CAR-CIK for ALL relapse after allogeneic transplantation

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Cuneo, May 19th 2023

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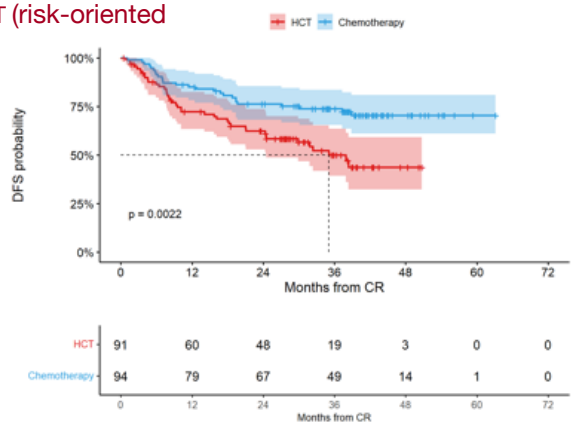
Disclosures

Amgen, Kite-Gilead, Novartis, Celgene-BMS, Sanofi,

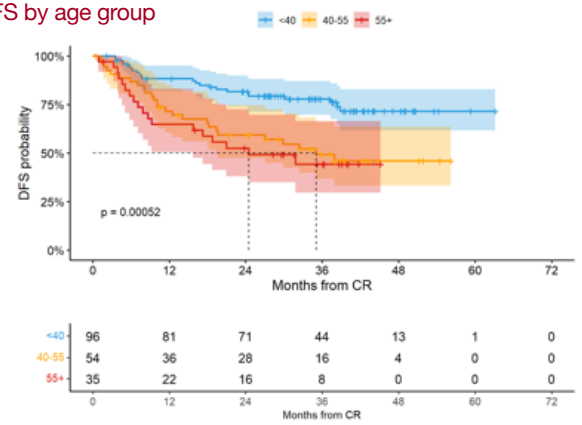
Jazz, Pfizer, Astellas, Abbvie, Incyte, Omeros, Roche

Final results of the national treatment program: the GIMEMA 1913 trial

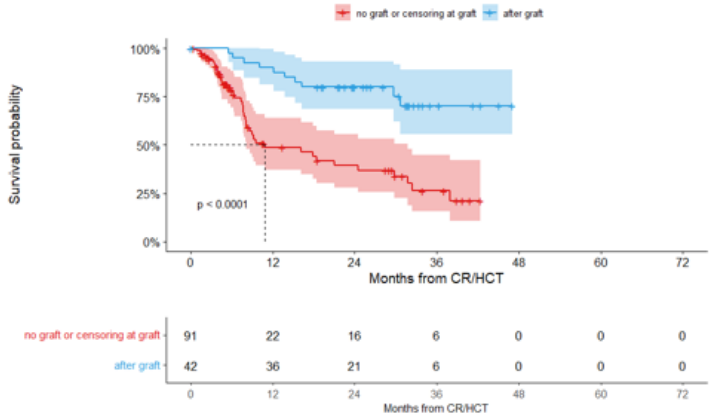
DFS by ITT (risk-oriented therapy)



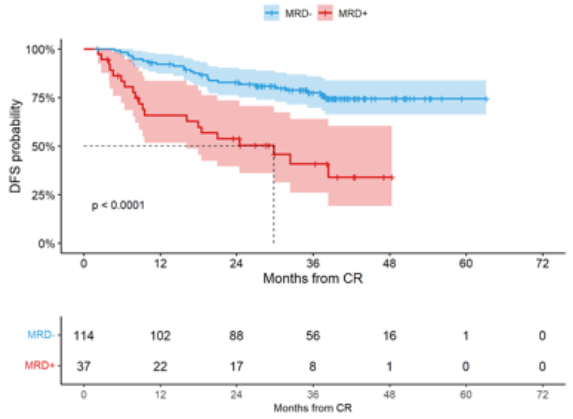
DFS by age group



DFS by HCT (ITT, time-dependent Simon-Makuch plot)



DFS by MRD response

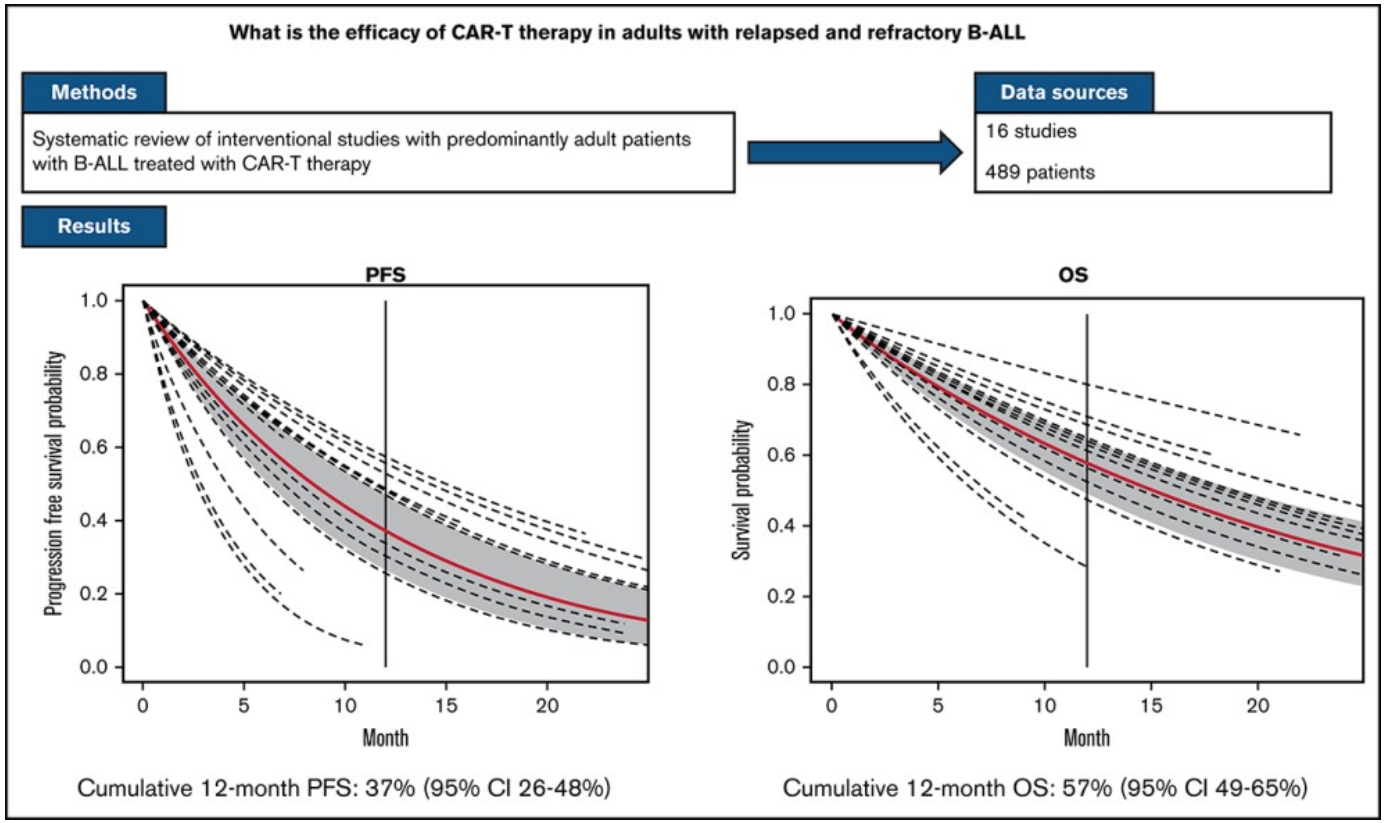


fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Bassan R et al.: EHA 2022 Vienna; abstr # S113

CAR-T cells in BP-ALL: where do we stand in adults?

