




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

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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



NO ONE FIGHTS ALONE.




Science
 Breakthrough of the Year
Cancer Immunotherapy
 T cells on the attack





**CAR T-Cell Therapy:
 ASCO's Advance of the Year**

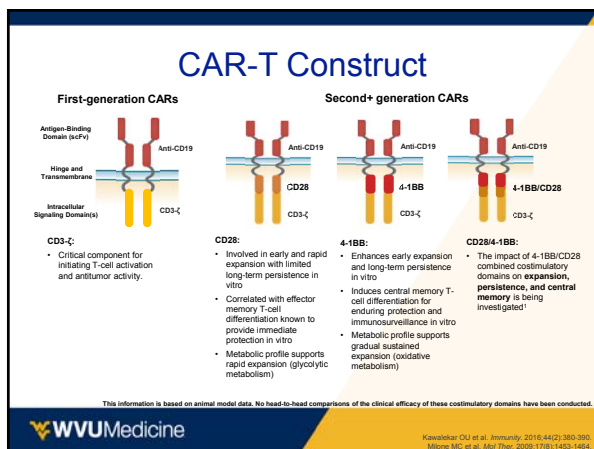
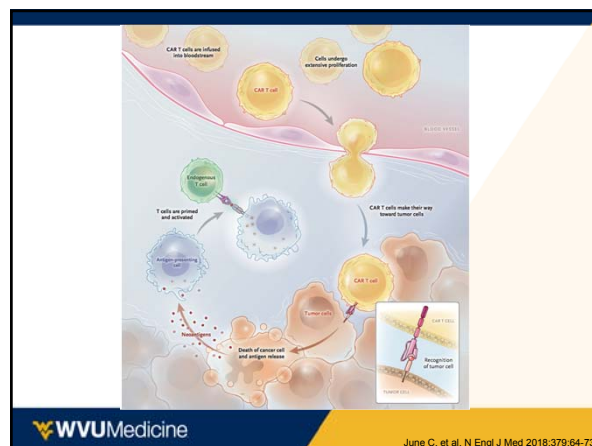
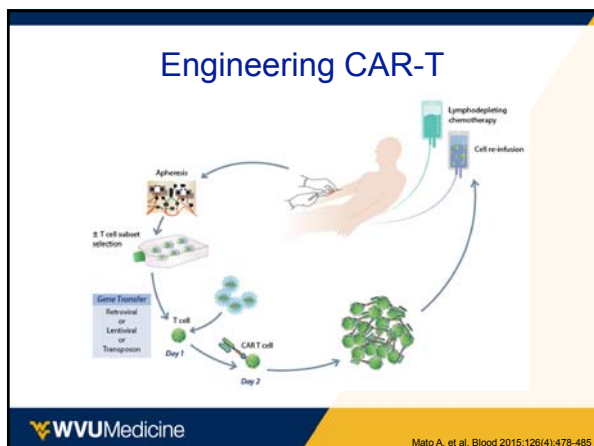


Chimeric Antigen Receptor T-Cells (CAR-T)

- 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.

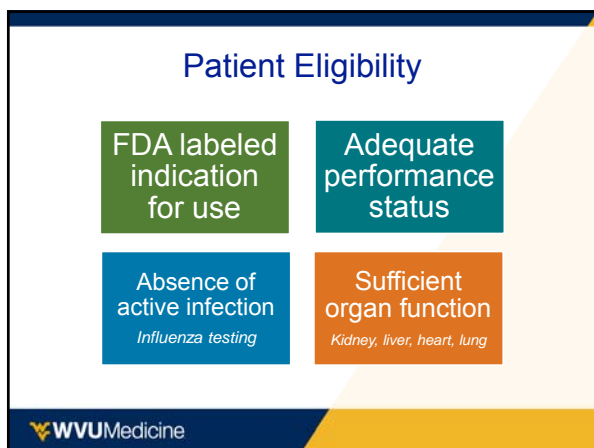


Mato A, et al. Blood 2015;126(4):478-485



Commercially Available Products

Tisagenlecleucel (Kymriah®)	Axicabtagene Ciloleucel (Yescarta®)
<ul style="list-style-type: none"> Treatment of relapsed or refractory large B-cell lymphoma in adults (after ≥2 lines of systemic therapy) Treatment of B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in patients <u>up to 25 years of age</u>. 4-1BB/CD3-ζ costimulatory domain Novartis Pharmaceuticals Corp. 	<ul style="list-style-type: none"> Treatment of relapsed or refractory large B-cell lymphoma in adults (after 2 or more lines of systemic therapy) Anticipation of B-cell ALL indication CD28/CD3-ζ costimulatory domain Kite Pharma, Inc



