

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

Friday, June 28, 2019
8:30 am – 4:30 pm

Rockefeller University
New York, NY

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

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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.

The Leukemia & Lymphoma Society (LLS) is recognized by the New York State Education Department's State Board for Social Work as an approved provider of continuing Education for licensed social workers #SW-0117. LLS maintains responsibility for this program. Social workers will receive 7.5 CE clinical contact hours for this activity.

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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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OVERVEIW

David L. Porter, MD (Chair)

Jodi Fisher Horowitz
 Professor in Leukemia Care Excellence
 Director, Blood and Marrow Transplantation
 Perelman School of Medicine
 University of Pennsylvania Health System
 Philadelphia, PA

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FACULTY

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Philadelphia, PA

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Hematology/Oncology Fellow
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Northwell Health Cancer Institute
Donald & Barbara Zucker School of Medicine
at Hofstra/Northwell
Lake Success, NY

Ira Braunschweig, MD

Director, Stem Cell Transplantation
Clinical Program Director Hematologic Malignancies
Montefiore Medical Center
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Senior Director, Professional Education & Engagement
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Rye Brook, NY

Adam D. Cohen, MD

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Medical Oncologist
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Hematology/Oncology Fellow
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Heather DiFilippo, MSN, CRNP

Certified Adult Nurse Practitioner
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Philadelphia, PA

Sergio A. Giralt, MD

Melvin Berlin Family Chair in Myeloma Research
Professor of Medicine, Weill Cornell Medical College
Chief Attending, Adult BMT Service
Memorial Sloan Kettering Cancer Center
New York, NY

Sukhdeep Kaur, MD

Hematology/Oncology Fellow
Rutgers Cancer Institute of New Jersey
New Brunswick, NJ

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Attending Physician
Division of Leukemia
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Hackensack University Medical Center
Hackensack, NJ

Deepu Madduri, MD

Assistant Professor of Medicine
Hematology and Medical Oncology
Mount Sinai Medical Center
New York, NY

Nigina Mirazimova, MSN, RN, OCN®

Patient Care Director
New York-Presbyterian
Weill Cornell Medicine
New York, NY

Gwen L. Nichols, MD

Executive Vice President, Chief Medical Officer
The Leukemia & Lymphoma Society
Rye Brook, NY

Ran Reshef, MD, MSc

Associate Professor of Medicine at CUMC
Director, Translational Research
Blood and Marrow Transplantation and
Cell Therapy Program
Division of Hematology/Oncology and
Columbia Center for Translational Immunology
New York-Presbyterian
Columbia University Irving Medical Center
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Adult Bone Marrow Transplant Service & Center for
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Director, Bone Marrow and Hematopoietic
Stem Cell Transplant
Chief, Bone Marrow Transplant Service
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Professor of Pathology and Laboratory Medicine
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Elizabeth A. Weber, BSN, RN

Commercial Cellular Therapy Coordinator
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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

Steven Bair, MD, has nothing to disclose. He does intend to include either non-FDA-approved or investigational use for the following products/devices: We will discuss the results of the bb2121 BCMA CAR product. We will also discuss other cellular therapy products in development, but not approved for myeloma (to be determined).

Jacqueline C. Barrientos, MD, MS, is a Consultant for: AstraZeneca; Bayer; Genentech; Gilead Sciences, Inc.; Pharmacytics, An AbbVie Company and Sandoz, Inc., a Novartis Division. Received an honorarium for a Medical Education Speaker Event for Janssen, Pharmaceutical Companies of Johnson & Johnson. 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.

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

Adam D. Cohen, MD, is a Consultant for: Celgene Corporation; Janssen, Pharmaceutical Companies of Johnson & Johnson; Kite Pharma, A Gilead Company; Seattle Genetics; and Takeda. Research Support and Intellectual property related to CAR T cells licensed by University of Pennsylvania for Novartis. He does intend to include either non-FDA-approved or investigational use for the following products/devices: BCMA-directed CAR T cells for myeloma.

Dennis L. Cooper, 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.

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

Heather DiFilippo, MSN, CRNP, 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.

Sergio A. Giralt, MD, is a Consultant for: Amgen, Celgene Corporation, Jazz Pharmaceuticals, Johnson & Johnson, Sanofi, and Takeda. 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.

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

Jamie L. Koprivnikar, MD, is on the Speaker's Bureau for: AbbVie, Alexion, Amgen, and Novartis. 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.

Deepu Madduri, MD, is a Consultant for Foundation Medicine and Takeda. She does not intend to include any non-FDA-approved or investigational use of any products/devices.

Nigina Mirazimova, MSN, RN, OCN®, has nothing to disclose. She does not intend to include any non-FDA-approved or investigational use of any products/devices.

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

Ran Reshef, MD, MSc, is on the Advisory Board for Atara Biotherapeutics and Pfizer. He is a Consultant for Kite, A Gilead Company and Magenta Therapeutics. He does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR-T cells in off label indications.

Joanna M. Rhodes, MD, received a fee as a Medical Reviewer for Medscape. She does intend to include either non-FDA-approved or investigational use for the following products/devices: CJL-019 for CLL and CAR T for CLL.

Larysa Sanchez, MD, has nothing to disclose. She does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR T in Multiple Myeloma.

Gunjan L. Shah, MD, has done Research Funding for Amgen and Janssen, Pharmaceuticals Companies of Johnson & Johnson. She does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR T for non-FDA approved indications.

Mari Lynne Silverberg, MPA, RN, BSN, OCN®, has nothing to disclose. She does intend to include either non-FDA-approved or investigational use for the following products/devices: CAR T-cells/Immune Effector Cell.

Koen van Besien, MD, PhD- has done research support for AlfyImmune Therapeutics and Consultant and on the Advisory Board for Cellectis. He does not intend to include any non-FDA-approved or investigational use of any products/devices.

Elizabeth A. Weber, BSN, RN, is a Consultant for Novartis. She does not intend to include any non-FDA-approved or investigational use of any products/devices.

Catherine Wei, MD, 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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AGENDA

8:00 – 8:30 am	Breakfast and Registration
8:30 – 8:35 am	Welcome and Overview <i>David L. Porter, MD (Chair) and Lauren Berger, MPH</i>
8:35 – 8:45 am	LLS Impact: Advancing Cures <i>Gwen L. Nichols, MD</i>
8:45 – 9:15 am	CAR T-cell Clinical Applications: Is it Right for My Patients? <i>Sergio A. Giralt, MD</i>
9:15 – 9:45 am	CAR T Toxicity and Management <i>Ran Reshef, MD, MSc</i>
9:45 – 10:15 am	CAR T-cells for ALL <i>Jamie L. Koprivnikar, MD</i>
10:15 – 10:30 am	Break
10:30 – 11:00 am	CAR T-cells: A Major Advance for Patients with Refractory DLBCL <i>Ira Braunschweig, MD</i>
11:00 – 11:45 am	It Takes a Village: Panel Presentations & Discussion <i>Heather DiFilippo, MSN, CRNP, Nigina Mirazimova, MSN, RN, OCN®, Mari Lynne Silverberg, MPA, RN, BSN, OCN® and Elizabeth A. Weber, BSN, RN</i>
11:45 – 12:15 pm	CAR T-cells for CLL <i>Jacqueline C. Barrientos, MD, MS and Joanna M. Rhodes, MD</i>
12:15 – 12:30 pm	Lunch Break
12:30 – 1:15 pm	Meet the Experts: Roundtable discussions facilitated by fellows and symposium faculty <i>Fellows: Steven Bair, MD, Susan Dewolf, MD, Sukhdeep Kaur, MD, Joanna M. Rhodes, MD, Larysa Sanchez, MD and Catherine Wei, MD</i>
1:15 – 2:15 pm	Case Presentations: NHL and Myeloma: Referral, Treatment and Follow-up <i>Koen van Besien, MD, PhD and Deepu Madduri, MD</i>
2:15 – 2:45 pm	CAR T-cells for Myeloma: The Next Major Disease Target? <i>Adam D. Cohen, MD</i>
2:45 – 3:15 pm	CAR T cells, Jump-starting your program <i>Dennis L. Cooper, MD</i>
3:15 – 3:30 pm	Q & A <i>Dennis L. Cooper, MD</i>
3:30 – 4:00 pm	Value, Cost & Reimbursement for CAR T cells: Overcoming the Obstacles <i>Gunjan L. Shah, MD</i>
4:00 – 4:30 pm	Interactive Panel Discussion and Q & A <i>David L. Porter, MD and Panel</i>

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MEET THE EXPERTS: ROUNDTABLE DISCUSSIONS

Setting up a program

Sergio A. Giralt, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Catherine Wei, MD

Rutgers Cancer Institute of New Jersey
New Brunswick, NJ

Financial Considerations

Susan Dewolf, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Gunjan L. Shah, MD

Memorial Sloan Kettering Cancer Center
New York, NY

Nursing and Coordination of Care

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University of Pennsylvania Health System
Philadelphia, PA

Elizabeth A. Weber, BSN, RN

University of Pennsylvania Health System
Philadelphia, PA

Nursing and Coordination of Care

Nigina Mirazimova, MSN, RN, OCN®
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Weill Cornell Medicine
New York, NY

Mari Lynne Silverberg, MPA, RN, BSN, OCN®

Memorial Sloan Kettering Cancer Center
New York, NY

CAR T and CLL

Jacqueline C. Barrientos, MD, MS
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Donald & Barbara Zucker School of Medicine
at Hofstra/Northwell
Lake Success, NY

Joanna M. Rhodes, MD

University of Pennsylvania Health System
Philadelphia, PA

CAR T and Lymphoma

Ira Braunschweig, MD
Montefiore Medical Center
Bronx, NY

Mohammad Kazemi, MD

Montefiore Medical Center
Bronx, NY

Koen van Besien, MD, PhD

New York-Presbyterian
Weill Cornell Medicine
New York, NY

CAR T and Myeloma

Steven Bair, MD
University of Pennsylvania Health System
Philadelphia, PA

Adam D. Cohen, MD

University of Pennsylvania Health System
Philadelphia, PA

CAR T and Myeloma

Deepu Madduri, MD
Mount Sinai Medical Center
New York, NY

Larysa Sanchez, MD

Mount Sinai Medical Center
New York, NY

CAR T and ALL

Jamie L. Koprivnikar, MD
Hackensack University Medical Center
Hackensack, NJ

Toxicity and Management: CRS and Neurotoxicity

Ran Reshef, MD, MSc
New York-Presbyterian
Columbia University Irving Medical Center
New York, NY

Toxicity and Management: CRS and Neurotoxicity

Dennis L. Cooper, MD
Rutgers Cancer Institute of New Jersey
New Brunswick, NJ

Sukhdeep Kaur, MD

Rutgers Cancer Institute of New Jersey
New Brunswick, NJ

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CAR-T SYMPOSIUM 2019

Gwen L. Nichols, MD
Executive Vice President
Chief Medical Officer

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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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WHY ARE WE SO EXCITED ABOUT IMMUNOTHERAPY?

THE LEUKEMIA & LYMPHOMA SOCIETY

- 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.

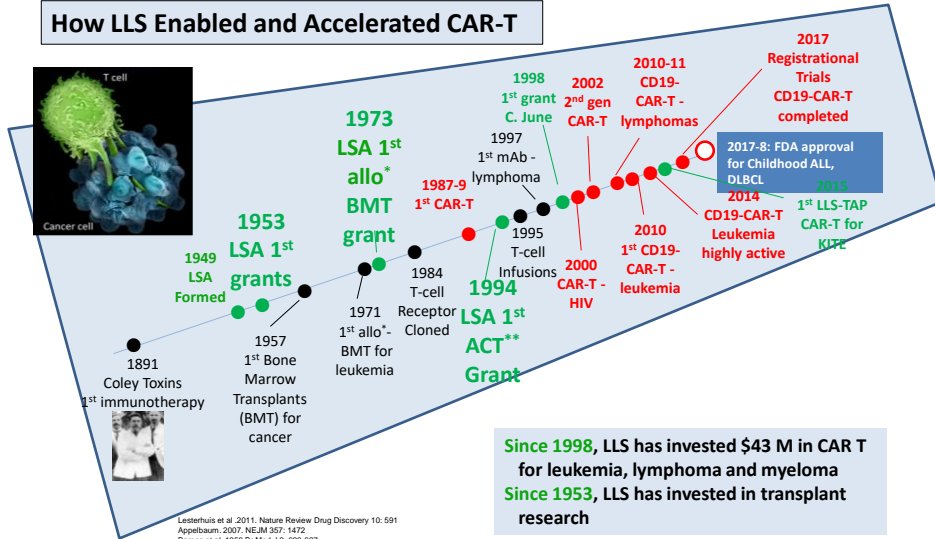
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CUTTING-EDGE RESEARCH TAKES TIME

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. 1998. Br Med J 2: 926-927
 Barrett et al. 2014. Annu Rev Med 65: 333-47
 June, Riddell and Schumacher. 2015. Sci Trans Med 7: 280ps7

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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



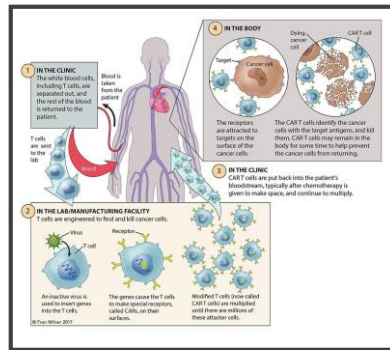
LLS EDUCATION RESOURCES FOR CAR-T

For patients:

- www.LLS.org/CART

For healthcare professionals:

- www.LLS.org/CE



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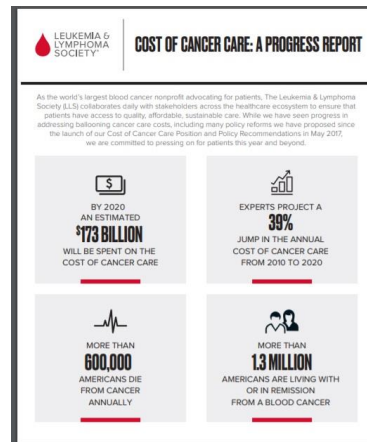
LLS POLICY EFFORTS SUPPORTING ACCESS TO CAR-T

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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LLS INFORMATION RESOURCE CENTER (IRC)

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

- Disease information

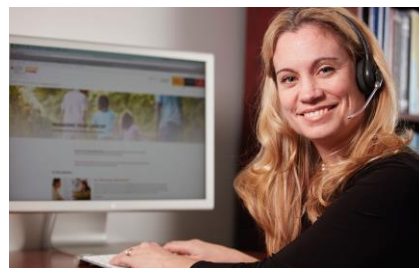
www.LLS.org/IRC **800.955.4572**

- Emotional support

- Local support through our patient access field teams

- Financial, travel and co-pay assistance

- Referral to clinical trial navigation



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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.

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



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ENJOY THE PROGRAM!





Memorial Sloan Kettering
Cancer Center

CAR T- CELL CLINICAL APPLICATIONS

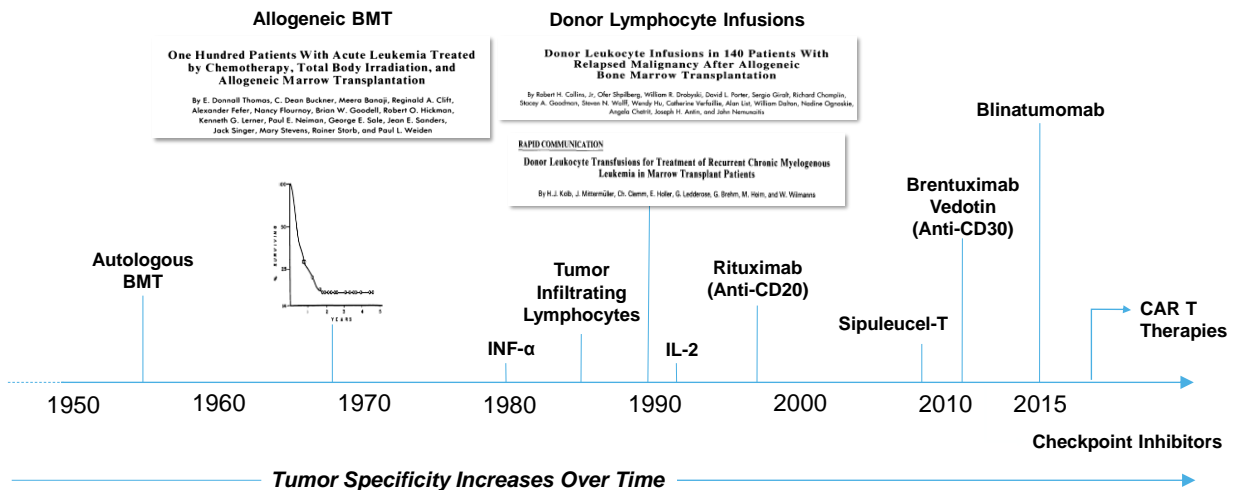
Is It Right For My Patients?

Sergio Giralt, MD

Melvin Berlin Family Chair in Myeloma Research
Professor of Medicine Weill Cornell Medical College
Chief Attending, Adult BMT Service
Memorial Sloan Kettering Cancer Center
New York, NY

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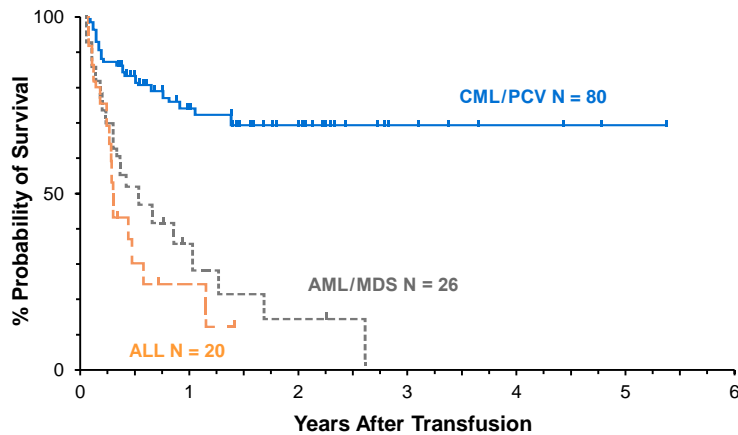
Timeline of Advances in Immunotherapy



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Donor Lymphocyte Infusions Are Associated With Poor Efficacy in ALL

Response to DLI in Patients With Recurrent Leukemia After Bone Marrow Transplant



Kolb HJ, et al. *Blood*. 1995;86(5):2041-2050.

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Paradigm Shift in Oncology



Target the Tumor

- Chemotherapy and AutoHCT
- Monoclonal Antibodies
 - Rituximab and Herceptin
- Antibody-Drug Conjugates
 - Brentuximab
- Tumor Checkpoint Blockade – PD-L1



Target the Host

- Vaccination
 - Gardasil (anti-HPV16&18)
 - Sipuleucel-T (anti-PSA)
- Immune Modulators
 - Lenalidomide
- Immune Checkpoint Blockade
 - PD1, CTLA4



Target Both Tumor & Host

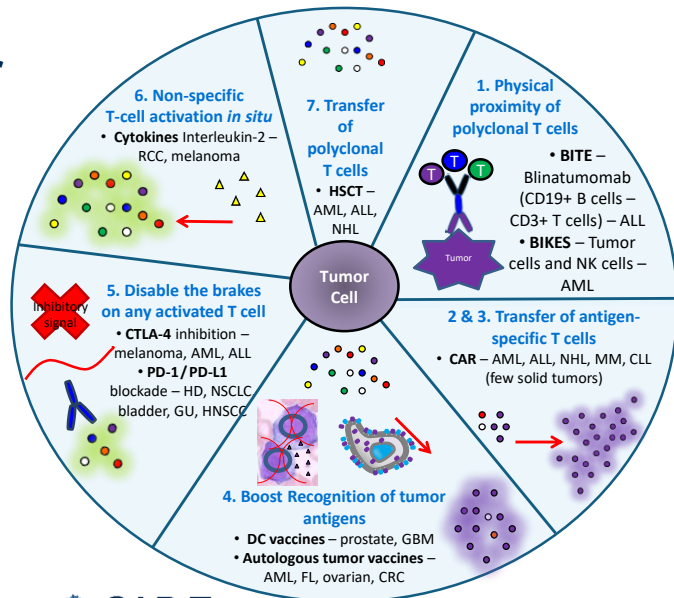
- Allogeneic HCT
- Bispecific Antibodies
 - Blinatumomab
- **CAR T Therapy**

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How to Optimally Harness Antitumor Immunity

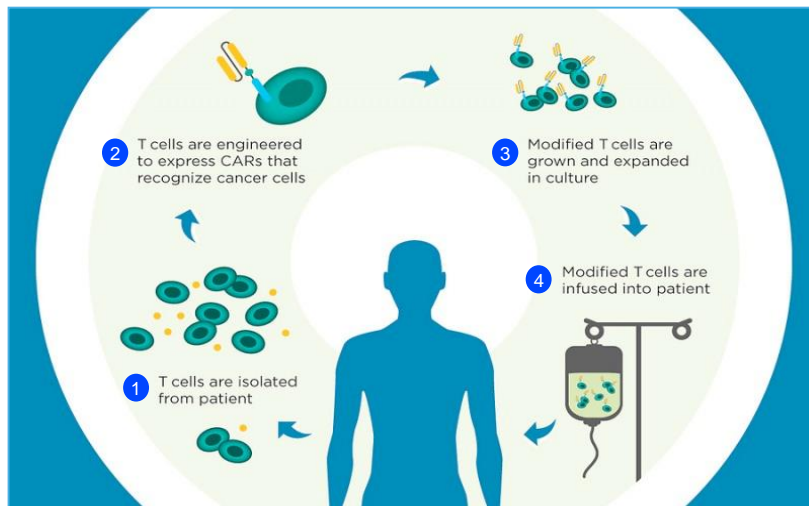


Available on the ASTCT Website.

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CAR-Modified T Cells as Cancer Therapy

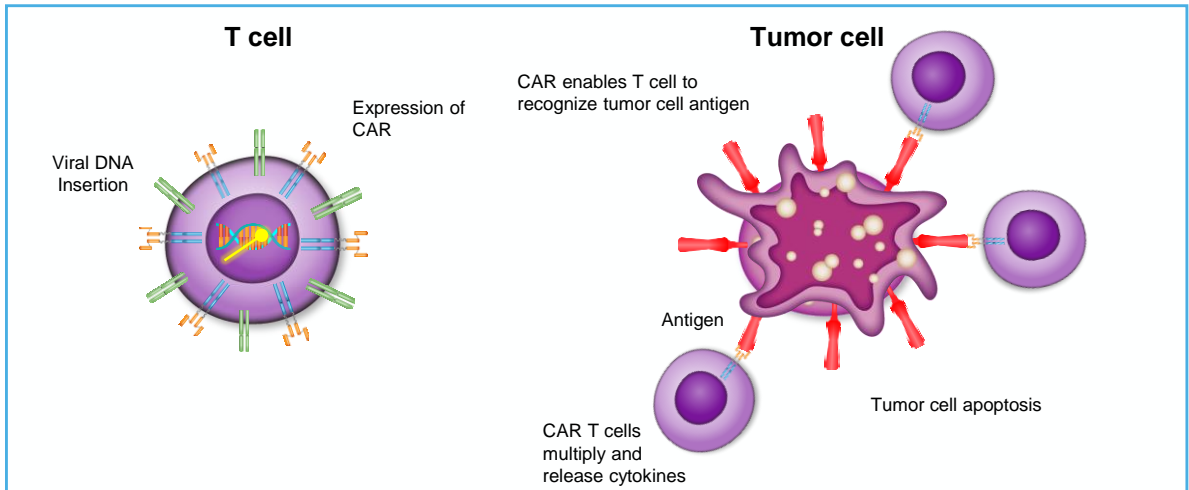


Source: mskcc.org

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CAR T Cells: Mechanism of Action



Available on the ASTCT Website.



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CD19-Targeted CAR Therapies Approved or Under Investigation in the United States

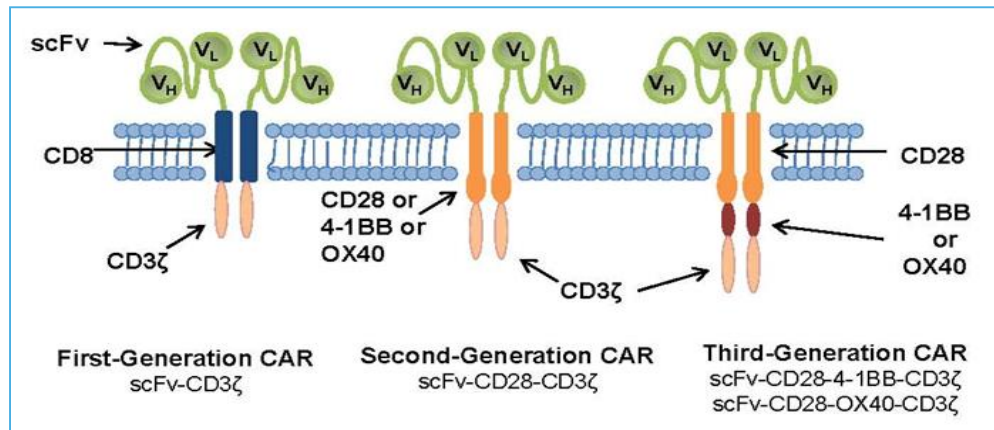
Academic Group	Company (Drug)	Co-Stimulatory Domain	Vector Delivery	Indications
UPenn	(Tisagenlecleucel) (CTL019) Novartis	4-1BB	Lentiviral	ALL, CLL, DLBCL, FL
Fred Hutchinson	(JCAR017) Juno	4-1BB	Lentiviral	ALL, CLL, various B-cell malignancies
NCI (NIH)	(Axicabtagene Ciloleucel) (KTE-C19) Kite, A Gilead Company	CD28	Retroviral	DLBCL, ALL, MCL
MDACC	Intrexon/Ziopharm	CD28 → 4-1BB	Transposon/transposase	B-cell malignancies
Institute Pasteur	(UCART19) Collectis/Pfizer	4-1BB	Lentiviral	ALL, CLL, AML, MM
Baylor	(BPX-401) Bellicum	MyDBB + CD40	Retroviral	Various
Dartmouth	Cardio3	DAP-10	Retroviral	AML, MDS, MM



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Evolution in CAR Design



Park J, et al. *Discov Med*. 2010;9(47):277-288.



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CTL019 (Tisagenlecleucel, KYMRIA[®])

- **Indication:** Tisagenlecleucel (KYMRIA[®]) is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- **Dose:**
 - For patients 50 kg or less: administer 0.2 to 5.0×10^6 CAR-positive viable T cells per kg body weight
 - For patients above 50 kg: administer 0.1 to 2.5×10^8 CAR-positive viable T cells
- **Conditioning Chemotherapy:** Fludarabine (30 mg/m² IV daily for 4 days) and cyclophosphamide (500 mg/m² IV daily for 2 days starting with the first dose of fludarabine). Infuse tisagenlecleucel (KYMRIA[®]) 2 to 14 days after completion of the lymphodepleting chemotherapy



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CTL019 (Tisagenlecleucel, KYMRIA[®])

- Pivotal phase 2 study:
 - ELIANA (NCT02435849)
- Evaluable patients: N = 63
 - 10% primary refractory disease
 - 48% one prior stem cell transplantation
 - 8% two prior stem cell transplantations

Results	N = 63
CR/Cri ^{a,b} (95% CI)	52 (83%) (71%, 91%) <i>P</i> < 0.0001
CR ^c	40 (63%)
CRi ^d	12 (19%)
CR or Cri with MRD-negative bone marrow ^{e,f} (95% CI)	52 (83%) (71%, 91%) <i>P</i> < 0.0001
Duration of Remission ^g	N = 52
Median (months) (95% CI)	Not reached (7.5, NE ^h)

^aCR/Cri was calculated based on all patients who received KYMRIA[®] and completed at least 3 months follow-up, or discontinued earlier prior to the data cutoff. Requires remission status to be maintained for at least 28 days without clinical evidence of relapse. ^bThe null hypothesis of CR/Cri less than or equal to 20% was rejected. ^cCR was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and ANC >1,000/microliter) without blood transfusion. ^dCri (complete remission with incomplete blood count recovery) was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion. ^eMRD negative was defined as MRD by flow cytometry less than 0.01%. ^fThe null hypothesis of MRD-negative remission rate less than or equal to 15% was rejected. ^gDuration of remission was defined as time since onset of CR or Cri to relapse or death due to underlying cancer, whichever is earlier, censoring for new cancer therapy including stem cell transplantation (N = 52). ^hNot Estimable.

1. KYMRIA[®] [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2017.
2. Buechner J, et al. *Haematologica*. 2017;102(s2): Abstract S476.



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Additional Anti-CD19 CAR T Therapies in Commercial Development for R/R B-ALL

	KTE-C19		JCAR017
Clinical Trial	ZUMA-3 NCT02614066	ZUMA-4 NCT02625480	NCT01865617
Phase	Phase 1/2	Phase 1/2	Phase 1/2
Dose Level	0.5 × 10 ⁶ CAR T cells/kg 1 × 10 ⁶ CAR T cells/kg 2 × 10 ⁶ CAR T cells/kg	1 × 10 ⁶ CAR T cells/kg 2 × 10 ⁶ CAR T cells/kg	2 × 10 ⁵ to 2 × 10 ⁷ EGFR ⁺ cells/kg
Conditioning Chemotherapy	Cyclophosphamide (900 mg/m ² × 1 day) + fludarabine (25 mg/m ² /day × 3 days)	Cyclophosphamide (900 mg/m ² × 1 day) + fludarabine (25 mg/m ² /day × 3 days)	Low-dose Cy/Flu or Cy ± etoposide
Evaluable Patients (N)	R/R adult ALL (n = 24)	R/R pediatric and adolescent ALL (N = 7)	R/R adult B-ALL (N = 30)
Response Rates	CR = 71%	CR = 100%	CR = 93%

1. Shah BJ, et al. ASH 2017. Abstract 888.
2. Lee DW, et al. ESMO 2017. Abstract 1008PD.
3. Turtle C, et al. *J Clin Invest*. 2016;126(6):2123-2138.



32

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

Neelapu SS, et al. *N Engl J Med.* 2017 Dec 28;377(26):2531-2544.



33

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

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

Schuster SJ, et al. *N Engl J Med.* 2017;377(26):2545-2554.



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Several Anti-B-Cell Maturation Antigen (BCMA) CAR T Therapies Are in Development for Multiple Myeloma

	bb2121	CART-BCMA	LCAR-B38M	CAR-BCMA	KTE-585
Clinical Trial	NCT02658929 (CRB-401 study)	NCT02546167	NCT03090659	NCT02215967	NCT03318861
Phase	Phase 1	Phase 1	Phase 1/2	Phase 1	Phase 1
Dose Level	Dose escalation: 50, 150, 450, 800, and 1,200×10 ⁶ CAR T cells	Cohort 1: 1-5×10 ⁸ CAR T cells alone Cohort 2: Cy + 1-5×10 ⁷ CAR T cells Cohort 3: Cy + 1-5×10 ⁸ CAR T cells	0.17 or 1.05×10 ⁶ CAR T cells/kg	4 dose levels, 0.3×10 ⁶ , 1×10 ⁶ , 3×10 ⁶ , and 9×10 ⁶ CAR+ T cells/kg	Dose escalation
Infusion	Single infusion	Split-dose infusions (10% on day 0, 30% on day 1, and 60% on day 2)	Infused on 3 days (d0, d2, and d6)	Single infusion	Single infusion
Conditioning Chemotherapy	Fludarabine (30 mg/m ²) and cyclophosphamide (300 mg/m ²) daily for 3 days	Cohort 2 and 3: Cy (1.5 g/m ²) on day -3	Fludarabine (25 mg/m ²) and cyclophosphamide (250 mg/m ²) daily for 3 days	300 mg/m ² of cyclophosphamide and 30 mg/m ² of fludarabine daily for 3 days	Fludarabine and cyclophosphamide for 3 days
Response Rates	ORR = 89% (N = 18)	Cohort 1: 6/9 patients responded Cohort 2: 2/5 patients responded	ORR = 100% (N = 5)	Dose level 4: 9/11 patients responded	

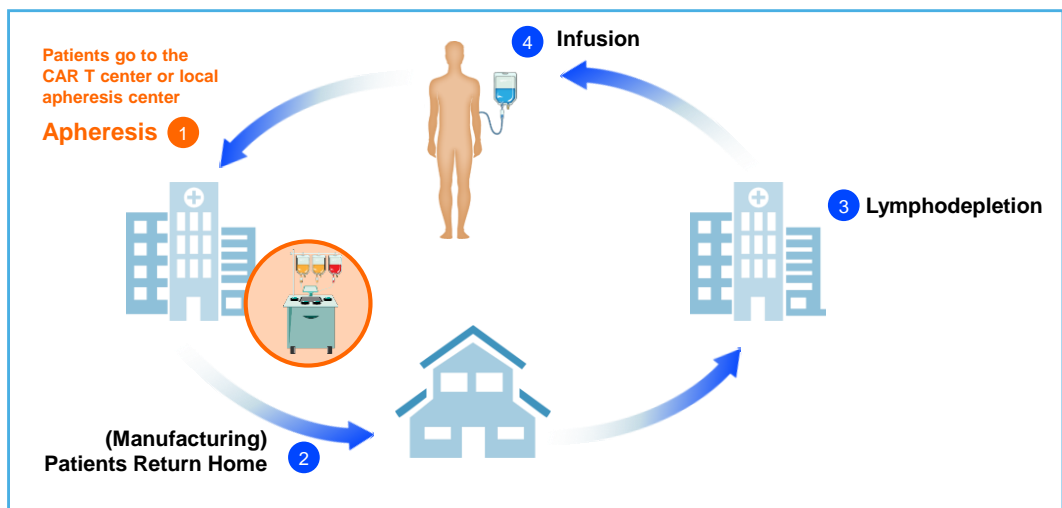
1. Kochenderfer JN, et al. ASH 2017. Abstract 740.
2. Cohen AD, et al. ASH 2017. Abstract 505.
3. Mi JQ, et al. ASH 2017. Abstract 3115.
4. Brudno J, et al. ASH 2017. Abstract 524.
5. <https://clinicaltrials.gov/ct2/show/record/NCT03318861>. Accessed March 2018.



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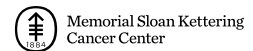
Patient Journey: Manufacturing to Infusion



36

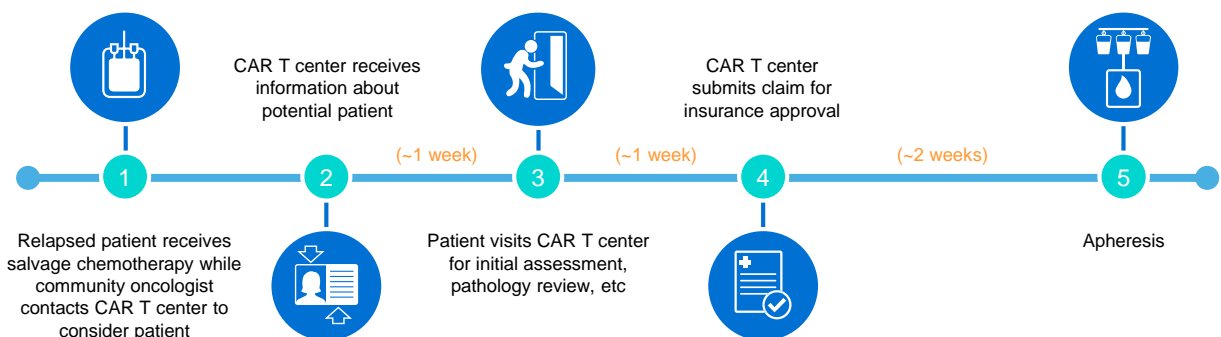
Key Questions to Consider When Thinking About Referring a Patient for CAR T Cell Therapy

- Does the patient qualify for a currently licensed product?
 - Tisagenlecleucel (Kymriah®):
 - RR ALL <25 years of age
 - RR CD19 + DLBCL
 - Axicabtagene Ciloleucel (Yescarta®)
 - RR CD19 + DLBCL
- What other treatment alternatives are there?
 - Commercial
 - Investigational
- Can the patient get CAR T cell therapy?
 - Qualify physically
 - Psycho-social support
 - Insurance coverage
- Do I have a place I can send them?