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN ADULTS WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA



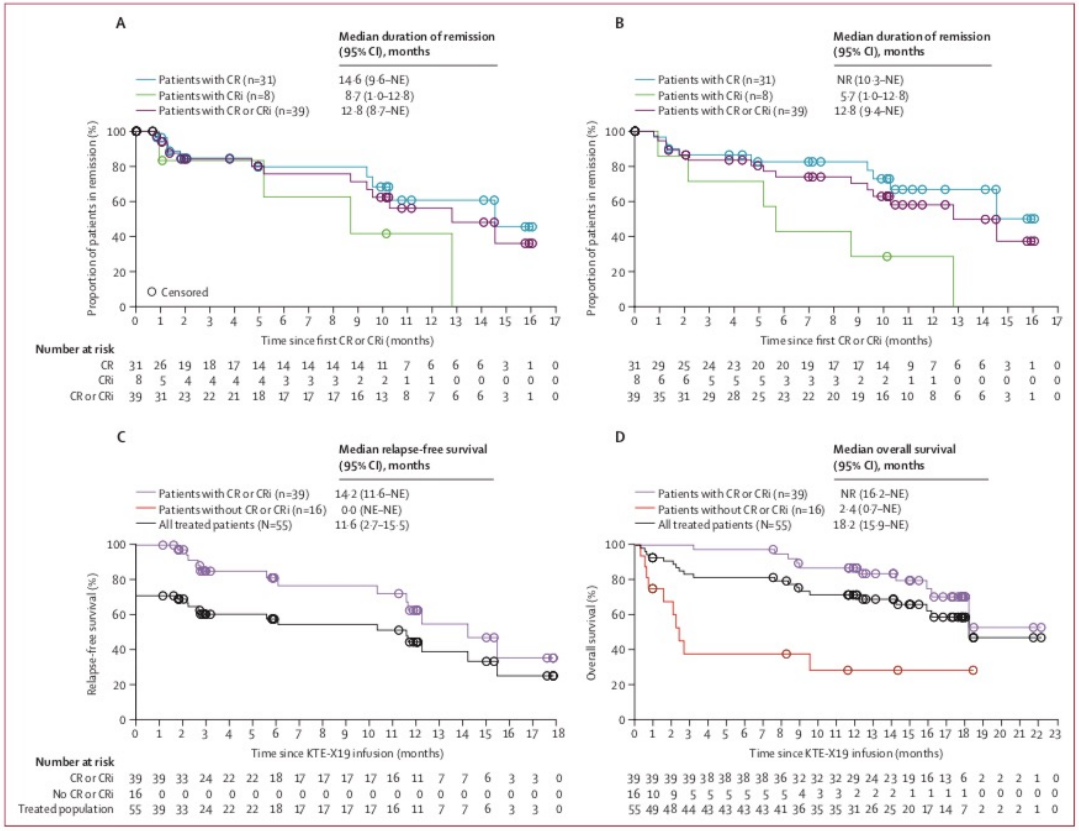
Punita Grover et al. Blood Adv, 2022

KTE-X19 for relapsed or refractory adult B-cell ALL: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study

- **The median age of treated patients was 40 years**
- **71% had complete remission**
- **median duration of remission was 12·8 months**
- **median RFS was 11·6 months**
- **median OS was 18·2 months**

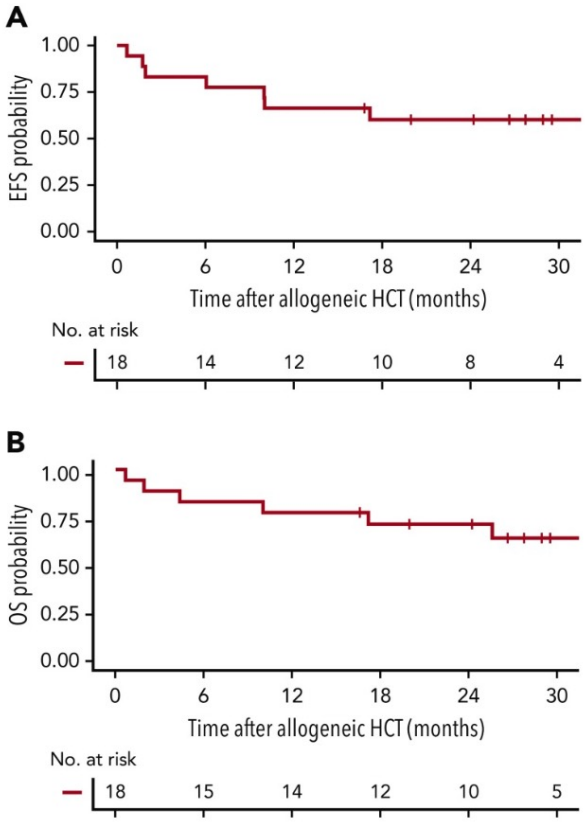
Among responders
- **the median OS was not reached**
- **97% had MRD negativity**
- **10 patients (18%) received allo-SCT after KTE-X19**

- **The most common adverse events of grade 3 or higher were anaemia (49%) and pyrexia (36%)**
- **Two grade 5 events occurred (brain herniation and septic shock)**
- **CRS of grade 3 or higher occurred in 24% and neurological events of grade 3 or higher occurred in 25%**

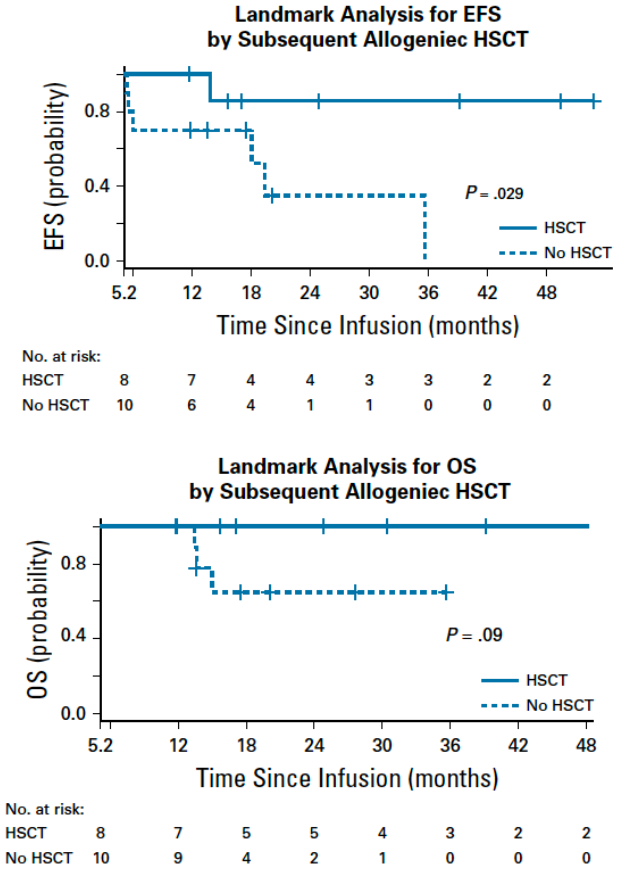


Shah BD Lancet 2021; 398: 491–502

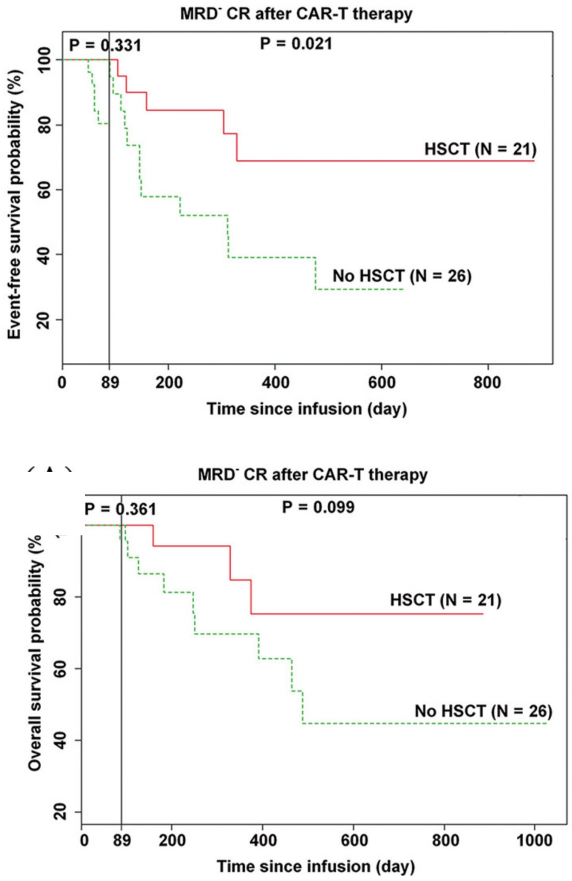
HCT may improve EFS following CD19 CAR in some published studies



Hay, et al. Blood 2019



Frey, et al. JCO 2020

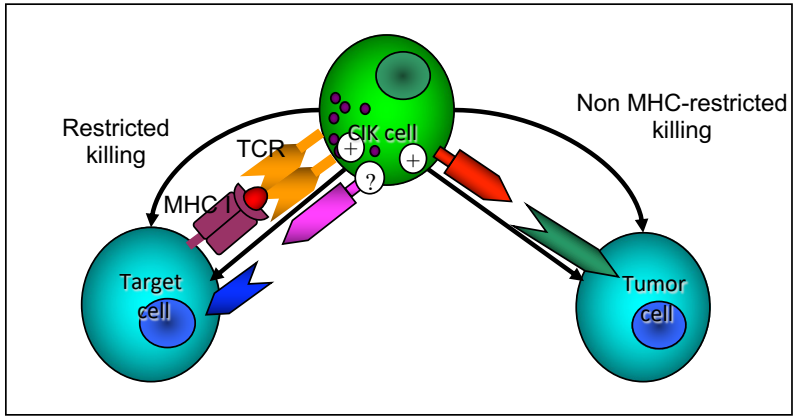


Jiang, et al. AJH 2019

Background for new allogeneic CARs

- Chimeric antigen receptor (CAR) T cell immunotherapy has achieved complete remission and durable response in highly refractory patients.
- Results are particularly exciting in DLBCL and pediatric ALL. The outcome in adult ALL are less impressive particularly in patients relapsing after allogeneic stem cell transplantation.
- Furthermore, patient-derived CAR T cell production may be limited due to failure to collect sufficient T cells or to expand products in selected patient populations who received intensive chemotherapy
- Patients with high leukemic blast contamination might benefit from healthy allogeneic lymphoid cells.
- Ready to go, off the shelf allogeneic CARs represent an ambitious goal of the ongoing research

