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MD Anderson Cancer Center
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The Role of CAR T cells in DLBCL

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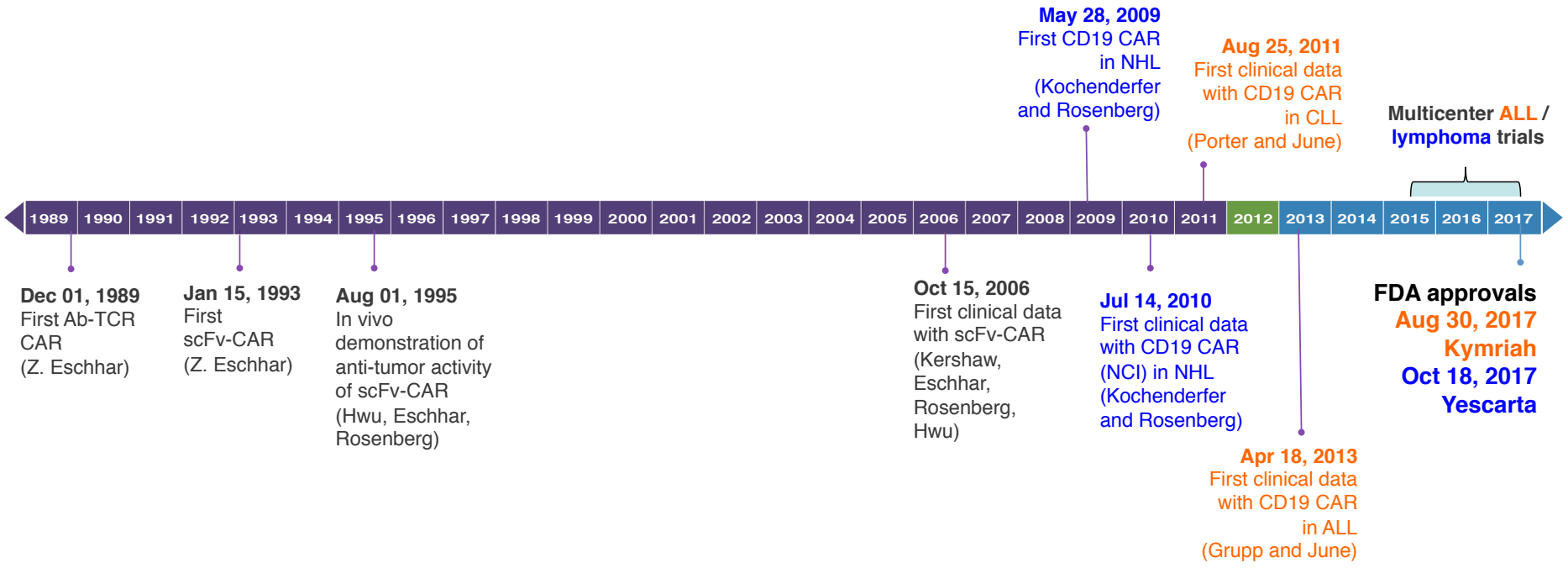
4th Postgraduate Lymphoma Conference, Rome, Italy
March 15-16, 2018

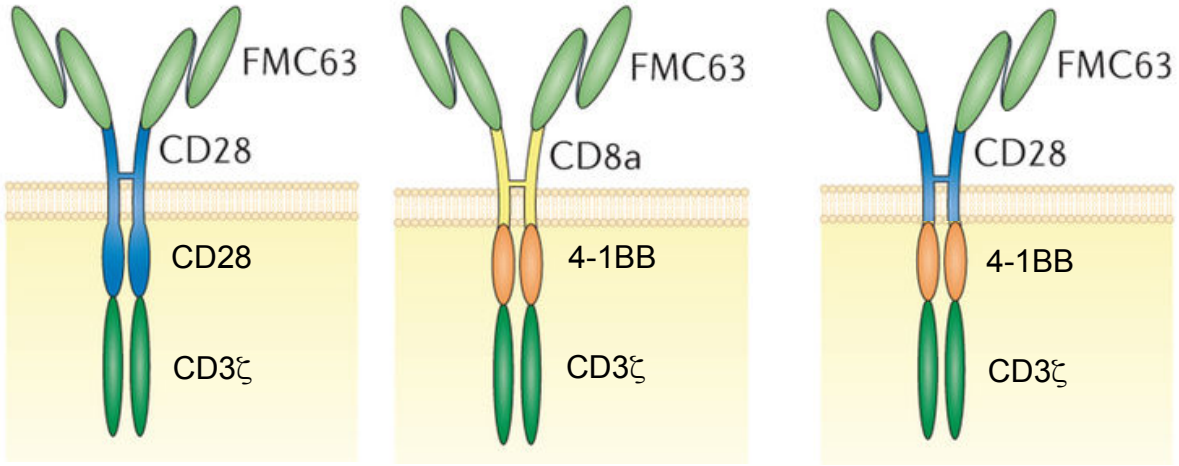
CAR T development: From discovery to FDA approval

Discovery to FDA approval ~25 years



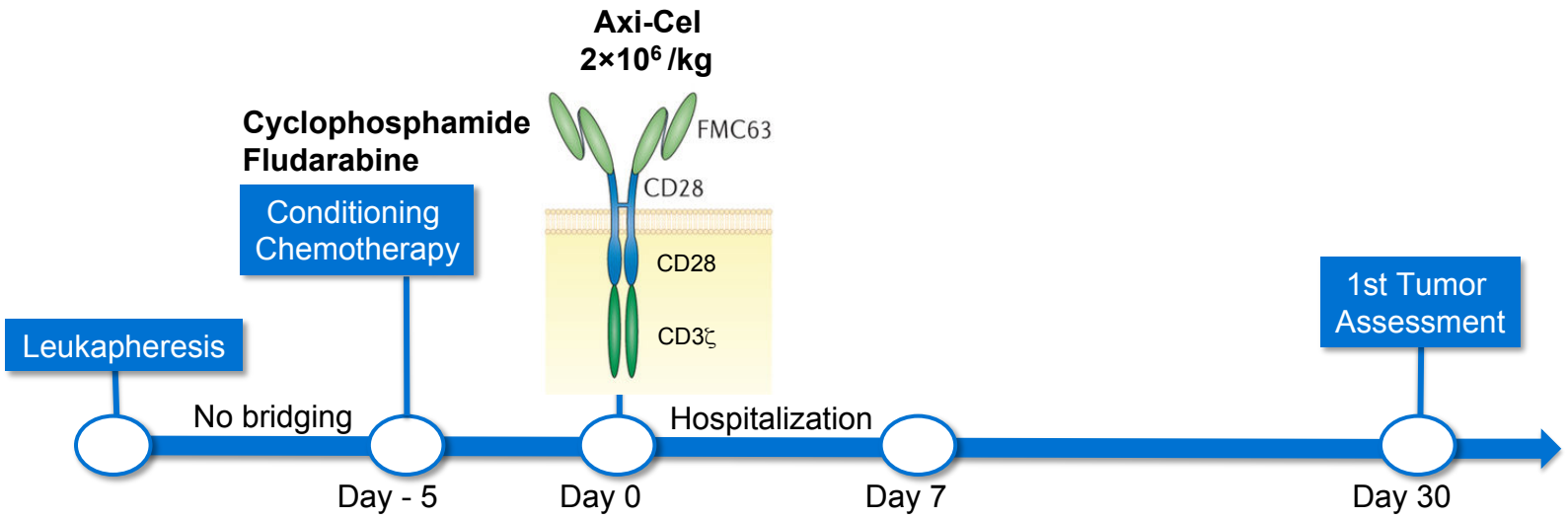
CD19 CAR T products in pivotal trials in NHL

