Demystifying Medicine 2018

Is Childhood Leukemia Curable?

Challenges and Milestones in Current Approaches

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Tuesday, January 16, 2018

Disclosures

- No disclosures to report

Educational Objectives

- Provide a general overview of pediatric ALL and current treatment approaches
- Review advances in immunotherapeutic approaches for treatment of ALL
- Discuss future directions and challenges in immunotherapy for ALL

Lets meet our special guests…

****All patients/parents have provided consent/assent or permission as appropriate to share their pictures and their stories****

BJ

- 18 year old male
- Diagnosed in October 2015
- Previously healthy
- No known risk factors
- Friend to all, loved son and brother
- Came to the NIH at age 19

Images courtesy of BJ's mother

MM

- 3 ½ year old female
- Diagnosed in March 2012
- Previously healthy
- No known risk factors
- Loves to dance, and is the heart and soul of her family
- Came to NIH at age 8

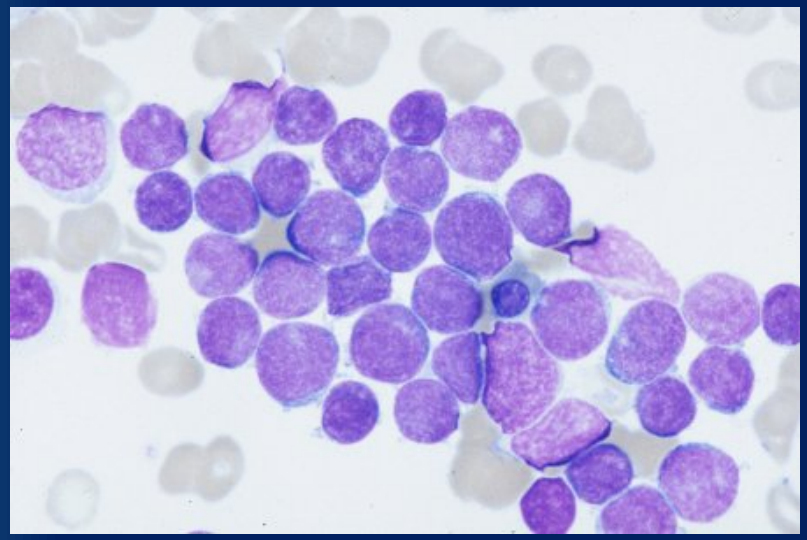
Images courtesy of MM's parents

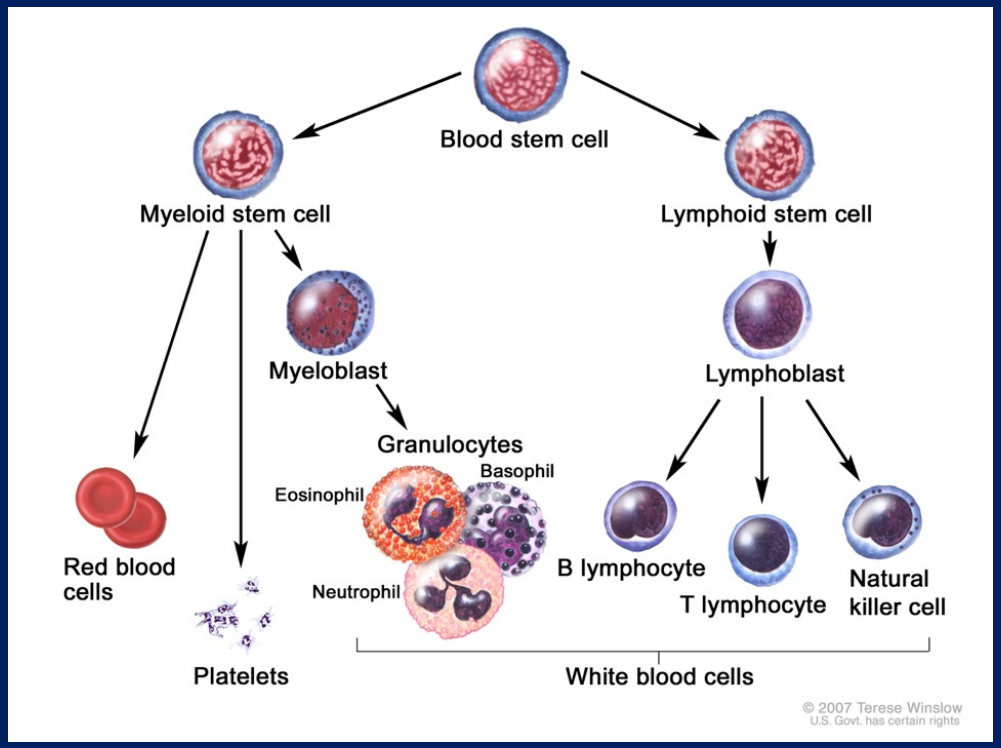
Sunny

- 6 year old male
- Diagnosed in June of 2010
- Previously healthy
- No known risk factors
- Loves X-box, food, challenges and is a loving brother and son
- Came to the NIH at age 12

Images courtesy of Sunny's parents

What are Lymphoblasts?

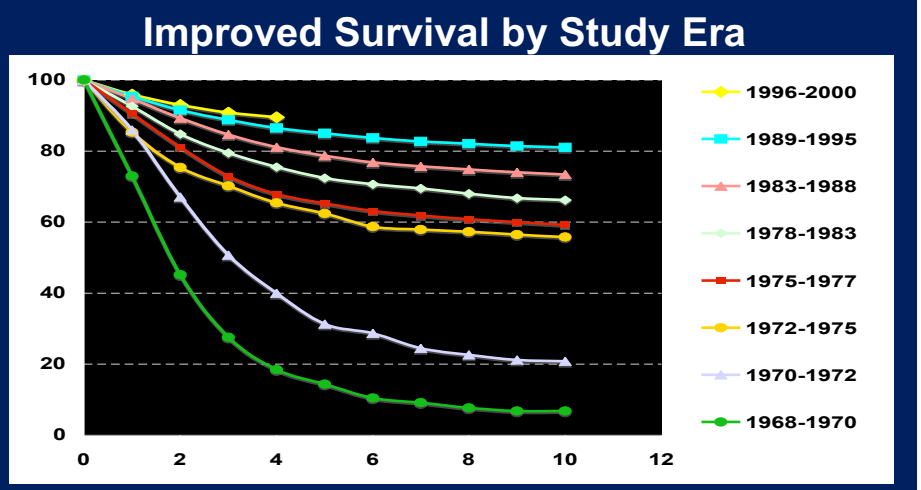




Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute

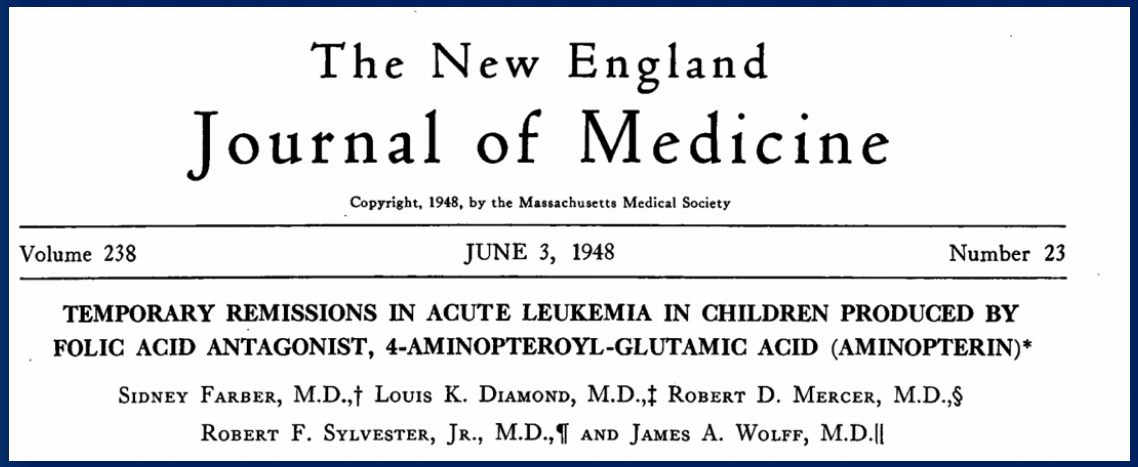
Childhood Acute Lymphoblastic Leukemia (ALL)

- Most common cancer diagnosed in children.
  - 41 cases/million in children aged < 14
  - 17 cases/million in teens between ages 15-19
  - 25% of all new cancer diagnosis
- 85-90% of patients will be cured.
- "Poster-child" for efficacy and importance of cooperative groups and clinical trial participation.



Data courtesy of GH Reaman, H Sather, Children's Oncology Group

Origin of ALL Therapy



The New England
Journal of Medicine

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Volume 238 JUNE 3, 1948 Number 23

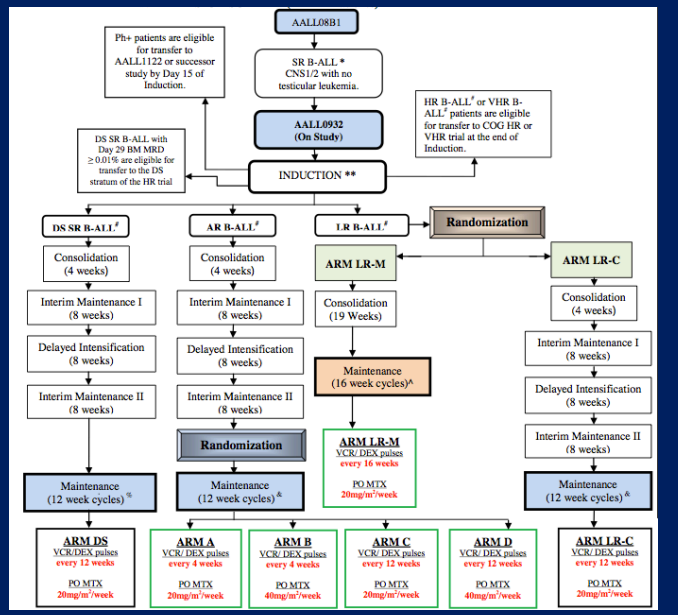
TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.||

- Based on the observation of folic acid agonists leading to an "acceleration" of leukemia progression
- This report outlined the cases of 5 children who attained a temporary remission with use of folic acid antagonists

Current Treatment Plan

- Combinatorial chemotherapy treatment strategy with non-competing mechanisms of action.
- Series of intensified/de-intensified treatment cycles.
- Prolonged maintenance phase (2-3 years)
- Risk-adapted approach



4.2.1 Induction (35 days).- B-ALL Patients

All patients without DS receive common Induction Therapy.

