

CAR T cells directed to CD19 in hematologic malignancies

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Abramson Cancer Center



Penn Medicine



UNIVERSITY OF PENNSYLVANIA

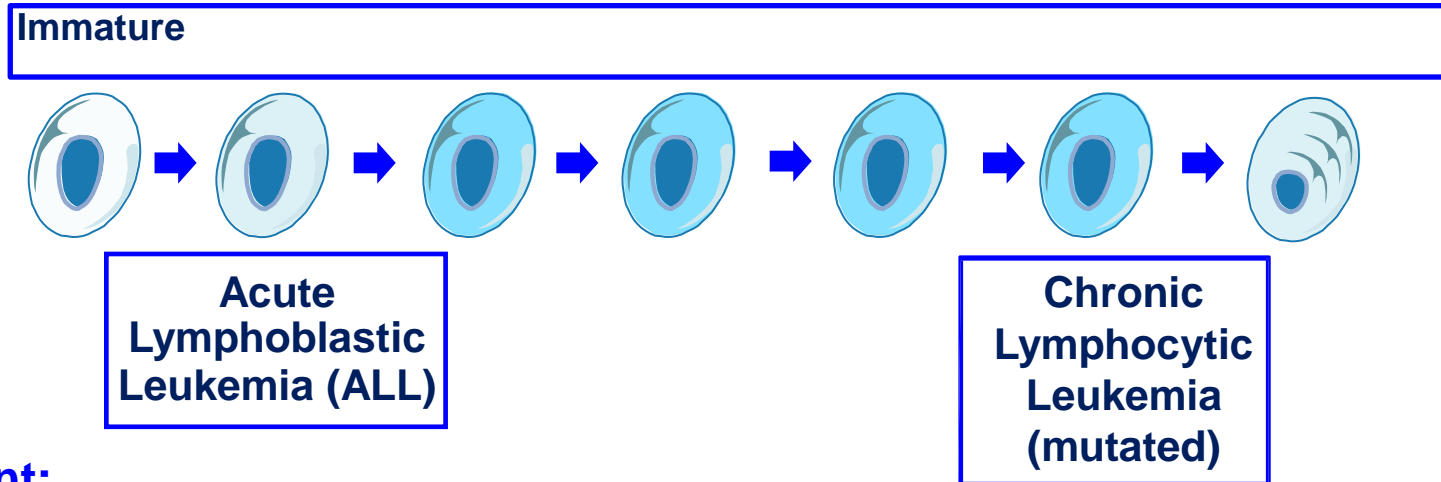
COI Disclosure Information

- Novartis has licensed the use of CARs in oncology from University of Pennsylvania
- Speaker and members of study team have financial interest due to potential upstream IP and patents and licensure to Novartis
- Novartis provides research funding for my lab at Penn
- COI managed in accordance with University of Pennsylvania policy and oversight

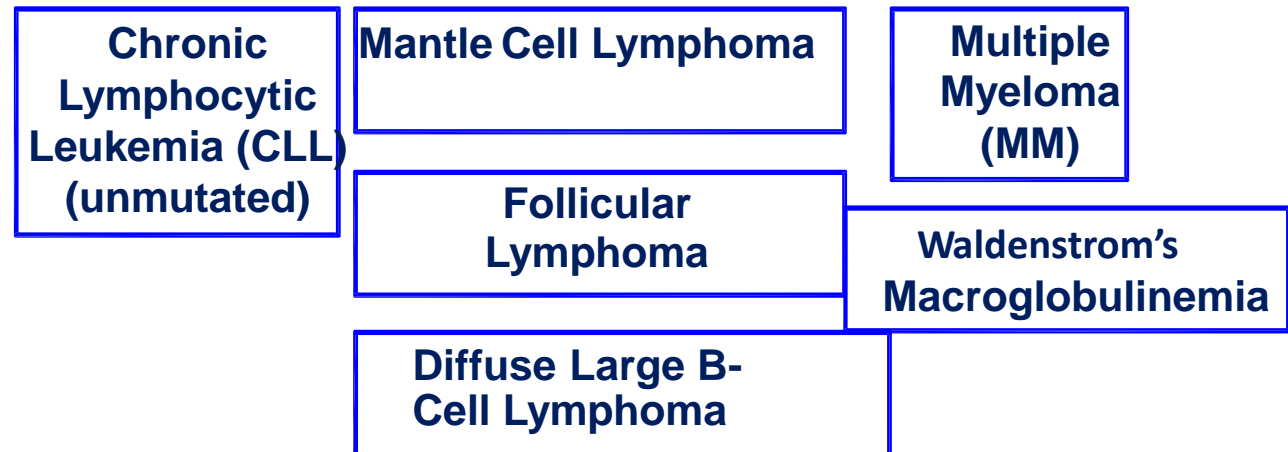
Human CD19 Expression by Hematopoietic Cells (Opportunities for CART19 Intervention)

Normal:

Pro-B Pre-B Immature B Naïve B Germinal Center B Memory B Plasma Cell



Malignant:



CD19 Expression

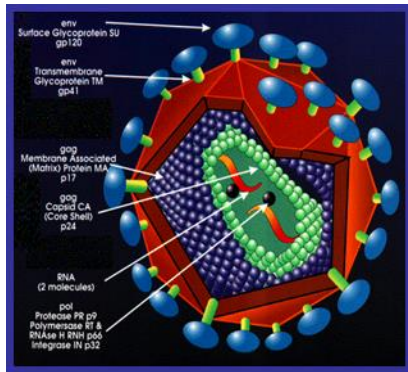
CD19 Expression

Abramson Cancer Center

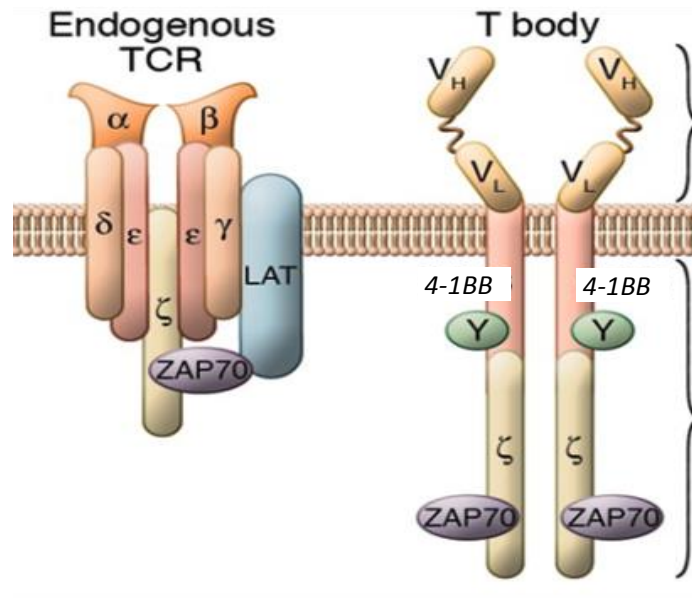


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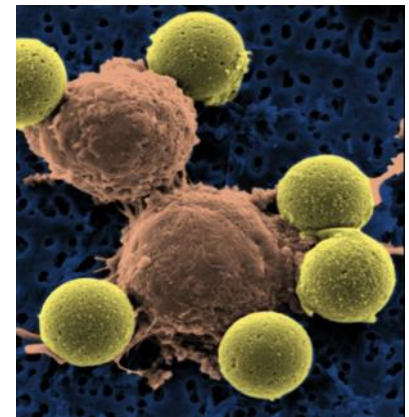
To engineer a T cell, you need...



