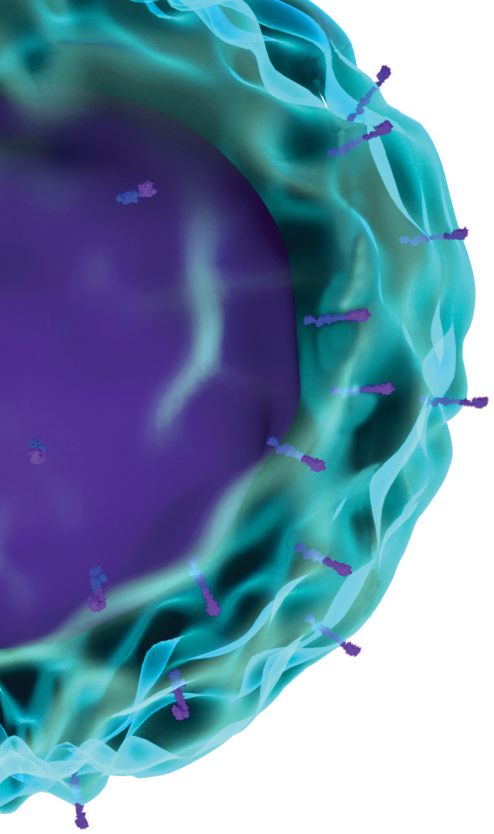


Latest Approaches to
Treating Lymphoma and Myeloma with CAR T-Cell Therapy
Strategies for Integrating Into Practice

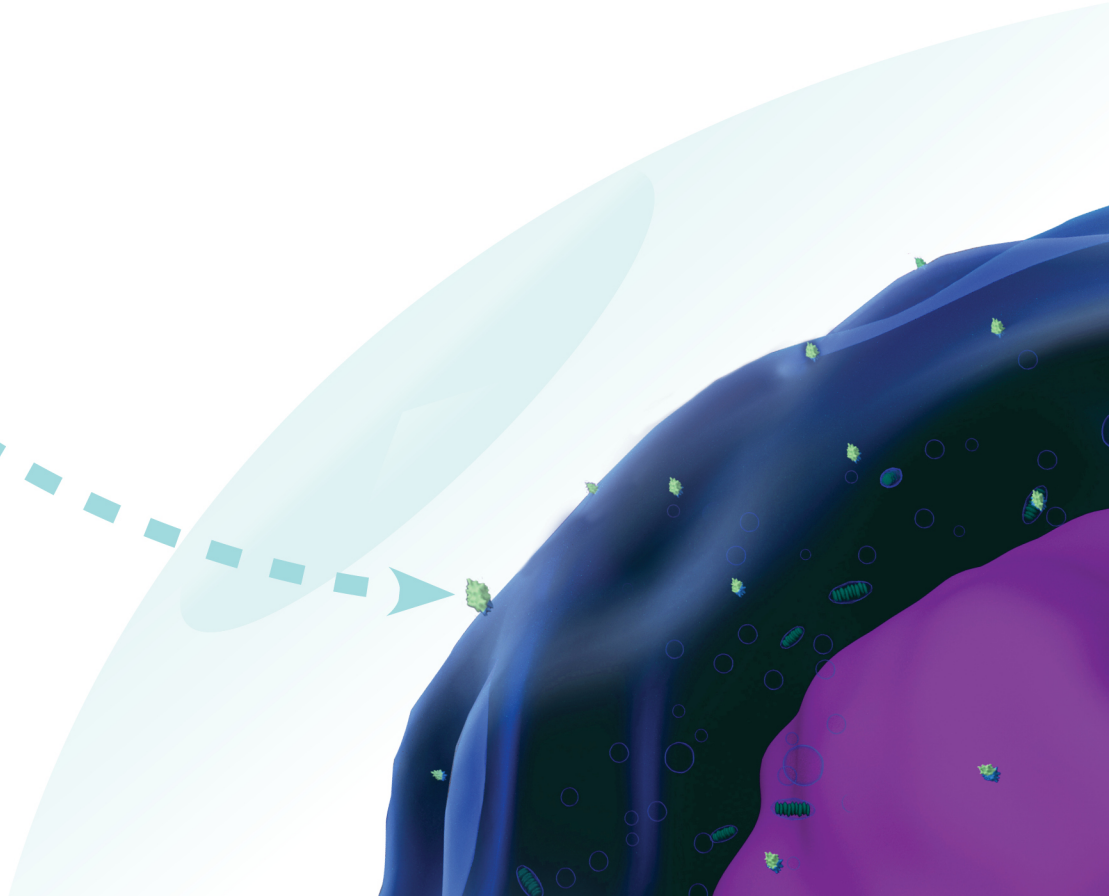
Friday, September 13, 2019

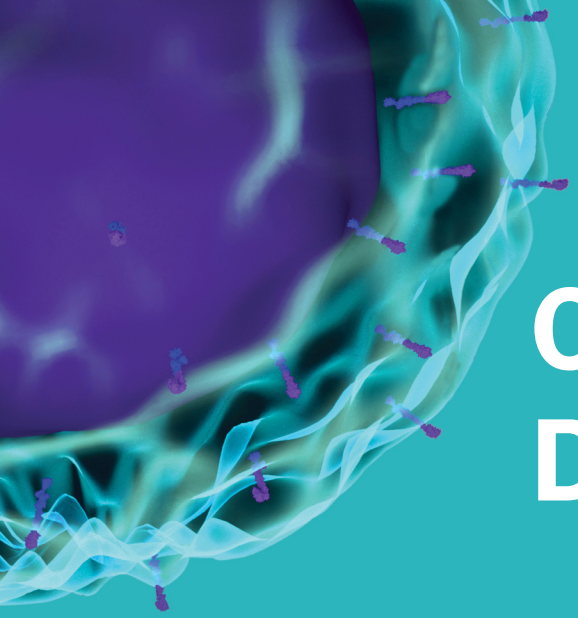
Time: 6:15 AM – 7:45 AM
Grand Ballroom, Level 4, A/B/D/E

This activity is jointly provided by The Postgraduate Institute for Medicine (PIM) and Bio Ascend.

PIM Postgraduate Institute for Medicine

Bio Ascend





Overview of CAR T Cells and Current Data of Patients with Lymphoma

Julie Vose, MD, MBA

Neumann M. and Mildred E. Harris Professor
Chief, Division of Oncology and Hematology Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

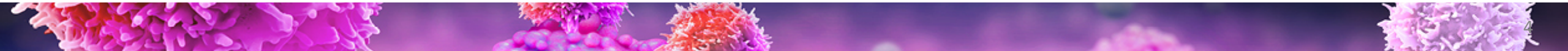
Overview of CAR-T cells and Lymphoma Trials

Julie M. Vose, M.D., M.B.A.
Chief, Hematology/Oncology
University of Nebraska Medical Center

Disclosures

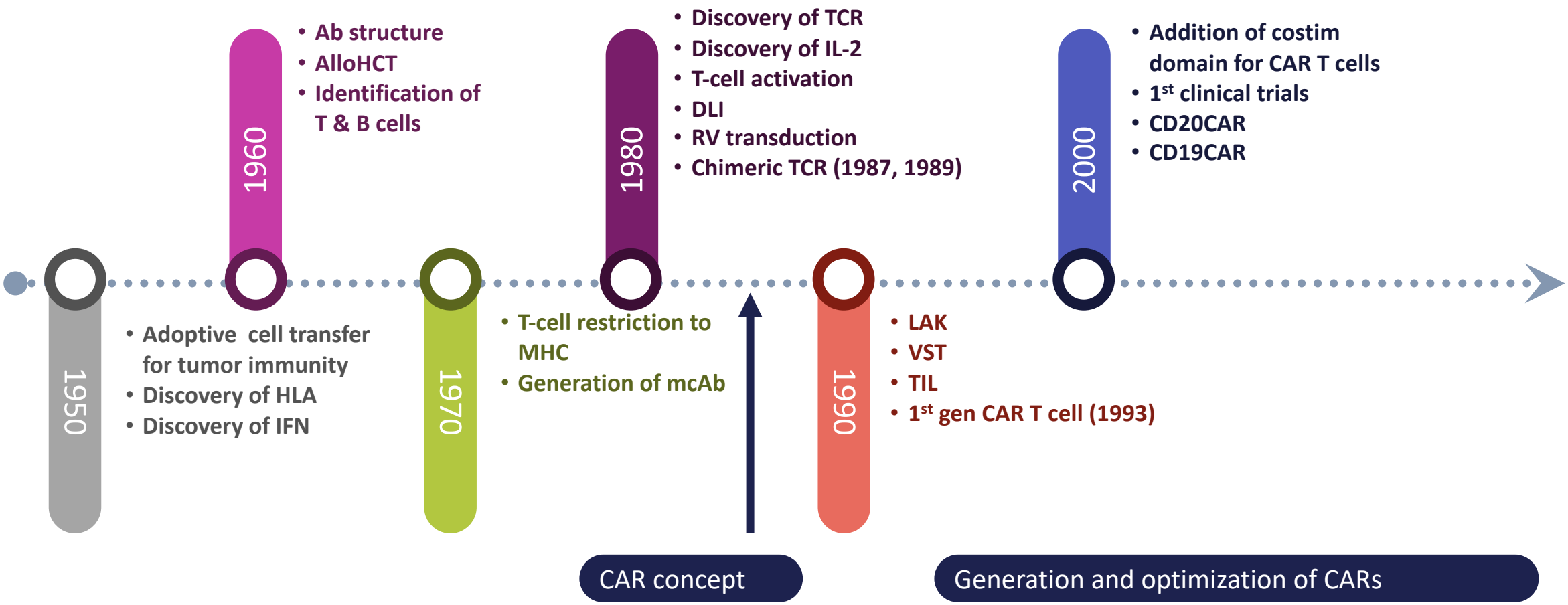
Research: Astra-Zeneca, BMS, Celgene, Incyte, Kite Pharma, Novartis, Merck, Seattle Genetics

Honorarium/Consulting: Astra-Zeneca, Abbvie, Epizyme, Legend, Janssen, Kite Pharma, Nordic Nanovector, Verastem



