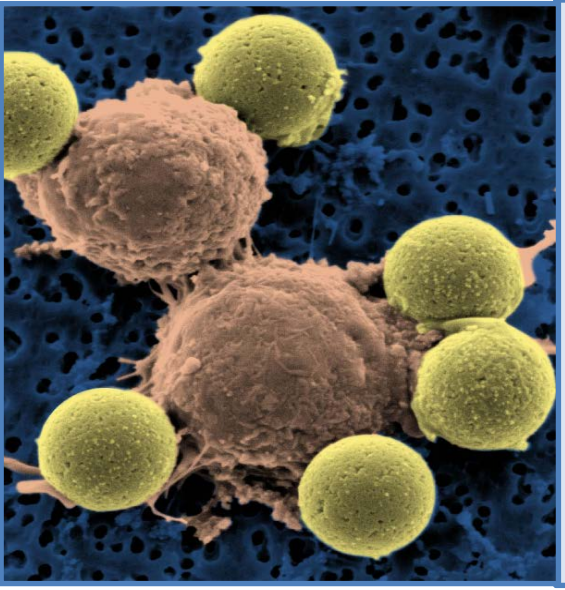

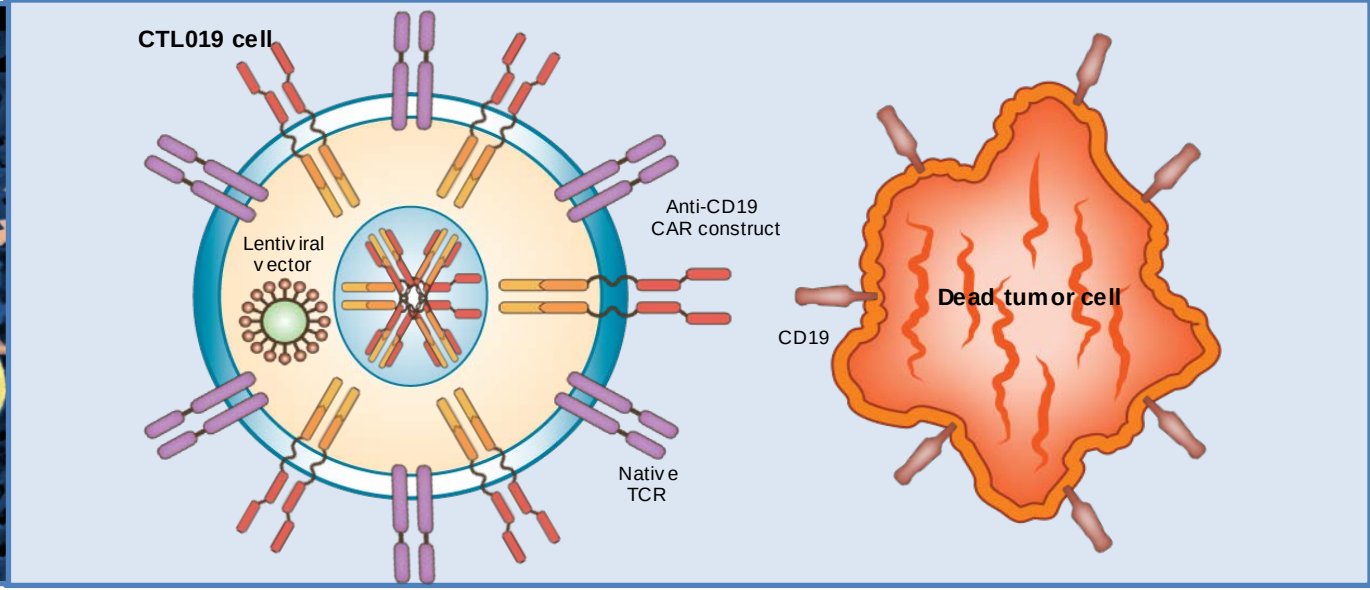

CAR T-cell Therapy: A Personalized Immunotherapy Approach to Cancer

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OptumHealth Education
April 12, 2019

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Disclosures

- Consultancy:
  - Novartis – advisory boards, clinical trial development
  - Kite – advisory board

- CTL019 (now known as Kymriah, tisagenlecleucel) licensed by Novartis
- CTL119 (investigational product) licensed by Novartis

