



**MAZUMDAR-SHAW
CANCER CENTER**

CAR-T Therapy In B Cell Malignancy

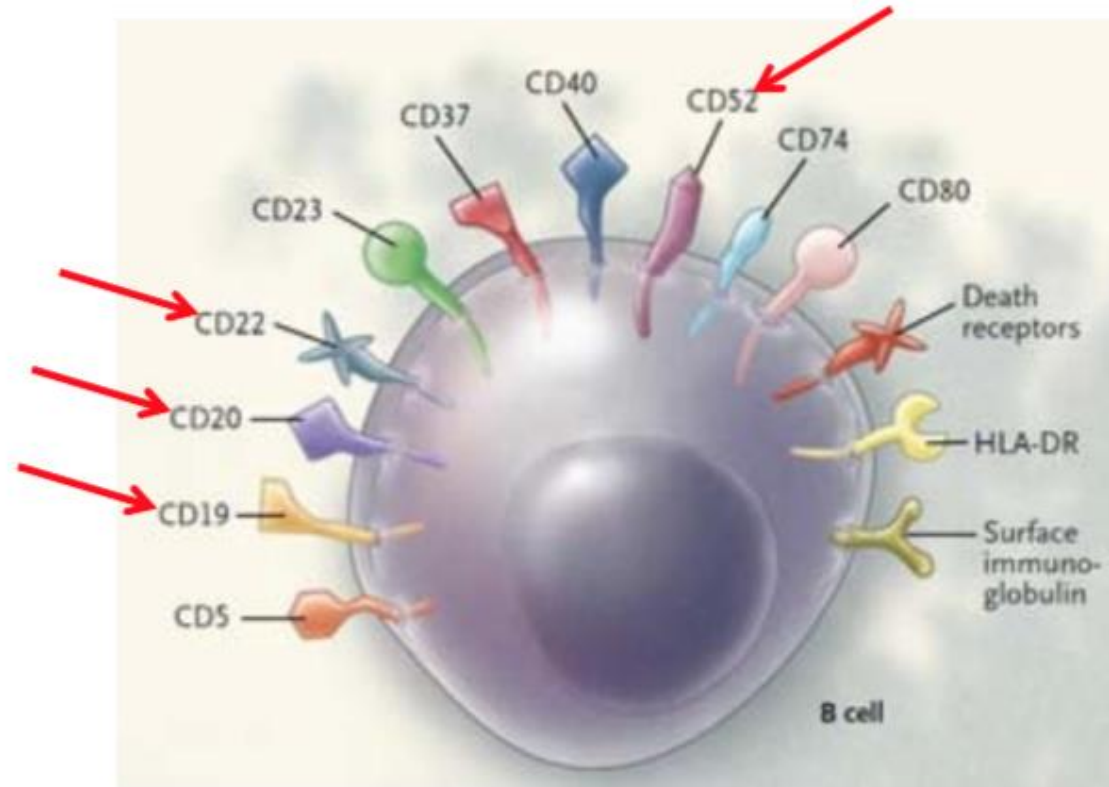
- *Sunil Bhat*
- *Vice-Chair Oncology Collegium, Narayana Group of Hospitals*
- *Director and Clinical Lead*
- *Paediatric Haematology, Oncology and Bone Marrow Transplantation*
- Narayana Health Network Hospitals
- SRCC Mumbai and MSMC NH Bangalore
- Ex Secretary Pediatric Hematology & Oncology Chapter of India (IAP)
- Secretary Karnataka Hematology Oncology Society



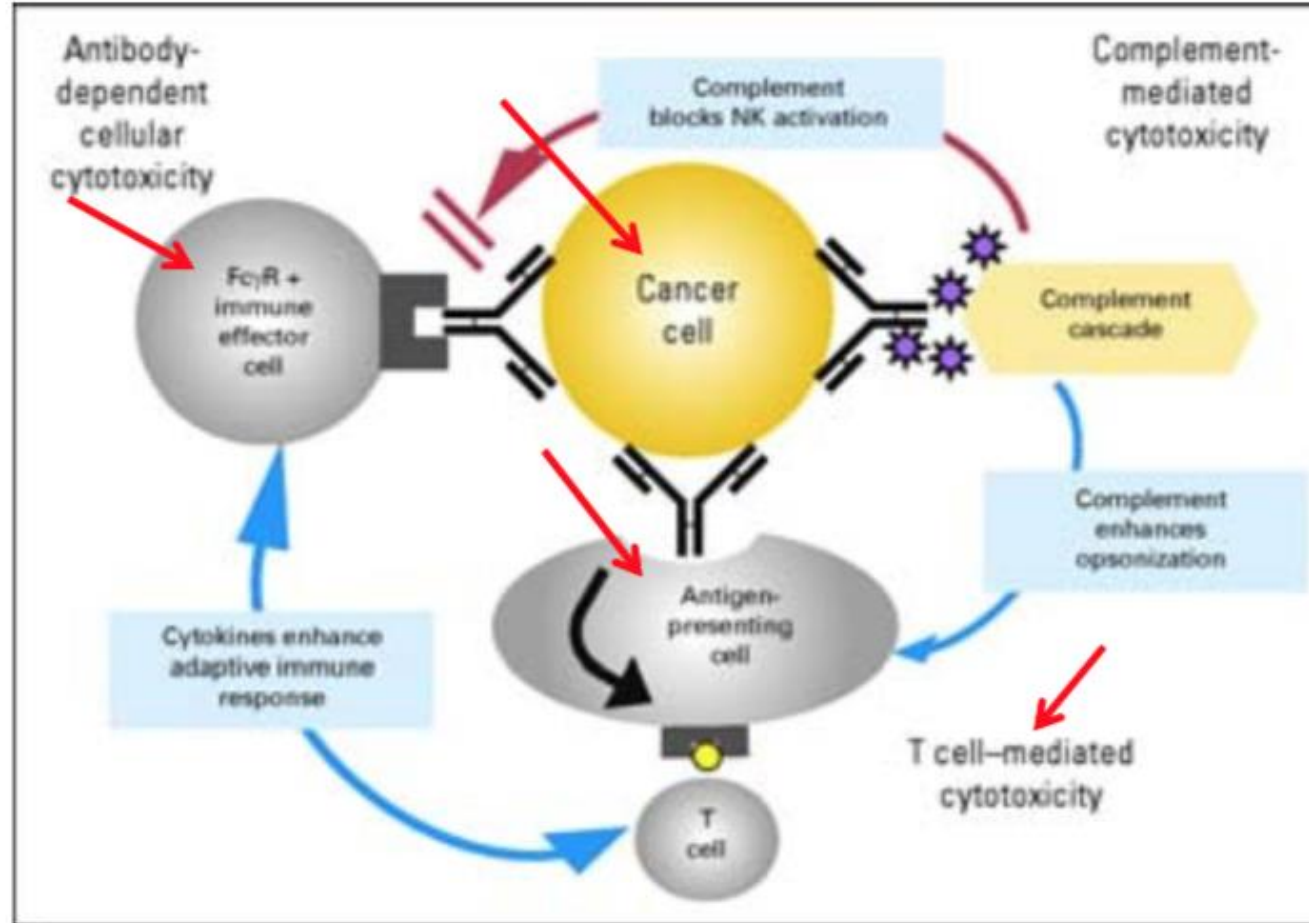
Overview of presentation

- Dwell in the history
- Evolution of CAR T cell therapy
- Indian Data
- Relapse and other challenges with CD19 CARTs
- Other strategies

Potential B Cell Antigen Targets !!