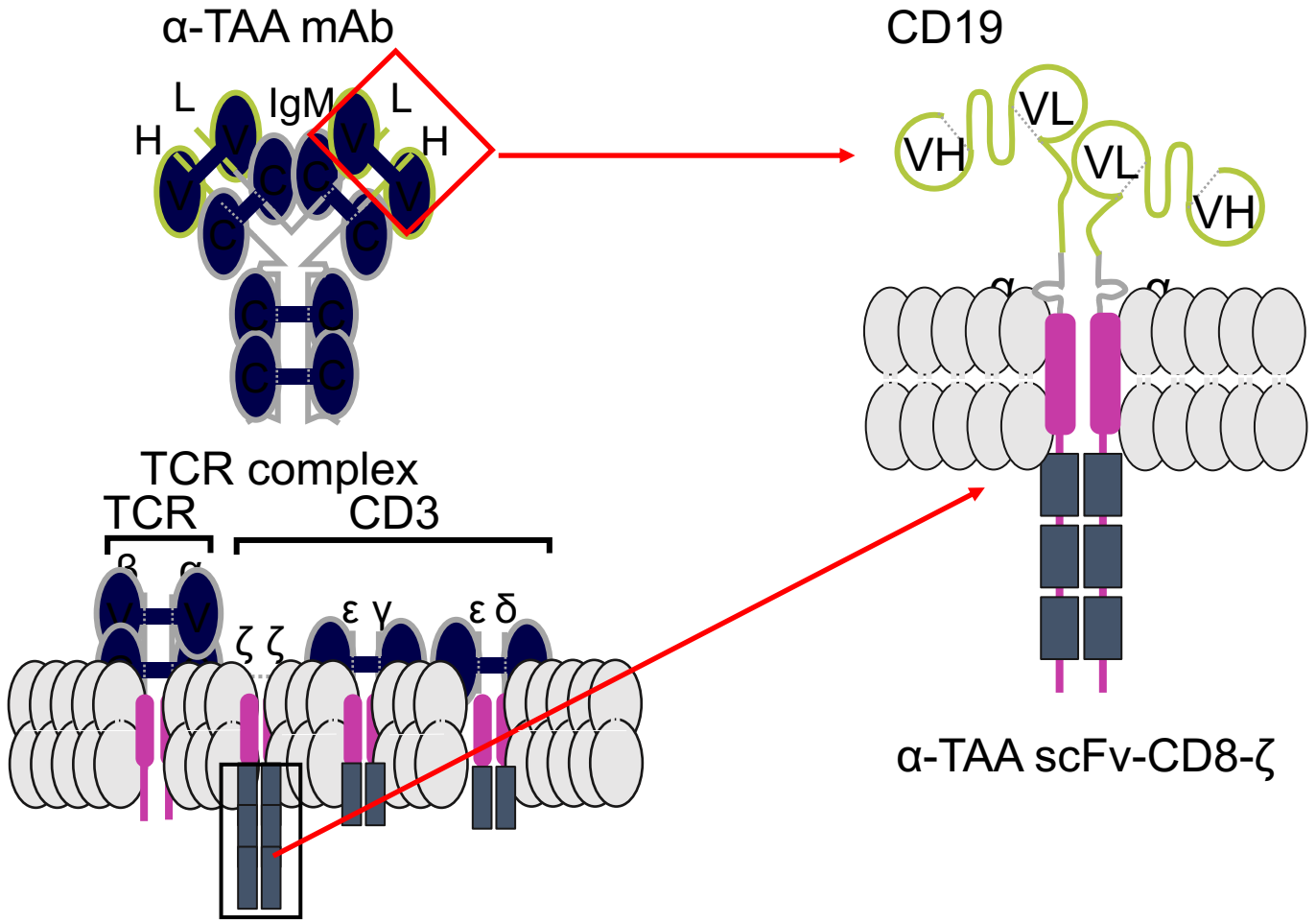
Overview of CAR T Cells

Development of Adoptive Cellular Therapy



Slide courtesy of Elizabeth Budde

Basic Structure of a Tumor-Targeted CAR



CAR =

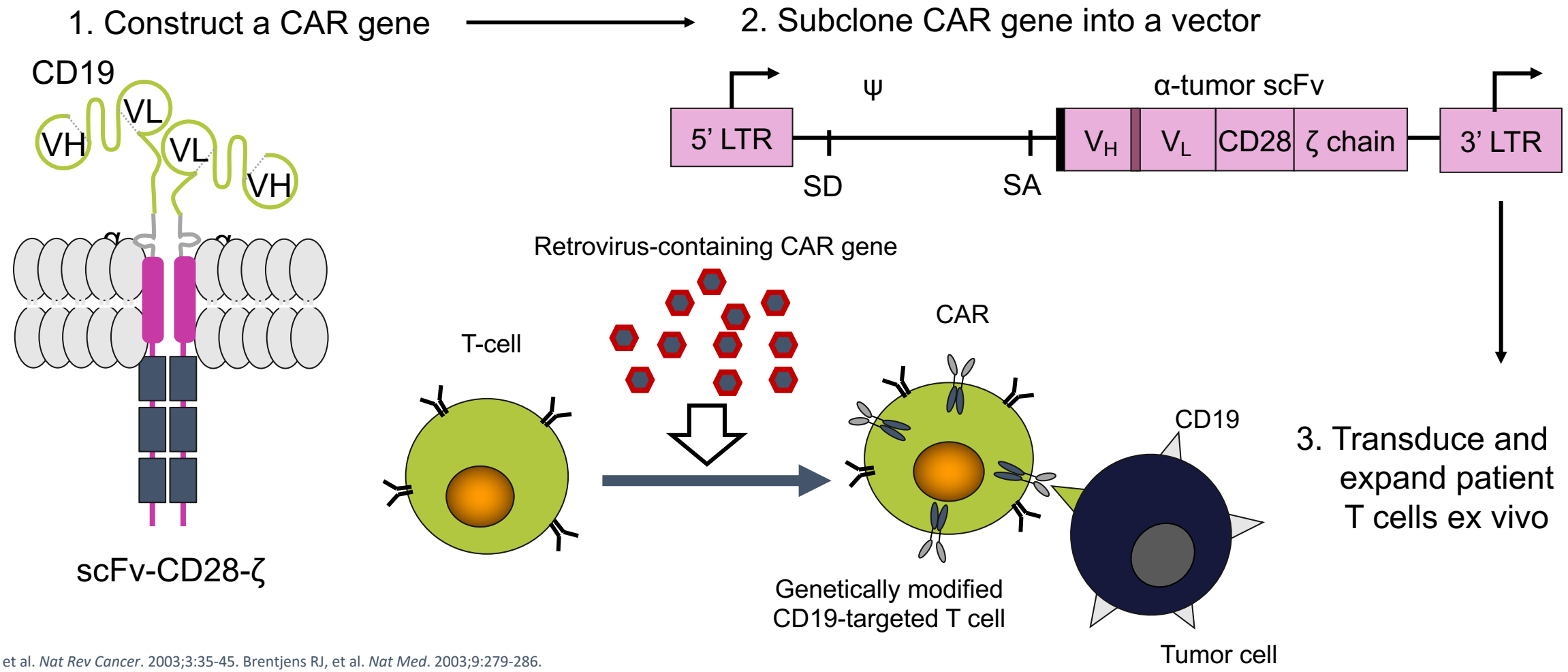
Specificity of antibody target recognition

+

Effector mechanisms of T cell

Sadelain M, et al. *Nat Rev Cancer*. 2003;3:35-45.

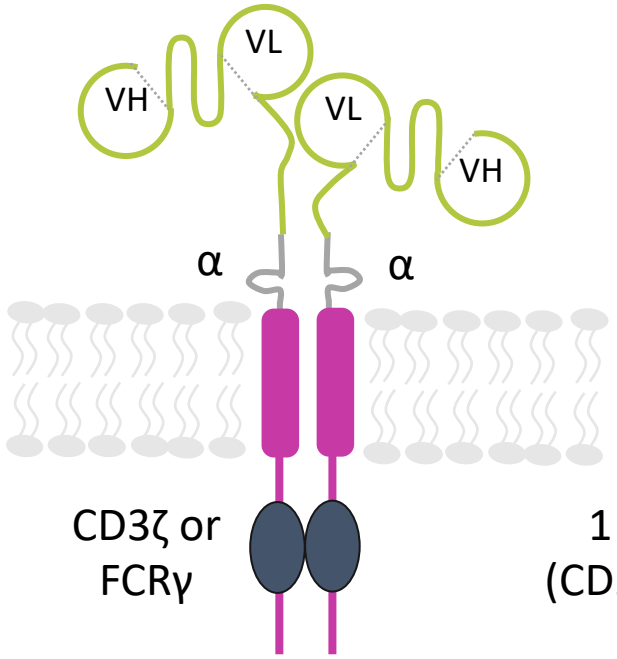
Generation of TAA-Targeted T Cells for Treatment of Cancer



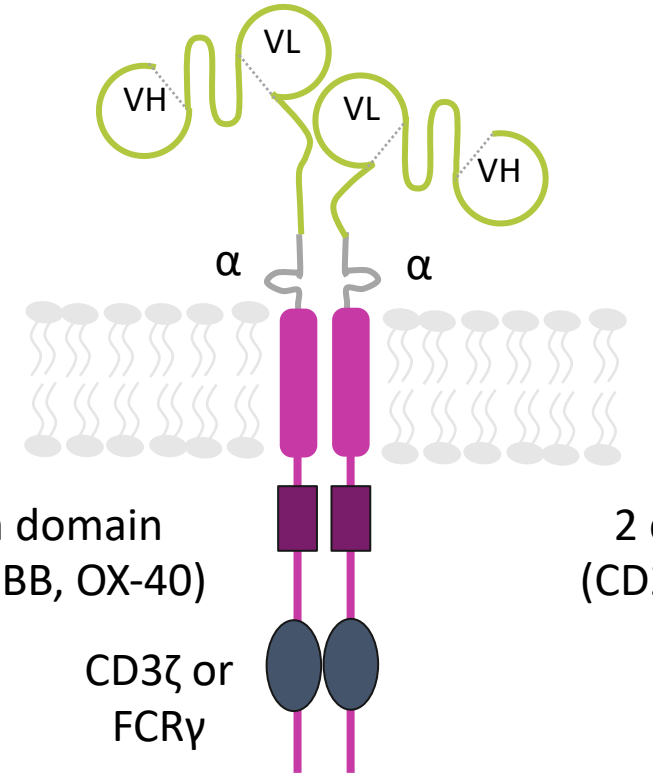
Sadelain M, et al. *Nat Rev Cancer*. 2003;3:35-45. Brentjens RJ, et al. *Nat Med*. 2003;9:279-286.