***A gene delivery
system
(lentiviral vector)***

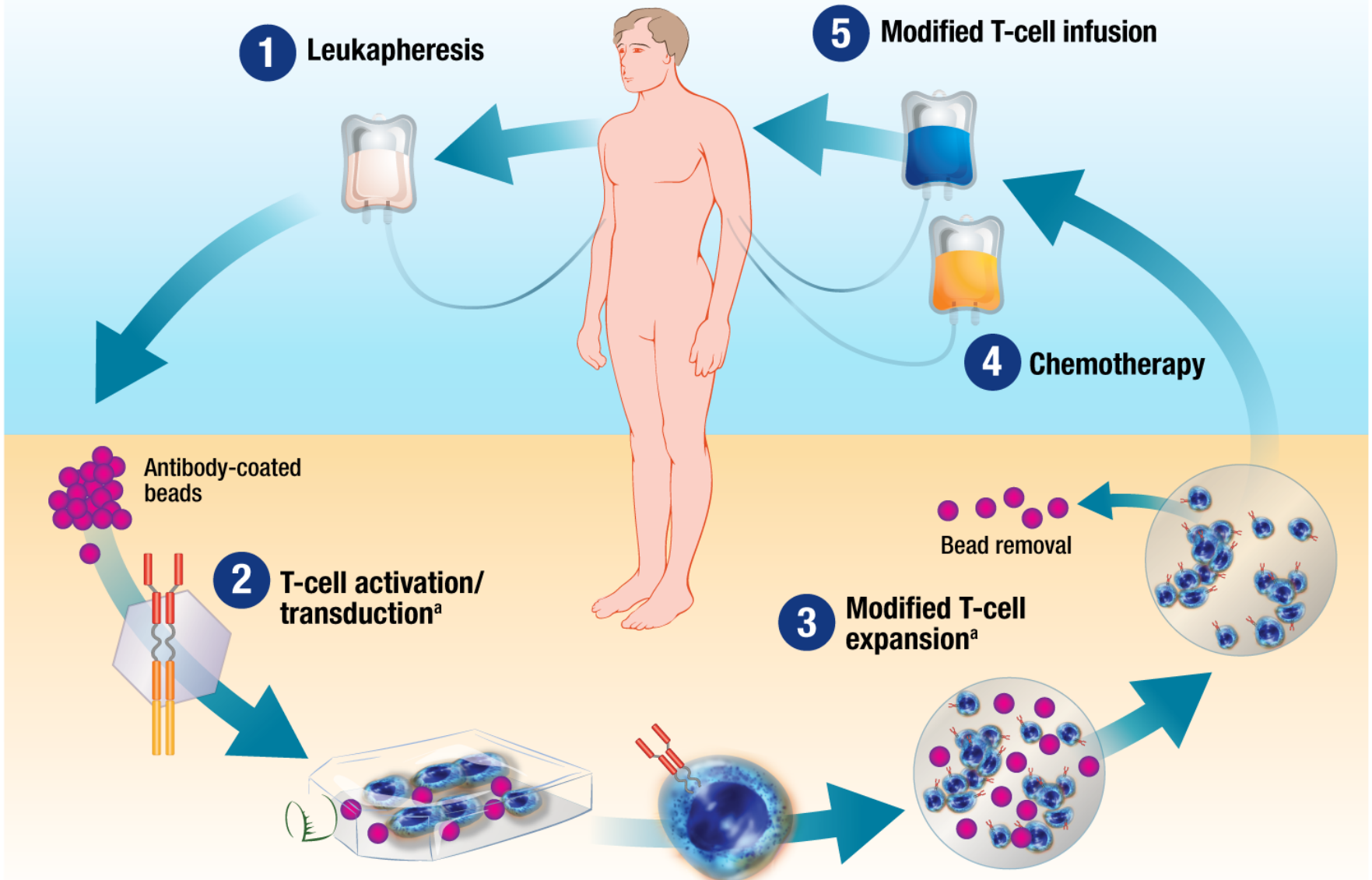


***An antigen receptor
(natural ligand,
TCR or CAR)***



***Ex vivo culture
system (anti-
CD3/28 beads)***

Overview of CTL019 Therapy

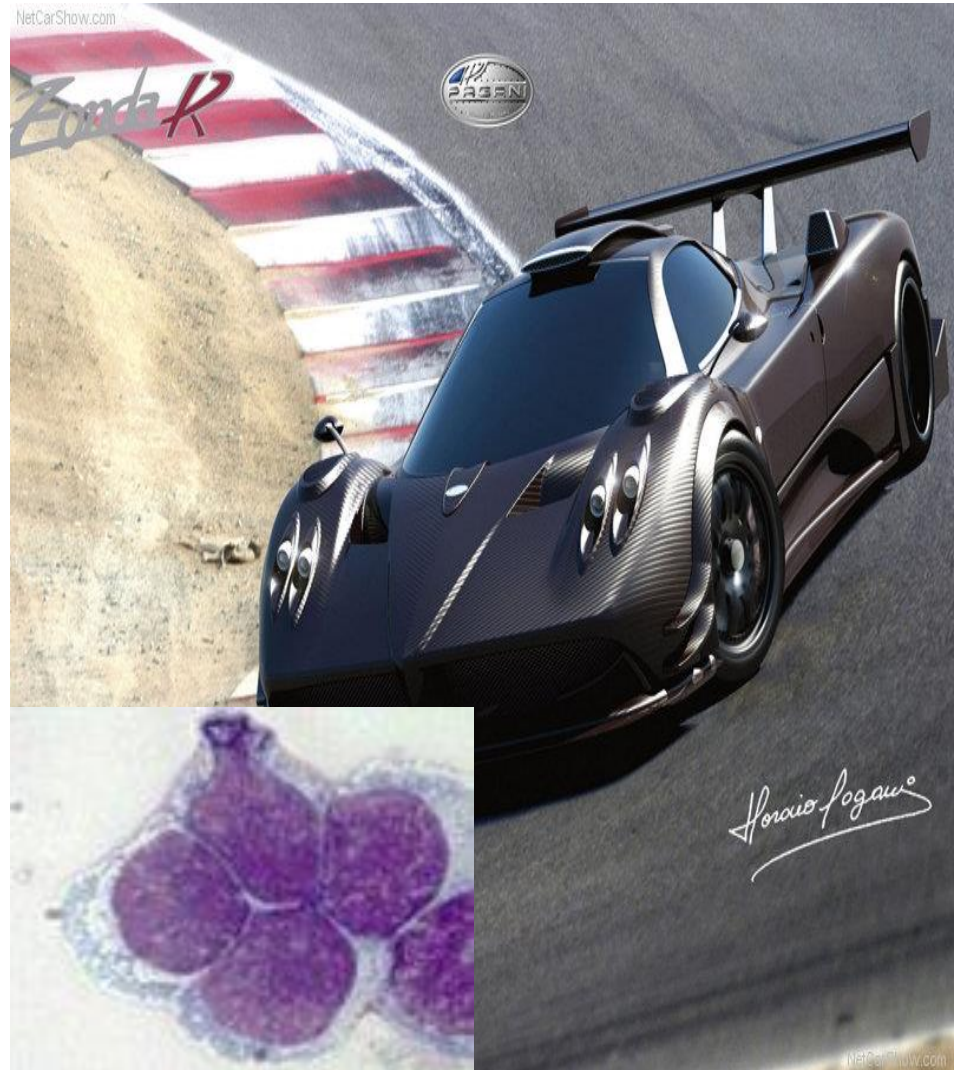


^a Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

CARs Meet Leukemia/Lymphoma

107 CTL019 Recipients

- ALL:
 - 30 kids
 - 15 adults
- CLL:
 - 42 adults
- NHL:
 - 18 adults
- MM
 - 2 adults

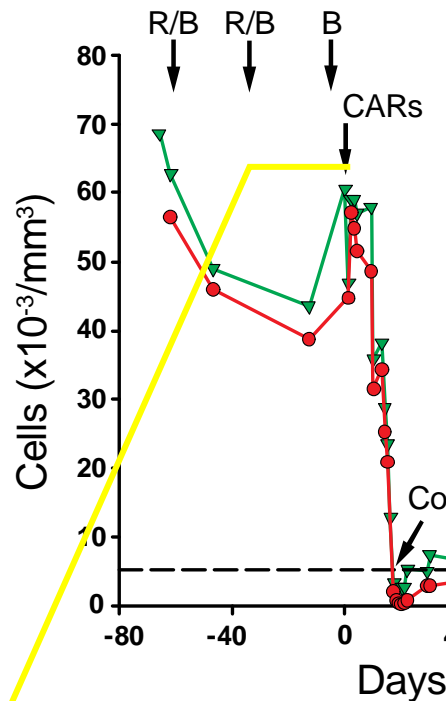


CLL Pilot Study Design and Considerations