Outline

CAR T cell Therapy

- Chimeric Antigen Receptor (CAR) Design
- CAR T cell Trials and Outcomes

Toxicity

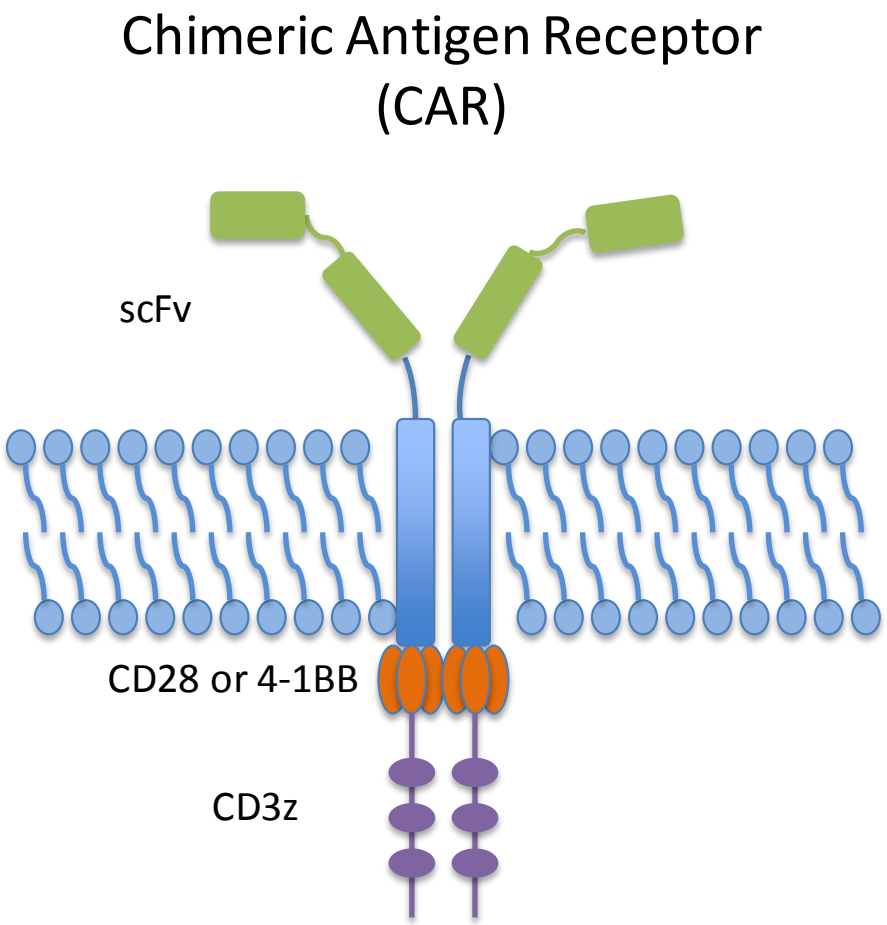
- Cytokine Release Syndrome (CRS)
- Neurotoxicity

Logistics

- Getting patients to CAR T cell therapies

What's next for CAR T cell Therapy?

Cellular Immunotherapy with CAR T cells



CAR links extracellular antibody to intracellular T cell signaling domains

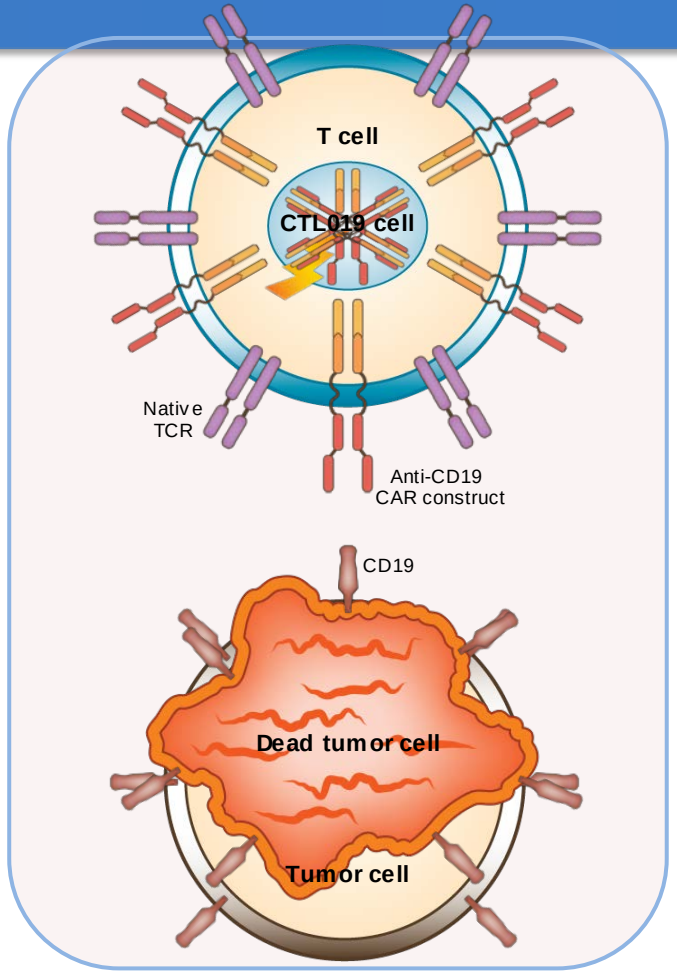
- Recognition: scFv binds antigen on tumor cell
- Activation: linked to activation signals

Selecting a target antigen:

- Ideally, universally expressed on tumor cells and not expressed on normal cells, but RARE
- Close to ideal – CD19 as example:
  - *Expressed on most B cell malignancies*
  - *Expression restricted to B cells*

