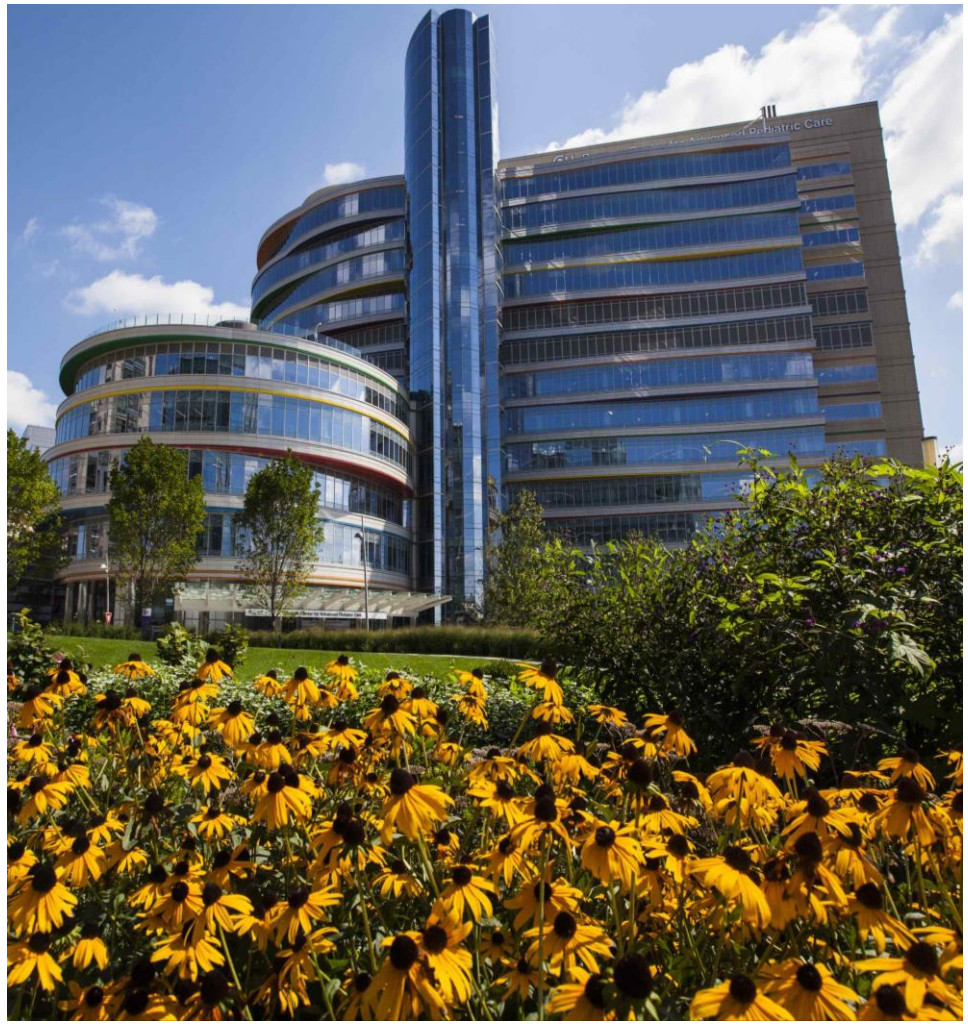
The Children's Hospital of Philadelphia®



The CAR T Cell Revolution in Leukemia – Reverse Engineering Exceptional Patient Responses

Stephan Grupp MD, PhD

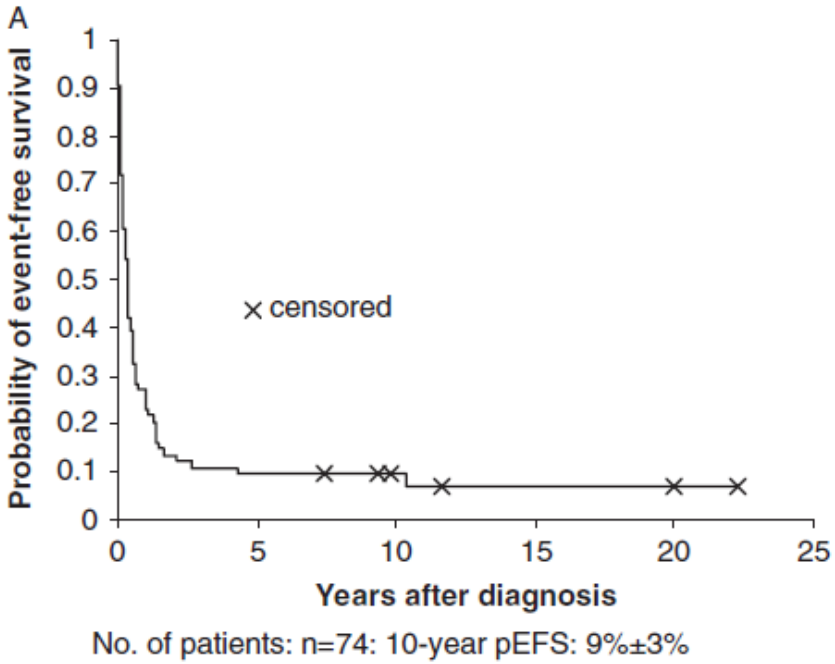
Director, Cancer Immunotherapy Frontier Program
Chief, Cell Therapy and Transplant Section

Perelman School of Medicine
University of Pennsylvania

cancer immunotherapy FRONTIER PROGRAM

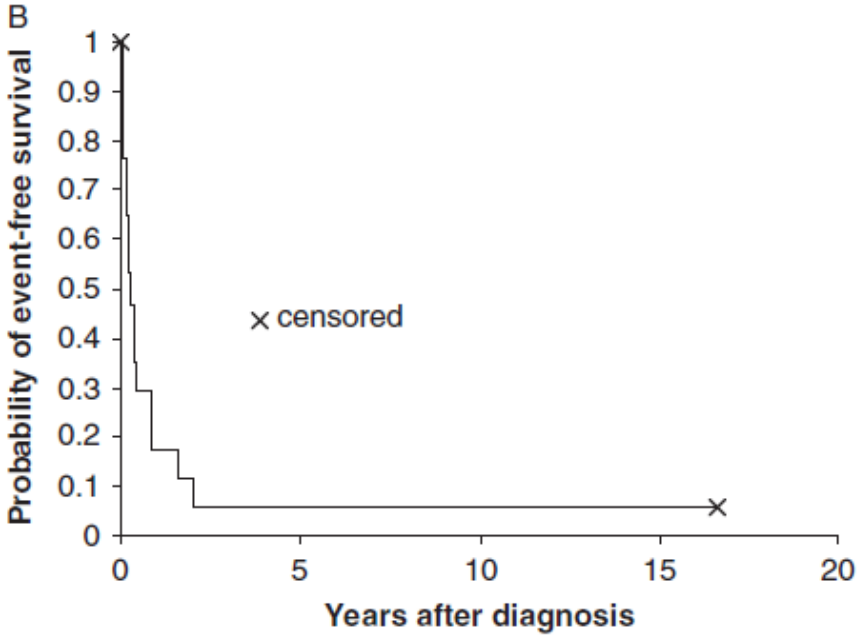
Dismal Outcome for 2nd+ Relapse of ALL

10 year EFS



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 (CNS #1) of pediatric cancer mortality: NOVEL THERAPIES ARE NEEDED

Resimuller et al. JPHO 2013

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 RESIONS AND T-CELL RECEPTOR-DERIVED C REGIONS

Yoshihisa Kuwana[1], Yoshihiro Asakura[1,2], Naoko Utsunomiya[2], Mamoru Nakanishi[2], Yohji Arata[2], Seiga Itoh[3], Fumihiko Nagase[4] and Yoshikazu Kurosawa[1*]

[1]Institute for Comprehensive Medical Science, Fujita-Gakuen Health University, Toyoake, Aichi, 470-11
[2]Faculty of Pharmaceutical Science, University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113
[3]Tokyo Research Laboratories, Kyowa Hakko Co., Asahimachi, Machida, Tokyo, 194
[4]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

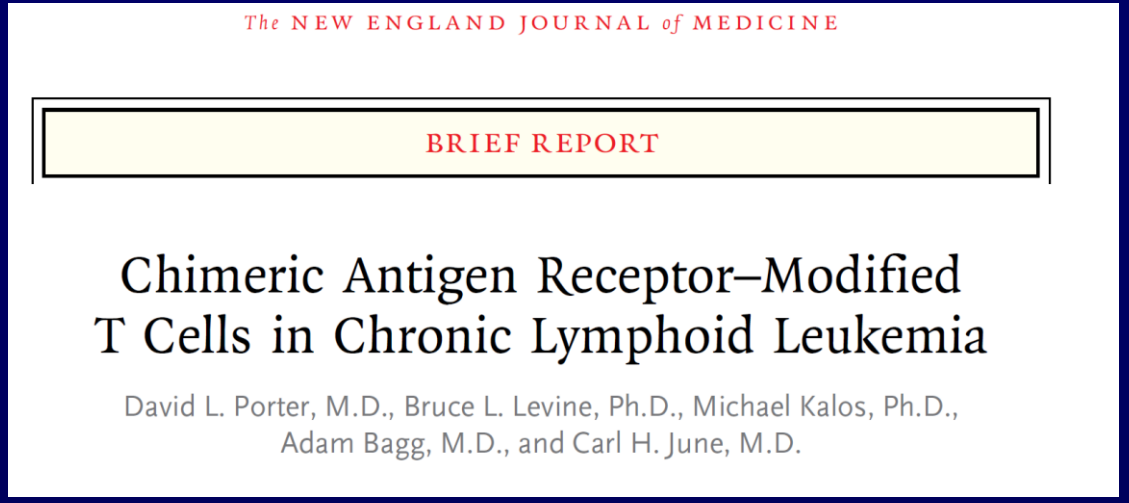
Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

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

2011



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.

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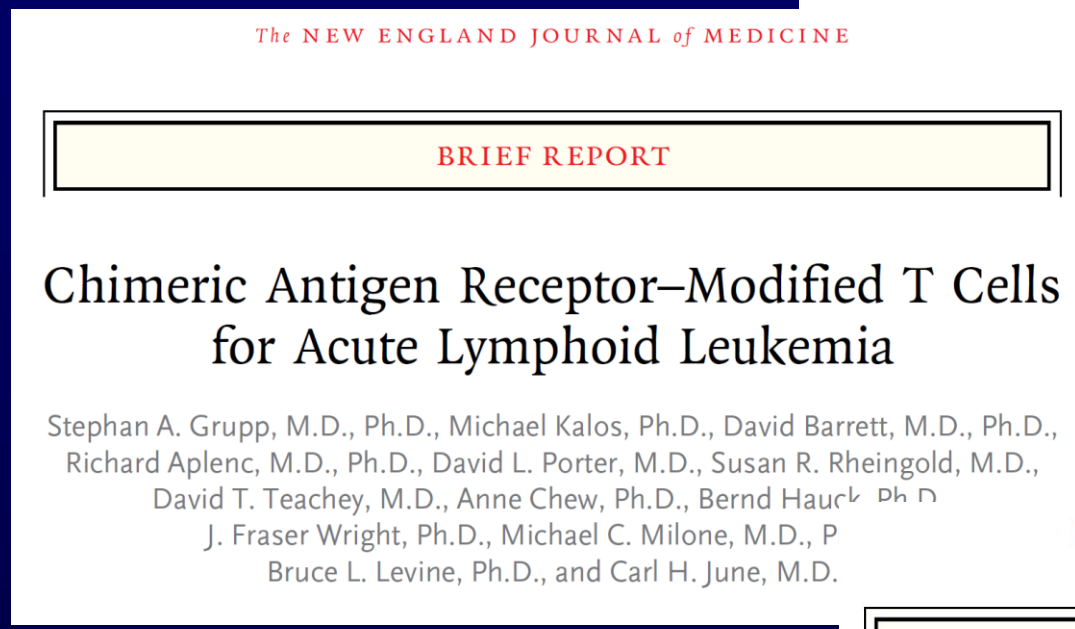
ic Antigen Receptor–Modified n Chronic Lymphoid Leukemia