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

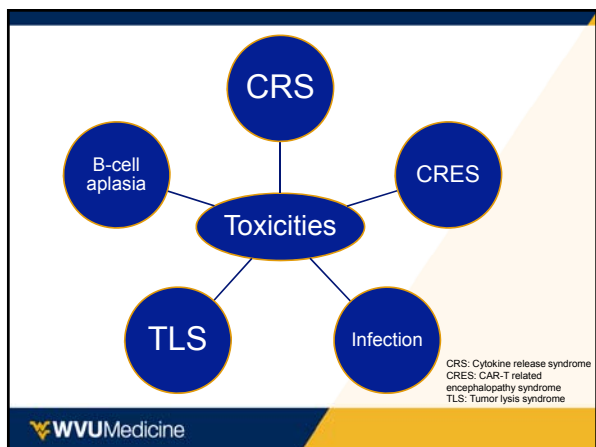
Regimens:

- Fludarabine 25-30 mg/m²/day x 3-4 doses
- Cyclophosphamide 250-500 mg/m²/day x 2-3 doses
- Bendamustine 90 mg/m² x 2 days
- No lymphodepletion

Kymriah (tisagenlecleucel) Package Insert, May 2018

CAR-T Infusion

- Cryopreservation of CAR-T product
- Currently no standard dose (may depend on indication)
 - 2 x 10⁵ – 6 x 10⁸ cells/kg
- Single vs multiple infusion bags



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 FiO ₂ <40% Grade 2 organ toxicity
3	Hypotension requiring high dose vasopressors FiO ₂ ≥ 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

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

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 2653].
Schuster SJ et al. Blood. 2017;130(suppl 1) [abstract 577].
Data on file, Novartis Pharmaceuticals Corp.

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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

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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

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REVIEW OF CLINICAL DATA

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Disease	Response Rate <i>percent</i>	Comments	Reference
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. ¹⁰ Davila et al. ¹⁶ Turtle et al. ¹⁷
B-cell acute lymphoblastic leukemia (in children)	68-90	Approximately 23% 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. ¹⁸ Maude et al. ¹⁹ Fry et al. ²⁰ Lee et al. ²¹
Chronic lymphocytic leukemia	57-71	Relapse is rare in patients who have a complete response; ibrutinib appears to increase response rates	Porter et al. ⁴ Turtle et al. ¹¹
Lymphoma			
Diffuse large B-cell lymphoma	64-86	Approximately 40-50% of patients reported to have a durable complete response	Turtle et al. ¹⁶ Kochenderfer et al. ²² Schuster et al. ¹² Neelapu et al. ¹³
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. ¹²
Transformed follicular lymphoma	70-83	A total of 3 of 3 patients with transformed follicular lymphoma had a complete response	Turtle et al. ¹⁶ Schuster et al. ¹² Neelapu et al. ¹³
Refractory multiple myeloma	25-100	B-cell maturation antigen CAR T cells; stringent complete response in approximately 25% of patients	Ali et al. ²³ Fan et al. ²⁴ Berdeja et al. ¹⁴
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. ²⁵
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. ¹¹