Mechanism of Action



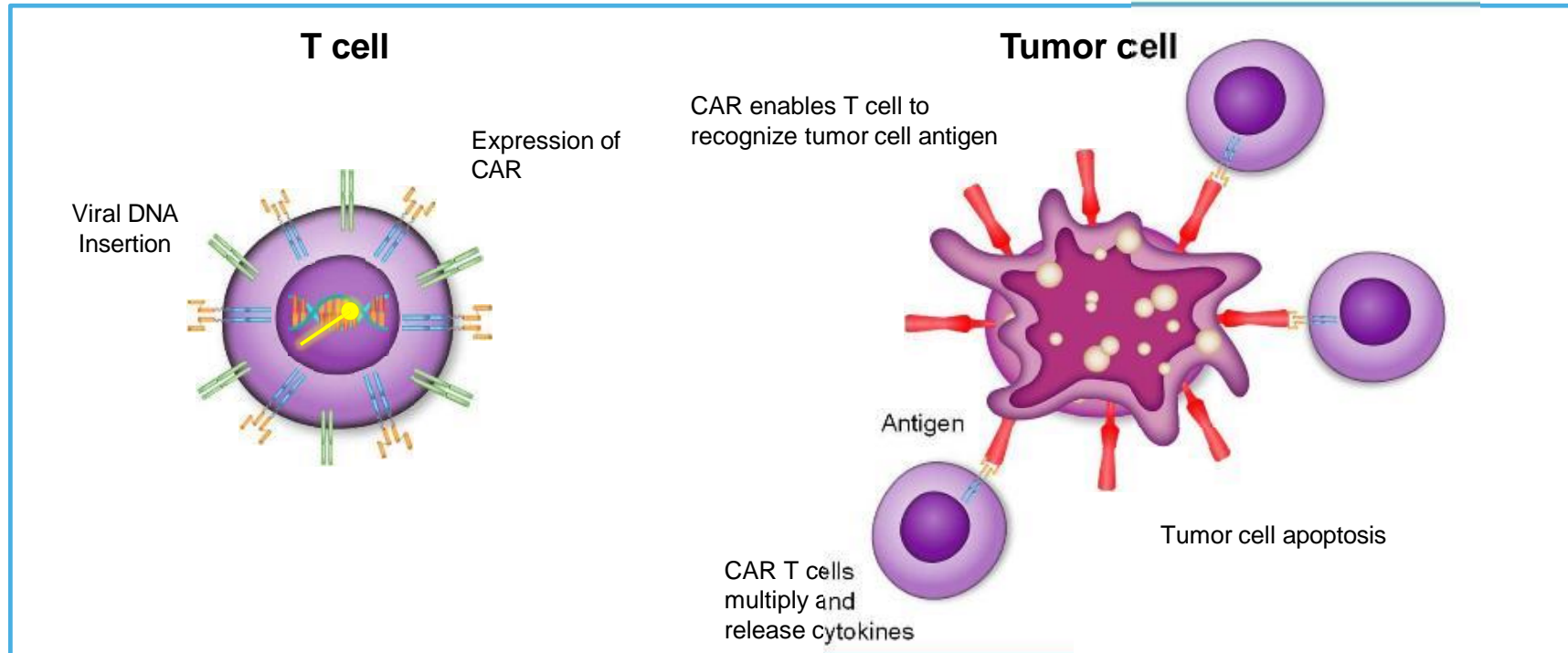
Zelig Eshhar – Israeli Immunologist



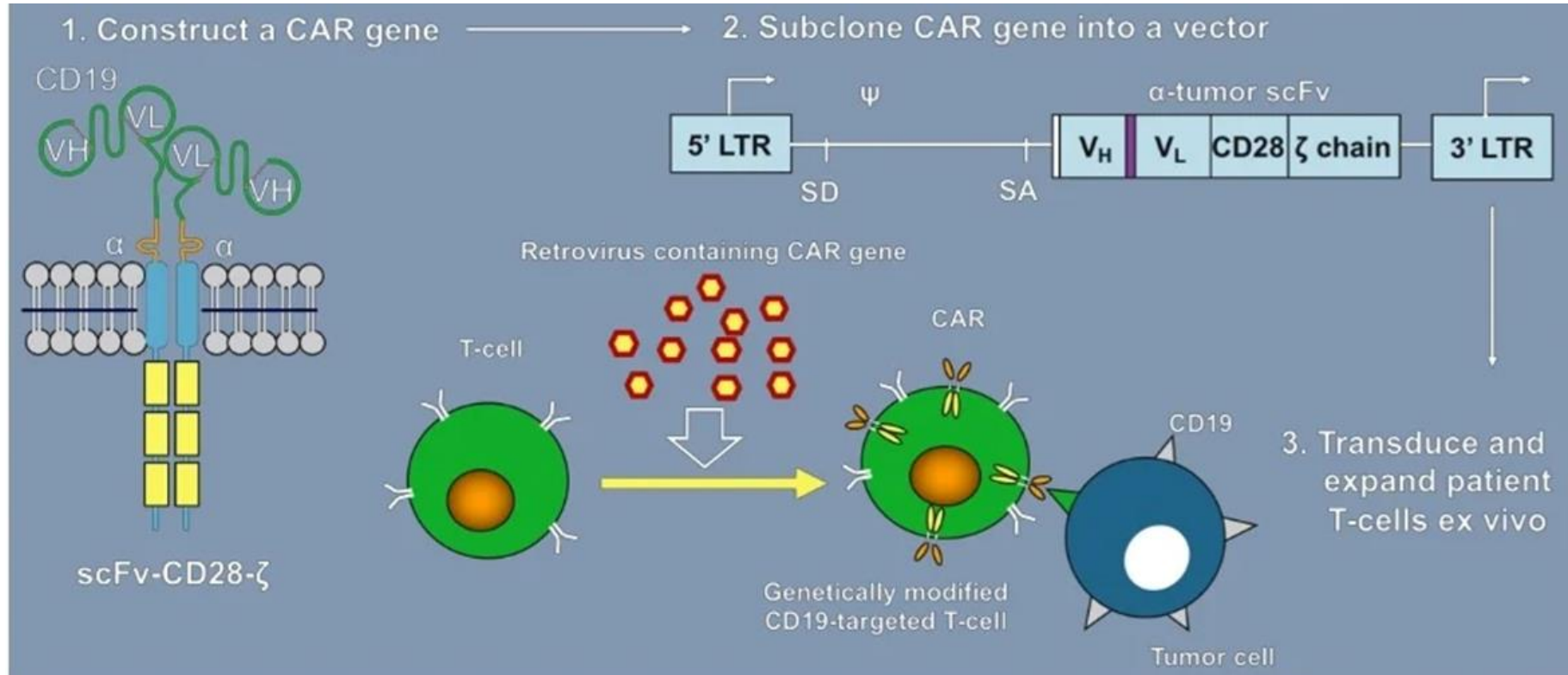
In 1989, Israeli immunologist Dr Zelig Eshhar reported the “Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity.” Subsequently, in 1991, Eshhar reported “Targeting of T lymphocytes to Neu/HER2-expressing cells using chimeric single chain Fv receptors.”

However, these initial reports faced challenges as the structure lacked components to effectively activate and proliferate T cells in response to stimuli.

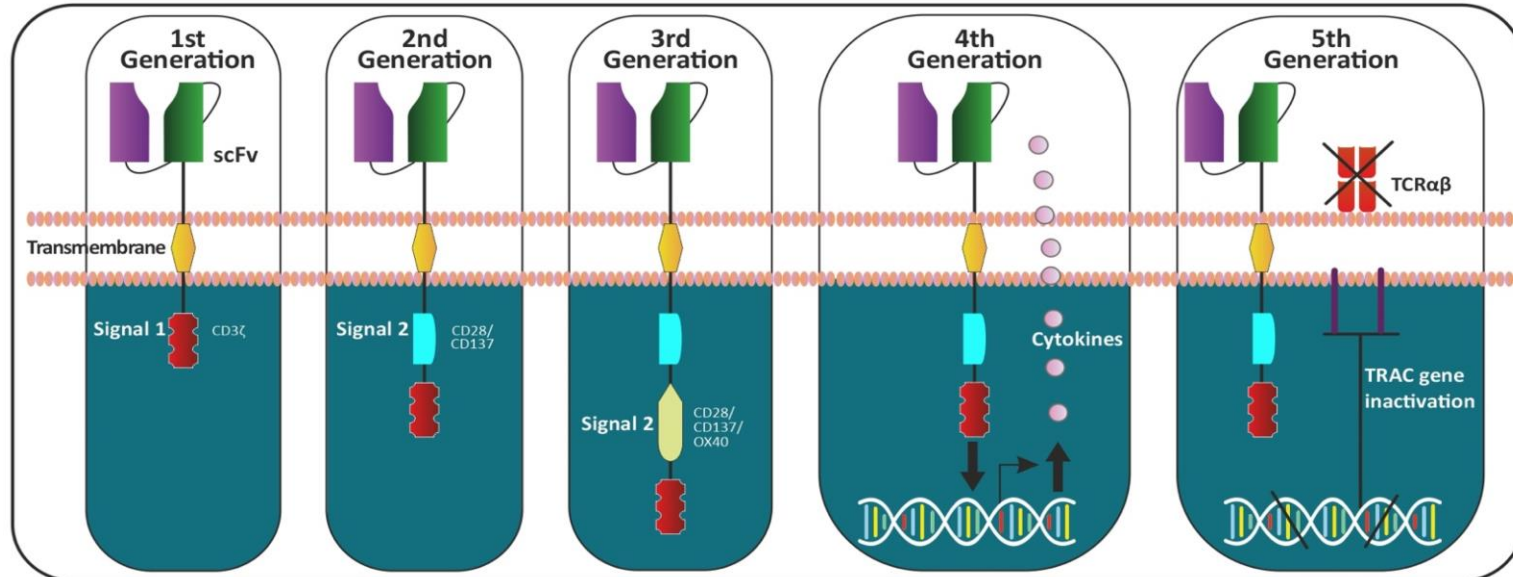
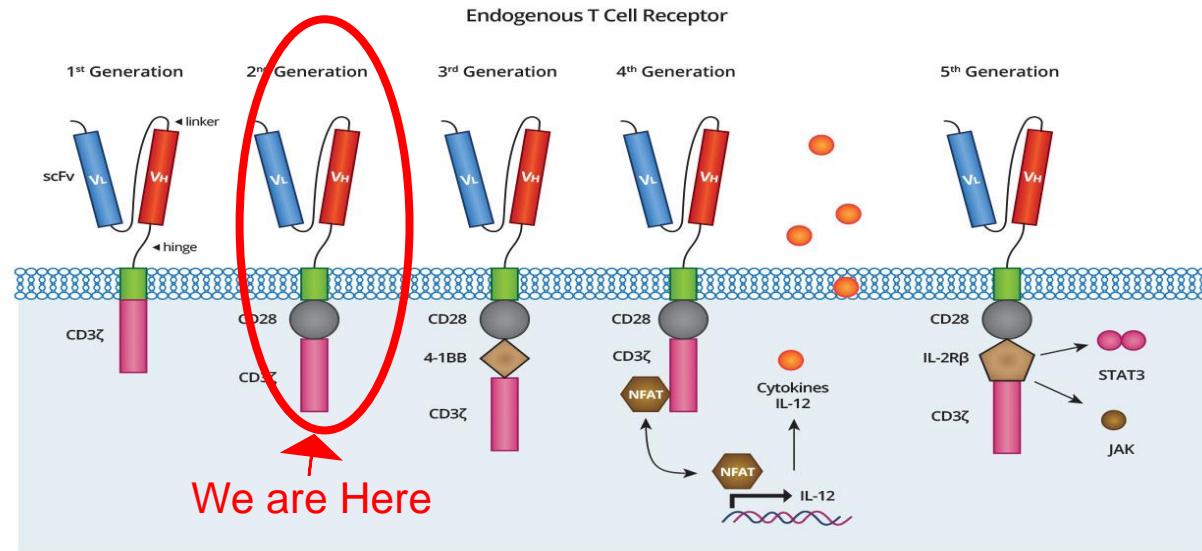
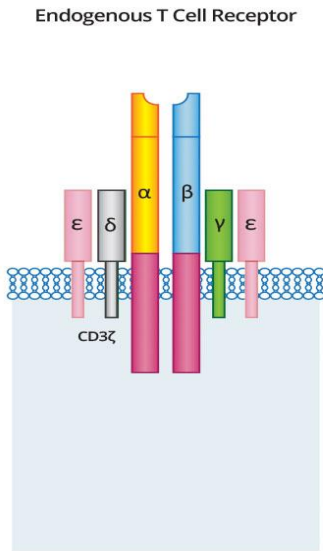
CAR T Cells: Mechanism of Action



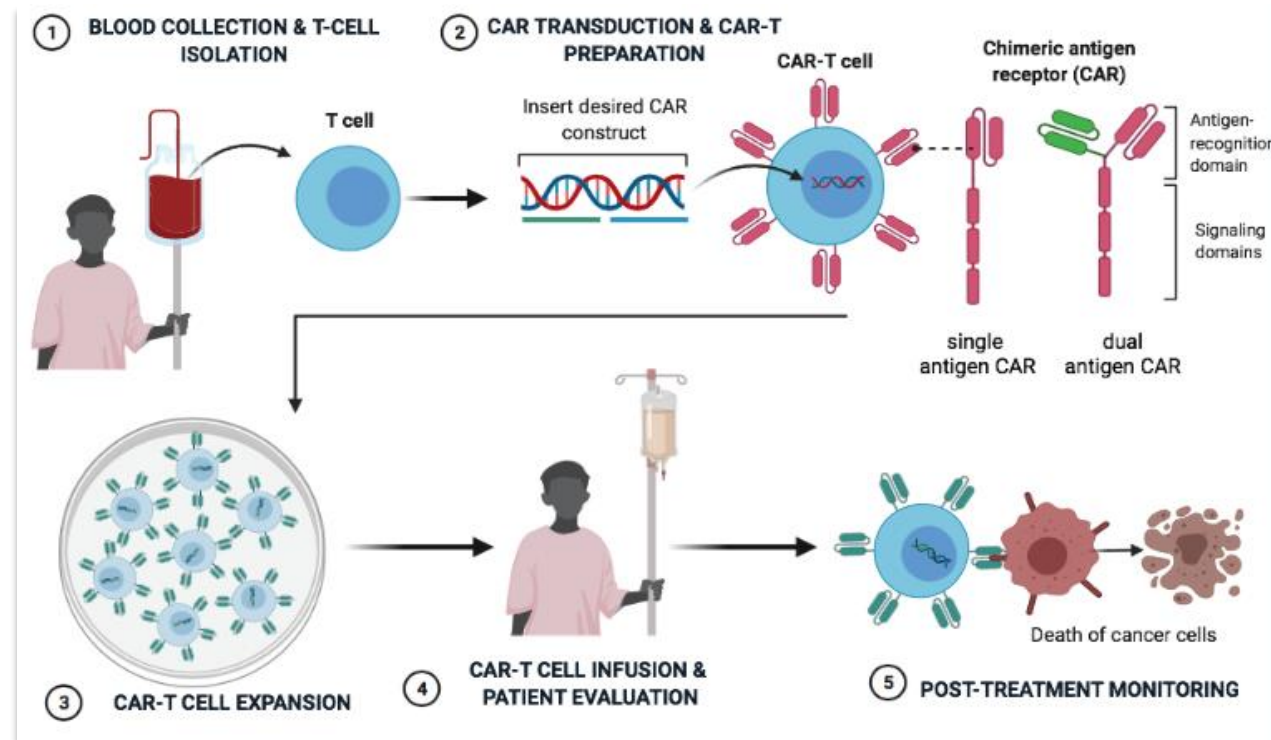
CAR Gene Transduction



Generations of CAR T cell therapy



CAR-T cell therapy workflow



Hematologic Malignancies

- Diffuse large B-cell lymphoma (DLBCL)
- Acute lymphocytic leukemia (ALL)
- Mantle **cell** lymphoma (MCL)
- Chronic lymphocytic leukemia (CLL)
- Multiple Myeloma (MM)
- **AIDS**

