Il futuro del trapianto di cellule staminali allogeniche

Alessandro Rambaldi

UNIVERSITÀ DEGLI STUDI DI MILANO

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Conflict of interest

Fees for consultancies and participation into meetings, boards and symposia sponsored by

- Jazz
- Pfizer
- Astellas
- Abbvie
- Novartis
- Amgen
- Incyte
- Omeros
- Roche
- Celgene BMS
- Sanofi

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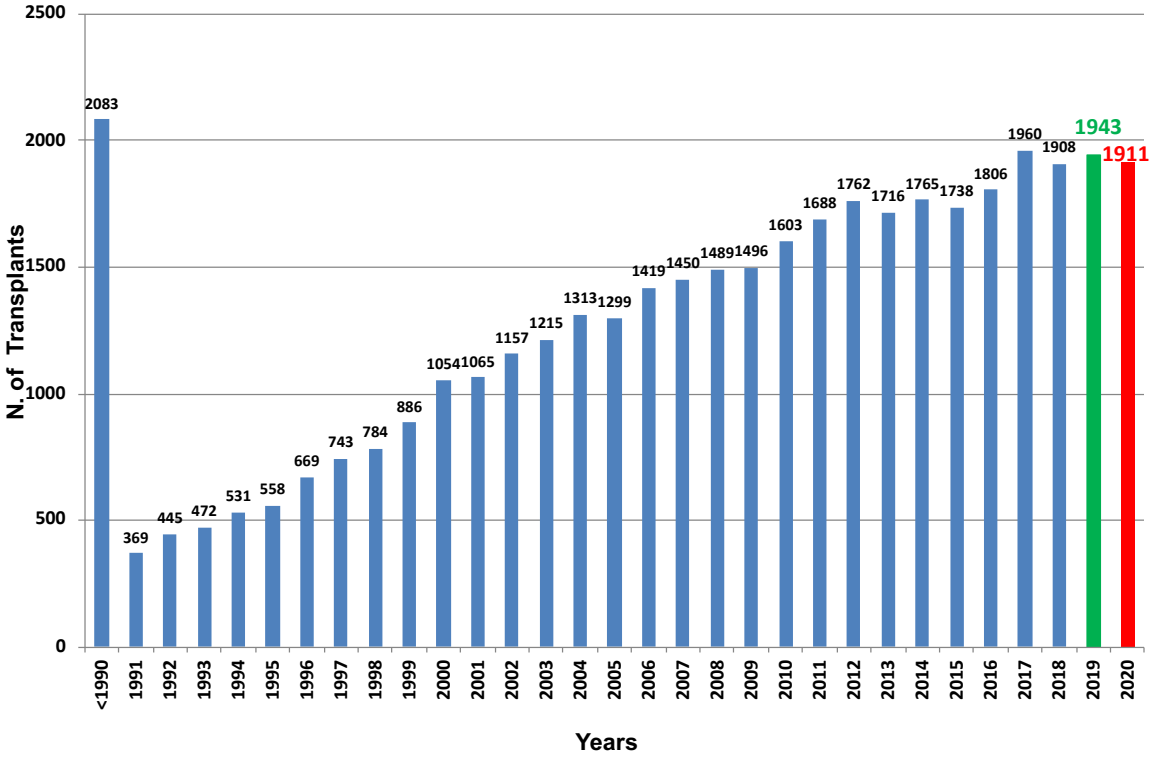
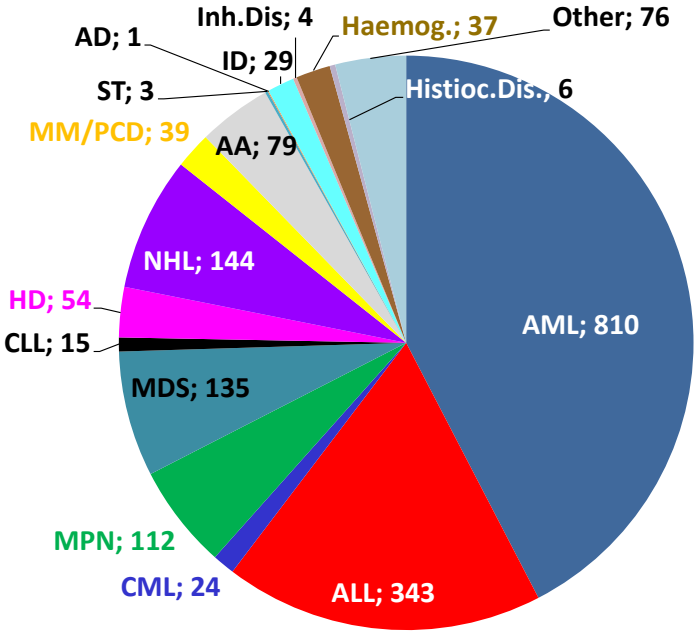
Attività di Trapianto allogenico in Italia
Procedure (N= > 41000) e Indicazioni

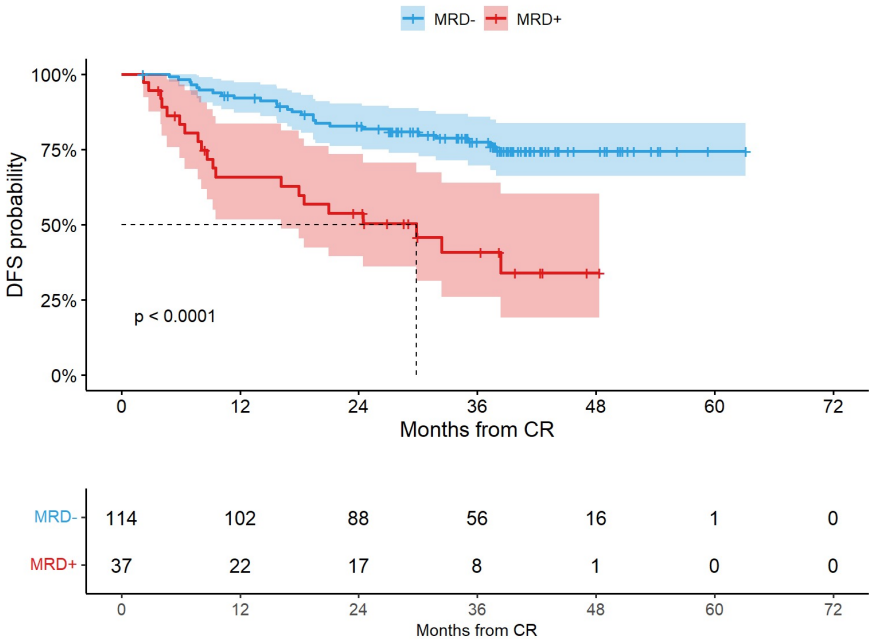




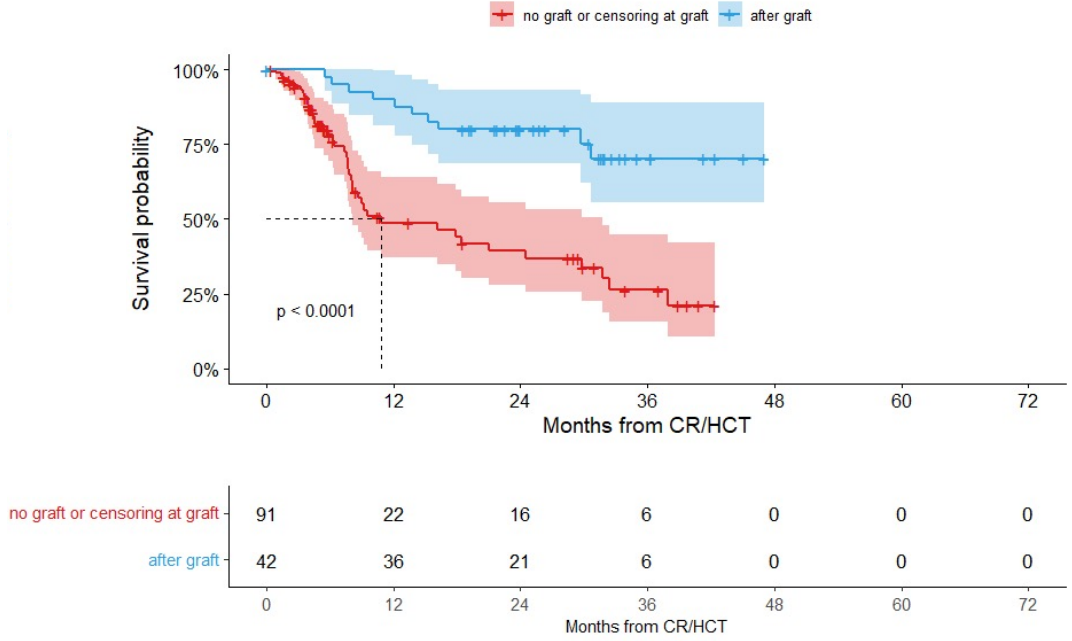
GITMO

National Pegaspargase-modified risk-oriented program for Ph-negative ALL/LL: GIMEMA LAL 1913 final results

DFS by MRD response



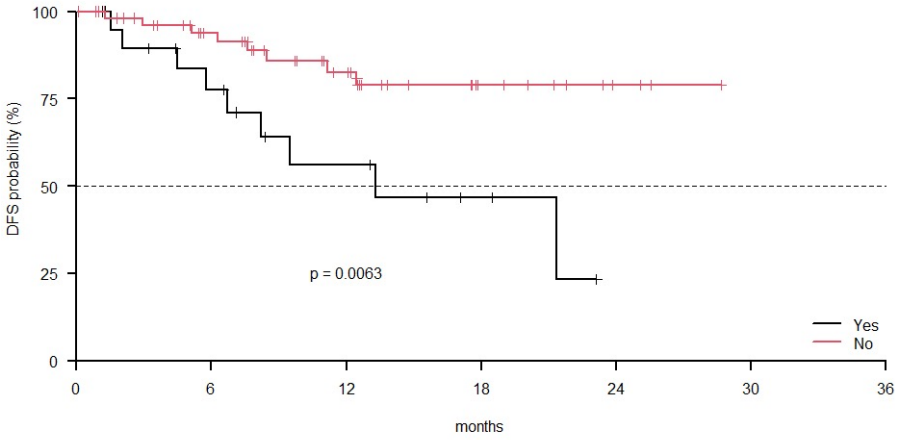
DFS by HCT (ITT, time-dependent Simon–Makuch plot)



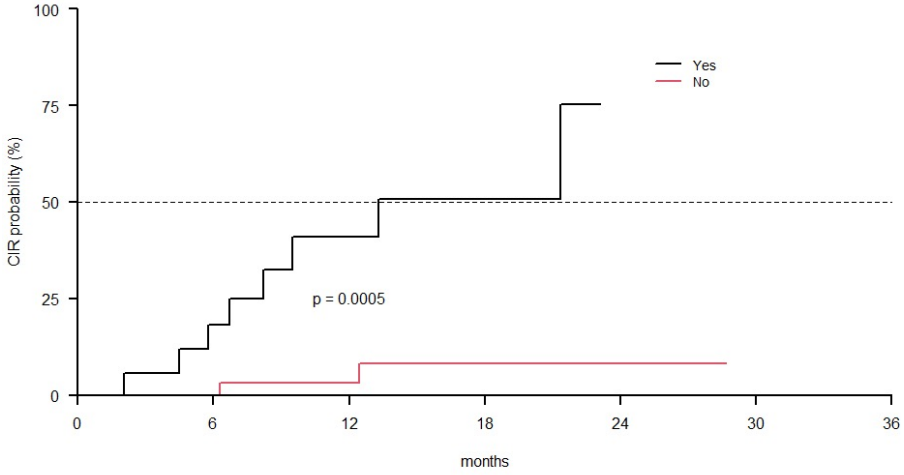
Bassan R, et al. EHA 2022; Abstract S113 and oral presentation.