Evolution in CAR Design

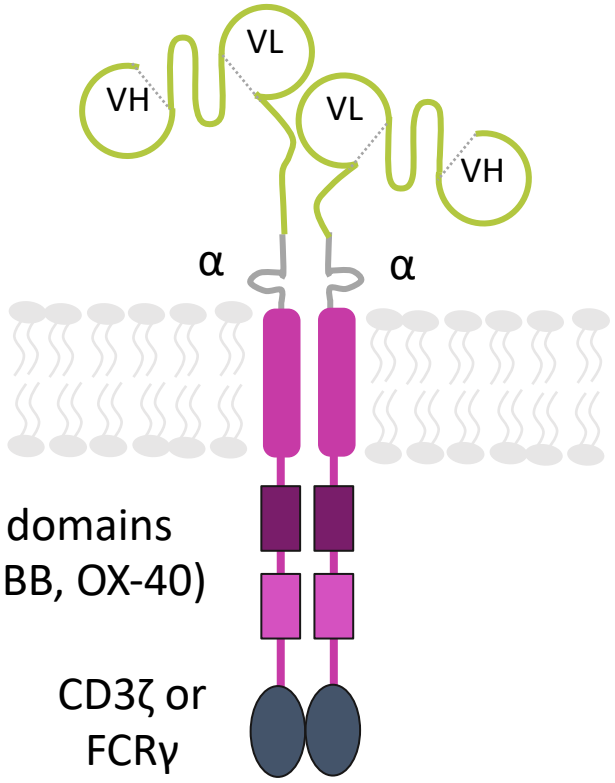
First Generation



Second Generation

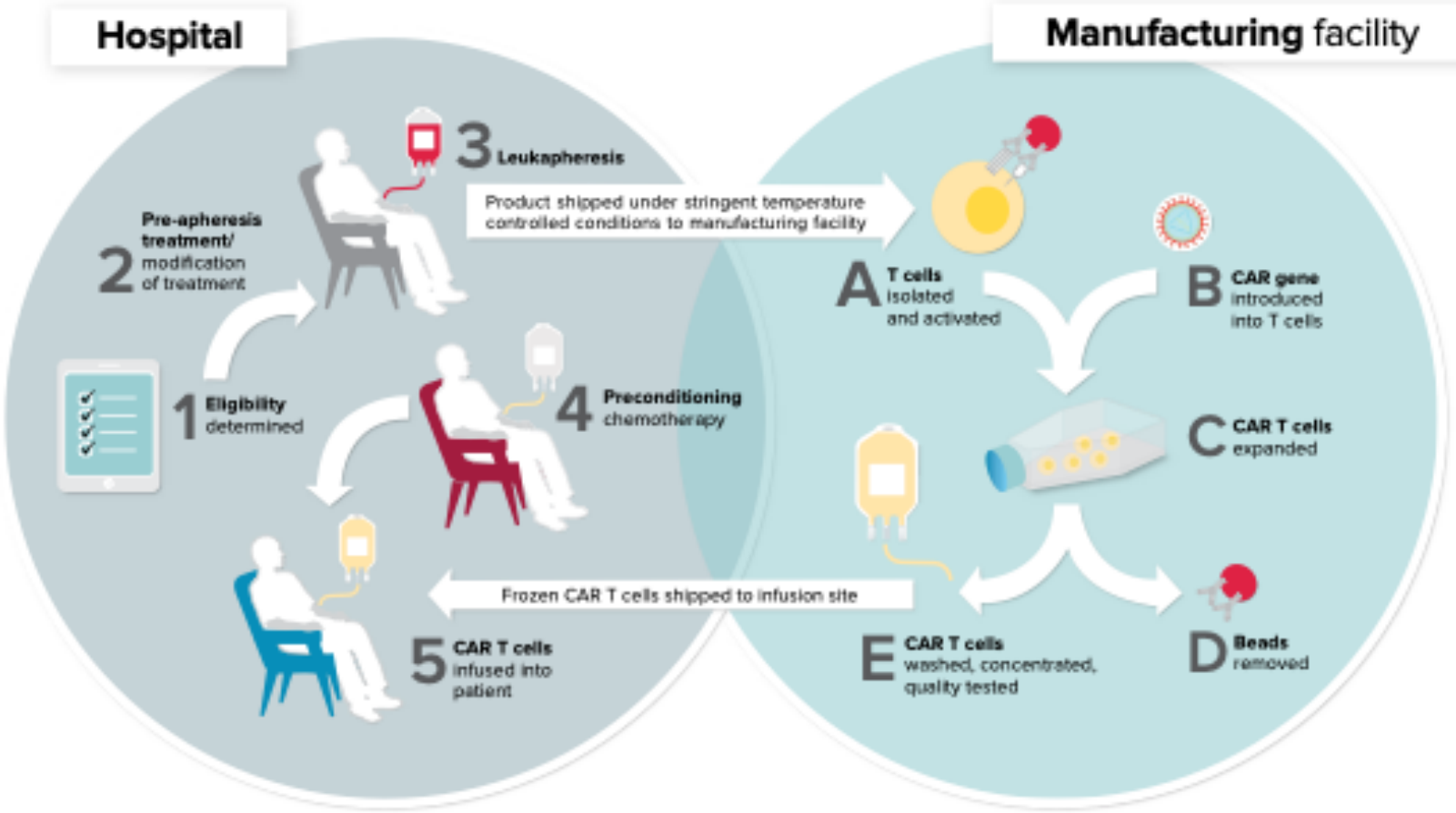


Third Generation



Park J, et al. *J Clin Oncol*. 2015;33:651-653.

How Are CAR T Cells Manufactured/Engineered?

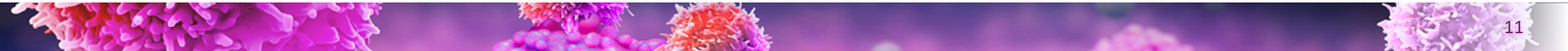


- On average, the production of CAR T cells takes approximately 10 to 14 days
- The time from endogenous T-cell collection to CAR T-cell infusion varies, but typically ranges from 1 to 4 weeks

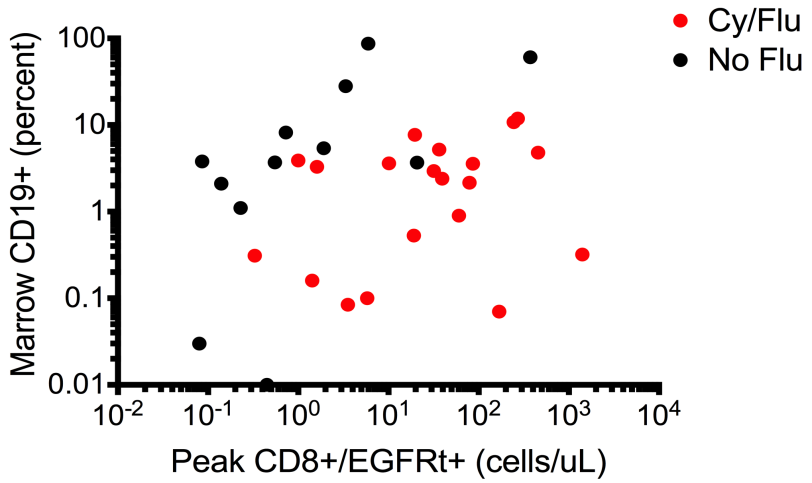
Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FSHP1_CART_Factsheet_June2018_FINAL.pdf. Accessed July 3, 2019.

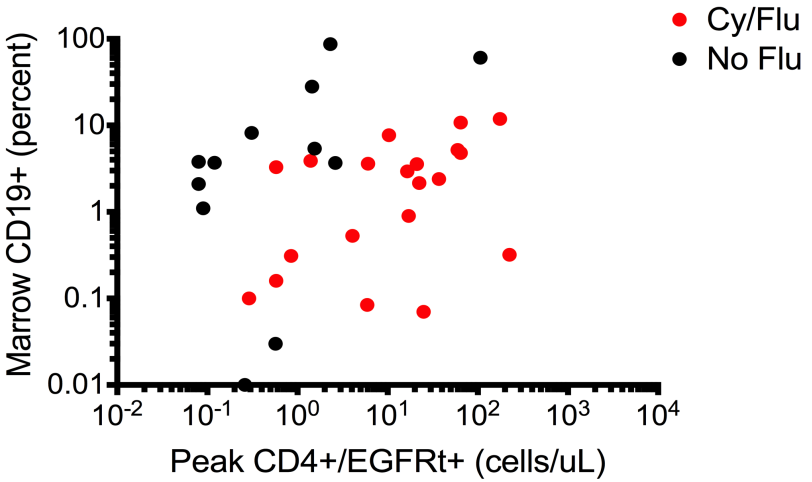
CD19-Directed CAR T-Cell Therapy: Schema

- **Collection of cells by resting state leukapheresis**
  - T cells from patients often compromised in number or subsets
- **Cell manufacture (2-4 weeks)**
  - May include isolation of T-cell subsets
  - T-cell stimulation
  - Transduction with viral vector (gamma or lentivirus containing the CAR)
  - Cell growth to target numbers (generally 1-2 million/kg)
  - Pass release criteria for safety and FDA specifications
- **Lymphodepletion chemotherapy**
  - Given to deplete endogenous T cells and increase engraftment of CAR T cells
  - Generally with cyclophosphamide and fludarabine
- **CAR T-cell infusion (usually cryopreserved and contain low-level DMSO)**
- **Monitoring for CRS and neurotoxicity – for 10- 14 days up to 2 months**

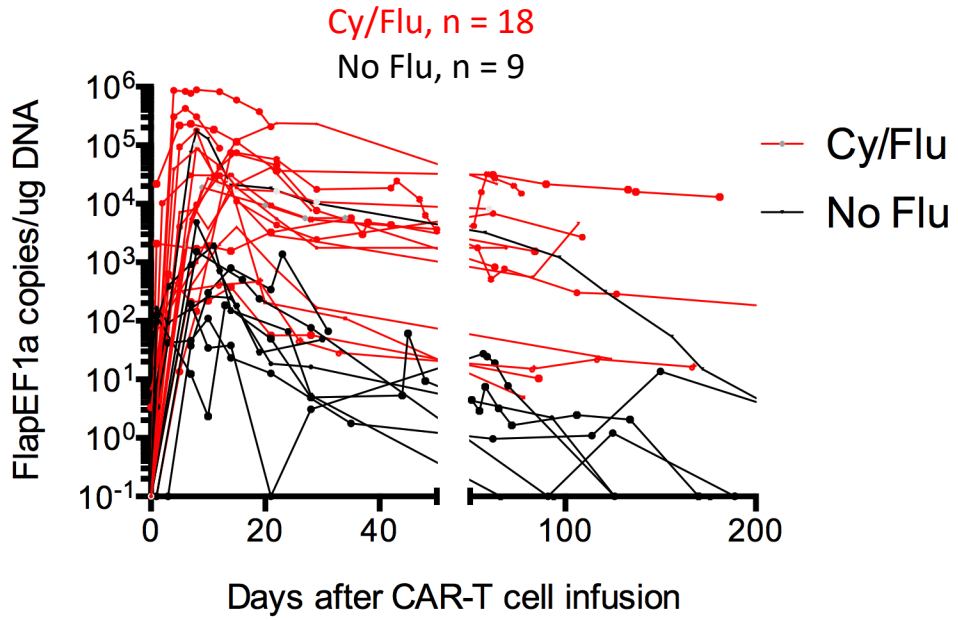


Cy/Flu Lymphodepletion Improves CAR T-Cell Expansion and Persistence





Cy/Flu: higher serum IL-7 ($P = 0.014$) and IL-15 ($P < 0.001$) on the day of CAR T-cell infusion



Turtle CJ, et al. *Sci Transl Med*. 2016;8:355ra116.

What Makes a Cancer a Good CAR T-Cell Candidate?

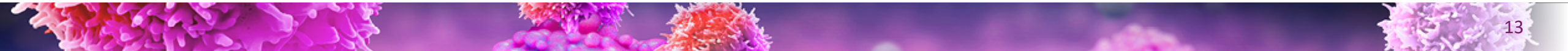
Tumor antigen that is present on all, or most, of the cancer cells and is necessary for that cancer cell's survival

+

Tumor antigen that is not present on normal healthy cells such that immune attack on those normal healthy cells would lead to unacceptable toxicity

=

A good CAR T-cell candidate



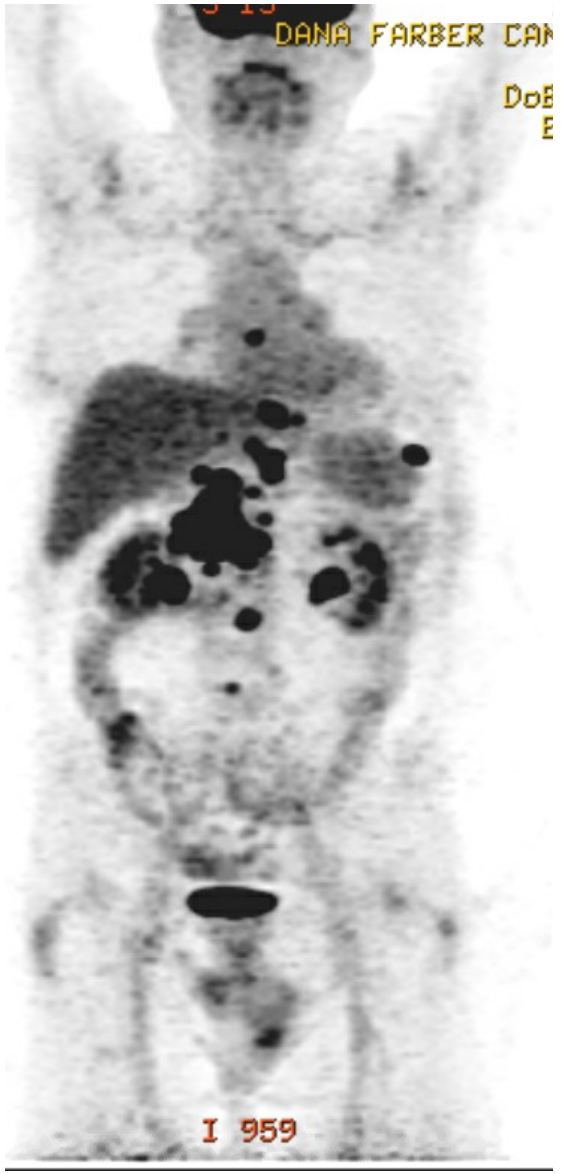
CAR T Cells for Non-Hodgkin Lymphoma (NHL)

