CDDF 10TH ALPINE CONFERENCE
CURRENT AND FUTURE CHALLENGES OF INNOVATIVE ONCOLOGY DRUG DEVELOPMENT
26 - 28 February 2018
Innsbruck, Austria

The Early Chimeric Antigen Receptor (CAR) T-cell Experience From An Academic Perspective

CARs: LEARNING TO DRIVE

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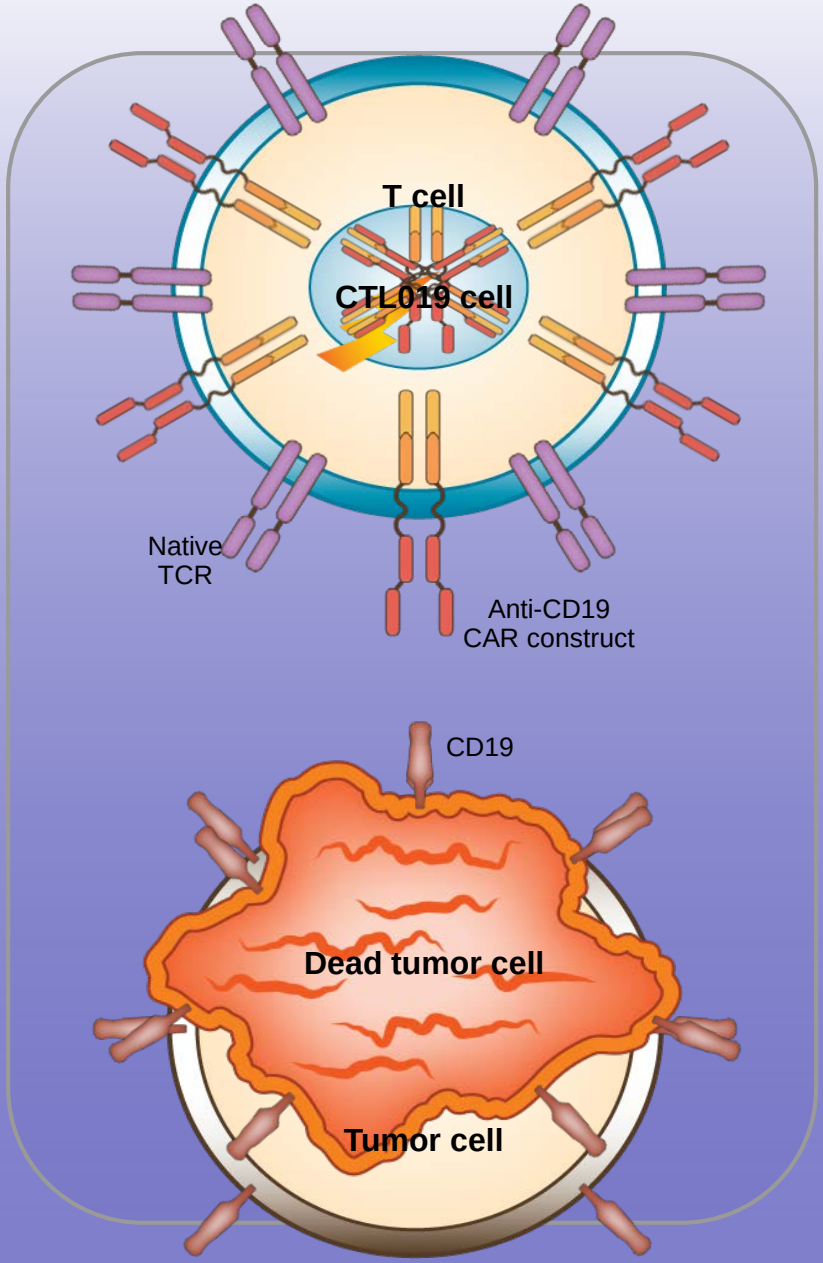
Cancer Drug Development Forum
February 28, 2018

CASE:

- Diagnosed with follicular lymphoma in 2006 at age 61
- Active observation until 2010
- Treatment history
  - Rituximab (R) monotherapy in 1/2010 (PD after 6 months)
  - R-bendamustine in 3/2012 (CR)
  - R-CHOP in 3/2013 (PR)
  - Ibrutinib (clinical trial) 10/2013 (PR)
  - R-lenalidomide 3/2014 (PD)
  - Progression 3/2015 – hospice evaluation
  - **Enrolled on UPCC13413 in 2015 with anti-CD19 CAR T-cells**
  - Remains in CR

Targeting CD19+ B-cells with CAR-Modified T-cells

- Gene transfer (lentiviral vector) to stably express CAR on T cells confers novel antigen specificity
- CAR modified T cells can now recognize and kill CD19+ cells



