CAR-T and other innovative treatments for ALL

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Disclosures

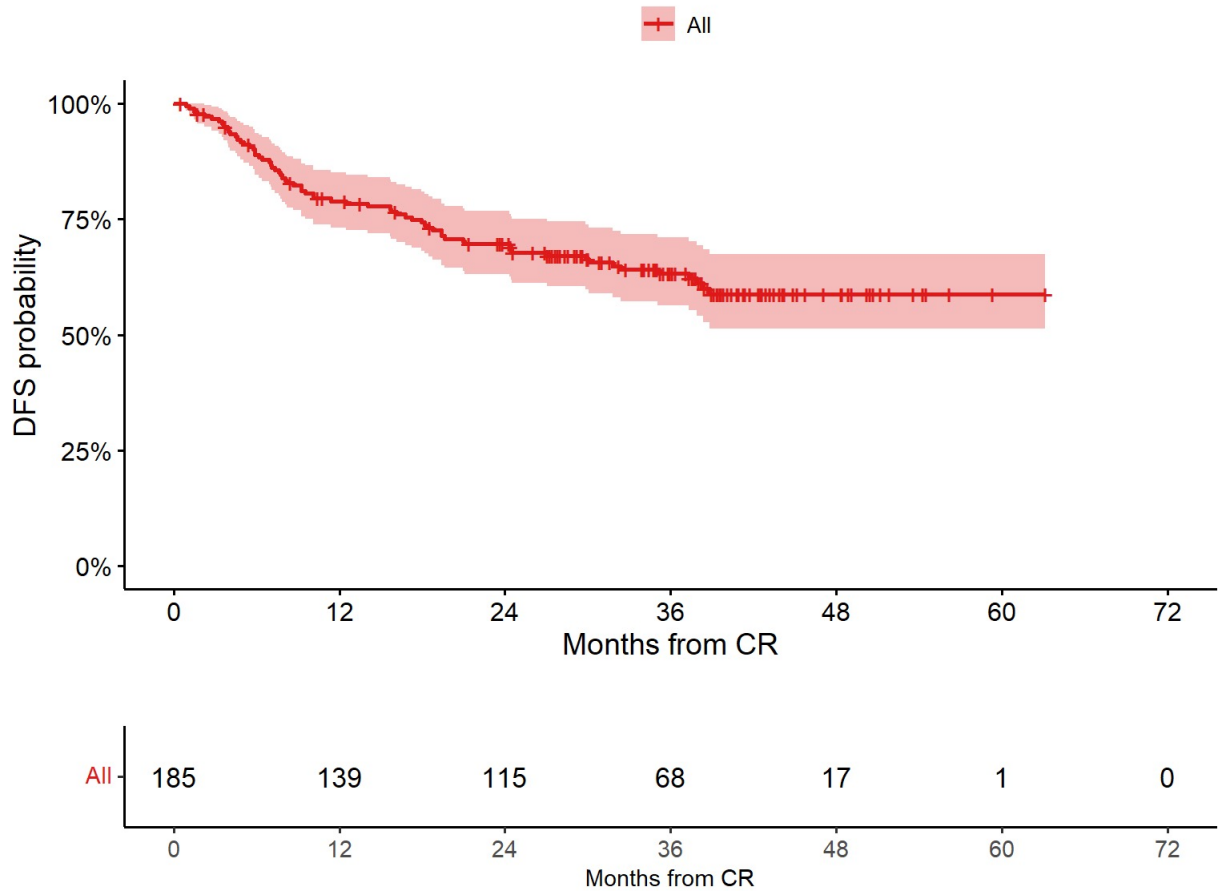
Amgen, Kite-Gilead, Novartis, Celgene-BMS, Sanofi,

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

Primary endpoint: DFS

Median follow-up: 38.7 months (2.2 - 64.2)

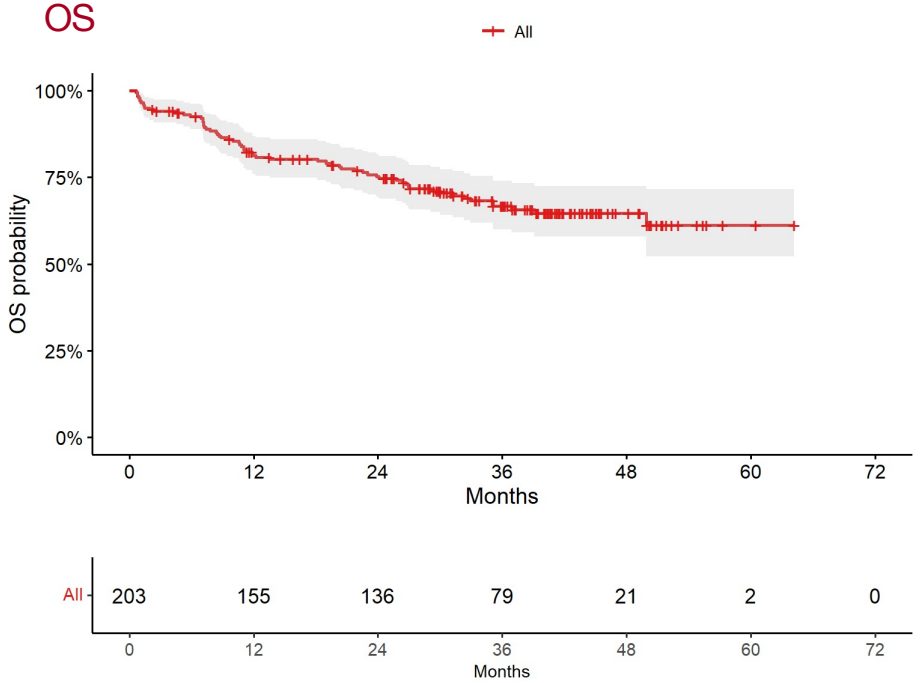
* Primary objective reached



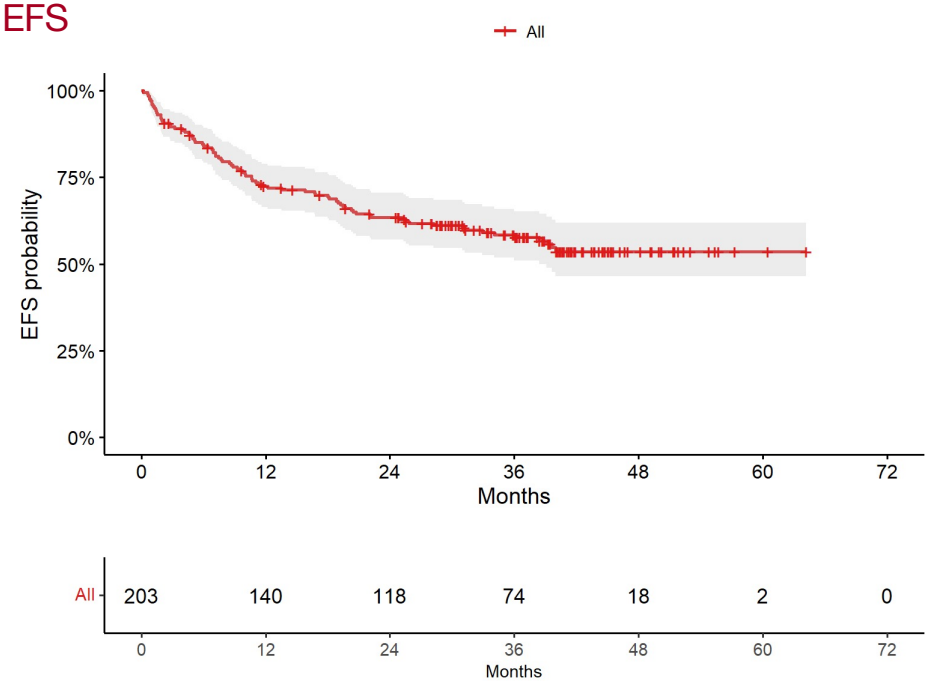
	24 Months	36 Months
Estimate (95%CI)	70% (63%, 77%)*	63% (56%, 71%)

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

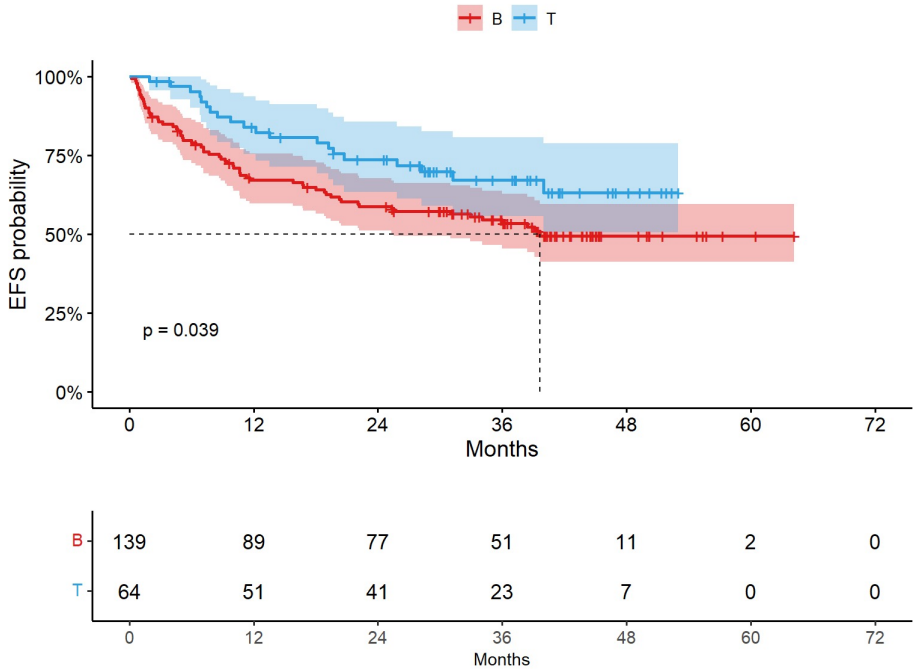
OS



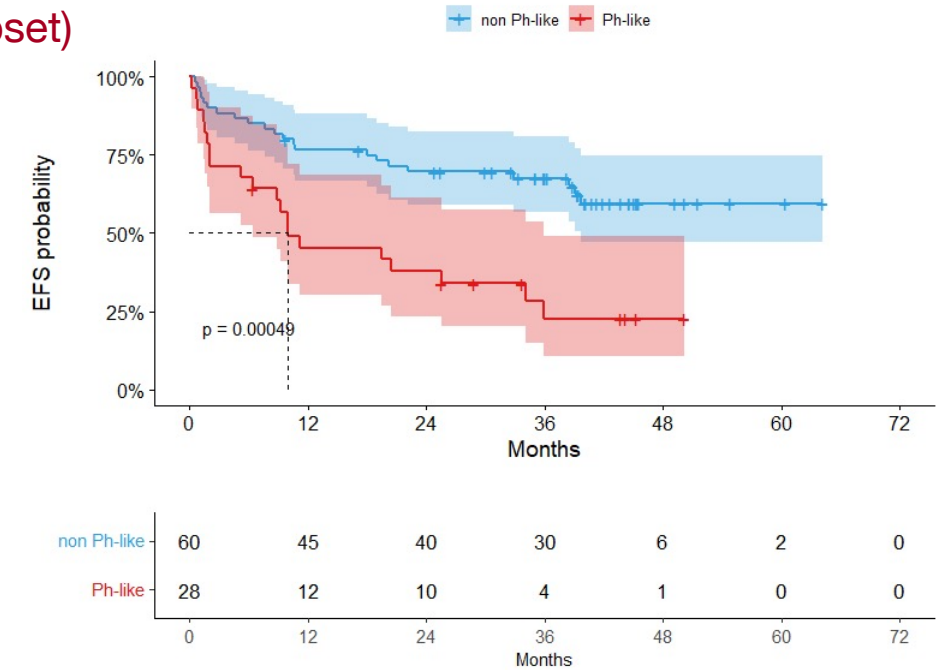
EFS



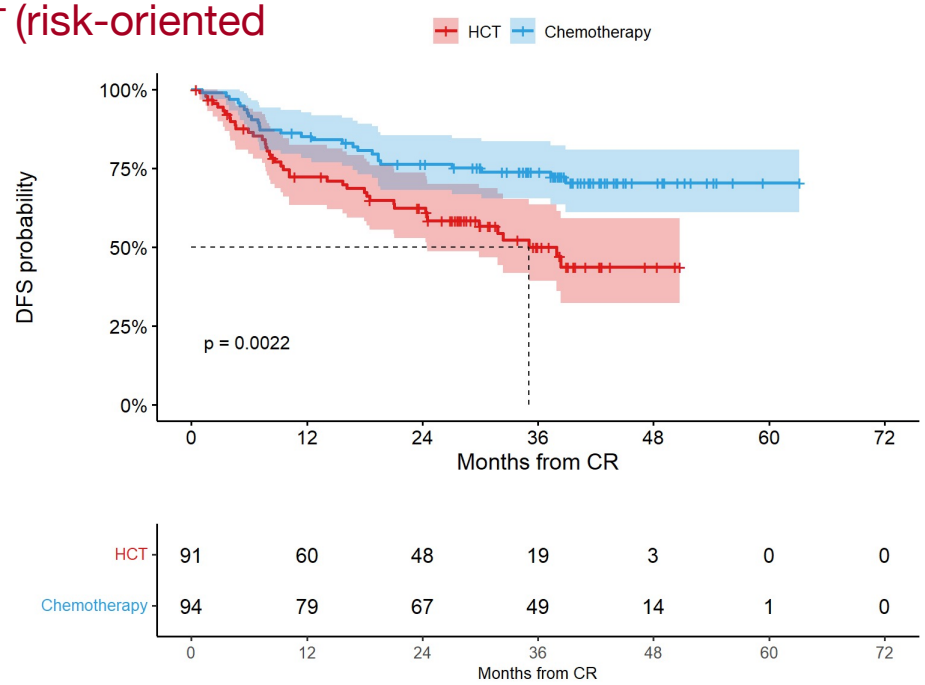
EFS by B/T subset



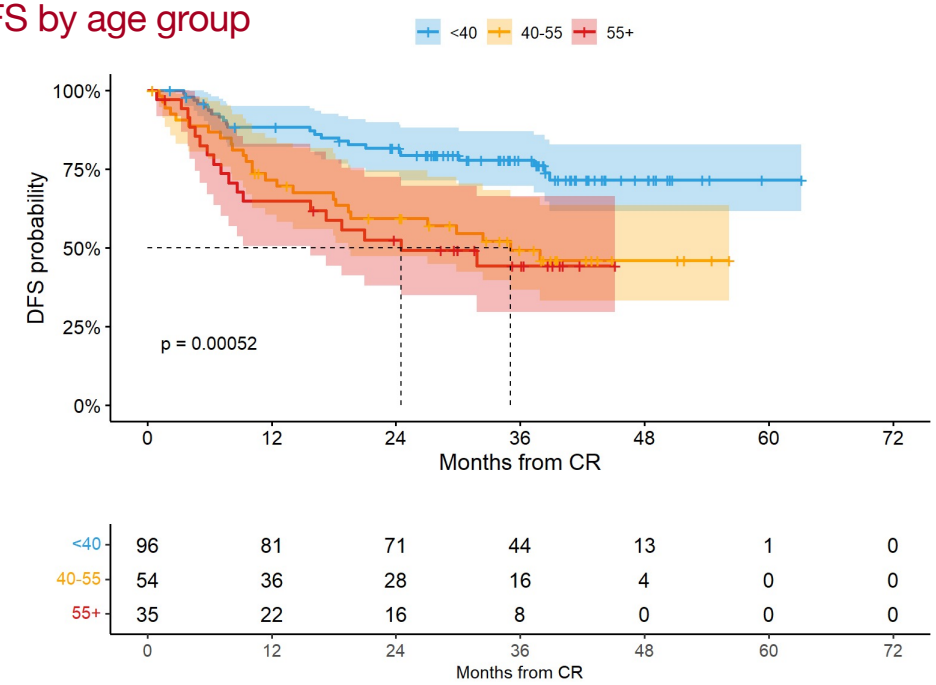
EFS by Ph-like signature (B subset)



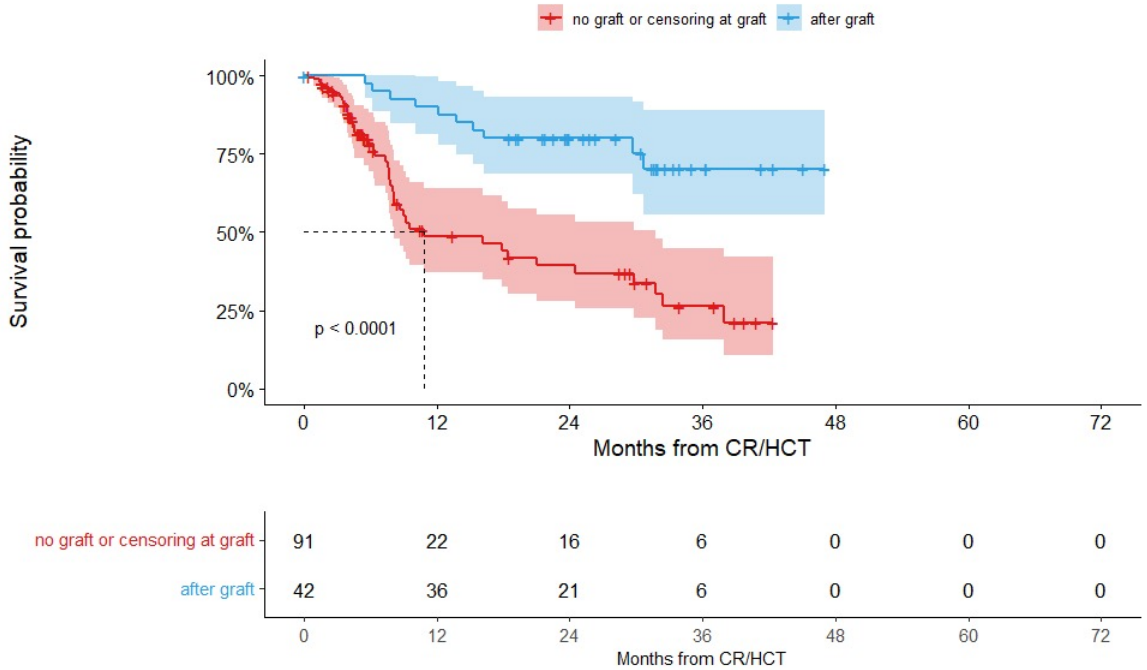
DFS by ITT (risk-oriented therapy)



