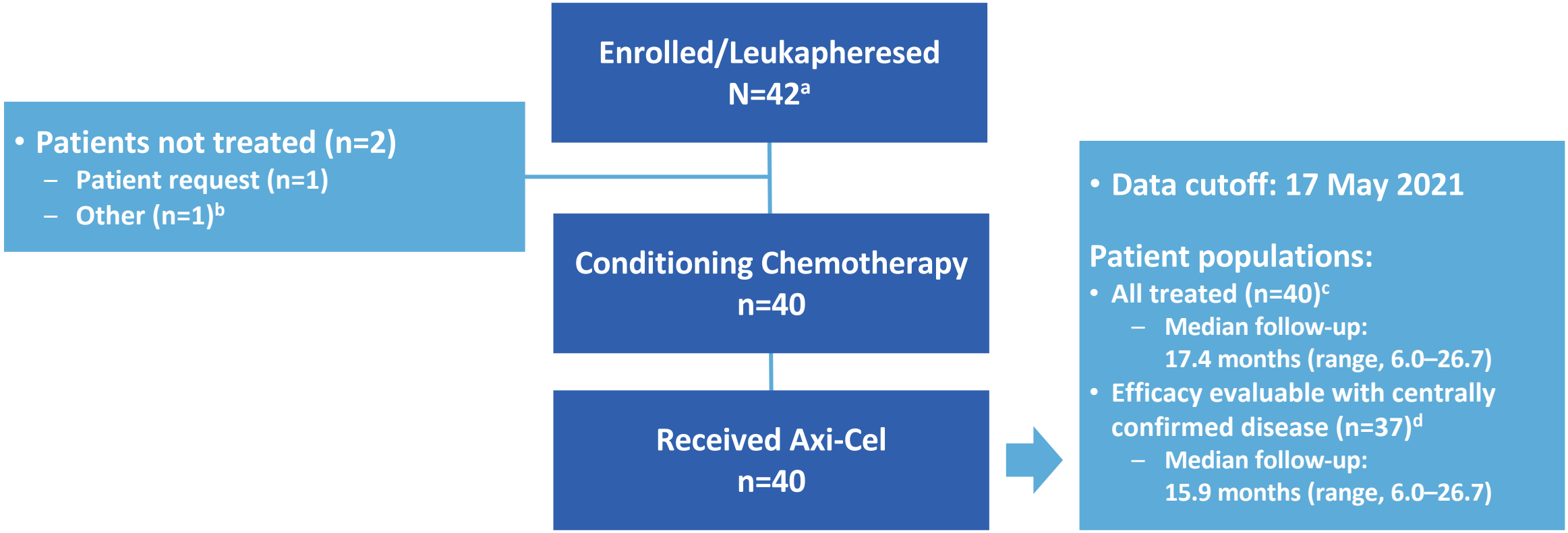
Budka et al, *AACR* 2021, Abstract #CT166

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: Disposition



[a] Prior to conditioning chemotherapy, 7 patients received non-chemotherapy bridging therapy. [b] Patient was withdrawn from study due to additional biopsy which revealed a second primary tumor. [c] Includes all treated patients who received any dose of axi-cel. [d] Includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1 × 10^6 CAR T cells/kg. Of all 40 treated patients, 3 were excluded from the efficacy analysis: 2 had an IPI score of 2 and neither double-/triple-hit lymphoma per central review; 1 patient had an IPI score of 2 and no central confirmation of disease type.

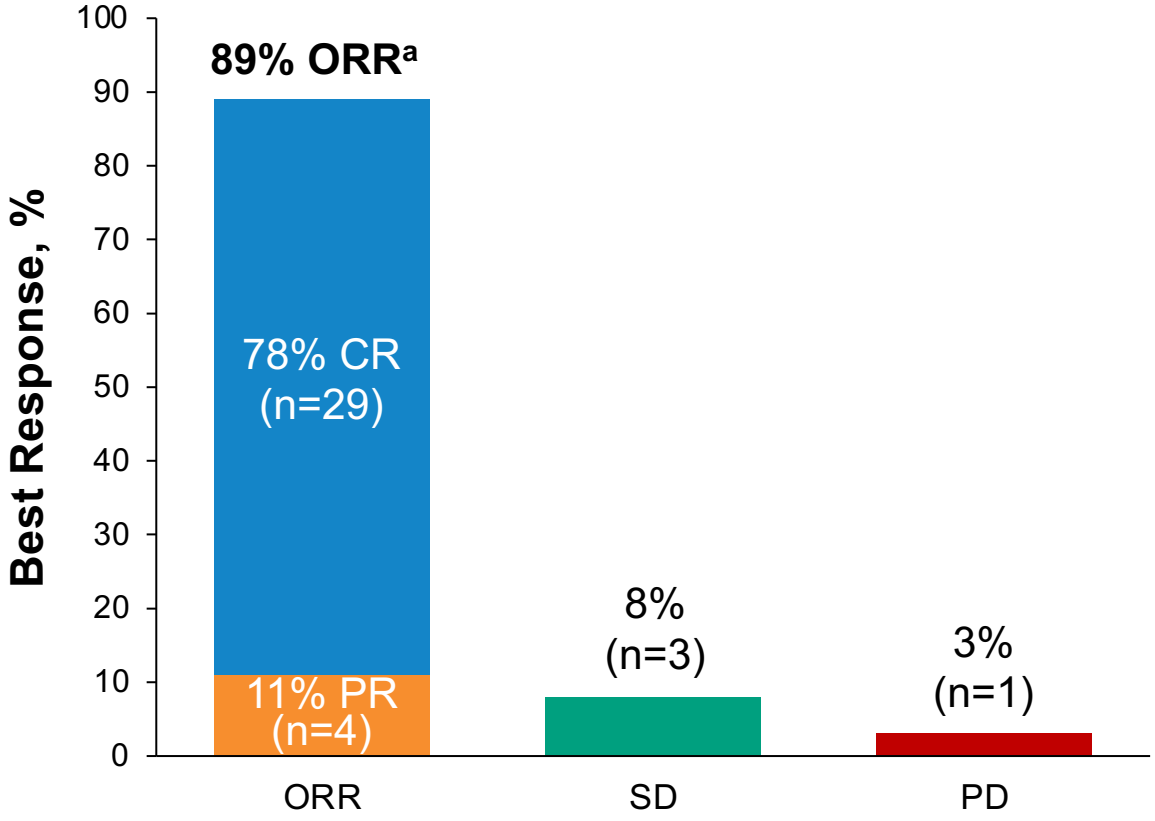
Neelapu et al, ASH 2021, Abstract 739

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 et al, ASH 2021, Abstract 739

ZUMA-12 primary analysis: Efficacy



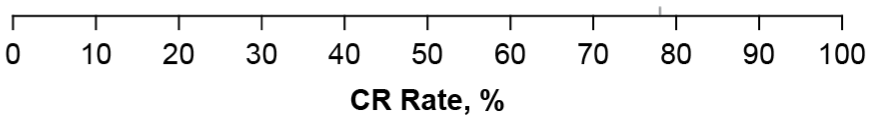
	Efficacy Evaluable N=37[b]
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)[c]	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

- Among all treated patients (N=40), ORR was 90% (95% CI, 76–97); CR rate was 80% (95% CI, 64–91)

Neelapu et al, ASH 2021, Abstract 739

ZUMA-12: CR rate was consistent among key subgroups

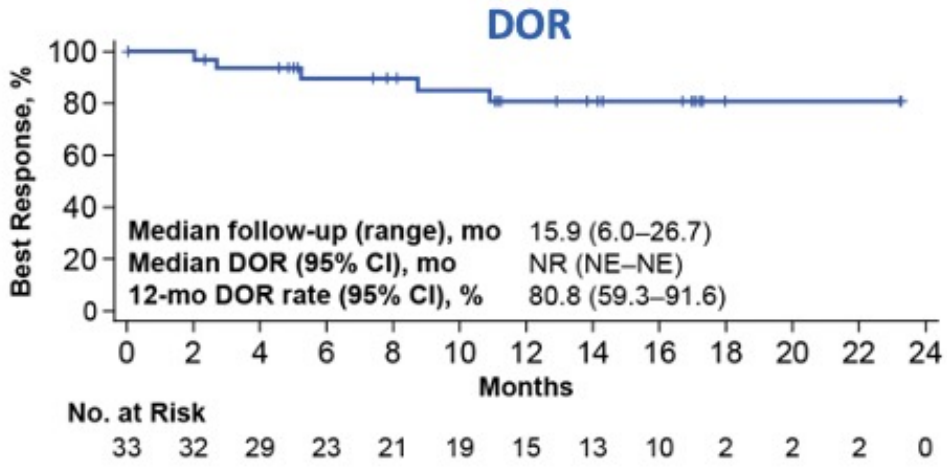
		Evaluable Patients	Patients With a CR	CR Rate (95% CI)
Overall		37	29	78 (62-90)
Age, years	<65	24	17	71 (49-87)
	≥65	13	12	92 (64-100)
Sex	Male	25	18	72 (51-88)
	Female	12	11	92 (62-100)
Double- or triple-hit status per central lab and IPI score	Double- or triple-hit only	6	3	50 (12-88)
	IPI ≥3 only	27	22	81 (62-94)
	Double- or triple-hit and IPI ≥3	4	4	100 (40-100)
Double- or triple-hit status per local lab[b]	Double- or triple-hit	13	10	77 (46-95)
	Neither double- nor triple-hit	20	16	80 (56-94)
ECOG performance status	0	15	13	87 (60-98)
	1	22	16	73 (50-89)
Deauville five-point scale	4	18	15	83 (59-96)
	5	19	14	74 (49-91)
Prior therapy category	DA-EPOCH-R/EPOCH-R	17	13	76 (50-93)
	R-CHOP	19	15	79 (54-94)
	Other	1	1	100 (3-100)
Best response to prior therapy	PR/SD	21	17	81 (58-95)
	PD	15	11	73 (45-92)

