

# **CAR T-CELL THERAPY FOR ALL: IDENTIFYING APPROPRIATE PATIENTS AND MAXIMIZING OUTCOME**

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Transplant Section

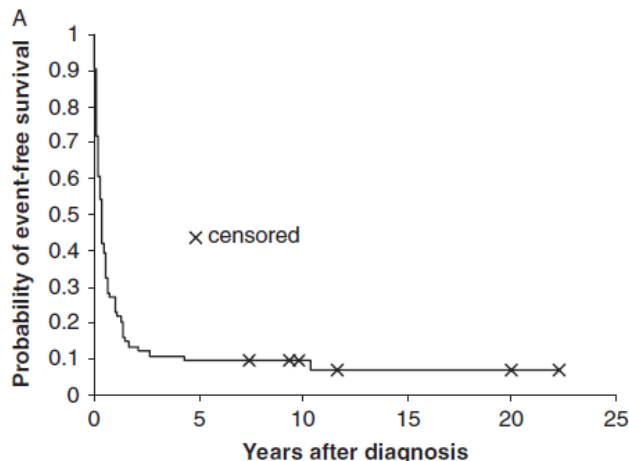


# Disclosures

- Research and/or clinical trial support from Novartis, Servier, Vertex and Kite
- Study steering committees, consulting, or scientific advisory boards: Novartis, Adaptimmune, Eureka, TCR2, Juno, CRC Oncology, Cure Genetics, GlaxoSmithKline, Cellectis, Janssen, Vertex, Roche
- Toxicity management patent managed by U Penn policies

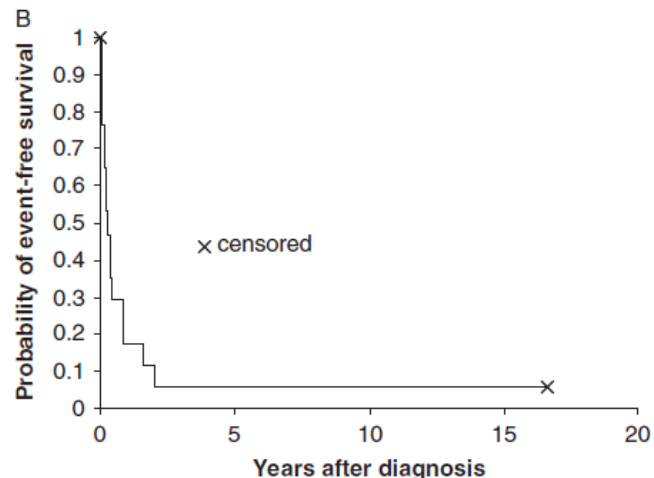
# Why do we need CAR T for ALL?