Outcome according to Ph-like signature

Disease-free survival by Ph-like signature



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

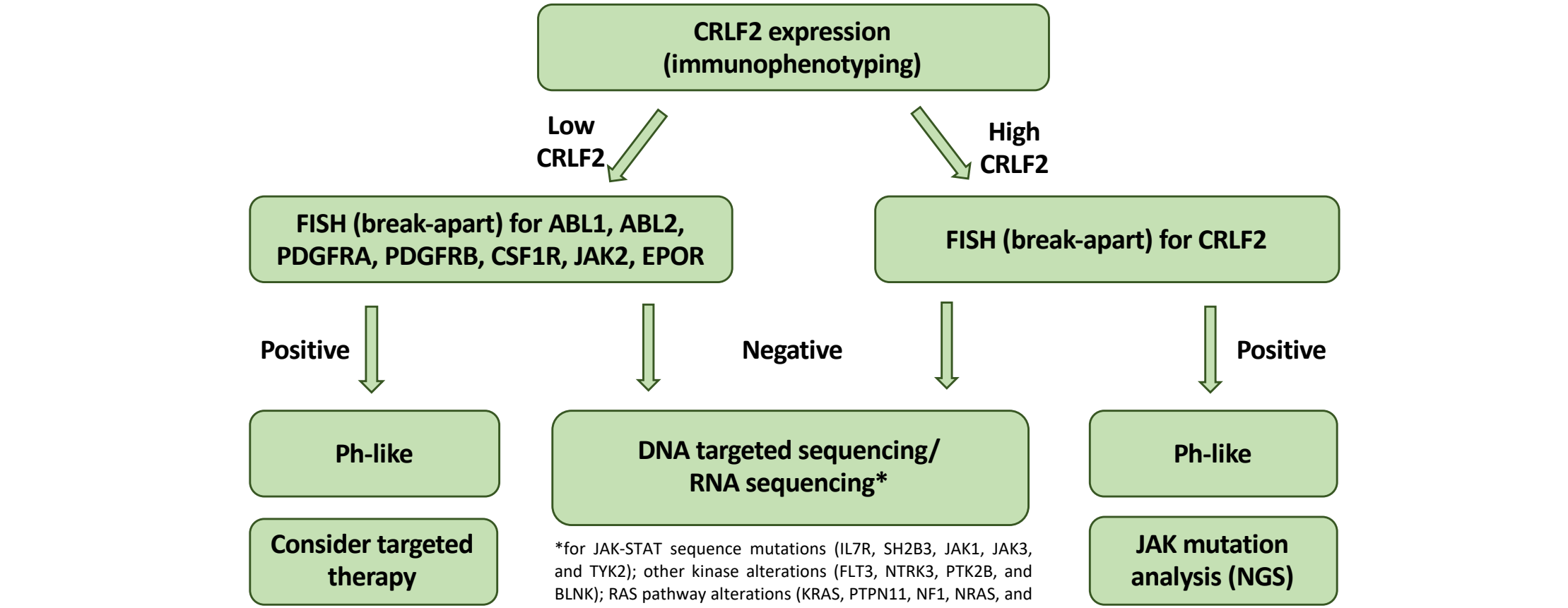


1-year relapse rate:	Ph-like	40.1%
	Not Ph-like	3.2%

P=0.0005

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

Screening of newly diagnosed cases of ALL

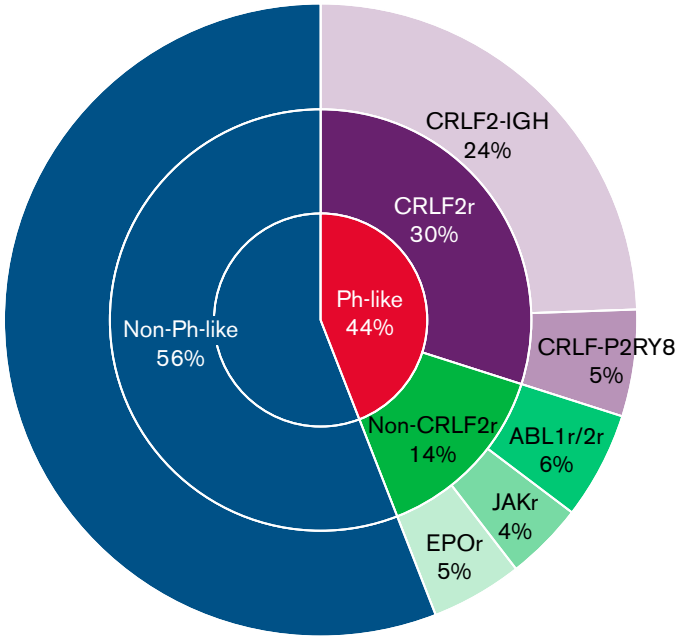


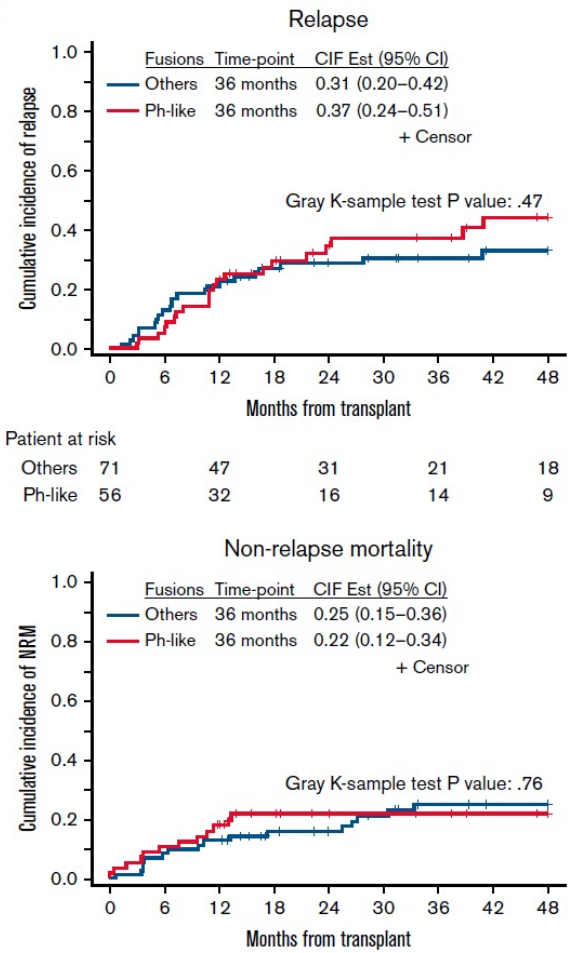
*for JAK-STAT sequence mutations (IL7R, SH2B3, JAK1, JAK3, and TYK2); other kinase alterations (FLT3, NTRK3, PTK2B, and BLNK); RAS pathway alterations (KRAS, PTPN11, NF1, NRAS, and CBL)

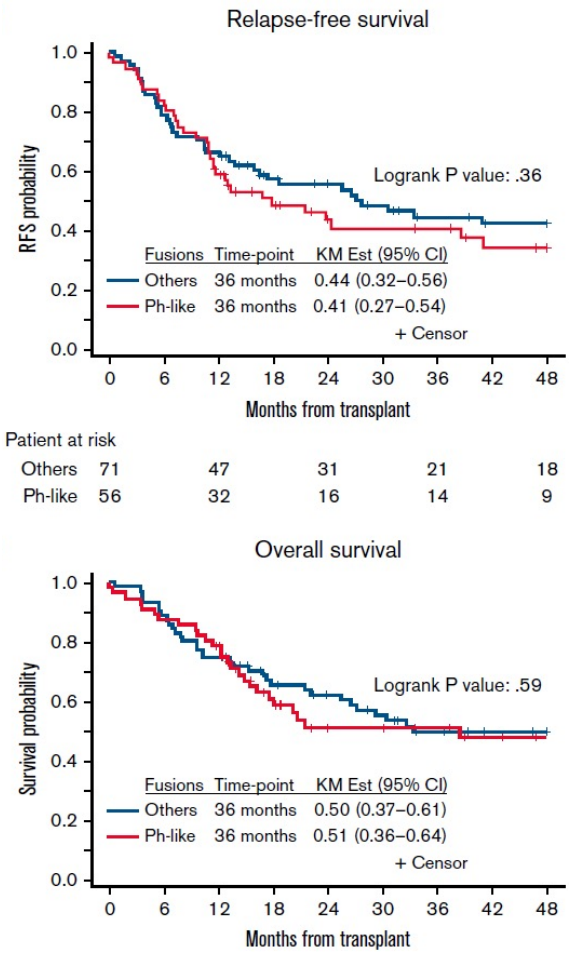
Harvey RC, Tasian SK. Blood Adv 2020;4:218–28;
Frisch A, Ofran Y. Haematologica 2019;104:2135–43.