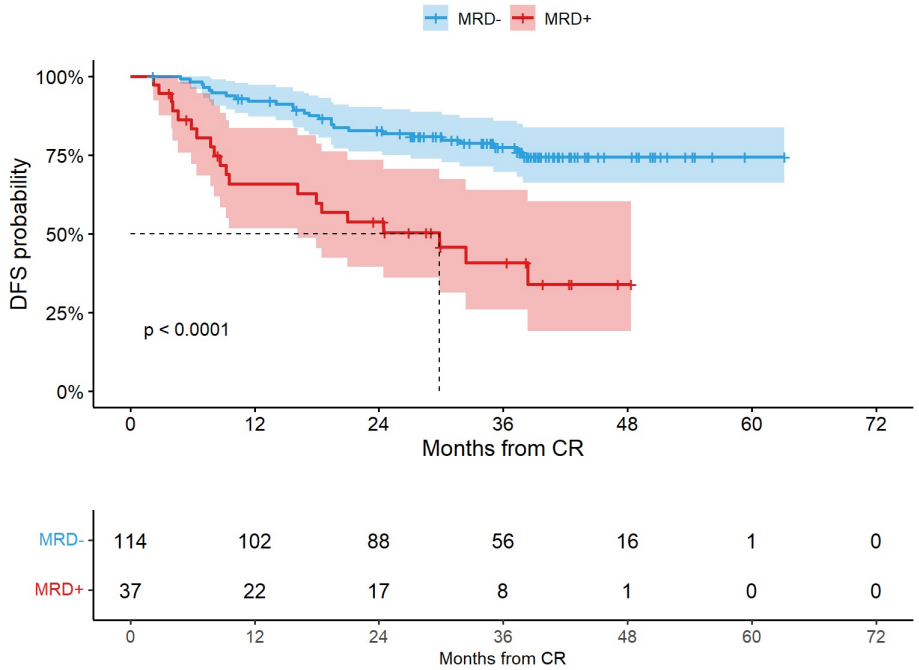
DFS by age group



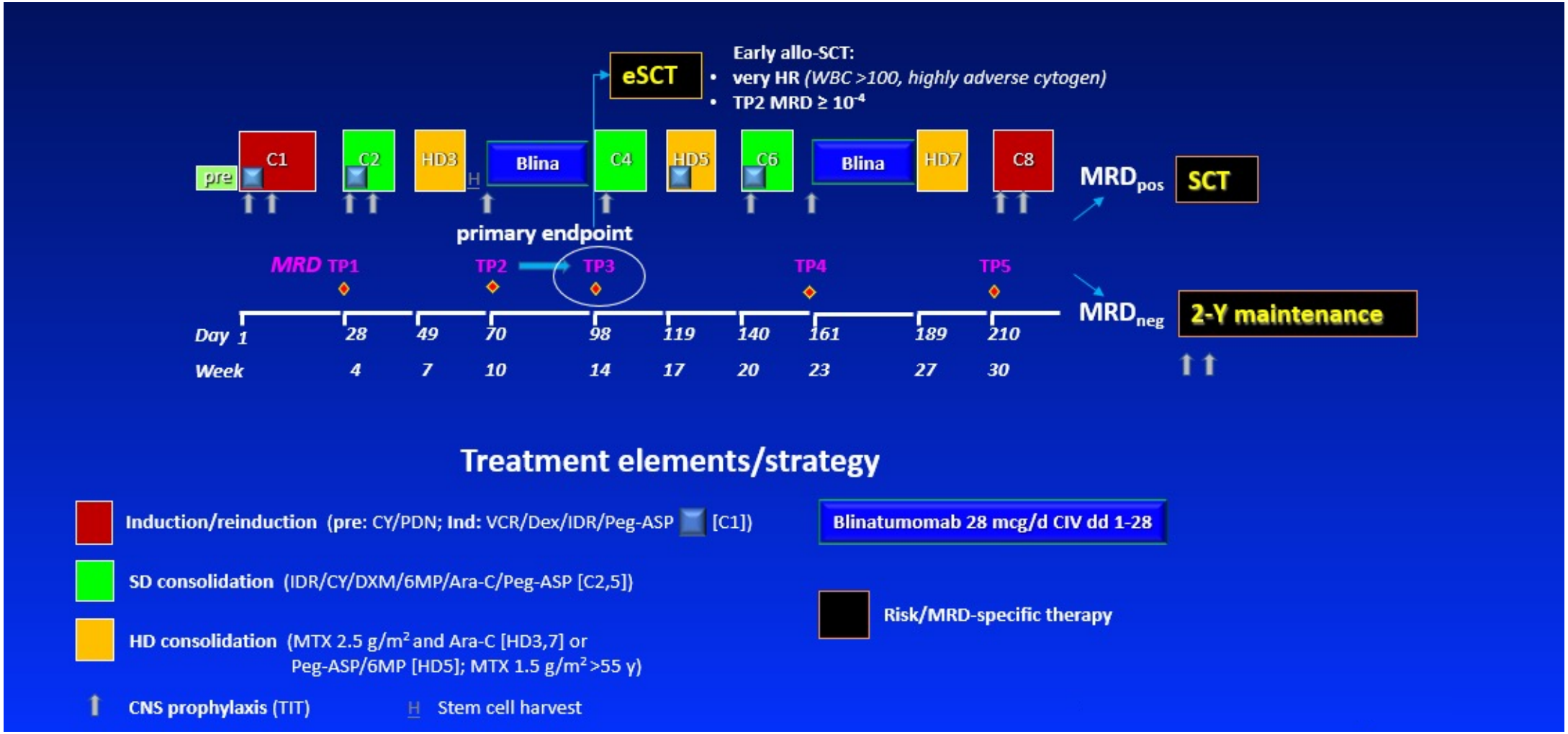
DFS by HCT (ITT, time-dependent Simon-Makuch plot)



DFS by MRD response



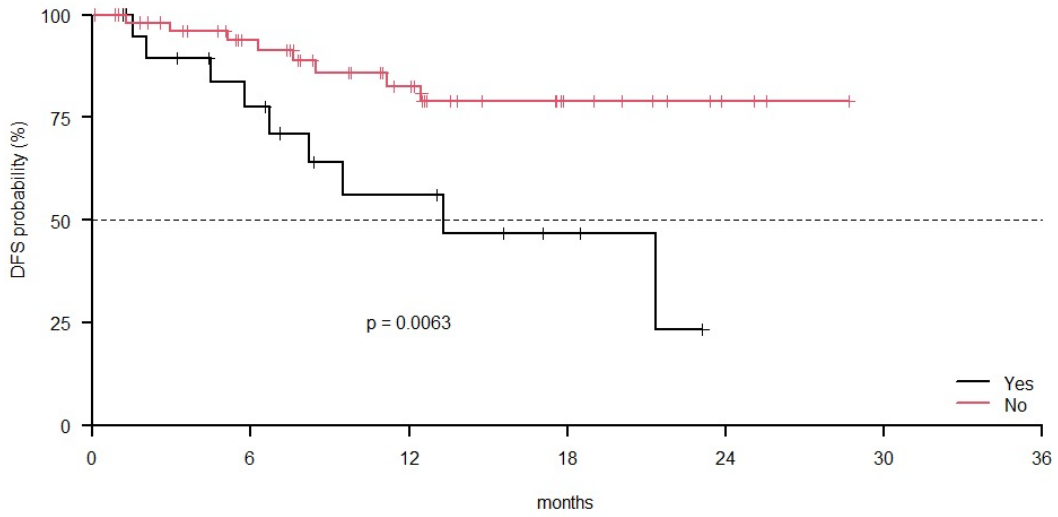
GIMEMA 2317 study protocol



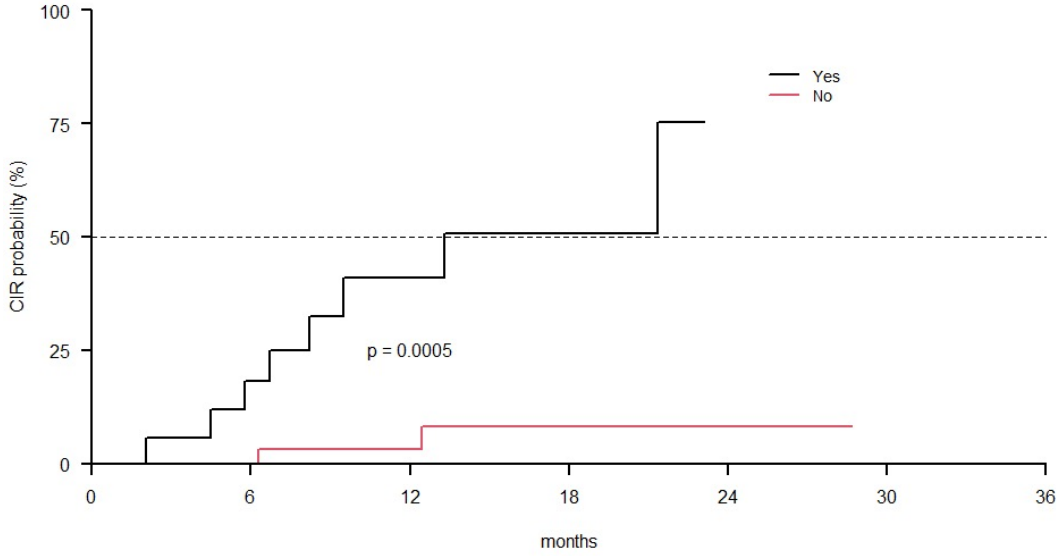
Bassan R, et al. EHA 2021; Abstract S114 and oral presentation;
ClinicalTrials.gov: NCT03367299.

Outcome according to Ph-like signature

Disease-free survival by Ph-like signature



Relapse incidence in MRD_{neg} group by Ph-like signature



1-year relapse rate:	Ph-like	40.1%
	Not Ph-like	3.2%
		P=0.0005

Bassan R, et al. EHA 2021; Abstract S114 and oral presentation.

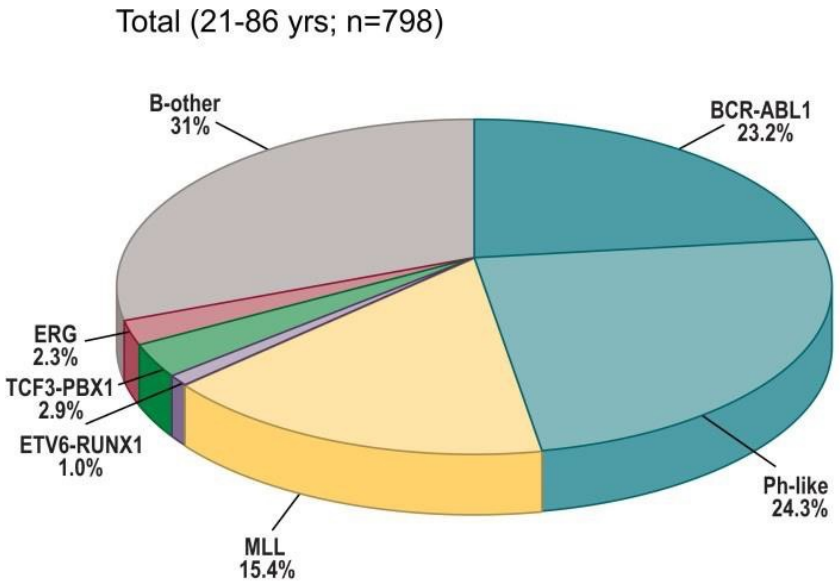
Ph-like ALL

- In 2009, “Ph-like” or “BCR-ABL1-like” ALLs were independently described by the Children’s Oncology Group (COG)/St. Jude Children’s Research Hospital[1] and the Dutch Childhood Oncology Group[2] using gene expression profiling
- Ph-like ALL is a subtype of B-cell precursor ALL characterized by a poor outcome and a diverse group of genetic alterations that activate cytokine receptor and kinase signaling similar to that of BCR-ABL1-positive ALL[3].
- These alterations result in a poor response to standard chemotherapy, with response rates similar to those found in BCR-ABL1-positive ALL[3]
- Over 90% of patients with Ph-like ALL harbor genetic alterations that are amenable to treatment with targeted inhibition (TKI therapy)[4]

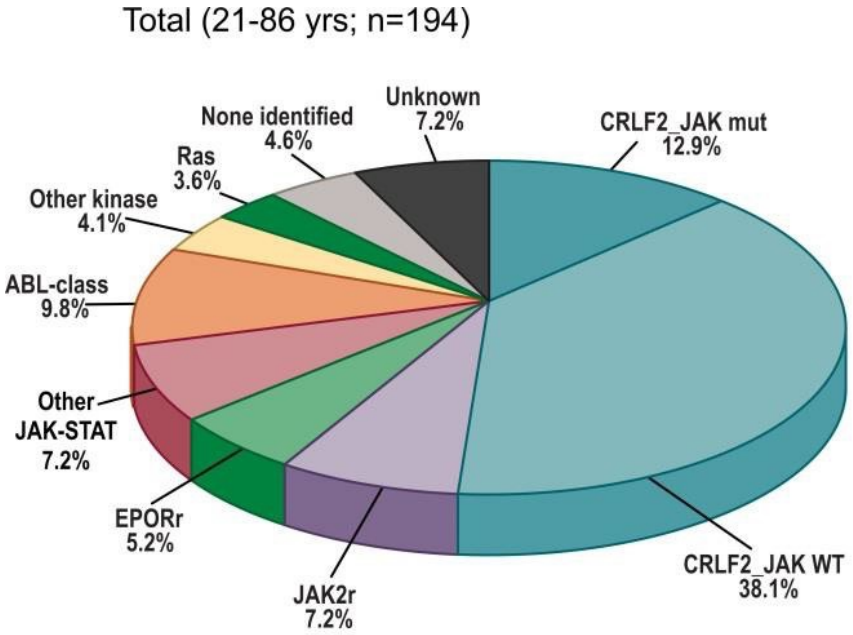
[1]Mullighan CG, Su X, Zhang J, et al; N Engl J Med. 2009;360(5):470-480., [2]Den Boer ML, et al. Lancet Oncol. 2009;10(2):125-134, 17;35:975–83. [3] Iacobucci I and Mullighan CG.; J Clin Oncol 2017;35: 975-983 [4] Roberts K Best Practice & Research: Clinical Haematology, 2018; (31): 351-356,

BP-ALL subtypes in Adult patients

Frequency of ALL subtypes in adult patients



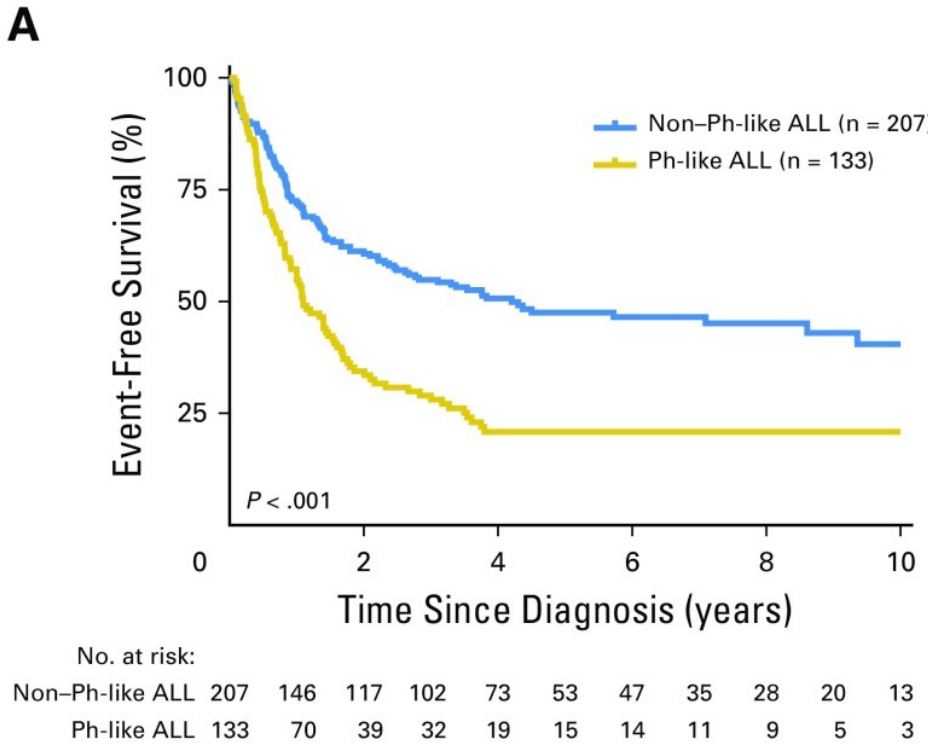
Frequency of Ph-like ALL subtypes in adult patients



Roberts, K et al.: J Clin Oncol. 2017 Feb;35(4):394-401

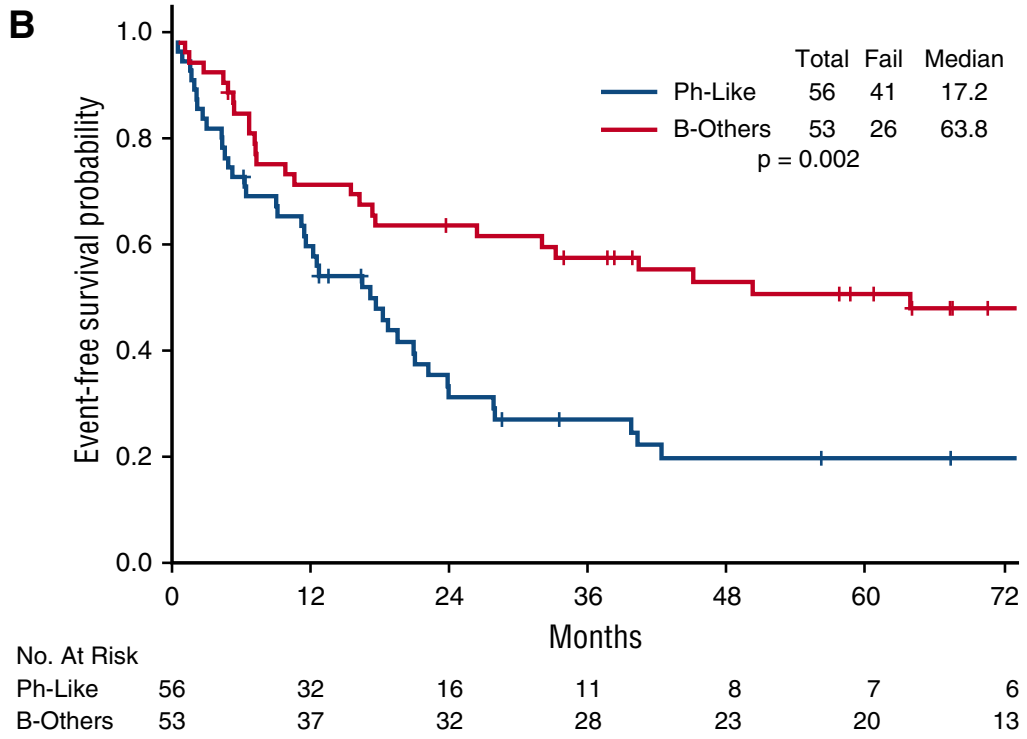
Ph-like ALL: a high-risk subtype in adults