Solid Tumors

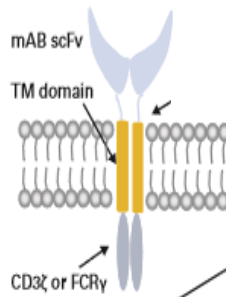
- Lung Cancer
- Breast Cancer
- Glioblastoma
- Oral Cancer
- RCC

Evolution of CAR T Cells



1980-1990s:
Altering T-cell receptor can lead to targeted cell killing

1990s:
First Generation CARTs – slow tumor growth in mice



2000s:
Second Generation CARTs – improved in vitro killing and persistence in mice



2012:
Adult studies begin showing promise of CD19 CAR (Seattle, NCI, MSKCC, Penn)

2013:
2 children with refractory ALL, achieve remission

2017:
FDA Approves first CART product

CD19
YESCARTA[®]
(axicabtagene ciloleucel) Suspension for IV infusion
For B-NHL (DLBCL)

CD19
TECARTUS[®]
(brexucabtagene autoleucel) Suspension for IV infusion
For B-NHL (MCL) 2020,
and B-ALL 2021

BCMA
Abecma[™]
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION
For Multiple Myeloma

BCMA
CARVYKTI
(ciltacabtagene autoleucel)
For Multiple Myeloma



CD19
KYMRIAH[®]
(tisagenlecleucel) Suspension for IV infusion
For B-ALL 2017, and
B-NHL (DLBCL) 2018

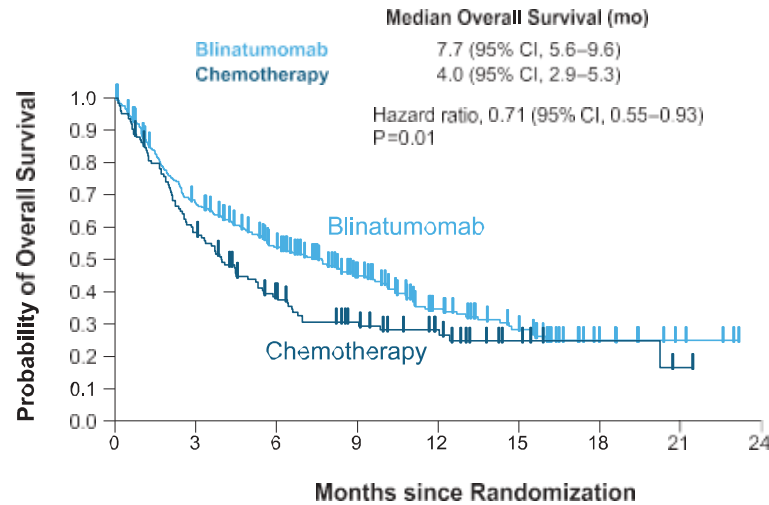
CD19
Breyanzi[®]
(lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION
For B-NHL (LBCL)

ARI-0001 **CD19**
For B-ALL (Spain)

US FDA approvals
• CD19 - 04
• BCMA - 02

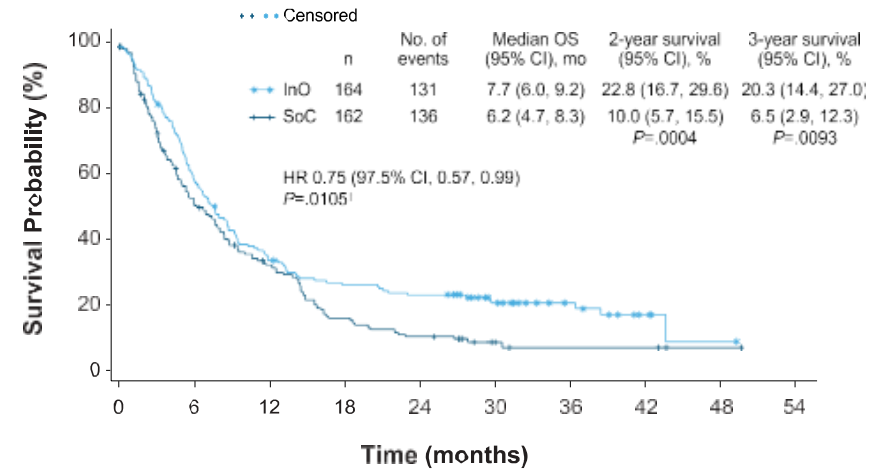
Overall Survival With Novel Agents in R/R ALL

Overall Survival¹



No. at Risk	0	3	6	9	12	15	18	21	24
Blinatumomab	271	176	124	79	45	27	9	4	0
Chemotherapy	134	71	41	27	17	7	4	1	0

Overall Survival²



No. at Risk	0	6	12	18	24	30	36	42	48	54
InO	164	95	54	41	36	23	12	5	1	0
SoC	162	75	45	22	14	5	3	3	1	0

1. Kantarjian HM, et al. *N Engl J Med*. 2017;376(9):836-847.
 2. Kantarjian HM, et al. *Cancer*. 2019 Mar 28. doi: 10.1002/cncr.32116. [Epub ahead of print].

ELIANA Trial

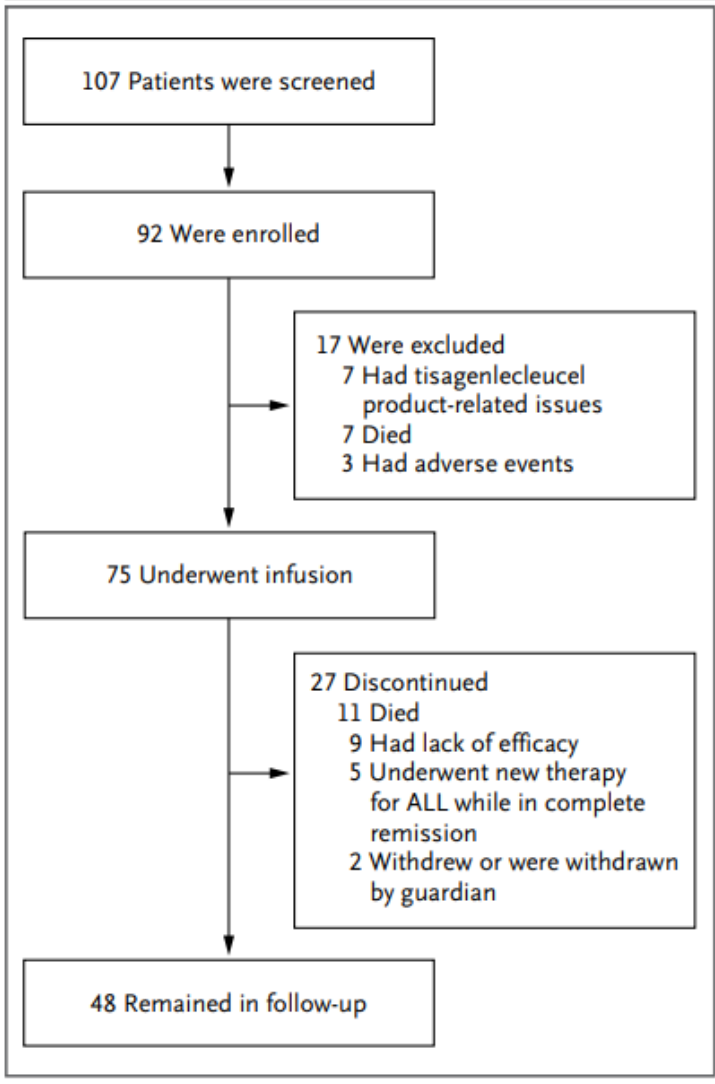


Figure 1. Screening, Enrollment, Treatment, and Follow-up.

The first patient's first visit occurred on April 8, 2015. The median time from tisagenlecleucel infusion to data cutoff was 13.1 months. The reasons for patients not enrolling in the study after screening included not meeting the inclusion criteria or meeting the exclusion criteria (11 patients, including <5% blasts in the bone marrow in 8 patients), death before acceptance of the apheresis sample at the manufacturing facility (2 patients; 1 who died from pulmonary hemorrhage and 1 who died from multiorgan failure), physician decision (1), and apheresis-related issue (1). All patients who completed screening and whose apheresis product was received and accepted by the manufacturing facility were enrolled in the study. Of the 75 patients who received an infusion, 65 (87%) received bridging chemotherapy between enrollment and infusion, and 72 (96%) received lymphodepleting chemotherapy (fludarabine–cyclophosphamide [71 patients] or cytarabine–etoposide [1]). Seventeen enrolled patients did not receive a tisagenlecleucel infusion because of product-related issues (7 patients), death (7 patients; 4 from disease progression and 1 each from sepsis, respiratory failure, and fungemia), and adverse events (3 patients; 1 each from graft-versus-host disease, systemic mycosis, and fungal pneumonia). Tisagenlecleucel product-related issues included an inability to manufacture as a result of poor cell growth for 6 patients and a technical issue unrelated to cell growth for 1 patient. Patients who received the infusion but discontinued follow-up were followed for survival. At the time of data cutoff, 27 patients had discontinued follow-up owing to death (11 patients; 7 from disease progression and 1 each from encephalitis, cerebral hemorrhage, systemic mycosis, and hepatobiliary disorders related to allogeneic hematopoietic stem-cell transplantation), lack of efficacy (9 patients; nonresponse or relapse), new therapy while in complete remission (5), and patient or guardian decision (2); 48 patients remained in follow-up. ALL denotes acute lymphoblastic leukemia.