	NCI	U Penn	FHCRC / SCH
CD19 Ab	FMC63	FMC63	FMC63
Hinge Transmembrane	CD28	CD8a	CD28
Signal 2	CD28	4-1BB	4-1BB
Signal 1	CD3ζ	CD3ζ	CD3ζ
Gene transfer	Retrovirus	Lentivirus	Lentivirus
	Kite Pharma **KTE-C19** **Axicabtagene ciloleucel** **Axi-cel**	**Novartis** **CTL-019** **Tisagenlecleucel**	**Juno Therapeutics** **JCAR017 (CD4:CD8 = 1:1)** **Lisocabtagene maraleucel** **Liso-cel**

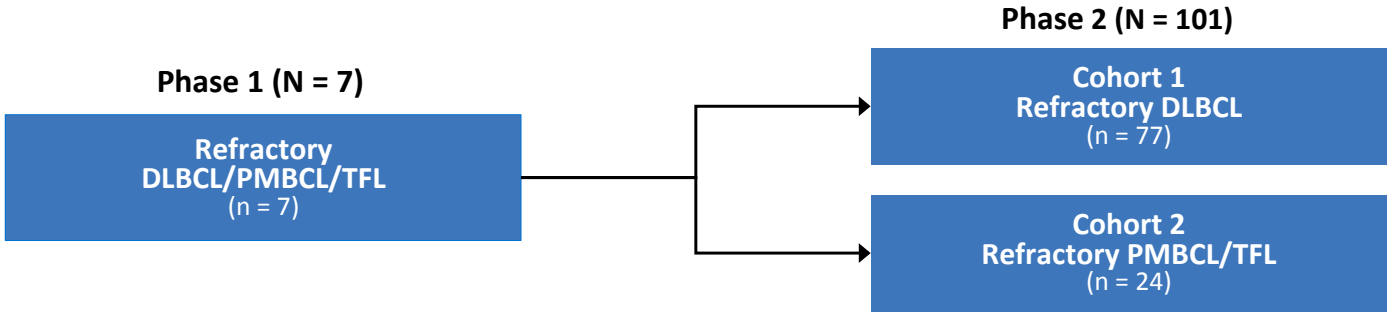


Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

ZUMA1: Multicenter trial of axi-cel CD19 CAR T therapy in refractory aggressive B-cell NHL



ZUMA1: Phase 1/2 study design



Key eligibility criteria

- No response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

- **N = 108**
- **Data cutoff: August 11, 2017**
- **Median follow-up: 15.4 months**

Conditioning regimen

- Cyclophosphamide 500 mg/m^2 + fludarabine 30 mg/m^2 for 3 days

Axi-cel: 2 × 10^6 CAR+ cells/kg

- 99% enrolled were successfully manufactured
- 91% enrolled were dosed
- 17-day average turnaround time from apheresis to delivery to clinical site

ASCT, autologous stem cell transplant.

ZUMA1: Baseline patient characteristics

Characteristic	Phase 1 and 2 N = 108
Median (range) age, y	58 (23 – 76)
≥ 65 y, n (%)	27 (25)
Male, n (%)	73 (68)
ECOG 1, n (%)	62 (57)
Disease stage III/IV, n (%)	90 (83)
IPI score 3-4, n (%)	48 (44)
≥ 3 prior therapies, n (%)	76 (70)
Refractory Subgroup Before Enrollment	**Phase 1 and 2 N = 108**
Refractory to second- or later-line therapy, n (%) Best response as PD to last prior therapy	80 (74) 70 (65)
Relapse post-ASCT, n (%)	25 (23)

ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index.

Neelapu et al. ASH 2017

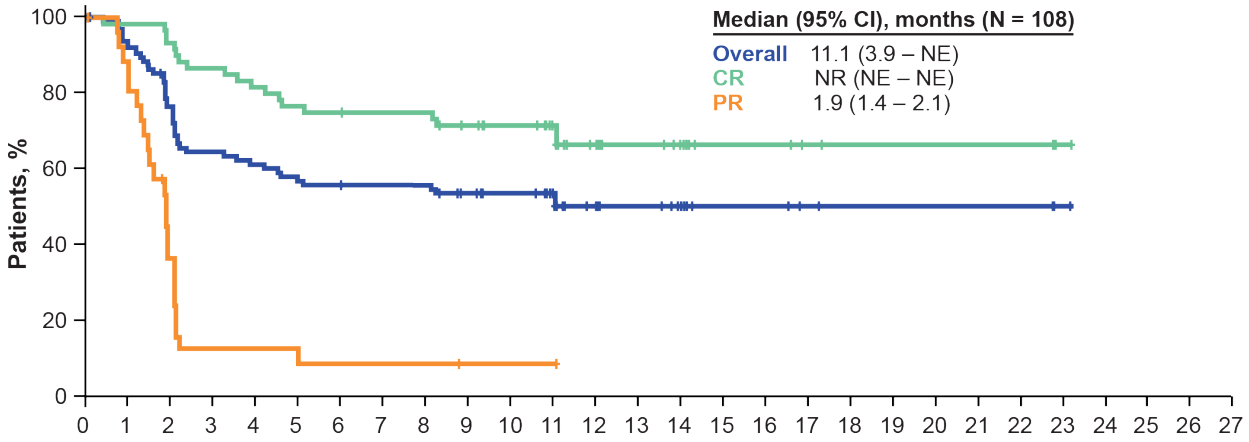
ZUMA1: Efficacy

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, mo	8.7		15.4	
	ORR	**CR**	**ORR**	**CR**
Best objective response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49 – 424) days
- Study met primary endpoint for ORR ($p < 0.0001$) at primary analysis