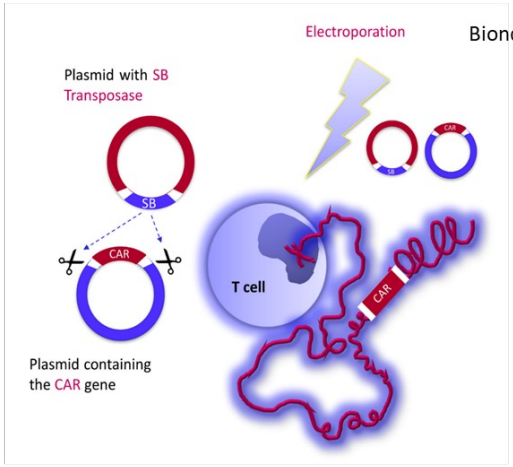
A non-viral platform to generate allogeneic CAR-T cells



Introna et al, BMT, 2006, Marin et al, Exp. Hematol,2006, Franceschetti et al, Exp Hematol, 2009, Introna et al, BBMT, 2010, Pievani et al, Blood, 2011, Pievani et al, Blood, 2011, Rambaldi Leukemia 2015, Introna et al, BBMT 2017

Cytokine induced killer cells

Non-viral vector to generate CAR-CIK cells



Biondi, Magnani (2017) J Aut

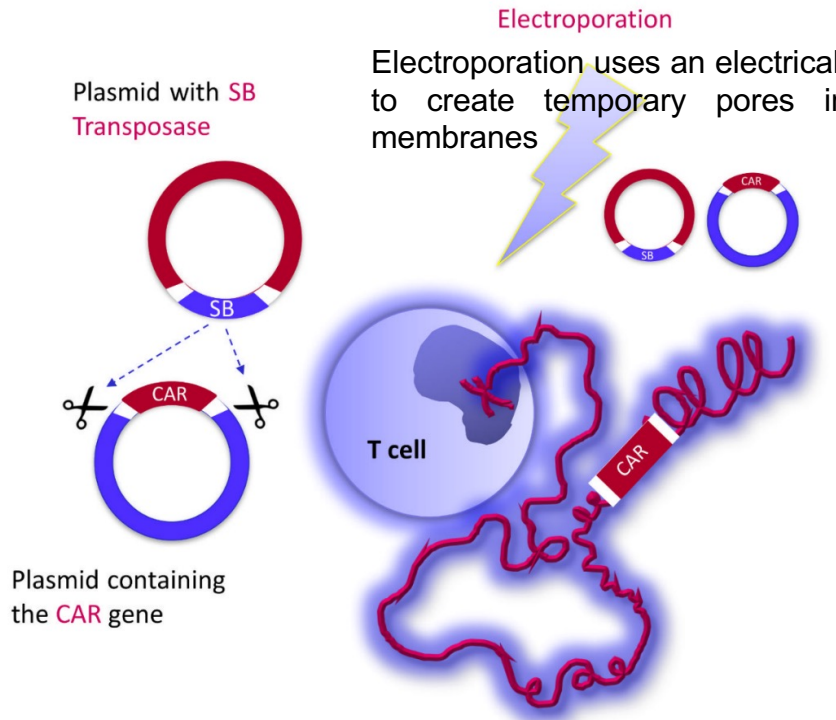
WO2016/071513; Magnani CF, Oncotarget. 2016;7(32):51581-51597; Turazzi N, Br J Haematol. 2017;182(6):939-943; Magnani CF, Hum Gene Ther. 2018; 29(5):602-613; Rotiroti MC, Mol Ther. 2020 Sep 2;28(9):1974-1986

Non-Viral Sleeping Beauty (SB) Transposon System

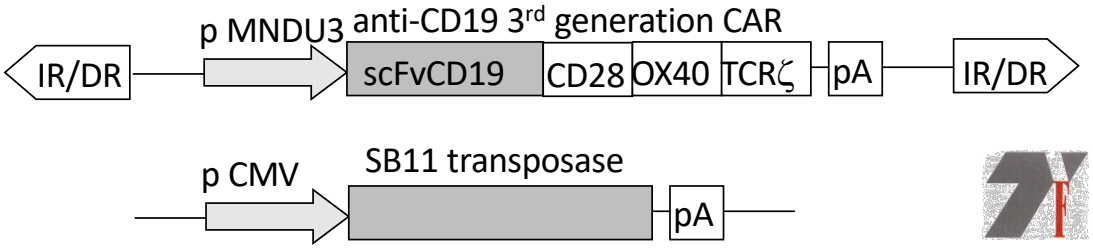
Sleeping Beauty (SB)

a non-viral vector derived from the Tc1/mariner family of DNA transposon validated in clinics for CAR T

Ivics Z (1997) Cell 91(4):501-10; Kebriaei P (2016) J Clin Invest. 126(9):3363-76

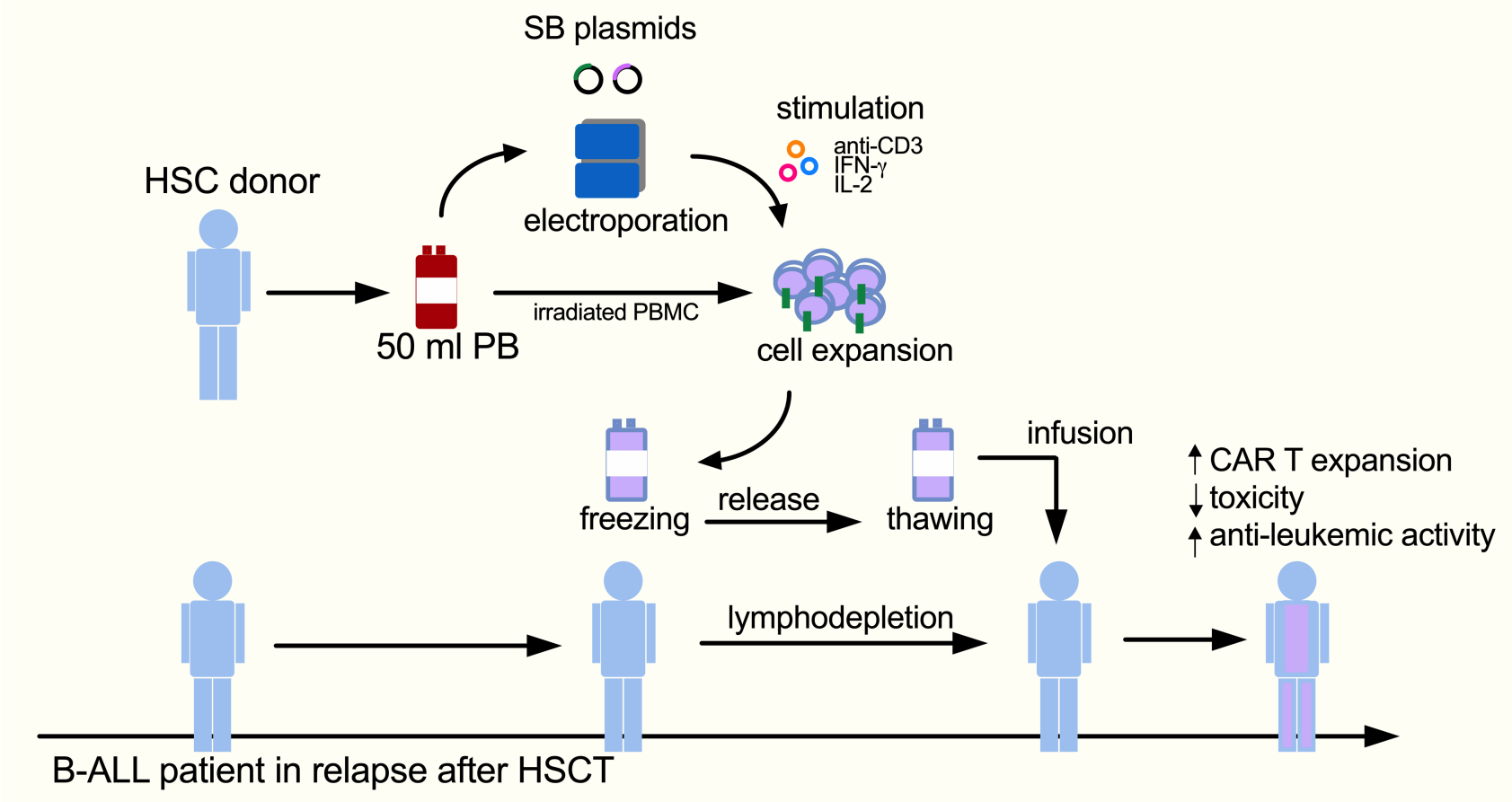


VECTOR DESIGN



Magnani CF et al : Hum Gene Therapy 2018;
Magnani CF et al : Oncotarget (2016)