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

2013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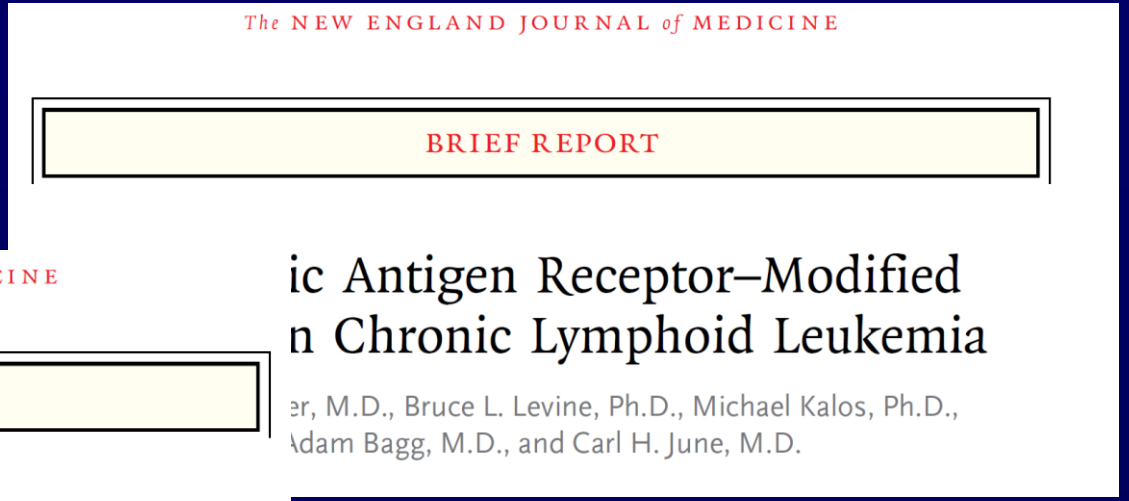
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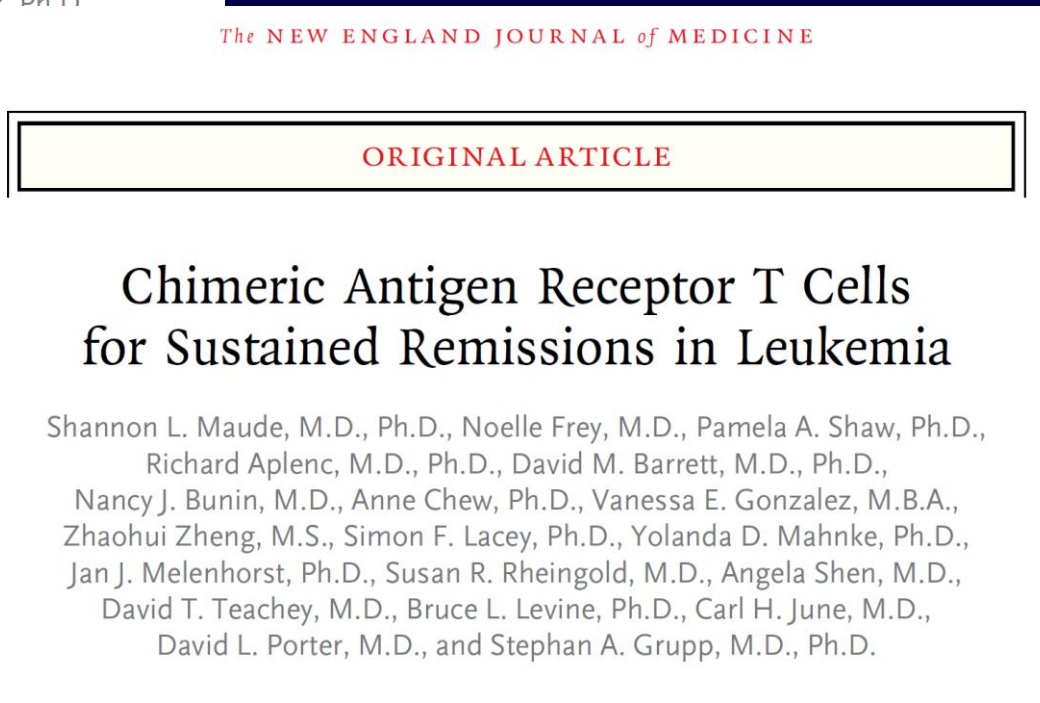
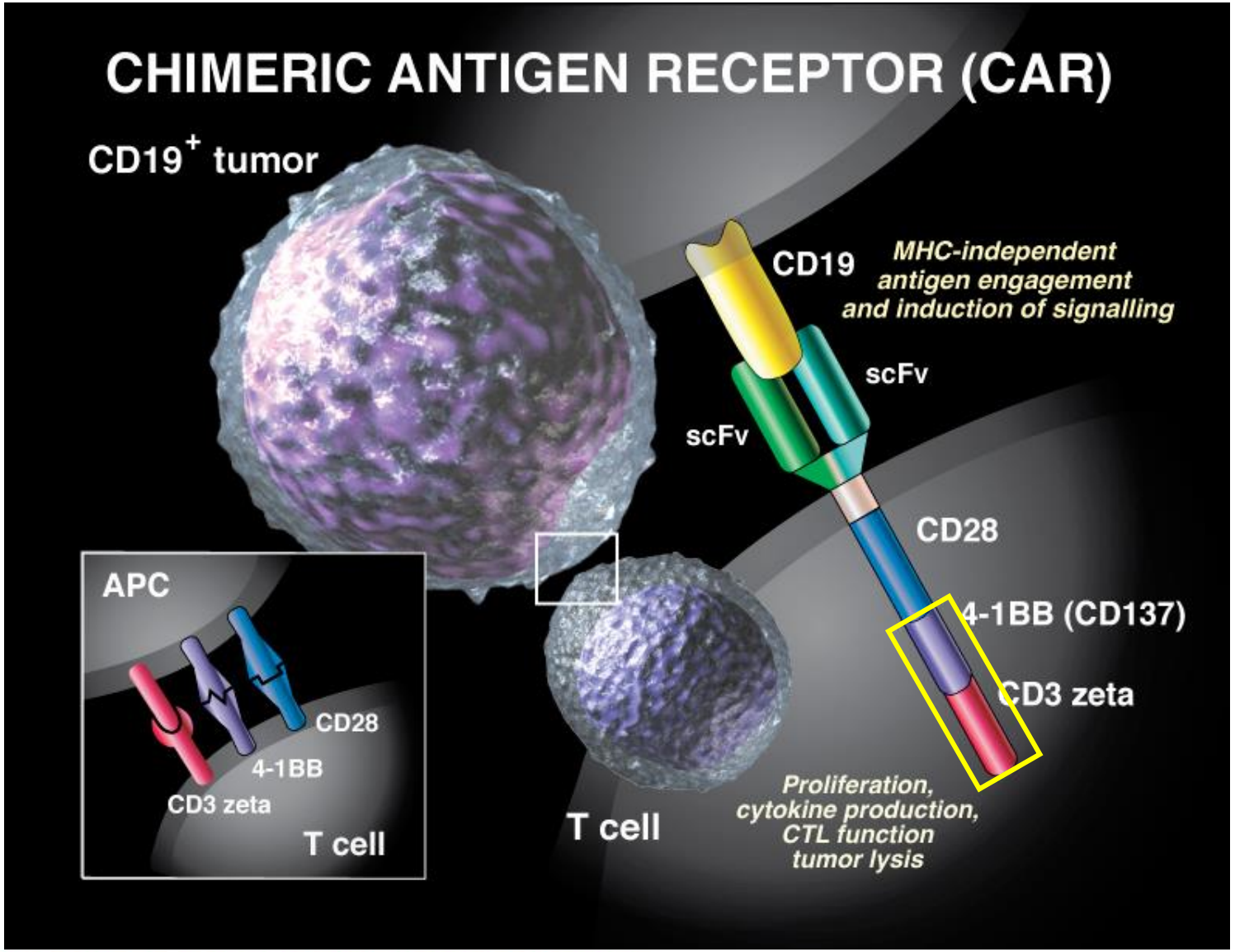

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia
Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D.,
Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D.,
Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa 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.

2014

CART19: Chimeric Antigen Receptor T cells against CD19

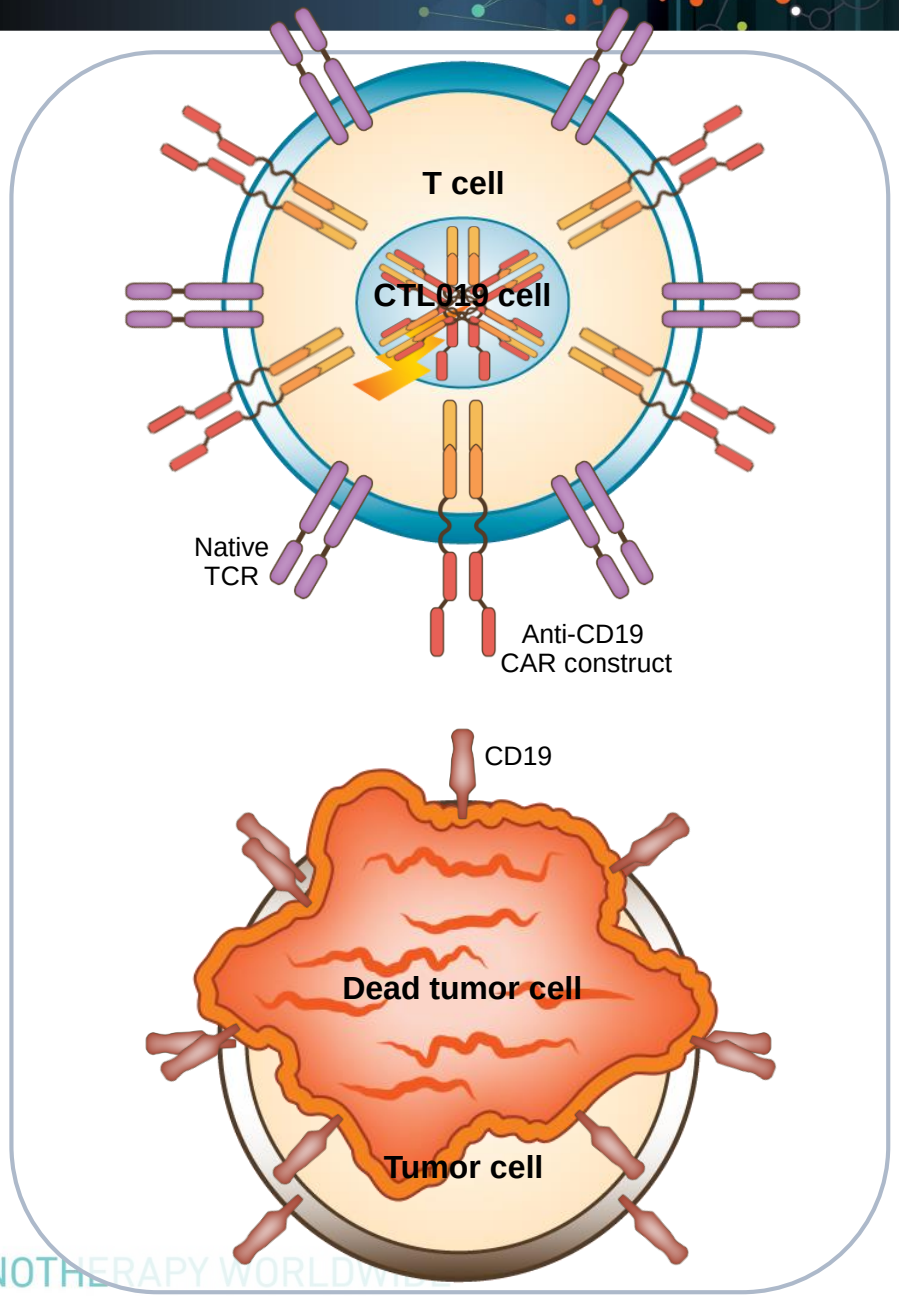


Redirecting T cell Specificity in CTL019 cells

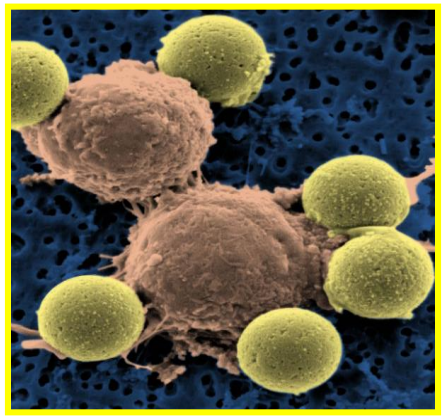
Goals for modern, highly active cell therapy:

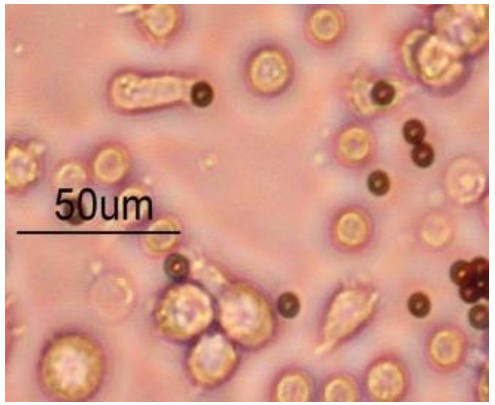
- Proliferation – high level of in vivo proliferation correlates with high response rates
- Persistence – longer term persistence may allow longer term disease control.