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

Frequency of genomic alterations (adults with Ph-like ALL)

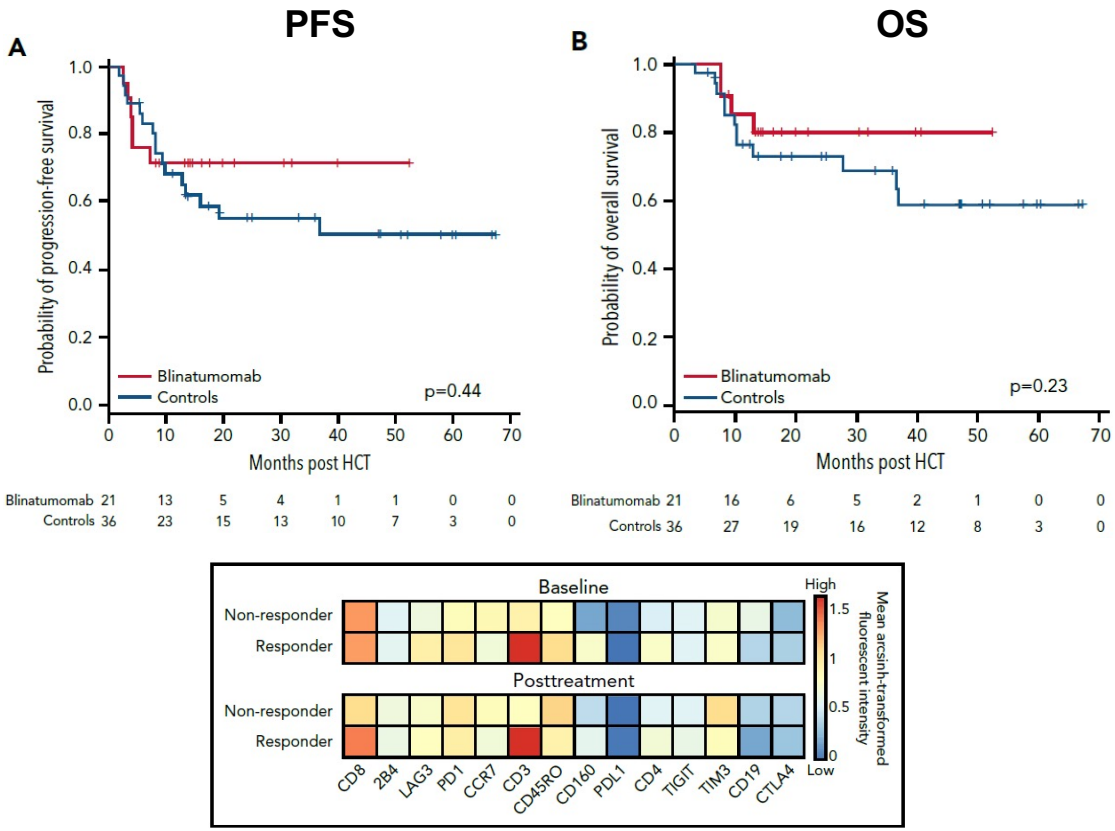






Aldoss I, et al. Blood Adv 2022;6:4936–48.

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

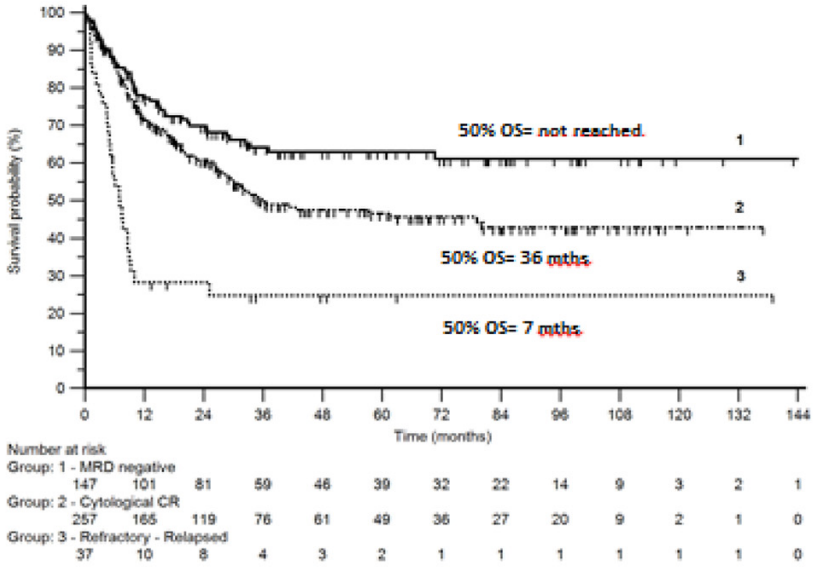


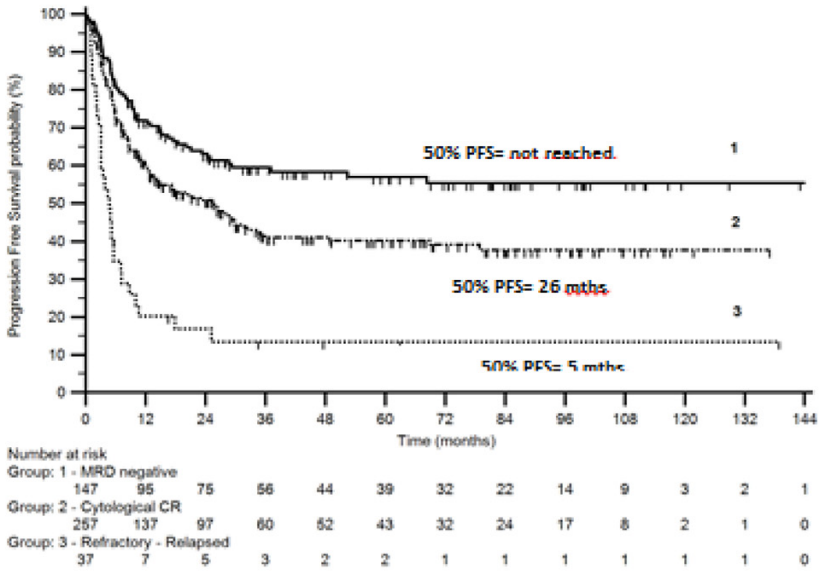
Main results

- 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 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 may be indicative of whether they will respond to blinatumomab

Gaballa MR, et al. Blood 2022;139:1908–19.

A challenging choice: consolidation in Ph+ ALL

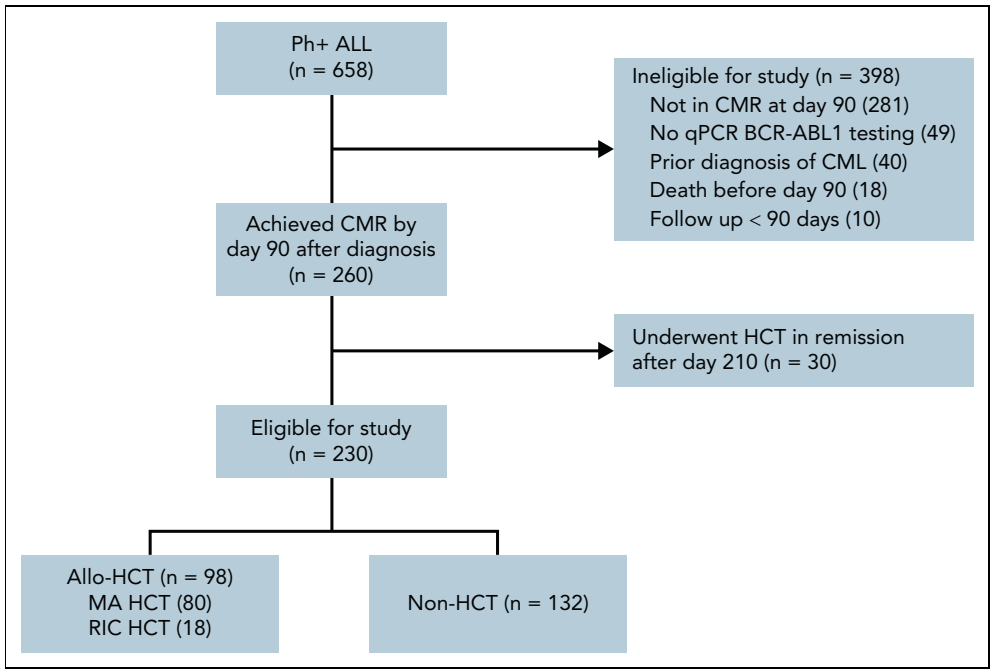


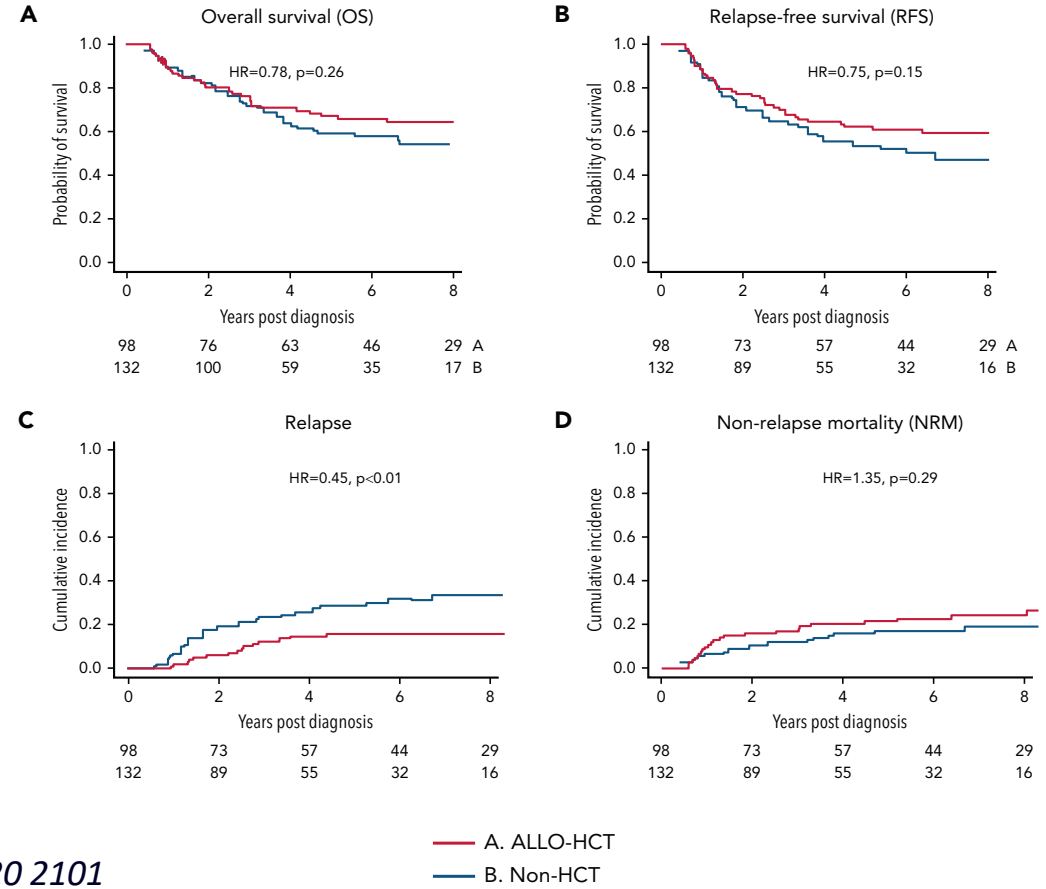


Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Ph+ ALL in the Era of Tyrosine Kinase Inhibitors: A Registry-Based Study of the Italian Blood and Marrow Transplantation Society (GITMO)

