Understanding CAR T-cell Therapy as a Treatment Option for Blood Cancer Patients

Friday, June 21, 2019
8:30 AM - 4:30 PM

Hilton Nashville Downtown
Nashville, TN

This activity is supported by educational grants from Celgene Corporation and Kite, a Gilead Company.

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1

INTRODUCTIONS AND WELCOME

Lauren Berger, MPH
Senior Director
Professional Education & Engagement
The Leukemia & Lymphoma Society
Rye Brook, NY

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LEARNING OBJECTIVES

At the conclusion of this program, participants will be able to:

- Explain the emerging role of chimeric antigen receptor (CAR) T-cell treatment as an option for patients with relapsed/refractory blood cancer
- Discuss treatment plans for patient care
- Explain potential short- and long-term side effects and management
- Identify patients who could potentially be treated with CAR therapy
- Engage patients and caregivers in discussions on CAR T-cell therapies including benefits, risks, and barriers to entry

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CME/CPE/CE INFORMATION & CREDIT DESIGNATION

Target Audience
This activity has been designed to meet the educational needs of hematologists-oncologists, medical oncologists, oncology fellows, pharmacists, physician assistants, nurse practitioners, nurses, and oncology social workers at the intermediate and advanced level involved in the care of patients with hematologic malignancies.

Providers
Jointly provided by The Leukemia & Lymphoma Society and Medical Learning Institute, Inc.

Commercial Support Acknowledgement
This activity is supported by educational grants from Celgene Corporation and Kite, a Gilead Company.

CME/CPE/CE Continuing Education Information
Physician Credit Designation
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Medical Learning Institute, Inc. and The Leukemia & Lymphoma Society. The Medical Learning Institute, Inc. is accredited by the ACCME to provide continuing medical education for physicians.

The Medical Learning Institute, Inc. designates this live educational activity for a maximum of 7.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Pharmacist Credit Designation
The Medical Learning Institute, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Completion of this knowledge-based activity provides 7.5 contact hours (0.75 CEUs) of continuing pharmacy education credit. The Universal Activity Number for this activity is 0468-9999-19-007-L01-P.

Registered Nurse Designation
Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society National Office under provider number CEP 5832 to award 7.5 continuing education contact hours through the California Board of Registered Nursing.

Social Work Credit Designation
The Leukemia & Lymphoma Society (LLS), provider number #1105 is approved as a provider for social work continuing education by the Association of Social Work Boards (ASWB) www.aswb.org. Approved Continuing Education Program (ACE). Approval Period: 12/10/2017 - 12/10/2020. LLS maintains responsibility for the program. Social workers should contact their regulatory board to determine course approval. Social workers will receive 7.5 CE clinical contact hours.

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INSTRUCTIONS FOR CREDIT

There is no fee for this educational activity. To receive credit for this CME/CPE/CE activity, complete the preassessment, course, post- assessment, and evaluation and return it to the on-site coordinator. Your certificate of credit will be e-mailed to you within 4 weeks. For pharmacists, MLI will accept your completed evaluation form for up to 30 days and will report your participation to the NABP only if you provide your NABP e-Profile number and date of birth. Within 6 weeks, view your participation record at the NABP website: mycpemonitor.net.

For questions regarding the accreditation of this activity, please contact Medical Learning Institute, Inc. at (609) 333-1693 or ndane@mlicme.org.

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FACULTY

David L. Porter, MD (Chair)
Jodi Fisher Horowitz
Professor in Leukemia Care Excellence
Director, Blood and Marrow Transplantation
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University of Pennsylvania Health System
Philadelphia, PA

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Research Nurse Specialist II
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Nashville, TN

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Nurse Practitioner
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for Blood Cancer at TriStar Centennial
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Director of Multiple Myeloma Research
Sarah Cannon Research Institute at
Tennessee Oncology and Sarah Cannon Center
for Blood Cancer at TriStar Centennial
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Clinical Program Manager
Sarah Cannon Blood Cancer Network
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Medical Director, Pediatric Stem Cell Transplantation Program
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Nashville, TN

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Physician-in-Chief Hematology
Senior Vice President, Market Operations
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Co-Director, Immune Effector Cell Therapy (CAR-T) Program
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Clinical Trial Nurse Navigator
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Memphis, TN

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Professor of Medicine
Medical Oncology and Pathology Director
Bone Marrow Stem Cell Transplant Center
Director, Division of Stem Cell Transplantation
and Immunotherapy
Emory University School of Medicine
Atlanta, GA

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DISCLOSURE

Before the activity, all faculty and everyone who is in a position to have control over the content of this activity and their spouse/life partner will disclose the existence of all financial interest and/or relationship(s) they might have with any commercial interest producing healthcare goods/services to be discussed during their presentation(s): honoraria, expenses, grants, consulting roles, speakers bureau membership, stock ownership, or other special relationships. Presenters will inform participants of any off-label discussions. All identified conflicts of interest are thoroughly vetted by Medical Learning Institute, Inc. for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations.

The associates of Medical Learning Institute, Inc., the accredited provider for this activity and The Leukemia & Lymphoma Society do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this CME/CPE/CE activity during the past 12 months

Name of Planner or Manager	Title	Reported Financial Relationship
Patricia Ensor, RPh	Content Expert Reviewer	Has nothing to disclose. She does not intend to include any non-FDA-approved or investigational use of any products/devices.
Teresa Haile, RPh, MBA	Lead Pharmacy Planner	Has nothing to disclose. She does not intend to include any non-FDA-approved or investigational use of any products/devices.

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FACULTY DISCLOSURES

David L. Porter, MD, is on the Advisory Board for: Glenmark; Kite, A Gilead Company; and Novartis. Research Support for Novartis, receives royalty payments for patent licensed by Penn to Novartis and his wife is employed with Genentech as a Division Sales Manager for the Breast Cancer Group. He does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR T cells for CLL.

Brittney Baer, RN, BSN, has nothing to disclose. She does not intend to include any non-FDA-approved or investigational use of any products/devices

Lesley Camille Ballance, MSN, FNP-BC, has nothing to disclose. She does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR T-cells are not approved for multiple myeloma.

Jesús G. Berdeja, MD, is a Consultant for: Amgen; Bioclinica; Bristol-Myers Squibb; Celgene Corporation; CRISPR Therapeutics; Janssen, Pharmaceutical Companies of Johnson & Johnson; Karyopharm Therapeutics; Kite, A Gilead Company; Prothena Corporation; Servier; Takeda. Research Funding for: AbbVie, Amgen, Acetylon Pharmaceuticals, Inc, Bluebird Bio, Bristol-Myers Squibb, Celgene Corporation, Constellation; CURIS, Inc; Genentech; Glenmark; Janssen; Kesios Therapeutics; Lilly; Novartis; Poseida Therapeutics; Sanofi; Takeda; Teva Pharmaceutical Industries; Vivolux. He does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR T therapy for multiple myeloma.

Trista Carelock, RN, BSN, BMT-CN®, OCN®, has nothing to disclose. She does intend to include either non-FDA-approved or investigational use for the following products/devices: novel agents currently on clinical trial for CAR T therapy.

Luciano J. Costa, MD, PhD, is a Consultant for Celgene Corporation and Karyopharm Therapeutics and received a Speaker's Fee for Amgen. He does intend to include either non-FDA-approved or investigational use for the following products/devices: novel agents currently on clinical trial for CAR T therapy.

Bhagirathbhai R. Dholaria, MBBS, has nothing to disclose. He does intend to include either non-FDA-approved or investigational use for the following products/devices: novel agents currently on clinical trial for CAR T therapy.

Rebecca Epperly, MD, has nothing to disclose. She does not intend to include any non-FDA-approved or investigational use of any products/devices.

Mykala Heuer, BSN, RN, has nothing to disclose. She does not intend to include any non-FDA-approved or investigational use of any products/devices.

Gerhard C. Hildebrandt, MD, is a Consultant/Advisor for: Incyte; Jazz Pharmaceuticals; Kite, A Gilead Company; and Pfizer. Research Funding for Jazz Pharmaceuticals, Pharmacyclics, and Takeda. Stock/Ownership Interests: AbbVie; Aetna; Bluebird Bio; Bristol-Myers Squibb/Medarex; Cardinal Health; Celgene Corporation; Cellectis; Clovis Oncology; CRISPR Therapeutics; CVS Health; Endocyte, A Novartis Company; GW Pharmaceuticals; IDEXX Laboratories; Immunomedics; INSYS Therapeutics, Inc; Jazz Pharmaceuticals; Johnson & Johnson; Juno Therapeutics, A Celgene Company; Kite, A Gilead Company; Novartis; Pfizer; Procter & Gamble; Sangamo Therapeutics; and Vertex. He does not intend to include any non-FDA-approved or investigational use of any products/devices.

Carrie L. Kitko, MD, is on the Advisory Board for Novartis and received a Speaker's Fee for Mallinckrodt. She does intend to include either non-FDA-approved or investigational use for the following products/devices: novel agents currently on clinical trial for CAR T therapy.

C. Fred LeMaistre, MD, has nothing to disclose. He does intend to include either non-FDA-approved or investigational use for the following products/devices: tisagenlecleucel and (axicabtagene ciloleuce).
Amitkumar Mehta, MD, is a Consultant for Bristol-Myers Squibb; Celgene Corporation; Kite Pharma, A Gilead Company, and Spectrum. He received Speaker's Fee from AstraZeneca; Gilead Sciences, Inc.; Kite, A Gilead Company; Kyowa Kirin, SGN NanoPharma, and Spectrum. He does not intend to include any non-FDA-approved or investigational use of any products/devices

Dilan A. Patel, MD, has nothing to disclose. He does not intend to include any non-FDA-approved or investigational use of any products/devices.

Ayman Qasrawi, MD, has nothing to disclose. He does intend to include either non-FDA-approved or investigational use for the following products/devices: novel agents currently on clinical trial for CAR T therapy.
Laura Romundstad, CRNP, MSN, RN, has nothing to disclose. She does not intend to include any non-FDA-approved or investigational use of any products/devices.

M. Paulina Velasquez, MD, has nothing to disclose. She does intend to include either non-FDA-approved or investigational use for the following products/devices: novel agents currently on clinical trial for CAR T therapy.

Edmund K. Waller, MD, PhD, FACP, is a Consultant for: Novartis, Kalytera Therapeutics, Humanagen Inc., and Founder for Cambium Medical Technologies. He does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR T for non-FDA approved indications.

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AGENDA

8:00 – 8:30 am	Breakfast and Registration
8:30 – 8:35 am	Welcome & LLS Impact: Advancing Cures *Lauren Berger, MPH*
8:35 – 8:45 am	Overview *David L. Porter, MD (Chair)*
8:45 – 9:15 am	CAR T-cell Clinical Applications: Is it Right for My Patients? *Bhagirathbhai R. Dholaria, MBBS*
9:15 – 9:45 am	CAR T Toxicity and Management *M. Paulina Velasquez, MD*
9:45 – 10:15 am	CAR T-cells for ALL *Carrie L. Kitko, MD*
10:15 – 10:30 am	Break
10:30 – 11:00 am	CAR T-cells for NHL *Amitkumar Mehta, MD*
11:00 – 11:30 am	CAR T-cells for Myeloma: The Next Major Disease Target? *Jesús G. Berdeja, MD*
11:30 – 12:00 pm	CAR T-cells for CLL *David L. Porter, MD*
12:00 – 12:15 pm	Q & A *David L. Porter, MD*
12:15 – 12:30 pm	Lunch Break
12:30 – 1:15 pm	Meet the Experts: Roundtable discussions facilitated by fellows and symposium faculty *Brittney Baer, RN, BSN; Lesley Camille Ballance, MSN, FNP-BC; Jesús G. Berdeja, MD; Trista Carelock, RN, BSN, BMT-CN®, OCN®; Luciano J. Costa, MD PhD; Rebecca Epperly, MD; Mykala Heuer, BSN, RN; Gerhard C. Hildebrandt, MD; Carrie L. Kitko, MD; C. Fred LeMaistre,MD; Amitkumar Mehta, MD; Dilan A. Patel, MD; Ayman Qasrawi, MD; Laura Romundstad, CRNP, MSN, RN; M. Paulina Velasquez,MD; Edmund K. Waller, MD, PhD, FACP*
1:15 – 2:15 pm	Case Presentations: NHL and Myeloma: Referral, Treatment and Follow-up *Gerhard C. Hildebrandt, MD and Luciano J. Costa, MD, PhD*
2:15 – 2:45 pm	Getting Started: A CAR T Team's Experience *Edmund K. Waller, MD, PhD, FACP*
2:45 – 3:15 pm	Commercial CAR-T Coverage and Reimbursement: What a Clinician Needs to Know *C. Fred LeMaistre, MD*
3:15 – 4:00 pm	It Takes a Village: Panel Presentations & Discussion *Brittney Baer, RN, BSN; Lesley Camille Ballance, MSN, FNP-BC; Trista Carelock, RN, BSN, BMT-CN®, OCN® and Mykala Heuer, BSN, RN*
4:00 – 4:30 pm	Interactive Panel Discussion and Q & A *David L. Porter, MD and Panel*

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9

MEET THE EXPERTS: ROUNDTABLE DISCUSSIONS

Getting Started/Setting up a CAR T program
Edmund K. Waller, MD, PhD, FACP
Emory University School of Medicine
Atlanta, GA

Financial Considerations
C. Fred LeMaistre, MD
Sarah Cannon Blood Cancer Network
Nashville, TN

Nursing and Coordination of Care
Brittney Baer, RN, BSN
Vanderbilt University School of Medicine
Nashville, TN

Mykala Heuer, BSN, RN
Vanderbilt-Ingram Cancer Center
Nashville, TN

Nursing and Coordination of Care
Lesley Camille Ballance, MSN, FNP-BC
Sarah Cannon Research Institute at
Tennessee Oncology and Sarah Cannon Center
for Blood Cancer at TriStar Centennial
Nashville, TN

Trista Carelock, RN, BSN, BMT-CN®, OCN®
Sarah Cannon Blood Center Network
Nashville, TN

CAR T and Lymphoma
Ayman Qasrawi, MD
University of Kentucky HealthCare
Lexington, KY

Gerhard C. Hildebrandt, MD
University of Kentucky HealthCare
Lexington, KY

CAR T and Myeloma
Jesús G. Berdeja, MD
Sarah Cannon Research Institute at Tennessee Oncology
and Sarah Cannon Center for Blood Cancer at TriStar Centennial
Nashville, TN

Luciano J. Costa, MD, PhD
University of Alabama Birmingham School of Medicine
Birmingham, AL

CAR T in ALL
Dilan A. Patel, MD
Vanderbilt University School of Medicine
Nashville, TN

Carrie L. Kitko, MD
Vanderbilt University School of Medicine
Nashville, TN

Toxicity and Management: CRS and Neurotoxicity
Rebecca Epperly, MD
St. Jude Children's Research Hospital
Memphis, TN

M. Paulina Velasquez, MD
St. Jude Children's Research Hospital
Memphis, TN

General Questions for the Experts
Amitkumar Mehta, MD
University of Alabama Birmingham School of Medicine
Birmingham, AL

Laura Romundstad, CRNP, MSN, RN
Clinical Trial Nurse Navigator
Clinical Trial Support Center
The Leukemia & Lymphoma Society
Rye Brook, NY

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10

11

OUR MISSION

The mission of The Leukemia & Lymphoma Society (LLS) is: Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.

We fund **RESEARCH** to advance lifesaving treatments

We drive **ADVOCACY** for policies that protect patient access to lifesaving treatment

We provide patients and families with hope, guidance, education and **SUPPORT**

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12

WHY ARE WE SO EXCITED ABOUT IMMUNOTHERAPY?

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- **20+ years of support is finally leading to therapeutics.**
- **CAR-T proves we can harness our own immune system to help fight cancer.**
- **It's the beginning; adding a new arm in our treatment armamentarium to combine with chemotherapy, targeted therapy.**
- **LLS is not satisfied. We need to know how to turn non-responders into responders and to make the therapy safer and more accessible.**

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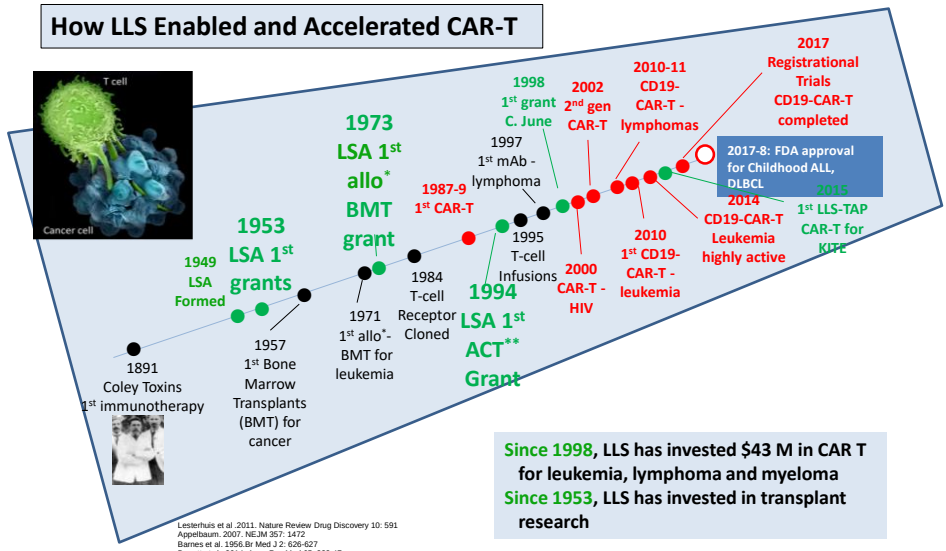
13

CUTTING-EDGE RESEARCH TAKES TIME

How LLS Enabled and Accelerated CAR-T



Since 1998, LLS has invested $43 M in CAR T for leukemia, lymphoma and myeloma
Since 1953, LLS has invested in transplant research

Lesterhuis et al .2011. Nature Review Drug Discovery 10: 591
Appelbaum. 2007. NEJM 357: 1472
Barnes et al. 1956.Br Med J 2: 626-627
Barrett et al., 2014. Annu Rev Med 65: 333-47
June, Riddell and Schumacher. 2015.Sci Trans Med 7: 280ps7

Leukemia Society of America (LSA) = The Leukemia & Lymphoma Society (LLS)
Chimeric Antigen Receptor T cell therapy
General Immunotherapy

- allo = allogeneic (donor is not the patient)
- ** ACT = adoptive cellular therapy

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14

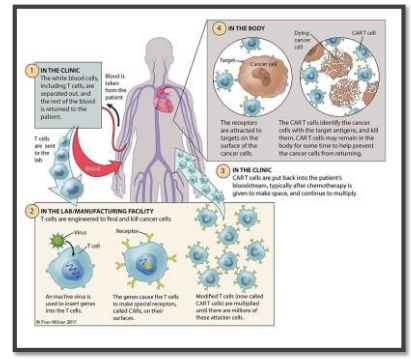
LLS EDUCATION RESOURCES FOR CAR-T

For patients:

- www.LLS.org/CART

For healthcare professionals:

- www.LLS.org/CE



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15

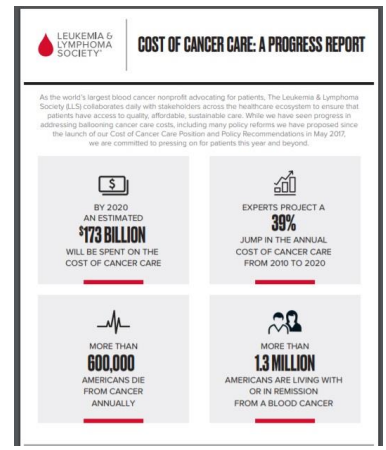
LLS POLICY EFFORTS SUPPORTING ACCESS TO CAR-T

LLS Cost of Care (www.LLS.org/cancercost)

- We are focused on costs for patients, both financial and personal, throughout the cancer care continuum.

Supporting Value-Based Pricing and Care

- We are proud to represent blood cancer patients during ICER's ongoing review of CAR-T therapy.



ICER - Institute for Clinical and Economic Review

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16

LLS INFORMATION RESOURCE CENTER (IRC)

Last year alone, LLS Information Specialists responded to nearly 20,000 inquiries from patients and caregivers.

- **Disease information**
- **Emotional support**
- **Local support through our patient access field teams**
- **Financial, travel and co-pay assistance**
- **Referral to clinical trial navigation**

www.LLS.org/IRC 800.955.4572

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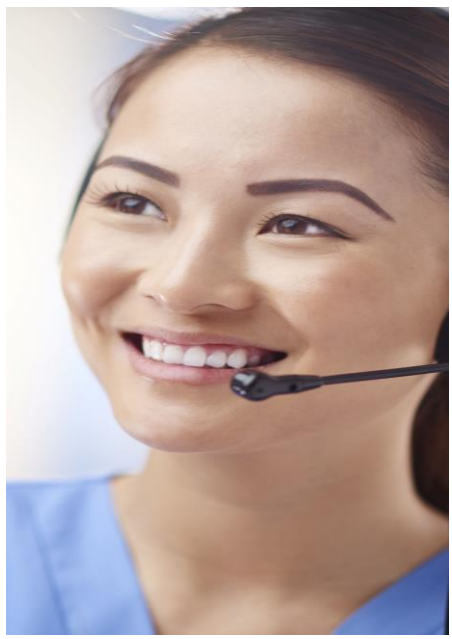
17



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CLINICAL TRIAL SUPPORT CENTER

Personal guidance to help patients find clinical trials.

Our **Clinical Trial Support Center (CTSC)** provides specially trained nurses to help patients find and enroll in clinical trials based on highly detailed, individualized assessments.

562

patients provided with in-depth clinical trial navigation and support in past year

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18

ENJOY THE PROGRAM!

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19

CAR T-cell Clinical Applications: Is it Right for My Patients?

Bhagirathbhai Dholaria, MBBS
Assistant Professor of Medicine
Hematology/Stem Cell Transplant
Vanderbilt University School of Medicine
Nashville, TN

June 21, 2019

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VANDERBILT HEALTH

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20

Overview

- CAR T: new frontier in cancer immunotherapy
- Development of CAR T -cell therapy
- Clinical applications
- Limitations and future directions

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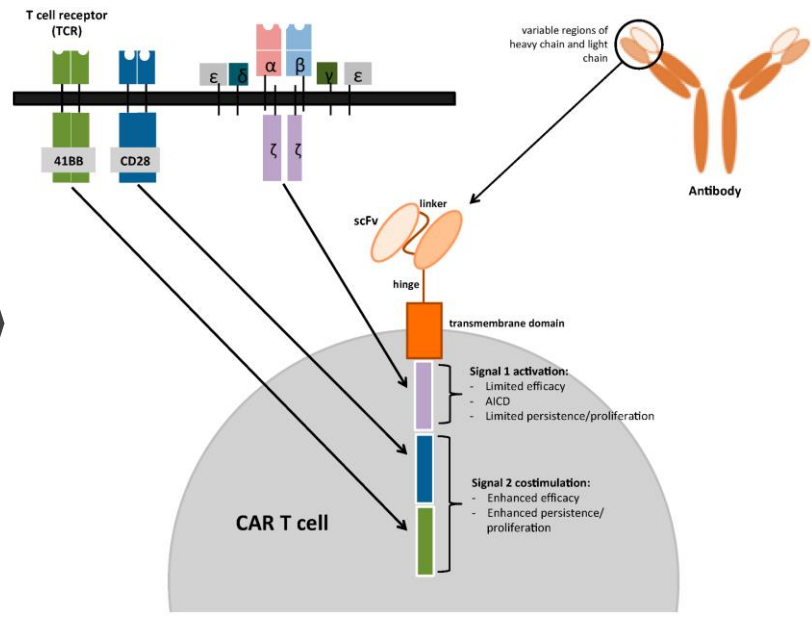
21

Chimeric Antigen Receptor



Cancers 2017, *9*(9), 115.

22

Why CARs?

- Specific and potent: B- specific, T- toxic
- Overcome immune tolerance
- Targets surface molecules in native confirmation
- Independent of antigen-presenting cell and MHC complex

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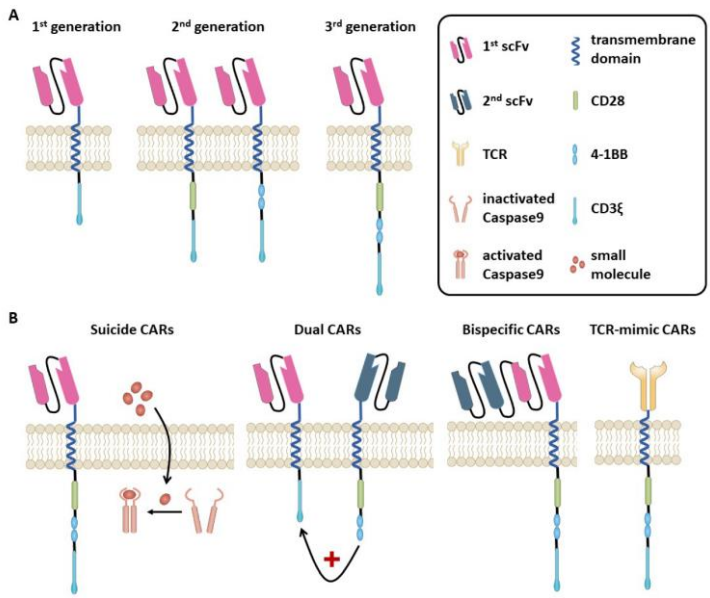
23

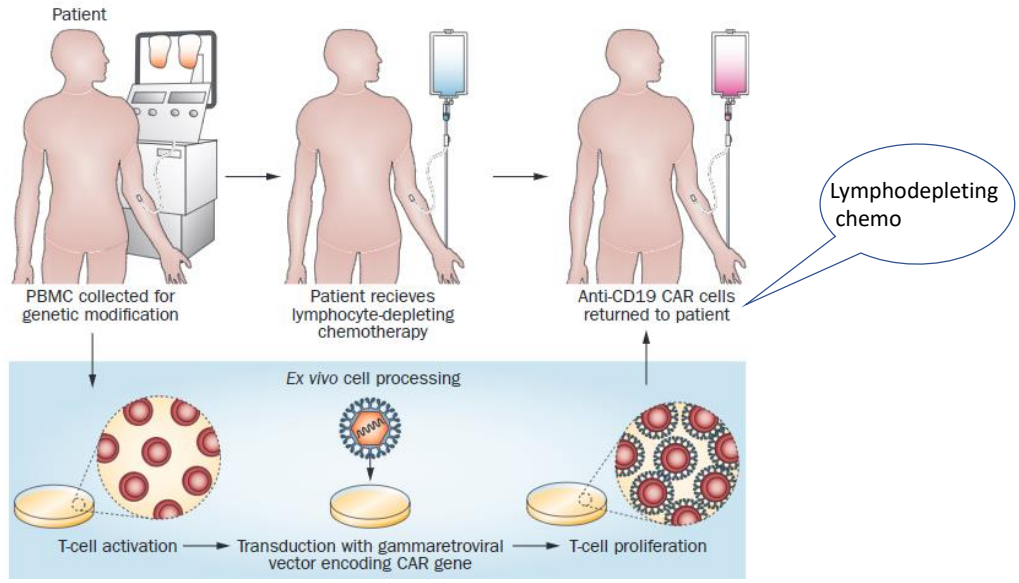
Evolution of CAR Constructs



J. Clin. Med. 2019, *8*(2), 200.

24

CAR T Manufacturing and Administration



PBMC- peripheral blood mononuclear cell

Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2013.46.

25

Early Phase Trials

- Highlighted the efficacy of 2nd generation CARs
- Confirmed the role of lymphodepleting chemotherapy
- Formed the basis for single-arm phase II trials
- Started the debate to expand to other tumors

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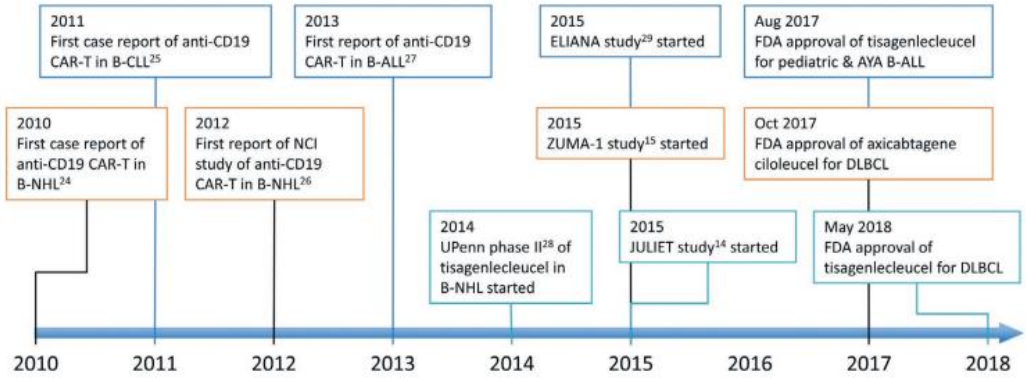
26

Development of CD19 CAR T-cell therapy



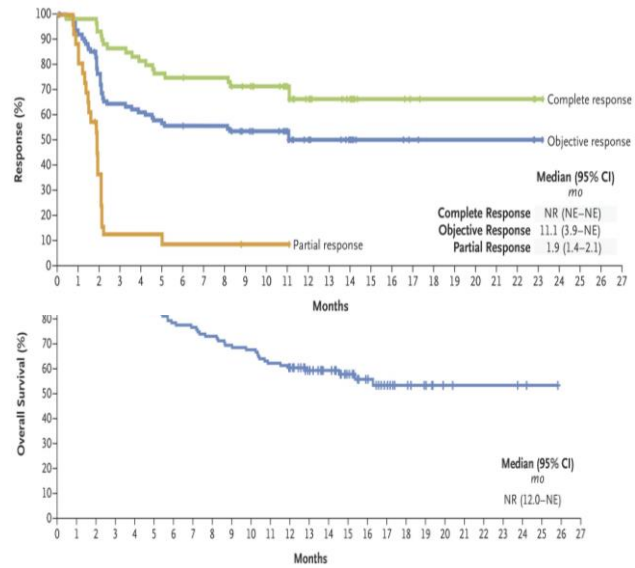
Drugs in Context 2019; 8: 2125-67.

27

CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

- N=101/111
- Production time=17 days
- No bridging rx
- ORR=82%
- CR=54%
- 1.5-yr estimated OS=52%
- CRS grade ≥3=13%
- neurotox grade ≥3=28%

Package insert
- N=101
- ORR=72%
- CR=51%
- Manufacturing failure=1



CR- complete response; CRS- cytokine release syndrome; ORR- overall response rate; OS- overall survival.

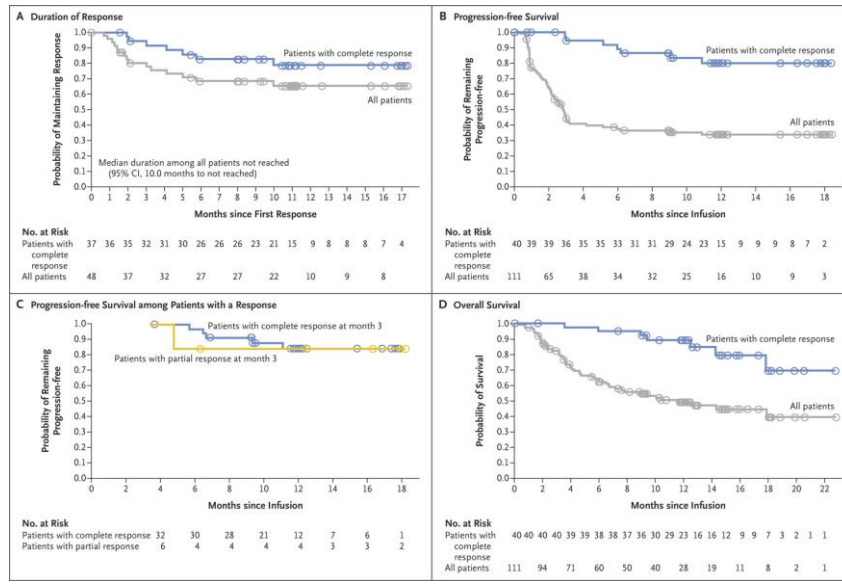
N Engl J Med 2017; 377:2531-2544.

28

CD19 CAR in DLBCL- JULIET (Tisa-cel)

- N=95/165
- Production time=39 days
- 92% received bridging rx
  -ORR=52%
- CR=40%
- 1-yr estimated OS=49%
- CRS grade ≥3=18%
- neurotox grade ≥3=11%

Package insert
- N=68
- ORR=50%
- CR=32%
- Manufacturing failure=11



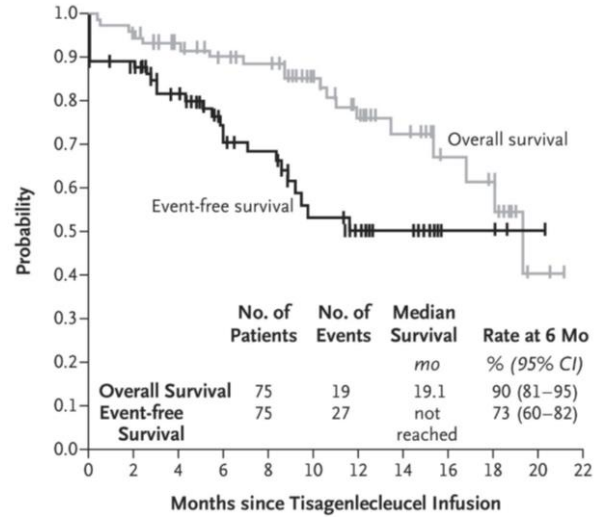
N Engl J Med 2019;380:45-56.

29

CD19 CAR in B-ALL: ELIANA (Tisa-cel)

- N=75/107
- ORR=81%
- CR=60%, CRi= 21%
- CRS grade ≥3= 47%
- neurotox grade ≥3=13%

Package insert
- N=63
- CR/CRi=83%
- Manufacturing failure=6



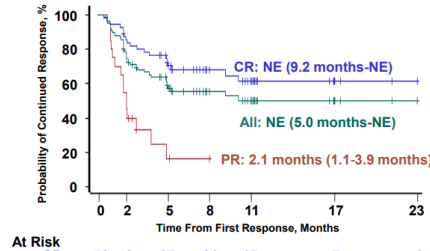
	No. of Patients	No. of Events	Median Survival mo	Rate at 6 Mo % (95% CI)
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

Maude et al. N Engl J Med 2018; 378:439-448.

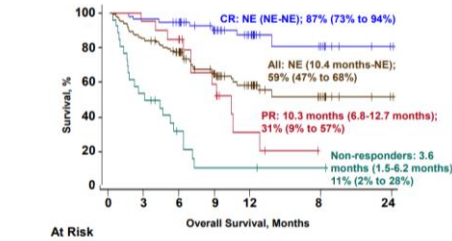
30

CD19 CAR in DLBCL- TRANSCEND (Liso-cel)

- N=102/134
- Majority received bridging rx
- ORR=75%
- CR=55%
- 1-yr estimated OS=59%
- CRS grade ≥3=1%
- neurotox grade ≥3=13%
- Manufacturing failure=2



At Risk							
CR	56	48	37	21	15	7	1
PR	20	11	2	1	0		
All	76	59	39	22	15	7	1



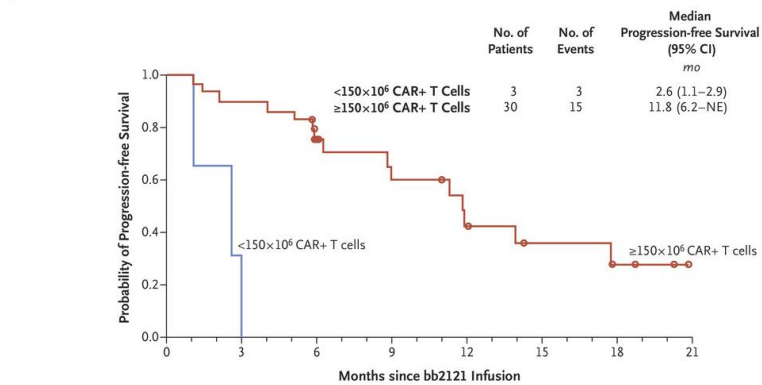
At Risk								
All	102	86	68	48	28	11	0	
CR	56	54	47	37	23	10	0	
PR	20	19	15	9	3	0		
Nonresponder	26	13	6	2	2	1	0	Nonres

Abramson JS, et al. HemaSphere. 2018;2(S1): Abstract S800.

31

BCMA CAR T Therapy for Myeloma

- bb2121
  - B cell maturation antigen (BCMA)
  - Phase I CRB-401 study
  - Previously treated patients with relapsed/refractory multiple myeloma
  - ORR: 85%, CR: 45%

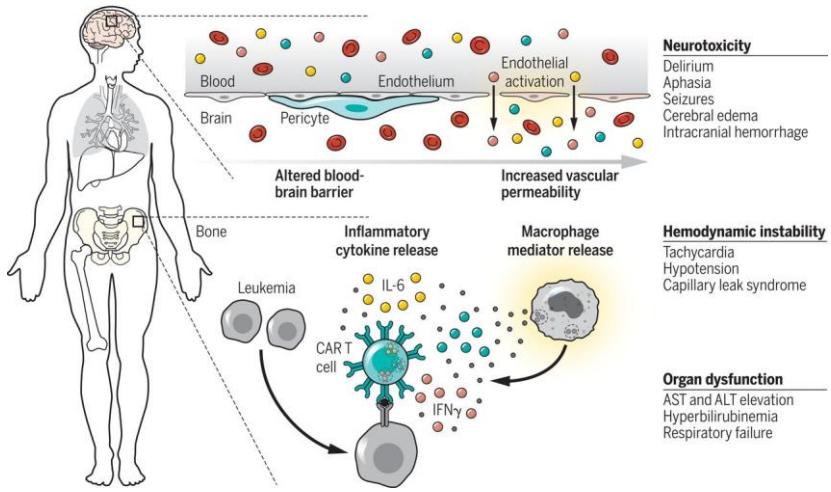


No. at Risk																					
<150×10⁶ CAR+ T cells	3	3	2	0																	
≥150×10⁶ CAR+ T cells	30	30	28	27	26	26	17	14	14	12	12	11	8	7	6	5	5	5	3	2	2	0

N Engl J Med 2019; 380:1726-1737.