For patients with Down syndrome see Section 4.20.

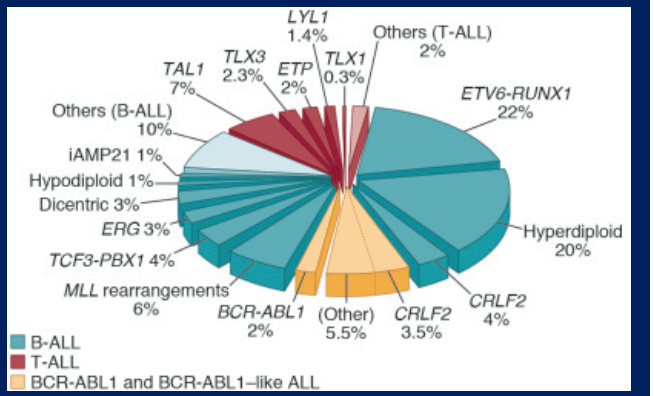
Patient name or initials _____ DOB _____

Induction therapy lasts 5 weeks (35 days). See Section 4.1 for full details regarding assignment to treatment arms and subsequent therapy. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) Dose 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	Given at time of diagnostic LP OR Day 1*	See Section 4.2 for administration guidelines **Note age-based dosing**	a. Hx, PE, Wt, Ht b. CBC/diff[1]platelets c. BM eval[1] d. PB sample[1] e. CSF cell count, cytospin[2] f. Creatinine, Bili, Albumin & ALT g. Varicella titer h. TPMT genotype (optional) [1]See Section 7.1 for details [2] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Cytarabine (IT ARAC)	IT	CNS2 patients ONLY Age (yrs) Dose 1-1.99 20 mg 2-2.99 30 mg ≥ 3 40 mg	**CNS2:** twice weekly†	† The initial dose is followed by twice weekly IT ARAC except during weeks when Days 8 & 29 IT MTX is administered **Note:** IT therapy is administered until 3 consecutive CSF samples are clear of blasts.	
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 8, 15 &22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	3 mg/m²/dose BID	Days 1-28 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.2 for administration guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4	**Note: pegaspargase should be administered on Day 4.** Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8 and 29	See Section 4.2 for administration guidelines **Note age-based dosing** **Note:** All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation.	

Risk Factors

- Standard NCI
  - Age 1-10 years
  - White blood cell count < 50,000
- Central nervous system disease
- Testicular involvement
- Down syndrome
- Sex
- Race/Ethnicity
- Immunophenotype (B v T-cell)



- Cytogenetics
  - Ph+; t(9;22)
  - *MLL/KMT2A*; 11q23
  - *ETV6-RUNX*1; *TEL-AML*; t(12,21)
  - Hypo/hyperdiploid
  - Newcomers:
    - Ph+ like
    - iAMP21
- Response to therapy

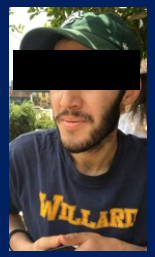
Challenges

- Curative options for relapsed/refractory disease remains a therapeutic challenge
- Outcomes for the adolescent young adult (AYA) population remain particularly poor
- Toxicity from cumulative therapy not insignificant
- Novel therapies are needed

Our Patients

BJ

- High-risk by age and presenting WBC (121K)
- Response to chemotherapy was suboptimal:
  - End-induction + disease→ high risk arm
  - Disease burden increased after consolidation

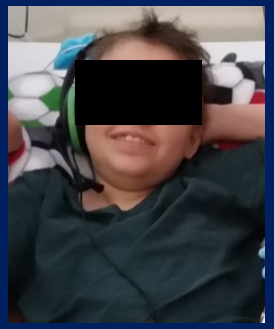


MM

- Standard risk at presentation
- Response to chemotherapy was suboptimal:
  - End-induction + disease→ high risk arm
  - Continued on therapy
- Relapsed in 2014 with CNS only disease

Sunny

- Standard risk at presentation
- Relapsed towards the end of therapy in September 2013