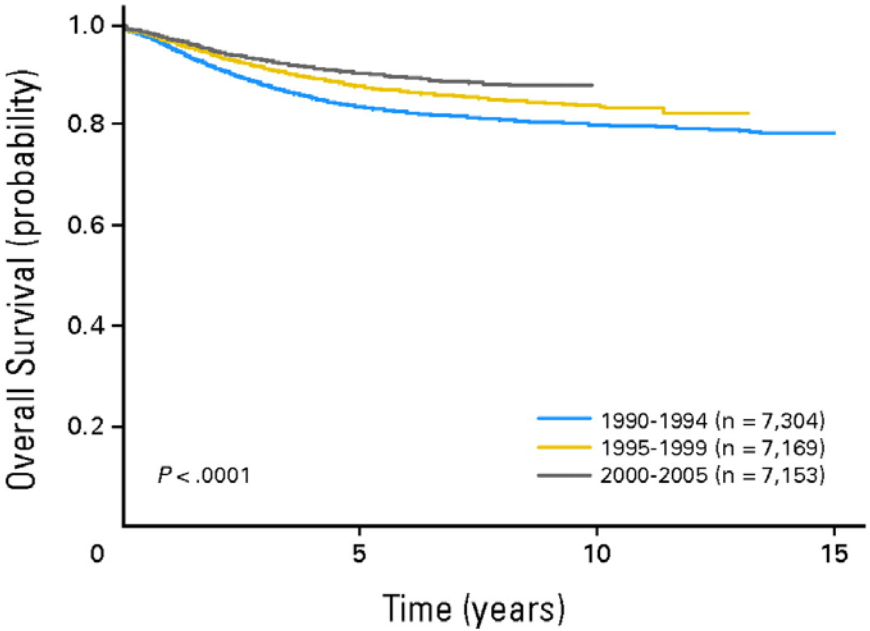
CAR T cell Engineering

- T cells collected from patient
- Lentiviral vector introduces gene encoding CAR
- CAR links extracellular antibody to intracellular T cell signaling domains
- T cells expanded ex vivo
- Reinfused ➔ come in contact with antigen ➔ engage CAR ➔ cytotoxic response and in vivo proliferation
- Persistent CART19 (CTL019) cells may allow long-term disease control



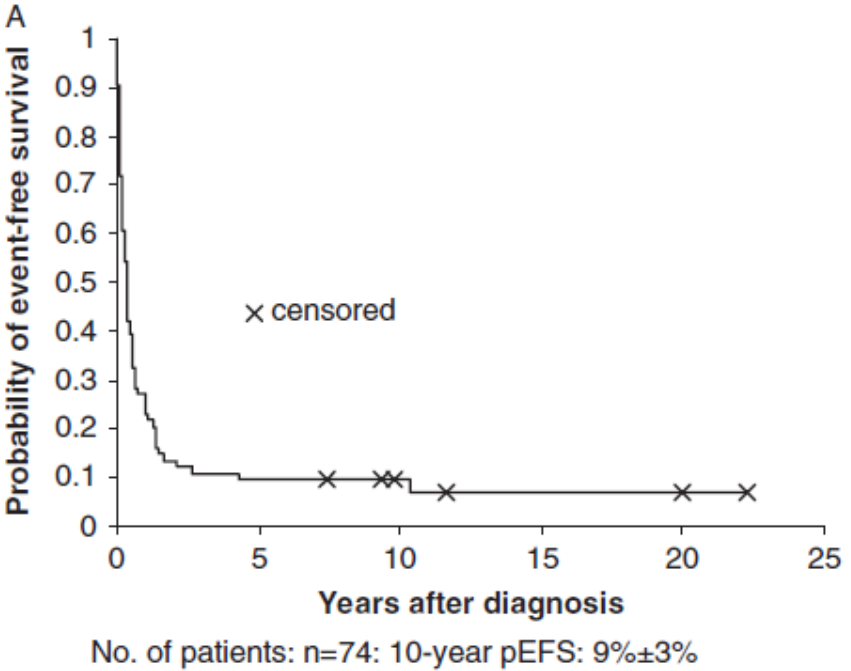
Pediatric Acute Lymphoblastic Leukemia (ALL)

Survival for newly diagnosed ALL



Hunger S P et al. JCO 2012;30:1663-1669

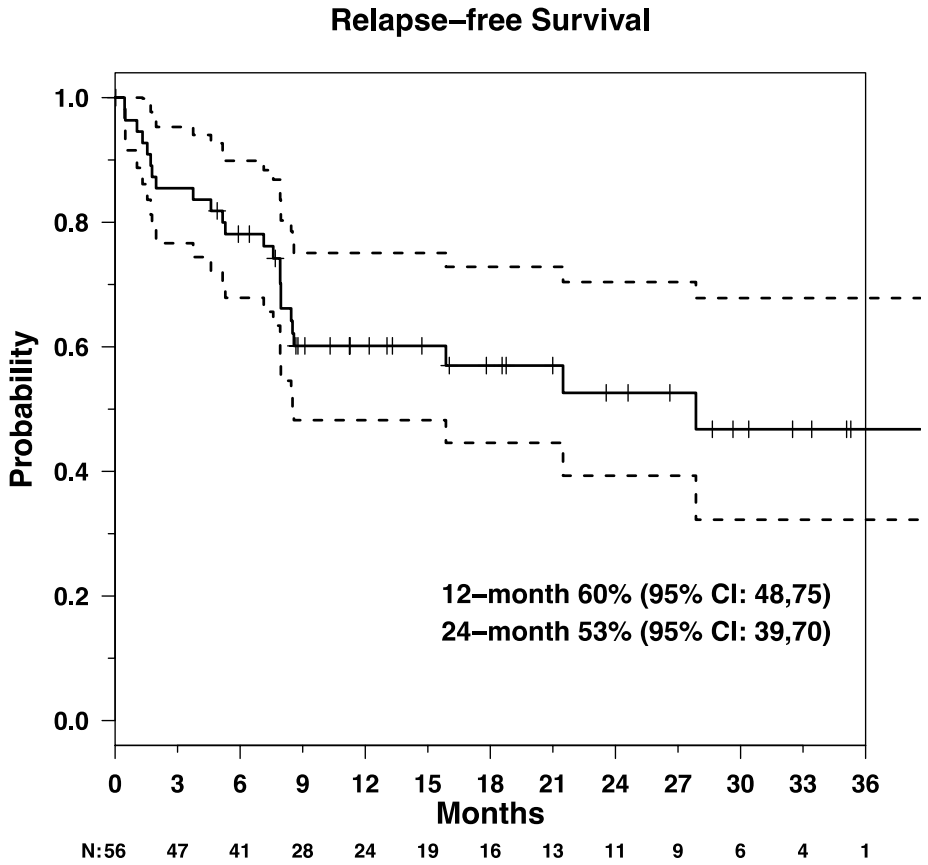
Survival for 2nd relapse



Resimuller et al. JPHO 2013

- Outcomes remain poor for pediatric ALL that is refractory or in second or greater relapse