CAR, chimeric antigen receptor; TCR, T-cell receptor.
Slide: Courtesy of Dr. David Porter

Timeline of Cellular Therapy at Penn

Preclinical work in laboratory of Dr. Carl June and early cellular therapy trials:

- Immunology of bone marrow transplant
- Adoptive T-cell therapy for HIV
- Adoptive T-cell therapy in oncology patients

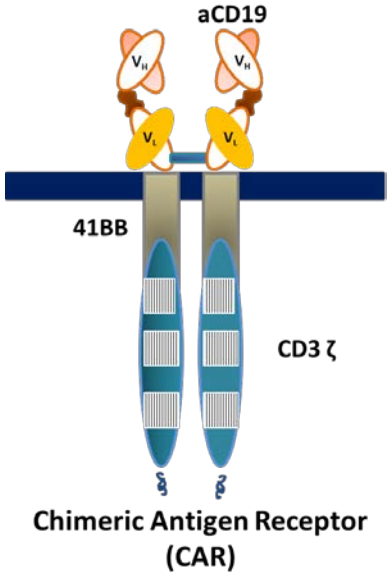
  CD3/CD28 co-stimulated T-cells

Timeline of Cellular Therapy at Penn

CAR T-cell trials:

- 2006 First draft of clinical trial written
- 2009 IRB approval of protocol
- 2010 First 3 CLL patients treated
- 2011 No patients treated (lack of funding)
- 2011 First publication

First Publication



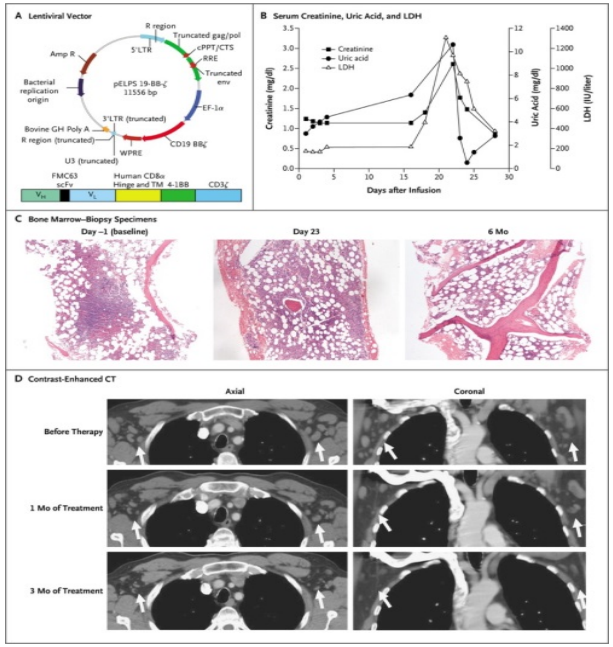
Chimeric Antigen Receptor (CAR)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

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



From Porter et al. N Engl J Med 2011; 365:725-733

Timeline of Cellular Therapy at Penn

- 2012 Penn-Novartis Alliance formed
- 2012 Institutional trials for B-ALL at CHOP/HUP and CLL at HUP
- 2013 Institutional trial for B-cell lymphomas

Timeline of Non-Institutional Cellular Studies

- 2014 Receives FDA breakthrough therapy designation
- 2015 Multisite Novartis/CTL019 trials
  - » Eliana study for B-ALL
  - » Juliet study for DLBCL (27 centers, 10 countries)

  Other CART19 trials (Kite, Juno)
- 2017 FDA approval

  tisagenlecleucel (Novartis) for r/r B-ALL (age: up to 25)

  axicabtagene ciloleucel (Kite) for r/r DLBCL

LEARNING FROM INSTITUTIONAL TRIALS

1. Toxicities/Management

2. Collaboration:
   Academic and Industry

3. Other Challenges

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

N Engl J Med 2014; 371:1507-1517

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.

N Engl J Med 2017; 377:2545-2554

TOXICITIES

- Recognition of unique side effects of cellular therapy
  - Cytokine release syndrome
  - Neurotoxicity
  - Hypogammaglobulinemia

- Development of management strategies

DEVELOPMENT OF PENN CRS GRADING SYSTEM

Grade	
1	Supportive care only
2	IV therapies +/- hospitalization
3	Hypotension requiring IV fluids or low dose vasoactive or hypoxemia requiring supplemental oxygen
4	Hypotension requiring high-dose vasoactives or hypoxemia requiring mechanical ventilation
5	Death

- CRS:
  - ALL (100%)
  - Lymphoma (57%)
    - Less severe
    - Not associated with response in DLBCL
- Neurotoxicity

Table 2. Adverse Events of Special Interest That May Have Been Related to CTL019 Therapy.*