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

The NEW ENGLAND JOURNAL of MEDICINE

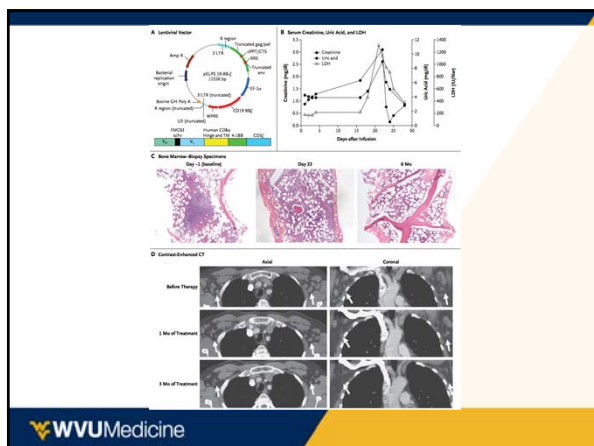
BRIEF REPORT

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



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, P. 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. Lebowitz, M.A. Pulsipher, and S.A. Grupp

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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)
- 80% achieved CR; 21% achieved CRi
- Engineered T-Cells detected up to 20 months out

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

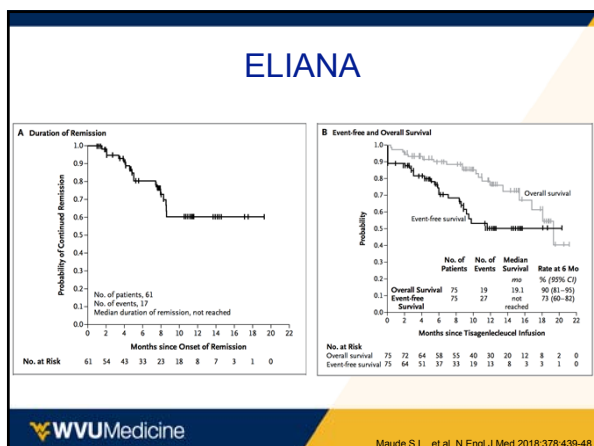


Table 2. Grade 3 or 4 Adverse Events Suspected to Be Related to Tisagenlecleucel That Occurred in at Least 5% of Patients.

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)	—	—
Hypertension	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)	—	—	—

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



FDA Approval Brings 1st Gene Therapy to the United States

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ZUMA 3

Design	<ul style="list-style-type: none"> Multicenter, single arm, open-label Phase I/II R/R B-Cell ALL
Patients	<ul style="list-style-type: none"> n=24 18 years and older
Endpoints	<ul style="list-style-type: none"> Primary: Overall complete remission rate Secondary: DOR, RFS, OS, MRD negative remission rates, Allo HSCT rate,
Response	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 17/24 patients (71%) with complete tumor remission (CR) 100% of responders were MRD negative
Adverse Events	<ul style="list-style-type: none"> 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


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DIFFUSE LARGE B-CELL LYMPHOMA

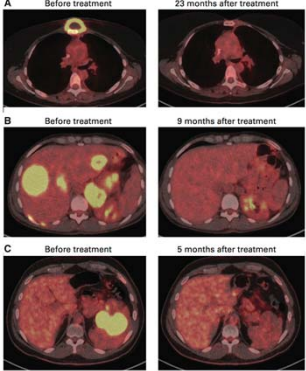



SCHOLAR-1

- 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

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

ZUMA 1 – Phase 1

Molecular Therapy
Original Article



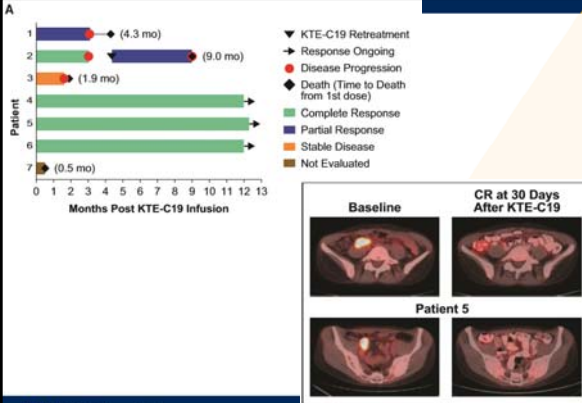

Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma

Frederick L. Locke,^{1,2} Sattva S. Neelapu,^{1,3} Nancy L. Bartlett,¹ Taryia Siddiqi,⁴ Julio C. Chavez,⁵ Chitra M. Hosing,⁶ Armin Ghobadi,¹ Lihua E. Budde,⁴ Adrian Bot,⁷ John M. Rossi,⁸ Yizhou Jiang,⁹ Allen X. Xue,⁷ Meg Elias,⁷ Jeff Aycock,⁷ Jeff Wieszorek,⁷ and William Y. Ge⁷