EFS in the cooperative study group



Roberts, K et al.: J Clin Oncol. 2017 Feb;35(4): 394-401

EFS at MD Anderson



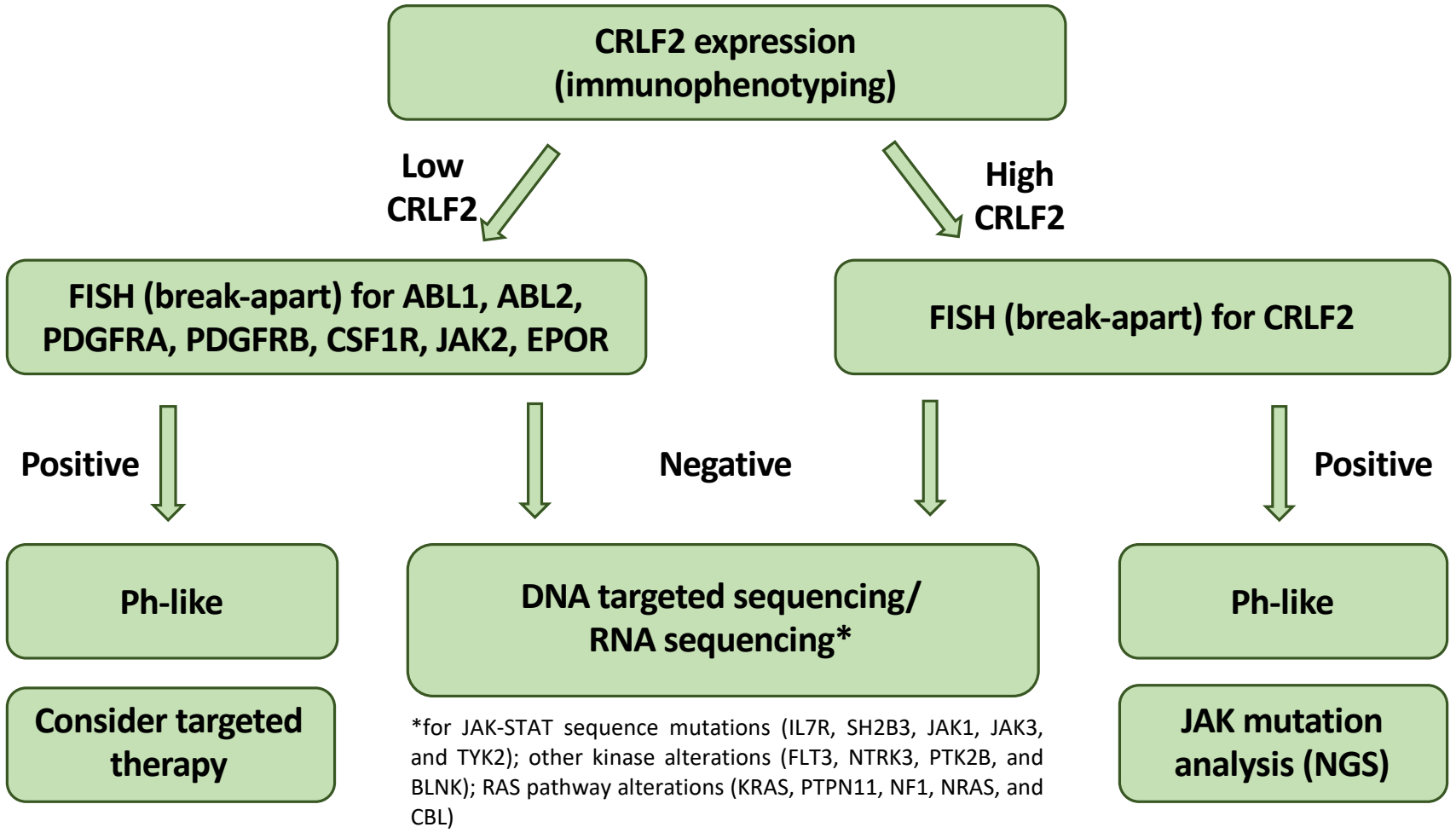
Jain N et al.: Blood. 2017;129(5):572-581

No consensus exists regarding the preferred approach to be used for the diagnosis of Ph-like ALL

- Screening for the Ph-like pattern should be adopted in routine clinical practice
- Patients should be informed that current screening methods may miss rare gene mutations
- If the ABL-activating aberration is identified, adding TKI to therapy is advised.
- All patients with identified kinase-activating aberrations should be defined as high risk; hence, intensification of chemotherapy, treatment with kinase targeting agents and/or antibody-derived novel agents may be considered.

Avraham Frisch and Yishai Ofran, Haematologica 2019 Volume 104(11):2135-2143

Screening of newly diagnosed cases of ALL (our current approach)



*for JAK-STAT sequence mutations (IL7R, SH2B3, JAK1, JAK3, and TYK2); other kinase alterations (FLT3, NTRK3, PTK2B, and BLNK); RAS pathway alterations (KRAS, PTPN11, NF1, NRAS, and CBL)

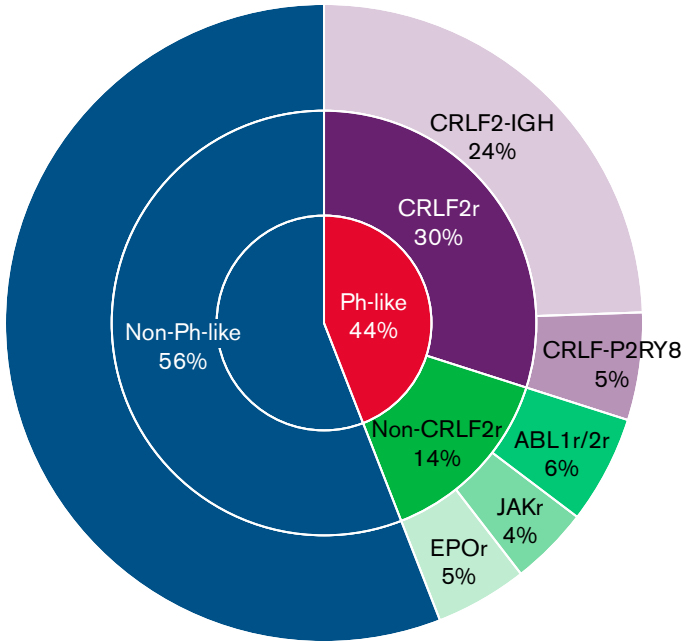
Current clinical trials of kinase inhibitor therapies for children and adults with Ph-like ALL

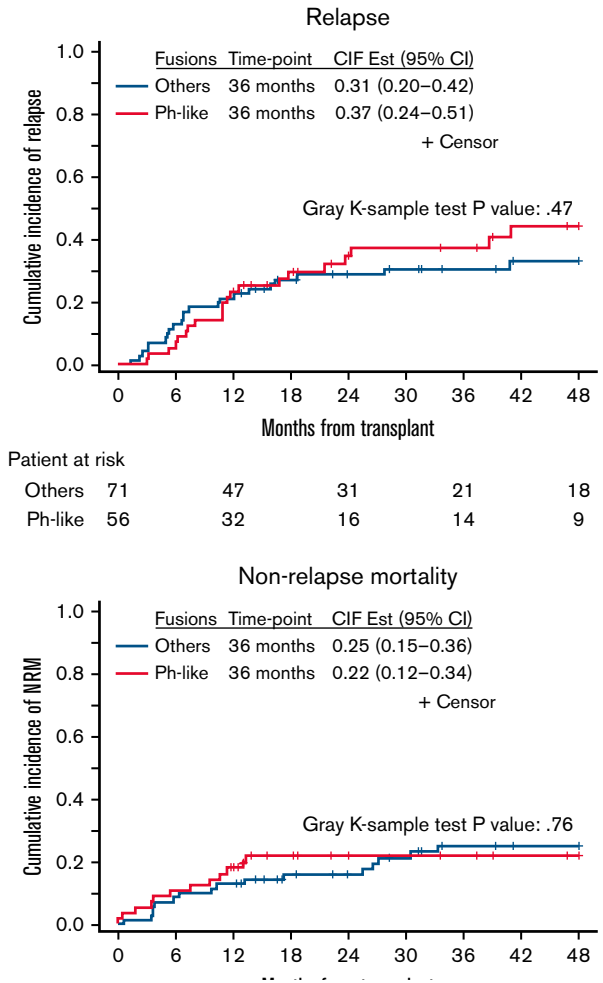
Ph-like alteration	Kinase inhibitor	Disease status	Age, y	Clinical trial	Trial phase	
ABL class	Dasatinib	Newly diagnosed	1-30	NCT01406756 (COG AALL1131)	3 (dasatinib subarm)	*
	Dasatinib	Newly diagnosed	1-18	NCT03117751 (SJCRH Total XVII)	3 (dasatinib subarm)	**
	Dasatinib	Relapsed	≥10	NCT02420717 (MDACC)	1/2	←
CRLF2/JAK pathway	Ruxolitinib	Newly diagnosed	1-21	NCT02723994 (COG AALL1521)	2	**
	Ruxolitinib	Newly diagnosed	1-18	NCT03117751 (SJCRH Total XVII)	3 (ruxolitinib subarm)	**
	Ruxolitinib	Newly diagnosed	18-39	NCT03571321	1 (planned phase 2 expansion)	**
	Ruxolitinib	Relapsed	≥10	NCT02420717 (MDACC)	1/2	←

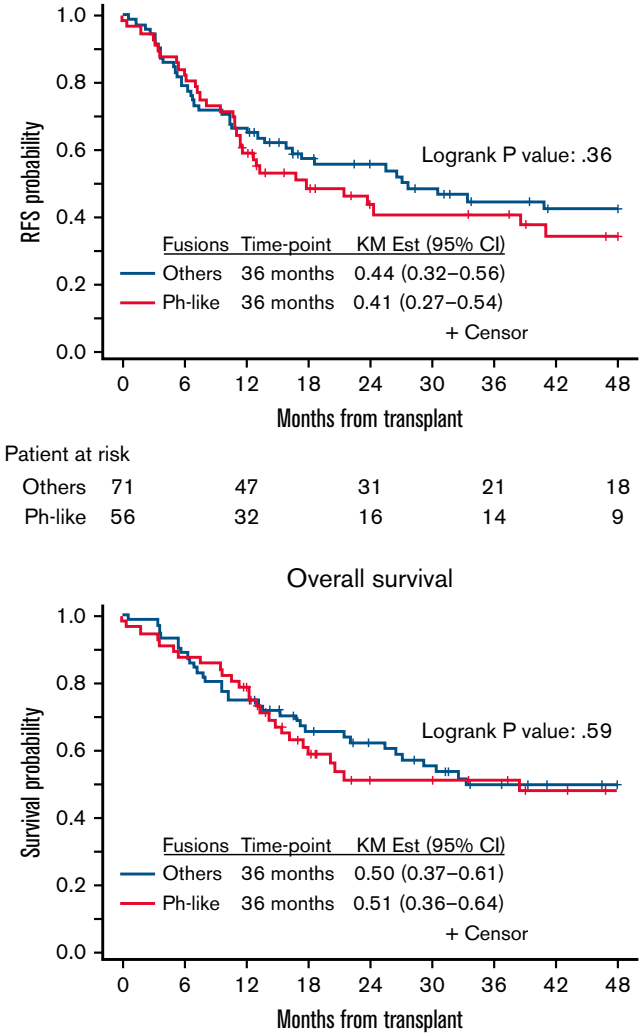
Active not recruiting*
Active recruiting **
Terminated has results (updated May 2022) ←

Harvey RC and Tasian SK, Blood Adv, 14 January 2020 • Volume 4, Number 1, 218-228

Outcomes of allogeneic hematopoietic cell transplantation in adults with fusions associated with Ph-like ALL

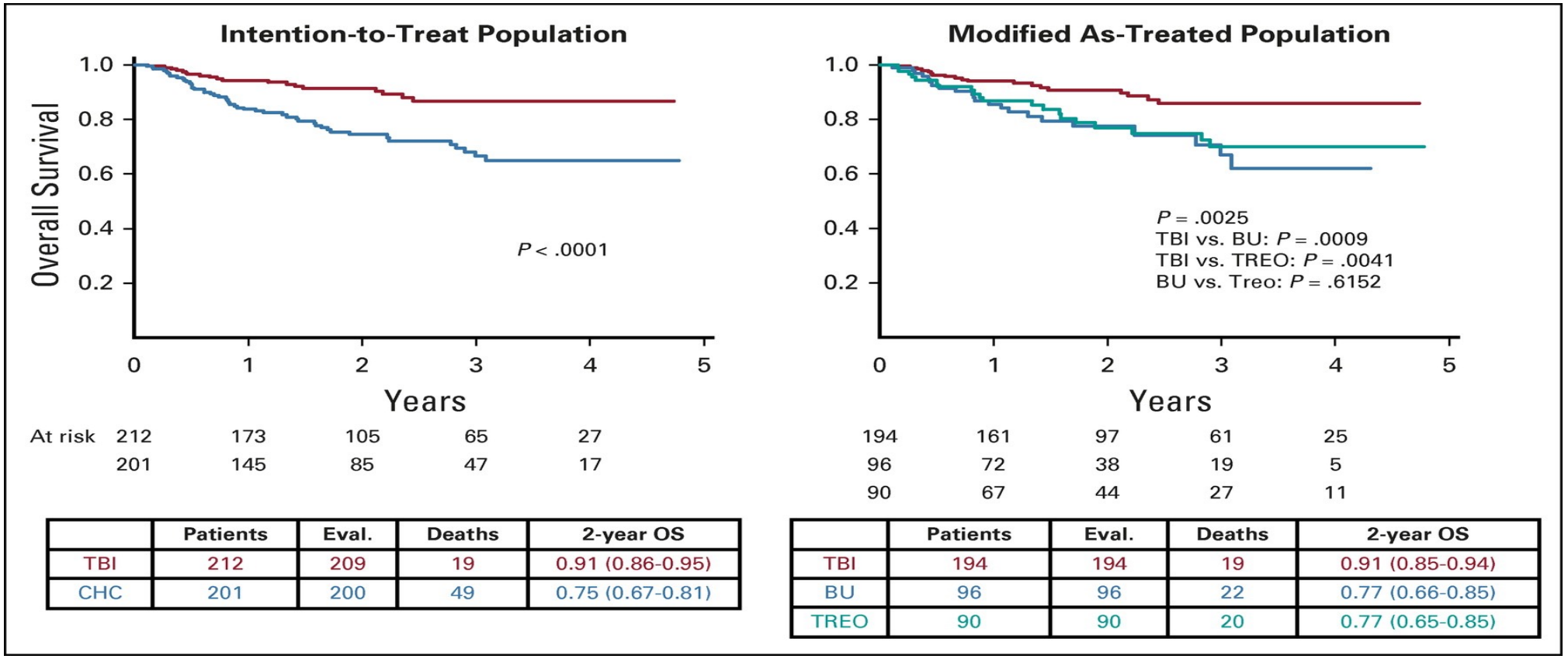






Aldoss I et al:, Blood Adv, 13 September 2022 • Volume 6, Number 17, 4936-4948

The role of conditioning regimen: the pediatric trial

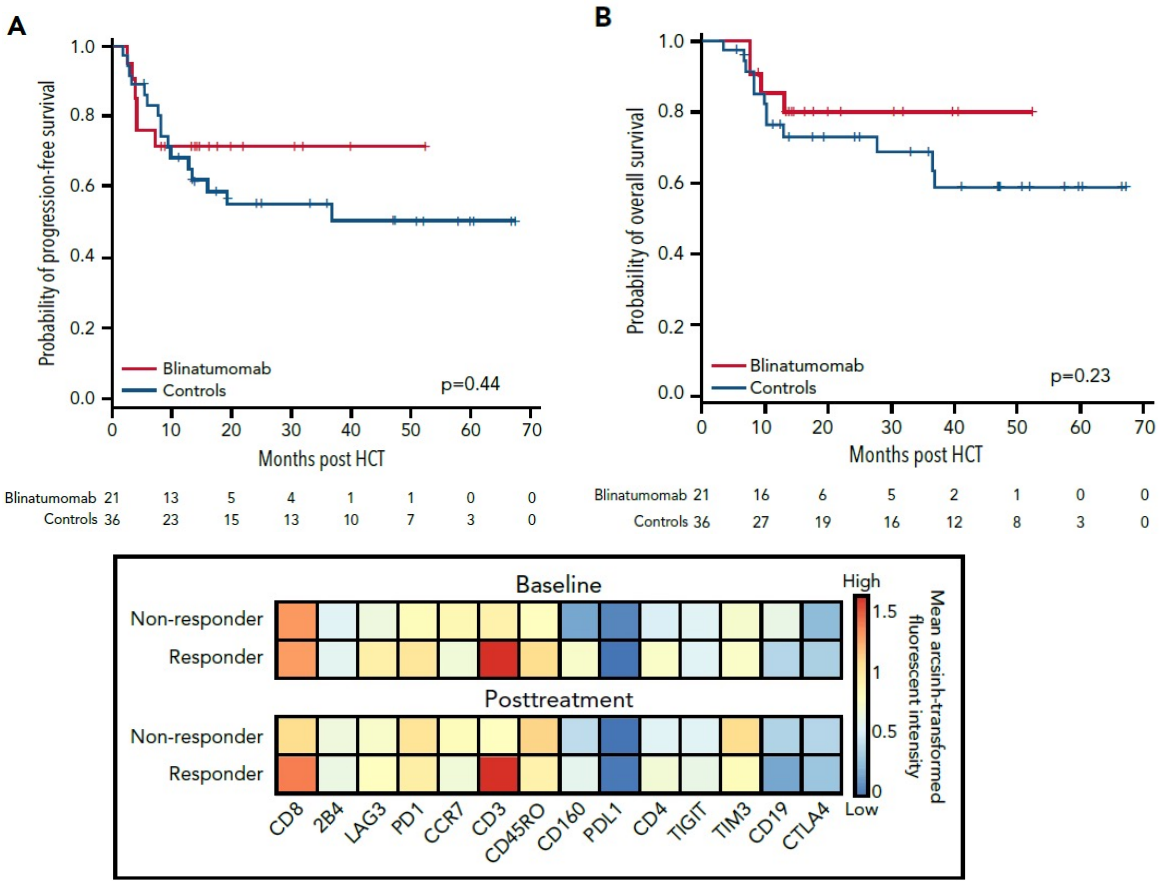


	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

Peters C et al. Journal of Clinical Oncology 2021 39295-307

Blinatumomab maintenance after allogeneic hematopoietic cell transplantation for B-lineage ALL



