T Cell Engaging Therapies for Relapsed and Refractory B ALL BiTEs and CARTs

May 15, 2017

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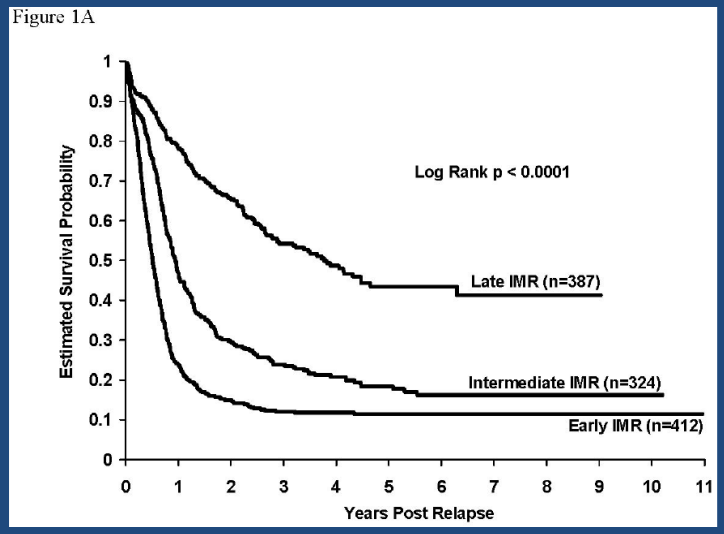
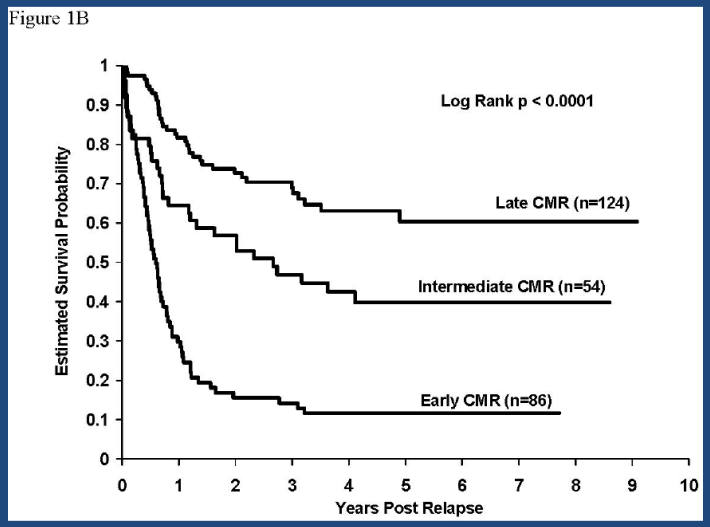
POGO
PEDIATRIC ONCOLOGY GROUP OF ONTARIO

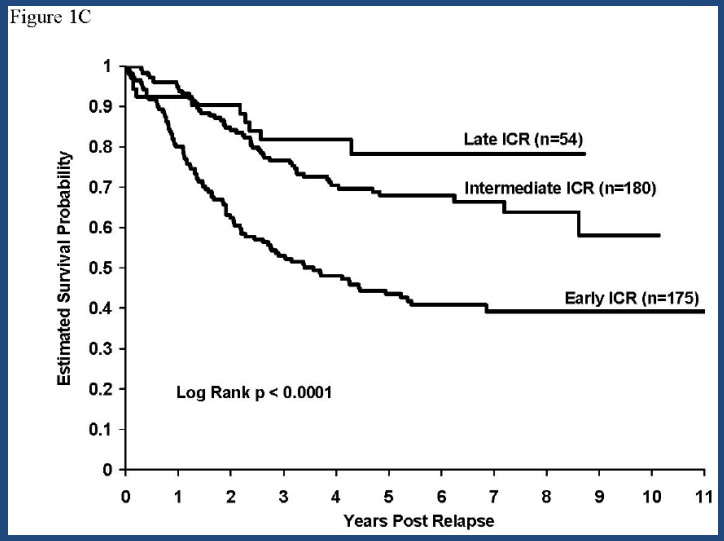
IBM 57.3% of Relapses



CMR 20.9% of Relapses



IEM 13.5% of Relapses



Early: <18 months from initial dx
Intermediate: 18-36 months from initial dx
Late: >36 months from initial dx

