CAR-T Therapy: The Past, The Present, and The Future

Nilay Shah, MD
Michael Chargualaf, PharmD, BCOP
WVU Medicine
Mary Babb Randolph Cancer Center

Objectives

- Review indications for FDA approved CAR-T therapy
- Become familiar with the CAR-T engineering process and administration processes
- Analyze clinical data for CAR-T therapy
- Outline place in therapy of CAR-T
- Create plans for the management of CAR-T toxicities

Emily Whitehead


Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS
20 December 2013
Science
Vol. 342 | No. 6165 | Pages 1405–1544
Breakthrough of the Year
www.sciencemag.org

CAR T-Cell Therapy:

ASCO's Advance of the Year

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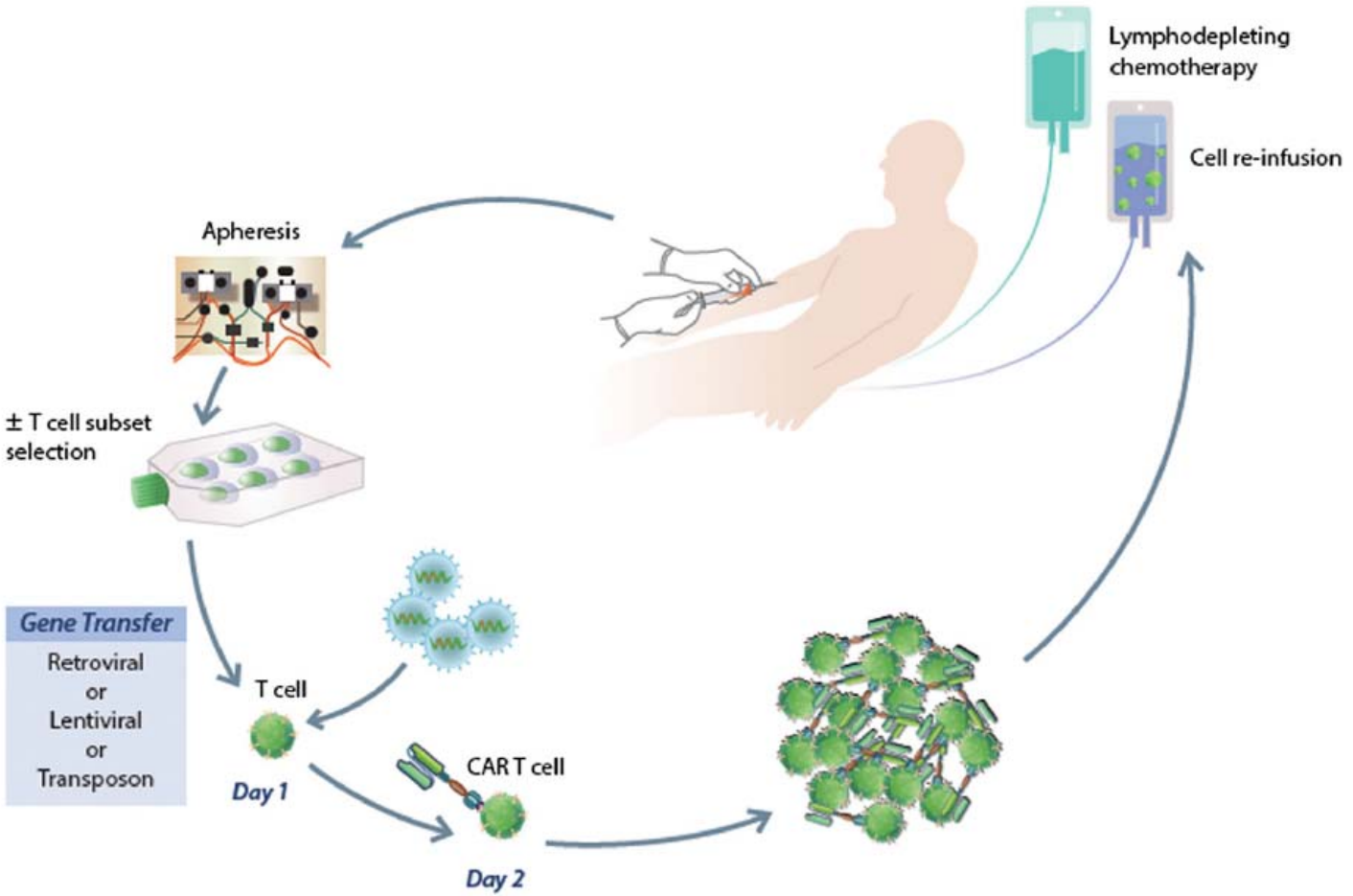
Chimeric Antigen Recepetor T-Cells (CAR-T)

- Chimeric Antigen Receptor (CAR): fusion protein containing T-cell signaling domains and an antigen recognition moiety

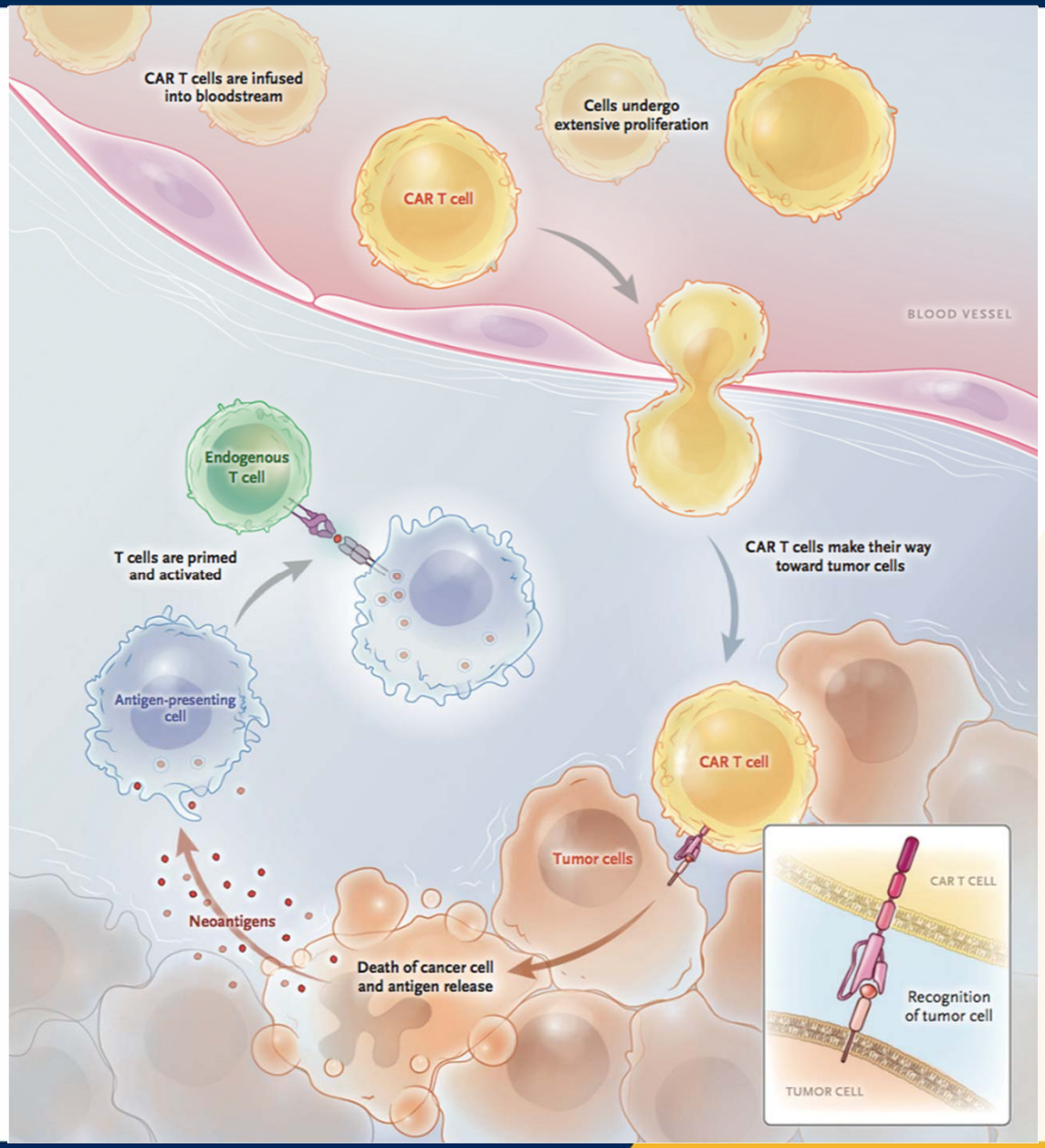
- CAR-T therapy modifies a patient's own immune system (T cells) to fight cancer.

Mato A, et al. Blood 2015;126(4):478-485

Engineering CAR-T



Mato A, et al. Blood 2015;126(4):478-485



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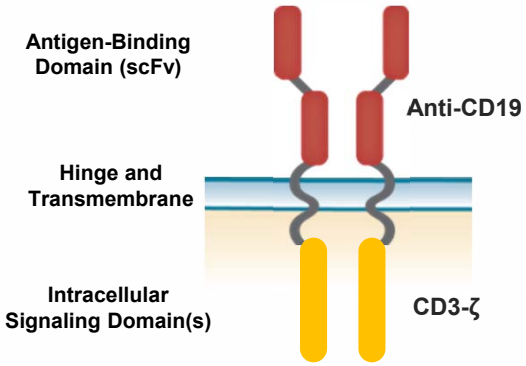
June C, et al. N Engl J Med 2018;379:64-73

CAR-T Construct

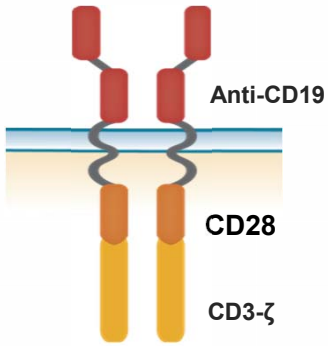
First-generation CARs



CD3-ζ:

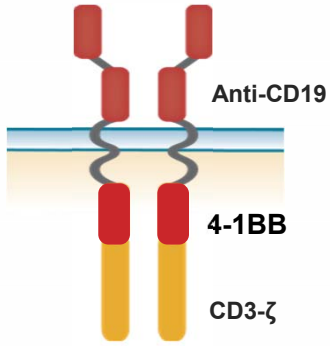
- Critical component for initiating T-cell activation and antitumor activity.