MAIN RESULTS

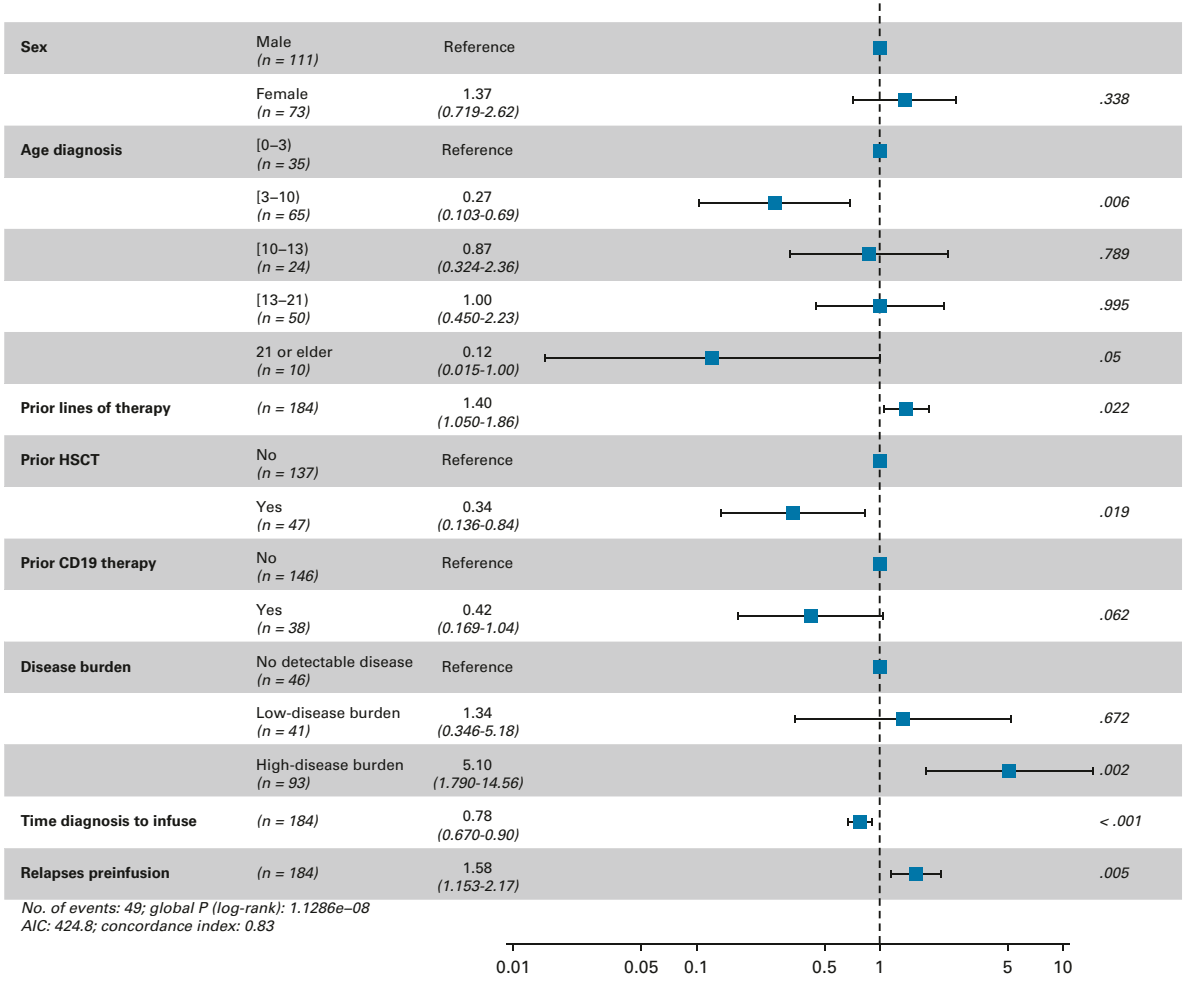
- 12/ 23 pts (57%) completed all 4 cycles (17 pts were alive at the end of the study; 6 pts relapsed)
- With a median follow up of 14 3 months, the 1year OS, PFS, and non relapse mortality rates were 85%, 71% and 0%. CIR,29%
- The cumulative incidence of acute GVHD grades 2 to 4 and 3 to 4 were 33% and 5%, respectively; 2 cases of mild (10%) and 1 case of moderate (5%) chronic GVHD were noted
- In a matched analysis with a contemporary cohort of 57 patients, no significant difference between groups regarding blinatumomab's efficacy
- Responders had greater numbers of CD3, CD4, CD160 T cells compared with non responders. In addition, responders had higher levels of CD8 T cells after therapy
- Blinatumomab is safe and feasible for use in B-ALL after allogeneic HCT
- The composition of a patient's T-cell subsets at the time of treatment is indicative of whether they will respond to blinatumomab

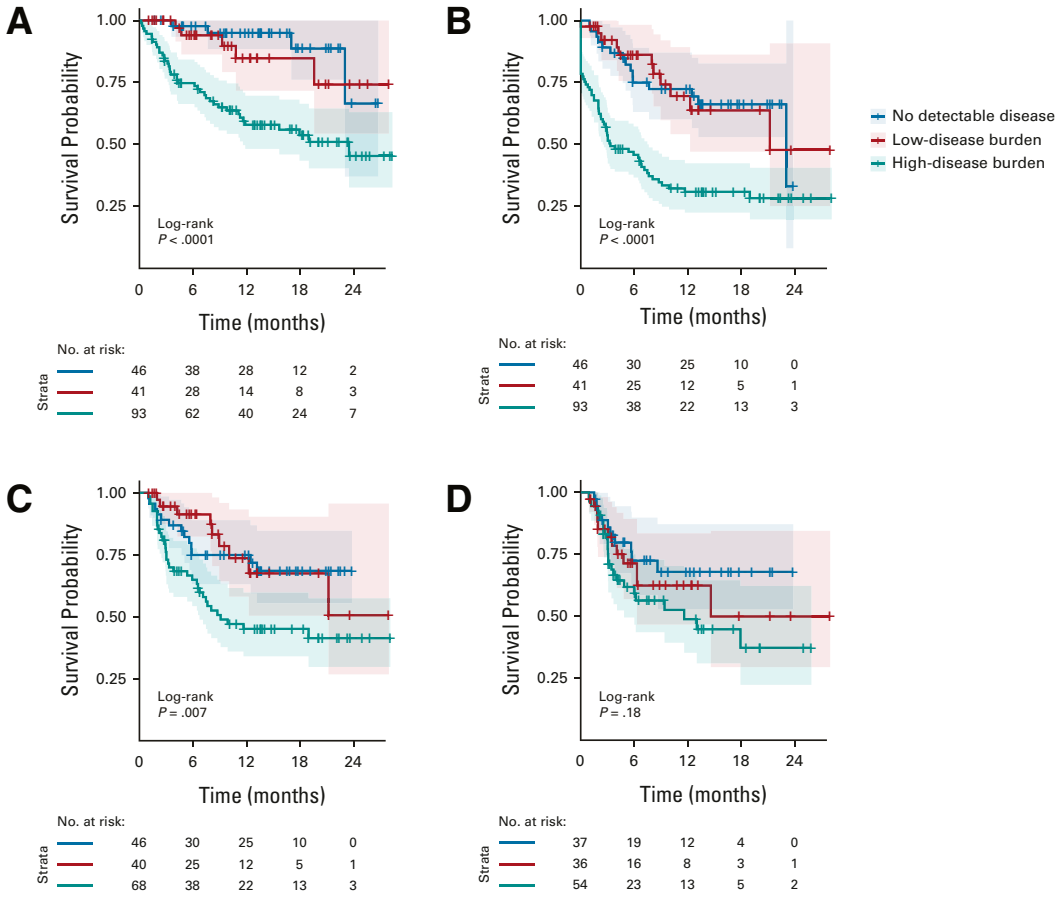
ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; HCT, hematopoietic stem cell transplantation; HR, high-risk; PFS, progression free survival; OS, overall survival; NRM, non relapse mortality

Gaballa M, et al. Blood 2022 Mar 24;139(12):1908-1919 .

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

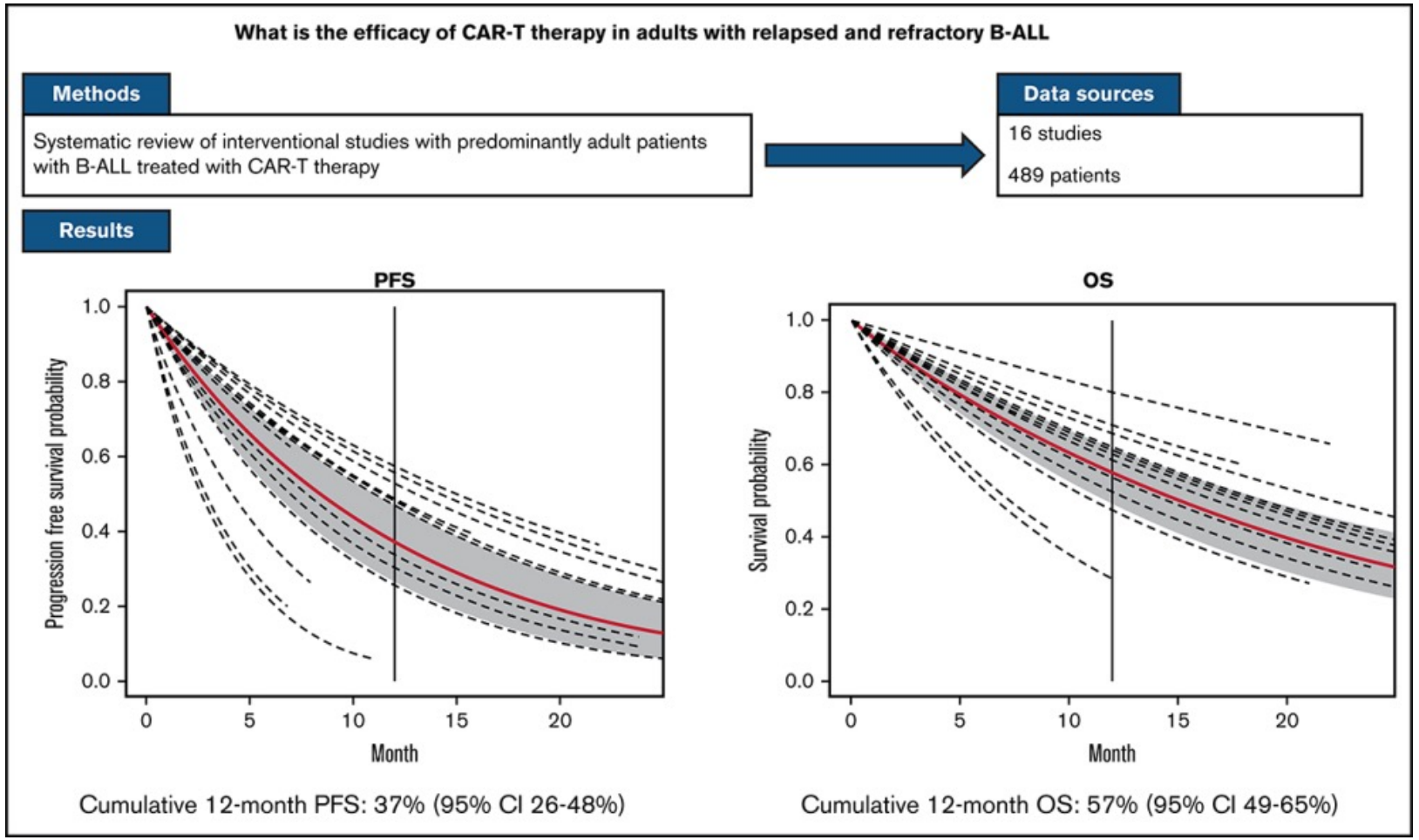
Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report





Schultz, LM et al.: J Clin Oncol 2021

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



Punita Grover et al. Blood Adv, 2022

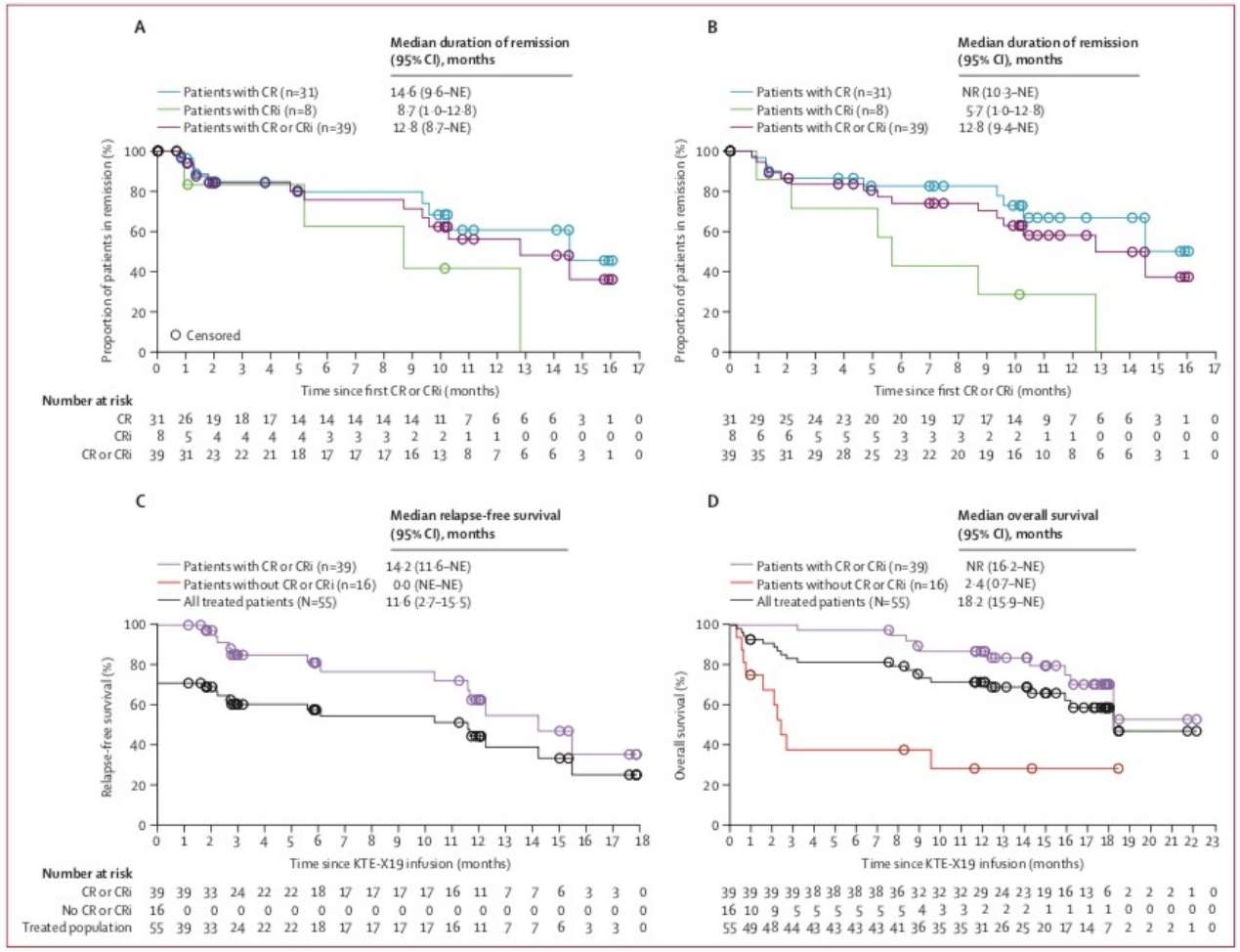
KTE-X19 for relapsed or refractory adult B-cell ALL: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study

- **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**

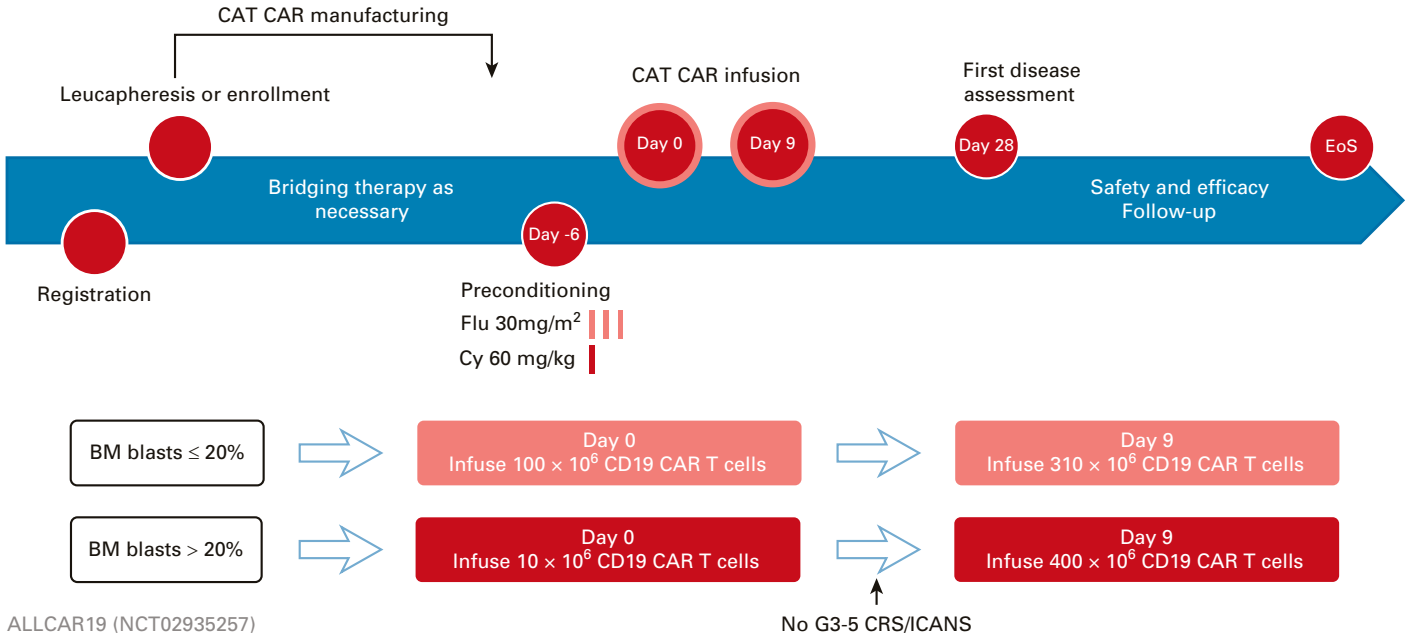
- **The most common adverse events of grade 3 or higher were anaemia (49%) and pyrexia (36%)**
- **Two grade 5 events occurred (brain herniation and septic shock)**
- **CRS of grade 3 or higher occurred in 24% and neurological events of grade 3 or higher occurred in 25%**