- 9585 patients with B ALL or T cell ALL registered on COG clinical trials 1988-2002
- 1961 patients experienced a relapse (20.45%)

Nguyen et al. (2008) Leukemia

Outcome of Patients Treated for Relapsed or Refractory Acute Lymphoblastic Leukemia: A Therapeutic Advances in Childhood Leukemia Consortium Study

Richard H. Ko, Lingyun Ji, Phillip Barnette, Bruce Bostrom, Raymond Hutchinson, Elizabeth Raetz, Nita L. Seibel, Clare J. Twist, Elena Eckroth, Richard Sposto, Paul S. Gaynon, and Mignon L. Loh

Results

Complete remission (CR) rates (mean ± SE) were 83% ± 4% for early first marrow relapse, 93% ± 3% for late first marrow relapse, 44% ± 5% for second marrow relapse, and 27% ± 6% for third marrow relapse. Five-year DFS rates in CR2 and CR3 were 27% ± 4% and 15% ± 7% respectively.

VOLUME 28 · NUMBER 4 · FEBRUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Goal: Achieve Clinical Remission with Therapeutic Attempts

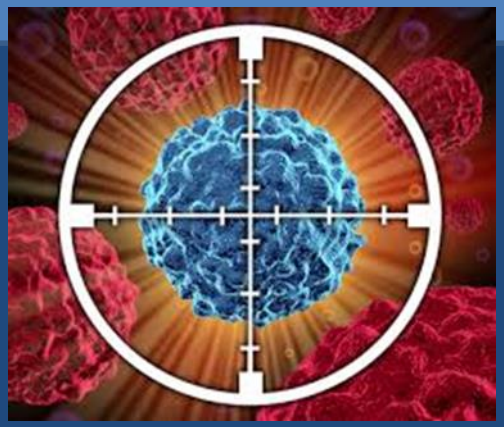
Ideal: Minimal Residual Disease Negative (MRD)

Difficult: Shorter time to relapse and when multiple relapses

The Dream….

A New Agent that will:

1. Target just the Leukemia Cells
2. Will work! –have ability to achieve MRD negative remissions
3. Have no (minimal) acute or long term toxicity
4. Readily available (quick access), easy to give and not cost too much



T Cell Engagers: CD19 targets

- Almost all B Lymphoblasts express CD19
- Not expressed on other cells/tissue (limits off target effects)
- Can harness cytotoxic immunity with directed T cells against CD 19 malignant cells
  - BiTE Blinatumomab
  - CART Chimeric Antigen Receptor T cells