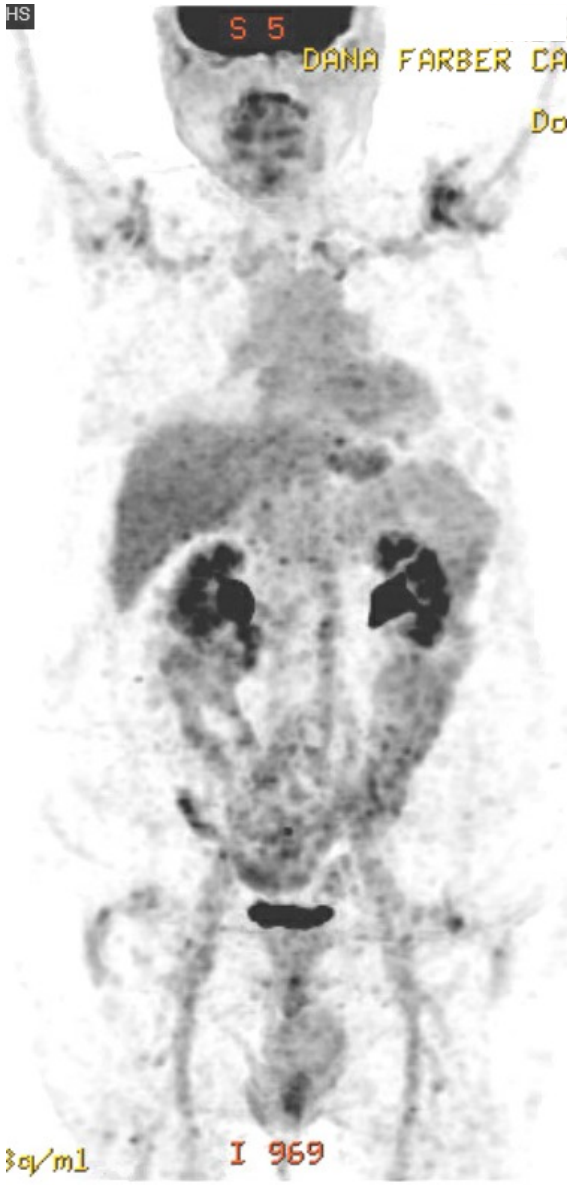
Case Presentation

68-year-old man diagnosed with stage III, DLBCL, GCB subtype

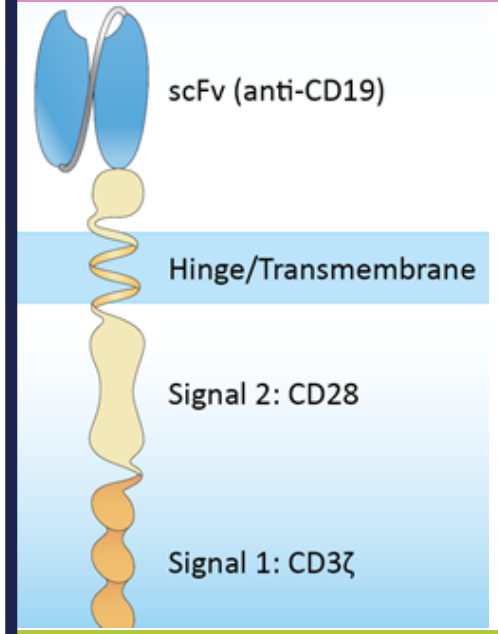
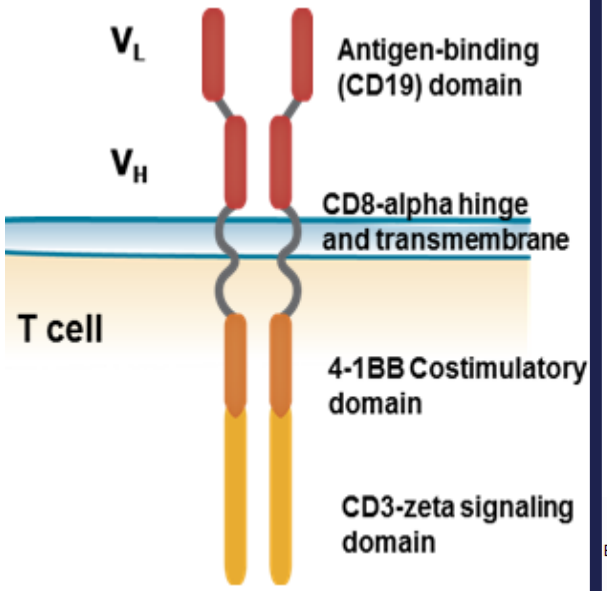
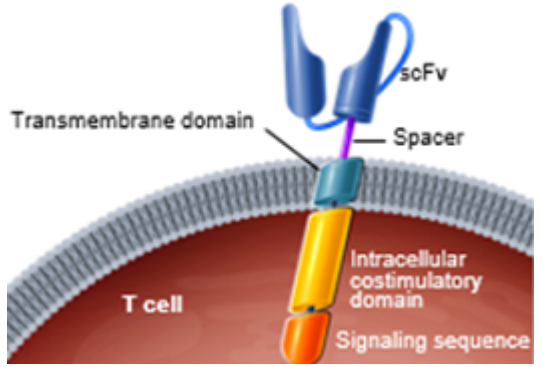
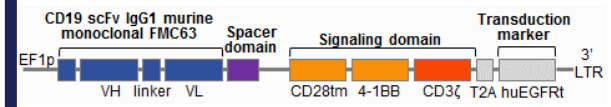
- Treated with RCHOP with a CR
- Relapsed at 2 years
- Treated with RICE with SD; R-GDP + radiation with a CR, which was consolidated with an auto transplant
- Relapsed within 1 year
- Treated with axicabtagene ciloleucel (axi-cel)
  - Pretreatment echo with critical AS; stress test with critical findings; underwent cardiac catheterization with percutaneous aortic valve replacement and RCA stenting
  - Axi-cel infusion further delayed due to enteroviral infection on day -5
  - Course complicated by grade 2 CRS and grade 3 neurotoxicity as well as Takasubo's cardiomyopathy and a transient ischemic attack

Scans at 1 mo showed a CR
Scans at 9 mo showed ongoing CR



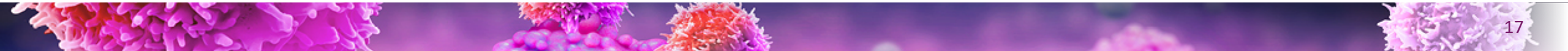


CD19-Directed CAR T Cells

KTE-C19 *axicabtagene ciloleucel* ***(axi-cel)***	**CTL019** ***tisagenlecleucel***	**JCAR017** ***lisocabtagene maraleucel*** ***(liso-cel)***
		 
Kite Pharma	**Novartis**	**Juno Therapeutics**
scFv = anti-CD19	**scFv = anti-CD19**	**scFv = anti-CD19**
CD28-CD3ζ	**4-1BB-CD3ζ**	**4-1BB-CD3ζ**
FDA approved	**FDA approved**	**Investigational**

Multicenter CD19 CAR T-Cell Trials in Aggressive NHL

Study/Sponsor	ZUMA1/Kite	JULIET/Novartis	TRANSCEND/Juno
Reference	Neelapu et al. NEJM 2017 Locke et al. Lancet Oncol 2019	Schuster et al. NEJM 2019	Abramson et al. ASCO 2018
CAR T-cell design	CD19/CD3z/CD28	CD19/CD3z/4-1BB	CD19/CD3z/4-1BB
CAR T-cell dose	2×10^6/kg	Up to $1\text{-}5 \times 10^8$	$0.5\text{-}1 \times 10^8$
Conditioning therapy	Cy/Flu	Cy/Flu or bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL/PMBCL/TFL	DLBCL/TFL	DLBCL/TFL
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	23%	49%	38%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	94%	99%
Treated/Enrolled	109/120 (90%)	111/165 (67%)	114/134 (85%)



ZUMA-1 Trial: Eligibility and End Points *Axicabtagene Ciloleucel (KTE-C19)*

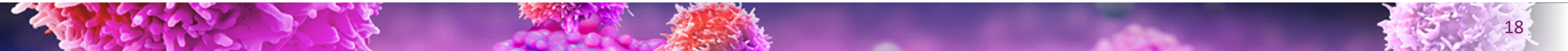
Key Eligibility Criteria

- ZUMA-1 phase 2 portion
  - Cohort 1: patients with refractory DLBCL (n = 77)
  - Cohort 2: patients with refractory PMBCL or transformed FL (n = 24)
- Key inclusion criteria
  - No response to last CT or relapsed within 12 mo of ASCT
  - Prior treatment with anthracycline and anti-CD20 monoclonal antibody

Secondary End Points

- Assess time to response for patients with both objective response and CR
- Assess PR and CR at month 3 as PFS prognostic factor

Locke, et al. ASCO 2018 (abstr 3003).



ZUMA-1: Patient Characteristics

Characteristic	Overall N = 101
Median age (range), yr	58 (23-76)
Male, n (%)	68 (67)
ECOG PS 1, n (%)	59 (58)
Disease stage III/IV, n (%)	86 (85)
IPI score 3-4, n (%)	46 (46)
≥ 3 prior therapies, n (%)	70 (69)
Median SPD of index lesions (range), mm^2	3721 (171-23, 297)
Refractory to ≥ 2 lines of therapy, n (%)	77 (76)
Best response as PD to last therapy, n (%)	67 (66)
Relapse post-ASCT, n (%)	21 (21)

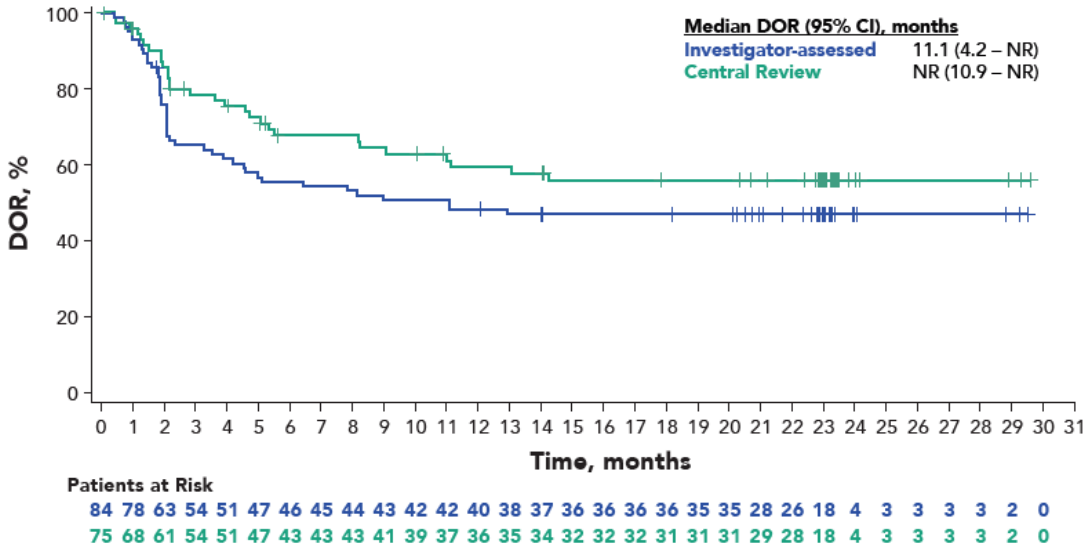
Locke, et al. ASCO 2018 (abstr 3003).