ZUMA 3 Trial

KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, randomised, controlled, phase 2 trial



Findings Between Oct 1, 2018, and Oct 9, 2019, 71 patients were enrolled and underwent leukapheresis. KTE-X19 was successfully manufactured for 65 (92%) patients and administered to 55 (77%). The median age of treated patients was 40 years (IQR 28–52). At the median follow-up of 16·4 months (13·8–19·6), 39 patients (71%; 95% CI 57–82, $p < 0·0001$) had complete remission or complete remission with incomplete haematological recovery, with 31 (56%) patients reaching complete remission. Median duration of remission was 12·8 months (95% CI 8·7–not estimable), median relapse-free survival was 11·6 months (2·7–15·5), and median overall survival was 18·2 months (15·9–not estimable). Among responders, the median overall survival was not reached, and 38 (97%) patients had MRD negativity. Ten (18%) patients received allo-SCT consolidation after KTE-X19 infusion. The most common adverse events of grade 3 or higher were anaemia (27 [49%] patients) and pyrexia (20 [36%] patients). 14 (25%) patients had infections of grade 3 or higher. Two grade 5 KTE-X19-related events occurred (brain herniation and septic shock). Cytokine release syndrome of grade 3 or higher occurred in 13 (24%) patients and neurological events of grade 3 or higher occurred in 14 (25%) patients.

Interpretation KTE-X19 showed a high rate of complete remission or complete remission with incomplete haematological recovery in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia, with the median overall survival not reached in responding patients, and a manageable safety profile. These findings indicate that KTE-X19 has the potential to confer long-term clinical benefit to these patients.

Survival and durability of response

- **ELIANA trial** : Tisagenlecleucel for pediatric and young adult patients, 75 patients were treated, with a CR rate of 81%.

EFS and OS at 12 months of 50% and 76%, respectively.

- **Multicenter ZUMA-3** study treating 55 adults with r/r ALL with KTE-X19, CR rate was 71% and median OS was 18.2 months.

The median duration of remission for responders was 12.8 months.

- Another multicenter study treated 38 adult and pediatric patients with CART19 with a CR rate of 71%, with OS and progression-free survival of 67% and 47%, respectively, at 1 year. The median duration of response was 14.8 months

Ortíz-Maldonado V, Rives S, Castellà M, et al. CART19-BE-01: a multicenter trial of ARI-0001 cell therapy in patients with CD19+ relapsed/refractory malignancies. Mol Ther. 2021;29(2):636-644.

Anti-CD19 CAR T Cells Have Dramatic Activity in R/R ALL

Signaling Domain	Gene Transfer	Population	Prior HSCT/GVHD ^a	CR/MRD- CR Rate	Grade 3/4 ^a Cytokine Release Syndrome	Grade 3/4 ^b Neurotoxicity	Site/Ref
1BB-CD3ζ	Lentiviral	N = 43 (ALL) Peds and AYA	62% / 4% ^e	NR / 93%	29%	21%	MSKCC ¹ Park JH, et al. <i>NEJM</i> 2018
CD28-CD3ζ	retrovirus	N = 30 (ALL) N = 21 (ALL) Peds and AYA	36% / NR 37% / 0	83% / 67% ^c 93% / 86% NR / 85%	26%	42%	Seattle ^{2,3} Turtle CJ, et al. <i>JCI</i> 2016 Hay KA, et al. <i>Blood</i> 2019
4-1BB-CD3ζ	Lentiviral	53 (ALL) N = 21 (ALL) Peds and AYA	43% / 72%	70% / 60% (ITT)	83% 19%	23%	NCI ⁴ Lee DW, et al. <i>Lancet</i> 2015
CD28-CD3ζ	retrovirus	N = 75 (ALL) Peds and AYA	61% / NR	60% / 60%	76% CRS (29% severe)	29%	ELIANA Study ⁵ Maude SL, et al. <i>NEJM</i> 2018
CD3ζ 4-1BB-CD3ζ	retrovirus	N = 75 (ALL) Peds and AYA	61% / NR	NR / 93%	61% ^d	13%	Seattle Children's Hospital ⁶ Gardner RA. <i>Blood</i> 2017

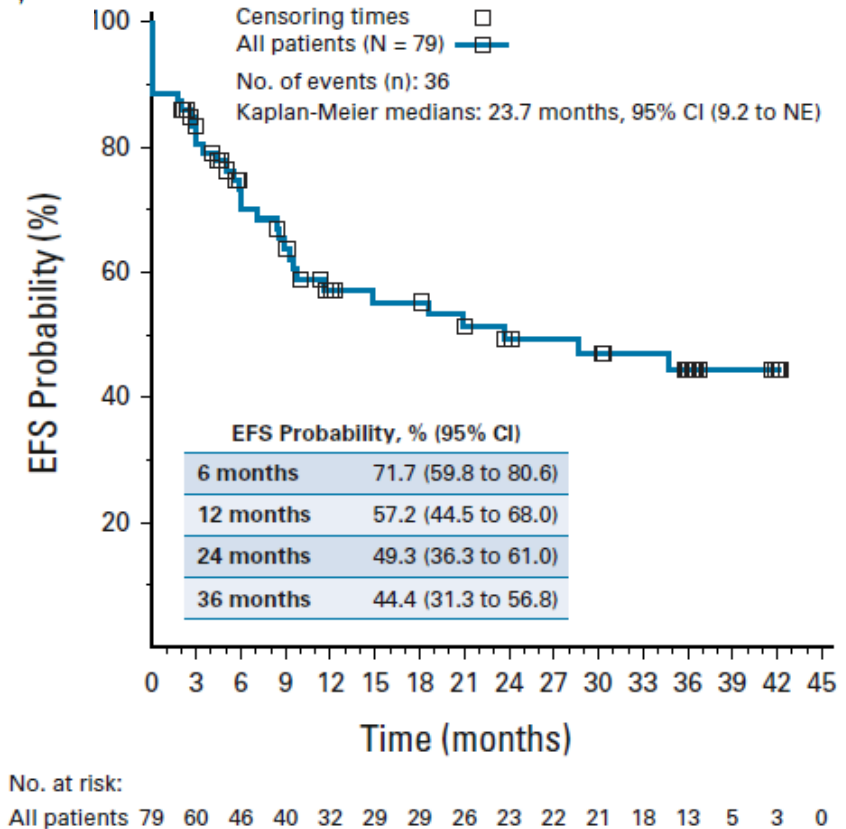
NR, not reported.
^a A difference in the rate or severity of toxicity in patients with a prior allogeneic HSCT was not apparent.
^b The grading criteria were different in all the studies. Please refer to the original publication for additional details.
^c Minimal residual disease assessed on a total of 48 patients who had sufficient bone marrow samples.
^d Severe CRS required intensive care with varying degrees of respiratory support (from placement of a nasal cannula to mechanical ventilation).
^e GVHD in 1 out of 27 patients who received previous HSCT.

1. Park JH, et al. *N Engl J Med*. 2018;378(5):449-459. 2. Turtle CJ, et al. *J Clin Invest*. 2016;126(6):2123-2138. 3. Hay KA, et al. *Blood*. 2019;133(9):1652-1663. 4. Lee DW, et al. *Lancet*. 2015;385(9967):517-528. 5. Maude SL, et al. *N Engl J Med*. 2018;378(5):439-448. 6. Gardner RA, et al. *Blood*. 2017;129(25):3322-3331.

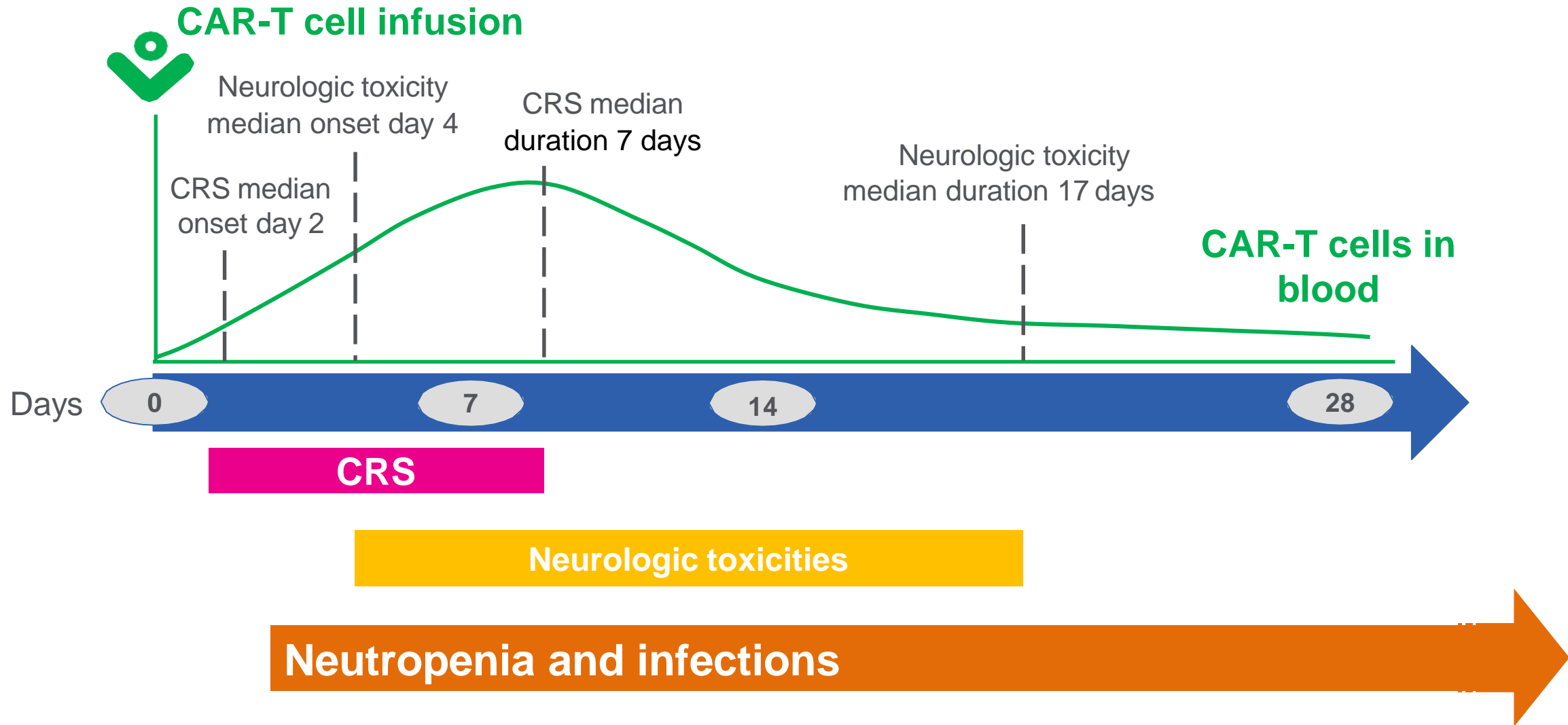
Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial

Theodore W. Laetsch, MD^{1,2}; Shannon L. Maude, MD, PhD¹; Susana Rives, MD, PhD³; Hidefumi Hiramatsu, MD, PhD⁴; Henrique Bittencourt, MD, PhD^{5,6}; Peter Bader, MD⁷; André Baruchel, MD⁸; Michael Boyer, MD⁹; Barbara De Moerloose, MD, PhD¹⁰; Muna Qayed, MD¹¹; Jochen Buechner, MD, PhD¹²; Michael A. Pulsipher, MD^{13,14}; Gary Douglas Myers, MD¹⁵; Heather E. Stefanski, MD, PhD¹⁶; Paul L. Martin, MD, PhD¹⁷; Eneida Nemecek, MD¹⁸; Christina Peters, MD¹⁹; Gregory Yanik, MD²⁰; Seong Lin Khaw, MBBS(Hons), PhD²¹; Kara L. Davis, DO²²; Joerg Krueger, MD²³; Adriana Balduzzi, MD²⁴; Nicolas Boissel, MD, PhD²⁵; Ranjan Tiwari, MSc²⁶; Darragh O'Donovan, PhD²⁷; and Stephan A. Grupp, MD, PhD^{1,2}

