

*OBA Protocol 1102-1091(MSKCC IRB 11-038)*

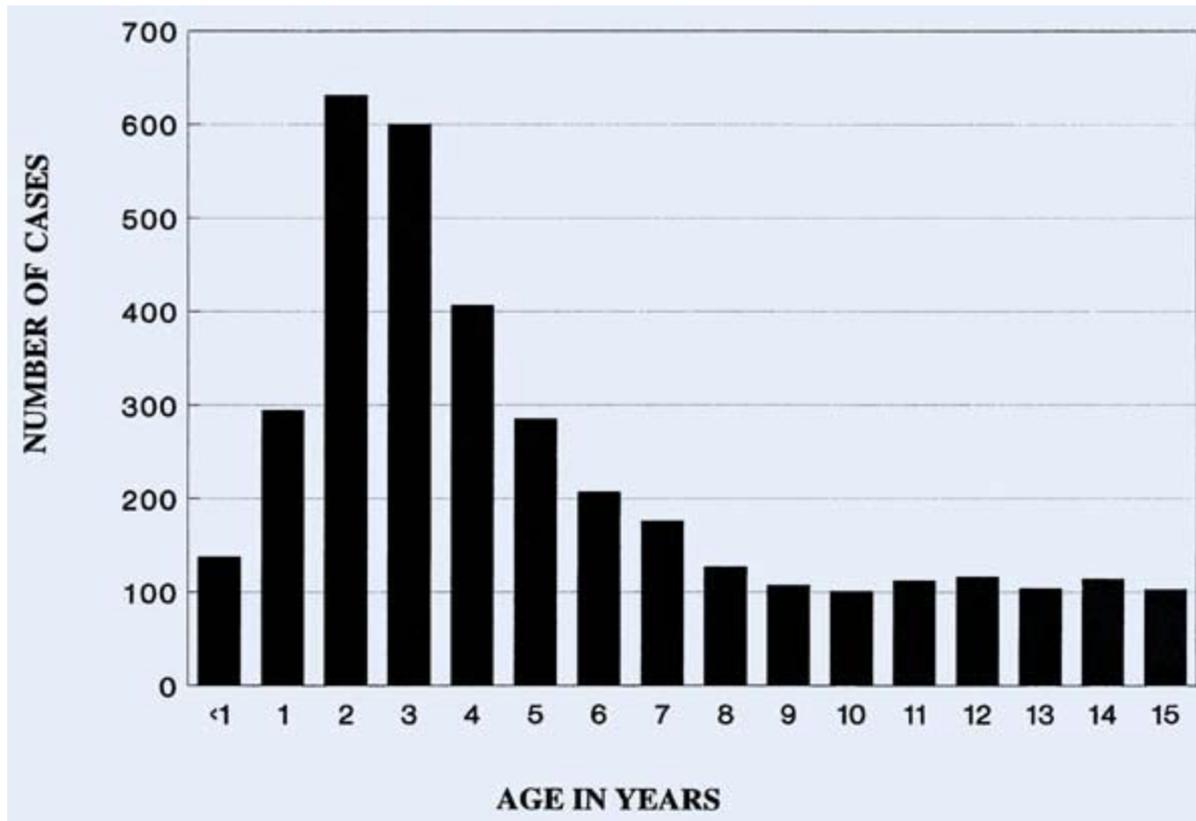
Phase I study of *In Vitro* expanded allogeneic Epstein-Barr Virus specific Cytotoxic T-Lymphocytes (EBV-CTLs) genetically targeted to B cell specific antigen CD 19 ~~positive for *In Vivo* treatment of~~ residual or relapsed acute lymphoblastic leukemia after allogeneic blood stem cell transplantation

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# Agenda

- Demographics of CD19+ leukemia
- Concerns raised with the Protocol
- Concerns raised with Patient Consent
- Concerns raised with Donor Consent



**Figure 19.2** Age distribution of 3,620 children with acute lymphoblastic leukemia.  
(Data from the Children's Cancer Group)

Acute Leukemia

Predominance of blast cells in bone marrow

Assignment of B, T, or Myeloid- Ontogeny

B cell

Tdt+, PAS+/-, FAB L1,L2

Pro-B/early preB

CD34+/CD19+  
t(4;11)+, t(9;22), hyper-  
Diploid and others  
(Table 19.1)

Common ALL(cALL)

CD 34+/-,CD19+/CD10+  
FAB L1 (occasionally L2)  
Hyperdiploid, t(12;21), t(9;22),6q-

Pre-B ALL

CD 34-/CD19+/CD20+/CD22+  
FAB L1/L2  
Cytogenetics frequently similar to  
cALL but often t(1;19) or t(9;22)