Shah BD Lancet 2021; 398: 491–502

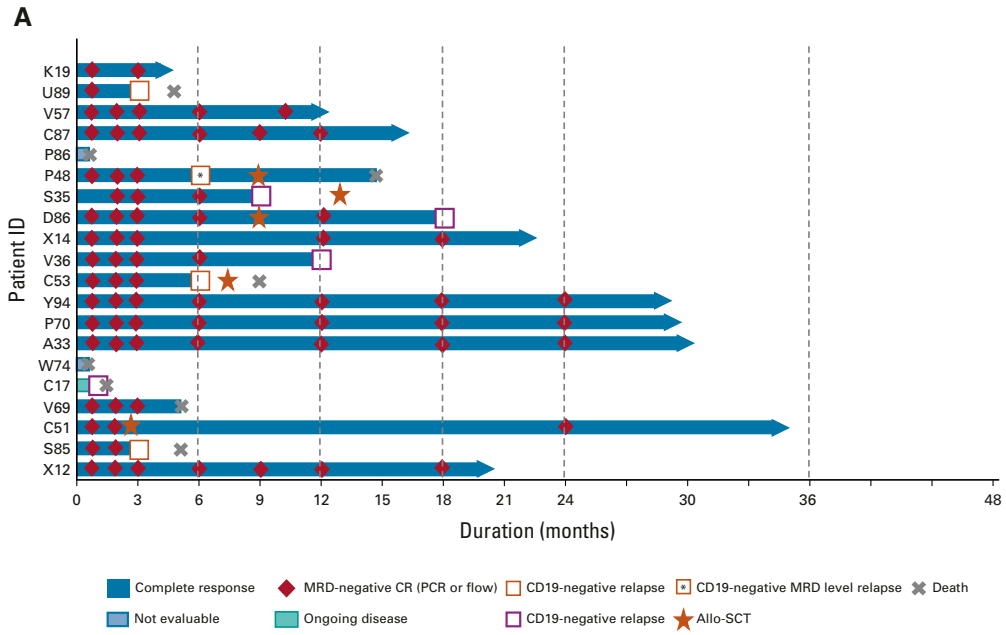
Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell ALL

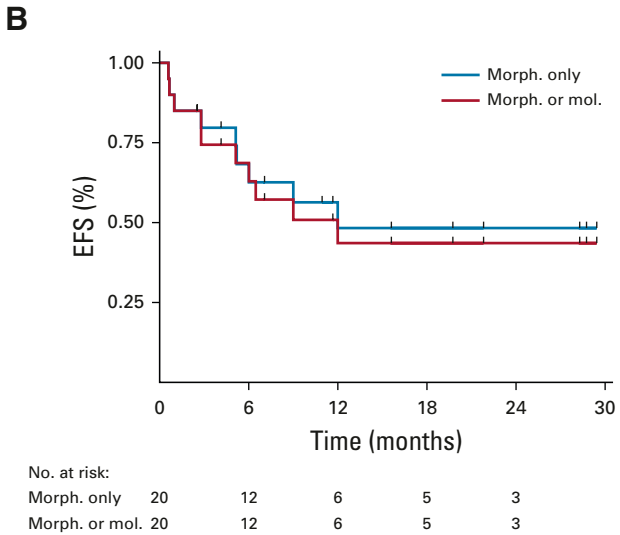
Baseline Characteristic	n = 20
Sex, No. (%)	
Female	7 (35)
Male	13 (65)
Median age, years (range)	41.5 (18-62)
Chromosomal or molecular status, No. (%)	
Ph+ (bcr-abl)	6 (30)
MLL	1 (5)
Others	8 (40)
Normal	4 (20)
Failed	1 (5)
Previous treatment	
Median previous lines (range)	3 (2-6)
Inotuzumab ozogamicin exposure, No. (%)	10 (50)
Blinatumomab exposure, No. (%)	5 (25)
Previous allo-SCT, No. (%)	13 (65)

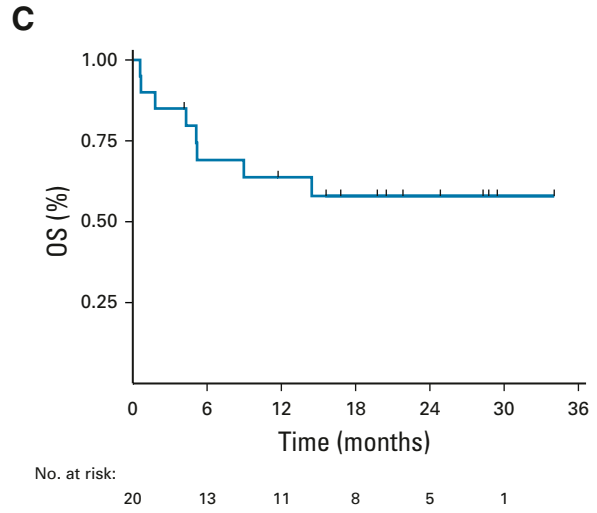


Roddie C et al.: Journal of Clinical Oncology 39:3352-3363. 2021

Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell ALL



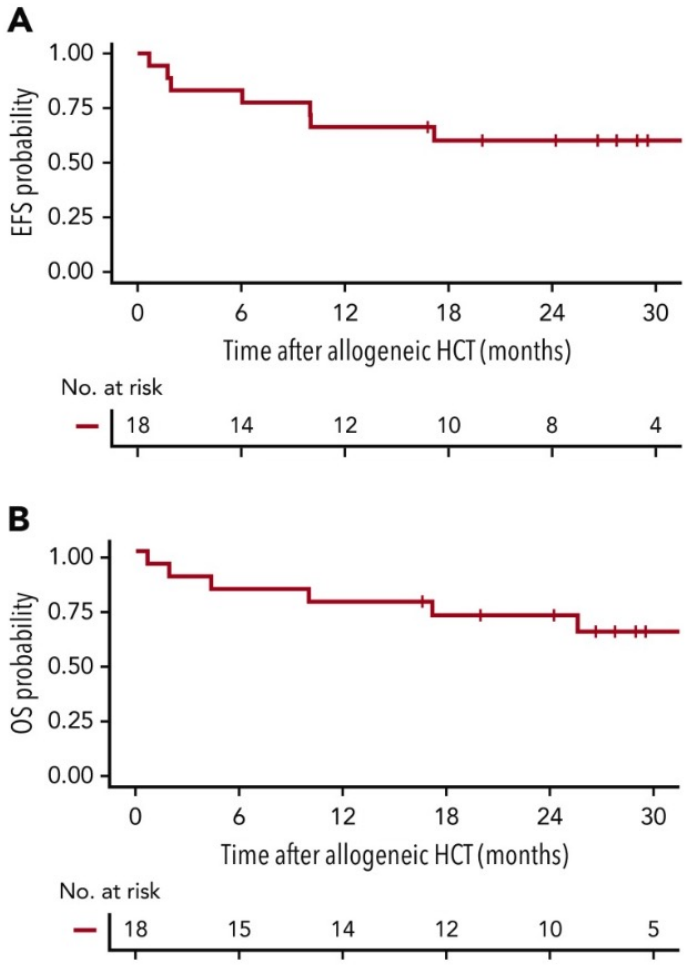




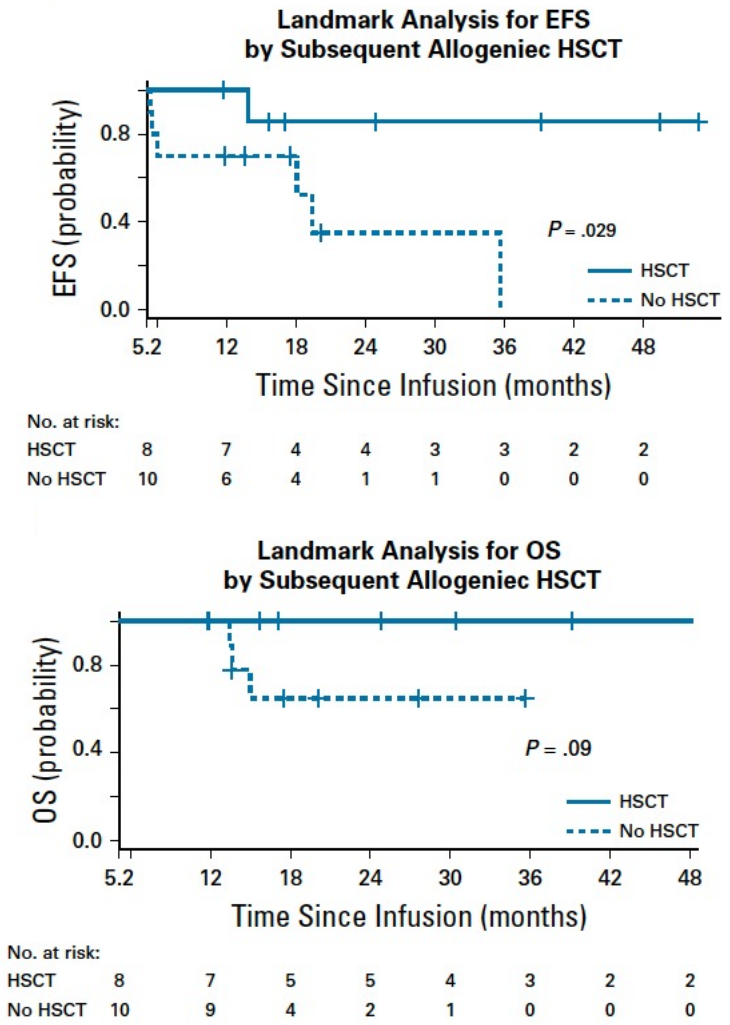
Roddie C et al.: Journal of Clinical Oncology 39:3352-3363. 2021

Should we advise an alloHSCT to every patient achieving CR?

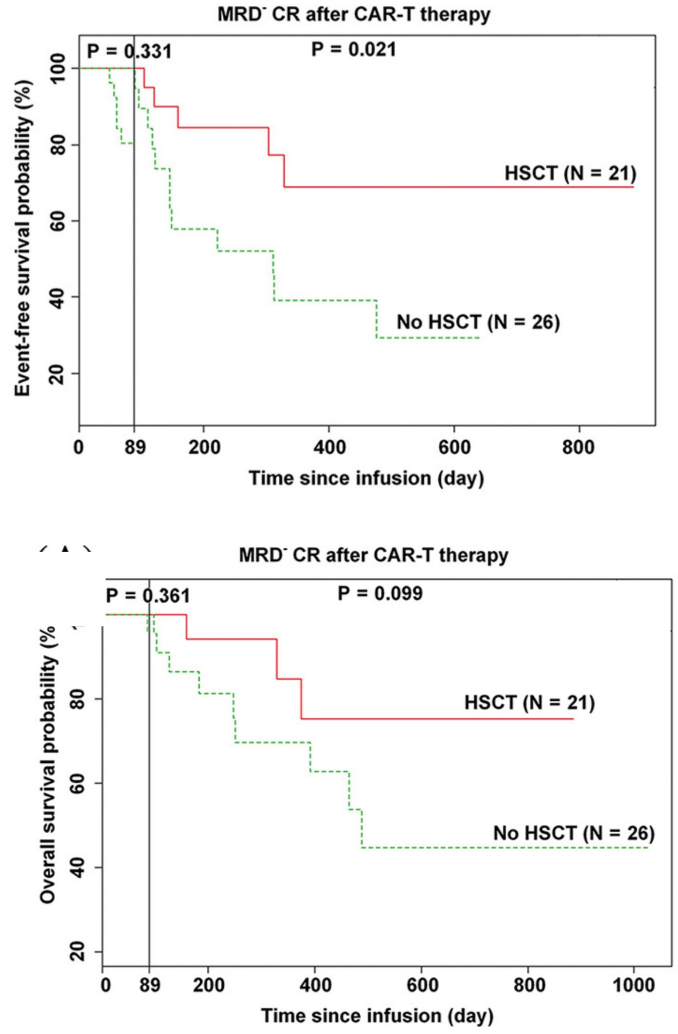
HCT may improve EFS following CD19 CAR in some published studies



Hay, et al. Blood 2019



Frey, et al. JCO 2020



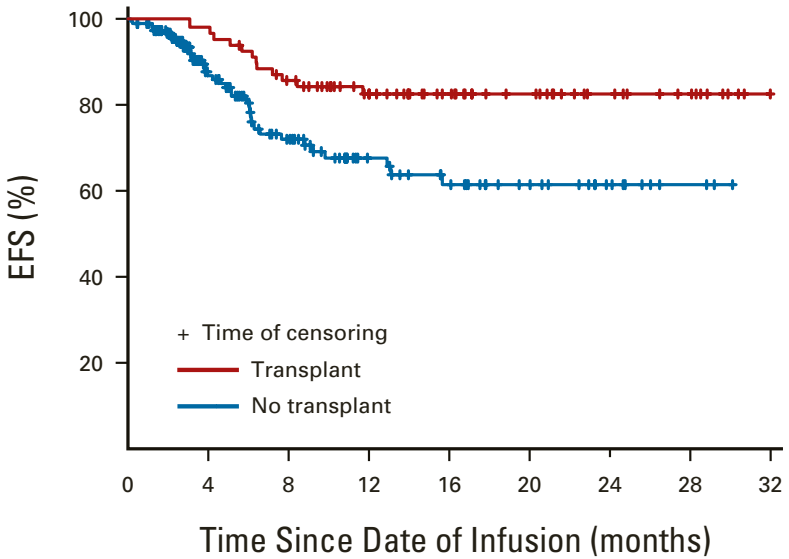
Jiang, et al. AJH 2019

What’s next in BP-ALL?

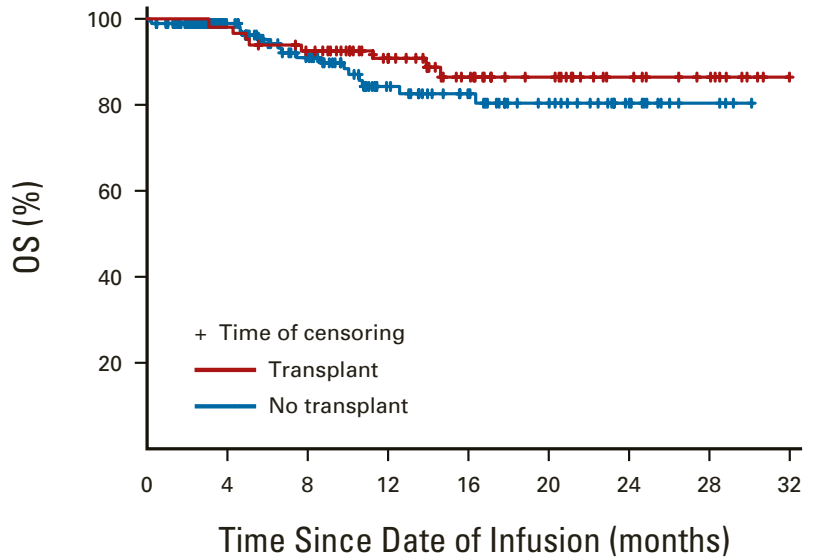
Co-administration of CD19- and CD22-Directed CAR-T Cell Therapy in Childhood B-Cell ALL: A Single-Arm, Multicenter, Phase II Trial

Results

- Patients registered (N = 232); infused (N= 225); achieving CR (N= 192);
- Patients consolidated with transplant (N= 78) (due to KMT2A rearrangement, (n = 22), ZNF384 fusion (n = 2), parent request (n = 54)



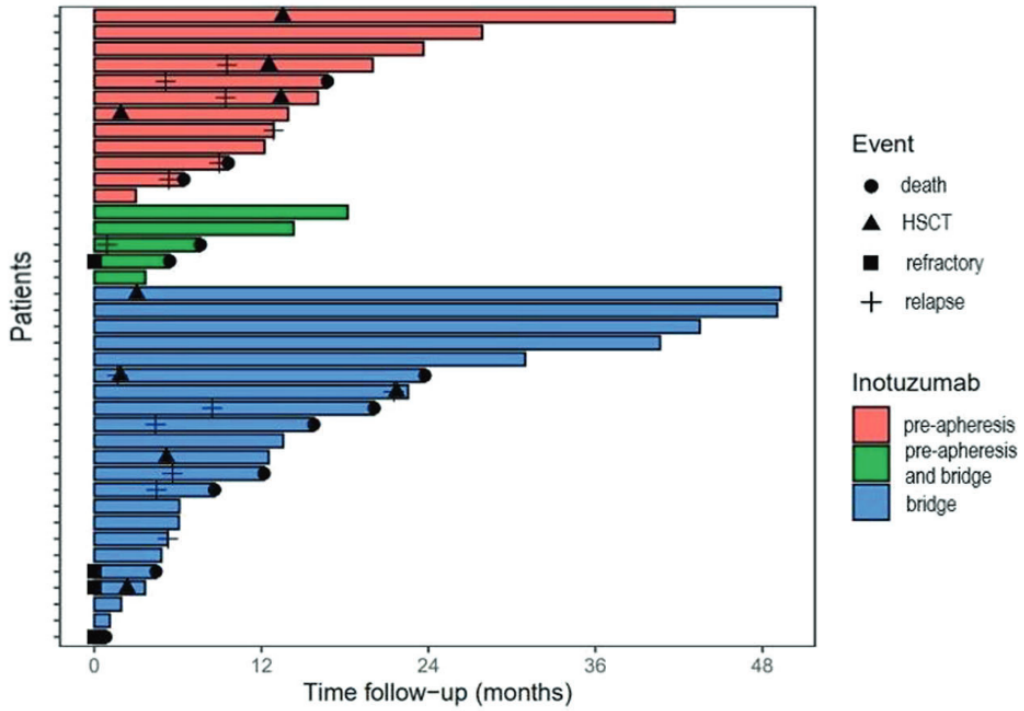
No. at risk (No. censored):									
Transplant	78 (0)	77 (0)	66 (2)	50 (16)	34 (32)	24 (42)	15 (51)	10 (56)	1 (65)
No transplant*	194 (0)	104 (72)	64 (97)	39 (119)	29 (126)	18 (137)	11 (144)	4 (151)	0 (155)