Characteristic	All Patients (N = 79)	Post-Infusion alloSCT (n = 17)	No Post-Infusion alloSCT (n = 62)
Age, years, median (range)	11 (3-24)	9 (4-21)	12 (3-24)
Sex, male, No. (%)	45 (57)	13 (77)	32 (52)
Prior HSCT, No. (%)	48 (61)	6 (35)	42 (68)
Previous lines of therapy, No., median (range)	3 (1-8)	2 (2-4)	3 (1-8)
Disease status, No. (%)			
Primary refractory	6 (8)	1 (6)	5 (8)
Relapsed	73 (92)	16 (94)	57 (92)
Morphologic blast count in bone marrow, %, median (range) ^a	74 (5-99)	84 (9-99)	72 (5-96)
CNS status classification, No. (%)			
CNS-1 ^b	68 (86)	16 (88)	52 (84)
CNS-2	10 (13)	1 (6)	9 (15)
Unknown	1 (1)	0	1 (2)
High-risk genomic lesions, ^c No. (%)	30 (38)	9 (53)	21 (34)
Down syndrome, No. (%)	6 (8)	1 (6)	5 (8)



CAR-T Cell Therapy – Timing of toxicities



Where do we stand in the race of CAR T cells

S. No.	Institute/Company	Location	CAR-Design	Vector	Manufacturing	Status	Approved
1	IIT Mumbai ACTRAC	Mumbai	2 nd Gen CD19 (humanized CD19)	Unknown	Manual	Clinical trial started on 05- 06-2021	YES (>15 years old)
2	Immuneel in collaboration with HCB & IDIBAPS, Spain	Bangalore	2 nd Gen CD19 CAR	Same as in Kymriah	Prodigy	Phase II trial completed	YES for NHL
3	Intas Biopharmaceuticals (Intas, TMC Kolkata, ICMR)	Ahmedabad	2 nd Gen CD19 CAR Miltenyi product	No data	No data available	No data available	No
4.	CMC Vellore Miltenyi Biotech	Vellore	2 nd Gen CD19 CAR Miltenyi product	Lentigen	Prodigy	Phase II CT initiated	No
5.	Dr Reddy's in collaboration with Pregene Biopharma	Hyderabad	2 nd Gen BCMA CAR	Lentiviral	? Prodigy	Phase I CT started	No
6.	Cellogen Therapeutics	Delhi	3 rd and 4 th Gen CAR	Indigenous Lentiviral vector	Prodigy and in-house	Pre-clinical – completed Phase I CT to be initiated	No

A PHASE 2 STUDY TO DETERMINE THE SAFETY AND EFFICACY OF VARNIMCABTAGENE AUTOLEUCEL (IMN-003A) IN PATIENTS WITH RELAPSED AND REFRACTORY CD19 POSITIVE B CELL MALIGNANCIES

Principal Investigators:

Dr. Sharat Damodar, NH-MSMC,
Bengaluru

Dr. Raja Thirumalairaj, Apollo Cancer Centre, Chennai
Dr. Pankaj Malhotra, PGIMER, Chandigarh

Dr. Sunil Bhat, NH-MSMC, Bengaluru

Sites

- Narayana Health – Mazumdar Shaw Medical Center, Bengaluru
- Apollo Cancer Centre, Chennai
- Postgraduate Institute of Medical Education and Research, Chandigarh (Public Hospital)

Sponsor

Immuneel Therapeutics Private Limited

29/P2, 8th Floor, Narayana Health City, Hosur Road, Bommasandra Industrial Area, Bengaluru, Karnataka, India, 560099.

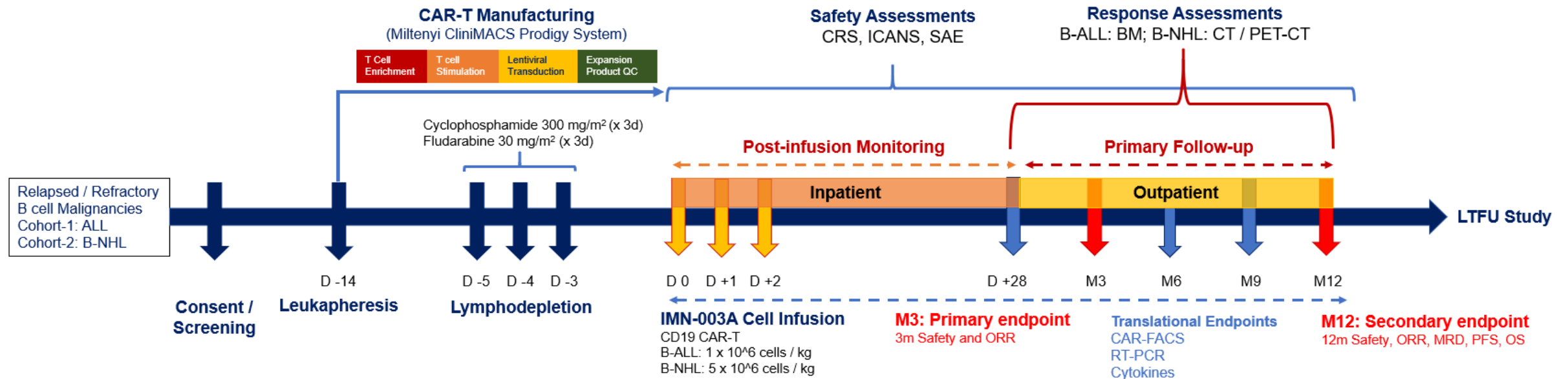
PHASE-2 FIRST-IN-INDIA INDUSTRY STUDY OF VARNIMCABTAGENE AUTOLEUCEL (IMN-003A) IN RELAPSED REFRACTORY B CELL MALIGNANCIES (IMAGINE STUDY): B-ALL PEDIATRIC SUBANALYSIS

Primary Objectives:

- Safety at 3 months
- Objective response rate (ORR) at 3 months

Primary Endpoints:

- Adverse events, specifically cytokine release syndrome (CRS) and Immune effector Cell Associated Neurotoxicity Syndrome (ICANS) and Treatment Related Mortality (TRM) after infusion
- Efficacy at 3 months based on NCCN criteria (CR, CRi, MRD)



Inclusion Criteria

- 3 to 45 years
- Beyond first relapse
- Primary refractory disease
- Philadelphia positive ALL intolerant of TKI
- Ineligible or declines allogeneic transplant
- MRD positive
- ECOG 0 or 1
- Adequate organ function

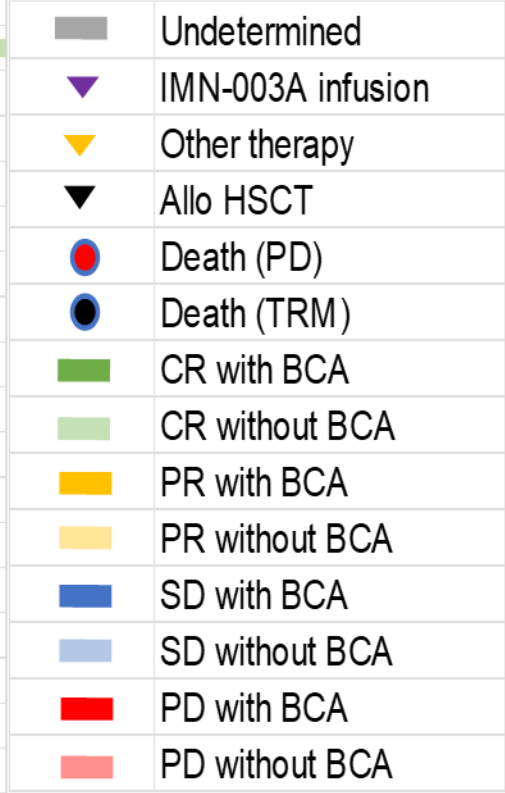
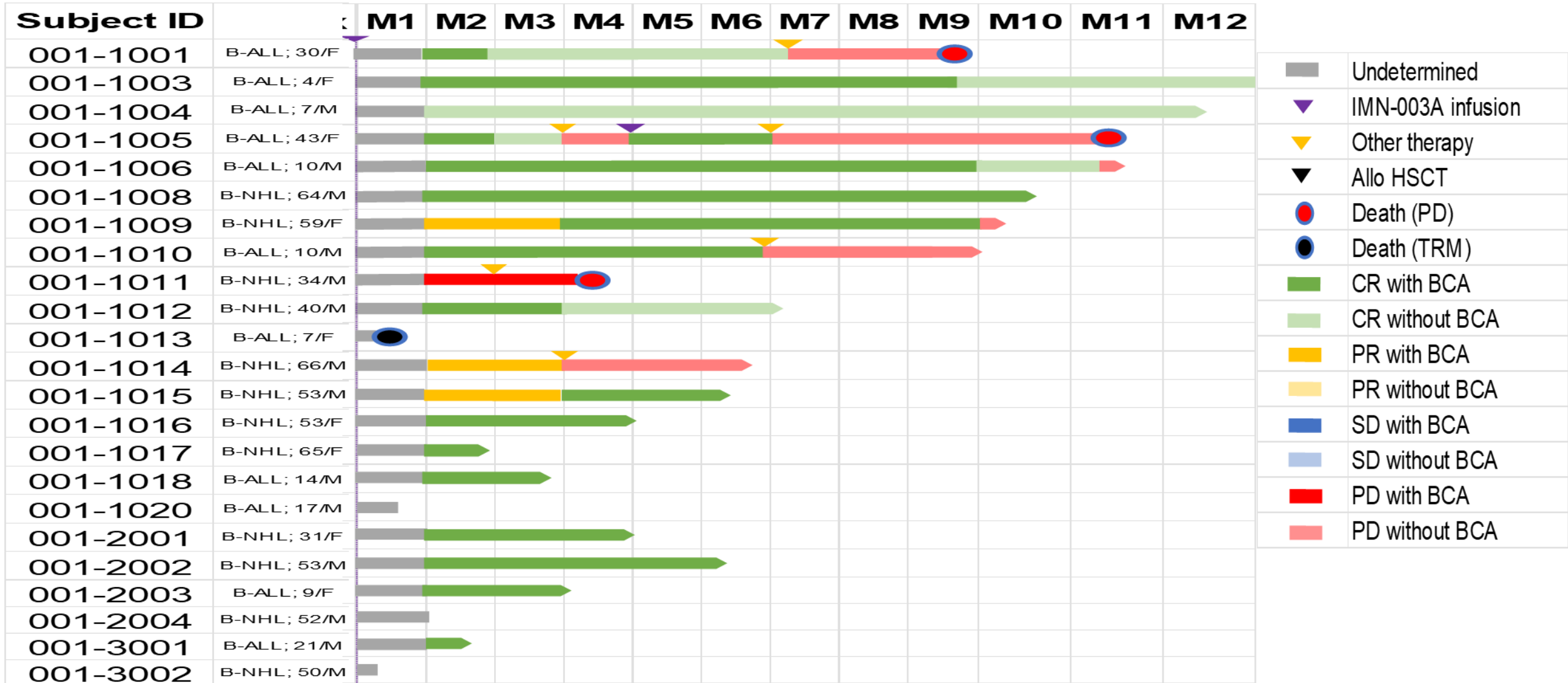
Exclusion Criteria