Neelapu et al. N Eng J Med 2017

ZUMA1: Duration of response by best objective response



Patients at Risk

Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
PR	26	21	9	3	3	2	2	2	2	1	1	1	0												

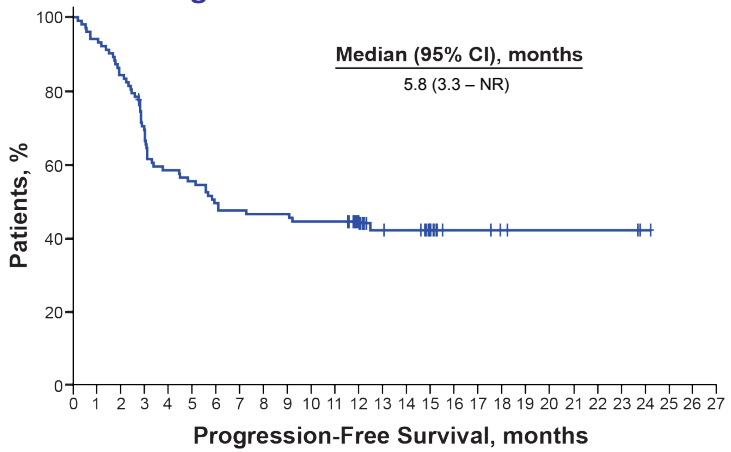
- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients have ongoing CR at 24 months

CR, complete response; NR, not reached; PR, partial response.

Neelapu et al. N Eng J Med 2017

ZUMA1 at median f/u of 15.4 months: 42% progression-free and 56% alive

Progression-Free Survival

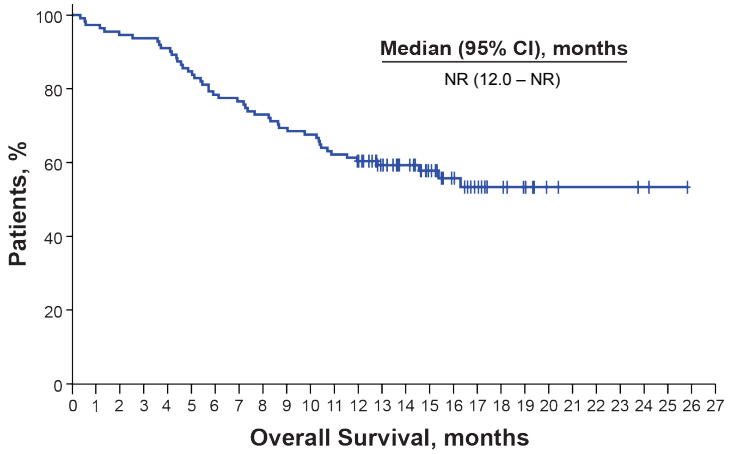


Patients at Risk

108 90 61 52 49 47 34 20 6 4 3 3 1

Landmark	PFS
6-month	49
12-month	44
18-month	41

Overall Survival



Patients at Risk

108 102 98 84 78 72 63 40 23 11 4 3 2 0

Landmark	OS
6-month	78
12-month	59
18-month	52

NR, not reached; OS, overall survival; PFS, progression-free survival.

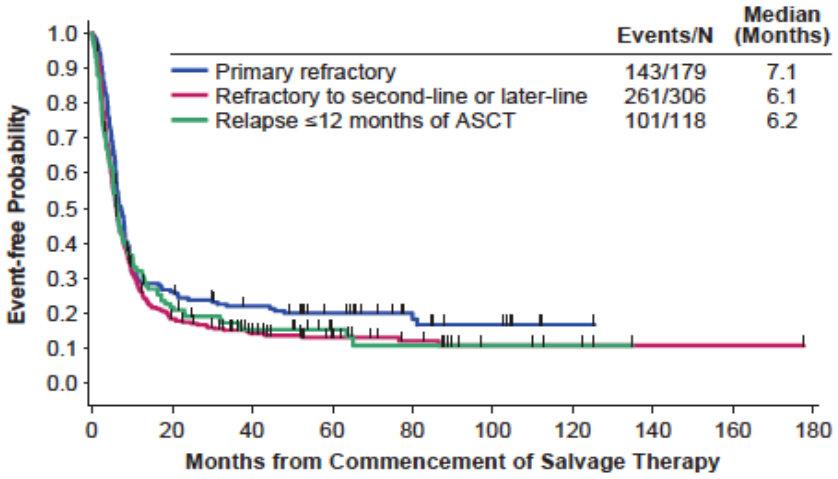
Neelapu et al. N Eng J Med 2017

SCHOLAR-1: Outcomes in refractory aggressive B-cell NHL

(SCHOLAR - Retrospective Non-Hodgkin Lymphoma Research)

- Meta-analysis to evaluate the outcomes in chemorefractory DLBCL
- CORAL, CCTG-LY12, MDACC, Mayo-Iowa
- Chemorefractory patient population
  - ✓ SD/PD after primary or later-lines of therapy
  - ✓ Relapse ≤12 months after ASCT
- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

Overall survival



Crump, Neelapu et al, Blood 2017

Multicenter CD19 CAR T-cell trials in aggressive NHL

Study / Sponsor	ZUMA1 / Kite	JULIET / Novartis	TRANSCEND / Juno
Reference	Neelapu et al, NEJM 2017	Schuster et al, ASH 2017	Abramson et al, ASH 2017
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	Up to 1-5 x 10^8	0.5-1 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL / FL Gr 3B
Treated/Enrolled	101/111 (91%)	99/147 (67%)	108/140 (77%)
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	21%	47%	42%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	94%	98%

Efficacy in multicenter CD19 CAR T trials in adult NHL

		Best response			Durability				
Study/Sponsor	**Product**	**N**	**Best ORR**	**Best CR rate**	**F/U mo**	**N**	**Durable ORR**	**Durable CR rate**	**Ref**
ZUMA1 / Kite	CD19/CD3ζ/ CD28	108	82%	58%	12	108	42%	40%	Neelapu et al, NEJM 2017
JULIET / Novartis	CD19/CD3ζ/ 4-1BB	81	53%	40%	6	46	37%	30%	Schuster et al, ASH 2017
TRANSCEND / Juno	CD19/CD3ζ/ 4-1BB	65	80%	55%	6	38	47%	42%	Abramson et al, ASH 2017