Targets just the Leukemia Cells 

Blinatumomab

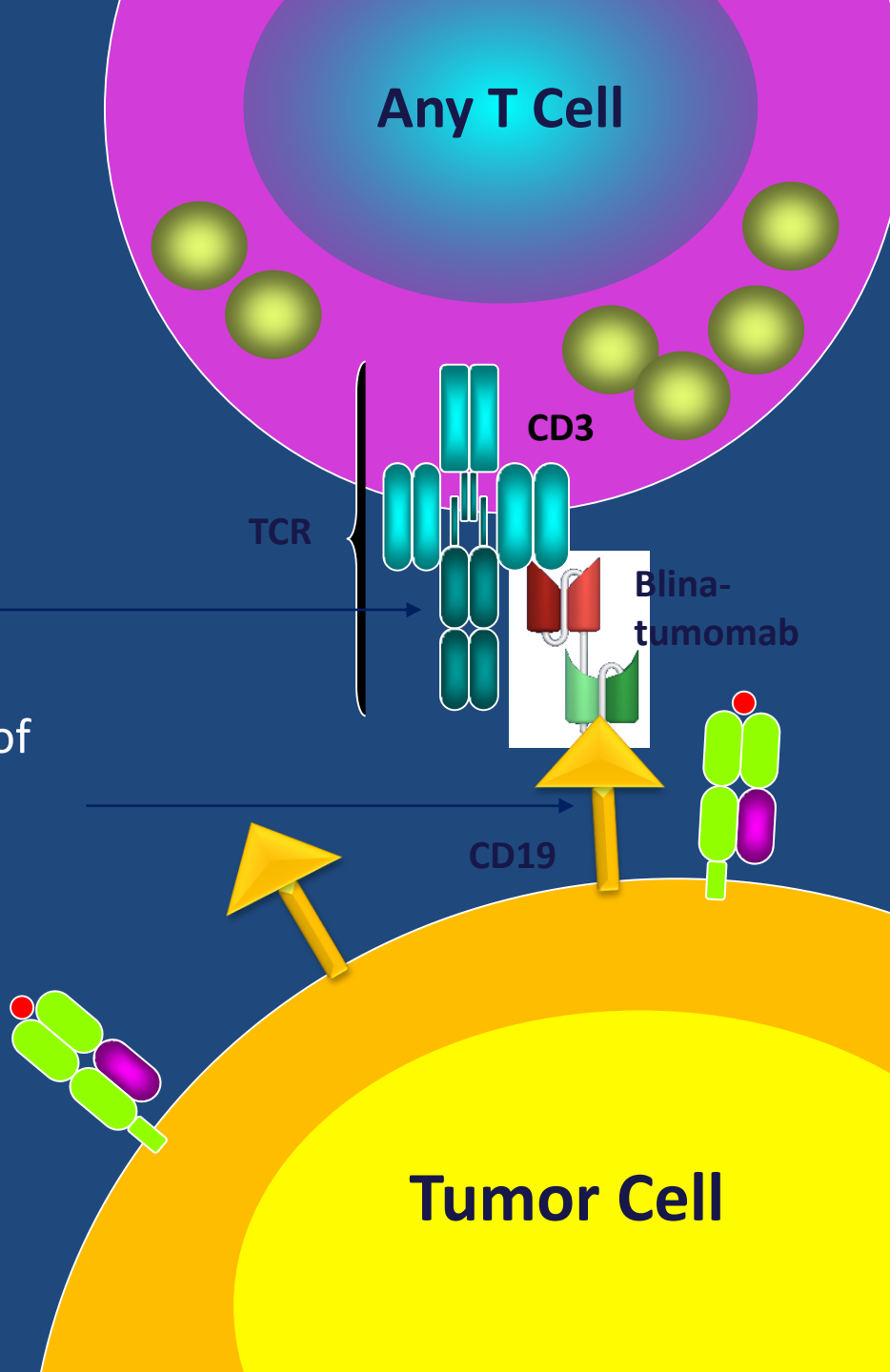
Mechanism of Action

(BiTE® = Bi-specific T-Cell Engager)

acts independently of specificity of T Cell Receptor (TCR)

allows T cells recognition of tumor-associated surface antigen (TAA)

does not require MHC Class I and/or peptide antigen



Courtesy of Dr. Lia Gore

Early Peds Experience with BiTE

Author	Number of Patients	Phase	Reported Outcomes
Handgretinger (2011)	• 3 All post HSCT	• 3 patient cohort • Compassionate	• All 3 achieved MRD CR at day 28
Shlegel (2014)	• 9 - All patients prior HSCT	• Cohort study • Compassionate	• 5/9 achieved MRD CR at day 28
Von Stackelberg (2016)	• N=49 at phase I • n=44 treated at phase II dose	• Phase I/II • Primary endpoint CR within 2 cycles	• 70 evaluable – (27/70) achieved CR • Those in CR (14/27) 53% MRD negative