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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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Common Eligibility Criteria for CAR T Clinical Trials

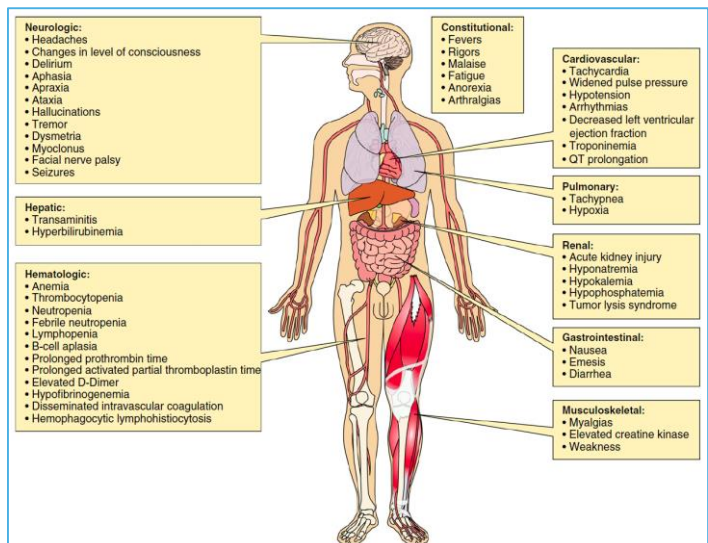
Key Inclusion Criteria	Key Exclusion Criteria
<ul style="list-style-type: none"> Life expectancy ≥ 12 weeks ECOG performance status of 0-1 at screening Adequate bone marrow reserve <ul style="list-style-type: none"> ANC $\geq 1000/\mu\text{L}$ ALC $> 100-300/\mu\text{L}$ Platelet count $\geq 50,000-75,000/\mu\text{L}$ Hemoglobin $> 8.0 \text{ g/dL}$ Adequate renal function <ul style="list-style-type: none"> Serum creatinine $\leq 1.5 \times \text{ULN}$ eGFR $\geq 60 \text{ mL/min/1.73 m}^2$ Creatinine clearance (as estimated by Cockcroft Gault) $> 60 \text{ mL/min}$ Adequate hepatic function <ul style="list-style-type: none"> Serum ALT/AST $< 2.5-5 \times \text{ULN}$ Total bilirubin $< 1.5-2 \text{ mg/dL}$, except in subjects with Gilbert's syndrome Adequate cardiac function <ul style="list-style-type: none"> Cardiac ejection fraction $> 45-50\%$, no evidence of pericardial effusion as determined by an ECHO Adequate pulmonary function <ul style="list-style-type: none"> Baseline oxygen saturation $> 91-92\%$ on room air Adequate vascular access for leukapheresis procedure 	<ul style="list-style-type: none"> History of allogeneic stem cell transplantation Prior CAR therapy or other genetically modified T-cell therapy Active CNS involvement by malignancy Active hepatitis B, hepatitis C, or HIV infection Uncontrolled acute life threatening bacterial, viral or fungal infection (eg, blood culture positive ≤ 72 hours prior to infusion) Cardiovascular disease <ul style="list-style-type: none"> Unstable angina and/or myocardial infarction within 6 months Cardiac arrhythmia not controlled with medical management Patients on oral anticoagulation therapy Previous or concurrent malignancy with the following exceptions: <ul style="list-style-type: none"> Adequately treated basal cell or squamous cell carcinoma In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study A primary malignancy which has been completely resected and in complete remission for ≥ 5 years History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement

www.clinicaltrials.gov. Accessed July 10, 2017.



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CRS Toxicities by Organ System



Budno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330.



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Patients Who Are Appropriate for CAR T Therapy

Factors to consider when selecting patients for CAR T therapy:

1. Age
2. Organ function
3. ECOG PS
4. Underlying neurological disorders, including seizures
5. Active infections
 - Uncontrolled infections may exacerbate certain toxicities, such as CTCAE grade 5 infections
6. CNS disease
 - Exclusion varies by CAR T therapy and indication



Many of the perceived barriers to CAR T therapy are generally not real barriers for patients

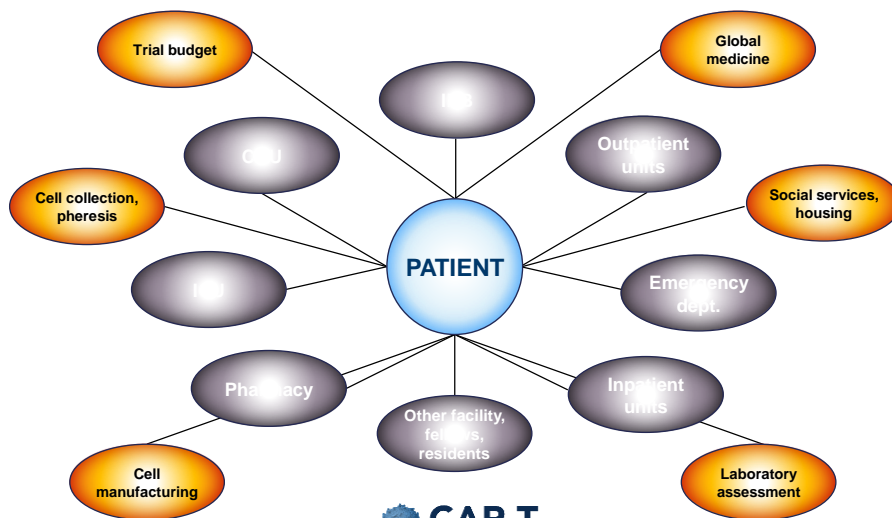
CTCAE, Common Terminology Criteria for Adverse Events;
ECOG PS, Eastern Cooperative Oncology Group Performance Status



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Best Practices: Ensure Crosstalk Between Clinical, Nursing, Financial, and Coordination Teams



www.clinicaltrials.gov. Search term "chimeric antigen receptor." Accessed May 18, 2017.



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Ongoing CAR Trials in Hematologic Malignancies

	Number of Clinical Trials			Targets Currently Being Investigated
	Total	Phase 1	Phase 2	
Lymphoma	105	89	44	
B-cell lymphoma	56	47	25	CD19, CD20, CD22, CD30
ALL	43	37	17	CD19, CD22, CD7
CLL	36	30	18	CD19, CD20, CD22
Non-Hodgkin lymphoma	67	58	29	CD19, CD30, CD22, CD20
DLBCL	24	20	14	CD19, CD20, CD22
MCL	16	14	11	CD19, CD20, CD22
FL	15	13	9	CD19, CD20, CD22
Burkitt lymphoma	14	13	5	CD19, CD20, CD22
Hodgkin lymphoma	11	9	3	CD19, CD30, NY-ESO
Leukemia	90	76		
B-cell leukemia	36	30	17	CD19, CD5, CD20, CD22, CD30, CD33, CD123, BCMA
AML	12	9	3	CD7, CD33, CD123
MM	13	11	4	CD19, BCMA, CD138, NY-ESO



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Ongoing CAR Trials in Solid Tumors

	No. of Clinical Trials	Targets Currently Being Investigated
Astrocytoma	7	HER2, EGFRvIII, IL13Rα2
Glioblastoma	7	HER2, EGFRvIII, IL13Rα2, NY-ESO
Breast	13	HER2, EpCAM, cMET, Mesothelin, ROR1, MUC1, CEA, CD70, CD133, NY-ESO
Colorectal	9	CEA, EGFR, MUC1, HER2, CD133,
HCC	11	Glypican-3 (GPC3), MUC1, EPCAM, NY-ESO
NSCLC	5	PD-L1, MUC1, ROR1, CEA, NY-ESO
Melanoma	3	cMET, GD2, CD70, NY-ESO
Mesothelioma	4	FAP, mesothelin
Neuroblastoma	8	GD2, CD171, NY-ESO
Ovarian	7	Mesothelin, CD70, HER2, CD133, CEA, NY-ESO
Pancreatic	13	Mesothelin, Prostate Stem Cell Antigen (PSCA), CD70, MUC1, HER2, CD133, NY-ESO
Stomach	8	EPCAM, CEA, MUC1, HER2, NY-ESO
Thoracic	5	MUC1, ROR1, PD-L1



www.clinicaltrials.gov. Search term "chimeric antigen receptor." Accessed May 18, 2017.

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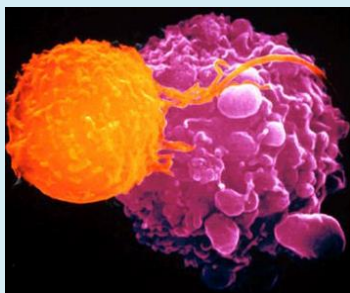
Memorial Sloan Kettering
Cancer Center

THANK YOU!

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CAR-T Cell Toxicity



Ran Reshef, MD, MS
BMT and Cell Therapy Program
Columbia University Medical Center
New York, NY

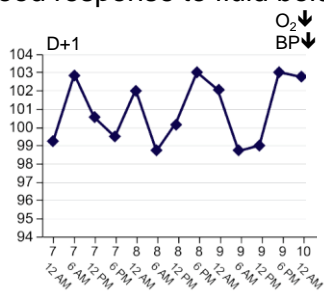
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John, A 52-Year-Old Man with DLBCL

- Presented in December 2017 with epigastric pain and fatigue.
- Imaging showed extensive lymphadenopathy, 18cm mesenteric mass and bone marrow involvement.
- Biopsy - DLBCL with myc amplification, TP53 mutation
- 2 cycles of R-EPOCH -> Progressive disease
- 2 cycles of R-DHAP -> Progressive disease
- Cells collected for CD19-targeting autologous CAR-T cells.
- Bridging therapy – high dose dexamethasone, complicated by clostridium difficile colitis and influenza
- CAR-T cells infused on June 6th, 2018 after lymphodepleting chemotherapy.

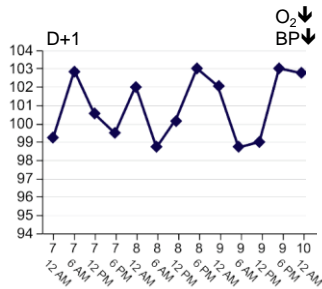
John, A 52-Year-Old Man with DLBCL

- CAR-T infusion well-tolerated.
- On day +1 new onset of high fevers. Infectious workup negative and empiric antibiotics started. Around-the-clock acetaminophen started.
- On day +4 fevers ongoing. O₂ saturation drops to 89% and BP 90/50 without good response to fluid bolus.



John, A 52-Year-Old Man with DLBCL

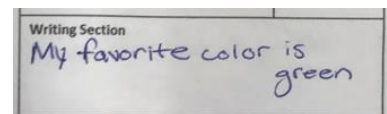
- Tocilizumab (IL-6R inhibitor) is administered i.v. for grade 2/3 **Cytokine Release Syndrome (CRS)**.
- Resolution of symptoms within several hours.



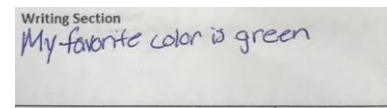
John, A 52-Year-Old Man with DLBCL

- On Day+5 the patient appears sleepy.
- Slight tremor on exam.
- On Day+6 unable to name certain objects, operate smartphone, write a sentence.
- On exam no focal symptoms, MRI brain and EEG without findings.
- Dexamethasone 10mgQ6hr started for **Immune Effector Cell-Associated Neurotoxicity (ICANS)**.
- On Day+7 neurological exam back to baseline.

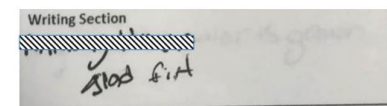
Day 0



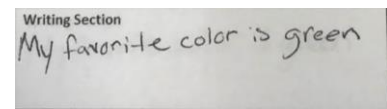
Day +5



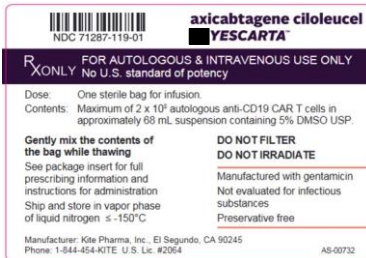
Day +6



Day +7



First FDA-Approved CAR-T Cells

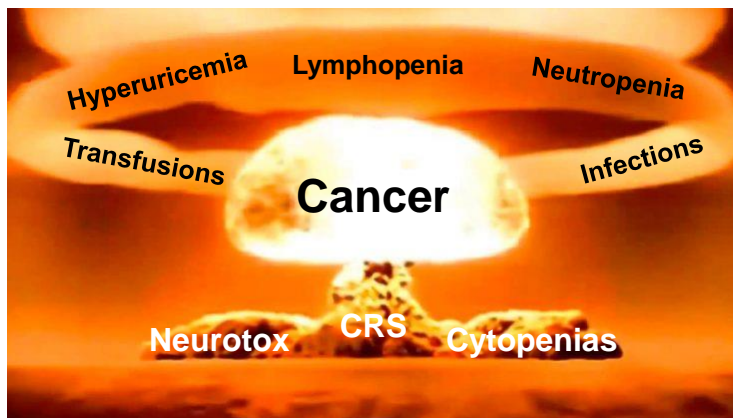


Oct. 17, 2017 – adult lymphoma



Aug. 30, 2017 – ALL up to age 25
May 1, 2018 – adult lymphoma

CAR T Cell Therapy: Toxicity



CAR T Cell Therapy: Toxicity

Cytokine Release Syndrome (CRS)

- Common; requires careful monitoring and management.

Neurologic Side Effects

- Changes in mental status, confusion, delirium, aphasia. Cerebral edema and seizures rare.

Cytopenias

- Generally from chemotherapy regimen. Reversible but frequently prolonged

HLH/MAS – uncommon. Generally considered a severe form of CRS.

Prolonged hypogammaglobulinemia due to B-cell aplasia

Infusion reactions - rare

Tumor Lysis Syndrome – rare but important to monitor in high tumor burden

HLH - Hemophagocytic lymphohistiocytosis; MAS - Macrophage activation syndrome



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Cytokine Release Syndrome (CRS)

CRS is a condition resulting from the release of cytokines from activated CAR T cells, as well as bystander immune cells.

Most patients who respond to CAR T therapy develop CRS.

Blocking IL-6 signaling with a monoclonal antibody (tocilizumab) is effective therapy. Steroids are used for severe or refractory CRS.

Patients treated inpatient or requested to be close to the hospital.

REMS, Risk Evaluation and Mitigation Strategy

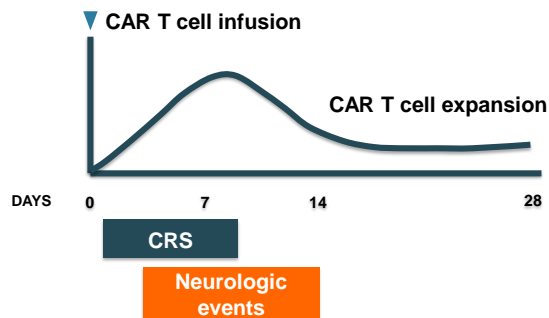


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Typical Onset and Resolution of CRS and Neurotoxicity

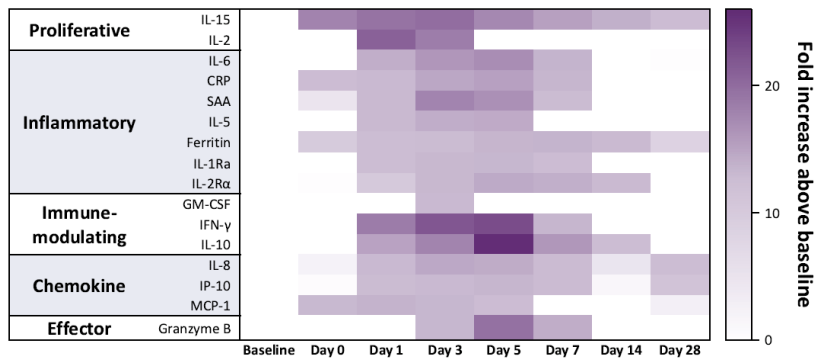
- CRS may occur within hours but generally appears within days (day 1-14)
- Coincides with maximal T-cell expansion
- Median time to CRS onset for commercial CAR-T cells: 2 – 3 days



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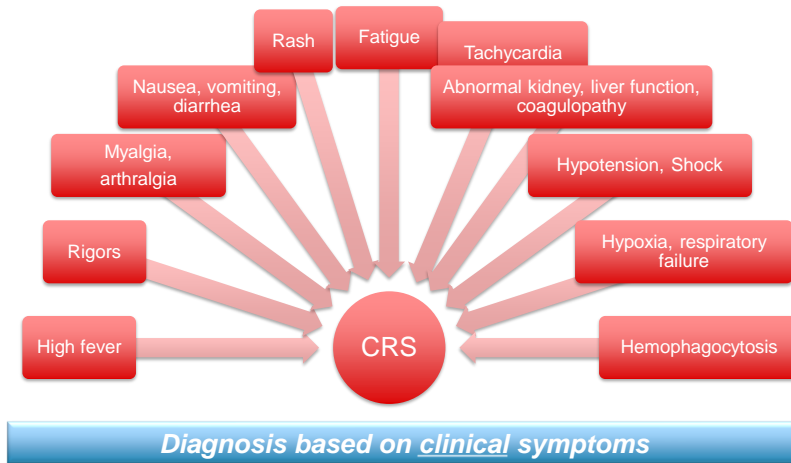
Cytokine Storm After CAR-T Infusion

Elevation of multiple cytokines and markers of inflammation observed following CAR-T infusion.



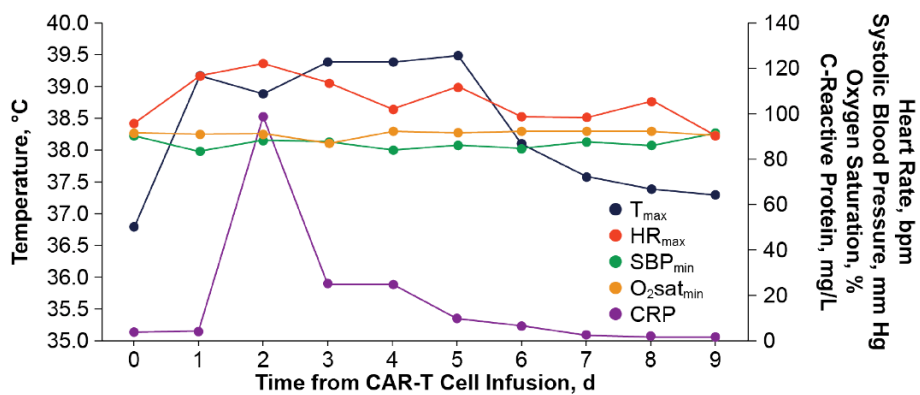
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Signs and Symptoms of CRS



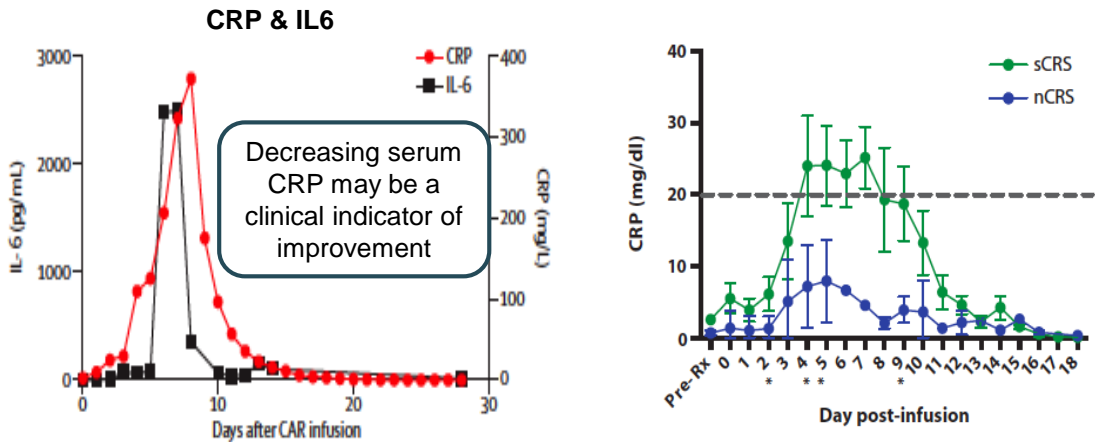
57

CRS – Typical Course



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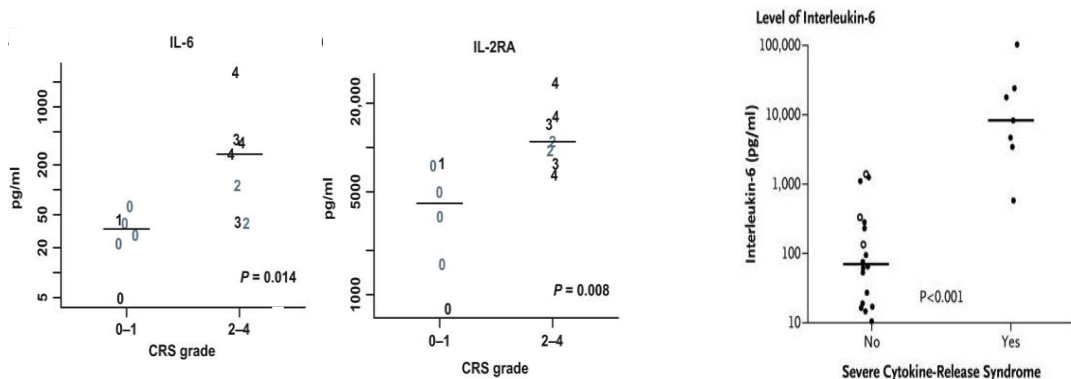
C-Reactive Protein (CRP) is a Biomarker for CRS



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Peak Cytokine Levels Correlate with CRS Severity

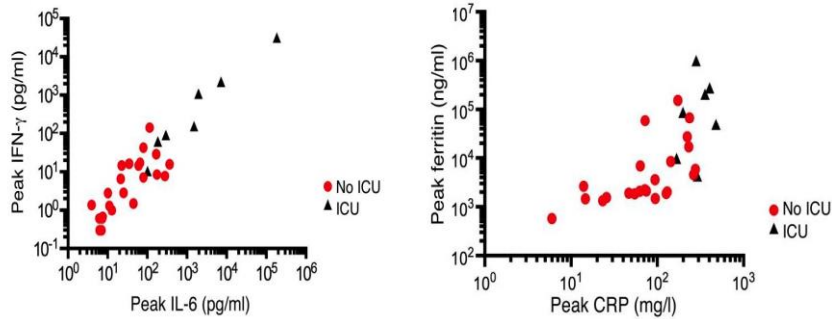
CRS grade correlates with peak IL-6 and IL-2RA levels



60

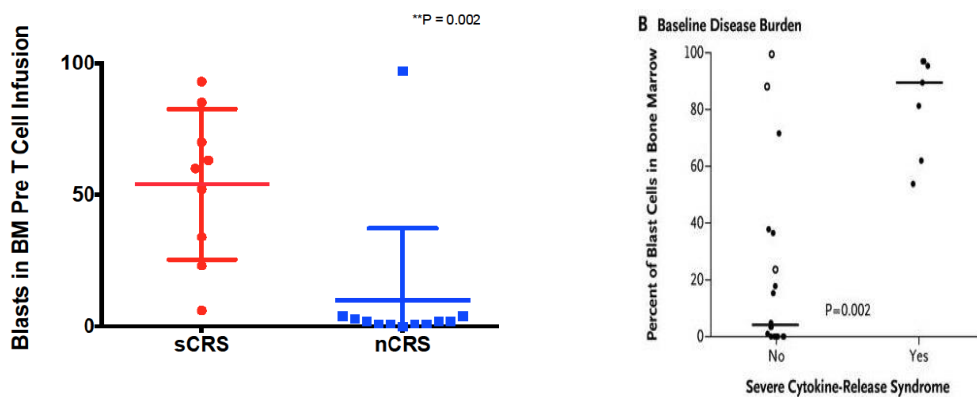
Peak Cytokine Levels Correlate with CRS Severity Requiring ICU Care

- Higher peak IL-6 and IFN- γ levels are observed in patients requiring ICU care.
- Elevations of serum C-reactive protein (CRP) and ferritin correlate with the occurrence of severe CRS requiring ICU care.



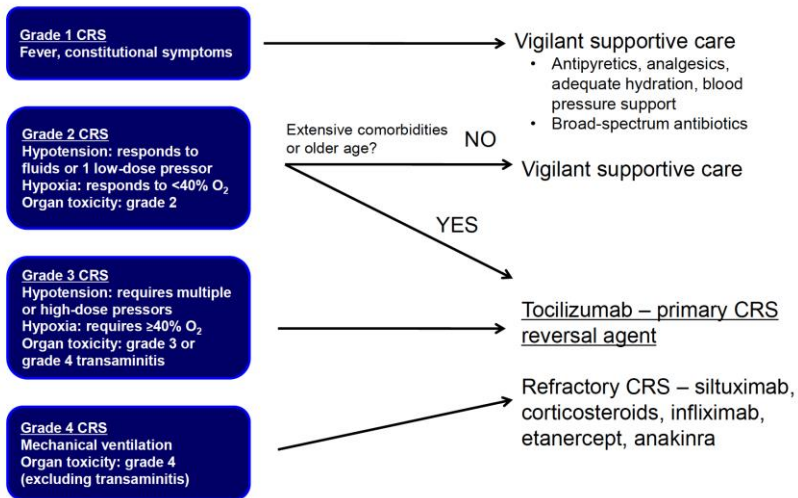
61

CRS Severity Correlates with Disease Burden



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CRS Management

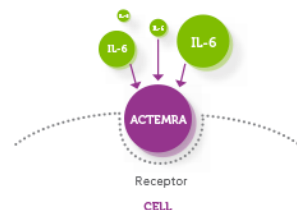


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Tocilizumab for Treatment of CRS

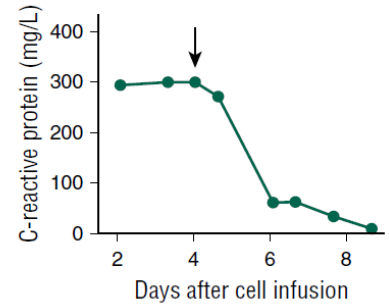
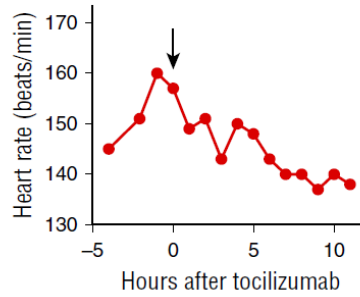
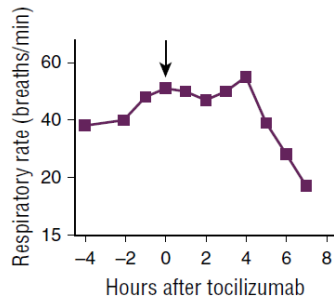
Tocilizumab	
MOA	IL-6 receptor antagonist (monoclonal antibody)
Approved indication	Polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and rheumatoid arthritis, CRS
AEs	Transaminitis and neutropenia (uncommon)
Dosage in CRS management	<ul style="list-style-type: none"> • 8 mg/kg IV over 1 hour (maximum dose of 800 mg) • Some patients may require a second or third dose

- Tocilizumab is approved by the FDA for the treatment of CAR T-cell–induced CRS
- Steroids are indicated in patients with life-threatening CRS or failure of tocilizumab
- Treatment of CRS does not impact the in vivo expansion of CAR-T cells and does not seem to impair efficacy



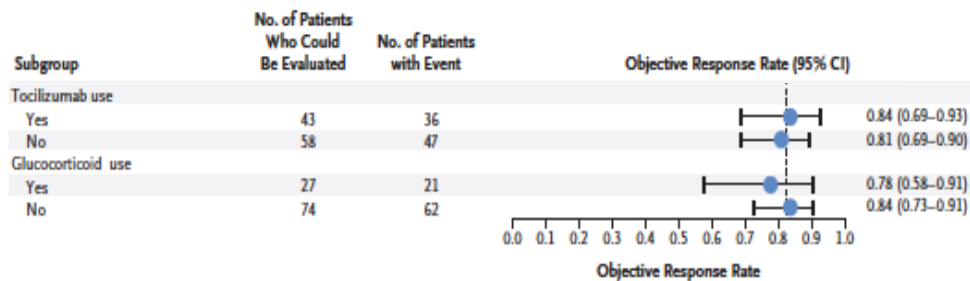
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Response to Tocilizumab



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Impact of CRS Treatment on Response to CAR-T Cells



From ZUMA-1 study – axi-cel in aggressive NHL

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CAR-T Neurotoxicity

- Neurotoxicity resembles a toxic/metabolic encephalopathy
- Symptoms include diminished attention, headache, anxiety, tremor, aphasia, dysphasia, difficulty in performing complex tasks (handwriting), memory loss, confusion, somnolence, altered mental status
- Nearly all neurotoxicity events occur within the first 4-8 weeks following infusion
- The median time to onset is 3-10 days
- Prolonged symptoms lasting up to 6 months anecdotally observed
- Serious events including cerebral edema and seizures have occurred

Neurotoxicity Management

MONITORING and WORKUP

All patients with grade ≥ 2 neurologic toxicity should be evaluated by the neurology consult service.

Neurological examination q 4 hours

Rule out other causes of neurologic symptoms.

Brain MRI

EEG

Examination of the cerebrospinal fluid (CSF)

TREATMENT

Reassurance

Severe neurologic toxicities are frequently treated with systemic corticosteroids.

- Dexamethasone is commonly used for grade ≥ 2 neurologic toxicity.
- Life-threatening neurotoxicity (e.g., cerebral edema) is treated with high-dose methylprednisolone.

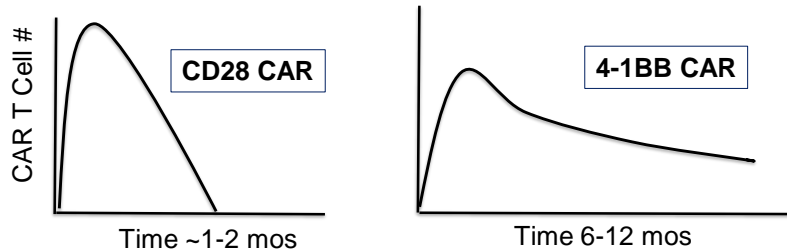
Initiate non-sedating antiseizure prophylaxis (e.g., levetiracetam) in patients with active neurotoxicity.

Monitor patients for 4 weeks close to the center.

Patients should not drive for 8 weeks.

Do all CAR-T Cells Have the Same Toxicity?

- Costimulatory domain affects expansion and persistence.
- These differences also determine the kinetics of toxicities: CD28 early and rapid; 4-1BB gradual.
- New CAR-T targets may have additional off-target effects based on their expression in healthy tissues.



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Toxicity – Are the Products Different??

CAR-T product	KTE-C19 (Kite) CD28, bulk T	CTL019 (Novartis) 4-1BB, bulk T	JCAR017 (Juno) 4-1BB, CD4/CD8 subsets
Study populations	DLBCL, TFL, PMBCL (N=101)	DLBCL (N=115)	DLBCL, tFL, FL3B (N=102)
Any CRS	<ul style="list-style-type: none"> • Comparisons across trials • Different grading schemas • Different toxicity management algorithms • Learning curve over time 		
≥ Grade 3 CRS			
Any NT			
≥ Grade 3 NT			
Grade 5 CRS or NT			
Tocilizumab	43%	15%	17%
Steroids	27%	11%	21%

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Evolution of CRS Grading

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, IV fluids); prophylactic medication 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 infarction)	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 IV fluids or low dose of one vasopressor OR • Grade 2 organ toxicity ¹	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 ¹ or grade 4 transaminitis	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity ¹ (excluding transaminitis)
Penn criteria [17]	Mild reaction: Treated with supportive care, such as antipyretics, antiemetics	Moderate reaction: Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including sepsis-like fever and need for IV therapies (not including fluid resuscitation for hypotension)	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation
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 ¹	Hypotension responds to IV fluids or low-dose vasopressor Hypoxia requiring FIO ₂ <40% Grade 2 organ toxicity ¹	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FIO ₂ >40% Grade 3 organ toxicity ¹ or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity ¹ except grade 4 transaminitis



National Cancer Institute. Common terminology criteria for adverse events (CTCAE); Lee et al., BBMT 2019; Lee et al., Blood 2014; Neelapu et al. Nat Rev Clin Oncol 2018; Park et al. NEJM 2018; Porter et al. J Hematol Oncol 2018

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Revised Grading Scales for CRS

	2014 NCI Consensus Revised Grading Scale ¹	Penn Grading Scale (PGS-CRS) ²
Grade 1	<ul style="list-style-type: none"> Symptoms are not life threatening Symptomatic treatment only (ex: fever, nausea, fatigue, headache, myalgias, malaise) 	<ul style="list-style-type: none"> Mild reaction Treated with supportive care (anti-pyretics, antiemetics)
Grade 2	<ul style="list-style-type: none"> Symptoms require and respond to moderate intervention <u>Hypoxia</u>: responsive to <40% oxygen <u>Hypotension</u>: responsive to fluids or one low dose vasopressor Grade 2 organ toxicity 	<ul style="list-style-type: none"> Moderate Requires IV therapies or parenteral nutrition Some signs of organ dysfunction (i.e. grade 2 Cr or grade 3 LFTs) related to CRS Hospitalization for CRS-related symptoms including fevers with associated neutropenia
Grade 3	<ul style="list-style-type: none"> Symptoms require and respond to aggressive intervention <u>Hypoxia</u>: requires oxygen >40% <u>Hypotension</u>: requires high dose or multiple vasopressors Grade 3 organ toxicity Grade 4 transaminitis 	<ul style="list-style-type: none"> More severe reaction requiring hospitalization Moderate signs of organ dysfunction (grade 4 LFTs or grade 3 Cr) related to CRS <u>Hypotension</u> treated with IV fluids or low dose pressors Coagulopathy requiring FFP or cryoprecipitate <u>Hypoxia</u> requiring supplemental O₂ (nasal cannula oxygen, high flow O₂, CPAP or BiPAP)
Grade 4	<ul style="list-style-type: none"> Life-threatening symptoms Requirement for ventilator support Grade 4 organ toxicity (excluding transaminitis) 	<ul style="list-style-type: none"> Life-threatening complications <u>Hypotension requiring high dose pressors</u> <u>Hypoxia requiring mechanical ventilation</u>
Grade 5	Death	Death



Lee DW et al. Blood. 2014.
Porter DL et al. Sci Transl Med. 2015.

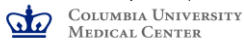
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ASTCT CRS Consensus Grading 2019

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
			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)

ASTCT American Society of Transplantation and Cell Therapy

Lee et al., BBMT 2019.



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Prevent or Treat CAR-T Toxicity? Which is Better?

Prophylactic Tocilizumab

- ZUMA-1 Safety Management Cohort examined prophylactic tocilizumab on day +2 in patients receiving axi-cel for aggressive NHL.
- N=34
- Response rates and CAR-T expansion not significantly different from expected.
- Severe CRS reduced. Neurotoxicity not reduced (possibly increased!).

Event, n (%)	ZUMA-1 Primary Analysis (N = 101)	SMS Cohort 3 (N = 34)	
Any CRS	94 (93)	32 (94)	
Worst grade ≥ 3	13 (13)	1 (3)	↓
Any NE	63 (62)	29 (85)	↑
Worst grade ≥ 3	28 (28)	14 (41)	↑



Locke et al., ASH 2017.

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Prevent or Treat CAR-T Toxicity? Which is Better?