B-ALL

CD10+/-CD19+,Tdt-  
FAB L3  
Burkitt translocations: t(8;14) and  
alternatives t(2;8), t(8;20) between  
Ig receptors and cmyc (Table 19.1)

T cell

PAS (block positivity)

Pro-T

CD3+/CD7+  
Multiple TF /TCR  
translocations  
(Table 19.1)

Pre- T

CD2+/CD5+//CD8+  
Multiple TF/TCR  
(Table 19.1)

Common T

CD2+/CD5+/8+  
Multiple TF/TCR

Late T-ALL

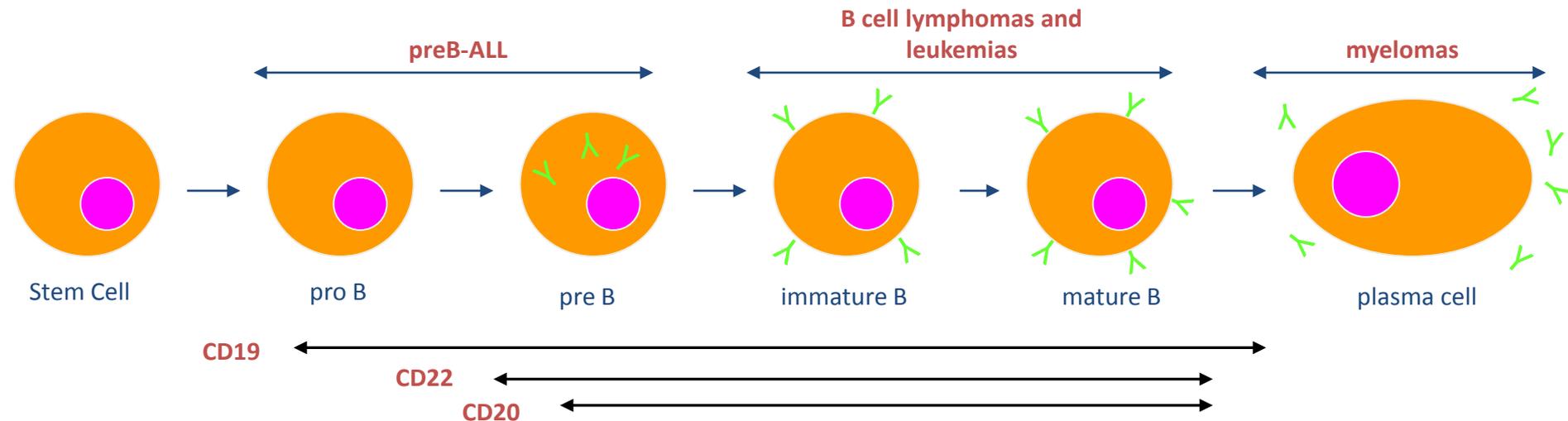
TCR  $\alpha/\beta$  +,  $\gamma/\delta$ +