CRS and NT in multicenter CD19 CAR T trials in adult NHL

Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Ref
ZUMA1 / Kite	CD19/CD3ζ/ CD28	101	93%	13%	64%	28%	Neelapu et al, NEJM 2017
JULIET / Novartis	CD19/CD3ζ/ 4-1BB	99	58%	23%	21%	12%	Schuster et al, ASH 2017
TRANSCEND / Juno	CD19/CD3ζ/ 4-1BB	67	36%	1%	21%	15%	Abramson et al, ASH 2017

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism

ZUMA1: Tocilizumab/Steroid use did not impact responses but was associated with higher CAR T cell levels

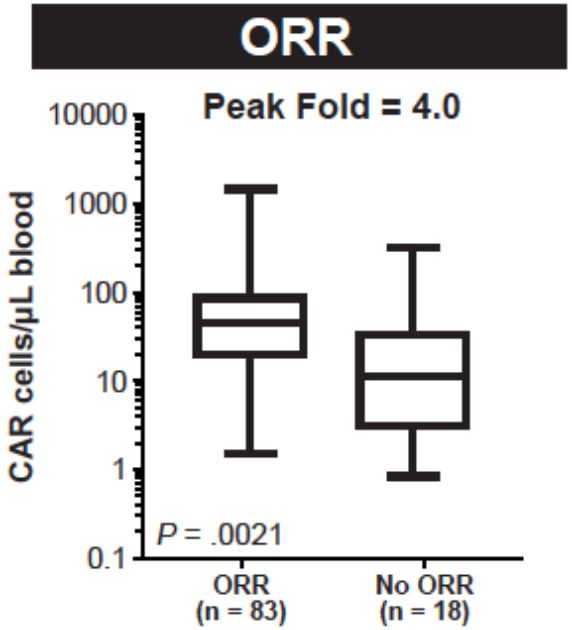
	Tocilizumab			Steroids		
	Without n = 58	With n = 43	*P* Value	Without n = 74	With n = 27	*P* Value
ORR, n (%)	47 (81.0)	36 (83.7)	.8	62 (83.8)	21 (77.8)	.56
CR, n (%)	33 (56.9)	22 (51.2)	.69	40 (54.1)	15 (55.6)	1
Ongoing, n (%)	28 (48.3)	16 (37.2)	.31	33 (44.6)	11 (40.7)	.82
Median peak CAR, cells/μL (range)	27 (1-1226)	61 (1-1514)	.0011	32 (1-1226)	50 (1-1514)	.0618
Median CAR AUC, cells/μL days (range)	290 (17-14329)	744 (5-11507)	.0022	408 (17-14329)	725 (5-11507)	.0967

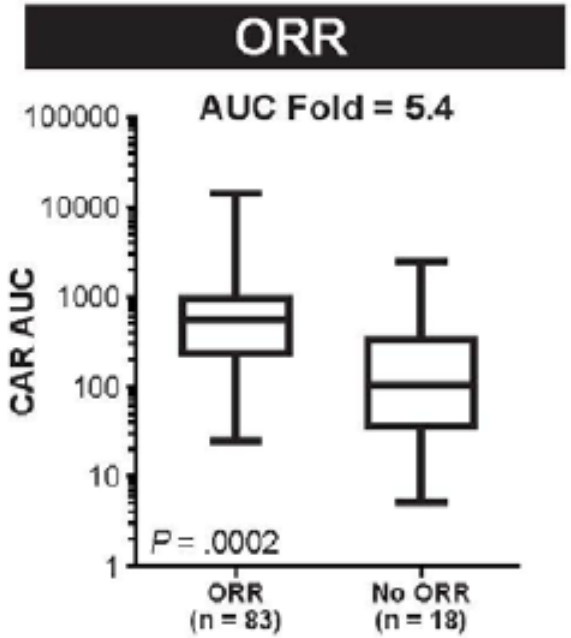
Neelapu et al. ICML 2017, Abstract 8

ZUMA1: Biomarkers of response after axi-cel

Covariate	Impact on efficacy
Clinical prognostic markers	
Age, stage, IPI, bulky, extranodal, refractory subgroup, primary refractory, prior ASCT	No
Product characteristics	
CD4:CD8 ratio	No
Phenotype	No
T-cell doubling time	No
Tumor characteristics	
Cell of origin (ABC vs. GCB)	No
DLBCL vs. PMBCL vs. TFL	No
CD19 H score	No
Post-infusion	
Peak CAR and CAR-AUC	Yes
Tocilizumab and steroid use	No

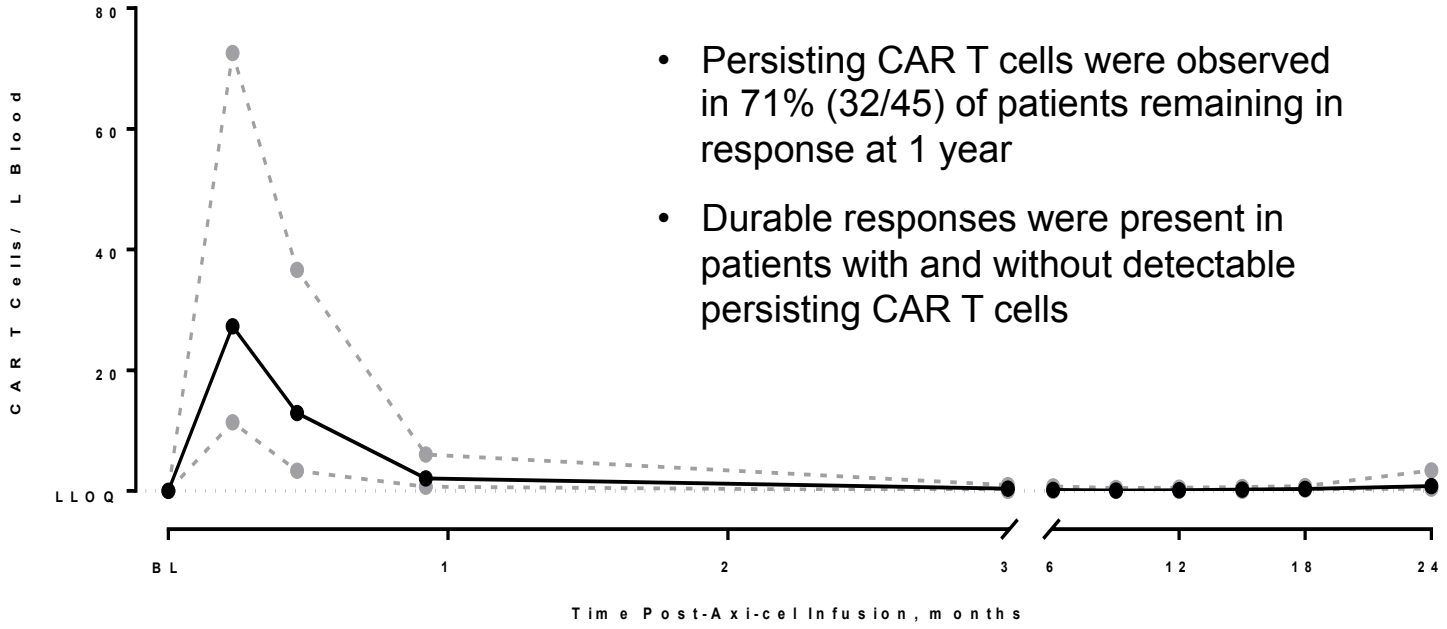
ZUMA1: CAR T-cell expansion after axi-cel infusion is associated with response