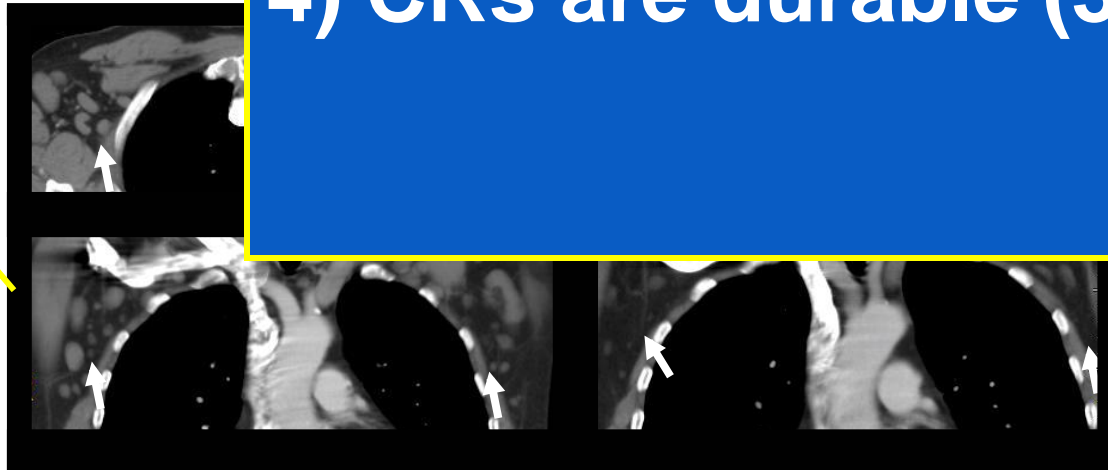
- Single center pilot trial of CTL019 (formally CART19) cells
- Primary objective:
 - Safety, feasibility and immunogenicity of CTL019 in patients with CD19+ leukemia and lymphoma
- Detailed inclusion/exclusion at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01029366) (NCT01029366)
 - CD19+ B cell malignancies with no available curative options (such as autologous or allogeneic SCT)
 - CLL: failed ≥ 2 prior therapies, progression within 2 years of last treatment.
 - Limited prognosis (<2 year) with available therapies.