Early Steroid Use

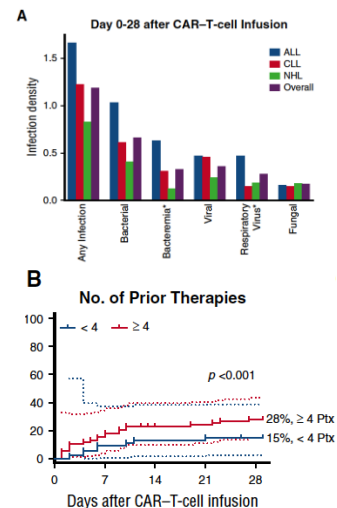
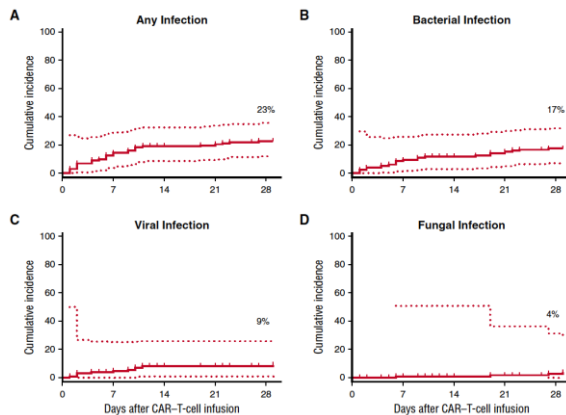
- ZUMA-1 Revised AE Management Cohort examined early use of steroids and tocilizumab for grade 1 CRS and neurotoxicity.
- N=21
- Tocilizumab used in 86%; steroids used in 76%.
- Response rates and CR rates similar to expected.
- Severe CRS eliminated. Severe neurotoxicity significantly reduced.

AE Grade, n (%)		ZUMA-1 Standard Algorithm (N = 108)	Early Intervention Cohort (N = 21)
NEs	Grade 1 or 2	37 (34)	10 (48)
	Grade ≥ 3	35 (32)	2 (10) ↓
CRS	Grade 1 or 2	88 (81)	21 (100)
	Grade ≥ 3	12 (11)	0 (0) ↓

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Other Toxicities

Infections



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Other Toxicities

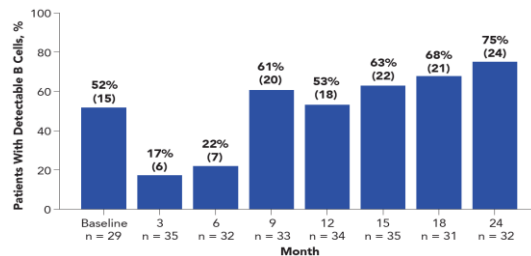
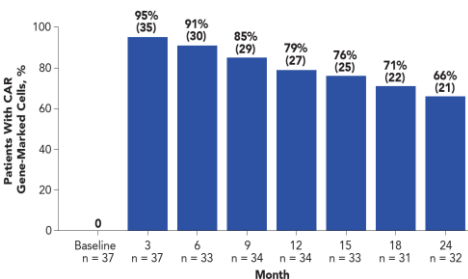
Prolonged Cytopenias

- Up to a quarter of patients will still have grade 3-4 cytopenias 3 months after CAR-T infusion.
- Transfusions and growth factor support are allowed and recommended.

Other Toxicities

Hypogammaglobulinemia

- Persistence of CD19-targeting CAR-T cells may lead to prolonged depletion of healthy B cells in addition to protection against cancer cells.
- Monitoring of IgG levels and IVIG repletions are recommended until recovery.
- Many patients will recover B cells and antibody production over time.



CAR-T Cells Real World Experience

- N=295 (17 centers). Commercial axi-cel (non-clinical trial patients)
- Median time from leukapheresis to LD chemo – 21.5 days
- Manufacturing failure 2%
- 55% received bridging chemotherapy
- Median age 60 (range 21-83)
- 19% ECOG performance status > 1

CAR-T cells Real World Experience

43% of patients would not have met eligibility for ZUMA-1.

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)

CAR-T cells Real World Experience - Safety

Toxicity was no different compared to the ZUMA-1 pivotal trial

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

Treatment-related deaths – 2 (<1%)

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Future Developments: Safety

- Better understanding of risk factors, dosing, manufacturing
- Split dosing
- Prophylactic/ Pre-emptive tocilizumab or steroid treatment
- Alternative agents – siltuximab, JAK inhibitors, anakinra
- Safety switches – iCasp9 suicide gene, CD20 suicide gene
- Block Trafficking to CNS – Natalizumab (α 4 integrin inhibitor)
- “Armored” CARs that express IL-12 or IL-15 locally

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REMS Requirements

REMS – Risk Evaluation and Mitigation Strategy

- Site certification
- Training for all personnel caring for CAR-T patients
- Availability of tocilizumab – 2 doses per patient with immediate availability
- Patients should carry a wallet card and
- Quality assurance plan

Collaborative Management is Critical



Back to Our Patient John...

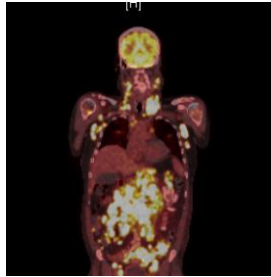
52 yo male

DLBCL with myc amplification, TP53 mutation. Failed 2 lines of therapy.

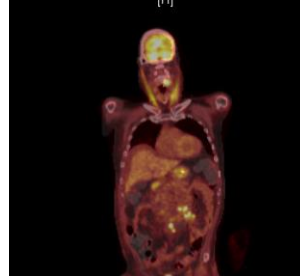
2 lines of therapy – best response PD

Grade 2 CRS; Grade 2 ICANS. Treated successfully with tocilizumab and short steroid course.

Baseline



D+30



Risks Should be Assessed in the Context of the Potential Benefit

CRS - Cytokine Release Syndrome; ICANS – Immune Effector Cell-Associated Neurotoxicity



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Thank you!



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CART THERAPY IN ALL

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Overview

- Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia Clinical Trial Results
- Tisagenlecleucel indications
- Tisagenlecleucel administration
- Tisagenlecleucel monitoring
- Mechanisms of relapse
- Limitations of CART therapy
- Role of AlloHSCT
- Clinical Trials of CART including adults

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Original Article

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

Shannon L. Maude, M.D., Ph.D., Theodore W. Laetsch, M.D., Jochen Buechner, M.D., Ph.D., Susana Rives, M.D., Ph.D., Michael Boyer, M.D., Henricque Bittencourt, M.D., Ph.D., Peter Bader, M.D., Michael R. Verneris, M.D., Heather E. Stefanski, M.D., Ph.D., Gary D. Myers, M.D., Muna Qayed, M.D., Barbara De Moerloose, M.D., Ph.D., Hidefumi Hiramatsu, M.D., Ph.D., Krysta Schlis, M.D., Kara L. Davis, D.O., Paul L. Martin, M.D., Ph.D., Eneida R. Nemecek, M.D., Gregory A. Yanik, M.D., Christina Peters, M.D., Andre Baruchel, M.D., Nicolas Boissel, M.D., Ph.D., Françoise Mechinaud, M.D., Adriana Balduzzi, M.D., Joerg Krueger, M.D., Carl H. June, M.D., Bruce L. Levine, Ph.D., Patricia Wood, M.D., Ph.D., Tetiana Taran, M.D., Mimi Leung, M.P.H., Karen T. Mueller, Pharm.D., Yiyun Zhang, Ph.D., Kapildeb Sen, Ph.D., David Lebwohl, M.D., Michael A. Pulsipher, M.D., and Stephan A. Grupp, M.D., Ph.D.

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Study Overview

- CD19-specific CAR T cells were produced centrally for a global study in young people with relapsed B-cell ALL.
- The overall remission rate was 81%, and patients with a response were negative for minimal residual disease.
- High-grade toxic effects were frequent but treatable.

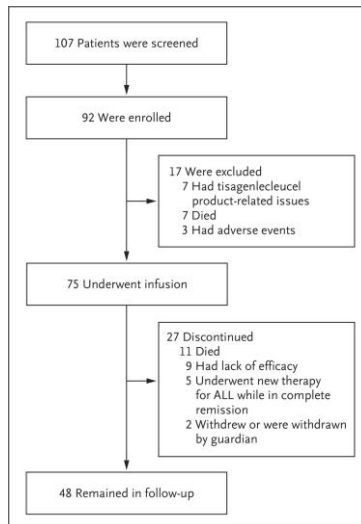
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Screening, Enrollment, Treatment and Follow-up



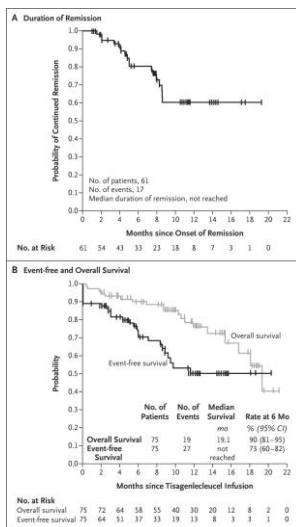
Maude SL et al. N Engl J Med 2018;378:439-448.

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Duration of Remission, Event-free Survival, and Overall Survival



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

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Overall Safety of Tisagenlecleucel

Table 1. Overall Safety of Tisagenlecleucel.

Event	Any Time (N = 75)	≤8 Wk after Infusion (N = 75)	>8 Wk to 1 Yr after Infusion (N = 70)
		<i>number of patients (percent)</i>	
Adverse event of any grade	75 (100)	74 (99)	65 (93)
Suspected to be related to tisagenlecleucel	71 (95)	69 (92)	30 (43)
Grade 3 or 4 adverse event	66 (88)	62 (83)	31 (44)
Suspected to be related to tisagenlecleucel	55 (73)	52 (69)	12 (17)

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

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

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

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

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

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Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel

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)
	<i>number of patients (percent)</i>		
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."

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

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Conclusions

- In this global study of CAR T-cell therapy, a single infusion of tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects.

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Indications

- FDA label indication for the use of tisagenlecleucel is for patients <26 years of age and CD19+ B-ALL that is refractory or with ≥ 2 relapses.
 - Limited published experience with the use of CAR T-cell therapy in infants <12 mo of age.
 - Relapse includes medullary and/or extramedullary disease. CAR T cells have shown activity against extramedullary disease.
- Treatment course consists of lymphodepleting chemotherapy (with fludarabine and cyclophosphamide) followed by tisagenlecleucel 2 to 14 days following completion of the fludarabine/cyclophosphamide regimen.
- Dosing is based on weight reported at the time of leukapheresis
 - ≤ 50 kg: IV: 0.2 to 5 x 10⁶ CAR-positive viable T cells per kg body weight
 - >50 kg: IV: 0.1 to 2.5 x 10⁸ CAR-positive viable T cells

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Administration

- Prior to apheresis for T-cell collection, consider avoidance of agents that may significantly impact the absolute lymphocyte count and/or T-cell function.
- The following lymphodepletion regimen is suggested prior to infusion of tisagenlecleucel (with alternatives allowed):
- Fludarabine (30 mg/m² IV daily for 4 days)
- Cyclophosphamide (500 mg/m² IV daily for 2 days starting with first dose of fludarabine)
- Infuse tisagenlecleucel 2 to 14 days after completion of the lymphodepleting chemotherapy.
- Recommend evaluation of response 28 days after tisagenlecleucel infusion.

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Monitoring

- Hypogammaglobulinemia: Monitor IgG levels after treatment with tisagenlecleucel and replace with IV or subcutaneous immunoglobulin per standard guidelines (generally accepted to replete for IgG <400 mg/dL).
- Patients may be monitored for B-cell aplasia (BCA) as a surrogate measure of functional CAR T-cell persistence.
- There is no consensus of the role of subsequent vaccination in patients with functional persistence of CAR T cells.

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Relapse Mechanisms

- CD19-negative relapse when CD19 antigen is lost due to the immunologic pressure exerted by CD19 CART
 - Results in alternatively spliced isoform of CD19 that is no longer recognized by the CART
- CD19-negative relapse with acquisition of an AML phenotype in KMT2A-rearranged B-ALL
 - In 7 patients with KMT2A-rearranged B-ALL treated with CD10 CART therapy, all patients initially achieved a CR, however, 2 patients developed CD19-negative AML (clonally related to their ALL)
- CD19-positive relapse
 - Seems to occur exclusively in patients who do not have engraftment and persistence of CART
 - May be due to immune-mediated rejection

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Limitations

- Manufacturing challenges
 - Autologous lymphocyte collection can be challenging depending on patient size, absolute lymphocyte count, recent exposure to chemotherapy, prior HCT
 - “Off the shelf” product
- Patients requiring ongoing immunosuppression for GVHD are ineligible
 - Product resistant to immunosuppressive agents such as calcineurin inhibitors
- CD19 Antigen escape
 - Alternative B-cell targets such as CD22 (shows promise in phase I trial even in patients previously treated with CD19 targeted CART)
 - Bi-specific CART constructs CD19/CD22
- Poor response or poor persistence of CART
 - Addition of checkpoint inhibitors
- Toxicity
 - CRS
 - CRES

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

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Role of AlloHSCT

- 52 patients (25%) proceeded to HCT following CART
 - 40 (77%) disease free survival
 - 8 (15%) relapsed
 - 4 (8%) alive with unknown disease status
- 128 patients survived CART therapy, achieved a hematologic CR and did not proceed to HCT
 - 42% with eventual disease relapse
- EFS and OS of 50% at 12 months
- HCT can offer improvement upon the 12-month EFS and OS provided by CART therapy alone
- CART is a bridge to HCT, but does not replace it
 - Expedient HCT recommended for KMT2A-rearranged B-ALL due to high risk of relapse with AML phenotype

CR, Complete Response; EFS, Event-Free Survival; HCT, Hematopoietic Cell Transplant; OS, Overall Survival

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Clinical Trials including Adults

- Modified receptor, termed 19-28z—which links the CD19 binding receptor to the costimulatory protein CD28
- CR in 14 out of 16 patients with relapsed or refractory B-cell ALL following infusion with CAR T cells
- 7 out of 16 patients were able to receive an allogeneic HCT
 - None have relapsed
- Follow-up data of adult patients enrolled on this trial (n = 53) showed a 83% CR rate after the infusion
 - 32 patients achieved an MRD-negative CR
 - At a median follow-up of 29 months (range, 1–65), the median OS was 12.9 months (95% CI, 8.7–23.4 months)
 - Subsequent allogeneic HCT did not appear to improve survival
- KTE-C19 uses a similar anti- CD19 CAR construct, and demonstrated an MRD-negative CR in 6 of 8 efficacy-evaluable adult patients with R/R ALL

MRD, Minimal Residual Disease

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Clinical Trials including Adults

- A second receptor construct defined by the attachment of an alternative costimulatory protein, 4-1BB, to the CD19 binding protein has shown similar results to the 19-28z CAR T cells
- CTL019, were infused into 16 children and 4 adults with R/R ALL; a CR following therapy was achieved in 14 patients
- No response of the disease to treatment in 3 patients and disease response to therapy was still under evaluation for 3 patients
- A follow-up study of 25 children and 5 adults showed a morphologic CR of 90% (27 out of 30) patients within a month of treatment and an OS of 78% (95% CI, 65%–95%) and EFS of 78% (95% CI, 51%– 88%) at 6 months.
- There were 19 patients in sustained remission, of which 15 received no further therapy.

Grupp SA, Frey NV, Aplenc R, et al. T Cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) produce significant in vivo proliferation, complete responses and long-term persistence without GVHD in children and adults with relapsed, refractory ALL [abstract]. Blood 2013;122:Abstract 67.
Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-1517.

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Conclusions

- CART represents a valuable therapy in children and young adults with relapsed/refractory ALL
- At the present time, alloHSCT still plays a role in therapy following CART
- Newer constructs are needed and under development to address CD19 antigen escape, manufacturing difficulties, and the treatment of patients requiring immunosuppression
- Promising results seen in the adult population, however, the toxicity profile needs to be better defined

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THANK YOU!

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CAR T-cells: A Major Advance for Patients with Refractory DLBCL

Ira Braunschweig, MD

Director, Stem Cell Transplantation
Clinical Program Director Hematologic Malignancies
Montefiore Medical Center
Bronx, NY

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2 FDA Approved CAR-Ts for Relapsed or Refractory Large B-cell Lymphomas

- Axicabtagene ciloleucel (Axi-cel)
- Tisagenlecleucel
- costimulatory domain: CD28 in axicabtagene ciloleucel; 4-1BB in tisagenlecleucel
- gene transfer method: retrovirus in axicabtagene ciloleucel; lentivirus in tisagenlecleucel

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Zuma-1

The Study That Started It All

- 111 patients with refractory DLBCL, PMBCL, or Transformed FL were treated with Axi-cel after lymphodepleting chemotherapy
- Refractory was defined as stable or progressive disease to last chemotherapy regimen or relapsing within 12 months of autologous stem cell

Neelapu SS et. al. NEJM 2017; 377:2531-44.

DLBCL, Diffuse large B-cell lymphoma
PMBCL, Primary mediastinal B-cell lymphoma

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Characteristics

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Age			
Median (range) — yr	58 (25–76)	57 (23–76)	58 (23–76)
≥65 yr — no. (%)	17 (22)	7 (29)	24 (24)
Prior therapies — no. (%)			
≥Three prior lines of therapy	49 (64)	21 (88)	70 (69)
History of primary refractory disease**	23 (30)	3 (12)	26 (26)
History of resistance to two consecutive lines	39 (51)	15 (62)	54 (53)

Neelapu SS et. al. NEJM 2017; 377:2531-44.

111

How Do These Patients Typically Do? Scholar-1 Study

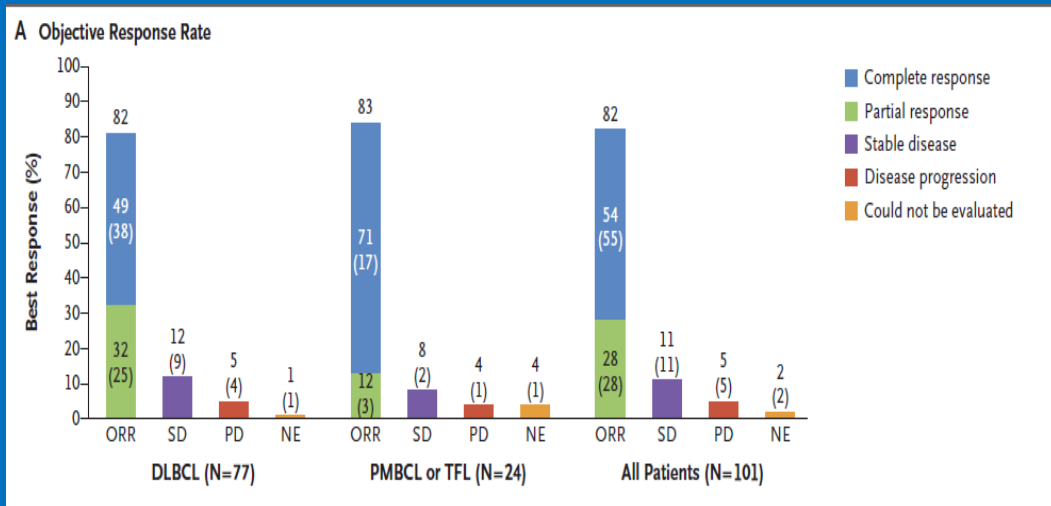
- Retrospective Study that pooled data from 2 phase 3 clinical trials and 2 observational cohorts
- Definition of refractory similar to Zuma-1
- Looked at 636 refractory patients
- RR 26%; CR 7%; Median OS 6.3 months

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

RR, Response Rate; CR, Complete Response; OS, Overall Survival

112

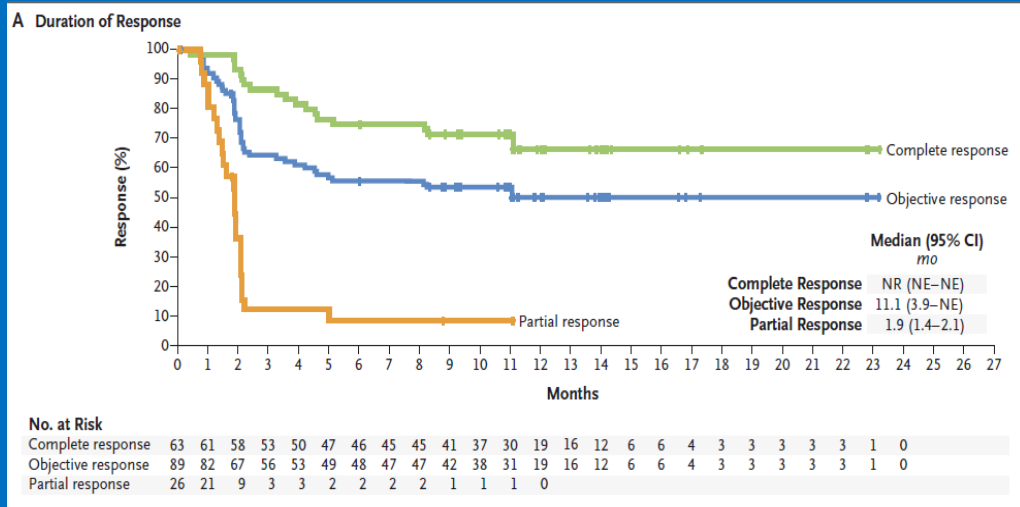
Responses



Neelapu SS et. al. NEJM 2017; 377:2531-44.

113

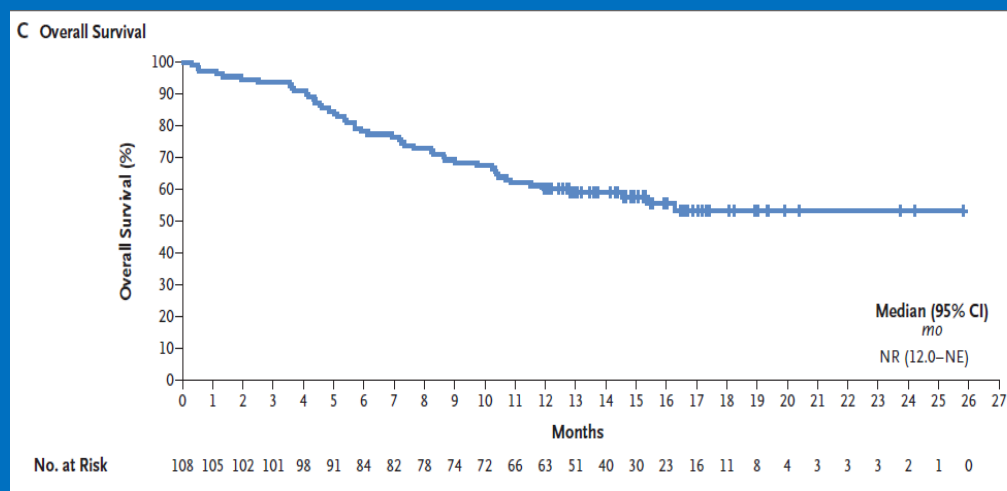
Duration of Response- At Least 1 Year of Follow-up



Neelapu SS et. al. NEJM 2017; 377:2531-44.

114

Survival With Minimum 1 Year of Follow-Up



Neelapu SS et. al. NEJM 2017; 377:2531-44.

115

High Risk Genetics

- Assessed in 47 evaluable patients with pre-treatment samples
- 37 had either double expressor, double or triple hit, or myc-but >70% ki-67
- CRs 68%
- Median follow up of 15.4 months 49% of responses were ongoing

Neelapu SS et. al. Blood 2018 132:2967.

116

2 Year Follow-Up

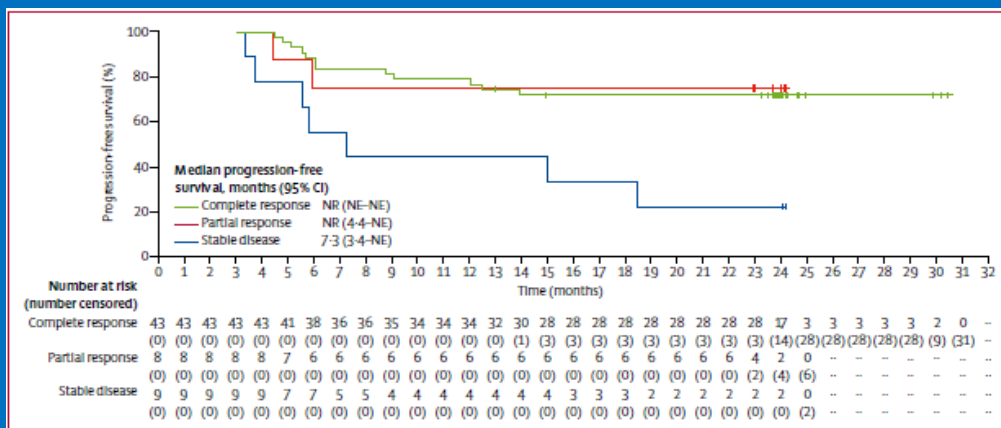
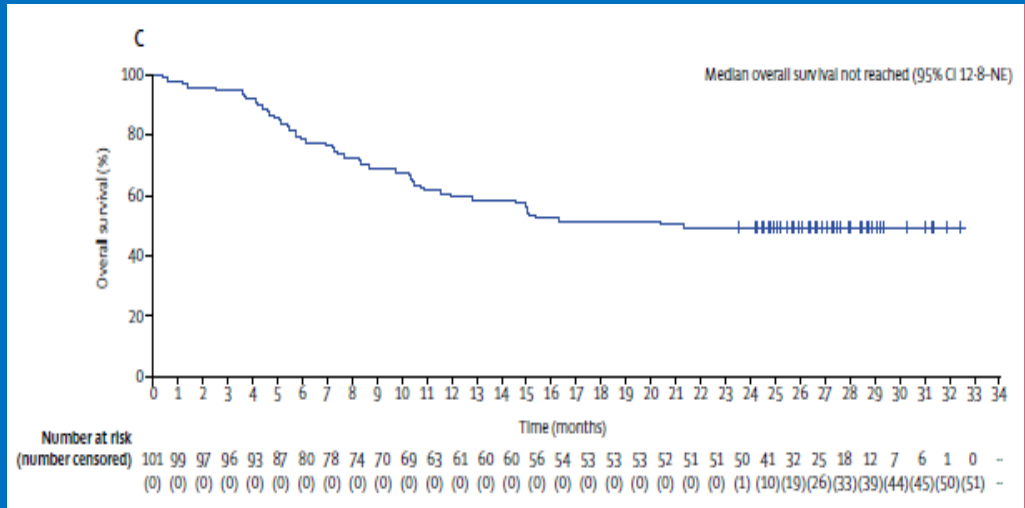


Figure 2: Post-hoc analysis of Investigator-assessed progression-free survival by response status at 3 months after axicabtagene ciloleucel. 60 patients with ongoing complete response, partial response, or stable disease month 3 in phase 2 are shown. The x-axis shows time since infusion of chimeric antigen receptor T cells. Four of eight patients with partial responses and four of nine patients with stable disease at 3 months subsequently converted to complete responses. NR-not reached, NE-not estimable.

Locke FL et. al. Lancet Oncology Jan 1 2019 Vol 20 P31-42.

117

Survival 2 Year Follow-Up



Locke FL et. al. Lancet Oncology Jan 1 2019 Vol 20 P31-42

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Tisagenlecleucel-JULIET Study

- Progressed after 2 or greater lines of chemotherapy
- Ineligible for Auto or relapsed post Auto
- 99 patients infused
- Median age 56 (22-76)
- 77% had stage III or IV
- Median number of prior lines was 3

Schuster SJ et. al. Blood 2017 130:577.

119

JULIET-Results

- Best ORR 53. 1% with 39.5% CR
- For patients evaluable at 6 months CR rate was 30%
- Response rates consistent across prognostic subgroups(prior auto, double hit)
- Median duration of response not reached
- Median OS was not reached
- 6 month probability of survival was 64.5%

Schuster SJ et. al. Blood 2017 130:577.

ORR, Overall Response Rate

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Characteristics Differentiating Patients in the Real World from ZUMA-1

- 124 of 286* (43%) 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 LJ et. al. ASH 2018 Abstract 91.

121

Subject with Multiple Co-morbidities

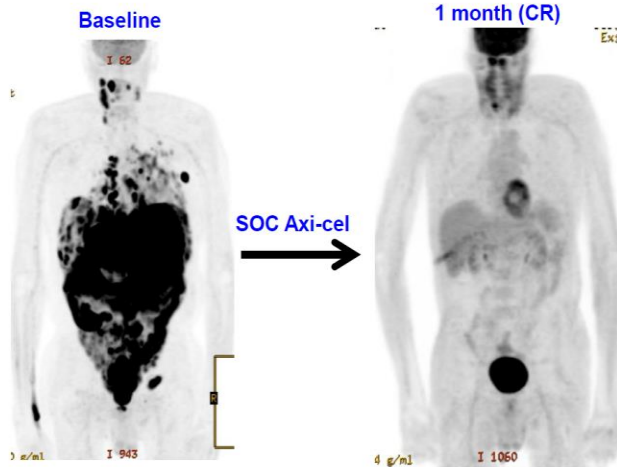
68 yo M with DLBCL-GCB

Prior therapies – 7

- R-CHOP
- ICE → Zevalin
- R-ESHAP
- R-Hypercytoxin
- Gemcitabine
- Bendamustine
- R-Hypercytoxin

Co-morbidities

- ECOG PS 3
- EF – 45%
- Pulmonary embolism
- GI bleed
- Obstructive jaundice → Biliary catheter



Nastoupil LJ et. al. ASH 2018 Abstract 91.

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American Society of Hematology
Helping hematologists conquer blood diseases worldwide

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

Loretta J. Nastoupil*, Michael D. Jain*, Jay Yaakov Spiegel, Armin Ghobadi, Yi Lin, Saurabh Dahiya, Matthew Lunning, Lazaros Lekakis, Patrick Reagan, Olalekan Oluwole, Joseph McGuirk, Abhinav Deol, Alison R. Sehgal, Andre Goy, Brian T. Hill, Andreadis Charalambos, Javier Munoz, Jason Westin, Julio C Chavez, Amanda Cashen, Nabil N. Bennani, Aaron Rapoport, Julie M Vose, Lei Feng

David B Miklos**, Sattva S. Neelapu**, Frederick L. Locke**

*LIN and IMDJ are co-first authors
**DBM, SSN, and FLL are co-senior authors

ASH 2018 Abstract 91

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Auto, Allo, or Chemo?

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Chemotherapy Sensitive Relapse

- Auto has a long track record of curing these patients with decades of follow up
- Better tolerated?
- We know we'll get paid for an auto

125

Sometimes the Lines Blur

- 72 yo woman presented with a mesenteric mass> DLBCL
- R-CHOP X 6 residual disease
- R-ICE X 2 further improvement but residual disease
- “ No ASCT with PET FPS 4/5”

R/CHOP, rituximab, cyclophosphamide, vincristine, prednisone
RICE, rituximab, ifosfamide, carboplatin, etoposide

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Intolerant To Chemo

- 74 yo woman was dxed with Stage IIIB FL in 2013
- R-CHOP X 6>CR
- 1/19:Extensive relapse Biopsy>Transformation
- R-EPOCH X2 complicated with PNA and sepsis
- “I’m done with chemo”
- Received Axi-Cel with only Grade 1 CRS

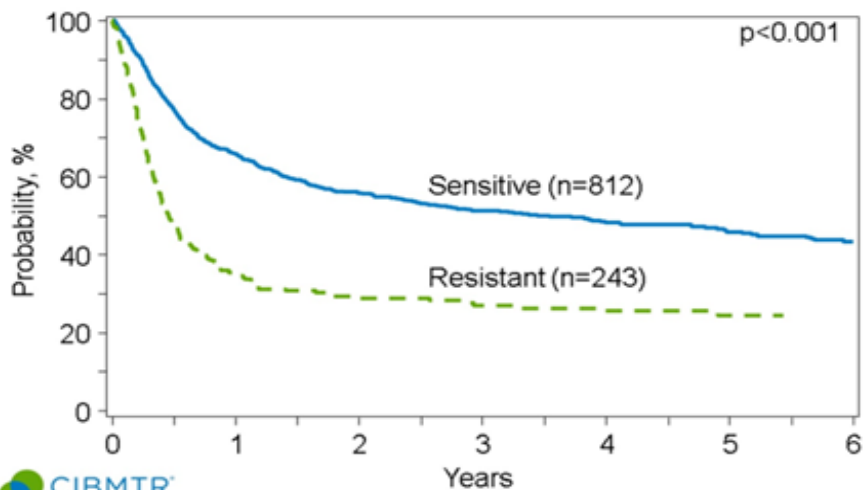
R-EPOCH, rituximab plus etoposide, prednisone, vincristine,
cyclophosphamide, and doxorubicin

127

Relapse Post Auto

128

Survival after HLA-Matched Sibling HCT for Diffuse Large B-cell Lymphoma (DLBCL), 2004-2014

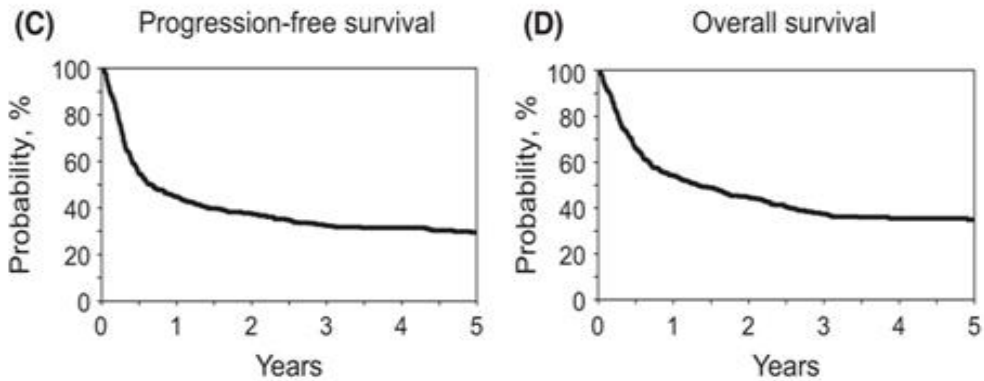


D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016. Available at: <http://www.cibmtr.org>

40

129

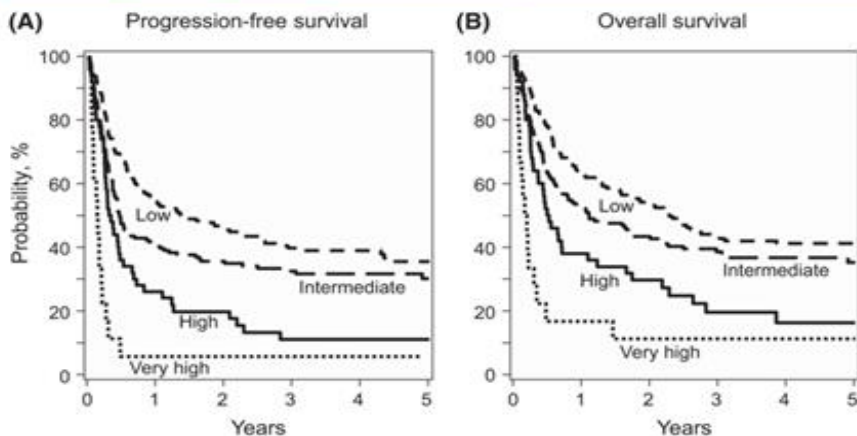
Outcomes for DLBCL patients undergoing allogeneic HCT after prior failed ASCT



Fenske T et al., *British Journal of Haematology* 2016; 174(2):234-248

130

Prognostic index for DLBCL patients undergoing allo-HCT after prior failed ASCT



KPS < 80; Interval < 12 months; chemoresistant at alloHCT



Fenske T, et al, *British Journal of Haematology* 2016; 174(2):234-248

131

Primary Refractory/Relapsed Refractory

- 83 yo man presented with large neck mass> DLBCL
- He walks with a walker and lives in assisted living facility
- Mini-RCHOP > minimal response
- Benda/Obinutuzumab> Minimal response
- “Not a candidate for CAR-T”

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Thank You!