32

CAR T Side Effects



Science AAAS

Published by AAAS

Carl H. June et al. Science 2018;359:1361-1365.

33

CAR T Side Effects

- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- B Cell aplasia
- Macrophage Activation Syndrome (MAS)/HLH

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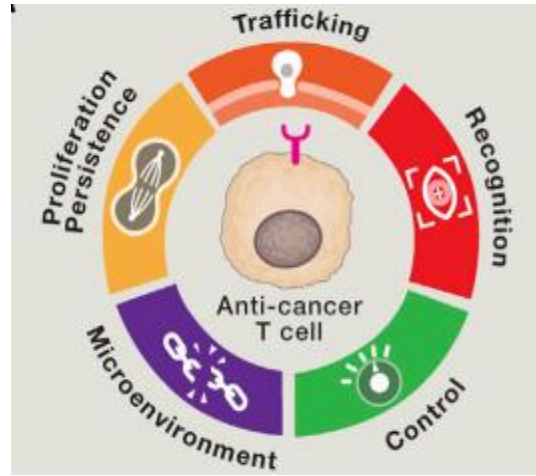
Study Eligibility Considerations

- Disease
  - Relative stability during CAR T manufacturing
  - Bridging therapy
  - ?CNS control
- Patient
  - Adequate cell counts
  - DVT, bleeding, infection, neurological disorders
  - Functional status: at screen vs. day of CAR T infusion
- Other
  - Social support

Future Directions

- New indications: frontline therapies, randomized with transplant
- New diseases: AML, solid organ malignancies…
- Off-the-shelf CARs, Armored CARs
- Novel combinations: checkpoint inhibitors, TKI



Cell. 2017 Feb 9;168(4):724-740.

Conclusions

- CAR T is here to stay
- Think of CAR in every patient: commercial or trial
- Toxicity and logistical challenges
- Future: safer and stronger

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37

Thank You

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38

CAR T-cell Toxicity and Management

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39

Objectives

Following this activity, participants will be able to:

- Identify potential toxicities of CAR T-cells*
- Recognize ASTCT**'s CRS^ and Neurotoxicity Grading systems
- Describe monitoring and management strategies for CRS/neurotoxicity

* CAR. - Chimeric Antigen Receptor
** ASTCT. - American Society for Transplant and Cellular Therapy
^ CRS. - Cytokine Release Syndrome

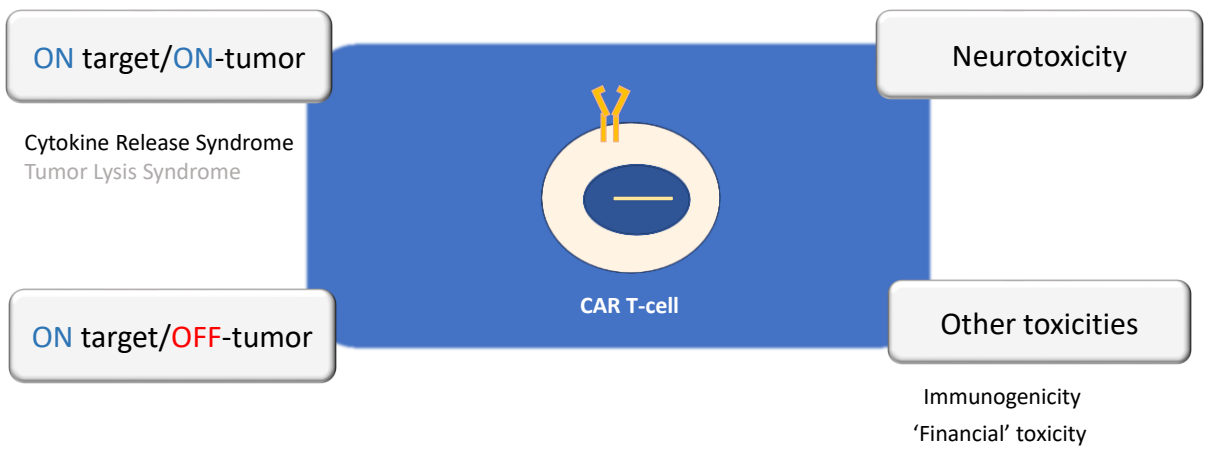
40

Outline

- Toxicities
  - ON target/OFF-tumor
  - ON target/ON tumor
  - Neurotoxicity
  - Other
- Conclusions

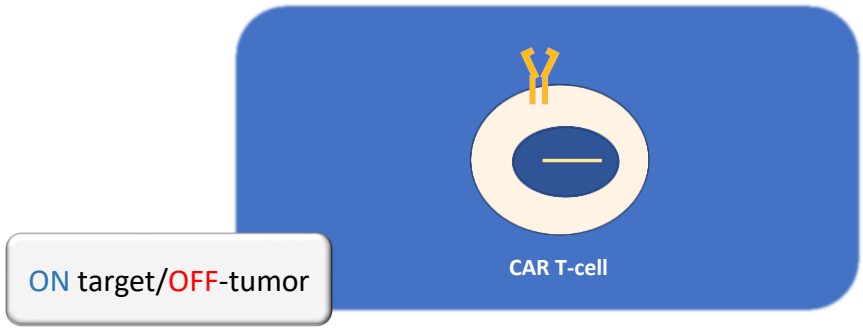
41

Summary



42

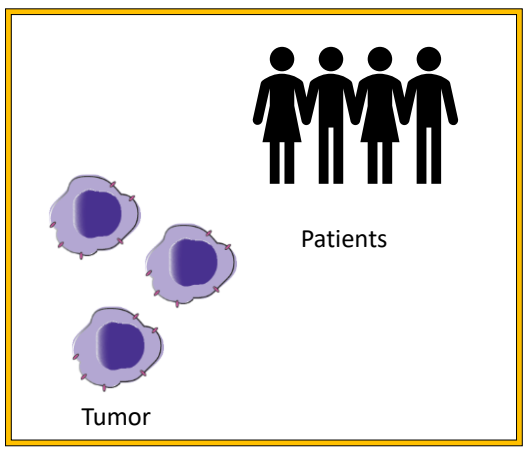
Summary



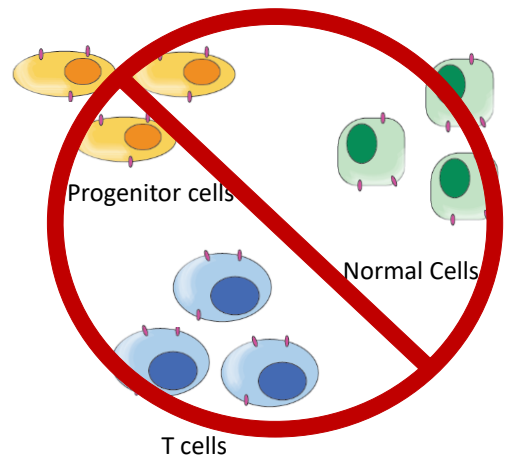
ON target/OFF-tumor

43

CAR T-cell Therapy : Antigen Selection



Efficacy

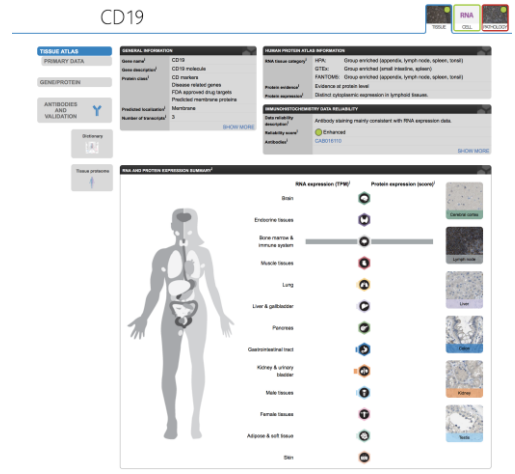


Safety

44

CD19 As An Antigen Target

https://pecan.stjude.cloud/proteinpaint/cd19

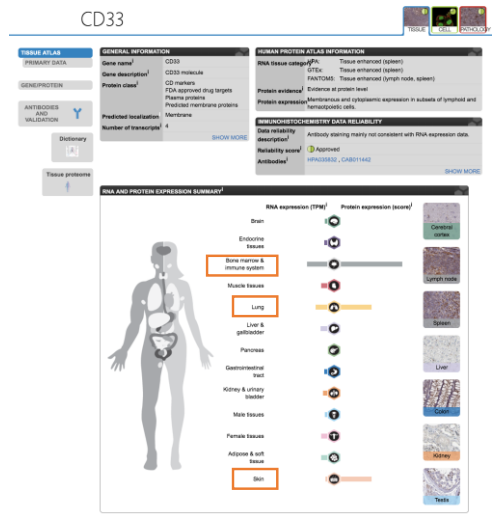


https://www.proteinatlas.org/ENSG00000177455-CD19/tissue

45

The Ideal Target is More Elusive in AML

https://pecan.stjude.cloud/proteinpaint/cd33



https://www.proteinatlas.org/ENSG00000105383-CD33/tissue

46

ON-Target/OFF-Tumor Toxicities: Mitigation strategies

- Antigen selection
- Safety switches
- CAR T-cell ablation with steroids or Antithymocyte Globulin (ATG)

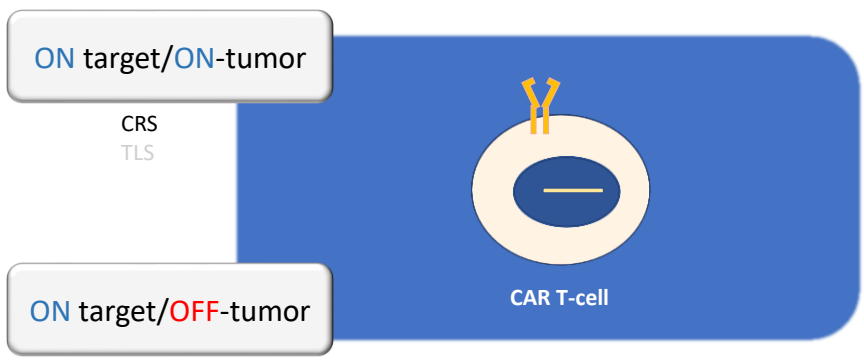
Preclinical efforts:

- Inducible CAR T-cells

Perna.Cell.2017.
DiStasi. NEJM.2011.
Wu, et al. *Science*, 2015.
Cho, et al. 2018.

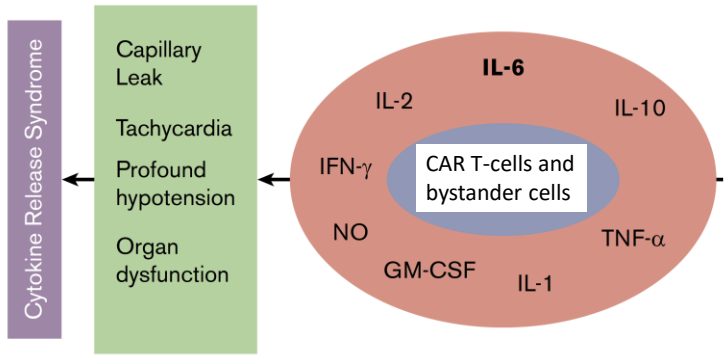
47

Summary



48

CRS: Pathophysiology



IL-6: Interleukin-6
IL-2: Interleukin-2
IFNG: Interferon gamma
NO: Nitrous oxide
GM-CSF: Granulocyte Macrophage Colony Stimulating Factor
IL-1: Interleukin 1
IL-10: Interleukin 10
TNFα: Tumor necrosis Factor alpha

Variable symptoms
2 days to 2 weeks after T-cell infusion

Figure adapted from: Jain, Litzow. *Blood Adv*, 2018.
Additional references: Teachey, et al. *Blood*, 2013.
Maude, et al. *Blood*, 2015.
Shah, Fry. *Nat Rev Clin Oncol*. 2019.

49

CRS: Clinical Presentation

	Signs/symptoms
Constitutional	Fever, malaise, anorexia, myalgias, HLH-like syndrome*
Cardiac	Tachycardia, arrhythmias, heart block, low ejection fraction
Respiratory	Tachypnea, pleural effusion, pulmonary edema
GI	Nausea, vomiting, diarrhea
Hepatic	Increased serum ALT, AST, or bilirubin levels
Renal	Acute kidney injury, decreased urine output
Coagulation	Disseminated intravascular coagulation (less common)
Dermatological	Rash (less common)

*HLH-Hemophagocytic lymphohistiocytosis

Lee. *Blood*. 2014
Brudno. *Blood*. 2016
Maude. *Cancer J*.2014
Neelapu. *Nat Rev*. 2018
Shah, Fry. *Nat Rev*. 2019
Lee, *Biol Blood Marrow Trans*. 2019

50

CRS: Correlation with Disease and Outcome

- Its presence has been linked to CAR T-cell efficacy
- The degree of CRS has NOT
- Factors influencing presence of CRS:
  - Tumor burden
  - CAR T cell dose
  - Lymphodepletion
  - Product phenotype

Lee. Blood. 2014.
Grupp. Blood. 2014.
Maude. NEJM. 2014.

51

CRS: Published Grading Scales

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE version 4.03 [11]	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrate)	Life-threatening consequences; pressor or ventilatory support indicated
CTCAE version 5.0 [13]	Fever, with or without constitutional symptoms	Hypotension responding to fluids. Hypoxia responding to <40% FiO_2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO_2	Life-threatening consequences; urgent intervention needed
Lee criteria [14]	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO_2 OR • Hypotension responsive to i.v. fluids or low dose of one vasopressor OR	Symptoms require and respond to aggressive intervention: • Oxygen requirement ≥40% FiO_2 OR • Hypotension requiring high-dose or multiple vasopressors OR • Grade 3 organ toxicity[c] or grade 4 transaminitis	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity[c] (excluding transaminitis)
Penn criteria [		tropenic fever and need for i.v. therapies (not including fluid resuscitation for hypotension)	Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	complications ssion requiring pressors ng mechanical
MSKCC criteria [16]	Mild symptoms requiring observation or supportive care only (eg, antipyretics, antiemetics, pain medication)	Hypotension requiring any vasopressors <24 h Hypoxia or dyspnea requiring supplemental oxygen <40%	Hypotension requiring any vasopressors ≥24 h Hypoxia or dyspnea requiring supplemental oxygen ≥40%	Life-threatening symptoms Hypotension refractory to high dose vasopressors Hypoxia or dyspnea requiring mechanical ventilation
CARTOX criteria [12]	Temperature ≥38°C Grade 1 organ toxicity[f]	Hypotension responds to i.v. fluids or low-dose vasopressor Hypoxia requiring FiO_2 <40% Grade 2 organ toxicity[f]	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO_2 ≥40% Grade 3 organ toxicity[f] or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity[f] except grade 4 transaminitis

Heterogeneity among grading systems makes comparison between studies difficult

Table from:
ASTCT Guidelines
Lee, et al. *Biol Blood Marrow Trans*. 2019.

Additional references:
CTCAE v. 4.03 and 5.0.
Lee. *Blood*. 2014.
Park. *NEJM*.2018.
Porter. *J Hematol Oncol*. 2018.
Neelapu. *Nat Rev Clin Oncol*. 2018.

52

CRS: ASTCT Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Hypotension and hypoxia determine severity of CRS

CRS as long as symptoms that led to diagnosis persist even if afebrile

Lee, et al. *Biol Blood Marrow Trans*. 2019.

53

CRS: Monitoring

- CRS grading at least once every 12 hours
- Increase frequency with clinical status changes
- Frequent monitoring of:
  - CBC, coagulation studies, chemistry profiles, LFTs
  - CRP, ferritin, LDH
- Blood cultures

Teachey, et al. *Blood*, 2013.
Mahadeo, et al. *Nat Rev Clin Oncol*. 2018.

54

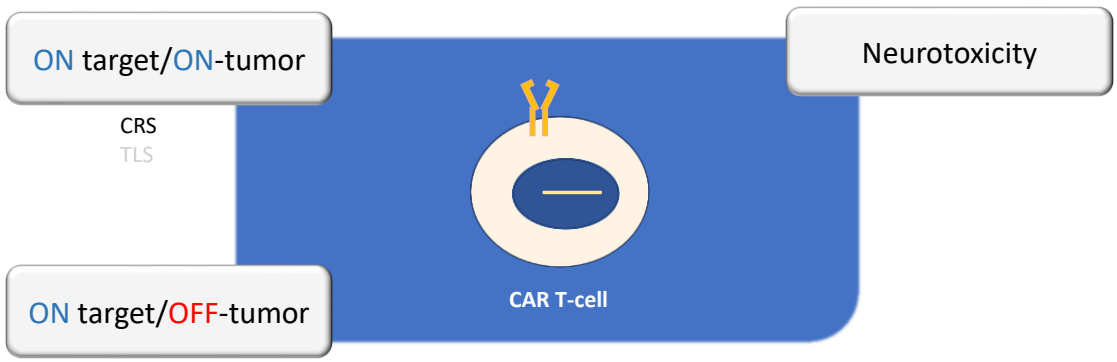
CRS: Management (Based on CRS grading)

- If febrile: start empiric broad antibiotic coverage
- If hypotension
  - →initial bolus 10-20mL/kg*
  - →Start anti IL-6 therapy (tocilizumab-FDA approved for CRS)
  - →Consider starting vasopressors
  - →Consider use of colloids
  - →Consider adrenal insufficiency when choosing corticosteroids
- Transfer to ICU early

https://www.fda.gov/drugs/informationondrugs/ approveddrugs/ucm574154.htm
Neelapu. *Nat Rev Clin Oncol*. 2018.
Mahadeo, et al. *Nat Rev Clin Oncol*. 2018.

55

Summary



56

Neurotoxicity: Pathophysiology

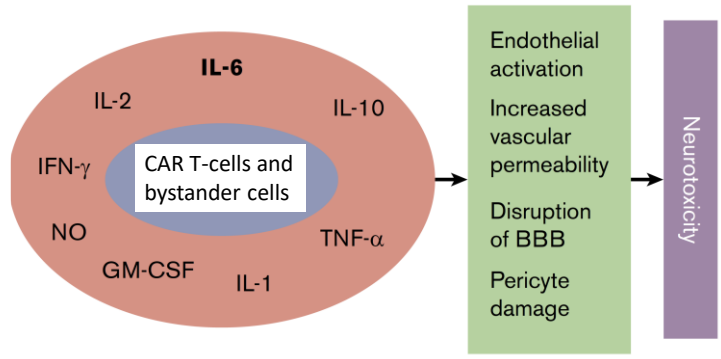


Figure adapted from: Jain, Litzow. *Blood Adv*, 2018.
Additional references: Turtle, et al. *Cancer Discov*, 2017.
Taraseviciute. *Cancer Discov*, 2018.

57

Neurotoxicity: Considerations

- CRES: CAR-T-cell-related encephalopathy syndrome (CARTOX)
- ICANS: Immune effector cell associated neurotoxicity syndrome (ASTCT)
- Timing: can be concurrent with CRS or after CRS has resolved
- Serum levels of cytokines/inflammatory markers correlate with severity (retrospective study)

Neelapu. *Nat Rev Clin Oncol*. 2018,
Lee, et al. *Biol Blood Marrow Trans*. 2019,
Karschnia. Blood. 2019.

58

Neurotoxicity: Reported Side Effects in FDA-Approved CD19-CAR T-cells

Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)
Encephalopathy: includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism **Delirium:** includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness **Headache:** includes headache and migraine **Anxiety** **Sleep disorder:** includes sleep disorder, insomnia, nightmares	**Encephalopathy:** includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbed attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor **Delirium:** includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness **Headache** **Dizziness:** includes dizziness, presyncope, syncope **Aphasia:** includes aphasia, dysphasia **Motor dysfunction:** includes muscle spasms, muscular weakness **Tremor** **Ataxia** **Seizure** **Dyscalculia** **Myoclonus**

Lee, et al. *Biol Blood Marrow Trans*. 2019.

59

Neurotoxicity: ASTCT Grading System

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score for children age ≥12 years*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score for children age <12 years	1-8	1-8	≥9	Unable to perform CAPD
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor weakness (any age)‡	N/A	N/A	N/A	Deep focal motor weakness, such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging§	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

Lee, et al. *Biol Blood Marrow Trans*. 2019.

60

Adults: Immune Effector Cell Associated Encephalopathy Score (ICE)

ICE

- **Orientation:** orientation to year, month, city, hospital: 4 points
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- **Attention:** ability to count backwards from 100 by 10: 1 point

Lee, et al. *Biol Blood Marrow Trans*. 2019.

61

Children <12yo: Cornell Assessment of Pediatric Delirium (CAPD)

Answer the following based on interactions with the child over the course of the shift					
	Never, 4	Rarely, 3	Sometimes, 2	Often, 1	Always, 0
1. Does the child make eye contact with the caregiver?					
2. Are the child's actions purposeful?					
3. Is the child aware of his/her surroundings?					
4. Does the child communicate needs and wants?					
	Never, 0	Rarely, 1	Sometimes, 2	Often, 3	Always, 4
5. Is the child restless?					
6. Is the child inconsolable?					
7. Is the child underactive; very little movement while awake?					
8. Does it take the child a long time to respond to interactions?					

Lee, et al. *Biol Blood Marrow Trans*. 2019.
Traube. *Crit Care Med*.2014.

62

Neurotoxicity: Monitoring

- Severity: No predictive factors identified so far
- Assessment: at least 2x inpatient, at least 1x outpatient
- Increase monitoring frequency with any changes/concerns
- Educate caretaker how to identify symptoms once outpatient

Mahadeo, et al. *Nat Rev Clin Oncol*. 2018.

63

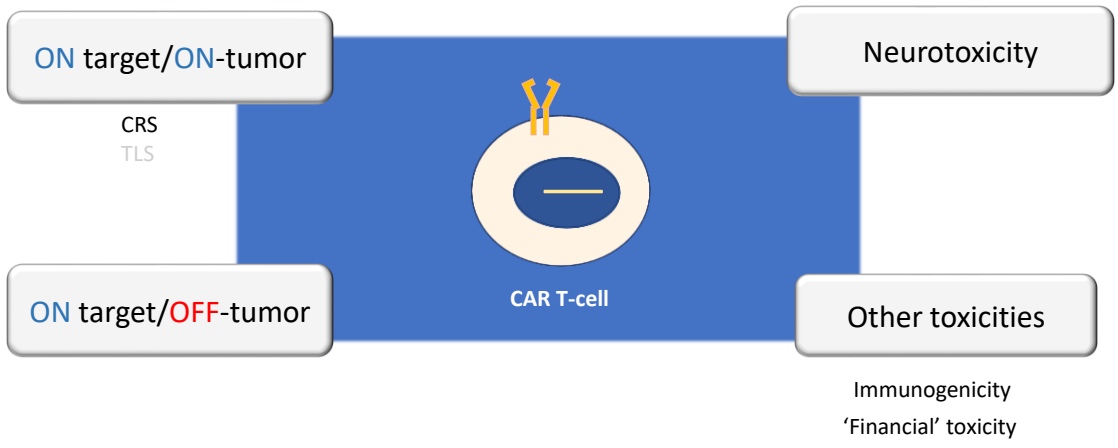
Neurotoxicity: Management

- Supportive care
- Tocilizumab potentially helpful if neurotoxicity associated with CRS
- Preclinical studies → potential effect of anakinra (IL-1 blocker)
- Levetiracetam recommended in patients with history of seizures
  - 10 mg/kg, up to a maximum of 500 mg per dose) every 12 hours for 30 days.
- Consider neurology/neurosurgery consult

Mahadeo, et al. *Nat Rev Clin Oncol*. 2018
Giavidris. *Nat Med*. 2018.

64

Summary



65

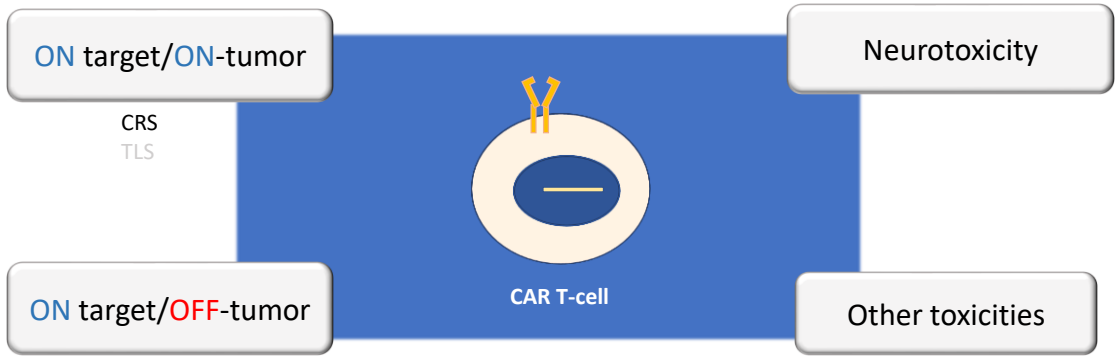
Other Toxicities:

- Immunogenicity
  - Human anti-mouse antibody (HAMA) monitoring
    - not a common complication
  - Humanized single chain variable fragment (scFv)
- 'Financial toxicity'

Jain, Litzow. *Blood Adv*, 2018.

66

Conclusion



Immunogenicity

'Financial' toxicity

67

Conclusion

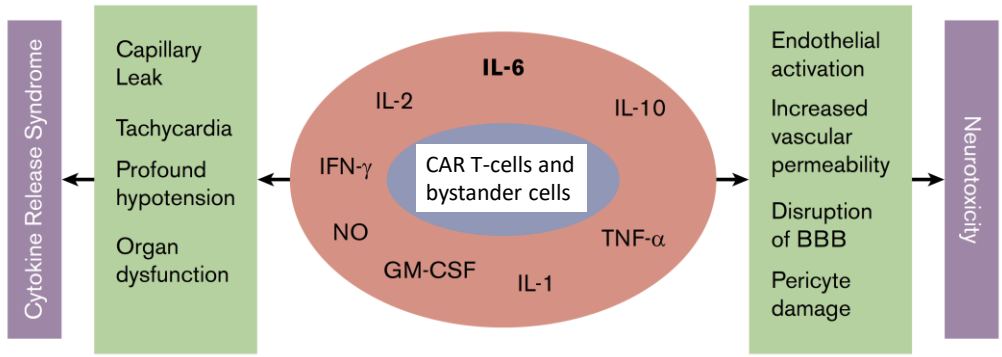


Figure adapted from: Jain, Litzow. *Blood Adv*, 2018.

Additional references:
Teachey, et al. *Blood*, 2013.
Maude, et al. *Blood*, 2015.
Shah, Fry. *Nat Rev Clin Oncol*. 2019.

68

Questions?

Paulina.Velasquez@STJUDE.ORG

69

Chimeric Antigen Receptor (CAR) T Cell Therapy for B cell Acute Lymphoblastic Leukemia (ALL)

Carrie L. Kitko, MD
Associate Professor
Medical Director, Pediatric Stem Cell Transplant
Vanderbilt University Medical Center
Nashville, TN

June 21, 2019

70

Outcome of Pediatric Pre-B cell ALL

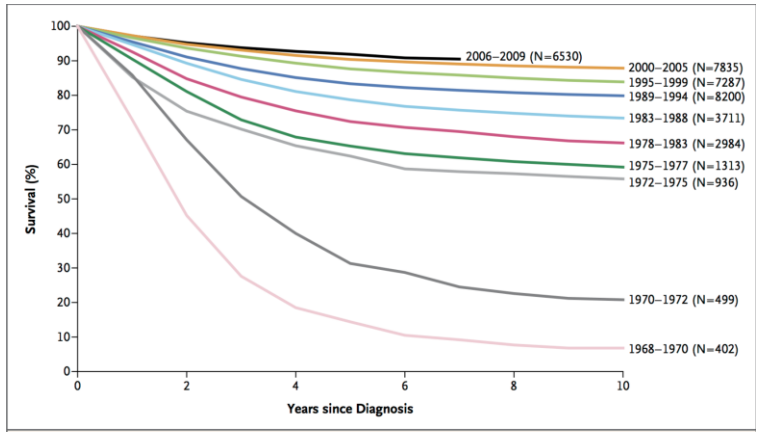


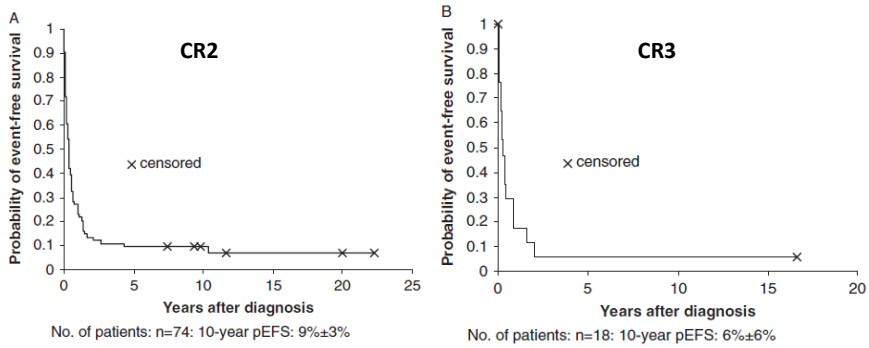
Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

Hunger and Mullighan. NEJM. 2015. 373:1541-1552.

71

Dismal Outcome for Relapse ALL in Pediatric

- **Leukemia is the #1 cause of pediatric cancer mortality**
- **30-40% achieve another remission**
- **Novel therapies are needed**

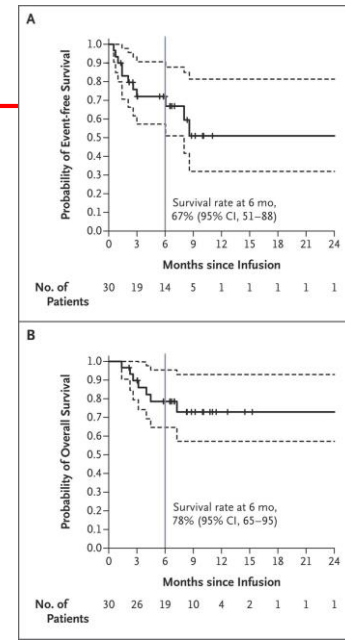


CR, complete response; pEFS, probability of event-free survival.
Reismüller et al. JPHO. 2013; 35(5);e200-4.

72

Phase I Trial

- 25 pediatric & 5 adult patients
  - Children's Hospital of Philadelphia & Univ of Penn
- 60% failed prior allo stem cell transplant (SCT)
- 80% had detectable disease
- CD19 directed CAR, 4-1BB co-stim
- 0.76×10^6 to 20.6×10^6 CTL019 cells/kg
- All patients had cytokine release syndrome (CRS), 27% severe
- 13 patients had neurologic toxicity
- 27/30 were in morphologic CR at D30
  - 22 were minimal residual disease (MRD) neg



CRS, cytokine release syndrome; MRD, minimal residual disease; SCT, stem cell transplantation.
Maude SL et al. N Engl J Med 2014;371:1507-1517.

73

ELIANA - tisagenlecleucel

- Pts age > 3 yo at screen and < 21 years at dx @ 25 institutions
- > 5% blasts
- 61% infused failed a prior SCT
- 113 pts screened, 97 enrolled, 18 did not receive infusion (toxicity = 10, manufacturing failure = 8)
- 0.2×10^6 to 5.4×10^6 cells/kg
- CRS in 77%, 48% received tocilizumab
- CR/Complete Remission with incomplete hematologic recovery (CRi) in 65 pts, 64 were MRD neg
- Median duration of CR was not reached
- Overall Survival (OS) at 18 mo was 70%

OS, overall survival.
SL Maude et al. N Engl J Med 2018;378:439-448.

74

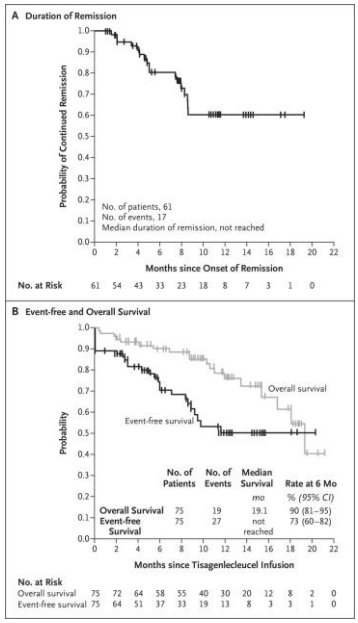


Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

Type of Event	Any Grade (N = 75)	Grade 3 (N = 75)	Grade 4 (N = 75)
	number of patients (percent)		
Any adverse event of special interest	67 (89)	26 (35)	30 (40)
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Neurologic event	30 (40)	10 (13)	0
Infection	32 (43)	16 (21)	2 (3)
Febrile neutropenia	26 (35)	24 (32)	2 (3)
Cytopenia not resolved by day 28	28 (37)	12 (16)	12 (16)
Tumor lysis syndrome	3 (4)	3 (4)	0

* The criteria for defining adverse events of special interest were based on experience from ongoing clinical studies. The cytokine release syndrome includes the Medical Dictionary for Regulatory Activities preferred terms "cytokine release syndrome," "cytokine storm," "shock," "macrophage activation," and "hemophagocytic lymphohistiocytosis." Neurologic events include the standardized Medical Dictionary for Regulatory Activities query terms "noninfectious encephalopathy" and "delirium."

SL Maude et al. N Engl J Med 2018;378:439-448.

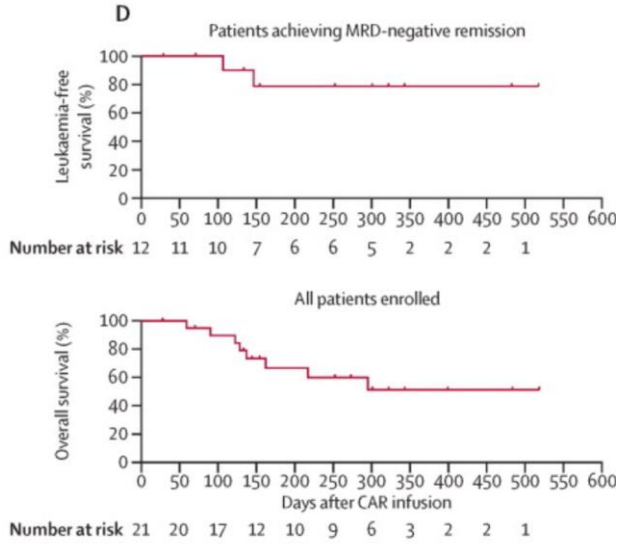
75

National Cancer Institute Experience

- Phase I dose escalation
- Relapse/Refractory (R/R) ALL
- Eligible age 1 – 30 years
- Measurable disease
- 8 failed prior SCT
- 21 enrolled, 2 failed manufacturing
- CD19 directed CAR, CD28 co stim
- Cell dose: 1 X 10^6/kg (n= 15), 3 X 10^6/kg (n =4)
- CRS in 16 patients
  - Grade 3 or 4 in 6 (including 2 of 4 in 3 X 10^6 group, DLT)
- Neurotoxicity in 6
- CR: 67%, MRD neg 12/20
- 10 MRD neg patients underwent SCT, still in CR
- 2 MRD neg patients did not undergo SCT, but relapsed

Lee DW et al. Lancet 2015; 385: 517–28.

76



Lee DW et al. Lancet 2015; 385: 517–28.

77

ZUMA -3 (KTE-X19)

- End of Phase 1 results
- 45 Adult for R/R pre B cell ALL (> 5% blasts)
- Median age: 46 (18-77y)
- 66% of patients received > 3 therapies
- 29% (n=13) failed allo SCT
- Cell dose
  - 2 X 10^6 - 6
  - 1 X 10^6 - 23
  - 0.5 X 10^6 – 16
- ≥ Grade 3 CRS in 29%, Neurotox in 38%
  - 2 previously reported G5 – cerebral infarction and MSOF in context of CRS
- 41 pts w/ > 2 mo f/u – 68% CR/CRi, 73% MRD neg
- Phase 3 ongoing at the 1 X 10^6 dose – 84% CR/CRi rate, 15 mo median EFS
- Previously reported to difference in response or side effects based on prior blinatumomab

Shah et al. ASCO. 2018 & 2019.