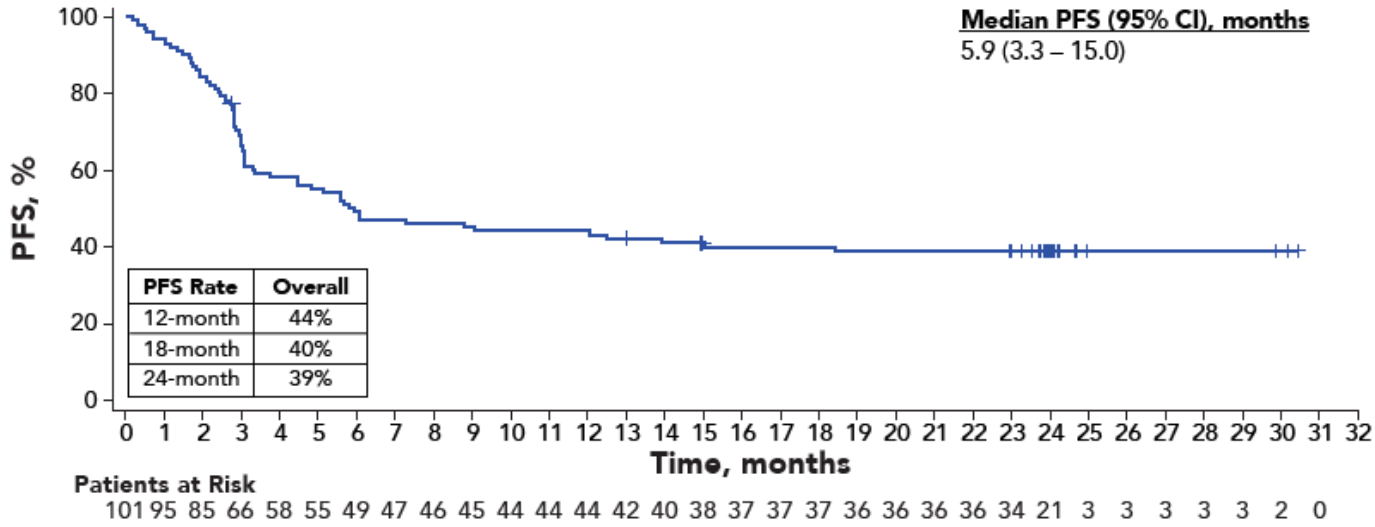
ZUMA-1: Response Rates

Neelapu, et al. ASH 2017	Phase 2 (Primary Analysis) N = 101	
Median follow-up, mo	8.7	
	ORR	**CR**
Best objective response, %	82	54
Ongoing, %	44	39

Neelapu, et al. ASH 2017 (abstr 578).

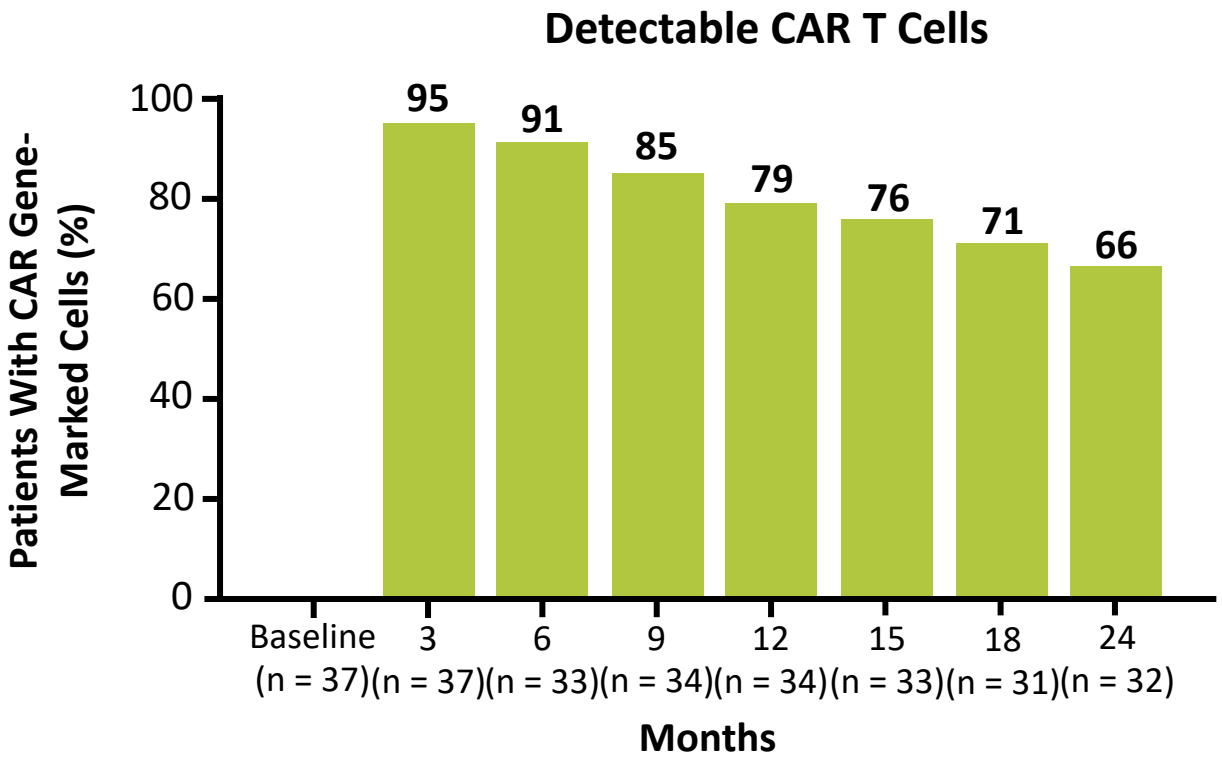
ZUMA-1 Two-Year Results

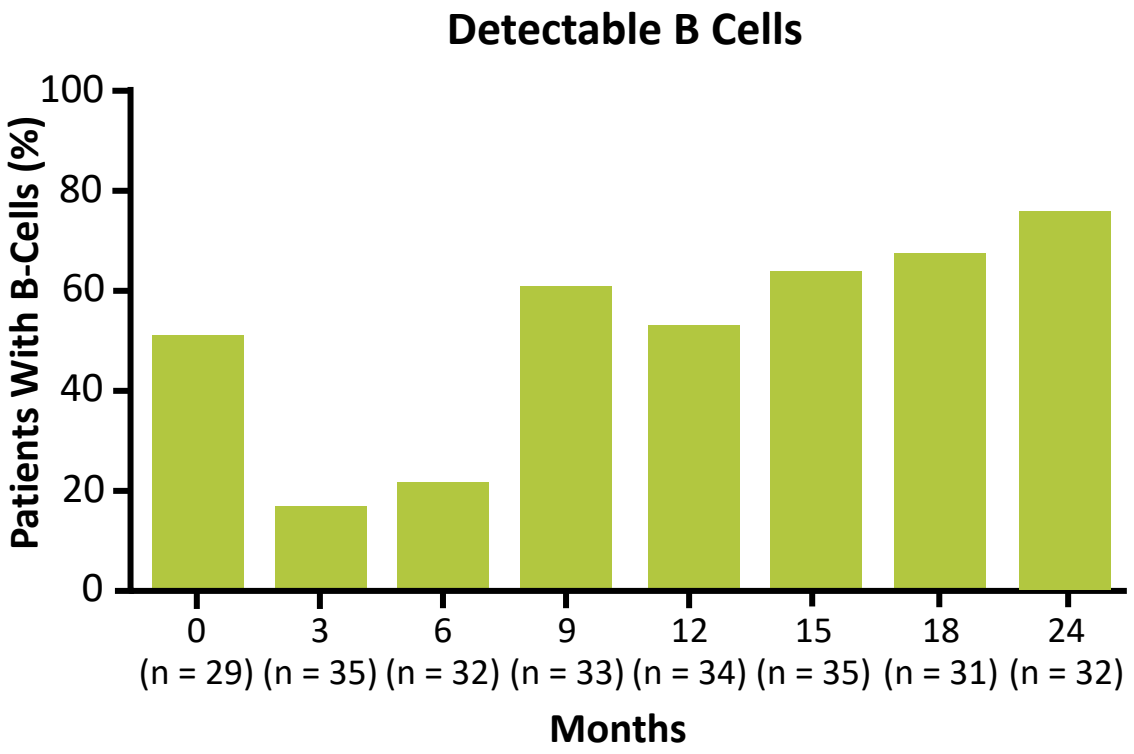




Locke, et al. *Lancet Oncol*. 2019;20:31.

ZUMA-1 Extended 2-Year Follow-Up: CAR T-Cell Persistence and B-Cell Recovery in Responding Patients