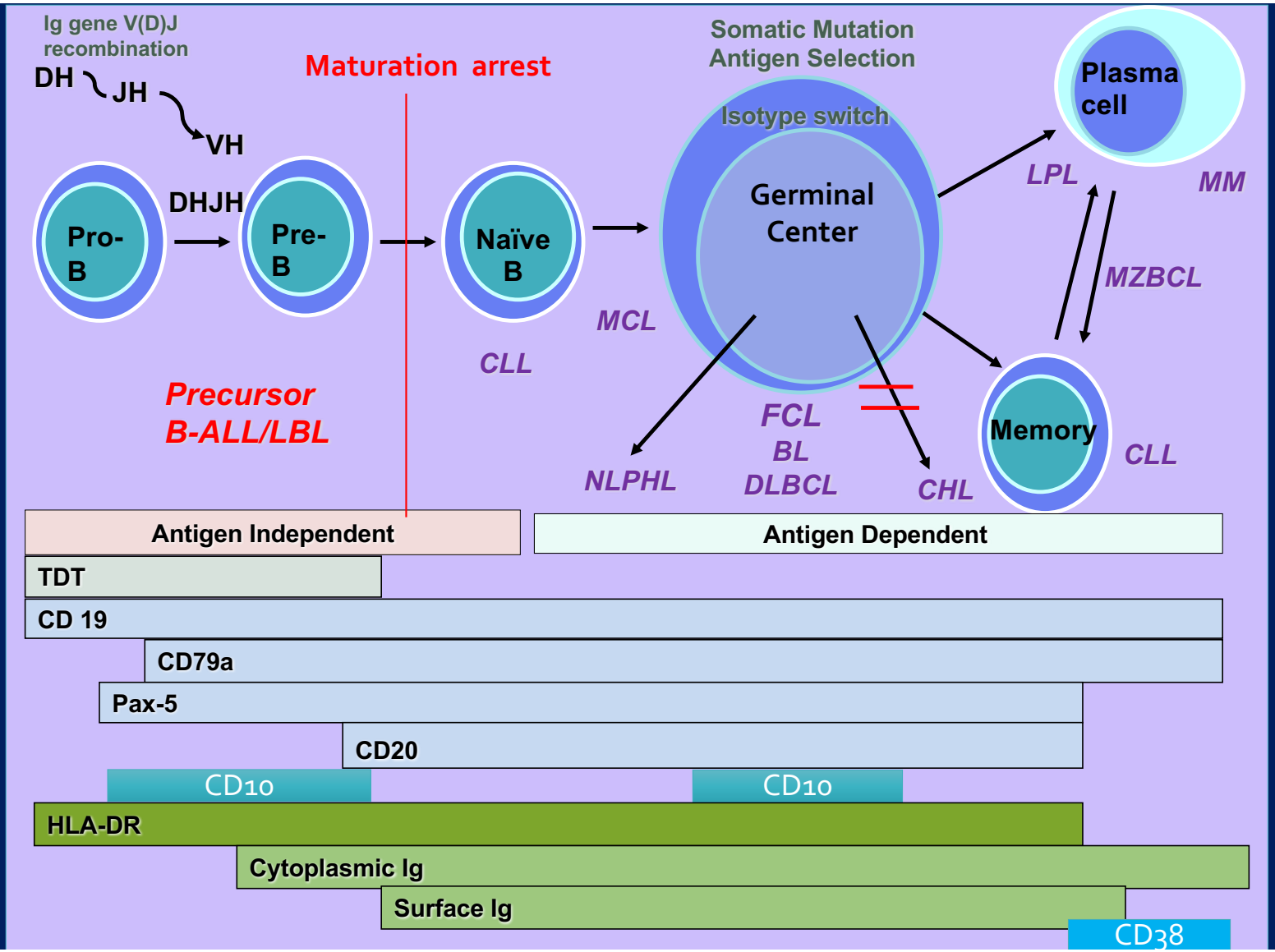


Novel Therapies: FDA Approval

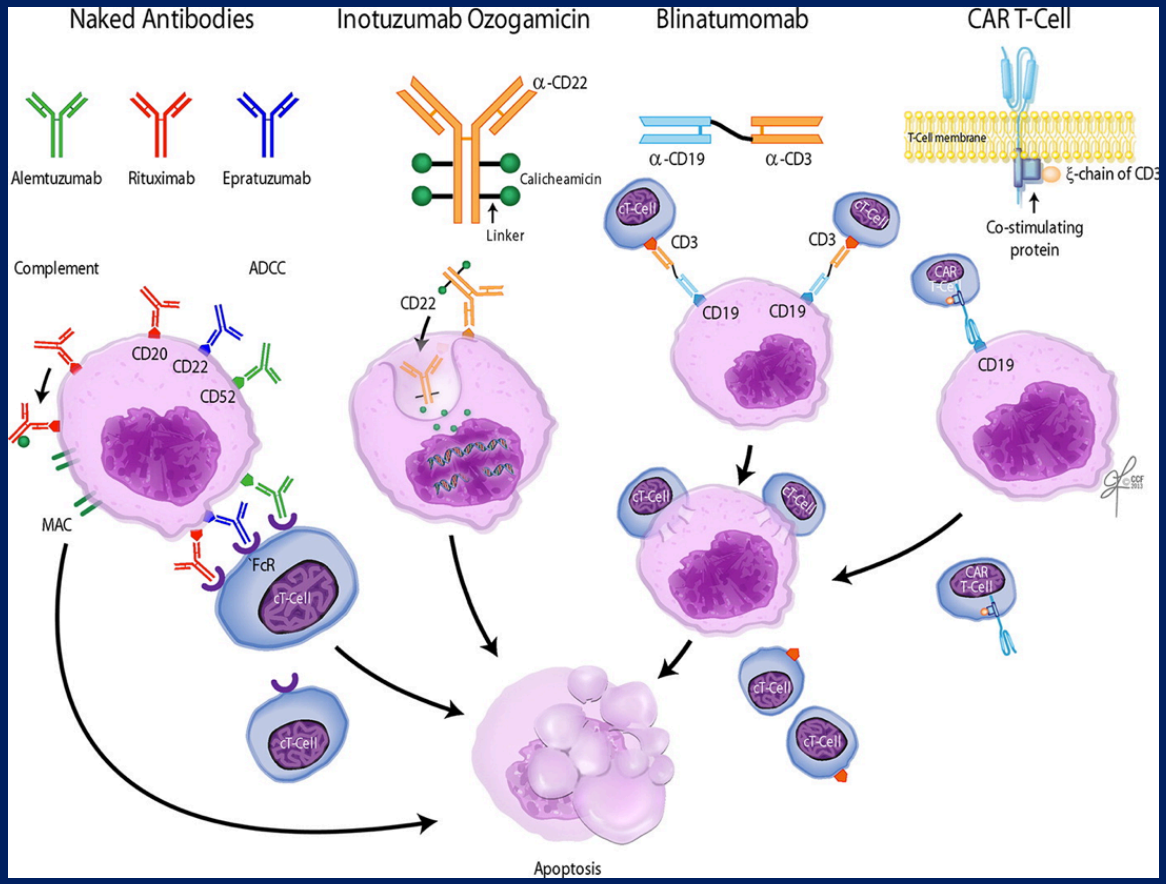
- Clofarabine: Purine nucleoside antimetabolite
- Nelarabine: Purine nucleoside antimetabolite, T-cell
- Vincristine Sulfate Liposome Injection (Marqibo®): ALL, in adults

- **Complete remission rates: +/- 20%**

B Cell Surface Antigens



Immunotherapy for ALL

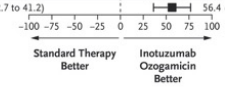


Portell C. Leukemia & Lymphoma 2013

Inotuzumab

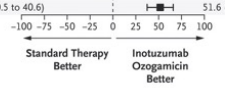
A Rate According to Stratification Factors at Randomization

Subgroup	No. of Patients: Inotuzumab Ozogamicin Group	No. of Patients: Standard-Therapy Group	Complete Remission: Inotuzumab Ozogamicin Group, % (95% CI)	Complete Remission: Standard-Therapy Group, % (95% CI)	Between-Group Difference (97.5% CI), percentage points	P Value
All patients	109	109	80.7 (72.1 to 87.7)	29.4 (21.0 to 38.8)	51.4 (38.4 to 64.3)	<0.001
Duration of first remission						
<12 mo	71	71	77.5 (66.0 to 86.5)	23.9 (14.6 to 35.5)	53.5 (37.6 to 69.4)	<0.001
≥12 mo	38	38	86.8 (71.9 to 95.6)	39.5 (24.0 to 56.6)	47.7 (25.8 to 69.0)	<0.001
Salvage-treatment phase						
First	73	73	87.7 (77.9 to 94.2)	28.8 (18.8 to 40.6)	58.9 (44.2 to 73.6)	<0.001
Second	36	36	66.7 (49.0 to 81.4)	30.6 (16.3 to 48.1)	36.1 (11.5 to 60.7)	0.002
Age						
<55 yr	66	69	80.3 (68.7 to 89.1)	31.9 (21.2 to 44.2)	48.4 (31.7 to 65.1)	<0.001
≥55 yr	43	40	81.4 (66.6 to 91.6)	25.0 (12.7 to 41.2)	56.4 (36.1 to 76.7)	<0.001



B Rate According to Patient Characteristics at Baseline

Subgroup	No. of Patients: Inotuzumab Ozogamicin Group	No. of Patients: Standard-Therapy Group	Complete Remission: Inotuzumab Ozogamicin Group, % (95% CI)	Complete Remission: Standard-Therapy Group, % (95% CI)	Between-Group Difference (97.5% CI), percentage points	P Value
All patients	109	109	80.7 (72.1 to 87.7)	29.4 (21.0 to 38.8)	51.4 (38.4 to 64.3)	<0.001
Peripheral blasts						
0	42	48	90.5 (77.4 to 97.3)	41.7 (27.6 to 56.8)	48.8 (29.9 to 67.7)	<0.001
>0 to 1000	32	35	71.9 (53.3 to 86.3)	20.0 (8.4 to 36.9)	51.9 (28.5 to 75.3)	<0.001
>1000	34	25	76.5 (58.8 to 89.3)	20.0 (6.8 to 40.7)	56.5 (32.2 to 80.7)	<0.001
Bone marrow blasts						
<50%	30	29	86.7 (69.3 to 96.2)	41.4 (23.5 to 61.1)	45.3 (20.5 to 70.1)	<0.001
≥50%	77	78	77.9 (67.0 to 86.6)	24.4 (15.3 to 35.4)	53.6 (38.4 to 68.8)	<0.001
CD22 expression						
<90%	24	24	79.2 (57.8 to 92.9)	25.0 (9.8 to 46.7)	54.2 (27.0 to 81.3)	<0.001
≥90%	74	63	82.4 (71.8 to 90.3)	36.5 (24.7 to 49.6)	45.9 (29.1 to 62.8)	<0.001
Karyotype						
Normal	20	20	95.0 (75.1 to 99.9)	30.0 (11.9 to 54.3)	65.0 (39.6 to 90.4)	<0.001
Ph-positive	14	18	78.6 (49.2 to 95.3)	44.4 (21.5 to 69.2)	34.1 (−1.8 to 70.1)	0.08
t(4;11)-positive	3	6	33.3 (0.8 to 90.6)	33.3 (4.3 to 77.7)	0.0 (−74.7 to 74.7)	1.00
Other abnormalities	49	46	85.7 (72.8 to 94.1)	26.1 (14.3 to 41.1)	59.6 (41.3 to 78.0)	<0.001
Previous stem-cell transplantation						
Yes	17	22	76.5 (50.1 to 93.2)	27.3 (10.7 to 50.2)	49.2 (17.8 to 80.6)	0.004
No	92	87	81.5 (72.1 to 88.9)	29.9 (20.5 to 40.6)	51.6 (37.4 to 65.9)	<0.001



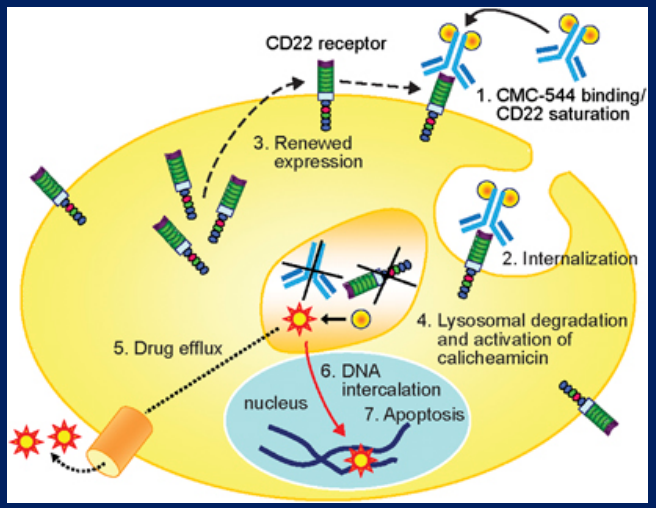
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

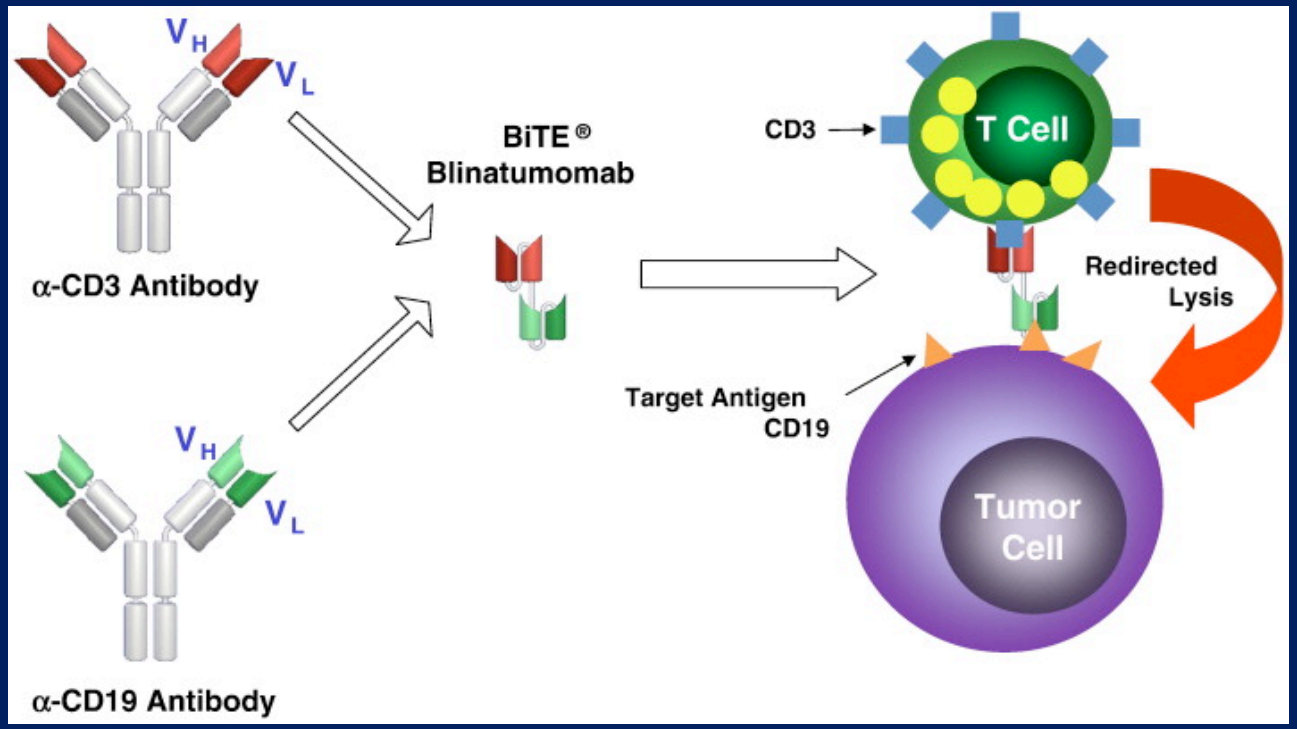
Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., Erik Vandendries, M.D., Ph.D., and Anjali S. Advani, M.D.