Myeloid

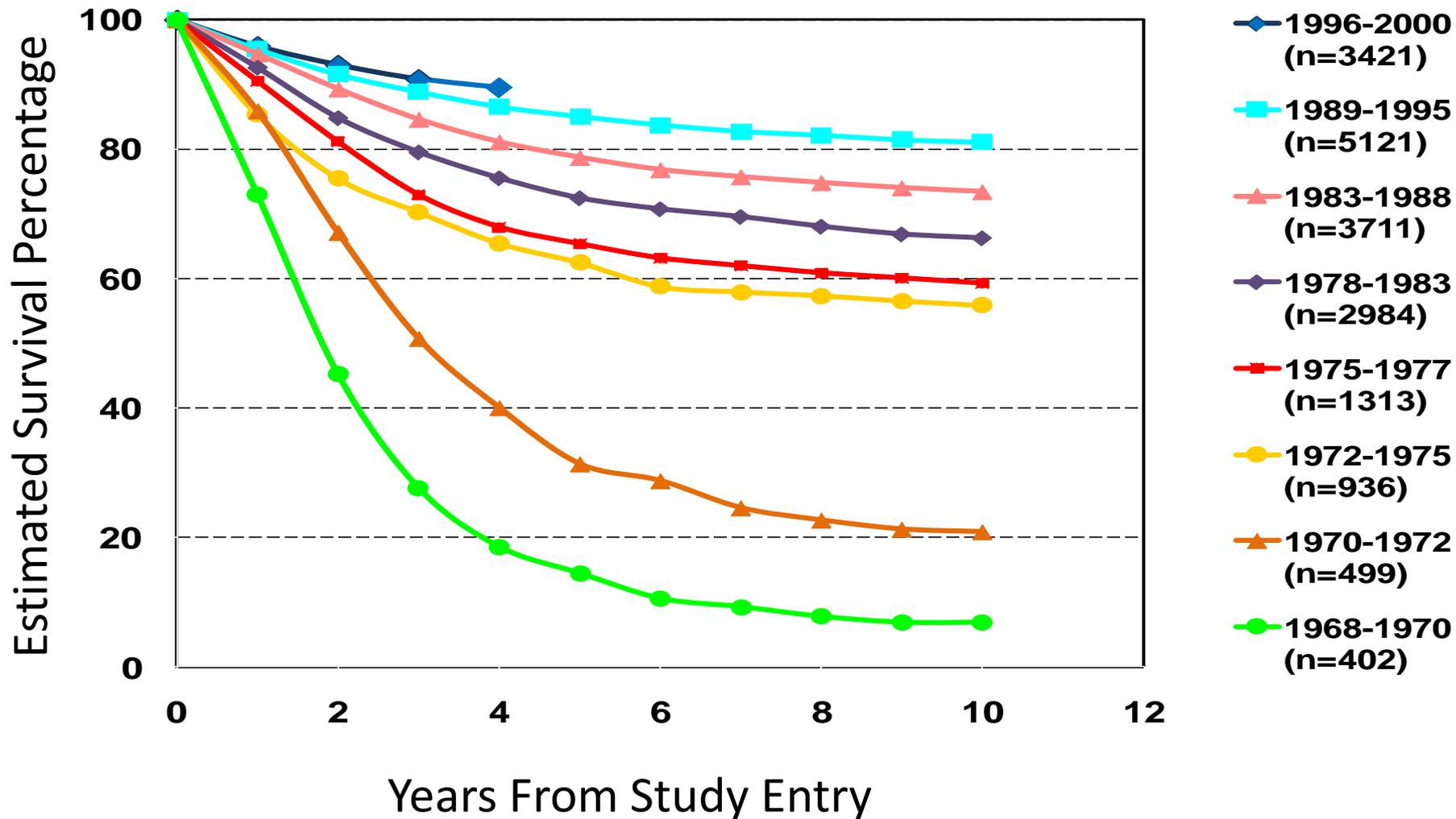
granules,  
Auer rods,  
Sudan Black+  
Esterase +/-  
(See Chapter 20)

# CD19

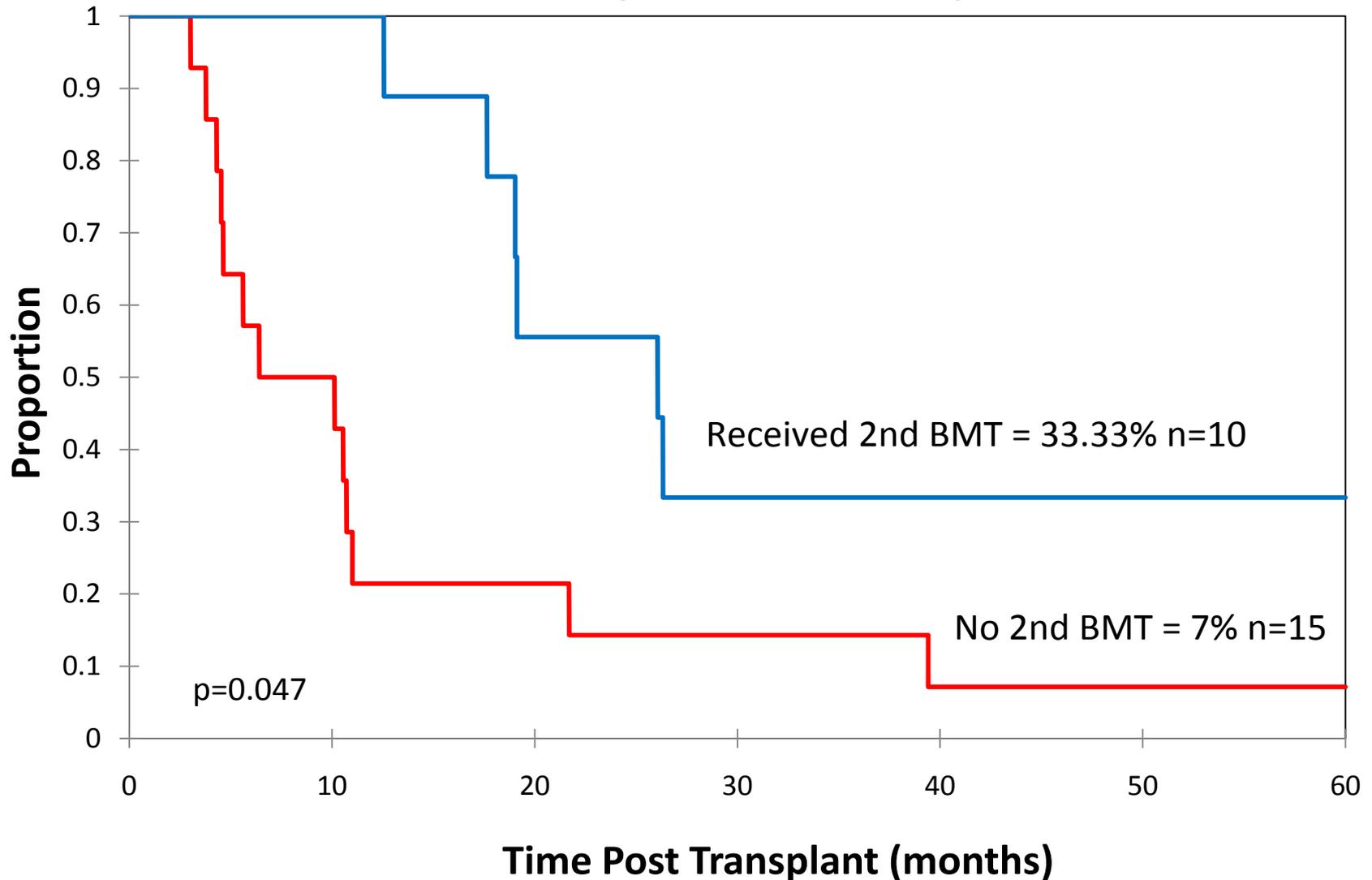
- CD19 expression is restricted to B cells and possibly follicular dendritic cells
- CD19 is not expressed on pluripotent bone marrow stem cells
- CD19 is expressed on the surface of most B cell malignancies