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The CAR T Cell Journey: It Takes A Village

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Bone marrow transplant and Cellular Therapy

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Commercial Cellular Therapy Nurse Coordinator
Cellular Therapy and Transplant
Penn Medicine Abramson Cancer Center

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Getting the Hospital...Commercial CAR T Cells



- Large City Medical Center (LCMC) Hematopoietic Stem **Transplant Program—15 years experience**
- **FACT accredited:** Clinical, Collections (Apheresis/Donor Room) and Processing (Cell Lab)
- **Independent Cellular Service vs. Embed CAR T cells within Transplant Service**
 - Dedicated BMT in-patient units, large outpatient BMT Day hospital staffed with BMT-trained Oncology Certified RN's
 - Existing, robust BMT electronic order sets and clinical documentation
 - **Advantageous to begin by embedding CAR T cells within BMT service**

135

Getting the Hospital Ready.... Commercial CAR T Cells

- **Vendor Qualification:** Manufacturers (Vendors) conduct site visits to “qualify” the hospital
 - Apheresis and Cell Processing Lab inspection et al
- Cell Chain
- **Hospital Certification:** Manufacturers ensure hospital meets REMS program
 - Authorized
 - Safety Training
 - Tocilizumab (ACTEMRA®) tracking
 - REMS training and tracking

REMS, Risk Evaluation and Mitigation Strategy

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Getting the Hospital Ready.... Commercial CAR T Cells

- **Targeted Education:** For appropriate stakeholders manning the designated CART patient care areas
- **Generic CAR T Cell training for all nursing staff** of those areas
 - Specifics for axicabtagene/tisagenlecleucel introduced at an additional session
- **REMS training** for those who prescribe, dispense and administer the construct
 - BMT Service and CART patient care areas
 - Providers, Pharmacy, Nursing

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Getting the Hospital Ready.... REMS

- **REMS—Risk Evaluation Mitigation Strategies**
 - **FDA required program:** when a drug/construct has possible side effects that have the potential for significant harm
 - **Strategies** must be put into place to **mitigate** the potential for harm
- REMS program
 - **Content:** potential side effects with grading and treatment algorithms; mandatory patient education, Wallet card
 - **Knowledge Assessment:** 100% correct responses required to be compliant

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Getting the Hospital Ready.... REMS Infrastructure

- **Patient Education**
 - What? Required content: wallet cards, staying within 2 hours of treating facility, avoid operation of heavy machinery; additional care instructions
 - Who has responsibility for teaching? Nurse Coordinators (Primary), MDs, APPs, and unit RNs
 - How recorded? EMR documentation
 - Resources? Wallet Cards for CART staff, patient education materials/binders/brochures
- **Dedicated Tocilizumab doses for each treated patient set aside prior to infusion**
 - Required: Tracking process and log managed by pharmacy department

139

Getting the Hospital Ready.... REMS Infrastructure

- **Patient monitoring for at least 7 days post-infusion**
 - Coordination of care process or policy that details all phases of CART cell therapy
 - Best practice: establish clinical milestones/pathways to guide inpatient/outpatient follow-up, including long-term follow-up and return to referring provider
- **Adverse Event Reporting**
 - Utilize established processes with addition of registry (CIBMTR) reporting and document the process (SOP)

CIBMTR, Center for International Blood and Marrow Transplant Research

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Getting the Hospital Ready.... REMS Rollout

- **EMS content slides and knowledge assessment**
 - **REMS website vs. paper document** submission to Vendor* *OR*
 - Using **own electronic learning system**
 - Advantages: Compliance reports easily generated; testing statistics obtainable--required for vendor audits for axicabtagene (Yescarta®)
 - **Determine target audience**
 - Staff, providers in dedicated CART cell patient care areas.
 - ? Staff/providers in support units
 - Include all new staff onboarding in designated CART cell patient care areas
 - **Create a policy/SOP**—will need to share with vendor
- **Determine compliance threshold before Patient #1 treated**
 - Min. 80% compliance
- **Quality Officer/Manager**
 - To track compliance
 - To assist with SOPs, vendor audits, data tracking/metrics
 - * Required for tisagenlecleucel (KYMRIAH®) REMS. Best practice: institution reconciliation of site compliance

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Getting the Hospital Ready....FACT Compliance



- **FACT**--Foundation for the Accreditation of Cellular Therapy
 - Standards for Hematopoietic Cellular Therapy (HCT) **AND** Immune Effector Cell Therapy (IEC)
 - **7th Edition of HCT Standards *INCLUDE* IEC Standards**
 - Include Clinical, Apheresis Collection Facility and Processing Facility Standards (also Marrow Collection Facility Standards)
 - **Successful accreditation significance:**
 - Standards meet or exceed most government regulations
 - Insurance carriers are increasingly looking for FACT accreditation when designating hospitals Centers of Excellence
 - Required for participation in NCI, ECOG, SWOG, and COG clinical trials
 - A factor in the ranking of "America's Best Hospitals" by U.S. News and World Report

NCI, National Cancer Institute; ECOG, Eastern Cooperative Oncology Group; SWOG, Southwest Oncology Group; COG, Children's Oncology Group

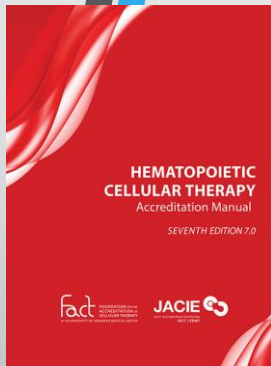
142

Getting the Hospital Ready.... FACT Compliance

- **Accreditation versus compliance with standards**
 - *Must* comply for accreditation as per FACT
 - *Expected to comply* in order to treat as per FACT
- **IEC Accreditation versus Dual Accreditation**
 - Can be sought *with* re-accreditation of established HCT program on cycle
 - Seek IEC accreditation when ready off cycle of HCT reaccreditation
 - Entire cellular program will be inspected (HCT & IEC) at time of request for IEC accreditation—be ready
 - Programs can seek IEC accreditation solely, with or without HCT program in existence/accredited

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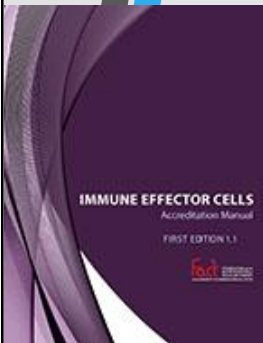
Getting the Hospital Ready....FACT Compliance



- **HPC Program established and/or FACT Accredited...**
 - **IEC standards similar to HPC Standards**
 - Advantage: minimal changes/adaptions necessary
 - Examples:
 - Patient selection and screening
 - Physical plant requirements, consultative services requirements, et al (Clinical Standards section)
 - Most, HPC Apheresis processes/standards
 - Most Processing Facility processes/standards
 - **"Exception":**
 - Processing Facilities producing investigational IEC products are expected to be FACT compliant

144

Getting the Hospital Ready....FACT Compliance



- **Select Standards Specific to IECs (CART cells, et al)**
 - **Physician and APP competencies:** patient care, use of products
 - **RN competencies** on certain oncologic emergencies and Cytokine Release Syndrome and Neurotoxicity
 - **Patient care:** Guidelines and/or processes on the **Management of Cytokine Release syndrome and Neurotoxicity**; communication & guidelines for escalation of care, communication of initial IEC therapy plan with referring physician, regular assessment of patients
 - Policies and procedures addressing the **administration of Immune Effector Cells**
 - **Collection of data** similar to CIBMTR data points and report to such an institutional repository

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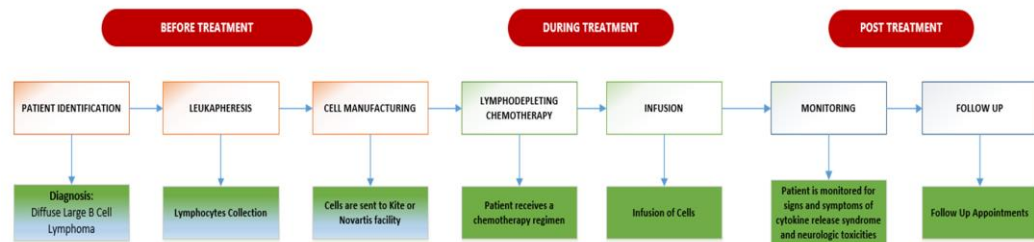
Getting the Hospital Ready.... FACT Compliance

- **Quality Management**
 - **Quality Plan**—robust document. Advantage: Can edit if established for HCT program
 - **Metrics**
 - Outcome Analyses including an endpoint of clinical function
 - Overall and treatment-related morbidity and mortality at 30 days, 100 days and 1 year after cellular therapy product administration
 - Annual audits of safety endpoint and immune effector cell therapy toxicity management
- Quality Officer/Manager with Data Team support ideal

REFERENCES: FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration Seventh Edition (FACT, Omaha, NE, 2018)
 FACT-JACIE Cellular Therapy Product Collection, Processing, and Administration Accreditation Manual Seventh Edition (FACT, Omaha, NE, 2018)
 FACT Standards for Immune Effector Cells First Edition 1.1 (FACT, Omaha, NE, 2018)
 FACT Accreditation Manual for Immune Effector Cells First Edition 1.1 (FACT, Omaha, NE, 2018)

146

CAR – T PROCESS



147

Case Study: CB

- CB, a 55 y.o. male, originally diagnosed with DLBCL
 - S/P 3 different chemo regimens and auto transplant
 - Relapsed with surgical pathology confirmation
 - Otherwise stable; no interim lymphoma therapy
 - Lives in suburb of NYC app. 2 hours away without traffic, with wife. 2 grown sons. Has commercial health insurance through employment

“Where do I start?”

148

Getting the Patient Ready....The Journey
has started

External Referral Process

Required documents for CAR T Consultation

149

Initial Evaluation

- Referred to Large City Medical Center (LCMC) for CART cell evaluation
- Purpose of appointment is to determine if CAR-T is a safe and appropriate option for this patient.
 - Disease/eligibility assessment?
 - Performance Status?
 - Psychosocial Supports?

150

Case Study: CB con't

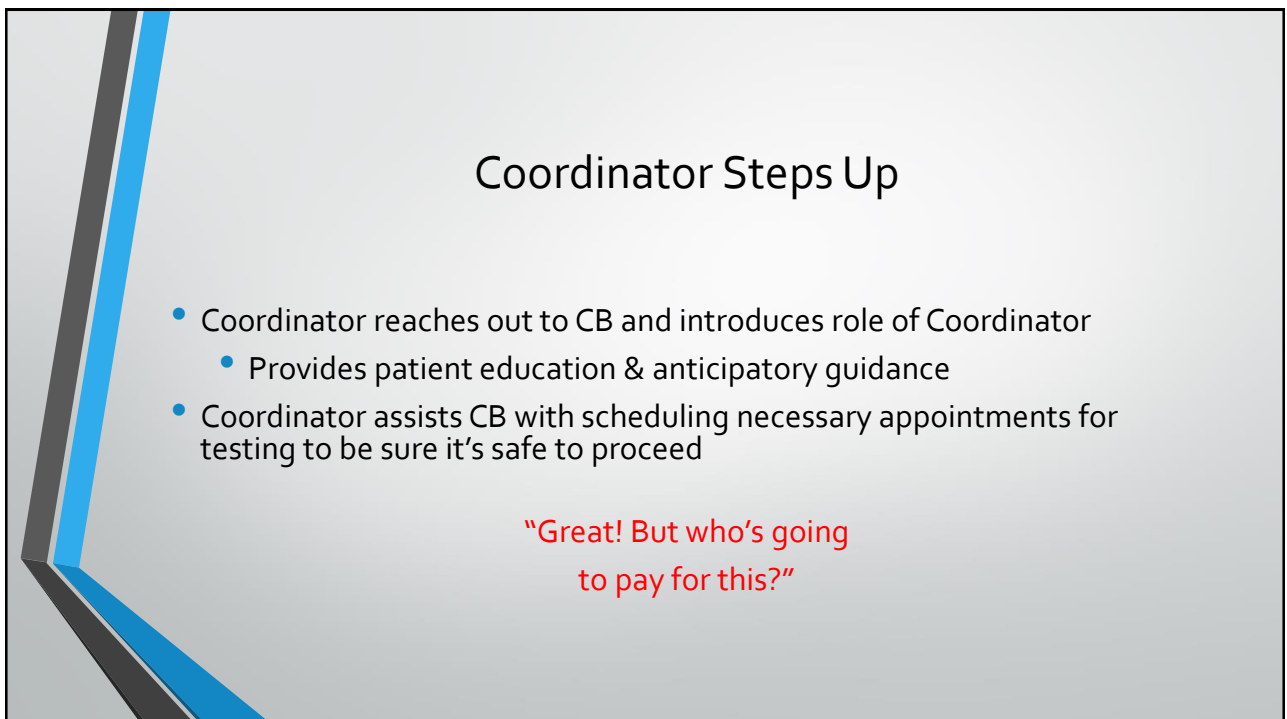
- CB meets with Lymphoma Specialist at Large City Medical Center
- Determined that patient is appropriate candidate for CART Therapy

"What's next?"

151



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153

Financial Quarterback

- Collaboration between Cellular Therapy Coordinator, Designated Financial Coordinator, Business Office, Billing Department, Financial Advocacy, and Social Work

154

Case Study: CB con't

- CB completes required testing and meets criteria
- He has signed consent and remains motivated to proceed with CART Therapy

"Can I get CAR-T tomorrow?"

155

Logistical Navigation- Timing Matters

- Collaborate with all departments when involved in the process as well as coordinate with manufacturer to get the patient in ASAP
 - Manufacturing slot availability
 - Register patient in manufacturing portal

156

Case Study: CB con't

- CB's case is submitted to insurance
- Insurance provides authorization for CAR-T 5 days after submission
 - Coordinate with manufacturer for shipment of necessary equipment
 - Arrange product pick-up time with manufacturer

"Am I ready to collect?"

157

Getting the Patient Ready....The Nurse Visit

Nurse Coordinators meet with CB and provides patient teaching

- **Patient education**
- **Treatment calendar**
- **Course of treatment**

Central line placement

Nurse Coordinator notifies pharmacy to make sure 2 doses of tocilizumab (ACTEMRA®) is available

158

Getting the Patient Ready....Cells Collection

CB comes to the apheresis unit for leukapheresis

- Lymphocytes Collection
- Cells are sent to Kite or Novartis for Cell manufacturing



159

Case Study: CB con't

- CB has his pre-donor evaluation performed in apheresis and it is decided that he can have cells collected via peripheral veins
- A few days later, CB's cells are collected in Apheresis Lab
- Cells are processed by stem cell lab and picked up by courier to be transported to manufacturer

"What am I supposed to do while I wait?"

160

The Waiting Period

- Period of high-stress for patients
- CT Coordinator should provide frequent updates regarding plan and manufacturing
- Close monitoring by MD
 - Consider bridging therapy and/or delaying infusion as clinically appropriate
- CT Coordinator to assist patient with coordinating lodging for self and caregiver for 28 days post anticipated infusion date.
 - Provide resources and referrals as needed



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Case Study: CB con't

- Cellular Therapy Coordinator receives call from manufacturer that CB's product is ready to be shipped
- CB's MD is notified and confirms that CB's condition remains appropriate for treatment
- Stem Cell Lab is notified that CB's cells will be returning to Penn
- Patient is notified that his product is returning

"Am I ready for infusion now?"

162

Pre-Infusion Planning

- Appointments scheduled pre-chemo and pre-infusion with MD or NP
- Lymphodepleting (LD) chemo scheduled
- Infusion visit scheduled in our Apheresis Lab
- Verification of Toci availability confirmed with Pharmacy 1 week prior to anticipated start of LD chemo

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Pre-Infusion Education

- Prior to CART cell infusion, Coordinator will re-educate patient and caregivers about signs/symptoms of CRS & Neurotoxicity
- Patient will receive a wallet card containing information about CAR-T toxicities as well as contact information to reach their provider during and after working hours.
- Important to educate patients and family members about information on their card and to instruct them to keep the wallet card with them at all times.

164

Case Study: CB con't

- Arrangements made for CB to stay at a local hotel from Day -5 through Day 28 post-infusion
- CB receives his completed wallet card and is instructed to carry it for 28 days post infusion
- CB visits with NP Heather on day of planned LD chemo start

165

CAR-T Cell Infusion & Follow-Up Care in Outpatient Setting

166

Pre-infusion Patient Journey

- There is typically a minimum of 1 month between collection and start of Lymphodepleting chemotherapy
 - Initial Criteria screening (which typically occurs at least 2 weeks prior to collection) cannot account for complications that may arise for complex patients with aggressive disease
 - Some of these complications can impact safety of proceeding with CAR-T treatment
 - Eg; rapidly progressive disease, infection, deteriorating performance status
 - Important that patient receives thorough evaluation by NP prior to start of LD chemo
 - Assessing for changes; new symptoms, reviewing re-staging scans, constitutional symptoms, performance status, psychosocial changes

167

Cell Therapy NP Visits

- NP visit day prior to or at LD chemotherapy
 - Establish relationship and contact information
 - Educate patient on what to anticipate the day of the infusion
 - Review chemotherapy side effects (nausea)
- Evaluate pt day of and prior to infusion
 - Ensure appropriate candidate
 - Free of infection
 - Resolved toxicity from chemotherapy
 - Ongoing patient education
 - Document that it is okay for the infusion to proceed

168

Patient Management

- On the day of infusion:
 - Allopurinol: Tumor lysis can be a complication
 - Baseline blood work
 - CRP/Ferritin baseline and then weekly. They can elevate during CRS
 - CBC Plts > 20 for T cell infusion
 - Contact information during working hours and after hours/on weekends
- On the day of infusion:
 - Prophylactic antibiotics for infection risk
 - Review respiratory viral swab
 - Free of infection

CRP, C-Reactive Protein

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Cell Therapy NP Visits

- Cytokine release syndrome is a systemic inflammatory response associated with CAR T-cell therapy
- Symptoms include fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, fast breathing, rapid heartbeat, low blood pressure, seizures, headache, confusion, delirium, hallucinations, tremor, and loss of coordination

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Cell Therapy NP Visits

- Cytokine release syndrome typically occurs between day 2-14 following the CAR T cell infusion
- More rapid onset with axicabtagene ciloleucel (Yescarta®)
- Low grade fevers that can escalate
- Flu like symptoms
- Therefore, important to see regularly after the infusion

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Cell Therapy NP Visits

- Evaluate pt day 2 and 4 following infusion and weekly out through day 28
- Contact info for symptom management
- Reiterate signs and symptoms of CRS and neurotoxicity
- Physical exam
- Evaluate for CRS, infection and neurotoxicity

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Neurological Toxicity

- Less well defined; less defined management
- Symptoms
 - Expressive aphasia (esp naming objects/people); can progress to perseveration, global aphasia
 - Often alert and oriented
 - Tremors, myoclonus, seizures
 - Apraxia, dysgraphia
 - Encephalopathy
- Onset: within days to 2-3 weeks post CART
 - During or after systemic CRS
- Self limited; Rare cases of cerebral edema and death

173

Case Study: CB

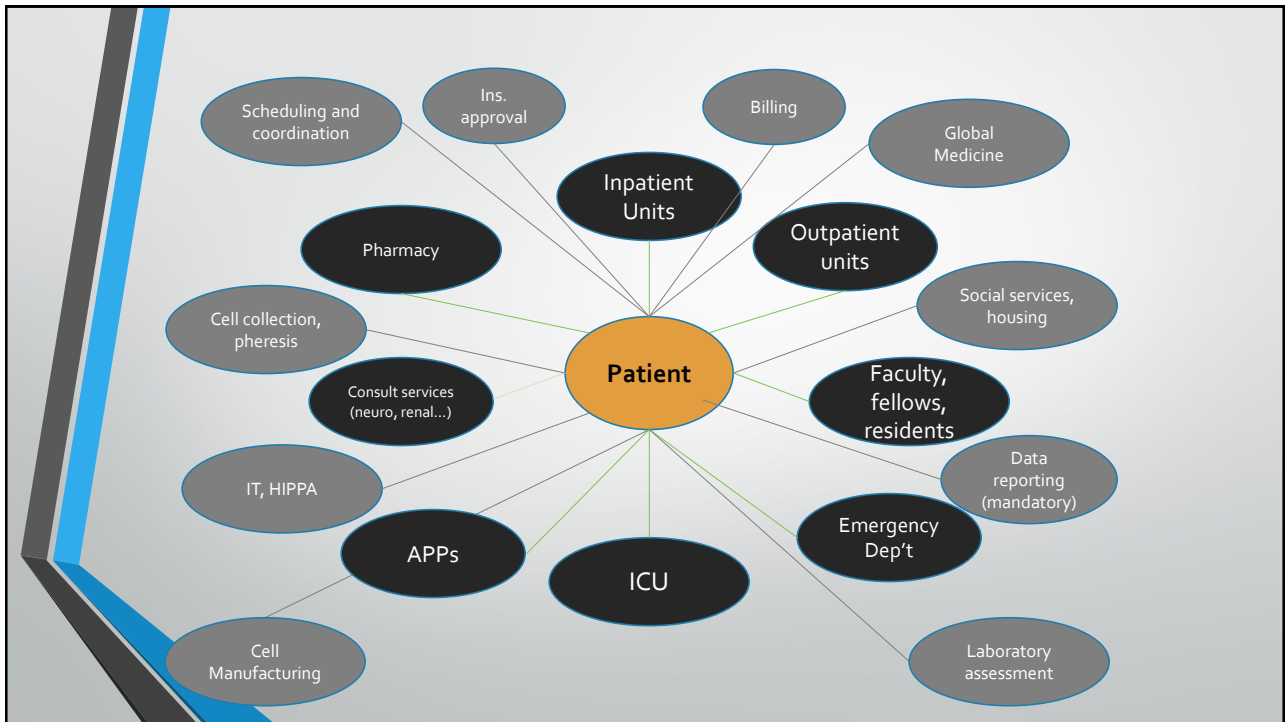
- CB is a 55 year old male with DLBCL.
- Received chemotherapy followed by his T cell infusion
 - Tolerated chemotherapy and T cells without any complications
- On day 5, CB developed fevers of 103.0 with flu-like symptoms
- Evaluated by NP in office.
 - Hemodynamically stable, received IVF's
 - No obvious infection. Infectious workup initiated
 - Presumed CRS (Cytokine release syndrome)
- Admitted to the hospital

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Access Points

- A patient may travel through
 - Outpatient Clinic
 - Emergency Room
 - Oncology Evaluation Center (OEC)
 - Intensive Care Unit
 - Outside Facilities (which we prefer to avoid)
- Staff may interact with
 - Physicians:
 - Residents/Attendings, APP's
 - ER, Floor, ICU, ID, Neuro
 - Nurses
 - Pharmacists

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Case Study: CB

- The patient is admitted to our transplant /cellular therapy service
 - Run by APP's and an Attending physician who all specialize in transplant and cellular therapy
 - REMs training for all providers
- Per our policy, an infectious workup was initiated despite our strong suspicion for CRS.
 - The patients are at a high risk for infections and CRS which can lead to poor outcomes.
- CB was started on intravenous hydration, antibiotics as well as Tylenol around the clock
- Fevers improved

177

Case Study: CB

- On Day 6, CB developed high fevers again despite Tylenol ATC
- Developed low blood pressure not responding well to multiple fluid boluses
 - He was given tocilizumab
- 12 hours following Toci, the patient's blood pressure normalized and was stable without fevers and not requiring IV fluids

178

Case Study: CB

- On Day 7, CB developed word finding difficulty with somnolence. This is considered a neurotoxicity from CAR-T cell therapy
 - The patient was treated with corticosteroids

179

Case Study: CB

- On Day 10, the patient's neurological status returned to baseline
- CBC and Ocomp normalized
- The patient was discharged to home on day 12
 - Instructed to stay within the immediate area for up to day 28
 - Seen in the office weekly for the next two weeks

CBC, Complete blood count; Ocomp, Comprehensive metabolic

180

Thank You!

181

CAR T-cells for Chronic Lymphocytic Leukemia

Jacqueline C. Barrientos, MD, MS

CLL Research and Treatment Center at the Northwell Health Cancer Institute

Associate Professor of Medicine

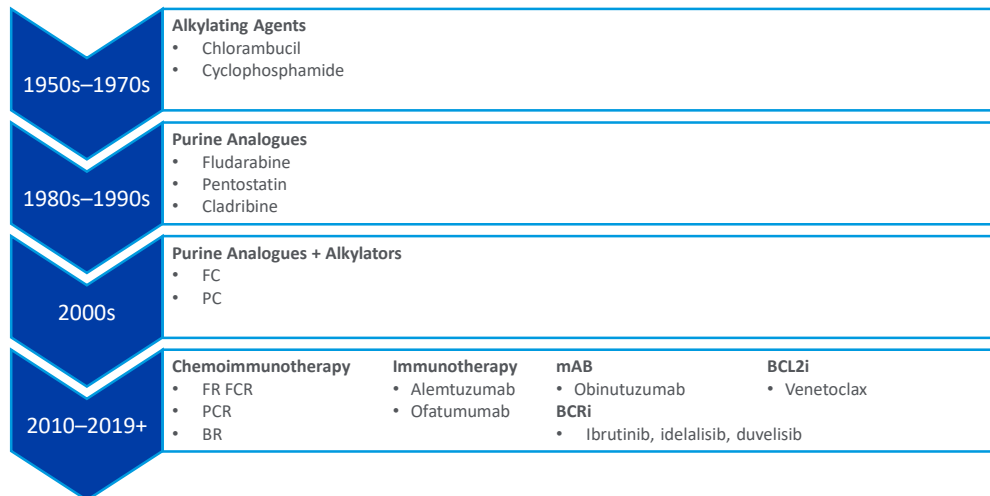
Feinstein Institute for Medical Research and Zucker School of Medicine at Hofstra/Northwell



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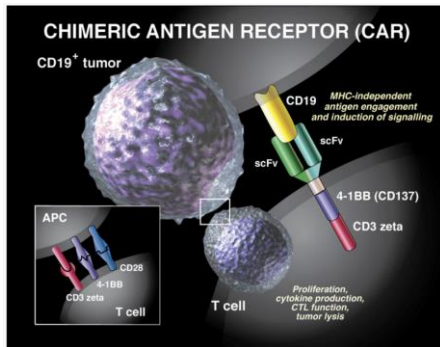
CLL Drug Development Timeline



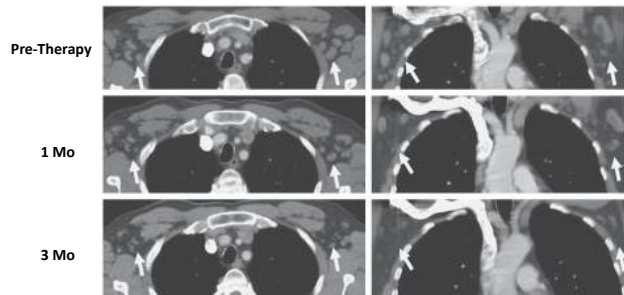
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Chimeric Antigen Receptor T-Cell Therapy

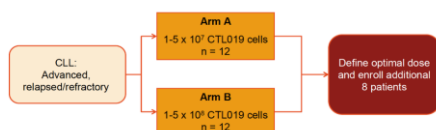
- 2011: First case report of successful CAR T-cell therapy in CLL



Bone Marrow Biopsy Specimens



CTL019 Dose Optimization in R/R CLL Phase 1 (Penn): Study Design and Patients



Eligibility criteria

- R/R CLL/SLL
- Anticipated survival <2years
- Age ≥ 18
- Relapsed ≥ 2 prior therapies
- Within 2 yrs of last regimen

Primary objectives

- CR rate at 3 months

2ry objectives

- Safety
- Manufacturing feasibility
- Antitumor activity (ORR, PFS,OS)
- T-cell expansion and persistence

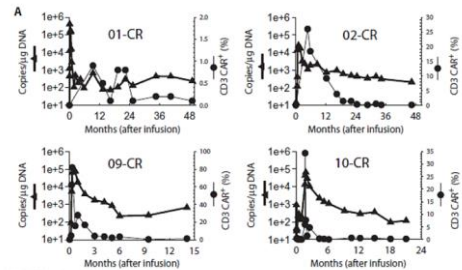
Baseline characteristics	N=28 (Eval 24)
Median (range) age, y	62 (51-76)
Prior lines of therapy, median (range)	4 (2-9)
Prior lbr, n (%)	3 (12)
Any high-risk cytogenetics, n (%)	12 (75)
TP53 mutation	9(38)
Lymphodepleting Chemotherapy	
Bendamustine	5
FC/PC	18

- In Stage 1 of the trial, patients received either a high (n = 11) or low (n = 13) dose of CTL019 cells

Response	High dose (5 × 10 ⁸ cells)	Low dose (5 × 10 ⁷ cells)
CR or PR	6/11 (54%)	4/13 (31%)
NR	5/11 (46%)	9/13 (69%)

Phase 1/2 CTL019 in R/R CLL (U Penn): Summary

Study Design	A randomized phase 2 study of two CTL019 doses in R/R CLL.
Patients	Eligible patients had > 2 prior therapies and progressed within 2 years of > 2 nd line therapy. Stage 1 (n = 28) was used to determine optimal dose. Stage 2 (n = 6) involved treatment with the optimal dose.
Efficacy	<ul style="list-style-type: none"> 5 × 10⁸ CTL019 cells was determined to be the optimal dose Of the evaluable patients treated at the optimal dose, 6 achieved a CR and 3 achieved a PR At the time of data cutoff, 5 remained in CR with a median follow-up of 26 months (range, 5-34) and 1 progressed with CD19⁺ disease
Safety	<ul style="list-style-type: none"> All patients (n = 35) were evaluable for toxicity and 19 patients experienced delayed CRS <ul style="list-style-type: none"> Of these patients, 7 experienced grade 3 or 4 CRS Tocilizumab successfully reversed CRS in 4 patients while 15 patients did not require intervention Dose was not associated with CRS development or severity

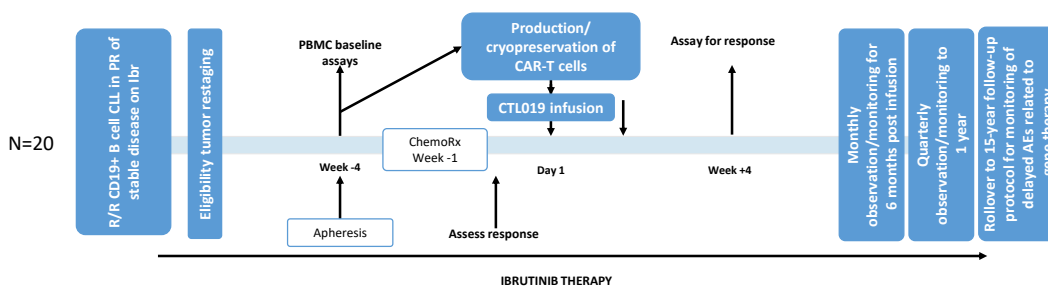


NCT01029366
Figure from Porter DL, et al. *Sci Transl Med.* 2015;7(303):303ra139. Reprinted with permission from AAAS.
1. Porter DL, et al. *Sci Transl Med.* 2015;7(303):303ra139.

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

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CTL119 in R/R CLL Previously Treated with Ibr: Study Design and Patients



- Target dose = 1.5 × 10⁸ CTL119
 - CTL119 split dose 10/30/60%
- Patients must have been receiving ibrutinib for 6 months prior to enrollment
- 17/19 patients had adverse prognostic markers

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CTL119 in R/R CLL Previously Treated with Ibr: Baseline Characteristics of Infused Patients

Baseline characteristics of infused patients	N=19
Median (range) age, years	62 (42-76)
Female	4
Prior therapies	
First-line ibrutinib n=5	0
Other n=14	2 (1-16), including 3 patients with prior CART-19 (CT 019)
Poor prognostic features	
Del17p or mutated <i>TP53</i>	11
Del11q22 or mutated <i>ATM</i>	3
Median (range) marrow burden	21% (7-63)
Median (range) tumor area by CT (mm²) in 9 patients with enlarged lymph nodes	1471 (178-2220)

NCT02640209. 1. Gill et al. *ASH*. 2018-Abstract 298.

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CTL119 in R/R CLL Previously Treated with Ibr: Key Safety Results

Characteristics	N=19
Cytokine release syndrome (CRS)	18
Penn grade 1-2	15
Penn grade 3-4	3
Penn grade 5	0
Tocilizumab treatment	2
Encephalopathy (CTCAE)	5
Grade 1	2
Grade 2	2
Grade 3	0
Grade 4	1
Cardiac grade 5 arrhythmia	1
Total grade 3	49
Total grade 4	22

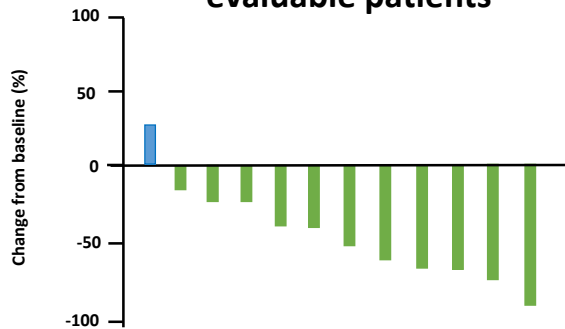
- 1 patient died due to cardiac arrhythmia in the setting of grade 4 neurotoxicity
- 18/19 patients experienced CRS

CTCAE: common terminology for adverse events
NCT02640209. 1. Gill et al. *ASH*. 2018-Abstract 298.

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CTL119 in R/R CLL Previously Treated with Ibr: Key Efficacy Results

Sum Target Lesion % Change from Baseline at 3 Months, in 12 evaluable patients



NCT02640209. 1. Gill et al. ASH. 2018:Abstract 298.

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CTL119 in R/R CLL Previously Treated with Ibr: Key Efficacy Results *Continued*

iwCLL response rates, n/N (%)	
At 3 months post-CTL119	
CR	6/14 (43)
PR	4/14 (29)
SD	3/14 (21)
PD	1/14 (7)
At 12 months post-CTL119	
CR	2/7 (29)
PR	5/7 (71)
SD	0
PD	0
Bone marrow response rates, n/N (%)	
Bone marrow at 3 months post-CTL119	
Morphologic CR	17/18 (94)
Flow MRD CR	15/17 (88)
Bone marrow at 12 months post-CTL119	
Morphologic CR	10/11 (91)
Flow MRD CR	7/10 (70)

- Median (range) follow-up was 18.5 months (8-28)
- Of the 10 patients with bone marrow morphologic CR at 12 months:
 - 7/10 were MRD-ve
 - 3/10 were 3.58, 2.34 or 3.79 log₁₀ reduction
- Of the 3 patients previously treated with CTL019, at 12 months:
 - 2 were in MRD+ CR
 - 1 was refractory (PD)
- In total, 16/18 patients remain in morphologic and/or flow CR at last follow-up

PD, progressive disease

NCT02640209. 1. Gill et al. ASH. 2018:Abstract 298.

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CTL119 in R/R CLL Previously Treated with Ibr: Authors' Conclusions

- CTL119 showed promising activity in patients not achieving CR despite ≥ 6 months of ibrutinib
- The iwCLL CR rate was 43%
- At 3 months, the bone marrow remission rate was 94%, including a 78% MRD negative response by deep sequencing
- These findings compare favorably to prior CART19 cell studies in patients with progressive CLL (iwCLL CR rates of 21-29%)
- CRS was frequent but mild-moderate and did not commonly require anti-cytokine therapy

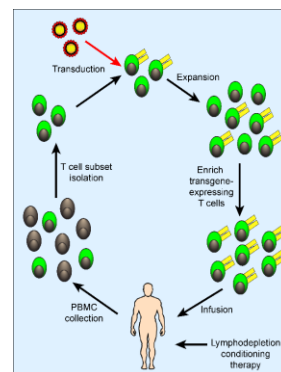
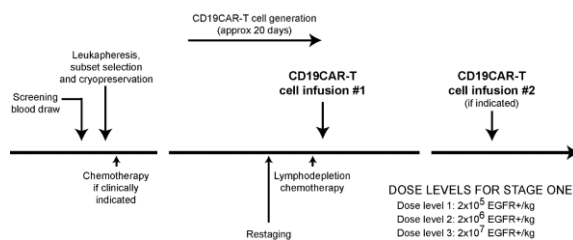
NCT02640209. 1. Gill et al. ASH. 2018:Abstract 298.