Neelapu et al. N Eng J Med 2017

ZUMA1: CAR T-cell expansion and persistence after axi-cel infusion



- Persisting CAR T cells were observed in 71% (32/45) of patients remaining in response at 1 year
- Durable responses were present in patients with and without detectable persisting CAR T cells

BL, baseline; LLOQ, lower level of quantification.
Solid line indicates median. Dashed lines indicate Q1 and Q3.

Neelapu et al. ASH 2017

ZUMA1: CD19 loss at progression suggests a potential mechanism of axi-cel resistance in NHL

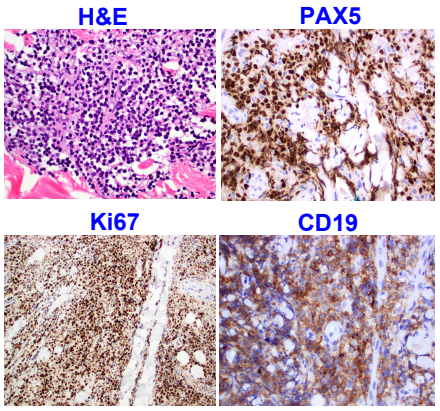
Progression Biopsies

N = 21

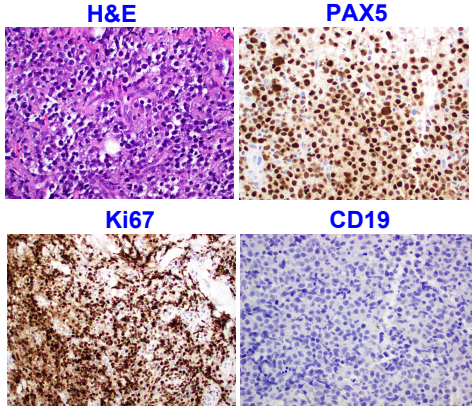
CD19 (n = 21)

- **CD19+** 14/21 (67)
- **CD19-** 7/21 (33)

Pre-axi-cel



Post-axi-cel



Neelapu et al. ASH 2017

Alternatively spliced variants of CD19 after CAR T therapy

- At relapse, 15/16 (94%) patients assessed had CD19 loss on ELIANA trial

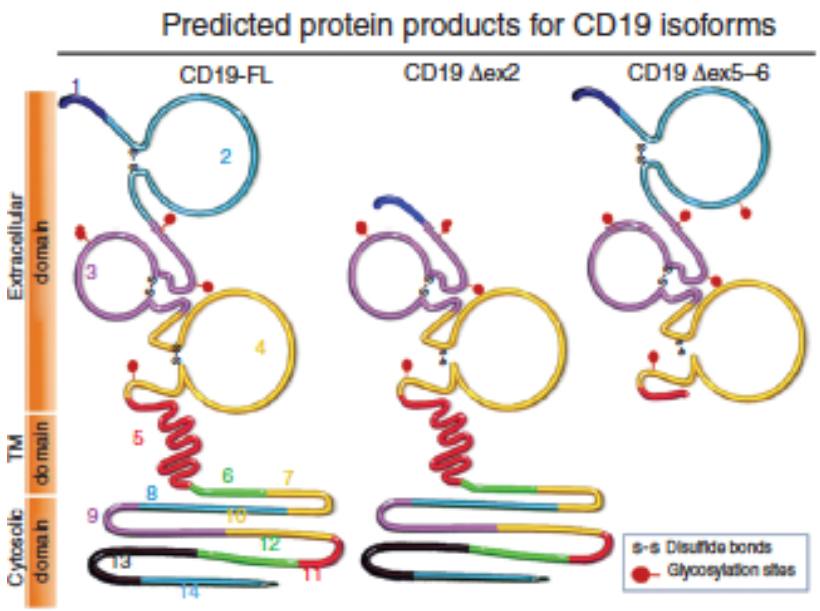
Maude et al, N Eng J Med 2018

Cancer Discov 2015

Convergence of Acquired Mutations and Alternative Splicing of *CD19* Enables Resistance to CART-19 Immunotherapy

Elena Sotillo[1], David M. Barrett[2], Kathryn L. Black[1], Asen Bagashev[1], Derek Oldridge[2], Glendon Wu[1,3], Robyn Sussman[2], Claudia Lanauze[1,4], Marco Ruella[5], Matthew R. Gazzara[6,7], Nicole M. Martinez[7], Colleen T. Harrington[1,4], Elaine Y. Chung[1], Jessica Perazzelli[2], Ted J. Hofmann[2], Shannon L. Maude[2] Pichai Raman[1,2], Alejandro Barrera[6], Saar Gill[5,8], Simon F. Lacey[8], Jan J. Melenhorst[8], David Allman[9], Elad Jacoby[10], Terry Fry[10], Crystal Mackall[10], Yoseph Barash[5], Kristen W. Lynch[6], John M. Maris[2], Stephan A. Grupp[2], and Andrei Thomas-Tikhonenko[1,3,4,9]