August 2016



- Pediatric: Retrospective study presented at ASCO 2017
- Phase II COG Study planned

Blinatumomab



- 50-70% CR rate in adults
- 30-40% CR rate in children

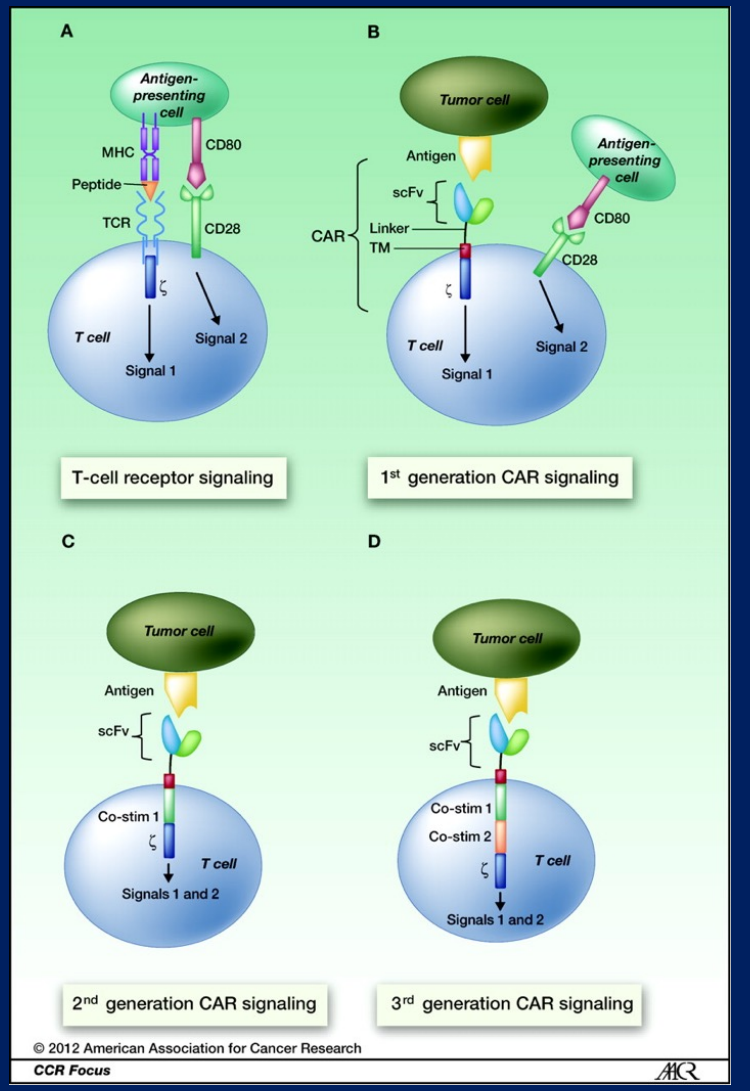
Novel Therapies: FDA Approval

- Blinatumomab: Accelerated approval in 2014, regular approval 2017.
- Inotuzumab: Approval in 2017, adults only

- **Complete remission rates: +/- 40-50%**

CAR-T Cell Therapy

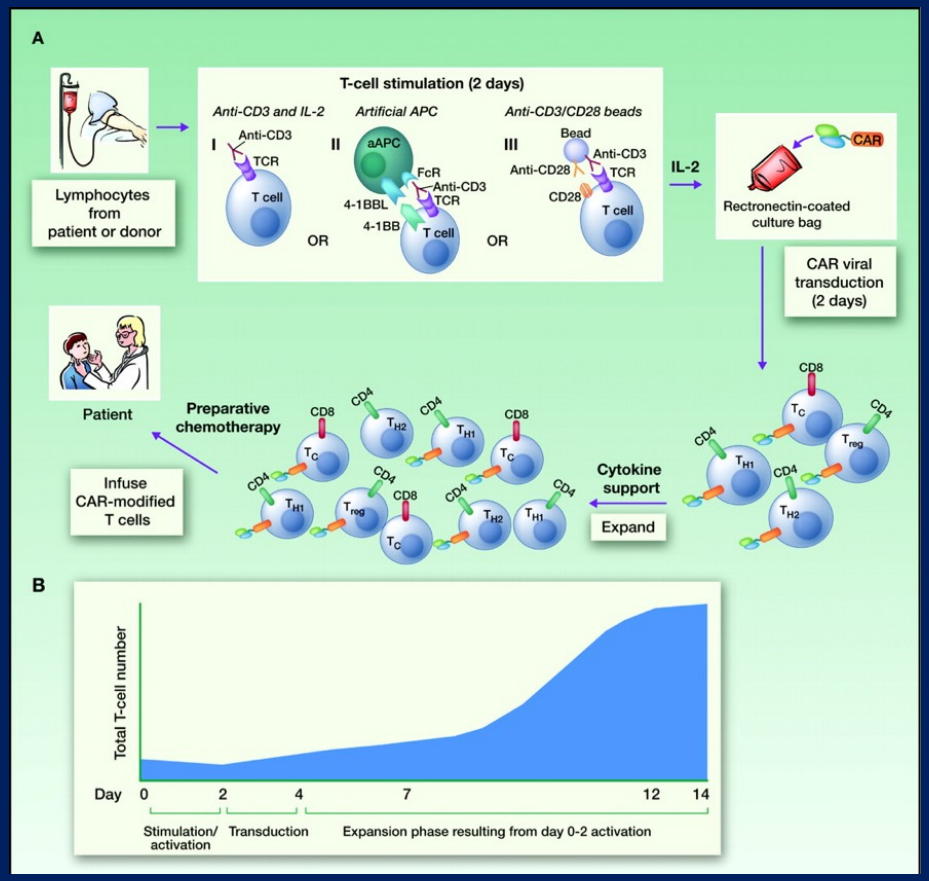
- What is a CAR
  - Chimeric Antigen Receptor
- Retains the functionality of a T-cell with the antigen recognition properties of antibody
- Customized receptor
  - Extracellular antigen-binding domain
  - Intracellular signaling domain of T cells



Lee DW, et al. Clin Cancer Res 2012

Making a CAR-T Cell

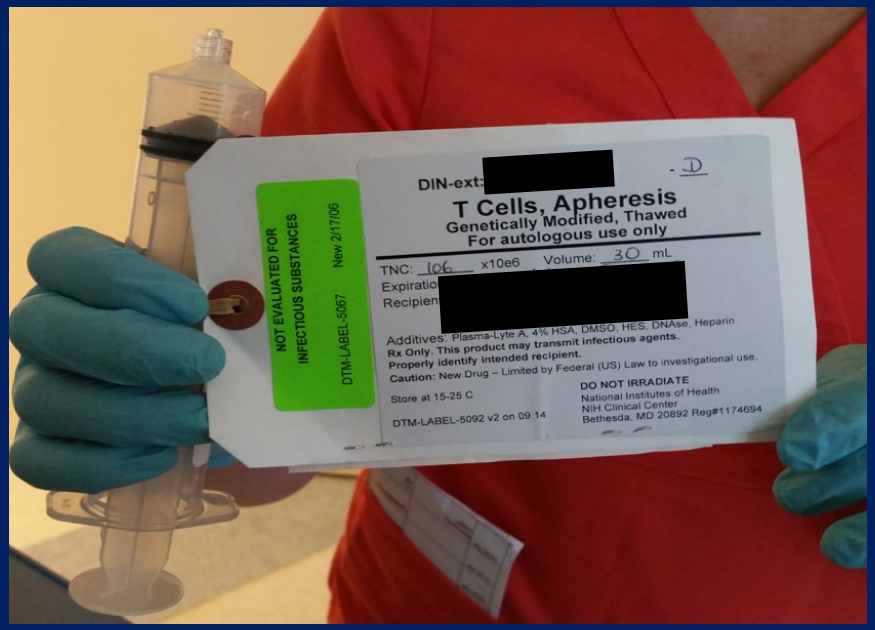
1. Patient undergoes apheresis for collection of lymphocytes
2. Lymphocytes are put into culture, stimulated and transduced (lenti/retrovirus)
3. Cells expand in vitro
4. Patient receives lymphodepleting chemotherapy prior to cell infusion
5. CAR-T Cell infusion on Day 0