survival <10%



No. of patients: n=74: 10-year pEFS: 9%±3%

30-40% can obtain another remission

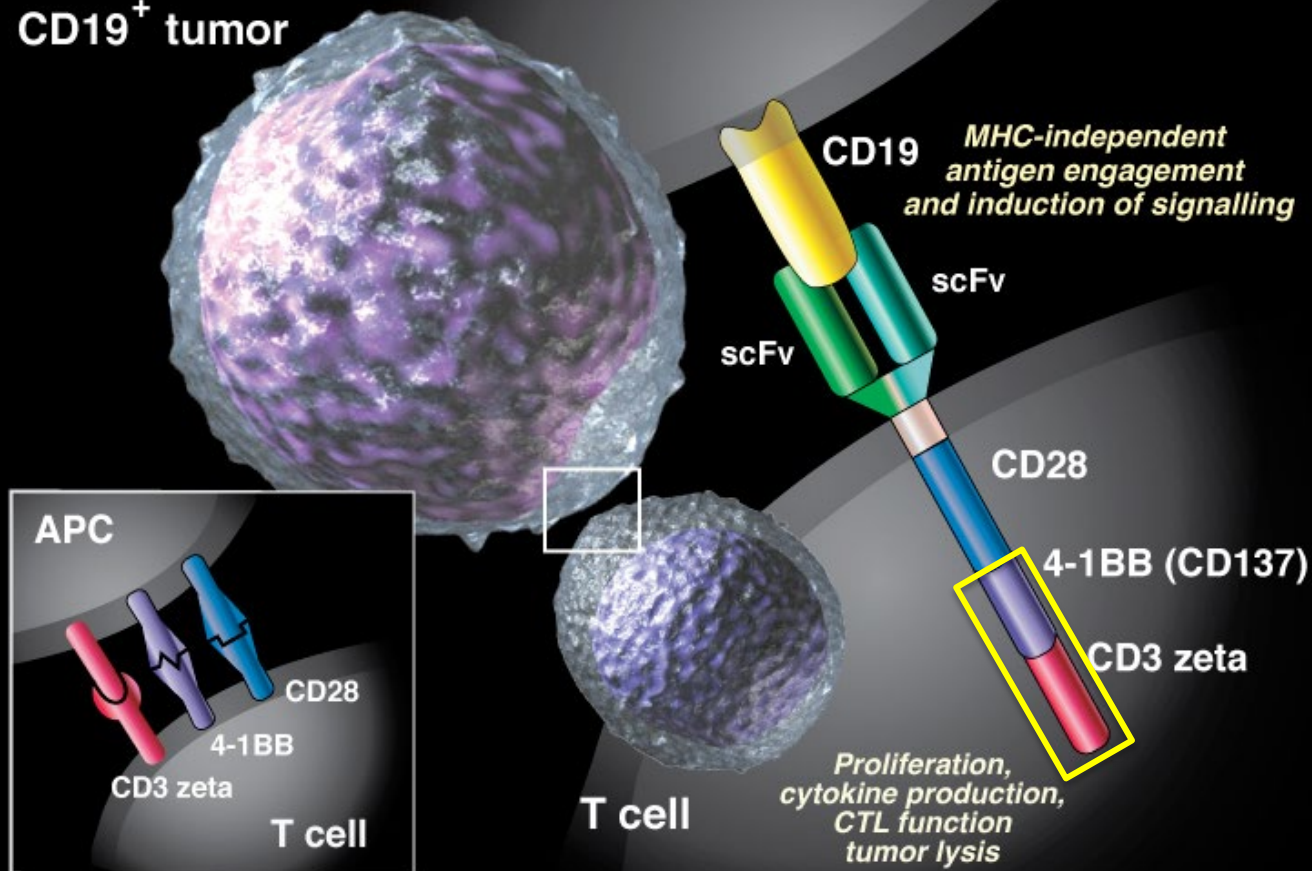


No. of patients: n=18: 10-year pEFS: 6%±6%

**Leukemia is still the #2 cause of pediatric cancer mortality:  
NOVEL THERAPIES ARE NEEDED**

# CHIMERIC ANTIGEN RECEPTOR (CAR)

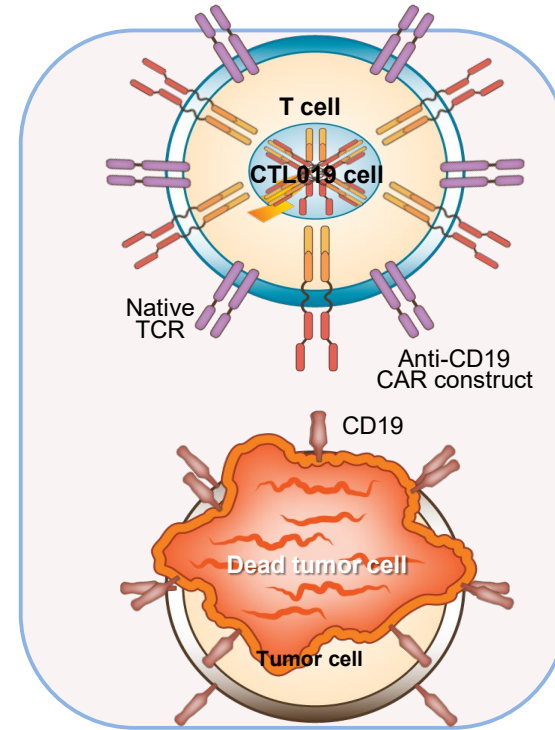
CD19<sup>+</sup> tumor



# Making CAR T cells work

## Goals for modern, highly active cell therapy

- Proliferation: leads to 90%+ complete responses (CHOP studies)
- Persistence: longer term persistence leads to 50-60% long term disease free, and no need for BMT in most
- Length of persistence required is unknown ?? 6mo??



# In the Beginning: CAR-T Cells

Vol. 149, No. 3, 1987  
December 31, 1987

BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS  
Pages 960-968

EXPRESSION OF CHIMERIC RECEPTOR COMPOSED OF IMMUNOGLOBULIN-DERIVED  
V REGIONS AND T-CELL RECEPTOR-DERIVED C REGIONS

Yoshihisa Kuwana<sup>1</sup>, Yoshihiro Asakura<sup>1</sup>, Naoko Utsunomiya<sup>2</sup>,  
Mamoru Nakanishi<sup>2</sup>, Yohji Arata<sup>2</sup>, Seiga Itoh<sup>3</sup>,  
Fumihiko Nagase<sup>4</sup> and Yoshikazu Kurosawa<sup>1\*</sup>

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<sup>3</sup>Tokyo Research Laboratories, Kyowa Hakko Co., Asahimachi,  
Machida, Tokyo, 194

<sup>4</sup>Department of Immunology, Nagoya University School of Medicine,  
Tsurumai, Showa-ku, Nagoya, 466, Japan

*Proc. Natl. Acad. Sci. USA*  
Vol. 86, pp. 10024-10028, December 1989  
Immunology

## Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR\*

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel



ORIGINAL ARTICLE

### Chimeric Antigen Receptor-Modified T Lymphomas

Stephen J. Schuster, M.D., Özlem Anak, M.D., Landsburg, M.D., Mark A. Anderson, M.D., David L. Porter, M.D., and Richard A. Clendinning, M.D. N Engl J Med 2017; 376:245-254

for Adults

Stephan A. Grupp, M.D., Richard Aplenc, M.D., David T. Teachey, M.D., J. Fraser Wright, M.D., Bruce D. Camitta, M.D., and David L. Porter, M.D.