¹Department of Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL 33613, USA; ²Division of Cancer Medicine, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; ³Stewart Cancer Center, Washington University School of Medicine, St. Louis, MO 63110, USA; ⁴Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA 91010, USA; ⁵Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL 33613, USA; ⁶Division of Cancer Medicine, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; ⁷Xile Pharma, Santa Monica, CA 90404, USA



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

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, J.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. Wieszorek, and W.Y. Ge



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

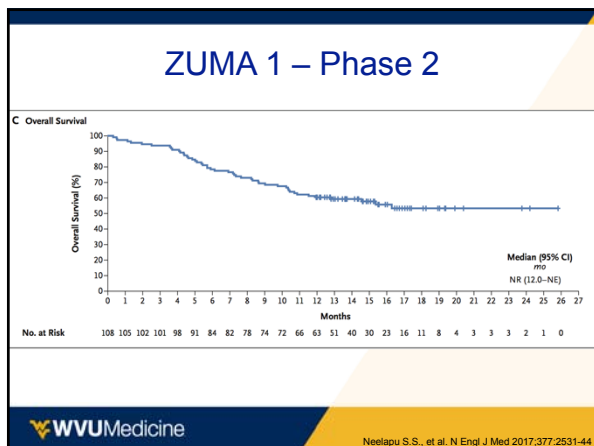
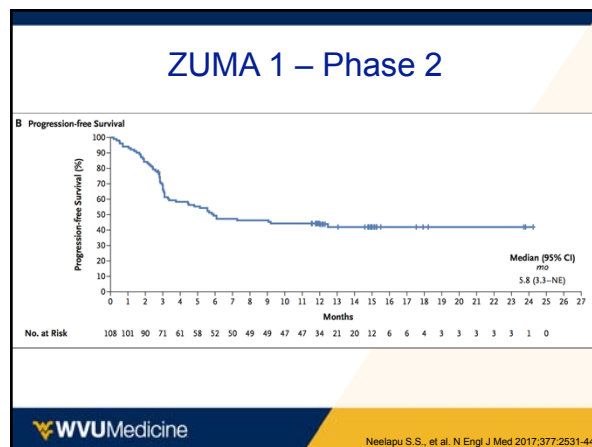
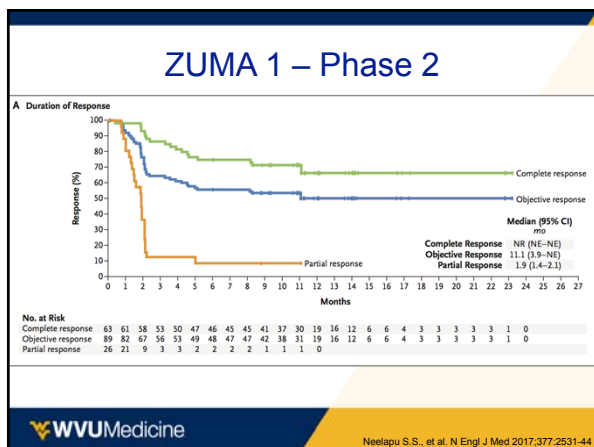
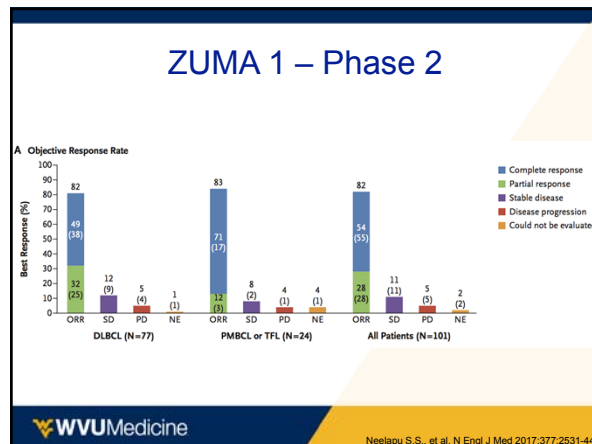
Patients