Ability to achieve MRD negative remission 

Easy to Give:

- Complicated
- Continuous infusion for 28 days

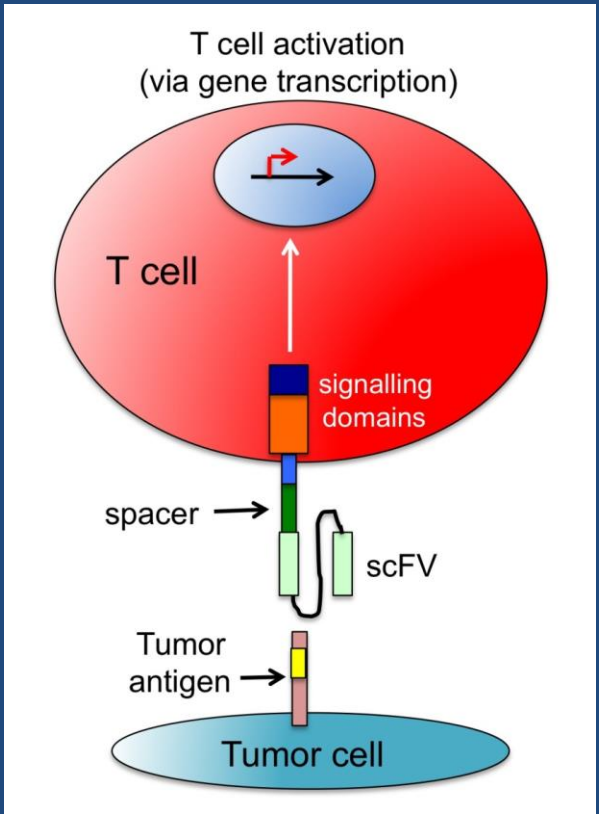
Available:

- Clinical Trial: AALL1331
- Compassionate access
- FDA approval Sept. 1, 2016 for Relapsed Pediatric B ALL (non Ph+)

Cost:

- unknown

Chimeric Antigen Receptor (CAR)



Easy?