Examples of Clinical Responses

UPN 02



UPN 03

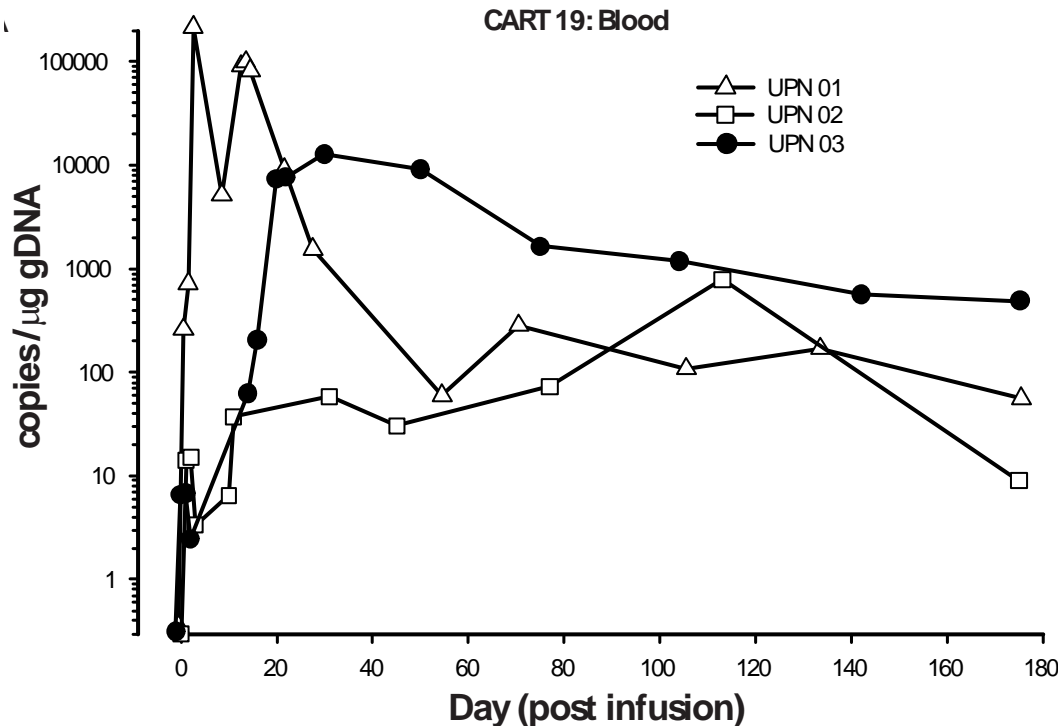


UPN 01

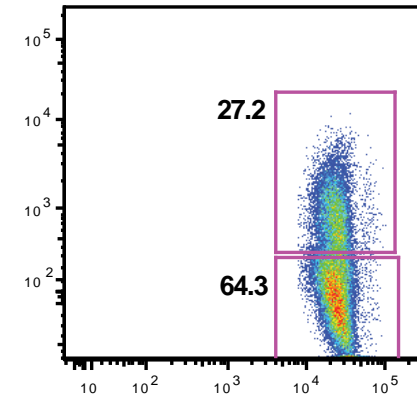
- Lessons from first 3 pts:
- 1) Advanced r/r CLL w 3 to 8 prior regimens
 - 2) Two pts w 17p deletion (p53)
 - 3) Bulk disease eradicated (3 to 7 lbs of tumor/pt !)
 - 4) CRs are durable (3 years)

Pharmacology and Pharmacokinetics of CTL019

CD8 Day 56



CART19 cells proliferate
2 to 4 log10 in all patients in vivo



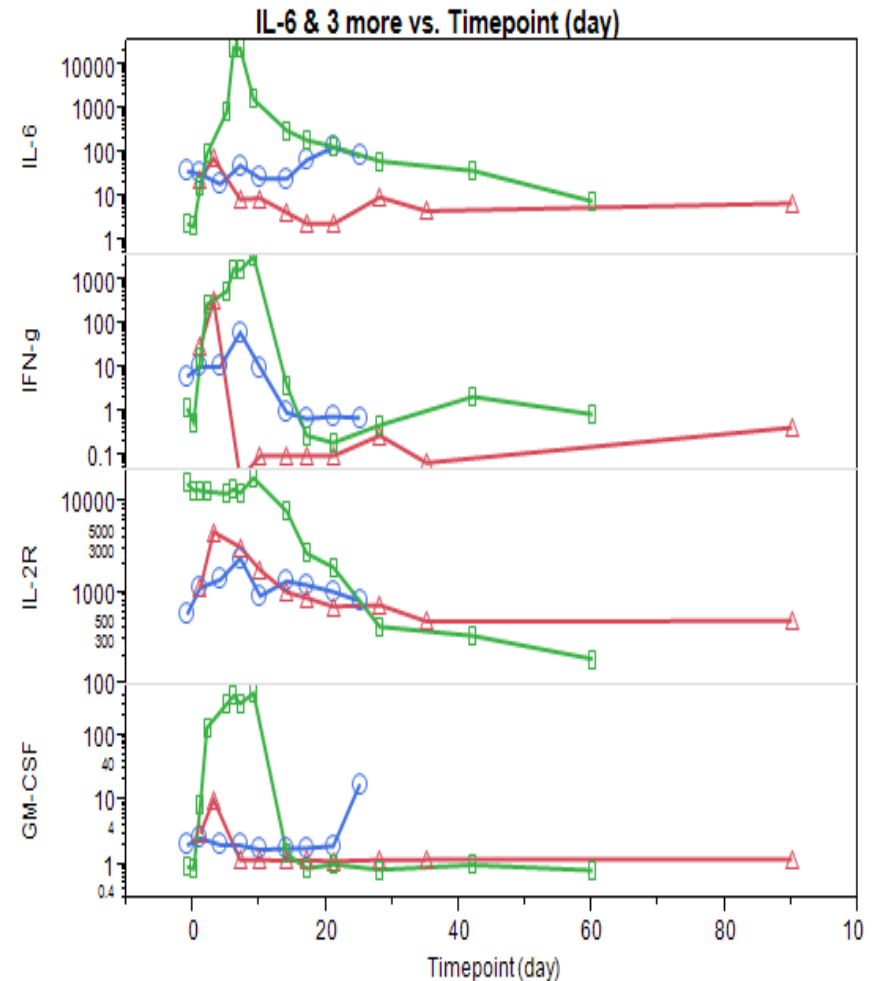
1. CAR moiety expressed for at least 6 months
2. Sustained antibody delivery with a single infusion of engineered T cells!
3. CARs expressed for at least 3 years

CART19 Toxicities

- **B cell aplasia**
 - observed in all responding patients to date
 - managed with replacement therapy
- **Tumor lysis syndrome (TLS)**
 - Can be delayed by weeks; usually coincident with CRS
- **Cytokine release syndrome (CRS)**
 - reversible, on-target toxicity
 - Severity related to tumor burden: Treat MRD as outpatient?
- **Macrophage activation syndrome (HLH / MAS)**
 - elevated serum ferritin (>500,000 ng/ml), CRP, D-dimer
 - elevated cytokines: IL-6, IFN-gamma
 - Reversed with tocilizumab

Massive Elevations in IL-6 After CTL019 in Responding Patients

- Almost all responding patients developed a CRS
 - High fevers, myalgias, nausea, hypotension, hypoxia, etc.
 - Very high levels of IL6
 - IFN-g, modest TNF-a
 - Mild increases in IL-2