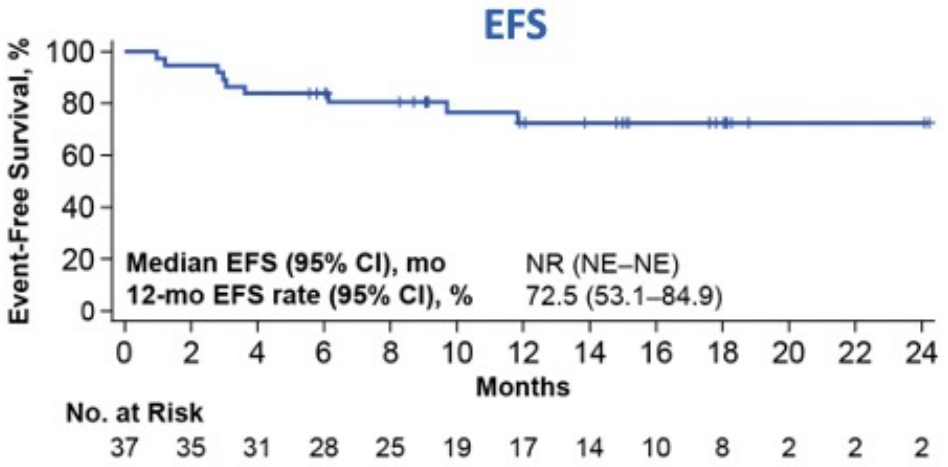


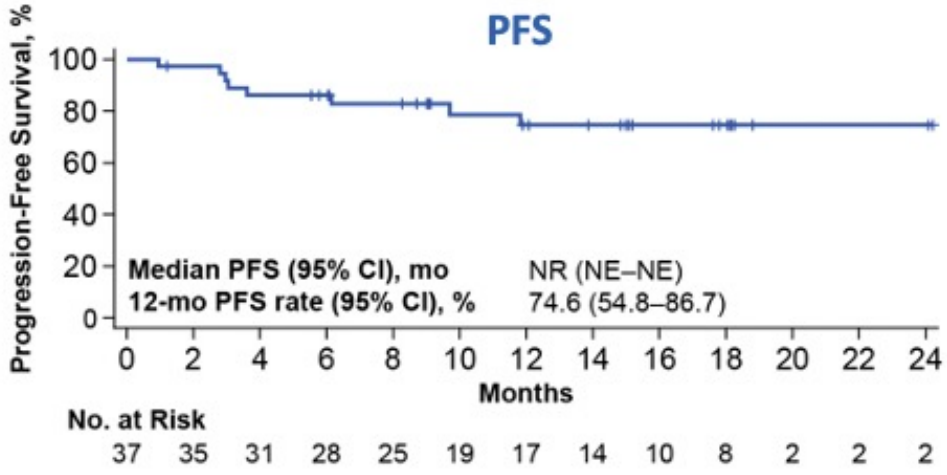
[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1 × 10^6 CAR T cells/kg. [b] The CR rate among patients with or without double- or triple-hit lymphoma per central laboratory was 70% (95% CI, 35-95) and 80% (95% CI, 56-94), respectively.

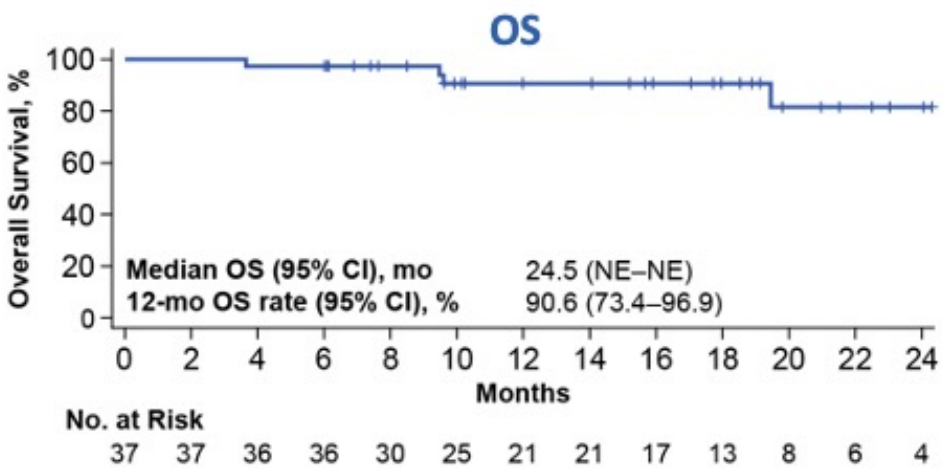
Neelapu et al, ASH 2021, Abstract 739
Neelapu et a, *Nat Med*, 2022; 28(4): 735-742

ZUMA-12 primary analysis: Efficacy









Neelapu et al, ASH 2021, Abstract 739

ZUMA-12: CRS

Parameter	All Treated (N=40)
Any grade CRS, n (%)[a]	40 (100)
Grade 3	3 (8)
Most common any-grade symptoms of CRS, n (%)	
Pyrexia	40 (100)
Hypotension	12 (30)
Chills	10 (25)
Hypoxia	9 (23)
AE management for CRS, n (%)	
Tocilizumab	25 (63)
Steroids	14 (35)
Vasopressors	1 (3)
Median time to onset (range), days	4 (1–10)
Median duration of events (range), days	6 (1–18)
Patients with resolved events by data cutoff, n/n (%)	40/40 (100)
Patients with resolved events by Day 14 post–axi-cel, n/n (%)	39/40 (98)

- No Grade 4 and 5 CRS occurred

Neelapu et al, ASH 2021, Abstract 739
Neelapu et a, *Nat Med*, 2022; 28(4): 735-742

ZUMA-12: Neurological Events

Parameter	All Treated (N=40)
Any grade NE, n (%)[a]	29 (73)
Grade ≥3	9 (23)
Grade ≥2	15 (38)
Most common any-grade symptoms of NE, n (%)	
Confusional state	11 (28)
Encephalopathy	10 (25)
Tremor	10 (25)
AE management for NE, n (%)	
Steroids	13 (33)
Tocilizumab	1 (3)
Median time to onset (range), days	9 (2–44)
Median duration of events (range), days	7 (1–280)
Patients with resolved events by data cutoff, n/n (%)	28/29 (97)
Patients with resolved events by Day 21 post–axi-cel, n/n (%)	20/29 (69)

- Grade 4 NEs occurred in 2 patients (5%[b]); no Grade 5 NEs occurred
- One event of Grade 1 tremor was ongoing at data cutoff

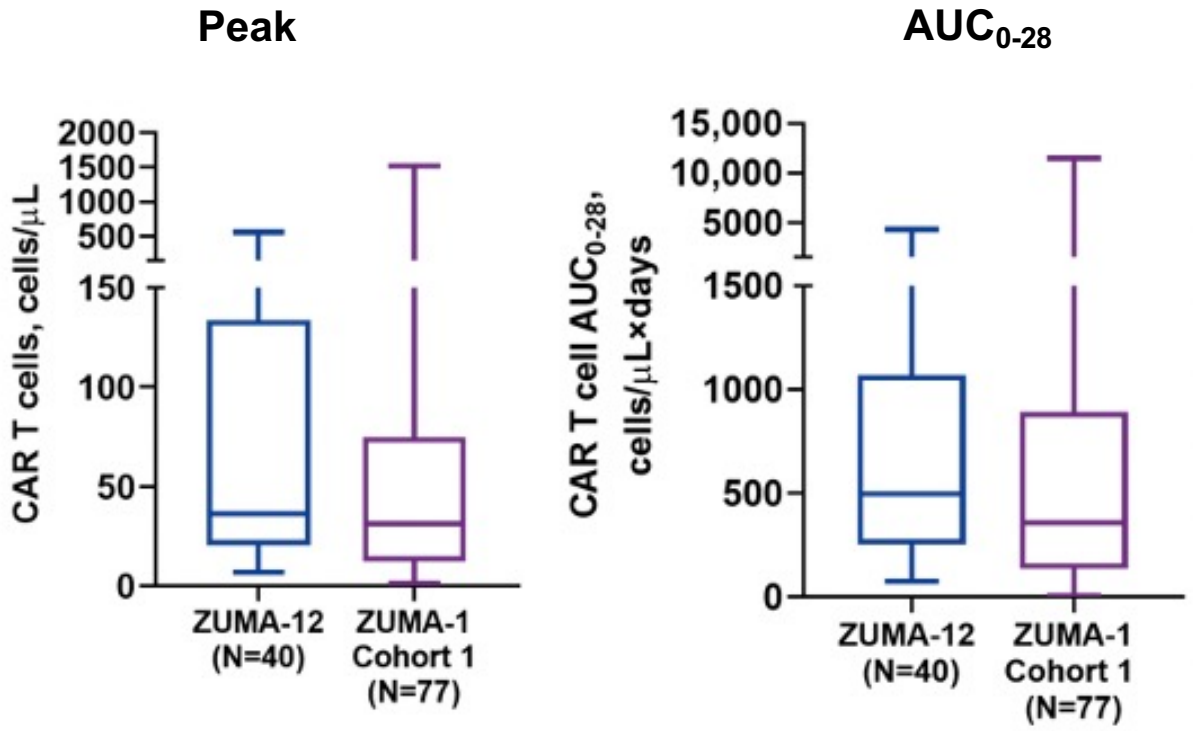
Neelapu et al, ASH 2021, Abstract 739
Neelapu et a, *Nat Med*, 2022; 28(4): 735-742