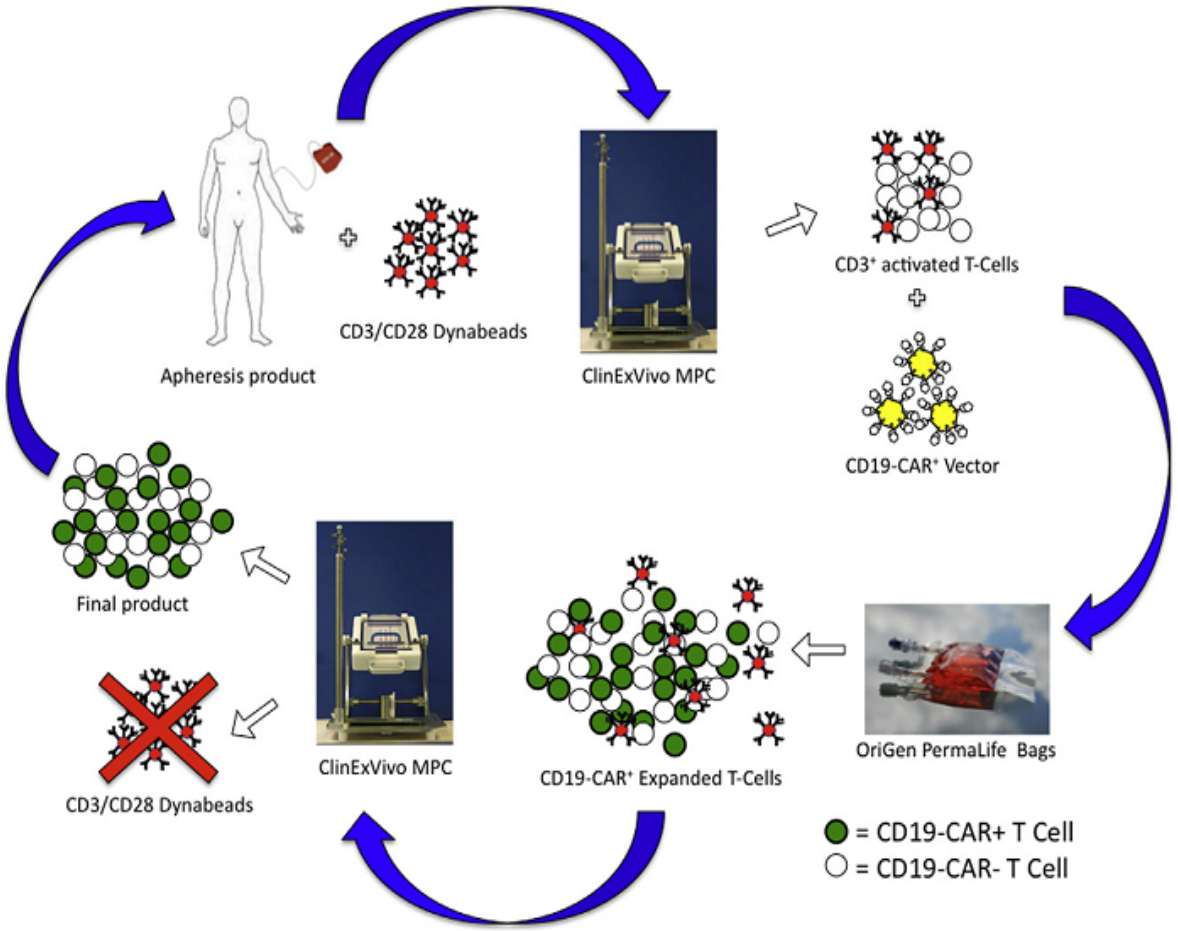


Figure 1. Scheme of the manufacturing process. On day 0, the apheresis product was incubated with anti-CD3/anti-CD28 paramagnetic Dynabeads at a ratio of beads: CD3+ cells of 3:1. The suspension of cells and beads was then exposed to a magnet (ClinExVivo MPC) to select the CD3+ fraction. The selected cells were washed and resuspended in initiation medium, with low IL-2 concentration. After 2 days of culture, the cells and beads were added to culture bags (PermaLife) that had been treated with RetroNectin and loaded with anti-CD19 CAR viral vector and incubated for at least 24 h. The transduction step was repeated the day after, and the cells and beads were then transferred to new culture bags and expanded for 9 more days. At the completion of the cell expansion, the beads were removed and discarded with the ClinExVivo MPC magnet, and the cells were washed and prepared for the infusion.

Tumaini, Cryotherapy, 2013

Do They Work?

- There are different CARTs
  - Designed with varying co-stimulatory domains
  - CHOP and Novartis: Persistence of CARTs
  - NIH and KTE-C19: 1-3 month persistence

Do they work?

CD019 (CHOP)	Maude et al. NEJM, October 16, 2014
Patient Population	25 patients aged 5-22 plus 5 adult patients
Morphologic Response	27/30 (90%) M1 Marrow at 1 month post infusion
MRD Response	22/30 (73%) MRD negative remission at 1 month post infusion
CNS3 excluded (2 CNS2)	No CNS relapses at 6 month time point
6 month EFS	67% (short follow-up)

NIH	Lee et al. (2015) Lancet
Patient Population	21 patients aged 1-30 (B ALL B NHL)
MRD Response	12/20 MRD negative remission at 1 month post infusion (10/12 went on to receive transplant)
6 month Leukemia Free Survival	76% (short follow-up)

CART cells detected in CSF

When they don’t work…

- CD19 negative relapses
- Early loss of T Cell persistence
  - Return of CD19 population
- 6 month EFS reported
  - Need longer survival data!!!