78

Incidence of Treatment-Emergent CRS- and NE-Specific Symptoms (≥ 25% Overall)

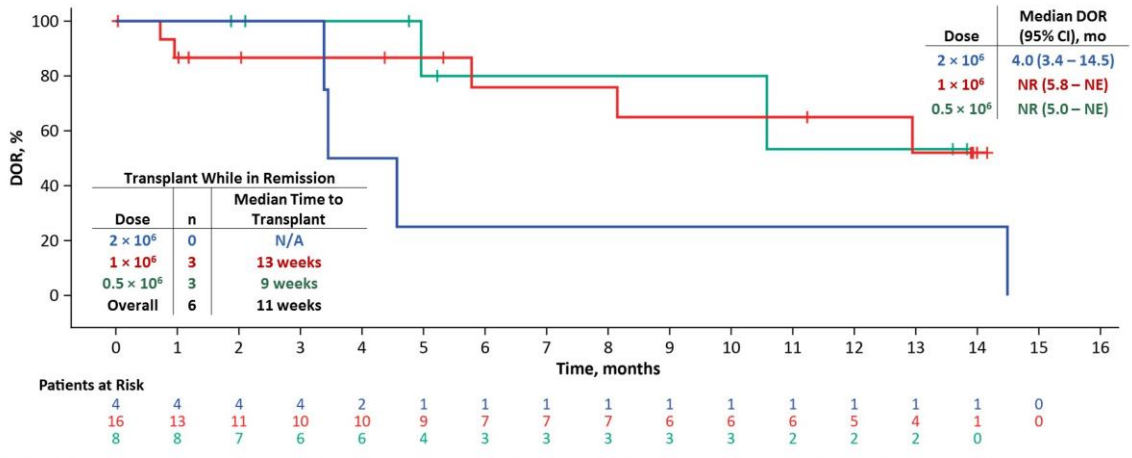
Event, %	2×10^6 (n = 6) Any	2×10^6 (n = 6) Grade ≥ 3	1×10^6 (n = 23) Any	1×10^6 (n = 23) Grade ≥ 3	0.5×10^6 (n = 16) Any	0.5×10^6 (n = 16) Grade ≥ 3	Overall (N = 45) Any	Overall (N = 45) Grade ≥ 3
Any CRS[a,b]	**100**	**50**	**100**	**26**	**81**	**25**	**93**	**29**
Pyrexia	100	50	87	39	63	31	80	38
Hypotension	67	50	74	39	50	19	64	33
Sinus tachycardia	33	0	43	4	13	0	31	2
Chills	17	0	39	0	13	0	27	0
Any NE[b]	**83**	**50**	**87**	**43**	**63**	**25**	**78**	**38**
Encephalopathy	67	33	48	26	13	13	38	22
Confusional state	33	17	39	4	31	13	36	9
Tremor	17	0	35	0	25	0	29	0

[a]CRS was graded per a modified grading system proposed by Lee DW, et al. *Blood*. 2014;124:188-195. [b]Individual symptoms of CRS and NEs were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03.
CRS, cytokine release syndrome; NE, neurologic event.

Presented By Bijal Shah at 2019 ASCO Annual Meeting

79

Duration of Remission Not Censored at Transplant



- Of the 6 patients who received transplant, 3 have ongoing remission as of the data cutoff

Figure includes all patients who achieved a CR + CRi with at least 2 months of follow up (n = 28) without censoring at transplant. Ticks indicate censored events.
DOR, duration of remission; N/A, not applicable; NE, not evaluable; NR, not reached.

Presented By Bijal Shah at 2019 ASCO Annual Meeting

80

ZUMA 4

- End of Phase I results
- Age 3-20 years
- 24 patients received KTE-X19 (20 = 1 X 10^6/kg; 4 = 2 X 10^6/kg)
- 25% failed prior SCT
- CR + CRi rate was 64-100% (2 X 10^6 vs 1 X 10^6 dose)
- Hypotension and anemia were common
- ≥ 3 neuro toxicity in 11-36%
- 3 Grade 5 events, unrelated to KTE-X19

Wayne et al. ASPHO. 2019.

81

Memorial Sloan Kettering 19-28z CAR T

- Phase 1
- 53 adult patients
- CR in 83%, MRD neg 67%
- CRS in 26%, 1 died
- CD19 directed CAR, CD28 co-stim
- Median f/u 29 mo, median OS was 12.9 mo, EFS 6.1 mo
- Pts with < 5% blasts, median OS was 20.1 mo, EFS was 10.6 mo
- More intense bridging therapy associated w more severe infections, but not other outcomes, including CRS or OS

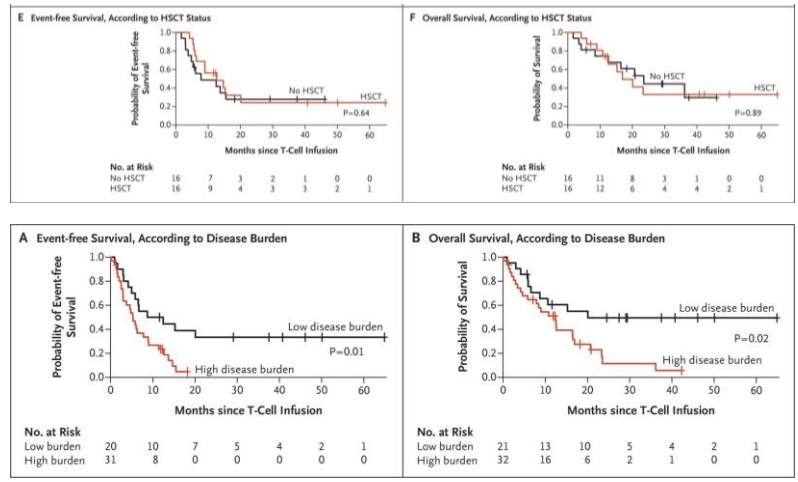
JH Park et al. N Engl J Med 2018;378:449-459. Perica et al. ASCO. 2019.

82

Table 1. Characteristics of the 53 Patients at Baseline.*

Characteristic	Value
Age	
Median (range) — yr	44 (23–74)
Distribution — no. (%)	
18–30 yr	14 (26)
31–60 yr	31 (58)
>60 yr	8 (15)
No. of previous therapies — no. (%)	
2	21 (40)
3	13 (25)
≥4	19 (36)
Primary refractory disease — no. (%)	
Yes	12 (23)
No	41 (77)
Previous allogeneic HSCT — no. (%)	
Yes	19 (36)
No	34 (64)
Previous treatment with blinatumomab — no. (%)	
Yes	13 (25)
No	40 (75)
Pretreatment disease burden†	
Median bone marrow blasts (range) — %	63 (5–97)
Bone marrow blasts — no. (%)	
≥5%	27 (51)
<5% with extramedullary disease	5 (9)
≥0.01% and <5%	15 (28)
<0.01%	6 (11)
Philadelphia chromosome–positive — no. (%)	
Yes	16 (30)
No	37 (70)

* Percentages may not total 100 because of rounding. HSCT denotes hematopoietic stem-cell transplantation.
† The value for the median bone marrow blasts was assessed in patients who had bone marrow blasts of 5% or more. A high disease burden was defined as 5% or more bone marrow blasts or extramedullary disease, and a low disease burden as less than 5% bone marrow blasts. Minimal residual disease was assessed by means of multiparameter flow cytometry,[11,12] and negative status with regard to minimal residual disease was defined as less than 0.01% bone marrow blasts.



JH Park et al. N Engl J Med 2018;378:449-459.

83

CD22 CAR

- CD19 negative relapse remains a significant issue
- CD22 directed CAR, 4-1BB co-stim
- Enrolled age 1-55, 31/34 failed prior CD19 directed CAR
- 13/34 failed prior SCT
- Median cell dose: 1 X 10^5 CAR/kg (SCT recipients), 7.5 X 10^5 CAR/kg (non SCT recipients)
- 30 patients survived for 30 days or longer and were evaluated, 24 (80%) achieved CR/CRi

Pan J et al. Leukemia. 2019. May 20. [Epub ahead of print].

84

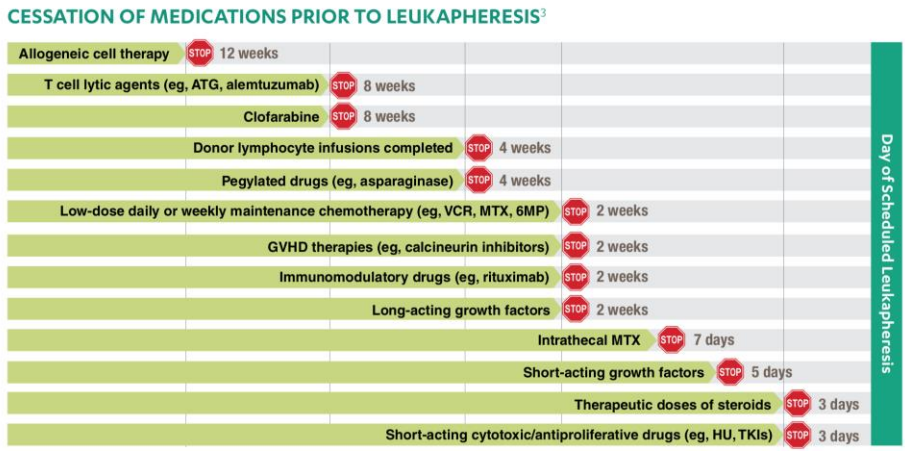
Challenges

85

Lack of Expansion

- 5-10% of patients T-cells will not successfully expand
- Absolute lymphocyte counts of 100-500 typically required prior to collection
  - What type of T cell is most important?
- Prior chemotherapy exposure is also critical
- Patients with rapidly progressing disease struggle to find window for collection

86



- An example of medications to avoid leading up to leukapheresis
- Taken from the tisagenlecleucel Provider Resources
- https://www.hcp.novartis.com/globalassets/products2130/kymriah/dcbcl/resources/kymriah_ref_physician_guide_digital.pdf

87

Off The Shelf CAR T Therapy

- Healthy donors
- Would allow access to CAR T therapy immediately
- Requires genetic modification to construct the CAR as well as eliminate potential for Graft vs Host Disease (GVHD)
  - CRISPR/Cas9 gene editing to remove T cell receptor alpha chain (TRAC) expression
  - Also potential for addition of suicide/safety switch

88

Universal CAR T

- Phase 1 study
- Age 6 mo to 18 yo with R/R B cell ALL
- Previously failed leukapheresis or ineligible for other CAR therapy
- CD19 directed, 4-1BB co-stim; Rituximab sensitive ”safety switch”
- Fixed dose: 2 X 10^7 total cells
- Goal: Bridge to allo SCT with 6-12 weeks
- 5 patients infused – all with reversible CRS, 2 with neurotox
- 5 patients received allo SCT
  - 2 relapsed post-SCT (1 CD19+, 1 CD19-)
  - 1 died from TRM, 2 with very short follow-up

Qasim W. et al. ASH 2017.

89

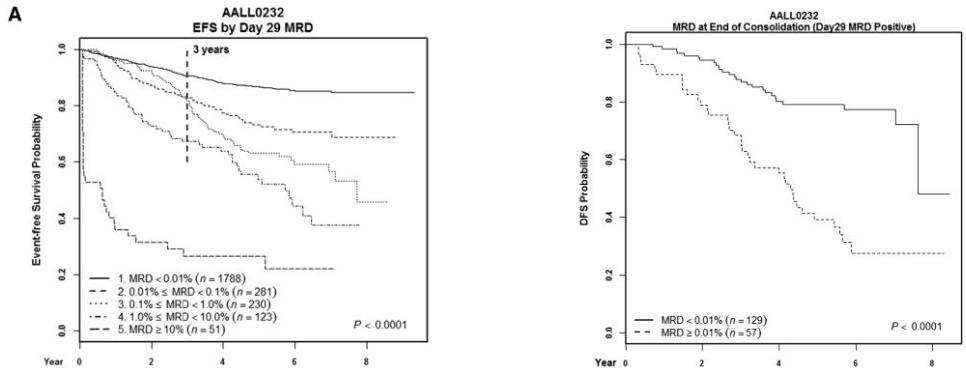
Role for Allogeneic Transplant

- Early loss of CAR T cells is associated with relapse (CD19+)
  - Lack of expansion post-infusion
    - What cells should be infused
  - Potential for immunologic rejection
  - T-cell exhaustion
- Patients with MRD- remission and persistence of CAR at risk for CD19- relapse
  - At present no way to pre-emptively monitor

90

Future Directions

- Bring CAR T therapy earlier in treatment – AALL1721
- Pediatric patients with MRD positive at end of consolidation have poor outcomes



Michael J. Borowitz et al. Blood 2015;126:964-971.

91

Questions

92

CAR-T FOR LYMPHOMA

UAB Lymphoma Program

Amitkumar Mehta, MD

Assistant Professor, Lymphoma Program
Co-Director, Immune Effector Cell Therapy (CAR-T) Program
Division of Hematology/Oncology
University of Alabama Birmingham School of Medicine
Birmingham, AL

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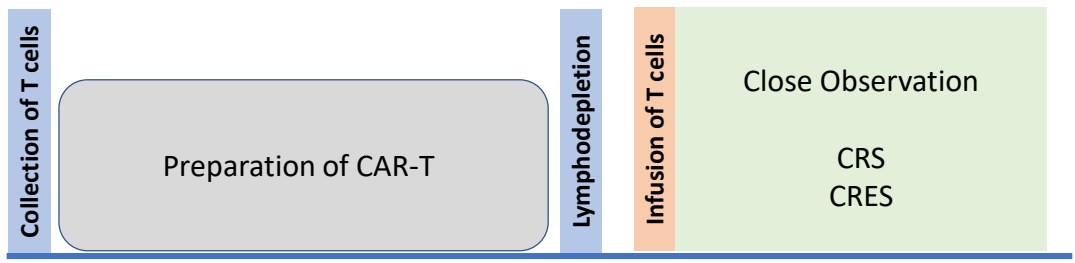
93

Process of CAR-T



CRS, Cytokine Release Syndrome; CRES, CAR-T related Encephalopathy syndrome.

94

CAR-T Products

	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel	bb2121
Company	Kite, a Gilead Company (now Gilead)	Novartis (U Penn partnership)	JUNO (Now Celgene Corporation)	Blue Bird (Now Celgene Corporation)
Indication	Aggressive B cell Lymphoma	Aggressive B - cell Lymphoma Acute B- cell Lymphoblastic Leukemia	Aggressive B- cell Lymphoma	Multiple Myeloma
Target	CD19	CD19	CD19	BCMA
FDA Approval	Approved	Approved	Not Approved	Not Approved
Cost	$373,000	$373,000 (Lymphoma) $475,000 (Leukemia)		

95

Tisagenlecleucel in Lymphoma (Novartis)

- Approved by FDA in May 2018
- Indications: DLBCL, Transformed follicular Lymphoma, Primary Mediastinal B cell Lymphoma (PMBL) who have failed 2 lines of treatment
- This was based on JULIET study, a phase II trial (n=147)[7]

JULIET Trial (n=147)	
Overall response rate	53.1% (complete response: 39.5%)
CR rate at 6 months	CR : 30%, PR: 7%
Adverse Events	Grade ≥3: Cytopenia (27%), Infections (20%) and Febrile Neutropenia (13%)
CRS	Grade ≥3: 23% (with Penn grading scale)
CRES	Grade ≥3: 12%

DLBCL, diffuse large B-cell lymphoma; CRS,Cytokine Release Syndrome; CRES, CAR-T related Encephalopathy syndrome.
[7]NSchuster et al., Blood 2017 130:577.

96

Axicabtagene Ciloleucel in Lymphoma (Kite, a Gilead Company)

- Approved by FDA in October 2017
- Indications: DLBCL, Transformed follicular Lymphoma, Primary Mediastinal B-cell Lymphoma (PMBL) who have failed 2 lines of treatment.
- This was based on ZUMA-1 trial, Phase II trial (n=111)[6]

ZUMA-1 trial (n=111)	
Overall response rate	82% (complete response: 54%)
At median 15.4 months	42% continued to have response, 40% still in CR
Adverse events	Grade ≥3: neutropenia (78%), anemia (43%), and thrombocytopenia (38%)
CRS	Grade ≥3: 13%
CRES	Grade ≥3: 28%

CRS, Cytokine Release Syndrome; CRES, CAR-T related Encephalopathy syndrome.
[6]Neelapu et al., N Engl J Med 2017; 377:2531-2544.

97

CAR-T Therapy in Lymphoma

	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Construct	anti-CD19-CD28-CD3z	anti-CD19-4-1BB-CD3z	anti-CD19-4-1BB-CD3z
T cells	Bulk	Bulk	1:1::CD4:CD8
Dose	2 X 10^6 to 2 X 10^8	0.6-6.0 X 10^8	DL1: 0.5 X 10^7 DL2: 5 X 10^8
Bridging	Not allowed	Allowed on study	Allowed on study
Lymphodepletion	FluCy: 500/30 X 3 days	FluCy: 250/25 X 3 days Or BR	FluCy: 300/30 X 3 days
Treatment location	Inpatient only	Inpatient/outpatient	Inpatient/outpatient

98

CAR-T Therapy in Lymphoma

%	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
ORR	82	52	80
CR	54	40	59
Toxicities			
Grade ≥3 CRS	13	22	1
Grade ≥3 NT	31	12	13
Toci/Steroids	29/45	11/15	15/21

CR, complete response; CRS, cytokine release syndrome; Toci, tocilizumab.

99

Why 80% ORR and 50% CRR is So Important?

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100

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]

DLBCL:

- 5-year survival rate: 50%-70%
- 50% of patients are refractory to or relapse after first line treatment
- What is the outcome of these patients?

SCHOLAR-1 (Retrospective international study)

- Pooled data from LY.12-CORAL study, MDA, and University of Iowa/Mayo Clinic)

101

Study Design

Retrospective study

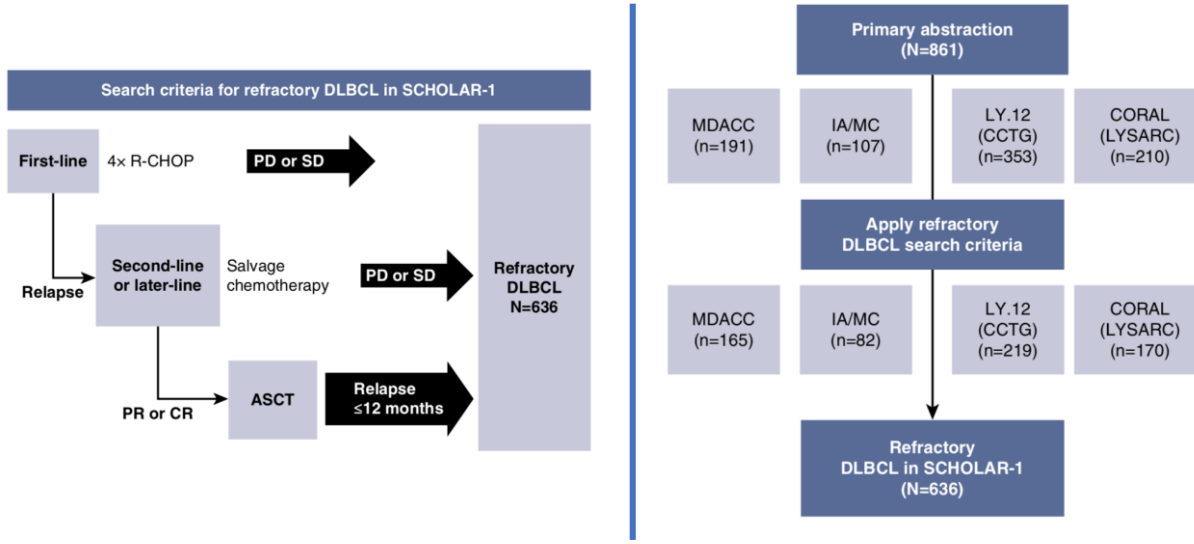
Refractory LCL: tFL and PMBL

Refractory DLBCL: PD/SD as best response to first-line treatment or relapse ≤12 months after ASCT

Patients must have received anti-CD20 and anthracyclines as first line therapy

Exclusion: Primary CNS lymphoma

102



ASCT, autologous stem cell transplantation; CCTG, Canadian Cancer Trials Group; CORAL, Collaborative Trial in Relapsed Aggressive Lymphoma; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; IA/MC, Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence; LYSARC, Lymphoma Academic Research Organization; MDACC, MD Anderson Cancer Center; PD, progressive disease; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, stable disease.

103

Patient Characteristics (pertinent)

Characteristic	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled (N = 636)
Median age, y (range)	56 (20-81)	60 (20-80)	54 (24-70)	54 (19-65)	55 (19-81)
Male sex, %	64	62	61	69	64
Primary diagnosis, %					
DLBCL*	76	89	84	100	87
PMBCL	1	0	5	0	2
TFL	3	0	10	0	4
Indeterminate/missing	19	11	1	0	7
Refractory category, %					
Primary refractory	0	24	51	28	28
Refractory to ≥ second-line therapy	90	51	21	46	50
Relapsed ≤12 mo post-ASCT	10	24	28	26	22
Total no. of lines of chemotherapy and ASCT received, %‡					
1	0	24	51	28	28
2-3	90	50	21	46	49
≥4	0	1	0	0	<1

104

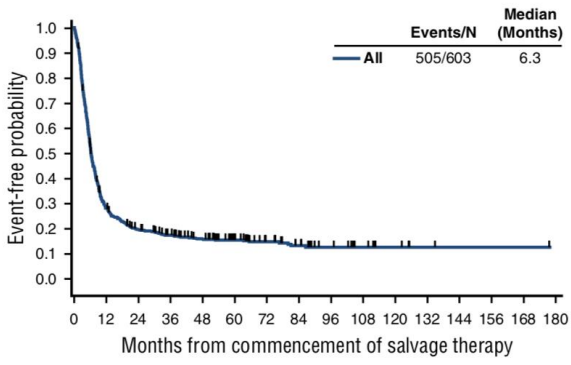
RR to Chemotherapy After Refractory Disease

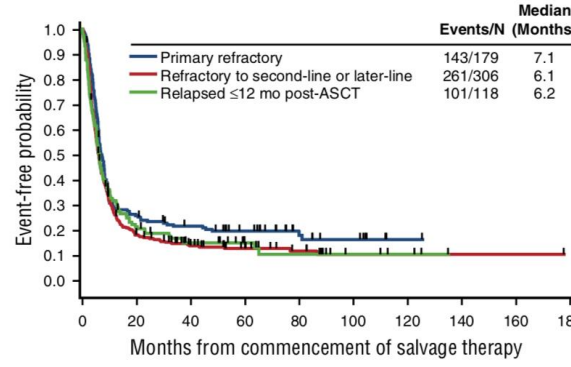
Table 2. Rate of response to chemotherapy after refractory disease

	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)
Patients evaluated for response, n†	165	82	106	170
Response rate, % (95% CI)	20	26	26	31
CR rate	7	7	2	15
PR rate	13	18	25	16
Response rate by refractory category, % (95% CI)				
Primary refractory				
RR	—	25	27	10
CR rate	—	10	1	2
Refractory to second-line or later-line therapy				
RR	20	21	20	40
CR rate	7	5	20	18
Relapse ≤12 mo post-ASCT				
RR	19	35	—	39
CR rate	6	10	—	25

105

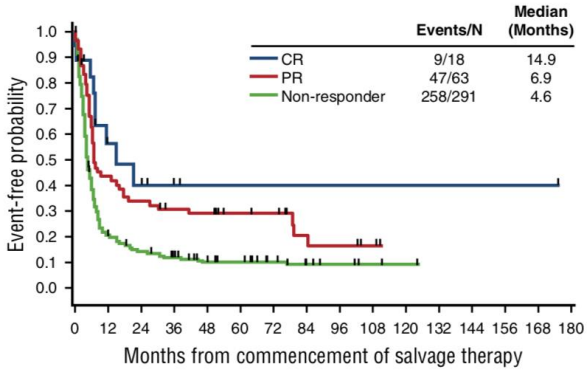
Survival

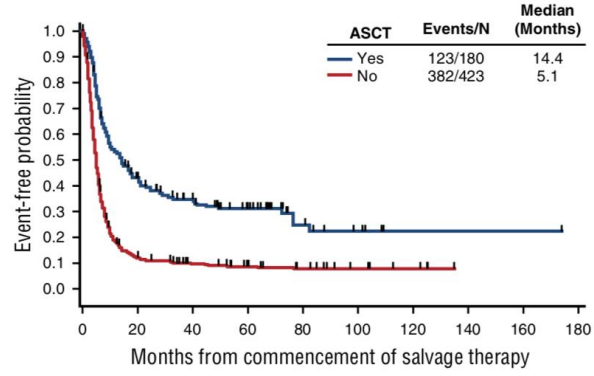




106

Survival





107

Is the Response Durable?

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108

Long-term Follow-up: ZUMA-1

Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial

Frederick L Locke, Armin Ghobadi, Caron A Jacobson, David B Miklos, Lazaros J Lekakis, Olalekan O Oluwole, Yi Lin, Ira Braunschweig, Brian T Hill, John M Timmerman, Abhinav Deol, Patrick M Reagan, Patrick Stiff, Ian W Flinn, Umar Farooq, Andre Goy, Peter A McSweeney, Javier Munoz, Tanya Siddiqi, Julio C Chavez, Alex F Herrera, Nancy L Bartlett, Jeffrey S Wiezorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu**

109

ZUMA-1

- Single-arm, multicenter, registrational study (22 sites)
- DLBCL, PMBL and tFL: Refractory or relapse after ASCT

	ORR	CR
Median follow-up of 15.4 months (n=108)	82%	58%

110

Long-Term Follow-up (median 27.1 months)

Median follow-up of 27.1 months (n=101)	ORR	CR
	83%	59%

111

Long-Term Follow-up (median 27.1 months)

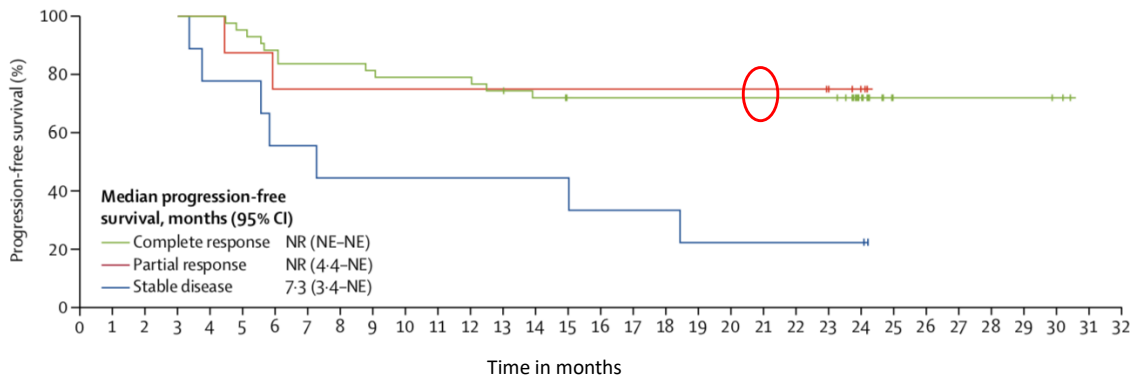
Median overall survival	Not reached (12.8-NE)
Median PFS	5.9 months (95% CI: 3.3-15.0)
Median duration of response	11.1 months (4.2-NE)

112

Long-Term Follow-up (median 27.1 months)

	Investigator-assessed (n=101)	IRC-assessed (n=101)
Objective response*	84 (83%)	75 (74%)
Complete response†	59 (58%)	55 (54%)
Partial response	25 (25%)	20 (20%)
Ongoing response‡	39 (39%)	36 (36%)
Complete response	37 (37%)	35 (35%)
Partial response	2 (2%)	1 (1%)
Median duration of response, months (95% CI)	11·1 (4·2–NE)	NR (10·9–NE)
Median duration of complete response, months (95% CI)	NR (12·9–NE)	NR (NE–NE)
Median overall survival, months (95% CI)	NR (12·8–NE)	NR (12·8–NE)

113



114

Long-Term Follow-up (median 27.1 months)

Toxicity of interest	
CRS (Grade >3)	12 (11%)
NT (Grade >3)	35 (32%)

115

How About Real World?

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116

Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real World Experience

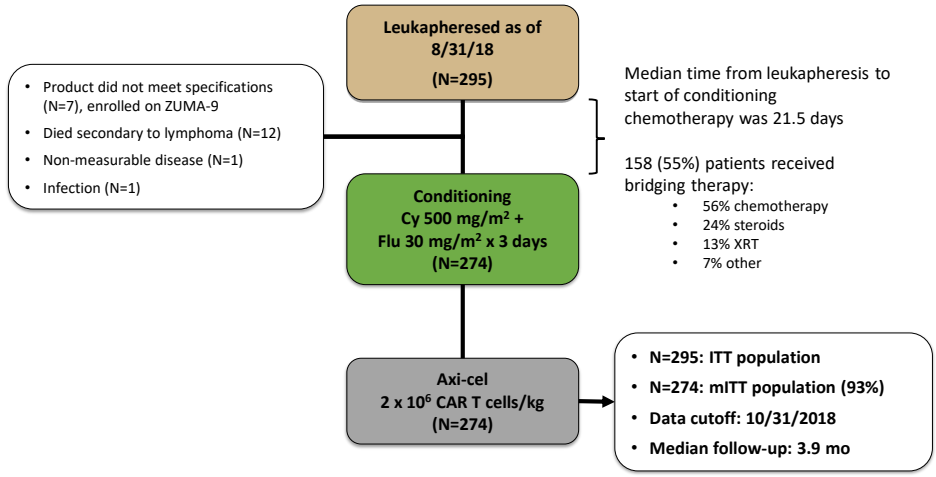
Abstract #: 91 (ASH 2018)
Author: Nastoupil LJ, et al. (MD Anderson Cancer Center)

Study Background

- Axi-cel (Yescarta®) is an autologous anti-CD19 CAR T-cell therapy approved in the US for the treatment of adult patients with relapsed/refractory DLBCL after two or more lines of systemic therapy.
- Axi-cel was approved based on the pivotal ZUMA-1 trial of 108 patients.
- The objective of the current study was to delineate the characteristics and real-world outcomes of patients undergoing standard of care axi-cel.
- This was a retrospective analysis of data from 295 patients at 17 US academic centers.

Nastoupil et al. ASH 2018.

Consort Diagram



Nastoupil et al. ASH 2018.

119

Patient Characteristics

Characteristic, n (%)	SOC Axi-Cel n=293	ZUMA-1 n=108
Patients infused / leukapheresed	275 / 295 (93%)	108 / 119 (91%)
Median age, yrs (range)	60 (21-83)	27 (25)
≥65 yrs		
Male	189 (65%)	73 (25%)
ECOG PS		
0-1	232 (81%)	108 (100%)
2 / 3-4	44 (15%) / 12 (4%)	0
Disease stage III/IV	240 (84%)	90 (83%)
DLBCL	197 (68%)	77 (76%)
PMBCL / tFL	17 (6%) / 75 (26%)	8 (7%) / 16 (15%)
IPI ≥3	158 (55%)	48 (44%)
>3 prior therapies	215 (75%)	76 (70%)
Primary refractory	100 (35%)	27 (25%)
Refractory to second line or later	121 (42%)	80 (74%)
Relapsed post-ASCT	95 (33%)	25 (23%)

Nastoupil et al. ASH 2018.

120

Patient Characteristics

124 of 286 (43%) of patients would not have met eligibility for ZUMA-1 at the time of leukapheresis.

Criteria excluded from ZUMA-1	N=124 n (%)
Platelets <75	37 (13%)
Active DVT/PE	27 (9%)
Prior CD19 or CAR T -cell therapy	24 (8%)
GFR <60	22 (8%)
History of CNS lymphoma	22 (8%)
Symptomatic pleural effusion	11 (4%)
LVEF <50%	10 (4%)
Prior allogeneic SCT	7 (2%)

Nastoupil et al. ASH 2018.

121

Safety of Axi-Cel in the Real World

	SOC Axi-cel N=274	ZUMA-1 n=108
All grades of CRS	240 (92%)	100 (93%)
Grade ≥3 CRS	18 (7%)	14 (13%)
Median time to onset of CRS	3 days	2 days
All grades of NT	181 (69%)	70 (65%)
Grade ≥3 NT	85 (33%)	33 (31%)
Median time to onset of NT	6 days	5 days
Tocilizumab usage	63%	45%
Corticosteroid usage	55%	29%
Median hospital stay	14 days	N/A
ICU stay	85 (32%)	N/A
Grade 5 AEs	7 (3%)	4 (4%)
Treatment-related deaths	2 (1%)	2 (2%)

Nastoupil et al. ASH 2018.

122

Efficacy of Axi-Cel in the Real World

	SOC Axi-cel Evaluable	SOC Axi-cel	ZUMA-1 n=108
Median follow-up, months		3.9	15.4
Day 30 ORR	238	191 (80%)	N/A
Day 30 CR		113 (47%)	N/A
Best ORR at Day 90	248		
Best CR at Day 90		2 (1%)	2 (2%)

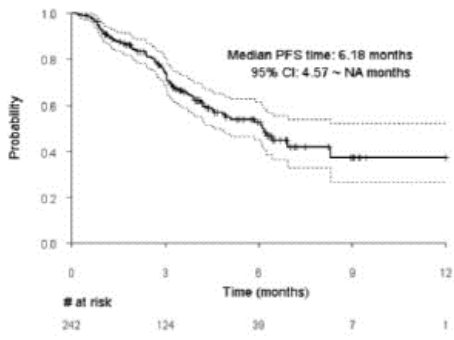
Nastoupil et al. ASH 2018.

123

Efficacy of Axi-Cel in the Real World

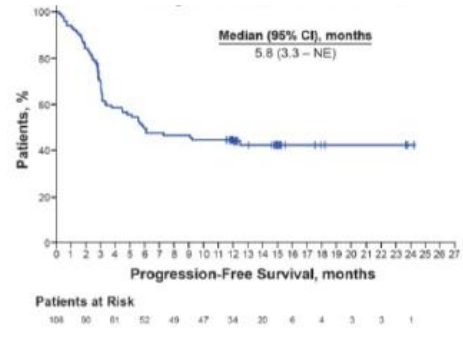
Progression-Free Survival

Real World



Median Follow-up: 3.9 months

ZUMA-1



Median Follow-up: 15.4 months

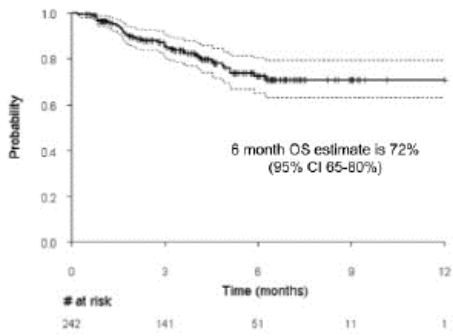
Nastoupil et al. ASH 2018.

124

Efficacy of Axi-Cel in the Real World

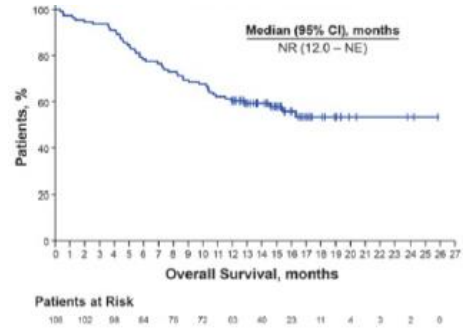
Overall Survival

Real World



Median Follow-up: 3.9 months

ZUMA-1



Median Follow-up: 15.4 months

Nastoupil et al. ASH 2018.

125

Cytokine Release Syndrome

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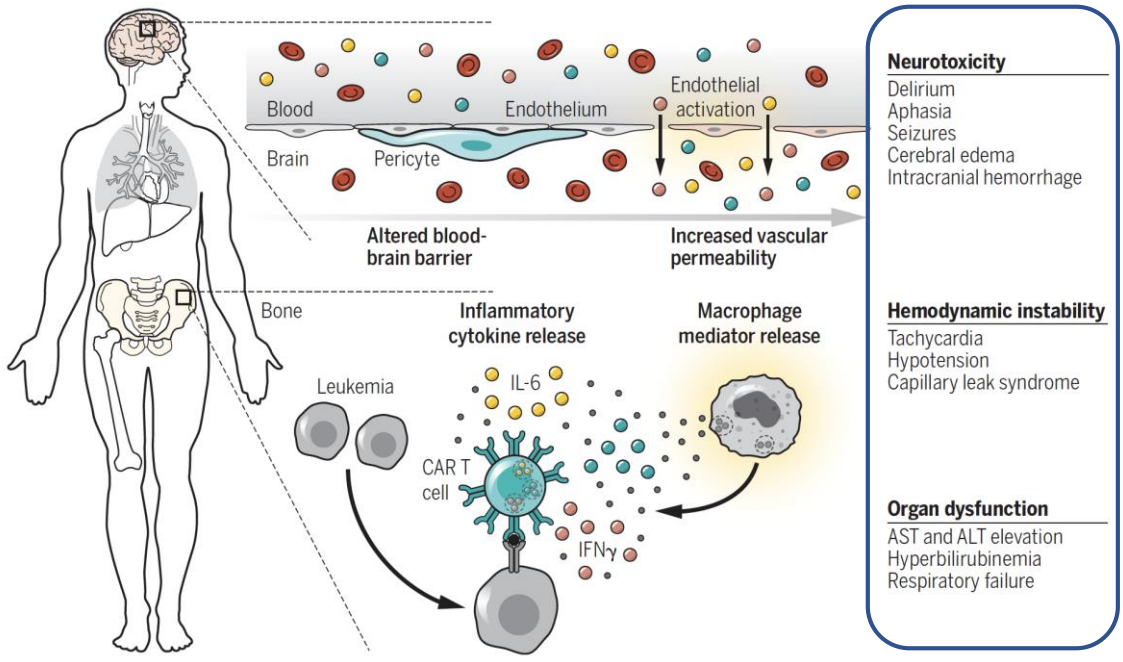
126



June et al., Science, 2018.