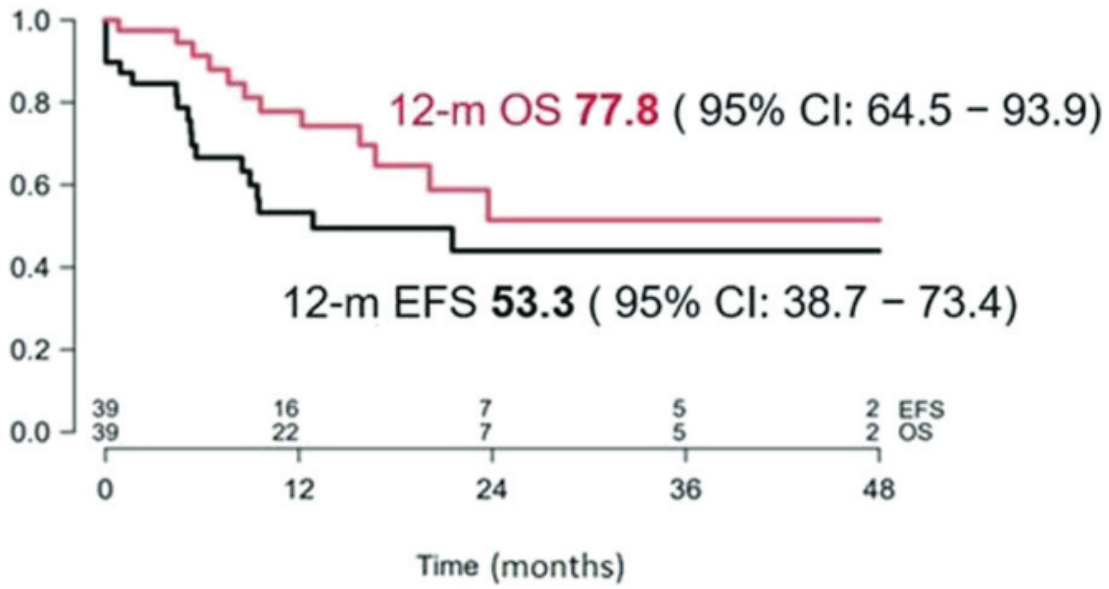
No. at risk (No. censored):									
Transplant	78 (0)	77 (0)	71 (2)	54 (18)	35 (35)	25 (45)	15 (55)	10 (60)	1 (69)
No transplant*	194 (0)	120 (72)	86 (98)	55 (124)	42 (136)	26 (151)	15 (162)	5 (172)	0 (177)

Wang T et al.: JCO 2022 DOI https://doi. org/10.1200/JCO.22. 01214

Outcome of chimeric antigen receptor T-cell therapy following treatment with inotuzumab ozogamicin in children with R/R ALL



Duration of response after CAR-T

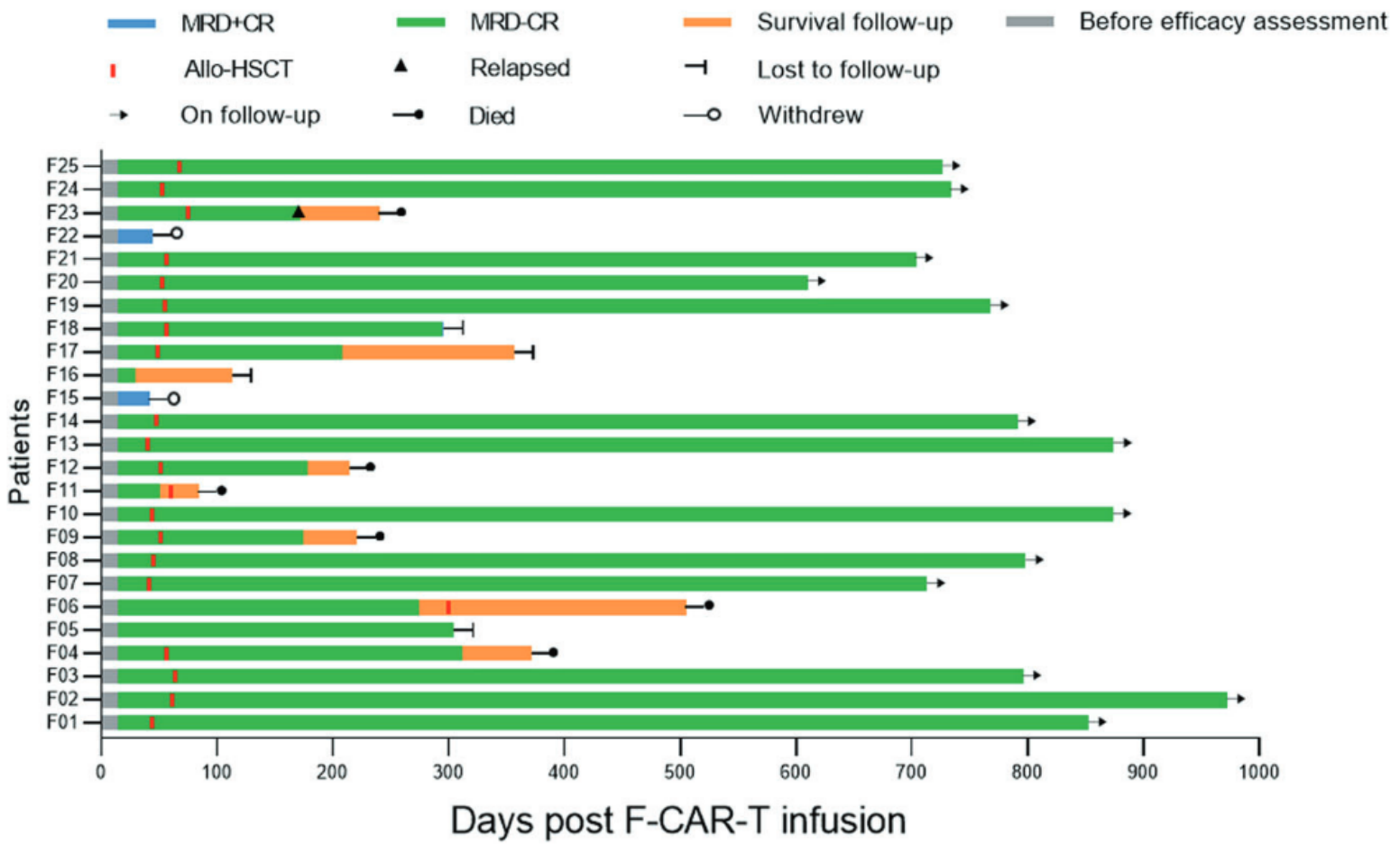


Outcome of the entire cohort

Ceolin V et al.: Leukemia; https://doi.org/10.1038/s41375-022-01740-9

Next-day manufacture of a novel anti-CD19 CAR-T therapy for B-ALL: first-in-human clinical study

Clinical outcome



Yang J et al.: Blood Cancer Journal (2022) 12:104 ; https://doi.org/10.1038/s41408-022-00694-6

Phase I, open label, multicenter, dose escalation study of YTB323 in adult patients with CLL/sLL, DLBCL and ALL

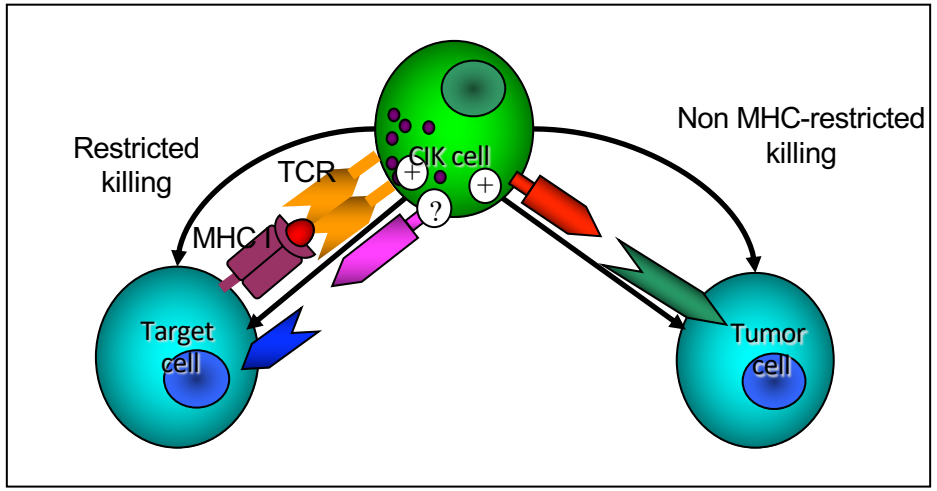
- A first-in-human study to evaluate the feasibility, safety and preliminary antitumor efficacy of YTB323, a Novel, Autologous CD19-Directed CAR-T Cell Therapy Manufactured Using the Novel T-Charge™ Platform

- T-Charge™ minimizes the ex vivo culture time and reduces the manufacturing process time to **< 2 days**

- Starting from cryopreserved leukapheresis, T cells are transduced with a lentiviral vector encoding for the same CAR used for tisagenlecleucel

- The T-Charge™ platform preserves naive/T_{scm} cells, leading to potentially higher potency and longer persistence

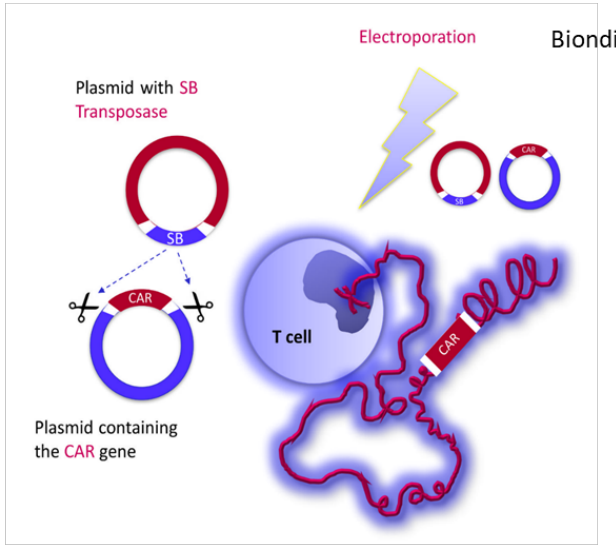
A non-viral platform to generate allogeneic CAR-T cells



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

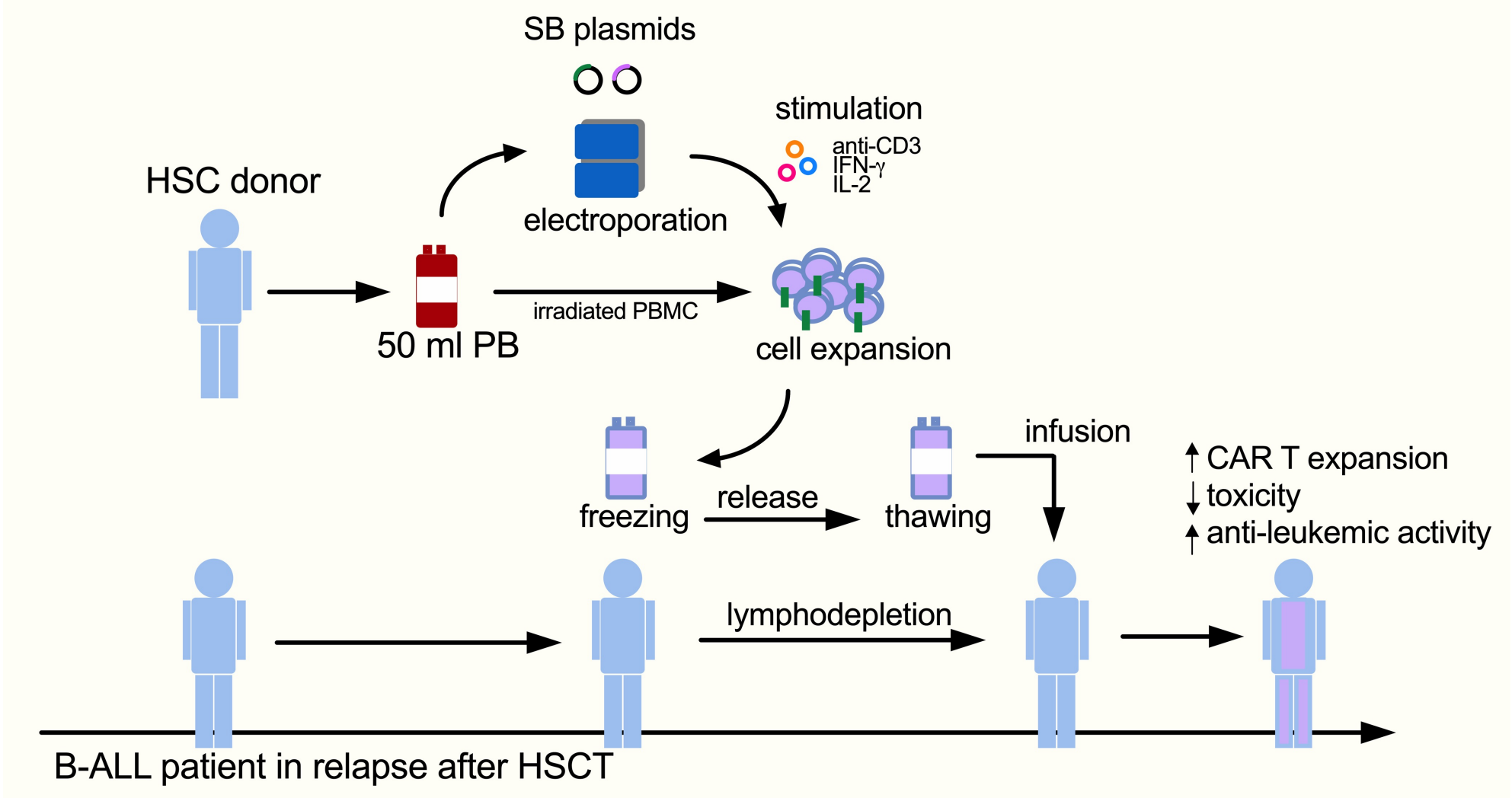
Non-viral vector to generate CAR-CIK cells



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

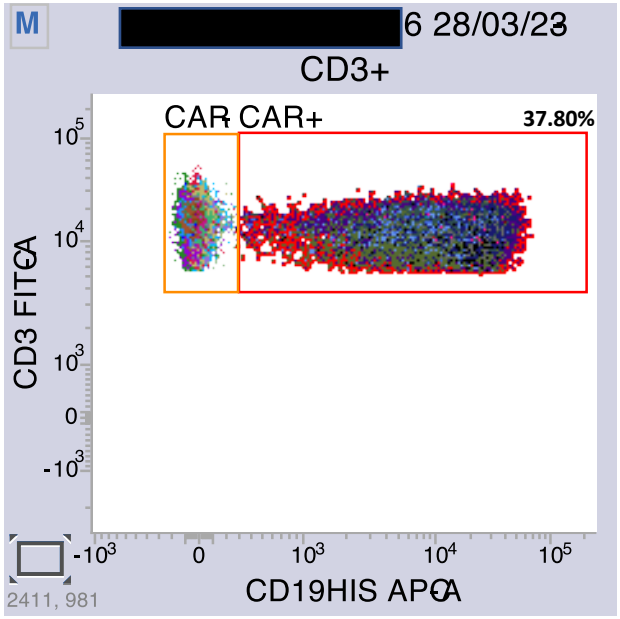
SLEEPING BEAUTY-ENGINEERED CARCIK CELLS ACHIEVE ANTI-LEUKEMIC ACTIVITY WITHOUT SEVERE TOXICITIES



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

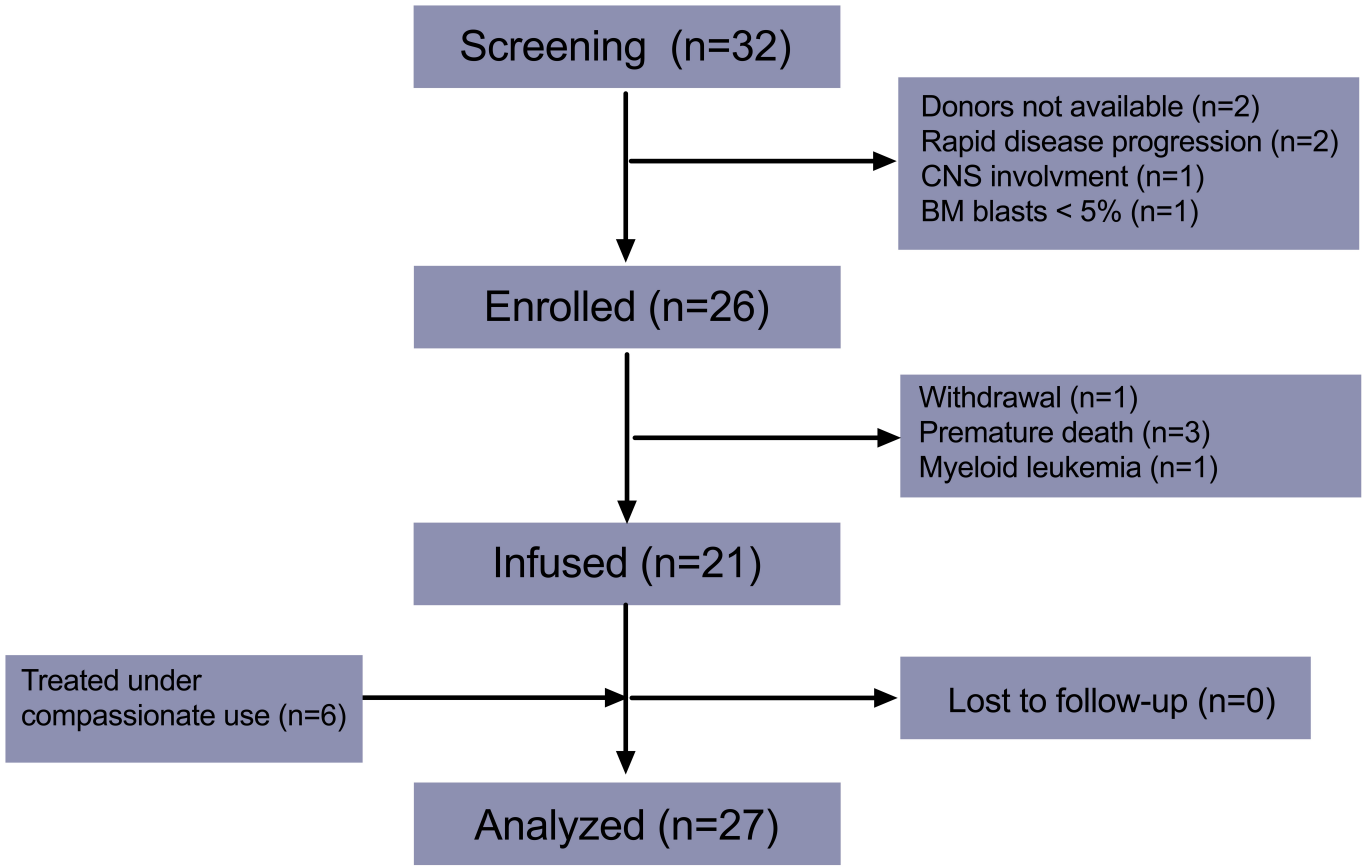
Early peak of CAR-CIK19

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)

Study profile and baseline characteristics



Patients characteristics:

- No. of prior lines (median, range): 4(2-8)
- No. of previous alloHSCT, n (%):
  - 1 (18, 66.6%);
  - 2 (9, 33.3%)
- Type of transplant, n (%):
  - Haplo 10 (37%)
  - MUD 10 (37%)
  - Sib 7(26%)
- aGvHD post last tx:
  - Grade I and II (n=8, 29%), GIII %(n=1, 4%)
- cGvHD post last Tx:
  - Grade I and GII (n=4, 15%); GIII (n=0, 0%)
- BM blasts at the enrollment, median (range): 40 (0-100)
- Extramedulary disease, n (%): 7 (26%)