Candoni A et al.: Biol Blood Marrow Transplant 25 (2019) 2388-2397

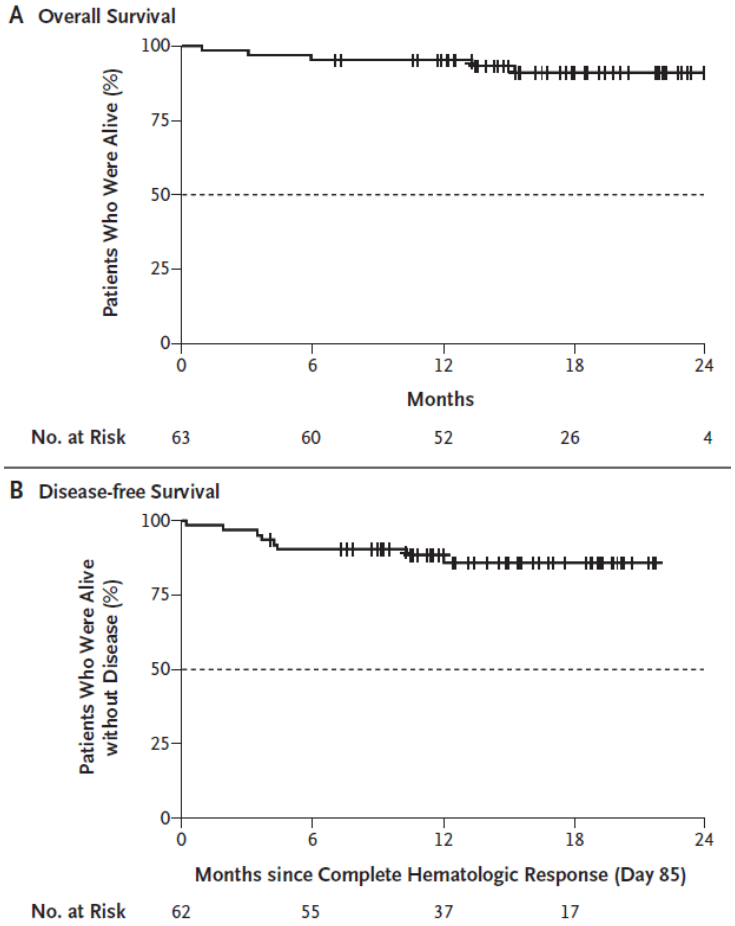
The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis





Ghobadi A et al.: Blood 17 november 2022 | volume 140, number 20 2101

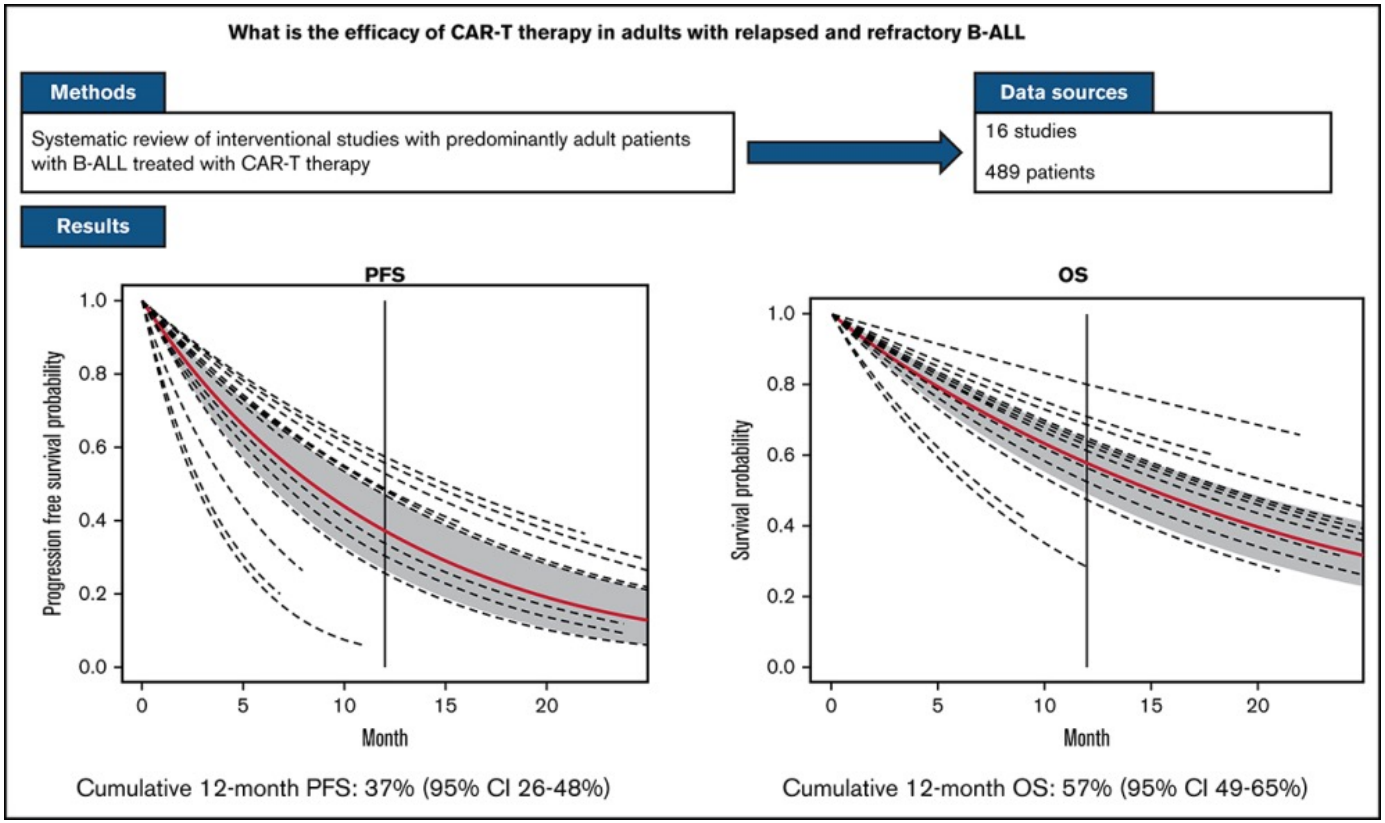
D-ALBA: results



- At the end of the second cycle of blinatumomab, a molecular response was reported in **52%** of patients that further increased at **81%** after the fourth cycle
- The 18-month OS and RFS were **95%** and **88%**, respectively
- **Very low non-relapse mortality** : 1/24 **(4%)** patients who received allografts from veno-occlusive disorder

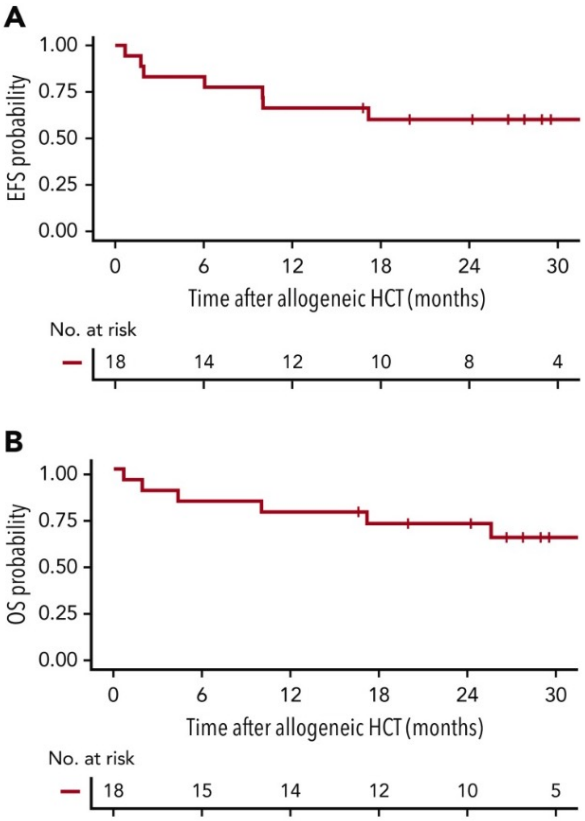
Foà, et al. N Engl J Med. 2020

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

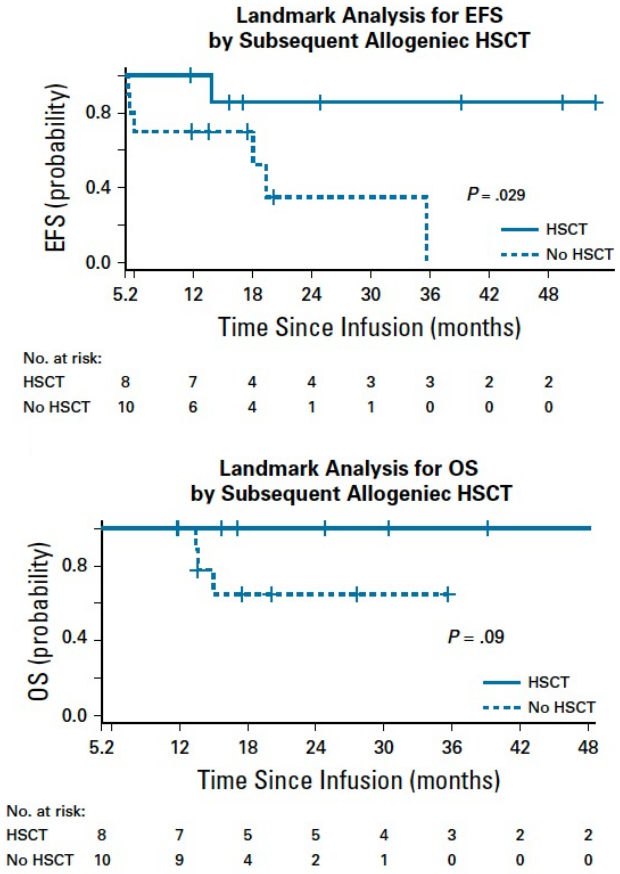


Punita Grover et al. Blood Adv, 2022

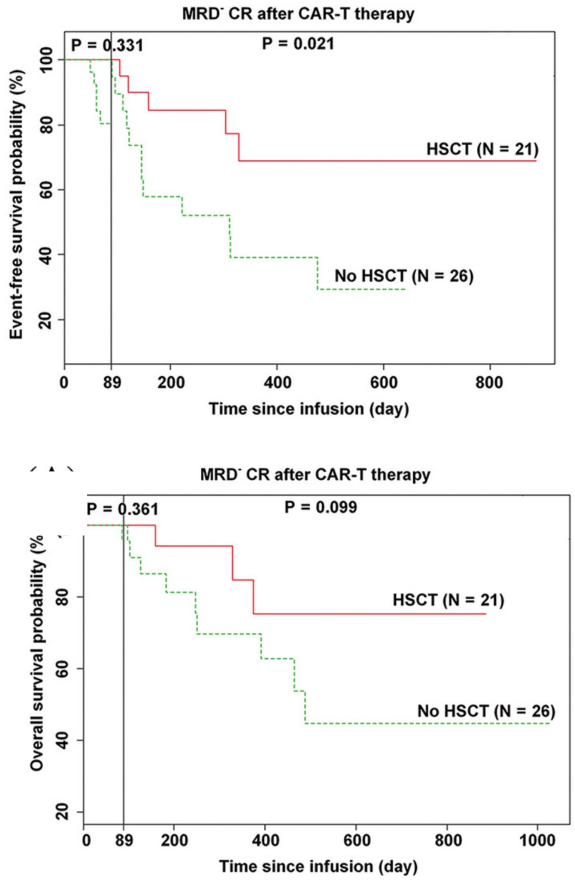
HCT may improve EFS following CD19 CAR in some published studies