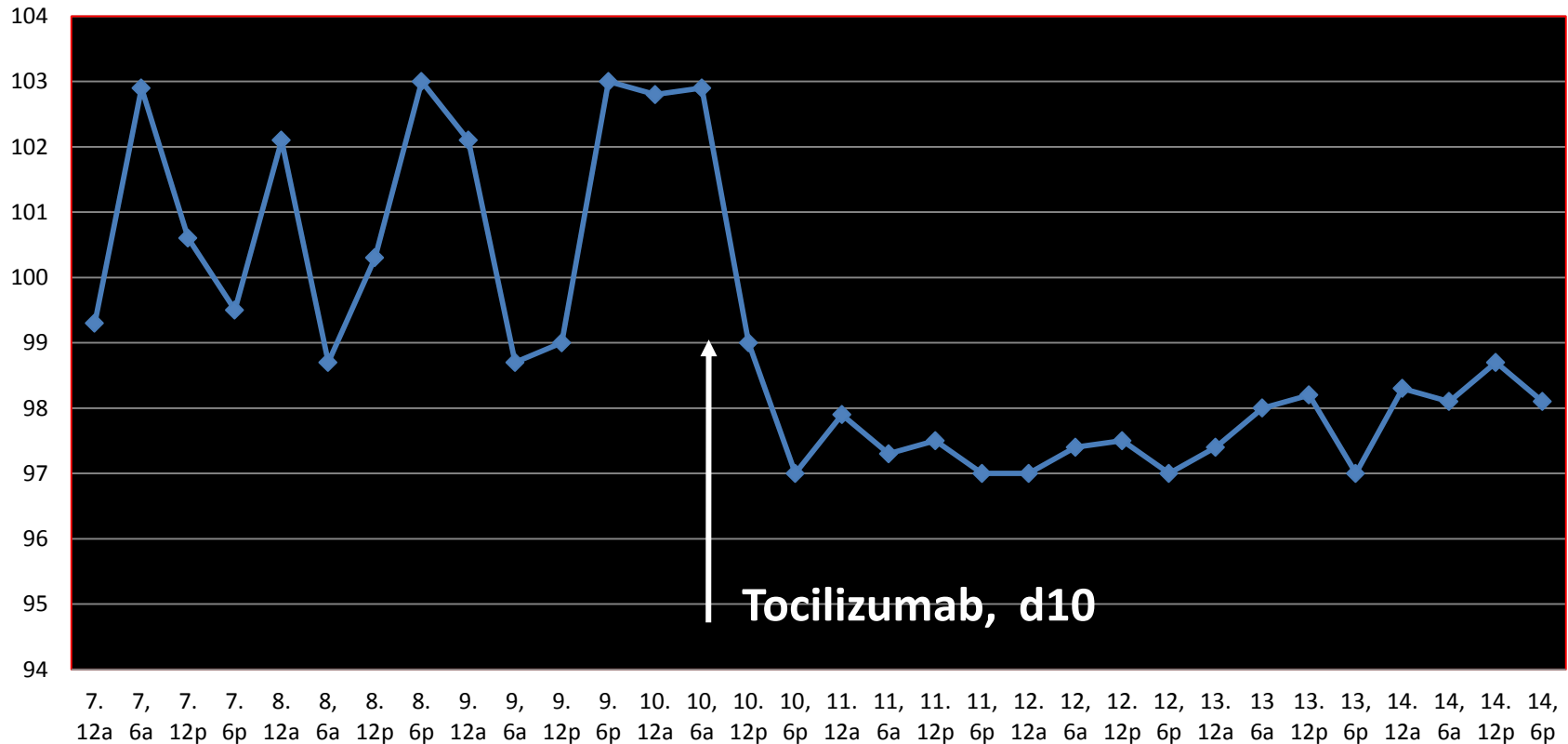
CHP959-117 NR

CHP959-118 CR mild CRS

CHP959-120 CR severe CRS

Tocilizumab Anti-Cytokine Therapy for Cytokine Release Syndrome

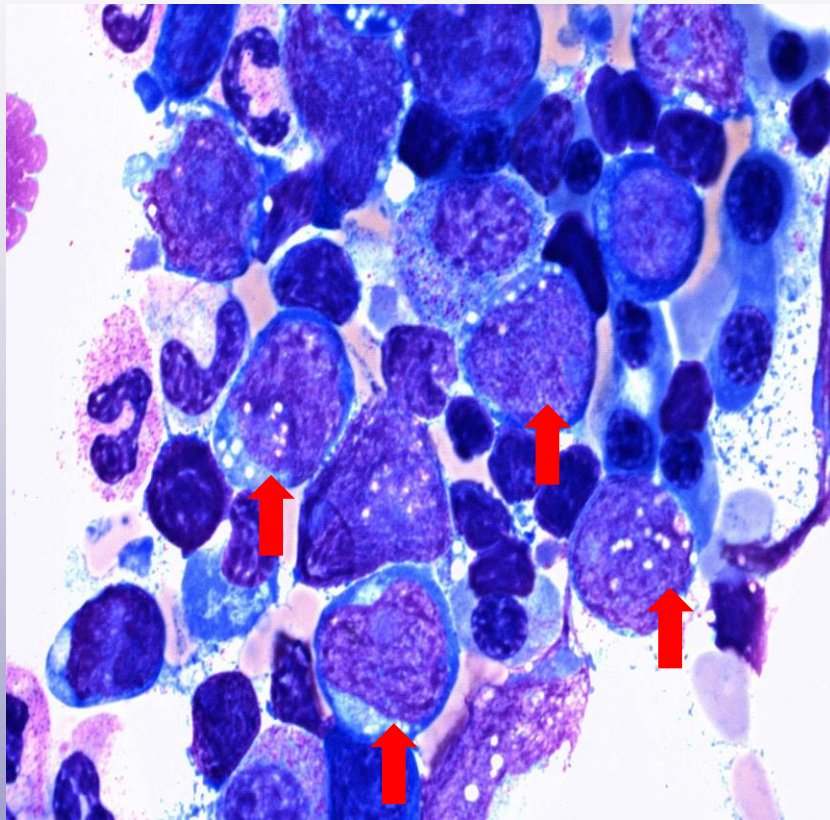
Temp (deg F)