Length of persistence needed for long-term disease control is unknown

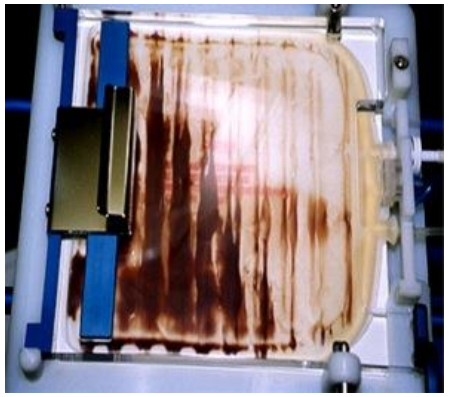


Cell manufacturing matters





Bead addition

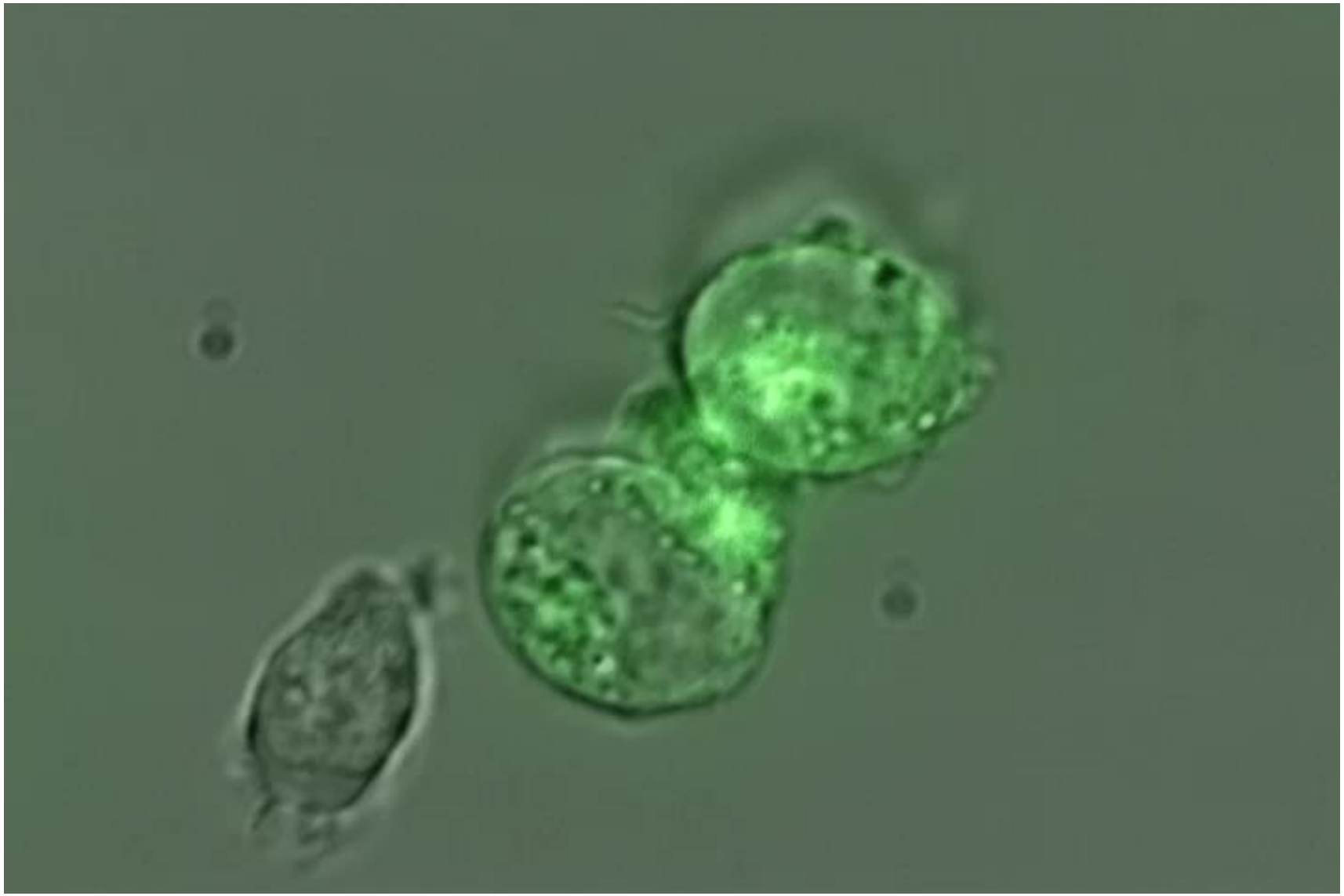


Bead removal

T-cell infusion

- **CD3/CD28 beads: clinical scale up, no feeder cells required**
- **Expansion >10^6-fold**
- **Repertoire preserved**
- **Maintains earlier T cell memory states**
- **Induction of telomerase: minimize replicative senescence**

Levine BL, et al. *J Immunol.* 1997; 159: 5921-5930.
Carroll RG, et al. *Science.* 1997; 276: 273-276.
Weng NP, et al. *Immunol. Rev.* 1997; 160: 43-54.
Humeau LM, et al. *Mol. Ther.* 2004; 9; 902-913.

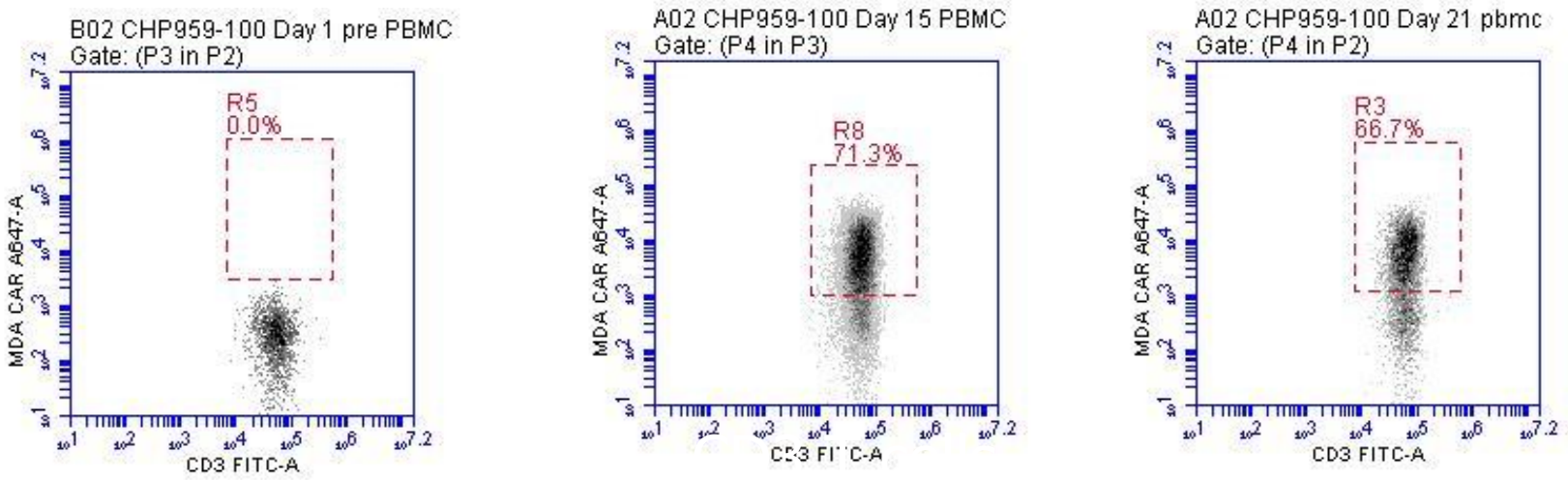


Credit to Mike MIlone

Proliferation is key to highly active CAR therapy

D+1 **D+15** **D+21**

CTL019



CD3 T cells

Persistence of CTL019 and B cell aplasia out to 5 years in responding patients

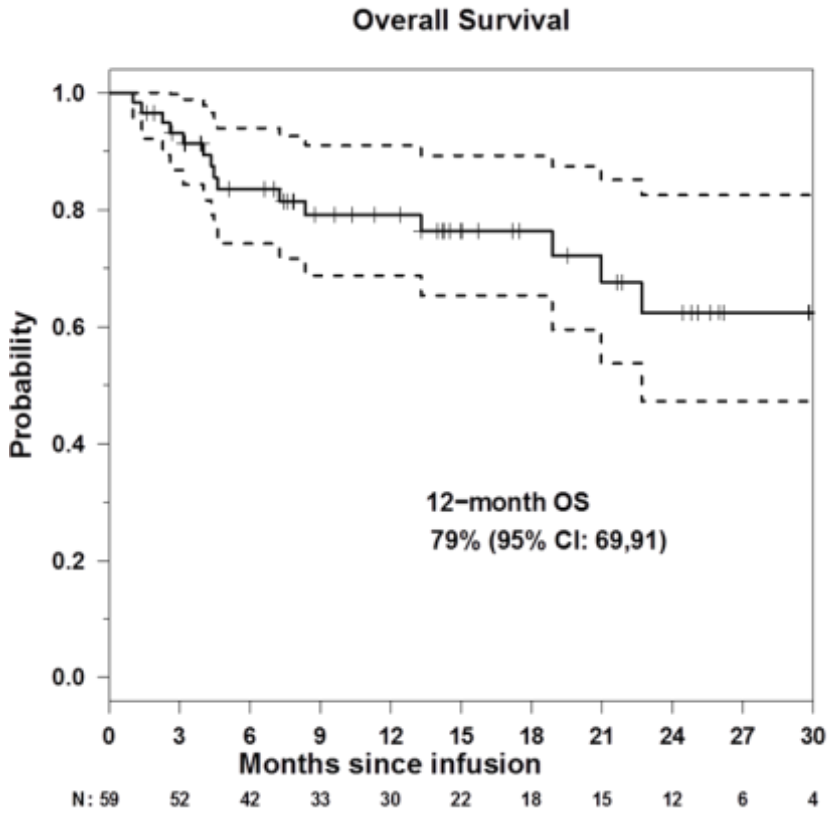
CD19 CAR CTL019 in relapsed/refractory pediatric ALL: 93% complete response rate

Results presented at ASH 2015

- CR in 55 of 59 patients (93%) at 1 month; median follow-up of 12 months
- 6 patients went to subsequent transplant, 1 to DLI
- 12 month OS: 79% (95% CI: 69, 91)

- Relapse-free survival (RFS)
  - 6 month RFS: 76% (95% CI: 65,89)
  - 12 month RFS: 55% (95% CI: 42,73)

- No relapses past 1 year
- 18 patients in remission beyond 1 year, 13 without further therapy



Kaplan-Meier survival curve of OS with number (N) of patients at risk at each time point indicated below x-axis.

- Humanized CTL119 – 22/22 CR in same population, early F/U

CTL019 impact on CNS disease

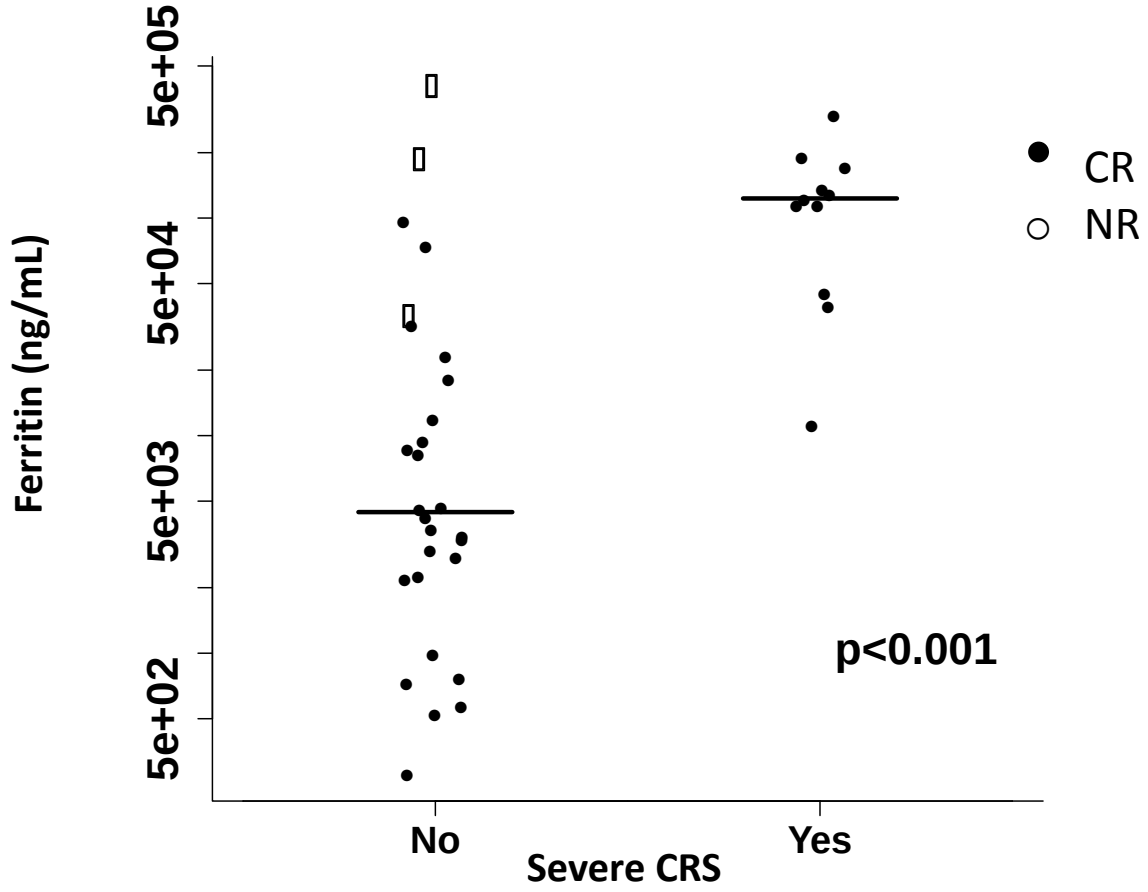
- 12 patients w/ prior CNS3 status
- These pts ranged from 1st to 6th relapse pre-CTL019
  - 1st CNS relapse=1, 2nd= 6, 3rd= 3, 4+= 2
- 4 pts were CNS2 on d-1, all CNS 1 on D28
- 0 CNS relapses
- 1 pt with Ph+ disease and 6 prior CNS relapses remains in CR at 2.5 years
- 98% of all pts have CTL019 in CSF
- 9/9 pts in CR at 1 yr have CTL019 in CSF (2177 to 15,727 copies/ug genomic DNA)

