Clinical Development and Innovation in Engineered T Cell Therapies

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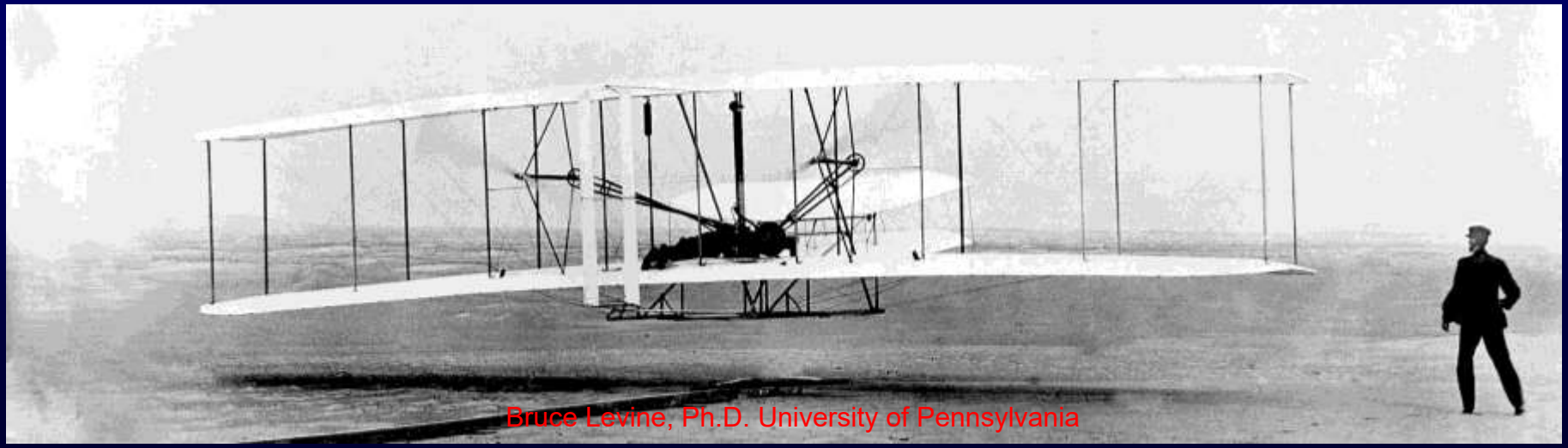
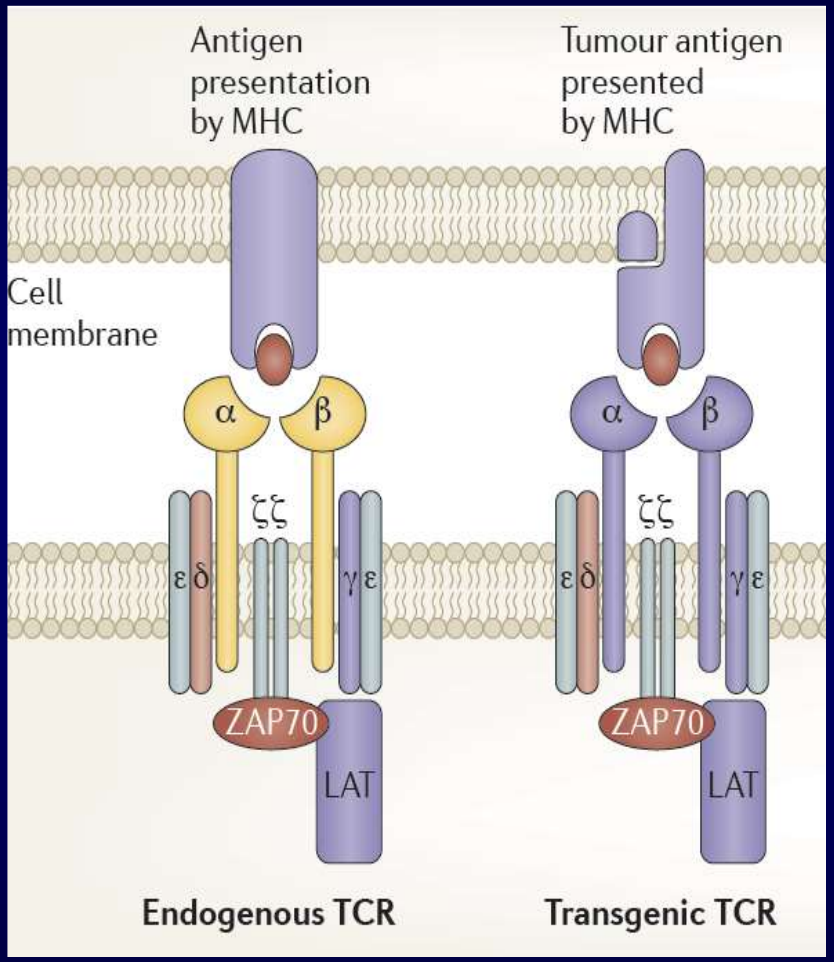
Conflict of Interest Statement

- Declaration of financial interest due to intellectual property and patents in the field of cell and gene therapy.
- Consultant for GE Healthcare
- Founder Tmunity Therapeutics
- Conflict of interest is managed in accordance with University of Pennsylvania policy and oversight

A Technological Advance That Required Power and Control



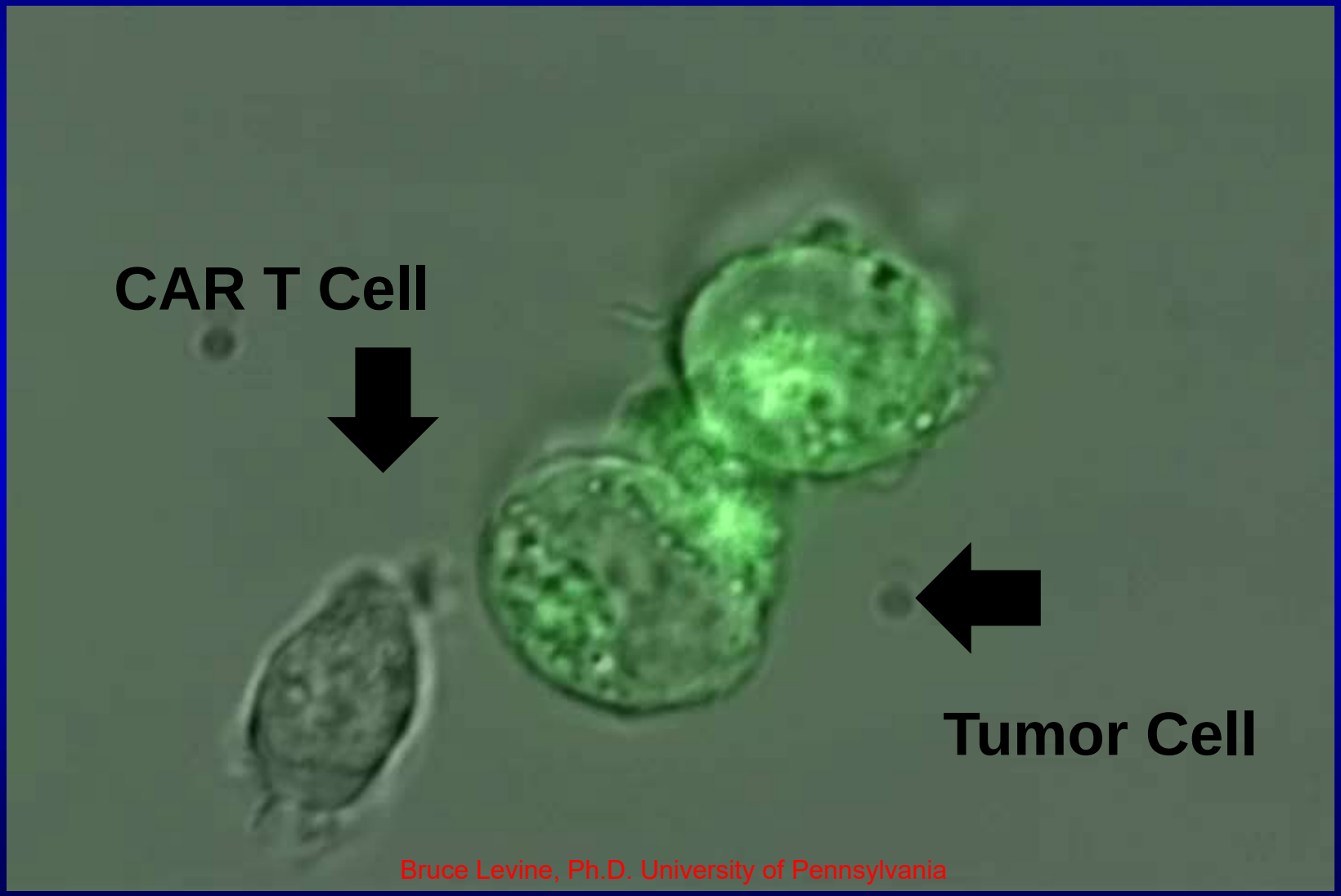
Overcoming the Scarcity of Tumor Specific Immunity and Tumor Suppression: Creation of Re-directed T cells