Hay, et al. Blood 2019

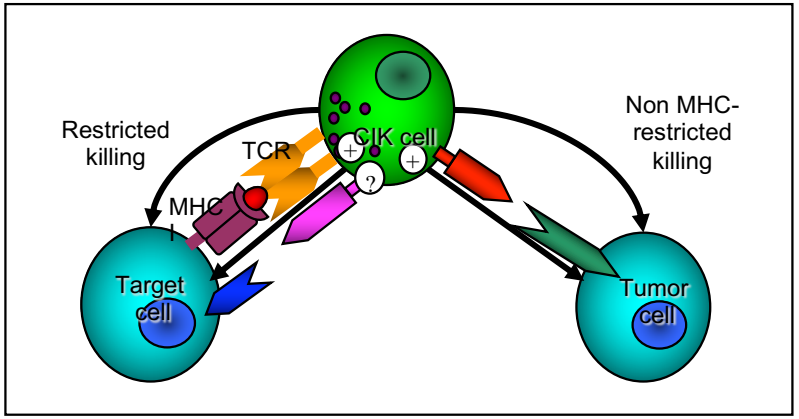


Frey, et al. JCO 2020



Jiang, et al. AJH 2019

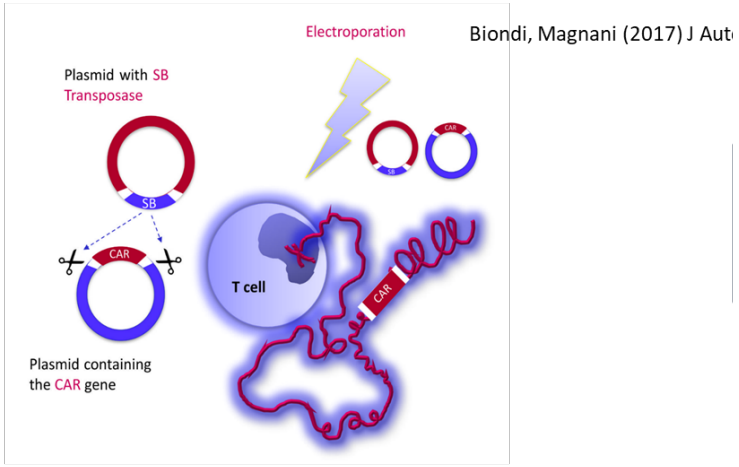
Sviluppo di cellule CAR-T allogeniche in Italia: un network lombardo



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

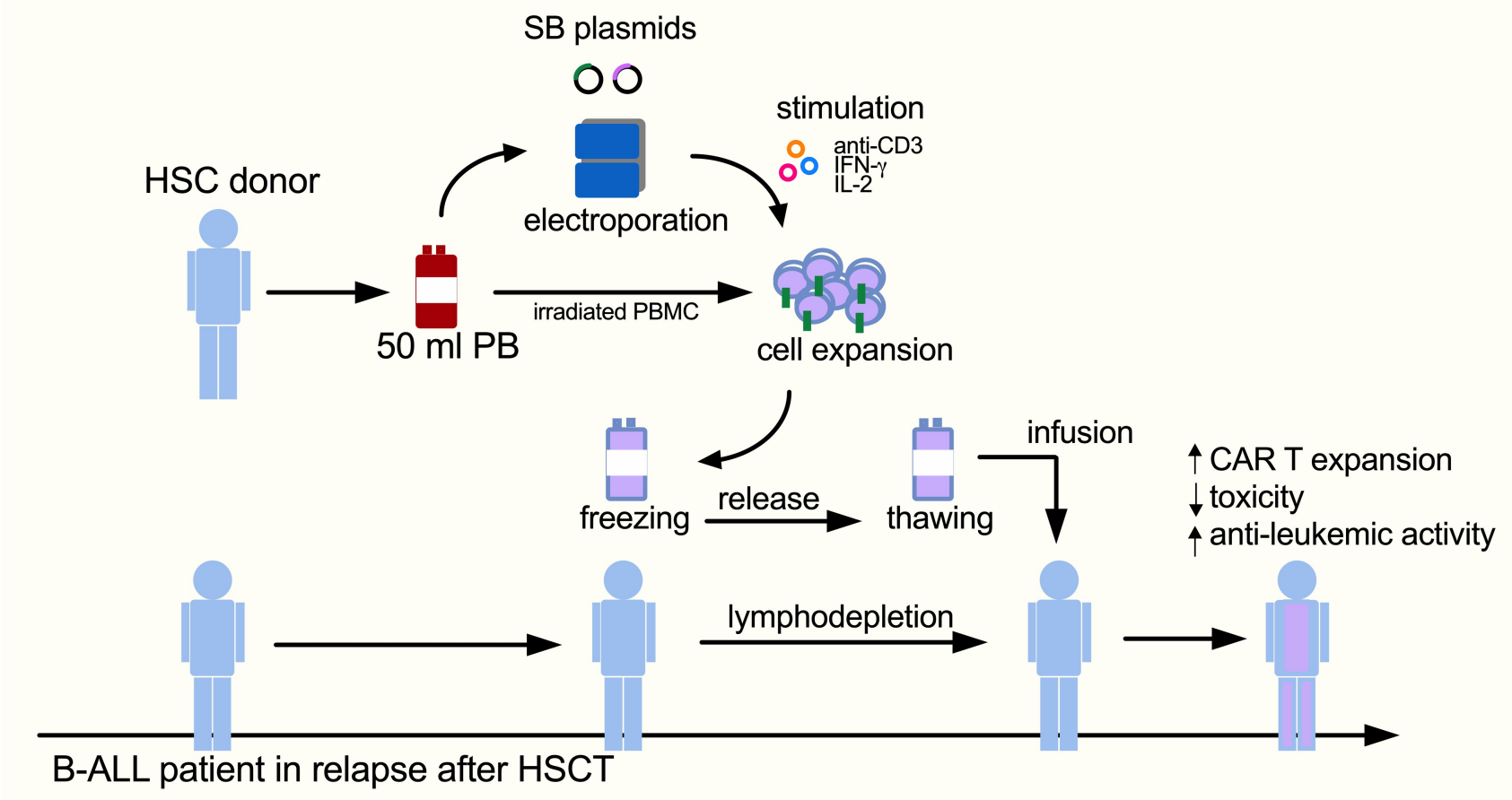
Non-viral vector to generate CAR-CIK cells



Biondi, Magnani (2017) J Aut

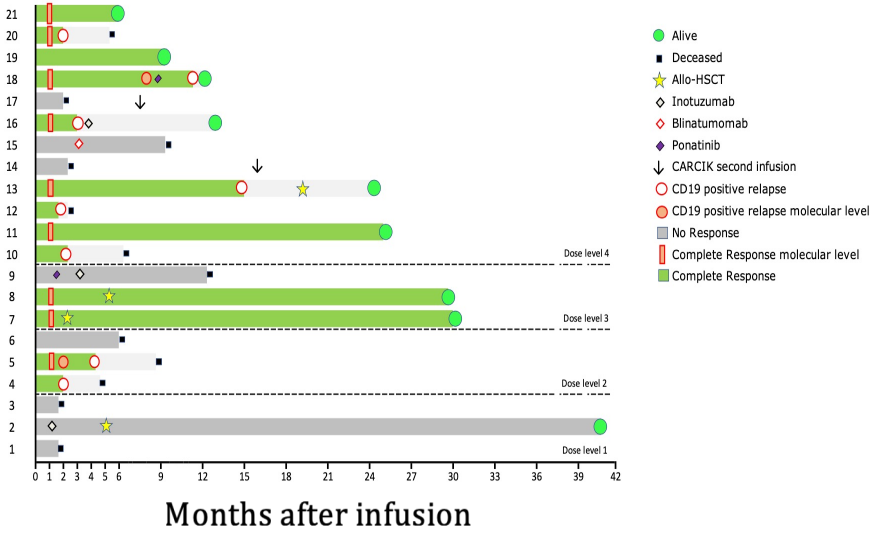
WO2016/071513; Magnani CF, Oncotarget. 2016;7(32):51581-51597; Turazzi N, Br J Haematol. 2017;182(6):939-943; Magnani CF, Hum Gene Ther. 2018; 29(5):602-613; Rotiroti MC, Mol Ther. 2020 Sep 2;28(9):1974-1986

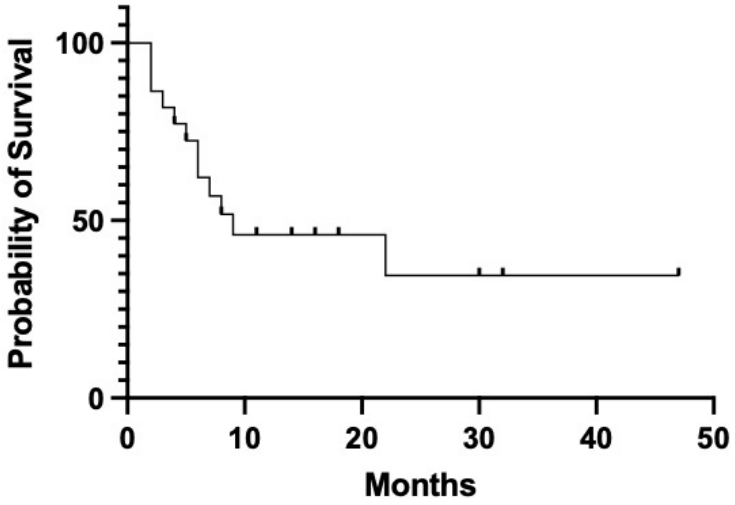
SLEEPING BEAUTY-ENGINEERED CARCIK CELLS ACHIEVE ANTI-LEUKEMIC ACTIVITY WITHOUT SEVERE TOXICITIES