127

Definition

DEFINITION OF CRS

The CTCAE v4.03 defines CRS as "a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells [11]." Although inclusive of many of the features of immune effector cell-associated CRS, this definition does not include fever, the hallmark of immune effector cell-associated CRS. CTCAE v5.0 refined the definition as "a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines [13]."

different ways to activate T and/or other immune effector cells, CRS as we have described it appears to be an immune effector cell-associated phenomenon. Therefore, we define CRS as "a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, Lee, Daniel W. et al.,Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

128

ASBMT Consensus Grading of CRS

ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Tocilizumab

Steroids

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells
Lee, Daniel W. et al. Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

129

ICANS: IEC-Associated Neurotoxicity Syndrome

symptoms, as well as to acknowledge other cellular immunotherapies and therapeutics, such as bispecific antibodies, that may have similar neurologic side effects. We define ICANS as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema." Similar to CRS, ICANS should be applied to any immune effector cell engaging therapy, not just CAR T cells.

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells
Lee, Daniel W. et al.,Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

130

ICANS: IEC-Associated Neurotoxicity Syndrome

Neurologic and Psychiatric Adverse Reactions Reported with Approved CAR T Products

Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)
Encephalopathy: includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism **Delirium:** includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness **Headache:** includes headache and migraine **Anxiety** **Sleep disorder:** includes sleep disorder, insomnia, nightmares	**Encephalopathy:** includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbed attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor **Delirium:** includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness **Headache** **Dizziness:** includes dizziness, presyncope, syncope **Aphasia:** includes aphasia, dysphasia **Motor dysfunction:** includes muscle spasms, muscular weakness **Tremor** **Ataxia** **Seizure** **Dyscalculia** **Myoclonus**

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells
Lee, Daniel W. et al.,Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 - 638.

131

Grading ICANS: Encephalopathy

Encephalopathy Assessment Tools for Grading of ICANS

CARTOX-10 [12]	ICE
• **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points • **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention:** ability to count backwards from 100 by 10: 1 point	• **Orientation:** orientation to year, month, city, hospital: 4 points • **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention:** ability to count backwards from 100 by 10: 1 point

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.
Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells
Lee, Daniel W. et al.,Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 – 638.

132

Grading ICANS: Encephalopathy

ASBMT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

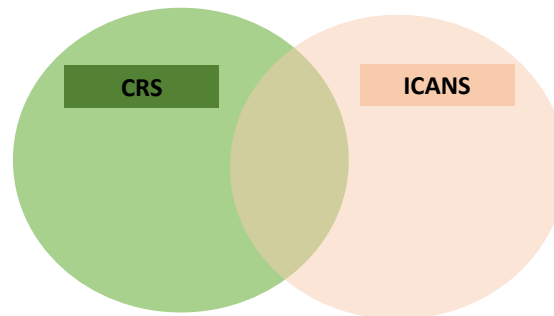
Steroids

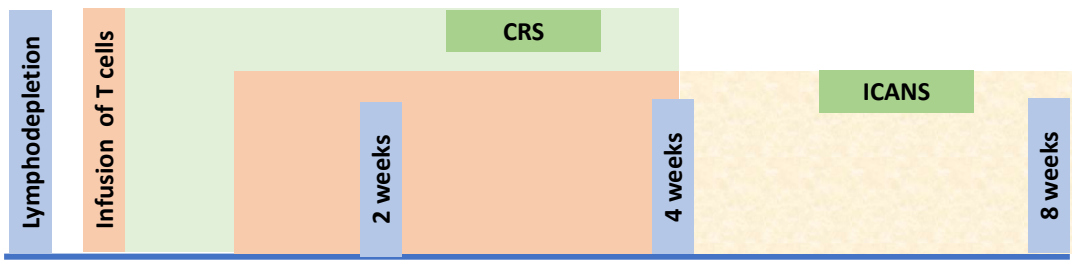
Tocilizumab

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, Lee, Daniel W. et al.,Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 - 638

133

CRS and ICANS





CRS, Cytokine Release Syndrome; CRES, CAR-T related Encephalopathy syndrome.

134

Thank You

O'NEAL COMPREHENSIVE CANCER CENTER
UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

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135

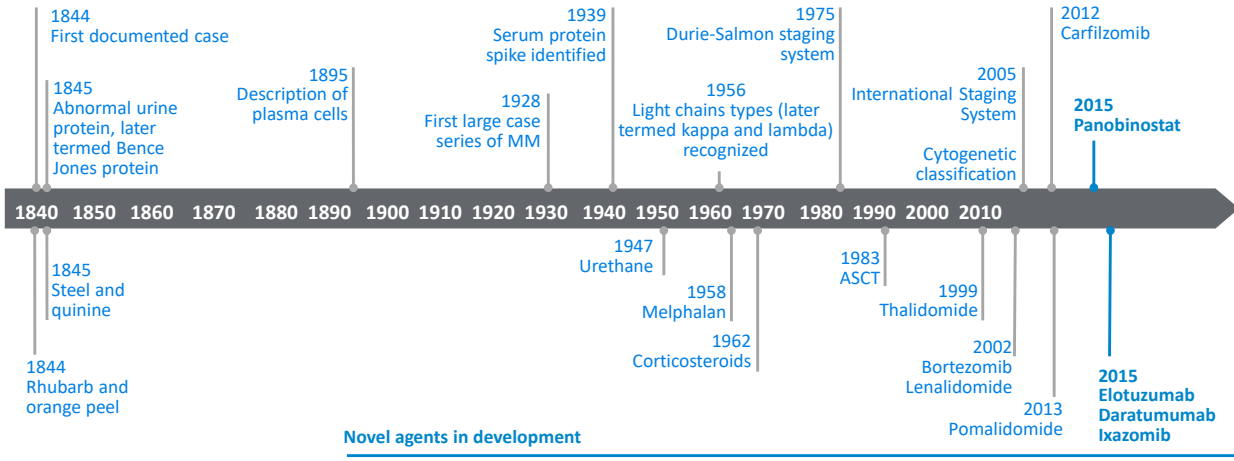
SARAH CANNON
Research Institute

CAR T-CELLS FOR MM: THE NEXT MAJOR DISEASE TARGET?

Jesús G. Berdeja, MD
Director of Multiple Myeloma Research
Sarah Cannon Research Institute at Tennessee Oncology and
Sarah Cannon Center for Blood Cancer at TriStar Centennial
Nashville, TN, USA

136

Timeline History of Myeloma

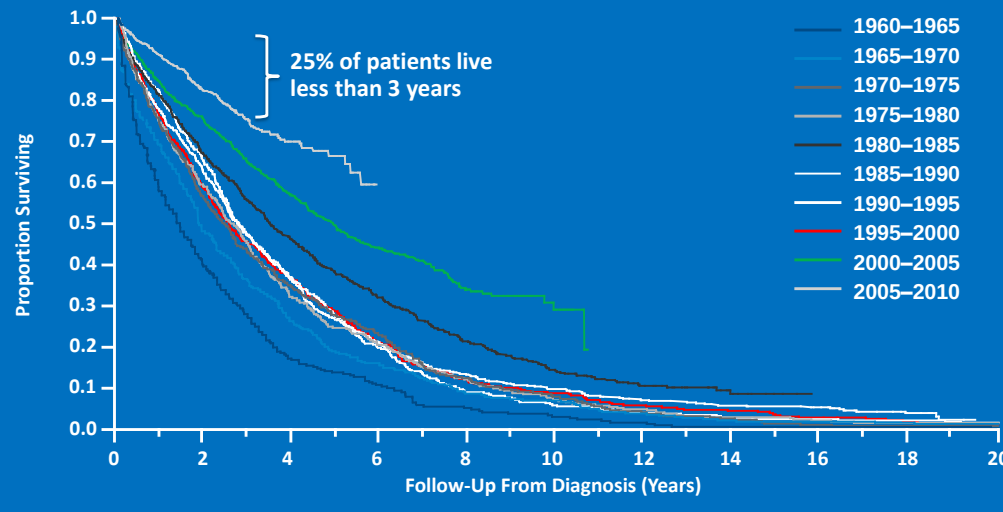


Kyle RA, Rajkumar SV. *Blood.* 2008;111:2962; Durie BGM. Concise Review of the Disease and Treatment Options: Multiple Myeloma. International Myeloma Foundation; 2011/2012 edition; KYPROLIS [package insert]. Onyx Pharmaceuticals, Inc. July 2012; POMALYST [package insert]. Celgene Corporation. February 2012.

Slide courtesy of the MMRF

137

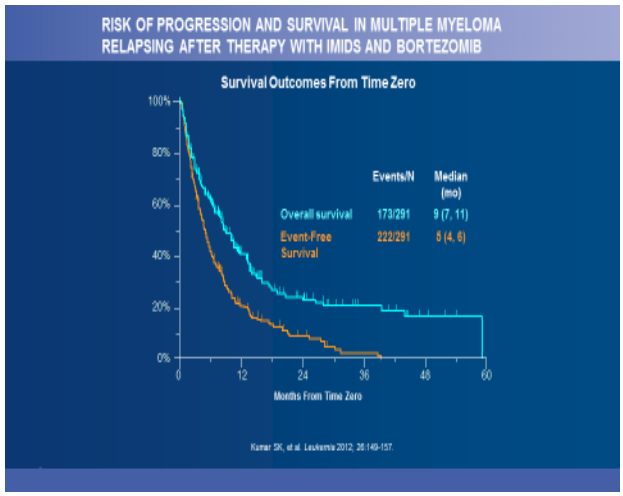
Improving Survival in MM



Adapted from Kumar SK et al. *Leukemia.* 2014;28:1122.

138

Despite Progress in Multiple Myeloma There Remains a Need for New Therapies



Analysis of Real-World Data on Overall Survival in Multiple Myeloma Patients With ≥3 Prior Lines of Therapy Including a Proteasome Inhibitor (PI) and an Immunomodulatory Drug (IMiD), or Double Refractory to a PI and an IMiD.

"Although newer PIs and IMiDs, such as carfilzomib and pomalidomide, have been introduced into the treatment regimen, our study of real-world data from electronic medical records of two independent U.S. databases suggests that ***median OS*** *durations remain poor (approximately* ***8 months****) in patients with MM who are heavily pretreated, those refractory to a PI and an IMiD, or both."*

Usmani, et al. Oncologist. 2016

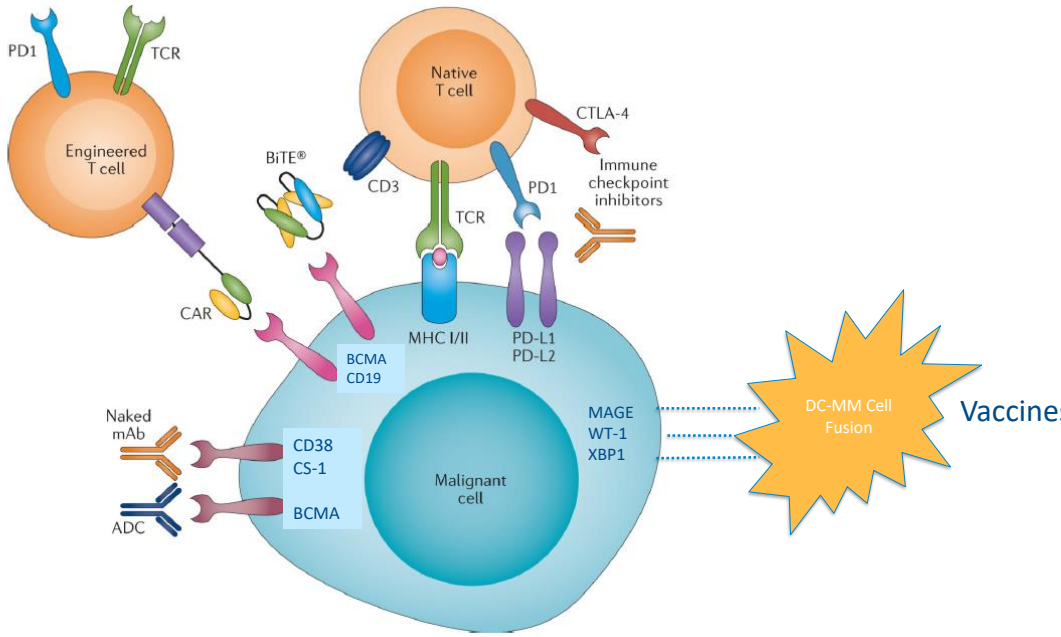
139

Most Recent New Drug Approvals for 3rd or 4th Line MM

Current U.S. Standards of Care For Multiple Myeloma 4th Line of Therapy		
	pomalidomide (Pomalyst) and dexamethasone (Pomalyst Product Monograph)	daratumumab (*Lancet* 2016, Lonial S)
N	452	106
Inclusion Criteria	• ≥2 prior therapies, including lenalidomide (REVLIMID) and bortezomib • Relapsed and refractory multiple myeloma • Disease progression on or within 60 days of last therapy	• Previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or were refractory to both proteasome inhibitors and immunomodulatory drugs
Prior Tx	5 (2-14)	5 (2-14)
CR Rate (%)	<1%	~3%
ORR (%)	23.5%	29%
PFS (mos)	3.6 months	3.7 months

CR, complete response; ORR, overall response rate; PFS, progression-free survival.

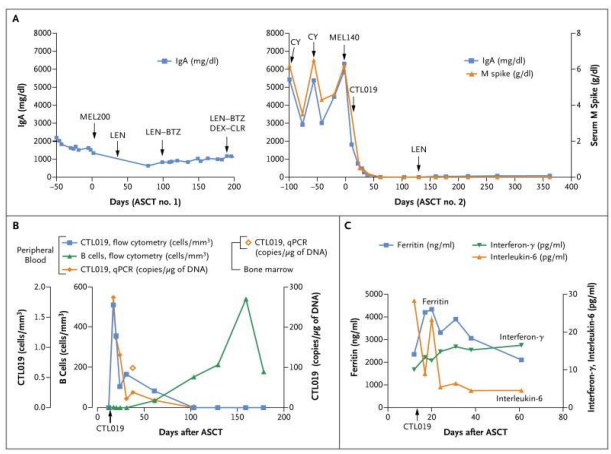
140



Adapted from Batlevi et al, Nat Rev Clin Oncol 2016.

141

CAR T- Cells Against CD19 for Multiple Myeloma: CASE Report



"A patient with refractory multiple myeloma received an infusion of CTL019 cells, a cellular therapy consisting of autologous T cells transduced with an anti-CD19 chimeric antigen receptor, after myeloablative chemotherapy (melphalan, 140 mg per square meter of body-surface area) and autologous stem-cell transplantation.

Four years earlier, autologous transplantation with a higher melphalan dose (200 mg per square meter) had induced only a partial, transient response. Autologous transplantation followed by treatment with CTL019 cells led to a complete response with no evidence of progression and no measurable serum or urine monoclonal protein at the most recent evaluation, 12 months after treatment.

This response was achieved despite the absence of CD19 expression in 99.95% of the patient's neoplastic plasma cells."

Garfall et al: N Engl J Med. 2015 Sep 10;373(11):1040-7. doi: 10.1056/NEJMoa1504542.

142

Designing a MYELOMA CAR: Possible Targets

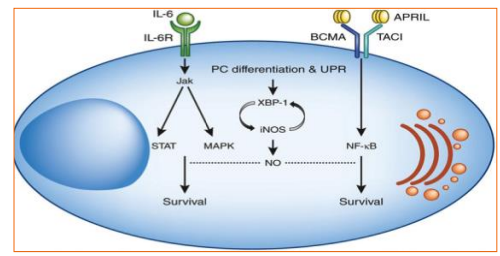
- The Classics
  - CD 38
  - CD 138
  - CD 56
  - Kappa light chain
  - CD 19
- New Targets
  - Lewis Y
  - CD 44v6
  - CS1/SLAMF7
  - BCMA
  - CD 229
  - Integrin

BCMA, B-cell maturation antigen.

143

BCMA Biology

- B-cell maturation antigen (BCMA) is a member of the TNF receptor superfamily
- Receptor for BAFF and APRIL
- Expressed on cell surface
- Expression largely restricted to plasma cells and some mature B cells (absent on naive and memory B cells)
- Important in B-cell maturation and long-lived plasma cell survival



APRIL, a proliferation-inducing ligand; BAFF- B-cell activating factor belonging to the TNF family; TNF, tumor necrosis factor.

Njau & Jacob. Nat Immunol 2014. 15:219.

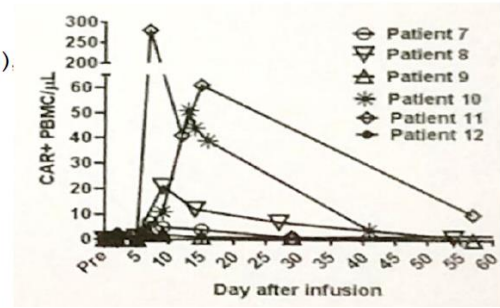
144

NCI BCMA-specific CAR in rel/ref MM

Cyclophosphamide 300 mg/m² Fludarabine 30 mg/m² QD for 3 days → CAR-BCMA T cells* Single infusion

*Dose escalation of CAR+ T cells/kg
0.3 x 10^6
1.0 x 10^6
3.0 x 10^6
9.0 x 10^6

- Responses in 4/12 pts.
  - PR (2wks), VGPR (8wks), sCR (17wks), VGPR (26+ wks)
- Associated with CART expansion
- Severe CRS and delirium



Ali et al. ASH 2015. LBA #1: Blood 2016.

CRS, cytokine release syndrome; PR, partial response; sCR- stringent compete response; VGPR, very good partial response.

145

2019 CART TRIALS IN MULTIPLE MYELOMA

BCMA

NCI	2215967	Closed	
NCI	3602612	Open	
UPEN/Novartis	2546167	Closed	
Multiple/Bluebird2658929		Closed	
Multiple/Celgene	3361748	Closed	
Multiple/Bluebird3274219		Open	
Multiple/Nanjing Legend	3758417	Open	
Multiple/Janssen/Legend	3548207	Open	
MSK/Juno		Closed	
UW/Juno	3338972	Open	
Multi/Juno	3430011	Open	
Multi/Poseida	3288493	Open	
Multi/Kite	3318861	Closed	
Multi/Cartesian Ther		Open	
Multiple/Celgene	3601078	Open	
Multiple/Celgene	3651128	Open	
Mult hosp/co in China	3492268	Open	
	3711864	Open	
	3815383	Open	
	3380039	Open	
	3716856	Open	
	3661554	Open	
	3664661	Open	
	3093168	Open	
	3751293	Open	
	2954445	Open	
Shanghai Bioray Labs	3752541	Open	Allo CART

OTHER

APRIL	Multi/Autolus	3287804	Open
BCMA+	MSK/Juno	3070327	Open
	UW/NCI		Open
CD19	UPenn/Novartis	2794246	Closed
CD138	UNC	3672318	Open
	General Hosp PLA, China	1886976	Closed
CD38	Multi/Sorrento Ther	3464916	Open
CS1	COH/NCI	3710421	Open
CD19/BCMA	UPenn/Novartis	3549442	Open
CD19/BCMA	Soochow Univ, China	3455972	Open
CD19/BCMA	Shanghai/HRAIN	3706547	Open
CD138/BCMA	Soochow Univ, China	3196414	Open
CD38/BCMA	General Hosp PLA, China	3767751	Open
Multi	Shenzhen/China	3271632	Open
Multi	Multiple sites/China	3473496	Open

www.clinicaltrials.gov, March 2019.

146

BCMA-DIRECTED CAR T CELLS IN MULTIPLE MYELOMA

	BB2121 BLUEBIRD	LCAR-B38M LEGEND	JCARH125 JUNO
Target	BCMA	BCMA	BCMA
Ag-binding domain	scFv (M)	2-VHH (C)	scFv (H)
Vector	Lentiviral	Lentiviral	Lentiviral
Costimulatory Domain	CD3/41BB	CD3/41BB	CD3/41BB
Special Qualities	Low tonic activity	2 epitopes	Equal # CD4/CD8
# Cell Doses	1	1 (20/30/50)	1
Lymphodepletion	Flu/Cy	Cy	Flu/Cy
Indication	R/R	R/R	R/R

SARAH CANNON Research Institute

Raje et al, NEJM 2019; Zhao et al, ASH 2018, Mailankody et al, ASH 2018.

147

BCMA-DIRECTED CAR T CELLS IN MULTIPLE MYELOMA

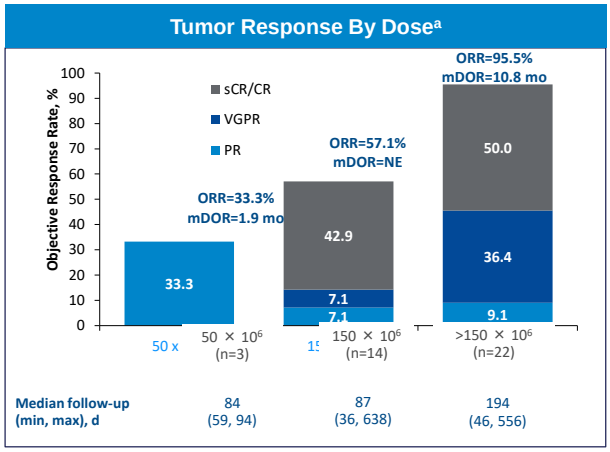
	BB2121(BLUEBIRD)	LCAR-B38M(LEGEND)	JCARH125(JUNO)
Population	33	57	44
# Prior Tx	7	3	7
CART Dose	50-800 x 10^6	0.07-2.1 x 10^6/kg	50-450 x 10^6
ORR	85%	88%	82%
CR	45%	74%	27%
CRS All Grades (Grade 3/4)	76% (6%)	89% (7%)	80% (9%)
Med Onset of CRS	2 d	9 d	3 d
Neurotox All Grades (Grade 3/4)	42% (3%)	2% (0%)	25% (7%)
Med PFS	11.8 mos	15 mos	-

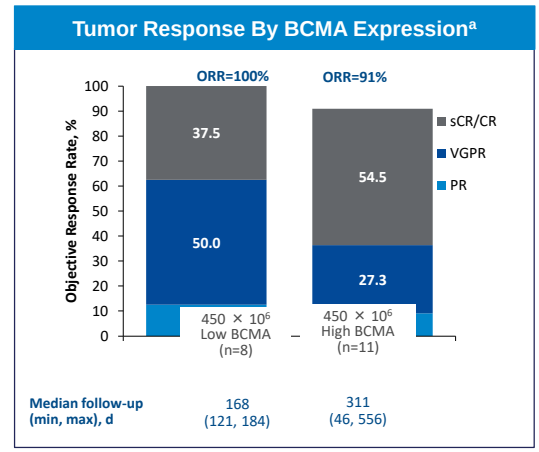
SARAH CANNON Research Institute

Raje et al, NEJM 2019; Zhao et al, ASH 2018, Mailankody et al, ASH 2018.

148

BB2121 Tumor Response: Dose-Related; Independent of Tumor BCMA Expression





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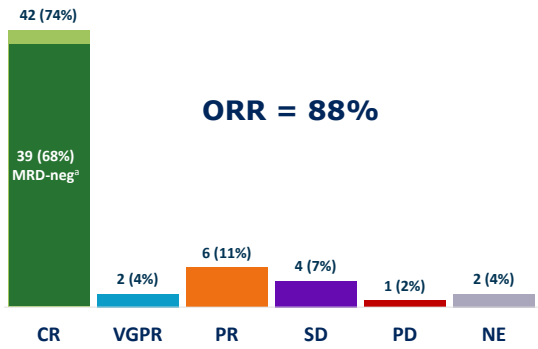
Berdeja, et al: EHA 2018.

149

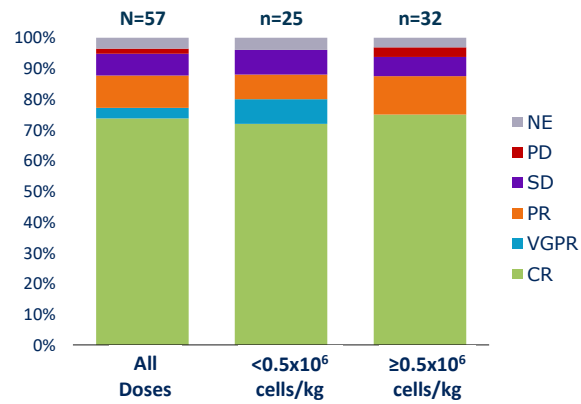
Efficacy

Best Overall Response (N=57)



- mDOR = 16 mo (95% CI, 12–NR)
- mDOR for MRD-neg CR = 22 mo (95% CI, 14–NR)
- Median time to initial response = 1 mo (0.4–3.6)

Best Overall Response by Dose



BCMA <40% (n=26/53)[b] = 92% ORR
BCMA ≥40% (n=27/53)[b] = 82% ORR

[a]8-color flow cytometry with cell count up to 500,000 cells; [b]BCMA expression data available for 53 patients.

60th ASH Annual Meeting 2018, Zhao W-H, et al. Abstract #955.

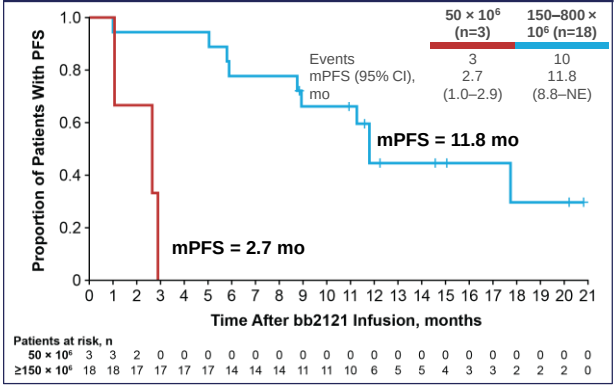
CR, complete response; mDOR- median duration of response; MRD-neg, minimal residual disease-negative; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

150

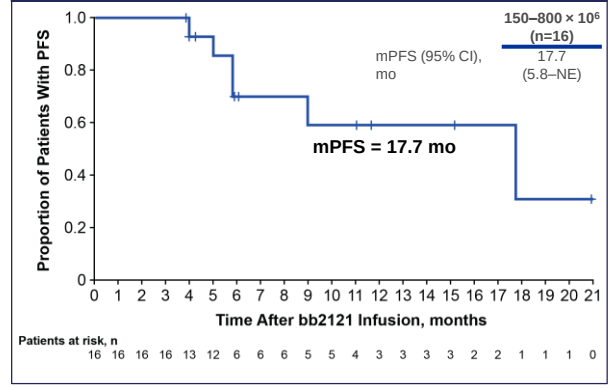
Progression-Free Survival

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



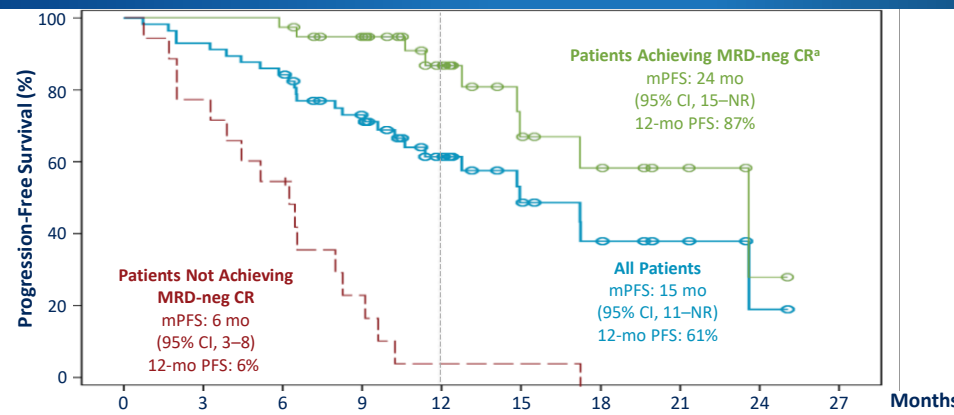
PFS in MRD-Negative Patients



Berdeja, et al: EHA 2018.

151

Progression-Free Survival



Patients at risk:										
All Patients	57	53	48	37	21	11	7	4	1	0
Patients Achieving MRD-neg CR	39	39	38	33	20	10	7	4	1	0
Patients Not Achieving MRD-neg CR	18	14	10	4	1	1	0	0	0	0

[a]30/39 patients still in remission

60th ASH Annual Meeting 2018, Zhao W-H, et al. Abstract #955.

mPFS, median progression-free survival.

152

Future Directions of Most Advanced CAR T Products

- Race to FDA Approval in the USA
  - Global Pivotal Trial (KarMMa) just completed enrollment
    - bb2121 dose range: 150-450 × 10^6 CAR+ T cells
  - Legend/Janssen enrolling on pivotal trial of LCAR-B38M or JNJ-68284528
- Use Beyond the Refractory Setting
  - Trials in earlier phase of disease
    - KarMMa 3 – randomized Phase 3 of bb2121 vs SOC in pts with 2-4 priors
    - KarMMa 2 – cohort of pts with early relapse, bb2121 as 2nd line
  - In conjunction with ASCT/Consolidation in MRD
    - KarMMa2, SZ-CART-MM 02 (BCMA and CART19)
  - Upfront in high risk patients
    - UPENN/Novartis (BCMA CART and/or CART19) [NCT03549442]
    - Several others in development

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153

Does the T-cell Composition of the Product Matter?

- Does infusion of a fixed ratio of 1:1 CD4:CD8 cells in the infused CAR T product lead to more active and durable product?[1,2]
- Does selecting for T cell memory phenotype result in longer duration of response, decrease toxicity?

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[1]Sommermeyer et al: Leukemia 2015;30:492. [2]Turtle et al: Sci Transl Med 2016;8(355).

154

JUNO - CD4:CD8 1:1 RATIO

- MCARH171
- JCARH125
- FCARH143

- Early results encouraging – awaiting longer follow-up

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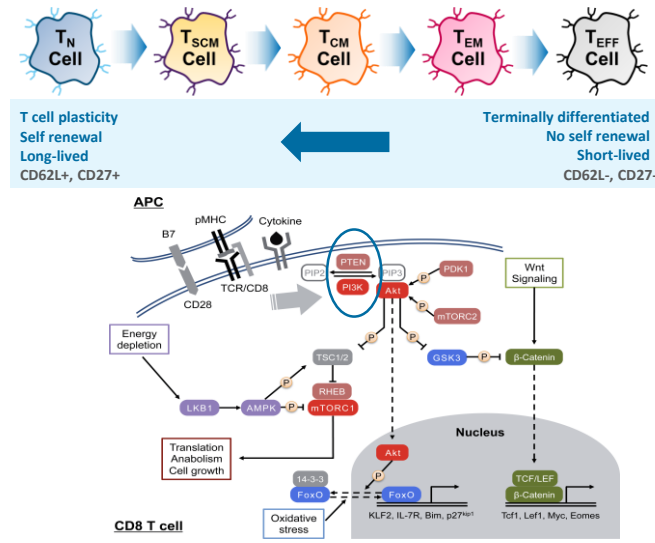
155

bb21217: Next-Generation Anti-BCMA CAR T Cell Therapy

- bb21217 uses the same CAR construct design as bb2121[1]
- bb21217 is cultured with PI3 kinase inhibitor, bb007, to enrich for T cells displaying a memory-like phenotype
- CAR T cells enriched for this phenotype may persist and function longer than non-enriched CAR T cells[2]
- Could persistence of functional CAR T cells translate to a longer duration of response?



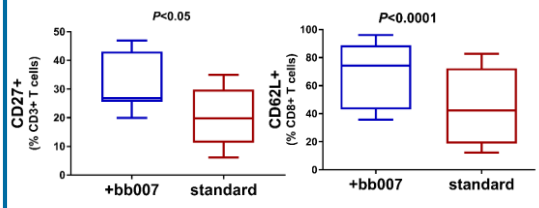
BCMA, B-cell maturation antigen; PI3K, phosphoinositide 3 kinase.
1. Friedman et al. *Hum Gene Ther* 2018;29:585-601. 2. Fraietta JA, et al. *Nat Med*. 2018 May;24:563-571

Shah et al: ASH 2018, Abstract 488.

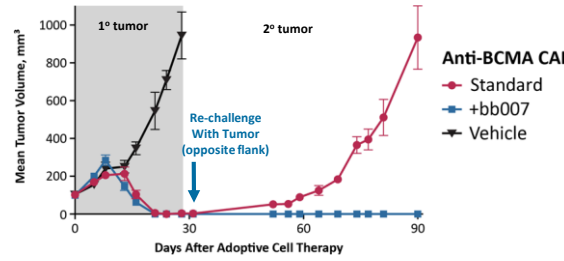
156

PI3K Inhibition Enriches for Memory-Like (CD27+ and CD62L+) T Cells and Extends CAR T Cell Activity

Prevalence of CD27+ and CD62L+ T Cells



Tumor Volume in Mouse Xenografts After a Single Treatment



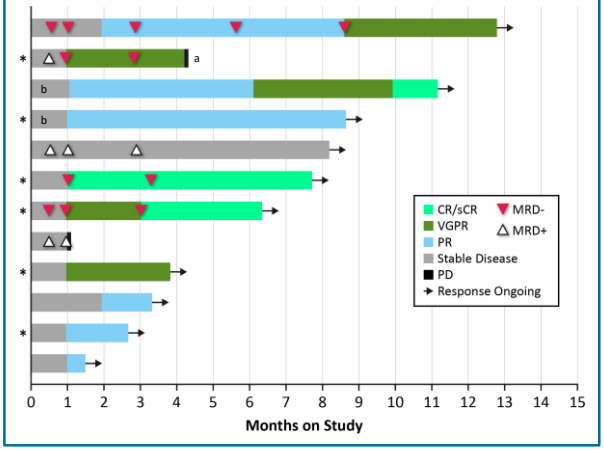
- Culturing with PI3K inhibitor, bb007, significantly increases the percentage of CD27+ and CD62L+ T cells
- T cell surface markers CD27+ and CD62L+ are associated with less differentiated, central memory T cells

- CAR T cells manufactured with and without bb007 eliminate tumors in established MM xenografts equally well
- Opposite flank tumor re-challenge resulted in no tumor growth in mice treated with bb007 cultured CAR T cells, suggesting longer persistence of anti-tumor effect

157

Clinical Responses and Duration of Response at the 150 × 10^6 CAR+ T Cell Dose

Clinical Responses Over Time



CR, complete response; MRD, minimal residual disease; ORR, objective response rate; PR, partial response; VGPR, very good partial response. *Patients with high tumor burden. [a]Progression based exclusively on appearance of new bone lesions. [b]MRD status not available. [c]Includes unconfirmed responses. [d]Patients with ≥PR and valid MRD assessments. [e]Two MRD-neg. responses at 10^{-6} and 2 at 10^{-5} sensitivity level by Adaptive next-generation sequencing. [f]Among 10 responders with ≥PR.

Clinical Response

	bb21217-Treated (N=12)
ORR,[c] n (%) [95% CI]	10 (83.3) [51.6, 97.9]
sCR/CR	3 (25)
≥VGPR	6 (50)
MRD status in bone marrow, n	
MRD-evaluable responders[d]	4
MRD-neg	4[e]
Median time to first response (min, max),[c,f] mo	1 (1, 2)
Median time to best response (min, max),[c,f] mo	1 (1, 10)
Median follow-up duration (min, max), mo	5.9 (1.0, 11.8)

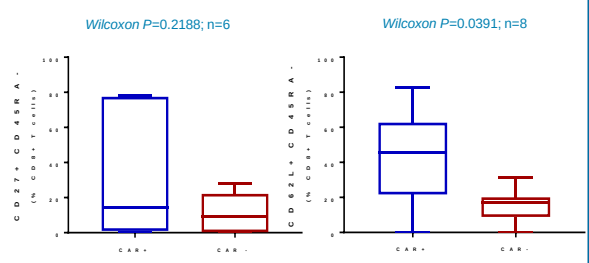
- 10/12 patients (83%) achieved an objective response at the first tested dose (150 × 10^6 CAR+ T cells)
- Responses deepening over time; CR achieved as late as month 10
- Responses ongoing in all but 1 responder; first patient dosed continues in response >1 year after treatment
- 100% MRD negativity in 4/4 responders evaluable for MRD status; 2/2 non-responders were MRD positive

Data Extract: 18OCT2018

158

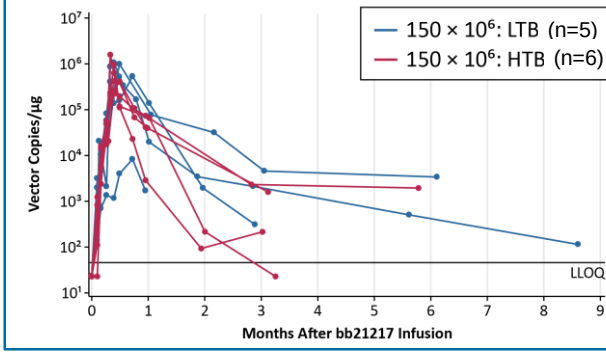
Robust Expansion of Infused CAR+ T Cells Enriched for Memory-Like T Cells

CD27+ or CD62L+ CD45RA– CD8+ Cells[a]



- Enrichment for memory-like cells within CAR+ cell population in blood post-infusion
- Robust and consistent CAR+ T cell expansion post-infusion independent of tumor burden
- Detectable CAR + T cells up to 9 months post-infusion

Vector Copy Number Over Time by Baseline Tumor Burden



	Month 1	Month 3	Month 6	Month 9
At risk, n	9	7	3	1
With detectable vector, n (%)	9 (100)	6 (**86**)[b]	3 (100)	1 (100)

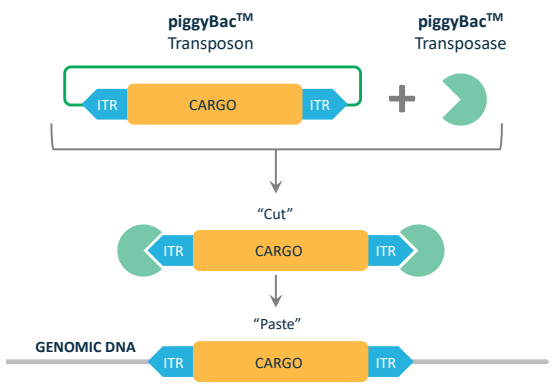
HTB- high tumor burden; LLOQ- lower limit of quantitation; LTB- low tumor burden.
[a]Immunophenotyping occurred at time of peak CAR T expansion. [b]One patient with undetectable vector received cyclophosphamide on day 15 for grade 4 encephalopathy.