-intracellular Ags
-MHC dependent

Fesnak, June, Levine; Nature Reviews Cancer, Aug, 2016

CAR T Cells Killing Tumor Cells

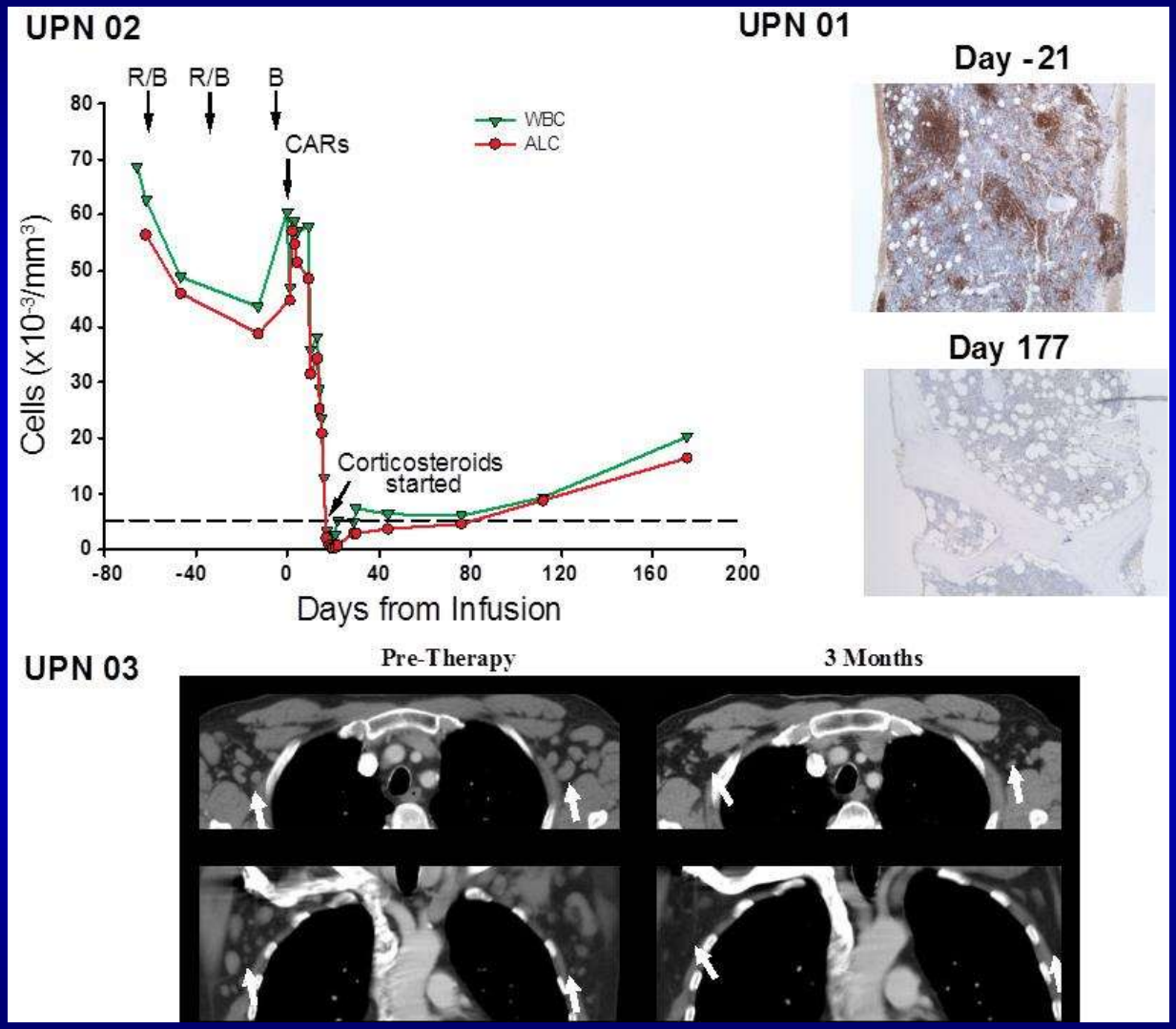


Engineered T Cell Therapies:
Considerations in Development

- How to Dose a Dividing Drug?
- Persistence (Durability) & Escape as Mechanisms of Relapse
- Engineered T Cell Combinations
- Phenotype and Biomarkers
- Comparability and Globalization
- Safety of Potent T Cells, Gene Modification in T Cells

Relapsed/Refractory Chronic Lymphocytic Leukemia

CART19 Subjects Infused Aug, Sept 2010



2.9 to 7.7 pounds of tumor killed

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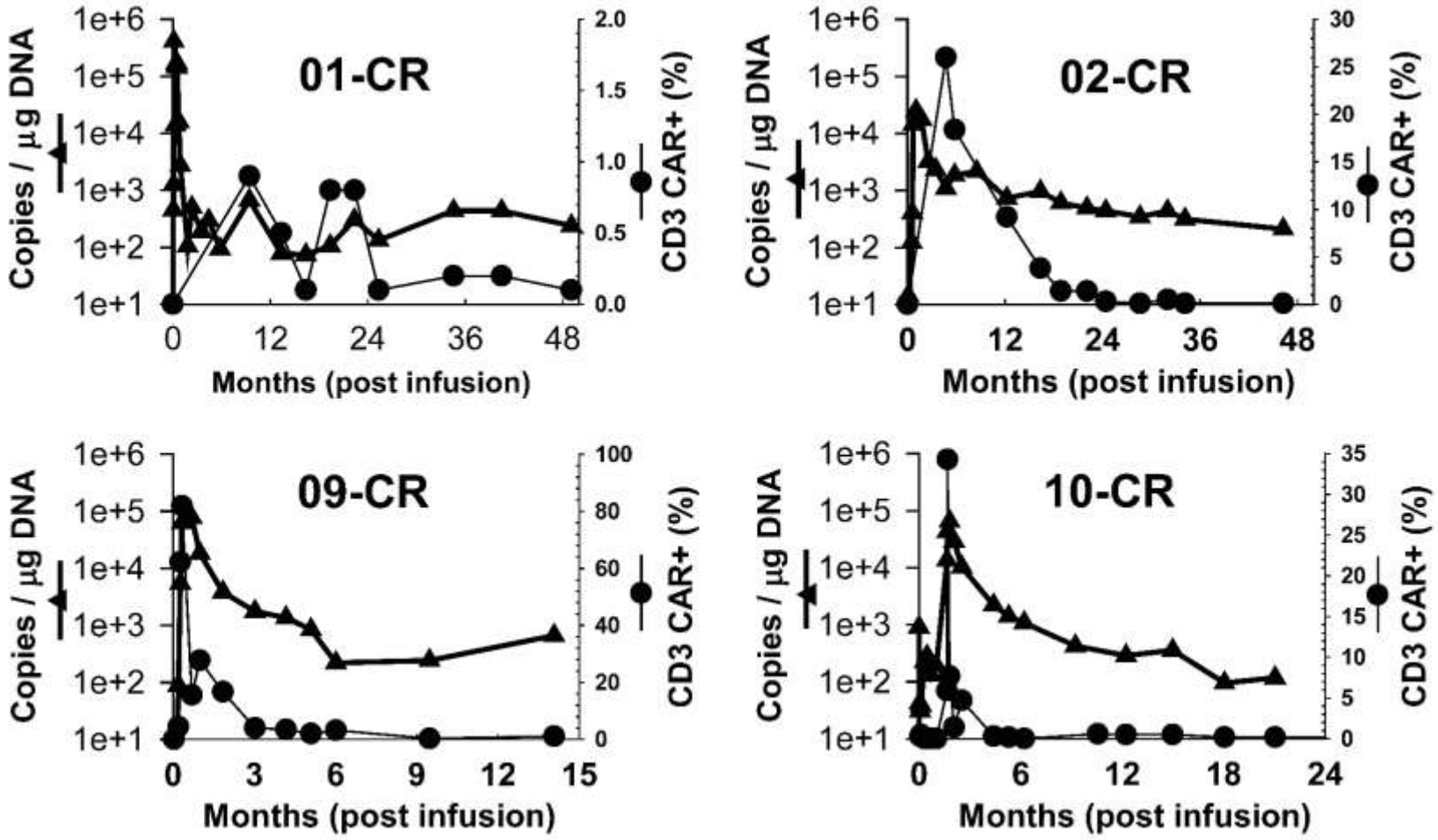
NEJM 365:725, 2011, Science Translational Med 3:95ra73, 2011

Long term persistence and expression of CTL019 in CLL patients with durable remission