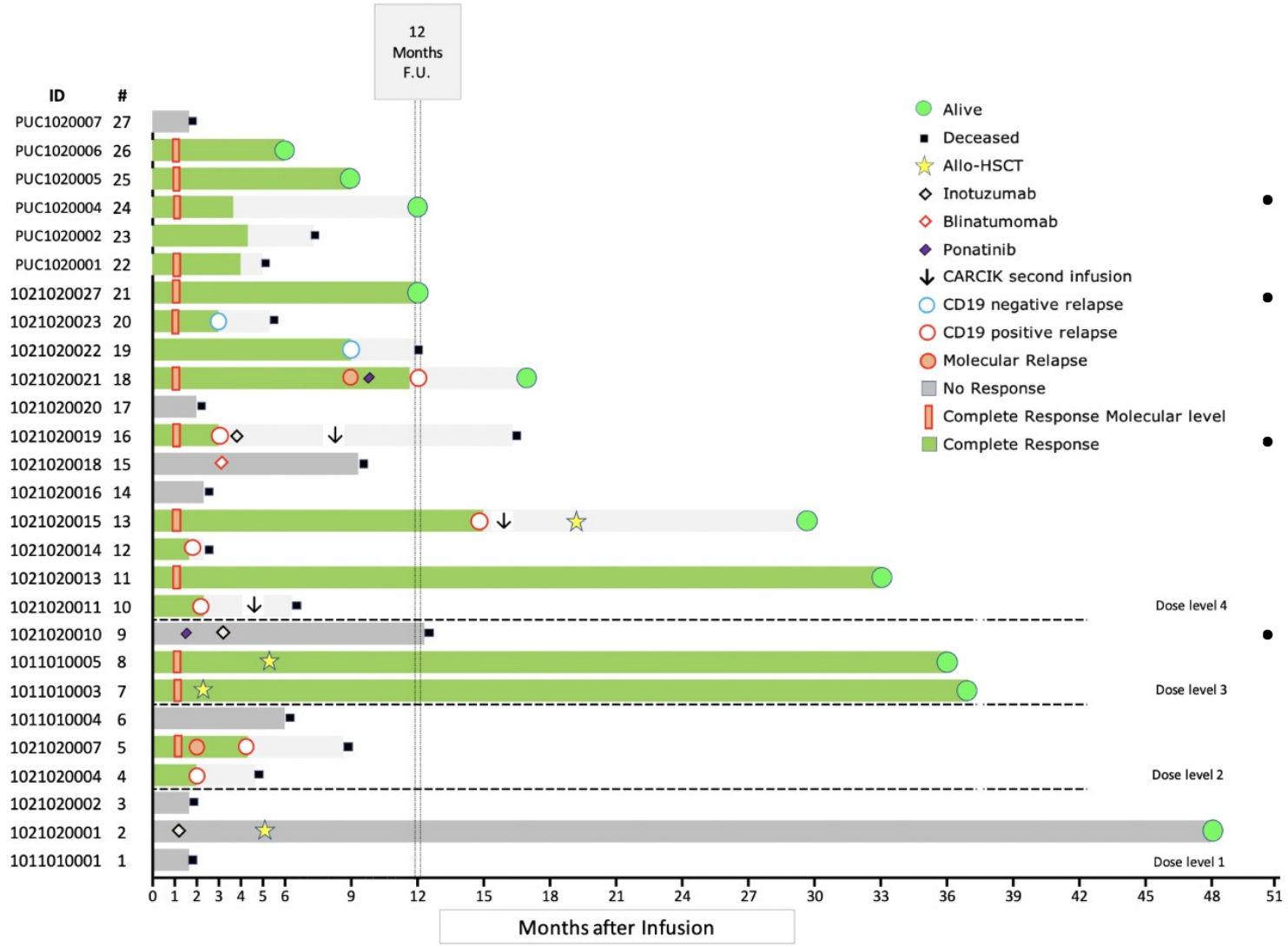
CARCIK-CD19 in B-ALL post HSCT: selected adverse event

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

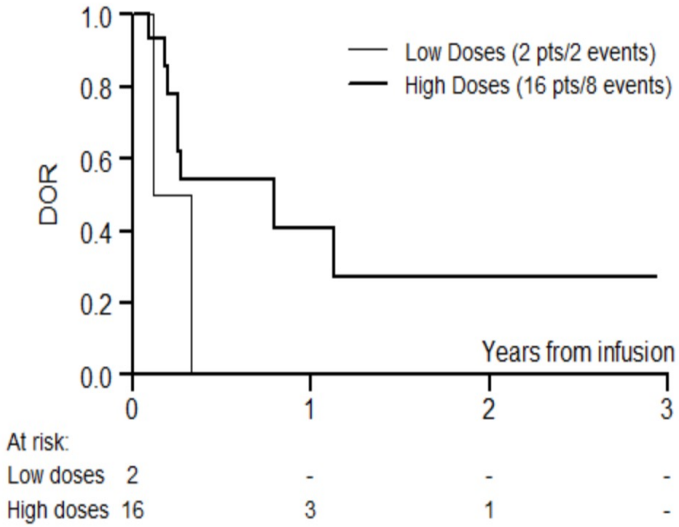
Response data



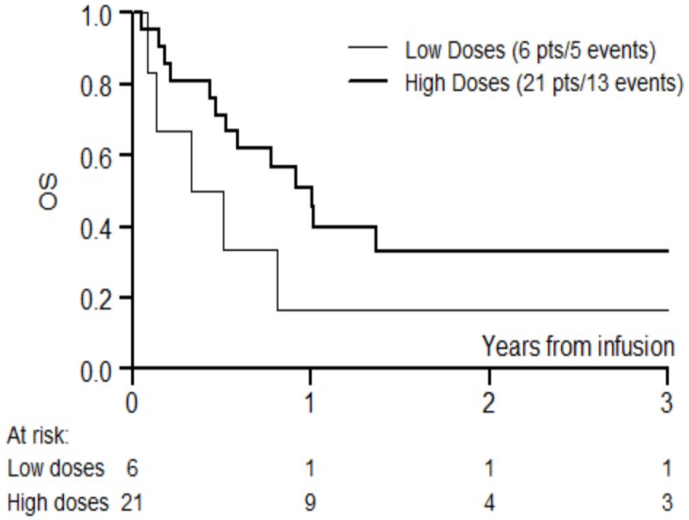
- CR: 18/27 patients (66.7%, 95%CI=46-84%)
- CR: 16/21 patients (76.2%, 95%CI=53-92%) treated with the 2 highest doses
- Fourteen (77.8%) of the overall responders and 13 of the responders at the highest doses (81.3%) achieved MRD negativity
- The type of donor did not influence the achievement of CR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

Main outcomes

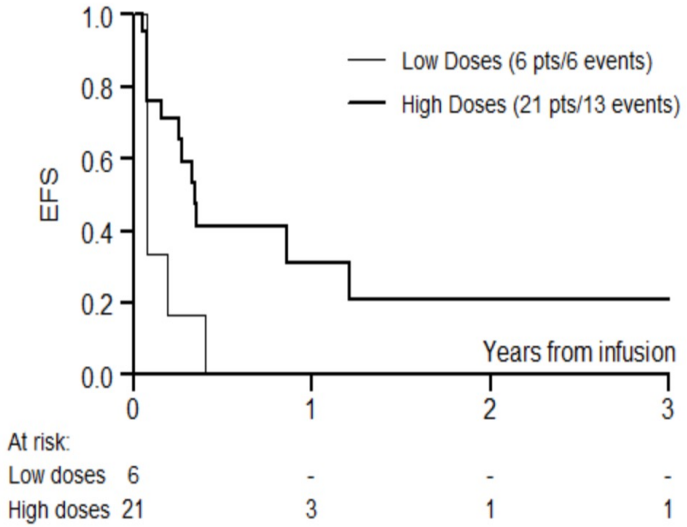
Duration of remission



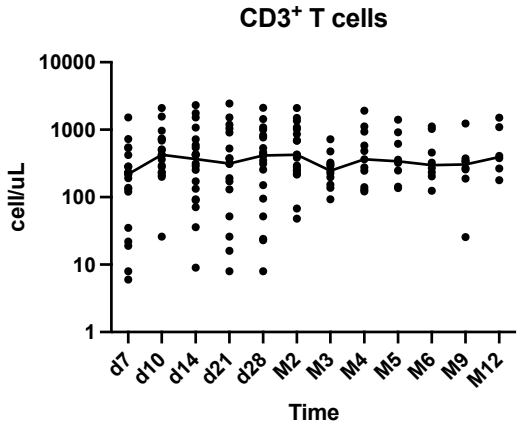
Overall survival

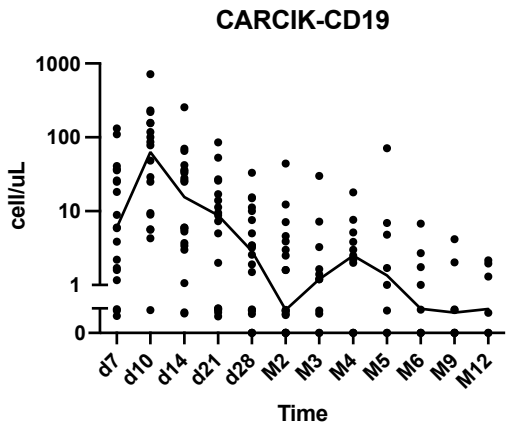


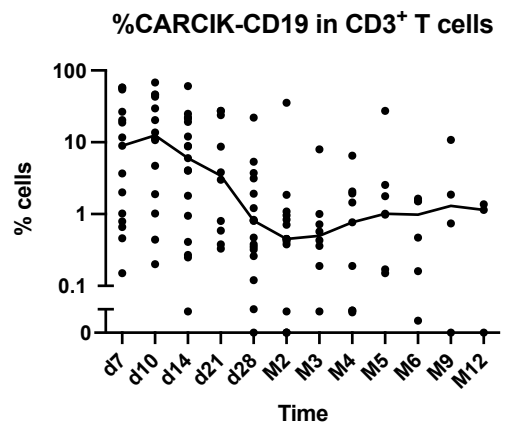
Event free survival

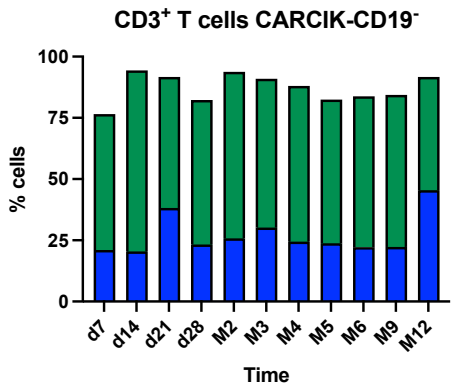


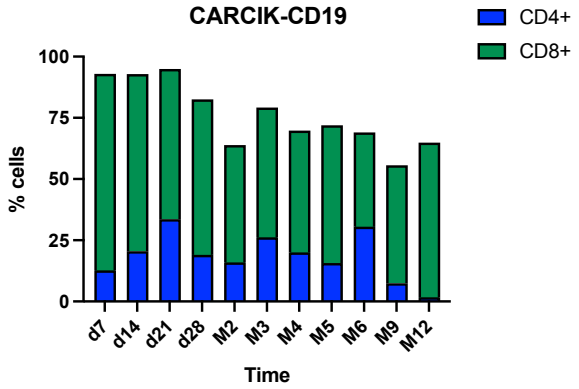
CD3+ T cells and CARCIK-CD19 reconstitution

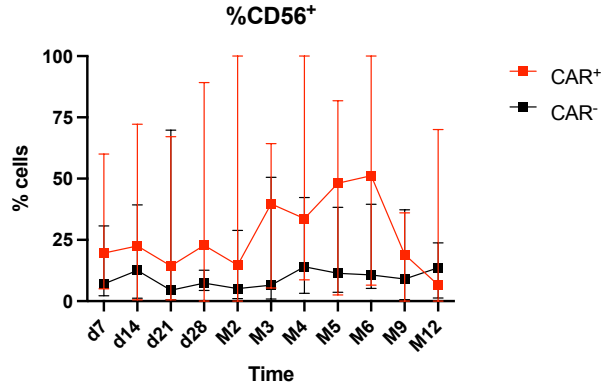




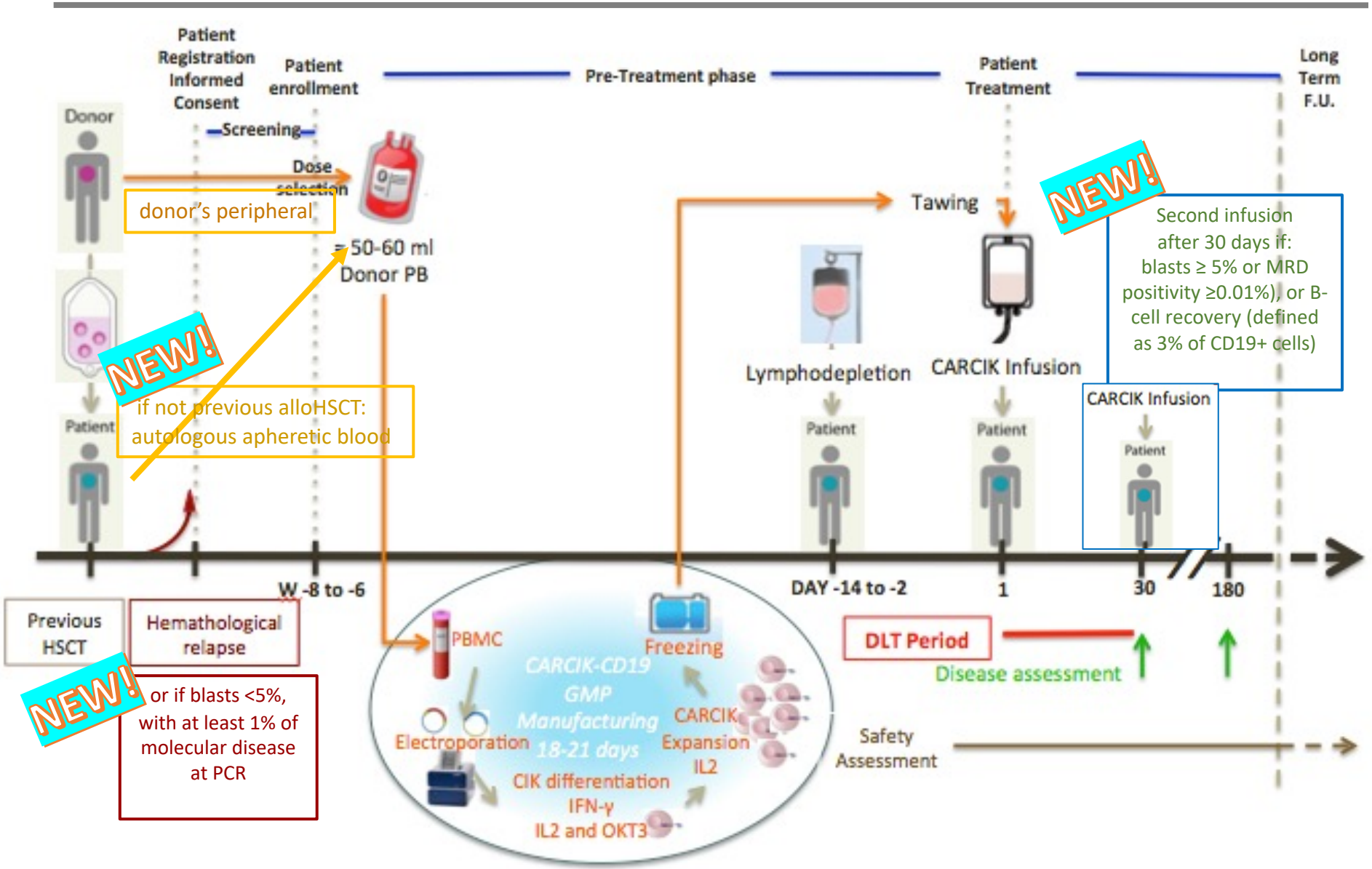








FT03CARCIK Phase 2: Flow-chart



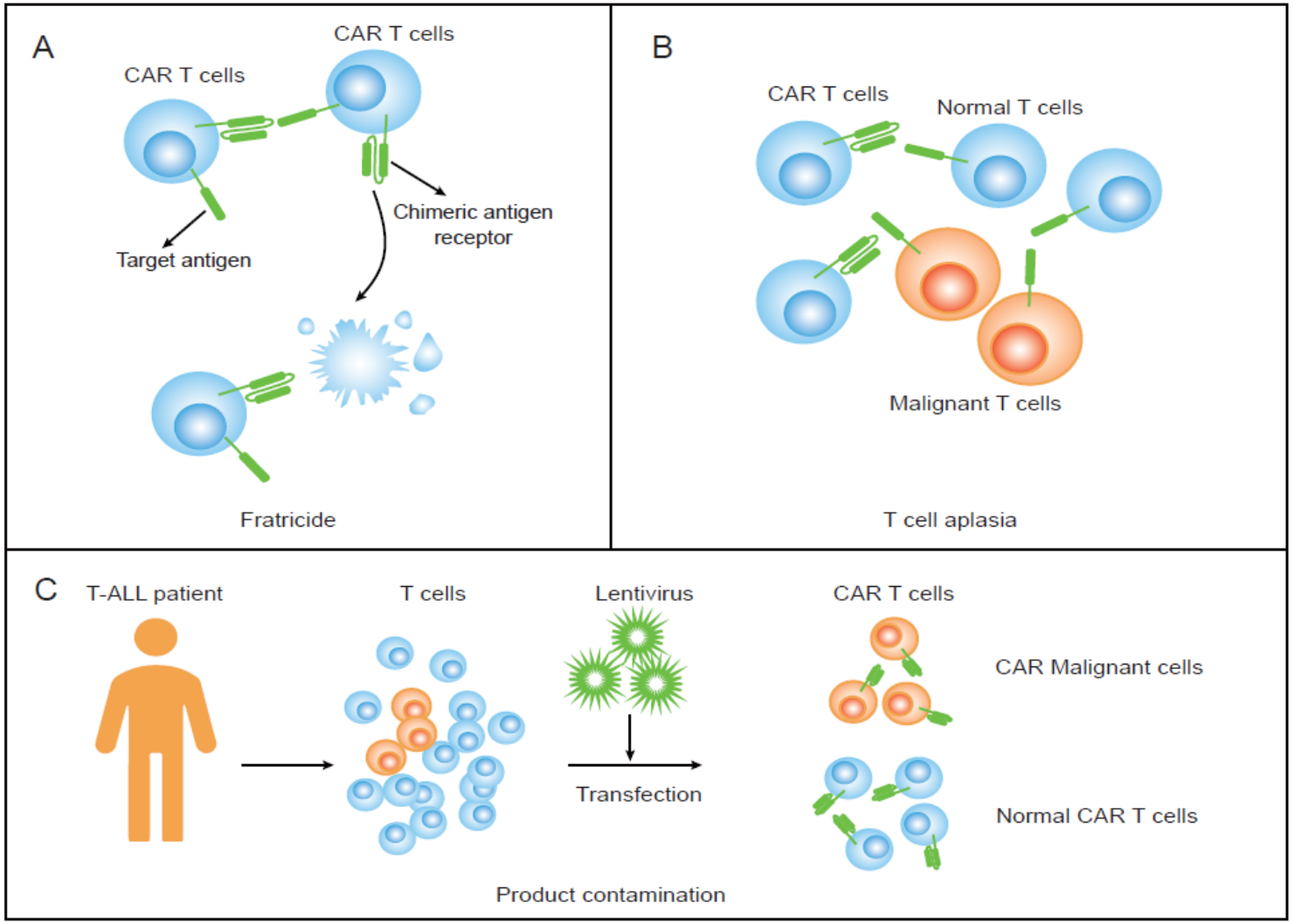
Conclusions

- Major improvements have been achieved by the National Treatment Program for ALL
- Ph-like ALL represents the major problem in the setting of B precursor ALL. Although no consensus exists regarding the preferred approach to be used for the diagnosis of Ph-like ALL, screening for the Ph-like pattern should be adopted in routine clinical practice
- MRD drives the daily clinical practice. Allo HSCT remains mandatory for patients not achieving MRD negativity after intensive chemotherapy.
- Immunotherapy with blinatumomab, Inotuzumab and CAR-T cells are changing the treatment landscape of adult ALL