Phase 1/2a Trial of CTL019 in Pediatric ALL



CR: 56/60 (93%)

CNS control: 11/15 pts with CNS disease within 12 mo remained in continuous CR

RFS:

12 mo – 60% (48, 75)

24 mo – 53% (39, 70)

7 pts proceeded to SCT, 1 to DLI

– 2 relapses after SCT

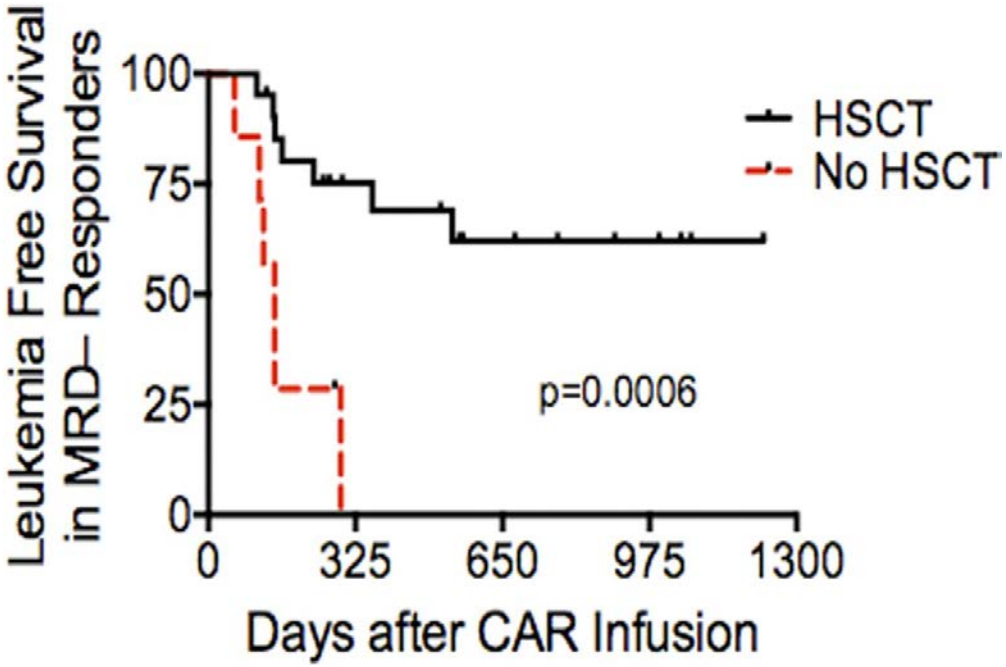
Median f/u: 15 mo (1-48 mo)

Maude et al., ASCO 2016

CRs with CD19 CARs

NCI CD19-28 CAR

- 31/51 (60.8%) CR, 28 MRD- in children and young adults with R/R B-ALL
- Median Leukemia-free survival 18 mo in 28 MRD- CR
- 21/28 receiving subsequent SCT



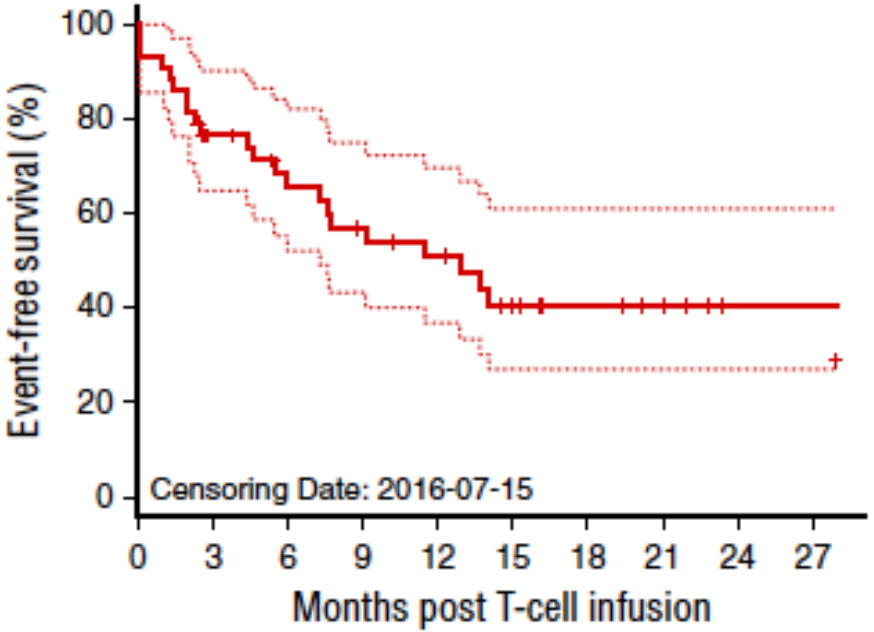
Lee D et al. ASH 2016

CRs with CD19 CARs

FHCRC CD19-4-1BB CAR

- 40/43 93% MRD- CR in children and young adults with R/R B-ALL
- 12mo EFS 50.8% (95% CI, 36.9-69.9%)
- 11 underwent HSCT

Gardner RA et al. Blood 2017; 129: 3322-3331.