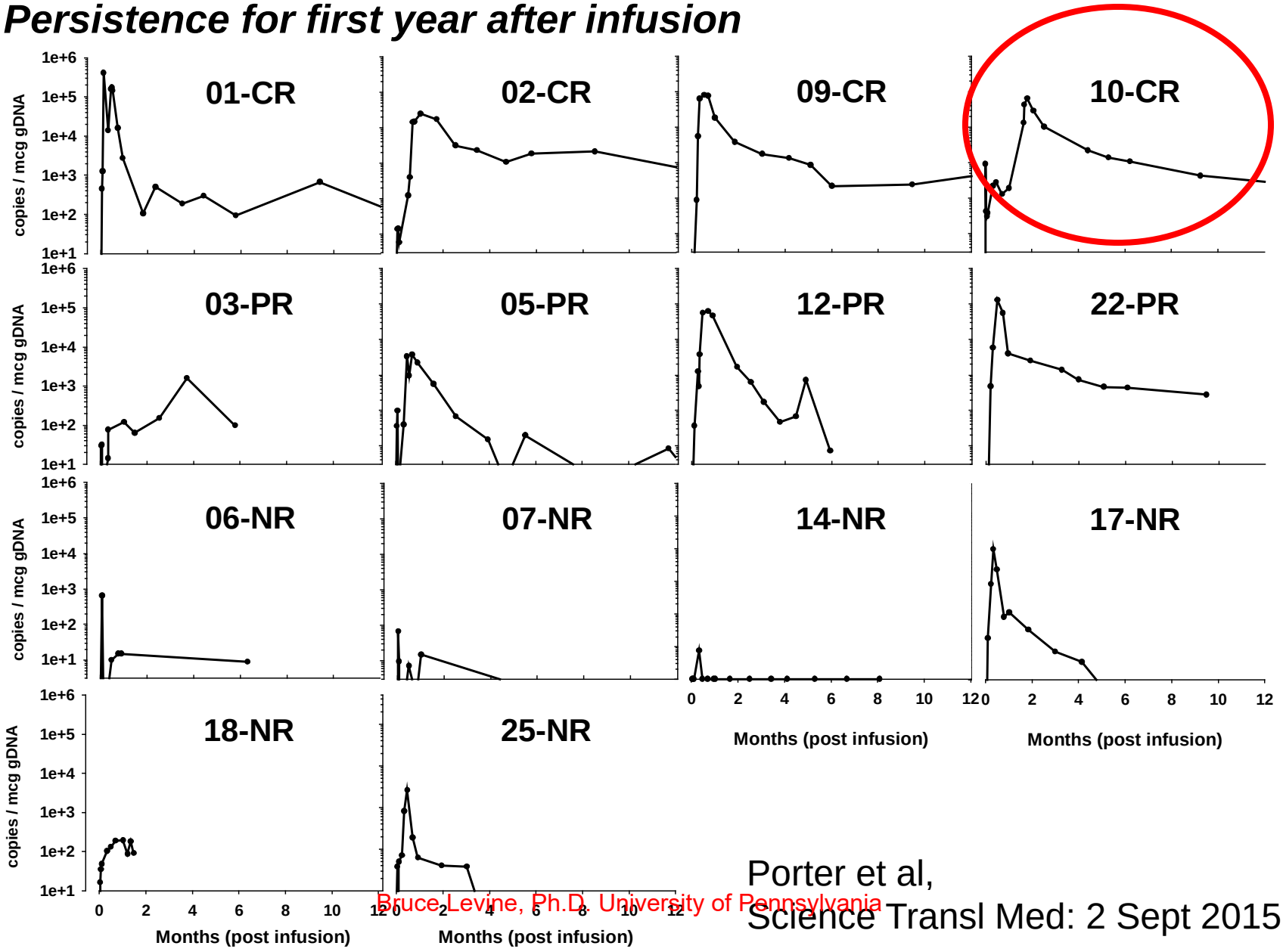
CLL subjects with persistence beyond one year



Porter et al,
Science Transl Med: 2 Sept 2015

Bedside Back to Bench Lessons

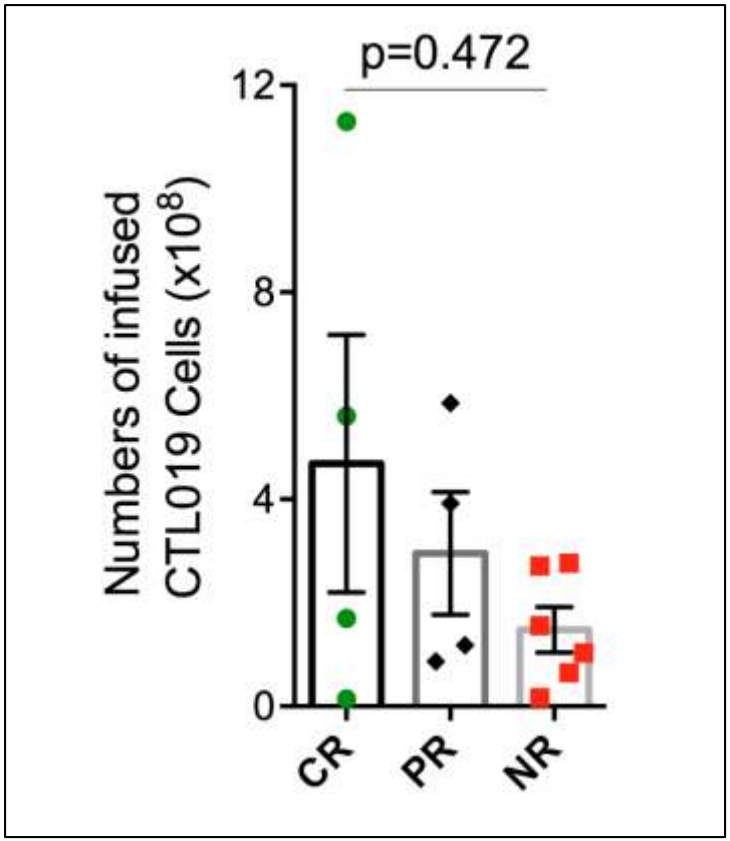
Persistence for first year after infusion



Porter et al,
Science Transl Med: 2 Sept 2015

CTL019 Therapy in R/R Chronic Lymphoid Leukemia

For a Dividing Drug - Quality Counts!



- No statistical difference in the numbers of CTL019 cells infused per patient and clinical outcome of therapy (Exact's Unpaired Mann-Whitney statistical test).

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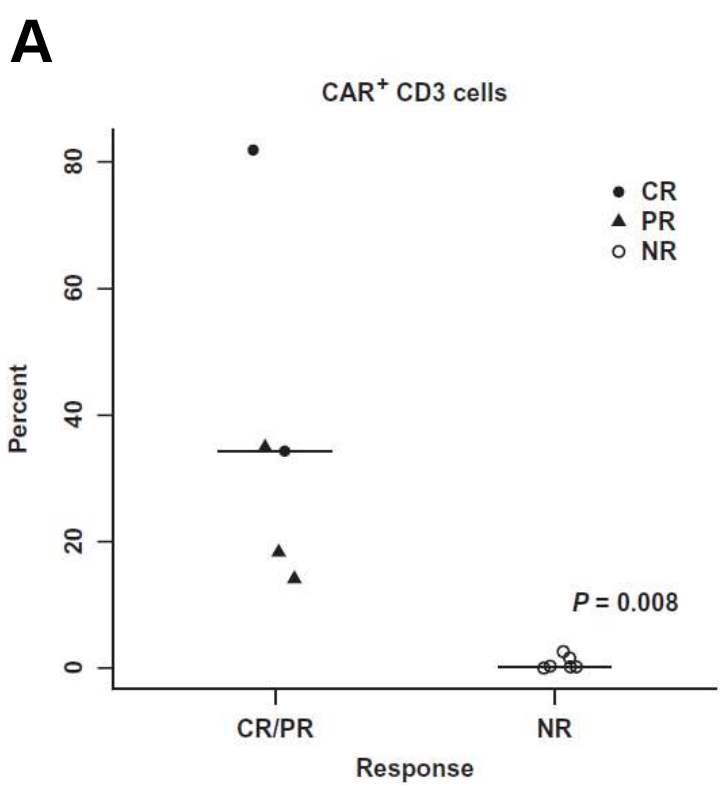
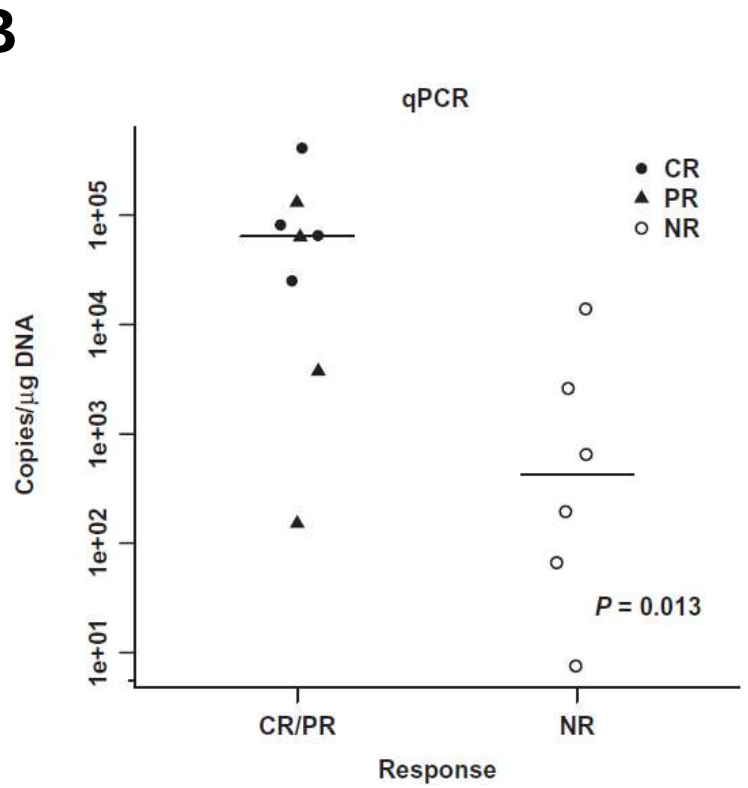
Porter D. L. *et al.*, Science TM (2015)

CTL019 Therapy in R/R Chronic Lymphoid Leukemia
Peak CTL019 Expansion Correlates With Clinical Response