Magnani, J Clin Invest. 2020

RESPONSE DATA AND SURVIVAL



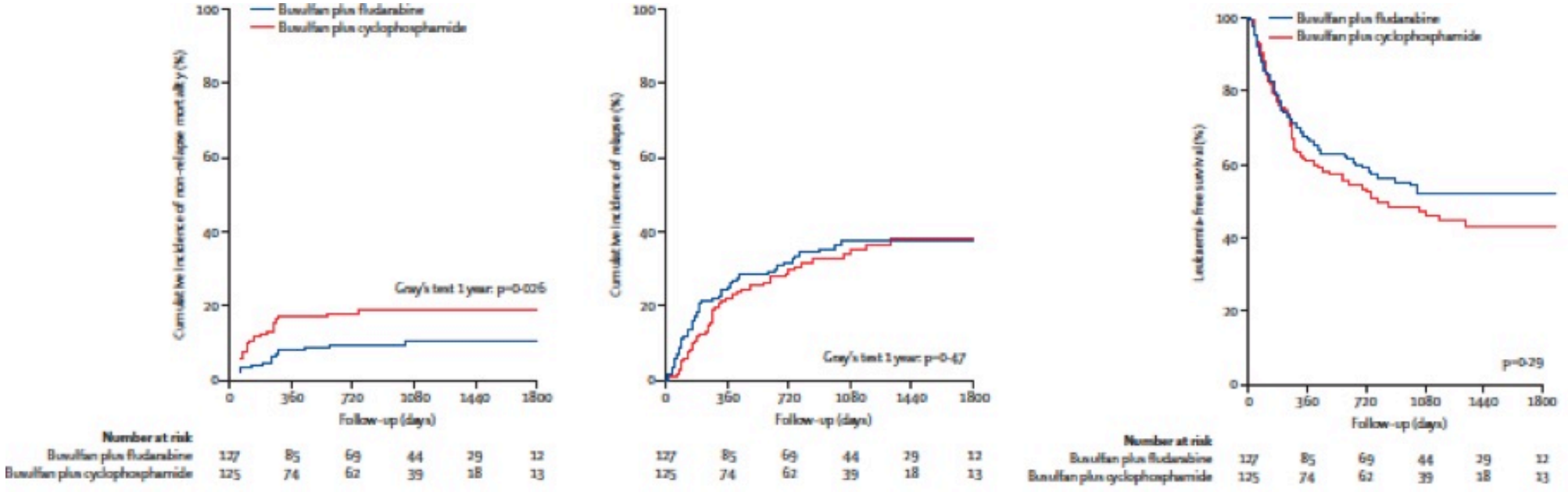


77% achieved a CR, of these 76% were MRD negative

@ 12 mo OS: 43%

Lussana F et al.: ASH 2022

In AML AlloHSCT is the most effective consolidation treatment but leukemia relapse remains high



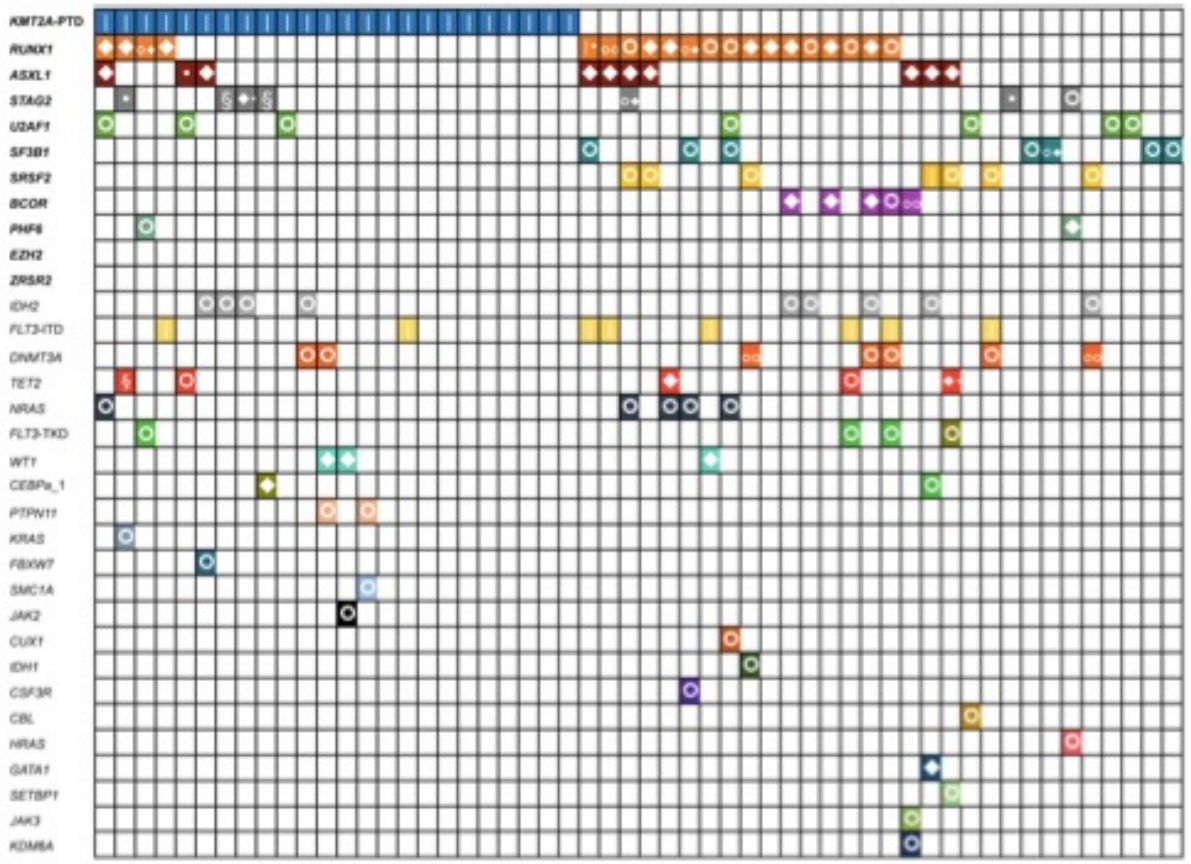
A. Rambaldi et al.: The Lancet Oncology, 2015

How to improve these results

1. Accurate definition of the disease biology
2. Reducing the tumor burden (MRD)
3. Reducing the incidence of refractory AML
4. Improving the conditioning regimen
5. Making alloHSCT a platform for further treatments (post transplant strategies)

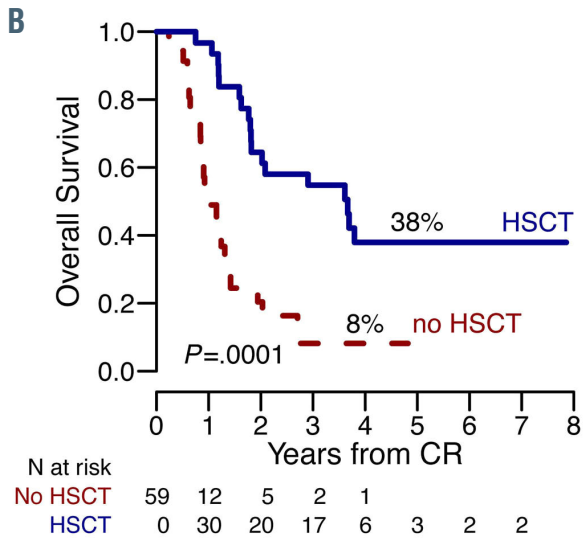
Clinical significance of chromatin-spliceosome AML: a report from the NILG randomized trial 02/06

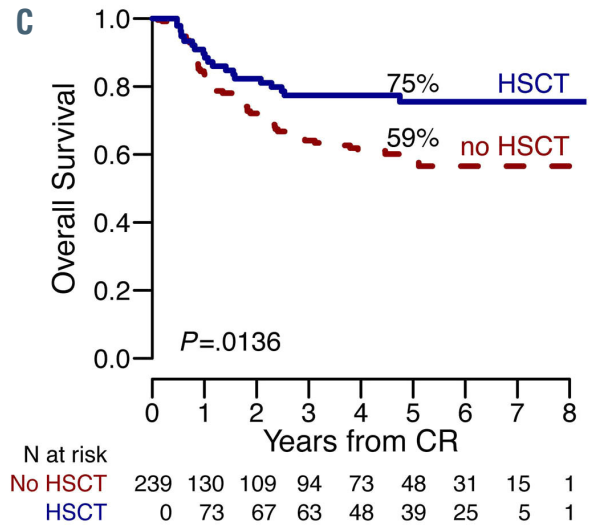
- We analyzed a prospective cohort of 413 newly diagnosed AML patients who were enrolled in a randomized clinical trial (NILG AML 02/06)
- Among clinically defined *de novo* AML, 17.6% carried CS mutations (CS-AML) and showed clinical characteristics closer to sAML (older age, lower white blood cell counts and higher rate of multilineage dysplasia)



Caprioli C et al.: Haematologica 2021 Volume 106(10):2578-2587

Clinical significance of chromatin-spliceosome AML: a report from the NILG randomized trial 02/06