Cytokine Release Syndrome (CRS) in Pediatric r/r ALL

- Infusion is the easy part –
  can routinely be done outpatient
- CRS is a reversible, on-target toxicity
- High fever, myalgias
- Fever is the first event
- Severe CRS – unstable hypotension, can proceed to need for mechanical ventilation

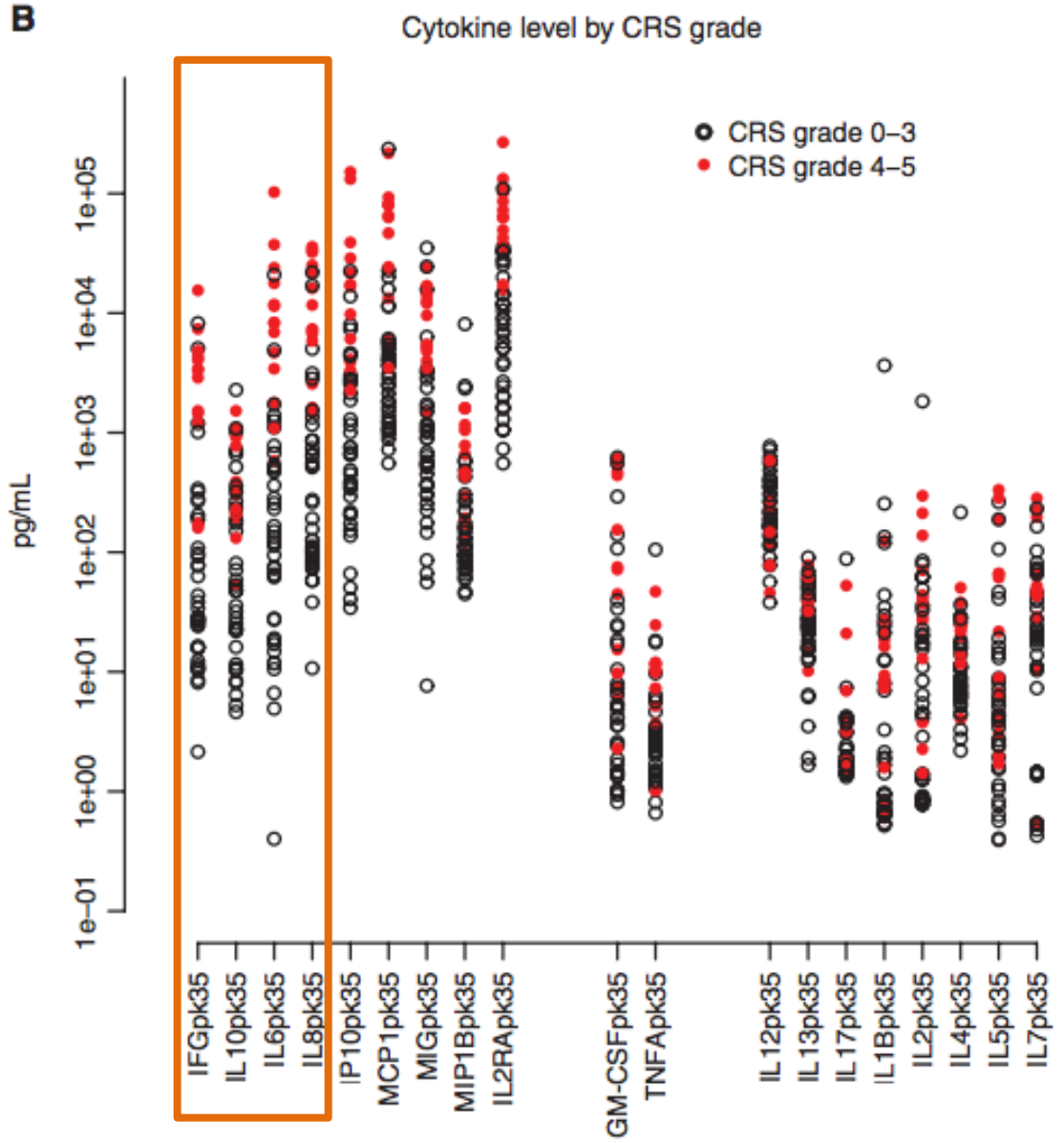
CRS:
high ferritins suggest Macrophage Activation Syndrome

CRS & MAS overlap



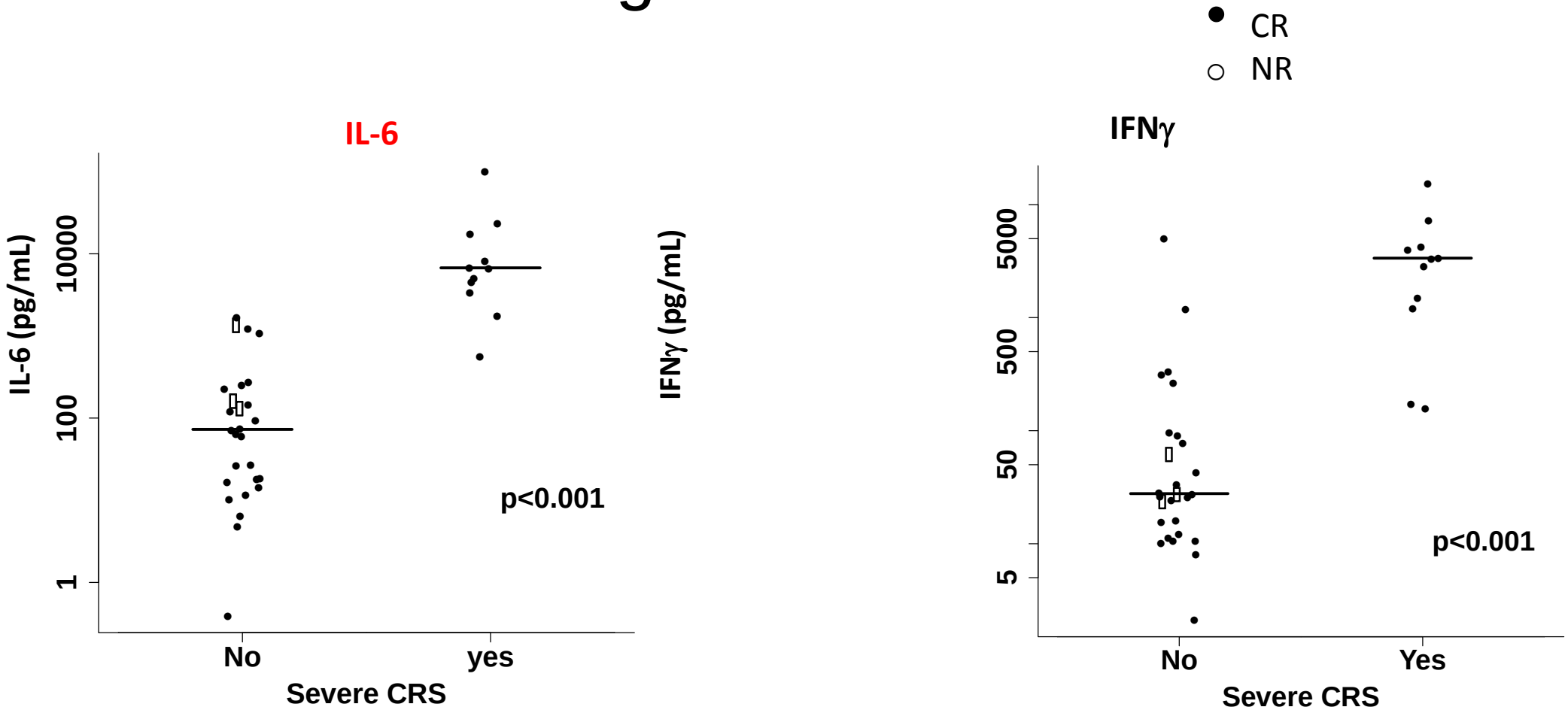
Maude et al, NEJM 2014

Cytokine profiles in CRS patients match patterns seen in MAS/HLH patients



Teachey, et al., *Cancer Discovery,* 2016

CRS associated with IFN-g and IL-6

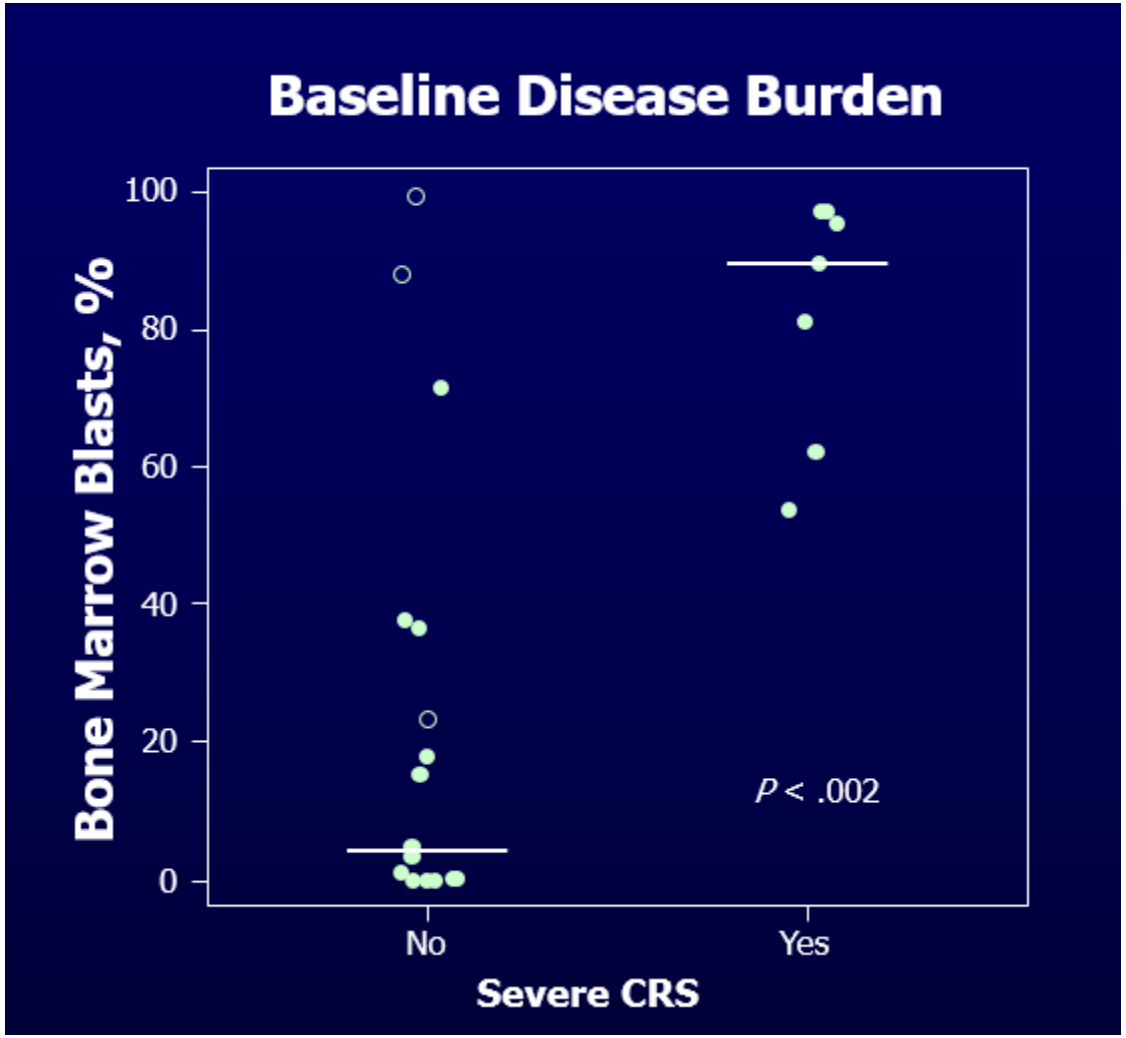


Maude et al, NEJM 2014

Tocilizumab (Actemra)