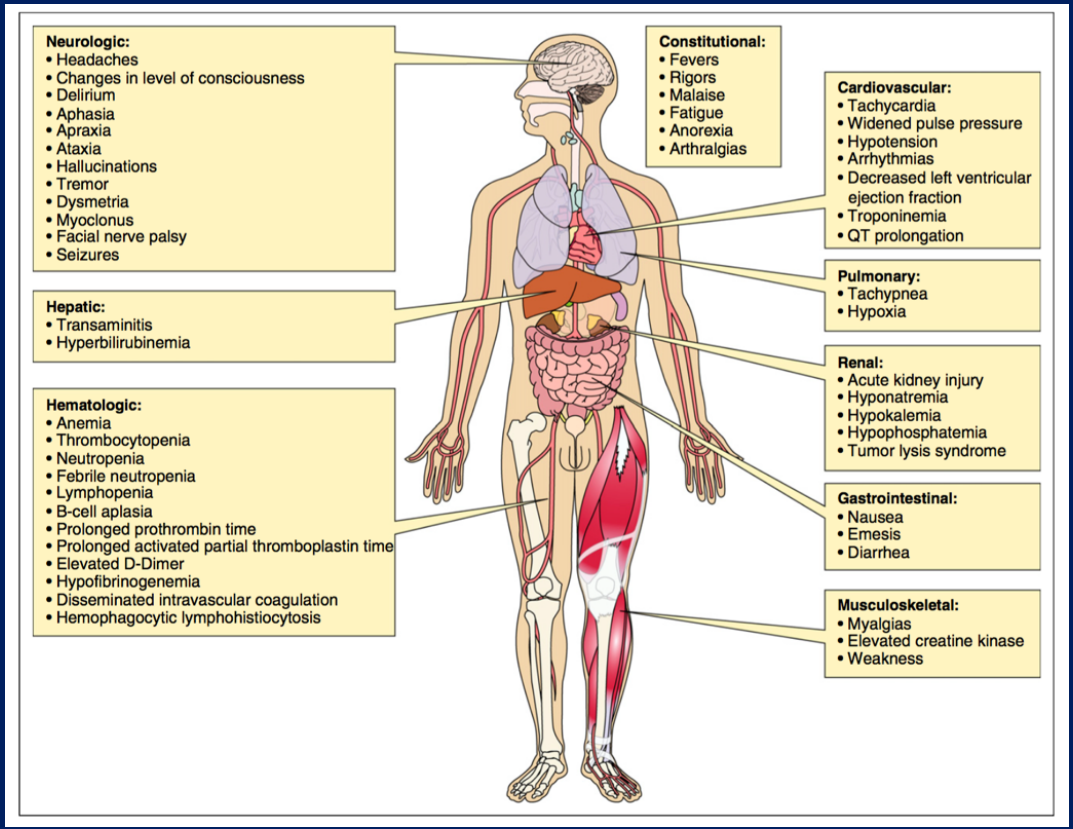
Lee DW, et al. Clin Cancer Res 2012

Infusion Day!!

Bench to Bedside

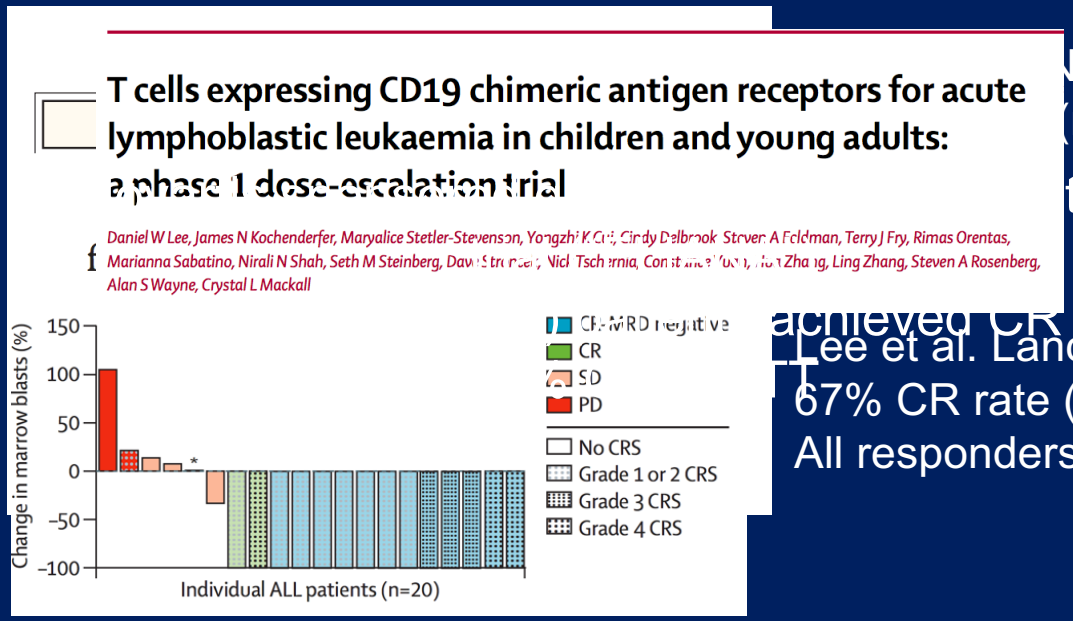


Cytokine Release Syndrome



Brudno/Kochenderfer Blood 2017

CD19 CAR Clinical Updates



NEJM 2014
(not ITT)
tration

achieved CR
Lee et al. Lancet 2015
67% CR rate (ITT)
All responders with CRS

CAR Therapies: FDA Approval

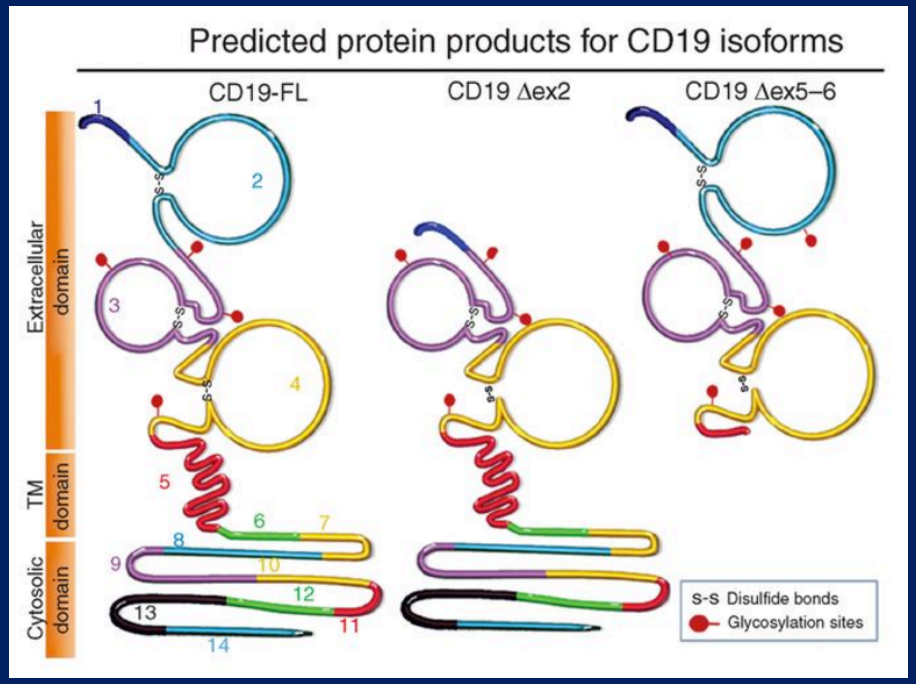
- Kymriah™ (tisagenlecleucel, Novartis): For children up to age 25 with ALL (August 2017)
- Tocilizumab: To treat CAR T-cell related CRS (August 2017)
- Yescarta™ (axicabtagene ciloleucel, KITE): For adults with Diffuse Large B Cell Lymphoma (October 2017)
- **Complete remission rates: +/- 50-80%**

Will CD19 CAR be "THE" Answer?

CAR-T in April 2012

Oh Where… Oh Where… Has my CD19 gone?

- At least ONE identified mechanism:
  - Loss of the surface epitope, but retention of the target protein (in part)
  - Due to clustering of nonsense and missense mutations in exon 2 of CD19
  - Specific frameshift mutation eliminates full-length CD19 but allows expression of an isoform
    - Mostly cytosolic and hidden from T cells
  - Hallmark of relapsed leukemia post CAR was lack of the full-length isoform



Sotillo/Thomas-Tikhonenko, Cancer Discovery 2015

Lineage Switch (ALL→ AML)

- *MLL*-rearranged B-ALL (11q23) rearrangement
  - "Infant" ALL→ VERY poor prognosis
- Gardner et al.
  - 7 of 7 with *MLLr*-ALL attained MRD neg CR post –CD19 CAR
  - Relapses seen in 2 with myeloid phenotype
- Similar experience seen in *MLLr*-ALL treated with blinatumomab
- Jacoby et al.
  - CD19 CAR immune pressure induces lineage switch

Gardner/Turtle, Blood 2015
O'Brien, Pediatric Blood Cancer 2016
Jacoby/Fry Nat Commun 2016

CD22 on ALL

- 140 kDa B-lineage differentiation antigen
- Expressed on vast majority of pre-B ALL
- Targetable antigen for immunotherapy
  - Epratuzumab
  - Inotuzumab
  - Moxetumomab (HA22)

Pediatr Blood Cancer 2015;62:964–969

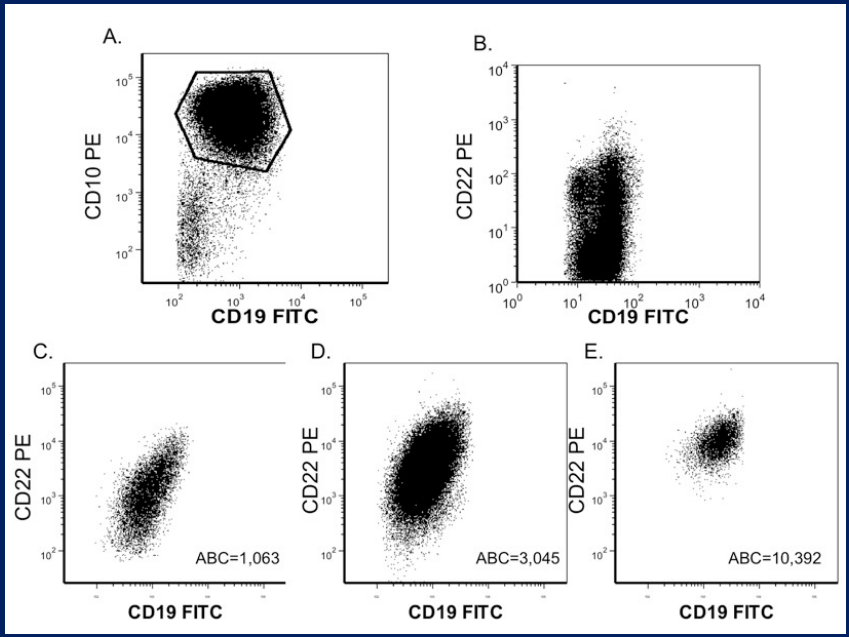
Characterization of CD22 Expression in Acute Lymphoblastic Leukemia