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

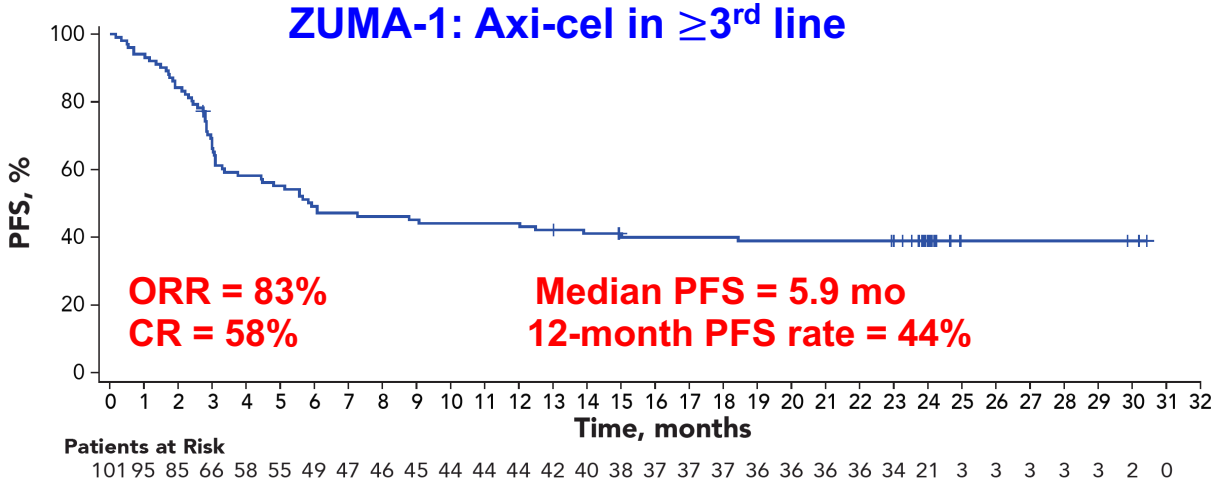


- Suggests T-cell fitness may be better in earlier lines of therapy

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

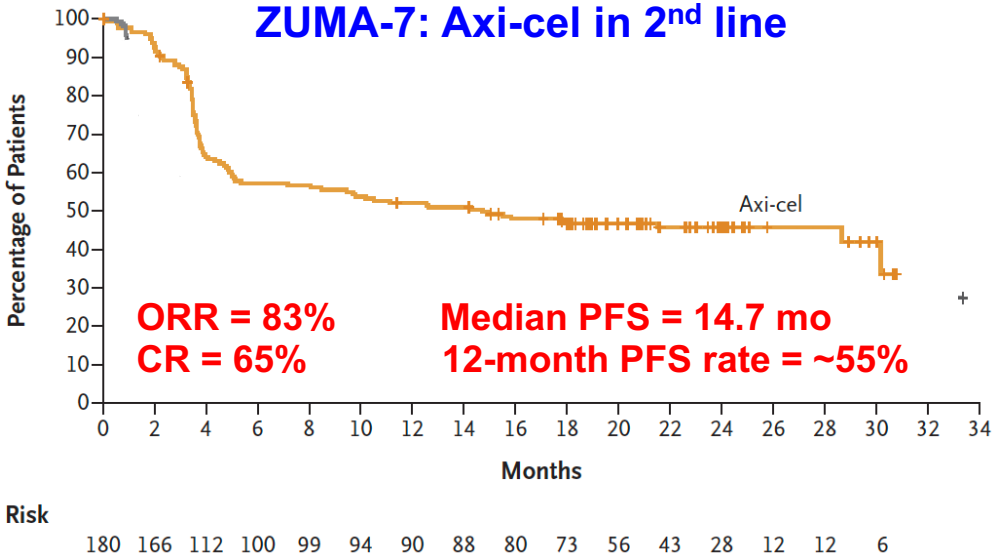
ZUMA-1: Axi-cel in ≥3rd line



ORR = 83%
CR = 58%

Median PFS = 5.9 mo
12-month PFS rate = 44%

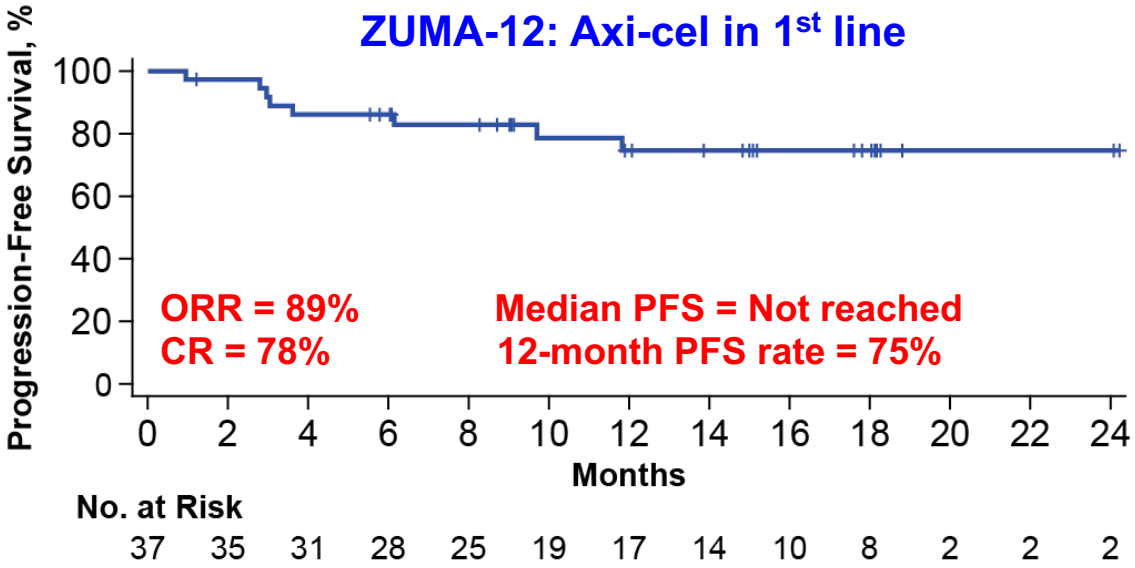
ZUMA-7: Axi-cel in 2nd line



ORR = 83%
CR = 65%

Median PFS = 14.7 mo
12-month PFS rate = ~55%

ZUMA-12: Axi-cel in 1st line



ORR = 89%
CR = 78%

Median PFS = Not reached
12-month PFS rate = 75%

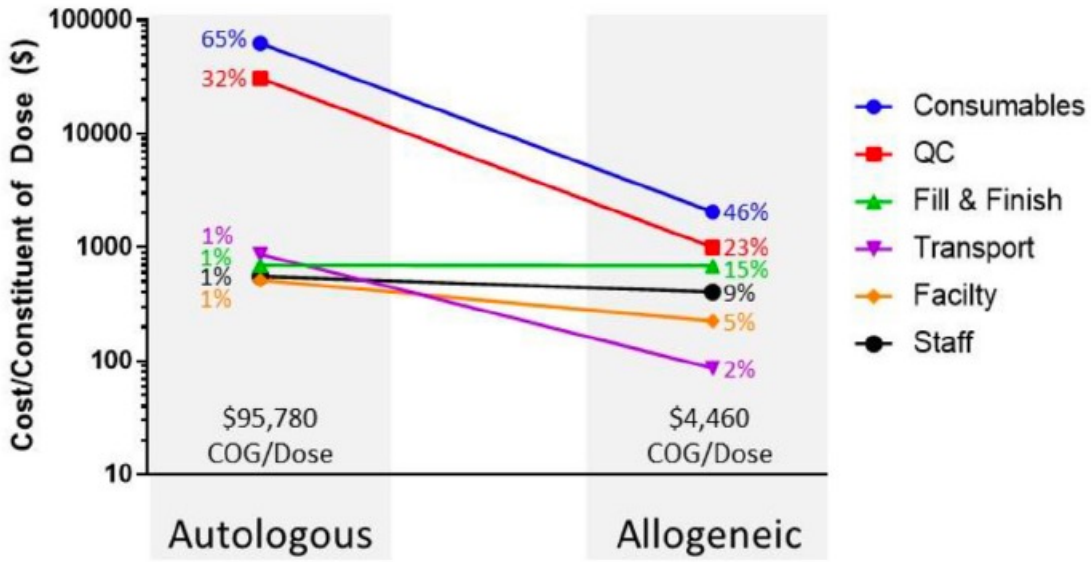
- ZUMA-23: Phase 3 randomized study in 1L high-risk LBCL launched