Second+ generation CARs



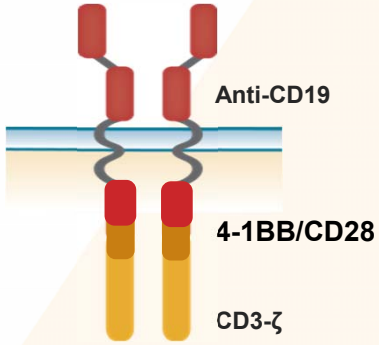
CD28:

- Involved in early and rapid expansion with limited long-term persistence in vitro
- Correlated with effector memory T-cell differentiation known to provide immediate protection in vitro
- Metabolic profile supports rapid expansion (glycolytic metabolism)



4-1BB:

- Enhances early expansion and long-term persistence in vitro
- Induces central memory T-cell differentiation for enduring protection and immunosurveillance in vitro
- Metabolic profile supports gradual sustained expansion (oxidative metabolism)



CD28/4-1BB:

- The impact of 4-1BB/CD28 combined costimulatory domains on **expansion, persistence, and central memory** is being investigated[1]

This information is based on animal model data. No head-to-head comparisons of the clinical efficacy of these costimulatory domains have been conducted.

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Kawalekar OU et al. *Immunity*. 2016;44(2):380-390.
Milone MC et al. *Mol Ther*. 2009;17(8):1453-1464.

Commercially Available Products

Tisagenlecleucel (Kymriah®)	Axicabtagene Ciloleucel (Yescarta®)
▪ Treatment of relapsed or refractory large B-cell lymphoma in adults (after ≥2 lines of systemic therapy)	▪ Treatment of relapsed or refractory large B-cell lymphoma in adults (after 2 or more lines of systemic therapy)
▪ Treatment of B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in patients up to 25 years of age.	▪ *Anticipation of B-cell ALL indication*
▪ 4-1BB/CD3-ζ costimulatory domain	▪ CD28/CD3-ζ costimulatory domain
▪ Novartis Pharmaceuticals Corp.	▪ Kite Pharma, Inc

Patient Eligibility

FDA labeled indication for use

Adequate performance status

Absence of active infection

Influenza testing

Sufficient organ function

Kidney, liver, heart, lung

Bridging to CAR-T

- May be necessary to control disease burden during manufacturing process

Lymphodepletion

Purpose:

- Depletion of endogenous lymphocytes with low-dose chemotherapy
- Enhance proliferation of infused CAR-T

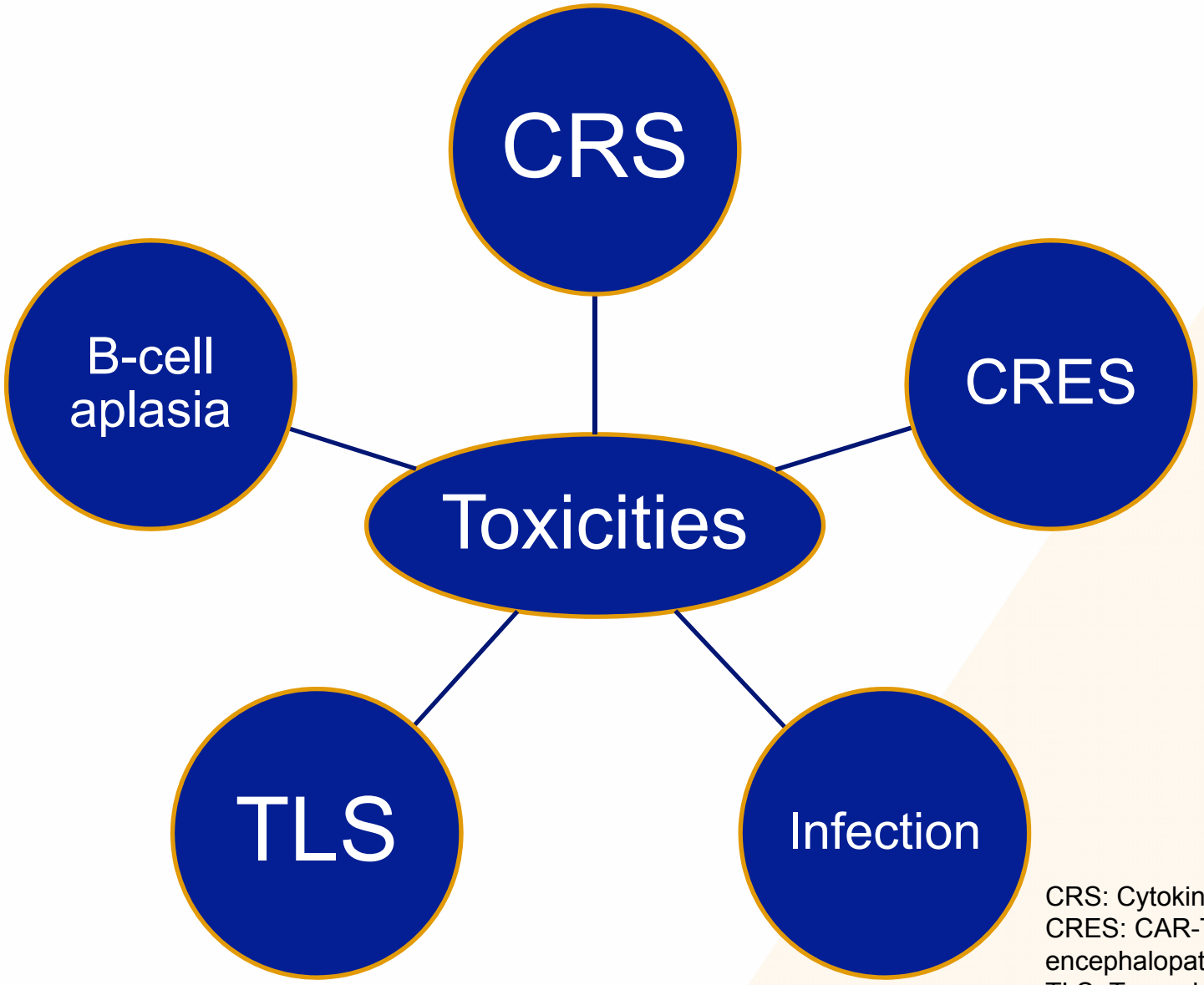
Regimens:

- Fludarabine 25-30 mg/m^2/day x 3-4 doses
  Cyclophosphamide 250-500 mg/m^2/day x 2-3 doses
- Bendamustine 90 mg/m^2 x 2 days
- No lymphodepletion

Kymriah (tisagenleleucel) Package Insert. May 2018

CAR-T Infusion

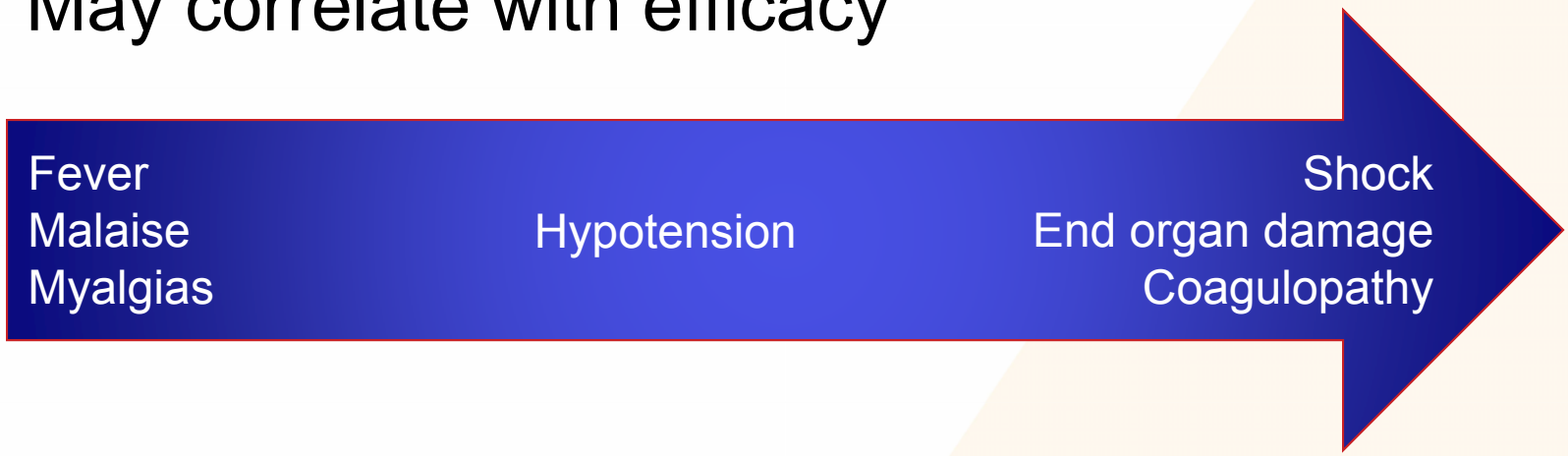
- Cryopreservation of CAR-T product
- Currently no standard dose (may depend on indication)
  - 2 x10^5 – 6 x 10^8 cells/kg
- Single vs multiple infusion bags



CRS: Cytokine release syndrome
CRES: CAR-T related encephalopathy syndrome
TLS: Tumor lysis syndrome

Cytokine Release Syndrome (CRS)

- Well-documented entity with CAR-T
- Usually reversible, but potentially life-threatening
- Related to T-cell expansion
- May correlate with efficacy