Acute Lymphoblastic Leukemia

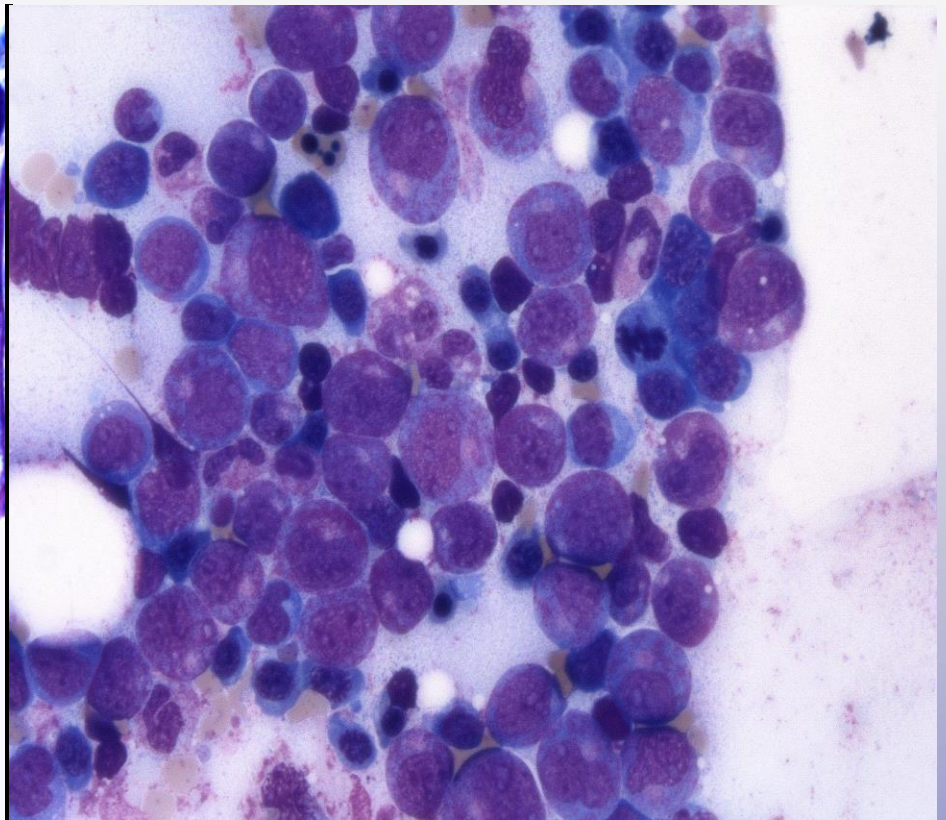
- 30 percent of all childhood malignancies
- 2500 to 3500 new cases of ALL/yr in children
- 85% or more are cured
- In adults, 11 cases/million people yearly
- Cure rate in adults variable, ~40% with standard chemotherapy
- Prognosis for relapsed or refractory ALL is poor (median survival <1 year)

ALL (04409-23), Pre-infusion



10% blasts

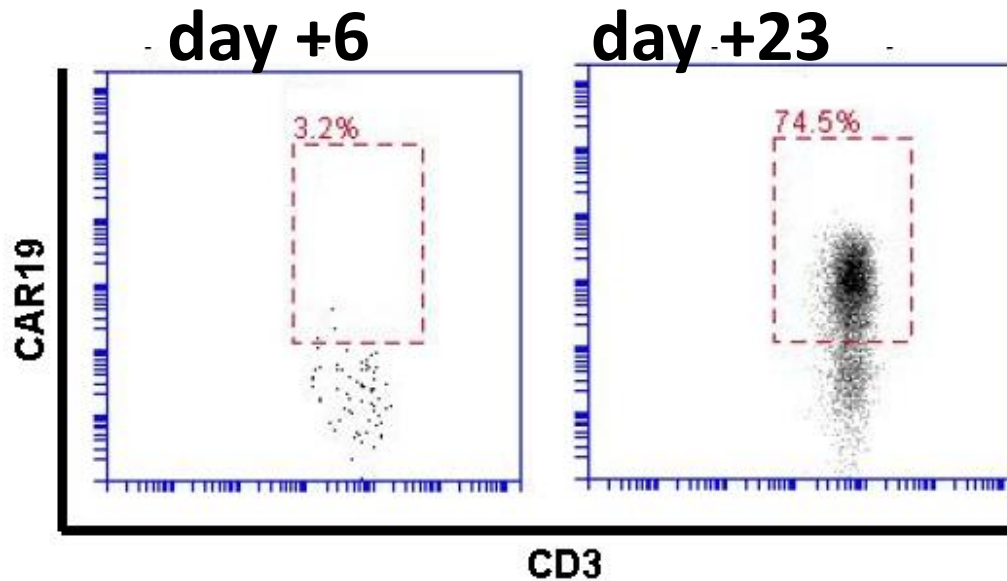
ALL (04409-23), Day 27



Complete Remission

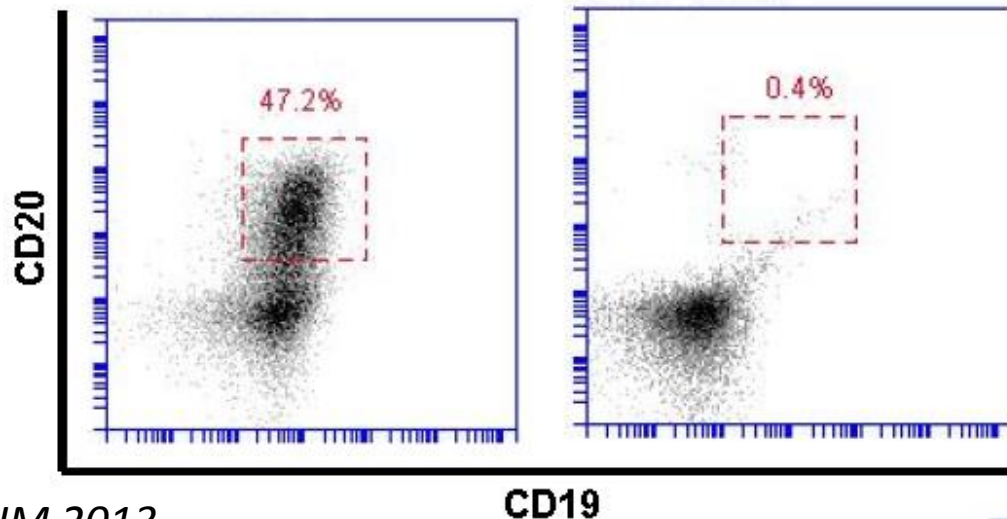
Rapid Induction of Remission in pre-B ALL: pt #1

**Marrow
T Cells**

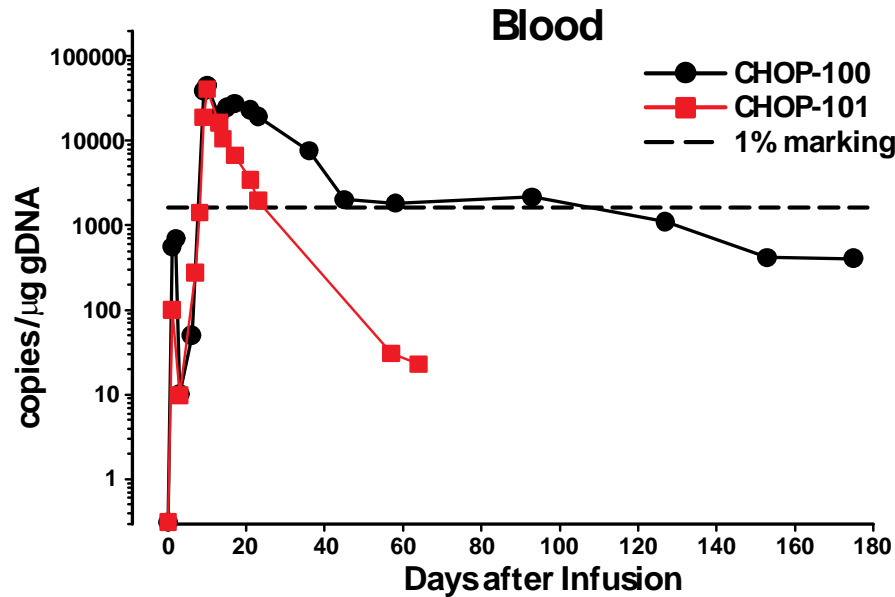


- Deep remission induced in 23 days
- No chemotherapy was given
- Status: CR (12+)
- MRD <0.01% cells