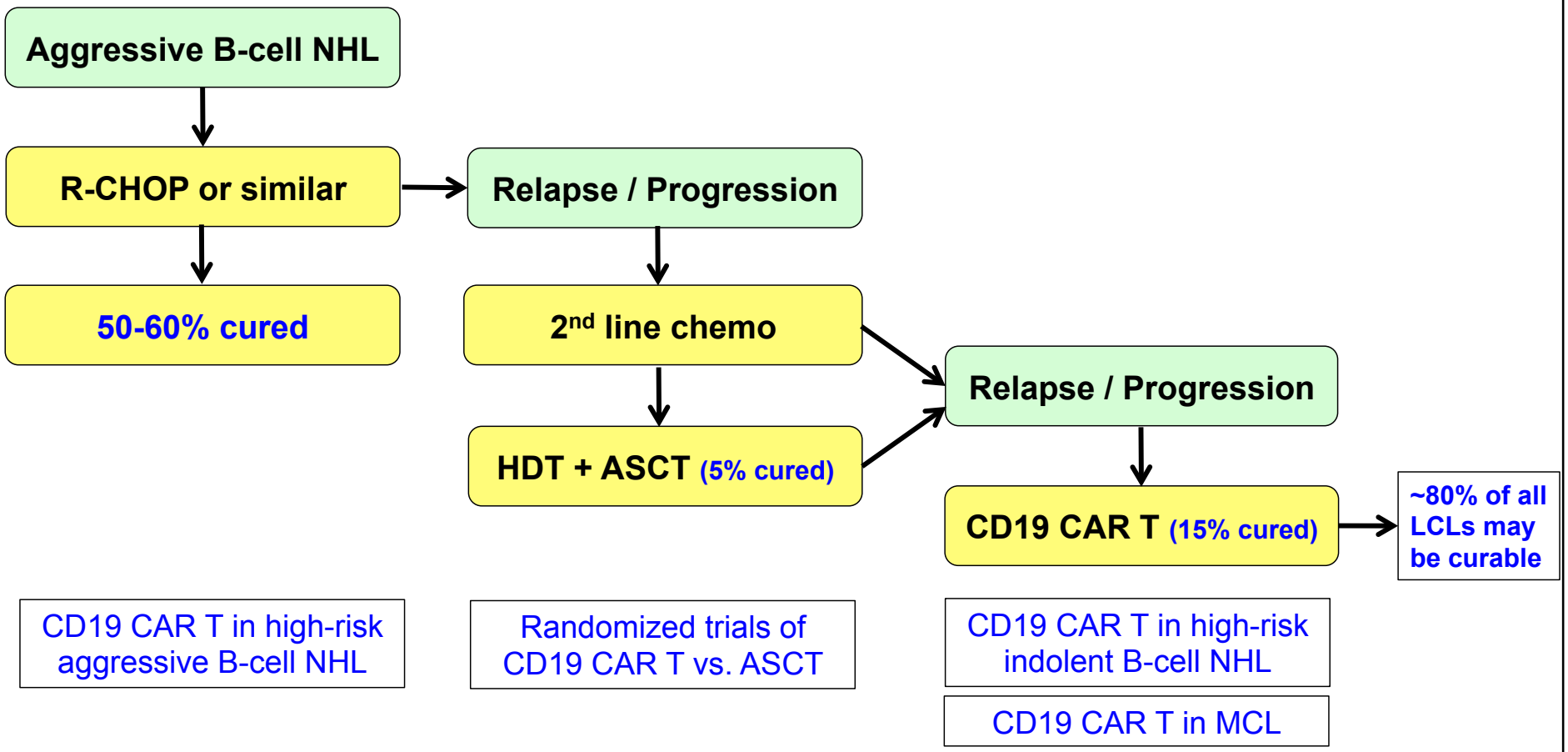
Loss of exon 2 or exons 5-6



CD19 CAR T in NHL: Key Takeaways

- Pivotal trials in adult aggressive NHL met primary endpoints for ORR and one product has been approved by the FDA
- Centralized manufacturing is feasible with turnaround time of ~2-3 weeks
- Durable remissions in ~40% of aggressive NHL patients
- Effective in multiple aggressive NHL subtypes – GCB, ABC, PMBCL, TFL, DHL, THL, CNS lymphoma
- CRS and neurotoxicity are the major toxicities but generally reversible
- Responding patients return to near-normal quality of life
- CD19 loss may be a common mechanism of escape after axi-cel therapy

CD19 CAR T in NHL: Beginning of a paradigm shift



Future directions

Improving efficacy

- Understand mechanisms of resistance
- Bi/multi-specific CAR T cells to overcome antigen escape (CD19+CD22 or CD19+CD20)
- CAR T + Immunomodulators

Improving safety

- Toxicity management guidelines
- Prophylactic interventions
- Safety switches to induce suicide or eliminate CAR T

CARTOX Guidelines REVIEWS

Nat Rev Clin Oncol, Jan 2018

Chimeric antigen receptor T-cell therapy — assessment and management of toxicities

Sattva S. Neelapu[1], Sudhakar Tummala[2], Partow Kebriaei[3], William Wierda[4], Cristina Gutierrez[5], Frederick L. Locke[6], Krishna V. Komanduri[7], Yi Lin[8], Nitin Jain[4], Naval Daver[4], Jason Westin[1], Alison M. Gulbis[9], Monica E. Loghin[2], John F. de Groot[2], Sherry Adkins[1], Suzanne E. Davis[10], Katayoun Rezvani[3], Patrick Hwu[10], Elizabeth J. Shpall[3]

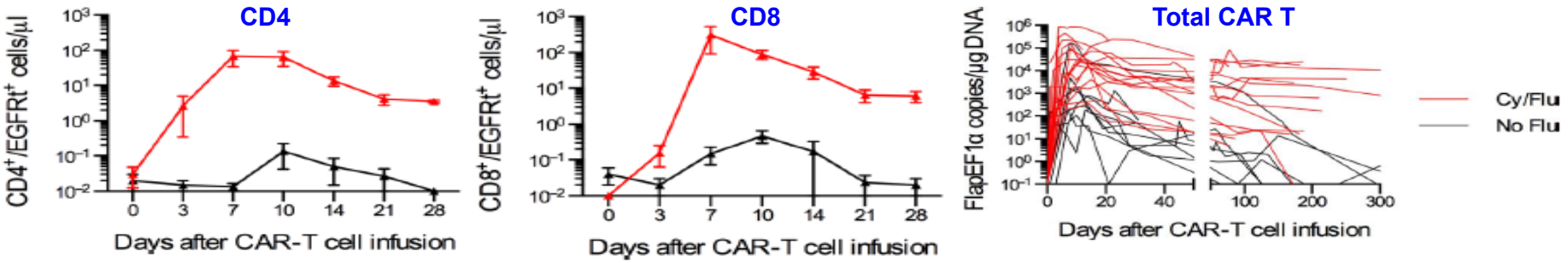
Improving access

- CAR T therapy for other lymphomas and earlier stages of disease
- Allogeneic off-the-shelf CAR T
- Reducing cost of therapy

Thank you!