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CD19 CAR-T Cells (JCAR014) are Highly Effective in Ibrutinib-Refractory High-Risk CLL

Stage 1: Dose escalation/de-escalation, 3+3 design

Stage 2: Safety evaluation in expanded disease-specific cohorts



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Patient Characteristics: High-Risk CLL Population

Characteristic	N=24
Age at infusion, median [range], years	61 [40-73]
Prior lines of therapy, median [range]	5 (3-9)
Prior allogeneic HCT	4 (17%)
Prior Ibrutinib	24 (100%)
o Ibrutinib-refractory	19 (79%)
o BTK or PLCG2 mutation	9/19 (47%)
o Ibrutinib-intolerant	3 (13%)
Venetoclax-refractory	6 (25%)
High-risk cytogenetics, N (%)	23 (96%)
o Complex karyotype	16 (67%)
o 17p del	14 (58%)
High-risk histology (Richter's/IPC/PLL), N (%)	8 (33%)
Extramedullary disease, N (%)	23 (96%)
o Cross-sectional area, median [range], mm ²	3093 [546-20406]
o FDG-avid disease on PET, N (%)	14/15 (93%)
o SUV _{MAX} , median [range]	7.1 [3.4-27.5]
Marrow abnormal B cells, median [range], %	64.5 [0-96]

Pre-therapy absolute abnormal B cell count in blood:

- Median 1.1 (x103/ μ L)
- Range 0 - 76.68 (x103/ μ L)

• CD19 CAR-T cell product was manufactured in 100% of patients

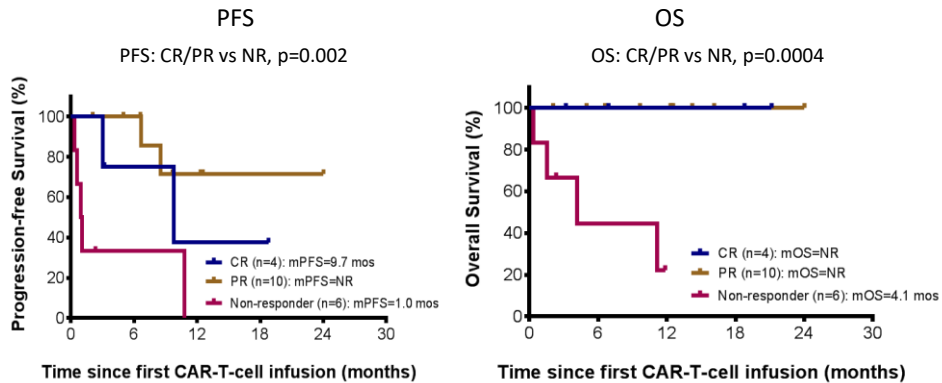
• 22/24 (92%) products were formulated in the defined CD4+:CD8+ composition

• No difference in CAR-T cell naive and memory subset phenotypes between patients on/off ibrutinib immediately prior to leukapheresis

High Response Rates in High-Risk CLL Patients Demonstrated at Four Weeks after JCAR014 Infusion

Lymphodepletion	Non-Cy/Flu (N=3 restaged)	Cy/Flu lymphodepletion (N=21)	
		All patients (N=19 restaged)	Ibrutinib-refractory (N=16 restaged)
Dose Level	All Doses	DL 1, 2	DL 1, 2
IWCLL restaging	N=3	N=19	N=16
ORR (CT at 4 weeks)	1/3 (33%)	14/19 (74%)**	11/16 (69%)**
CR (CT at 4 weeks)	0/3 (0%)	4/19 (21%)	4/16 (25%)
BM disease at baseline	N=3	N=17	N=14
Flow-negative (at 4 weeks)	1/3 (33%)	15/17 (88%)	12/14 (86%)
PET-avid disease at baseline	N=1	N=11	N=11
ORR (at 4 weeks)	0/1 (0%)	8/11 (73%)**	8/11 (73%)
CR (at 4 weeks)	0/1 (0%)	7/11 (64%)**	7/11 (64%)

Longer PFS and OS in High-Risk CLL Patients with a Lymph Node Response (IWCLL) to Cy/Flu and JCAR014



Cy/Flu, JCAR014 dose level 1 or 2 (n=20)
Lymph node response by IWCLL (CT scan) at 4 weeks

No responding patients underwent allogeneic HCT after JCAR014 immunotherapy.

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Cytokine Release Syndrome and Neurotoxicity in CLL Patients After JCAR014 Immunotherapy

CRS		CLL (n=24)	NT		CLL (n=24)
CRS grade (Lee et al, Blood, 2014)	0	4 (17%)	Neurotoxicity (CTCAE v4.03)	0	16 (67%)
	1	8 (33%)		1	0 (0%)
	2	10 (42%)		2	2 (8%)
	3	0 (0%)		3	5 (21%)
	4	1 (4%)		4	0 (0%)
	5	1 (4%)		5	1 (4%)

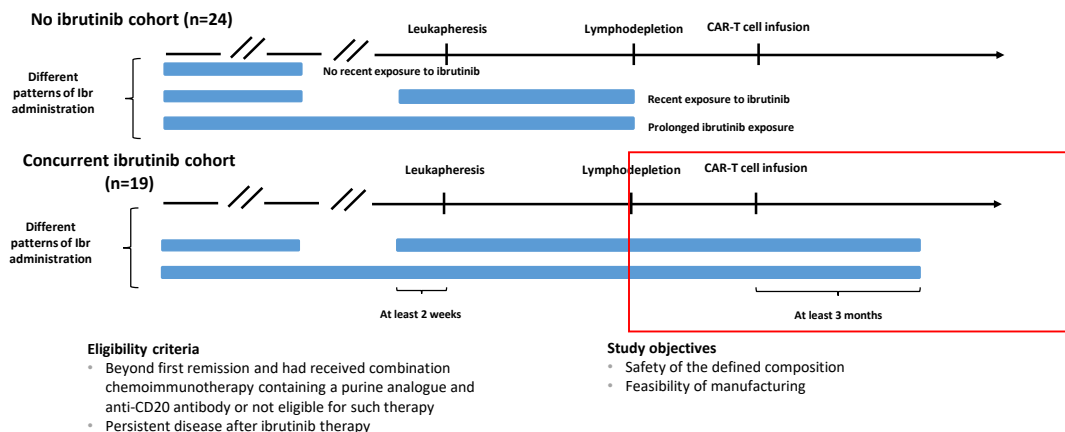
- 6 patients (25%) received tocilizumab and dexamethasone for CRS and/or neurotoxicity
 - 2 patients received vasopressors and required ICU care
 - 1 patient died (grade 5) with cerebral edema/severe CRS
 - Days in hospital: (median; all cause) = 9 days

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JCAR014 in R/R CLL in Ibrutinib-refractory CLL: Authors' Conclusions

- CD19 CAR-T cells can be administered with an accepted early toxicity profile
 - high-risk CLL patients (i.e., del17p, complex karyotype, ibrutinib-refractory, venetoclax-refractory)
- CAR-T cells + Cy/Flu lymphodepletion anti-tumor activity
 - bone marrow clearance
 - by flow cytometry in 88% and by IGH seq in 50%
 - 4 week evaluation
 - ORR 14/19 (74%), CR 4/19 (21%)
 - CR (PET-negative)- 7/11 (64%)

Phase 1/2 Study: 4-1 BB-EGFRt in R/R CLL Previously Treated with Ibr: Study Design and Patients



No ibrutinib cohort: ibrutinib was discontinued in all patients prior to leukapheresis or lymphodepletion.

CAR-T cell infusion (3 dose levels): dose level (DL1): 2x10⁵ EGFRt+ cells/kg; dose level (DL1): 2x10⁶ EGFRt+ cells/kg; dose level (DL1): 2x10⁷ EGFRt+ cells/kg
NCT01865617. 1. Gauthier et al. *ASH*. 2018:Abstract 299.

Phase 1/2 Study: 4-1 BB-EGFRt in R/R CLL Previously Treated with Ibr: Patient Disease Characteristics (1)

	Concurrent ibrutinib N=19	No ibrutinib N=24	P
Median age, years (IQR)	65 (56, 69)	61 (53, 64)	0.24
Female	7 (37)	9 (37)	1
ECOG 1 (n, %)	9 (47)	11 (46)	1
Richter's transformation (n, %)	4 (21)	4 (17)	1
17 p deletion (n, %)	14 (74)	17 (71)	1
11 q abnormality (n, %)	5 (26)	10 (43)	0.34
Complex karyotype (n, %)	14 (74)	18 (78)	1
Cross-sectional tumor area, mm ² , median (IQR)	2624 (1458, 4149)	3225 (1959, 4887)	0.36
Maximum SUV, median (IQR)	4.4 (3.4, 7.0)	5.1 (4.8, 9.6)	0.23
Serum LDH concentration, UI/L, median (IQR)	155 (135, 206)	234 (189, 322)	0.01

All variables assessed prior to lymphodepletion unless specified. Missing data not reported. P values per Fisher's or Wilcoxon Rank Sum as appropriate. NCT01865617. 1. Gauthier et al. *ASH*. 2018:Abstract 299.

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Phase 1/2 Study: 4-1 BB-EGFRt in R/R CLL Previously Treated with Ibr: Patient Disease Characteristics (2)

11 (58)	Concurrent ibrutinib N=19	No ibrutinib N=24	P
Blood absolute lymphocyte count (10 ⁹ cells/L), median (IQR)	1.12 (0.84, 3.95)	2.98 (1.00, 11.65)	0.19
Blood CLL cells (10 ⁹ cells/L), median (IQR)	0.45 (0.13, 3.13)	2.13 (0.18, 7.29)	0.41
Marrow CLL cells, %, median (IQR)	26 (12, 60)	59 (32, 78)	0.09
Prior therapies, number, median (IQR)	5 (4, 7)	5 (4, 6)	0.39
Prior stem transplantation (n, %)	3 (16)	3 (12)	1
Prior treatment with venetoclax (n, %)	11 (58)	6 (25)	0.06
Duration of last treatment with ibrutinib prior to leukemia, days, median (IQR)	248 (26, 764)	384 (120, 642)	0.50
CAR-T cell dose (n, %)			
2x10 ⁵ CAR-T cells/kg	0	5 (21)	0.06
2X10 ⁶ CAR-T cells/kg	19 (100)	19 (79)	
Cy/flu-based lymphodepletion (n, %)	19 (100)	24 (100)	1

Most patient and disease characteristics were comparable between the two cohorts

All variables assessed prior to lymphodepletion unless specified. Missing data not reported. P values per Fisher's or Wilcoxon Rank Sum as appropriate. Cy: cyclophosphamide; flu: fludarabine. NCT01865617. 1. Gauthier et al. *ASH*. 2018:Abstract 299.

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Phase 1/2 Study: 4-1 BB-EGFRt in R/R CLL Previously Treated with Ibr: Key Safety Results

Patient #	Cause of first ibrutinib dose reduction or discontinuation	Day of first ibrutinib dose reduction or discontinuation*	Total duration of ibrutinib therapy*
CLL-33	Abnormal liver function tests, disease progression	84	84
CLL-36	Thrombocytopenia [§]	7	89
CLL-35	Subdural hematoma, CAR-T cell-related neurotoxicity	12	19
CLL-44	CAR-T cell-related neurotoxicity	21	24
CLL-46	Disseminated intravascular coagulation during CRS	6	21
CLL-48	Microembolic strokes during neurotoxicity	8	8
CLL-45	Sudden death from presumed cardiac arrhythmia	4	4

- Concurrent ibrutinib was well tolerated in most patients
- In the concurrent ibrutinib cohort, 13/19 (68%) patients received ibrutinib as planned without discontinuation

*After CAR-T cell infusion
[§]CLL-36 continued on ibrutinib at a reduced dose
 NCT01865617. 1. Gauthier et al. *ASH*. 2018:Abstract 299.

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Phase 1/2 Study: 4-1 BB-EGFRt in R/R CLL Previously Treated with Ibr: Key Efficacy Results

	Concurrent ibrutinib n=18	No ibrutinib n=23	P
Evaluable for response			
iwCLL 2018 (CR/CRI/PR)	15/18 (83%)	15/23 (65%)	0.38
Marrow CR by flow cytometry	13/18 (72%)	17/23 (74%)	1
Marrow CR by <i>IGH</i> seq*	11/13 (85%)	7/14 (50%)	0.10
Nodal (CR/PR per iwCLL 2018 CT) [§]	10/14 (71%)	14/22 (64%)	0.73
PET (CR/PR per Lugano 2014 criteria) [¥]	8/10 (80%)	9/13 (69%)	0.66

- High response rates were seen at 4 weeks after CAR-T cell infusion

Two patients were not evaluable for response; p values per Fisher's test.
 *Among flow-negative patients with a trackable clone; [§]Among those with nodal disease before CAR-T cells;
[¥]Among those with available PET scans and nodal disease per Lugano 2014.
 NCT01865617. 1. Gauthier et al. *ASH*. 2018:Abstract 299.

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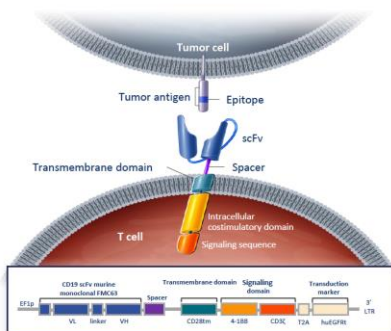
Phase 1/2 Study: 4-1 BB-EGFRt in R/R CLL Previously Treated with Ibr: Authors' Conclusions

- In this retrospective analysis of two sequential cohorts, concurrent administration of ibrutinib with CD-19-specific CAR-T cells for R/R CLL:
 - Was feasible in most patients
 - High response rates at 4 weeks were observed in this high-risk population
 - Higher *in vivo* expansion of CD4+ CAR-T cells was observed vs no ibrutinib, which may deepen responses
 - Lower rates of severe CRS (\geq grade 3 per Lee et al 2014 criteria) were seen vs no ibrutinib (0/19 vs. 6/24, respectively; $p=0.03$)
 - Lower serum concentrations of cytokines were correlated with severe CRS vs no ibrutinib
- Close cardiac monitoring (telemetry) might be considered in patients on ibrutinib developing CRS (potential risk of cardiac arrhythmia)
- The next step will be a prospective phase 1/2 study (TRANSCEND-CLL 17004, NCT03331198)

NCT01865617. 1. Gauthier et al. *ASH*. 2018:Abstract 299.

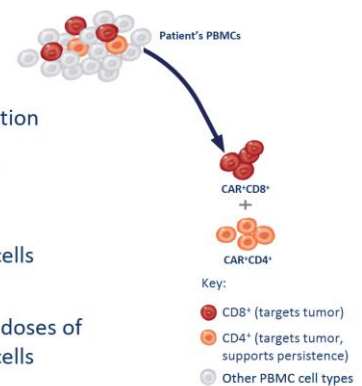
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Lisocabtagene Maraleucel (liso-cel; JCAR017) CD19-Targeted Defined Cell Product



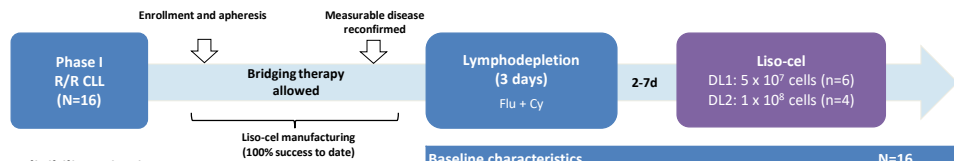
CAR, chimeric antigen receptor; CD, cluster of differentiation; huEGFRt, truncated human epidermal growth factor receptor; LTR, long terminal repeat; PBMC, peripheral blood mononuclear cells; scFv, single-chain variable fragment; VH, variable heavy chain; VL, variable light chain.

- Immunomagnetic selection
- Lentiviral transduction
- Expansion
- CD4+ and CD8+ CAR T cells formulated separately
- Administered at target doses of CD4+ and CD8+ CAR T cells



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TRANSCEND CLL 04: Liso-Cel in R/R CLL Previously Treated with Ibr: Study Design and Patients



Eligibility criteria

- R/R CLL/SLL
- Failed or ineligible for BTKi
- High-risk disease: failed ≥ 2 prior therapies
- Standard-risk disease: failed ≥ 3 prior therapies
- ECOG PS 0-1

Primary objectives

- Determine recommended dose
- Safety

Exploratory objectives

- Antitumor activity
- PK profile

Baseline characteristics	N=16
Median (range) age, y	65 (51-76)
Stage, n (%)	
Rai Stage III/IV	10 (63)
Binet Stage C	10 (63)
Any high-risk cytogenetics, n (%)	12 (75)
Del(17p)	7 (44)
TP53 mutation	10 (63)
Complex karyotype	8 (50)
Prior lines of therapy, median (range)	4.5 (2-11)
Prior Ibr, n (%)	16 (100)
Ibr R/R, n (%)	13 (81)
Ibr progression & prior Ven, n (%)	8 (50)

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TRANSCEND CLL 04: Liso-Cel in R/R CLL Previously Treated with Ibr: Key Results

Response rates, n (%)	
Best overall response	N = 16
ORR	13 (81)
CR/Cri	7 (44)
PR/nPR	6 (38)
SD	2 (13)
PD	1 (6)
Response at 30 days post liso-cel	N = 16
ORR	12 (75)
CR/Cri	5 (31)
PR/nPR	7 (44)
Response at 3 months post liso-cel	N = 10
ORR	8 (80)
CR/Cri	5 (50)
PR/nPR	3 (30)

uMRD4 at any time point	n/N (%)
Blood, flow cytometry	11/15 (73)
Bone marrow, NGS	7/8 (88)

- All 11 patients with uMRD4 in blood remain undetectable at last follow up
- All patients with post-dose follow-up at month 6 (n=5) have maintained uMRD response (CR, n=4)

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TRANSCEND CLL 04: Liso-Cel in R/R CLL Previously Treated with Ibr: Key Results *Continued*

TEAEs of ≥20% Incidence, n (%)	All Grades (N=16)	Grade ≥3 (N=16)	Treatment-related Grade ≥3
Any TEAE	16 (100)	16 (100)	9 (56)
Anemia	14 (88)	11 (69)	4 (25)
Thrombocytopenia	13 (81)	12 (75)	5 (31)
CRS	12 (75)	1 (6)	1 (6)
Neutropenia	10 (63)	10 (63)	6 (38)
Leukopenia	9 (56)	9 (56)	5 (31)
Hypokalemia	8 (50)	0	0
Pyrexia	6 (38)	0	0
Lymphopenia	5 (31)	5 (31)	5 (31)
Nausea	5 (31)	0	0
Diarrhea	4 (25)	0	0
Febrile neutropenia	4 (25)	3 (19)	1 (6)
Headache	4 (25)	0	0
Insomnia	4 (25)	0	0
Tremor	4 (25)	0	0

- 11 patients (69%) received tocilizumab and/or dexamethasone
- One DLT of grade 4 hypertension was reported in DL2
- No grade 5 AEs have been reported

SAEs, n (%)	N=16
All SAEs (all grade ≥3)	7 (44)
Lung infection	3 (19)
Aphasia	1 (6)
Blood fibrinogen decreased	1 (6)
Encephalopathy	1 (6)
Febrile neutropenia	1 (6)
Hypertension	1 (6)
Hyponatremia	1 (6)
AEs of Special Interest	N=16
CRS – any grade, n (%)	12 (75)
Median time to first onset, d (range)	6.5 (1-10)
Median duration, d (range)	5.5 (2-30)
Grade 3, n (%)	1 (6)
Neurologic events – any grade, n (%)	6 (38)
Median time to first onset, d (range)	10.0 (4-21)
Median duration, d (range)	6.5 (2-20)
Grade 3, n (%)	3 (18)
TLS – any grade, n (%) [all grade 3]	2 (13)

TRANSCEND CLL 04: Liso-Cel in R/R CLL Previously Treated with Ibr: Authors' Conclusions

- Liso-cel showed promising activity in heavily pretreated high-risk CLL patients, all of whom had prior Ibr treatment
 - High ORR (81.3%) and CR/CRi (43.8%)
 - Responses deepened from 3-mo to 6-mo follow-up
 - Continuing CR in 5/6 patients at 3 mo
- Early uMRD4 was observed in most patients (73.3%) and maintained at 3 and 6 mo
- Liso-cel toxicities were manageable at both dose levels with low rates of grade 3 CRS (6.3%) and NE (18.8%)
- After analysis of dose escalation data and selection of RP2D, Phase II will open for accrual (expected in 1st half of 2019)

Key Takeaways

- The field is rapidly changing with several novel targeted agents recently approved or in development
- In spite of these advances, patients with CLL may eventually relapse or become refractory to available therapies. Novel therapeutic strategies are needed.
- CAR T-cell therapy is currently in clinical development. Concurrent Ibrutinib may improve outcomes and reduce toxicity of CAR T-cell therapy in relapsed or refractory CLL
- Combination strategies appear to be safe and well-tolerated with sustained responses.
 - Is it possible to envision a future where CAR T-cell therapy can be safely incorporated into earlier lines of therapy to achieve a “cure”?

Thank you very much for your attention!
 Questions: jbarrientos@northwell.edu



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**Weill Cornell
 Medicine**

CAR-T for Lymphoma

Koen van Besien, MD, PhD

Director, Bone Marrow and Hematopoietic Stem Cell Transplant
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Axicabtagene Ciloleucel (YESCARTA®)

- Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

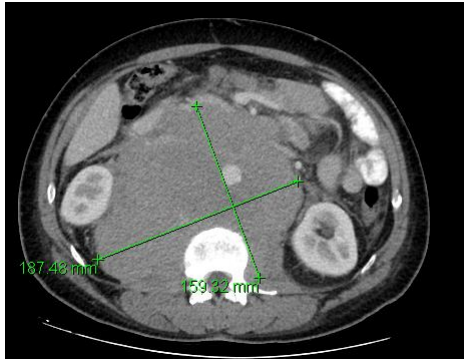
Tisagenlecleucel (KYMRIAH®)

- Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
- Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma

Case

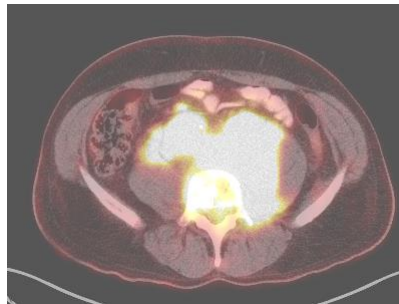
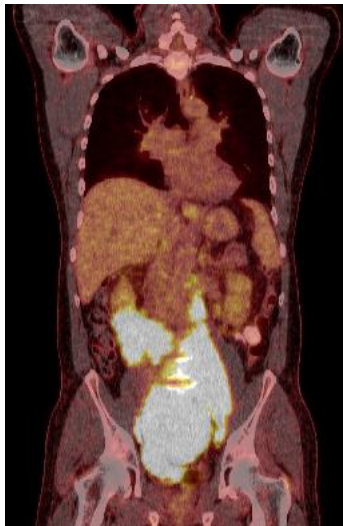
- **01/2015**
- **51 YOM**
- **Past Medical History: Hypertension- Gout**
- **Back Pain**
- **10 Lb weight Loss**
- **Non Smoker**
- **Alcohol Modest**
- **Family History: 1 Brother Coronary Artery Disease 1 Sister lymphoma**
- **WBC 7.4, Hgb 13.8, Plt 291, Cr 1.52, Ca 13**
- **LDH 1106**

At Diagnosis

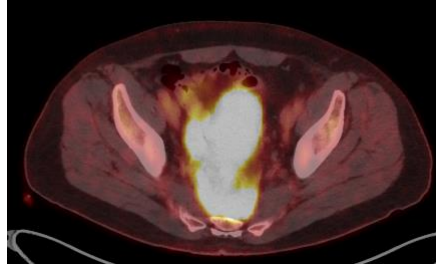


*Diffuse Large B-Cell Lymphoma
Myc and BCL-2 Rearranged
"Double-Hit Lymphoma"*

2/2016



After Selinexor RICE x 3

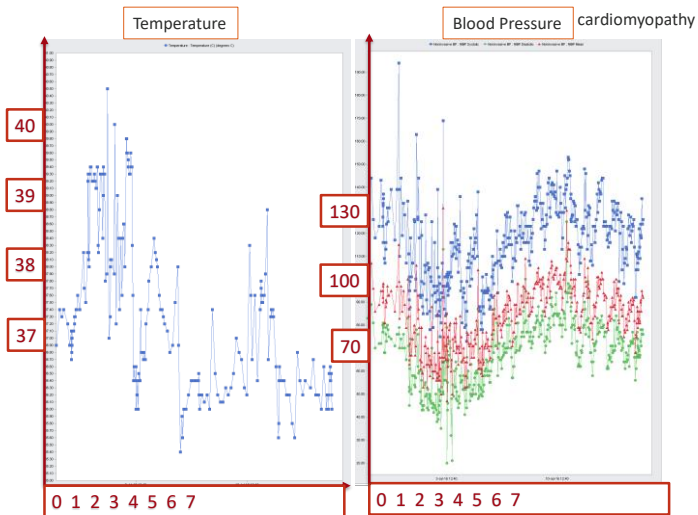


RICE, rituximab, ifosfamide, carboplatin, etoposide



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One month post CART

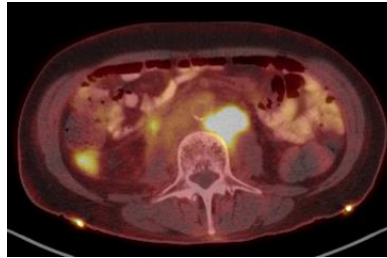
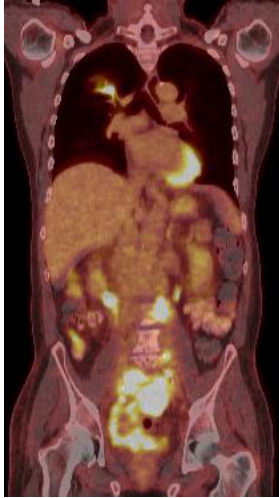
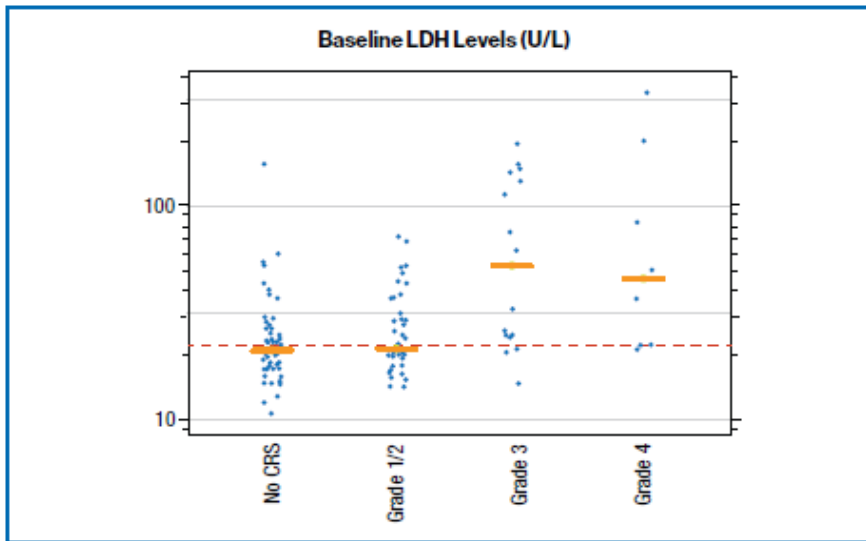


Figure 9. Predictivity of Baseline LDH for CRS Grades 3-4 vs Grades 0-2.



CRS, Complete Response Rate

Case 1: Lessons Learned

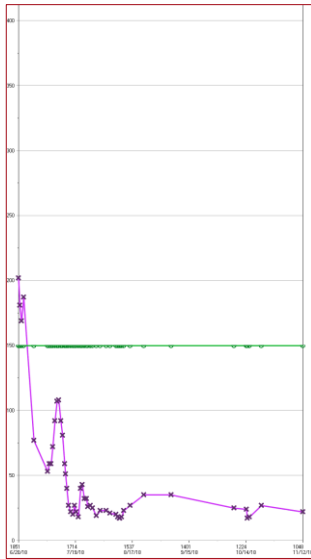
- **More Advanced Disease May Correlate with Higher Risk for CRS**

Case 2

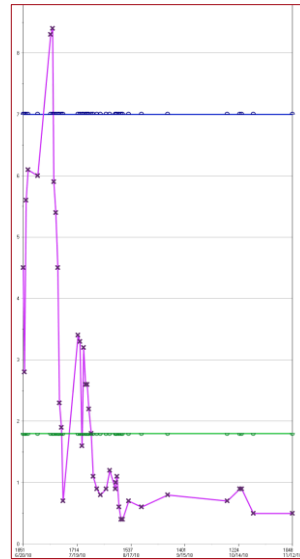
- **68 Year old female**
- 7/9/08 DLBCL: RCHOP x6.
- 5/4/2011 abdominal wall mass, excisional biopsy: extranodal marginal zone lymphoma of mucosal associated tissue. BRx6
- 7/23/15 Mediastinal mass: Diffuse large B-cell lymphoma R-DICE x2 – Autologous SCT BEAM
- 5/2018 Relapse: RDHAX – stable disease
- 7/11/2018 Fludarabine/Cyclophosphamide → Axi-/Cel
- CR

RCHOP, Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunomycin), Vincristine Sulfate (Oncov in), Prednisone;
BR Bendamustine/Rituximab; BEAM, BCNU (Carmustine), etoposide, cytarabine and melphalan; R-DICE Rituximab-dexamethasone, ifosfamide,
cisplatin, etoposide; R-DHAX, Rituximab, dexamethasone, cytarabine, and oxaliplatin

Platelets



Neutrophils

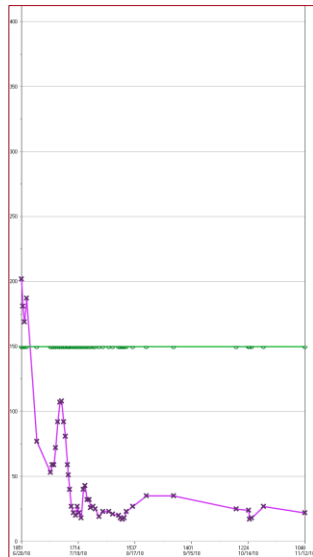


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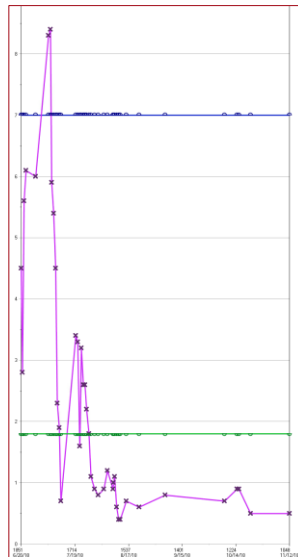
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Platelets



Neutrophils



Bone Marrow

Normocellular bone marrow with increased erythropoiesis and megakaryopoiesis and decrease in granulopoiesis.

45,XX,der(5;17)(p10;q10)[12]/46,XX[8]
12 of the 20 cells had a translocation involving 5p and 17q, resulting in loss of 5q and 17p.

Interphase FISH detected loss of EGR1 (54.5%) and TP53 (55%)

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Case 2: Lessons Learned

- Extensive Prior treatment may lead to occult MDS
- Consider Bone Marrow Analysis prior to treatment

MDS, Myelodysplastic Syndromes

Case 3:

- **86 Year Old Male**
- 07/2007 DLBCL Treated with RCHOP
- 03/2017 Recurrence left testicle
- Orchiectomy, REPOCH x3, HD methotrexate x 3
- 6/2018 recurrence on left leg. radiation 8/20--9/12/18 six sessions. No response
- 10/8/2018 received 16 additional XRT
- **2010 Bladder Cancer**
- **2001 Prostate cancer** Seed implant
- **1999 Left Nephrectomy**



REPOCH, rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride

Case 3:

- Echo: LVEF 64%
- Bone Marrow
 - Normocellular
 - Normal cytogenetics
- Geriatric Testing
 - No deficits
- MRI Brain:
- Neurology consult – **Normal findings**

LVEF, Left ventricular ejection fraction

Case 3: Lessons Learned

- Age is not a Contra-Indication

Case 4:

- **81 YO Female**
- PMH
- 2013 breast cancer s/p bilateral mastectomy
- Atrial Fibrillation – apixaban (Eliquis®)
- Hypertension
- Lymphoma History
- 3/2017 Mediastinal mass low grade B cell lymphoma of FCC origin
- 3/2017 prednisone
- 4/2017 PET CT marked regression in perihilar disease
- 5/2017 rituximab (Rituxan®)/bendamustine (Treanda®)
- 1/2018 R-CHOP*5 sessions
- 12/2017 - 1/2018 chest RT
- 1/2018 lenalidomide (Revlimid®) plus rituximab (Rituxan®)
- 5/13/2019 endobronchial lung biopsy NYU : DLBCL
- DICE x 1 day - confusion

Case 4



Work up

- **Echo Normal**
- **Bone Marrow Normal, normal cytogenetics**
- **Neurology:**
 - Exam notable for cognitive dysfunction, especially with attention and memory (MOCA 12/30).
 - MRI Brain shows severe microvascular ischemia and generalized atrophy.

Case 4: Lessons Learned?

- What constitutes a contra-indication?

Case 5:

- **69 year old female**
- 2005: stage I FL, localized to R groin and tx with RT. Was in remission until 3/2018
- 3/27/18: focal transformation to DLBCL, Diffuse adenopathy above and below diaphragm with bulky disease in abd/pelvis.
- 4/2018-7/2018: R-CHOP x6 cycles -9/2018: Recurrent Lower back pain → PD
- R-DICE, RDHAX →PD/SD
- 1/2019 FluCy – axicabtagene ciloleucel

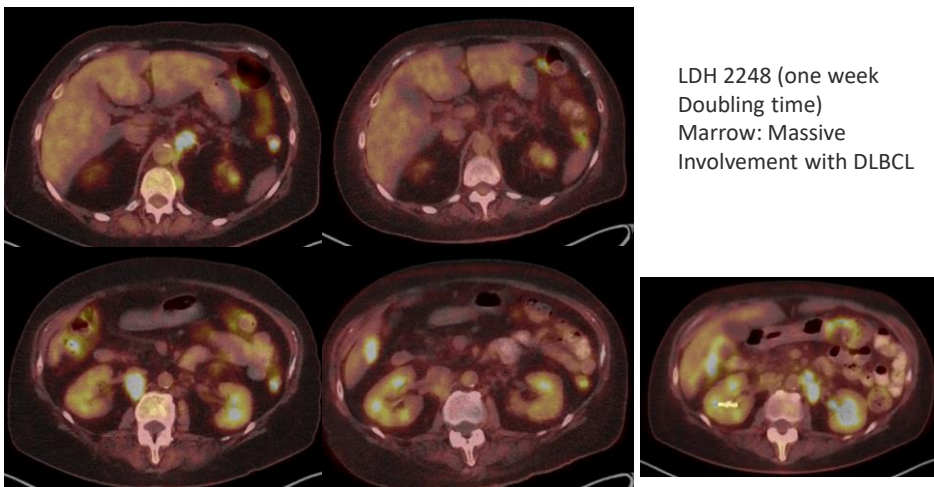
PD, Progressive Disease; SD, stable disease

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Pre

3 Months

6 Months



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Case 5: Lessons Learned

- **Should we have intervened at 3 months?**
- **What is salvage therapy after failure of CART?**

Conclusions

- **Experience with CAR T cell Therapy in DLBCL is rapidly accumulating.**
- **Many Questions remain regarding**
 - **Timing**
 - **Impact of Prior Therapy**
 - **Patient Selection**
 - **Indications are well defined**
 - **Contra-indications are not**
 - **Prediction of Long-Term Outcomes.**

THANK YOU!