2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

David T. Teachey, M.D., Bruce L. Levine, Ph.D., Can H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

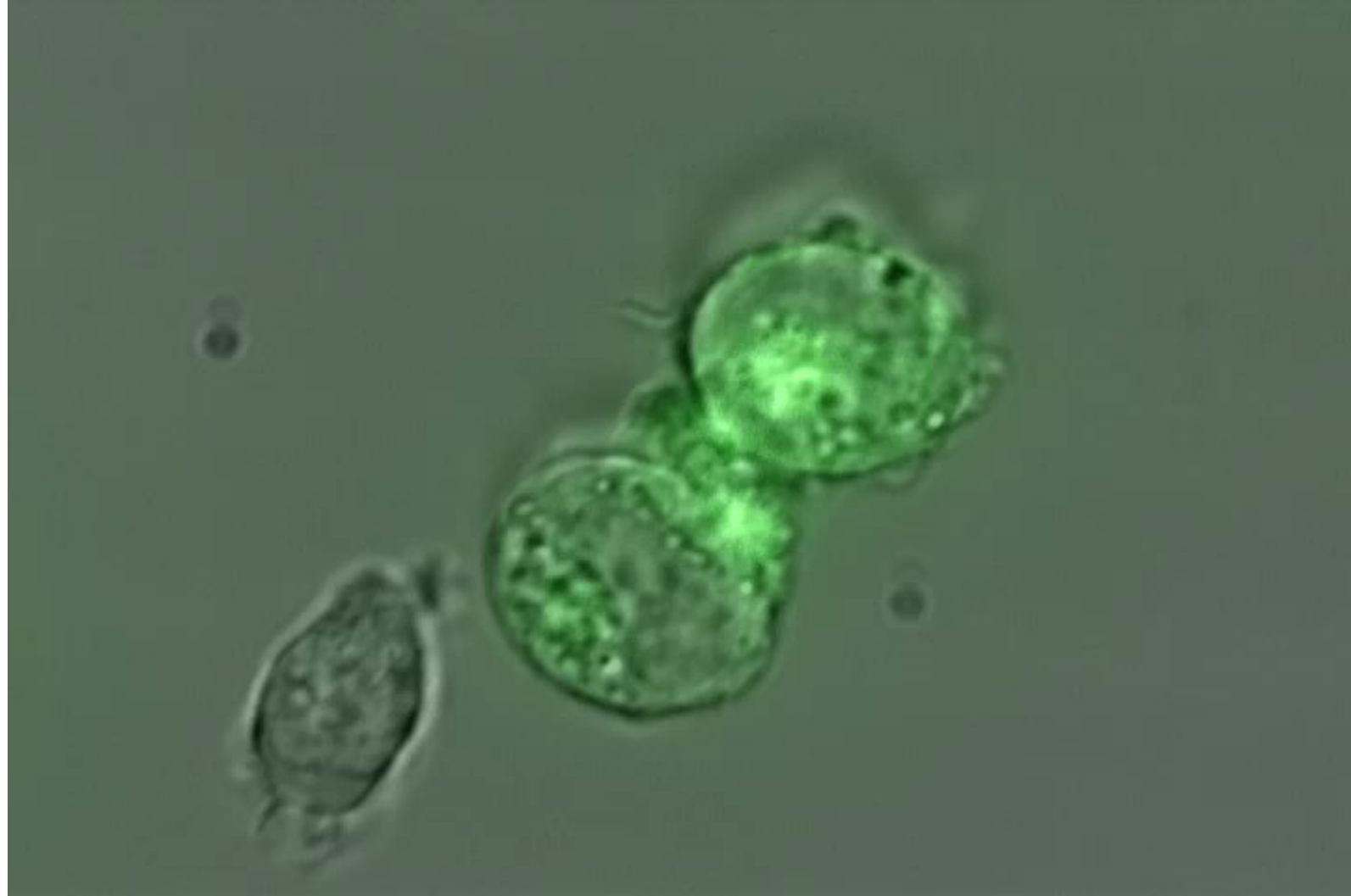
### Modified Hematopoietic Stem Cell Transplantation

for Acute Myeloid Leukemia

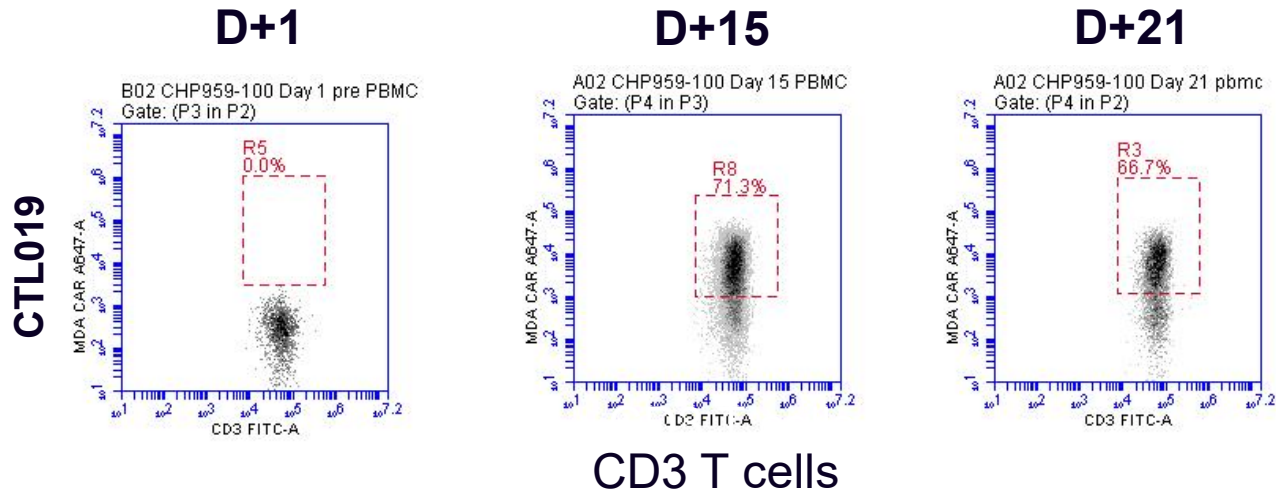
2017

### Refractory Acute Myeloid Leukemia

David T. Teachey, M.D., Bruce L. Levine, Ph.D., Can H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