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, *ASH 2021*, Abstract 739

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
- Potential to lower the cost of CAR T-cell therapy
- Improve access at non-transplant centers
- Long-term B-cell aplasia and hypogammaglobulinemia less likely
- Long-term risk of insertional mutagenesis less likely

Cost of goods/dose: Auto vs. Allo

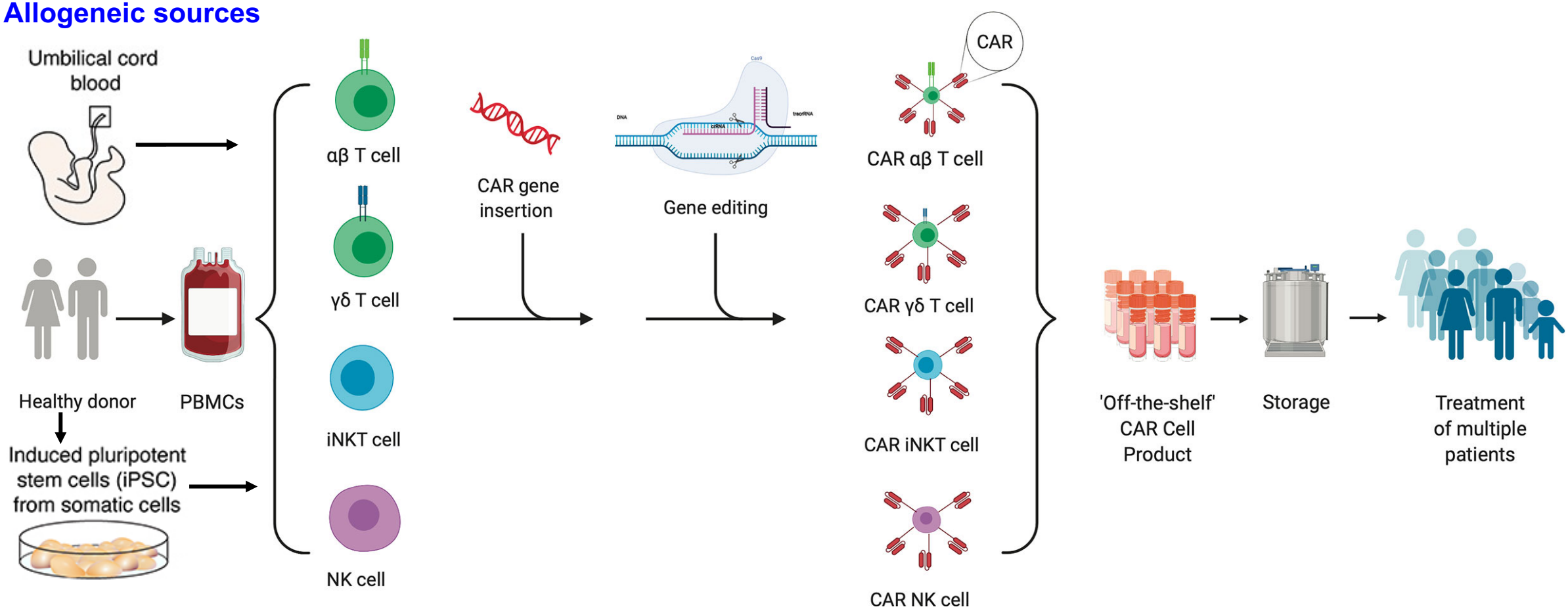


~100 doses/manufacturing run

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

Allogeneic CAR cell therapy

Allogeneic sources

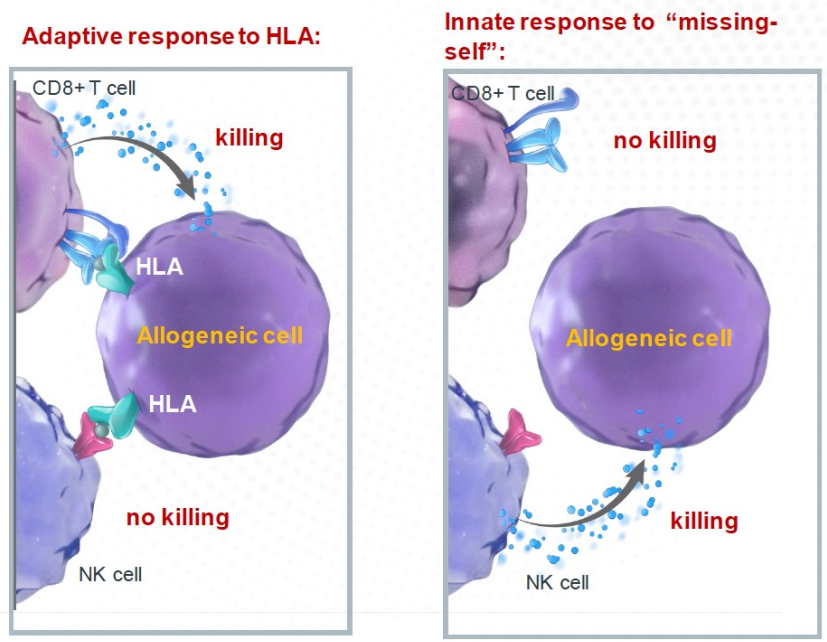


Bedoya DM et al. *Front Immunol.* 2021;12:640082.
Caldwell KJ et al. *Front Immunol.* 2021;11:618427.

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



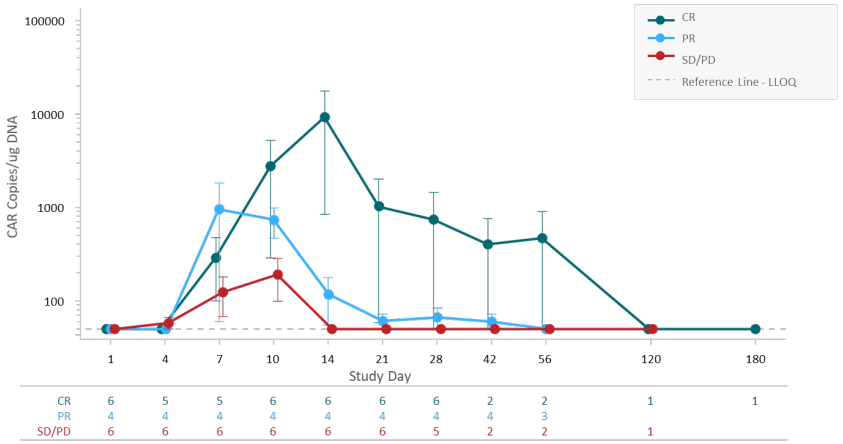
Depil et al. *Nat Rev Drug Discov*, 2020; 19(3) 185-199
Schrepfer et al, 2022 ASH Annual Meeting, Abstract 1690

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	

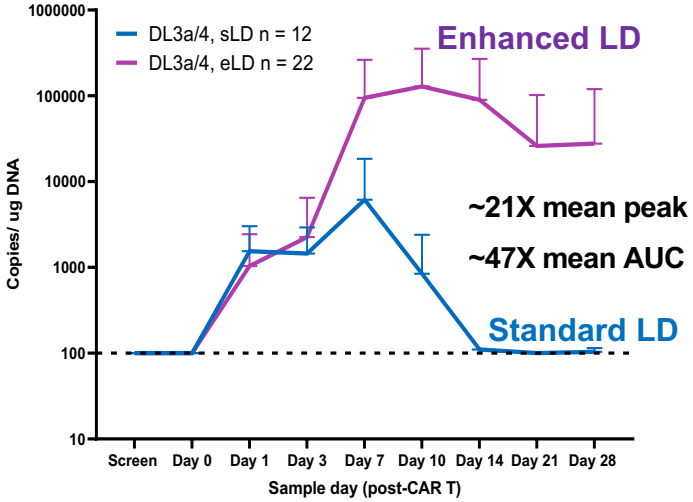
CAR-T expansion and persistence in phase 1 allogeneic CAR-T trials in r/r B-cell lymphomas

ALLO-501 (CD19 αβ CAR)