Nirali N. Shah, MD,[1]* Maryalice Stetler Stevenson, MD, PhD,[2] Constance M. Yuan, MD, PhD,[2]
Kelly Richards, RN,[1] Cindy Delbrook, RN,[1] Robert J. Kreitman, MD,[3]
Ira Pastan, MD,[3] and Alan S. Wayne, MD[1,3,4]

TABLE I. Characteristics of CD22 Expression on Patient Samples

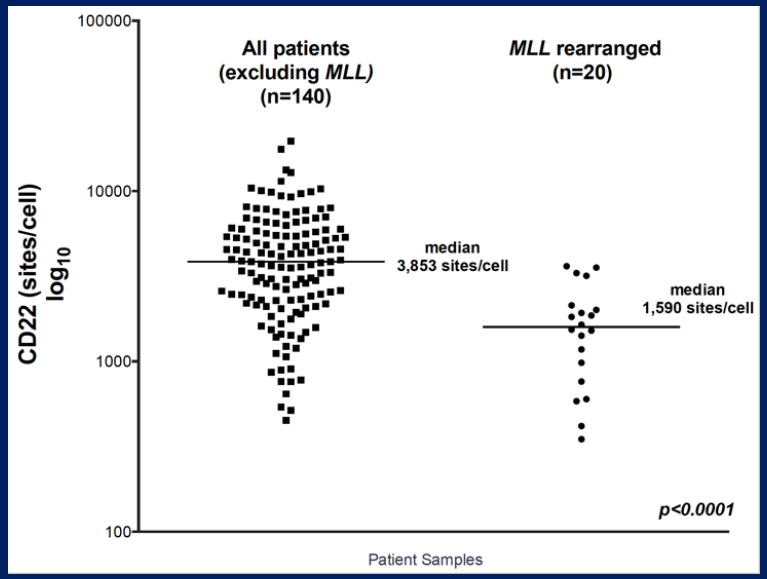
	n
Individual cases[a]	163
Median age of subjects (range), years	12.5 (0.6–25)
Median site density (range), sites/blast[b]	3,470 (349–19,653)
Median % CD22 expression (range)[c]	100% (22%–100%)
Cases with less than 90% CD22 expression[c]	7

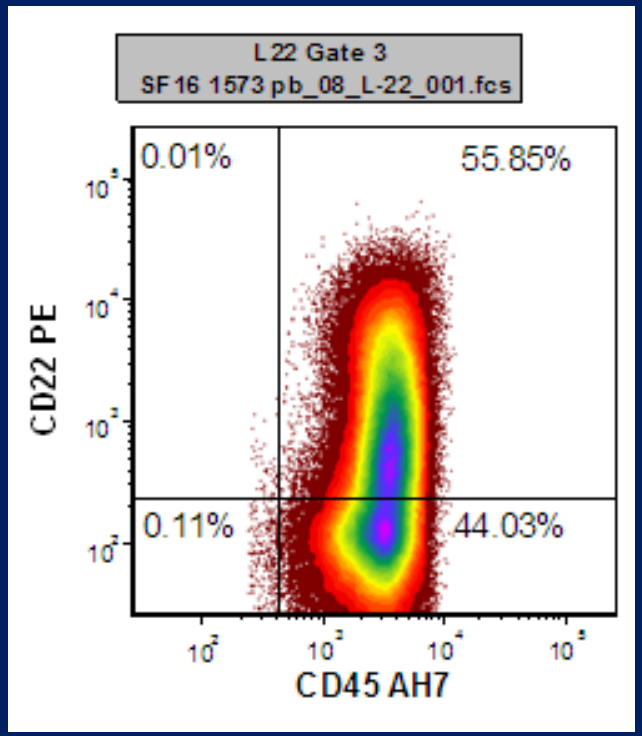
[a]337 samples analyzed from 163 individual subjects. 73 had serial evaluations, many with multiple samples, inclusive of 47 subjects who received treatment with anti-CD22 immunotoxin therapy. [b]160 of 163 samples had site density evaluable for analysis. [c]162 of 163 subjects had CD22% available for analysis.



MLL-rearranged ALL

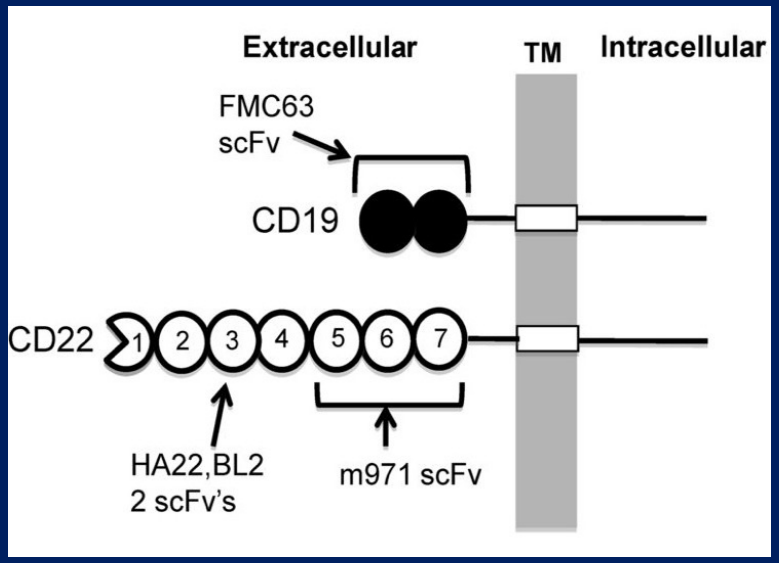
- Lower CD22 Site Density
- Partial positivity may be seen





Anti-CD22 CAR Construct

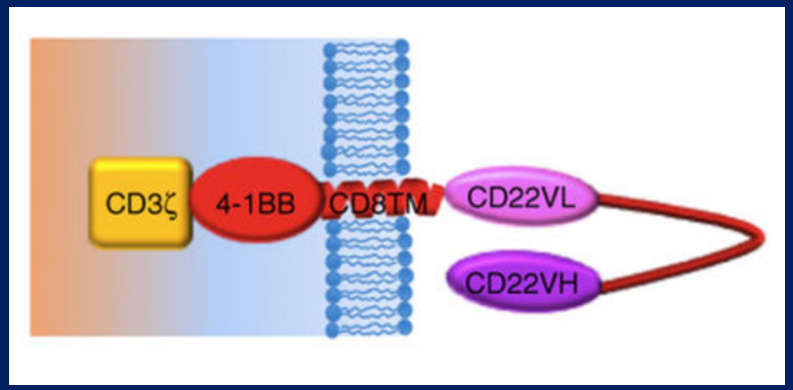
- Second generation CAR
- Utilizes m971 anti-CD22 scFv
- 4-1BB/CD3-zeta signaling



Haso et al, *Blood 2013*

NCI CD22 CAR Protocol

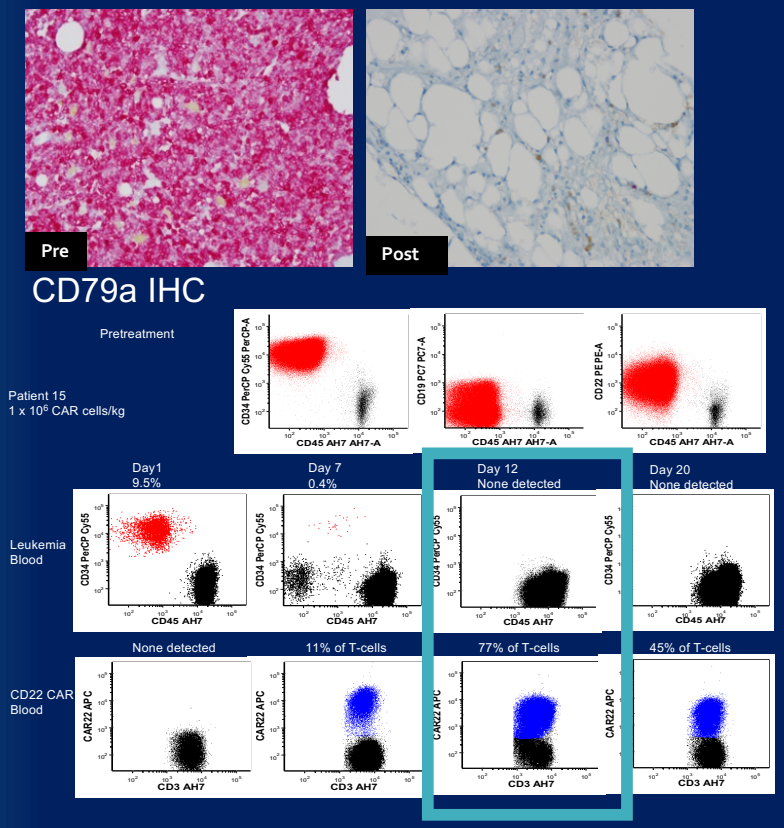
- Phase I, 3+3 dose escalation, CD22+, ages 1-30
- NCI-construct (41BB/m971)
- Enrolled first patient in 2014