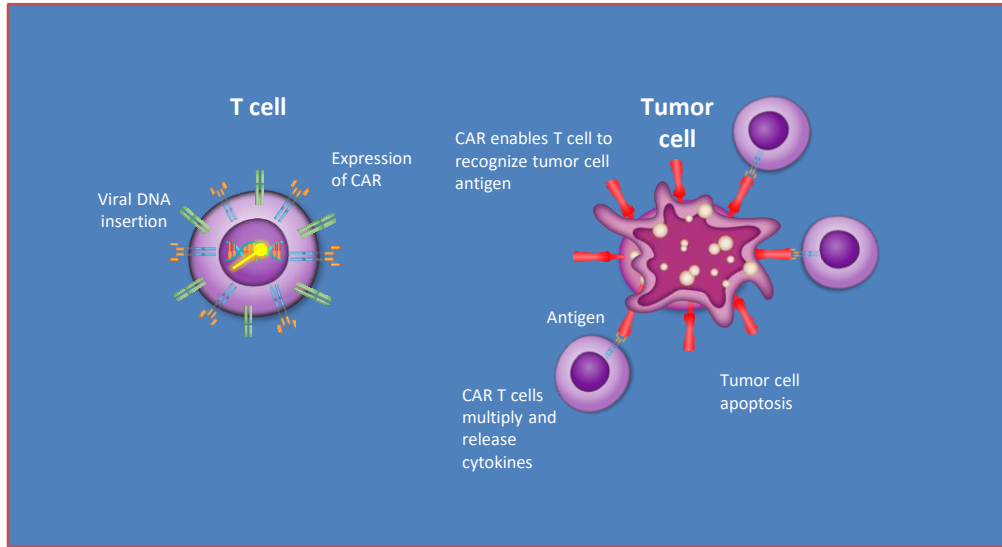
CAR T-Cell in Myeloma: Toxicity Management, Referral and Follow Up

Deepu Madduri, MD

**Assistant Professor of Medicine
Icahn School of Medicine at Mount Sinai
Tisch Cancer Institute
New York, NY**

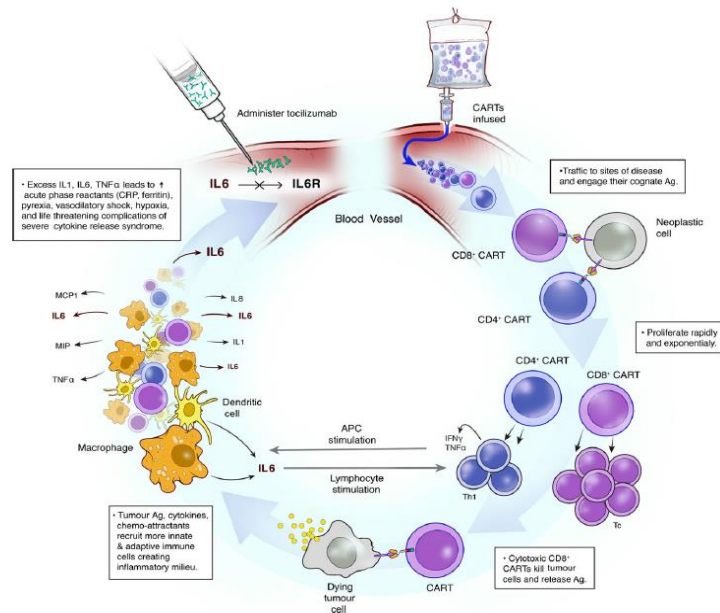


How CAR T-Cell Therapy Works



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Biological Consequences Following Car T-cell Infusion



Orlowski et al. Br J Haematol 2016.

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CAR T-cells Complications: Mechanisms



- Tumor associated antigen expressed on normal tissues
- Tumor lysis syndrome
 - Related to tumor burden and response
 - Management is same as tumor lysis syndrome in other settings
- Anaphylaxis
 - The T-cell is autologous but the receptor is foreign and one case of anaphylaxis has been reported
- **Cytokine release syndrome (CRS) - Most important !**

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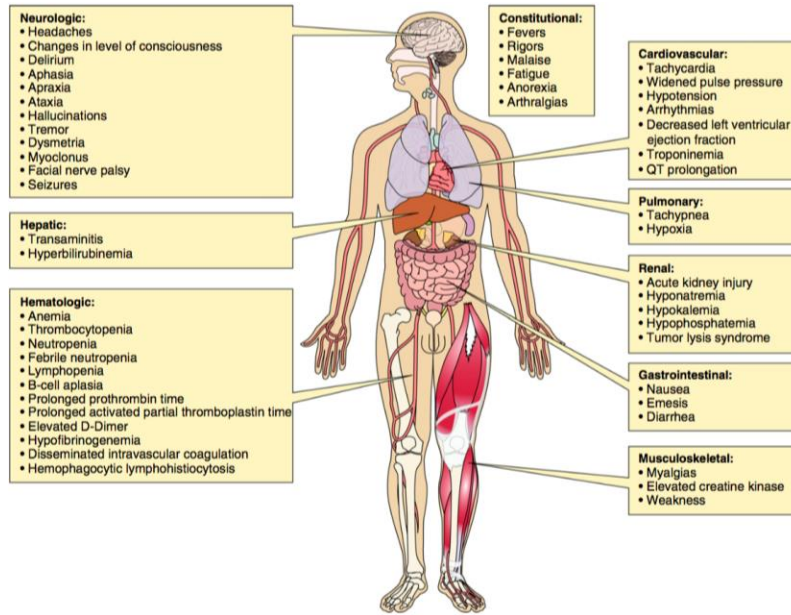
Cytokine Release Syndrome (CRS)



- Caused by cytokine production due to activation of the T-cells as well as other immune cells
- Principal mediators are interleukin-6, interferon- γ , tumor necrosis factor, interleukin-2, and interleukin-10
- Highest risk during first 10 days
- Severity may correlate with dose of T-cells and tumor burden
- Severity correlates with CRP, ferritin, IL-6, and soluble IL-2 receptor α

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Cytokine Release Syndrome Affects Multiple Organ Systems



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Table 2 CRS grading scales: Penn grading scale, CTCAE v4.0, and Porter et al. Journal of Hematology & Oncology (2018)

	Penn grading scale [16]	CTCAE v4.0 [35]	2014 Lee et al. [36]
Grade 1	Mild reaction; treated with supportive care such as antipyretics, antiemetics	Mild reaction; infusion interruption not indicated; intervention not indicated	Symptoms are not life-threatening and require symptomatic treatment only, eg., fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Moderate reaction; some signs of organ dysfunction (eg, grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including fevers with associated neutropenia, need for IV therapies (not including fluid resuscitation for hypotension)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	Symptoms require and respond to moderate intervention. Oxygen requirement < 40% or hypotension responsive to fluids or low-dose pressors or grade 2 organ toxicity
Grade 3	More severe reaction; hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other condition; this excludes management of fever or myalgias; includes hypotension treated with intravenous fluids (defined as multiple fluid boluses for blood pressure support) or low-dose vasopressors, coagulopathy requiring fresh frozen plasma or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS	Prolonged reaction (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 infiltrates)	Symptoms require and respond to aggressive intervention. Oxygen requirement ≥ 40% or hypotension requiring high-dose or multiple pressors or grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening complications such as hypotension requiring high-dose vasopressors, hypoxia requiring mechanical ventilation	Life-threatening consequences; pressor or ventilator support indicated	Life-threatening symptoms. Requirements for ventilator support or grade 4 oxygen toxicity (excluding transaminitis)

BiPAP bilevel positive airway pressure, CPAP continuous positive airway pressure therapy, CRS cytokine release syndrome, CTCAE Common Terminology Criteria for Adverse Events, IV intravenous, LFT liver function test, NSAID nonsteroidal anti-inflammatory drug
 *See specific definition of high-dose vasopressors

16-Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, Bagg A, Marucci KT, Shen A, Gonzalez V, Ambrose D, Grupp SA, Chew A, Zheng Z, Milone MC, Levine BL, Melenhorst JJ, June CH. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med.* 2015;7:303ra139

35- US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). V4.03. 2010. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_Sx7.pdf. Accessed 21 Sep 2017

36- Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124:188–95

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ASBMT CRS Grading



ASBMT CRS Consensus Grading##

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever††	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one 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, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

Lee DW, BBMT 2018.

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CRS Management: One of Many Proposed Guidelines

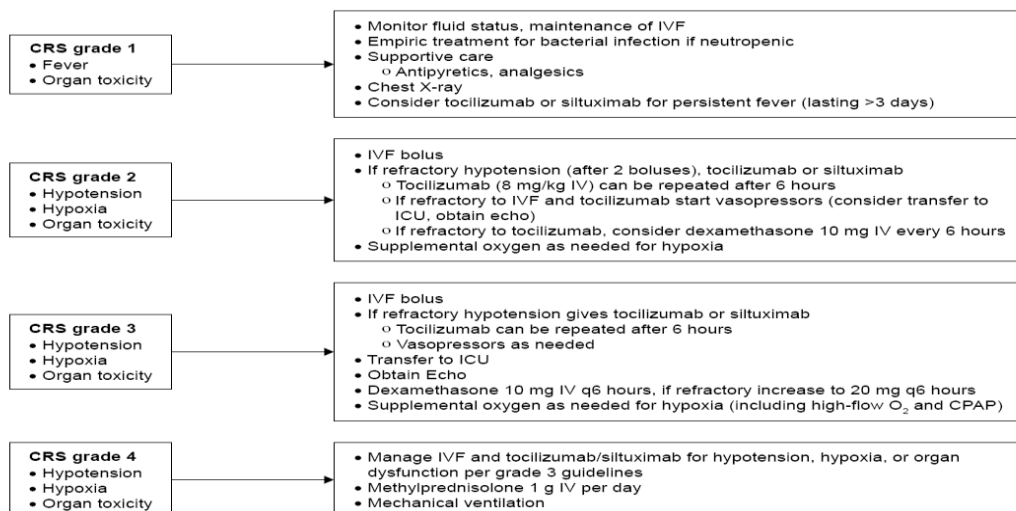


Figure 4 CRS management recommendations by Neelapu et al.²⁶

Notes: These recommendations suggest using anti-cytokine therapies for grade 1 CRS and require them for grade 2 or higher CRS. Supportive care is also suggested for each grade.

Abbreviation: CRS, cytokine release syndrome; IVF, intravenous fluid; ICU, intensive care units; q, every; CPAP, continuous positive airway pressure.

Lee DW, BBMT 2018.

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CRS Management: One of Many Proposed Guidelines



CRS Grading and Management Guidance

CRS Grade*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement less than 40% FiO ₂ or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity†	Administer tocilizumab‡ 8 mg/kg intravenous over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab
Grade 3 Symptoms require and respond to aggressive intervention Oxygen requirement greater than or equal to 40% FiO ₂ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenous twice daily or equivalent dexamethasone (eg, 10 mg intravenous every 6 hours) Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days
Grade 4 Life-threatening symptoms Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)	Per Grade 2	Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above

Abbreviation: CVVHD, continuous veno-venous hemodialysis.

*Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

†Refer to the table on the back for management of neurologic toxicity.

‡Refer to tocilizumab Prescribing Information for details.

From the YESCARTA® package insert.

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Case Scenario #1



- 61M with relapsed/refractory MM, penta-refractory, otherwise healthy
- Started fludarabine/cytosin conditioning chemotherapy 5 days ago
- Nursing notes showed a Tmax of 100.8 last night, blood and urine cultures drawn, CRP 105 mg/L, started on pip/tazo for presumed active infection

CRP, reactive protein; pip/tazo, piperacillin and tazobactam

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Don't Forget to r/o Infection Prior to CAR-T cell Infusion



- CT c/a/p
- Viral workup also sent
- ID consulted
- b2121 infusion delayed
- Called CRS/PI physician



CT, Computed tomographic; CAP, chest abdomen pelvis

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CRS Management is Key!!



- Infection workup negative, no further fevers, finished course of abx recommended by ID, on prophylactic cipro



- BCMA CAR-T cell infused 48h after last dose of pip/tazo
- Patient developed fevers on day+1, ANC 300, bp 135/80, HR 90, pulse ox 97% on room air

ANC, Absolute neutrophil count; BCMA, B cell maturation antigen.

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CRS Management



- Grade 1 CRS
- Pan cultures repeated
- Antibiotics changed to broad spectrum
- Acetaminophen for symptomatic relief
- Check CRP, ferritin
- 2am day+3, patient's pressures drop to 90/60, HR 130, PulseOx 91% ra, CRP now 230, ferritin 125

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CRS Management



- Grade 2 CRS
- 1L Fluid bolus to maintain pressures
- 2L nasal cannula
- Transfer to SICU if needs pressors or no response to bolus
- Tocilizumab 8 mg/kg x 1 started
- 10am day+3, bp 90s/60s, HR 145, pulse ox 95% on 2-4L NC, CRP 200, ferritin 500, 1+ bilateral pitting le edema

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CRS Management



- Started on levophed 10 mcg/min, titrated to 20 mcg/min soon thereafter
- Grade 3 CRS
- Second dose of toci given 10am after no improvement
- 2am day+4, bp 80s/50s, HR 150 in flutter, pulse ox 95% on 5L face mask, CRP 180, ferritin 2000, 2+ ble pitting edema, new small bilateral pleural effusions on cxr

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CRS Management



- Cardioverted, but pressures remain low
- Started on methylpred 1 mg/kg q12h or dex 10 mg IV q6 hours
- 6pm day+4, no improvement



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CRS Management



- Methylpred 1 g given
- 8am day+5, CRP now 60, ferritin 2100, pulse ox 95% weaned off facemask back onto NC, levophed titrated off
- Steroids tapered over next three days as patient continued to improve
- Discharged on day+10

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CARTOX-10 vs. ICE



Neurological assessment tools for grading of Neurotoxicity

CARTOX-10 (12)

Orientation: Orientation to year, month, city, hospital, President/Prime Minister of country of residence: **5 points**

Naming: Name 3 objects (e.g., point to clock, pen, button): **3 points**

Writing: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): **1 point**

Attention: Count backwards from 100 by ten: **1 point**

CARTOX-10 has been updated to the ICE tool. ICE replaces one of the CARTOX 10 orientation questions with a command-following assessment. Scoring unchanged.

10	No impairment
7-9	Grade 1 Neurotoxicity
3-6	Grade 2 Neurotoxicity
0-2	Grade 3 Neurotoxicity

0 with one of the additional events defined in Table 6: Grade 4 Neurotoxicity

ICE SCORE (IMMUNE EFFECTOR ENCEPHALOPATHY) ASSESSMENT

Orientation: Orientation to year, month, city, hospital: **4 points**

Naming: Name 3 objects (e.g., point to clock, pen, button): **3 points**

Following commands: (e.g., Show me 2 fingers or Close your eyes and stick out your tongue): **1 point**

Writing: Write a standard sentence (e.g., Our national bird is the bald eagle): **1 point**

Attention: Count backwards from 100 by ten: **1 point**



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Neurotoxicity Assessment



ASBMT Neurotoxicity (NT) Consensus Grading for Adults - Immune effect Cell-Associated Neurotoxicity Syndrome (ICANS)

NT Domain	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Assessment ICE Score	7-9	3-6	0-2	0 AND One of the events below
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 Non-convulsive 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
Raised ICP / Cerebral edema	N/A	N/A	Focal/local edema with or without hemorrhage on neuroimaging	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

- NT grade is determined by the most severe event not attributable to any other cause.
- A patient with a neuro-assessment score of 3 who has a generalized seizure is classified as having Grade 3 NT.
- A patient with a neuro-assessment score of 0 may be classified as having Grade 3 NT if the patient is awake with global aphasia. But a patient with a neuro-assessment score of 0 may be classified as having Grade 4 NT if the patient is unarousable.
- Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)
- Tremors and myoclonus associated with NT may be graded according to CTCAE v5.0 but they do not influence NT grading.



TRAINING & DEVELOPMENT | CIBMTR 2018

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Case Scenario #2



- 71M with primary refractory MM
- FC conditioning chemotherapy days -5 to -3
- BCMA CAR-T cell infusion on day 0
- Fevers started on day 0 (4-6 hours post infusion) treated with acetaminophen
- Fevers worsened with rapid rise in CRP to 80 on day +1, slight somnolence, severe fatigue, tremor – Toci given 8 mg/kg
- On day +1 8 pm, significant improvement, fevers disappeared, somnolence resolved; Neuro exams/CARTOX-10 normal
- Day+6 normal mentation during evening rounds, slight tremor in right hand
- 6am day+7 pt with AMS, unable to speak in full sentences with delayed responses, unable to write his daily sentence, fever 38

FC, fludarabine, cyclophosphamide; AMS, altered mental status

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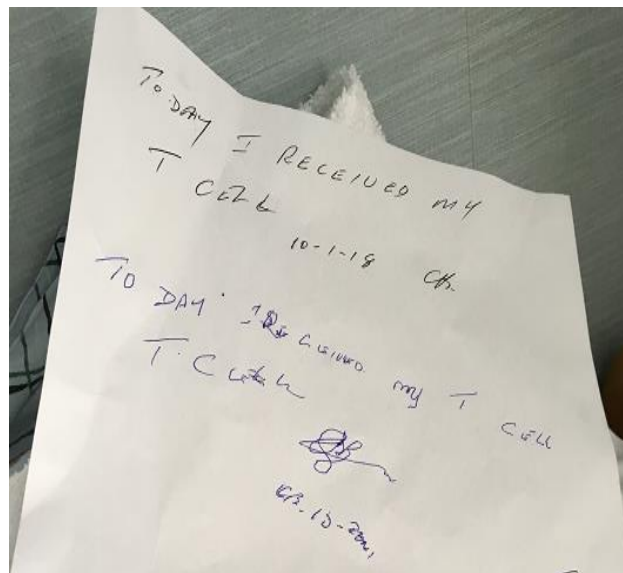
CRS Management



- Order CRP, ferritin, MRI brain
- CRP downtrending 120 → 65
- Ferritin increasing: 600 → 1200
- MRI brain neg
- Pt continues to deteriorate

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Daily Sentence is Key to Early Neurotoxicity Detection!!



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CRS Management

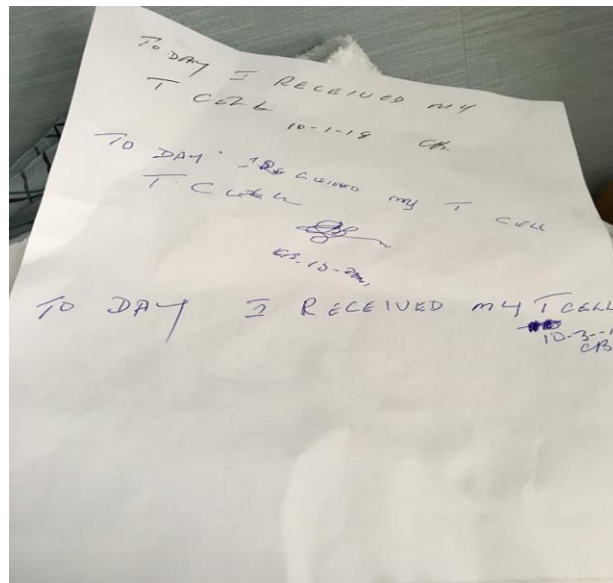


- Toci 8 mg/kg x 1 given again with Dex 10 mg IV q 6 hours
- By evening rounds, AMS significantly improved
- Pt no longer confused by day +8
- Dc'ed on day +14
- Month 1 biopsy: sCR, MRD neg, PET CT neg

(sCR), stringent complete response; MRD, minimal residual disease

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Look at the Transformation In His Handwriting!



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Case Scenario #3



- 44 y/o M with RRMM, VRD x 4 cycles f/b xrt to base of skull for PD, Dara KPD x 5 cycles, VDPACE with PD, then underwent BCMA CAR-T cell therapy
- +day 2 - S/p first dose toci at 828 am for rapid rise in CRP to 320. Subsequently, his CRP and ferritin downtrended but continued to have fevers, tachycardia to 150's. Increased pain all throughout esp with weakness of legs. ? Suspicion for tumor flare so MRI spine was done, which showed resolution of t10 lesion, but possible increase in size of L1 lesion.
- +day 3 - s/p second dose toci at 610 pm

RRMM, relapsed refractory multiple myeloma; PD, progressive disease; Dara KPd, daratumumab and carfilzomib, pomalidomide, and dexamethasone; VDPACE, bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide

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CRS Management: Anakinra



- + day 4 - Pt, however, still continues to have refractory fevers, tachycardia. His evening labs showed that his NA dropped to 126, albumin 2.3, rising LFT's, ferritin increased to 9469, and increased pain throughout his body. dexamethasone 10 mg x 1 given, at 1058 pm
- + day 5 - pt in am still had fever again at 825 am, discussed with medical monitor and decided to give 1st dose of anakinra 100 mg sc x1 at 837 am. Pt responded with improvement in his LFT's and slight improvement in ferritin. Pt spiked again at 11 pm to 39.3. Gave 2nd dose of anakinra at 2149 pm
- + day 6 - 3rd dose anakinra 1245 pm, 1114 pm anakinra 4th dose given
- + day 7 - all symptoms resolved with no fevers; ferritin and CRP downtrending. All labs normalized

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Tocilizumab Used for Initial CRS Management..



- Tocilizumab is a humanized, immunoglobulin G1 κ (IgG1 κ) anti-human IL-6R mAb approved for treatment of rheumatoid arthritis.
- Prevents IL-6 binding to both cell-associated and soluble IL-6Rs and therefore found to prevent severe or life-threatening CRS.
- The recommended dose of tocilizumab is 8mg/kg with an option to repeat the dose if no clinical improvement in symptoms within 24 to 48 hours.
 - Long half life so keep that in mind when repeating multiple doses especially if CRP is downtrending
- Within a few hours of administration of tocilizumab most patients symptoms resolve.

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Corticosteroids as Second-Line agent for CRS



- Corticosteroids are generally considered second-line therapy for CRS
- Can have widespread effects on the immune system and can cause a greater adverse effect on the antitumor activity of adoptively transferred T cells.
- So far, low dose steroids haven't been associated with negative responses, but data is still not fully mature
- Dexamethasone 10 mg IV every 6 hours and methylprednisolone 1mg/kg/day and occasionally 1 gm qday if severe refractory CRS

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Anakinra as a Second Line or Third Line Agent for CRS



- Anakinra neutralizes the biologic activity of IL-1 α and IL-1 β by competitively inhibiting their binding to IL-1R.
- It is administered by subcutaneous injection (1-2 mg/kg/day) using a graduated pre-filled syringe and can be given q6 hours or q12 hours.
- The pathophysiology of CRS and neurotoxicity suggest that macrophage-produced IL-1 plays a major role in triggering CRS and that IL1 blockade with anakinra may reduce both CRS and neurotoxicity, although this approach has yet to be tested in a clinical trial.
- Some mice studies have been done but need more clinical trial data in humans
- There are some promising data from a retrospective case series of 44 patients with secondary Haemophagocytic Lymphohistiocytosis (sHLH) for use of anakinra alongside intravenous immunoglobulins (IVIg's) and corticosteroids, with or without antimicrobial therapy. These are potentially relevant because CRS following CAR-T cell therapy can evolve into fulminant HLH.
- Although these data for anakinra in sHLH due to causes other than CAR-T cell therapy are promising, it is not clear if these data can be extrapolated to this scenario

Rajasekaran S., Pediatric Blood and Cancer Societies 2014..

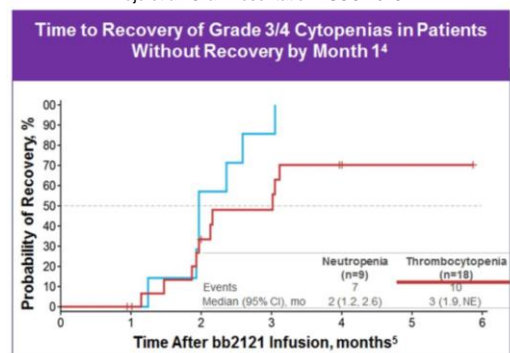
267

CAR-T is Done, What to Look Out For in Your Clinic?



- Pancytopenia
 - Could persist for months
 - Transfusions as needed
 - Hgb >7, plts > 10 if asymptomatic
 - Filgrastim (Neupogen®) for ANC < 500
 - Sargramostim (Leukine®) as needed if severe cytopenias
- Hypogammaglobulinemia
 - IVIG pre-lymphodepletion
 - Every month for 6 months
- Infections
 - CMV PCR check q month
 - Viral panel and blood cultures, abx if fevers
 - Vaccines schedule?

Raje et al. Oral Presentation ASCO 2018



- 31/40 (78%) recovered ANC to $\geq 1,000/\mu\text{L}$ by Day 32
- 22/40 (55%) recovered PLT to $\geq 50,000/\mu\text{L}$ by Day 32

CMV PCR, Cytomegalovirus polymerase chain reaction

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Current CAR-T cell Trials Open at Mount Sinai



- Bluebird CRB-402: Phase 1 trial with bb21217
- JNJ MMY2001: FIH, Phase 1 trial with JNJ-68284528
- Celgene bb2121-MM-002: Phase 2 trial with bb2121 in RRMM and Newly Dx MM
 - Only 1 line of prior therapy (PI, IMiD, +/- ASCT and progresses within 18 months of initial therapy)
- Celgene bb2121-MM-003: Phase 3 trial with bb2121 in RRMM (bb2121 vs Dara Pom Dex)
 - > 2 lines but < 4 lines of prior therapy
 - Needs prior exposure to dara
 - Randomized to dara pom vs. Car-T

Clintrials.gov: NCT# clinical trials (402 is NCT0327429), (JNJ is NCT03548207), Kamma 2 (NCT03601078), Kamma 3 (NCT 03651128).

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Eligibility: Who's a Good Candidate?



- Inclusion criteria
 - M spike >1.0 g/dL
 - FLC > 100 mg/dL
 - Progression of disease and/or refractory to last line of therapy
 - Must be exposed to PI, IMiD, and CD38
- Exclusion:
 - CNS involvement
 - Prior malignancy within 3 years
 - Active plasma cell leukemia
 - Non-secretory myeloma

FLC, Free light chains; PI, proteasome inhibitor; IMiD, immunomodulatory therapy

Raje et al. Oral Presentation ASCO 2018.

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Referral System at Mount Sinai



- Treated about 50 patients on various protocols
- Email me at deepu.madduri@mountsinai.org and/or RTCNPC@mountsinai.org

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CAR T Cells for Myeloma: The Next Major Disease Target?

Adam D. Cohen, MD
 Abramson Cancer Center
 University of Pennsylvania
 Philadelphia, PA

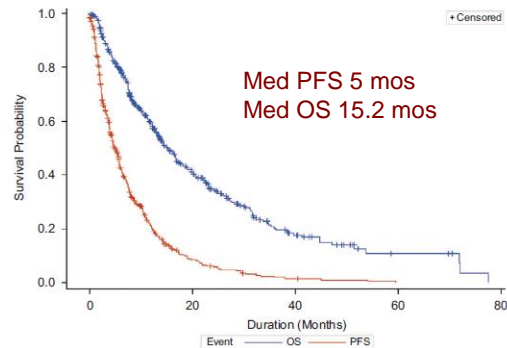
CAR T-cell Therapy for Blood Cancer Patients
 LLS Symposium
 New York, NY
 June 28, 2019



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Relapsed/Refractory Myeloma

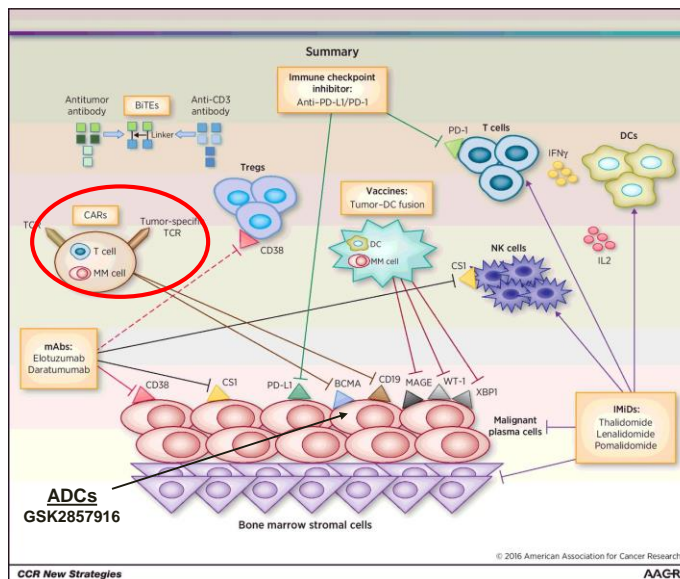
- ◆ **3+ prior lines, dual PI/IMiD-refractory, alkylator-exposed**
 - Traditionally poor outcomes
 - Short remission duration
- ◆ **Often altered biology**
 - Oligosecretory/light chain escape
 - Extramedullary/plasma cell leukemia
 - May need cytotoxics (eg VD-PACE)



PI, Proteasome Inhibitor; IMiD, Immunomodulatory Drug
VD-PACE, bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide

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Immunotherapy for MM: Targets and Tools



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Immunotherapy Targets for Myeloma

◆ The classics:

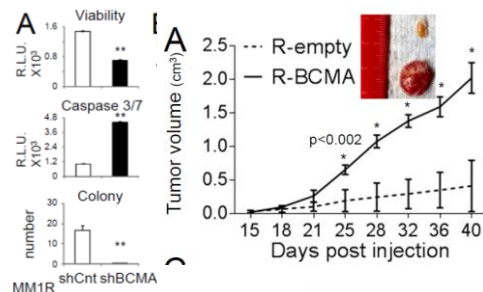
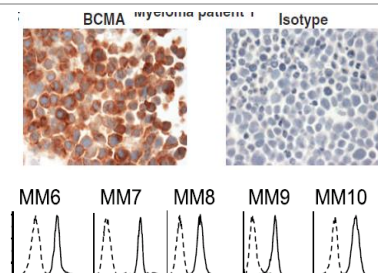
- CD138
- CD38
- CD56
- kappa light chain
- (CD19)

◆ The new models:

- Lewis Y
- CD44v6
- MAGE A3
- NY-ESO-1
- CS1/SLAMF7
- **BCMA**
- Integrin beta 7
- FcRH5
- CD48
- CD46
- CD229
- GPRC5D

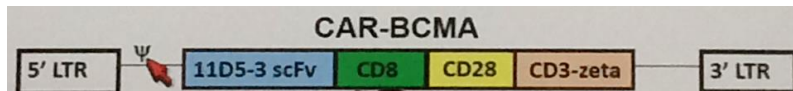
BCMA (B-cell Maturation Antigen)

- ◆ Receptor for BAFF (Blys) and APRIL
- ◆ Expressed on plasma cells, some mature B cell subsets, and plasmacytoid DC's
 - Maintains plasma cell homeostasis
- ◆ Highly expressed on myeloma cells
- ◆ Soluble BCMA in patient serum
- ◆ Promotes MM pathogenesis
 - ◆ Anti-BCMA ADCs
 - ◆ BiTEs / Bispecific Abs
 - ◆ CAR T cells



BAFF, B-cell Activating Factor, APRIL, A Proliferation Inducing Ligand; ADC's, Antibody Drug Conjugates

NCI BCMA-specific CAR in Rel/Ref MM

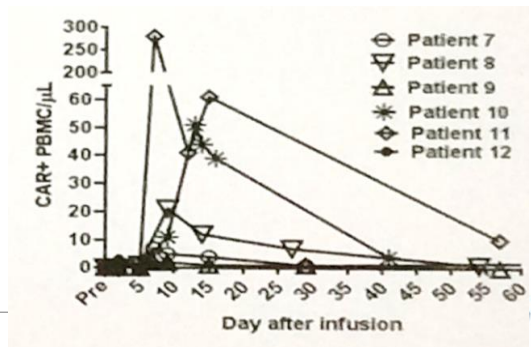


Cyclophosphamide 300 mg/m²
Fludarabine 30 mg/m²
QD for 3 days

CAR-BCMA T cells*
Single infusion

*Dose escalation of
CAR+ T cells/kg
0.3 x 10⁶
1.0 x 10⁶
3.0 x 10⁶
9.0 x 10⁶

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

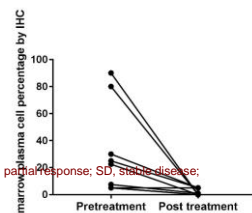
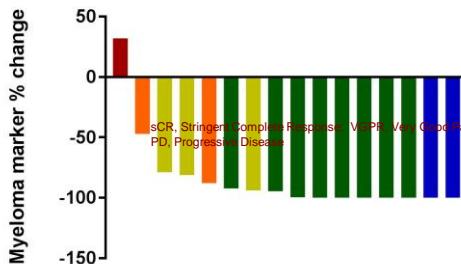


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Antimalignancy activity of the highest dose level of anti-BCMA CAR T cells-9x10⁶ CAR+ T cells/kg

Median 10 priors, low tumor burden
50% BCMA+ by IHC

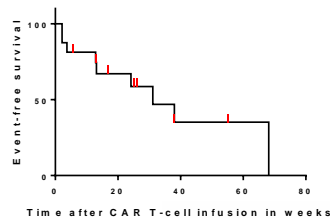
Change in bone marrow plasma cell percentage for 10 evaluable patients



13/16 (81%) ORR

Blue: sCR
Green: VGPR
Gold: PR
Orange: SD
Maroon: PD

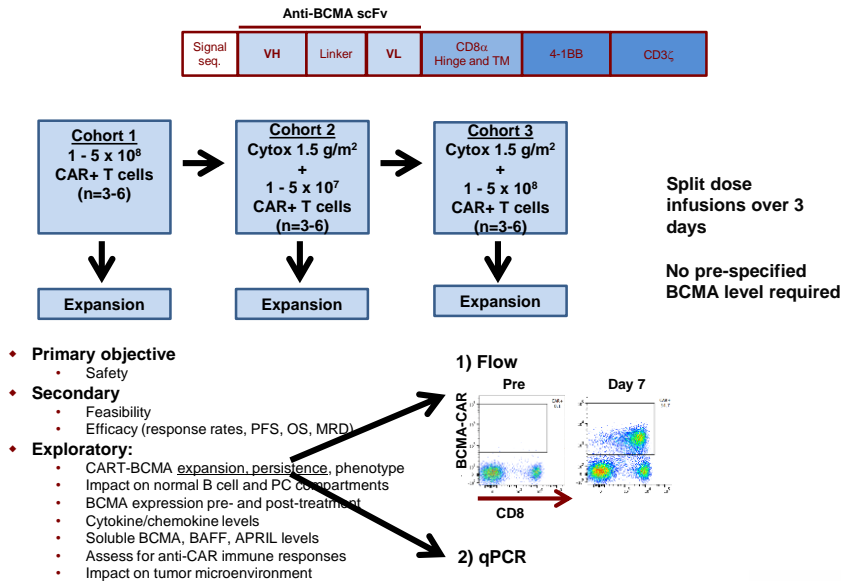
Median EFS = 31 weeks



sCR, Stringent Complete Response; VGPR, Very Good Partial Response; PR, partial response; SD, stable disease; PD, Progressive Disease

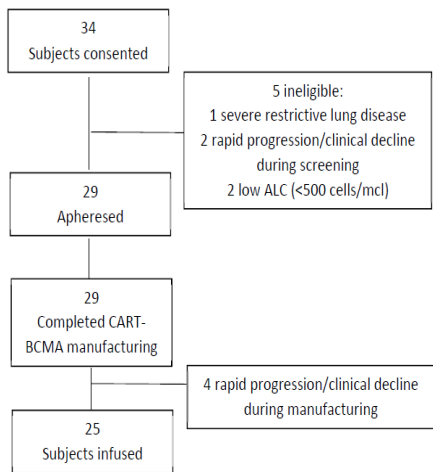
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Penn/Novartis CART-BCMA Trial



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Patients



	Treated patients (n=25)
Age	58 (44-75)
Gender	68% M; 32% F
Median years from diagnosis	4.6 (1.8 – 14.5)
Prior lines of therapy	7 (3-13)
Lenalidomide	100% (refr 76%)
Bortezomib	100% (refr 88%)
Pomalidomide	92% (refr 88%)
Carfilzomib or Oprozomib	96% (refr 80%)
Daratumumab	76% (ref 72%)
Dual- / Quad- / Penta-refractory	96% / 56% / 44%
Autologous / Allogeneic SCT	92% / 4%
Cyclophosphamide	100% (ref 68%)
Anti-PD1	28% (ref 24%)
High-risk genetics -17p or TP53 mutation	96% 68%
Extramedullary dz	28%
% BM plasma cells	65% (0 - 95)

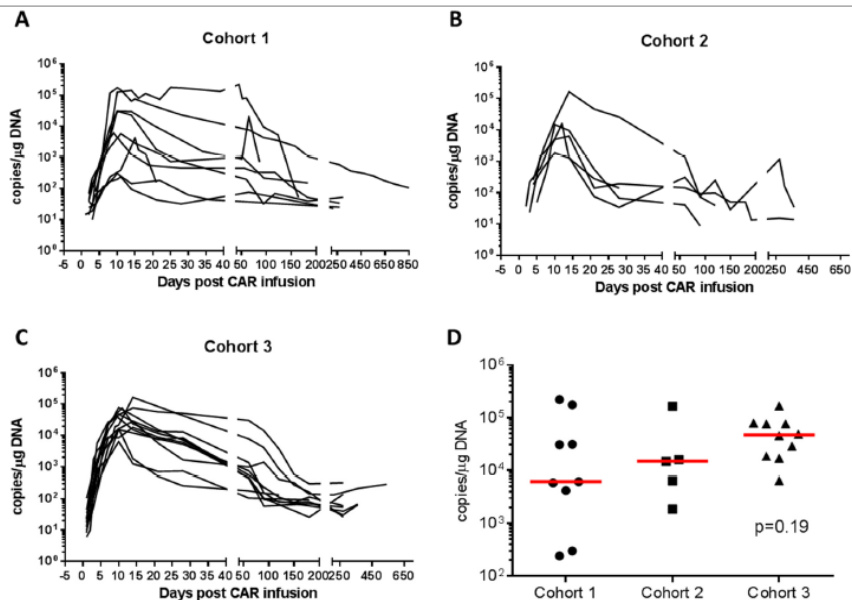


Cohen et al., J Clin Invest 2019.