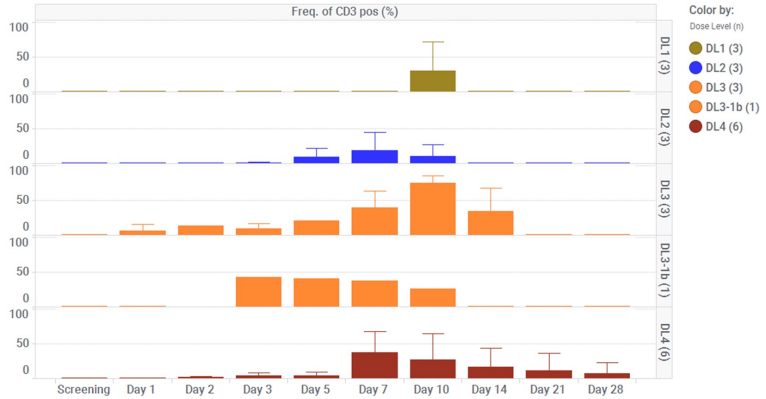
Neelapu et al. 2020 ASCO Annual Meeting, Abstract 8002

PBCAR0191 (CD19 αβ CAR)



Shah et al. 2021 ASH Annual Meeting, Abstract 302

ADI-001 (CD20 γδ CAR)



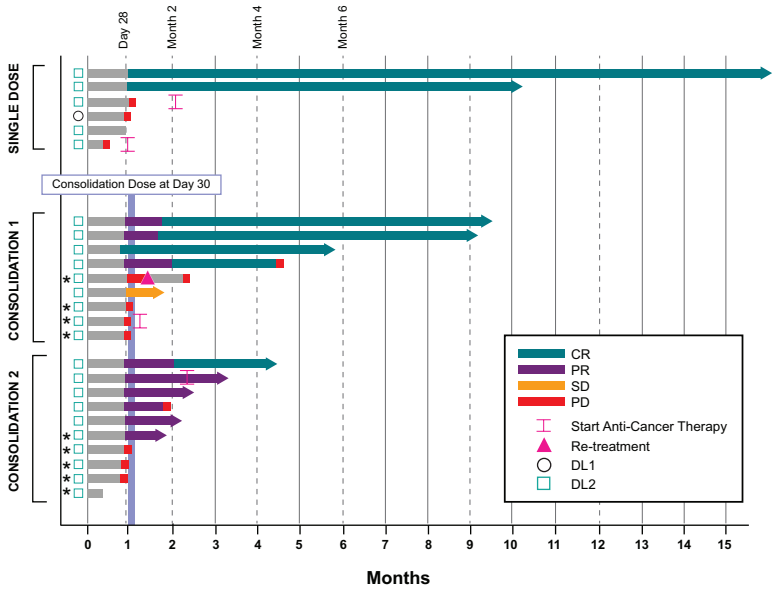
Neelapu et al. 2022 ASH Annual Meeting, Abstract 2018

- 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)

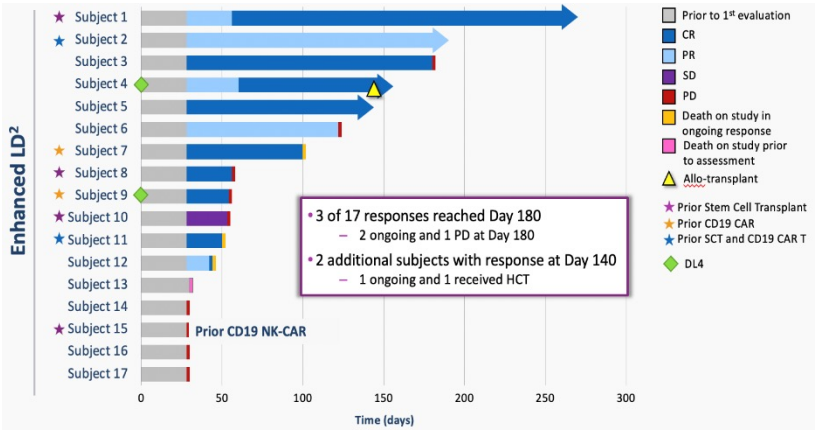
ORR/CR rate % = 48/28



Lekakis et al. 2021 ASH Annual Meeting, Abstract 649

PBCAR0191 (CD19 αβ CAR)

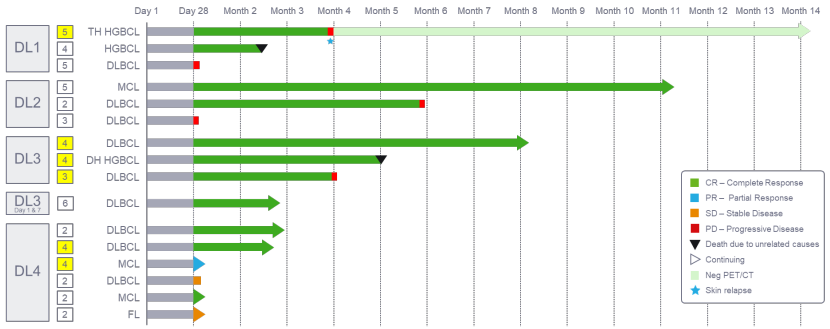
ORR/CR rate % = 69/56



Shah et al. 2021 ASH Annual Meeting, Abstract 302

ADI-001 (CD20 γδ CAR)

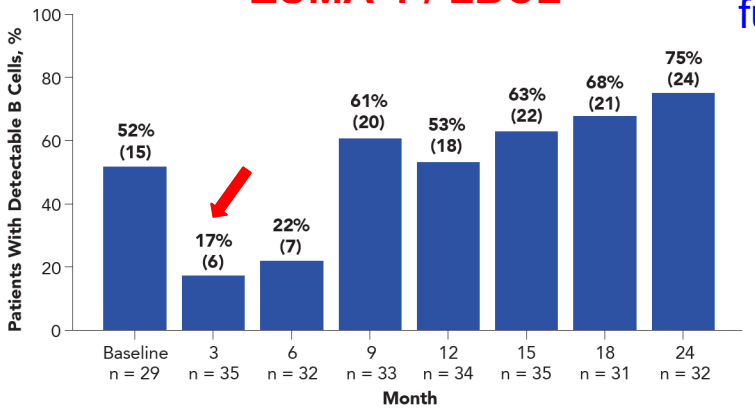
ORR/CR rate % = 75/69



Neelapu et al. 2022 ASH Annual Meeting, Abstract 2018

Auto CD19 CAR: B-cell recovery in patients with ongoing remission

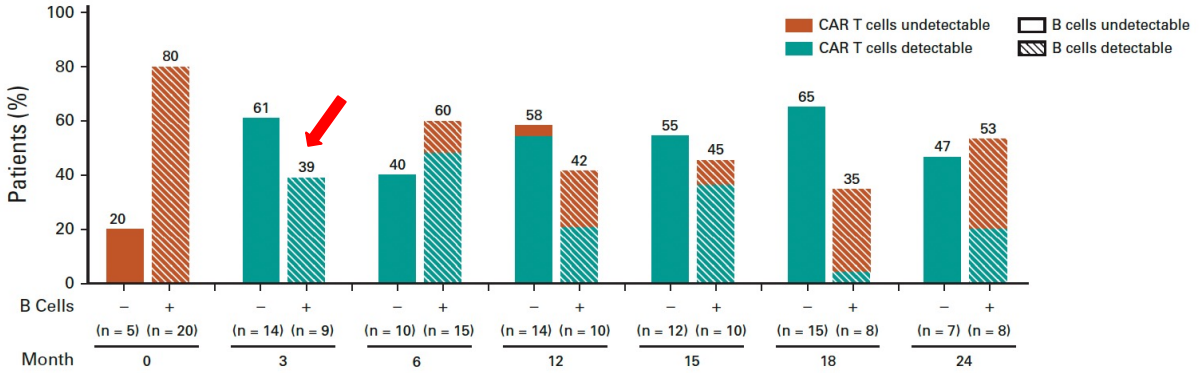
ZUMA-1 / LBCL



Locke et al Neelapu, *Lancet Oncol* 2019
Jacobson et al, *JSHCT* 2021, Abstract 009

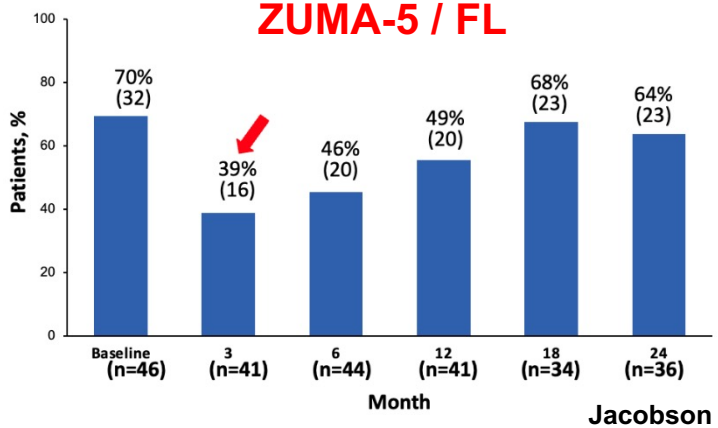
- B-cell recovery suggests loss of functional CAR-T persistence