- Lymphodepletion:
  - Fludarabine 25 mg/m²/day x 3 days (Days -4 to -2)
  - Cyclophosphamide 900 mg/m²/day x 1 days (Day -2)

Haso et al. Blood 2013
ClinicalTrials.gov NCT02315612

CD22 CAR is Active in CD19$^{neg/dim/+}$ ALL



Fry/Shah et al. Nature Medicine 2017

- Complete remission rate: 73%
- Limited CRS (Grades 1 & 2)
- Limited neurotoxicity
- Relapse associated with modulation in CD22**

Dose Escalation

Dose Level	Transduced CAR-T cells/kg	n	Dose Limiting Toxicity	Complete Remission	
1	3 x 10e5	6	1 (Gr 3 diarrhea)	1/6 (17%)	**Low Efficacy**
2	1 x 10e6	3	None	3/3 (100%)	
3	3 x 10e6	2	1 (Gr 4 hypoxia)	1/2 (50%)	**High Toxicity**
2	1 x 10e6	3*	None	1/3 (33%)	

Expansion at Dose Level 2: 1 x 10^6 CAR T cells/kg

**1 patient with DLBCL*

Patient Characteristics (n=22)

Dose level 2: 1 x 10^6 CAR-T cells/kg		n, (%)
	Median age, (range)	17.5 (4-30)
	Male, (%)	15 (68%)
Prior Therapy	Allo HSCT	18 (82%)
	Anti-CD19 therapy	20 (91%)
	Anti-CD22 CAR	2 (9%)
Disease Characteristics	CD19 negative/dim	12 (55%)
	≥ M2 marrow	17 (78%)
	Extramedullary disease	6 (27%)

Our Patients

BJ

- Received blinatumomab and achieved remission
- Went to hematopoietic stem cell transplant (HSCT)
- Relapsed with CD19 dim disease

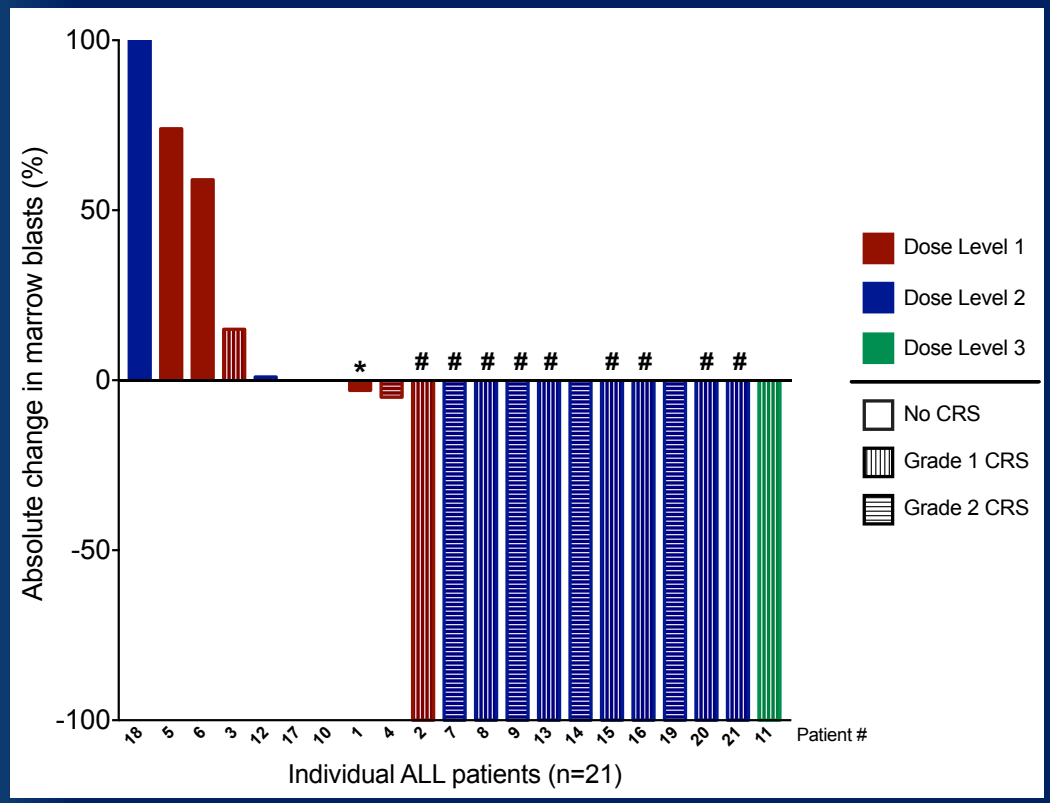
MM

- Relapsed again
- Received CD19 CAR T cells and went to HSCT after achieving remission
- Relapsed with CD19 + disease

Sunny

- Received CD19 CAR T cells and went to HSCT after achieving remission
- Relapsed almost 2 years post HSCT with CD19 negative disease

Response & CRS

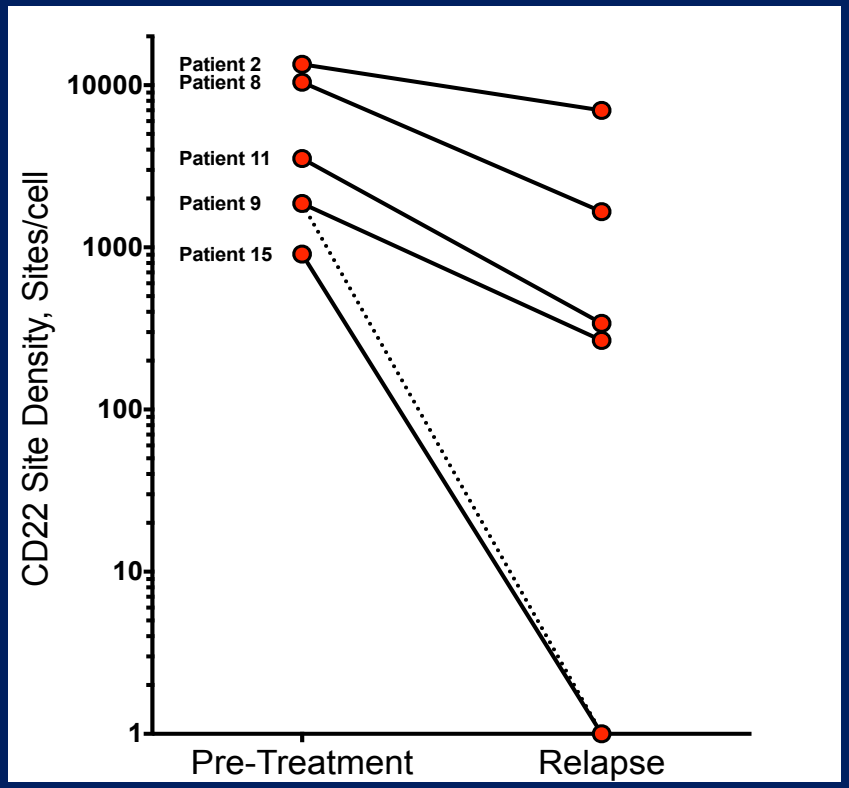


Complete Remission Rate: 78% (17/22)

- Longest remission is > 2 years post-CAR
- For those with relapse, generally 6+ months post-CAR
- Intensified lymphodepletion** → MRD neg CR

CD22 Antigen Expression at Relapse

- 5 patients with relapse
  - 1—CAR cell loss (dose level 1)
  - 4—with changes in CD22
    - 2 with relapse at 6 months
    - 2 with relapse at 2 months*
- Changes in CD22
  - Decrease in Site Density (n=2)
  - Antigen loss (n=1)
  - Both (n=1)

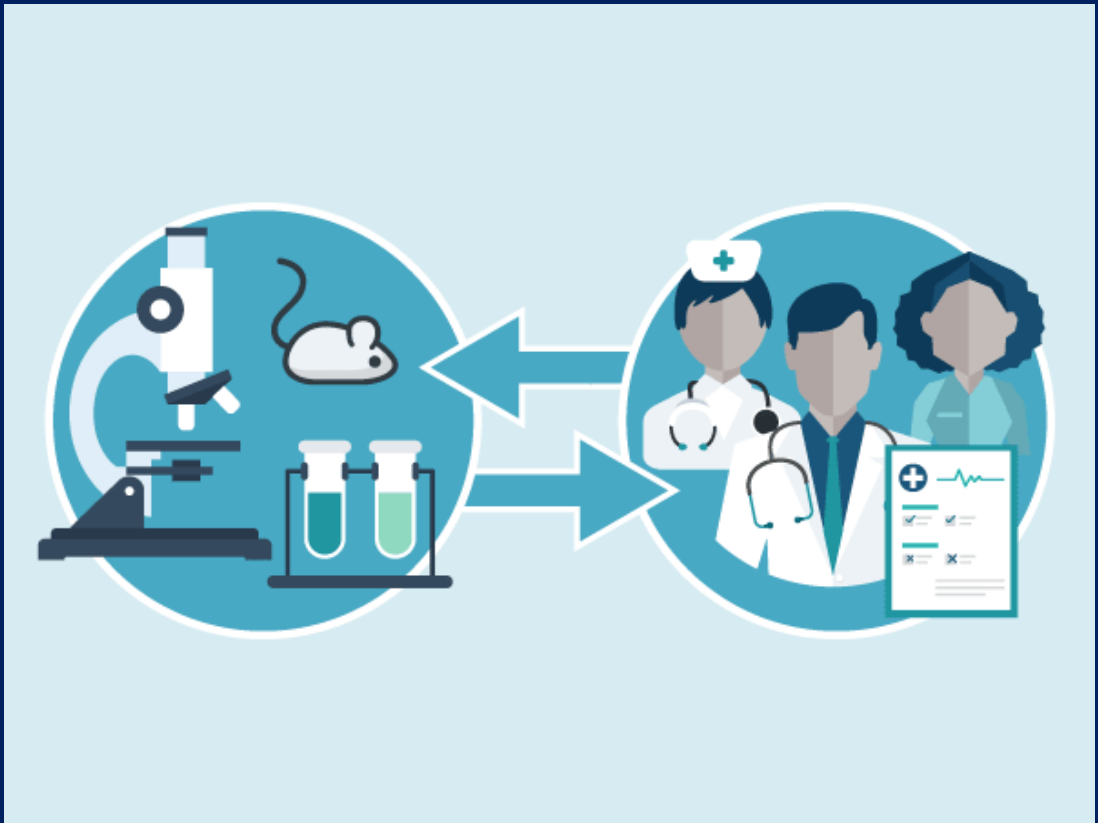


- *Received prior anti-CD22 targeted therapy

Experience to Date

- First successful salvage CAR therapy for CD19 negative B-ALL
- Preliminary experience suggests comparable potency to anti-CD19 CAR
- Response correlated with dose level
- No severe or irreversible neurotoxicity
- Relapse associate with changes in CD22 expression level
- Future Directions: Opportunities for multi-specific CAR targeting