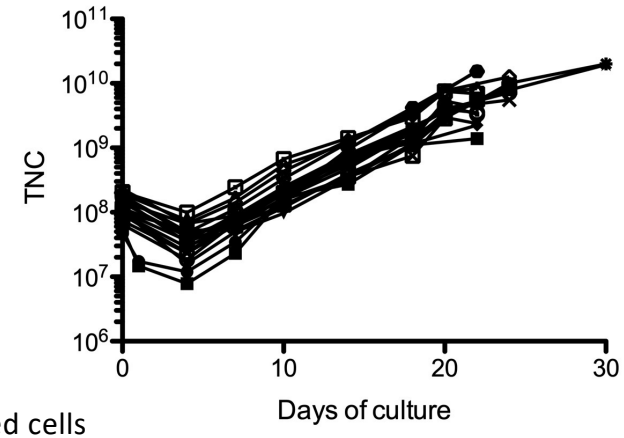
SLEEPING BEAUTY-ENGINEERED CARCIK CELLS ACHIEVE ANTI-LEUKEMIC ACTIVITY WITHOUT SEVERE TOXICITIES

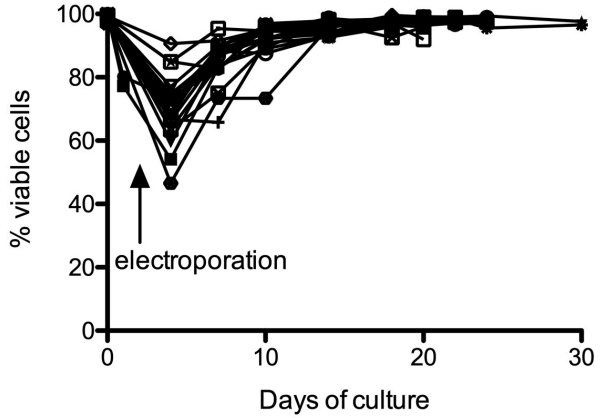


Magnani, J Clin InvestJ Clin Invest. 2020;130(11):6021-6033

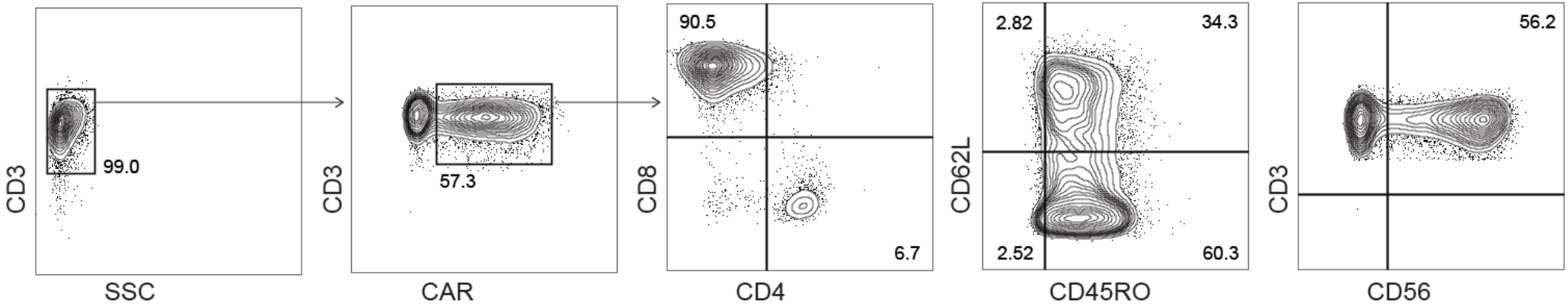
Manufacturing data: cell expansion and composition

N=19





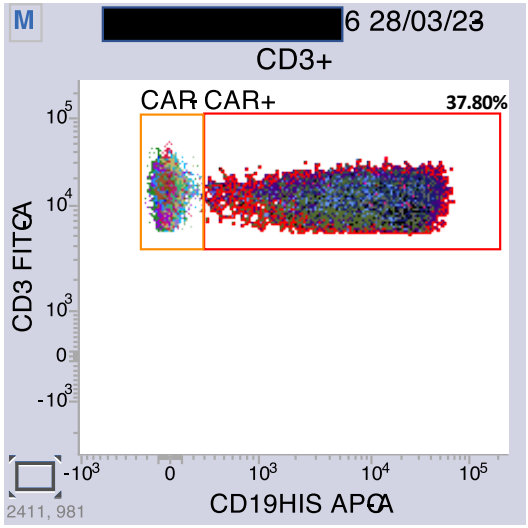
TNC= Total nucleated cells



Magnani C et al.: J Clin Invest. 2020. https://doi.org/10.1172/JCI138473

Early peak of CAR-CIK19

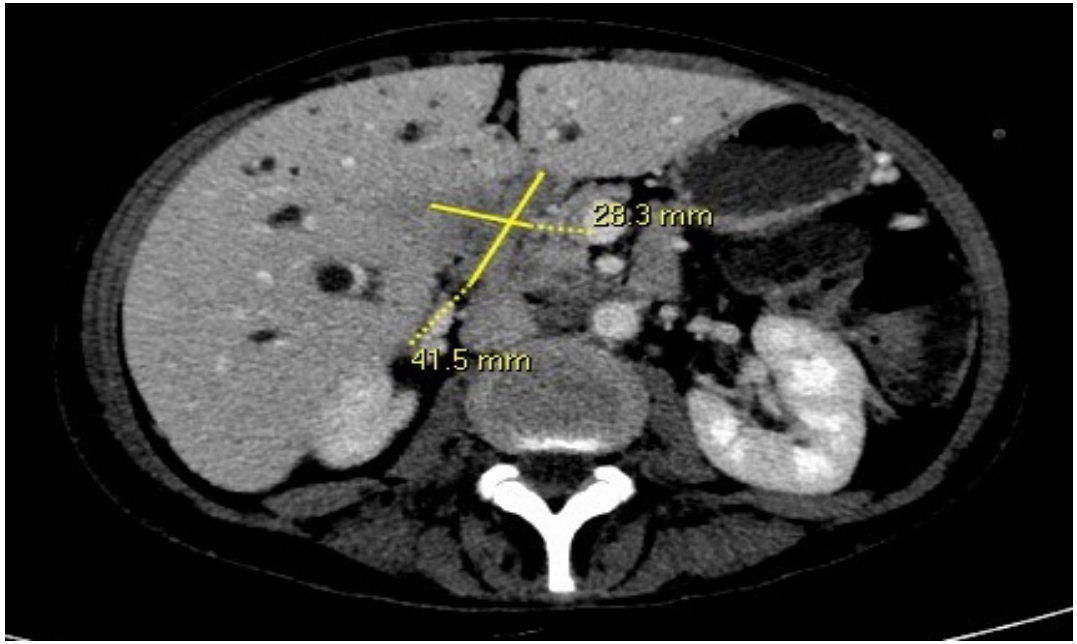
ID Patient: **PUC2002001**
Time Point: **Day 7** (28/03/2023)

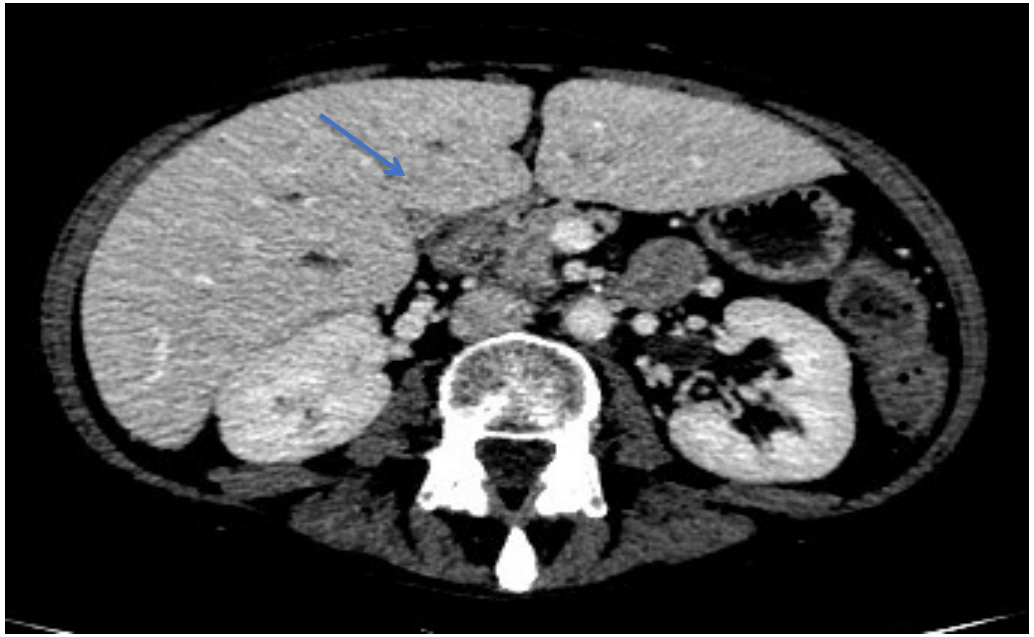


PERIPHERAL BLOOD (PB):
$CD3^+$ = 1041/µL
CAR^+ = 37.80% of $CD3^+$ (393.5/µL)
CAR^+ SUBSETS:
$CD8^+$ = 93.03% (366.1/µL)
$CD4^+$ = 4.97% (19.3/µL)