CRS Management

Grade	Signs/Symptoms
1	Constitutional symptoms (ie. fever)
2	Hypotension responsive to fluids or low dose vasopressors FiO2 <40% Grade 2 organ toxicity
3	Hypotension requiring high dose vasopressors FiO2 ≥ 40% and/or requiring BiPAP Grade 3 organ toxicity, Grade 3-4 transaminitis
4	Life-threatening hypotension Ventilator support Grade 4 organ toxicity
5	Death

Lee DW et al. Blood. 2014;124(2):188-95

CRS Management

Grade 1
- Vigilant supportive care
- Treat fever and pain

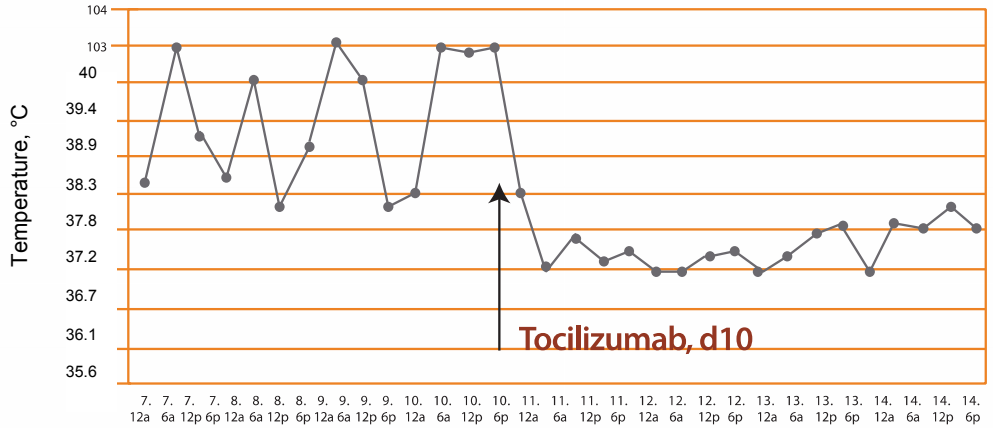
Grade 2
- Tocilizumab 8 mg/kg (max 800 mg) for hypotension refractory to fluid resuscitation
- +/- vasopressors
- Methylprednisolone 2 mg/kg if no clinical improvement after 12-18 hours of tocilizumab

Grade 3
- Tocilizumab +/- methylprednisolone per Grade 2
- Consider repeat tocilizumab dose
- Consider siltuximab 11 mg/kg IV

Grade 4
- Tocilizumab + high-dose steroids + siltuximab + vasopressors

Lee DW et al. Blood. 2014;124(2):188-95

Tocilizumab and CRS



- IL-6 receptor antagonist
- FDA approved for CAR-T induced CRS

Maude SL et al. Cancer J. 2014;20(2):119-122.
Lee C et al. Blood. 2017;130(suppl 1) [abstract 2553].
Schuster SJ et al. Blood. 2017;130(suppl 1) [abstract 577].
Data on file, Novartis Pharmaceuticals Corp.

CRES: CARTOX-10 Assessment

Orientation: 5 points	• Year, month, city, hospital, President
Identification: 3 points	• Name 3 separate objects
Writing: 1 point	• Ability to write a standard sentence
Counting: 1 point	• Count backwards from 100 by ten

CRES Management

Grade 1-2

- Vigilant supportive care
- Consider tocilizumab if associated with CRS

Grade 3

- Transfer to ICU

Grade 4

- Consider corticosteroids for severe neurotoxicity not associated with CRS

REVIEW OF CLINICAL DATA

Disease	Response Rate	Comments	Reference
	percent		
Leukemia			
B-cell acute lymphoblastic leukemia (in adults)	83–93	High initial remission rates; unresolved issue is whether CAR T-cell therapy is definitive therapy or should be followed by allogeneic hematopoietic stem-cell therapy	Park et al.,[35] Davila et al.,[36] Turtle et al.[37]
B-cell acute lymphoblastic leukemia (in children)	68–90	Approximately 25% of patients reported to have a relapse with CD19-negative or CD19-low leukemia; CD22 CAR T cells may improve survival among some patients with CD19 relapses	Maude et al.,[34] Maude et al.,[38] Fry et al.,[39] Lee et al.[40]
Chronic lymphocytic leukemia	57–71	Relapse is rare in patients who have a complete response; ibrutinib appears to increase response rates	Porter et al.,[41] Turtle et al.[42]
Lymphoma			
Diffuse large B-cell lymphoma	64–86	Approximately 40–50% of patients reported to have a durable complete response	Turtle et al.,[43] Kochenderfer et al.,[44] Schuster et al.,[45] Neelapu et al.[46]
Follicular lymphoma	71	At a median follow-up of 28.6 mo, the response was maintained in 89% of patients who had a response	Schuster et al.[45]
Transformed follicular lymphoma	70–83	A total of 3 of 3 patients with transformed follicular lymphoma had a complete response	Turtle et al.,[43] Schuster et al.,[45] Neelapu et al.[46]
Refractory multiple myeloma	25–100	B-cell maturation antigen CAR T cells; stringent complete response in approximately 25% of patients	Ali et al.,[47] Fan et al.,[48] Berdeja et al.[49]
Solid tumors			
Glioblastoma	ND	In case report from phase 2 study, complete response on magnetic resonance imaging after intravenous and cerebrospinal fluid administration of CAR T cells; response lasted 7.5 mo	Brown et al.[50]
Pancreatic ductal adenocarcinoma	17	In one patient with liver metastasis, CAR T-cell treatment produced a complete metabolic response in the liver but was ineffective against the primary pancreatic tumor	Beatty et al.[51]

June C, et al. N Engl J Med 2018;379:64-73

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

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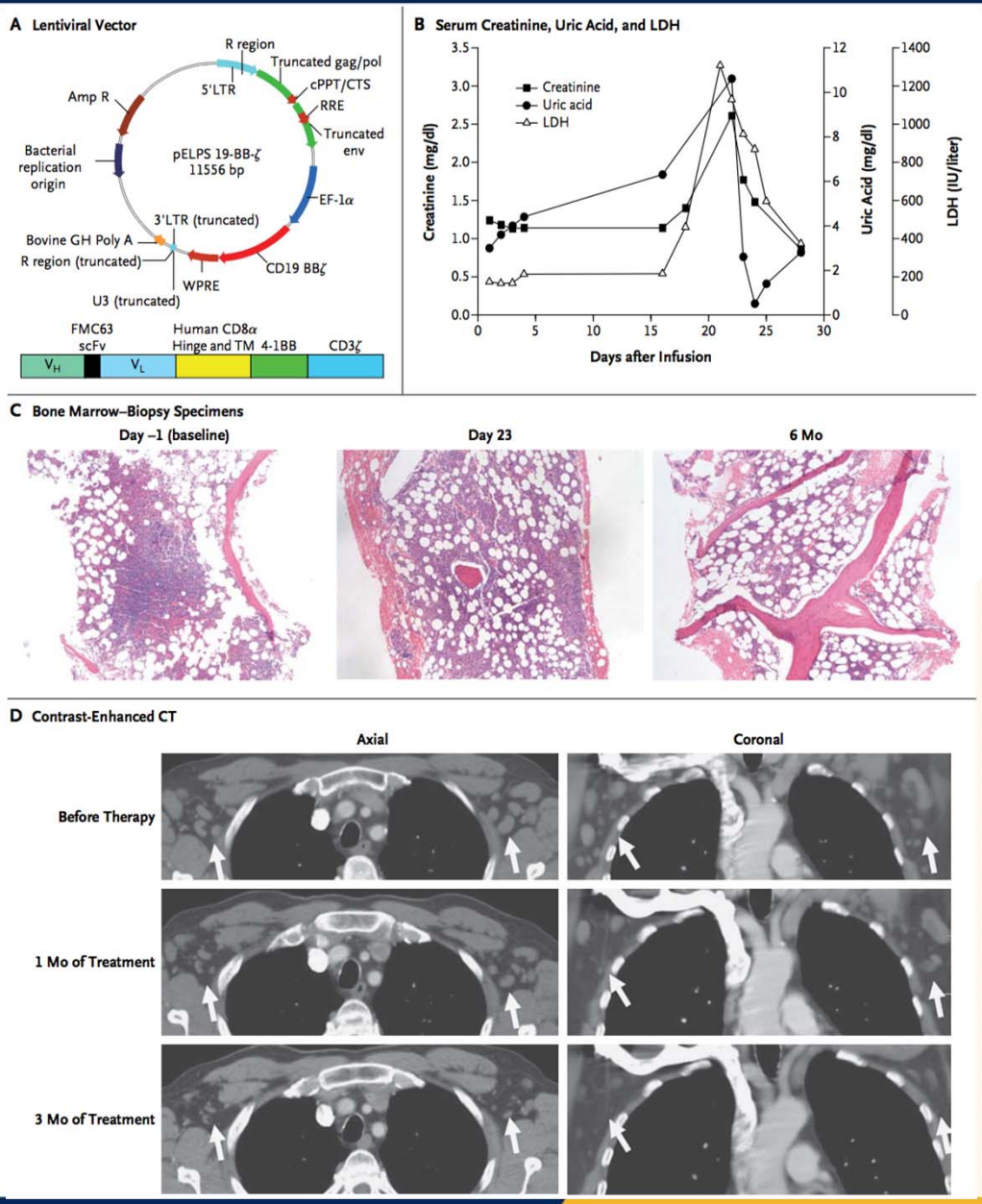
Porter D, et al. N Engl J Med 2011;365:725-33


A Lentiviral Vector
R region
Truncated gag/pol
5'LTR
cPPT/CTS
Amp R
RRE
Truncated env
Bacterial replication origin
pELPS 19-BB-ζ 11556 bp
EF-1α
3'LTR (truncated)
Bovine GH Poly A
R region (truncated)
CD19 BBζ
WPRE
U3 (truncated)
FMC63 scFv
Human CD8α Hinge and TM
4-1BB
CD3ζ
VH
VL
B Serum Creatinine, Uric Acid, and LDH
Creatinine
Uric acid
LDH
Creatinine (mg/dl)
Uric Acid (mg/dl)
LDH (IU/liter)
Days after Infusion
C Bone Marrow–Biopsy Specimens
Day –1 (baseline)
Day 23
6 Mo
D Contrast-Enhanced CT
Axial
Coronal
Before Therapy
1 Mo of Treatment
3 Mo of Treatment