Easy to Give:

- Complicated
- Time for manufacturing

Available:

- Limited
- Clinical Trials: CHOP, Expansion Novartis Trial CD019 (coming soon to SickKids), KTE-C19/ZUMA open at SickKids

Cost:

- Not Yet FDA approved – on the horizon
- Unknown?

Toxicity?

Cytokine Release Syndrome

- **Most common toxicity associated with both BiTE and CARTs**
- Constellation of inflammatory symptoms
  - Results from cytokine elevations
  - Associated with T cell proliferation
- CRS ranges from mild to severe to life threatening
  - Mild: flu-like symptoms, fever, myalgia
  - Severe: vascular leak, hypotension, pulmonary edema, coagulopathy
  - Life threatening: can lead to multi-system organ failure
- Cytokine elevations can be measured

Barrett, D. et al. (2014) Current Opinions in Pediatrics

CRS – How Common?

T Cell Engager	Grade 3 or higher	Reference
BiTEs	4% Grade 3 1% Grade 4 (n= 93 pediatric patients)	Von Stackelberg (2016), JCO
	2% (189 adult patients treated with Dexamethasone prephase)	Topp et al. (2015) Lancet Oncology
CARTs	27% Grade 3/4	Maude et al. (2014) NEJM
	16% Grade 3 16% Grade 4	Lee et al. (2015) Lancet

Not without toxicity! Delicate balance of risk and benefit!

Management of CRS

- Reported with first cycle of BiTE, typically within first 12-72 hours
- Post CART infusion – usually within 12-72 hours, but can be up to 14 days post
- Most Significantly elevated Cytokines:
  - IL10, IL6, IFNy
- Anti IL6 (tocilizumab) – resolution of CRS
  - Reversal and clinical improvement seen within 24 hours

Maude, Journal of Cancer, 2014; Barrett, Current Opinions in Pediatrics, 2014

Unique Neurotoxicity: BiTEs and CARTs

Temporary disturbances in CNS function :

- Trembling
- Disturbance or loss of movement of parts of the body
- Speech or coordination disorders
- Apraxia
- Dizziness
- Confusion, disorientation
- Reversible seizures
- Encephalopathy
- Somnolence, agitation

Neurotoxicity

T Cell Engager	Reported Neurotoxicity	Reference
BiTEs	24% reported events 4% Grade 3 No Grade 4/5 All reversible	Von Stackelberg et al. (2016) JCO
CART	6/21 patients (28%) 1/6 Grade 3 No Grade 4/5 All reversible	Lee et al. (2015) Lancet
	13/30 (43%) Grades not reported All reversible	Maude et al. (2014) NEJM

Other Toxicities

Persistent CARTs:

- No B cells – Acquired Hypogamaglobulinemia
- IVIG replacement
  - For duration of B cell aplasia

Late Effects of Immunotherapy Unknown

- Will need ongoing longitudinal studies

BiTE or CART

BiTE	CART
Available “off the shelf” FDA approval Sept. 1, 2016	Requires T cell collection and manufacturing (4 weeks to 4 months)
In Phase III trial (First Relapse)	In Phase I/II
Do not persist	Can persist – depends on type of CART
28 day continuous infusion	Short infusion (30 minutes)
No long term B cell aplasia	If CARTs designed to persist and patient does not go on to SCT – B cell aplasia and IVIG replacement indefinitely
Cytokine Release Syndrome (grade 3 or greater estimated 6-8%)	Cytokine Release Syndrome (grade 3 or greater estimated 30%)
Recommend follow BiTE with SCT	Varying opinions – also based on type of CART
Dexamethasone Prephase	No Steroids

The Dream…


STOP WORRYING
ABOUT WHAT CAN
GO WRONG, AND
GET EXCITED
ABOUT WHAT CAN
GO RIGHT.
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