CARCIK-CD19 mediated anti leukemic activity on extrahematologic disease

Patient #21020014: CT scan before and after CARCIK-CD19



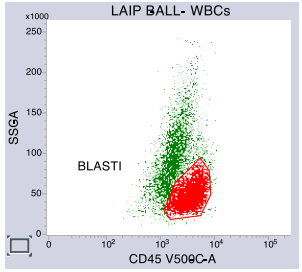


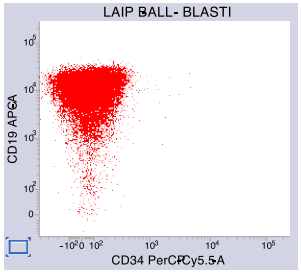
07 June 2019: Relapse post Allo-HSCT presenting liver adenopathy
27 June 2019:
- AST/ALT: 157/287 UI,
- γGT: 1183 UI
- Bilirubin: 18.8 mg/dl

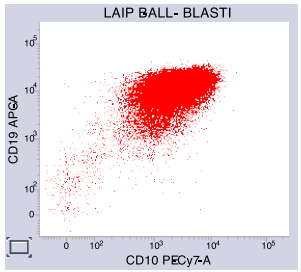
12 September 2019, day +44 after CARCIK-CD19 infusion:
- AST/ALT: 12/58 UI,
- γGT : 82 UI,
- Bilirubin 0,8 mg/dl

CARCIK-CD19 mediated anti leukemic activity on extrahematologic disease

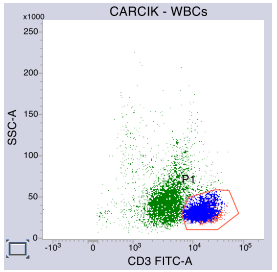
Patient #21020014: Flow Cytometry of pleural effusion

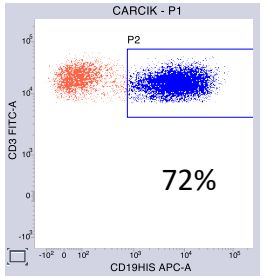


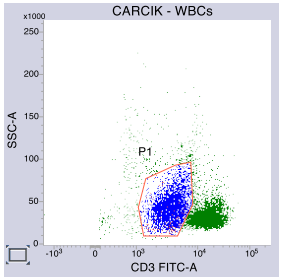


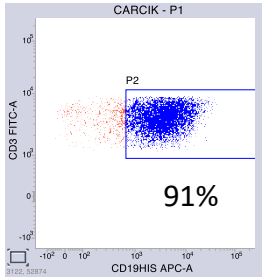


Baseline
Massive leukemic infiltration

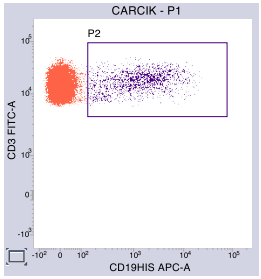


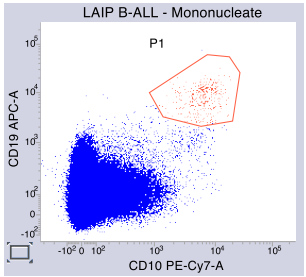






day +10
expansion of CARCIK-CD19 cells

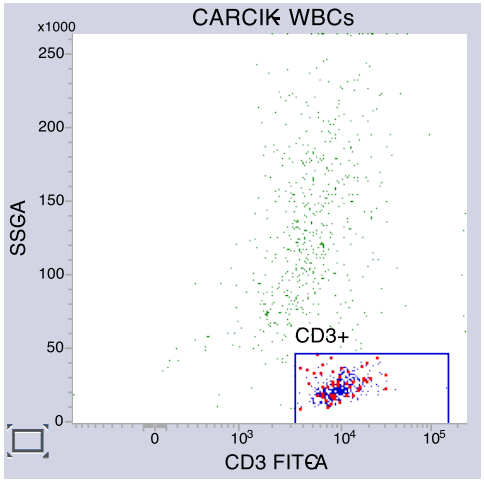




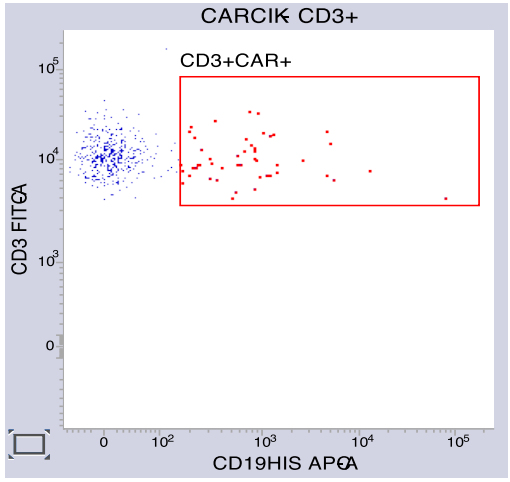
day +30
Persistence of CARCIK-CD19 cells
and leukemic clearance

CARCIK-CD19 mediated anti leukemic activity on extrahematologic disease

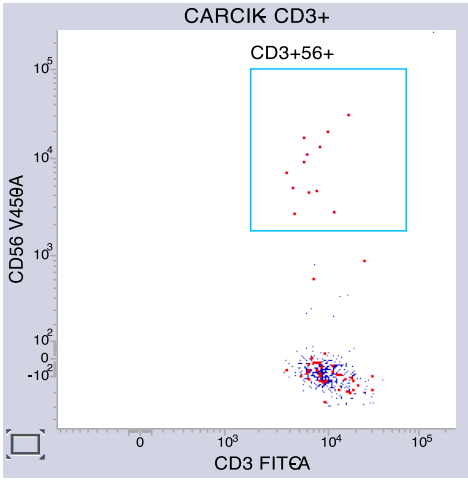
Patient #21020018: Flow Cytometry of CSF



Baseline
Massive leukemic infiltration



day +10
expansion of CARCIK-CD19 cells



day +30
Persistence of CARCIK-CD19cells
and leukemic clearance

CARCIKCD19 in adult ALL

Characteristics	All patients (22)
Age, median yo	40 (26 – 67)
Ph positive ALL, no. (%)	8 (36%)
Previous lines of treatment 2, No (%) 3-5, No (%) >5, No (%)	 3 (13) 14 (63) 5 (22)
Bridge therapy Inotuzumab, No (%) Blinatumomab, No (%) Low intensity Chemotherapy, No (%) TKI with or without Chemotherapy, No (%)	 5 (22) 1 (4) 14 (63) 2 (9)
Pre-infusion bone marrow blasts <5%, (%) ≥5%, (%)	 11 (52) 10 (48)

RESULTS OF SAFETY

Events	Patients (n°22)
CRS, n (%)	
Grade 1	3 (13%)
Grade 2	3 (13%)
Grade ≥ 3	0
ICANS n (%)	
Grade ≥ 3	2 (9%)
Infection, n (%)	
Grade 1	1 (4%)
Grade 3	2 (9%)
Grade 4	2 (9%)
GVHD n (%)	
Grade 1-3	0

- No dose limiting toxicity was observed
- CRS and ICANS were observed in patients treated with the highest doses and were manageable
- Tocilizumab was used in 4 patients
- Although 8 out of 22 had experienced GVHD after the previous HSCT, secondary GVHD was never observed