- GVHD or ongoing immunosuppressants
- Prior CD19 targeted therapy
- Clinically significant infection
- Current CNS disease / other CNS pathology

Varnimcabtagene Autoleucel – Summary

Endpoints	ITT Set (n = 11 B-ALL; 12 B-NHL)
Efficacy	
Overall Response Rate (ORR) @ Day 90 Primary endpoint	76.5% (n= 13 / 17) B-ALL 75% (n = 6 / 8); B-NHL 77.8% (n = 7 / 9) B-ALL Adult 50% (n = 1 / 2); B-ALL Paed 83.3% (n = 5 / 6) MRD neg (B-ALL): 75% (n = 6 / 8)
Overall Response Rate (ORR) @ Day 28	90.4% (n = 19 / 21) B-ALL 90% (n = 9 / 10); B-NHL 90.9% (n = 10 / 11) B-ALL Adult 100% (n = 3 / 3); B-ALL Paed 85.7% (n = 6 / 7) MRD neg (B-ALL): 90% (n = 9 / 10)*
Progression Free Survival	NR
Duration of Response	NR
Overall Survival	NR
Safety	
Cytokine Release Syndrome (CRS)	G4 4.3% (n = 1/23); G1 60.8% (n = 14/23)
Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)	G1 4.3% (n = 1/23); G3+ 0%
TRM	4.3% (n = 1/23); CRS
Tocilizumab Use	
CRS (n = 15 / 23)	39.1% (9 / 23)

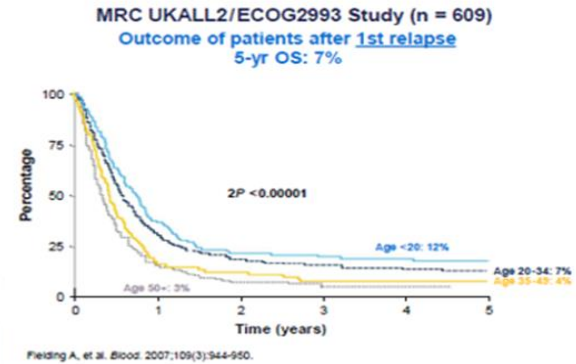
Varnimcabtogene Autoleucel – Swimmer Plot



Varnimcabtogene autoleucel – Only CAR-T in India to demonstrate superior OS in curative setting in B Cell Malignancies

No statistically significant improvement in OS in ~30 years

B-ALL



Statistically significant survival benefit

Var-cel

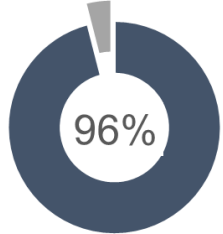
62%
reduction in risk of death
at 6 months

HR: 0.38
95% CI 0.22, 0.66

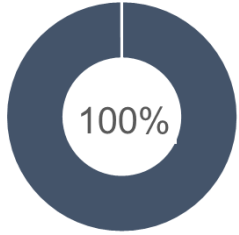
Var-cel is the first treatment in India to significantly improve OS in B cell malignancies

Robust manufacturing

IMAGINE Study



Received var-cel*



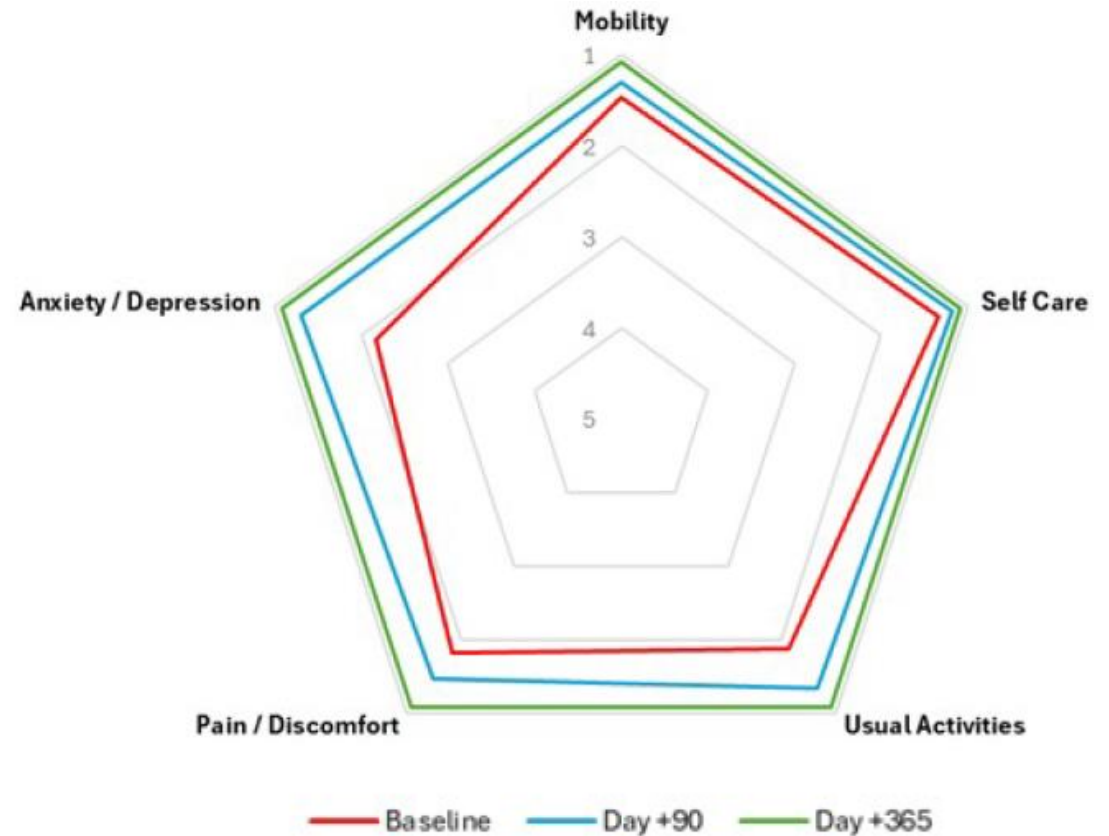
Manufacturing success

Survival benefit is reliant on manufacturing success and turnaround time

* 1 patient withdrawn before Infusion

Varnimcabtagene Autoleucel: Quality of Life (QoL) Outcomes

- Clinically meaningful improvements seen in all 5 dimensions including overall health score
 - Mobility, Self Care, Usual Activities, Pain / Discomfort, Anxiety / Depression
- Sustained through 3 to 12 months after varnim-cel infusion
- Early, sustained and significant improvements in EQ-5D parameters
- Benefits sustained across both age (paediatric and adult) and disease cohorts (B-ALL and B-NHL)

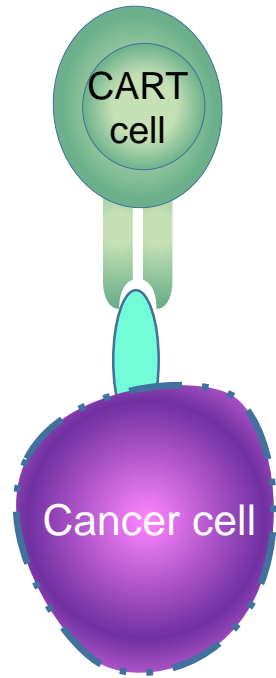


Mean change in QoL parameters from baseline to D+365 post varnim-cel infusion

Importance of persistence for durable remissions

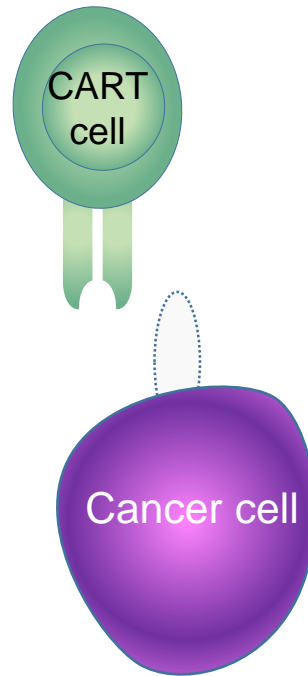
- Impact of prior blinatumomab on efficacy: CHOP reported outcomes from 166 patients treated with CART19. The CR rate was 93%, and 67 patients ultimately relapsed, 39 with CD19– disease due to antigen escaper. Prior therapy with blinatumomab was associated with a higher risk for CD19– relapse
- Rapid loss of CART persistence
- Duration of B-cell aplasia
- Fludarabine to cyclophosphamide lymphodepletion improved persistence and disease-free survival
- Murine vs Humanized anti-CD19

CD19 Antigen Escape

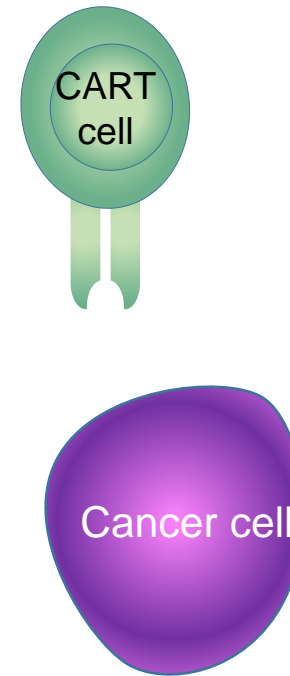


Antigen binding

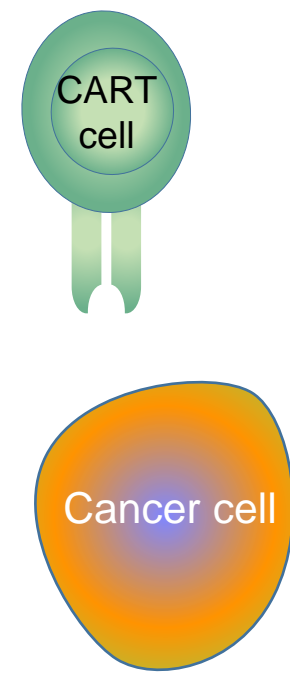
- CAR T cell activation
- Tumor cell killing