- Peak CTL019 expansion first 3 months measured by flow cytometry and qPCR
- No antibody (anti-CTL019) available for patients 01, 02, and 03

Penn Medicine

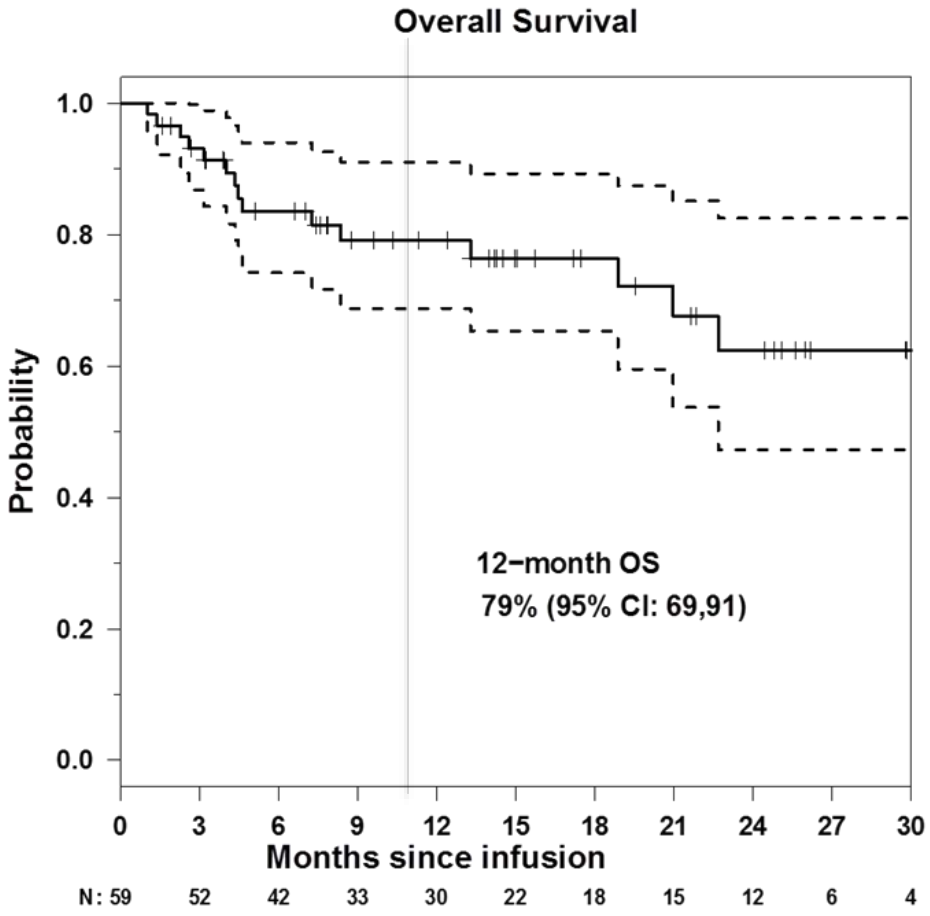
Porter D. L. *et al.*, *Science TM* (2015)

Persistence (Durability), or Not & Escape as Mechanisms of Relapse

Relapsed/refractory ALL: 93% CR rate after CTL019

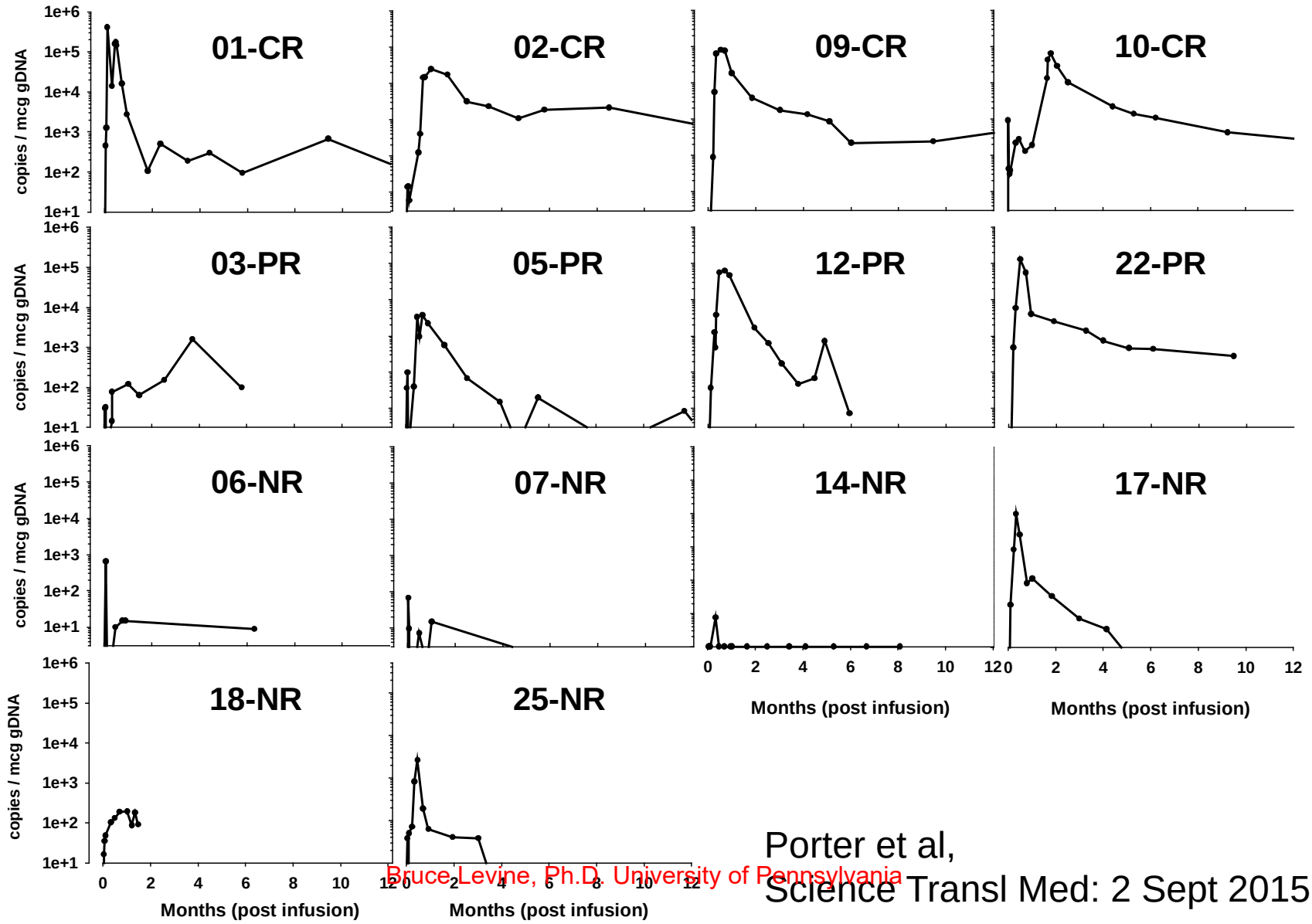
>350 patients with CLL, ALL, NHL, MM have gotten CTL019

- 60 r/r pediatric ALL pts:
  55 in CR at 1 mo (93%)
  median f/u 12 mo
- Only 6 went to subsequent transplant, 1 to DLI
- 6 mo RFS: 76% (95%ci 65-89%)
  12 mo RFS: 55% (95%ci 42-73%)
- No relapses past 1 year
- 18 patients in remission beyond 1 year,
  13 without further therapy



Predicting Responders (CLL): Expansion and Durable Persistance

Persistence for first year after infusion



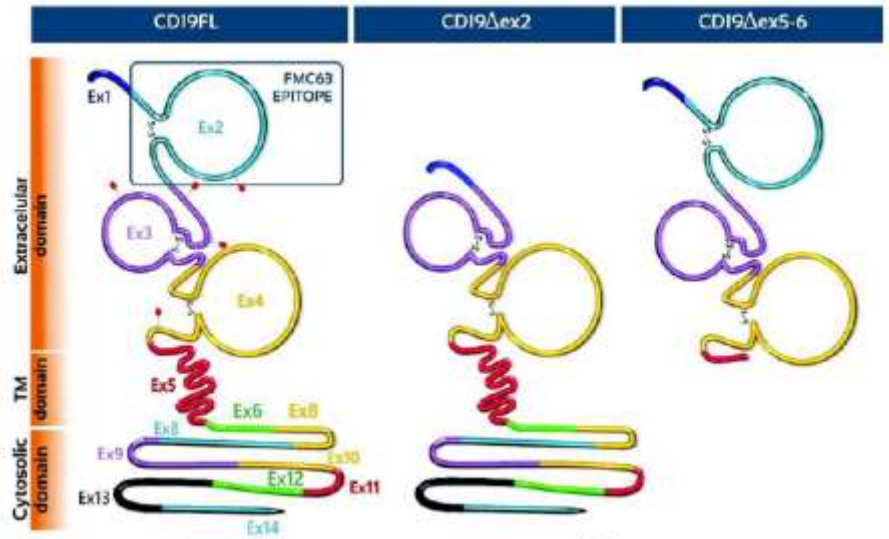
Porter et al,
Science Transl Med: 2 Sept 2015