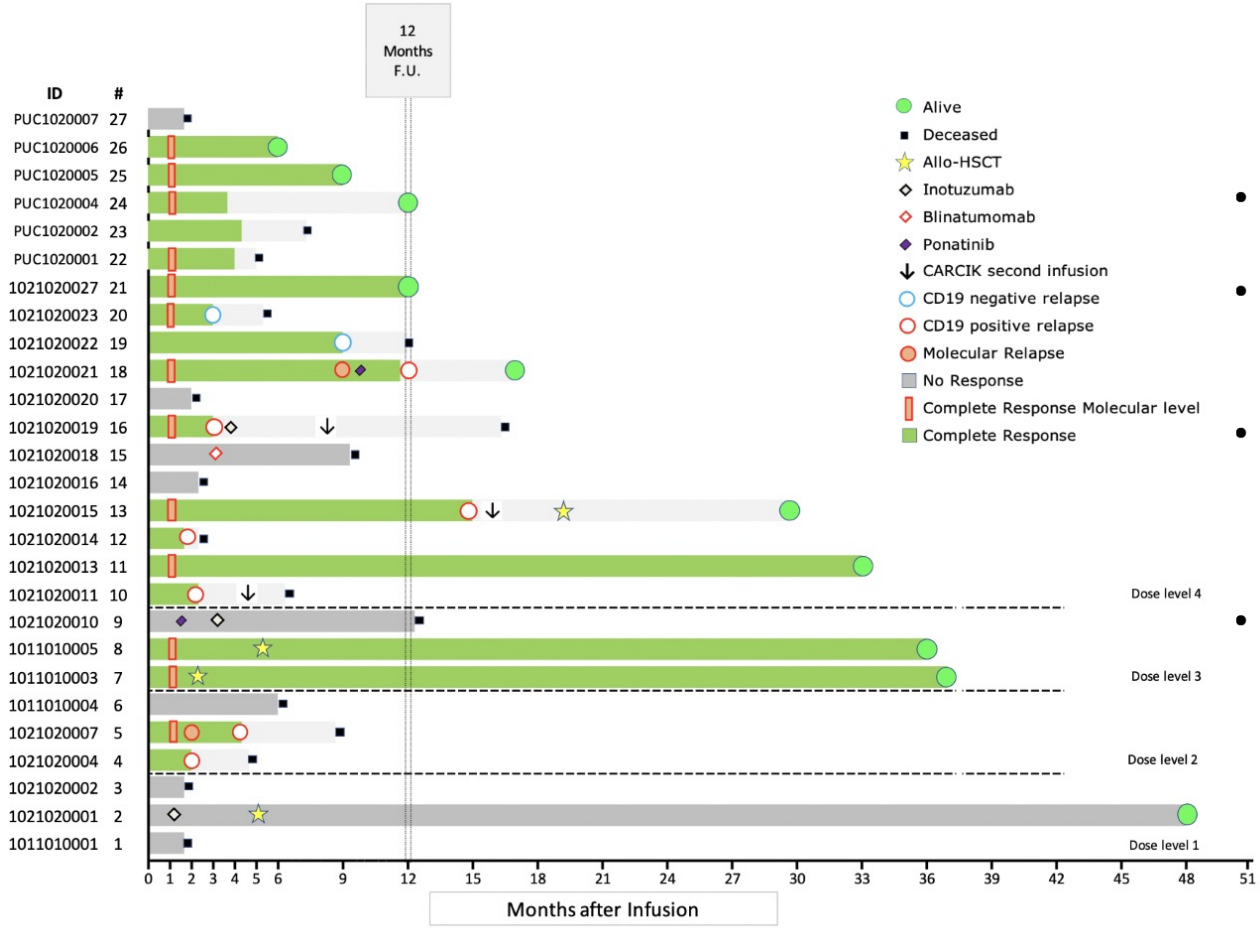
CARCIK-CD19 in B-ALL post HSCT: selected adverse event

Events	Patients
CRS, n (%)	
• Grade 1 • Grade 2 • Grade 3	4 (15%) 5 (19%) 0 (0%)
ICANS, n (%)	
Grade 3	2 (7%)
GvHD, n (%)	
Grade I-IV	0 (0%)
Infection, n (%)	
• Grade 1-2 • Grade ≥ 3	2 (7%) 7 (26%)
Prolonged cytopenia, n (%)	
Severe neutropenia, day 28 Severe thrombocytopenia, day 28	7 (32%) 17 (68%)

- no dose limiting toxicity was observed
- CRS and ICANS were observed in patients treated with the highest doses and were manageable
- Although 10 out of 27 had experienced GVHD after the previous HSCT, secondary GVHD was never observed
- 17 out of 25 patients remained with persistent cytopenia at day 28

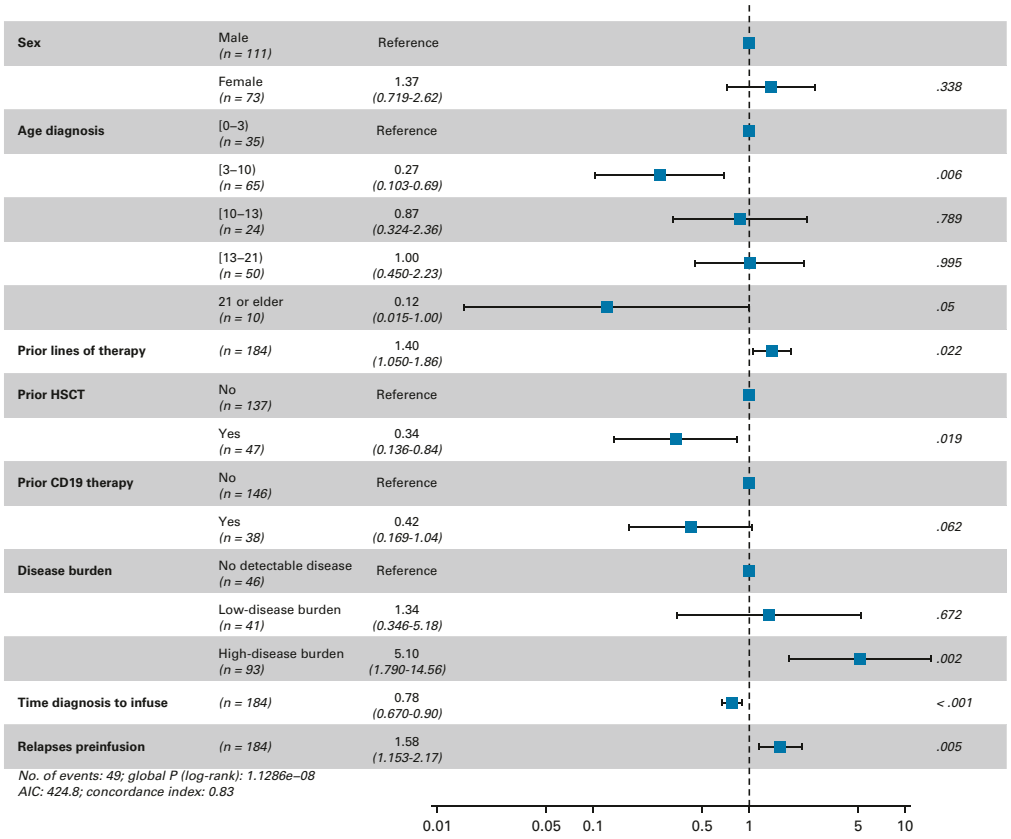
CRS criteria (Lee et al. Blood. 2014); ICANS, immune-effector cell-associated neurotoxicity syndrome; severe neutropenia <500/mmc; severe thrombocytopenia <50000/mmc

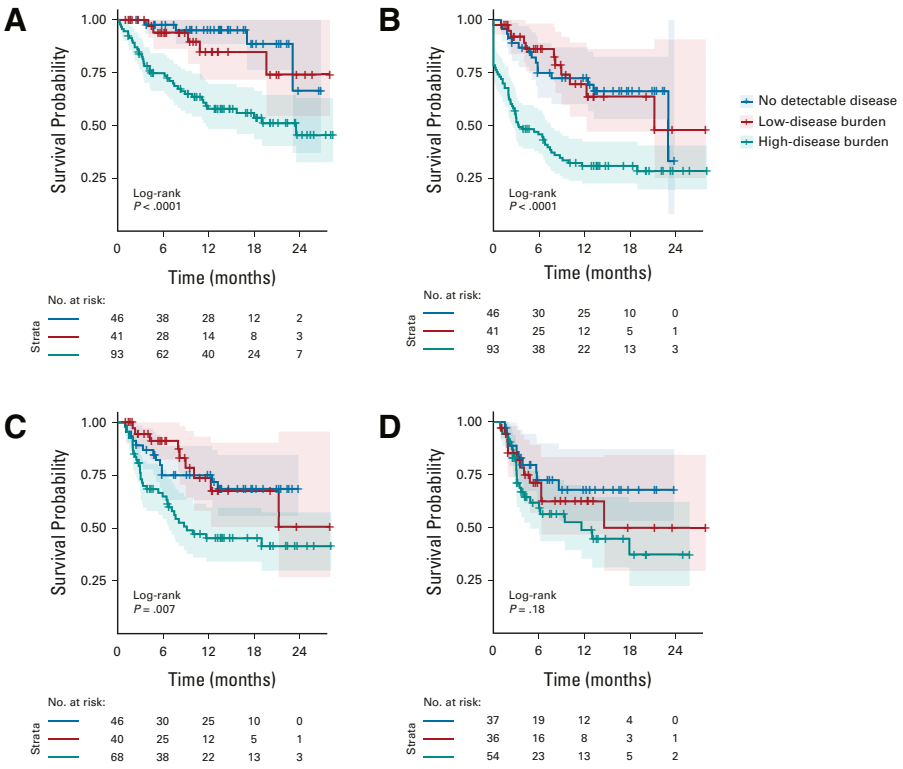
Response data



- CR: 18/27 patients (66.7%, 95%CI=46-84%)
- CR: 16/21 patients (76.2%, 95%CI=53-92%) treated with the 2 highest doses
- Fourteen (77.8%) of the overall responders and 13 of the responders at the highest doses (81.3%) achieved MRD negativity
- The type of donor did not influence the achievement of CR 28 days post-infusion