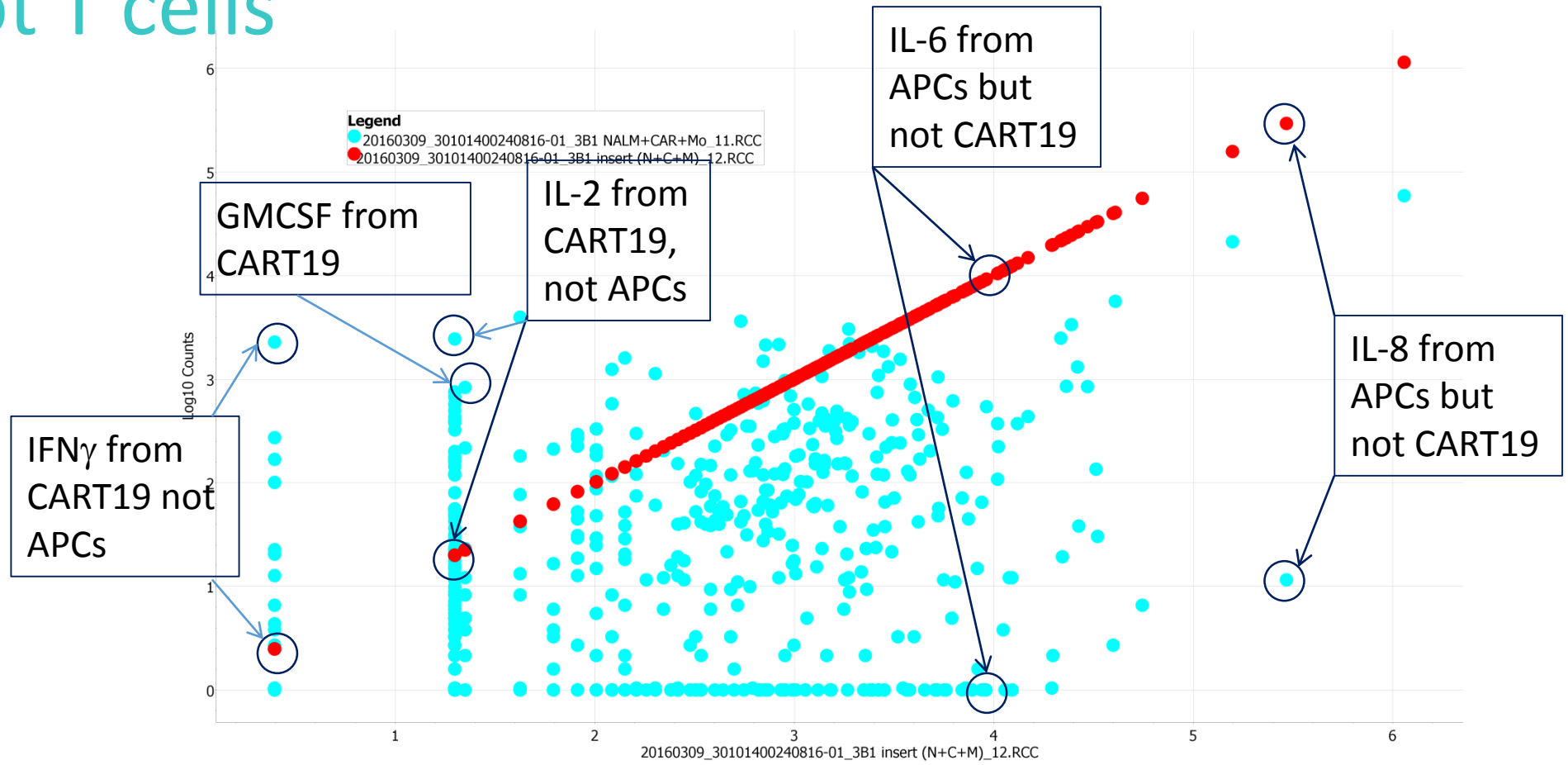
- **IL-6 receptor antagonist**
- **Blocks IL-6 mediated effects**
- **Indicated in:**
  - **juvenile idiopathic arthritis (JIA)**
  - **Rheumatoid arthritis (RA)**
  - **In Japan, indication for Castleman's Disease**
- **Given once or twice for CRS**
- **Rare side effects of transaminitis and neutropenia**
- **Now indicated for CRS treatment**

Disease Burden is Highly Predictive of Severe CRS

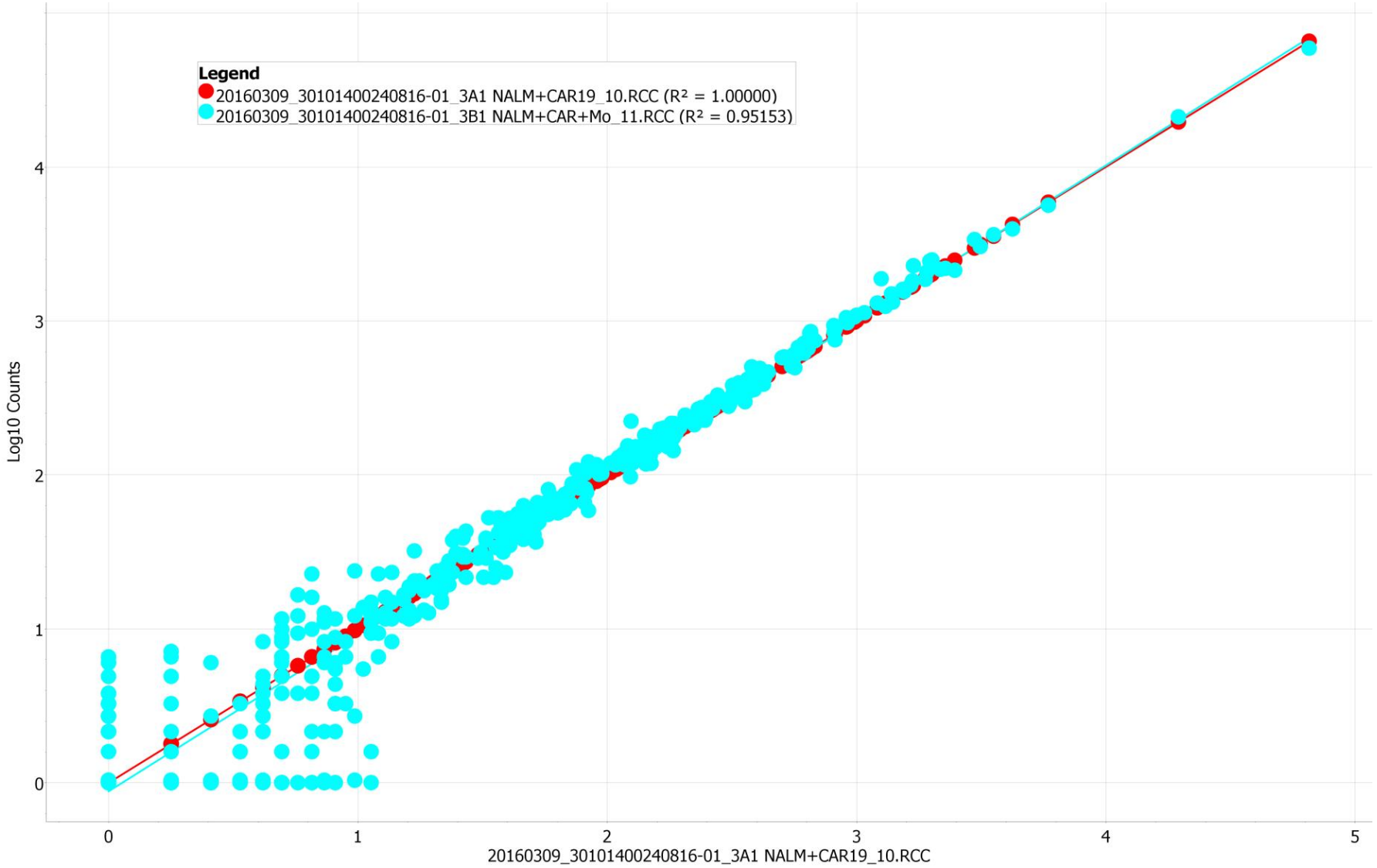


Maude et al. NEJM 2014

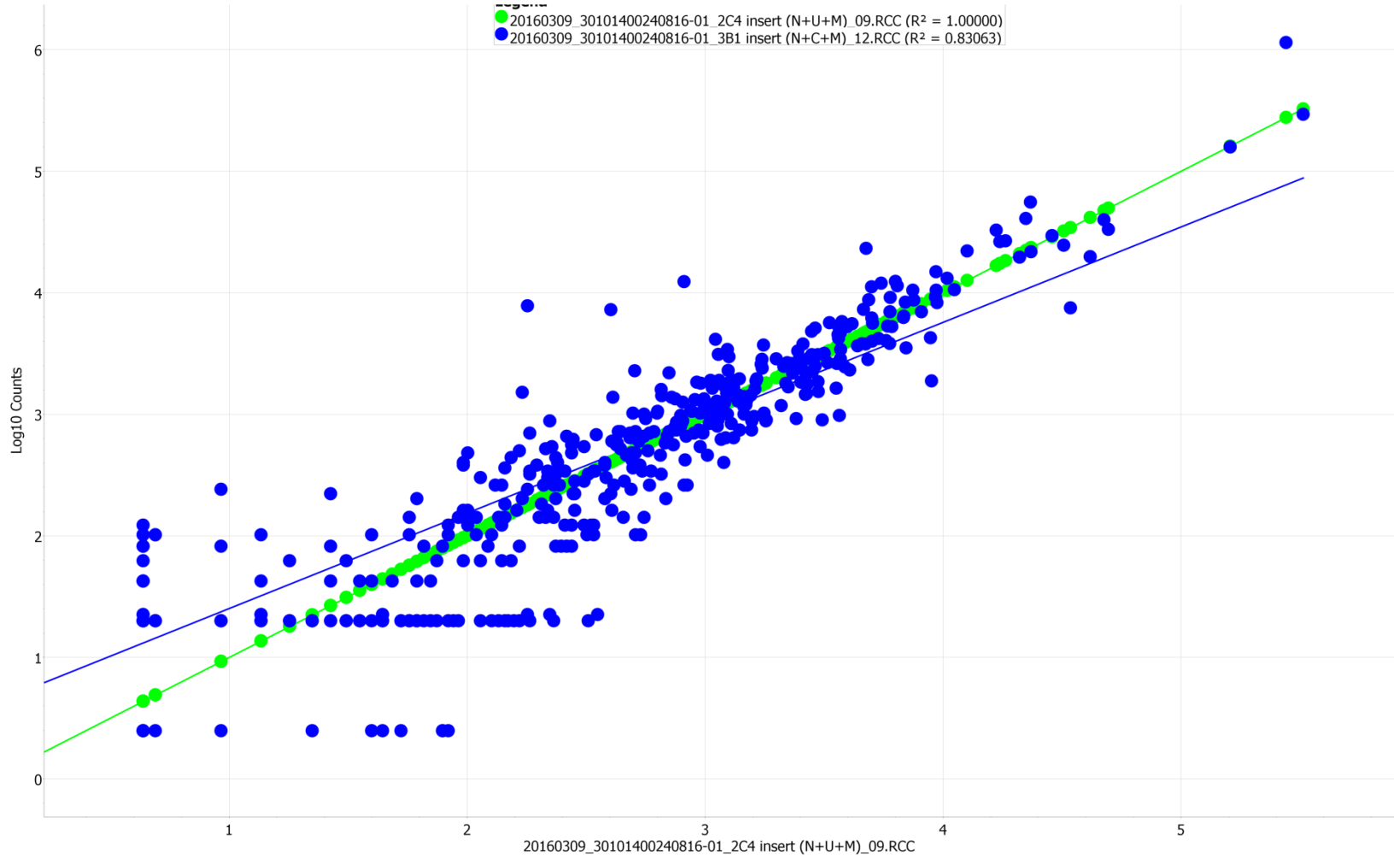
IL-6 and IL-8 are produced exclusively by APCs and not T cells



CART19 Nanostring: CART cell expression profile unaffected by proximity to APCs



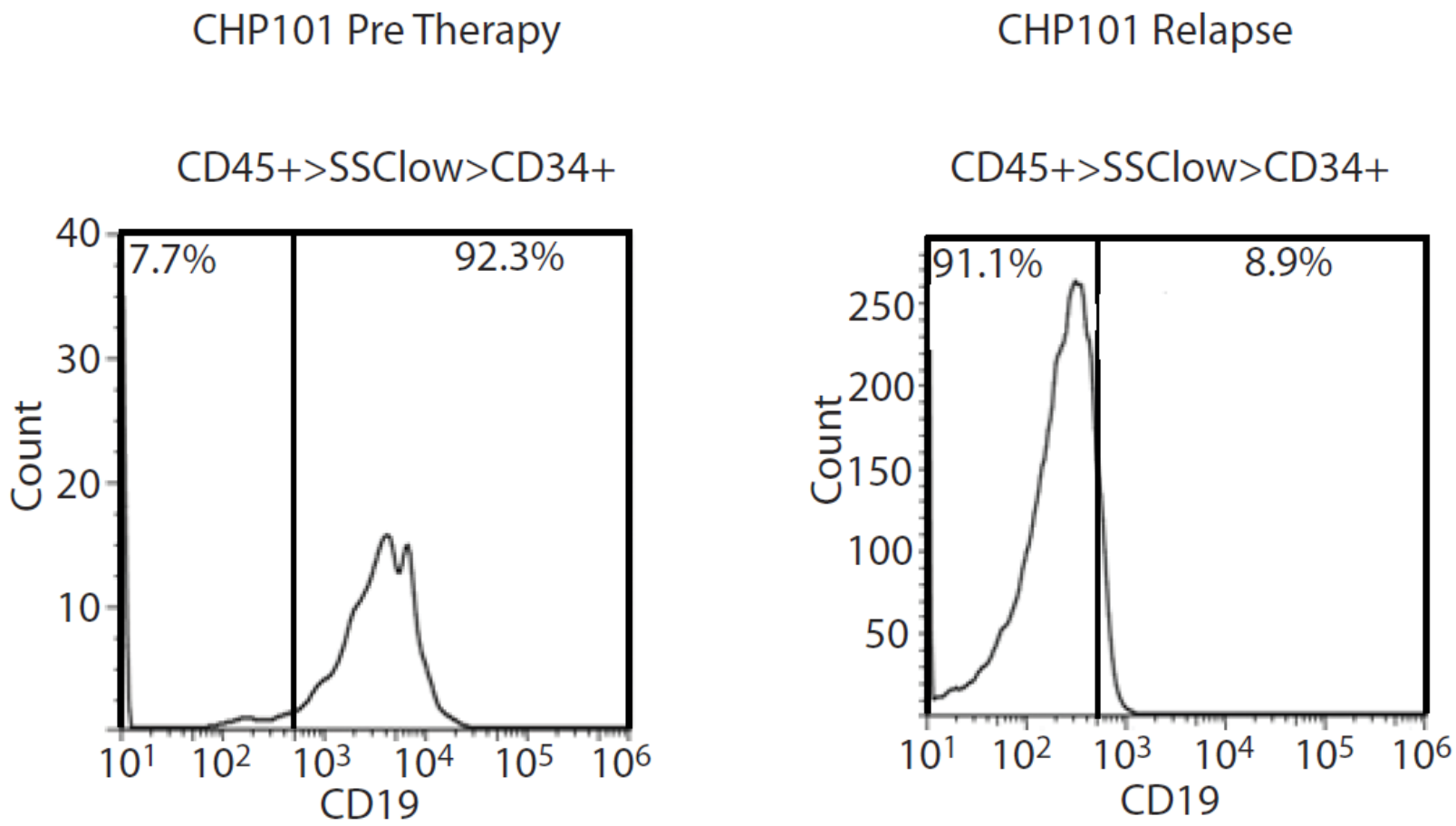
APC Nanostring: APC expression profile shows dozens of alterations when CAR T cells kill targets