# Improved Survival in Childhood ALL by CCG Study Era



# Overall Survival of CD19+ ALL CR2 Pediatric Patients Who Relapsed Post Transplant



# Donor Leukocyte Infusion (DLI) for Relapsed pediatric ALL following BMT

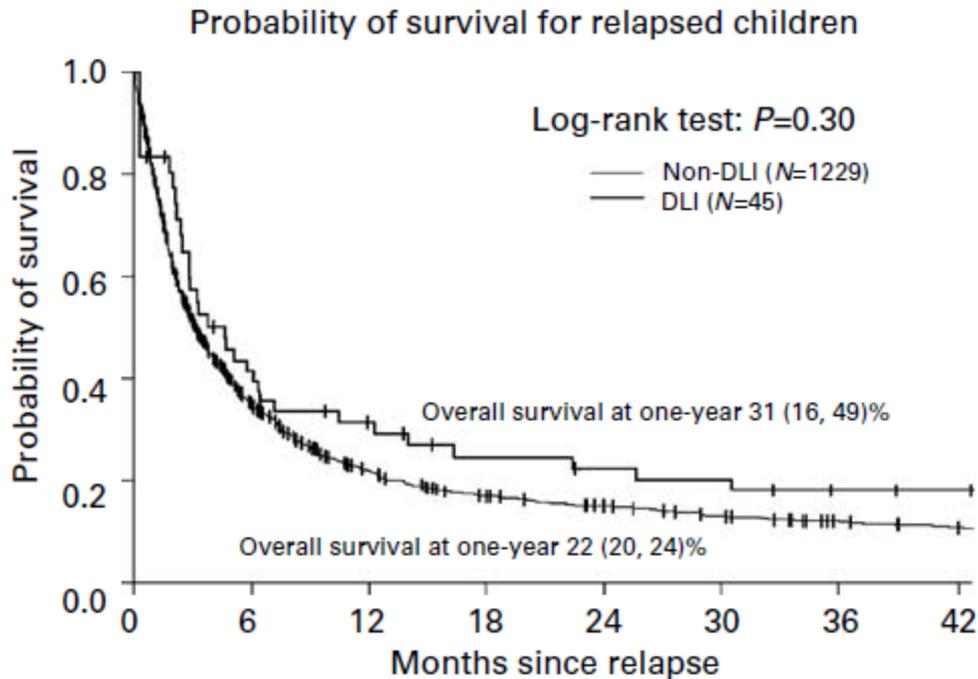
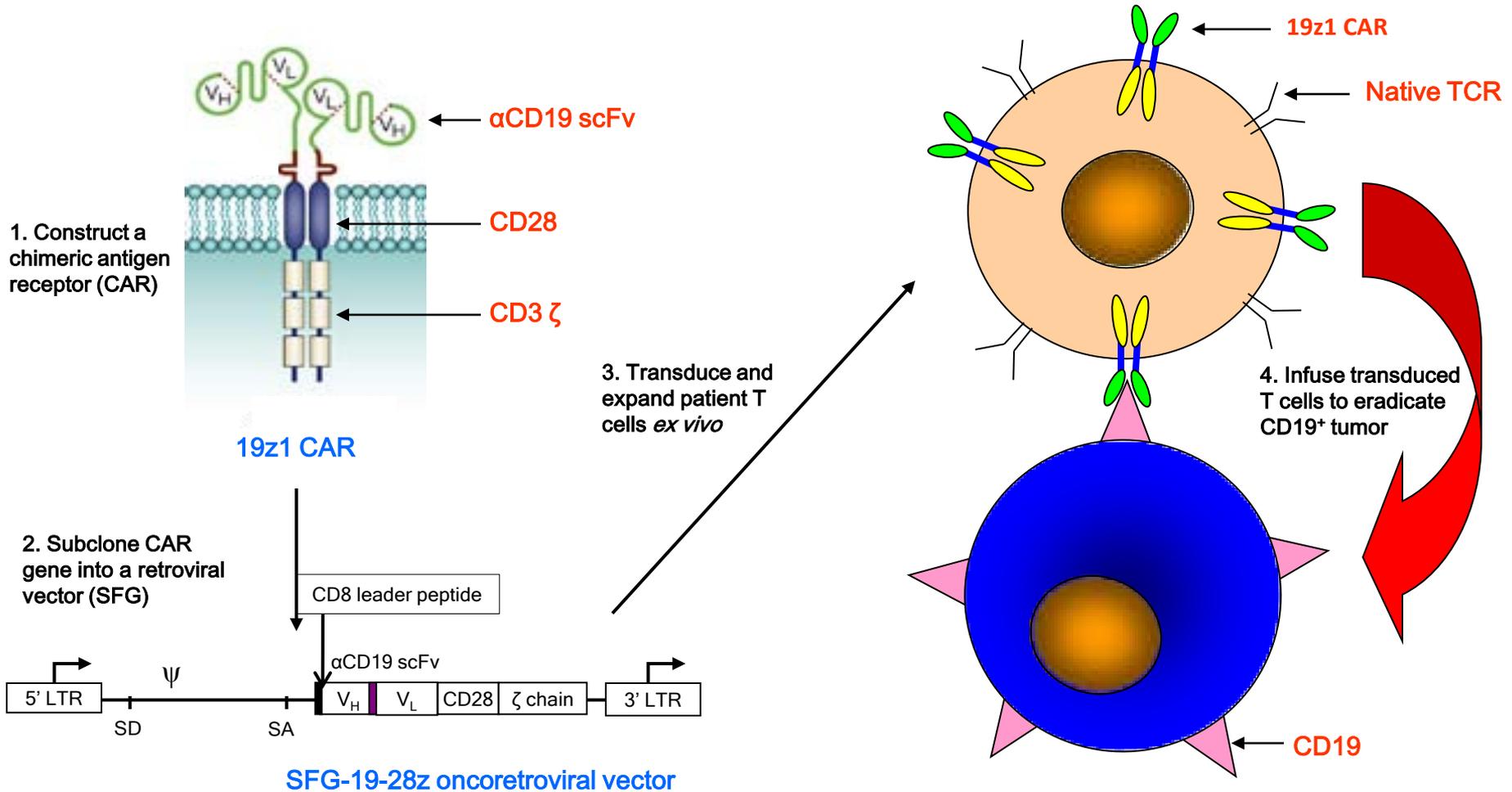


Figure 1 Probability of survival for relapsed children.