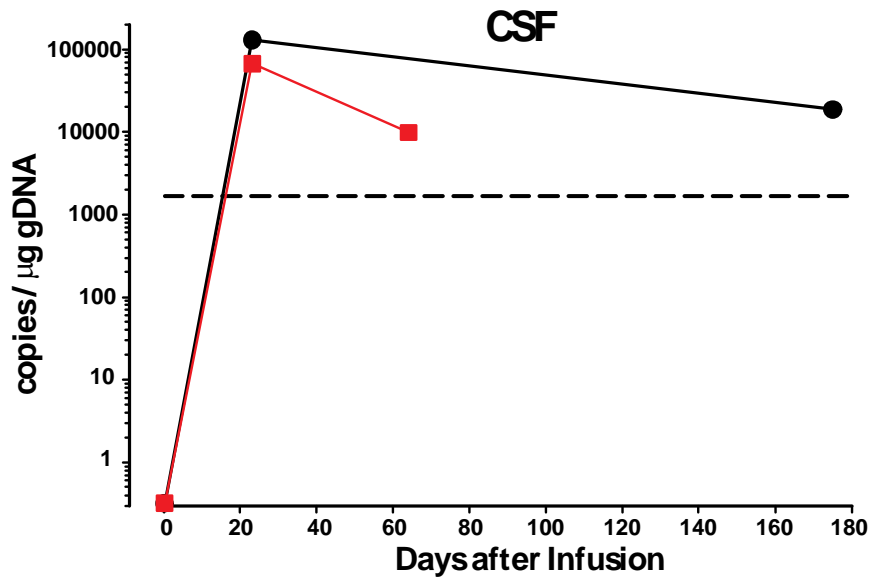
**Blasts
(ALL)**



Efficient Trafficking of CTL019 T Cells to CNS in ALL

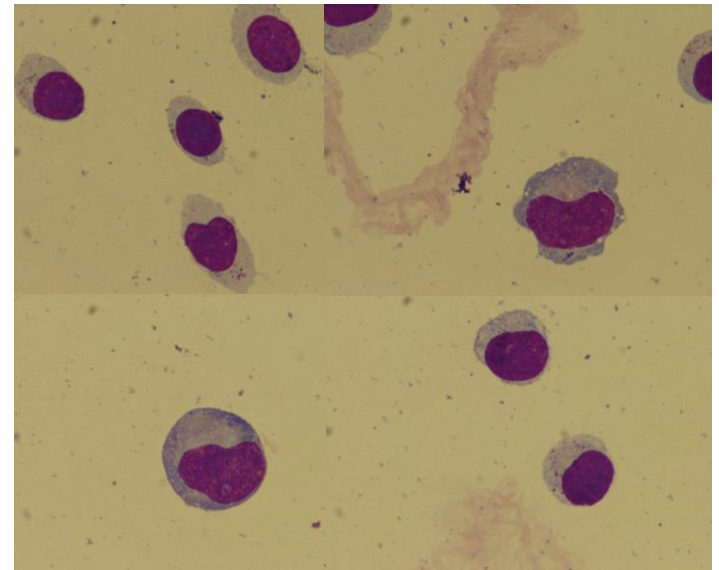
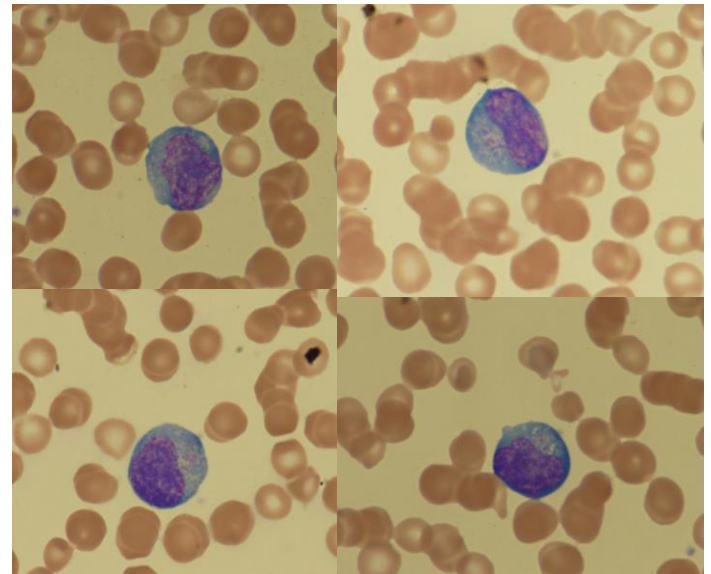