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CART-BCMA Expansion

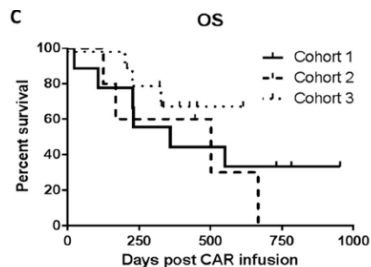
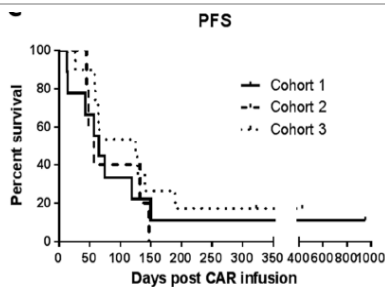
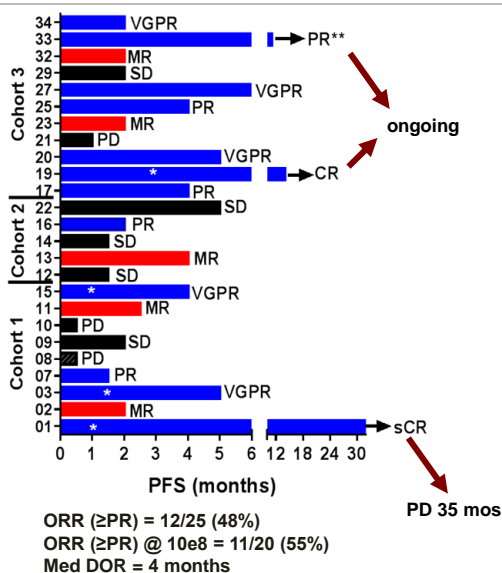


Cohen et al, J Clin Invest 2019.



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Clinical Outcomes



MR, Major Response; ORR, Objective Response Rate; DOR, Duration of Response



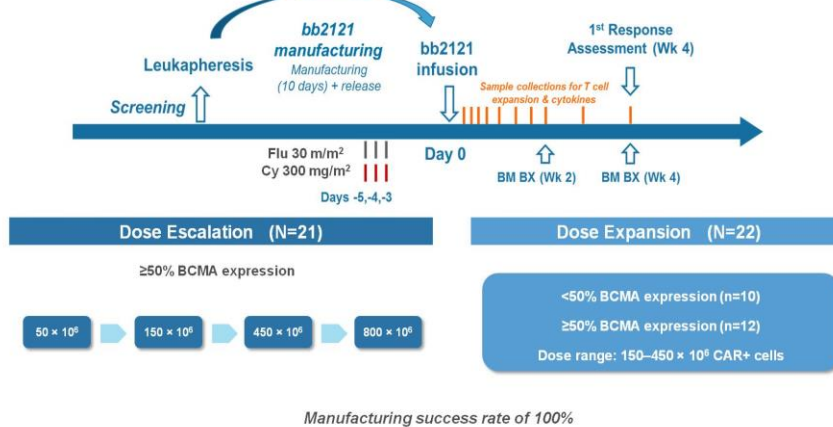
Cohen et al, J Clin Invest 2019.



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bb2121 BCMA-Specific CAR T cells

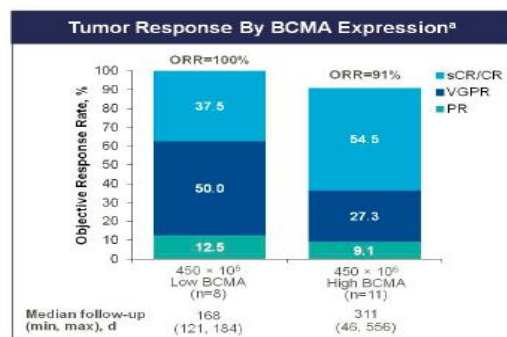
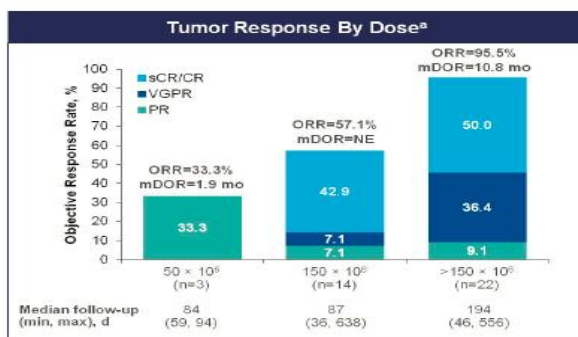
CRB-401 PHASE 1 STUDY DESIGN



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bb2121 BCMA-Specific CAR T cells

TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION



Data cutoff: March 29, 2018. CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. ^aPatients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow/plasma cells expression of BCMA; high BCMA is defined as ≥50%.

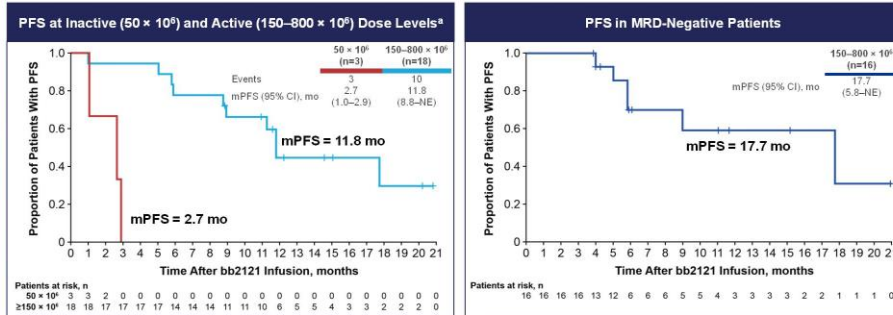
MRD-evaluable responders (n=16) – 100% were MRD-neg (< 1 × 10⁻⁴ by NGS)

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bb2121 BCMA-Specific CAR T cells

PROGRESSION-FREE SURVIVAL

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



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BCMA CAR T cells – Initial Studies, Refractory Pts

Trial	n	CAR	Conditioning	# lines	% hi risk [†]	Dosing	ORR	ORR (optimal doses)	VGPR/CR (optimal doses)
NCI ¹	26*	Murine, CD3/CD28	Cy/Flu	7.5	42%	0.3 – 9 x 10^6 /kg	58%	81% (13/16)	63% (10/16)
Penn ²	25	Human, CD3/41BB	None or Cy	7	76%	0.5 – 5 x 10^8	48%	64% (7/11)	36% (4/11)
Bluebird ³	43	Murine, CD3/41BB	Cy/Flu	7.5	40%	0.5 – 8 x 10^8	77% (30/39)	96% (21/22)	86% (19/22)

*2 treated twice; counted separately for response. [†] FISH +t(4;14), t(14;16), del 17p

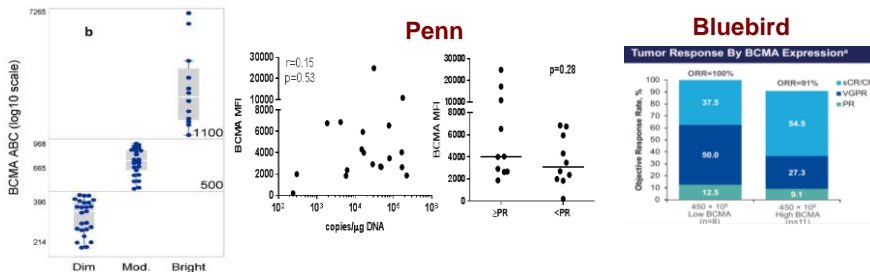
Trial	n	CRS %	CRS G3-4 %	Neuro tox %	Neuro tox G3-4 %	Tocilizumab
NCI ¹	26*	73%	23%	NR	12%	19%
Penn ²	25	88%	32%	32%	12%	28%
Bluebird ³	43	63%	5%	33%	2%	21%

*excluded high tumor burden in last 14 pts. NR = not reported

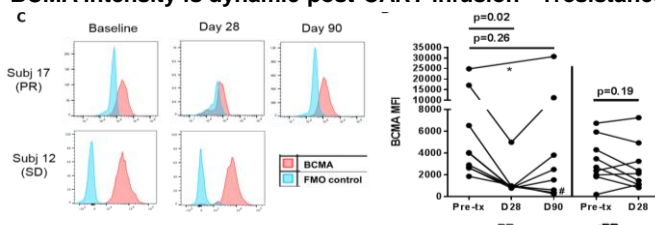
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BCMA CAR T cells – Lessons from Initial Studies

◆ BCMA intensity not predictive of CAR T expansion or response



◆ BCMA intensity is dynamic post-CART infusion - ?resistance mechanism



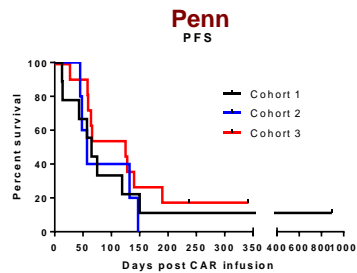
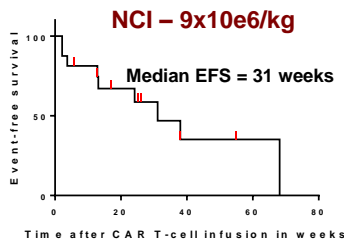
Salem et al, Leuk Res 2018; Cohen et al, J Clin Invest 2019; Rajee et al, ASCO 2018



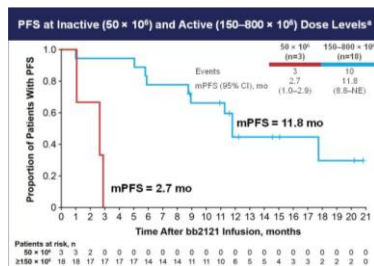
287

BCMA CAR T cells – Lessons from Initial Studies

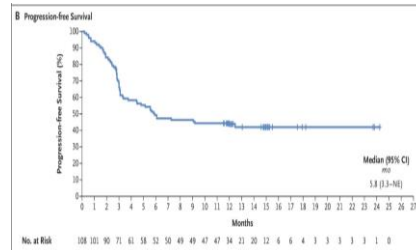
◆ Probably not curative in refractory patients



Bluebird – dose escalation



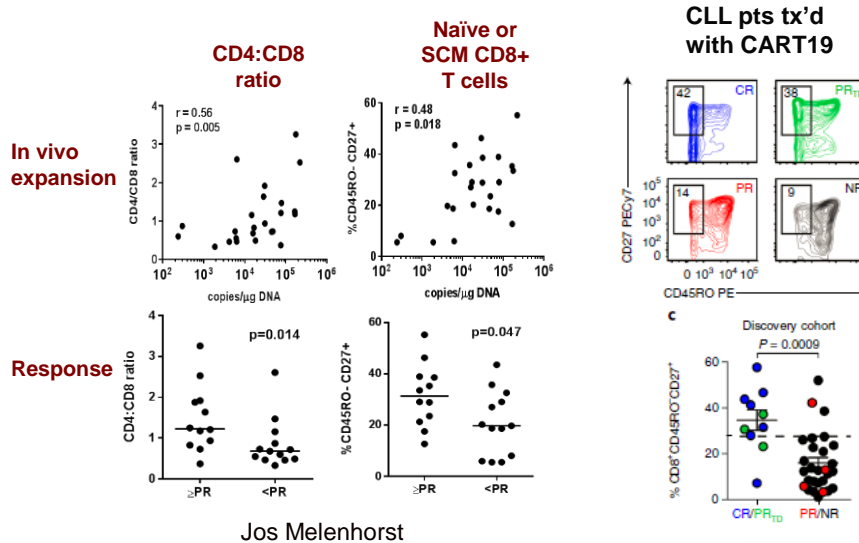
DLBCL ph2 Axicabtagene ciloleucel (YESCARTA®)



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BCMA CAR T cells – Lessons from Initial Studies

- ◆ Patients with “fitter” T cells may have better expansion/response



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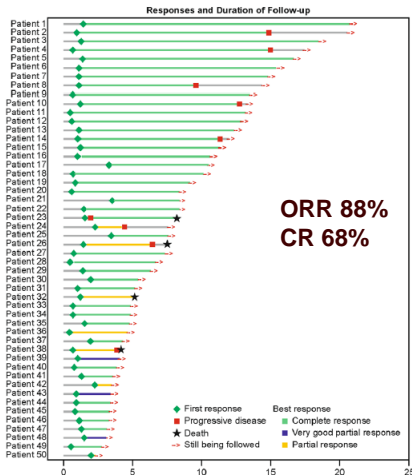
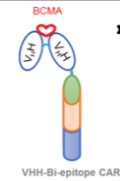
How to Improve Clinical Outcomes?

- Optimize CAR T product?
 - Dual epitope or dual antigen binding
 - Suicide genes/safety switches
 - Gene editing (e.g. PD-1 knockdown, allogeneic CARTs)
- Optimize manufacturing?
 - PI3K inhibitors? Transposon-based? Defined CD4:CD8 ratios? Cytokines?
- Optimize target expression?
 - Gamma-secretase inhibitors for BCMA?
- Optimize infusion schedule?
 - Serial infusions? Retreatment at progression?
- Patient selection?
 - Only high expressors? Earlier lines of therapy? High-risk?
- Lymphodepletion?
 - Is Cy/Flu the best?
- Rational combinations?
 - Checkpoint inhibitors? IMiDs? Other CAR T cells?

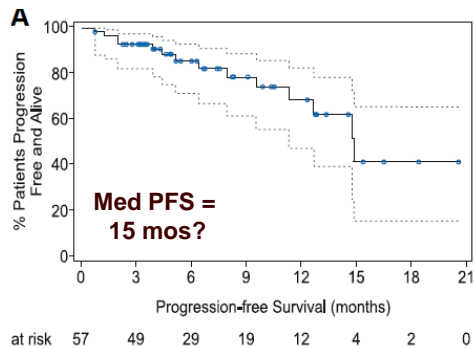
290

Phase 1 LCAR-B38M (BCMA CAR T cells)

- ◆ Single institution experience (n=57)
- ◆ CD3/41BB dual-binding CAR, Cy conditioning, med 3 priors
- ◆ 0.3 – 2.1 x 10⁶ CAR+ cells/kg



CRS 90% (7% Gr 3-4)
Neurotox 2% (Gr 1)

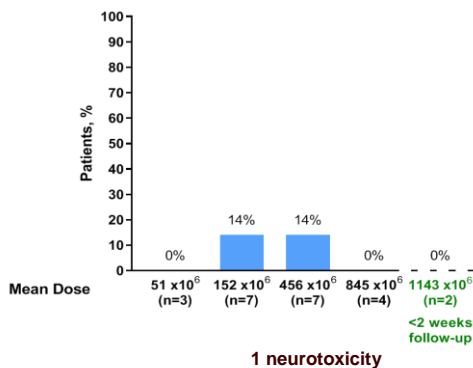


291

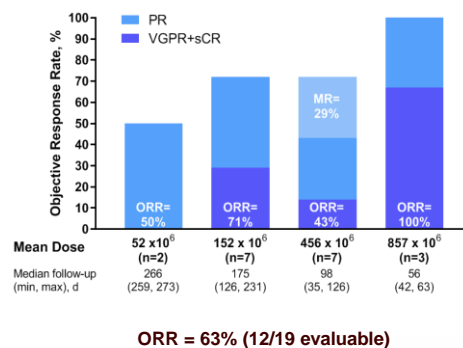
Transposon-Based BCMA CAR Construct (P-BCMA-101)

- Larger cargo capacity
- Preferentially transduces T_{SCM} and T_{CM}
- Slower in vivo expansion (peak day 14-21)

Cytokine Release Syndrome By Dose Level



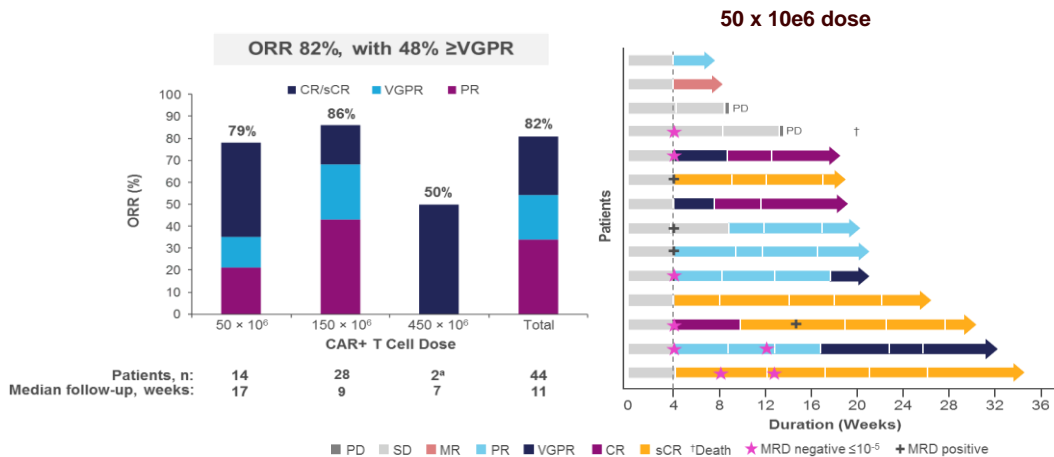
Tumor Response in Evaluable Patients by Dose



292

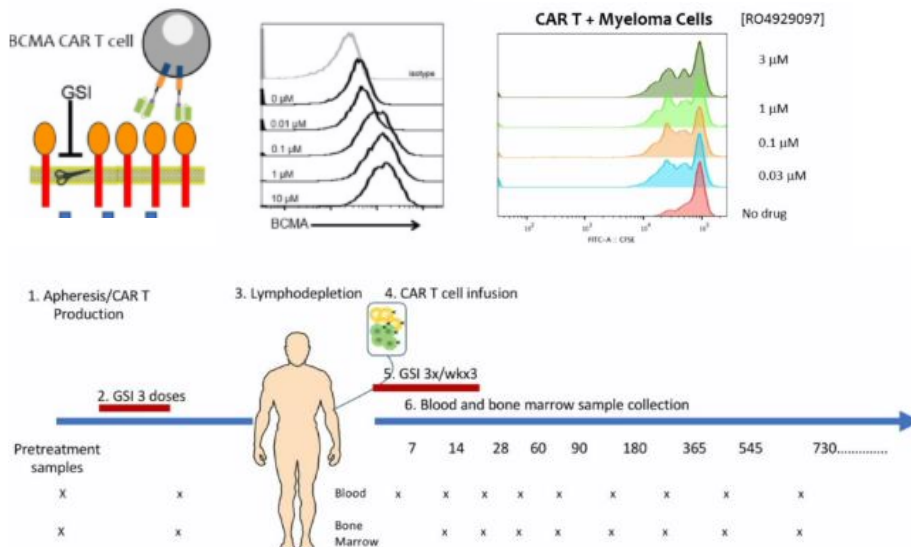
Ph 1/2 JCARH125 (Defined CD4:CD8 Pre-Manufacturing)

- CRS 80% (Gr 3-4 9%)
- Neurotox 25% (Gr 3-4 7%)



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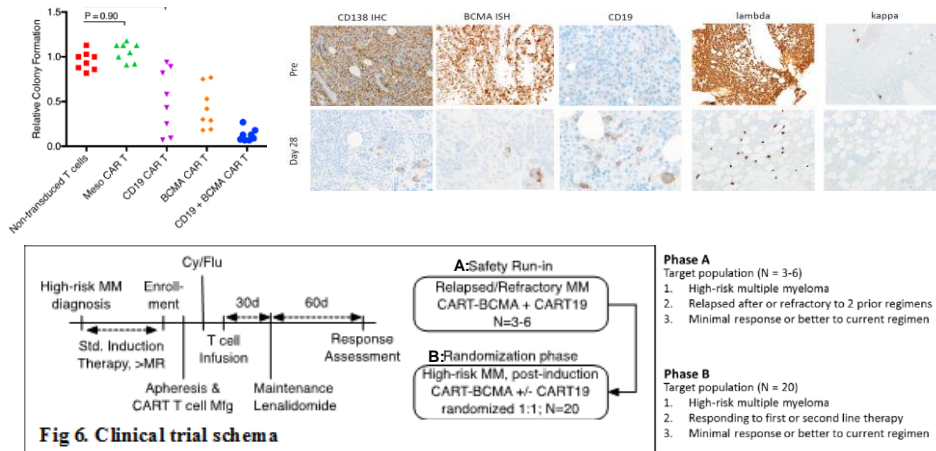
Gamma Secretase Inhibition to Maintain BCMA Expression



294

UPCC 46417: CART-BCMA +/- CART-19 for High-Risk MM

PI: Al Garfall



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Cellular Therapy in MM: What's Happening in 2019

- ◆ **BCMA CAR registration trials in rel/ref MM**
 - Celgene/Bluebird, Janssen/Legend, Celgene/Juno, Poseida
 - FDA approval early 2020?
- ◆ **Ongoing ph 1/2 for next-gen CAR products**
- ◆ **BCMA CAR trials for less-heavily treated patients**
 - 1-3 priors
 - Post-induction in hi risk
 - CART-BCMA +/- CART-19 (PI: Al Garfall)
- ◆ **BCMA CAR combo trials**
 - CART-19, IMiDs, gamma-secretase inhibitors, checkpoint inhibitors
 - Post-autoSCT
- ◆ **CAR T cells against CD38, SLAMF7, GPRC5D**
- ◆ **Gene-edited T cells**
 - "Off-the-shelf" allogeneic CAR T cells
 - PD-1 deficient NY-ESO1 TCR T cells

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Conclusions

- ◆ **BCMA validated as CAR target in myeloma**
 - CAR T cells manufactured, expand, persist
 - Activity in highly refractory MM
 - ORR 60-96% at optimal doses ($\geq 10^8$ cells)
 - CRS and neurotoxicity seen
 - No unexpected toxicities
 - Durability of responses an issue
 - T cell-intrinsic? MM cell-intrinsic? Microenvironment?

- ◆ **Multiple trials ongoing, including with new targets**

- ◆ **Need biomarkers of response, resistance**

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 Jennifer Brogdon
 Heather Huet
 Greg Motz
 Randi Isaacs
 Ewelina Morawa

CAR T Cell Therapy

Jump Starting Your Program

Dennis L. Cooper, MD

Chief, Blood and Marrow Transplantation
 Medical Oncologist
 Rutgers Cancer Institute of New Jersey
 New Brunswick, NJ

BEATING CANCER IS IN OUR BLOOD.



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Immunotherapy has Joined Chemotherapy, Radiation and Surgery as the Fourth Arm of Cancer Treatment

- Tisagenlecleucel CAR T approved for relapsed or refractory **acute lymphoblastic leukemia** (age < 25) 2017
 - Overall remission rate at 3 months 81%
 - Event free survival and overall survival at 12 months 73%
 - *These patients had essentially 0% prognosis as they had:*
 - *Median of 3 prior therapies and still had \geq 5% blasts*
 - *61% had prior allogeneic transplant*

BEATING CANCER IS IN OUR BLOOD.



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Diffuse Large B cell Lymphoma

- 2 Car T cell products are now approved for refractory diffuse large B cell lymphoma in the following settings:
 - Primary refractory
 - Remission followed by refractory relapse
 - Relapse within one year of autologous transplant
- With conventional therapy, the patients described above have a CR rate of 7% and a median survival of 6 months with conventional Rx
- CAR T cells show an overall response rate of 70-90% with $\geq 40\%$ in remission at 1 year and significant but unknown percentage possibly cured

BEATING CANCER IS IN OUR BLOOD.



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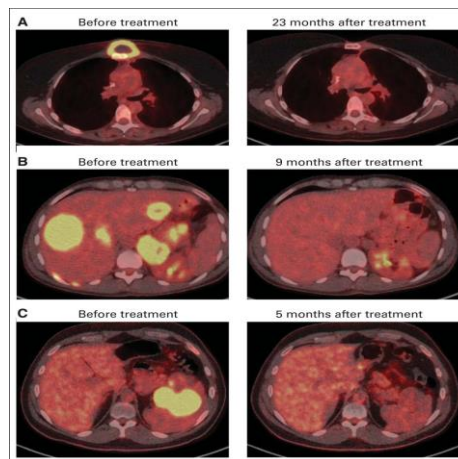


Fig 2. Complete remissions (CRs) of chemotherapy-refractory large-cell lymphomas in patients receiving anti-CD19 chimeric antigen receptor T cells. (A) Positron emission tomography (PET)/computed tomography (CT) scans show CR of chemotherapy-refractory primary mediastinal B-cell lymphoma (PMBCL) in patient No. 2. (B) PET/CT scans demonstrate CR of lymphoma in patient No. 8 who had chemotherapy-refractory PMBCL with extensive liver involvement. (C) PET/CT images show CR of diffuse large B-cell lymphoma, not otherwise specified, in patient No. 14, who had extensive splenic lymphoma.

Published in: James N. Kochenderfer; Mark E. Dudley; Sadik H. Kassim; Robert P.T. Somerville; Robert O. Carpenter; Maryalice Stetler-Stevenson; James C. Yang; Gao Q. Phan; Marybeth S. Hughes; Richard M. Sherry; Mark Raffeld; Steven Feldman; Lily Lu; Yong F. Li; Lien T. Ngo; Andre Goy; Tatyana Feldman; David E. Spaner; Michael L. Wang; Clara C. Chen; Sarah M. Kranick; Avindra Nath; Debbie-Ann N. Nathan; Kathleen E. Morton; Mary Ann Toomey; Steven A. Rosenberg; *JCO* 2015, 33, 540-549.
DOI: 10.1200/JCO.2014.56.2025
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“With Great Power, Comes Great Responsibility”

Uncle Ben, Spiderman

- In the acute lymphoblastic leukemia study, cytokine release syndrome (CRS) occurred in 77% of patients, 48% of whom received the anti-IL6R drug, tocilizumab
- Neurologic events occurred in 40% of patients
- In DLBCL, CRS occurred in 93% of patients with 13% \geq grade III, tocilizumab, vasopressors used in 43% and 17% of patients, respectively

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Financial Toxicity

- At present prices, CAR T cell therapy will increase health care costs by 10 billion dollars over 5 years
- CAR T cell therapy will increase health care spending on lymphoma by 68% from 2.9 to 4.9 billion dollars/yr
- In Hem/Onc we don't have another scenario in which the *lifetime* spending of a disease is dominated by a single day of treatment
- Don't screw it up

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Lin et al, JCO published on-line June 8, 2014
LEUKEMIA & LYMPHOMA SOCIETY

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Preparation for CAR T cells: It Takes Several Villages

- Medical Informatics
 - Order sets, alerts, templated notes that include CRS, CRES
- Hospital commitment
 - ICU bed on hold when patient admitted for CAR T cell therapy
 - Bed management for rapid admission or transfer to BMT floor vs ICU
 - Bed held on BMT floor for several days after discharge
- REMS Education: 350 people trained
 - All medical residents, neurology residents/Attendings given 1 hour lecture
 - ICU nurses, attending physicians and staff ("Train the trainer")
 - All Rapid Response Teams
 - BMT nurses, pharmacists
- Policies and procedures: jointly written by CINJ and RWJUH

Risk evaluation and mitigation strategy

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

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In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY DEC. 9, 2012



Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia.
Jeff Swensen for The New York Times

RELATED COVERAGE



An Exper
DEC. 9, 2012

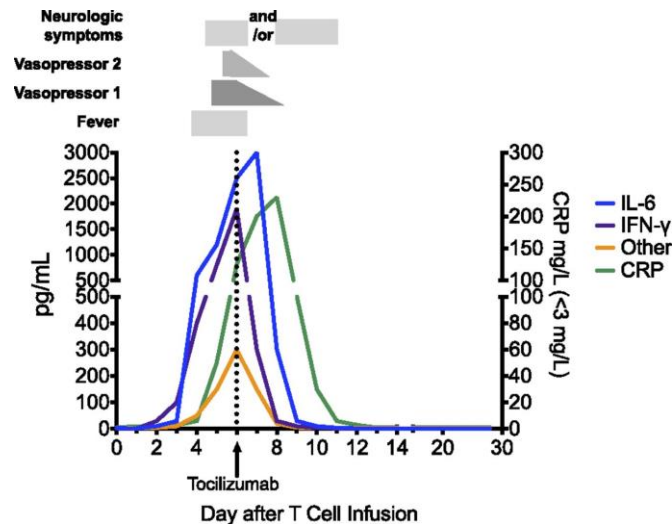


Immune!
cells, Van



306

Cytokine Changes Associated With Clinical Findings in a Hypothetical Patient with Grade 3 CRS. A Dramatic Rise in IL-6 and IFN γ Levels is Associated with the Onset of Fever at Day 3 After CAR T-cell Infusion



Daniel W. Lee et al. Blood 2014;124:188-195
©2014 by American Society of Hematology

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307

CRES: CAR T-cell-Related Encephalopathy Syndrome

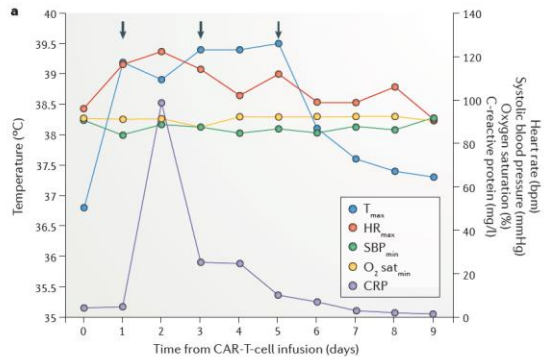
- Characterized by a toxic encephalopathy and delirium including diminished attention, language disturbance and impaired handwriting, may progress to seizures and herniation
- May occur during CRS, as CRS improves or completely unrelated to CRS
- Appears to **not be** IL-6 driven
 - Prophylactic tocilizumab does not decrease CRES
 - Mouse model shows no impact of IL-6 depletion¹
- Pathophysiology not understood: IL1 and anakinra?
- CRES treatment is generally with decadron/solumedrol, anti-convulsants and supportive care

1. Norelli et al. Nat Med 2018

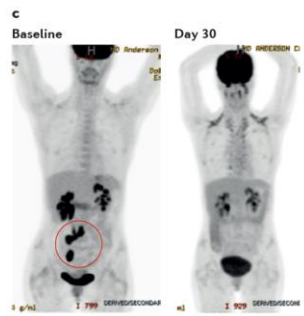
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b
 Day 4, MMSE 29/30
I love Shawnee, KS.
 Day 5, MMSE 27/30
Shawnee is a great town!
 Day 6, MMSE 29/30
I miss my kids.



Neelapu et al. Nat Review 2017.
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309

SCM RWJ Patient Alert - MOBILECARE, STEVE

This patient has received CAR-T therapy.
 Please notify Leukemia/Lymphoma fellow for recommendations and management @ 732-427-3906

<- Back Showing Alert 1 of 1 Next ->

Hide alert for 72 day(s)

v 1.3.2 Last Updated on: 10/16/18 Close

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ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp \geq 38	Temp \geq 38	Temp \geq 38	Temp \geq 38
		<i>With either</i>		
Hypotension	None	< 90 Systolic; No vasopressor	+ vasopressor	>1 vasopressor
		<i>And/or</i>		
Hypoxia	None	Low flow nasal cannula < 6L/m	High flow nasal cannula, non- rebreather	Requires positive pressure, CPAP, BIPAP, mechanical ventilation
		↑ Tocilizumab ICU SCREEN	↑ Decadron 10 mg QID, ICU	↑ Pulse solumedrol ICU

Lee et al. BBMT 2019.

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Cancer CARTOX
Toxicity Assessment and Management

Toxicity Grading Toxicity Management

Toxicity Grading

- CRS Grading
- CRS Reference Table
- ICANS Grading
- ICANS Reference Table

CRS Grading Summary Close

CRS GRADE

2

View Treatment

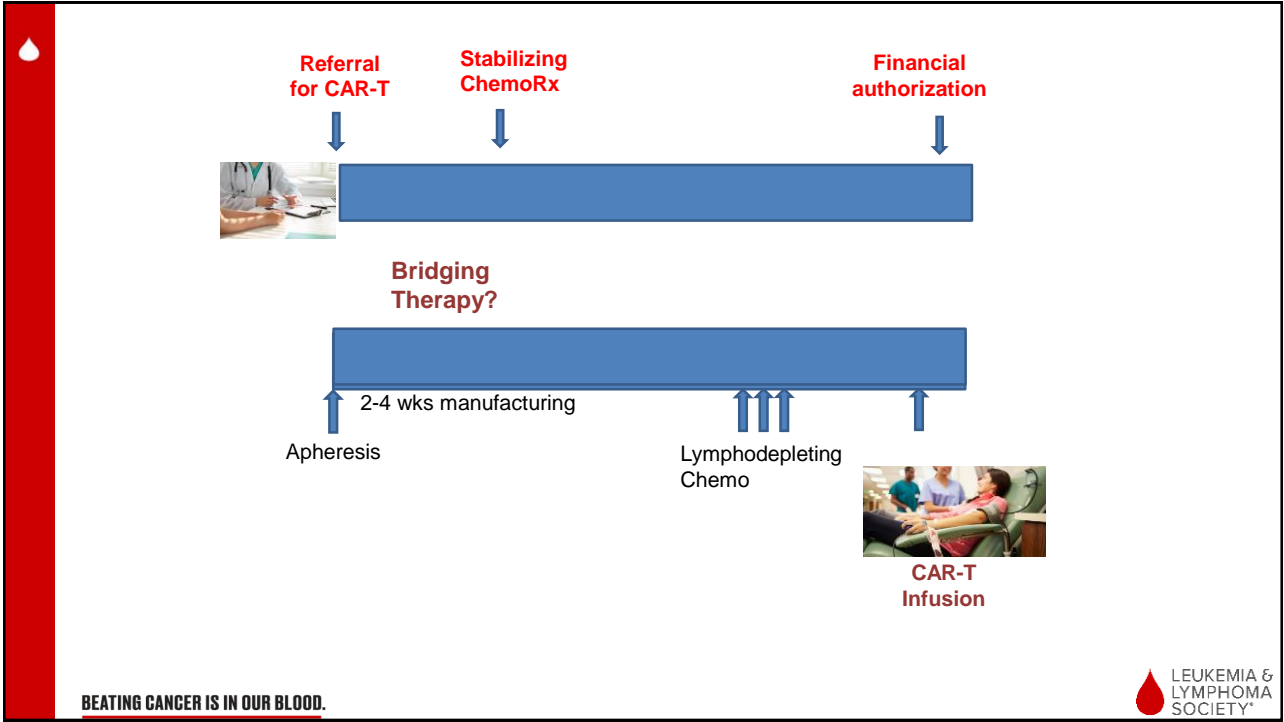
June 7, 2019 will be available to down-load from the Apple Store or Google Play

Sherry Adkins, Sattva Neelapu et al.