Antigen downregulation



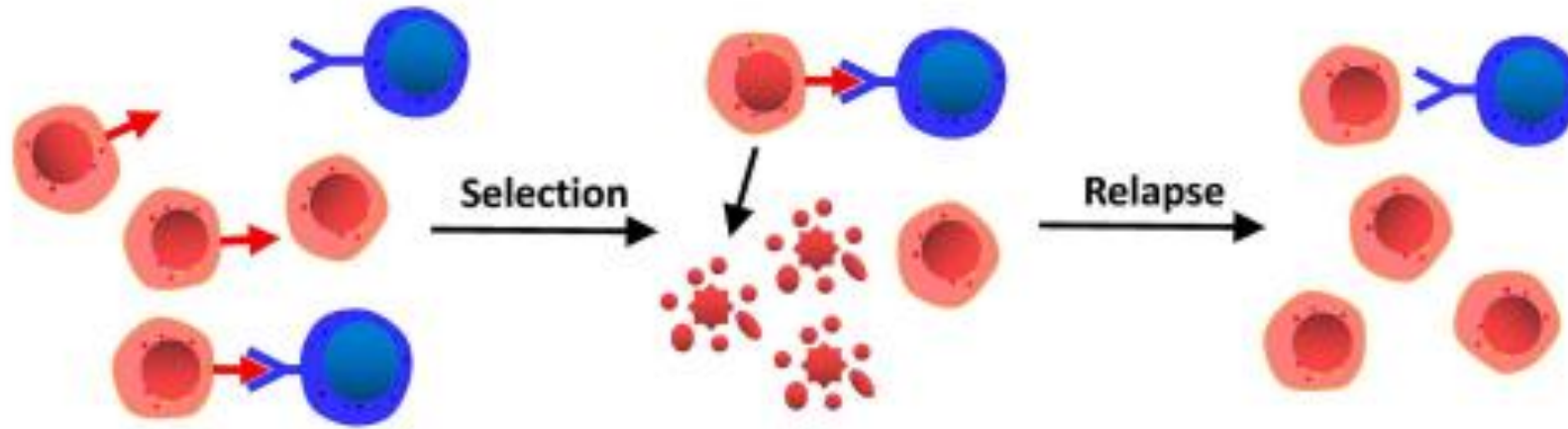
Antigen loss



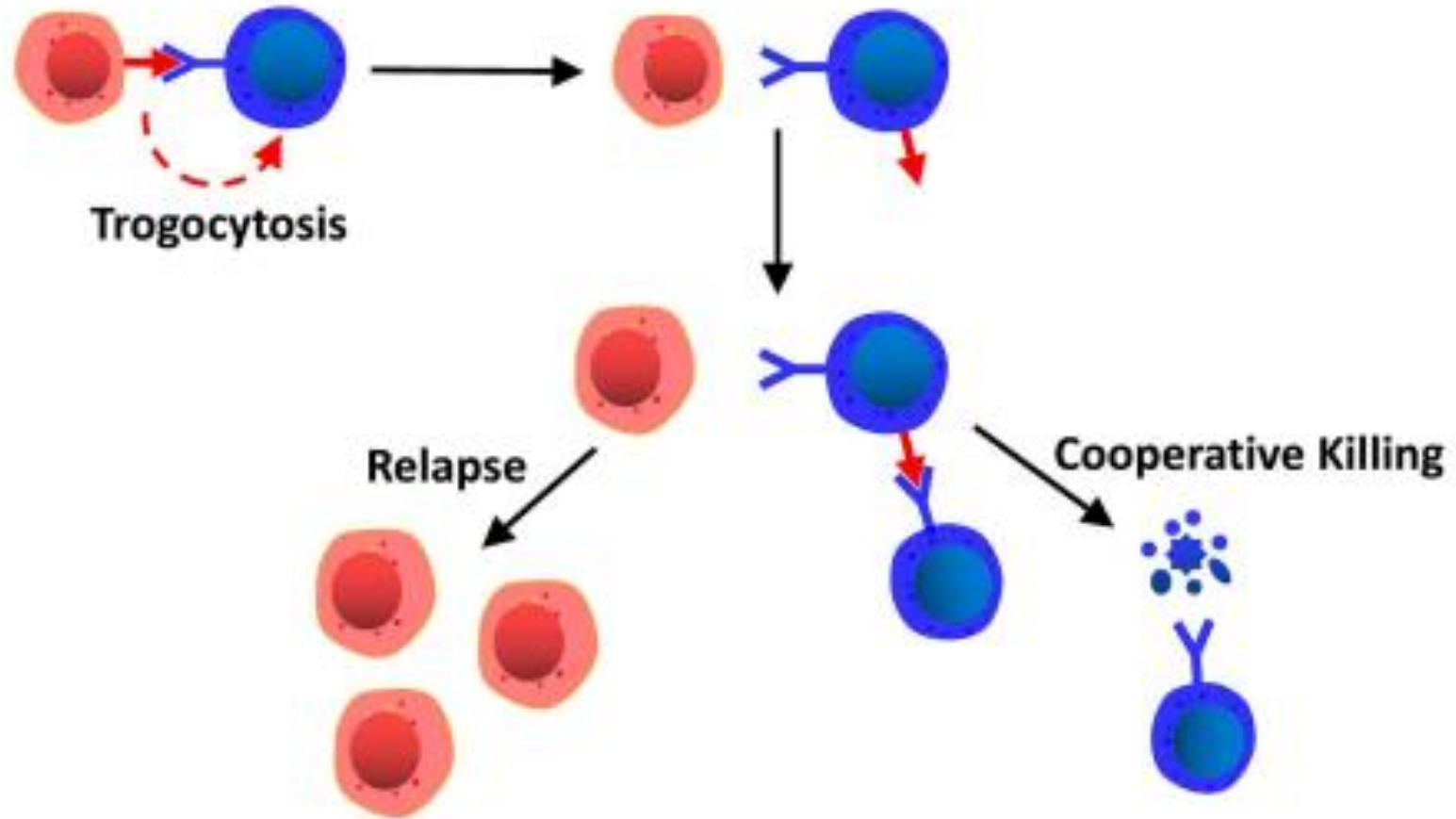
Lineage switching

Between 10-25% in ALL and between 20-30% in DLBNHL show recurrence after CD19 CAR T therapy due to CD19 antigen loss.

B

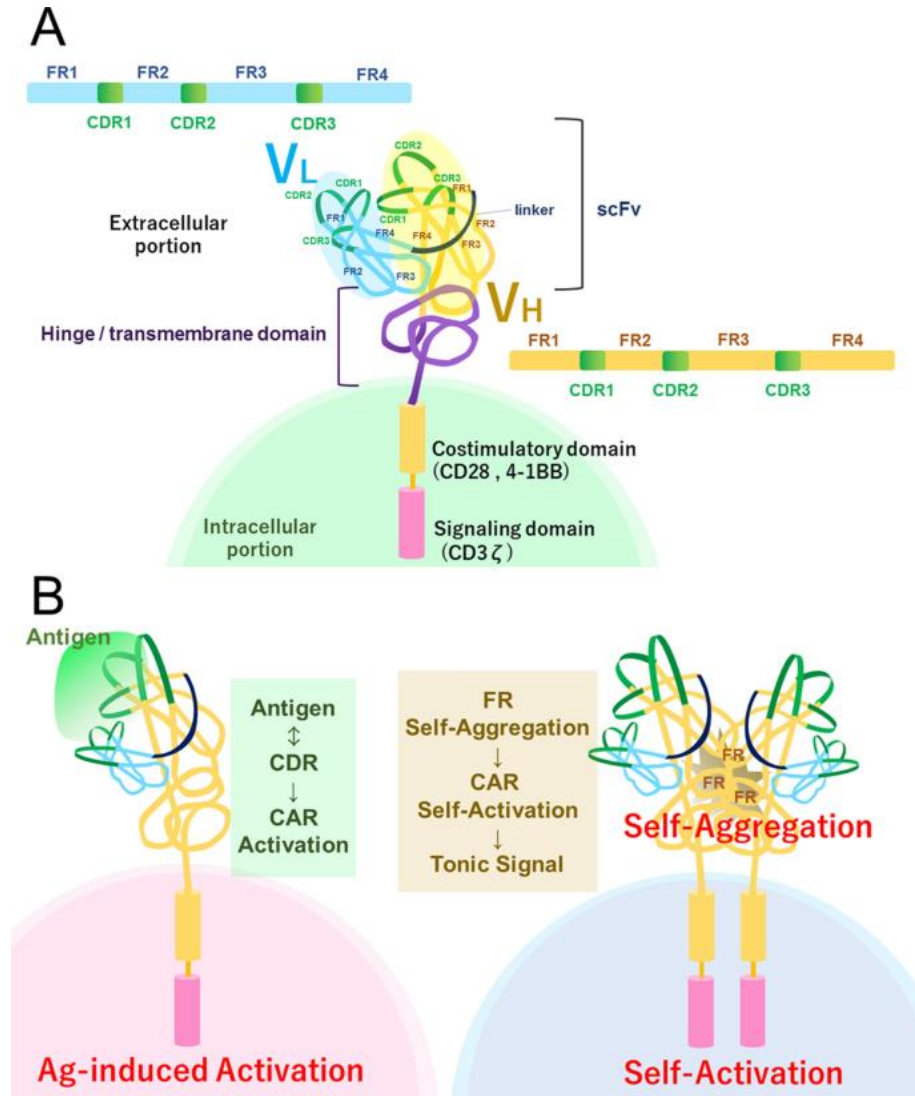


Selection by immune pressure. A small number of pre-existing CD19-negative tumor cells escape recognition of CD19 CAR T-cells and are transformed to dominant clones under selective therapeutic stress.



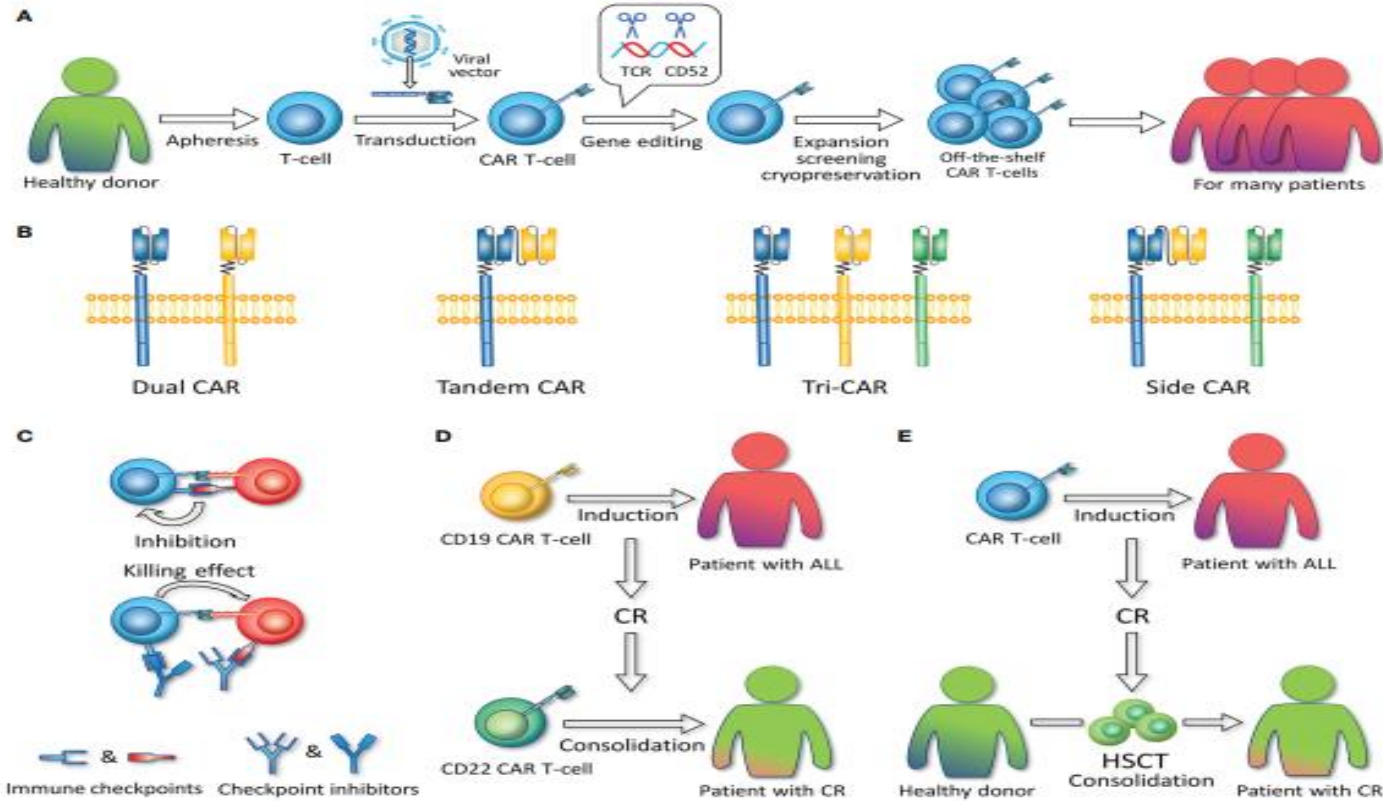
Trogocytosis and cooperative killing. B-ALL cells change CD19 to CD19 CAR T-cells, resulting in antigen escape and fratricide T cell killing.