ALL

- 18 patients
- GVHD: 48%
- Mortality: 17/18

# Generation of CD19-targeted Autologous T cells for treatment of B cell malignancies



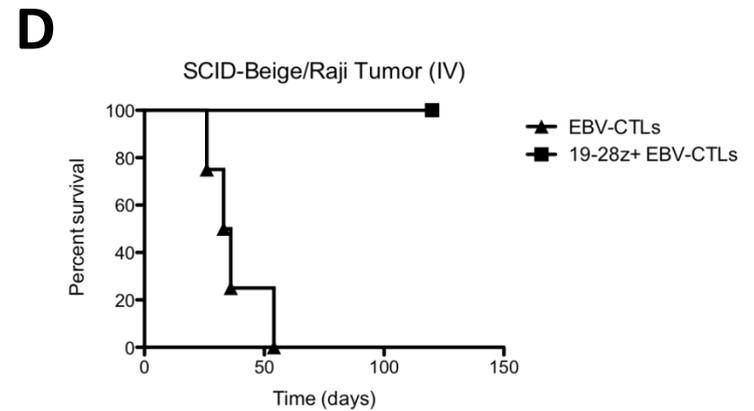
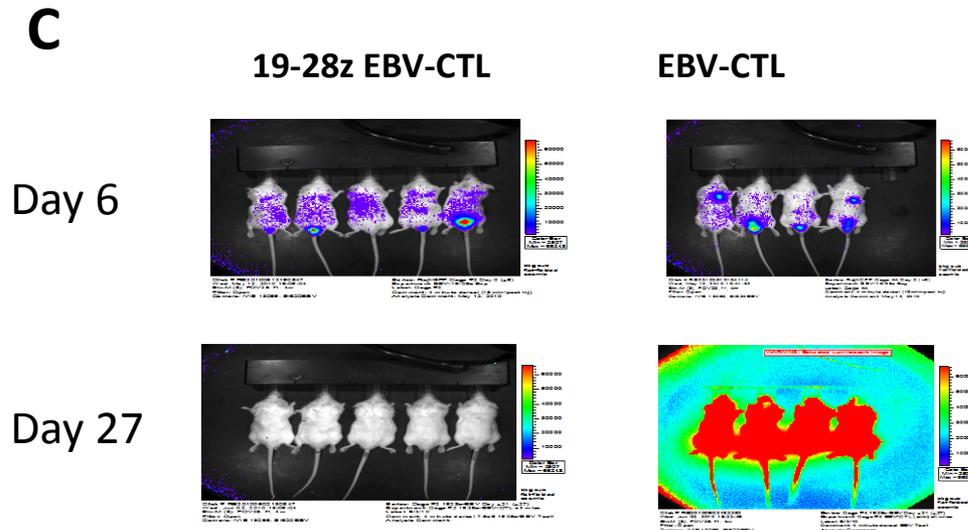
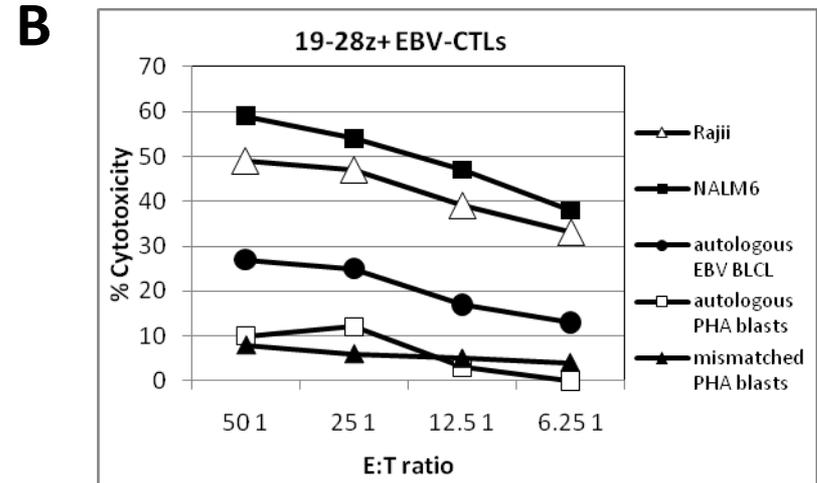
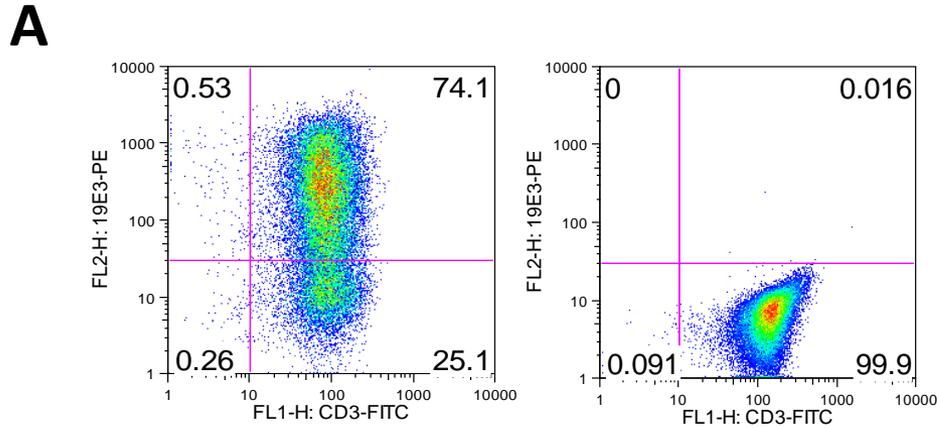
## Virus Specific T cells

- Epstein-Barr Virus (EBV)
  - 95% US population infected
  - Asymptomatic/Infectious Mononucleosis
- Donor EBV-CTLs (Epstein-Barr Virus Cytotoxic T-Lymphocytes)
  - Generated in Dr. Richard J. O'Reilly's Laboratory
  - MSKCC Clinical Trials treating EBV-PTLPD

**Table 1: Incidence of aGVHD following infusions of EBV CTL for treatment of PTLPD (IRB 95-024: Phase I/II study at MSKCC)**