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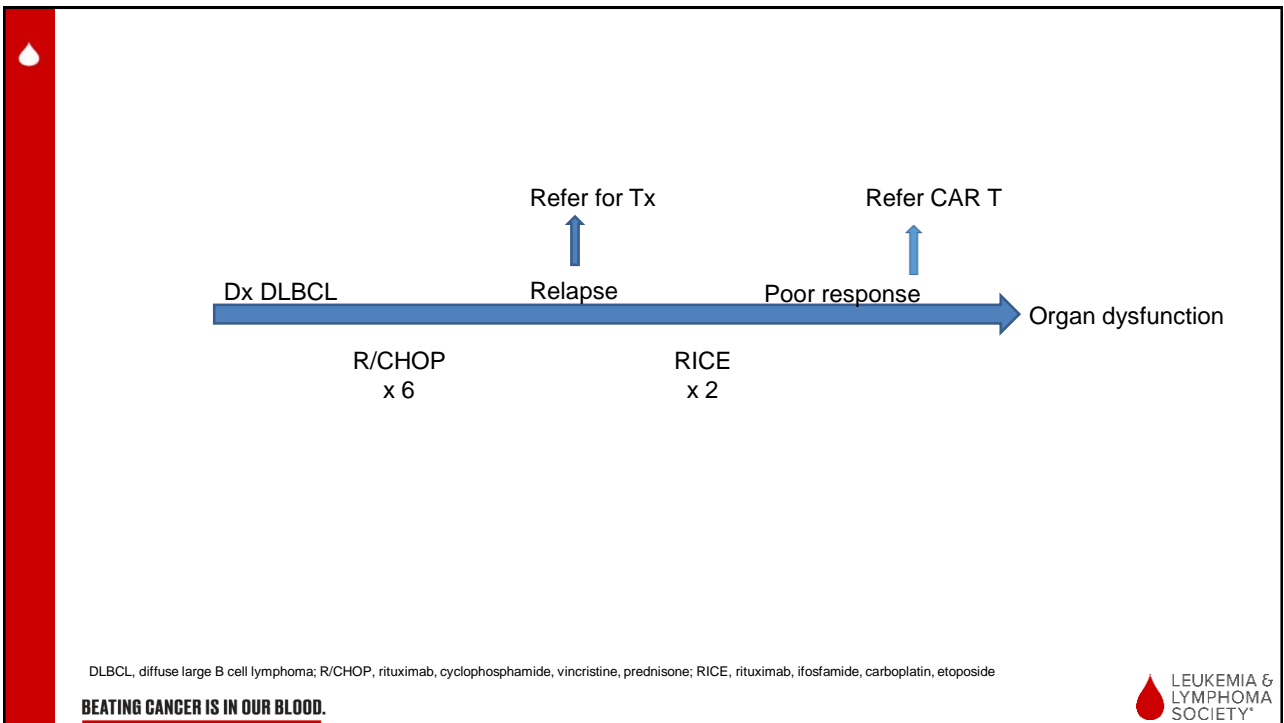
312



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DLBCL, diffuse large B cell lymphoma; R/CHOP, rituximab, cyclophosphamide, vincristine, prednisone; RICE, rituximab, ifosfamide, carboplatin, etoposide

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SAFETY OF AXI-CEL IN THE REAL WORLD

	SOC Axi-Cel (N = 274)	Zuma-1 (N = 108)
Tocilizumab usage	63%	45%
Corticosteroid usage	55%	29%
Grade 3 CRS/NT	7%/31%	13%/31%
Median Hospital Days	14 days	NA
ICU stay	85 (32%)	NA
Grade 5 AE	7 (3%)	4 (4%)
Treatment-related deaths	2 (1%)	2 (2%)
CR Rate day 90	57%	58%

SOC, Standard of Care; CRS, Cytokine release syndrome, NT, Neurotoxicity

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Nastoupil, Neelapu, Westin et al, ASH 2018.



315

A Real, Real-World Study (Presented by Anand et al. ASCO 2019)

- Search of FDA adverse events reporting system for all AE related to tisagenlecleucel and axicabtagene from 2013-2018 (Clinical trial & SOC)
- Total pts 636; 129 total deaths, 95 (15%) died from non-relapse mortality (NRM)
- *The 15% NRM is similar to expected NRM for allotransplant and 5X higher than autologous transplant (my comment)*
- *All patients treated on clinical trials had performance status 0-1; not likely to be the case in real world where CAR T is "only remaining hope" (my comment)*

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HEALTH

Hospitals are saving lives with CAR-T. Getting paid is another story

By IKE SWETLITZ / MARCH 12, 2019



An immunotherapy infusion (left) at the inpatient unit of the cellular immunotherapies and transplant program at VCU Massey Cancer Center in Richmond, Va.

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Which CAR T Should We Use?

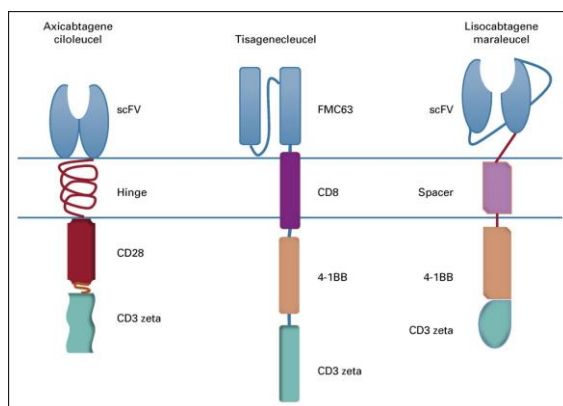


FIG 1. Depictions of three anti-CD19 CAR T-cell constructs in clinical development. Axicabtagene ciloleucel (left) contains a CD28 costimulatory domain in addition to a CD3 zeta domain, whereas tisagenlecleucel (middle) and lisocabtagene maraleucel (right) contain a 4-1BB costimulatory domain in addition to a CD3 zeta costimulatory domain. scFV, signal chain variable fragment.

Published in: Caron A. Jacobson; *Journal of Clinical Oncology* 2019 37328-335.
DOI: 10.1200/JCO.18.01457
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TABLE 1. Composition, efficacy and safety comparisons

	Axicaptagene ciloleucel ¹	Tisagenlecleucel ²	Lisocaptagene maraleucel ³
Study populations	DLBCL, TFL, PMBCL	R/R DLBCL	¹ CORE DL 2
Target Antigen	CD19	CD19	CD19
Lymphodepletion	Flu/Cy	Flu/Cy	Flu/Cy
Costimulatory Domain	CD28	4-1BB	4-1BB
T-cell Composition	Unspecified	Unspecified	1:1 CD4:CD8
Cell Dose	2 x 10 ⁶ cells/kg	5 x 10 ⁶	1 x 10 ⁶
OR (Best)	82% (N=108)	53% (N=81)	81% (N=27)
OR (6 Month)	41% (N=101)	37% (N=46)	50% (N=14)
CR (Best)	58% (N=108)	40% (N=81)	63% (N=27)
CR (6 Month)	36% (N=101)	30% (N=46)	50% (N=14)
Any Grade^{††} CRS / NT	94% / 87% (N=108)	58% / 21% (N=99)	24% / 17% (N=29)
≥ Grade 3 CRS^{††}	12% (N=108)	23% (N=99)	0% (N=29)
≥ Grade 3 NT^{††}	31% (N=108)	12% (N=99)	7% (N=29)
Grade 5 AEs	4% (N=108) [^]	none	-

¹Neelapu, *NEJM* 2017, ZUMA-1²Schuster, *ASH* 2017, JULIET³Abramson, *ASH* 2017, TRANSCEND[^]2 patients Grade 5 CRS[†]CORE Group (proposed pivotal pop'n) including DLBCL, NOS 1FL, FL3B, ECOG 0-1, and R/R patients^{††}CAR T toxicity grading scales differ across studies

Courtesy of and adapted from C. Turtle MBBS, PhD

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Which CAR T cell Product?

- Unlikely that products will be compared head-to-head
- CD-28 costimulatory molecule (Axicaptagene) seems to be associated with more rapid onset CRS, making outpatient treatment infeasible
- Tisagenlecleucel has had manufacturing issues with longer turn-around and with small percentage of products “out of specification”; requires companion “managed access protocol in place”
- Medicare currently pays 50% of price of CAR T product in hospital plus a sum for hospital stay; immediate \$185, 000 loss
- **Medicare pays 100% of drug delivered as outpatient (not admitted within 72 hours)**

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“Throwing Some Shade” on CAR T cells

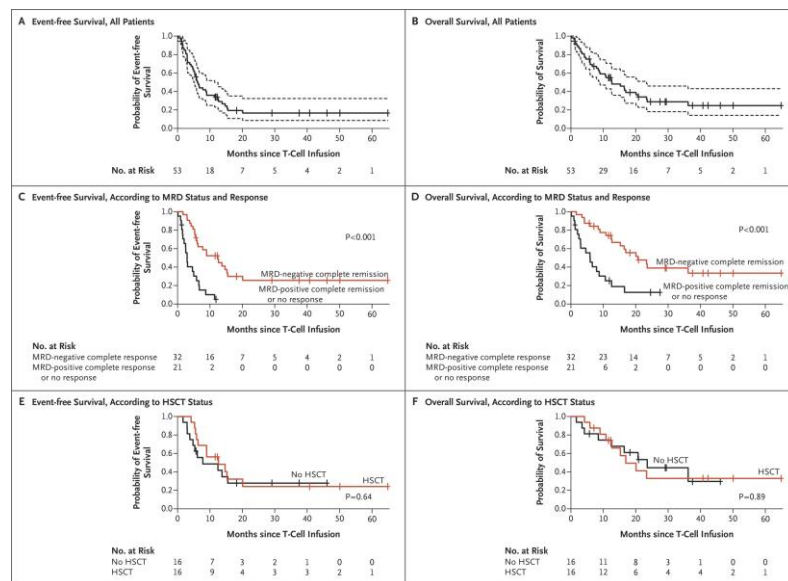
- Results in lymphoma in the “Real world” may not be as good as in clinical trials
- Results in adult ALL and CLL thus far not likely to justify cost
- Median PFS in myeloma patients < 1 year
- Current reimbursement for Medicare patients only 50% of the cost of the inpatient delivery of drug; proposed increase to 65% still represents at least a \$100,000 loss per patient; many Medicare-covered patients may not receive the best treatment

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Adult ALL study at Memorial

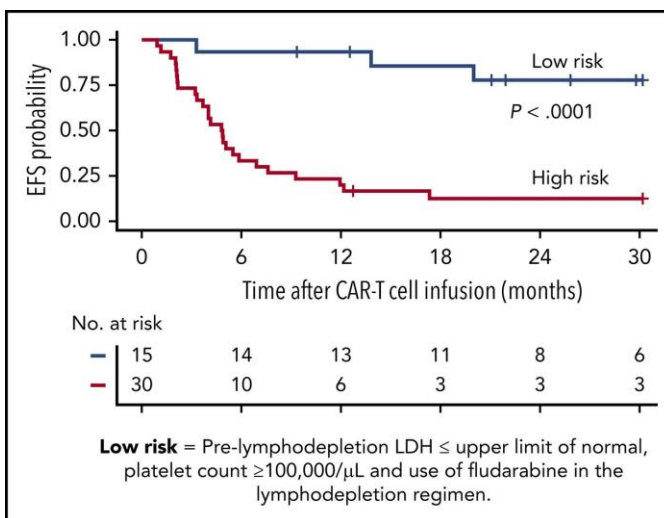


Park et al. NEJM 2018.

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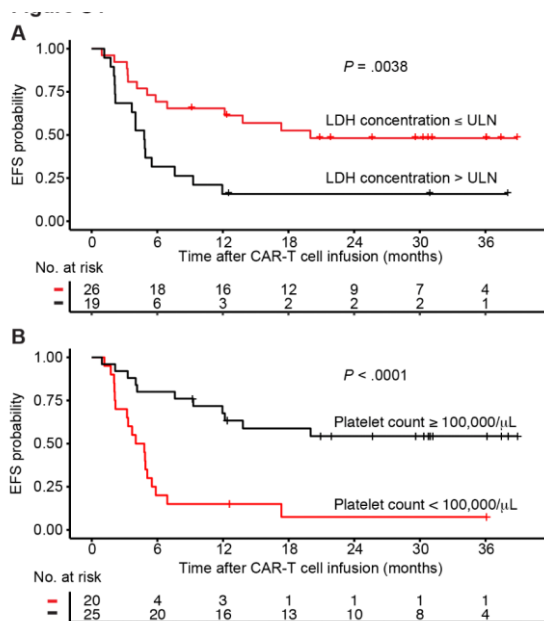
Kevin A. Hay et al. Blood 2019;133:1652-1663
©2019 by American Society of Hematology



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LDH and Platelet Count Pre-LD Chemotherapy Predicts Outcome



Hay et al. Blood 2019.

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ORIGINAL ARTICLE

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D.,
David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D.,
Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D.,
Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D.,
Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D.,
Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D.,
Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S.,
Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.

Raje et al. NEJM 2019.

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CAR T: Things We Would Like to See

- Price war among 3 or more products
 - At current prices an expansion of the indications would likely be unsustainable
- Clinical trials in which CAR T cells are tested as consolidation of initial treatment of adult ALL, multiple myeloma and unfavorable CLL
- Axicabtagene is currently being tested against SOC salvage chemo plus autologous transplant in first relapse

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Thank you very much
Any questions?

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Value, Cost, & Reimbursement for CAR T Cells: Overcoming the Obstacles

Gunjan L. Shah MD, MS

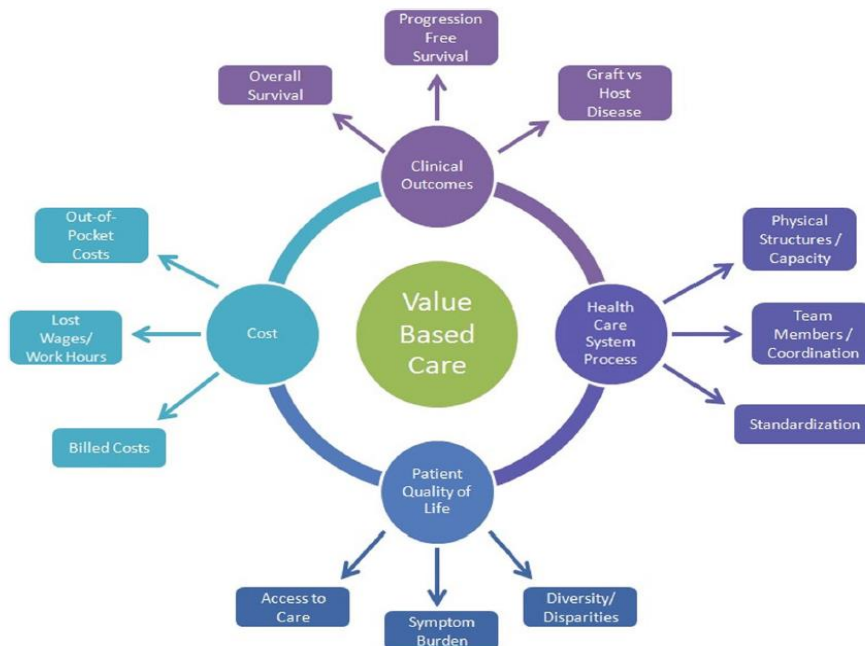
Adult Bone Marrow Transplant Service & Center for
Health Policy and Outcomes
Memorial Sloan Kettering Cancer Center
New York, NY

6.28.2019

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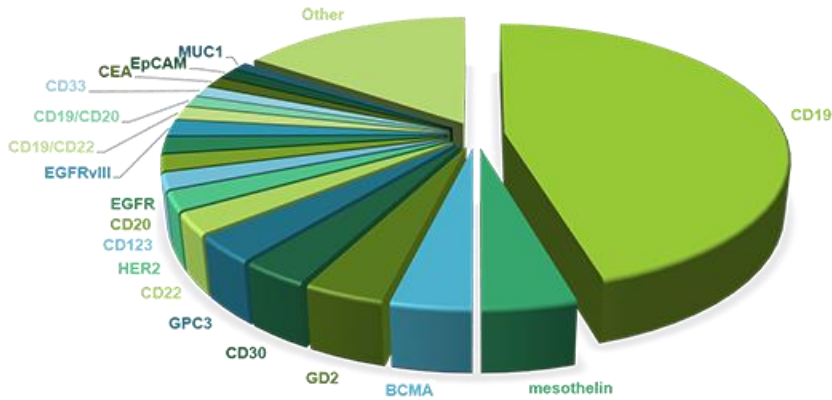
Memorial Sloan Kettering
Cancer Center



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Scope of CAR T cells

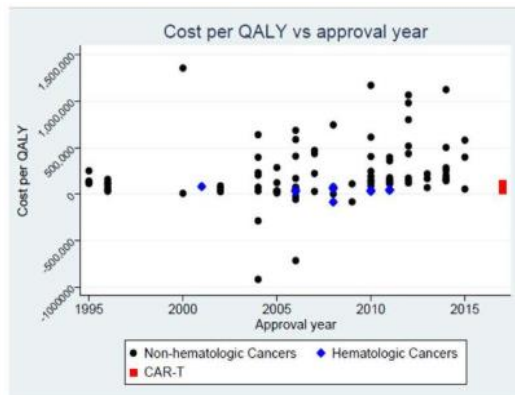
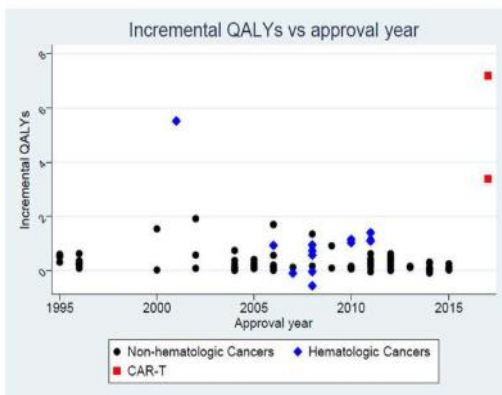
Product	Approval	Product Cost
Tisagenlecleucel	B-ALL, DLBCL	\$475,000
Axicabtagene ciloleucel	DLBCL	\$373,000



Creativebiomart.net

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Do CAR T Cells Provide More Value?



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Modeled Costs after CAR T cells

Table. Estimated Total Costs and Mean Expected Costs per Patient for Chimeric Antigen Receptor T-Cell Immunotherapies

Treatment Scenario	Total Cost, \$ ^a		
	Tisagenlecleucel		Axicabtagene Ciloleucel
	Base-Case Pricing	Outcomes-Based Pricing ^b	
Not treated	1207	1207	1207
Treated			
No CRS			
Response	478 777	478 777	377 253
No response	478 777	3777	377 253
Grade 1-2 CRS, received no tocilizumab ^c			
Response	502 464	502 464	400 940
No response	502 464	27 464	400 940
Grade 1-2 CRS, received tocilizumab ^c			
Response	504 276	504 276	404 564
No response	504 276	29 276	404 564
Grade ≥3 CRS, received no tocilizumab ^c			
Response	530 011	530 011	411 429
No response	530 011	55 010	411 429
Grade ≥3 CRS, received tocilizumab ^c			
Response	531 823	531 823	415 053
No response	531 823	56 823	415 053
Mean expected costs per patient treated	510 963	432 131	402 647

- Costs depend on rate of cytokine release syndrome & neurotoxicity → ICU days

JAMA Oncology July 2018 Volume 4, Number 7

333



MSKCC Resource Utilization

- Adult patients treated on investigator initiated trials
- Utilization data from day -7 to Day 30 from institutional billing system.
- 4 clinical trials across different indications and targets
 - CLL/NHL/ALL = CD19, CD28
 - MM = BCMA, 4-1BB
 - 6/2007 – 4/2018

	Total (n=106)	B-ALL (n=56)	CLL/NHL (n=37)	MM (n=13)
Age (yr, median, range)	53 (22-77)	45 (22-74)	64 (35-77)	58 (43-68)
Male Gender (n,%)	69 (65)	42 (75)	17 (46)	4 (31)

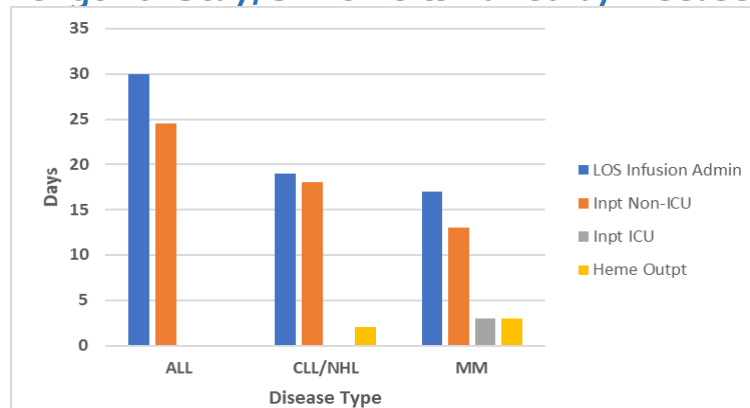
Shah et al, ASH Abstract 2018.

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Length of Stay/Clinic Visits Varied by Disease



Ranges	Total (n=106)	B-ALL (n=56)	CLL/NHL (n=37)	MM (n=13)
Non-ICU Inpatient	4-38	4-38	4-38	10-30
ICU Days	0-28	0-28	0-9	0-9

Shah et al, ASH Abstract 2018.

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Lab Work and Procedures

	Total (n=106)	B-ALL (n=56)	CLL/NHL (n=37)	MM (n=13)
Total Lab Panels	40,327	24,382	10,678	5,267
CBC/Chemistries	6,764 (17%)	4,238	1,851	675
Blood Cultures	563 (1.5%)	396	128	39
Bone Marrow Biopsy (n,%)	148	52 (93)	23 (62)	13 (100)
Median	148	1.5	1	2
ECHO (n,%)	72	33 (59)	15 (41)	1 (8)
median	72	1	0	0
EKG (n,%)	401	52 (93)	36 (97)	13 (100)
median	401	3.5	2	3
Lumbar Puncture (n,%)	54	29 (52)	5 (14)	0 (0)
median	54	1	0	0
EEG (n,%)	21	14 (25)	3 (8)	2 (15)
median	21	0	0	0

Shah et al, ASH Abstract 2018.

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CRS Management-Related Costs TRANSCEND-NHL Trial Micro-Costing Study



CRS: cytokine release syndrome; HRU: health resource utilization
 *TRANSCEND-NHL trial cytokine release syndrome guidelines
 †Total estimated CRS-related costs do not include the costs for HRU not in the trial guidelines.



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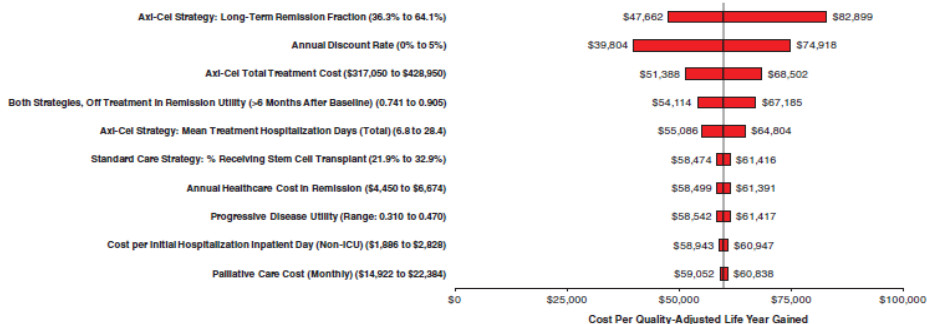
Siddiqui et al, ASH Abstract 2018.

337

Cost-Effectiveness of Axi-Cel vs Scholar -1

- Patient-level analyses of the ZUMA-1 and SCHOLAR-1 studies
- Decision model to estimate LY, QALY, Lifetime Cost
- US average sales prices and Medicare reimbursement schedules
- Axi-cel cost/QALY gained \$58,146

	Axi-Cel	Scholar-1
LY	9.5	2.6
QALY	7.7	1.1
Cost	\$552,921	\$172,737



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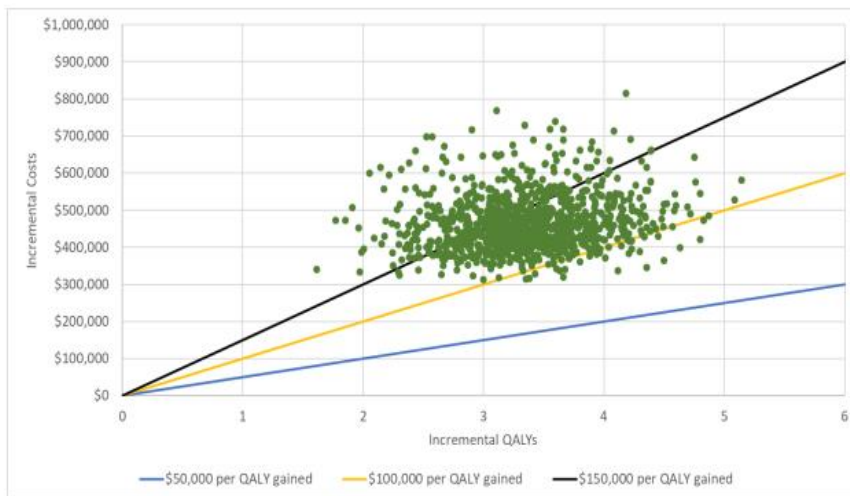
LY, Life Year; QALY, Quality Adjusted Life Year

Roth et al. J Med Econ 2018.

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Wide Range of Incremental Cost Effectiveness Ratios

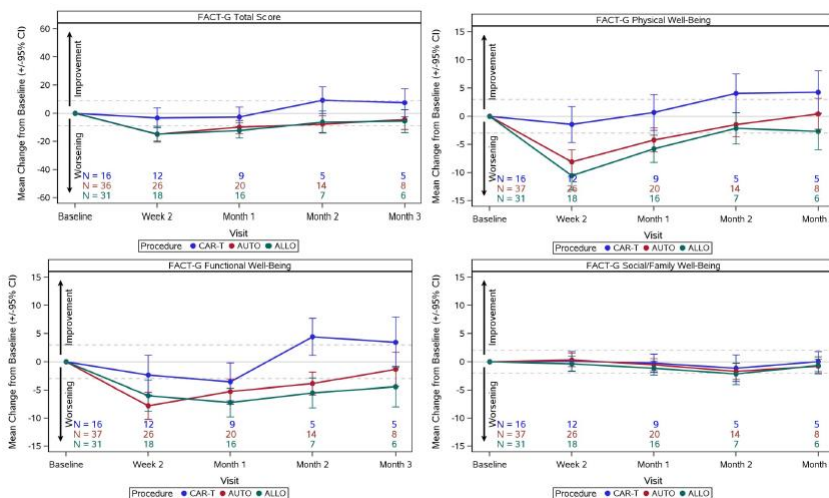
Figure D2. Cost-Effectiveness Cloud for Axicabtagene Ciloleucel Versus Chemotherapy



Tice et al, Inst Clin Econ Rev 2017.

339

QOL Decline Similar Across Cell Therapies



QOL, Quality of Life; FACT-G: Functional Assessment of Cancer Therapy - General

Sidana et al, ASCO Abstract 2019.

340

Ongoing Clinical Trials With PRO Endpoint

Clinicaltrials.gov Identification Nos.	Disease	PRO Instrument (Measures and Domains)	PRO Administration Time Point
NCT03086954	CD-19 positive lymphoma	EORTC quality of life of the core scale criteria QLQ-C30 (V3.0)	Time frame: 3 years
NCT03144583 NCT02919046	CD-19+ leukemia or lymphoma Neuroblastoma	Not provided EORTC quality of life measurement scale PedsQL4.0 children's quality of life of the core scale of the evaluation and comparison of physical condition before and after treatment	Time frame: months 3, 6, 12 Time frame: 3 years
NCT03355859 NCT03030001	B cell NHL Mesothelin-positive advanced malignancies	Not provided Not provided	Time frame: 2 years Time frame: 6 months
NCT02690545	CD30+ HL and NHL	NCI PRO-CTCAE, PROMIS GHS SF v1.0-1.1 (10-item), PROMIS Physical Function SF20a	At baseline and over time
NCT03361748	Multiple myeloma	EORTC-QLQ-C30, Euro-QoL-EQ-5D-5L, and EORTC-QLQ-MY20	Time frame: minimum of 24 months postinfusion
NCT03207178	B cell lymphoma	Not provided (Domains: Appetite, Sleep, Pain and Mental State)	Time frame: 1 year
NCT03179007	MUC1-positive advanced solid tumors	Not provided	Time frame: 2 years
NCT03182816 NCT03182803	EGFR-positive advanced solid tumors Mesothelin-positive advanced solid tumors	EORTC-QLQ-C30 EORTC-QLQ-C30	Time frame: 2 years Time frame: 2 years
NCT02208362	Malignant glioma	EORTC-QLQ-C30 and EORTC-QLQ-BN20	Time frame: 15 years (estimate the mean and standard error for change from baseline during treatment and post-treatment in the quality of life functioning scale, symptom scale, and item scores from the EORTC QLQ-C30 and the domain scale and item scores from the QLQ-BN20)
NCT03484702	Aggressive B cell NHL	EORTC-QLQ-C30, Euro-QoL-EQ-5D-5L, and FACT-Lym	Time frame: 2 years
NCT03016377	ALL	NCI PRO-CTCAE, PROMIS GHS SF v1.0-1.1 (10-item), PROMIS Physical Function SF20a	Time frame: 15 years
NCT03310619	B cell malignancies	EORTC-QLQ-C30 and Euro-QoL-EQ-5D-5L	Time frame: 2 years
NCT03331198	CLL/SLL	EORTC-QLQ-C30, Euro-QoL-EQ-5D-5L and QLQ-CLL	Time frame: 2 years
NCT03483103	Aggressive B cell NHL	EORTC-QLQ-C30 and Euro-QoL-EQ-5D-5L	Time frame: 2 years

QLQ-C indicates Quality of Life Questionnaire-Cancer; NCI, National Cancer Institute; GHS, Global Health Survey; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; ALL, acute lymphoblastic leukemia; EGFR, epidermal growth factor receptor.



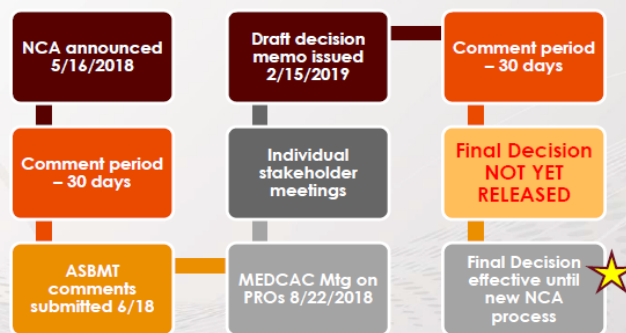
Memorial Sloan Kettering
Cancer Center.

PRO, Patient Reported Outcomes

Chakraborty et al, BBMT 2019.

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CMS/Medicare NCA for CAR-T: Process Flow



Follow the issue by visiting: <https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=291> or Visit www.CMS.gov – enter “chimeric” in the main search box at top of page



<https://www.asbmt.org/practice-resources/car-t-town-hall>

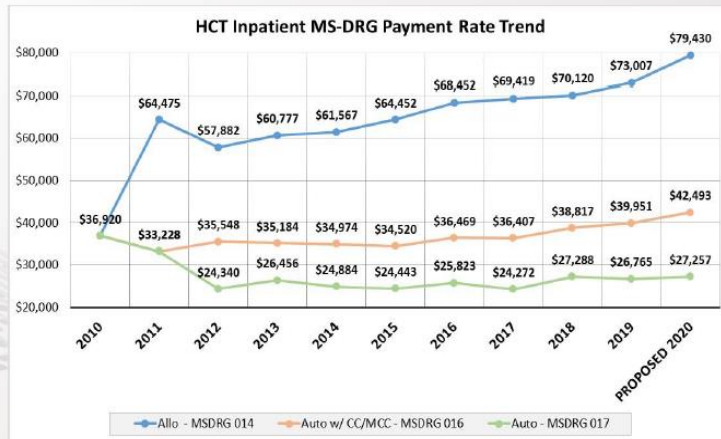


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CMS, Centers for Medicare & Medicaid Services; NCA: National Coverage Analysis

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FY 2020 Payment Rate Changes for Stem Cell Transplant MS-DRGs



<https://www.asbmt.org/practice-resources/car-t-town-hall>



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MS DRGs, Medicare Severity Diagnosis Related Groups

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Reminder: Current FY 2019 Medicare Inpatient CAR-T Payment

- 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 016 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

- In addition to the MS-DRG case payment, hospitals can receive additional payments through either the new technology add-on payment (maximum of \$186,500) and the outlier payment mechanism



* PPS-exempt hospitals have a different payment mechanism



<https://www.asbmt.org/practice-resources/car-t-town-hall>

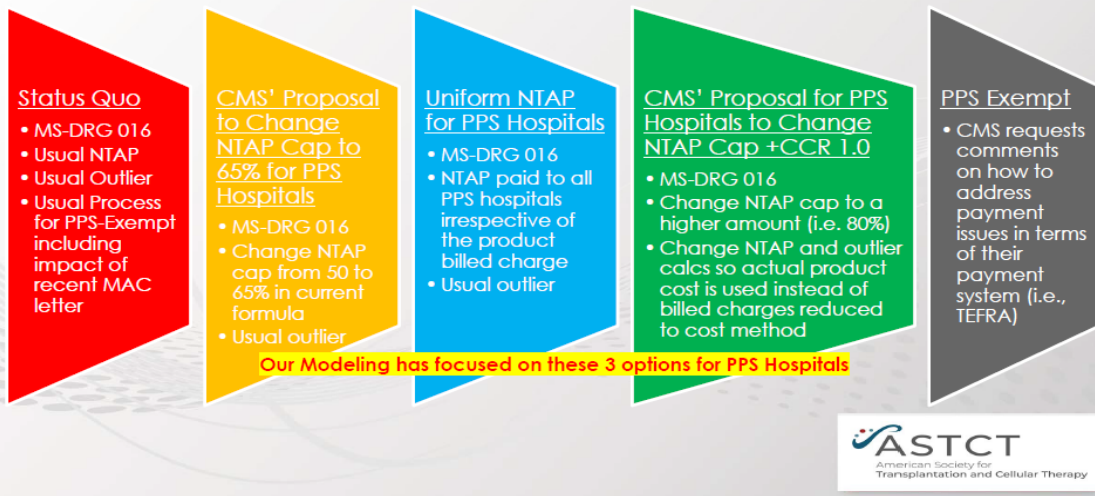


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PPS, Prospective Payment System

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Continuum of Options For Consideration For FY 2020



<https://www.asbmt.org/practice-resources/car-t-town-hall>



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NTAP, New Technology Add-on Payment ; MAC, Medicare Administrative Contractor

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Conclusions

- While providing potential clinical benefit, increasing use of this therapeutic modality can create **challenges** in **institutional resource capacity**
- Identifying these resources will allow for better **care delivery** and **allocation** of funds and ability to provide **value-based care**
- Further **refinement** of CART cell products and improvements in CART cell-related **toxicity management** may permit safer delivery of this therapy and reduce costs per patient
- Collection of **patient-reported outcomes** on research level is important and should be comparable
- **Reimbursement** and **coding** issues being addressed on national level



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

Interactive Panel Discussion Q & A

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THANK YOU!

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