ELIANA Phase 2 Trial of CTL019

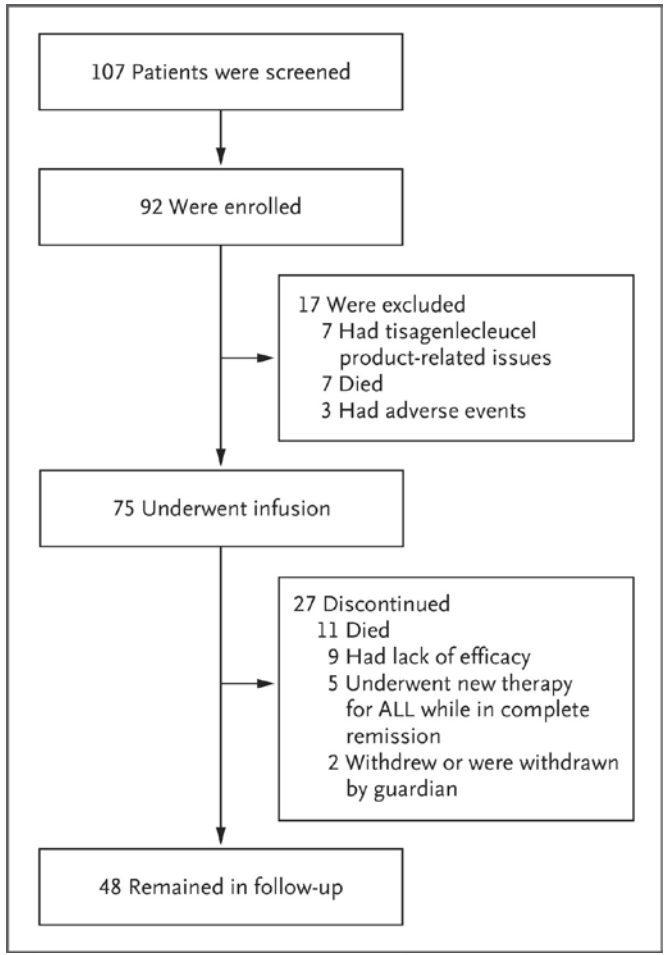


Table S1. Patient Demographics and Baseline Clinical Characteristics.

	Patients (N = 75)
Age, median (range), years	11 (3-23)
Male, n (%)	43 (57)
Prior stem cell transplant, n (%)	46 (61)
Previous line of therapies, median (range), n	3 (1-8)
Disease status, n (%)	
Primary refractory	6 (8)
Chemo-refractory or relapsed	69 (92)
Morphologic blast count in bone marrow, median (range), %	74 (5-99)
CNS status classification, n (%)*	
CNS-1	63 (84)
CNS-2	10 (13)
CNS-3	1 (1)
Unknown	1 (1)
High-risk genomic lesions, n (%)†	28 (37)
Down syndrome, n (%)	6 (8)

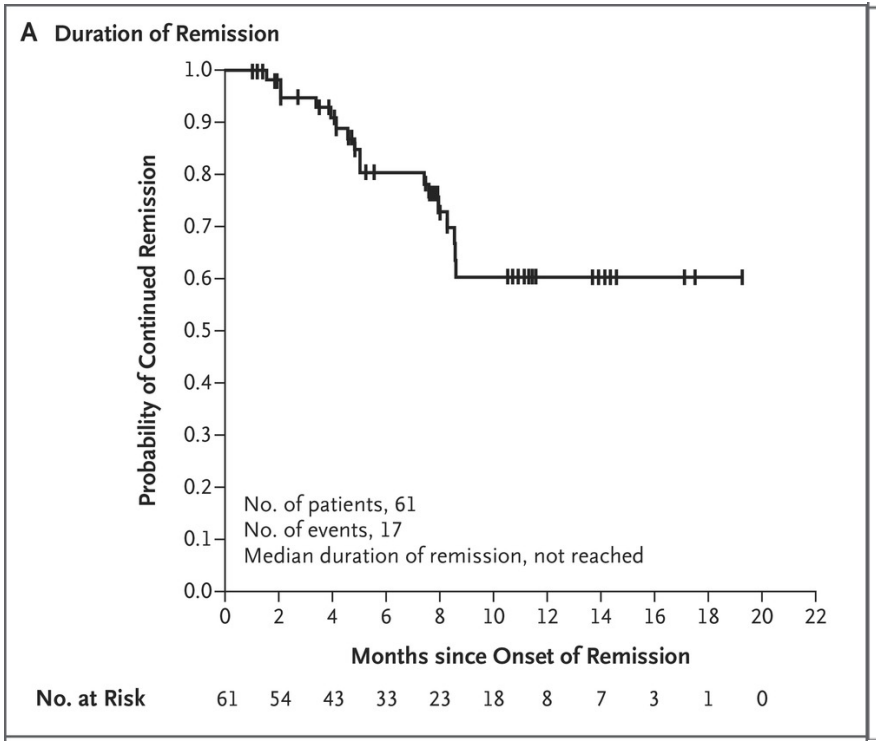
CNS, central nervous system.