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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ELIANA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

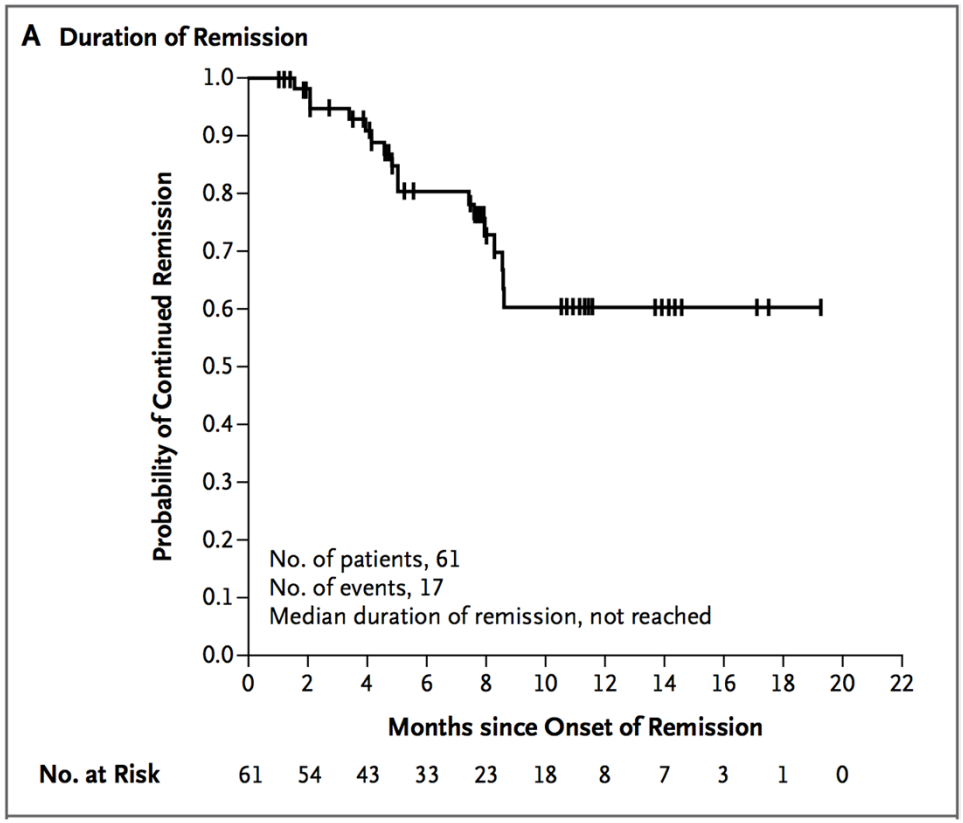
Maude S.L., et al. N Engl J Med 2018;378:439-48

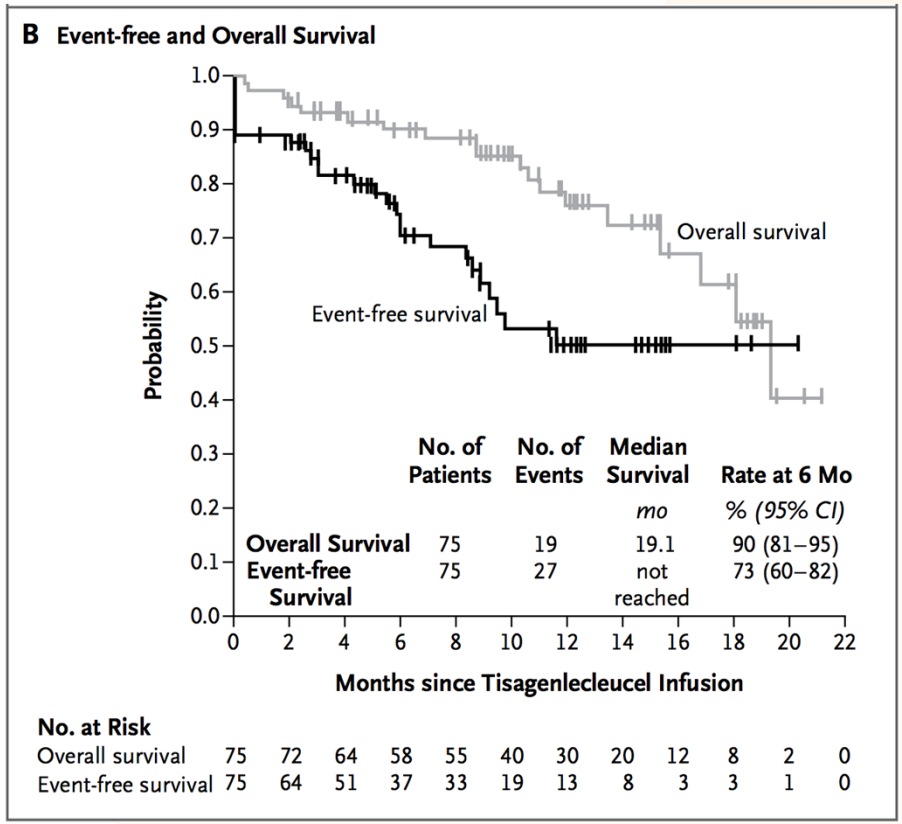
ELIANA

Design	• Global, single arm, open-label, multicenter • Phase II
Patients	• n=75 infused; 92 enrolled • Median age (range): 11 years (3-23) • Median prior therapies: 3 (46% had prior allogeneic HSCT) • Median marrow blast percentage: 74%
Endpoints	• Primary: Overall remission rate • Secondary: CR/Cri with MRD negativity; Duration or remission, EFS, OS
Response	• Overall remission rate (CR/CRi): 81% (median follow up 13.7 months) • 60% achieved CR; 21% achieved Cri • Engineered T-Cells detected up to 20 months out

Maude S.L., et al. N Engl J Med 2018;378:439-48

ELIANA





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Maude S.L., et al. N Engl J Med 2018;378:439-48

Table 2. Grade 3 or 4 Adverse Events Suspected to Be Related to Tisagenlecleucel That Occurred in at Least 5% of Patients.

Event	≤8 Wk after Infusion (N=75)		>8 Wk to 1 Yr after Infusion (N=70)	
	Grade 3	Grade 4	Grade 3	Grade 4
	number of patients (percent)			
Any grade 3 or 4 adverse event	19 (25)	33 (44)	8 (11)	4 (6)
Cytokine release syndrome	16 (21)	19 (25)	—	—
Hypotension	7 (9)	6 (8)	—	—
Decrease in lymphocyte count	5 (7)	4 (5)	1 (1)	—
Hypoxia	5 (7)	3 (4)	—	—
Increase in blood bilirubin	8 (11)	—	—	—
Increase in aspartate aminotransferase	5 (7)	2 (3)	—	—
Pyrexia	5 (7)	2 (3)	—	—
Decrease in neutrophil count	1 (1)	6 (8)	1 (1)	1 (1)
Decrease in white-cell count	—	7 (9)	—	—
Decrease in platelet count	3 (4)	4 (5)	—	—
Decrease in appetite	6 (8)	1 (1)	—	—
Acute kidney injury	3 (4)	3 (4)	—	—
Hypophosphatemia	5 (7)	1 (1)	—	—
Hypokalemia	6 (8)	—	—	—
Pulmonary edema	4 (5)	1 (1)	—	—
Thrombocytopenia	1 (1)	4 (5)	—	1 (1)
Encephalopathy	4 (5)	—	—	—
Increase in alanine aminotransferase	4 (5)	—	—	—
Fluid overload	4 (5)	—	—	—

Maude S.L., et al. N Engl J Med 2018;378:439-48

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ZUMA 3

Design	• Multicenter, single arm, open-label • Phase I/II • R/R B-Cell ALL
Patients	• n=24 • **18 years and older**
Endpoints	• Primary: Overall complete remission rate • Secondary: DOR, RFS, OS, MRD negative remission rates, Allo HSCT rate,
Response	• 17/24 patients (71%) with complete tumor remission (CR) • 100% of responders were MRD negative

Shah B, et al. ASH 2017;Abstract 888

ZUMA 3

Response	• 17/24 patients (71%) with complete tumor remission (CR) • 100% of responders were MRD negative
Adverse Events	• 8/29 (28%) Grade 3 or higher CRS • 18/29 (52%) with neurological toxicity • Two patients died – CVA (unrelated), fatal CRS

Shah B, et al. ASH 2017;Abstract 888

ZUMA 3

- In the subset of patients previously treated with Blinatumomab, 5/8 (63%) achieved CR/Cri and all 5 patients had MRD negative remissions
- KTE-C19 was also manufactured successfully in all patients
- Important to note that prior therapy directed against CD19 did not affect the manufacturing of the product

Shah B, et al. ASH 2017;Abstract 888

ZUMA 4

- Phase I/II
  - Actively recruiting
- Evaluating KTE-C19 (Yescarta) in pediatric and adolescent patients (age 2-21) with r/r B-Cell ALL
- Reported data on 4 treated patients:
  - All 4 patients MRD negative at 5 months
  - No dose limiting toxicity

Lee D.W., Ann Oncol 2017;28(suppl 5):v355-v371

Adult ALL

	Blincyto	Inotuzumab	19-28Z CAR	19-41BB CAR
Phase	III	III	I/II	II
Patients				
Age (year)	≥ 18	≥ 18	≥ 18	≤ 21
No. enrolled	271	141	83	92
No. evaluable	267	109	53	75
Follow-up (m)	11.7	NA	29	13.1
CR%	44	80.7	83	81
OS (m)	7.7	7.7	12.9	NR
CRS % (≥ grade 3)	4.9	NA	26	47
Neurotoxicity %	11	12	31	32