Data Extract: 18OCT2018.

159

Efficacy and Safety of P-BCMA-101 CAR-T cells

piggyBac™ is a non-viral DNA delivery system for developing CAR-T and other gene therapy products



- Creates CAR-T product candidates with a high percentage of **T Stem Cell Memory T cells (T_{SCM})**
- **Very large cargo capacity (potentially >20X lentivirus)** – large transgene - multiple CAR/TCR and armoring potential
  - **Fully functioning 4 CAR in one CAR-T cell produced as POC**
- Non-viral delivery system **– reduces the risk of mutagenesis and oncogenesis**
- **High insertion efficiency** and **stable transgene expression**

Gregory et al: ASH 2018.

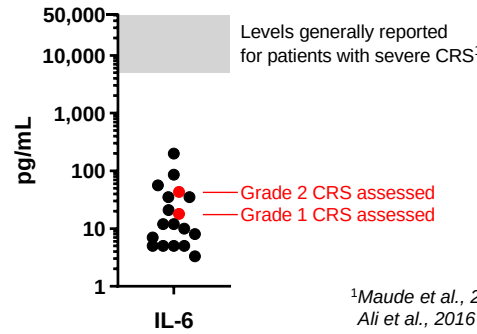
160

Cytokine Release Syndrome Negligible, Low Peak IL-6

Cytokine Release Syndrome Parameters

Parameter	Dosed Patients (n=21)
Patients with a CRS event, n	2 (9.5%)
Maximum CRS grade	
None	19 (90.5%)
1	1 (4.8%)
2	1 (4.8%)
Median time to onset, d	10.5
Median duration, d	3.5

Peak IL-6 Levels After P-BCMA-101



[1]*Maude et al., 2014*
Ali et al., 2016

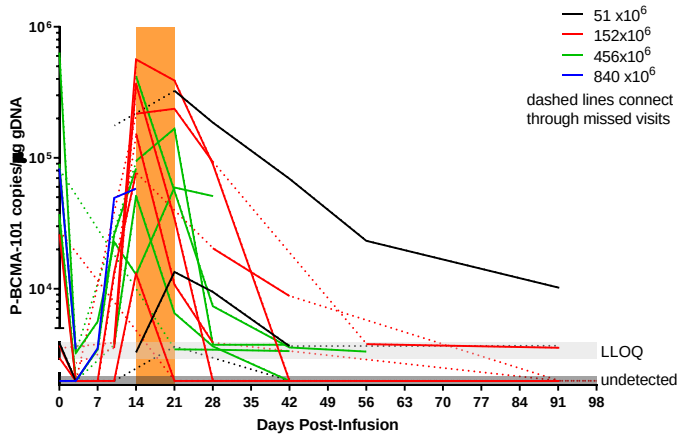
No use of tocilizumab, steroids, cytotoxic agents, rimiducid (safety switch) nor ICU admission for any patient for CRS
Only one use of tocilizumab and steroid to manage a patient with potential CRES

CRES, CAR-T cell-related encephalopathy syndrome; IL-6, interleukin 6.

161

P-BCMA-101 CAR-T Cell: Gradual Expansion

P-BCMA-101 in Peripheral Blood using PCR



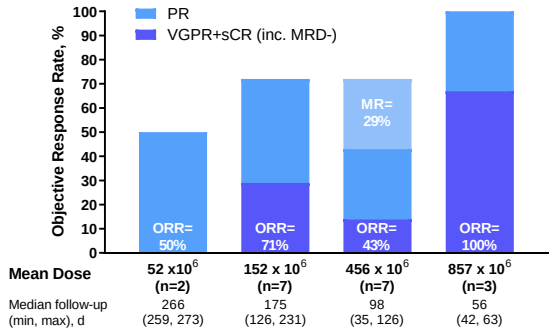
- Many CAR-T products show **peak expansion between 5-14 days**
- **Peak expansion of CAR-Ts often associated with CRS**
- P-BCMA-101 shows **peak expansion between 14-21 days**
- P-BCMA-101 reaches peak expansion gradually **without CRS**

Gregory et al: ASH 2018.

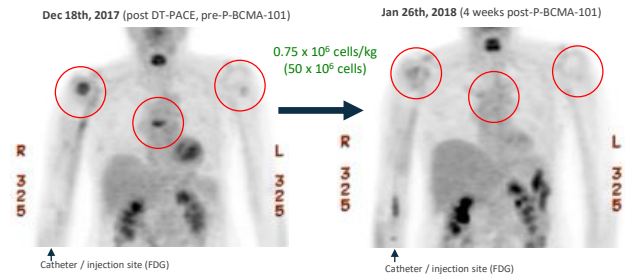
162

High Response Rates From the Lowest Dose Level

Tumor Response in Evaluable Patients by Dose



Patient 105-002 PET



Oligosecretory disease, M-protein, SPEP, UPEP, FLC not measurable/within normal limits.

Data cutoff: November 21, 2018.

ORR- objective response rate, attaining sCR (including. MRD-), CR, VGPR, or PR, including confirmed and unconfirmed responses. Evaluable patients: obtained first response assessment by IMWG m-protein criteria or PD/death.

2 patients with MR at 4 and 8 weeks follow-up with decreasing m-protein.

Gregory et al: ASH 2018.

163

CONCLUSIONS

- CAR T cells in MM are very active
  - High *ORR*, with high portion of CRs
  - Remission duration variable
- CAR T therapy is exciting but early with many unanswered questions
  - It does not appear curative in the R/R stage
    - Will it be different in earlier stages?
  - Need to understand mechanisms of relapse
  - Which is the best product?
    - Will new manipulations lead to better results: efficacy, safety, durability, access
  - Is benefit sufficient to justify cost?
  - How do CAR Ts compare with other immunotherapies (i.e., ADCs, bispecific antibodies)
- Toxicity management
  - Anticipation and early recognition is paramount
    - CRS, neurotoxicity, MAS, DIC, etc.
  - Post CAR T requires close follow-up
    - Best management yet to be defined (i.e., prophylaxis, use of IVIG, growth factors)
- The future looks bright!

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ADCs- antibody-drug conjugates; DIC- disseminated intravascular coagulation; MAS- macrophage activation syndrome.

164

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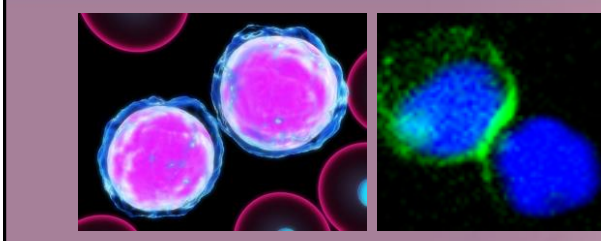
THANK YOU

165



CLL: Potential Roles for CAR T-Cell Therapy

David L Porter, MD
Director, Cell Therapy and Transplantation
University of Pennsylvania Health System
Abramson Cancer Center

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

166

CD19+ CLL: Rationale for Novel Therapies

- Median survival variable (2 to >20 years)
- Prognosis predictable based on many factors, including cytogenetics, numerous biomarkers, and response to therapy
- Incurable except by allogeneic BMT/SCT
  - Associated with extensive morbidity and mortality
  - Many patients not eligible (advanced disease, age, comorbidity, etc.)
- Patients with multiply relapsed or refractory disease or high-risk features have poor prognosis
- Newer, more effective therapies for advanced and high-risk CLL are necessary

BMT, bone marrow transplantation; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; SCT, stem cell transplantation.

167

CAR-T for CLL: UPenn Pilot Study Design and Considerations

- Single-center pilot trial of CTL019 (formally CART19) cells 2010
- Primary objective:
  - Safety, feasibility, and immunogenicity of CTL019 in patients with CD19+ leukemia and lymphoma
- Detailed inclusion/exclusion at clinicaltrials.gov (NCT01029366)
  - CD19+ B-cell malignancies with no available curative options (such as autologous or allogeneic SCT)
  - Failed >2 prior therapies, progression within 2 years of last treatment
  - Limited prognosis (<2 year) with available therapies

CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; UPenn, University of Pennsylvania; SCT, stem cell transplantation.

168

CLL: Overall Response to CTL019[1]

Response	N	%	Optimal dosing*
Complete response	13/46	28%	7/19 (37%)
Partial response	13/46	28%	3/19 (16%)
Overall response	26/46	56%	10/19 (53%)

CLL, chronic lymphocytic leukemia.
Porter et al, STM Vol 7 Issue 303 303ra139.
*Porter et al, ASCO 2016, Abstract #166699 and unpublished.

169

CAR-T for CLL: UPenn

- Can undergo massive expansion (1000-10,000 fold)
- Eradicate bulky tumor (2.5-7.5 lbs!)
- Can lead to long-term persistence (>7 yrs)
- Relapses after remission are uncommon
- Induce long-term remissions (>8 yrs) in patients with heavily pre-treated highly refractory CLL

CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; UPenn, University of Pennsylvania; SCT, stem cell transplantation.

170

SelectedTtrials of CD19-targeted CAR-T cells in CLL[1]

Source		N=	Co-stim Domain	LD Chemo	Dose (cells/kg)	ORR (%, iwCLL)	CR (%, iwCLL)
Autologous							
Kalos 2011	UPenn	3	4-1BB	Benda (n=1) Benda/R (n=1) PC (n=1)	$1.46x10^5$ to $1.6x10^7$	ORR: 3/3 (100%)	CR: 2/3 (67%)
Brentjens 2011	MSKCC	8	CD28	None (n=3) Cy (n=4)	$0.4x10^7$ to $1.0x10^7$	ORR: 1/8 (12%)	CR: 0/8 (0%)
Kochenderfer 2012; Kochenderfer 2015	NCI	8	CD28	FC (n=8)	$1.0x10^6$ to $5.5x10^7$	ORR: 7/8 (87%)	CR: 4/8 (50%)
Porter 2014	UPenn	14	4-1BB	FC (n=3) PC (n=5) Benda (n=6)	$0.14x10^8$ to $11x10^8$	ORR: 8/14 (58%)	CR: 4/14 (29%)
Porter 2016	UPenn	13	4-1BB	FC (n=13)	$5.0x10^7$	ORR: 4/13 (31%)	CR: 1/13 (8%)
		17		FC (n=17)	$5.0x10^8$	ORR: 9/17 (53%)	CR: 6/17 (35%)
Turtle 2016; Turtle 2017	FHCRC	24	4-1BB	Flu (n=2) Cy (n=1) FC (n=21)	$2.0x10^5$ to $2.0x10^7$	ORR: 14/19 (74%)	CR: 4/19 (21%)
Siddiqi 2018[a 39]	Multicenter	10	4-1BB	FC (n=10)	$5.0x10^7$ to $1.0x10^8$	ORR: 6/8 (75%)	CR: 4/5 (50%)
Gill 2018[b]	UPenn	14	4-1BB	FC (n=14)	$1.0x10^8$ to $5.0x10^8$	ORR: 10/14 (71%)	CR: 6/14 (43%)
Gauthier 2018[b]	FHCRC	17	4-1BB	FC (n=17)	$2.0x10^6$	ORR: 14/16 (88%)	NR
Allogeneic							
Brudno et al, 2015; Brudno et al, 2018	NCI	5	CD28	None	$0.4x10^6$ to $8.2x10^6$	ORR: 8/20 (40%)	CR: 4/20 (20%)
TOTAL		**133**				**12-100%**	**20-50%**

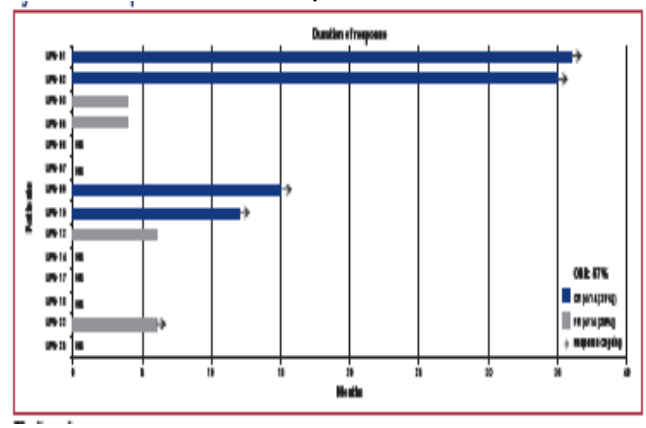
Benda, bendamustine; Benda/R, bendamustine/rituximab; CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CR, complete response; Cy, cyclophosphamide; FC, fludarabine/cyclophosphamide; FHCRC, Fred Hutchinson Cancer Research Center; iwCLL, International Workshop on CLL; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; NR, not reported; ORR, overall response rate; PC, pentostatin/cyclophosphamide; UPenn, University of Pennsylvania.
[a]CAR T cell product designed to contain 1:1 ratio of CD8+ and CD4+ cells; [b]Indicates combined treatment with ibrutinib.
1. Reproduced from Bair SM, Porter DL. *Am J Hematol*. 2019;94(S1):S10-S17.

171

Major Limitations to Success of CAR-T cells

- ALL
  - High CR rates (90%)
  - Relapse 20-50% (including CD19–)
- CLL
  - Lower CR rates
    - 25% to 35% in CLL
    - 40% to 70% in NHL
  - Relapse after CR unusual

CAR-T Cells for CLL: Relapse After Remission Unusual



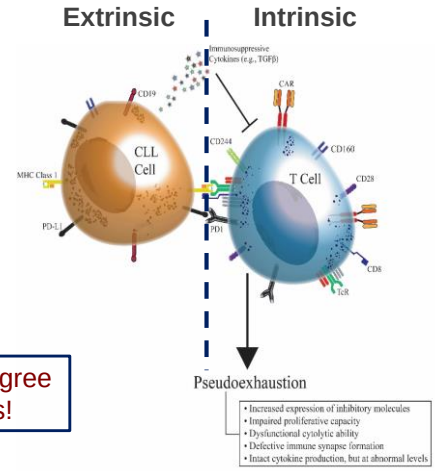
ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CR, complete response; NHL, non-Hodgkin lymphoma.

172

Identify Ideal T-cell Characteristics to Enhance Outcomes in CLL

- No obvious patient or disease factors predict response in CLL
  - Not age, prior therapy, cell dose, genetic risk profile, etc
- Responses may vary due to differences in innate, humoral, and cellular immune deficiencies
  - Inherent T-cell defects characteristic of CLL that worsen with disease progression

Potential Mechanisms of CAR-T Cell Dysfunction in CLL



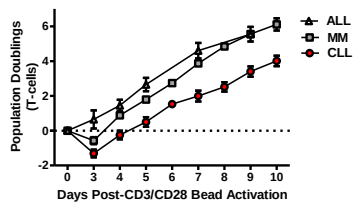
The best correlate of response so far is the degree of expansion of CAR-T cells in the patients!

CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; MHC, major histocompatibility complex; PD-L1, programmed death ligand 1; TcR, T-cell receptor; TGFβ, transforming growth factor beta.

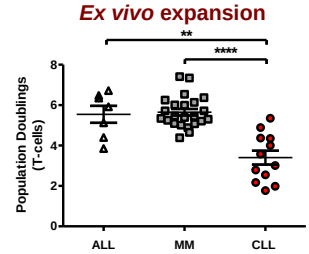
173

T cells in CLL Exhibit Proliferative Defects that Inhibit *ex vivo* and *in vivo* Expansion

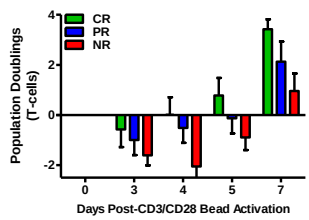
***Ex vivo* expansion**



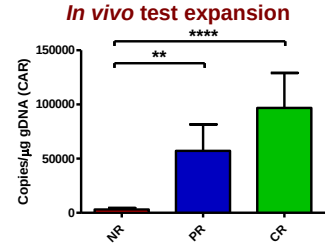
***Ex vivo* expansion**



***Ex vivo* test expansion**



***In vivo* test expansion**

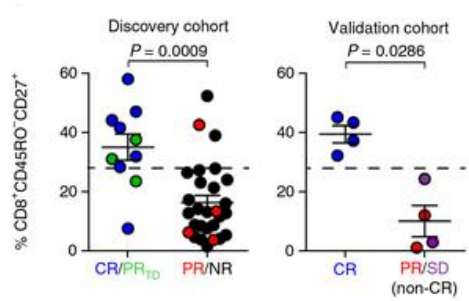


CLL, chronic lymphocytic leukemia.
Fraietta JA, et al. *Blood*. 2016;127(9):1117-1127.

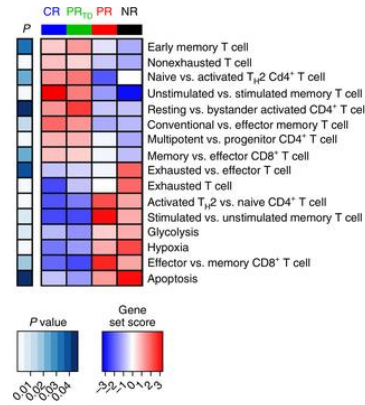
174

T-cell Markers and Response in CLL

Leukapheresis CD27+CD45RO-CD8+ T cell frequencies in patients by BOR



Heat map of selected pathways enriched in genes significantly upregulated or downregulated in CTL019 cells from patients by BOR

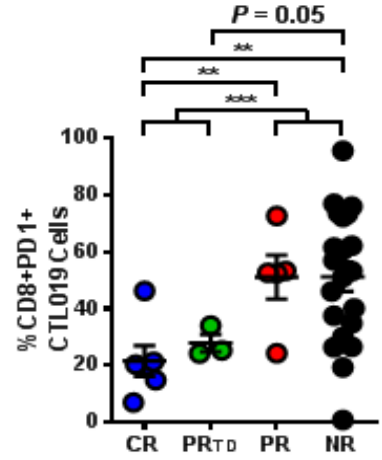


BOR, best overall response; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia.
Fraietta, JA et al. *Nat Med.* 24, pages 563–571 (2018).

175

PD-1 Expression on CAR-T cells and Response in CLL

- Lower PD-1 expression on CAR-T cells in responding patients with CLL
- Lower PD-1, Tim3, and Lag3 expression
- Will checkpoint blockage enhance or re-establish response?



CAR-T, chimeric antigen receptor-T; CLL, chronic lymphocytic leukemia; PD-1, programmed death receptor 1.
Fraietta, JA et al. *Nat Med.* 24, pages563–571 (2018).

176

Conclusions: Biomarker Assessment in CLL

- *In vivo* expansion and persistence are key quality attributes of CTL019
- Durable responses are associated with transcriptomic signatures of early memory T cells
  - T cells from non-responding subjects are enriched in genes of known pathways of exhaustion
- Frequency of CD27+CD45RO- CD8+ cells correlated strongly with complete and durable responses
- PD-1 and CD27 expression on CD8+ CTL019 in infusion product accurately predicts response
- It may be possible to identify patients most likely to respond to CTL019 prior to infusion based on T cell attributes
- Will it be possible to enhance T cell function prior to manufacturing to enhance response?

CD, cluster of differentiation; CLL, chronic lymphocytic leukemia.
Fraietta, JA et al. *Nat Med.*24, pages563–571 (2018).

177

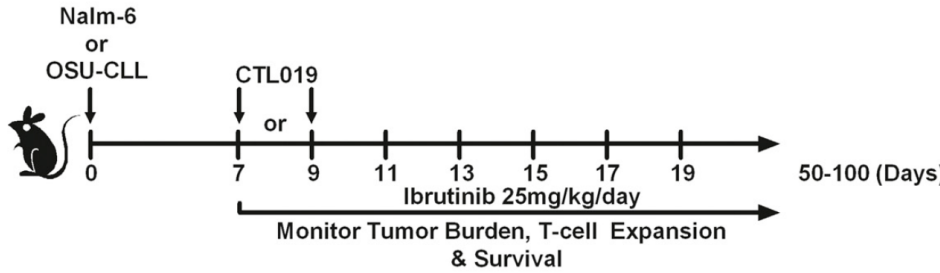
Improve Responses in CLL

Can T-cell Function and Targeting be Improved Before and After treatment?

178

Ibrutinib May Enhance CLL Response to CTL019[1]

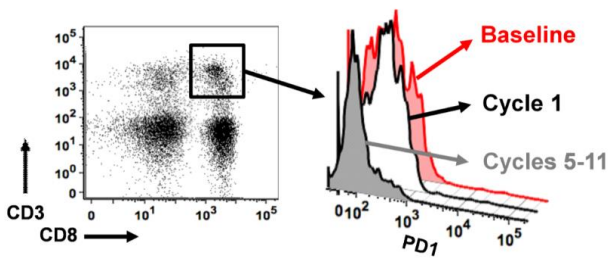
- T cells from CLL patients on ibrutinib for 6 to 12 months compared with baseline exhibit
  - Superior proliferative capacity *in vitro*
  - Superior survival *in vitro*
  - Reduced PD-1 expression on CD8+ T cells

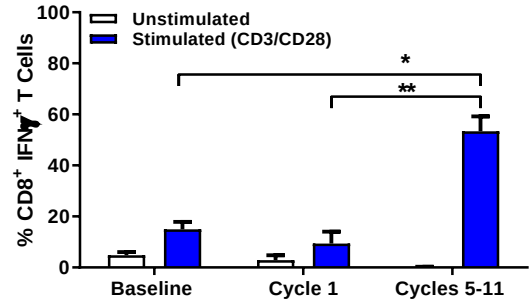


CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; PD-1, programmed death receptor 1.
1. Reproduced from Fraietta JA, et al. *Blood*. 2016;127(9):1117-1127.

179

Ibrutinib Decreases PD-1 Expression on CLL Patient CD8 T cells in Association with Improved Functional Activity



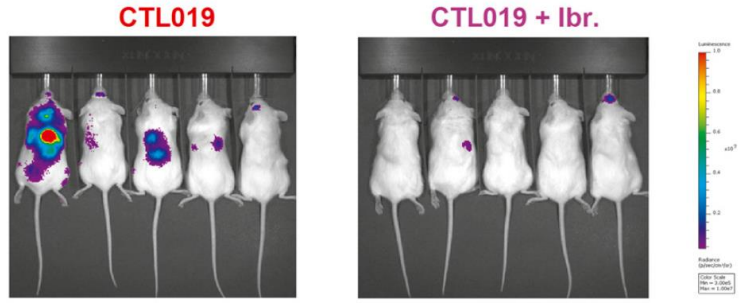


CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; PD-1, programmed death receptor 1.
Fraietta JA, et al. *Blood*. 2016;127(9):1117-1127.

180

Ibrutinib May Enhance CLL Response to CTL019[1]

- Reduces immunosuppressive molecule expression on T cells and B-cell CLL cells (CD200)
- Does not impair CAR gene transfer, T-cell expansion, or cytotoxic capacity in vitro, and may limit Th2 activation in CTL019
- Enhances CTL019 expansion, results in better CLL killing and increased survival in murine models
- Ibrutinib plus CTL019 may be synergistic in CLL patients

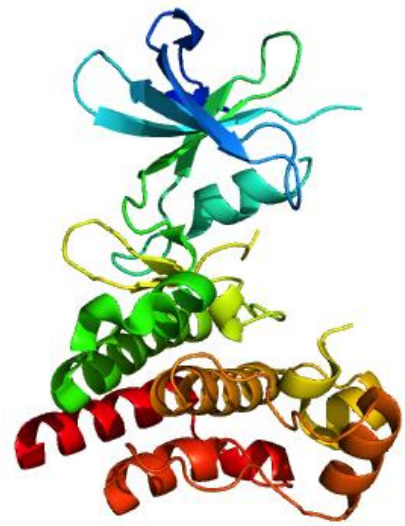


CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; Th2, type 2 helper T cell.
1. Reproduced from Fraietta JA, et al. *Blood*. 2016;127(9):1117-1127.

181

Hypothesis

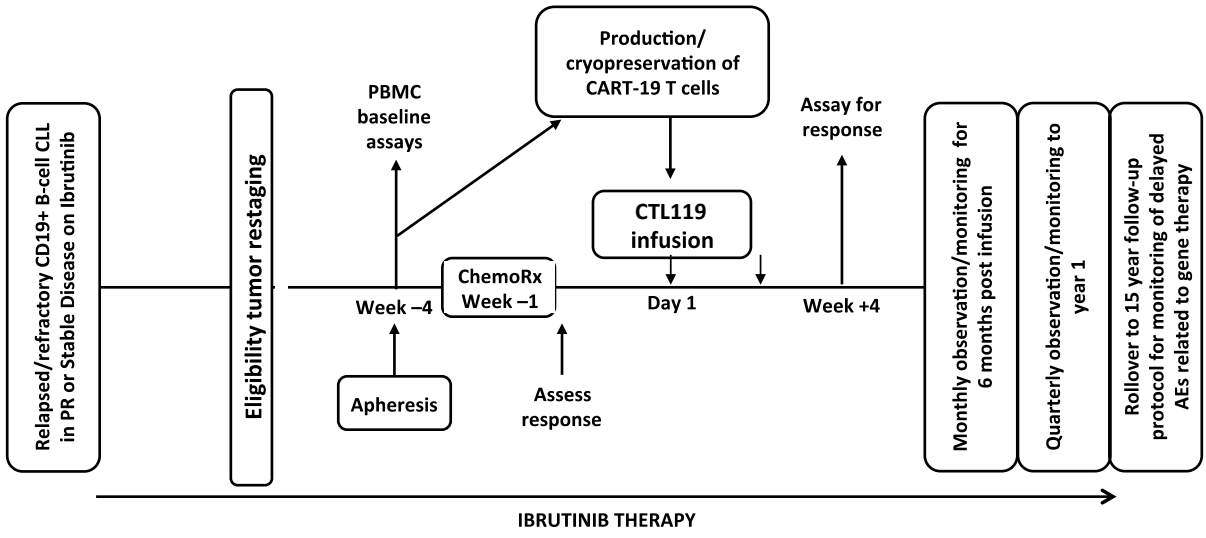
- Ibrutinib combined with CAR-T cells (CTL119) will improve clinical responses in patients with CLL



CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia.

182

Trial of ibrutinib Plus CTL119



AE, adverse event; CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; PBMC, peripheral blood mononuclear cell; Rx, therapy.

183

Ibrutinib and CTL119: Preliminary Data

- CTL119 (humanized CTL019/CART19)
- Target dose 5 x 10^8 CAR-T cells in split infusion (10%, 30%, 60%)
- Manufacturing successful in all patients
- 20 patients enrolled, 19 infused
  - 15 male, 4 female
  - Median age, 62 years
  - Median prior therapies, 2
  - TP53 or 17p abnormalities in 11 patients
  - Baseline marrow, 7% to 63% CLL (median 21%)
  - Median follow-up for 18 surviving patients, 18.5 months (8-28 months)

CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia.
Gill et al. ASH 2018. Abst 298; Unpublished data.

184

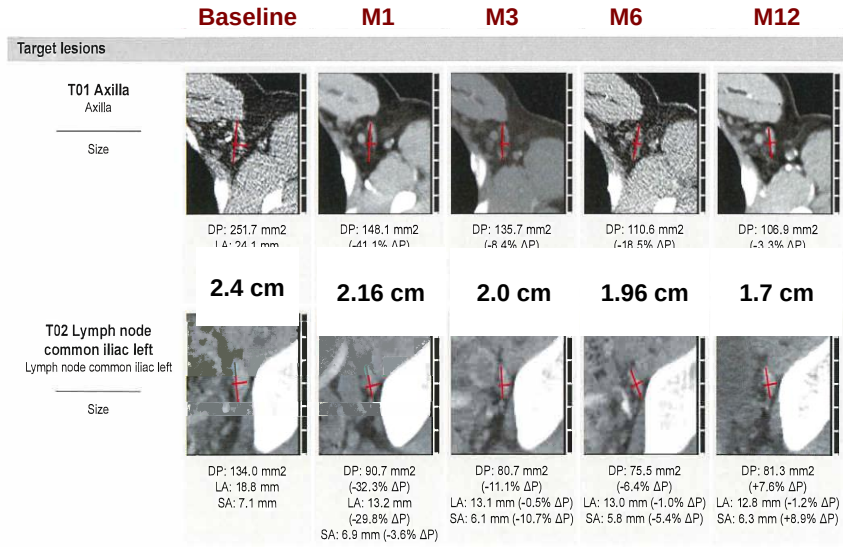
Ibrutinib and CTL119

- ORR at 3 months: 10/14 (71%)
- CR 3 months: 43% (6/14)
  - BM “CR”: 17/18 (94%)
- BM “CR” at 12 months: 10/11 (91%)
  - BM at 12 months MRD negative by NGS: 7/11 (64%)
- Several patients with stable or residual splenomegaly and/or adenopathy of unknown significance
- 16/18 remain in morphologic and/or flow CR at last follow-up

BM, bone marrow; CLL, chronic lymphocytic leukemia; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, objective response rate.
Gill et al. ASH 2018. Abst 298.

185

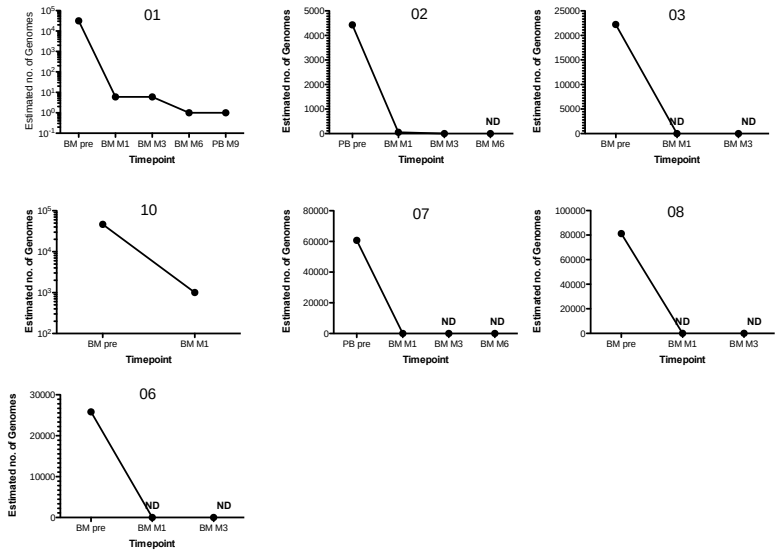
Efficacy: Imaging UPN 07: BM MRD-negative



BM, bone marrow; MRD, minimal residual disease. Gill et al. ASH 2018. Abst 298.

186

MRD by NGS



MRD, minimal residual disease; NGS, next-generation sequencing. Gill et al. ASH 2018. Abst 298.

187

Conclusions: CAR-T and ibrutinib

- Studied in patients not achieving CR despite at least 6 months of ibrutinib who were treated with humanized CART19
- iwCLL CR rate of 43%
- Bone marrow remission rate of 94%, including a 78% MRD-negative response by deep sequencing at 3 months
- This compares favorably to prior CART19 cell studies in patients with progressive CLL (iwCLL with CR rates of 21%-35%)
- CRS was frequent but mild-moderate and did not commonly require anticytokine therapy

CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CR, complete response; CRS, cytokine release syndrome; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease.

188

CAR-T cells and ibrutinib in CLL: ASH 2018

Abstract	CAR	N	Outcome
Gill (Penn) #298	CTL119 with ibrutinib for minimum 6 mo	20	ORR/CR 71%/43% BM CR 94%
Gauthier (Seattle) #299	JCAR14 Prog on Ibrutinib Min 2 wk Ib Compared to no Ib	17 w Ib 19 w/o Ib	ORR 88% vs 56% BM CR 75% vs 65%
Siddiqi (COH/Juno) #300	JCAR17 Previous Ib	10	iORR/CR 75%/50% MRD neg 6/7 pts tested

BM, bone marrow; CAR-T, chimeric antigen receptor-T; CLL, chronic lymphocytic leukemia; CR, complete response; MRD, minimal residual disease; ORR, overall response rate.

189

Future Possibilities for CAR-T cells for CLL

- CAR-T cells for multiply relapsed and refractory CLL patients
- CAR-T cells as early line (1st? 2nd? 3rd?) instead of other biological therapies because
  - Short-term treatment (“once and done”); no maintenance needed
  - **High rate of MRD-negativity (in CLL, MRD negativity may correlate with long-term PFS)**
  - Overall, may be financially preferable to years of expensive therapies
- CAR-T cells for patients not likely to respond to other therapies (ie, BTK mutations, ibrutinib resistance)
- Incorporate CAR-T cells in initial therapy with goal to cure CLL!

- **Future CAR-T cells: 2023**
  - Will be routine for B-cell malignancies including CLL, with defined dose and schedule of administration and readily identifiable patients most likely to benefit
  - Will have a defined product composition based on T-cell function and phenotype (Tcm?)
  - Will be combined with immune modifiers
  - Will have on and off switches

CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; MRD, minimal residual disease; PFS, progression-free survival; Tcm, central memory T cell.

190

Cell Therapy at Penn

It takes a village

Or a city

Penn, University of Pennsylvania.

191

Colleagues and Collaborators (too many to list)

ACC Translational Research
Carl June
Michael Milone
Carmine Carpenito
Anne Chew
Lester Lledo
Elizabeth Veloso
Joan Gilmore
Holly McConville
James Capobiancci
Amy Marshall
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Selina Luger
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January Salas McKee
Matt O'Rourke
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CTL019 Development Team

Study Participants

DSMC Members

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Questions and Discussion

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MEET THE EXPERTS: ROUNDTABLE DISCUSSIONS

Getting Started/Setting up a CAR T program
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Understanding CAR T-cell Therapy As A Treatment Option for Blood Cancer Patients

Case Presentation

LLS Nashville 06 21 2019

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Initial Presentation

- 29-year-old female
- Presented at outside hospital in 1/2017 with pericardial tamponade
- Found to have:
  - Mediastinal/pericardial mass, measuring 11×13 cm.
  - Multiple liver lesions, largest 5.5×5.1×4.2.
  - Cardiomyopathy, EF of 40%.
- Biopsy revealed PMBCL

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EF, ejection fraction; PMBCL, primary mediastinal B-cell lymphoma.

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Initial Treatment

- Hospital course was complicated by:
  - Septic shock
  - Acute hypoxic respiratory failure
  - Left PCA distribution ischemic stroke
- Treated with first cycle of R-CHOP with 50% dose reductions in vincristine and doxorubicin
- After cycle 1 → EF recovered
- Given cycle 2 of R-CHOP

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PCA, posterior cerebral artery; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

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Initial Treatment

- Cycle 3 (3/2017) → chemotherapy was changed to DA-EPOCH-R Complicated by *Mycobacterium avium* infection
- Cycle 4 (4/2017) → DA-EPOCH-R
- PET → CR
- Cycle 5 (5/2017)
- Patient then declined further therapy

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DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; PET, positron emission tomography .

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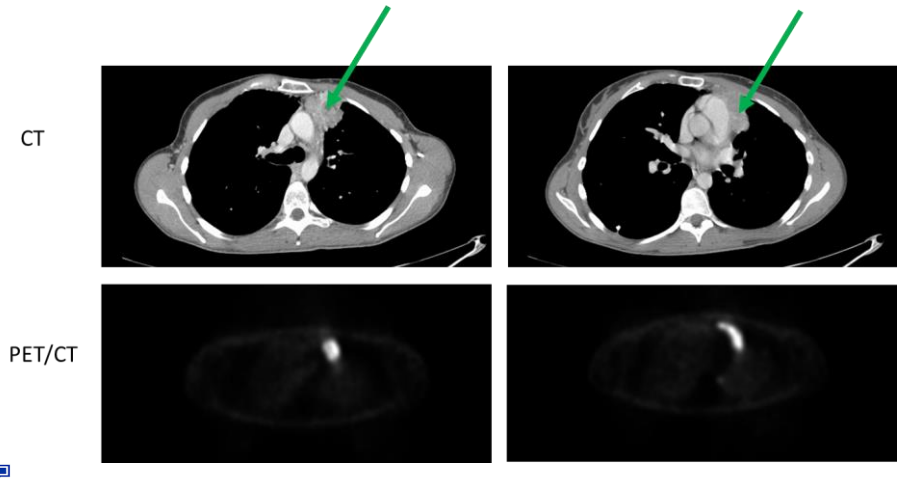
Follow-Up March 2018 (outside hospital)
Patient Denied Work-Up



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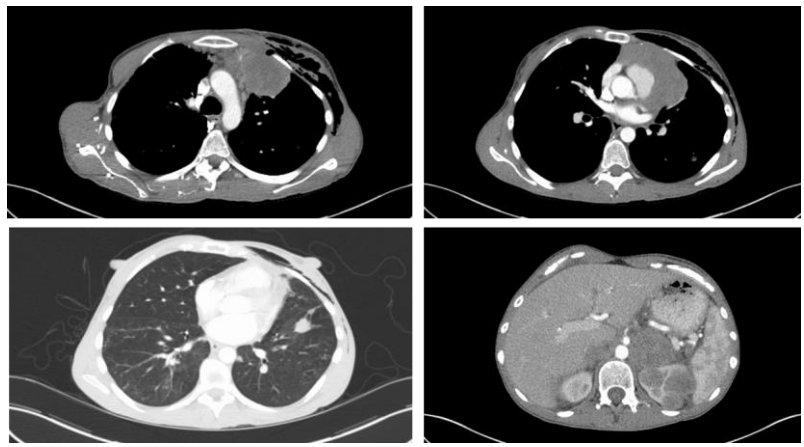
Follow-Up May 2018 (outside hospital)
Patient Agreed to Biopsy



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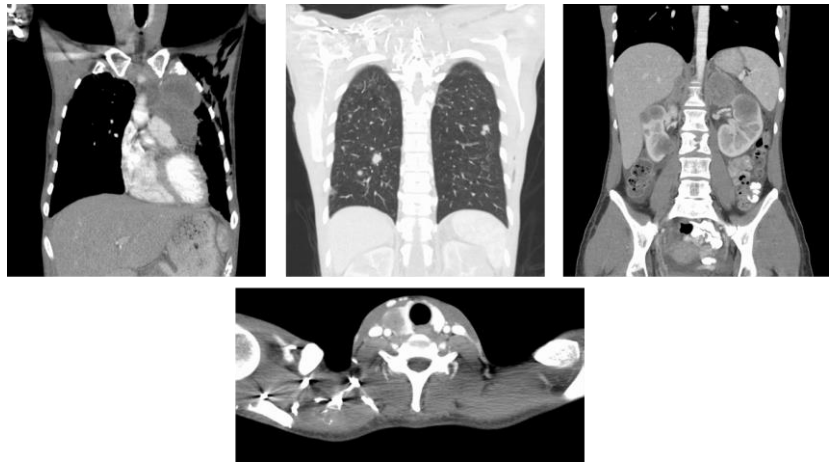
May 2018



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Subsequent Treatment at Outside Hospital

- Biopsy of mediastinal mass confirmed recurrent PMBCL
- Started on R-ICE C1 5/2018 with IT chemotherapy
- R-RICE C2 on 6/2018 with IT chemotherapy
- Auto collection performed
- PET/CT 7/2018 → persistent disease (Lugano 5)

RICE, rituximab, ifosfamide, carboplatin, and etoposide.