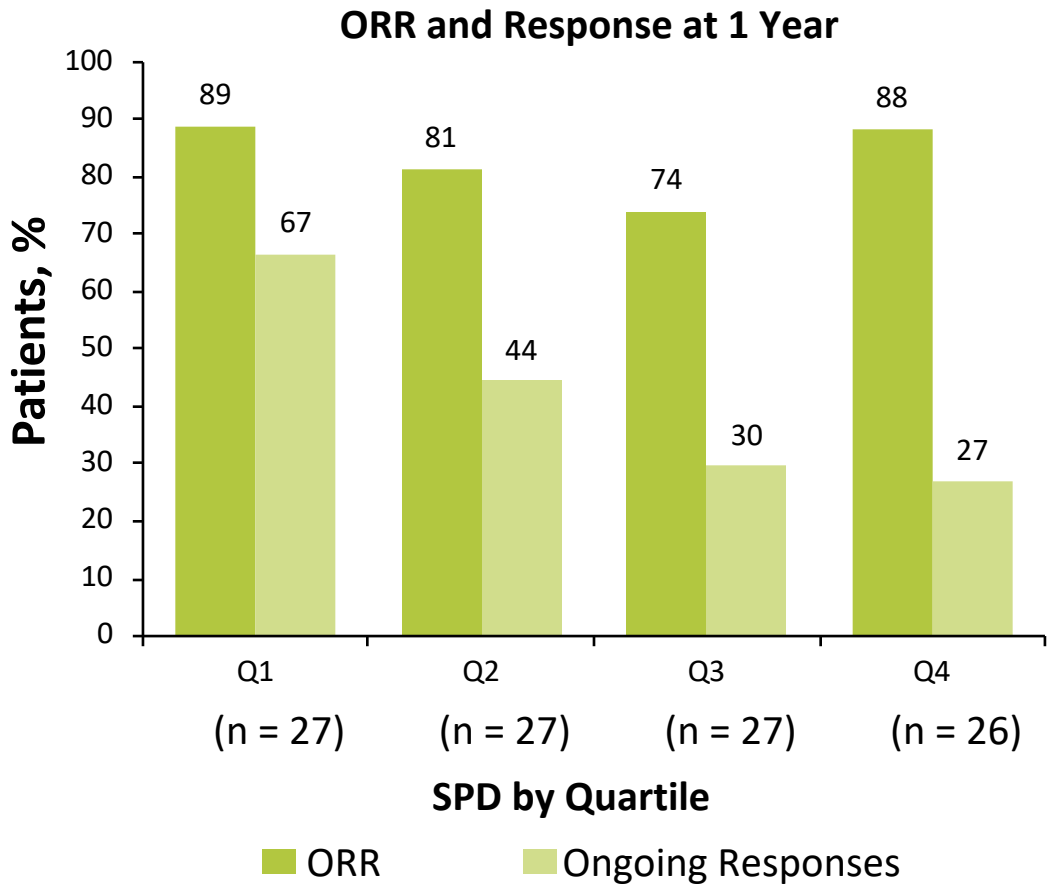


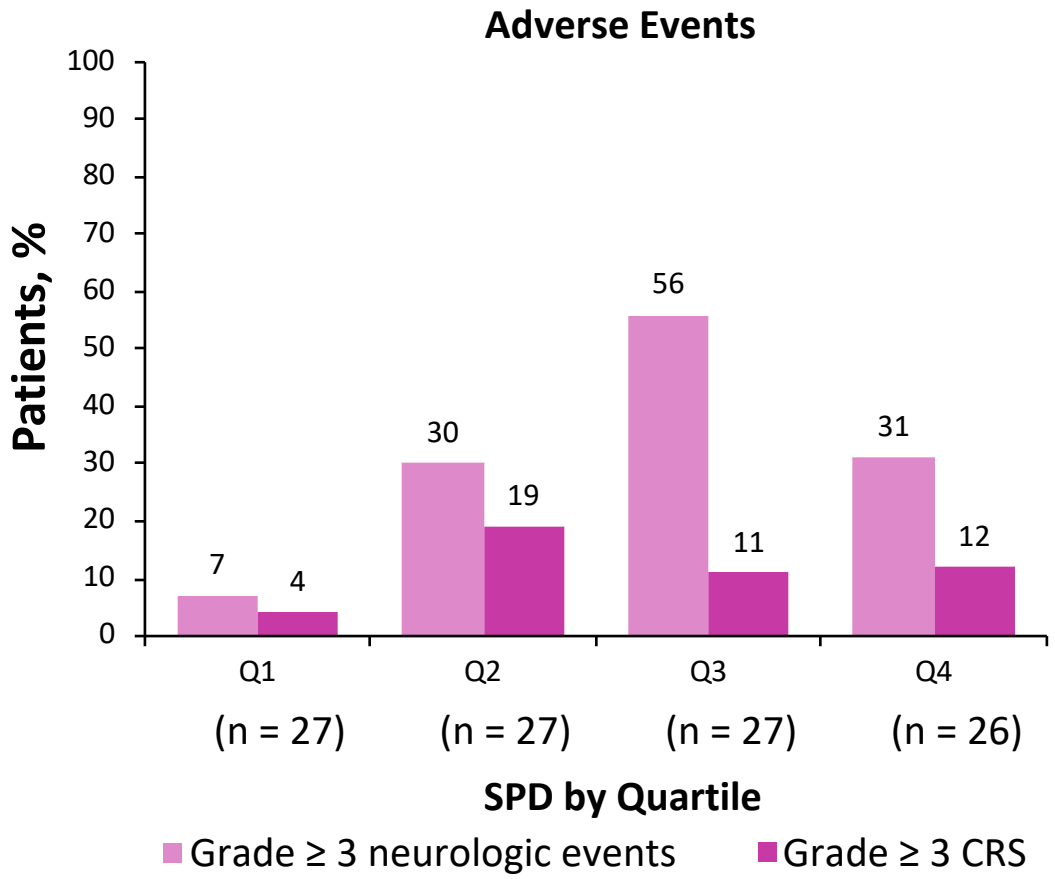


- 11/32 (34%) of evaluable patients with ongoing responses at 24 mo had no detectable CAR T cells
- 24/32 (75%) of evaluable patients with ongoing responses at 24 mo showed evidence of B-cell recovery

Neelapu. ASH 2018. Abstr 2967. Neelapu. *Lancet Oncol*. 2019;20:31.

ZUMA-1 Predictors: Baseline Tumor Burden *Efficacy and Safety*





CRS, cytokine release syndrome; Q, quartile; SPD, sum of product diameters.

Locke FL, et al. *J Clin Oncol*. 2018;36(suppl, abstr):3039.

JULIET Trial: Eligibility and End Points
Tisagenlecleucel (CTL019)

N = 111; Median follow-up, 14 mo (max, 23 mo)

Key Eligibility Criteria

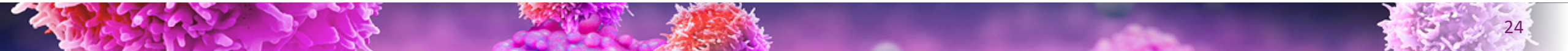
- ≥ 18 years of age
- Central confirmation of histology
- ≥ 2 prior lines of therapy for DLBCL
- PD after or ineligible for auto-SCT
- No prior anti-CD19 therapy
- No active CNS involvement

End Points

- Primary end point: best overall response rate (ORR: CR + PR)
  - Lugano criteria used for response assessment by IRC[1]
- Secondary end points: DOR, OS, safety

auto-SCT, autologous stem cell transplant; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response.

1. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3068.



JULIET: Patient Characteristics

Characteristic	Patients (N = 111)
Age, median (range), years	56 (22-76)
≥ 65 years, %	23
ECOG performance status 0/1, %	55/45
Central histology review	
Diffuse large B-cell lymphoma, %	**79**
Transformed follicular lymphoma, %	**19**
Double/triple hits in CMYC/BCL2/BCL6 genes, %	**17**
Cell of origin	
Germinal/Nongerminal center B-cell type, %	57/41
# of prior lines of antineoplastic therapy, %	
2/3/4-6	44/31/21
IPI ≥ 2 at study entry, %	72
Refractory/Relapsed to last therapy, %	**55/45**
Prior auto-SCT, %	**49**
Bridging chemotherapy, n	102
Lymphodepleting chemotherapy, n	103

Borchmann et al. EHA 2018 (abstr S799).

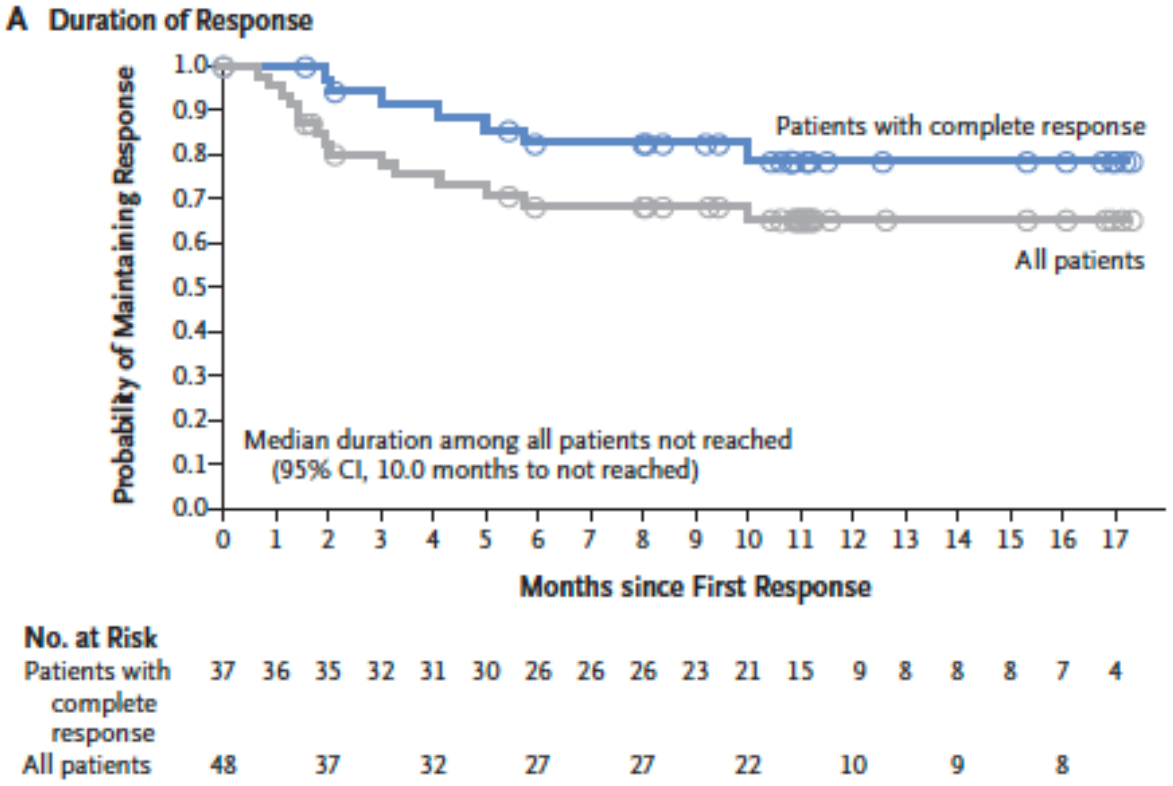
JULIET: Response Rates

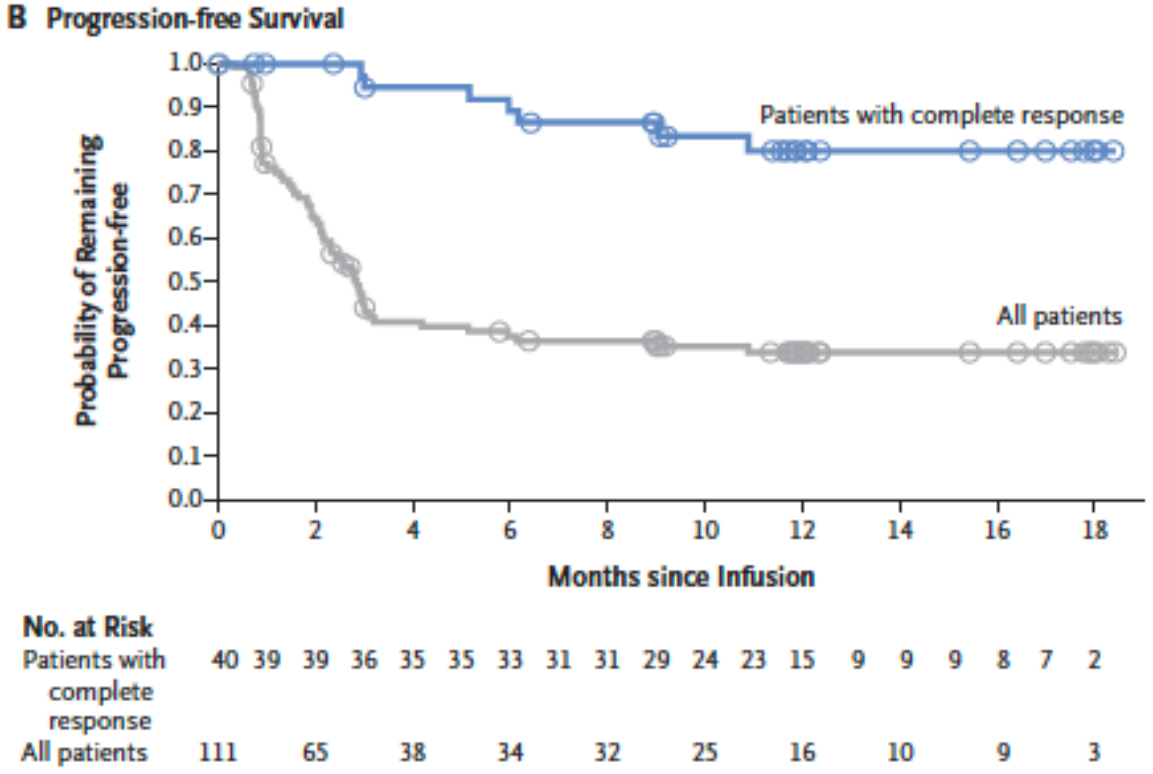
Best ORR within 3 months of infusion, 52% (95% CI, 41-62): 40% CR, 12% PR

	Null Hypothesis of ORR ≤ 20%	ORR n/N (%)
All patients		48/93 (52)
Age		
< 65 years		35/71 (49)
≥ 65 years		13/22 (59)
Sex		
Female		19/33 (58)
Male		29/60 (48)
Prior response status		
Refractory to last line		19/48 (40)
Relapsed to last line		29/45 (64)
IPI at enrollment		
< 2 risk factors		14/25 (56)
≥ 2 risk factors		34/68 (50)
Prior antineoplastic therapy		
≤ 2 lines		26/49 (53)
> 2 lines		22/44 (50)
Molecular subtype		
Activated B cell		21/40 (52)
Germinal cell		24/50 (48)
Prior HSCT therapy		
No		26/52 (50)
Yes		22/41 (54)
Rearranged *MYC/BCL2/BCL6*		
Double/Triple hits		8/16 (50)
Other		40/77 (52)

Borchmann et al. EHA 2018 (abstr S799).