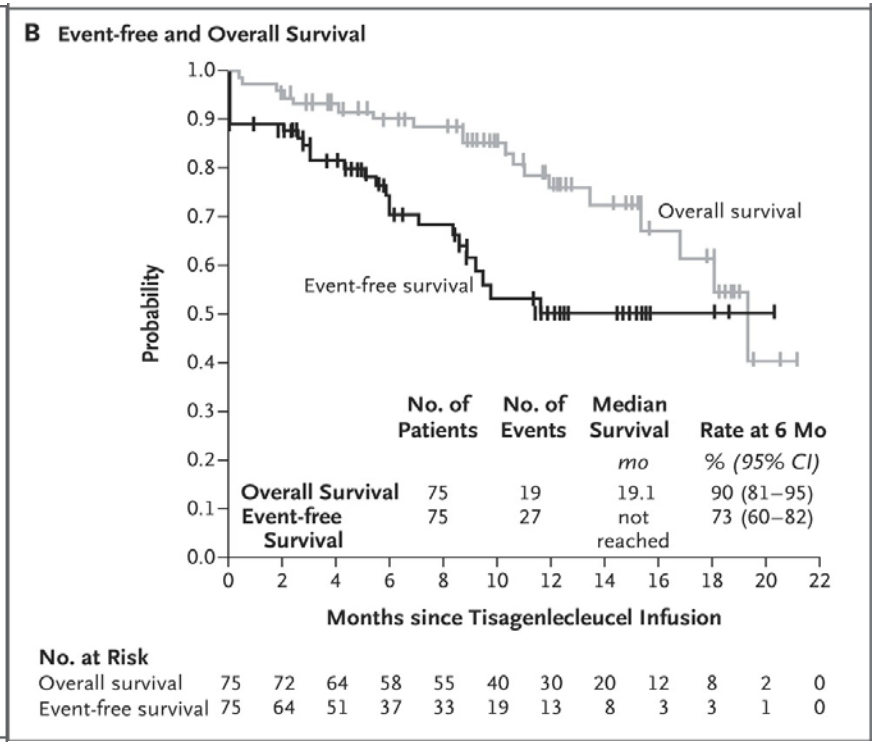
* The most current assessment on or prior to the date of enrollment. † *BCR-ABL1*, *MLL* rearrangement, hypoploidy, lesions associated with *BCR-ABL1*-like gene signature, or complex karyotype (≥5 unrelated abnormalities).

Maude SL et al. N Engl J Med 2018;378:439-448

Duration of Remission, Event-free and Overall Survival

Primary Endpoint: 61/75 CR/CRi (81%)





RFS: 59% (95% CI, 41 to 73) at 12 mo

8 underwent HSCT

Maude SL et al. N Engl J Med 2018;378:439-448

First US FDA approval of a CAR T cell therapy

August 30, 2017 – The FDA approved the first CAR T cell therapy, Kymriah™ for children and young adults up to age 25 with B-ALL that is refractory or in second or greater relapse

August 23, 2018 – EMA approval

September 6, 2018 – Health Canada approval

Outline

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Toxicity

- Cytokine Release Syndrome (CRS)
- Neurotoxicity

Logistics

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What's next for CAR T cell Therapy?

ELIANA Phase 2 Trial of CTL019 – Adverse Events

Table 2. Grade 3 or 4 Adverse Events Suspected to Be Related to Tisagenlecleucel That Occurred in at Least 5% of Patients.

Event	≤8 Wk after Infusion (N=75)		>8 Wk to 1 Yr after Infusion (N=70)	
	Grade 3	Grade 4	Grade 3	Grade 4
	number of patients (percent)			
Any grade 3 or 4 adverse event	19 (25)	33 (44)	8 (11)	4 (6)
Cytokine release syndrome	16 (21)	19 (25)	—	—
Hypotension	7 (9)	6 (8)	—	—
Decrease in lymphocyte count	5 (7)	4 (5)	1 (1)	—
Hypoxia	5 (7)	3 (4)	—	—
Increase in blood bilirubin	8 (11)	—	—	—
Increase in aspartate aminotransferase	5 (7)	2 (3)	—	—
Pyrexia	5 (7)	2 (3)	—	—
Decrease in neutrophil count	1 (1)	6 (8)	1 (1)	1 (1)
Decrease in white-cell count	—	7 (9)	—	—
Decrease in platelet count	3 (4)	4 (5)	—	—
Decrease in appetite	6 (8)	1 (1)	—	—
Acute kidney injury	3 (4)	3 (4)	—	—
Hypophosphatemia	5 (7)	1 (1)	—	—
Hypokalemia	6 (8)	—	—	—
Pulmonary edema	4 (5)	1 (1)	—	—
Thrombocytopenia	1 (1)	4 (5)	—	1 (1)
Encephalopathy	4 (5)	—	—	—
Increase in alanine aminotransferase	4 (5)	—	—	—
Fluid overload	4 (5)	—	—	—

Maude SL et al. N Engl J Med 2018;378:439-448

Cytokine Release Syndrome

CRS is related to T cell expansion

- Symptoms typically occur 1-14 days after CTL019 cell infusion in ALL

Fever
Myalgias
Nausea/Vomiting

Hypotension
Respiratory insufficiency
Renal insufficiency
Coagulopathy

- Severity scales with disease burden

Neurotoxicity

- Symptoms
  - Confusion/delirium
  - Expressive aphasia
  - Global encephalopathy
  - Tremor
  - Seizure
- Management
  - Supportive care/seizure management
  - Steroids?
- Pathophysiology
  - Cytokine-mediated?