CAR T-Cell Immunotherapy Treating T-ALL: Challenges and Opportunities

Thee major challenges for CAR-T cell therapy in T-ALL

A. Fratricide



B. T-cell aplasia

C. Product contamination

Ren, A.; Tong, X.; Xu, N.; Zhang, T.; Zhou, F.; Zhu, H. *Vaccines* **2023**

Donor-Derived CD7 Chimeric Antigen Receptor T Cells for T-Cell Acute Lymphoblastic Leukemia: First-in-Human, Phase I Trial

Design

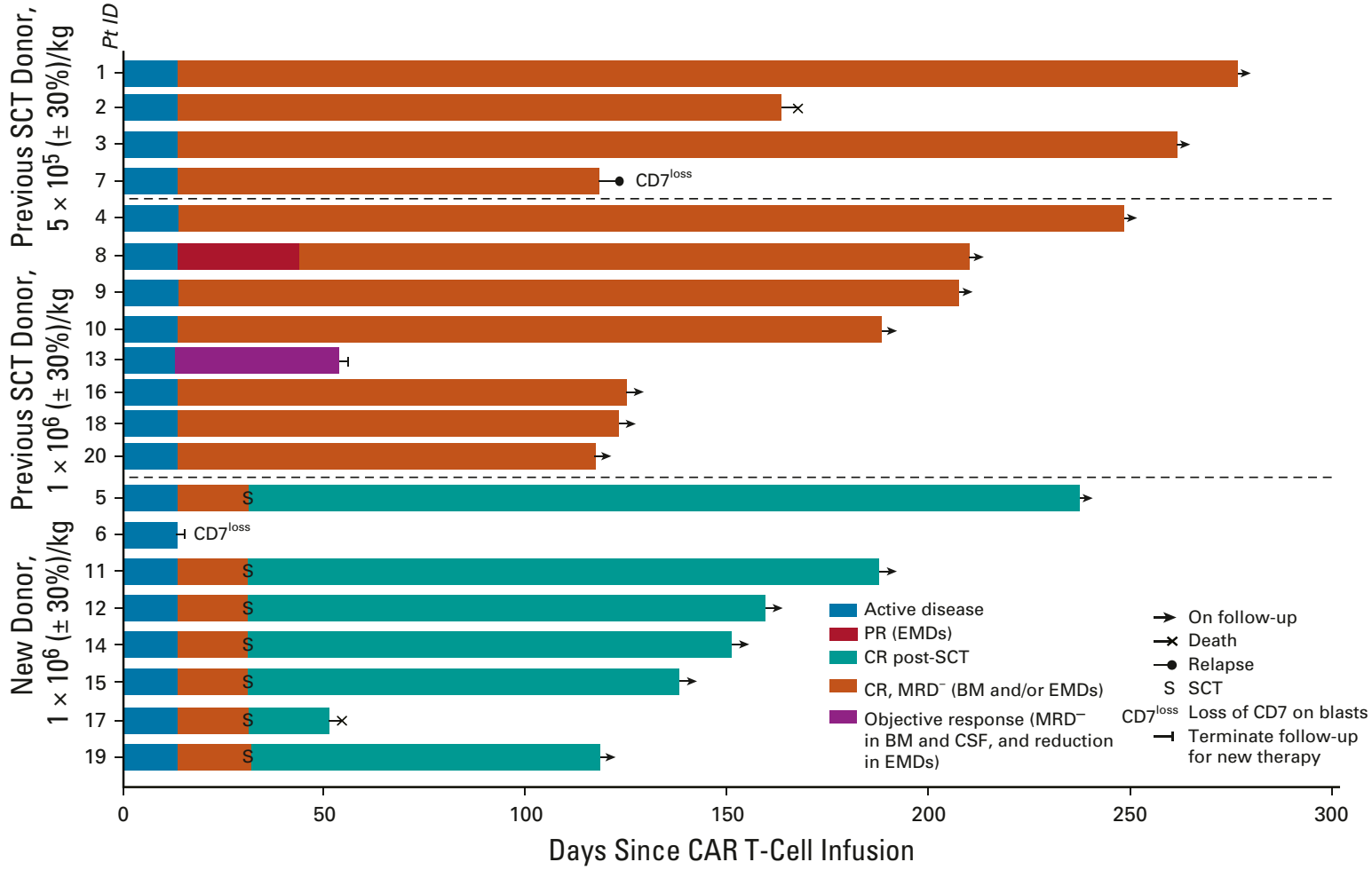
- To minimize CD7 CAR T-cell–mediated fratricide, a CD7-targeting CAR construct using IntraBlock technology, which prevents CD7 cell surface expression
- Anti-CD7 CAR T cells, manufactured from either previous stem-cell transplantation donors or new donors, to patients with r/r T-ALL
- Single infusions at doses of 5×10^5 or 1×10^6 (±30%) cells per kilogram of body weight
- The primary end point was safety with efficacy secondary

Safety

AE	Grade 1	Grade 2	Grade 3	Grade 4
CRS				
Total score	10 (50)	8 (40)	1 (5)	1 (5)
Fever	20 (100)	0	0	0
Hypoxia	0	8 (40)	1 (5)	1 (5)
Hypotension	0	0	2 (10)	0
ICANS				
Total score	3 (15)	0	0	0
ICE score	3 (15)	0	0	0
Depressed consciousness	0	0	0	0
Seizure	0	0	0	0
Motor weakness	0	0	0	0
Elevated ICP or cerebral edema	0	0	0	0
GVHD				
Total score	11 (55)	1 (5)	0	0
Skin	12 (60)	0	0	0
Liver	0	1 (5)	0	0
Intestinal	0	0	0	0

Pang J et al.: Journal of Clinical Oncology 39, no. 30 (October 20, 2021) 3340-3351

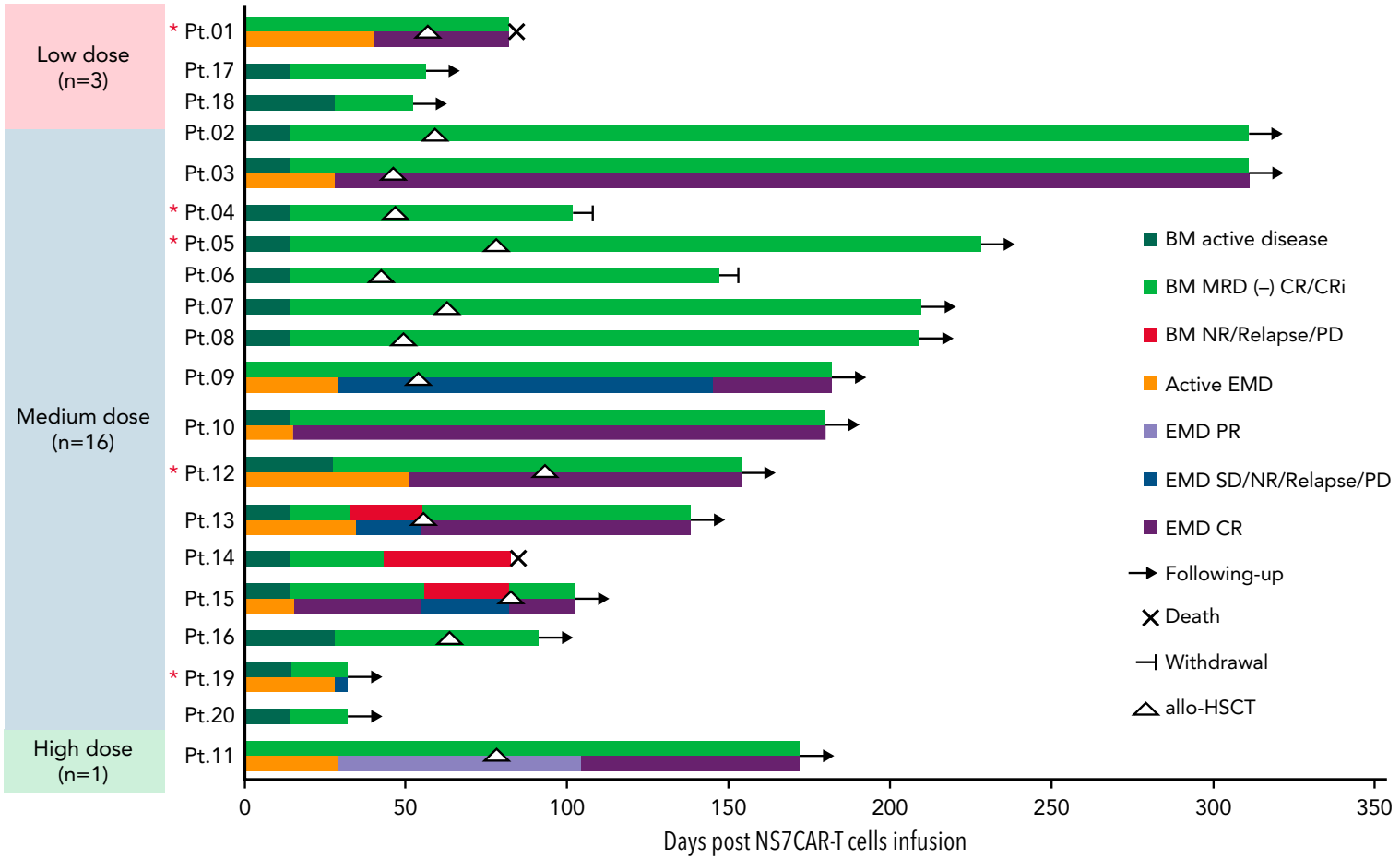
Donor-Derived CD7 Chimeric Antigen Receptor T Cells for T-Cell Acute Lymphoblastic Leukemia: First-in-Human, Phase I Trial



Pang J et al.: Journal of Clinical Oncology 39, no. 30 (October 20, 2021) 3340-3351

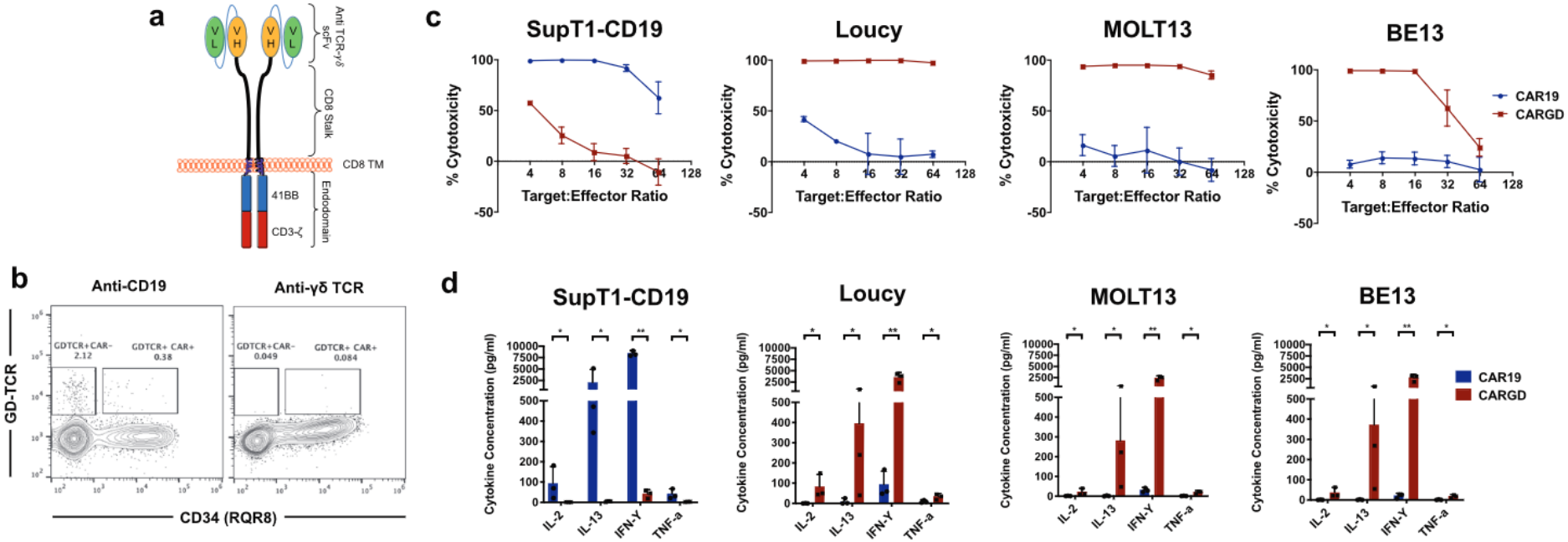
Naturally selected CD7 CAR-T therapy without genetic manipulations for T-ALL/LBL: first-in-human phase 1 clinical trial

- Naturally selected CD7 CAR T cells manufactured without additional genetic manipulations contained a high percentage of CAR1 cells.
- Naturally selected CD7 CAR T cells were safe and effective among T-ALL/LBL patients in a first-in-human phase 1 trial.



Peihua Lu et al.: Blood 140, (2022) 321-334

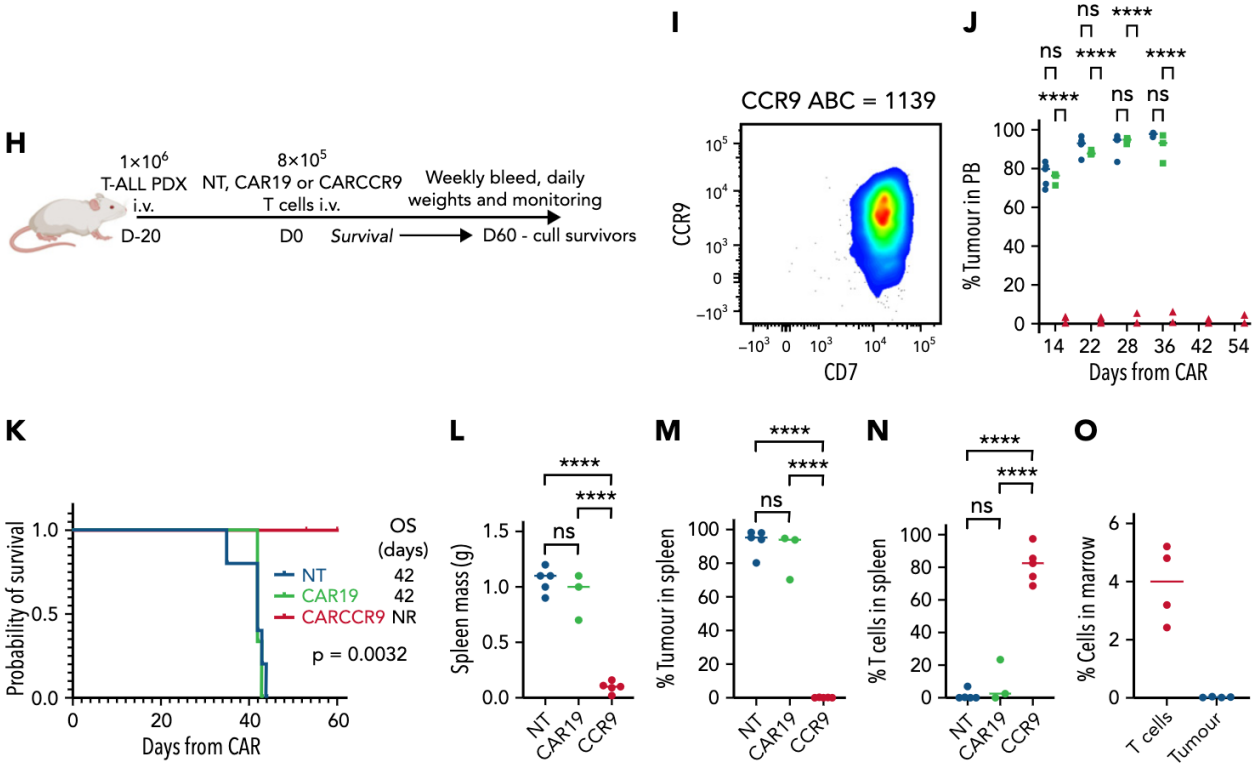
Chimeric antigen receptor T cells for gamma-delta T cell malignancies



P A Wawrzyniecka, L Ibrahim, G Gritti, M A Pule and P M Maciocia: Leukemia 2022 Feb;36(2):577-579

Anti-CCR9 chimeric antigen receptor T cells for T-cell acute lymphoblastic leukemia

- The chemokine receptor CCR9 is expressed in >70% of cases of T-ALL, including >85% of relapsed/refractory disease, and only on a small fraction (<5%) of normal T cells
- CAR-T cells targeting CCR9 are resistant to fratricide and have potent antileukemic activity both in vitro and in vivo
- anti-CCR9 CAR-T cells could be a highly effective treatment strategy for T-ALL, avoiding T cell aplasia and the need for genome engineering that complicate other approaches



PM Maciocia et al: Blood 2022 Jul 7;140(1):25-37.

Conclusions

- CAR-T cells are changing the treatment landscape of hematologic malignancies
- In ALL results are less impressive and patients can require a subsequent allogeneic transplant after achieving a complete hematologic response
- Rapid progress is ongoing with new generation of autologous CAR-T cells
- The use of different cell platforms and allogeneic donors is rapidly expanding including the setting of T-ALL