Blood
Day 10

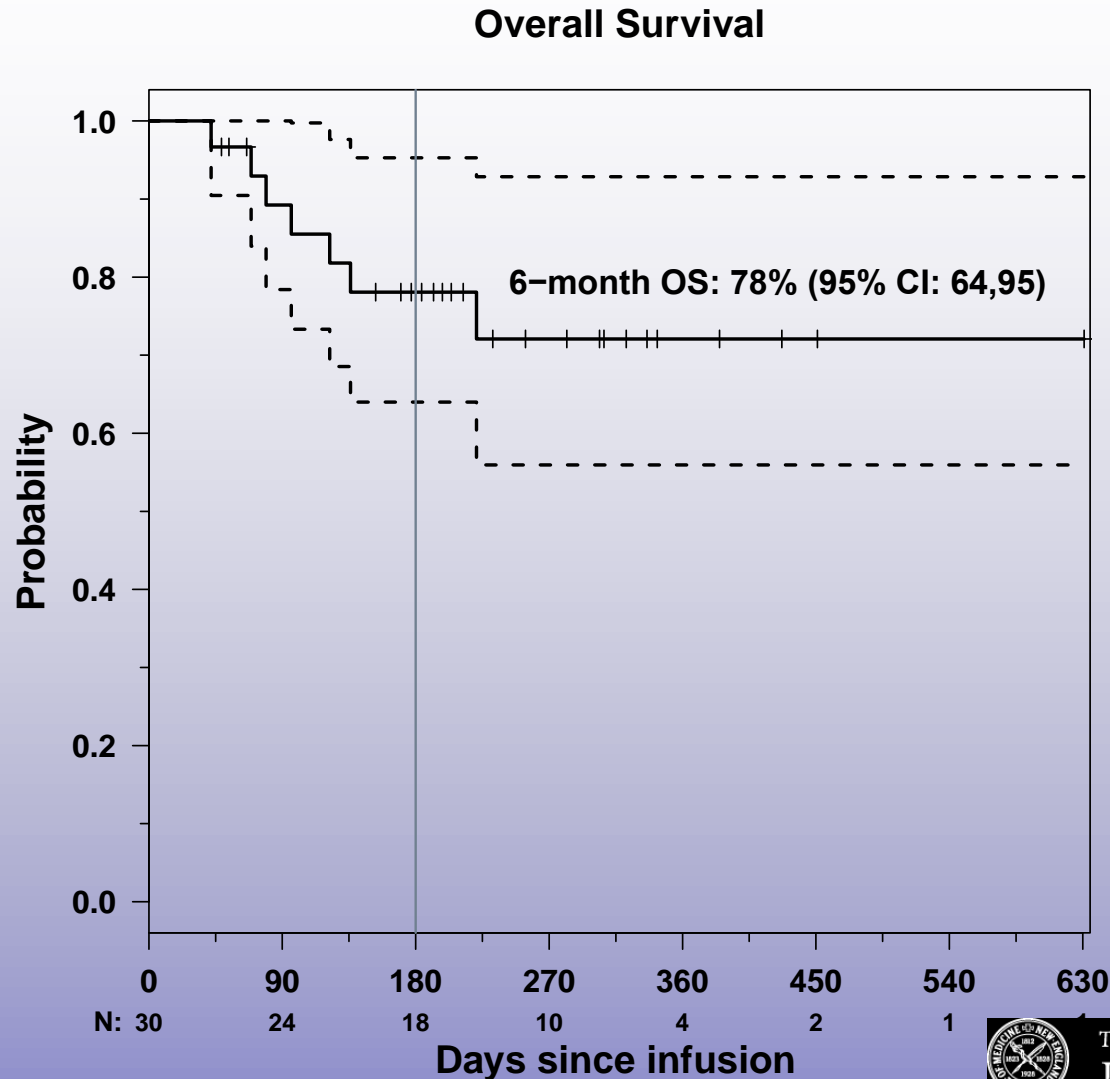


CSF
Day 23

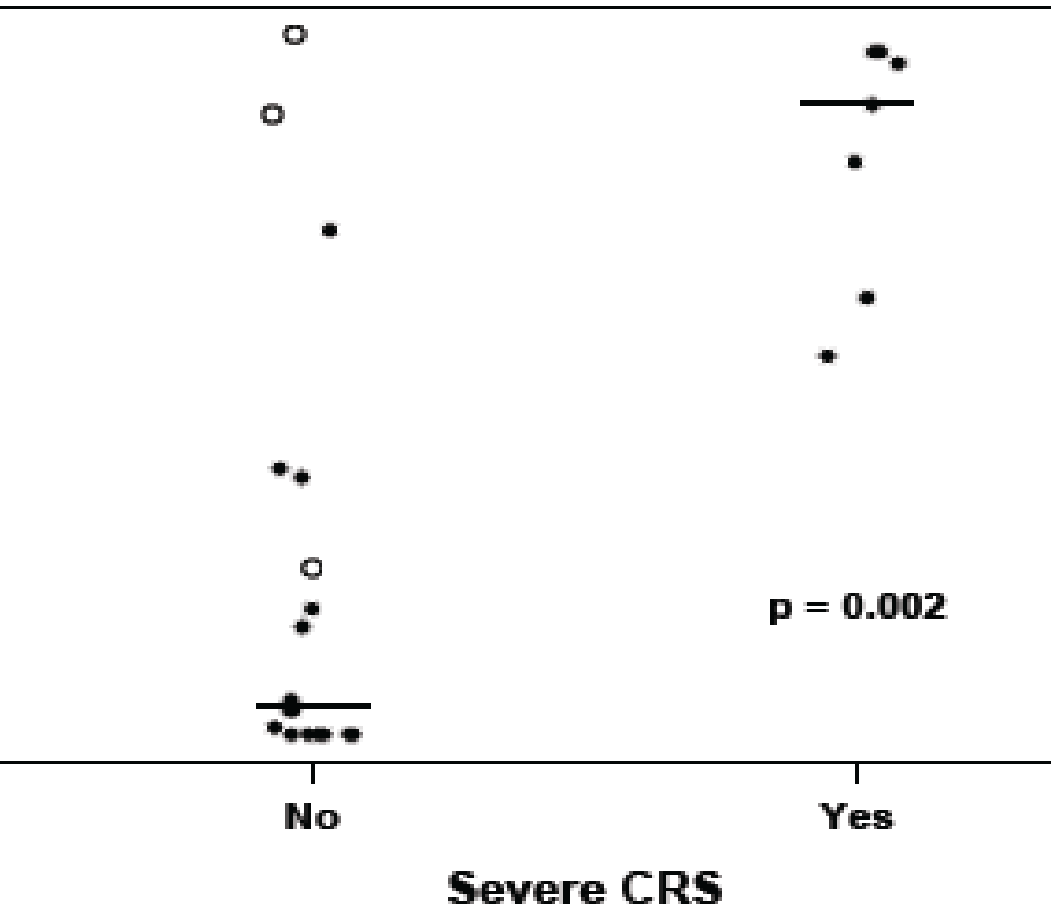
Morphology of CARs In Vivo



CTL019 for Relapsed Refractory ALL: Survival



The **NEW ENGLAND**
JOURNAL of **MEDICINE**



Rationale for CART-19 in Multiple Myeloma

1. Target clonotypic B-cells.

CD19+ B-cells with clonal relationship to myeloma plasma cells based on IgH sequence identity that may be a drug-resistant disease reservoir and/or stem-cell population.

2. Malignant myeloma plasma cells may express sufficient CD19 (at low levels) for CART-19 recognition.

Protocol with CART19 in myeloma open at Penn

Summary: CTL019 for B cell malignancies

- CAR T cells can eradicate large, bulky tumors in lymphomas and leukemias
- Response rates appear to be higher in ALL than lymphomas
- CAR T cells are living drugs and expand in vivo (1000 – 10,000 fold)
- Most responding patients develop cytokine release syndrome and B cell aplasia
 - Cytokine release syndrome can be managed with anti-cytokine therapy
 - Hypogammaglobulinemia can be managed with IVIG
- CAR T cells can persist for >36 months after a single treatment
- CAR therapy holds great promise for patients with advanced, relapsed and/or refractory CLL, ALL, NHL, (and maybe myeloma)

Colleagues and Collaborators (too many to list)

ACC Translational Research

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