JULIET: DOR and PFS at Median Follow-Up of 14 Months





Schuster SJ, et al. *N Eng J Med*. 2019;380:45-56.

TRANSCEND NHL 001 Trial: Eligibility and End Points

Lisocabtagene Maraleucel (liso-cel; JCAR017)

N = 73*; Median follow-up, 8 mo (CORE cohort)

Key Eligibility Criteria*

- DLBCL after 2 lines of therapy:
  - DLBCL, NOS (de novo or transformed FL)
  - High-grade B-cell lymphoma (double/triple hit)
- Prior SCT allowed
- Secondary CNS involvement allowed
- ECOG 0-2
- No minimum lymphocyte count requirement for apheresis

End Points

- Response rates
  - ORR, CR, PR
- DOR, OS, safety

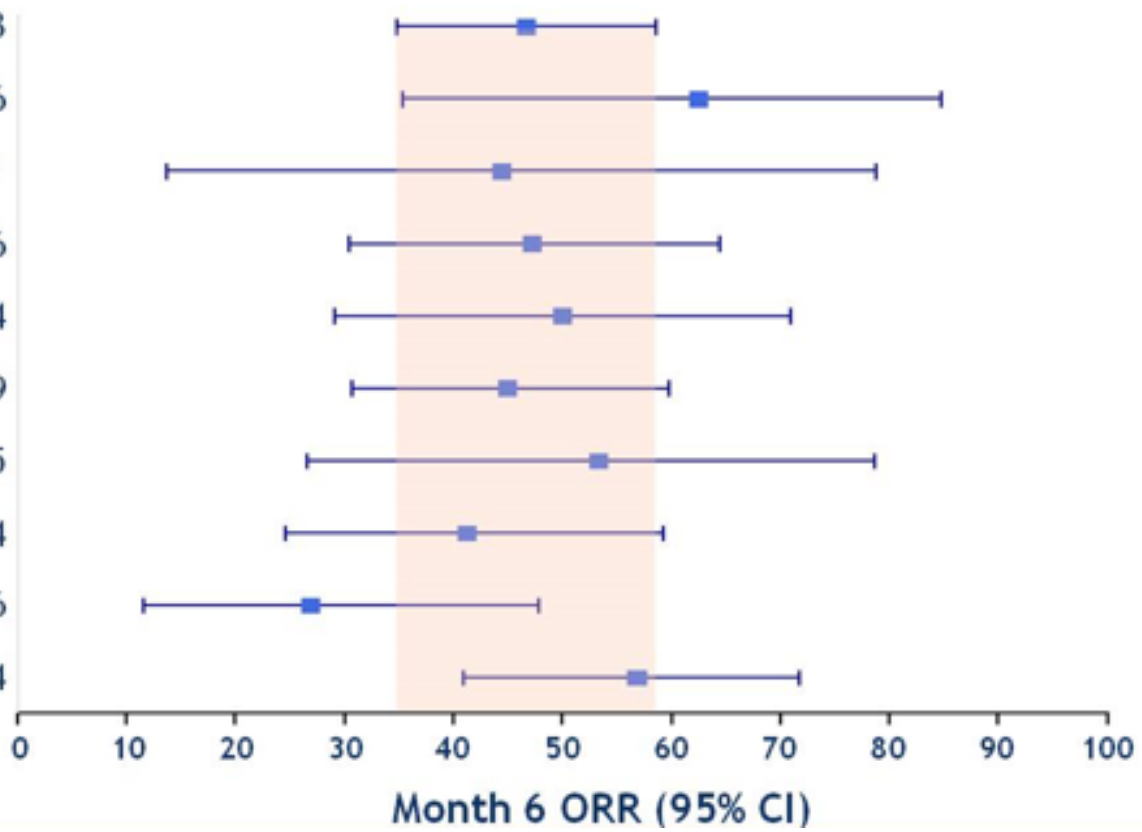
*CORE cohort

SCT, stem cell transplant; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ORR, overall response rate; OS, overall survival; PR, partial response.

TRANSCEND: Response Rates

ORR* at 3 months from infusion, 59% (95% CI, 47-70): 45% CR, 14% PR

Population	n
CORE patient population	73
Double/triple hit	16
Double expressor	9
Never in CR	36
Chemosensitive	24
Chemorefractory	49
Relapse < 12 mo from ASCT	15
SD/PD to last chemotherapy	34
IPI 3-5	26
IPI 0-2	44

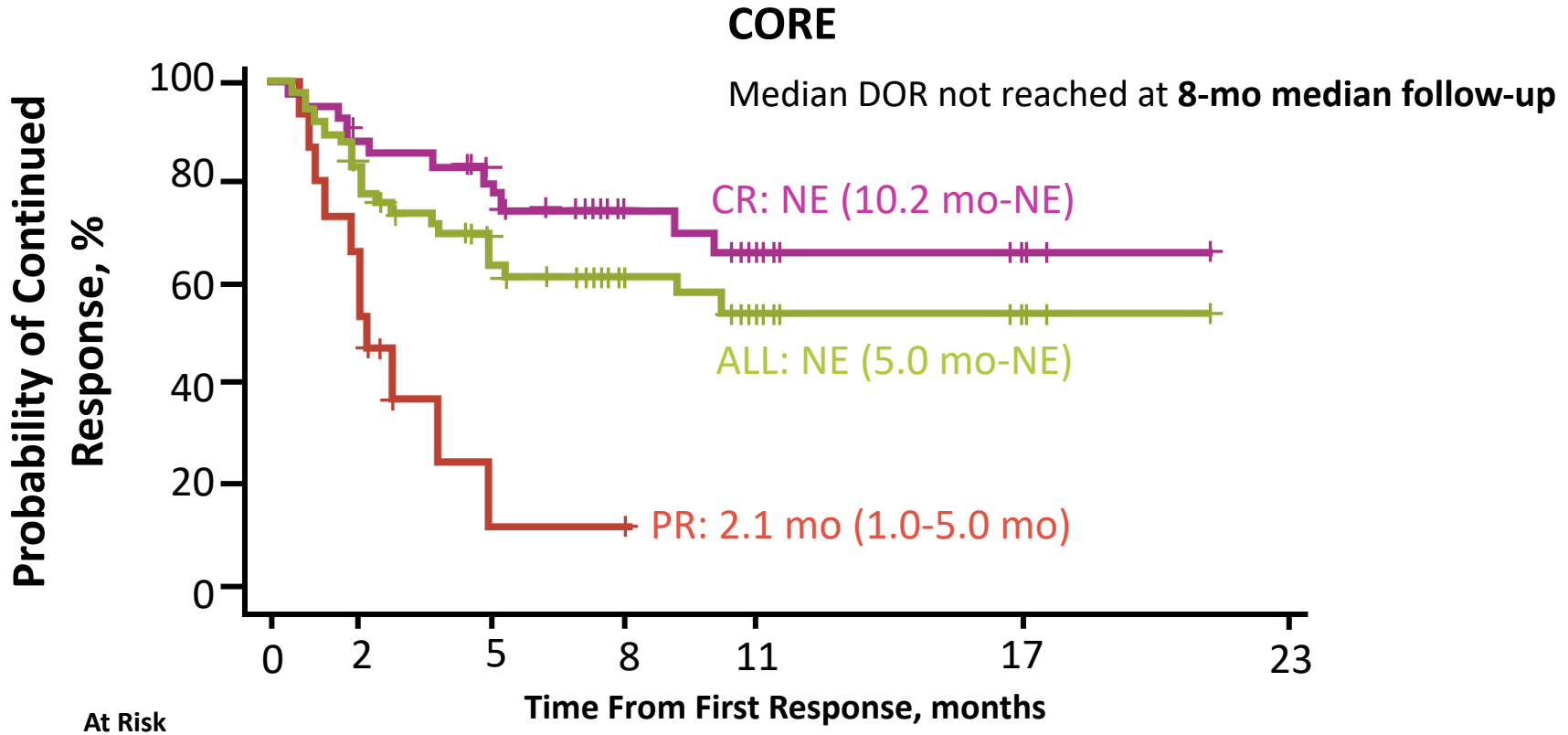


*Includes 2 dose levels in CORE cohort

Abramson, et al. ASCO 2018 (abstr 7505).

TRANSCEND: Lisocabtagene Maraleucel

Response Duration (TRANSCEND)



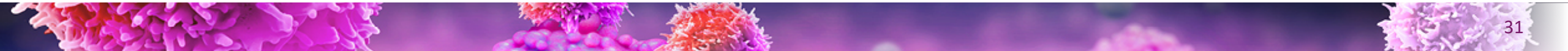
At Risk							
CR	43	37	30	18	12	6	0
PR	15	10	1	1	0		
ALL	58	47	31	19	12	6	0

Abramson, et al. ASCO 2018 (abstr 7505).

Current Results: CAR T-Cell Toxicity in DLBCL

	ZUMA-1	JULIET	TRANSCEND FULL	TRANSCEND CORE
Product	Axi-cel	T-cel	Liso-cel	Liso-cel
# treated	101	111	114	NR
CRS (%)	93	58	39	37
Gr 3+ CRS (%)	13	22	1	3
NT (%)	64	21	23	25
Gr 3+ NT (%)	28	12	13	15

Neelapu S. *Lancet Oncol*. 2019;20:31. Schuster SJ, et al. *N Eng J Med*. 2019;380:45-56. Abramson, et al. ASCO 2018 (abstr 7505).



Cross-Trial Comparisons: CD19 CAR T-Cell Therapy for Aggressive Lymphoma

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene Maraleucel++
Costim/Vector	CD28, retroviral	41BB, lentiviral	41BB, lentiviral
Cell product	Bulk T cells	Bulk T cells	CD4/CD8 subsets
Indication	DLBCL, High grade, PMBCL, tFL	DLBCL, High grade, tFL	DLBCL, High grade, PMBCL, tFL
Best ORR	82%	53%	80%
Best CR	58%	40%	59%
6-mo ORR	41%	37%	47%
6-mo CR	36%	30%	41%
CRS overall, 3/4	94%, 13%	58%, 23%*	37%, 1%
NT overall, 3/4	87%, 28%	21%, 12%	23%, 13%
Outpatient Rx	No	Yes (26%)	Yes
Reference	Neelapu S, et al. ASH 2017 (abstr 578).	Schuster SJ, et al. ASH 2017 (abstr 577).	Abramson J, et al. ASH 2017 (abstr 581). Abramson J, et al. ASCO 2018 (abstr 7505).