<b>Donor</b>	<b>Number of Patients</b>	<b>Number of Infusions</b>	<b>aGVHD post EBV-CTL</b>	<b>cGVHD</b>	<b>Survival</b>
Related HLA identical	3	1 - 3	none	0/3 evaluable	0
Related HLA non-identical	6	1 - 3	none	0/5 evaluable	3 128-135mos
Unrelated HLA identical	7	2 - 3	Gr I skin - 1	0/7 evaluable	5 21-175mos
Unrelated HLA non-identical	6	1 - 3	none	0/5 evaluable	1 81 mos
Third party	9	3-13	none	0/8 evaluable	5 4 - 27mos
<b>Total</b>	<b>31</b>	<b>1 - 13</b>	<b>zero grade III/IV</b>	<b>1/26 evaluable</b>	<b>14 4-175 mos</b>

# 19-28z EBV-CTLs: Preclinical validation



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# Concerns raised with the Protocol 1

- Title: deleted reference to treatment
- Design change
  - DLT: only grade 4 aGVHD changed to grade 3 or 4 aGVHD
  - Patients will be removed from study if transduction by CAR is <5%

## Concerns raised with the Protocol 2

- Clarifications: eligibility and conduct of study:
  - Age range for donors: unrelated vs related
  - Age of patients: < 19 at time of diagnosis
  - Eligibility criteria for patient organ function be determined on the day of initiation of conditioning regimen (Cyclophosphamide or fludarabine)
  - QC for release of transduced cells wrt endotoxin testing and level of transduction
  - Volume of blood to be drawn from pediatric patients as well as prioritization of studies
  - Number of patients to be enrolled: 26 patients and 26 donors

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# Concerns raised with Patient Consent

- Delete the word/concept of treatment or therapy
- Delete “patient” and insert “subject”
- Clarify number of patients and donors to be enrolled in study (26 patients and 26 donors)
- Provide time that research samples are to be stored (15 years)
- Insert a paragraph indicating the need for contraception during the course of the study
- Insert paragraph on our intent to request autopsy should patient die
- Clarification of costs related to participation

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**CONSENT FROM SCT DONOR FOR ESTABLISHMENT OF B and T CELL LINES**  
**(AICT facility)**

- Identification of SCT donor for MSKCC patient
- Assess patient's risk for post transplantation complication  
(e.g. HLA disparate donor or T cell depletion planned for prevention of GVHD)

EBV-PTLPD Y/N  
(IRB 95-024)

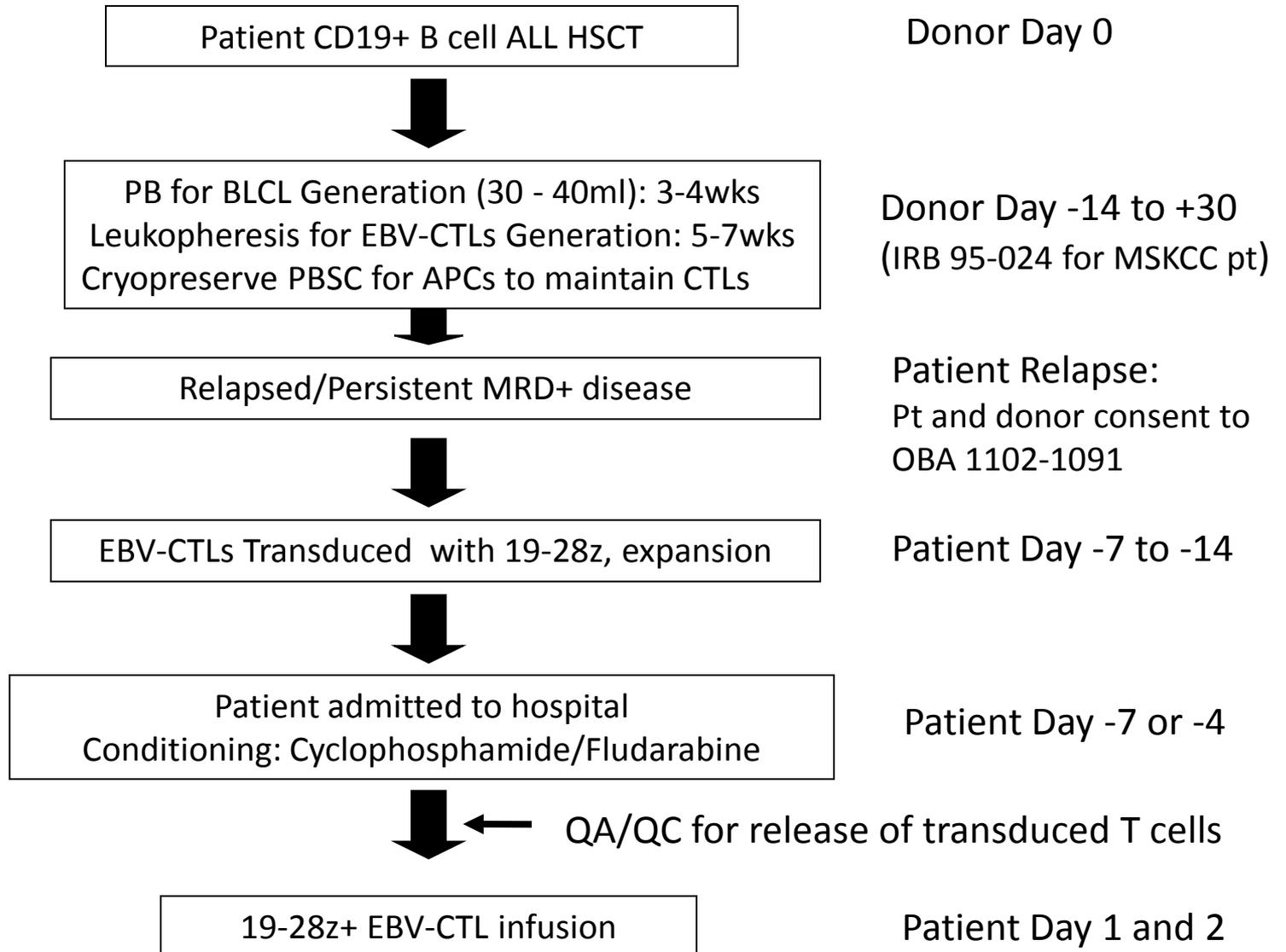
CMV Disease Y/N  
(IRB 05-065)