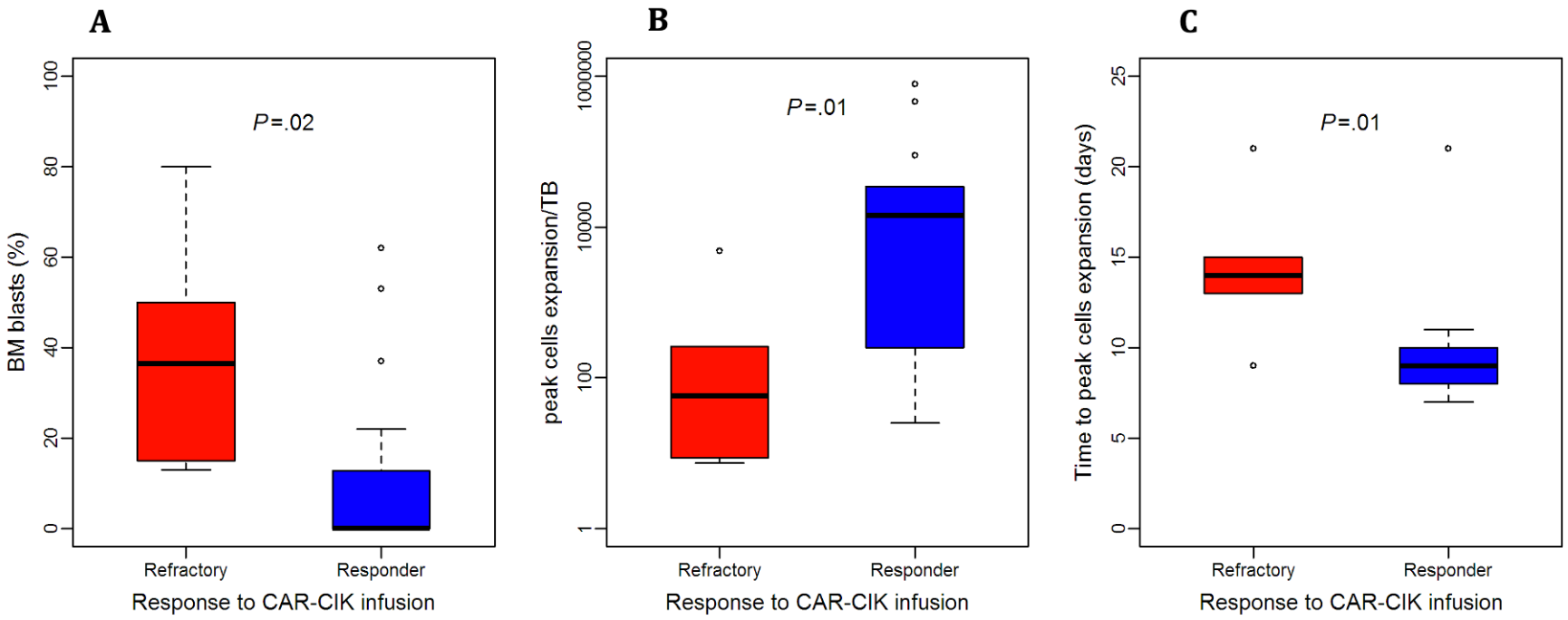
Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report





Schultz, LM et al.: J Clin Oncol 2021

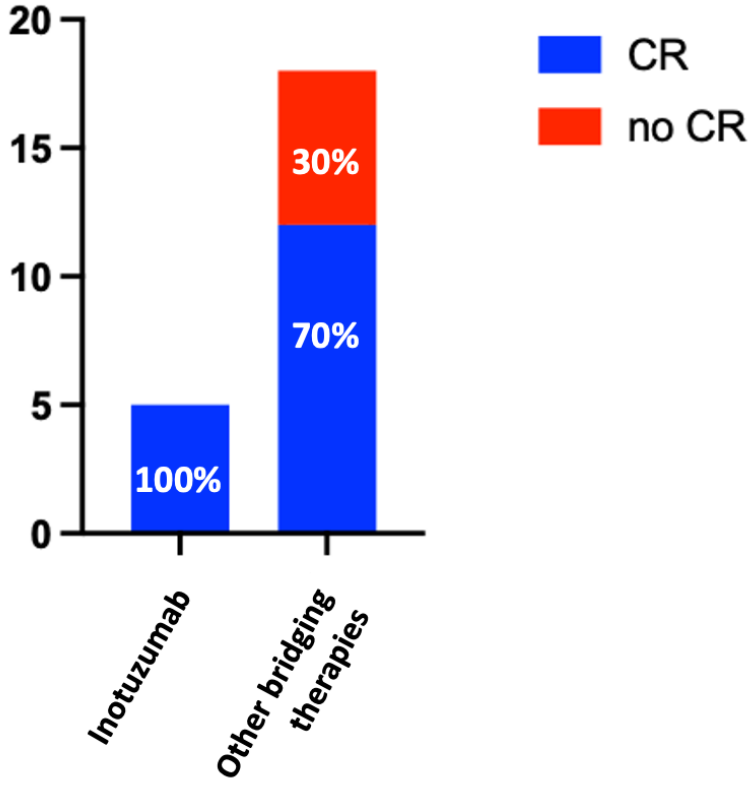
RESPONSE RATE ACCORDING TO TUMOR BURDEN, EFFECTOR-TO-TARGET AND TIME-TO-PEAK



INOTUZUMAB OZOGAMICIN AS BRIDGING THERAPY

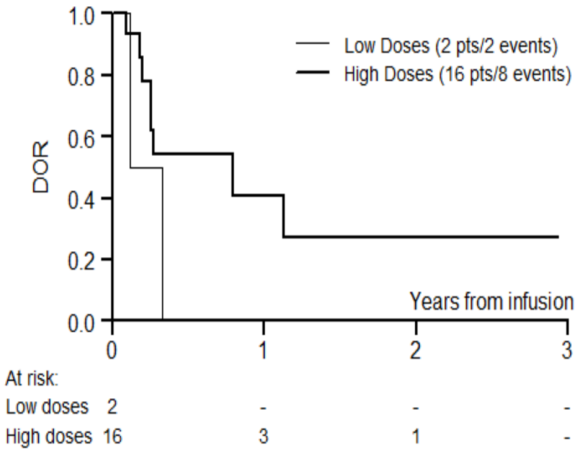
- Five adult patients who received inotuzumab had less than 5% BM blasts *before* CARCIK-CD19 infusion as compared to 6/15 (40%) of those who received other bridging therapies

- *After* CARCIK-CD19 infusion (**Figure**), all adult patients exposed to inotuzumab achieved a CR at day 28 as compared to 70% of those who received other bridging therapies