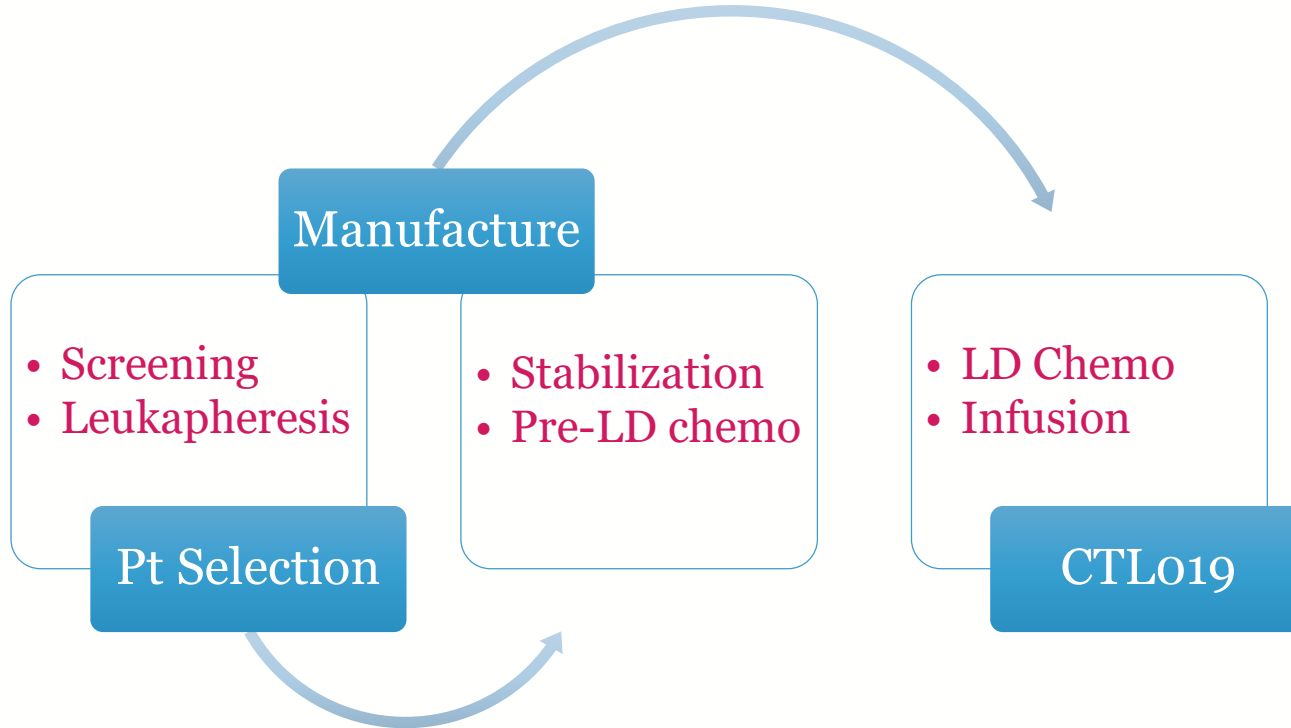


# Proliferation is key to highly active CAR therapy



**Persistence of CTL019 and B cell aplasia  
out to 7 years in responding patients**

# (NOT YOUR TYPICAL) TREATMENT PROCESS

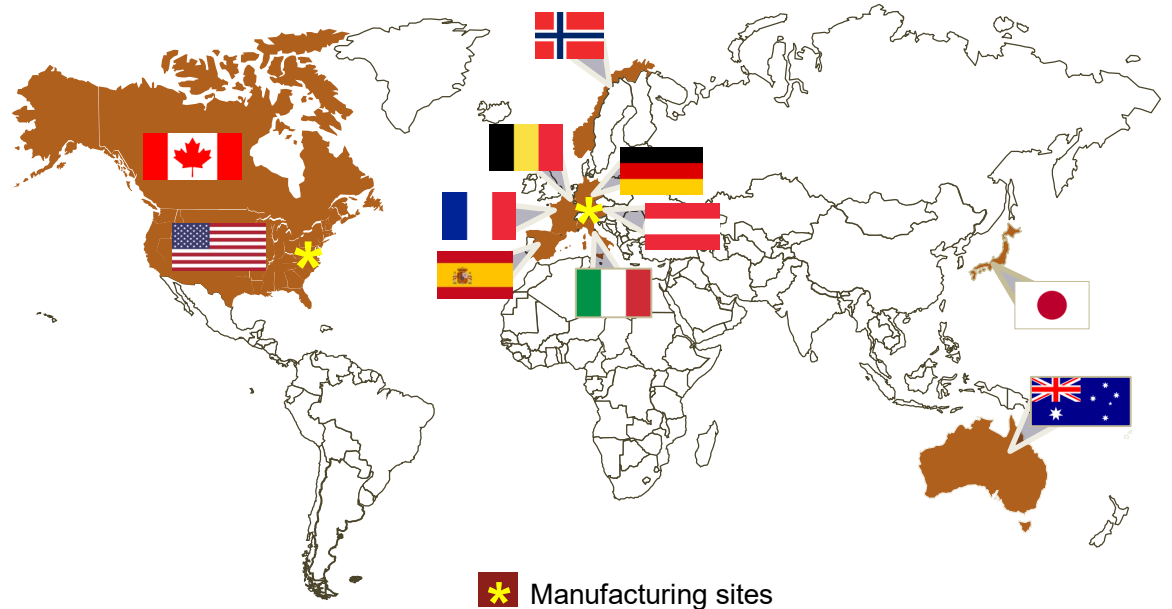


- Leukapheresis: often done ahead of time, can be months
- Pre-LD chemo:
  - goal is NOT remission
  - Keep the lid on
  - Consider not using blina
- Clear CD19 negative population is a contraindication – but hard to assess

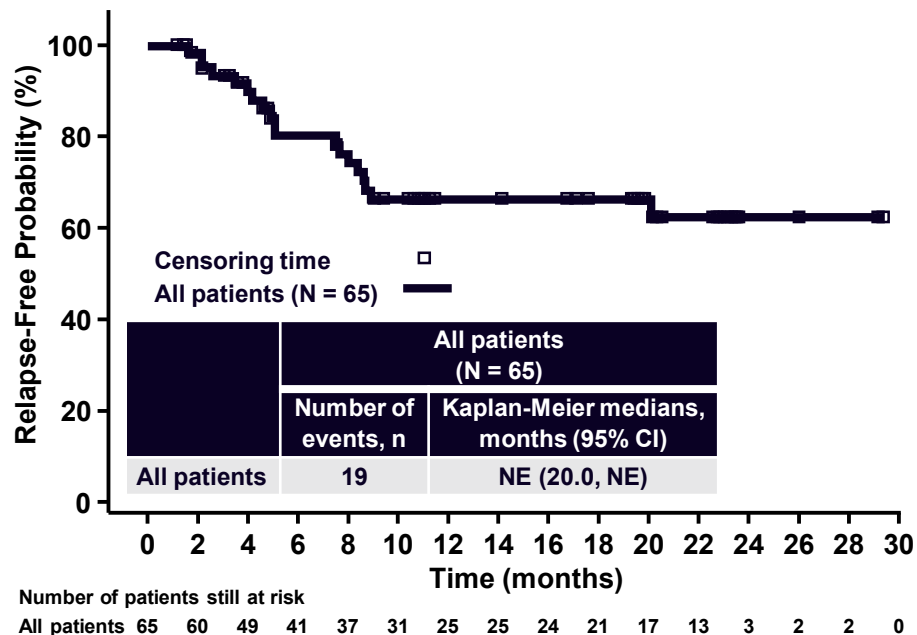
# ELIANA: Pivotal Phase 2 Study

**ELIANA is the first global, multicenter trial of CAR T cell therapy**

- Tisagenlecleucel (CTL019) produced at a central manufacturing site with global distribution
- 25 sites across 11 countries in North America, Europe, and Asia-Pacific



# High Response Rate; Median Duration of Remission Not Reached



- CR + CRi (within 3 months) 82% (65/79 infused; 95% CI, 72-90)<sup>a,b</sup>
- 98% (64/65) MRD(-)
- RFS among responders
  - 12-month: 66% (95% CI, 52-77)
  - 18-month: 66% (95% CI, 52-77)
  - 24-month: 62% (95% CI, 47-75)
- OS among all infused patients
  - 12-month: 76% (95% CI, 65-85)
  - 18-month: 70% (95% CI, 58-79)
  - 24-month: 66% (95% CI, 54-76)

Note: Only patients who achieved CR or CRi were included. Time is relative to onset of remission.

<sup>a</sup> The response was unknown in 6 patients.

<sup>b</sup> While in remission, 8 patients went on to stem-cell transplantation.

<sup>c</sup> MRD negative = MRD < 0.01%, as assessed by flow cytometry.

CR, complete remission; CRi, complete remission with incomplete blood count recovery