DIFFUSE LARGE B-CELL LYMPHOMA

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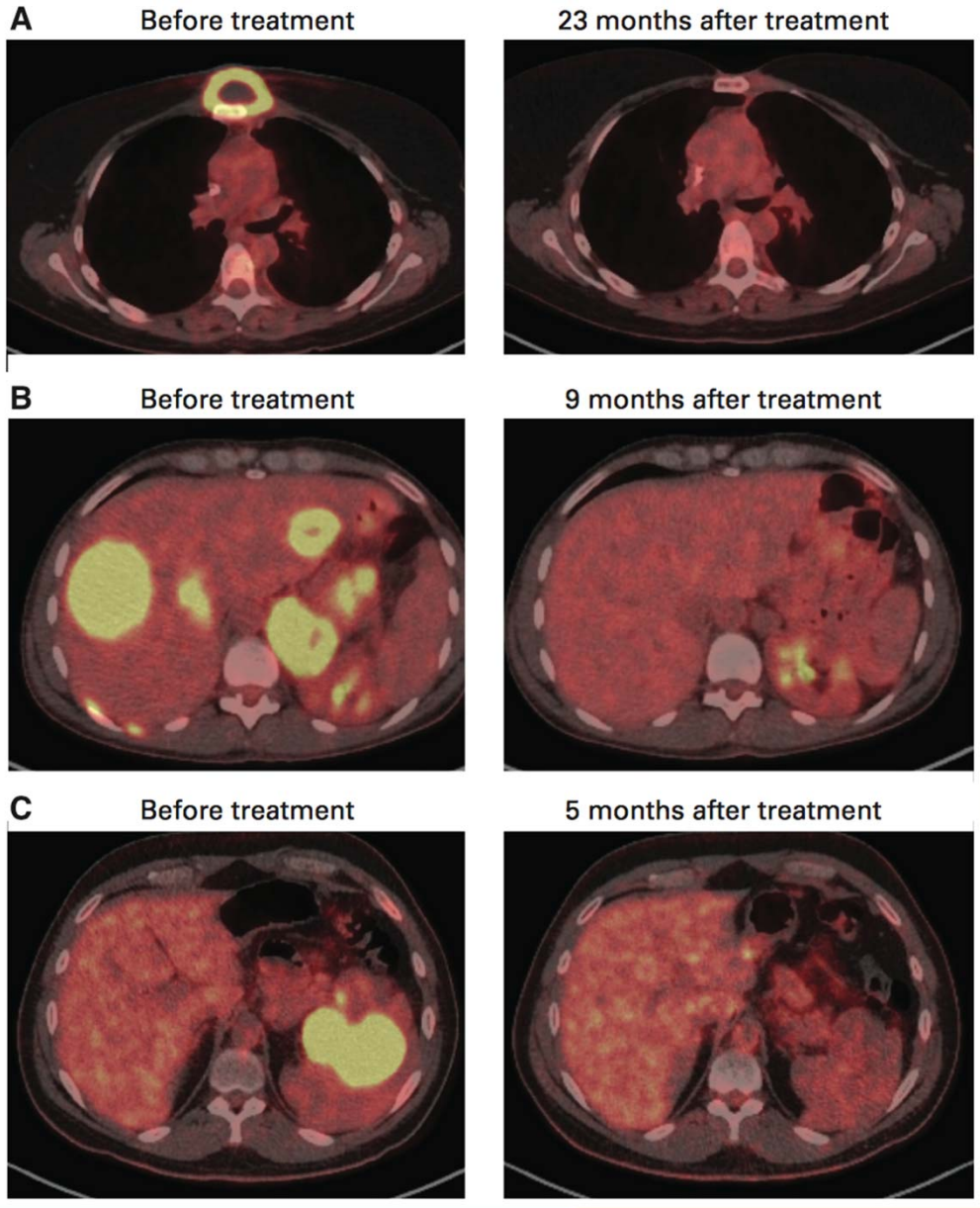
SCHOLAR-1

- Retrospective review of 636 patient with refractory NHL
  - Stable/progressive disease as best response to chemotherapy or relapse within 12 months of Auto-SCT
- ORR 26% with CR rate of only 7%
  - Lowest rates in patients with high IPI score or primary refractory disease
- Median OS 6.3 months
- 1 yr and 2 yr survival rates 28% and 20% respectively

Crump M, et al. Blood 2017;130:1800-8



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Kochenderfer J, et al. J Clin Oncol 2015;33(6):540-9

ZUMA 1 – Phase 1

Molecular Therapy
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma

Frederick L. Locke,[1,8] Sattva S. Neelapu,[2,8] Nancy L. Bartlett,[3] Tanya Siddiqi,[4] Julio C. Chavez,[5] Chitra M. Hosing,[6] Armin Ghobadi,[3] Lihua E. Budde,[4] Adrian Bot,[7] John M. Rossi,[7] Yizhou Jiang,[7] Allen X. Xue,[7] Meg Elias,[7] Jeff Aycock,[7] Jeff Wiezorek,[7] and William Y. Go[7]

[1]Department of Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL 33612, USA; [2]Division of Cancer Medicine, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [3]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO 63110, USA; [4]Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA 91010, USA; [5]Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL 33612, USA; [6]Division of Cancer Medicine, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [7]Kite Pharma, Santa Monica, CA 90404, USA

Locke F, et al. Mol Ther 2017;25:285-95

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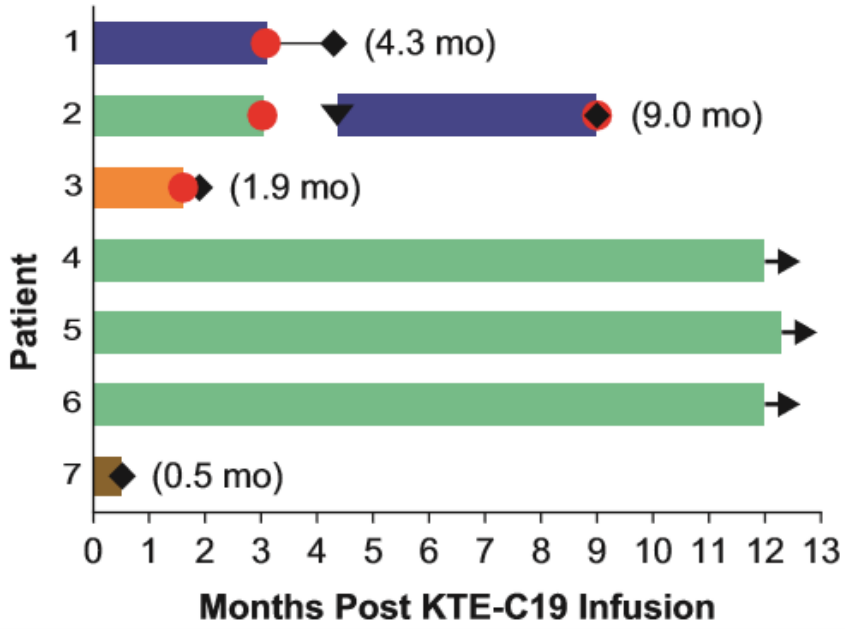

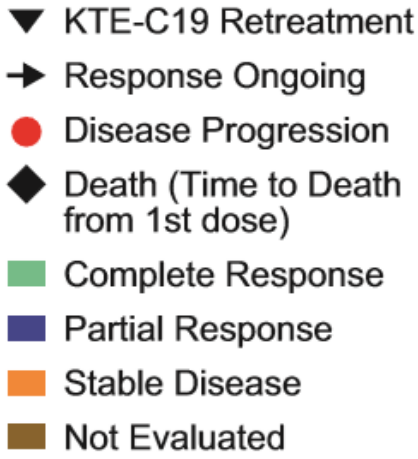

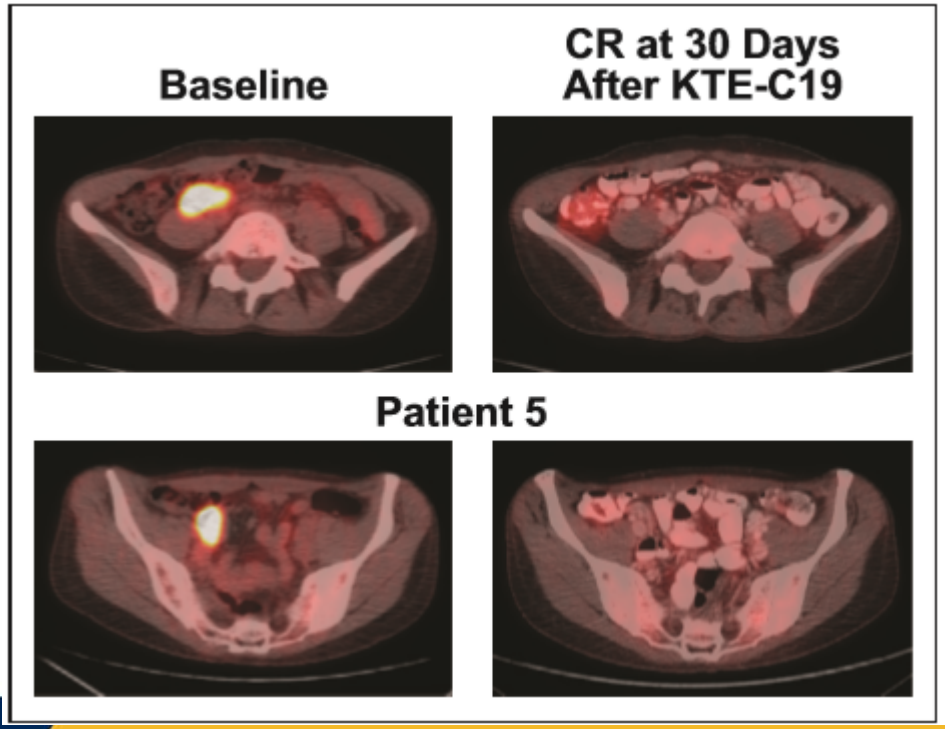

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Locke F, et al. Mol Ther 2017;25:285-95