* Penn grading scale, ++ Not FDA approved
Slide courtesy of David Maloney, MD

Factors Associated With Toxicity After CAR T-Cell Therapy

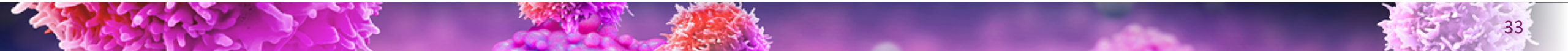
Host/Tumor Factors

- Type of malignancy (ALL > DLBCL)
- Tumor burden
- Baseline inflammatory state

Therapy-Related Factors

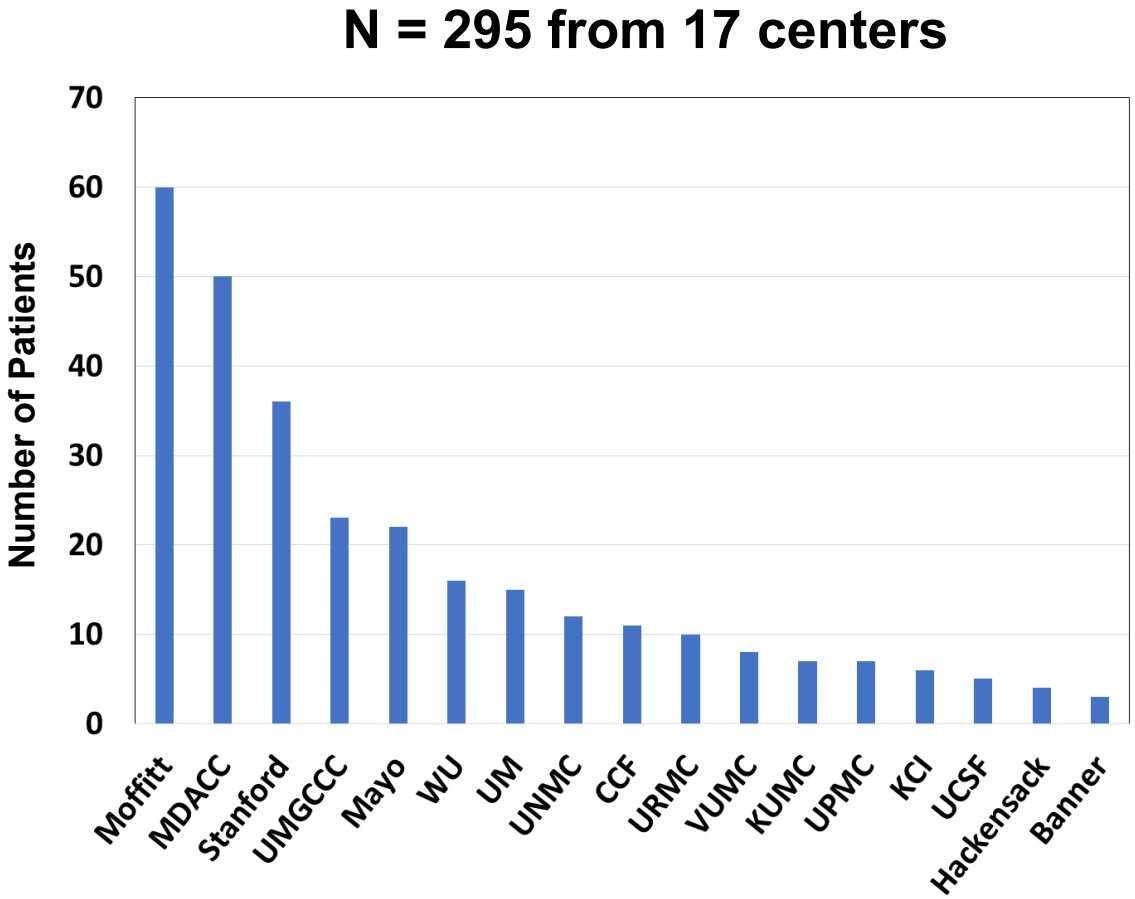
- Lymphodepleting/conditioning therapy
- CAR T-cell dose
- Peak blood CAR T-cell levels
- CAR T-cell design (CD28 > 4-1BB)
- CAR T-cell expansion
- Early and peak levels of certain cytokines
- Endothelial activation

Maude SL, et al. *N Engl J Med.* 2014; Davila ML, et al. *Sci Transl Med.* 2014; Lee DW, et al. *Lancet.* 2015; Teachey DT, et al. *Cancer Discov.* 2016; Turtle CJ, et al. *J Clin Invest.* 2016; Turtle CJ, et al. *Sci Transl Med.* 2016; Gust J, et al. *Cancer Discov.* 2017; Hay KA, et al. *Blood.* 2017; Neelapu SS, et al. *N Engl J Med.* 2017; Maude SL, et al. *N Eng J Med.* 2018; Park JH, et al. *N Engl J Med.* 2018; Santomasso BD, et al. *Cancer Discov.* 2018.



Real-World Experience With Axi-cel in Patients With R/R DLBCL

- Objective: Delineate the characteristics and real world outcomes of patients undergoing standard of care axi-cel
- Retrospective analysis of data from 17 academic centers based in the United States
- All patients leukapheresed as of August 31, 2018 with intention to manufacture commercial axi-cel were included in these analyses



Nastoupil LJ, et al. ASH 2018. Abstract 91.

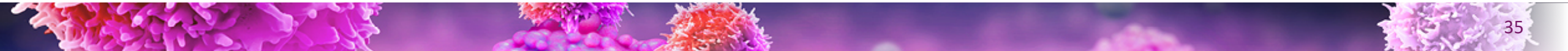
Safety of Axi-cel in the Real World

	SOC Axi-cel N = 274 (mITT)	ZUMA-1[1] N = 108
All Grades of CRS*, N (%)	240 (92%)	100 (93%)
Grade ≥3 CRS, N (%)	18 (7%)	14 (13%)
Median time to onset of CRS	3 days	2 days
All Grades of NT**, N (%)	181 (69%)	70 (65%)
Grade ≥3 NT, N (%)	85 (33%)	33 (31%)
Median time to onset of NT	6 days	5 days

* Lee criteria used for grading CRS

** CTCAE or CARTOX criteria used for grading neurotoxicity

Nastoupil LJ, et al. ASH 2018. Abstract 91.



Efficacy of Axi-cel in the Real World

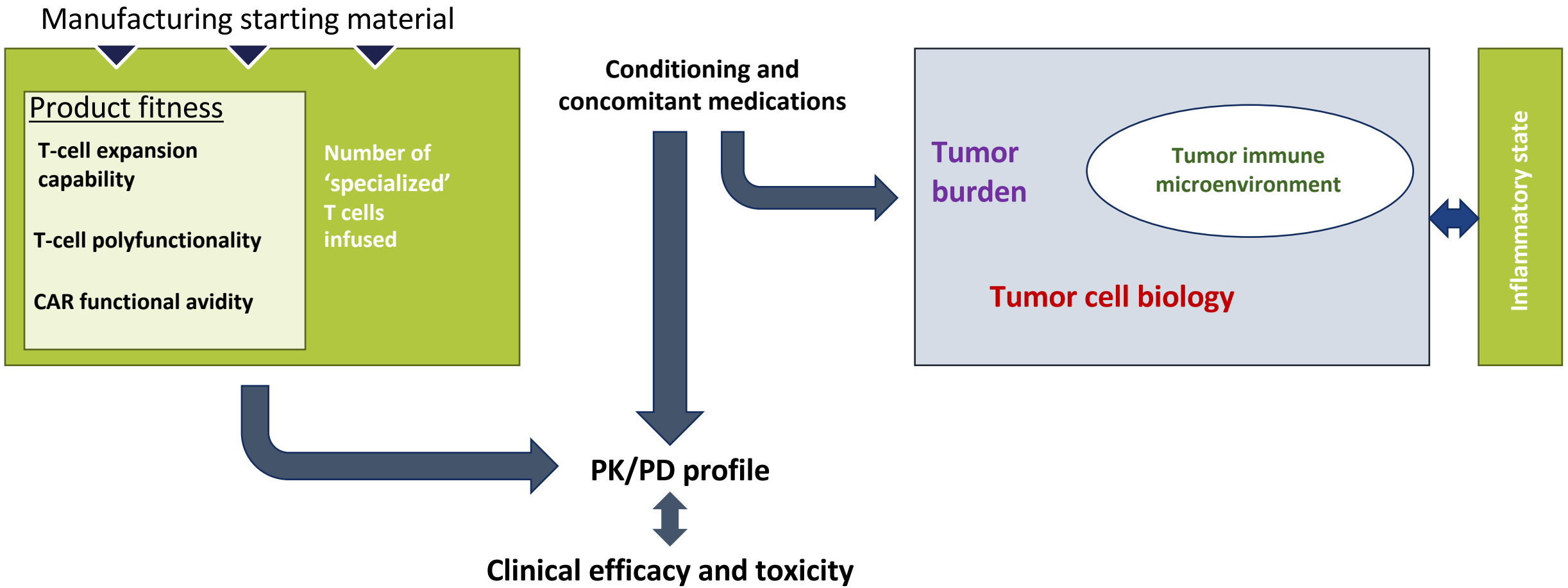
	SOC Axi-cel Evaluable	SOC Axi-Cel	ZUMA-1[1] N = 108
Median follow-up, months		**3.9**	**15.4**
Day 30 ORR, N (%)	**238**	**191 (80)**	**N/A**
Day 30 CR, N (%)		**113 (47)**	**N/A**
Best ORR at Day 90, N (%)	**248[a]**	**201 (81)**	**89 (82)**
Best CR at Day 90, N (%)		**142 (57)**	**63 (58)**

[a] Evaluable patients as of data cut-off date of October 31, 2018

Nastoupil LJ, et al. ASH 2018. Abstract 91.

Which Patients Are Most Appropriate for CAR T-Cell Therapy?

Factors That Influence Treatment Success and Failure to CAR T-Cell Therapy: A Hypothesized Model

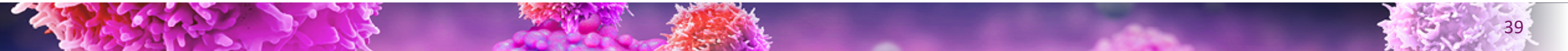


Adapted from Locke, et al. SITC 2018. #P212.

CAR, chimeric antigen receptor; PD, pharmacodynamics; PK, pharmacokinetics.

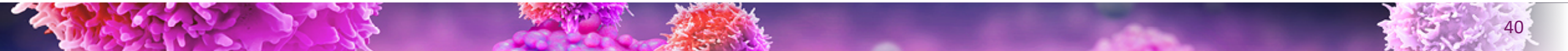
Who Should Be Referred for Commercial CAR T-Cell Therapy?

- FDA label very broad
  - Relapsed/refractory HGBL, DLBCL, PMBL (axi-cel only) or tFL after 2 lines of systemic therapy
  - No active CNS lymphoma
  - No upper age limit
  - No evidence that tumor must demonstrate CD19+
- Real-world studies suggest that expansion beyond clinical trial criteria preserves efficacy without an increase in toxicity
  - Eligibility criteria will be center dependent



Post-CAR T-Cell Therapy Management and Concerns

- Patients remain within 2 hours of treating center for 4 weeks, and abstain from driving for 8 weeks, following CAR T-cell infusion due to a low risk of recurrent CRS and/or NT
- After this, patients should be monitored for
  - Prolonged cytopenias – transfusions as indicated, G-CSF as needed for neutropenia
  - B-cell aplasia (IgG levels) – replete with IVIG for levels < 400
  - Relapse
  - Secondary malignancies
- Antibiotic (herpes virus and PJP) prophylaxis
  - For approximately 6 months (depending on the immunologic status of the patient)
- Upon relapse, patients should be biopsied
  - Immunomodulatory therapies have had success in salvaging CAR T-cell relapses; can check for PD-L1 on the tumor
  - Repeat CAR T-cell infusions have had limited testing in lymphoma and it is unclear if there is any role in this population



Patients with NHL: Possibly Eligible for CAR-T

- Before salvage is started, check with the CAR-T center
- Possible clinical trial eligibility and salvage therapy is dictated on these trials
- Close follow up at the CAR-T cell center needed
- Some toxicities are unique to CAR-T cells (CRS, NT)
- Relapse after CAR-T may also need different therapies