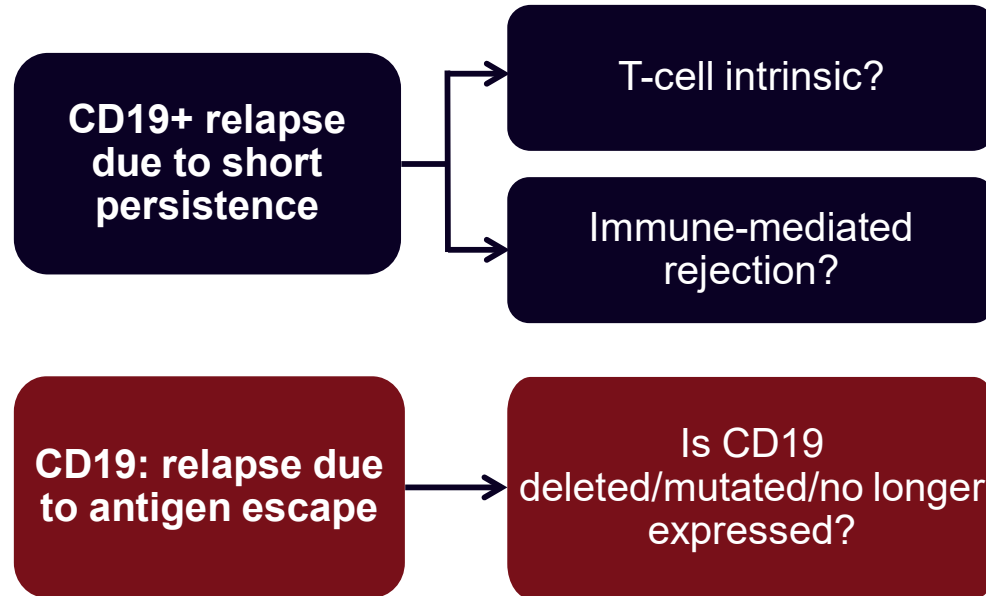
# Characteristics of Remission and Relapse

- Relapses tended to occur early (within the first year)
- The majority of relapses were CD19-negative:

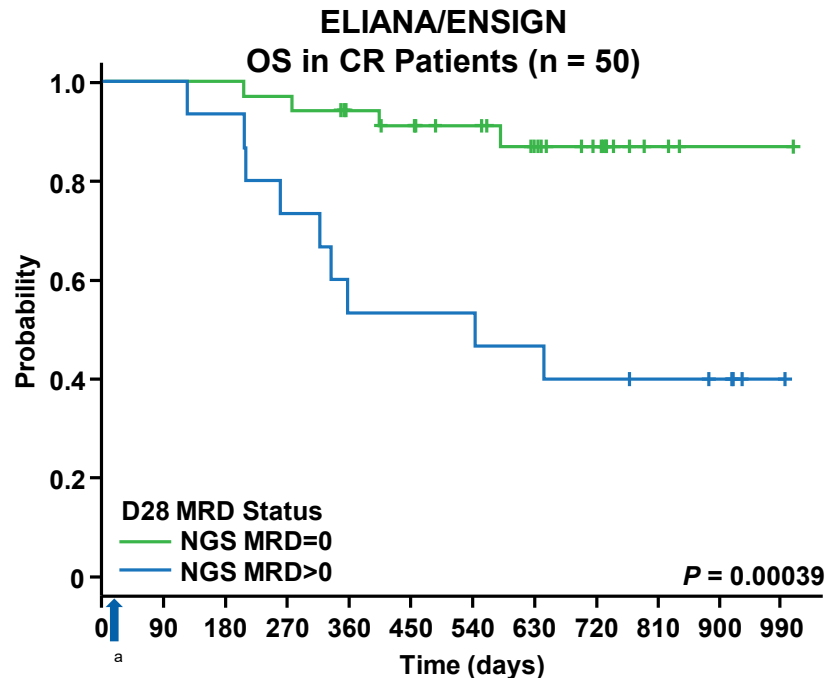
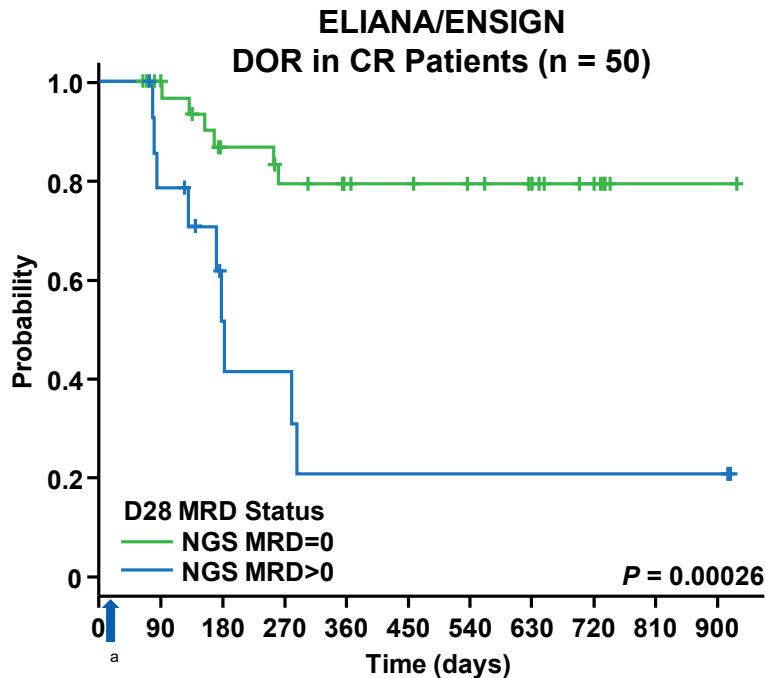
CD19-Negative	CD19-Positive	Unknown CD19 Status
14/19 (73.7% of relapses)	3/19 (15.8% of relapses)	2/19 (10.5% of relapses)

- All CD19-negative relapses occurred in the context of persistent B-cell aplasia
- One CR patient with B-cell recovery at 12 months is still in ongoing CR for 27 months at the time of data cut-off

# Mechanisms of Relapse



# Patients With No MRD Detected in D28 Bone Marrow by NGS Had Superior Outcomes



<sup>a</sup> Tisagenlecleucel infusion at Day = 1.  
CR, complete remission; DOR, duration of response;  
MRD, minimal residual disease; NGS, next-generation  
sequencing.