ZUMA 1 - Phase-2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

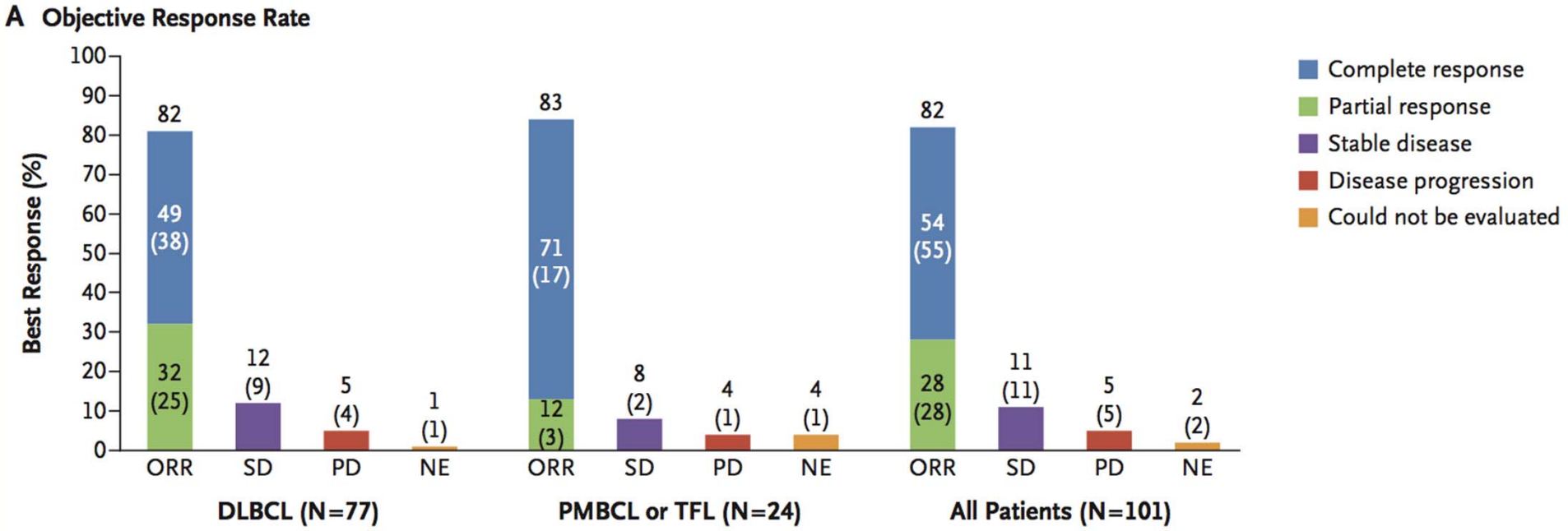
Neelapu S.S., et al. N Engl J Med 2017;377:2531-44

ZUMA – Phase 2

Design	•Global, multicenter, single arm, open-label •Phase II •r/r Diffuse Large B-Cell Lymphoma. Primary Mediastinal Lymphoma, or transformed Follicular Lymphoma
Patients	•n=101 (received infusion) and included in modified intention-to-treat analysis •At least 2 lines of therapy; progressive/stable disease to most recent therapy or relapse within 12 months of Auto-SCT •Median age: 58 (range 23-76) •85% with stage III/IV disease •77% resistant to second line or later therapies; 69% received at least 3 lines •21% of patients had prior auto-SCT
Endpoints	•Primary: Overall Response Rate (CR + PR) •Secondary: DOR, PFS, OS, Safety, Biomarker assessment

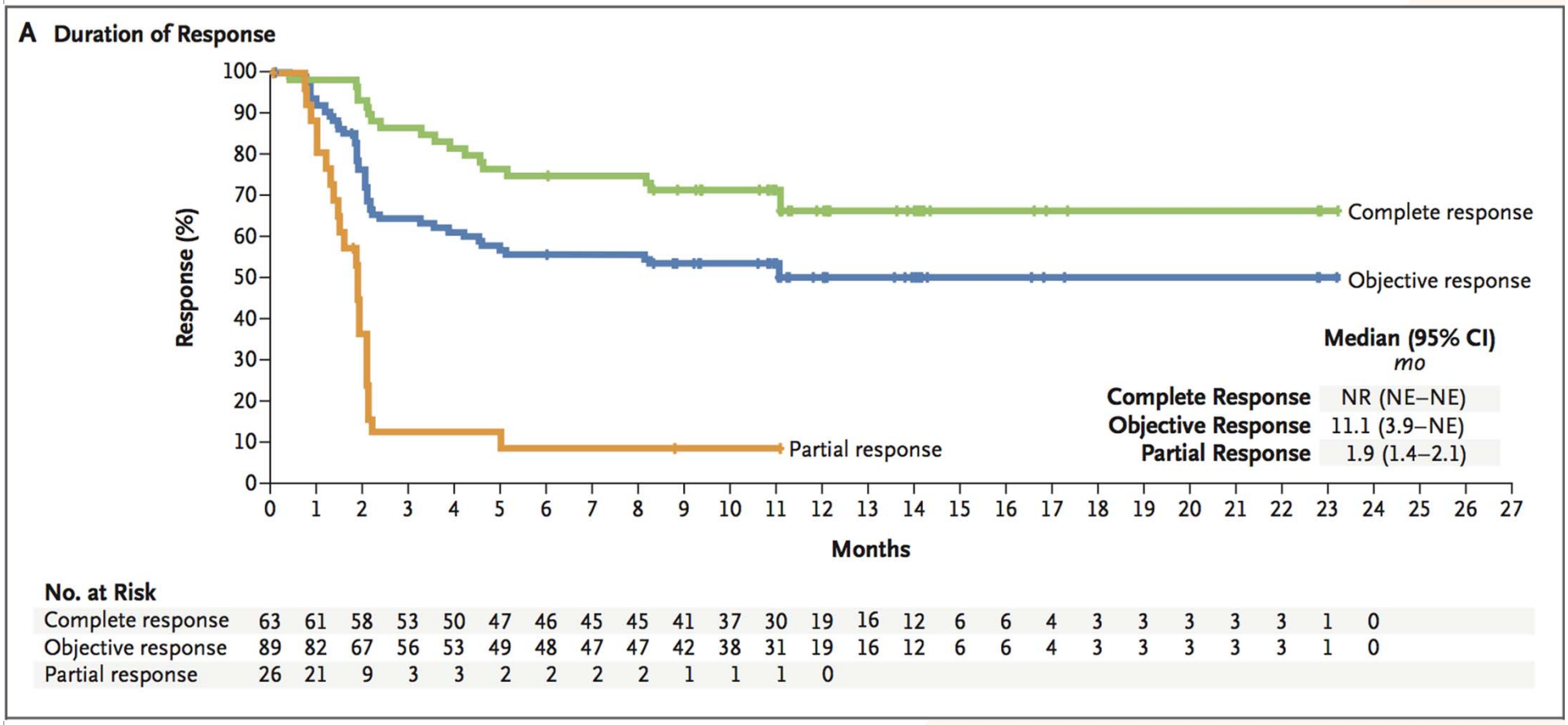
Neelapu S.S., et al. N Engl J Med 2017;377:2531-44

ZUMA 1 – Phase 2



Neelapu S.S., et al. N Engl J Med 2017;377:2531-44

ZUMA 1 – Phase 2



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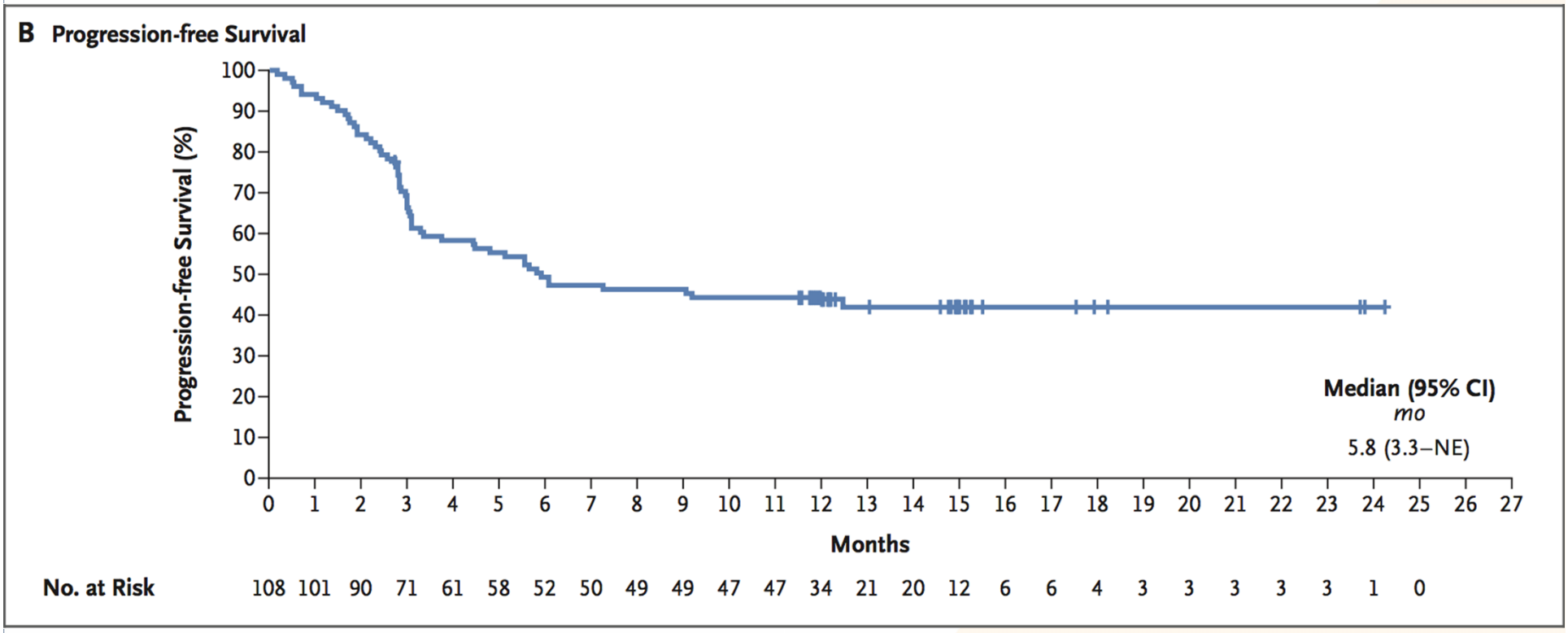
Neelapu S.S., et al. N Engl J Med 2017;377:2531-44