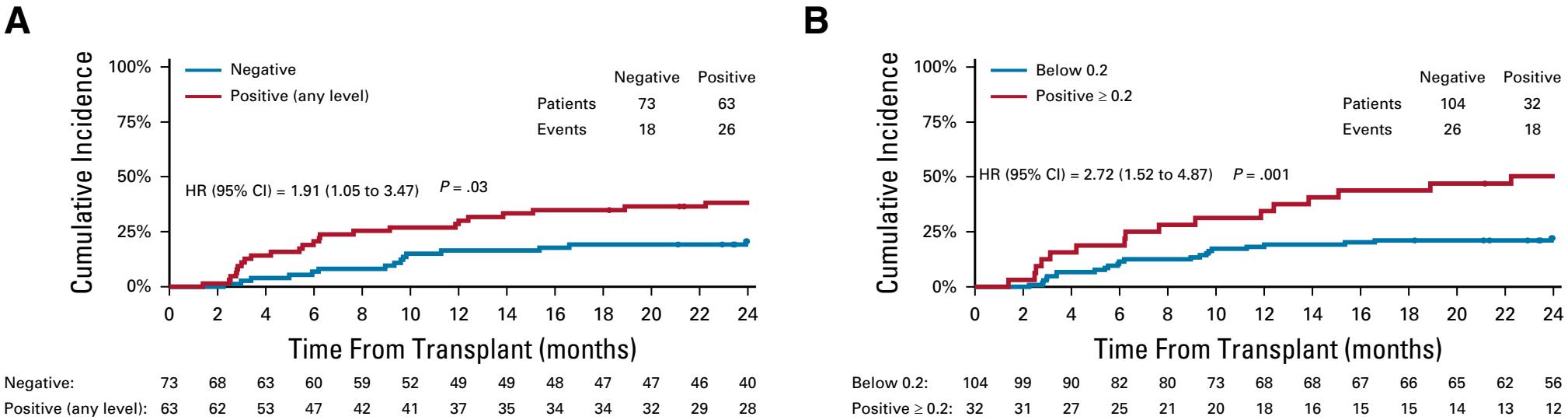




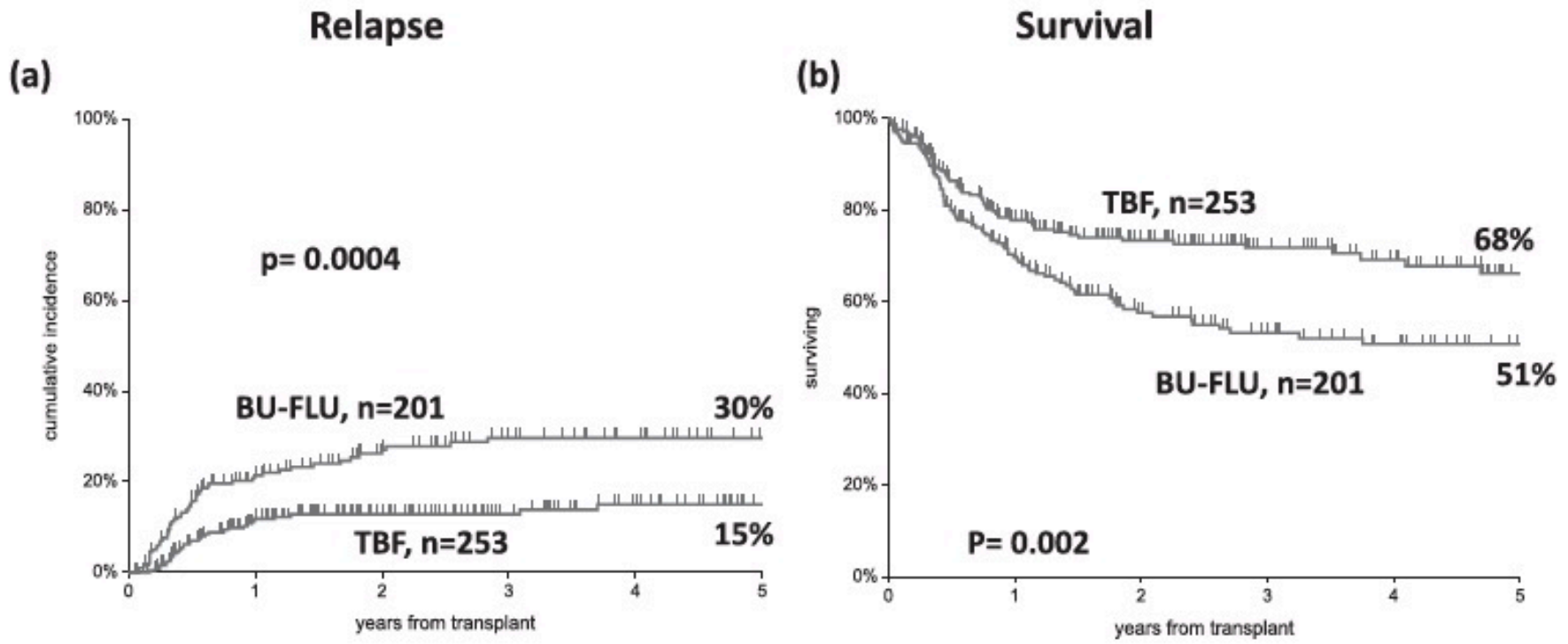
Transplant was considered as a time-dependent event

Caprioli C et al.: Haematologica 2021 Volume 106(10):2578-2587

Cumulative incidence of relapse by conventional MFC-MRD status



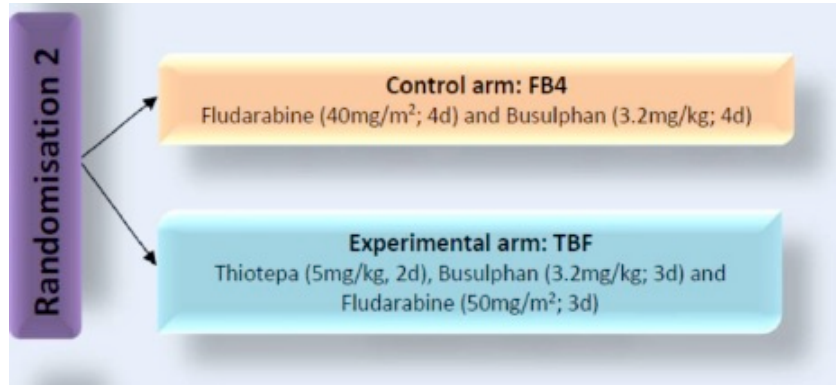
Cumulative incidence of relapse (a) and survival (b) for patients, with AML receiving TBF or BUFLU

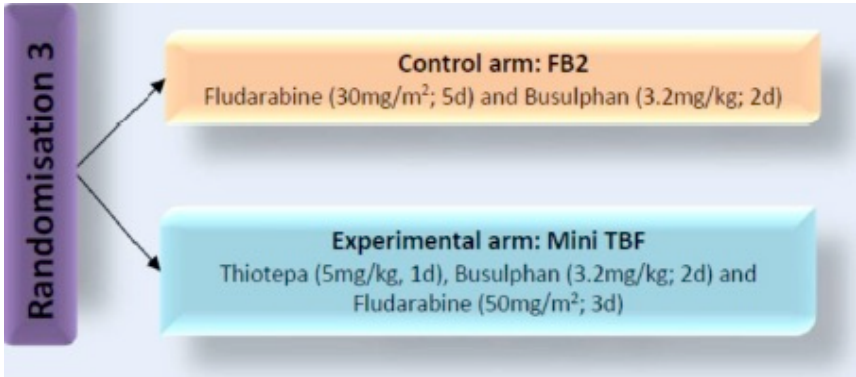


Sora F et al.: BBMT Biol Blood Marrow Transplant 26 (2020) 698703

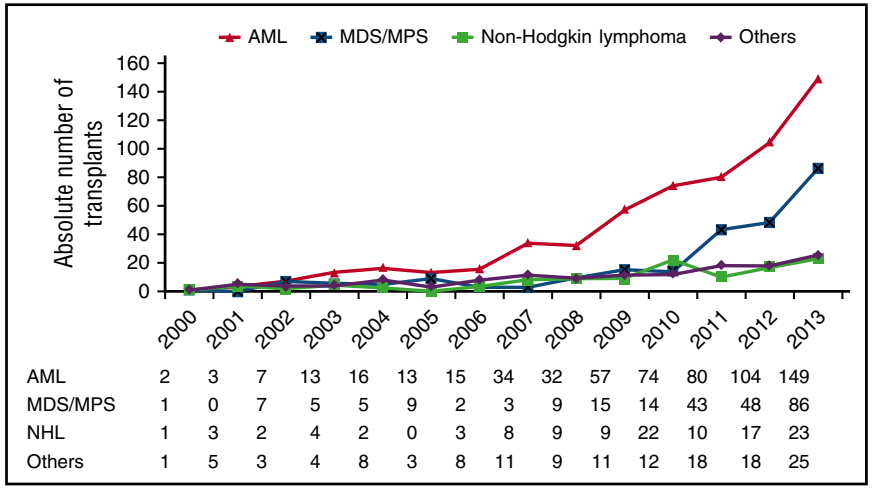
An International Randomised Clinical Trial of Therapeutic Interventions with the Potential to Improve Outcome in Adults with Acute Myeloid Leukaemia and High-Risk Myelodysplasia Undergoing Allogeneic Stem Cell Transplantation (COSI)

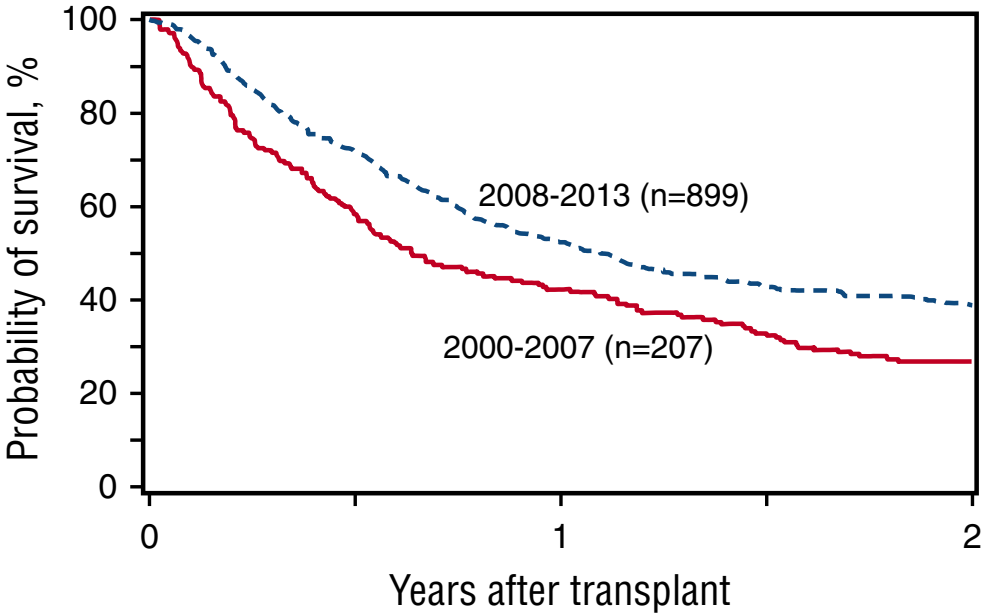
- **Chief Investigator: Professor Charles Craddock**
- **Sponsor: University of Birmingham**
- **EudraCT number: 2017-004801-42**
- **ClinicalTrials.gov number: NCT04217278**





HCTs in patients 70 years and older





Muffly, L. Et al.: Blood. 2017;130(9):1156-1164

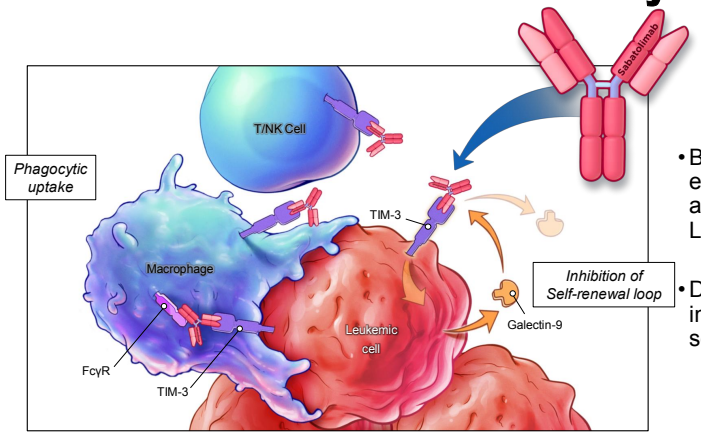
AlloHSCT as a platform for subsequent treatments

A Phase Ib/II, open label study of sabatolimab as a treatment for patients with AML and presence of measurable residual disease after allogeneic stem cell transplantation

(ClinicalTrials.gov Identifier: NCT04623216)

- Sabatolimab is a humanized, IgG4 (S228P) antibody targeting TIM-3.
- TIM-3 is expressed on immune cells as well as leukemic stem cells (LSCs) and blasts, but not normal hematopoietic stem cells.
- Sabatolimab is a potential first-in-class immunotherapeutic.
- Blockade of TIM-3 by sabatolimab may restore immune function while also directly targeting LSCs and blasts.