ZUMA-2 / MCL



Wang et al, *J Clin Oncol* 2022

ZUMA-5 / FL

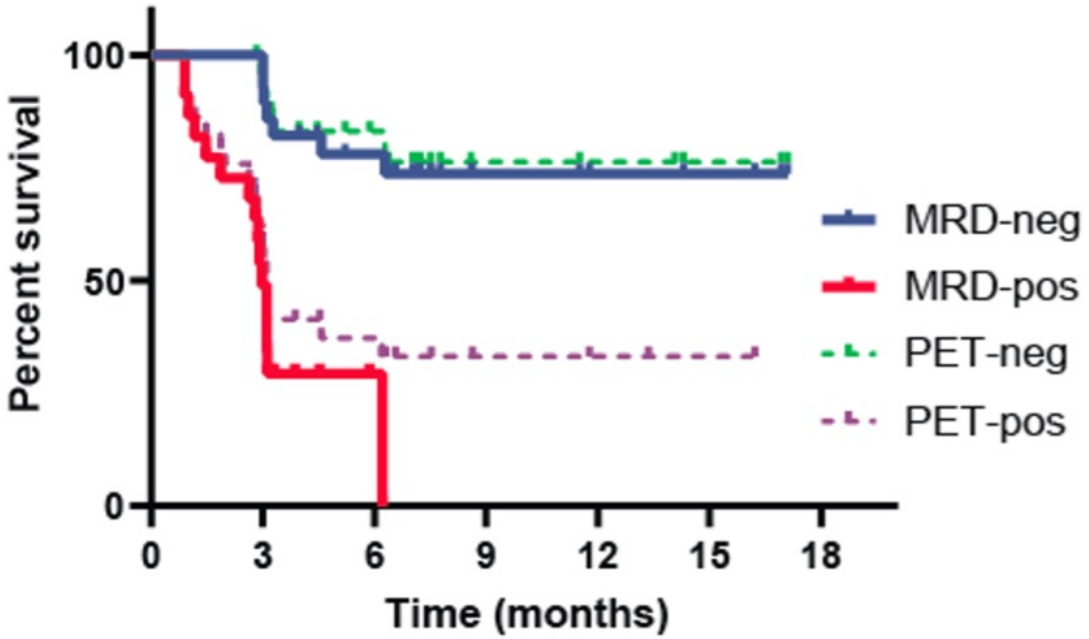


Neelapu et al, *ASH* 2021
Jacobson et al, *Lancet Oncol*, 2022

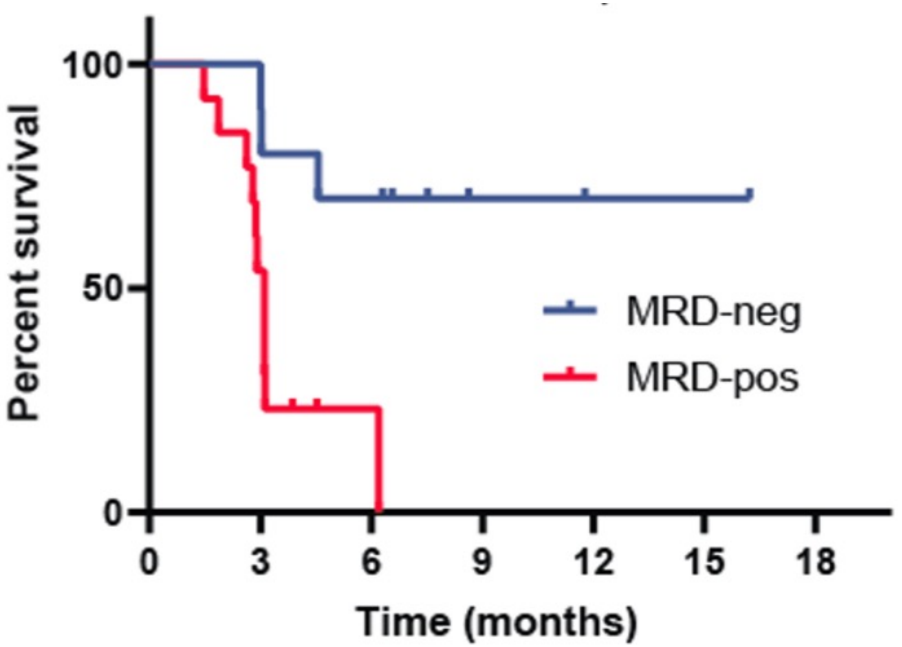
- **Supports the notion that functional CAR-T persistence for ≤3 months may be sufficient to maintain durability of responses in LBCL, MCL, and FL**

MRD negativity at day 28 strongly associated with durability in DLBCL after axi-cel

PFS by Day 28 MRD or Day 28 PET



PFS by Day 28 MRD in patients with PR/SD by D28 PET

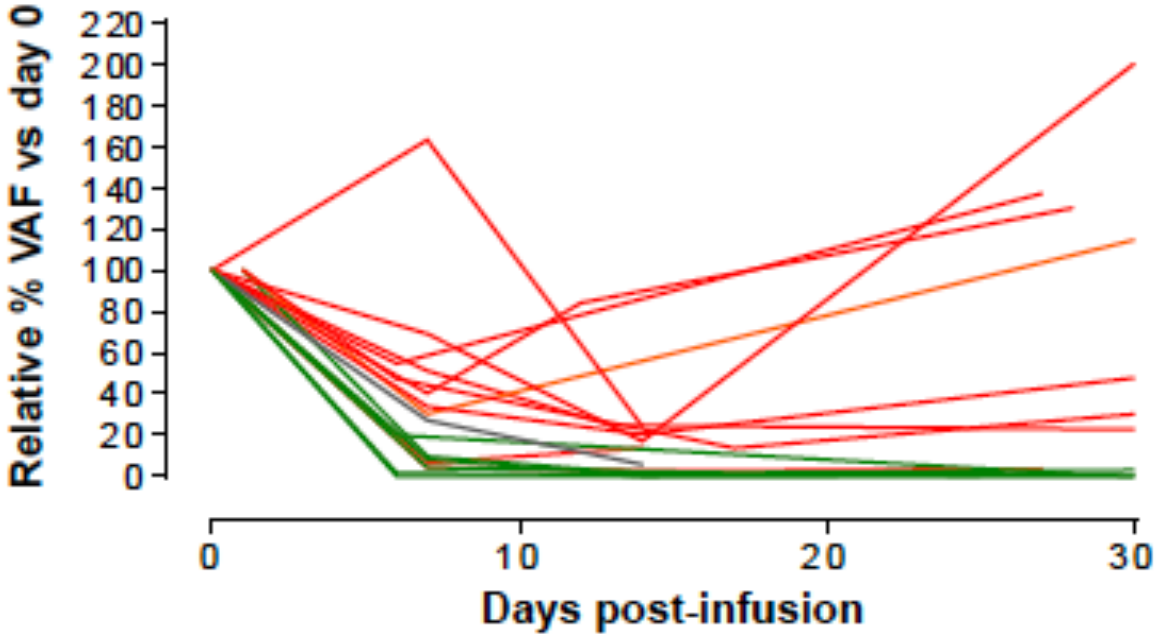


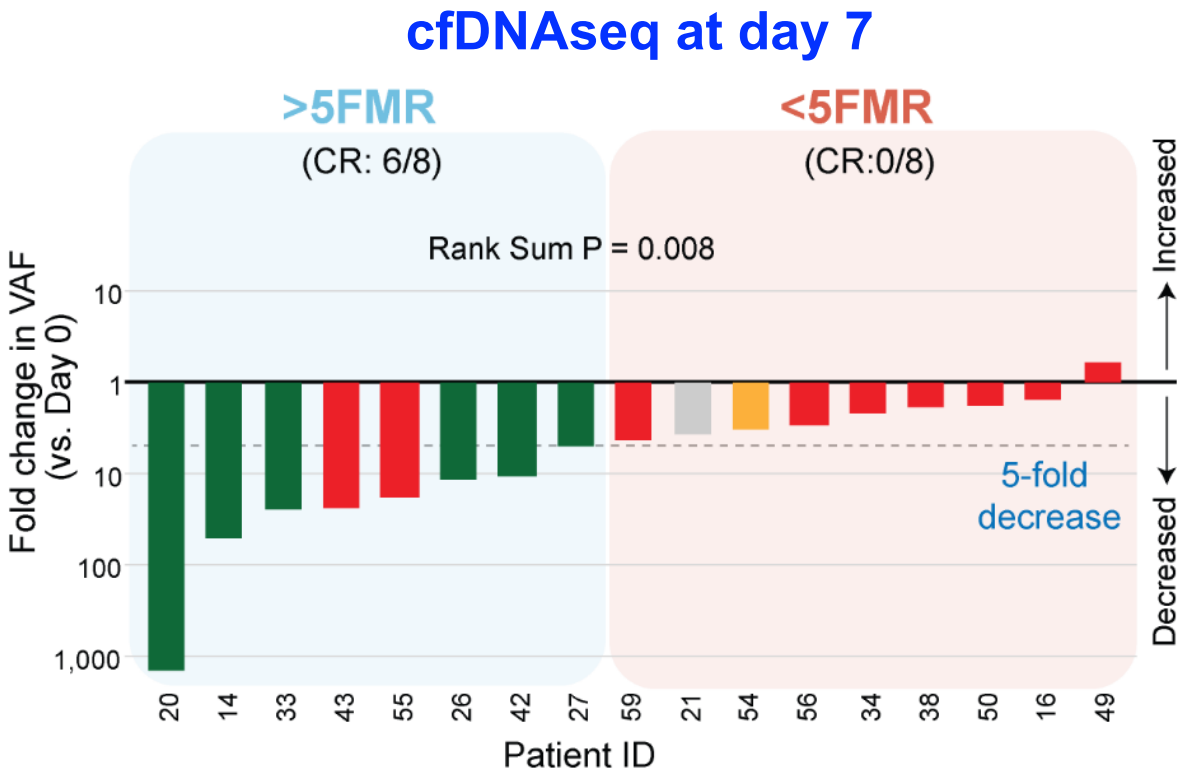
- Are cures occurring within the ***first month*** after CAR T?