ZUMA 1 – Phase 2



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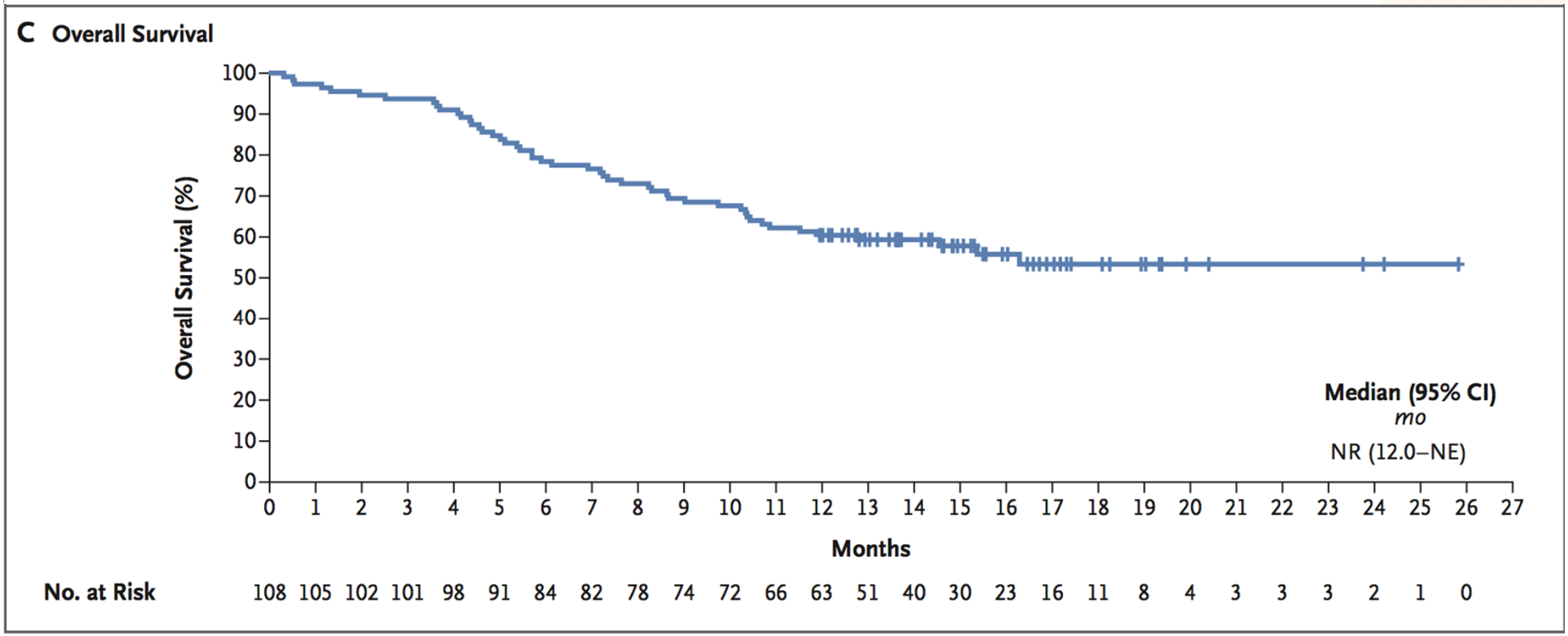
Neelapu S.S., et al. N Engl J Med 2017;377:2531-44

ZUMA 1 – Phase 2



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Neelapu S.S., et al. N Engl J Med 2017;377:2531-44

ZUMA 1 – Phase 2

Event	Any Grade	Grade 1 or 2	Grade ≥3
		number of patients (percent)	
Neurologic event			
Any	65 (64)	37 (37)	28 (28)
Encephalopathy	34 (34)	13 (13)	21 (21)
Confusional state	29 (29)	20 (20)	9 (9)
Tremor	29 (29)	28 (28)	1 (1)
Aphasia	18 (18)	11 (11)	7 (7)
Somnolence	15 (15)	8 (8)	7 (7)
Agitation	9 (9)	5 (5)	4 (4)
Memory impairment	7 (7)	6 (6)	1 (1)
Mental-status change	6 (6)	4 (4)	2 (2)
Cytokine release syndrome			
Any	94 (93)	81 (80)	13 (13)
Pyrexia	77 (76)	66 (65)	11 (11)
Hypotension	41 (41)	32 (32)	9 (9)
Hypoxia	22 (22)	13 (13)	9 (9)
Tachycardia	21 (21)	20 (20)	1 (1)
Chills	20 (20)	20 (20)	0
Sinus tachycardia	8 (8)	8 (8)	0
Headache	5 (5)	5 (5)	0

Neelapu S.S., et al. N Engl J Med 2017;377:2531-44

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KYMRIAH

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

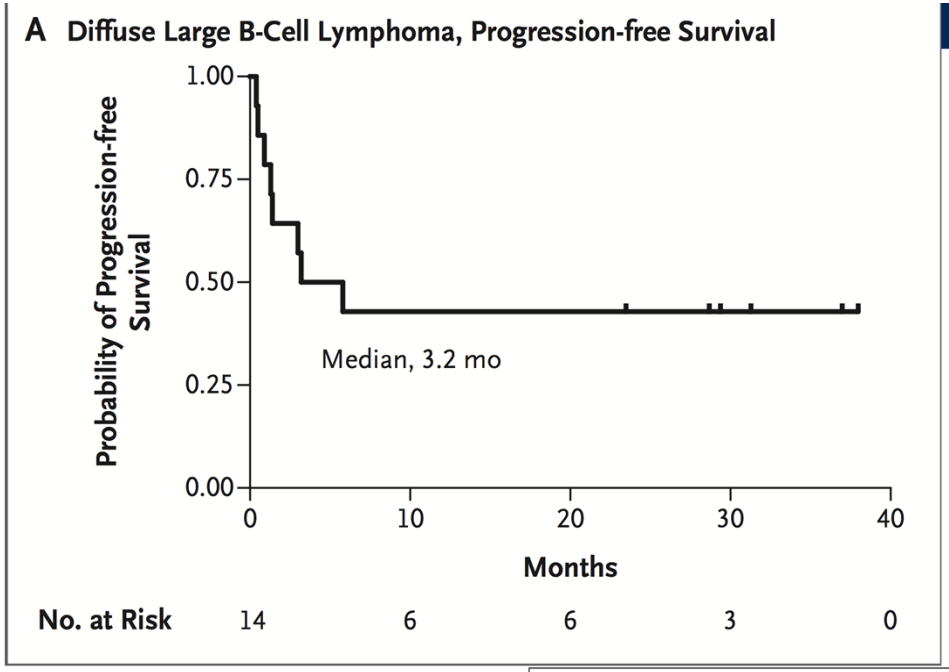
Stephen J. Schuster, M.D., Jakub Svoboda, M.D., Elise A. Chong, M.D., Sunita D. Nasta, M.D., Anthony R. Mato, M.D., Özlem Anak, M.D., Jennifer L. Brogdon, Ph.D., Iulian Pruteanu-Malinici, Ph.D., Vijay Bhoj, M.D., Ph.D., Daniel Landsburg, M.D., Mariusz Wasik, M.D., Bruce L. Levine, Ph.D., Simon F. Lacey, Ph.D., Jan J. Melenhorst, Ph.D., David L. Porter, M.D., and Carl H. June, M.D.

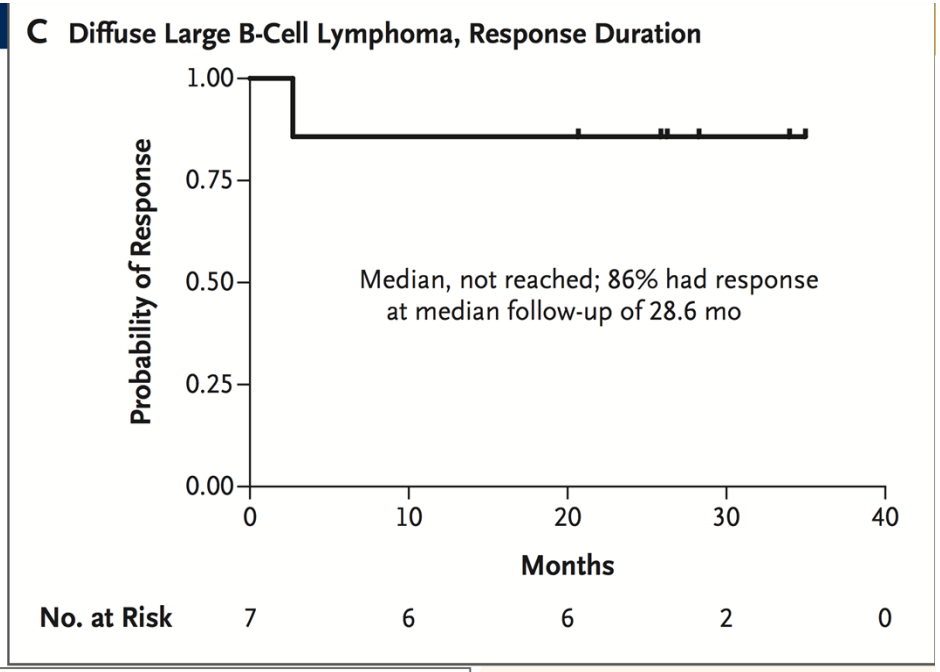
Schuster S, et al. N Engl J Med 2017;377:2545-54