Conditioning chemotherapy affects CAR T cell expansion, persistence, and clinical outcome

DLBCL, transformed LBCL, FL, MCL (**CD19/CD3ζ/4-1BB)**



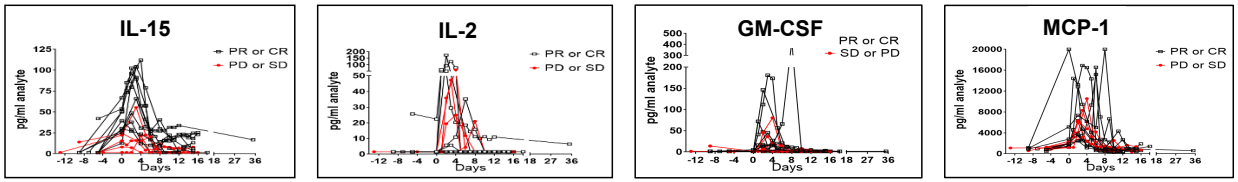
- CAR T cells reached higher peaks and persisted longer with Cy/Flu conditioning regimen compared with Cy regimen

Subgroup	N	ORR	CR
Cy or Cy/E	12	50%	8%
Cy/Flu	18	72%	50%

Turtle et al, Science Trans Med, 2016

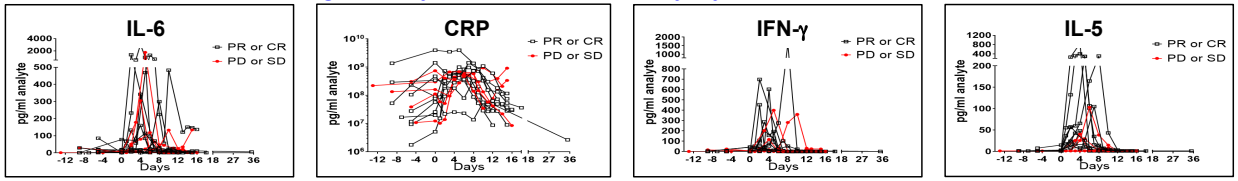
Cytokine storm after axi-cel CAR T infusion

Peaking on days 3-4: Immune homeostatic cytokines, chemokines



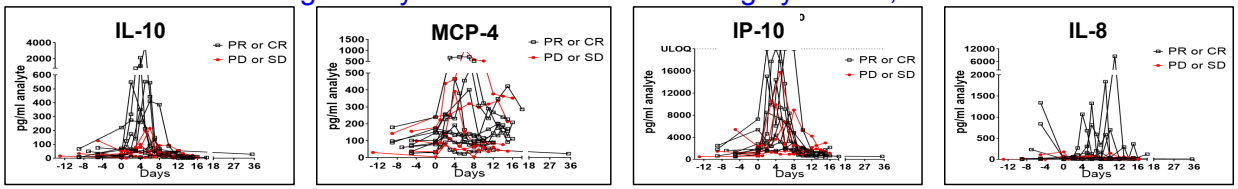
Help T cells grow

Peaking on days 5-7: Inflammatory cytokines and markers

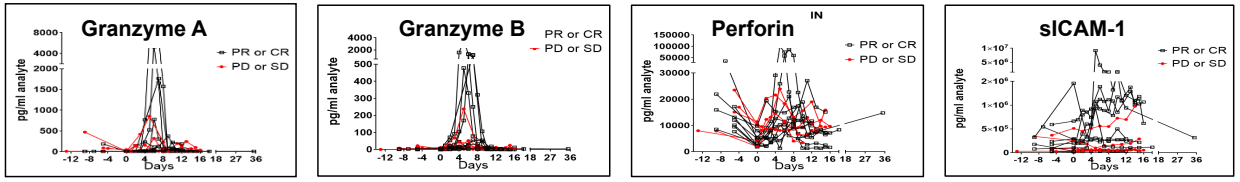


Make T cells more functional and help trafficking

Peaking on days 5-7: Immune modulating cytokines, chemokines



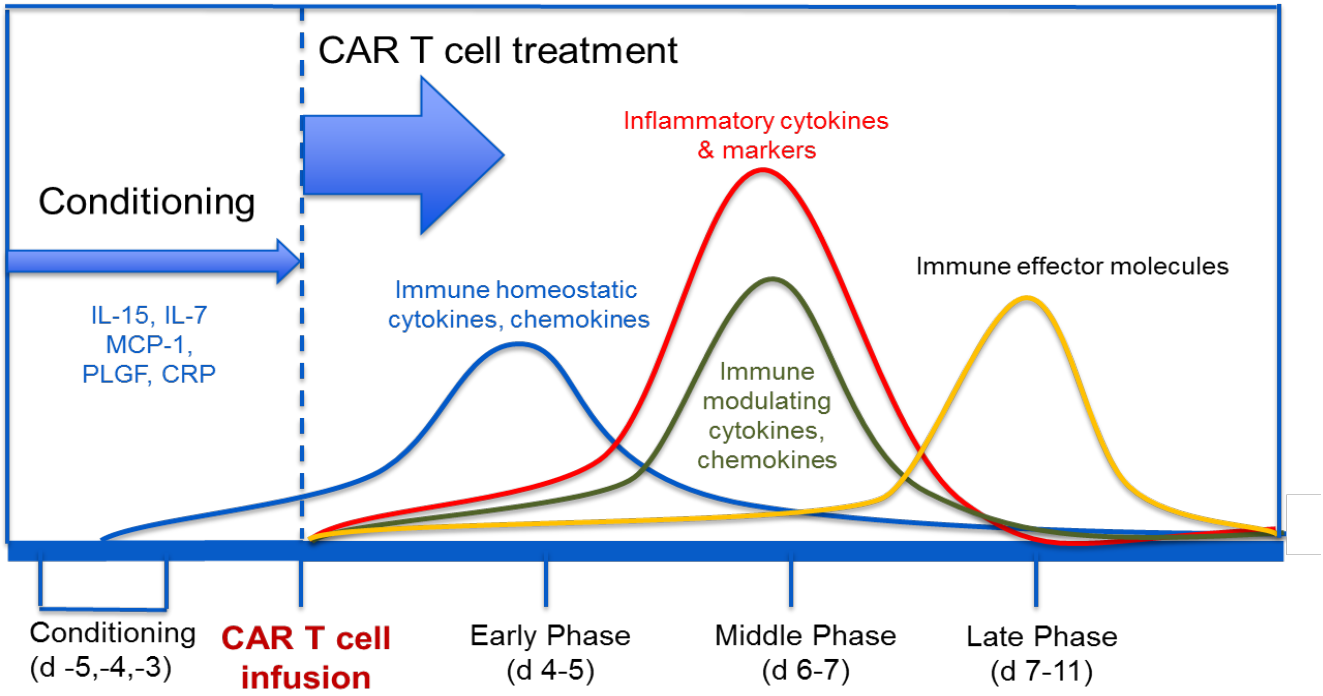
Peaking on days 7-11: Immune effector molecules