# Toxicity reporting in the commercial setting

- Large effect sizes have meant that CAR T indications are FDA approved on <100 patients
- Further data collection is paramount
- Data will not be collected in a research setting with research budgets and direct regulatory mandates on the centers
- Excessive, inconsistent, or conflicting data requests from companies or health authorities in the commercial setting may interfere with getting necessary data  
#Askforeverythinggetnothing

# Toxicity reporting in the commercial setting

- Large reporting mandates (all grade 4 and especially grade 3 tox, grade 1 or 2 CRS) will bury the signal in noise and are not feasible
- A registry approach is likely to be the best method of providing consistency and as complete data as possible.
- CIBMTR reporting should achieve this

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FDA News Release

# FDA approval brings first gene therapy to the United States

*CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia*

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**For Immediate  
Release**

August 30, 2017

Global access:

approved in the EU, UK, Canada in addition to US

- Kymriah (Novartis) for pediatric/young adult ALL
- Kymriah (Novartis) for DLBCL
- Yescarta (Kite/Gilead) for DLBCL

## Global access:

approved in the EU, UK, Canada in addition to US plus Australia (Kymriah only) and Japan

- Kymriah (Novartis) for pediatric/young adult ALL
- Kymriah (Novartis) for DLBCL
- Yescarta (Kite/Gilead) for DLBCL

# Indications for BMT for ALL patients we treat

- Plan for BMT all along
- MRD+ at D28 (rare)
- Early B cell recovery (<6 mo):  
BMT vs. reinfusion
- 2<sup>nd</sup> post-CAR remission
- ??? MLL rearranged?  
Concern for lineage switch

# What are the current labeled indications for Kymriah?

ALL up to age 25  
(CHOP treats to 29, but not w/ commercial product)

- Refractory, second relapse OR post-SCT relapse

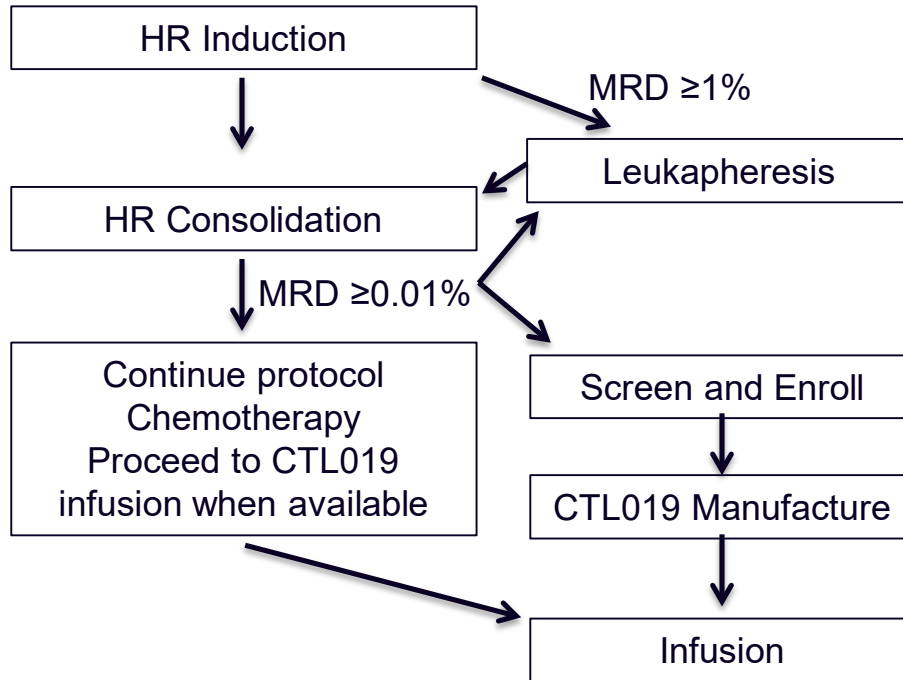
Other key points:

- Patients do not need to be in remission
- No donor is required
- Contraindications:
  - Rapidly progressing refractory disease
  - Active infection
  - Inadequate organ function suggesting inability to tolerate CRS (risk adjusted)