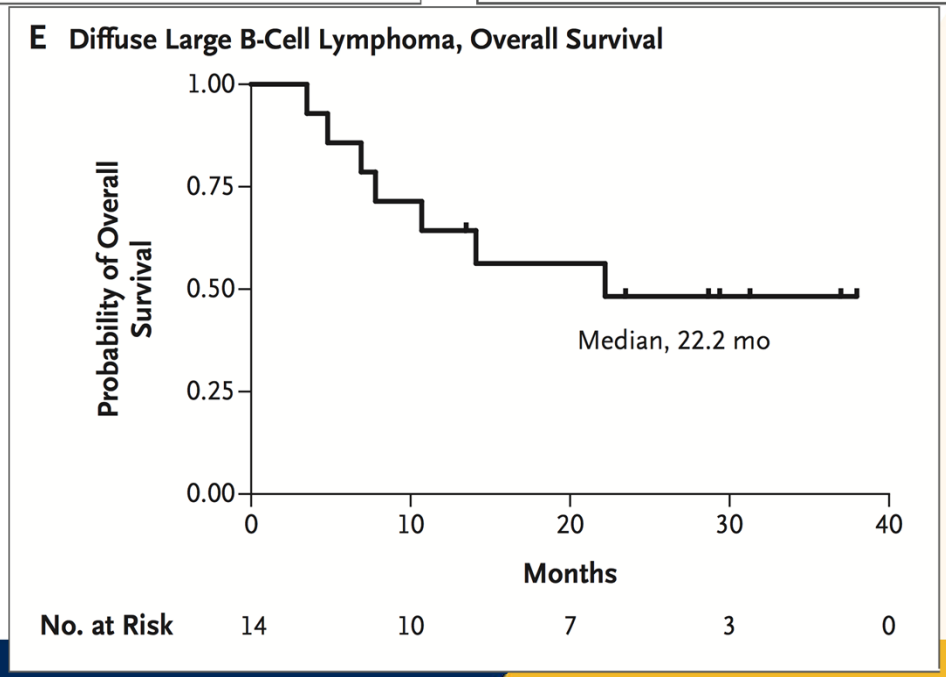
KYMRIAH

- Single center (U Penn) case series
- Evaluating CD19+ DLBCL/FL patients with no curative options, limited options, and partial/no resonse to most recent therapy
- Objectives: Overall Response Rate at 3 months
  - Secondary: PFS, DOR, Estimated OS
- 23 DLBCL patients enrolled, 14 received therapy
- Response: 50% had noted response.
  - 6/14 had complete response by 6 months (sustained)

Schuster S, et al. N Engl J Med 2017;377:2545-54







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Schuster S, et al. N Engl J Med 2017;377:2545-54

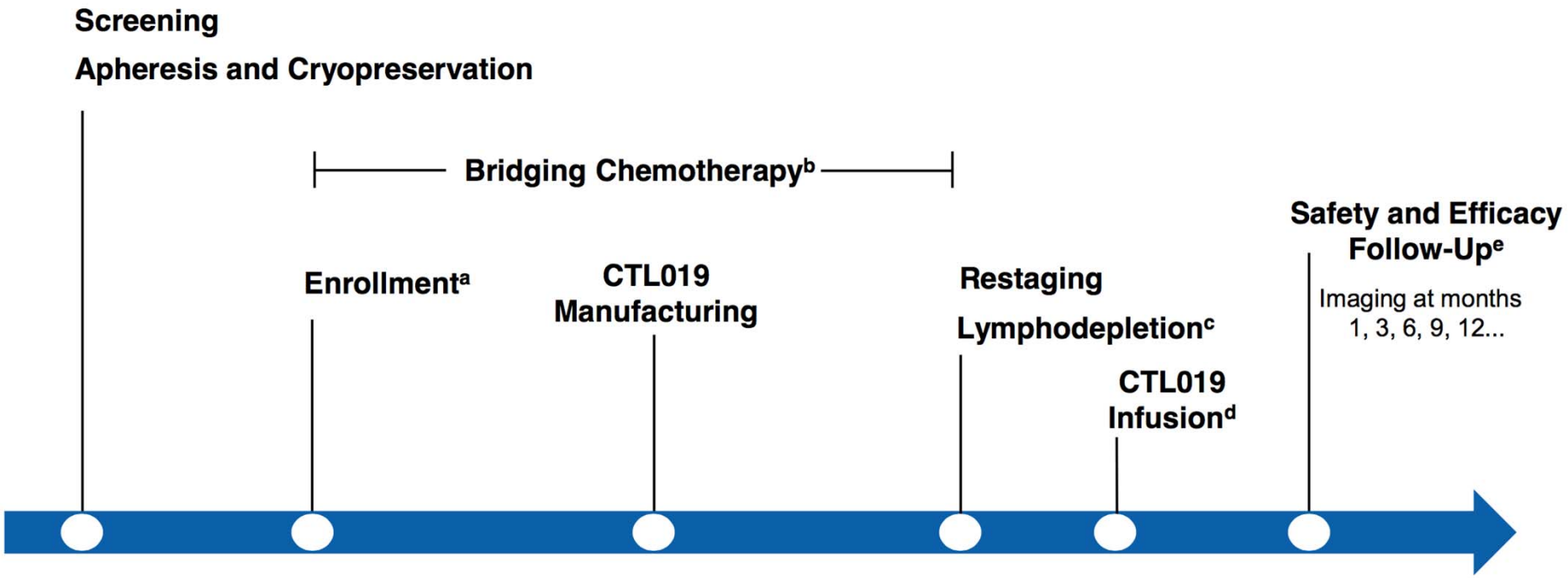
JULIET

Design	•Global, multicenter, single arm, open-label •Phase II •r/r Diffuse Large B-Cell Lymphoma (including transformed FL)
Patients	•n=81 (evaluated); 99 patients infused (18 outside US, not part of primary analysis) •At least 2 lines of therapy and ineligible for/failed Auto-SCT •Median age: 56 (23 patients > 65) •77% with stage III/IV disease •Median lines of therapy: 3 •47% of patients had prior auto-SCT
Endpoints	•Primary: Best Overall Response Rate •Secondary: DOR, OS, Safety

Schuster S, et al. Blood 2017;130(suppl 1):577

JULIET

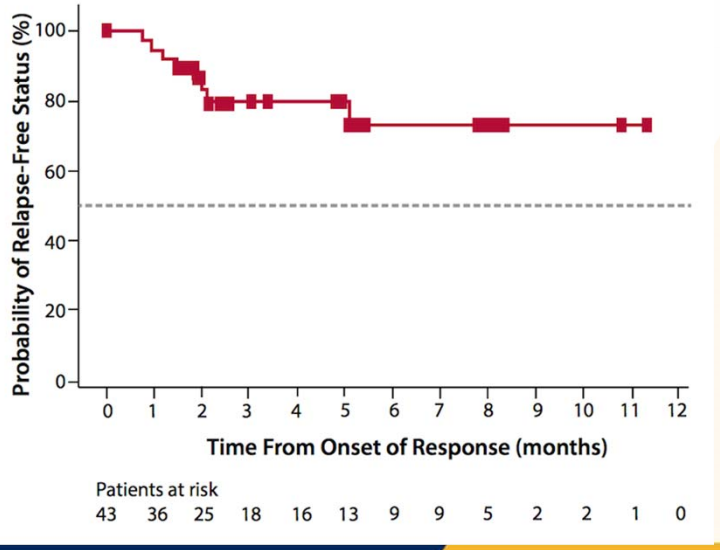
- Study Schema



Schuster S, et al. Blood 2017;130(suppl 1):577

JULIET

- Efficacy
  - ORR: 53%; CR 39.5%
  - Median DOR: Not reached; 6 mo relapse free rate 73.5%
  - Median OS: Not reached; 6 mo survival rate 64.5%



Schuster S, et al. Blood 2017;130(suppl 1):577

JULIET

- Safety
  - CRS: Grade 3 – 15%; Grade 4 – 8%
    - 15% received Tociluzumab; 11% received steroids
  - Neurologic events: Grade 3 – 8%; Grade 4 – 4%
  - No deaths from CRS of neurologic event

Schuster S, et al. Blood 2017;130(suppl 1):577

The first FDA-approved CAR-T cell therapy now has 2 indications

KYMRIAH®

(tisagenlecleucel) Suspension for IV infusion

NOW APPROVED in adults with relapsed/refractory DLBCL

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THERAPEUTIC ROLE for CAR-T

Acute Lymphoblastic Leukemia

- Currently only Kymriah (CTL-019) has approval for ALL
  - B-Cell ALL in second or later relapse in patients up to 25 years old

THERAPEUTIC ROLE for CAR-T

Diffuse Large B-Cell Lymphoma

- Both products (Kymriah and Yescarta) currently have indications in r/r Large Cell Lymphoma
  - At least two lines of therapy
  - Previously failed or not candidate for Auto-SCT
- Zuma 7 could answer question about efficacy vs Auto-SCT after first relapse

Obstacles and Limitations

- Manufacturing turnaround time
- Cost
- Lack of payment model
- Authorization

CAR-T in Multiple Myeloma

CAR-BCMA

- CD28/CD3ζ, γ-retroviral vector
- n=16,
- number of prior regimens (median): 9.5
- 63% refractory to last treatment regimen
- ORR=81%, CR+VGPR=63%

Brudno et al. JCO 2018

CARs in the Future

- Availability in numerous malignancies
- “Off the shelf” CAR-T
- Precise dosing (patient specific preferred)
- On/Off switch

Future Directions

Multiple Myeloma	• CRB-401: multicenter, phase 1 • Bb2121 targeting anti-B-cell maturation antigen (BCMA) • Number of prior regimens (median): 8 • ORR = 95.5%, sCR/CR = 50% • Median duration of response = 10.8 months
Acute Myeloid Leukemia	
Follicular Lymphoma	• JULIET, ZUMA

Future Directions

Breast cancer	• Targets: CEA, mesothelin • NCT02792114
Pancreatic cancer	• Anti-mesothelin • NCT02930993

Capabilities at WVU

- Kymriah product
  - Both indications
- First patient received cell infusion in September 2018 for DLBCL indication

Conclusions

- CAR-T available in specialized centers
- Novel treatment demonstrates significant clinical response
- Definitive place in therapy to be determined
- CAR-T technology is continuing to evolve
- Expansion of CAR-T into various malignancies

THANK YOU

WVUMedicine

QUESTIONS?