Kill target cells

Perez, et al, ASH 2015

Cytokine pattern after CAR T infusion

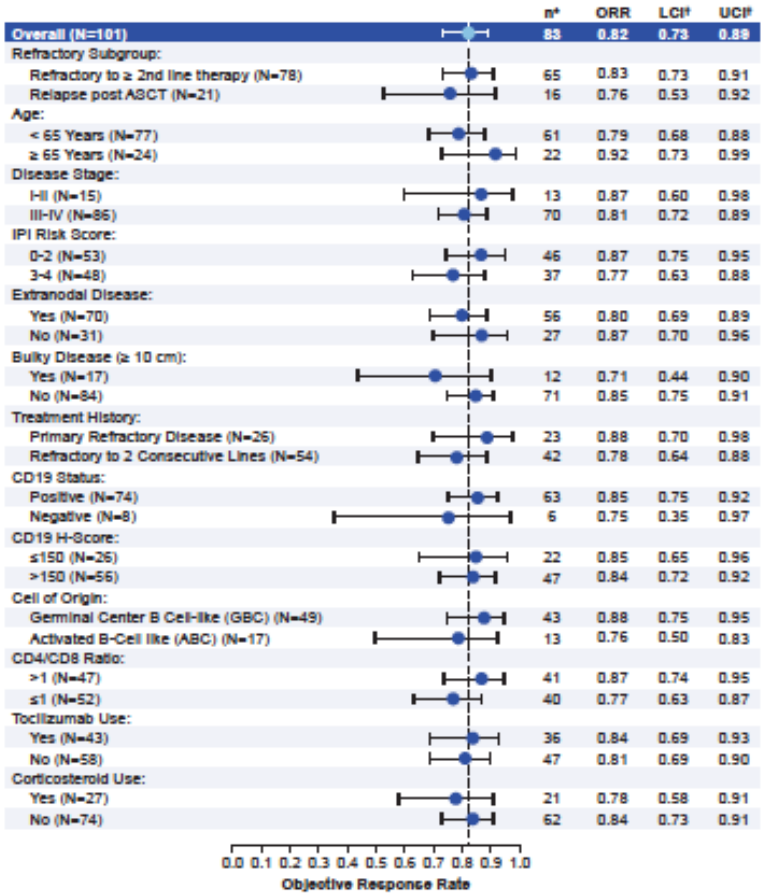


Perez, et al, ASH, 2015

Single and multicenter CD19 CAR T cell trials in adult NHL

Study/Sponsor	Product	Histology	N	ORR (%)	CR (%)	Ref
NCI	CD19/CD3ζ/CD28 with Cy/Flu (hi-dose)	DLBCL, iNHL, CLL	15	**80**	**53**	Kochenderfer et al, JCO 2015
NCI	CD19/CD3ζ/CD28 with Cy/Flu (lo-dose)	DLBCL, FL, MCL	22	**73**	**55**	Kochenderfer et al, JCO 2017
NCI	CD19/CD3ζ/CD28 post-alloSCT	DLBCL, MCL, CLL, ALL	20	**40**	**30**	Kochenderfer et al, JCO 2016
U Penn	CD19/CD3ζ/4-1BB variable conditioning	DLBCL, FL	28	**64**	**57**	Schuster et al, NEJM 2017
Fred Hutch	CD19/CD3ζ/4-1BB with Cy/Flu	DLBCL, FL, MCL	18	**72**	**50**	Turtle et al, SciTranMed 2016
ZUMA1 / Kite	CD19/CD3ζ/CD28 with Cy/Flu	DLBCL, TFL, PMBCL	108	**82**	**58**	Neelapu et al, NEJM 2017
JULIET / Novartis	CD19/CD3ζ/4-1BB with Cy/Flu	DLBCL	99	**53**	**40**	Schuster et al, ASH 2017
TRANSCEND / Juno	CD19/CD3ζ/4-1BB with Cy/Flu	DLBCL, MCL, PMBCL, FL	67	**80**	**55**	Abramson et al, ASH 2017

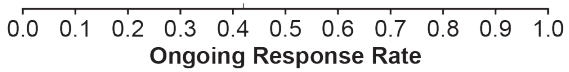
ZUMA1: Consistent responses across key covariates



Neelapu et al. N Eng J Med 2017

ZUMA1: Consistent ongoing responses (> 1 year) across key covariates

		n[a]	ORR	LCI[b]	UCI[b]
Overall (N=108)		**45**	**0.42**	**0.32**	**0.52**
Refractory Subgroup	Refractory to ≥ 2nd line therapy (N=80)	31	0.39	0.28	0.50
	Relapse post ASCT (N=25)	14	0.56	0.35	0.76
Age	< 65 Years (N=81)	32	0.40	0.29	0.51
	≥ 65 Years (N=27)	13	0.48	0.29	0.68
Disease Stage	I-II (N=18)	11	0.61	0.36	0.83
	III-IV (N=90)	34	0.38	0.28	0.49
IPI Risk Score	0-2 (N=60)	30	0.50	0.37	0.63
	3-4 (N=48)	15	0.31	0.19	0.46
Treatment History	Primary Refractory Disease (N=27)	11	0.41	0.22	0.61
	Refractory to 2 Consecutive Lines (N=55)	19	0.35	0.22	0.49
CD19 Status	Positive (N=77)	33	0.43	0.32	0.55
	Negative (N=10)	5	0.50	0.19	0.81
Cell of Origin	Germinal Center B Cell-like (GCB) (N=52)	23	0.44	0.30	0.59
	Activated B-Cell like (ABC) (N=18)	6	0.33	0.13	0.59
CD4/CD8 Ratio	>1 (N=51)	21	0.41	0.28	0.56
	≤1 (N=57)	24	0.42	0.29	0.56
Tocilizumab Use	Yes (N=49)	17	0.35	0.22	0.50
	No (N=59)	28	0.47	0.34	0.61
Corticosteroid Use	Yes (N=30)	10	0.33	0.17	0.53
	No (N=78)	35	0.45	0.34	0.57



- Median follow-up: 15.4 mo

[a]Indicates the number of evaluable patients. [b]The 95% lower confidence interval (LCI) and upper confidence interval (UCI) of the ongoing response rate were calculated using the Clopper-Pearson method. ASCT, autologous stem cell transplant; IPI, International Prognostic Index.

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