Tonic signaling in CAR T cells



How to ameliorate CD19 relapses

- CD
- Dual
- Tan
- Side
- Tri-
- Sec



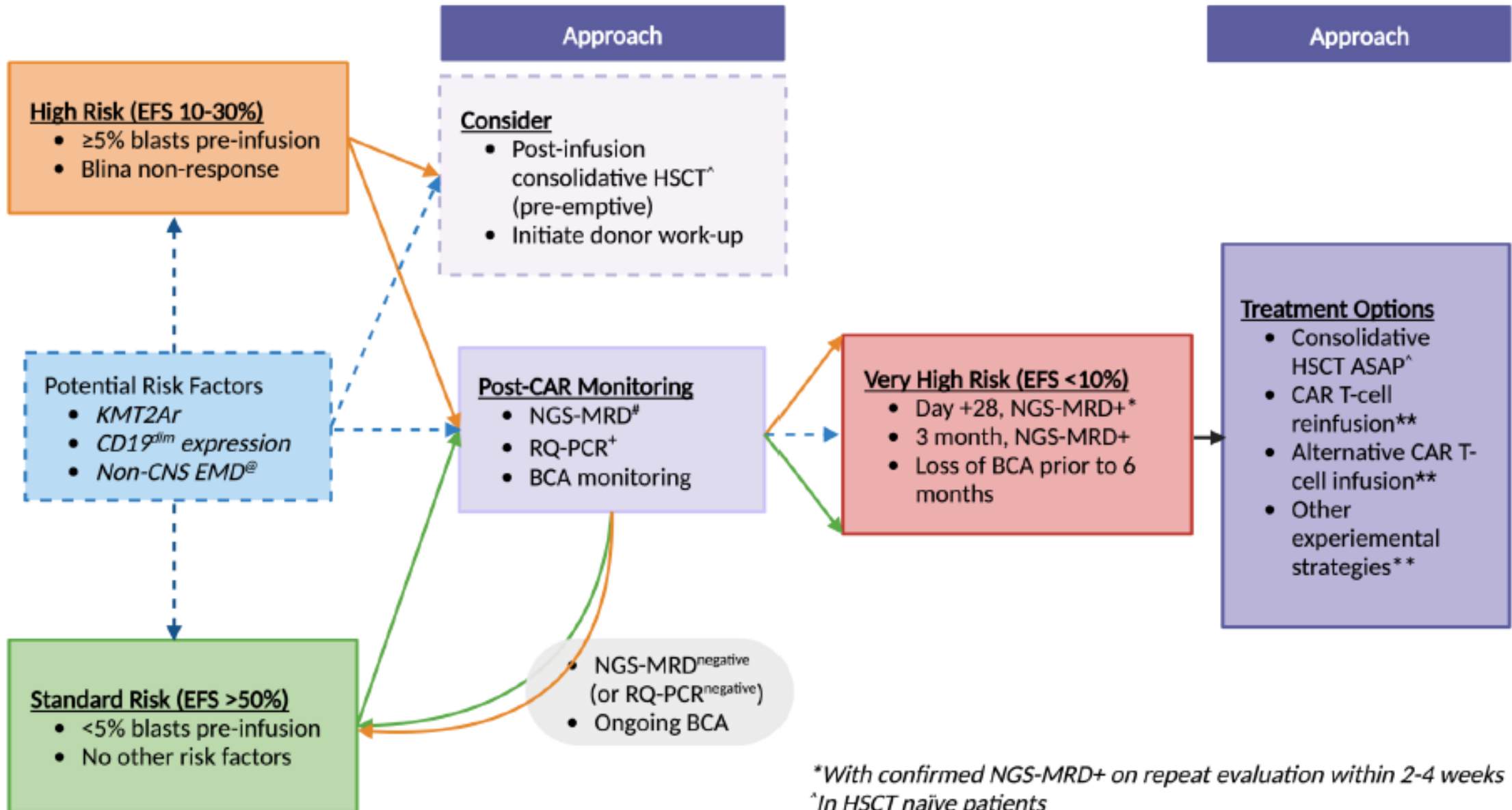
Cor **FIGURE 3 | (A)** Allogeneic, off-the-shelf CAR T-cells. The figure illustrates the general preparation process of allogeneic, off-the-shelf CAR T-cells. T-cells are extracted from healthy donors. Viral vectors are used to introduce CAR-encoding genes into T-cells. Gene editing technology is used to remove the gene fragments encoding TCR and CD52. CAR T-cells are expanded, screened, and cryopreserved. These CAR T-cell products can serve as timely treatment for many patients. **(B)** Multi-antigen targeted CAR. Dual CAR refers to two different mono-CARs in one T-cell. Tandem CAR refers to a CAR structure that contains two single-chain variable fragments. Tri-CAR T-cell coexpresses three different mono-CARs on a single T-cell. Side CAR T-cell expresses a Tandem CAR and a mono-CAR. **(C)** In combination with immune checkpoint inhibitors. Immune checkpoint inhibitors such as PD-1/PD-L1 inhibitors can specifically block the binding of CAR T-cell or ALL-expressed immune checkpoint molecules to the corresponding receptors on CAR T-cells, thereby enabling CAR T-cell activation and the killing of tumor cells. **(D)** Sequential infusion. CD19 CAR T-cells are first infused to induce CR, and after patients achieve CR, CD22 CAR T-cells are infused as consolidation. **(E)** Bridging to HSCT. CAR T-cells are infused to induce CR, and after patients achieve CR, hematopoietic stem cell transplantation (HSCT) is conducted as consolidation.

Role of consolidative SCT

- Treatment-related morbidity and mortality needs to be balanced against risk of relapse
- CARTs with functional persistence would be destroyed by SCT, losing their benefit of ongoing tumor surveillance
- There are no studies to randomize patients after CART therapy to allogeneic SCT or observation
- The decision is not likely generalizable across different CART19 products
- For example, patients taking 4-1BB CART19 products have better persistence (with potentially longer disease-free intervals, although more data are needed) than recipients of CD28-CART19 products

Pre-infusion Risk Factors

Post-infusion Risk Factors (for those achieving CR/CRi)



**With confirmed NGS-MRD+ on repeat evaluation within 2-4 weeks*

^In HSCT naïve patients

#Consider close monitoring Blood. 2022 Nov 23:blood.2022016937

***If NGS-MRD is not available*

Sequential CAR-T(Cocktail CAR-T)

- Sequential infusion
- Less complex
- Doesn't require

CLINICAL TRIALS AND OBSERVATIONS

Efficacy and safety of CAR19/22 T cell infusion in patients with refractory/relapsed B-cell malignancies

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Responses

MRD negative: 96%
31months OS: 95%

Sequential CAR-T cells for

KEY POINTS

- Sequential infusion of CAR19/22 T cell is highly active and well tolerated in patients with refractory/relapsed B-cell malignancies.
- Dual-targeting of CD19 and CD22 may represent a feasible solution to reduce antigen-escape relapse after CD19/CD22-directed therapies.

Antigen-escape relapse has emerged as a major challenge for long-term disease control after CD19-directed therapies, to which dual-targeting of CD19 and CD22 has been proposed as a potential solution. From March 2016 through January 2018, we conducted a pilot study in 89 patients who had refractory/relapsed B-cell malignancies, to evaluate the efficacy and safety of sequential infusion of anti-CD19 and anti-CD22, a cocktail of 2 single-specific, third-generation chimeric antigen receptor-engineered (CAR19/22) T cells. Among the 51 patients with acute lymphoblastic leukemia, the minimal residual disease-negative response rate was 96.0% (95% confidence interval [CI], 86.3-99.5). With a median follow-up of 16.7 months (range, 1.3-33.3), the median progression-free survival (PFS) was 13.6 months (95% CI, 6.5 to not reached [NR]), and the median overall survival (OS) was 31.0 months (95% CI, 10.6-NR). Among the 38 patients with non-Hodgkin lymphoma, the overall response rate was 72.2% (95% CI, 54.8-85.8), with a complete response rate of 50.0% (95% CI, 32.9-67.1). With a median follow-up of 14.4 months (range, 0.4-27.4), the median PFS was 9.9 months (95% CI, 3.3-NR), and the median OS was 18.0 months (95% CI, 6.1-NR). Antigen-loss relapse occurred in 1 patient during follow-up. High-grade cytokine release syndrome and neurotoxicity occurred in 22.4% and 1.12% patients, respectively. In all except 1, these effects were reversible. Our results indicated that sequential infusion of CAR19/22 T cell was safe and efficacious and may have reduced the rate of antigen-escape relapse in B-cell malignancies. This trial was registered at www.chictr.org.cn as #ChiCTR-OPN-16008526. (Blood. 2020;135(1):17-27)

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Allogenic CAR T Cell Therapy

- “Universal off-the-shelf” CAR T products derived from allogeneic sources (UCART)
- Alloreactivity can lead to rejection of the UCART mediated by the recipient T and NK cells, and alloreactivity from the UCART can lead to GVHD
- TCR as the main mediator of both rejection and GVHD, disruption of the TCR through one of a number of gene editing techniques has become the predominate means of preventing GVHD by UCART



Our “Emily” at more than 28
month follow up



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Question 1

The development of ICANS after CAR-T therapy in B-ALL is most closely linked to:

- A: Direct CART cell infiltration of brain parenchyma
- B: Blood-brain barrier disruption with endothelial activation
- C: Immune complex deposition in cerebral vessels
- D: Cerebral leukemia infiltration

Question 2

Compared with CD28 based CARs, 4-1BB based CAR-T cells used in B ALL are characterized by:

A: Faster expansion and higher early CRS rates

B: Greater terminal differentiation and exhaustion

C: Slower expansion with enhanced persistence

D: Reduced memory phenotype formation

Question 3

The pathophysiology of Cytokine Release Syndrome (CRS) following CART cell infusion is primarily mediated by :

- A: Direct tumour lysis by CAR-T cells
- B: Expansion of regulatory T cells
- C. Massive release of inflammatory cytokines
- D. Complement mediated cytotoxicity