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Initial Referral

- Seen first in Markey Cancer Center in July 2018 for consideration of CAR-T cell therapy with CD19 directed axicabtagene ciloleucel
- Underwent lymphapheresis by end of July 2018
- MRI brain July 2018 showed chronic left-sided PCA infarct
- Bridging therapy with GemOx early Aug 2018

GemOx, rituximab plus gemcitabine-oxaliplatin.

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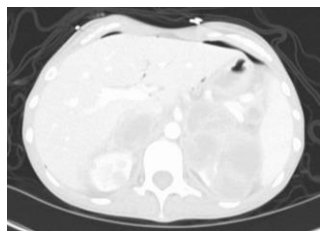
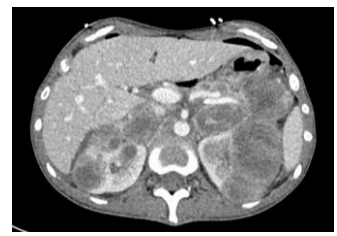
Course Prior to CAR-T

- Developed acute abdominal pain shortly after GemOx -> pneumoperitoneum





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Course Prior to CAR-T

- Discussions with surgery
- UGI series did not show contrast extravasations
- Decision on conservative management
- Discharged home 1 week later
- Initial cell manipulation failed; therefore tentative cell delivery pushed till end of Aug 2018

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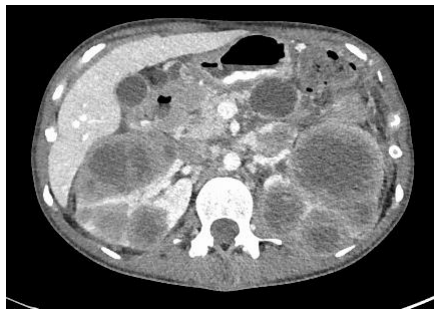
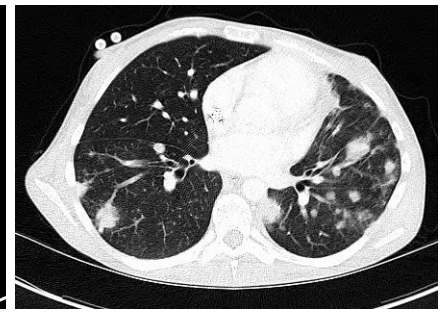
Course Prior to CAR-T

- Worsening symptoms in end of Aug 2018
- New scans with disease progression





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Course Prior to CAR-T

- Given dexamethasone 40 mg daily × 3 days
- Lymphodepleting chemotherapy with fludarabine and Cy given in end of Aug 2018
- Admitted in early Sep 2018 with fever, prostration, pneumonia and small pulmonary embolism
- CT chest with further disease progression
- CAR-T held due to active infection

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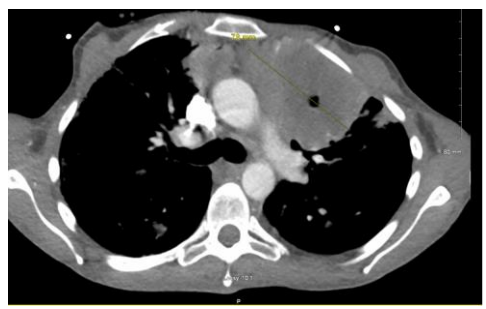

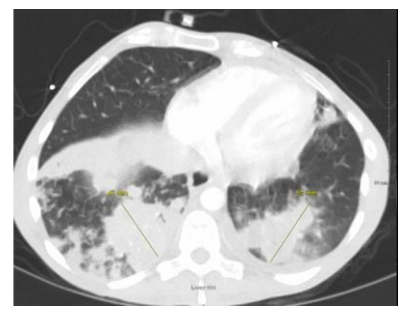

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So What To Do ?

- Patient specific challenges:
  - Hospice ?
  - Recent perforation ?
  - Deteriorating performance status ?
  - Active infection ?
  - Rapid disease progression
  - High patient expectation
- Patient specific challenges:
  - New CAR T program (first patient treated in August 2018)
  - Institutional anxiety
  - Team anxiety
  - Uncertainty on financial aspects
  - Outcomes?
  - Limited experiences?

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CAR-T Course

- Resolution of pneumonia with antibiotics
- Axicabtagene ciloleucel was given 12 days after Flu/Cy was completed (d0) (mid September 2018)
- Initially uncomplicated course
- On d+6, new anisocoria was noted
  - MRI brain showed new lesions
  - Intrathecal chemotherapy deferred due to concerns that intrathecal chemotherapy affects CAR T efficacy

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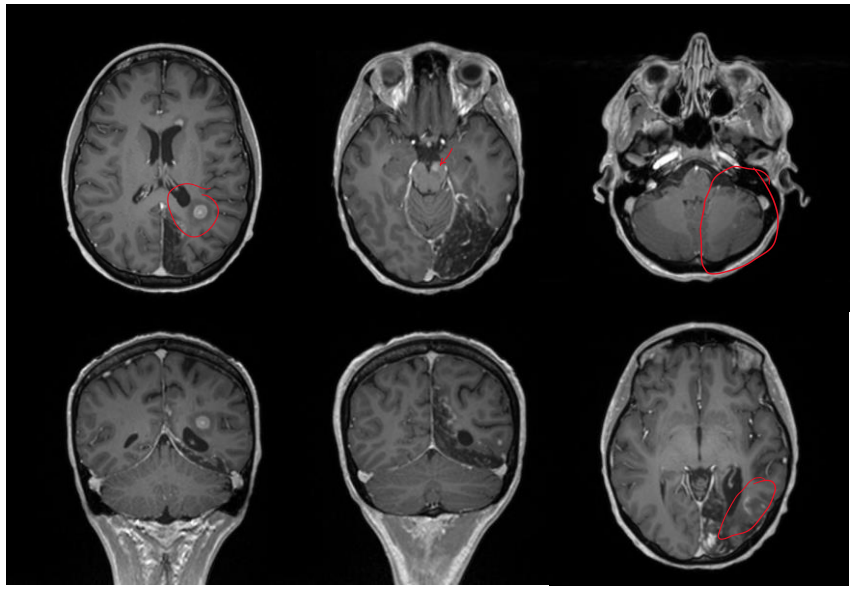


211

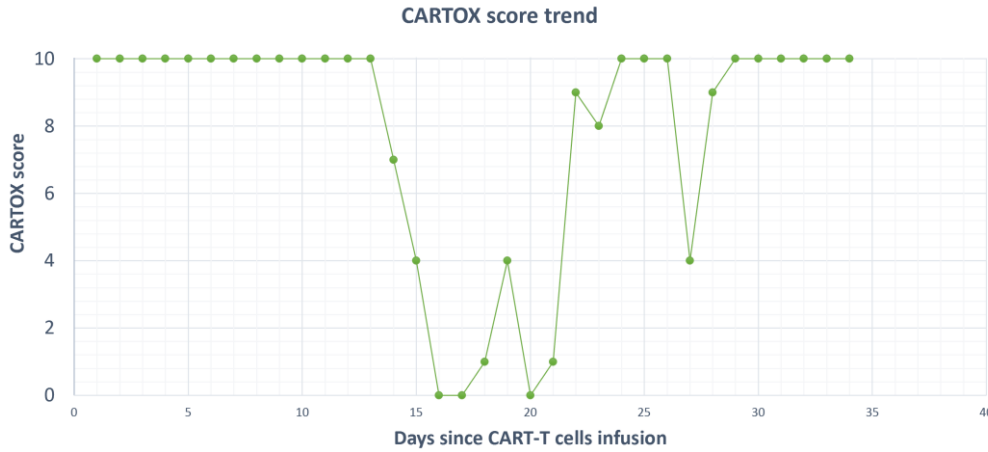
CAR-T Course

- LP deferred – patient declined
- Developed CRS grade I (d+7 to d+15)
  - △ No tocilizumab needed
- Developed CRES, up to grade III (d+14 to d+23).
  - △ Required 16 doses of dexamethasone
- Two doses of GCSF (d+23, d+24)
- Discharged on d+25
- Re-admitted d+26 to d+29 with grade III CRS

CRES, CAR-T cell-related encephalopathy syndrome; CRS, cytokine release syndrome.

212

CAR-T Course



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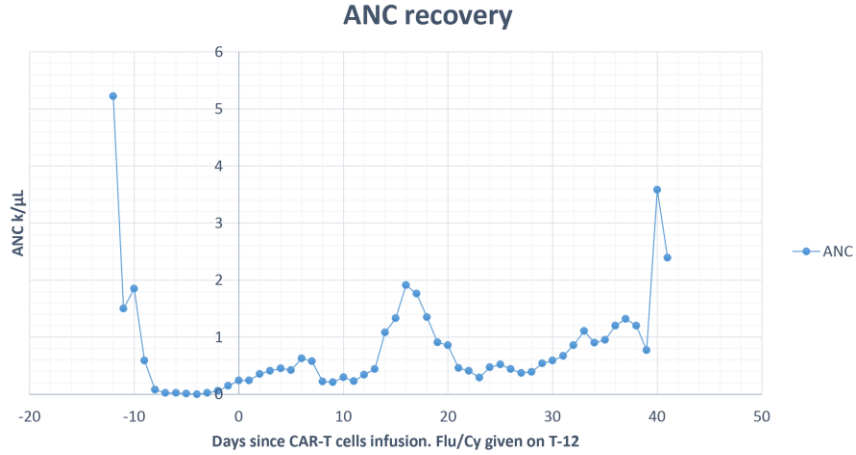
CAR-T Course



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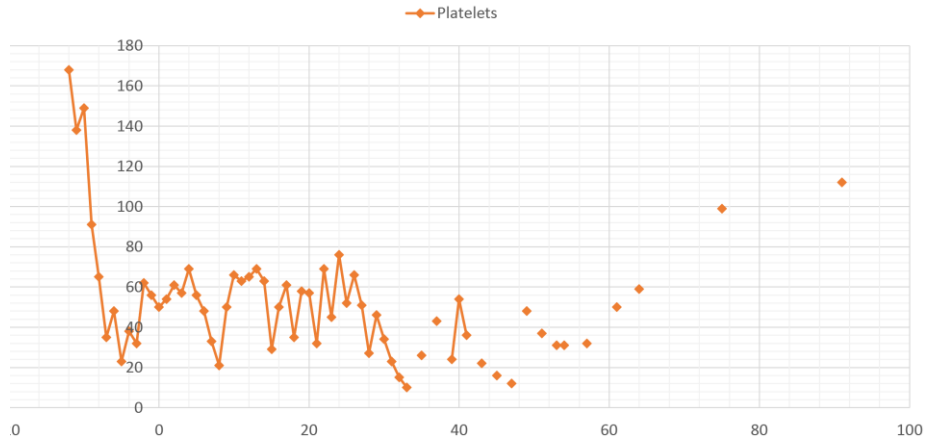
CAR-T Course



*Target goal: 50/nl due to anticoagulation for PE and GI bleed

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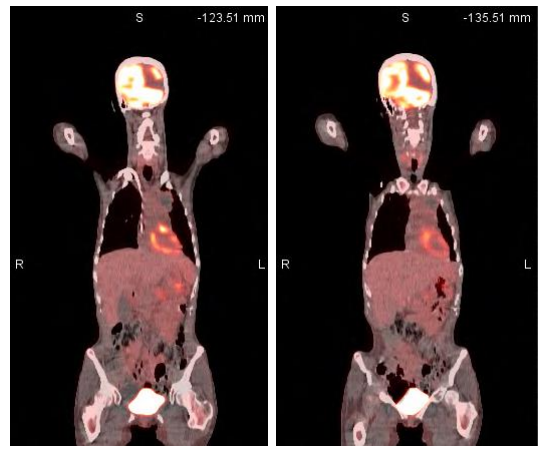
d+32 PET/CT



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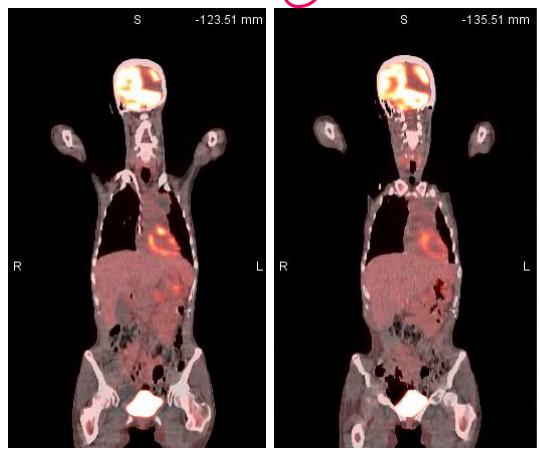
d+32 PET/CT

Lugano III



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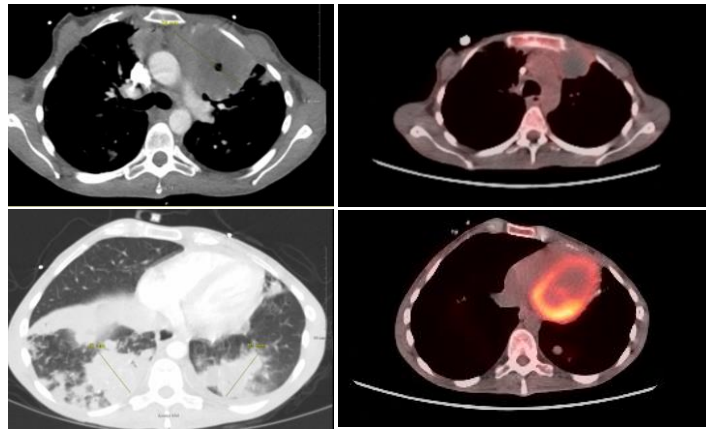
Comparison d+32 to prior

before

after



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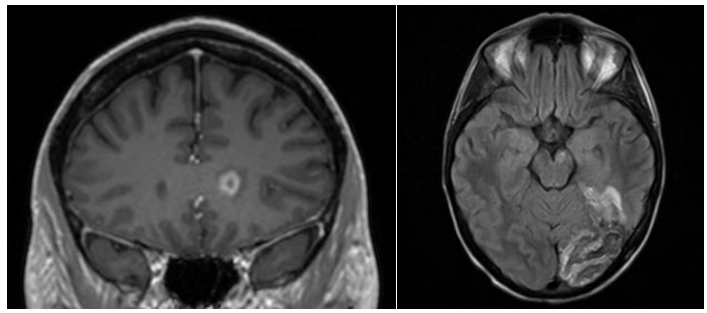
Post-CAR-T Course

- d+34 brain MRI showed a slight decrease in size of the lesions after CAR-T without CNS directed chemotherapy



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Post-CAR-T Course

- d+75 MRI brain
  - △ Further decrease in size of left parietal lobe lesion
  - △ Resolution of the left cerebral peduncle lesion
- Around days d+90 to 100, started having night sweats and itching
- PET/CT d+99 was obtained

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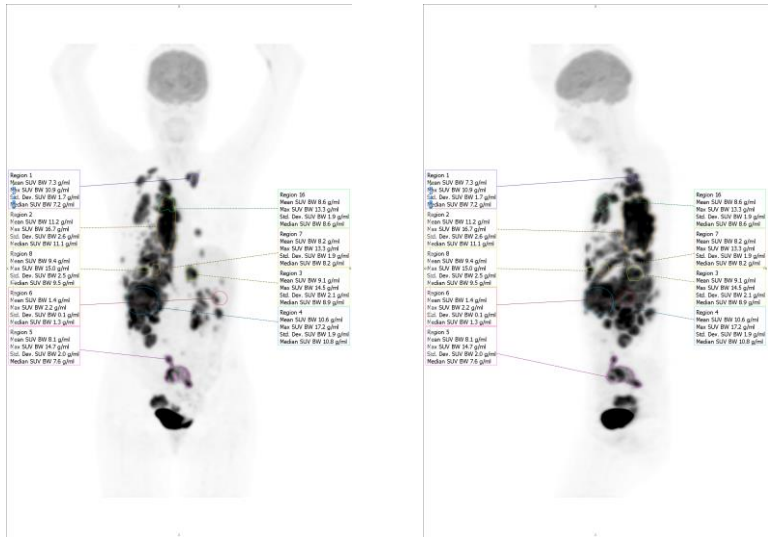

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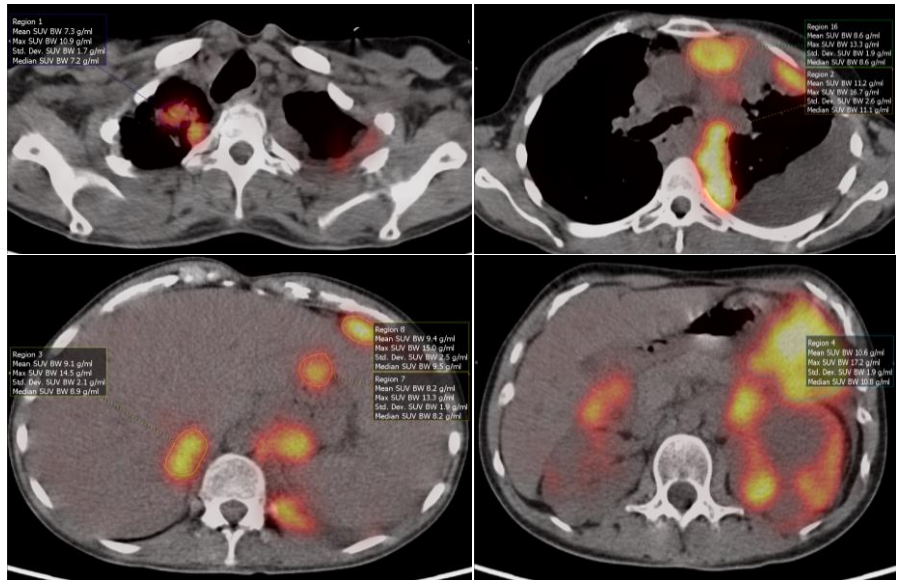

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Post-Relapse Course

- Off-label nivolumab 240 mg q2 weeks was started on d+112
- PET/CT and brain MRI repeated after 3 cycles

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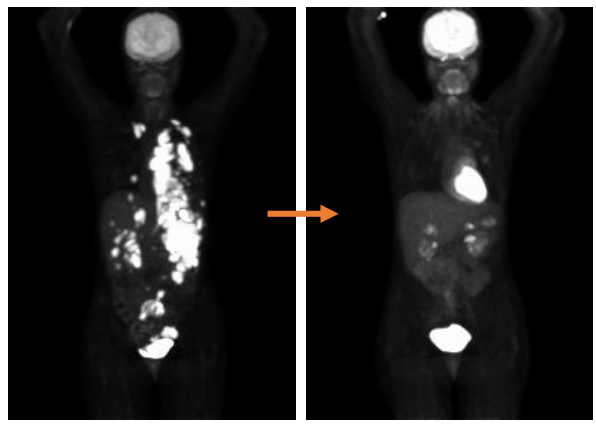
After 3 Cycles of nivolumab



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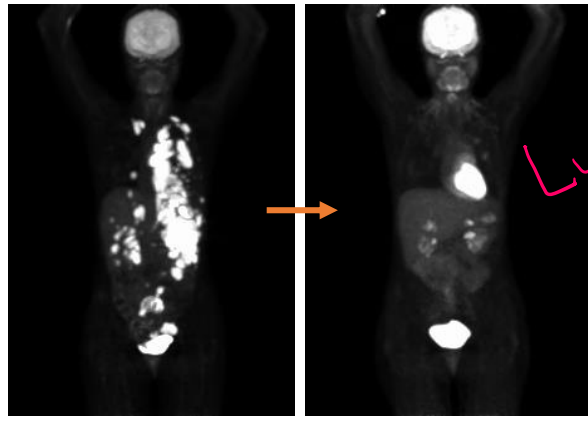
After 3 Cycles of nivolumab: PR



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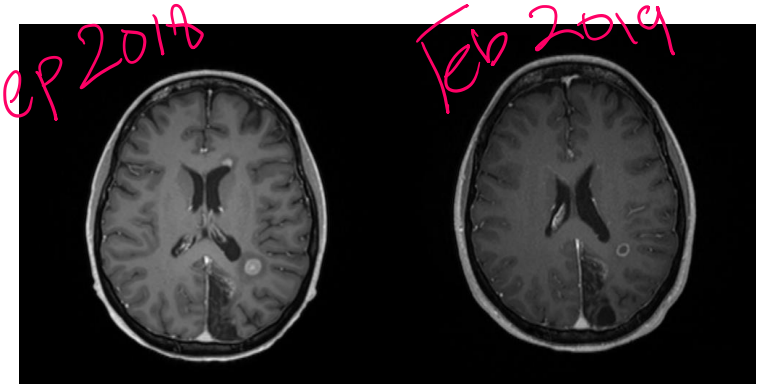
Post-relapse Course

- MRI with continued interval improvement in the left parietal lesion



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Post-Relapse Course

- Received 10 cycles of nivolumab so far, last in 5/2019
- Tolerated treatment well
- Plan for follow-up PET/CT and brain MRI
- Unfortunately, we did not check on CAR T persistence at time of nivolumab

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Summary

- CAR T cells can be effective in highly refractory disease
- Efficacy of CAR T for CNS disease has been reported, but experience is still limited
- It is not clear, whether post CAR T relapse management with checkpoint inhibitor results in response solely due to nivolumab or due to interactions between nivolumab and persisting CAR T
- CAR T cell patients are complex and need a multidisciplinary approach

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Thank you

- Our patients
- Hematology Program Markey Cancer Center
- University of Kentucky Health Care Business Partners
- All nurses, staff, fellows, pharmacists, physicians involved
- Dr. Qasrawi

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Case Presentation - Myeloma: Referral, Treatment and Follow-up

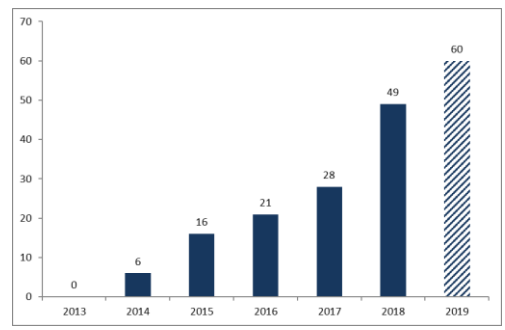
Luciano J. Costa, MD, PhD
Associate Professor of Medicine
University of Alabama at Birmingham
School of Medicine
Birmingham, AL

231

A Bit About Ourselves – UAB MM Program

- 4 core hematologists
- Comprehensive MM care
- ~300 individual patients/year
- 110 MM transplants/year
- Diverse clinical trials portfolio
- Emphasis on Phase 1, Phase 2, and immunotherapy trials

Accrual of MM patients to therapeutic trials



MM, multiple myeloma.

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Case #1 – "My Transplant Didn't Work"

42 yo, previously healthy

Presented with bone pain, found to have MM, ISS2, -13, del17p.
Serum M spike 3.4, IgGK

Managed in the community, ~4h from our center

1st line
Induction RVD x 4 (PR)-> ASCT (PR)-> KRd consolidation x3 (PD: 6 months post auto-HCT)

2nd line
DPd x3 (PD) – Sent for consideration of CAR T therapy

ASCT, autologous stem cell transplantation; DPd, daratumumab, pomalidomide, and dexamethasone; HCT, hematopoietic cell transplantation; IgGK, immunoglobulin G kappa; ISS2, International Staging System stage 2; KRd, carfilzomib, lenalidomide, and dexamethasone; PD, progressive disease; PR, partial response; RVD, lenalidomide, bortezomib, and dexamethasone.

233

Case #1 – "My Transplant Didn't Work"

ECOG is 0

Excellent organ function, excellent hematopoietic function

Secretory MM

No comorbidities

Excellent support system

Highly motivated

Myeloma rapidly progressing

ECOG, Eastern Cooperative Oncology Group.

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Case #1 – "My Transplant Didn't Work"

However…

Slot not immediately available

Trial requires at least 8 weeks off dara for cell collection

Other trials offered – rejected "I want CAR T"

Treated with conventional combination chemotherapy as "bridge"

Slot becomes available –> assigned to patient (at "top of list")

Responding to ongoing chemotherapy-> screen failure (not refractory), slot reassigned to other center 😟

Dara, daratumumab.

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Case #2 – "How Big is Your List?"

65 yo, hypertension, CHF, intermittent AFib on anticoagulation

Presented with anemia, found to have MM, ISS3, t(4;14). Serum M spike 5.7, IgGK

Managed in the community/academic center in neighboring state

1st line
Induction RVD x 4 (PR)-> ASCT (PR)-> R maintenance (PD after 18 months)

2nd line
Kd x1 – Not tolerated (dyspnea/ heart failure?)

3rd line
DPd (SD) – Pneumonia, ICU hospitalization, transient drop in EF, pacemaker/defibrillator.

4th line
IxaCyD (PD) – Referred for CAR T

AFib, atrial fibrillation; CHF, congestive heart failure; EF, ejection fraction; ICU, intensive care unit; ISS3, International Staging System stage 3; IxaCyD , Ixazomib –Cyclophosphamide-Dexamethasone; Kd , Carfilzomib - Dexamethasone SD, stable disease.

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Case #2 – "How Big is Your List?"

Patient had been in 3 other centers ("CAR Tour"); "complete workup" in two of the centers. Comes to clinic straight from airport

"Your program is smaller, so I thought I could get a higher place in your list"

ECOG is 1

Adequate EF, renal and hepatic function; excellent hematopoietic function

Secretory MM

Highly motivated

Myeloma rapidly progressing

237

Case #2 – "How Big is Your List?"

However…

Trial requires at least 4 weeks off anticoagulation

Mandatory brain MRI; however, pacemaker not MRI compatible

Patient disappointed. Refused other trials

Slot available, assigned to other patient

Return home to discuss stopping anticoagulation

MM progressed, renal deterioration, no longer a candidate

MRI, magnetic resonance imaging.

238

Cases #1 and #2 – Lessons Learned

"Slots" are the limiting factor

Patients not primarily managed at center – Need constant communication

Try to "sync" disease with eligibility/slot availability

Need to actively manage "wait list" – have a backup candidate

It is not for the fittest

It is not for the one who needs the most

It is for the one who can meet eligibility when slot available

239

Case #3 – "What's Next Doc?"

73 yo, HTN, BPH

Presented with anemia, hypercalcemia, bone lesions, found to have MM, ISS2, -13q. Serum M spike 2.8, IgGK

Managed in the community, locally

1st line
RVD x8 (SD)

2nd line
Kd x 2 (SD)

3rd line
KCd x 4 (SD)

4th line
KRd x8 (VGPR)->ASCT->R
Progression after 2 years

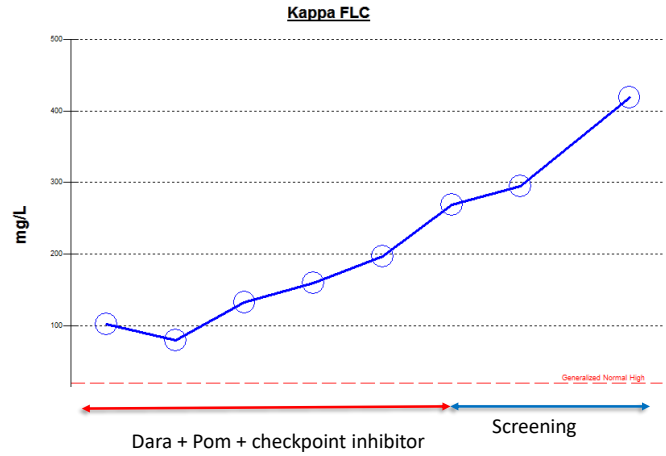
5th
Dara-Pom – Checkpoint inhibitor on trial (PR, then PD)

6th line
Consented for T cell engager trial, no slots

BPH, benign prostatic hyperplasia; Dara-Pom, daratumumab and pomalidomide; HTN, hypertension; KCd, carfilzomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response.

240

Case #3 – "What's Next Doc?"



FLC, free light chain.

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Case #3 – "What's Next Doc?"

Patient had never heard about CAR T-cells

"I will do what you tell me is best, doc"

ECOG is 1, yet sedentary, now 77 yo

Neuropathy grade 1-2 on gabapentin, chronic pain on narcotics

Prior DVT while on IMiDs, discontinued once pomalidomide interrupted

Secretory MM

Good family support

Myeloma slowly progressing

DVT, deep vein thrombosis; IMiDs, immunomodulatory drugs.

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Case #3 – "What's Next Doc?"

Despite being older, relatively frail, patient met eligibility

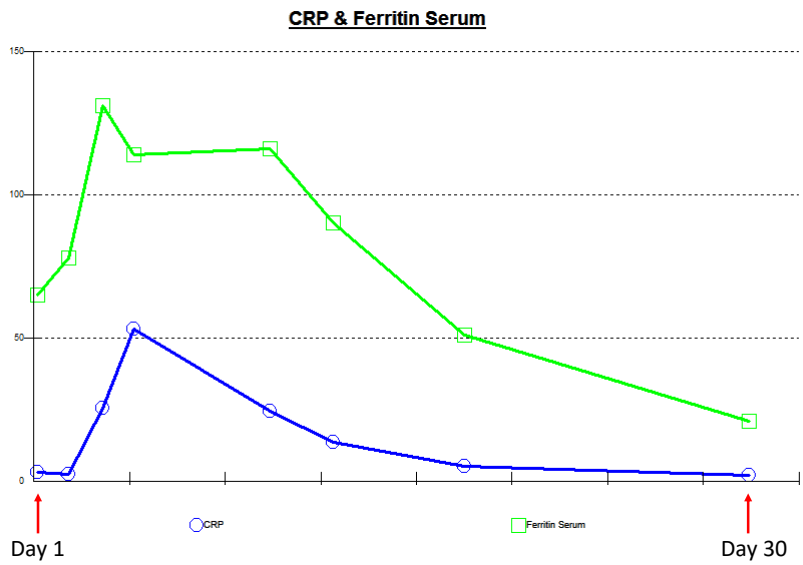
Successfully collected cells

Due to relatively slow pace of progression, no bridging chemotherapy employed

Patient tolerated well lymphodepleting chemotherapy (outpatient)

Admitted electively for infusion of cellular product and short-term monitoring of toxicities

243



CRP, C-reactive protein.

244

Case #3 – "What's Next Doc?"

Admission for 6 days for infusion and observation of early CRS

Patient had mild confusion, lethargy; traced back to attempts to optimize neuropathy meds.

No fever

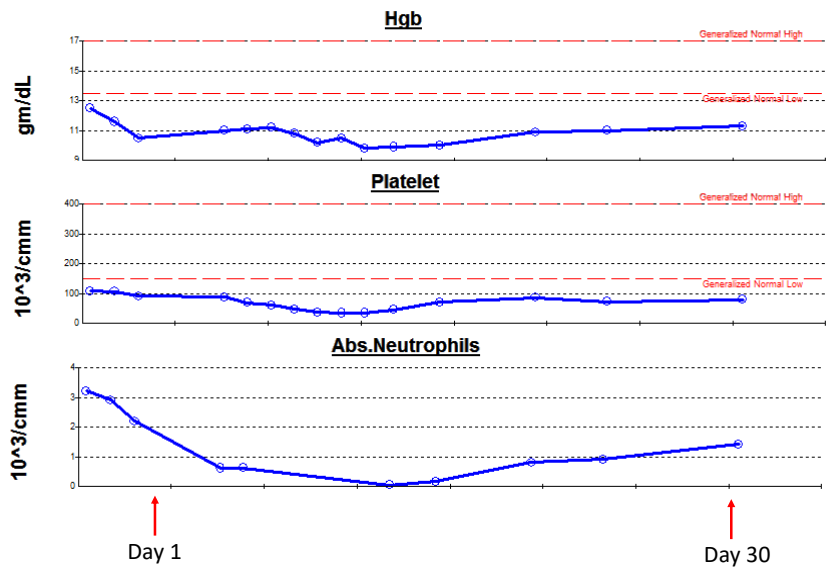
No infection

No transfusions

Transitioned to outpatient follow-up in cell therapy unit, initially twice a week, then once a week

CRS, cytokine release syndrome.

245



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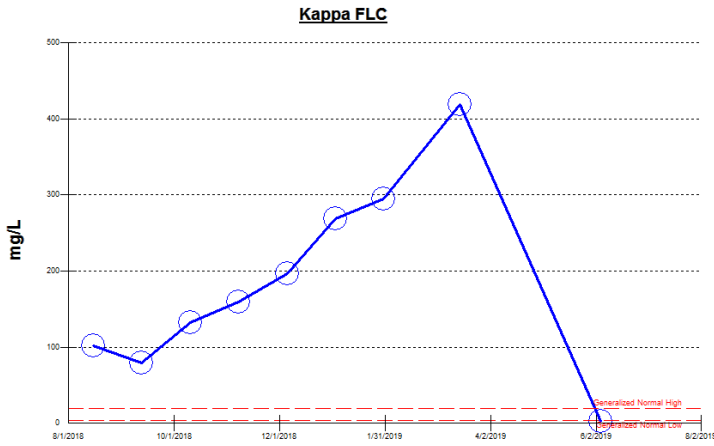

Marrow with <u>no plasma cells</u> on day 30

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Cases #3 – Lessons Learned

Integrate CAR T program with other institutional efforts
- Noncellular therapy trials
- Stem cell transplant program

Combat-proven warriors!

Disease burden and disease kinetics should inform your plan. (We get it wrong at times!)

Sometimes we get lucky – but we should not count on it

Unprecedented need for communication of oversight – we are <u>all</u> only starting to climb the learning curve

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Thank You!

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(205) 934-9695

@End_myeloma

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Getting You Ready for CART and Getting CART Ready for You

Edmund K. Waller , MD. PhD, FACP
Professor of Medicine
Medical Oncology and Pathology Director
Winship Cancer Center
Emory University
Atlanta, GA

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Don’t pass “GO” and you will lose money!

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Preparing the Institution for CAR T-cell Therapy

Financial & Reimbursements

- Aligning clinical practice to FDA label indications
- Negotiating with payors
- Dealing with the problem of Medicare patients

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Putting Together the CART Pit Crew

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Who is on the CART Team?

- Physicians
  - Become thoroughly educated in CAR T-cell therapy and AE management
  - Effectively communicate all aspects of CAR T-cell therapy to patients and families
  - Complete REMS training
  - Attend multidisciplinary team meetings
- Advanced Practice Providers
  - Become thoroughly educated in CAR T-cell therapy and AE management
  - Effectively communicate all aspects of CAR T-cell therapy to patients and families
  - Complete REMS training
  - Attend multidisciplinary team meetings
- Students and Trainees
  - Understand the principles of CART therapy
  - Close supervision if they are helping to grade CRS and Neurotoxicity
  - Identifying opportunities for research

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Who is on the CART Team?

- Nursing
  - Become thoroughly educated in CAR T-cell therapy and AE management
  - Effectively communicate all aspects of CAR T-cell therapy to patients and families
  - Undergo refresher training while on duty when patients are treated with CAR T cells
  - Attend multidisciplinary team meetings
- Emergency department and intensive care unit
  - Recognize the unique needs of patients receiving CAR T-cell therapy
  - Do not administer steroids
  - Follow CRS management algorithm and administer tocilizumab when needed
  - Attend multidisciplinary team meetings
- Pharmacy
  - Prepare plans for lymphodepleting chemotherapy and stock anti-cytokine therapy
  - Awareness of each CART patient to manage side effects
  - Attend multidisciplinary team meetings
- Social workers
  - Arrange lodging, transportation, and reimbursement
  - Provide emotional support
  - Attend multidisciplinary team meetings

Obtaining the Effector Cells for CAR T-cell Therapy

- Leukapheresis
- What is the target number of lymphocytes?
- Calculating the apheresis volume: how much is enough?
- The special case of lymphopenia

Pushing the CART "Go" Button For an Individual Patient

Managing patients during the intake process

- Insurance benefits pre-screening
- Timing of apheresis
  - To freeze or not to freeze
  - The problem of senescent T cells
- In-patient versus out-patient lympho-depleting chemotherapy

Coordination With the Manufacturing Facility

- Scheduling apheresis
- Shipping cells
- Waiting in line!
- Manufacturing
- Receipt of cells

Managing the CART In-Patient

- Developing a cellular therapy in-patient team
- REMS- who is the Authorized Representative?
- Discharge instructions

Managing the CART Out-Patient

- When to discharge?
- Instructions to the ER
- Instructions to the patient
- How to triage phone calls
- Atlanta traffic- how far is too far?