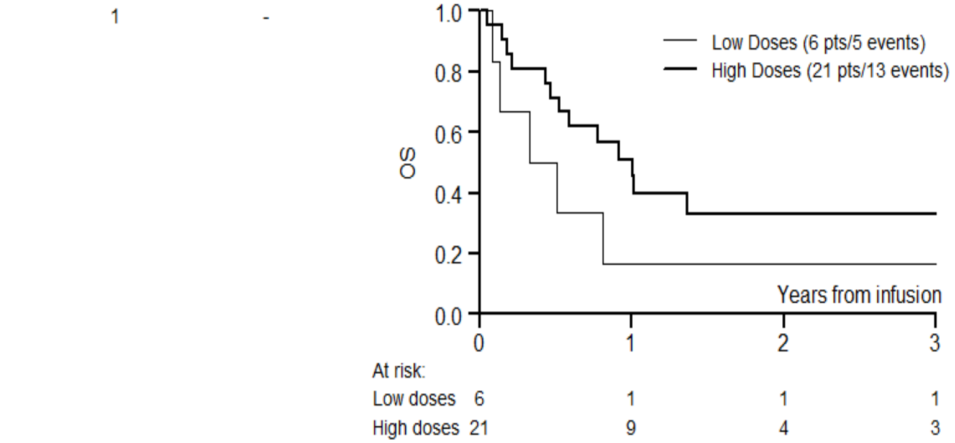


Main outcomes

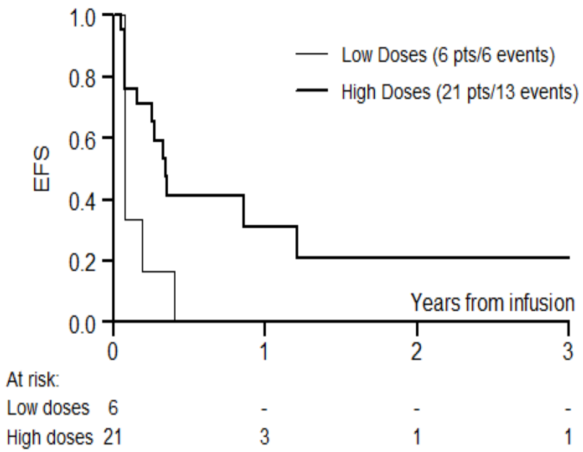
Duration of remission



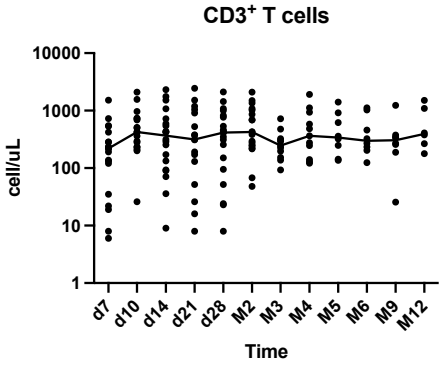
Overall survival

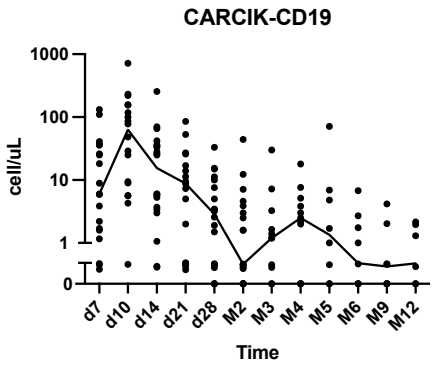


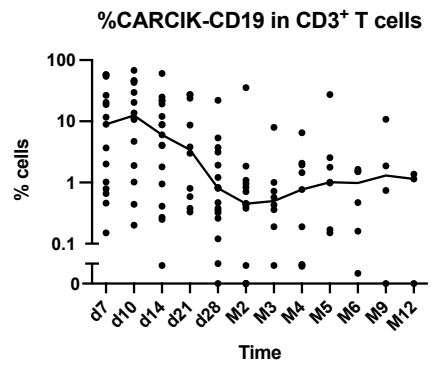
Event free survival

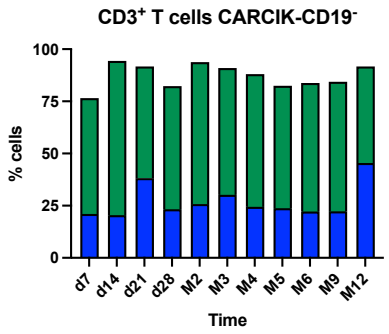


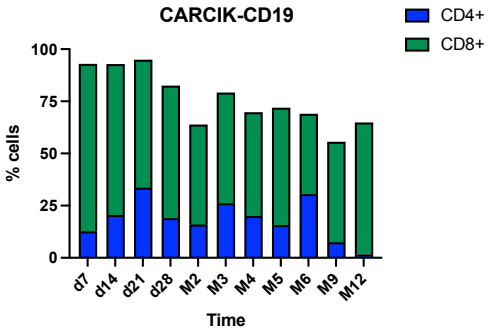
CD3+ T cells and CARCIK-CD19 reconstitution

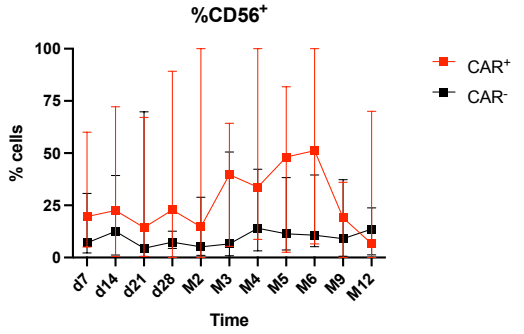




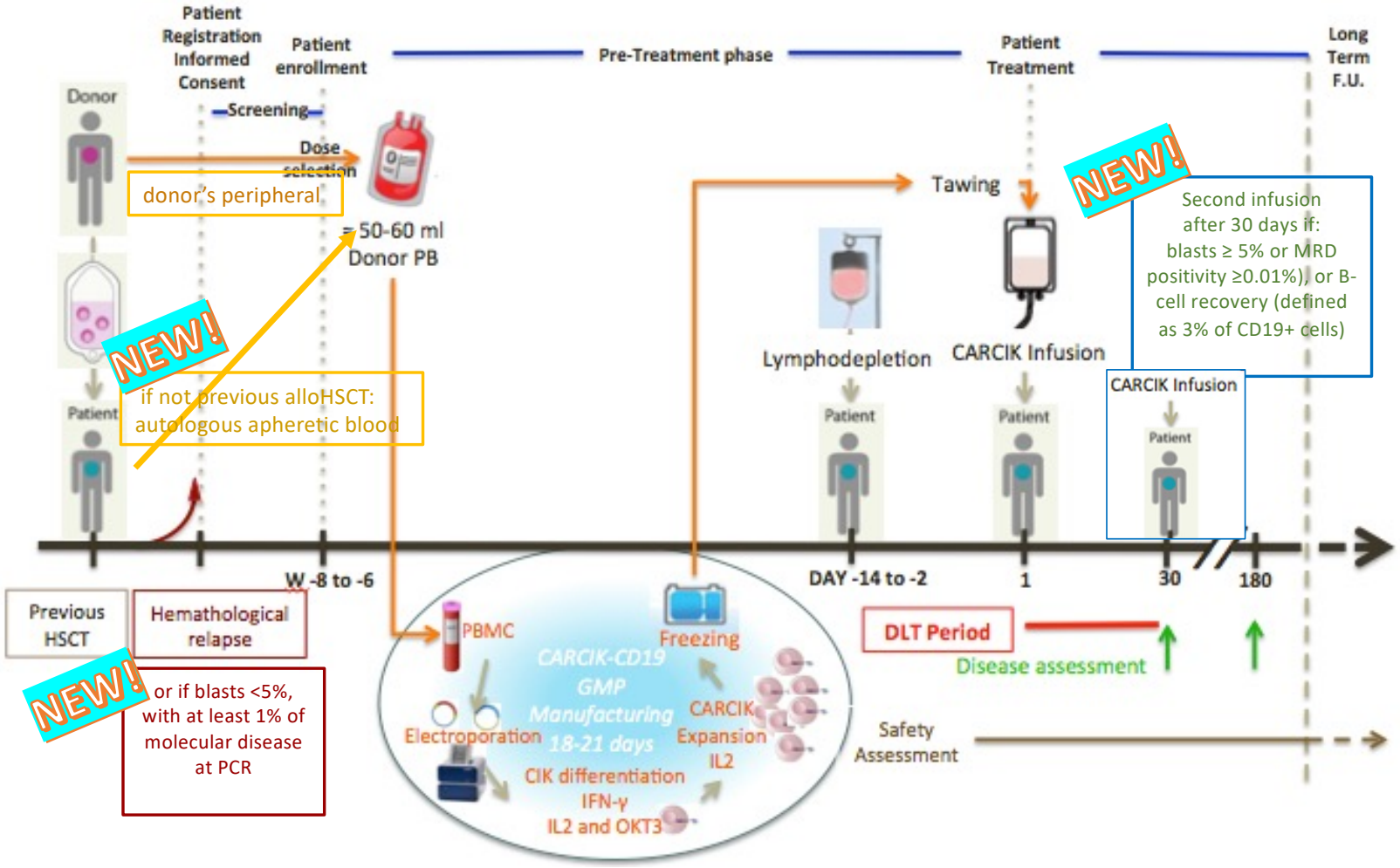








FT03CARCIK Phase 2: Flow-chart



ACKNOWLEDGMENTS

Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII, BG and University degli Studi di Milano, Milan, Italy

Alessandro Rambaldi
Giuseppe Gritti
Federico Lussana
Silvia Ferrari
Anna Grassi
Benedetta Rambaldi
Gian Maria Borleri

The Cell Therapy Lab, Gilberto Lanzani ASST Papa Giovanni XXIII, BG, Italy
Martino Introna
Chiara Capelli
Elisa Gotti
Josee Golay

Cell Factory- Laboratorio di Terapia Cellulare e Genica Stefano Verri, ASST-Monza, Ospedale San Gerardo, Monza, Italy
Chiara Magnani
Giuseppe Gaipa
Daniela Belotti
Giada Matera
Benedetta Cabiati
Stefania Cesana
Valentina Colombo
Michele Quaroni

COMITATO STEFANO VERRI
per lo studio e la cura della leucemia

Tettamanti Research Center, Department of Pediatrics, University of Milano-Bicocca, Monza, Italy
Andrea Biondi
Giuseppe Dastoli
Ettore Biagi
Sarah Tettamanti
Chiara Buracchi
Silvia Rigamonti
Grazia Fazio
Giovanni Cazzaniga