ALL: Mechanisms of Resistance to CART19

- **In pediatric and adult ALL, there is a >90% CR at 1 month**
- **To date, there have been 15 relapses in the first 50 patients given CART19:**
  - **No patient has relapsed beyond year**
  - **15 patients have relapsed, and 10 of these patients relapsed with CD19 negative leukemia**
- **What are the mechanisms of CD19 negative relapse in ALL?**

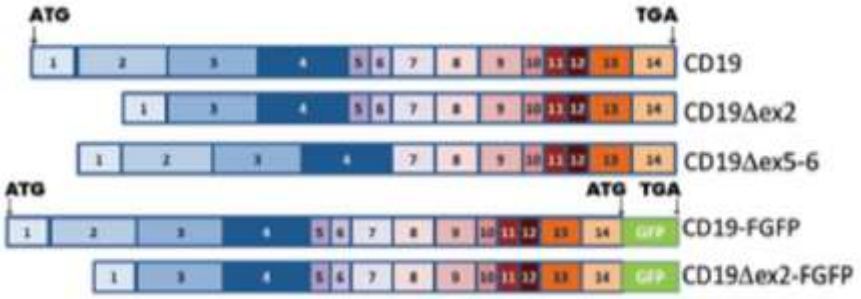
Mechanism of resistance in ALL: CD19 escape

PREDICTED PROTEIN PRODUCTS FOR ISOFORMS



- CD19 escape is a combination of mutations and shifts in splicing that favor retaining some CD19 protein
- DNA mutations can be subclonal, and may include splice factors sites

By flow cytometry, the CD19 escape variants lack the epitope recognized by the CAR T cell



Sotillo, E. et al, Convergence of Acquired Mutations and Alternative Splicing of CD19 Enables Resistance to CART-19 Immunotherapy. Cancer Discov. 2015 Dec;5(12):1282-95.

Challenging Malignancies: Rationale for Engineered T Cell Combinations

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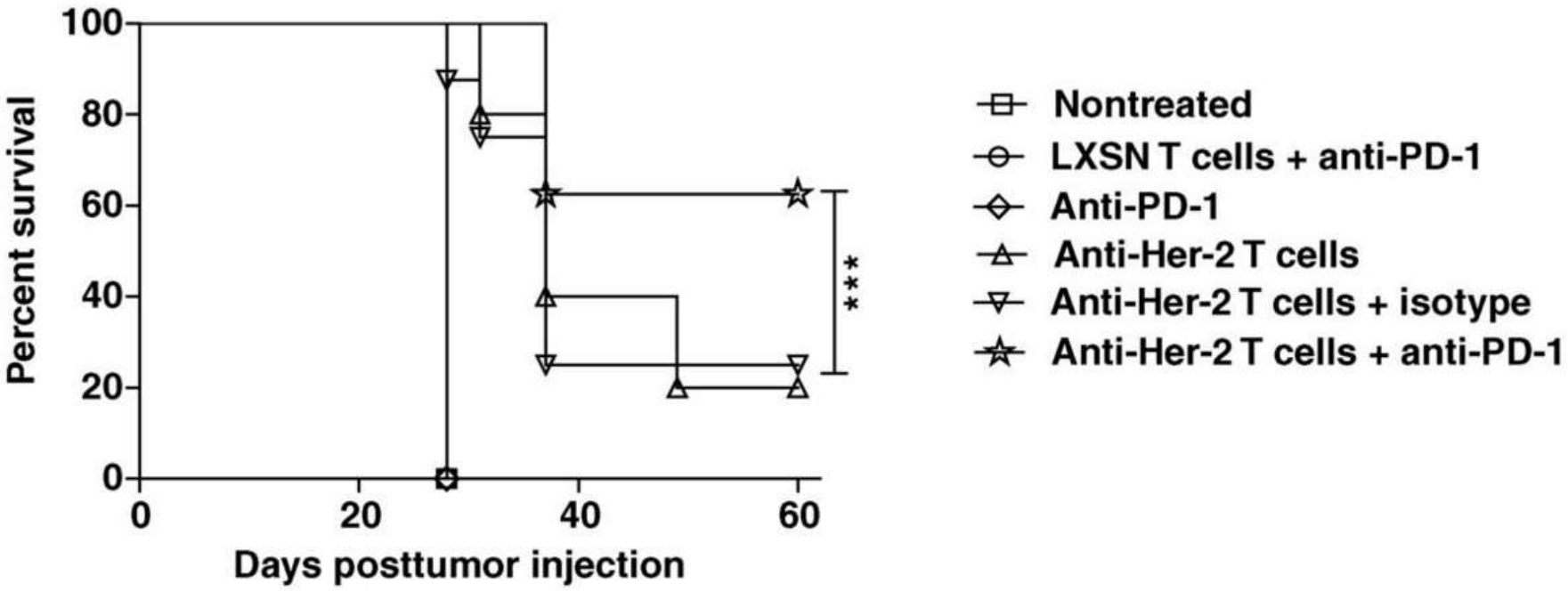
Lymphoma Phase IIa Study Design:
NCT02030834

- CAR T cells directed against CD19 (CTL019) in advanced CD19+ B-cell non-Hodgkin lymphomas (NHL)

Primary objective:
- Overall response rate (ORR) at 3 months
- Response rate by histology (DLBCL, FL, MCL)

Secondary objectives:
- Safety and tolerability of CTL019 in NHL subjects
- Persistence, trafficking and function of CTL019 *in vivo*
- Effects of B cells and CD19 expression *in vivo*
- CTL019 manufacturing feasibility
- MRD and survival rates

Engineered T Cells and Checkpoint Antibody Therapies: Potential Synergism



John LB. Anti-PD-1 antibody therapy potently enhances the eradication of established tumors by gene-modified T cells. Clin Cancer Res. 2013;19(20):5636-46.

Moon EK. Blockade of Programmed Death 1 Augments the Ability of Human T cells Engineered to Target NY-ESO-1 to Control Tumor Growth after Adoptive Transfer. Clin Cancer Res. 2015.

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CAR T in Lymphoma Conclusions

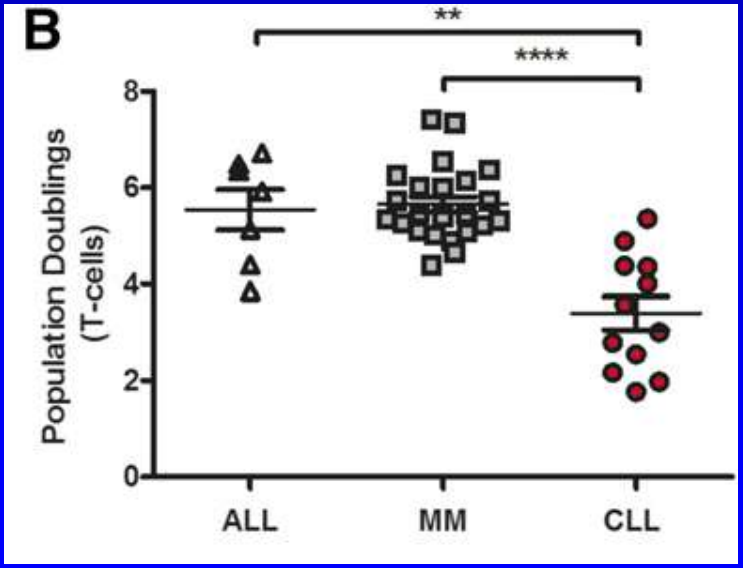
- CAR T cells directed against CD19 (CTL019) can achieve durable responses in patients with relapsed or refractory CD19+ DLBCL (ORR ~55%) and follicular lymphomas (ORR ~75%).
- All patients who achieved CR remain in CR.
- Toxicity appears to be acceptable. Cytokine release syndrome was generally grade 2.
- There were no deaths from cytokine release syndrome.
- Time to achieve best response in lymphoma is longer than in ALL
- Incidence of relapse with CD19-negative tumor appears to be less than with ALL
- Schuster (Penn) NCT02650999
  - Study of Pembrolizumab in Patients Failing to Respond to or Relapsing After Anti-CD19 Chimeric Antigen Receptor Modified T Cell Therapy for Relapsed or Refractory CD19+ Lymphomas

Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia

Joseph A. Fraietta,[1,2,*] Kyle A. Beckwith,[3,*] Prachi R. Patel,[1,2] Marco Ruella,[1,2] Zhaohui Zheng,[1,2] David M. Barrett,[4] Simon F. Lacey,[1,2] Jan Joseph Melenhorst,[1,2] Shannon E. McGettigan,[1,2] Danielle R. Cook,[1,2] Changfeng Zhang,[1,2] Jun Xu,[1,2] Priscilla Do,[3] Jessica Hulitt,[4] Sagar B. Kudchodkar,[1,2] Alexandria P. Cogdill,[1,2] Saar Gill,[1,5] David L. Porter,[1,2,5] Jennifer A. Woyach,[3] Meixiao Long,[3] Amy J. Johnson,[3] Kami Maddocks,[3] Natarajan Muthusamy,[3] Bruce L. Levine,[1,2,6] Carl H. June,[1,2,6] John C. Byrd,[3,*] and Marcela V. Maus[7,*]

[1]Center for Cellular Immunotherapies and [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [3]Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus, OH; [4]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA; [5]Division of Hematology-Oncology, Department of Internal Medicine and [6]Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; and [7]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