# AALL1721 Trial Design

## de novo NCI HR B-ALL



# Opportunities for improvement

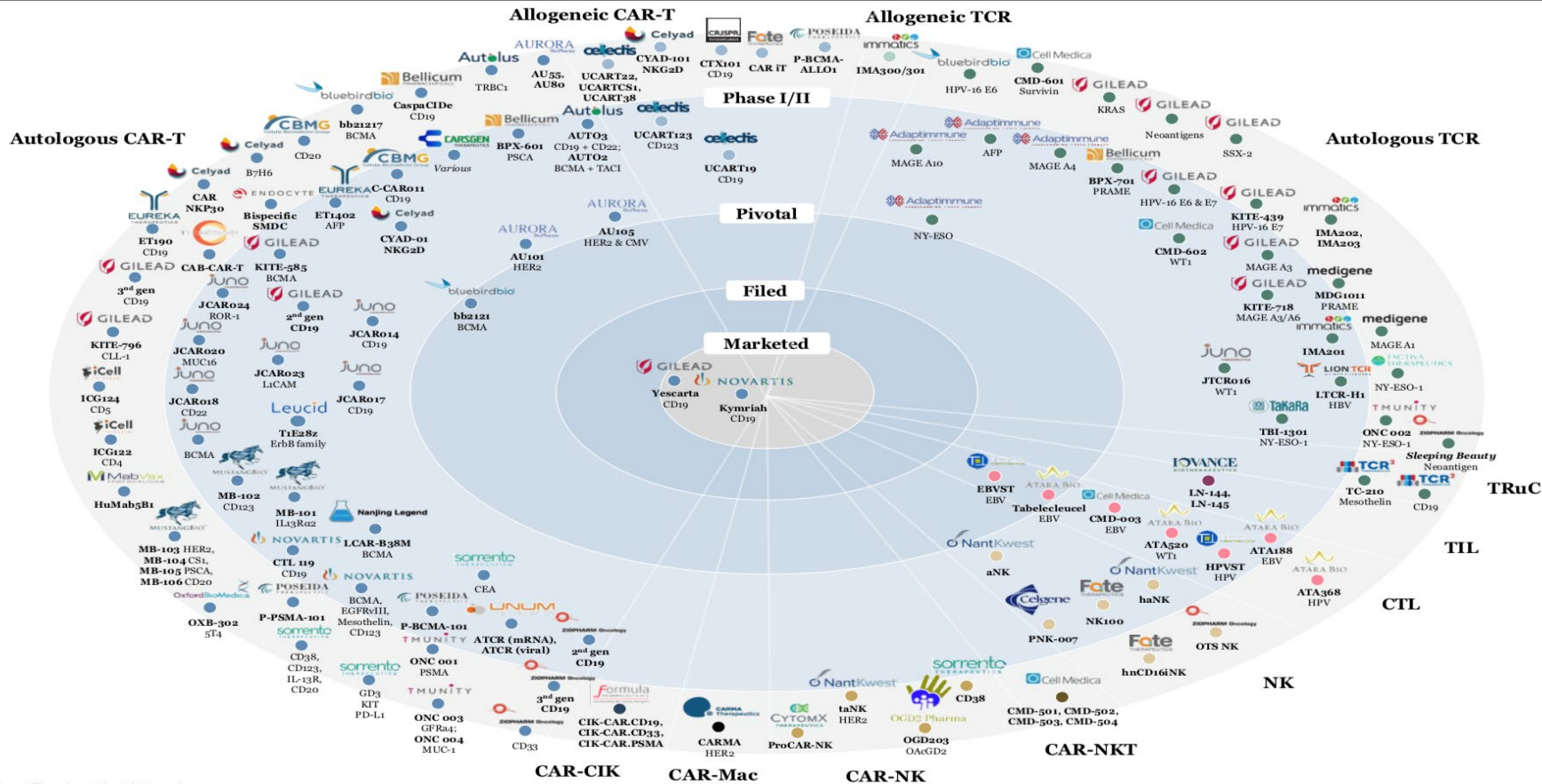
- Cost
- Manufacturing is first generation. There are HUGE opportunities for better process – speed, success rates, cost of goods, automation
- Release criteria
- We don't have a potency assay that predicts in vivo performance

# Opportunities for improvement

- Cost
- Manufacturing is first generation. There are HUGE opportunities for better process – speed, success rates, cost of goods, automation
- Release criteria
- We don't have a potency assay that predicts in vivo performance
- You can give CAR T cells in the clinic

# Rapidly Evolving CAR-T Landscape

## Adoptive Cellular Therapy Immuno-Oncology Landscape



# Penn/CHOP/NVS Cell Therapy

## Penn/ACC TRP

### **Carl June**

Anne Chew  
Amy Marshall  
Whitney Gladney  
Michael Milone  
Yangbing Zhao  
Elizabeth Veloso  
Dana Hammill  
**Pam Shaw**

## **CHOP Cell Therapy Lab**

### **David Barrett**

### **David Teachey**

Alix Seif  
Sarah Tasian  
Junior Hall  
Jessica Perazzelli  
Terri Ryan  
Jessica Lee

## CVPF

### **Bruce Levine**

### **Don Siegel**

## U Penn Clinical

David Porter  
Noelle Frey  
Elizabeth Hexner

## CHOP Clinical/Study Staff

### **Shannon Maude**

Richard Aplenc  
Sue Rheingold  
Colleen Callahan  
Amanda Dinofia  
Lisa Wray  
Diane Baniewicz  
Amy Barry  
Mark Duckworth  
Claire White  
Cate Girone  
Laura Motley  
Amazing CRC staff

## TCSL

### **Simon Lacey**

Jos Melenhorst  
Minnal Gupta  
Irina Kulikovskaya  
Jeff Finklestein  
Farzana Nazimuddin  
Vanessa Gonzalez

## Novartis Colleagues

## CHOP Stem Cell Lab

Yongping Wang  
Stephan Kaudake

## CHOP PICU

## Thomas-Tikhonenko

## Lab

## Adaptive TcR

**Patients and  
Families**