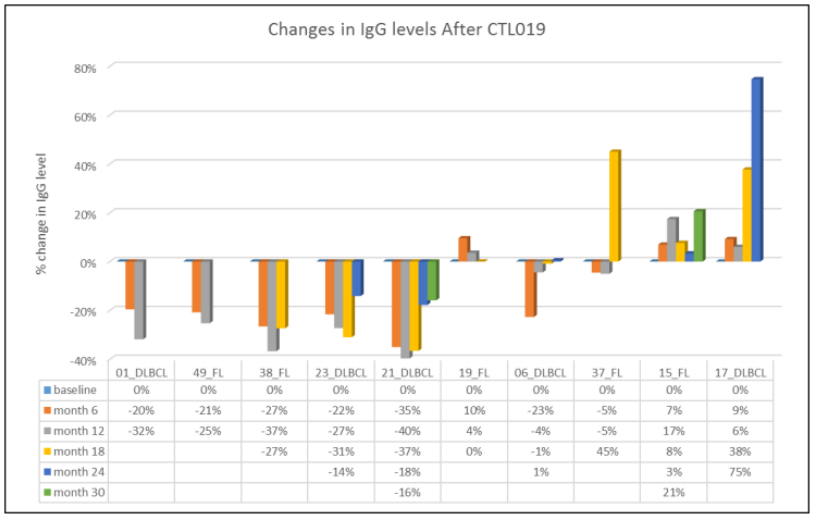
Adverse Event	Grade					Total Events	Grade 3 or Higher
	1	2	3	4	5	*number (percent)*	
Cytokine release syndrome	0	11	4	1	0	16 (57)	5 (18)
Neurotoxicity	4	4	1	1	1	11 (39)	3 (11)
Encephalopathy	0	0	1	1	1	3 (27)	
Delirium	0	2	0	0	0	2 (18)	
Tremor	2	0	0	0	0	2 (18)	
Cognitive disturbance	1	0	0	0	0	1 (5)	
Confusion	0	1	0	0	0	1 (5)	
Involuntary movements	1	0	0	0	0	1 (5)	
Memory impairment	0	1	0	0	0	1 (5)	

* A list of all adverse events is provided in the Supplementary Appendix.

From Schuster et al. N Engl J Med 2017; 377:2545-2554

HYPOGAMMAGLOBULINEMIA

- Differences depending on disease
  - In ALL
    - B-cell aplasia in all responding patients
    - IgG replacement given
  - In Lymphoma
    - Most patients do not need routine IgG replacement
    - Ig recovery noticed despite CTL019 persistence



	01_DLBCL	49_FL	38_FL	23_DLBCL	21_DLBCL	19_FL	06_DLBCL	37_FL	15_FL	17_DLBCL
baseline	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
month 6	-20%	-21%	-27%	-22%	-35%	10%	-23%	-5%	7%	9%
month 12	-32%	-25%	-37%	-27%	-40%	4%	-4%	-5%	17%	6%
month 18			-27%	-31%	-37%	0%	-1%	45%	8%	38%
month 24				-14%	-18%		1%		3%	75%
month 30					-16%				21%	

From Schuster et al. N Engl J Med 2017; 377:2545-2554

MANAGEMENT OF TOXICITIES

- The story of tocilizumab for CRS (Lisa Rosenblaum: “Tragedy, Perseverance, and Chance – the Story of CAR T-therapy” in N Engl J Med 2017; 377:1313-1315)
  - IL-6 receptor blocking antibody previously used in rheumatology

- Supportive care/steroids for neurotoxicity

- Immunoglobulin replacements for B-cell aplasia

COLLABORATION: ACADEMICS-INDUSTRY

- High quality control
- Documentation
- Monitoring
- Safety focus

OTHER CHALLENGES DURING DEVELOPMENT

- Patient volume after first reports of long term remissions
- Patients outside of US interested in trials
- Rapid growth of non-CTL019 trials (BCMA-CAR, solid oncology targets) and limited T-cell apheresis/production pace
- Patient selection
- Educating personnel within the Penn system
  - Research team
  - Non-oncology teams (ER, intensive care, neurology, house-staff)

FUTURE CHALLENGES

- Designing new clinical trials to improve efficacy
- Better understanding the toxicity profile of CAR T-cell therapies and developing effective management strategy
- Commercial product
  - Building structure and staffing within our division
  - Insurance reimbursement
  - Patient volume and selection

CARs: LEARNING TO DRIVE

- Case reports
  - Many unknowns, unexpected toxicities
- Smaller institutional trials for B-ALL, CLL, and lymphomas
  - Systemic monitoring of toxicities
  - Developed effective strategies to treat adverse events
- Larger multi-institutional trials
  - Efficacy/adverse events were similar to Penn trials
- Commercial CAR products