BLOOD, 3 MARCH 2016 x VOLUME 127, NUMBER 9



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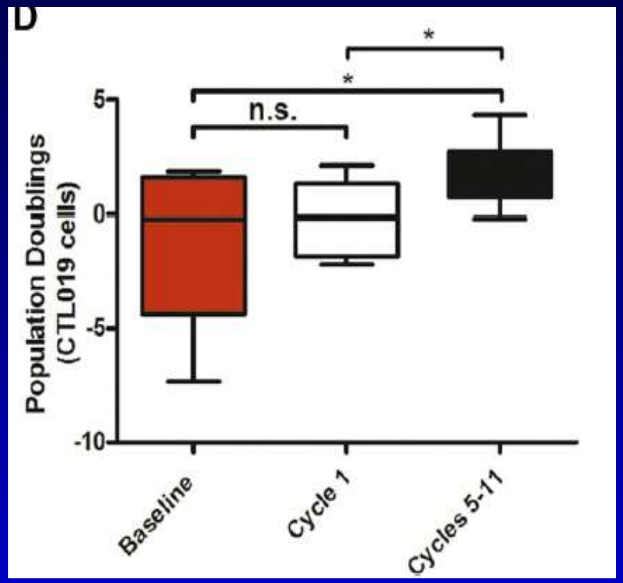
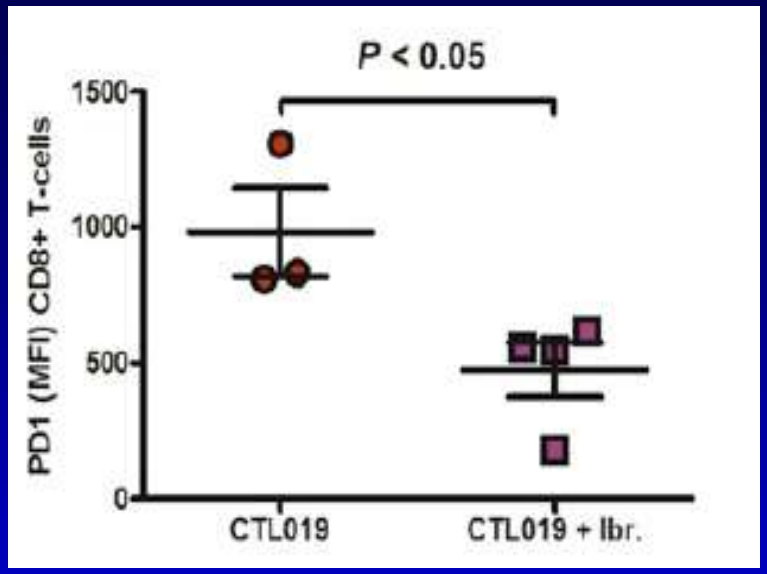
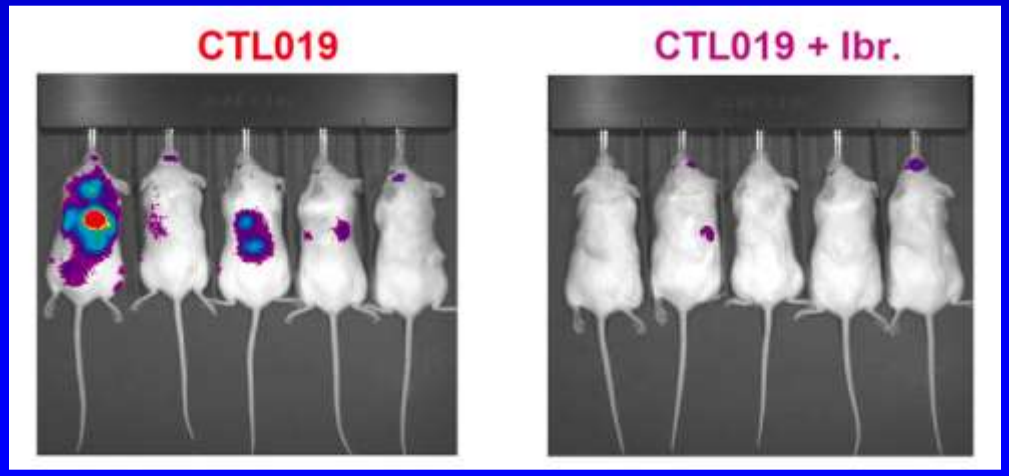
Long-term oral ibrutinib therapy corrects functional defects in CLL patient T cells





Ibrutinib increases engraftment and antitumor activity of CTL019 cells when administered concurrently



Pilot Trial Of Autologous T Cells Engineered To Express Anti-CD19 Chimeric Antigen Receptor (CART19) In Combination With Ibrutinib In Patients With Relapsed Or Refractory CD19+ CLL or SLL
NCT02640209

- To determine safety and efficacy of CART-19 cells in combination with ibrutinib.
- In subjects who have achieved partial response or stable disease on ibrutinib therapy

Principal Investigator: Saar Gill, MD
Abramson Cancer Center of the University of Pennsylvania

57 Biomarkers of Response to Anti-CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy in Patients with Chronic Lymphocytic Leukemia

CLL: Therapy, excluding Transplantation
Program: Oral and Poster Abstracts
Type: Oral
Session: 642. CLL: Therapy, excluding Transplantation: Ibrutinib Resistance, Transformation, and Cellular Therapy

Saturday, December 3, 2016: 8:00 AM

Room 6AB (San Diego Convention Center)

https://ash.confex.com/ash/2016/webprogram/

ASH | 58th Annual Meeting & Exposition
San Diego, CA · December 3-6, 2016

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Comparability and Globalization

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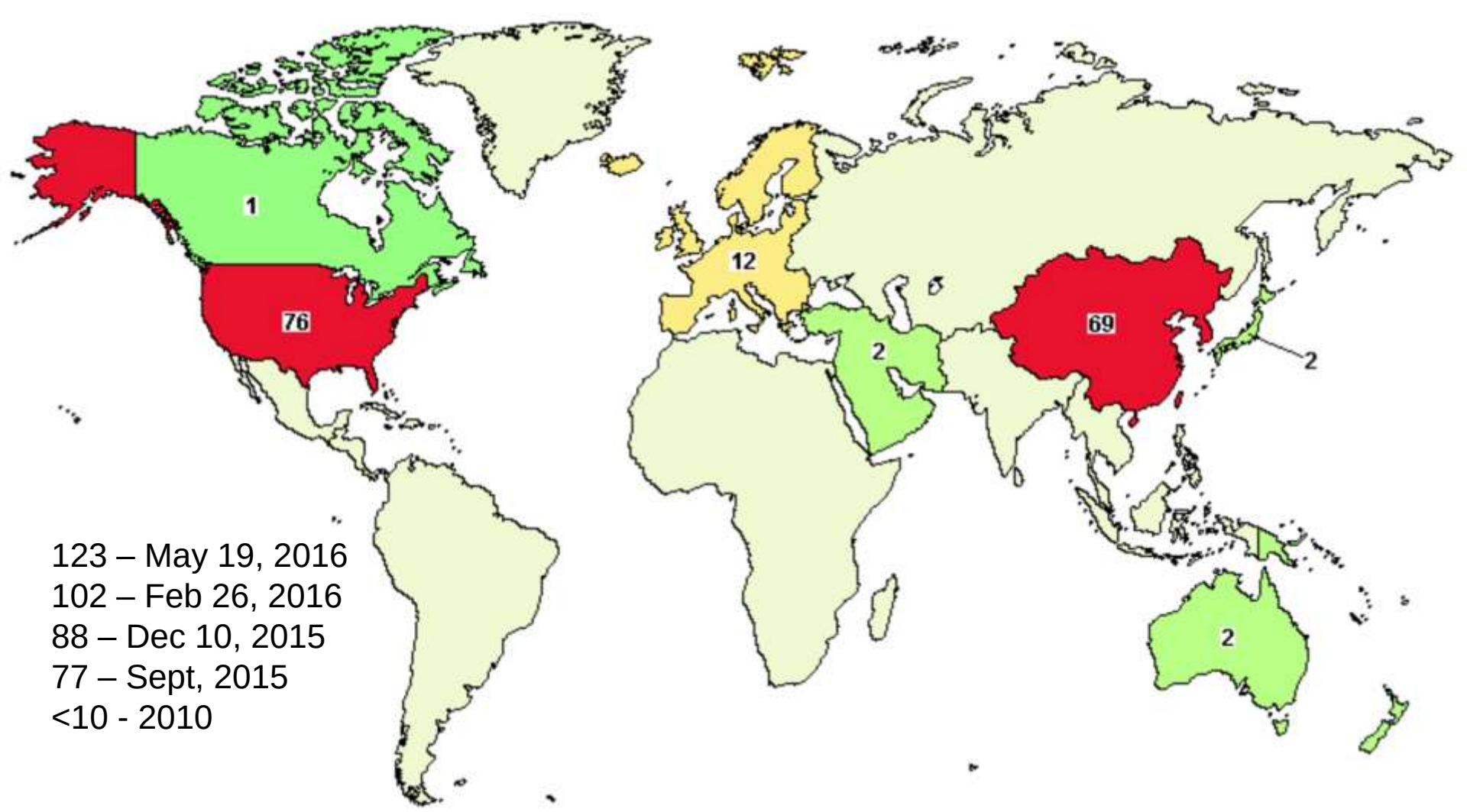
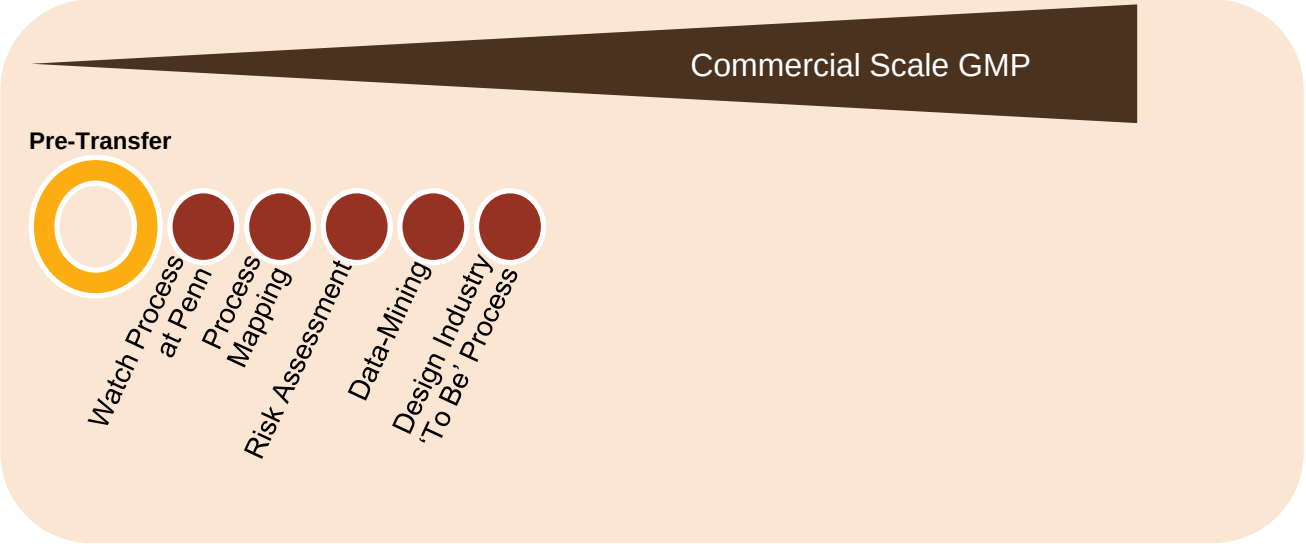
Clinicaltrials.gov search “chimeric antigen receptor” on November 8, 2016 yields 163 trials