Toxicity Summary

- CRS associated with CAR T cells can be safely managed
  - Requires specialized treatment
  - Cytokine blockade effective
  - Early cytokine data may be useful in CRS prediction models
  - Future studies will explore early intervention
- Neurotoxicity
  - Differs across diseases
  - Managed with supportive care
  - Just beginning to understand pathophysiology
  - Future studies needed to explore mechanism, which may inform prevention and treatment

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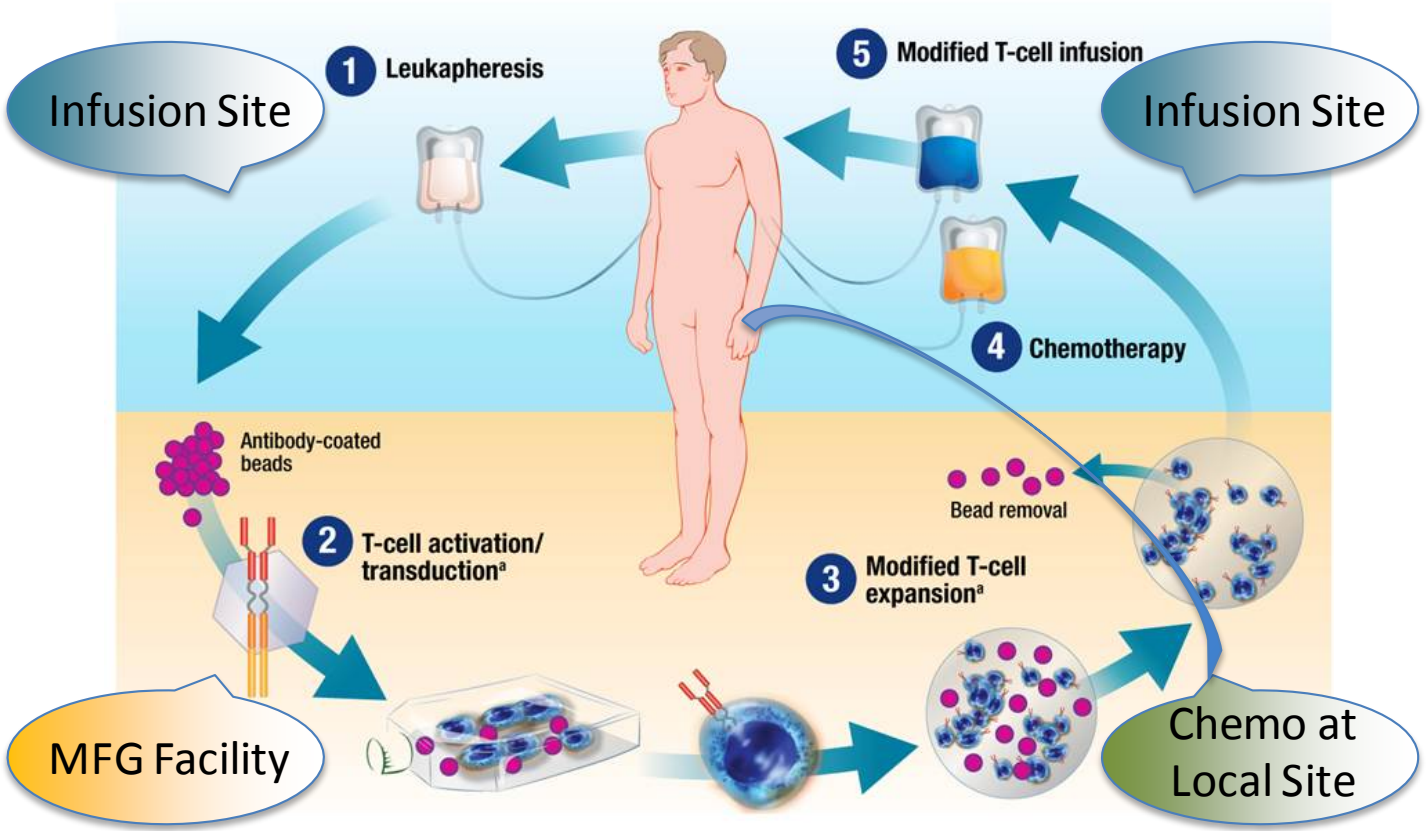
What's next for CAR T cell Therapy?

Logistics



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

Slide courtesy of Novartis

Patient Selection

- Population: Patients with B-ALL in 2nd or greater relapse or refractory
- Time from screening to treatment – weeks
- Need to stabilize and maintain eligibility

- Screen patients who have received prior CD19-directed therapy (eg blinatumomab) for CD19 expression

Timing of Leukapheresis

- At relapse
  - Considerations: WBC count, blast count
- After chemotherapy
  - Considerations: timing, type of chemotherapy, ALC
- After SCT
  - Considerations: timing, GVHD, immunosuppression

Patient Stabilization

Time from screening to treatment – weeks

- Goals:
  - Prevent rapid progression
  - Avoid organ toxicity and infectious complications
  - NOT to induce remission or reduce disease burden

Lymphodepleting chemotherapy

Given 1 week prior to infusion

- Purpose:
  - Disease control
  - Induce lymphopenia to facilitate engraftment and homeostatic expansion of CTL019 T cells
- Agents:
  - Cyclophosphamide 500 mg/m^2 IV daily Days 1-2, Fludarabine 30 mg/m^2 IV daily Days 1-4

CAR T Cell Infusion

- Premedication:
  - Tylenol and Benadryl
- Infusion:
  - Cell product thawed per Stem Cell Lab SOPs
  - Outpatient infusion center
  - Infused over 2-10 minutes by trained staff
  - Vital signs monitored every 15 minutes for 1 hour
  - Acute infusional toxicities rare

Management of Toxicity

- Cytokine Release Syndrome (CRS)
- Neurotoxicity

- Clinical care team:
  - Oncologists and BMT physicians
    - Core group focused on management of CAR T cell toxicities
  - Critical care
  - Neurologists