Relapse of WT1 positive relapse Y/N  
(IRB 07-055)

**Related donors** are consented to and enrolled on MSKCC IRB 95-024 (consent provided) that allows for BLCL and T cells to be used for generating any or all 3 specific CTLs. If recipient is subsequently enrolled on IRB 05-065 or IRB 07-055, the donor is also consented to specific protocol. Assent is obtained for all related donors  $\geq$  7 years and  $<$  18 years.

**Unrelated donors** are consented at NMDP Donor Centers (information sheet and consent provided) and donors agree to none, one, two or three options.

# 19-28z<sup>+</sup>-EBV-CTLs Phase I Clinical Trial



## Genetic Modification of Donor EBV CTL to express an anti-CD19 chimeric antigen receptor for donors with EBV-CTL already established

- Related: will be asked to consent to Protocol OBA# 1102-1091 (MSKCC IRB 11-038). Genetic modification would only occur when appropriate for recipient to proceed with chemotherapy regimen (Cyclophosphamide or Fludarabine)
- Unrelated donor will either have consented in peri-transplantation time period to utilize EBV-CTL for genetic modification or will be consented at time of patient relapse. This will be determined in collaboration with NMDP.

# Donor Consent Options

- Decline participation in any CTL study
- Agree to donate for CTL for one, two or three studies. (EBV, CMV, WT1)
- Agree for use for only the HSCT recipient for whom they donated

## Donor Consent Options for unused EBV CTLs

- Decline participation: CTLs are discarded when specific patient is no longer at risk for complication
- Agree to donate cells to laboratory research
- Agree for storage in central cell bank at MSKCC for treatment of other “third party” patients with EBV – PTLPD or CMV disease
- Up to now consent for storage for unrelated donors has been for 10 years. With establishment of central cell “third party” bank extending this time frame is under discussion with the NMDP and the IRB.

Non-MSKCC donors and patients  
Patient with post transplantation  
CD19+ leukemia relapse

- Determine patient has high probability of being eligible for protocol therapy in 7 - 9 weeks and donor meets donor eligibility criteria
- For related donor-recipient pair enroll both patient and donor simultaneously on CD19 protocol and donor proceeds with PB and leukopheresis.
- For unrelated donor recipient pair transfer NMDP search to MSKCC and request donor leukopheresis or unit of blood. Consent to be obtained as directed by NMDP.

## In summary Protocol 1102-1091 combines

- 30 years clinical expertise with conducting clinical trials in Pediatric Allogeneic HSCT with related and unrelated donors (since 1988). (Kernan and O'Reilly)
- 15 year experience with generation of and in vivo use of EBV CTL for treatment of EBV-PTLPD. (Kernan and O'Reilly)
- 10 year effort in development of T cells genetically modified to target tumor antigens (CAR). (Brentjens, Sadelain, and Riviere)
- 5 year experience of in vivo use of CAR T cells directed against CD19+ leukemia in the autologous setting (Brentjens and Riviere)