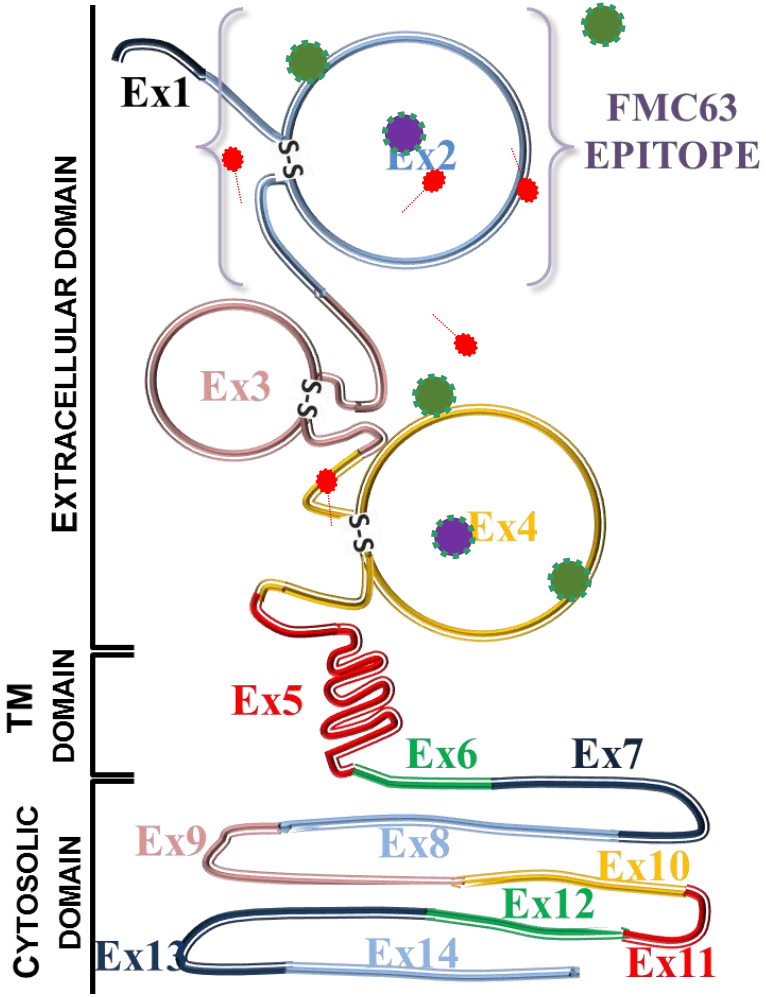
Resistance to CTL019

- No response
  - 7% of patients
  - ? T cell intrinsic - no proliferation=no response
- CD19+ relapse: 1/3 of recurrences
  - Highly enriched in pts who lose CARs before 3-6 mo
  - 1 CD19+ successful retrieval (of 3 attempts)
  - T cell intrinsic
- CD19 (-) relapse (antigen escape): 2/3 of recurrences
  - 5 within 3 mo, 4 at 9 mo (2 still CAR+), 3 after blina
  - ALL intrinsic

CD19 negative cells cause relapse



Grupp et al, NEJM 2013



ESCAPING CTL019

SPLICING

Exon 2
Exon 5-6
Partial exon 3

→ RESISTANT TO CTL019
(*in vitro* killing assay, Ruella & Gill)

MUTATIONS

Exons 2 and 4 seem to be hot-spots
1nt in/del: frameshift→truncated protein
Most are *de novo* in relapse sample

Frameshift mutations→Protein truncated shortly after mutation point
In frame mutation (substitutions, insertions of aa)

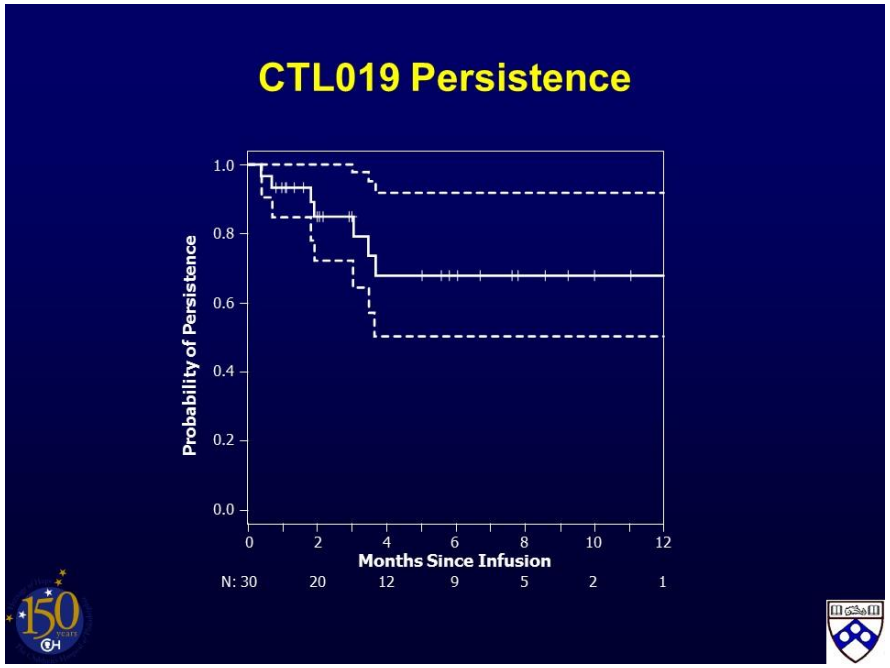
E. Sotillo et al Cancer Discovery 2015

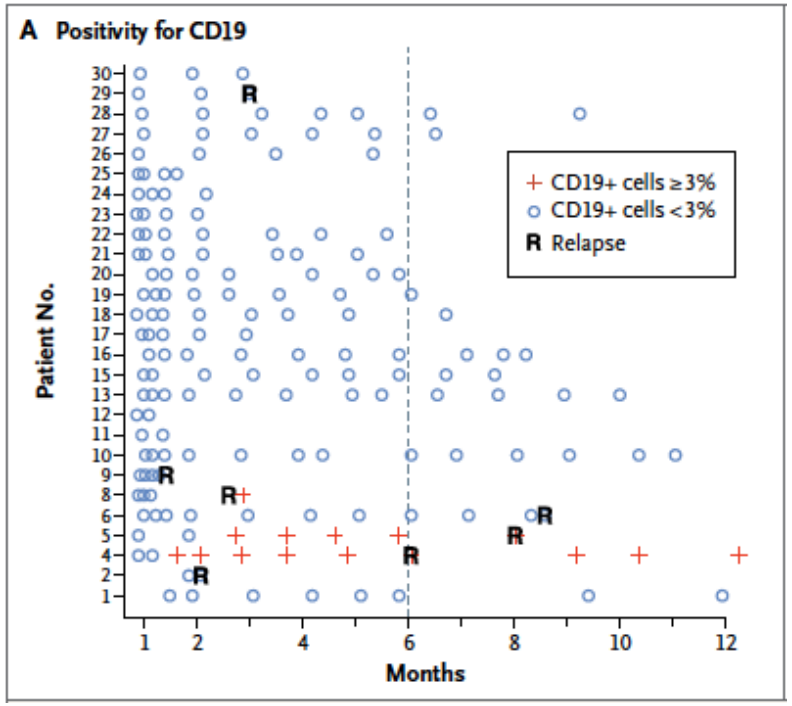
What to do about CD19 antigen escape?

- No evidence for epitope spreading
- Find a conserved epitope/exon in CD19
- Treat CD19 negative recurrence with CART22
- Combine CART19 with Inotuzumab
- Combine CART19 with CART22

Credit to Alan Wayne

CTL019 in Pediatric and Adult ALL: Long-Term Functional Persistence



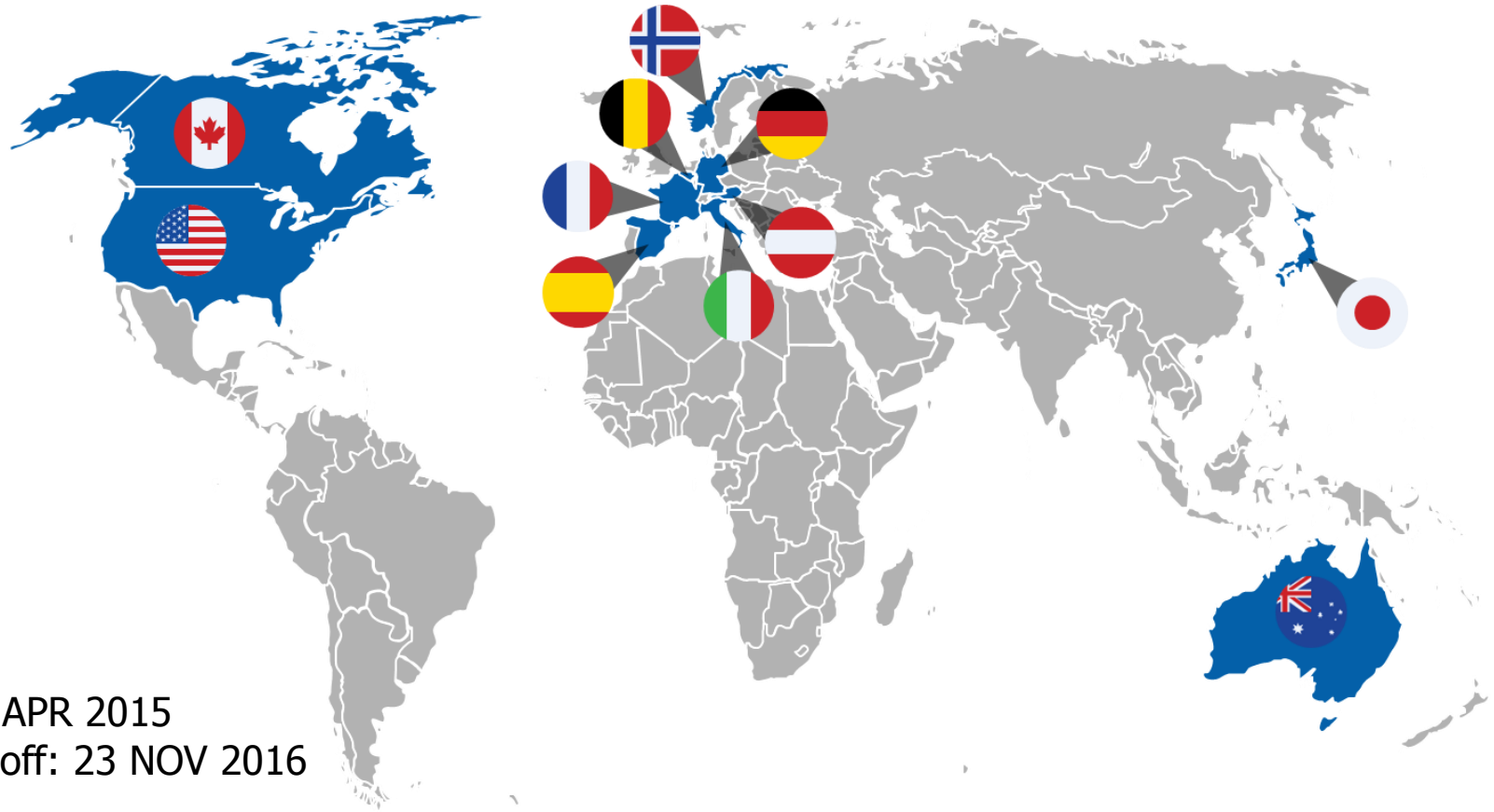


- CTL019 T cells robust in vivo expansion and persist in vivo
  - CTL019 detectable in the blood by flow cytometry for up to 11 months
  - B-cell aplasia occurred in all patients who had a response[1]
  - Long-term persistence may allow for long-term disease control[1,2]

1. Maude SL, et al. *N Engl J Med*. 2014;371(16):1507-1517. 2. Grupp SA, et al. Blood. 2015 [abstract 681].

- ELIANA is a Novartis single arm global study with centralized manufacturing of CTL019
- 25 sites in 11 countries across North America, Europe, Australia, and Asia