- 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 23-70)
- 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

WVUMedicine | 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	63 (64)	37 (37)	28 (28)	
Encephalopathy	24 (24)	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	

WVUMedicine | 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

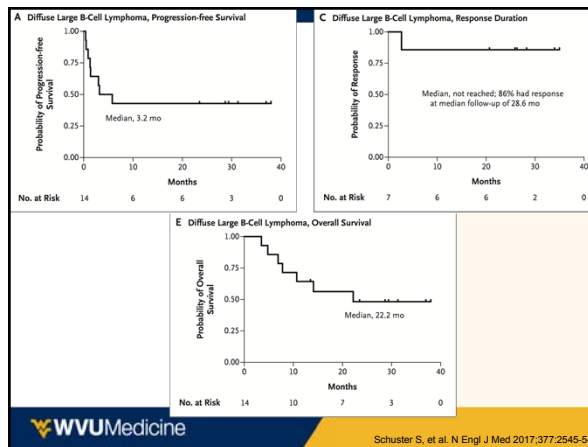
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KYMRIAH

- Single center (U Penn) case series
- Evaluating CD19+ DLBCL/FL patients with no curative options, limited options, and partial/no response 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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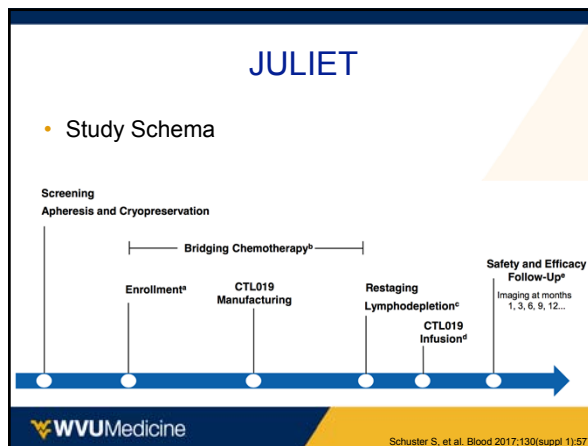
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JULIET

Design	<ul style="list-style-type: none"> • Global, multicenter, single arm, open-label • Phase II • r/r Diffuse Large B-Cell Lymphoma (including transformed FL)
Patients	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Primary: Best Overall Response Rate • Secondary: DOR, OS, Safety

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

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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%

Patients at risk
43 36 29 18 16 13 9 9 5 2 2 1 0

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

JULIET

- Safety**
 - CRS: Grade 3 – 15%; Grade 4 – 8%
 - 15% received Tocilizumab; 11% received steroids
 - Neurologic events: Grade 3 – 8%; Grade 4 – 4%
 - No deaths from CRS or 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

WVU Medicine

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

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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

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Obstacles and Limitations

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

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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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • JULIET, ZUMA

Future Directions

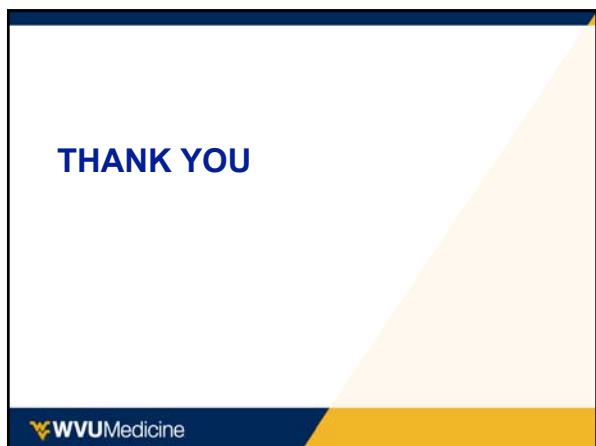
Breast cancer	<ul style="list-style-type: none"> • Targets: CEA, mesothelin • NCT02792114
Pancreatic cancer	<ul style="list-style-type: none"> • Anti-mesothelin • NCT02930993

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

 **WVU**Medicine



QUESTIONS?

 **WVU**Medicine