Frank et al, *ASH* 2019, Abstract 884

Molecular response at day 7 associate with durability of response or resistance after axi-cel in DLBCL

- Patients with >5-fold 7 day molecular response have 75% CR rate at 3 months
- Patients with <5-fold 7 day molecular response have 0% CR rate at 3 months

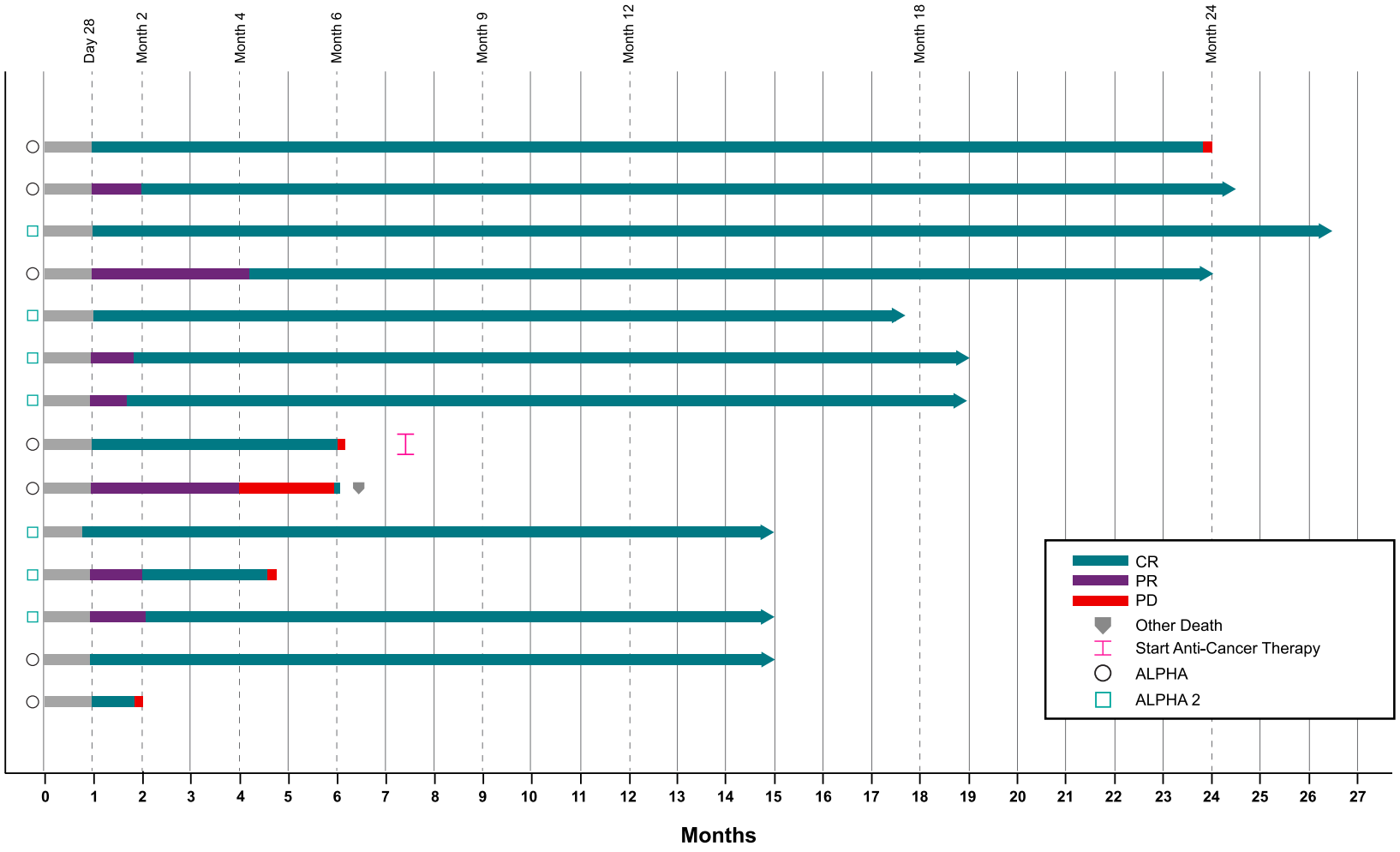




- Most of the antitumor effect likely occurring within the 1st week

Deng, Han, et al. *Nat Med* 2020

Durable remissions after allogeneic CD19 CAR-T (ALLO-501/A) in LBCL



Data Cutoff Date: October 25, 2022

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

Allogene press release, Dec 2022

Alloimmune defense receptor to resist host immune rejection

nature biotechnology

ARTICLES

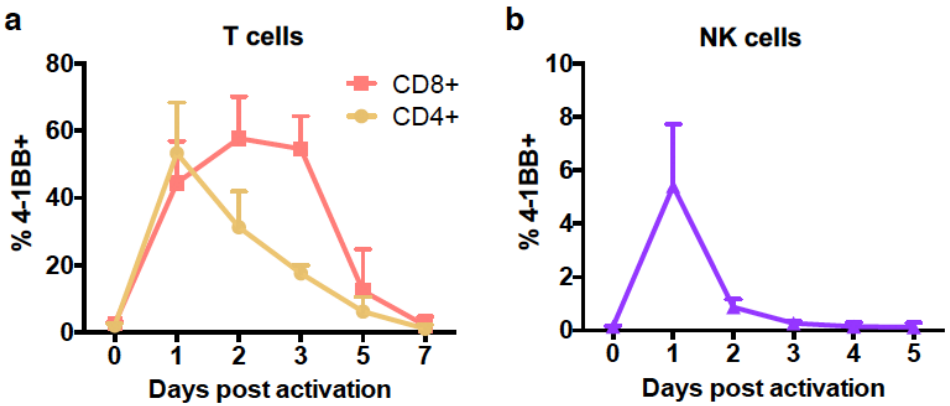
https://doi.org/10.1038/s41587-020-0601-5

July 2020

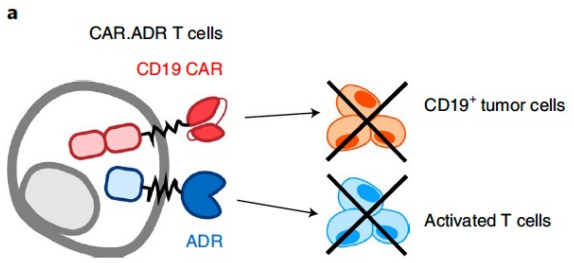
Engineered off-the-shelf therapeutic T cells resist host immune rejection

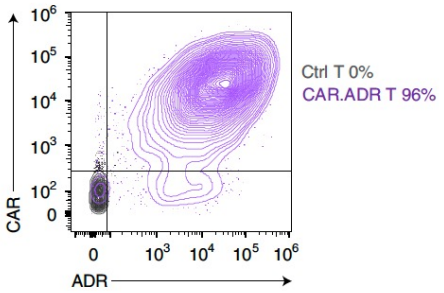
Feiyan Mo[1,2], Norihiro Watanabe[1], Mary K. McKenna[1], M. John Hicks[3], Madhuwanti Srinivasan[1], Diogo Gomes-Silva[1], Erden Atilla[1], Tyler Smith[1], Pinar Ataca Atilla[1], Royce Ma[1,4], David Quach[1], Helen E. Heslop[1,2], Malcolm K. Brenner[1,2] and Maksim Mamonkin[1,2,3,4] ✉