123 – May 19, 2016
102 – Feb 26, 2016
88 – Dec 10, 2015
77 – Sept, 2015
<10 - 2010

Effective Transfer of Technology Calls for Effective Collaboration

- Included areas of manufacturing process and analytical technology to consistently manufacture CTL019 with scale-up capabilities
- A step-based process transfer method was developed in collaboration with participants from diverse technology transfer teams (Academia, GMP production, Technical Development, QA and Regulatory)



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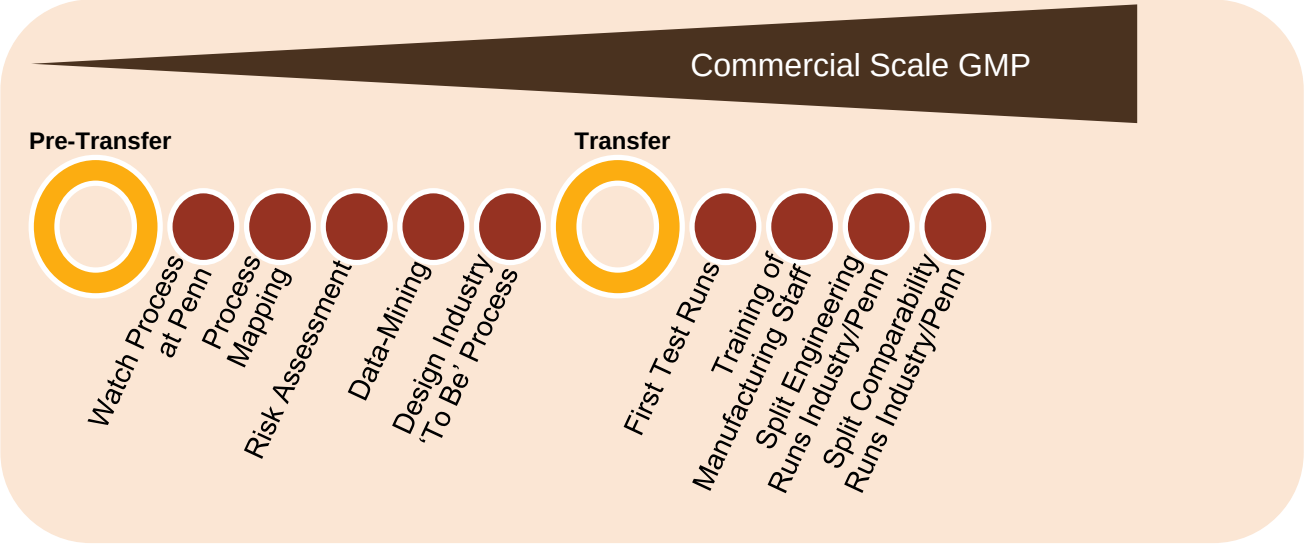

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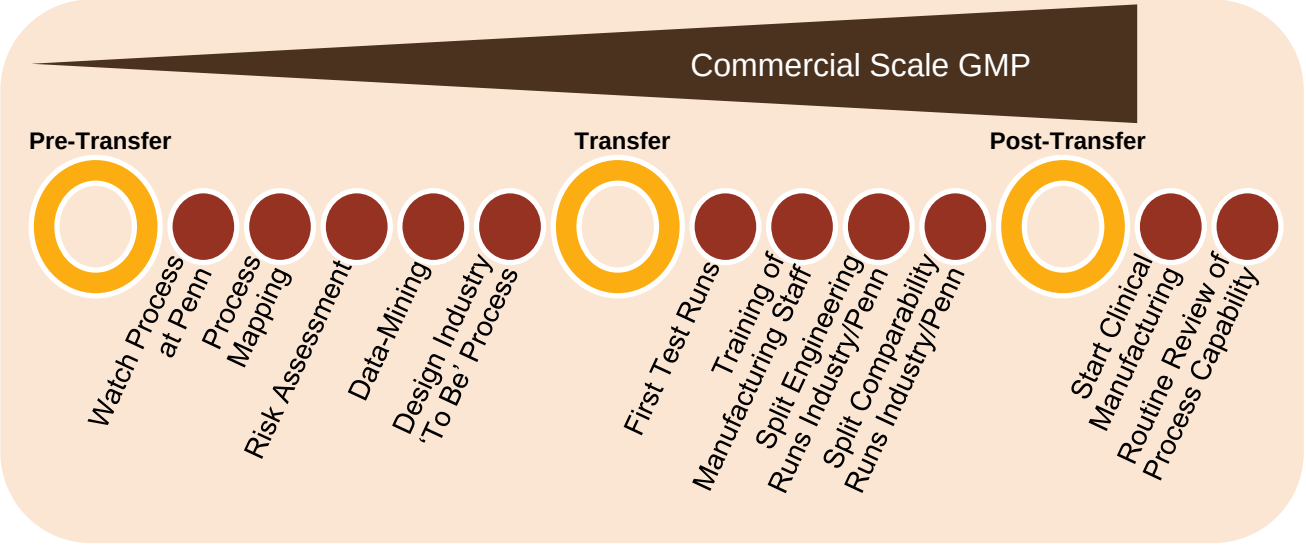

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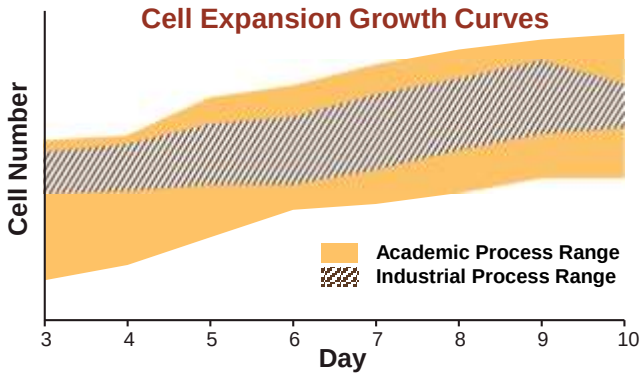
Ex Vivo Expansion Results

- Patient-derived autologous CTL019 cells for treatment of pediatric patients with r/r ALL enrolled in a US-based, multicenter, phase II clinical trial have now been processed in the industry setting and infused into patients
- The cell expansion growth curves and release criteria on the cell products obtained in this large scale manufacturing facility were within range of those obtained at the academic facility



ALL, acute lymphoblastic leukemia; r/r, relapsed/refractory.