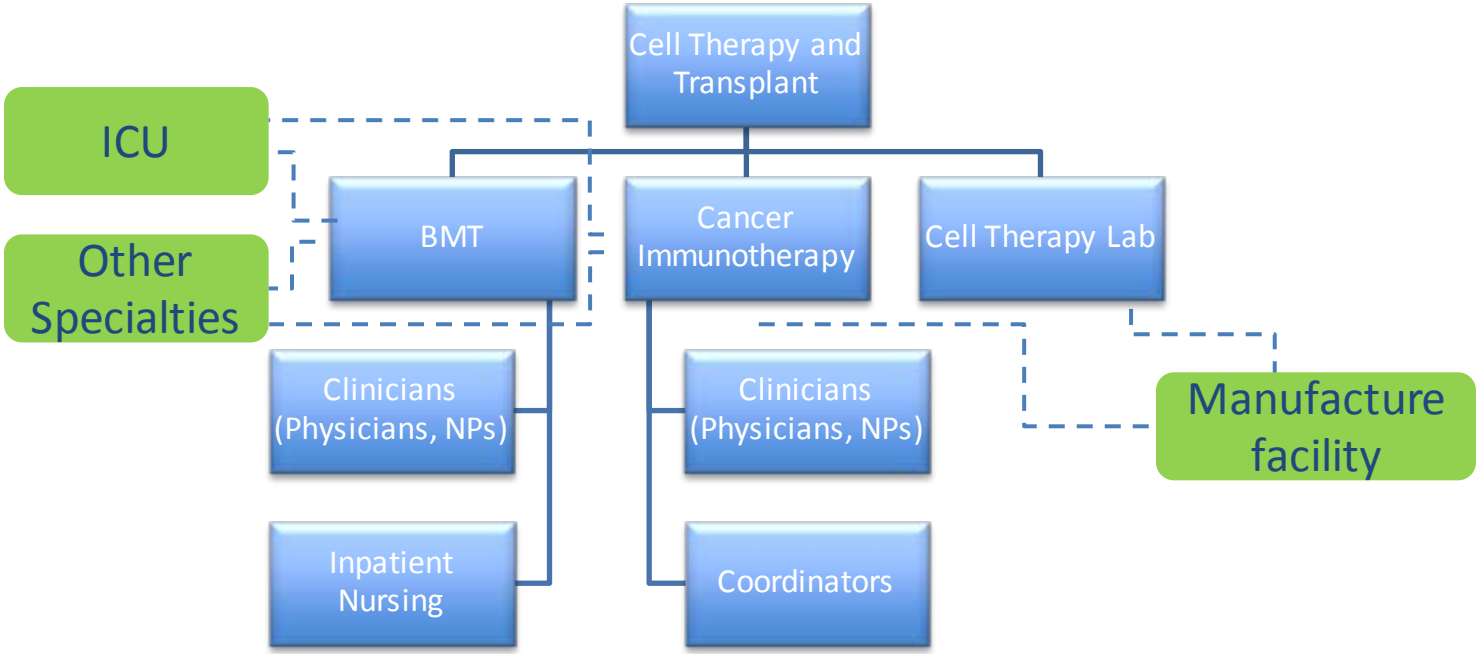
Long-term Management

- Monitoring response and persistence
  - B cell aplasia in first 6 months
- B cell aplasia:
  - Immunoglobulin replacement
    - Required in peds
    - Possibly not in adults?
  - Subcutaneous immunoglobulin for chronic B cell aplasia
  - Monitor IgG
  - Monitor for chronic sinusitis
- Prolonged cytopenias
  - More common in patients with prolonged cytopenias prior to infusion and post-SCT patients

Logistical Issues

- Transfer of care
  - Treatment at specialized care centers
  - Travel/housing
- Peri-infusion management
  - Limited group to focus on CAR T
  - Communication to other services
  - Spacing infusions
- Long-term management
  - Collaborative care: primary haematologist and infusion center

Cancer Immunotherapy Program



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What's next for CAR T cell Therapy?

What's next for cell therapy in pediatric cancers?

Expanding the role in B cell malignancies

- Moving into upfront therapy for VHR subsets at high risk of relapse
- Phase 2 trial in pediatric NHL
- Planning trials in other VHR populations
  - Down Syndrome B-ALL in first relapse
  - Hypodiploid B-ALL
  - B-ALL with t(17;19)

What's next for cell therapy in pediatric cancers?

Overcoming relapse

- CD19+ relapse - due to short persistence
  - Immune-mediated rejection?
  - T cell intrinsic?
- CD19- relapse - due to antigen escape

Persistence Variables

- CAR design
  - CD28 domain associated with more rapid early proliferation and more rapid loss (by 2 months in most cases)
  - 4-1BB domain associated with somewhat slower initial proliferation and prolonged persistence (years)
- Immune-mediated rejection
  - Anti-murine, anti-CAR
- T cell repertoire
  - Naïve and central memory T cells persist longer
  - Manufacture process may contribute or may be T cell intrinsic

What's next for cell therapy in pediatric cancers?

Overcoming relapse

- CD19+ relapse - due to short persistence
  - Immune-mediated rejection? *Humanized CAR trial ongoing at CHOP*
  - T cell intrinsic? *Combinations to improve T cell function*
- CD19- relapse - due to antigen escape
  - Alternative targets – CD22 CAR trials ongoing
  - Combination CARs

Conclusions

- CD19 CARs demonstrate the potential for cell therapy in pediatric cancers
  - High CR rates in refractory leukemias
  - Toxicity management for safe administration
- Cell therapies well-suited to pediatric cancers, which tend to be less heterogenous
- To expand the potential
  - Increase durable remission rates by overcoming relapse through
    - Improved persistence
    - Dual targeting
  - Combinations and innovative CAR designs may be needed to expand into other tumor types

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Adaptive TcR

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St. Baldrick's Foundation
Conquer Childhood Cancers

The Leukemia & Lymphoma Society
Fighting Blood Cancers