Global Registration trial of CTL019 in ALL - ELIANA



FPFV=8 APR 2015
Data cutoff: 23 NOV 2016

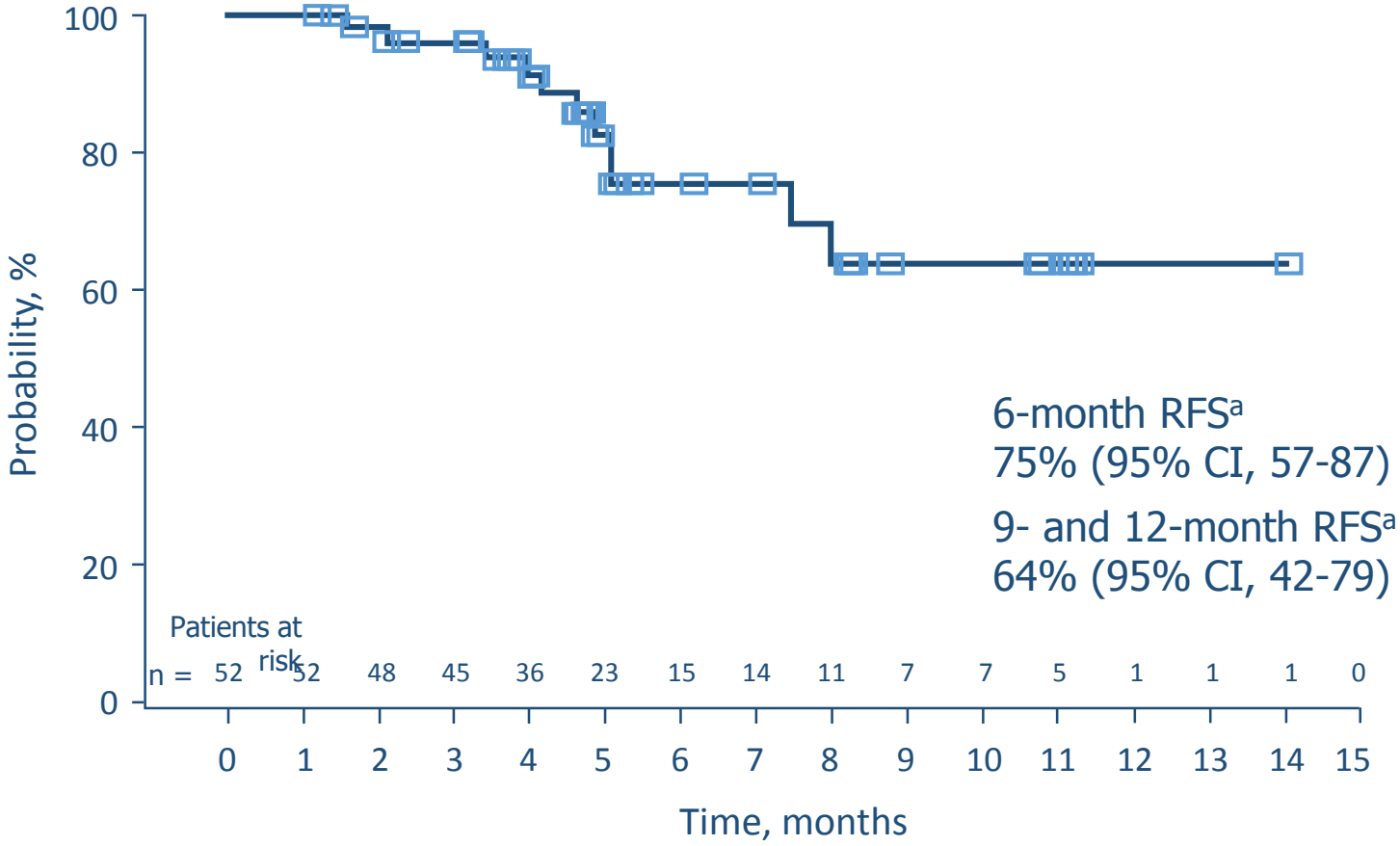
ELIANA: Primary Efficacy Analysis

Parameter	Efficacy Analysis Set[a] (n = 63)		
Primary endpoint	**% (n/N)**	**95% CI**	***P* Value**
Overall remission rate (CR + CRi) within 3 months	**83 (52/63)**	(71-91)	< .001[†]
Best overall response, %[b]			
CR	**63**		
CRi	**19**		
Secondary endpoint			
Best overall response of CR or CRi within 3 months with MRD-negative[c] BM	**83**	(71-91)	< .001[†]

[a] Patients infused with CTL019 ≥ 3 months prior to data cutoff. [b] The response was unknown in 6 patients. [c] MRD negative = MRD < 0.01%.
[†] Nominal *P* value is presented to test the null hypothesis of overall remission rate < 20% for comparison with historical control.

- The primary efficacy analysis was consistent with the interim analysis where the primary endpoint was met

ELIANA: Duration of Remission



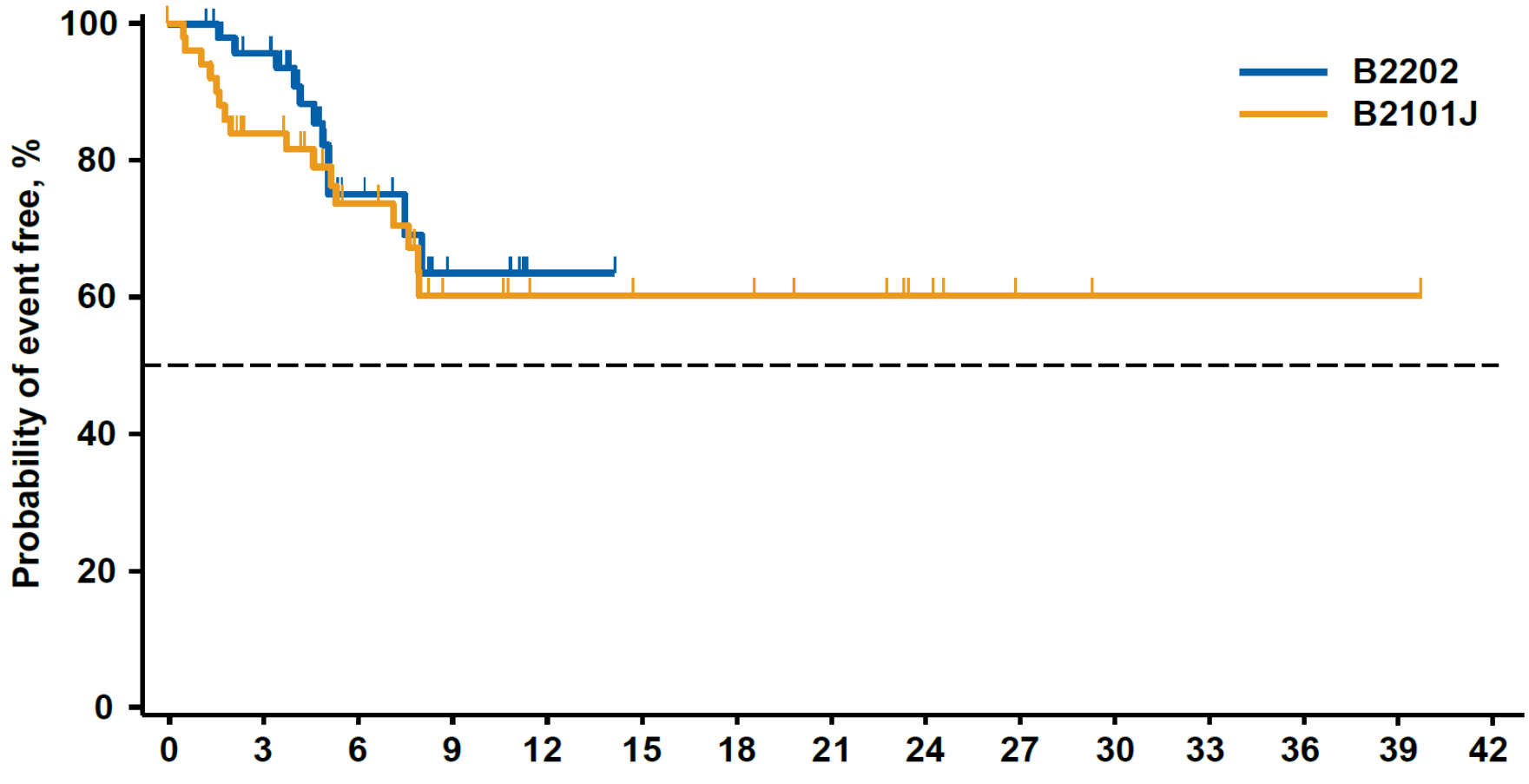
Patients (N = 52) Number of events (n = 11) Median follow-up, 4.8 months

Median DOR, not reached

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

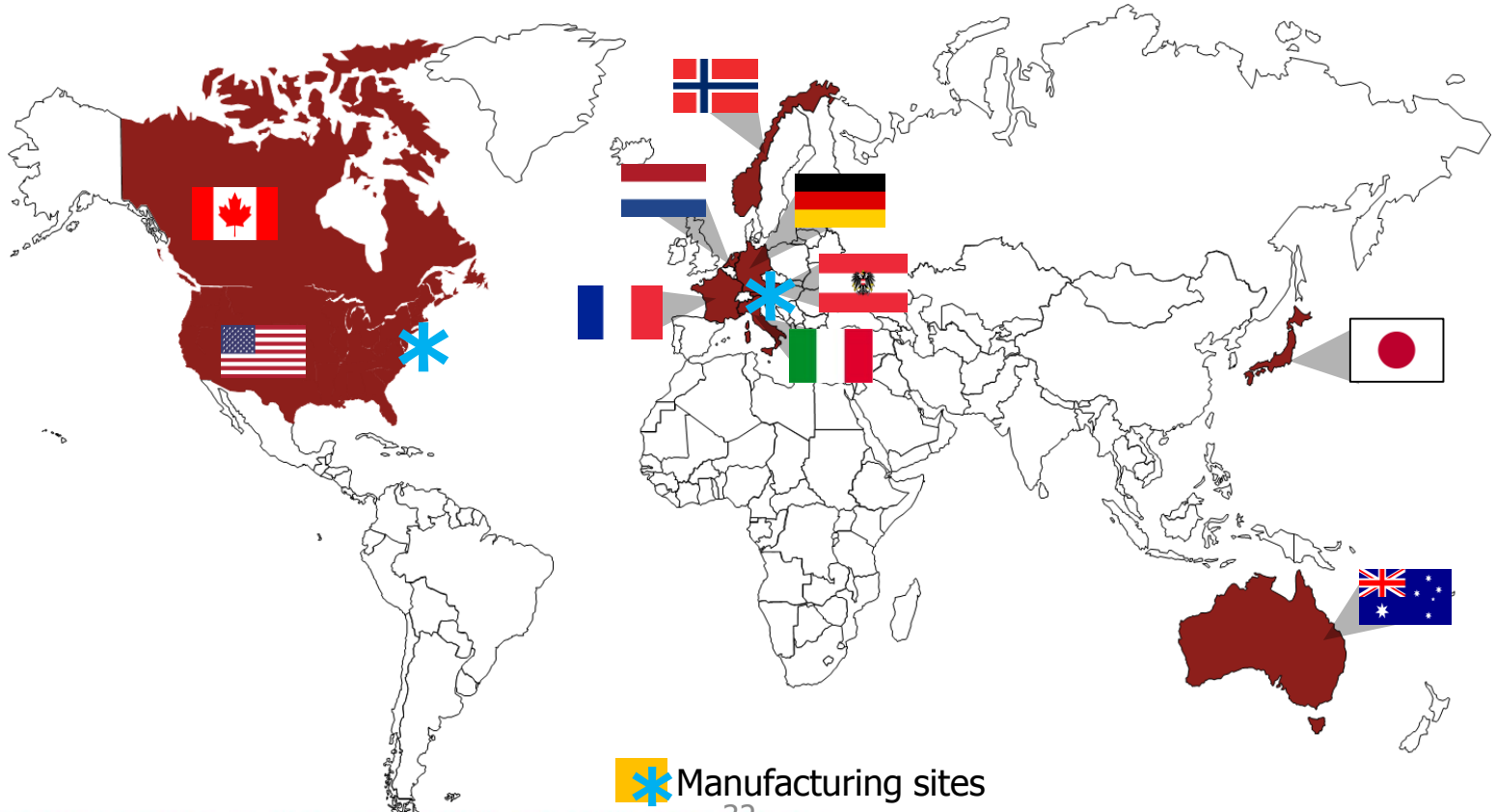
[a] Efficacy analysis set.