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Successful Transfer of CAR T Technology

- **Leveraged proven step-wise industry transfer process to capture academic experience along with extensive collaborative training and strong analytics**
- **Successful CAR T cell therapy process transfer from academia to industry**
- **CTL019 cell expansion growth curves at Novartis were within range of those observed at Penn, provides template for global scalability**
- **Key areas of enhancements within the large scale manufacturing process ensure production efficiency without compromising integrity and potency of the final product**

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Determine Efficacy and Safety of CTL019 in Pediatric Patients with Relapsed and Refractory B-cell ALL (ELIANA)

US sites

- **Children's Hospital of Philadelphia**
- **Cincinnati Children's Hospital**
- **University of Wisconsin**
- **Children's Medical Center of Dallas/UTSW**
- **Children's Mercy Kansas University**
- **Oregon Heath & Science University**
- **Stanford University**
- **University of Minnesota**
- **Children's Hospital Los Angeles**
- **University of Michigan**
- **Duke University**

Ex- US
(Canada, Australia, EU, Japan)

- **Royal Children's Hospital (Australia)**
- **Hospital St. Justine (Canada)**
- **Ghent University (Belgium)**
- **Oslo Univ. Hospital (Norway)**
- **Kyoto (Japan)**

Clinicaltrials.gov NCT02435849
Protocol closed to enrollment

NOVARTIS

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Single Arm, Open-Label, Multi-Center, Phase II Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients (JULIET)

US sites

- Emory Winship Cancer Institute
- University of Chicago
- University of Kansas
- University of Michigan
- University of Minnesota
- Duke University
- Ohio State James Cancer Hospital
- Oregon Health Sciences University
- MD Anderson Cancer Center

Ex- US
(Canada, Japan, EU)

- Montreal
- Sapporo
- Oslo

Clinicaltrials.gov NCT02445248

NOVARTIS

Safety of Potent T Cells and Gene Modification in T Cells

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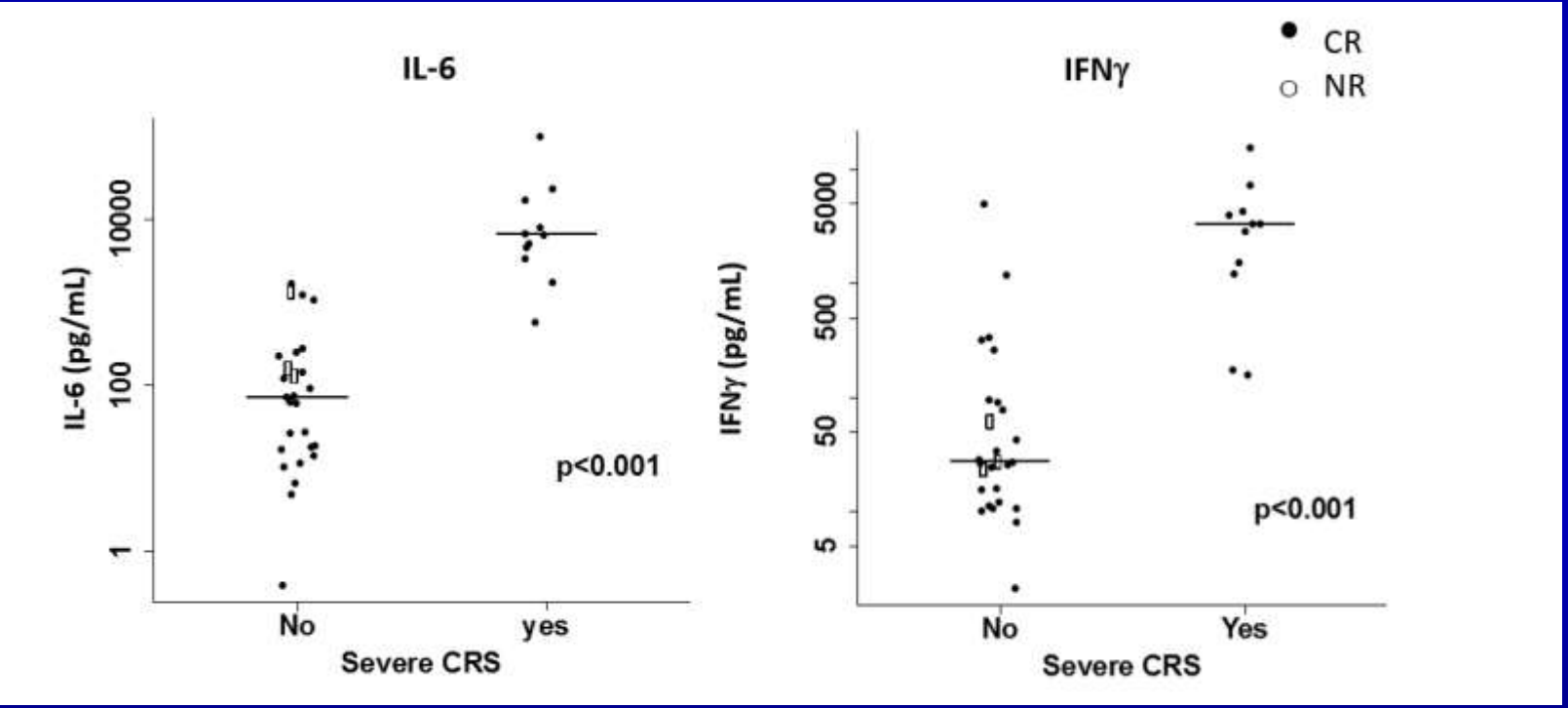
IL-6 levels correlate with Severe CRS, But Are Not Predictive



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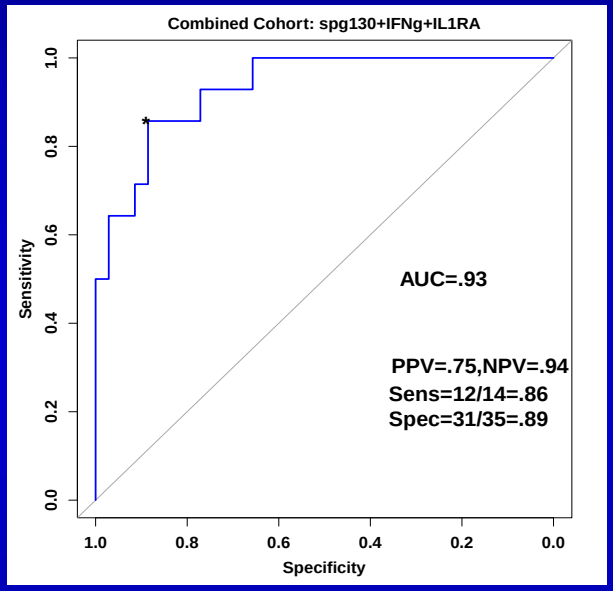
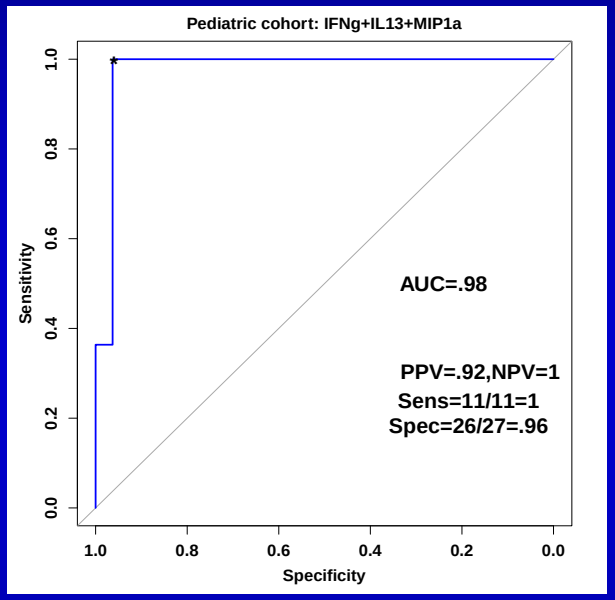
Cytokines other than IL-6 predict CRS



Full cohort (adults+peds)
Sgp130* + IFNg + IL1RA

*signal transducing receptor component IL-6 family



Pediatric cohort
IFNg + IL13 + MIP1a

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Teachey, DT et al. Cancer Discov. 2016 Apr 13

Chimeric Antigen Receptor T Cell Translation: Key Points

- CTL019 cells persist for years providing functional immunity
  - –Sci Transl Med. 2015 Sep 2
- CTL019 CARs have potent activity in refractory ALL, CLL, DLBCL, FL, myeloma
  - –Sci Transl Med. 2011, NEJM 2011, NEJM 2013, NEJM 2014, NEJM 2015
- Tech transfer from academia (Penn) to industry (Novartis) accomplished
- Novartis manufacturing for the pediatric r/r ALL global clinical trial and the DLBCL global clinical trial

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Penn Platform Technology: Academic CAR Clinical Trials

Lentiviral vector CAR's

- Adult Acute Lymphoblastic Leukemia NCT02030847
- **Acute Lymphoblastic Leukemia (CD22) NCT02650414, NCT02588456**
- Chronic Lymphocytic Leukemia NCT01747486
- **Chronic Lymphocytic Leukemia (CART19 + Ibrutinib) NCT02640209**
- Adult Lymphomas: NCT02030834
- **Myeloma**: NCT02135406 (CART19), **NCT02794246 (post-ASCT), NCT02546167 (BCMA)**
- Pediatric Leukemia and Lymphoma: NCT01626495
- Glioblastoma: NCT02209376
- Mesothelin expressing cancers: NCT02159716 (CARTmeso), NCT02465983 (CARTmeso19)
- Multi-center CTL019 trials NCT02228096

RNA CAR's

- Mesothelioma: NCT01355965
- Pancreatic Cancer: NCT01897415
- Breast Cancer: NCT01837602
- Hodgkin's Lymphoma: NCT02277522. NCT02624258
- AML: NCT02623582

- **Prostate cancer, Melanoma, Mesothelin positive cancers: pending**
- **More coming**

To Date from Penn
>275 CTL019 Patients
>65 other CAR's

http://www.penncancer.org/tcelltherapy

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