Bedside to Bench



Our Patients Inspire Change

Manufacturing Changes

- Variability in product composition between patients
- Despite this, we had successful manufacturing of products in > 90% of subject
- We could not manufacture cells for BJ
- In conjunction with the CC Cell Processing Section, we incorporated CD4/CD8 bead selection for the product
- This led to successful manufacture of the product
- We are now using this for all patients
- Early experience suggests that this may increase the potency of the cells

Images courtesy of BJ's mother

Intensified Lymphodepletion

- Sunny's first cell infusion led to an incomplete response.
- Second CAR-T cell infusions are generally ineffective.
- We modified the protocol to try an intensified lymphodepletion strategy… it **Worked.**
- We now use this for all second infusions moving forward.

Images courtesy of Sunny's parents

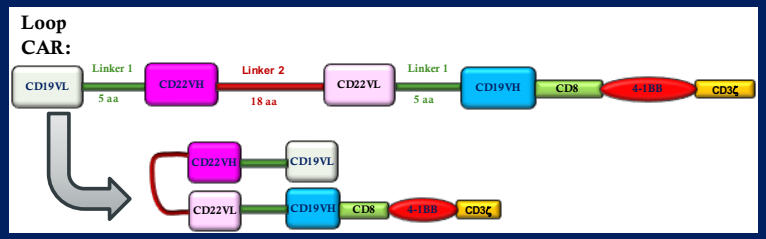
The "One-Two" Punch

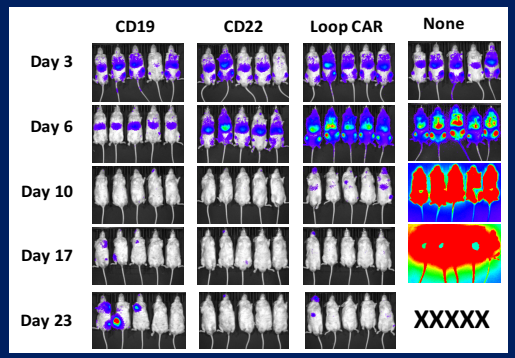
- Attained a complete remission but relapsed at approximately 6 months post CAR with CD19+/CD22 dim disease.
- Single antigen approach likely not sufficient for a sustained remission.
- We are currently weeks away from our Bi-specific CAR trial being open to enrollment

Images courtesy of MM's parents

Phase 1 Dose Escalation Study of Anti-CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Children and Young Adults with Recurrent or Refractory CD19/CD22-expressing B Cell Malignancies

- Hypothesis: Simultaneous targeting of CD19 and CD22 could diminish the risk of antigen loss escape
- Novel bivalent, bispecific CAR to be tested in the clinic
- Planning to open February 2018



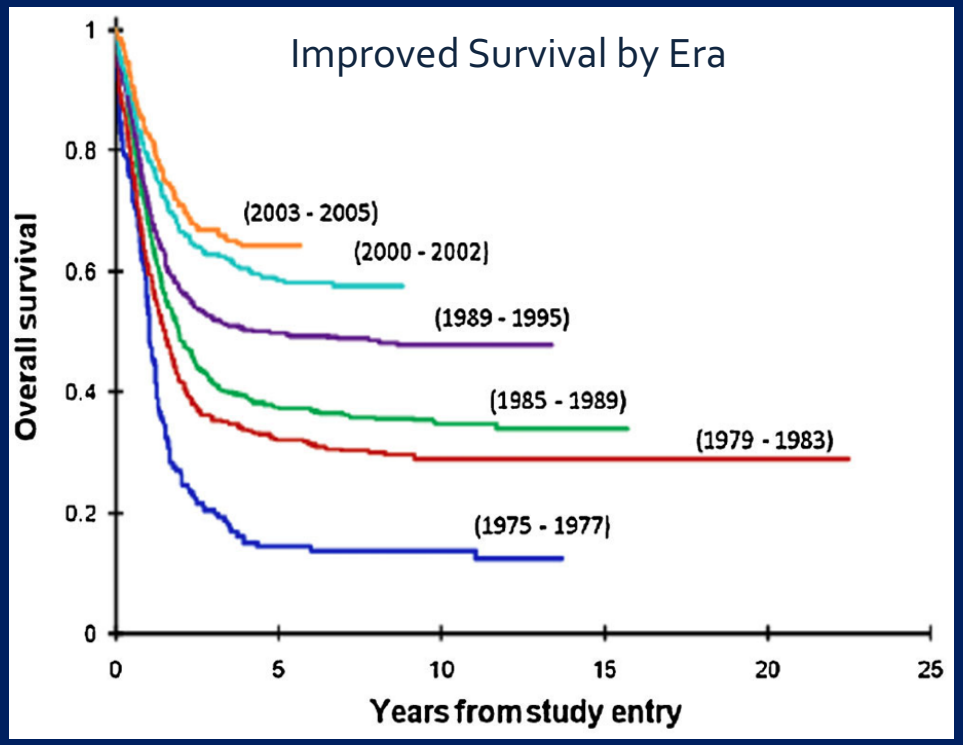


Activity of Bispecific CAR:
***In vivo* activity against CD19+/22+ B-ALL**

Data Courtesy of Haiying Qin

Acute Myelogenous Leukemia (AML)

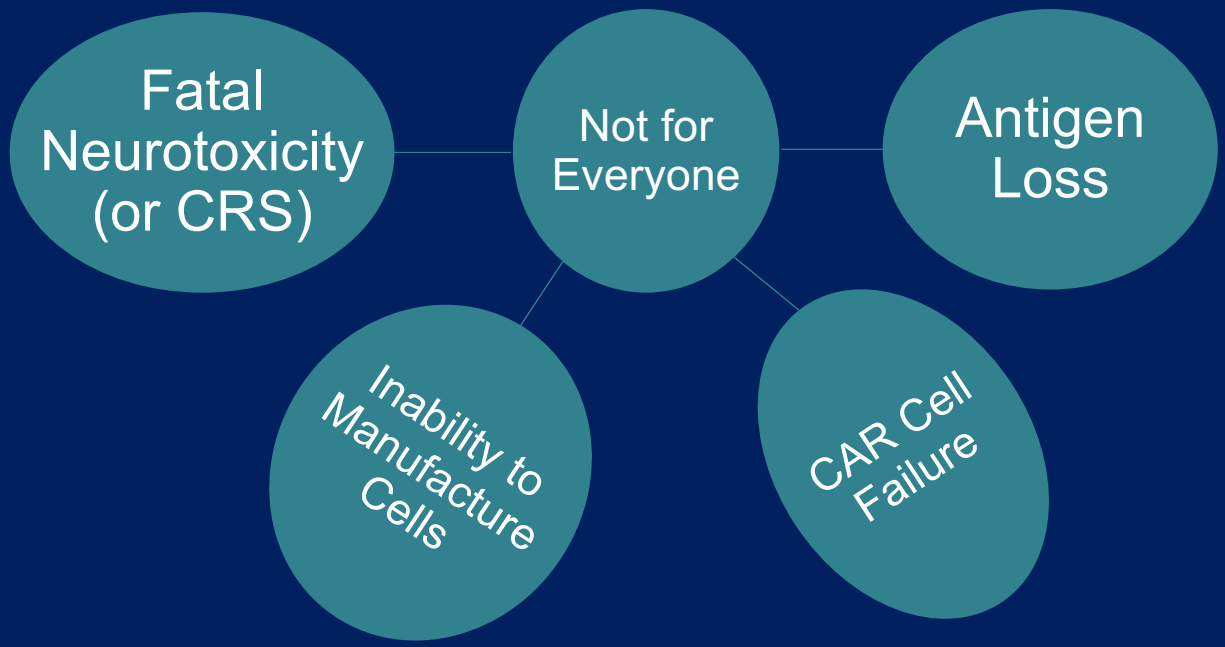
- 20% of all childhood leukemia
  - Childhood AML is 6% of all AML
- Overall survival: 60-70%
- Cytogenetics have an essential role in diagnosis and prognosis
- Intensive therapy is associated with high risk of infectious complications (5-7% treatment related mortality)
- Relapse is the greatest cause of failure
  - 30-40% relapse rates



AML, A New Frontier of CAR Therapy

- Outcomes for AML ~ 50-70% overall survival
- Immunophenotype more variable
  - CD33 (gemtuzumab target)
  - CD123
- B-cell aplasia as a consequence of CD19 targeted therapies can be supported
- Myeloid aplasia as a consequence of myeloid antigen targeted therapies, however, is much more difficult to manage
  - May need immediate stem cell transplantation to restore aplastic marrow

Will CARs be "THE" Answer?



30-40% Relapse Rate

Future Directions

- Novel CAR constructs:
  - AML CAR
  - Bi-specific CAR
- Optimizing second infusions
- Improving CAR persistence
- Increasing tumor sensitivity by enhancing antigen expression
- Bringing CAR constructs earlier into the therapeutic plan
- Exploring response in lymphoma and CNS disease
- Decreasing toxicity
- Improving access to therapy

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