DOR in B2202 and B2101J



Global Registration trial of CTL019 in DLBCL – JULIET

- JULIET is a Novartis global clinical trial with centralized manufacturing of CTL019
- 27 sites in 10 countries across North America, Europe, Australia, and Asia



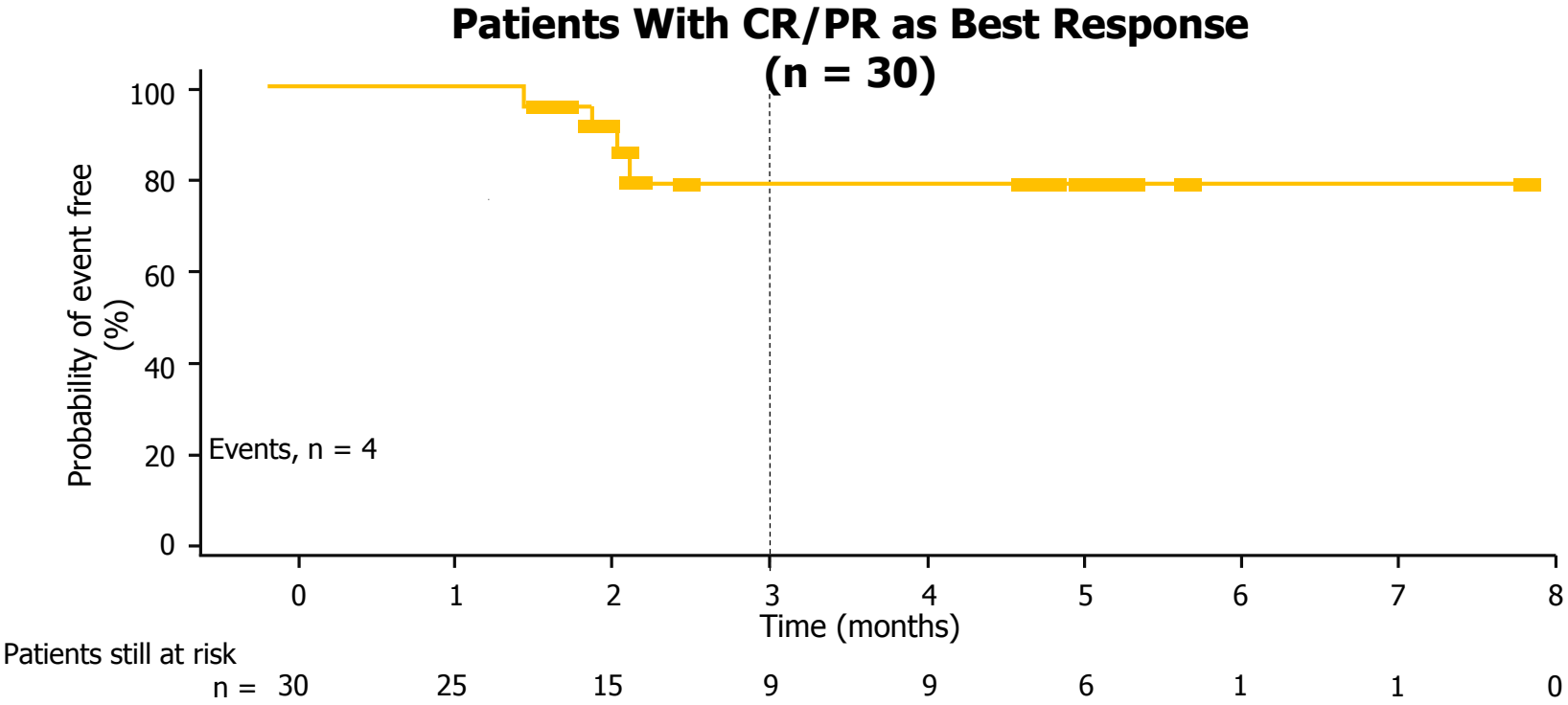
JULIET Primary Endpoint Met in DLBCL

Response Rate	Patients (N = 51)[a]	
Best overall response (CR + PR)	59%	*P* < .0001[b] (95% CI, 44-72)
CR	43%	
PR	16%	
SD	12%	
PD	24%	
Overall response rate (CR + PR) at 3 months	45%	
CR	37%	
PR	8%	

[a] The interim analysis was preplanned to include the first 51 patients treated with CTL019 and followed for at least 3 months or discontinued early.

[b] Null hypothesis of ORR ≤ 20%; the one-sided p-value threshold to reject the null hypothesis is 0.0047 (O'Brien-Fleming boundary) at the interim analysis and 0.0235 at the primary analysis.

DLBCL – Duration of Response: 79% Relapse-free at 6 Months



- All responses at 3 months were ongoing at the time of cut-off
- No responding patients went on to SCT
- Median DOR and OS not reached

Cytokine Release Syndrome in DLBCL

	Patients (n = 85)
Time to onset, median (range), days[a]	3.0 (1-8)
Duration, median (range), days[a]	7.0 (3-34)
Admitted to intensive care unit	24%
Hypotension that required intervention	29%
High dose vasopressors	7%
Intubated	8%
Anti-cytokine therapy[b]	18%
Tocilizumab	16%
Corticosteroids	11%

[a] Calculated based only on patients who had cytokine release syndrome (n = 48).
[b] 8 patients received both tocilizumab and corticosteroids.

CRS was graded using the Penn scale and managed by a protocol-specific algorithm.
Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139.

CTL019 Toxicity Summary

- Cytokine release syndrome (CRS)
  - Correlates with T cell proliferation and efficacy
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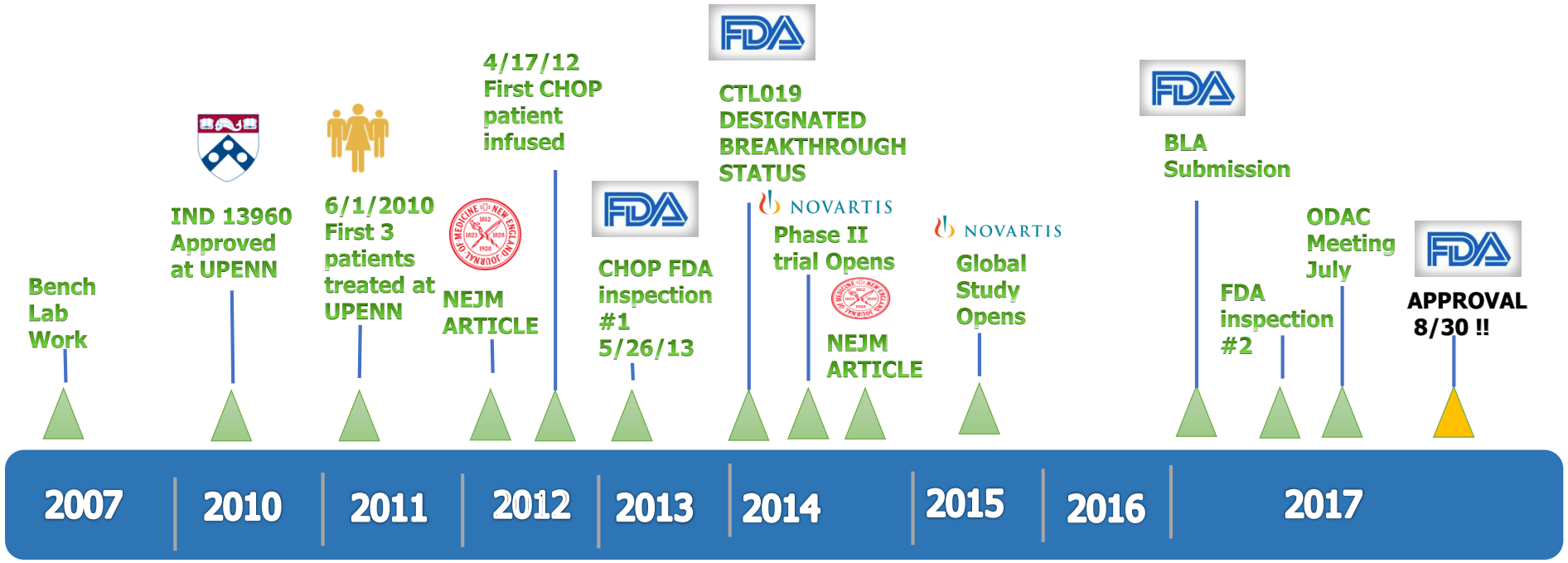
  - “Severe Neurotoxicity in the Phase 2 Trial of JCAR015 in Adult B-ALL (ROCKET Study)“
    Session 102, today, 11:10 – 11:30, Maryland Ballroom

From CART19 to Kymriah

Timeline to FDA Approval




F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment


The Chemicals in Your Mac and Cheese


Study of How We Look at Faces May Offer Insight Into Autism

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HEALTH

F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment

By DENISE GRADY JULY 12, 2017

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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

For Immediate Release August 30, 2017

FierceBiotech

BIOTECH RESEARCH IT CRO MEDTECH

Biotech

Novartis' stellar CAR-T efficacy data steamrolls safety doubts to power landmark cancer therapy toward approval

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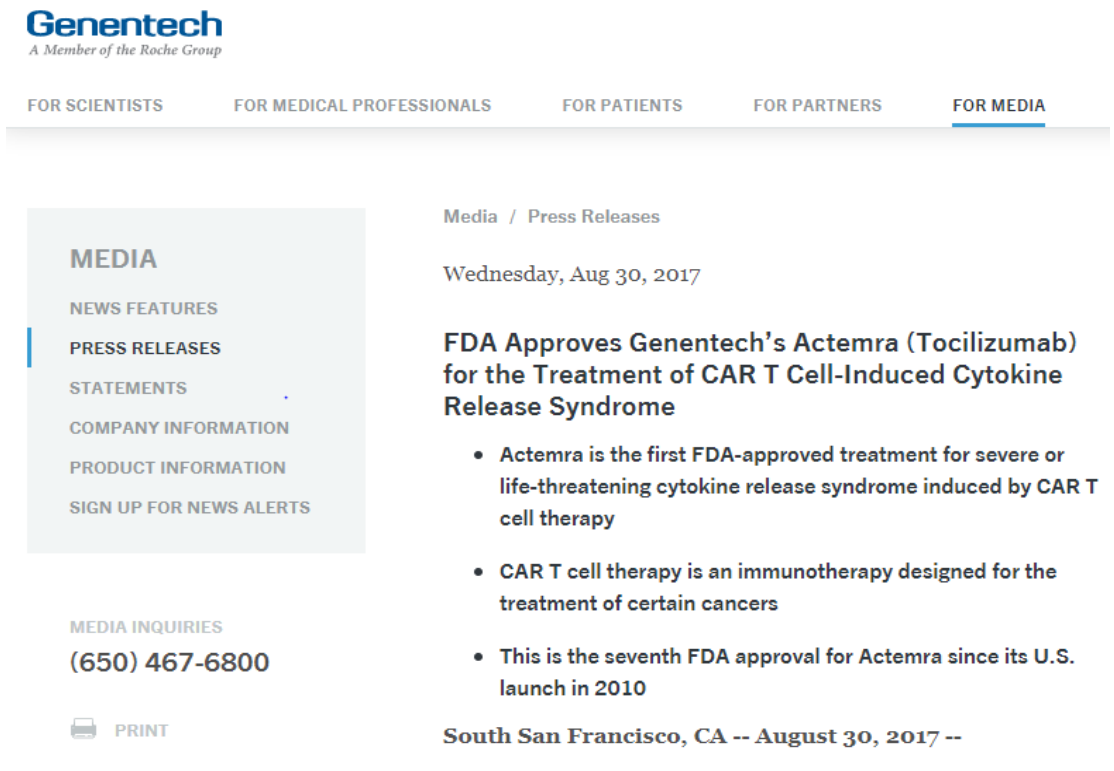

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Media / Press Releases

Wednesday, Aug 30, 2017

FDA Approves Genentech's Actemra (Tocilizumab) for the Treatment of CAR T Cell-Induced Cytokine Release Syndrome

- Actemra is the first FDA-approved treatment for severe or life-threatening cytokine release syndrome induced by CAR T cell therapy
- CAR T cell therapy is an immunotherapy designed for the treatment of certain cancers
- This is the seventh FDA approval for Actemra since its U.S. launch in 2010

South San Francisco, CA -- August 30, 2017 --

News & Events

FDA News Release

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

Yescarta is the second gene therapy product approved in the U.S.

For Immediate Release October 18, 2017

What is are the current labeled indications for CTL019/Kymriah?

- ALL up to age 25
- Refractory or second relapse

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Other key points:

- Patients do not need to be in complete remission to be treated
- No donor is required
- There is a plan for a registry
- No requirement for RCL testing

Are CAR T cells effective therapy? What have we shown we can do?

- Consolidate patients with MRD
- Reinduce remission
- Multicenter trial/s in pediatric ALL, registration trial, FDA approved product
- With adequate persistence, can we imagine a replacement for stem cell transplant?
- "What would this need to look like if we try to move this up front in ALL?" Steve Hunger, COG ALL Chair

Penn, CHOP, NVS Cell Therapy:

Penn/ACC TRP

Carl June
Anne Chew
Michael Milone
Yangbing Zhao
John Scholler
Elizabeth Veloso
Dana Hammill
Katie Marcucci
Pam Shaw

CHOP Cell Therapy Lab
David Barrett
David Teachey
Alix Seif
Shannon Maude
Junior Hall
Jessica Perazzelli
Terri Ryan
Sarah Tasian
Jessica Lee

CVPF

Bruce Levine
Anne Lamontagne
Matthew O'Rourke
Megan Suhoski

U Penn Clinical
David Porter
Noelle Frey

CHOP Clinical/Study Staff
Shannon Maude
Richard Aplenc
Colleen Callahan
Sue Rheingold
Anne Reilly
Christine Barker
Lauren Vernau
Mark Duckworth

NOVARTIS
David Lebwohl
Patricia Wood

TCSL

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

Thomas-Tikhonenko Lab

CHOP Nursing

CHOP CRSO Office

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cancer immunotherapy FRONTIER PROGRAM

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