4-1BB is temporarily upregulated by activated T and NK

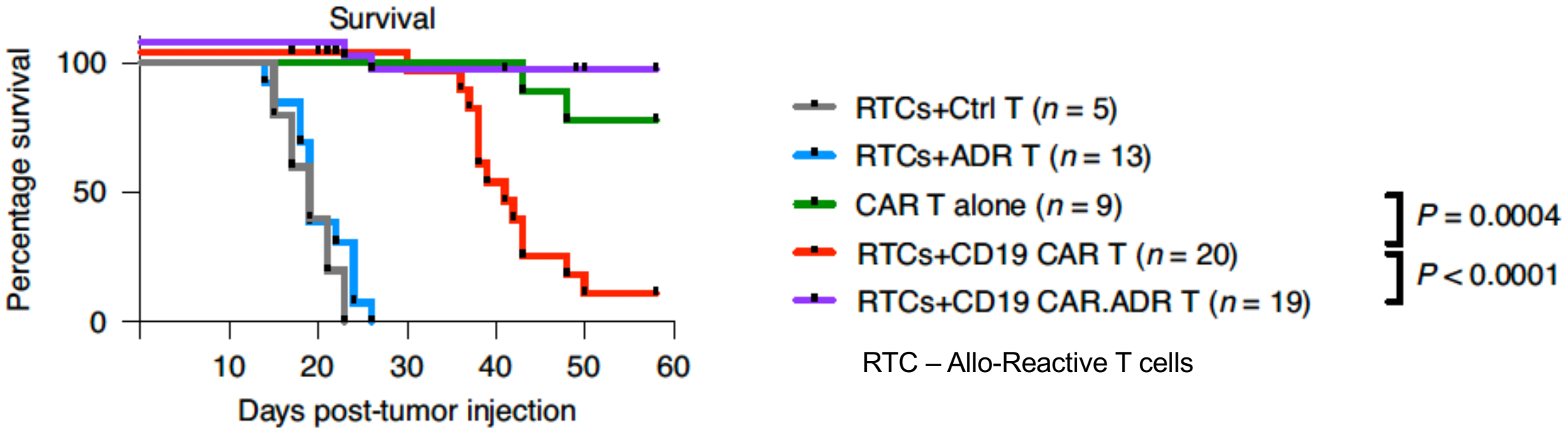


Alloimmune Defense Receptor
(ADR = 4-1BBL-spacer-CD3ζ)





Alloimmune defense receptor to resist host immune rejection



- ADR-expressing T cells resist cellular rejection by targeting alloreactive lymphocytes in vitro and in vivo, while sparing resting lymphocytes

Mo et al. *Nat Biotech* 2020

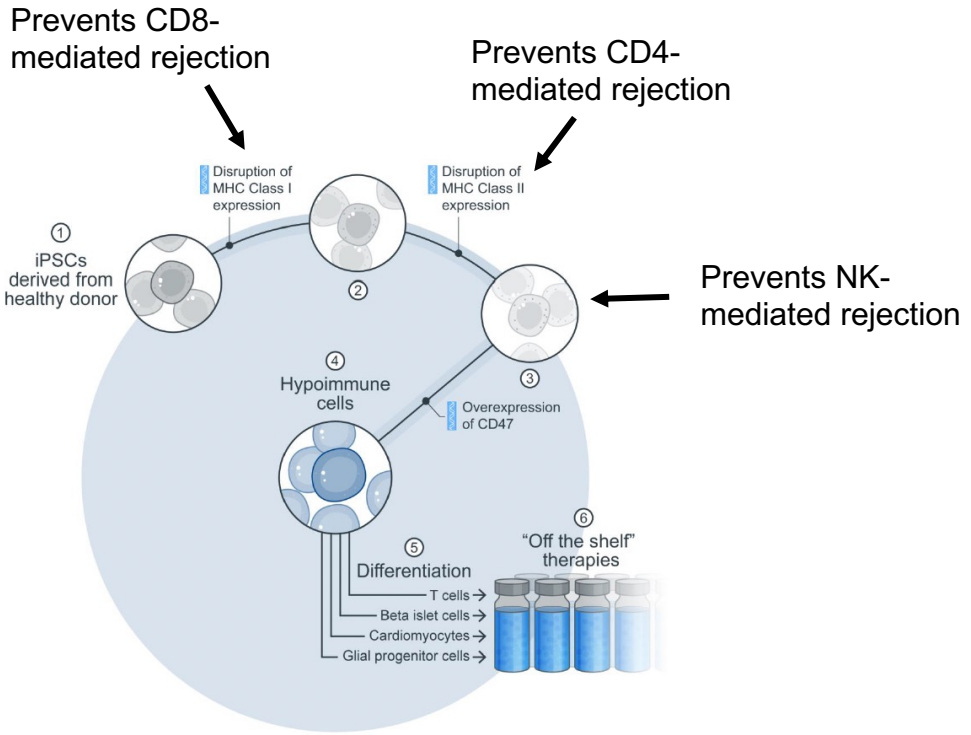
Hypoimmune platform to resist host immune rejection

LETTERS
https://doi.org/10.1038/s41587-019-0016-3
nature biotechnology
Mar 2019

Hypoimmunogenic derivatives of induced pluripotent stem cells evade immune rejection in fully immunocompetent allogeneic recipients

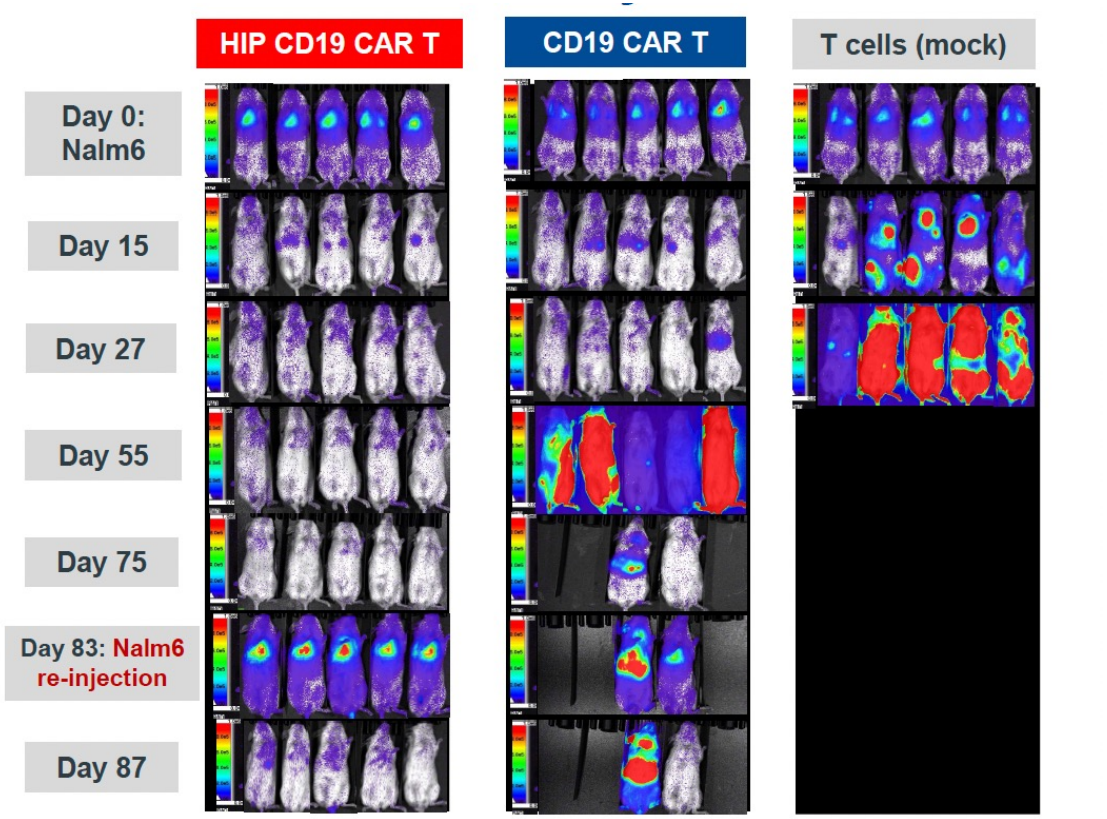
Tobias Deuse[1,7], Xiaomeng Hu[1,2,3,7], Alessia Gravina[1], Dong Wang[1,2], Grigol Tediashvili[1,2,3], Chandrav De[4], William O. Thayer[4], Angela Wahl[4], J. Victor Garcia[4], Hermann Reichenspurner[2,3], Mark M. Davis[5], Lewis L. Lanier[6] and Sonja Schrepfer[1*]

Hypoimmune platform



Hypoimmune CAR T cells resist immune rejection and mediate antitumor activity

Fully HLA-mismatched humanized mouse model



Bulk HIP CAR T cells survive in humanized mice and show function following Nalm6 re-injection at 83 days.

Schrepfer et al, ASH 2022, Abstract 1690

Summary

- ZUMA-12 is the first study to evaluate CAR T-cell therapy as part of first-line therapy in high-risk LBCL. In the primary analysis:
  - ORR was 89% and CR rate was 78%
  - With a median follow-up of 15.9 months, 73% of patients remained in response at data cutoff
- In ZUMA-12, higher frequency of CCR7+CD45RA+ T cells in axi-cel product was associated with greater CAR T-cell expansion than in ZUMA-1, suggestive of improved T-cell fitness in first-line treatment
- Early data suggests that allogeneic CAR cell therapies are safe and response rates in NHL appear to be comparable to autologous CAR T
- 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!

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