From Leukapheresis to CAR T-cell Infusion: Bridging Chemotherapy

- Lymphoma patients
- ALL patients
- How big is the window between bridging chemotherapy and CART?

Receipt of Manufactured CAR T-cell Products

- Receipt of CART product
- Cell therapy inventory management
- You break it you buy it!
- Where to thaw?

CART Infusion

- In-patient versus out-patient
- A note about filters
- Premeds- dos and don’ts
- Immediate toxicities

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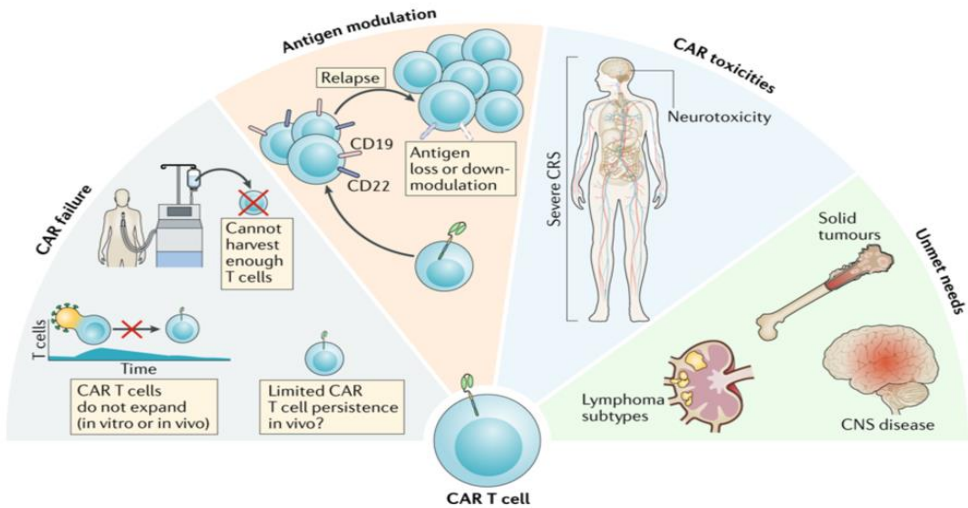
Limitations of CART Therapy



Shah and Fry Nat Rev Clin Oncol 2019.

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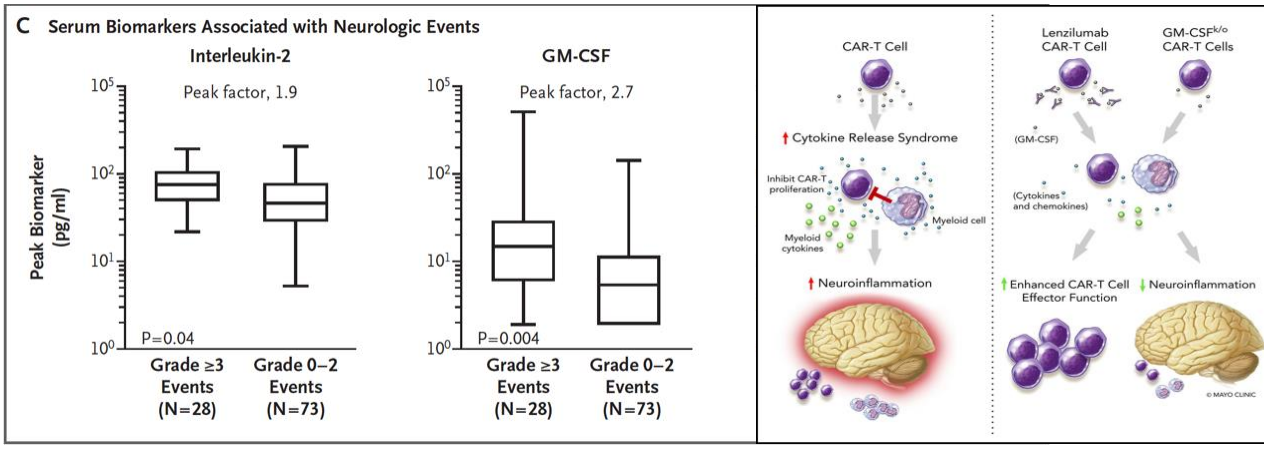
Cytokine Release Syndrome After CART

- Time course
- New grading scale
- Management: Anti-IL6 early and often
- Second line therapies

Neurotoxicity of CART

- Time course
- New grading scale
- Pathophysiology: is GM-CSF the key?
- Brand differences
- Treatment

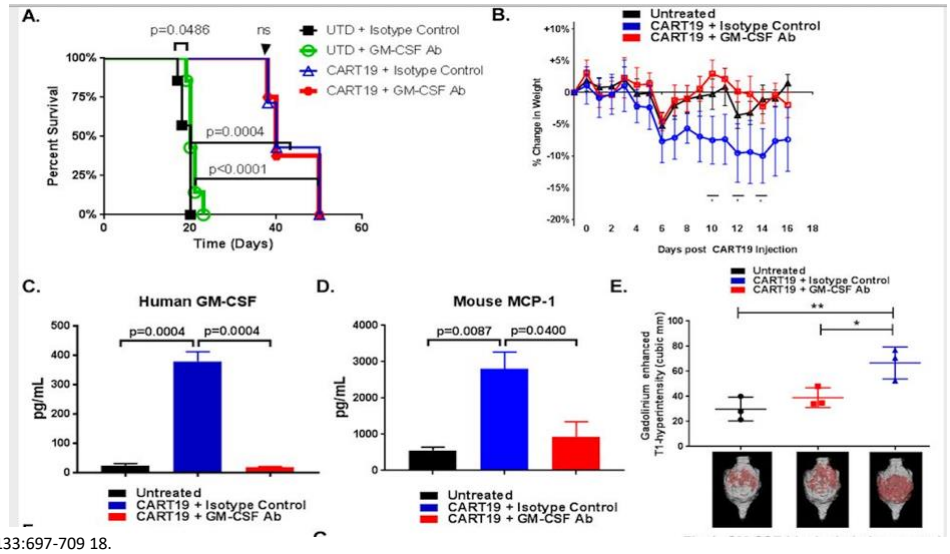
Blocking GM-CSF Signaling May Enhance CART Activity While Decreasing CRS



Neelapu 2017 NEJM 377:2531-2544; Sterner 2019 BLOOD 133:697-709 18.

267

Anti-GM-CSF Antibody Therapy Deceases Toxicity of CART Without Compromising Efficacy



Sterner 2019 BLOOD 133:697-709 18.

268

Managing the CART Patient

Planning for relapse

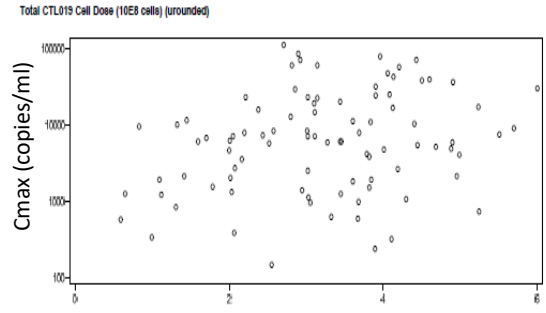
- Immune check-point blockade
- Small molecules that may enhance CART function
- CART re-treatment
- Is allo-transplant still an option?

What Can Be Done to Increase the Cell-Intrinsic Activity of CART therapy?

- Give more CART (with split dose to limit toxicity)
- Collect T cells earlier in the disease course, before they become senescent (Belinda and Transform trials)
- Improve manufacturing process- shorter expansion cultures with less senescence
- Immune check-point drugs to block co-inhibitory pathways
- TKI treatment to change metabolic profile of CART *in vivo*
- Next generation of dual CAR T, armored CART, etc…

Infusing larger numbers of Tisagenlecleucel did not increase *in vivo* expansion or response

Dose (0.6-6.0 × 10^8 CAR positive viable T cells)[a]



Exposure (maximal expansion from qPCR data)

Dose and exposure were independent

Awasthi 2018 BLOOD 132:899.

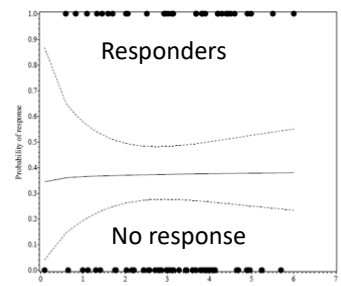
[a]1 patient received a dose < 0.6 × 10^8 CAR positive viable T cells.

271

Infusing larger numbers of Tisagenlecleucel did not increase *in vivo* expansion or response

Dose (0.6-6.0 × 10^8 CAR positive viable T cells)[a]

Response (Tumor response at month 3)



Responses were observed across full range of doses

Awasthi 2018 BLOOD 132:899.

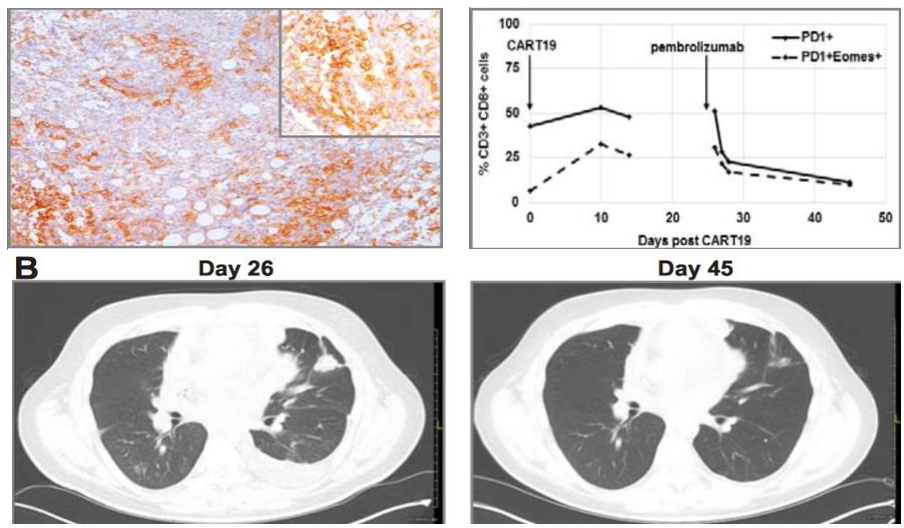
272

How to Manage DLBCL Relapsed After CART?

- Poor performance status and cytopenia's limit options: expect <25% survival
- Consider clinical trial
- Immune check-point blockade
- Rituximab and lenalidomide
- TKI: Ibrutinib, ?PI3K inhibitors
- Allo-transplant for fit patients with limited disease burden
- Involved field radiation

273

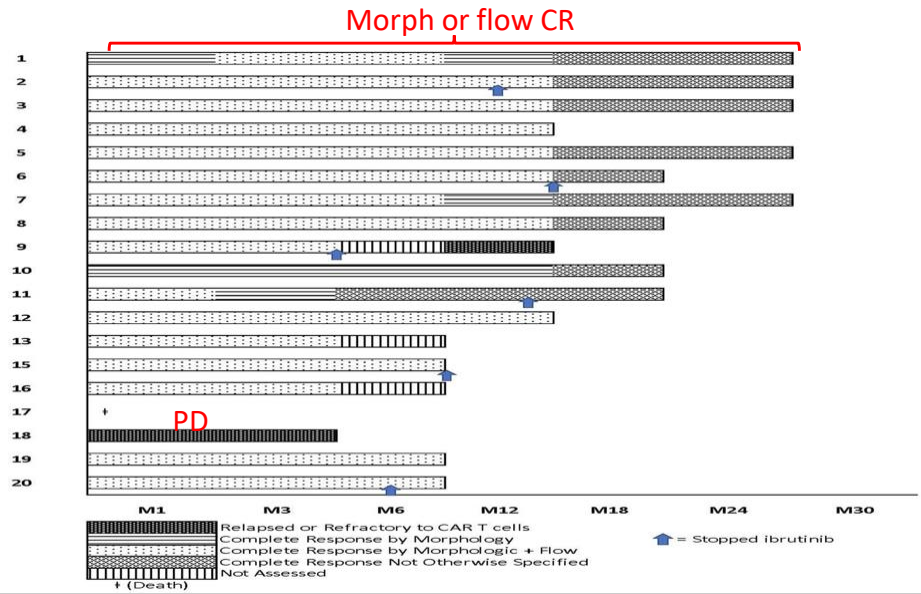
Anti-PD1 Pembrolizumab Therapy in a PDL1+ NHL Patient Relapsing After CART Infusion



Chong 2016 BLOOD 132:4198.

274

Prospective Clinical Trial of Anti-CD19 CAR T Cells in Combination with Ibrutinib for CLL



Gill BLOOD 2018
BLOOD 132:298.

275

Do anti-CART Immune Responses Affect CTL019 CART Efficacy?
Data from the Juliet tisagenlecleucel study

- No apparent impact of anti-CART humoral and cellular immunogenicity on exposure and response was observed
- Treatment-induced anti-mCAR antibodies were observed in 5% of the patients
- Pre-existing humoral immunity did not appear to impact duration of response
- T cell responses were consistent over time, and no impact on transgene expansion or patient outcome was observed.

Awasthi 2018 BLOOD 132:899.

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276

T cell phenotype and CART expansion and persistence

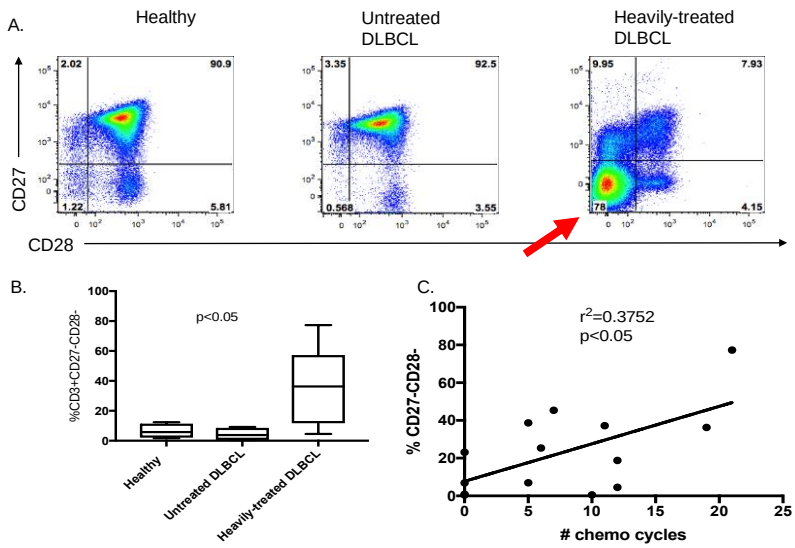
	T_N	T_{SCM}	T_{CM}	T_{EM}	T_{eff}
CD45RA	+	+	-	-	+
CD45RO	-	-	+	+	-
CCR7	+	+	+	-	-
CD27	+	+	+	-	-
CD28	+	+	+	-	-

Short lived
Terminally differentiated
Glycolytic metabolism

Long lived
Proliferative capacity
Oxidative metabolism

277

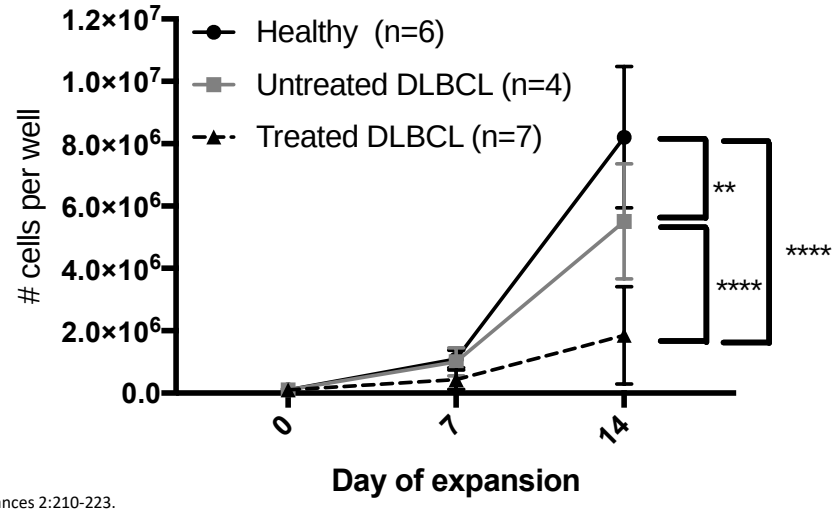
T cells from DLBCL patients show loss of CD27 and CD28



Petersen 2018 Blood Advances 2:210-223

278

T cells from heavily pre-treated DLBCL patients have decreased ex vivo growth



Petersen 2018 Blood Advances 2:210-223.

279

How Might Manufacturing of CART be Improved?

BEATING CANCER IS IN OUR BLOOD.

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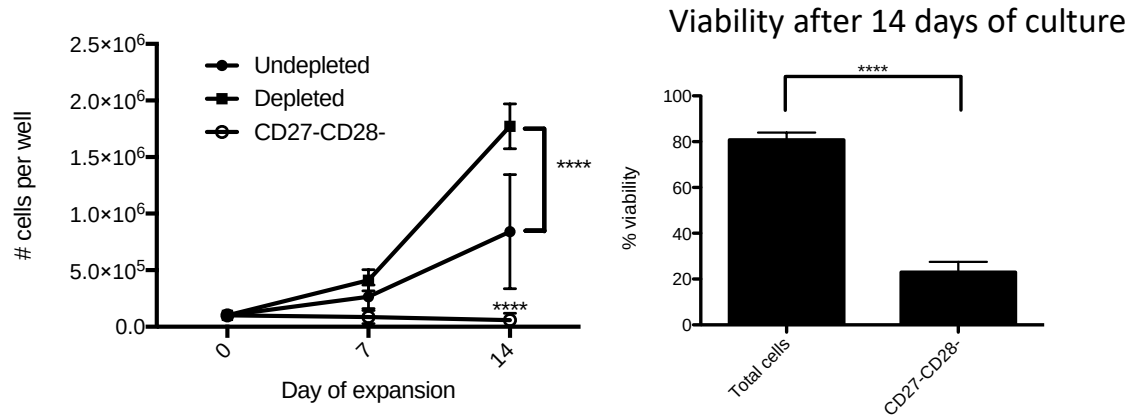
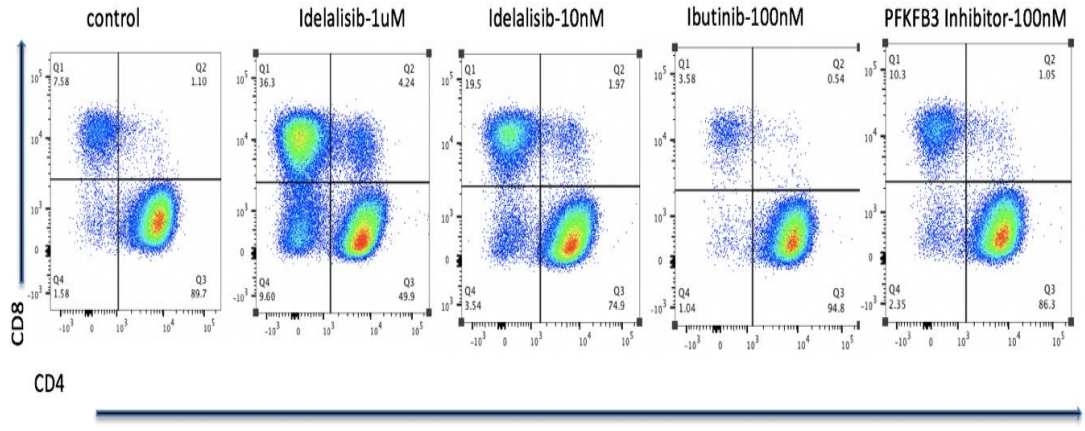
Depletion of CD27-CD28- Cells Improves the Expansion of T cells From DLBCL Patients



Petersen 2018 Blood Advances 2:210-223.

281

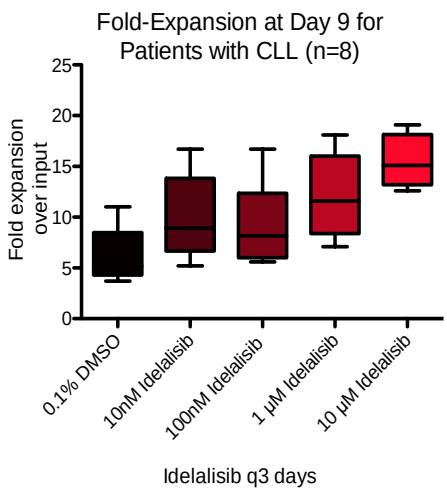
PI3Ki added to expansion cultures increased CD8+ T cell frequencies

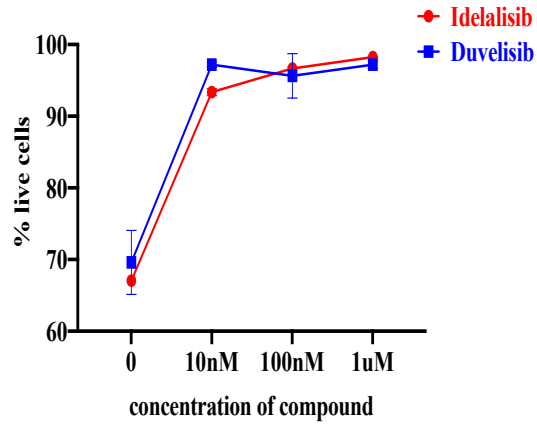


PI3Ki, phosphatidylinositol 3-kinase inhibitor.
Funk, Waller, and Waller, 2019 Regenerative Medicine Workshop Charleston SC.

282

PI3Ki enhanced expansion of viable T cells from CLL patients

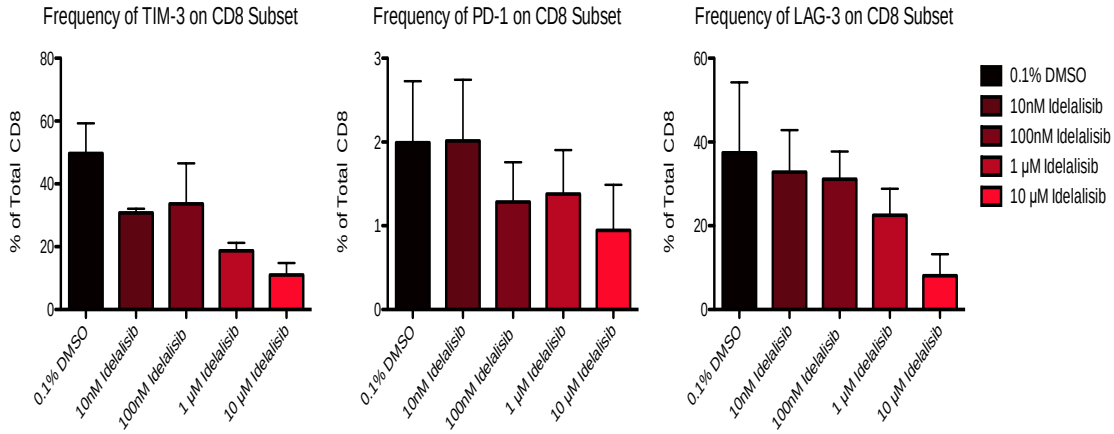




Funk, Waller, and Waller, 2019 Regenerative Medicine Workshop Charleston SC.

283

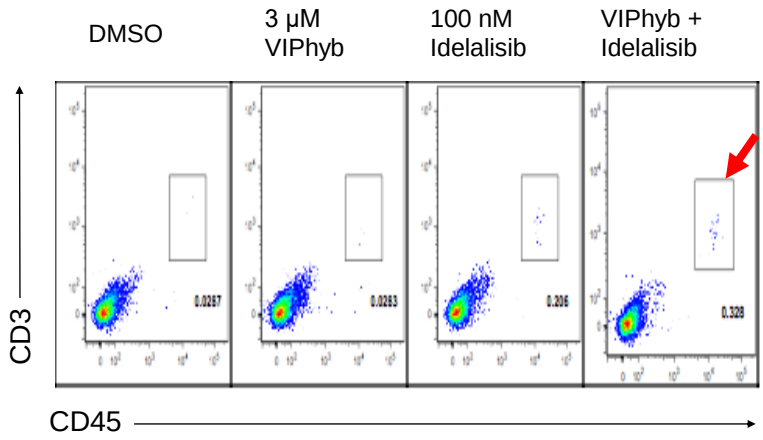
PI3Ki during T cell expansion decreased T cell expression of immune checkpoints in CLL patients

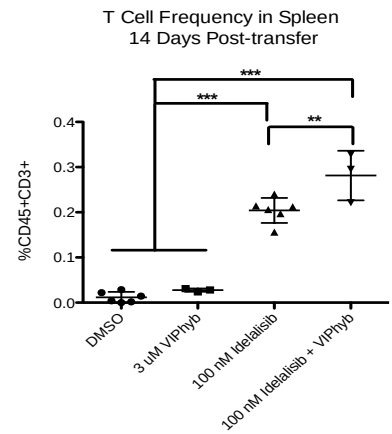


Funk, Waller, and Waller, 2019 Regenerative Medicine Workshop Charleston SC.

284

Improved *in vivo P*ersistence of Human T cells from DLBCL Patient Expanded with Idelalisib and VIP antagonist





Petersen 2018 Blood Advances 2:210-223.

285

ewaller@emory.edu

286

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Commercial CAR-T Coverage and Reimbursement: What a Clinician Needs to Know

C. Fred LeMaistre, MD
Physician-in-Chief Hematology
Senior Vice President, Market Operations
Sarah Cannon

287

WHY IS CAR-T REIMBURSEMENT IMPORTANT?

- 475+ cell and gene therapy companies in North America.
- ~ $20 billion in cell therapy deals, IPOs of ~ $1 billion and ~ $750 million in ~ company series funding.
- 400+ cell therapy partnerships related to development, commercialization, manufacturing.
- ~85 new cell therapy trials in 2018 in the US; > 400+ trials . ***By 2020, > 200 INDs per year; By 2025, FDA will be approving 10 to 20 cell and gene therapy products a year.***
- ***IECT will cause significant erosion in HCT, especially autologous HCT.***
- ***Hospitals are currently being asked to absorb the costs of commercial products.***

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IECT- IMMUNE EFFECTOR CELL THERAPY
https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics

288

OBJECTIVES

Are FDA-approved CAR-T products covered?	• Commercial Payers • Medicare • CMS CAR-T NCA
How are FDA- approved CAR-T products reimbursed?	• Commercial Payers • Medicare
SCBCN	• Our network structure • How we implemented commercial CAR-T

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ARE FDA-APPROVED CAR-T PRODUCTS COVERED?

290

TWO FDA APPROVED CAR T PRODUCTS

CAR T-cell therapy is only FDA approved for two indications:

- ≤ 25 years with acute lymphoblastic leukemia that is refractory or in 2nd or later relapse.
  Currently, fewer than 1 in 3 of these patients survive 5 years* $475,000
- ≥ 18 years and older with aggressive B-cell lymphoma that is refractory or in 2nd or later relapse.
  Palliative care is currently the only option for these patients* **$373,000**

- Commercial:
  - **Most** commercially insured patients have coverage for Yescarta® (*axicabtagene ciloleucel*) and/or Kymriah® (*tisagenlecleucel*)
  - May be limitations for specific plans and/or employer-sponsored groups (Experimental/Investigational denial may be attempted)
- Medicare:
  - In IPPS, it is a drug used in a part of a covered episode of care, i.e. an inpatient stay for treatment of lymphoma**
  - Q codes and payment for the OPPS setting

*INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW " *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value"*
***PPS exempt hospitals have a different payment mechanism*
IPPS - Inpatient Prospective Payment System; OPPS- Outpatient Prospective Payment System

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CMS COVERAGE PROPOSAL TO COVER AUTOLOGOUS T-CELLS WITH AT LEAST ONE CAR THROUGH CED

- Patient Must Have:
  - Relapsed or refractory cancer; and
  - Not currently experiencing any comorbidity that would preclude patient benefit
- Covered Indications:
  - FDA-approved indication furnished in a hospital that participates in a qualifying registry; OR
  - FDA-approved biological for use in the NCCN Drugs & Biologicals Compendium with grade 2 or after August 17 when patient enrolled in a CMS-approved clinical study
- Site of Service Requirements:
  - Has a Cellular Therapy Program
  - Has a designated care area
  - Written guidelines for patient communication, monitoring, and transfer to a ICU
- Coverage With Evidence Development (CED) Requirements:
  - Registries must be prospective, national, audited and approved by CMS
  - Accept all manufacture products and follow patient for 2 years
  - Answers specific questions with PRO for QOL and functional status for outpatients

https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=291

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How Are FDA Approved CAR-T Products Reimbursed?

293

CURRENT PAYMENT LANDSCAPE

	Inpatient	Outpatient hospital-based	Outpatient physician office
Commercial payers	• Case rate or SCA with % of billed • Drug cost as pass-through	• Case rate or SCA with % of billed • Drug cost as pass-through	• Not at this time - Biopharma & payers requiring FACT accreditation
Government	• DRG-based reimbursement ($39,000) • No additional drug payment except for NTAP, will cover up to 50% of drug cost • Depending on hospital charges the hospital may have the opportunity for outlier payment (chargemaster optics)	• Q code-based reimbursement – ASP + 6%. Drug cost covered. • Q code includes drug, leukapheresis and dose preparation procedures per infusion • Potential risk of admissions within 72 hours	• Not at this time - Biopharma requiring FACT accreditation

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294

TWO FDA APPROVED CAR T PRODUCTS

CAR T-cell therapy is only FDA approved for two indications:

- ≤ 25 years with acute lymphoblastic leukemia that is refractory or in 2nd or later relapse.
  Currently, fewer than 1 in 3 of these patients survive 5 years* $475,000
- ≥ 18 years and older with aggressive B-cell lymphoma that is refractory or in 2nd or later relapse.
  Palliative care is currently the only option for these patients* **$373,000**

- Inpatient CAR-T cases are grouped to MS-DRG 016 based on the presence of one of two CAR-T ICD-10-PCS codes (XW033C3 and XW043C3)

MS-DRG O16 Title	National Unadjusted PPS Payment*
Autologous Bone Marrow Transplant with CC/MCC or T-cell Immunotherapy	**$39,951**

- The national unadjusted PPS payment represents the payment amount before hospital specific adjustments are applied which will impact overall payment

- INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW " *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value*"
- *PPS exempt hospitals have a different payment mechanism*

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IPPS PAYMENT OVERVIEW

MS-DRG Unadjusted Payment + **NTAP Payment** + **Outlier Payment** = **Total Case Payment**

Both the NTAP and the outlier are dependent on the total billed charges for the case and the hospital's overall operating cost to charge ratio (CCR) which comes from each hospital's Medicare cost report.

The final MS-DRG payment is typically adjusted by one or more hospital specific factors such as the wage index, Indirect Medical Education (IME), and/or Disproportionate Share (DSH) as applicable

Source: Presentation by Jugna Shaw at the 2018 ASBMT BMT Administrator Meeting

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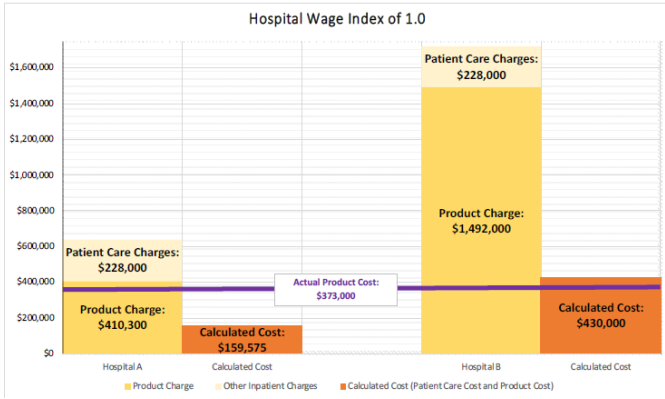
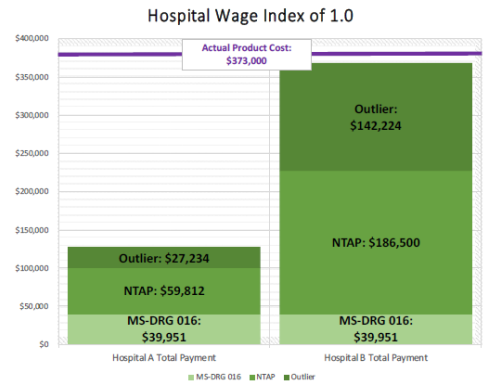
296

CALCULATED COST IMPACTS THE NTAP AND OUTLIER PAYMENT AMOUNTS RECEIVED





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PROPOSED FUTURE PAYMENT LANDSCAPE

	Inpatient	Outpatient hospital-based	Outpatient physician office
Commercial payers	• Included in your Program's master agreement with Payer • Drug cost remains a pass-through	• Included in your Program's master agreement with Payer • Drug cost remains a pass-through	• Not at this time - biopharma & payers requiring FACT accreditation
Government	• In 2020 IPPS, it will remain in MS-DRG 16 with a based reimbursement ($39,000) • No additional drug payment except for NTAP, will cover up to 65% of drug cost. NTAP goes away in Nov 2020. • Depending on hospital charges the hospital may have the opportunity for outlier payment (chargemaster optics)	• Q code-based reimbursement – ASP + 6%. Drug cost covered. • Q code includes drug, leukapheresis and dose preparation procedures per infusion • Potential risk of admissions within 72 hours	• Not at this time - biopharma requiring FACT accreditation

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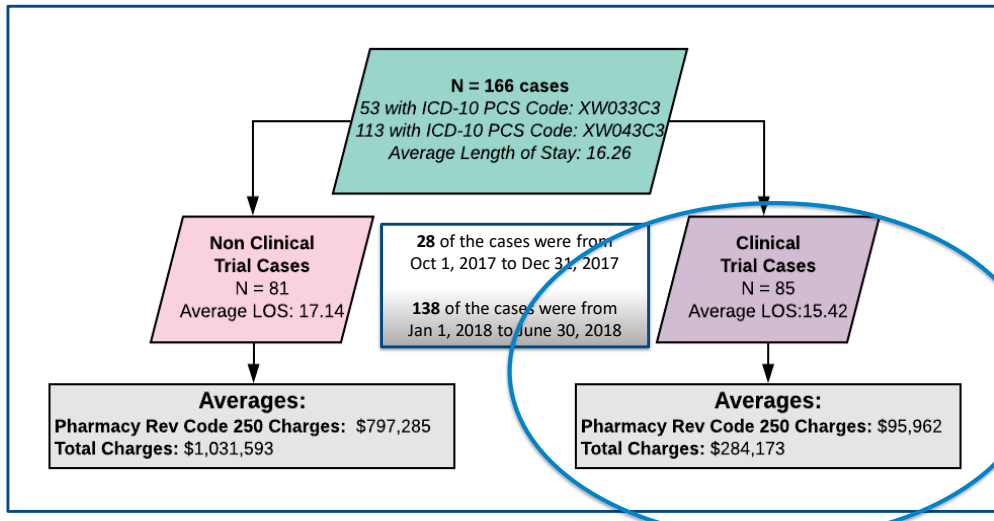
298

FY 2018 Medicare CAR-T Claims Data: What is Medicare Seeing?



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Source: Presentation by Jugna Shaw at the 2018 ASBMT BMT Administrator Meeting

299

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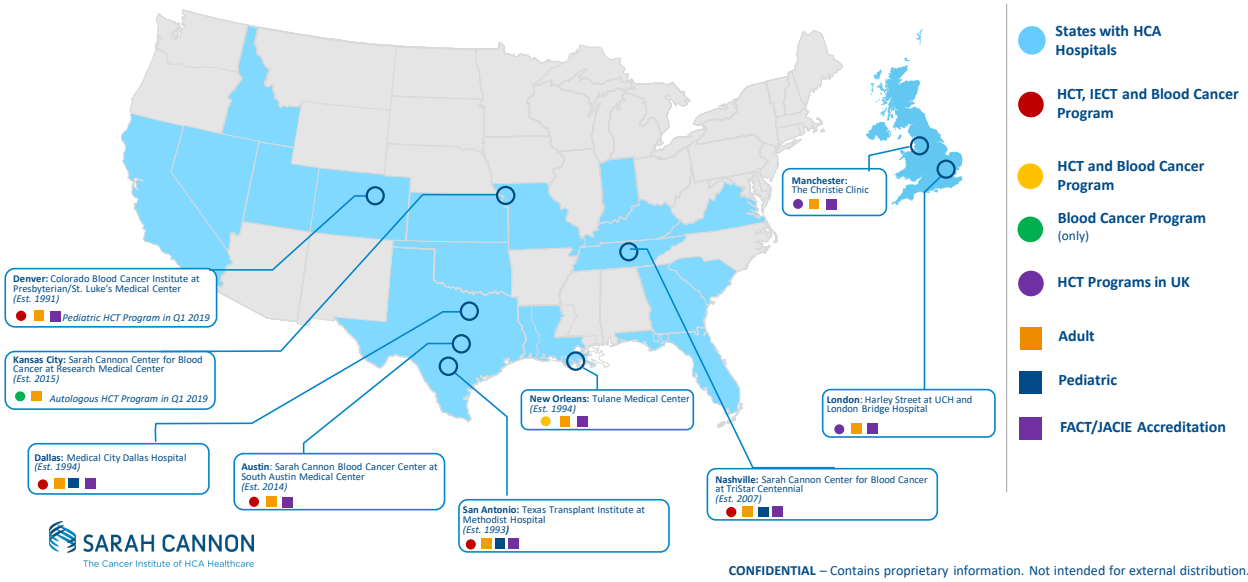
SARAH CANNON EXPERIENCE

300

SARAH CANNON BLOOD CANCER NETWORK PROGRAMS



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301

STANDARDIZATION ACROSS SARAH CANNON BLOOD CANCER NETWORK

- Standard QM plan and metrics
- Quarterly Network QM Committee meetings
- Standardized Clinical Pathways
- Standardized Patient Eligibility Criteria
- Mock FACT Survey Process

- Standardized Payer Contract Template and Language
- Network-level Vendor Contracting
- Implemented Revenue Optimization strategies
- Expense management committees

- Physician, APP privileging criteria and competencies
- Competencies for Nursing and Advanced Practice Clinicians

- Integrated Clinical Care and Research
- Abstracts/Presentations at ASCO, ASH & Tandem
- Pipeline development and operations support

- SOPs standardized
- Ongoing SOP Review process in place

- StafaCT: Developed HCT information solution for Cellular Therapy, Apheresis and Clinical operations
- Meet requirements from FACT, FDA, HRSA and Payers
- Developed Hematology Navigation software

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302

WHY SHOULD WE OFFER CAR T-CELL THERAPY

- Offering CAR T-cell Therapy is essential to maintaining our HCT referral patterns
- Many patients referred for CAR T-cell will not be eligible and will be evaluated for HCT
- Commercial Payers require CAR T-cell to be offered within their HCT COE Network
- Medicare/Medicaid reimbursement is a concern due to CMS having limited knowledge of CAR T-cell and the therapy receiving FDA approval so quickly.
- CAR T-cell therapy is only FDA approved for two indications
  - ≤ 25 years with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. Currently, fewer than 1 in 3 of these patients survive 5 years*
  - ≥ 18 years and older with aggressive B-cell lymphoma that is refractory or in second or later relapse. Palliative care is currently the only option for these patients*

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* INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW " *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value*"

303

SARAH CANNON IMMUNE EFFECTOR CELL THERAPY EXPERIENCE

Studies open in:

- Multiple Myeloma
- Diffuse Large B-Cell Lymphoma
- Mantle Cell Lymphoma
- Acute Lymphoblastic Leukemia
- B-Cell Non-Hodgkin Lymphoma
- Indolent Non-Hodgkin Lymphoma
- Multi Indication Solid Tumor
- Non Small Cell Lung Cancer
- CRISPR CS34+gene therapy Sickle Cell Anemia

Studies pending in:

- B-Cell NHL
- Multiple Myeloma
- AML/MDS
- Multi Indication Solid Tumor
- Outpatient setting

> 25

Immune Effector Cell Therapy studies opened since Dec 2015

> 120

patients enrolled since April 2016

- Myeloma
- Lymphoma
- NSCLC
- ALL
- Sarcoma

Immune Cell Therapy Committees

- Coordination and standardization of research processes across centers for both blood cancer and solid tumor indications
- Local committees comprised of site transplant, nursing, research staff and physicians meet monthly at each center
- Local committees report to Sarah Cannon Immune Effector Cell Therapy leadership monthly

Commercial CAR T-Cell Therapy

- 5 Programs in U.S. certified by Novartis
- 4 Programs in U.S. certified by Kite, 1 in process
- 1 Program in UK in process of Gilead certification

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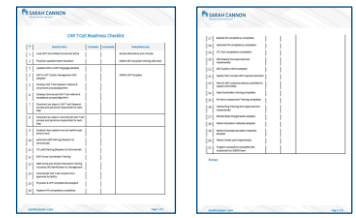
304

SCBCN REQUIREMENTS TO OFFER CAR T (RESEARCH & COMMERCIAL)

CAR T-cell therapy is only FDA approved for two indications:

- ≤ 25 years with acute lymphoblastic leukemia that is refractory or in 2nd or later relapse. Currently, fewer than 1 in 3 of these patients survive 5 years*
- ≥ 18 years and older with aggressive B-cell lymphoma that is refractory or in 2nd or later relapse. Palliative care is currently the only option for these patients*

- ❑ Implementation of SCBCN SOPs to meet Immune Effector Cell Therapy FACT Standards
- ❑ Implementation of SCBCN Annual Competencies for MDs and APPs
- ❑ Implemented local IECT Committee Structure
- ❑ Participate on SCBCN IECT Committee
- ❑ Appropriate number of staff to handle the complexity of CAR T patients, this includes BMT Coordinators, Research staff, BMT and ICU nursing staff, Oncology Pharm D.
- ❑ All physician specialties involved in the care of CAR T patients have been identified and appropriately trained
- ❑ Full adoption of all 3 modules of StafaCT by Physicians and Staff
- ❑ Completion of IECT Assessment by members of the SCBCN team



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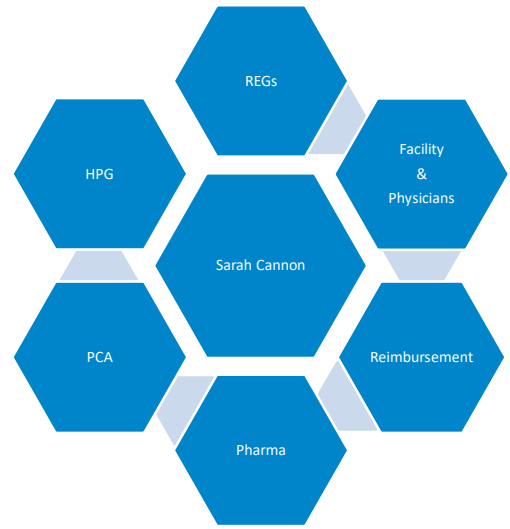
* INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW " *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value*"

305

PARTNERSHIP ACROSS HCA TO IMPLEMENT THIS NEW THERAPY

- **Regulatory Compliance**:
  - Standardized line items for all aspects of the CAR T process
  - FACT accreditation for all sites
- **HCT Physicians**:
  - Standardized Patient Eligibility Criteria developed
  - Monthly patient review of clinical and financial outcomes
- **Payer Contracting & Alignment:**
  - Negotiated a global with Cigna, Auto BMT rate with carve-out of CAR T
  - Developing standardized SCA template
  - Ops Counsel and Managed Government Contracting reviewing our options for Medicare and Medicaid
- **Reimbursement:**
  - Medicare Reimbursement modeling performed by Tom Bateman
- **Facility/Parallon:**
  - Setting up Pre-Authorization and Billing process to match our process for HCT patients. Bills will be closely reviewed prior to submission
  - Developing CAR T Patient Account audit process to ensure all charges were captured and appropriately billed
  - Developing individualized patient cost-containment reporting
- **HPG/Supply Chain:**
  - Working closely with Trina Kaylor and Brian Moran



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306

IECT OPERATIONS TOOLKIT DEVELOPED BY SARAH CANNON

Competencies & Privileges	SOPs & Resource Documents	Education & Training	Finance & Contracting
• RN • Apheresis • CTL Tech • Research RN • Clinical Pharmacist • APP • Physician privileges	• All FACT-required SOPs • Prep for vendor-required SOP management • Pre-site selection checklist • CRS Grading Tool • Patient Consent form • CAR T-Cell Readiness checklist • CARTOX 10 documentation tool	• HealthStream IECT Education module • Consulting Physician Training slide deck • Data Coordinator Training • Patient Education & Wallet Cards • Nurse neuro assessment training • Mock collection & Infusion case study	• Vendor Qualifications • Payer/Vendor contracting • Coding & Billing Updates

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SCBCN DEVELOPED TWO CAR T-CELL THERAPY NURSING EDUCATION MODULES

- **Car T-Cell Therapy: A New Frontier**
- **CAR T-Cell Therapy: Recognition and Management of Toxicities**
- Expert Clinical Advisory panel functioned as consultants & reviewers
- Free CNE hours provided
- Web-based, administered via HealthStream LMS
- Interactive
- Millennial learner-focused
- Designed to be updated as technology advances

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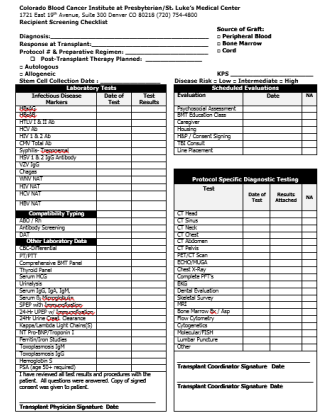
308

SARAH CANNON'S FORMAL PROCESS TO PROVIDE OVERSIGHT

- Standardized Patient Eligibility Form to be completed for each patient
- Each patient's eligibility form will be reviewed at the Program's multidisciplinary team meeting and at the Corporate level, to ensure patient meets our clinical and financial eligibility criteria
- The current IECT Committee will review each patient to ensure patient meets our clinical eligibility criteria, and review the expenses and payer mix of each patient

IECT Committee Members
- Fred LeMaistre, MD
- Carlos Bachier, MD
- Peter McSweeney, MD
- Aravind Ramakrishnan, MD
- Paul Shaughnessy, MD
- Vikas Bhushan, MD
- Rocky Billups
- Tonya Cox
- Paul Rein/Angie Taylor
- Program Administrators
- SC Support Team



Colorado Blood Cancer Institute at Presbyterian/St. Luke's Medical Center
1721 East 19th Avenue, Suite 300 Denver CO 80218 (720) 754-4800
Recipient Screening Checklist

Diagnosis:
Response at Transplant:
Protocol # & Preparative Regimen:
☐ Post-Transplant Therapy Planned:
Source of Graft:
○ Peripheral Blood
○ Bone Marrow
○ Cord
○ Autologous
○ Allogeneic
Stem Cell Collection Date
KPS
Disease Risk ○ Low ○ Intermediate ○ High

Laboratory Tests		
Infectious Disease Markers	Date of Test	Test Results
HBsAg		
HBsAb		
HTLV I & II Ab		
HCV Ab		
HIV 1 & 2 Ab		
CMV TDM Ab		
Syphilis- Treponemal		
HBV 1 & 2 IgG Antibody		
VZV IgG		
Chagas		
WNV NAT		
HEV NAT		
HCV NAT		
HBV NAT		
Compatibility Typing		
ABO / Rh		
Antibody Screening		
DAT		
Other Laboratory Data		
CBC-Differential		
PT/PTT		
Comprehensive BMT Panel		
Thyroid Panel		
Serum HCG		
UrinalysIs		
Serum IgA, IgG, IgM		
Serum Ig Monoglobulin		
SPEP with Immunofixation		
24-Hr UPEP w/ Immunofixation		
24Hr Urine Creat. Clearance		
Kappa/Lambda Light Chain(s)		
NT Pro-BNP/Troponin I		
Ferritin/Iron Studies		
Transferrin Sat		
Transferrin Sat		
Hemoglobin S		
PSA (age 50+ required)		

I have reviewed all test results and procedures with the patient. All questions were answered. Copy of signed consent was given to patient.

Transplant Physician Signature Date

Scheduled Evaluations		
Evaluation	Date	NA
Psychosocial Assessment		
BMT Education Class		
Caregiver		
Housing		
HSP / Consent Signing		
TEE Consult		
Line Placement		

Protocol Specific Diagnostic Testing			
Test	Date of Test	Results Attached	NA
CT Head			
CT Sinus			
CT Neck			
CT Chest			
CT Abdomen			
CT Pelvis			
PET/CT Scan			
ECHO/MUGA			
Chest X-Ray			
Complete PFT's			
EKG			
Dental Evaluation			
Skeletal Survey			
TEE			
Bone Marrow Bx / Asp			
Flow Cytometry			
Cytogenetics			
Molecular/FISH			
Lumbar Puncture			
Other			

Transplant Coordinator Signature Date

Transplant Coordinator Signature Date

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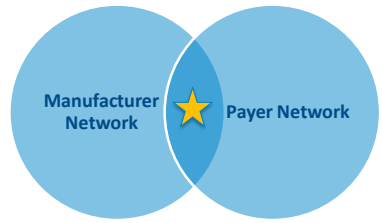
309

CREDENTIALS MATTER FOR PROVIDING CAR-T CELL THERAPY



Manufacturer
- Demonstrated expertise
- FACT Accreditation
- Contract to provide care in specific manner
- Clinical and administrative training for all involved staff

Payer
- Demonstrated expertise
- In-network facility with specific contract; Center of Excellence Network
- FACT Accreditation
- For some payers – use of manufacturer standards as proxy for specialized designation

Source: Presentation by Stephanie Farnia at the 2018 ASBMT BMT Administrator Meeting

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It Takes a Village

Lesley Camille Ballance, MSN, FNP-BC
Nurse Practitioner

Trista Carelock, RN, BSN, BMT-CN®, OCN®
Clinical Program Manager

315

CASE PRESENTATION

- 57-year-old female with a history of refractory multiple myeloma
- Presented in 2010 with renal failure and profound anemia
- Elevated lambda light chains in serum
- Bone marrow biopsy revealed 75% plasma cells
- Renal biopsy revealed lambda light chain nephropathy
- Referred by one of the practice partners to Dr. Ian Flinn shortly after diagnosis

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316

CASE PRESENTATION

Prior lines of therapy

- RVD + autologous stem cell transplant (1 year)
- Clinical trial w/ carfilzomib and panobinostat (6 months)
- Bortezomib (Velcade®), cyclophosphamide, and dexamethasone (11 months)
- Pomalidomide and dexamethasone (2 years)
- Clinical trial w/ antibody drug conjugate (5 months)

RVD-Lenalidomide, Bortezomib, and Dexamethasone.

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317

CASE PRESENTATION

- Enrolled in CAR T clinical trial, day 0, June 6, 2016
- No bridging chemotherapy
- Grade 1 CRS on day 16
- No neurotoxicity
- Day 14 light chains revealed VGPR
- Day 30 restaging revealed SCR
- Patient remains in an SCR per last restaging in April 2019

SCR, stringent complete response; VGPR, very good partial response; CRS, Cytokine release syndrome.

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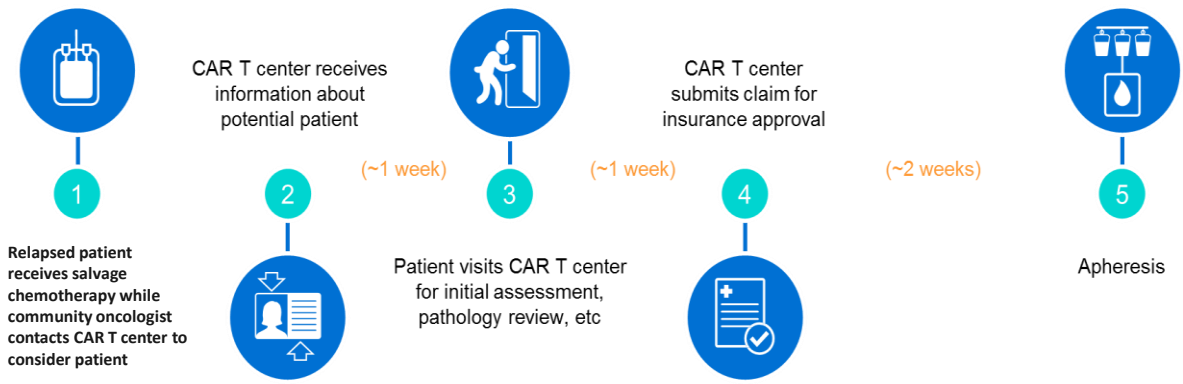
318

PATIENT JOURNEY AND LOGISTICS



Due to the characteristics of patients who are treated with CAR T therapy, the time pressure from patient identification to apheresis is expected to be a significant constraint

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319

GENERAL ELIGIBILITY CRITERIA

- Measurable disease
- ECOG score 0-1
- No history of significant neurological disease (seizures, CVA, TBI, etc.)
- Prior therapies (type and amount varies)
- Ejection fraction of 50%
- No active infections
- Adequate renal, kidney, and bone marrow function

ECOG, Eastern Cooperative Oncology Group; CVA, Cerebral Vascular Incident; TBI ,Traumatic BrainInjury.

COMMERCIAL ELIGIBILITY CRITERIA

- Standardized Patient Eligibility Form is completed for each patient
- Each patient's eligibility form is reviewed at the program's multidisciplinary team meeting and at the corporate level to ensure patient meets our clinical and financial eligibility criteria
- Clinical criteria reviewed include current disease state and history, medical history, chemotherapy treatment course, laboratory and radiologic results, ECOG score, infectious disease markers, stem cell transplant history, psychosocial assessment, etc.

MULTIDISCIPLINARY TEAM

Communication occurs throughout the continuum of care

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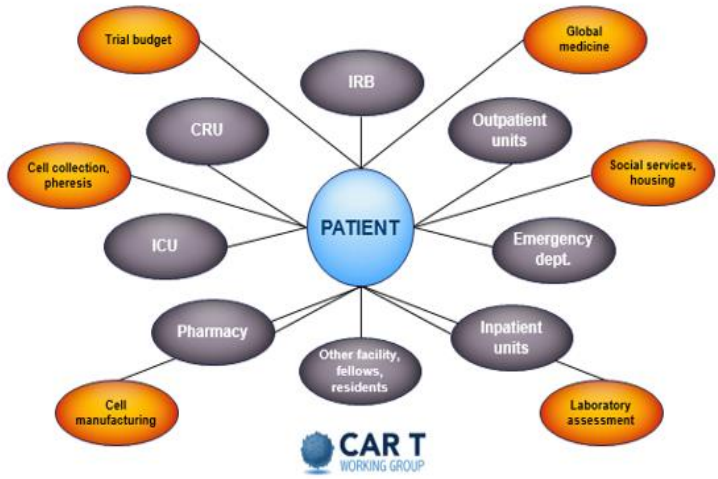
MULTIDISCIPLINARY TEAM



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MULTIDISCIPLINARY TEAM

- **Research Team/Transplant Coordinator**
  - Completes initial screening to determine if patient meets eligibility criteria
  - Develops plan for patient that includes lymphodepletion chemo, collection dates, shipping dates, and cell infusion
  - Research – educates team on protocol requirements
  - Communicates plan of care to leadership, clinical teams, and ancillary teams
- **ED**
  - Assesses patient for toxicities and initiates treatment when appropriate
- **Pharmacy**
  - Develops plan for sequestering tocilizumab (2 doses/patient)
  - STAT delivery of supportive medications (Toci) to BMT unit or ED

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324

MULTIDISCIPLINARY TEAM

- **Bed Control**
  - Ensure patient is placed on bone marrow transplant unit
- **Inpatient/Outpatient**
  - Chemo/infusion
  - Readiness plan for potential admit and clinical care requirements
  - Toxicity and supportive care management
  - CARTOX and CRS assessments with process for tracking grading and handwriting
  - Patient education
  - Handoff process for transfer of care from inpatient/outpatient

CARTOX, CAR-T-cell-therapy-associated TOXicity

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325

MULTIDISCIPLINARY TEAM

- **ICU**
  - Toxicity and supportive care management
  - CARTOX and CRS assessments
- **Social Work**
  - Patient/caregiver assessment and support
  - Housing
- **Case Management**
  - Assist with care needs at home
- **Financial Coordinator**
  - Assess financial responsibilities and patient needs

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REVISED GRADING SCALES FOR CRS

	2014 NCI Consensus Revised Grading Scale[1]	Penn Grading Scale (PGS-CRS)[2]

Grade 1	• Symptoms are not life threatening
	  • Symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgias, malaise)
		• Mild reaction
		  • Treated with supportive care (antipyretics, antiemetics)

Grade 2	• Symptoms require and respond to moderate intervention
	  • Hypoxia: responsive to <40% oxygen
	  • Hypotension: responsive to fluids or 1 low-dose vasopressor
	  • Grade 2 organ toxicity
		• Moderate
		  • Requires IV therapies or parenteral nutrition
		  • Some signs of organ dysfunction (ie, grade 2 Cr or grade 3 LFTs) related to CRS
		  • Hospitalization for CRS-related symptoms including fevers with associated neutropenia

Grade 3	• Symptoms require and respond to aggressive intervention
	  • Hypoxia: requires oxygen >40%
	  • Hypotension: requires high-dose or multiple vasopressors
	  • Grade 3 organ toxicity
	  • Grade 4 transaminitis
		• More severe reaction requiring hospitalization
		  • Moderate signs of organ dysfunction (grade 4 LFTs or grade 3 Cr) related to CRS
		  • Hypotension treated with IV fluids or low-dose pressors
		  • Coagulopathy requiring FFP or cryoprecipitate
		  • Hypoxia requiring supplemental O_2 (nasal cannula oxygen, high-flow O_2, CPAP or BiPAP)

Grade 4	• Life-threatening symptoms
	  • Requirement for ventilator support
	  • Grade 4 organ toxicity (excluding transaminitis)
		• Life-threatening complications
		  • Hypotension requiring high-dose pressors
		  • Hypoxia requiring mechanical ventilation

Grade 5	Death	Death

Lee DW, et al. *Blood*. 2014;124(2):188-195.
Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139.

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CRS MANAGEMENT GUIDELINES

CRS Grade	Symptom or Sign	Management
Grade 1	Fever or grade 1 organ toxicity	• Acetaminophen and hypothermia blanket for fever • Ibuprofen may be used as second option for fever if not contraindicated • Assess for infection with blood and urine cultures, and chest x-ray • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab 8 mg/kg or siltuximab 11 mg/kg IV for persistent (>3 days) and refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500 to 1000 mL normal saline • May give a second IV fluid bolus if SBP remains <90 mm Hg • Tocilizumab 8 mg/kg[b] IV or siltuximab 11 mg/kg IV for hypotension refractory to fluid boluses; may be repeated if needed • If hypotension persists after two fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain echocardiogram and initiate other methods of hemodynamic monitoring • In patients at high-risk[c] or if hypotension persists after 1 to 2 doses of tocilizumab/siltuximab, may use dexamethasone 10 mg IV every 6 hours • Manage fever and constitutional symptoms as in grade 1
	Hypoxia (FiO_2 <40%)	• Supplemental oxygen • Tocilizumab/siltuximab +/– corticosteroids and supportive care as in hypotension
	Grade 2 organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab/siltuximab +/– corticosteroids and supportive care as in hypotension

Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

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CRS MANAGEMENT GUIDELINES

CRS Grade	Symptom or Sign	Management
Grade 3	Hypotension	• IV fluid boluses as needed as in grade 2 • Tocilizumab/siltuximab as in grade 2 if not administered previously • Vasopressors as needed • Transfer to ICU, echocardiogram and hemodynamic monitoring as in grade 2 • Dexamethasone 10 mg IV every 6 hours; increase to 20 mg IV every 6 hours if refractory • Manage fever and constitutional symptoms as in grade 1
	Hypoxia (FiO_2 ≥40%)	• Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab/siltuximab + corticosteroids and supportive care as above
	Grade 3 organ toxicity or grade 4 transaminitis	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab/siltuximab + corticosteroids and supportive care as above
Grade 4	Hypotension	• IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as in grade 3 • Methylprednisolone 1 g/day IV may be used in place of dexamethasone • Manage fever and constitutional symptoms as in grade 1
	Hypoxia	• Mechanical ventilation • Tocilizumab/siltuximab + corticosteroids and supportive care as above
	Grade 4 organ toxicity excluding transaminitis	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab/siltuximab + corticosteroids and supportive care as above

Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

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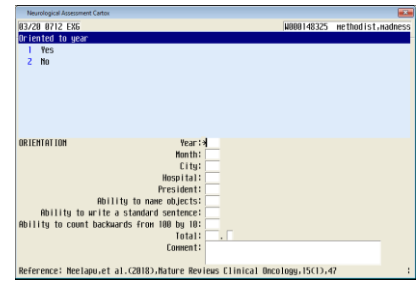
STAFF EDUCATION

- REMS training
- Role in identification and management of toxicities
  - Grading system and associated clinical management
- Assessment
  - Handoff on key findings
  - Handoff on Toxicity Scores (CRS/CRES)
    - CARTOX 10 (score, handwriting)
    - CRS
- Neutropenia and thrombocytopenia precautions
- Wallet card



REMS, Risk Evaluation and Mitigation Strategy; CRES, CAR T cell related encephalopathy syndrome.

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330

STAFF EDUCATION

- **Provider notification**
  - Fever ≥38 degrees C (100.4 degrees F)
  - Hypotension (SBP 90 mmHg or less): fluid bolus
  - Hypoxia (O_2 sat <90% on room air): O_2 requirement
  - Organ toxicity
  - Cardiac: tachycardia, arrhythmia, heart block, low ejection fraction – EKG
  - Respiratory: tachypnea, pleural effusion, pulmonary edema
  - Gastrointestinal: nausea, vomiting, diarrhea
  - Hepatic: increased AST/ALT or bilirubin
  - Renal: acute kidney injury (increased creatinine), decreased UOP
  - Skin: rash
  - Coagulopathy: disseminated intravascular coagulation (DIC)
  - Neurologic: headache, confusion, disorientation, agitation, dysphagia, tremor, seizures, motor weakness, incontinence, increased intracranial pressure, papilledema – levetiracetam; consult neuro; MRI

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331

PATIENT EDUCATION

- What is CAR T-cell therapy and what to expect
- When to call the MD
  - Fever of 100.4 or greater
  - Any changes in neurologic status (confusion, aphasia, etc.)
  - Uncontrolled bleeding r/t thrombocytopenia
  - Difficulty breathing
  - Chills or shaking chills
  - Dizziness or lightheadedness
  - Severe nausea, vomiting, or diarrhea
  - Fast or irregular heartbeat
  - Severe fatigue or weakness

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332

PATIENT EDUCATION

- Wallet card (carrying it at all times, providing to EMS, present at ED)
- No driving or participating in hazardous occupations or activities for 8 weeks
- No steroids without approval from BMT physician
- Neutropenic/thrombocytopenic precautions

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333

WHAT TO TELL THE REFERRING ONCOLOGIST

- Patients may be sent back to their primary oncologist after 28 days
  - Long-term CRS (post-day 28) is very rare
- Primary oncologist should closely monitor patients:
  - Blood counts
  - IgG levels
  - Signs of infection
- Hypogammaglobulinemia and prolonged B-cell aplasia is common
  - The utility of intravenous Ig (IVIg) replacement therapy needs to be further understood
  - The long-term sequelae of B-cell aplasia and IVIg replacement remain unknown
- Patients should follow up with the CAR T-cell therapy center per protocol

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334

SARAH CANNON IMMUNE EFFECTOR CELL THERAPY EXPERIENCE

Studies open in:

- Multiple Myeloma
- Diffuse Large B-Cell Lymphoma
- Mantle Cell Lymphoma
- Acute Lymphoblastic Leukemia
- B-Cell Non-Hodgkin Lymphoma
- Indolent Non-Hodgkin Lymphoma
- Multi Indication Solid Tumor
- Non Small Cell Lung Cancer
- CRISPR CS34+gene therapy Sickle Cell Anemia

Studies pending in:

- B-Cell NHL
- Multiple Myeloma
- AML/MDS
- Multi Indication Solid Tumor
- Outpatient setting

> 20

Immune Effector Cell Therapy studies opened since Dec 2015

> 120

patients enrolled since April 2016

- Myeloma
- Lymphoma
- NSCLC
- ALL
- Sarcoma

Immune Cell Therapy Committees

- Coordination and standardization of research processes across centers for both blood cancer and solid tumor indications
- Local committees comprising site transplant, nursing, research staff, and physicians meet monthly at each center
- Local committees report to Sarah Cannon Immune Effector Cell Therapy leadership monthly

Commercial CAR T-Cell Therapy

- 5 Programs in U.S. certified by Novartis
- 4 Programs in U.S. certified by Kite, 1 in process
- 1 Program in UK in process of Gilead certification

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336

Vanderbilt
FDA-Approved CAR-T Case Study

Brittney Baer, BSN, RN
Research Nurse Specialist II

Mykala Heuer, BSN, RN
Research Nurse Specialist II

337

Patient Background

56 year old male

Diagnosis: Diffuse Large B-cell Lymphoma 3B (Suggested follicular lymphoma origin)

- Treatment History:
  - *Jun. 2012:* Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (**R-CHOP**)
  - *Jan. 2014:* Bendamustine/Rituximab
  - *Jun. 2014-Oct. 2014:* Rituximab, Ifosfamide, Carboplatin, and Etoposide (**RICE**)
  - *Oct. 2014:* Autologous Stem Cell Transplant
  - *May 2015-Jul. 2015:* Rituximab, Gemcitabine, Oxaliplatin (**R-GemOx**)
  - *Oct. 2015-Nov. 2015:* **Clinical Trial -** HEMEP1558 (INC52793) – JAK1 inhibitor
  - *Nov. 2015:* Rituximab, Gemcitabine, Navelbine, and Doxorubicin (**R-GND**)

338

Recruitment Process

Patient had already established care at Vanderbilt

However, many patients for CAR-T are **outside** referrals

- **Challenges**:
  - Lack of new patient appointments in a timely manner
  - Receiving outside medical records
  - Getting the patient established in Vanderbilt's system

339

Interdisciplinary Teamwork

Presentation Meeting: To present all our patients for Allogeneic transplant, Autologous transplant, or CAR-T therapy

Includes:

- Physicians
- Research Nurses/Coordinators
- Transplant Nurse Practitioners/Nurses
- Transplant Coordinators
- National Marrow Donor Program (NMDP)
- Financial

340

Interdisciplinary Teamwork

Transplant Calendar Meeting: To coordinate the procedures required up to transplant or infusion date

Includes:

- Research Nurses/Coordinators
- Transplant Nurse Practitioners/Nurses
- Transplant Coordinators
- NMDP
- Financial
- Leukapheresis Charge Nurse
- Outpatient Transplant Unit Charge Nurse
- Processing Lab Manager

341

CAR-T Course

Leukapheresis: 18 JAN 2014

Lymphodepleting Chemotherapy: 28 JAN 2016 – 30 JAN 2016
Fludarabine and Cyclophosphamide

DAY ZERO: 03 FEB 2016

Hospitalization Post-CAR-T: 03 FEB 2016 – 13 FEB 2016

342

Cytokine Release Syndrome (CRS)

Fevers began on Day +4

Intermittent supplemental oxygen was given with sleep

CRS symptoms were treated with acetaminophen, IV fluids, cooling blankets, and ice packs

All CRS symptoms were **resolved** by Day +7

343

Neurotoxicity (CRES)

All patients at Vanderbilt University Medical Center are on prophylactic Keppra

Patient's symptoms were:

Headache

Abnormal gait

Slow to respond around Day +6

MRI of brain on Day +7 was **negative**

All CRES symptoms **resolved** by Day +7

344

Response to Therapy

Day +28 PET/CT

Good partial response to therapy with reduction in size of the right pelvic sidewall mass. Mild to moderate residual FDG uptake may be related to post-treatment changes. Attention on follow-up imaging is recommended. Right obturator node and right mesenteric node have resolved

345

Response to Therapy

Month 3 PET/CT

Complete response to therapy by Deauville criteria (score 2) with reduction in size of the right pelvic sidewall stromal scar. There are no abnormal areas of FDG uptake

346

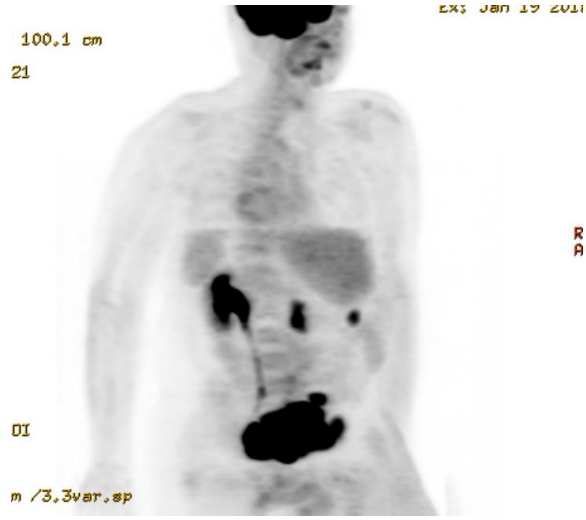
Response to Therapy

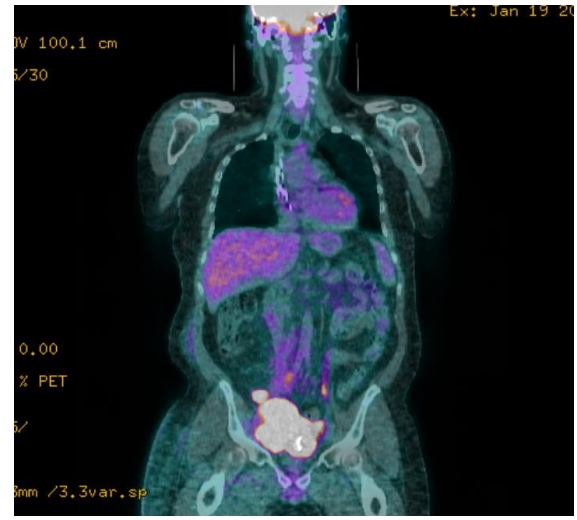
Month 24 (last study dictated follow up scan):

The examination is unchanged from multiple prior examinations, with surgical change in the right lower abdomen and thickening along the right lateral pelvic sidewall with FDG uptake comparable to blood pool background

347

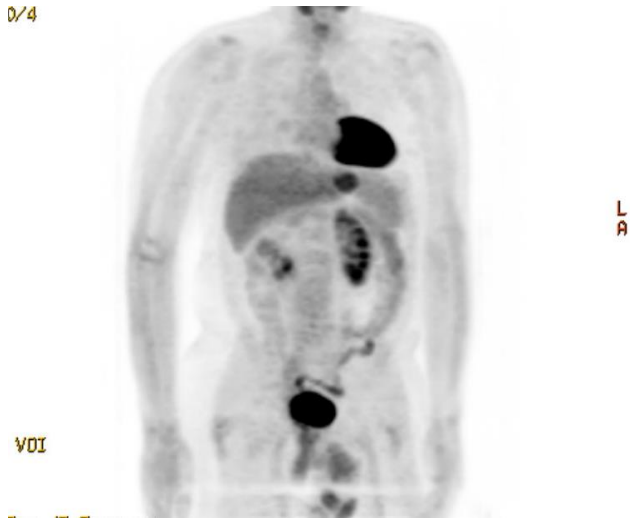
Prior to CART infusion PET/CT (19 JAN 2016)

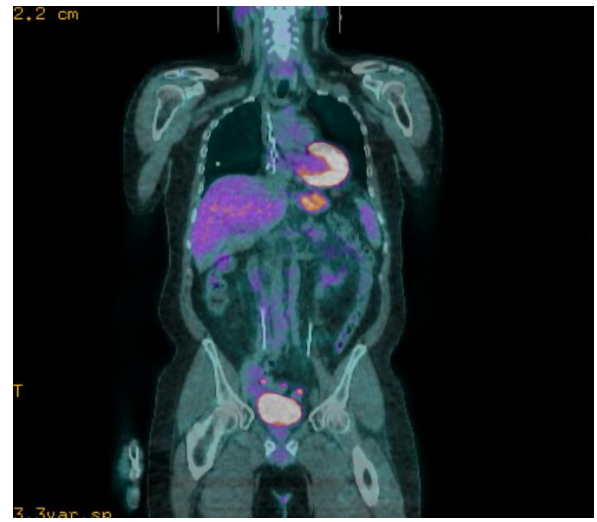




348

Month 3 post CART infusion PET/CT (02 MAY 2016)





349

Roadblocks

- Interdisciplinary communication
- Cell manufacturing dates
- Cell manufacturing failure
- Caregiver support
- Cost of local lodging
- Insurance approval/ reimbursement

350

Approved CAR-T:
Is the Treatment Really Accessible for Patients?

For **Medicaid and Medicare**: *covers a large amount of the Chimeric antigen receptor (CAR) T-cell therapy*

- These patients also require leukapheresis, hospitalization, additional labs, and more
- Although Medicaid and Medicare help cover the hefty fee of CAR-T, these other costs can add up
- Many insurance companies follow similar guidelines to Medicare and Medicaid

Additional potential financial hardships:

- Lodging - per Vanderbilt guidelines patients must stay within a 30 minute radius up to 30 days post CAR-T infusion
- Travel
- Food
- Length of time off work

Reference: Bennett, C. (2018, June). CAR T-Cell Therapies: Early Insights into Access and Affordability. Retrieved June 10, 2019, from http://obroncology.com/article/car-t-cell-therapies-early-insights-into-access-and-affordability/)

351

Approved CAR-T: Is the Treatment Really Accessible for Patients?

Vanderbilt's experience with insurance approval:

- Patients can sometimes get approved for CAR-T treatment quickly but determining approval for additional costs slows entire process
- Vanderbilt will assume the cost of the CAR-T treatment for patients whose insurance will not cover everything and still leave a large medical bill
- Vanderbilt had to have fewer patients receive commercial CAR-T therapy and encourage more CAR-T clinical trials due to insurance coverage issues and financial loss for Vanderbilt

352

Outpatient Treatment

- CART infusion is done outpatient with strict monitoring.
  - Clinic visits in Outpatient Transplant Unit at 0800 and 1600.
  - Telehealth visit with NP/PA at 2200.
  - Patient/caregiver are given equipment to take vital signs at local lodging.
- PA/NP are specially trained to assess CART patients.
  - Provider also has direct number and cell phone for patient/caregiver to contact with any issues.
- If problems arise, the patient is directly admitted to myelosuppression unit (*not* through ED)

353

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354

Interactive Panel Discussion
Q & A

355

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BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY®

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