Sabatolimab targets TIM-3 on immune and leukemic cells: a novel immuno-myeloid therapy



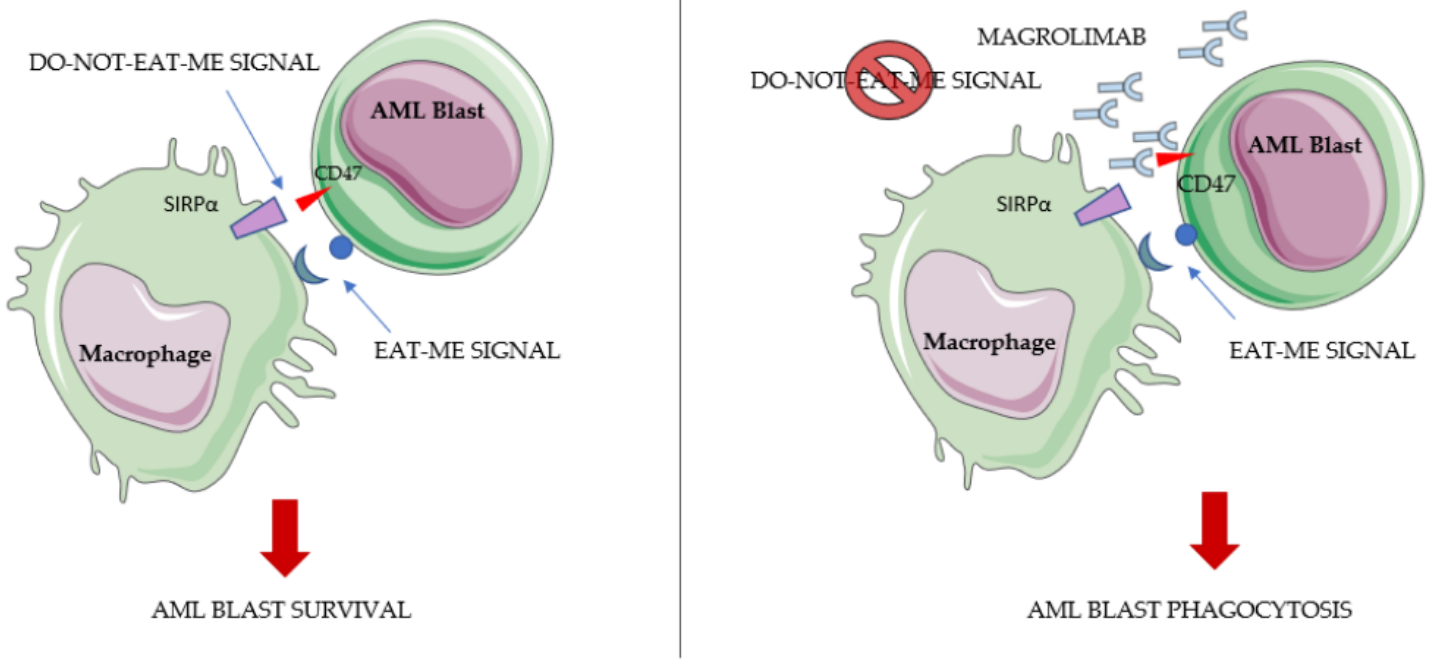
Sabatolimab

- Binds TIM-3 on immune cells, enhancing antileukemic immune activation and phagocytic killing of LSCs and blasts[1-4]
- Directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

FcγR, Fc gamma receptor.

1. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 2. Sabatos-Peyton C, et al. SITC 2020. Abstract 439; 3. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):Abstract S185; 4. Borate U, et al. EHA 2020. Oral presentation.

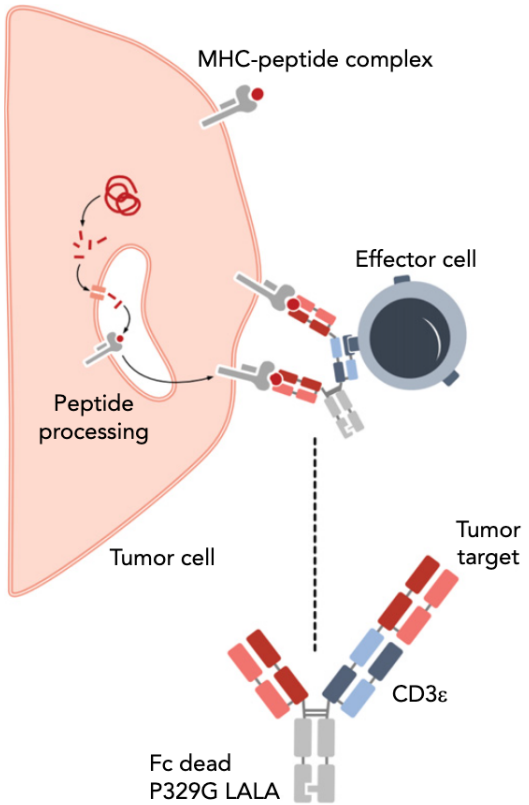
Magrolimab



Andreozzi, F.et al.: Int. J. Mol. Sci.2022,23,3887

Targeting intracellular WT1 in AML with a novel RMF-peptide-MHC-specific T-cell bispecific antibody

- Key Points
  - A T-cell bispecific antibody targeting intracellular WT1 presented on HLA-A2 for treatment of AML
  - The novel, clinical-stageWT1-TCB mediated high-level killing of primary AML cells, which was enhanced by the addition of lenalidomide
  - These properties led to the initiation of an entry-into-human clinical trial (#NCT04580121) for the treatment of relapsed/refractory AML

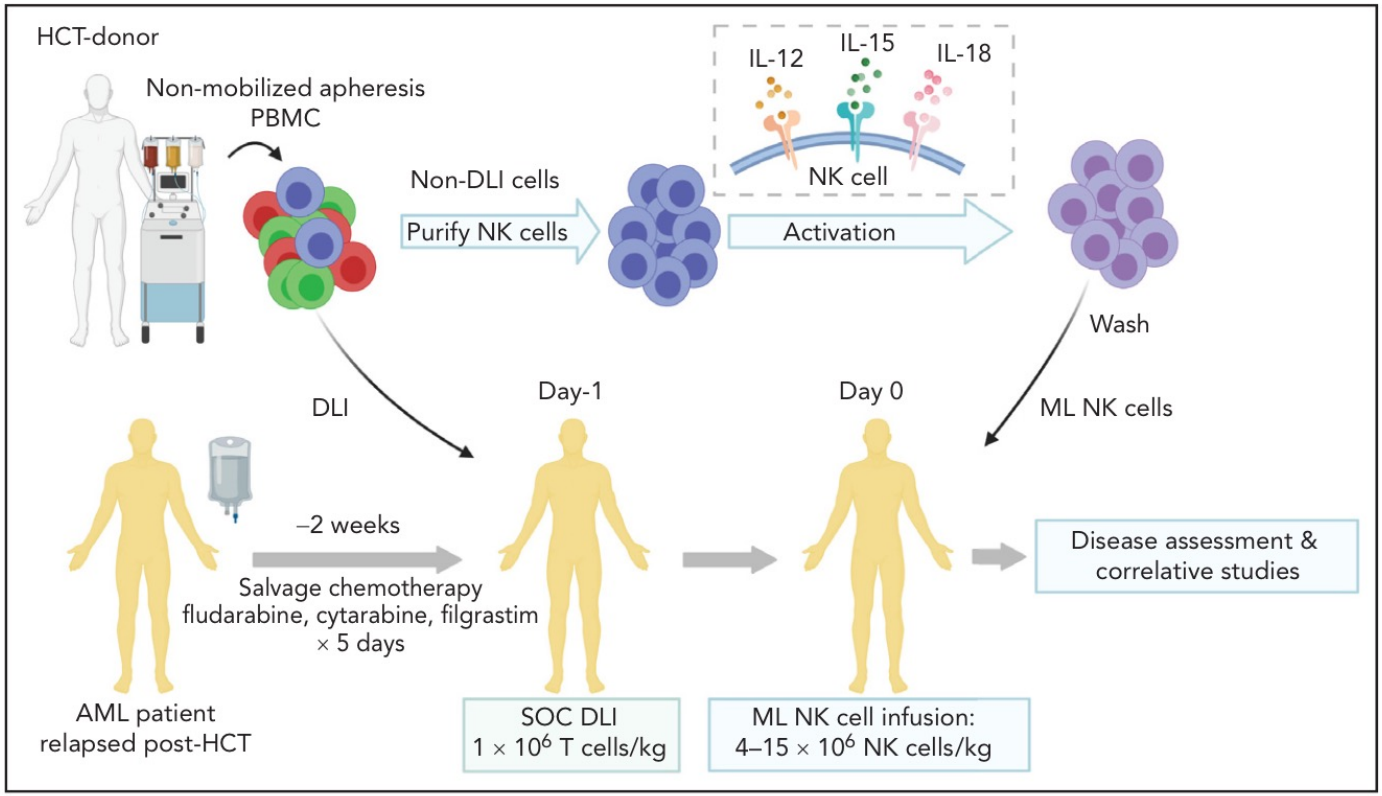


Augsberger C et al.: Blood 138, 25, 2655-2669, 2021

Cellular Therapies in AML

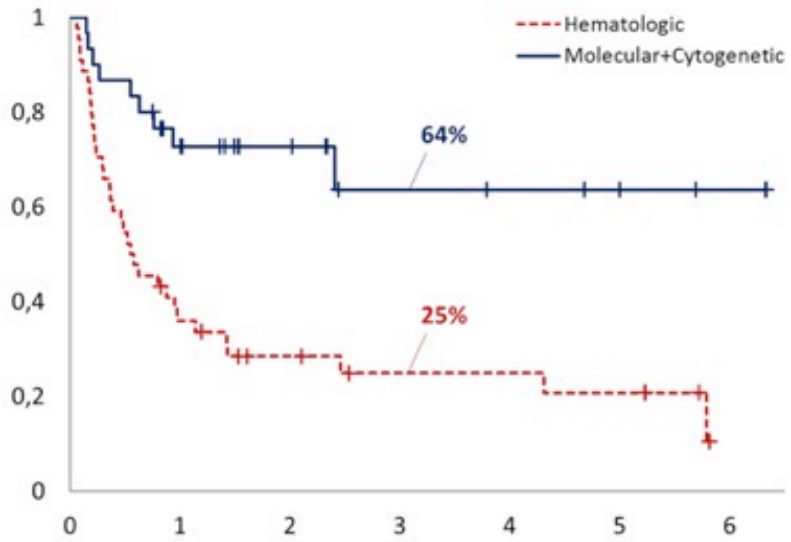
IMMUNOBIOLOGY AND IMMUNOTHERAPY

Donor memory-like NK cells persist and induce remissions in pediatric patients with relapsed AML after transplant

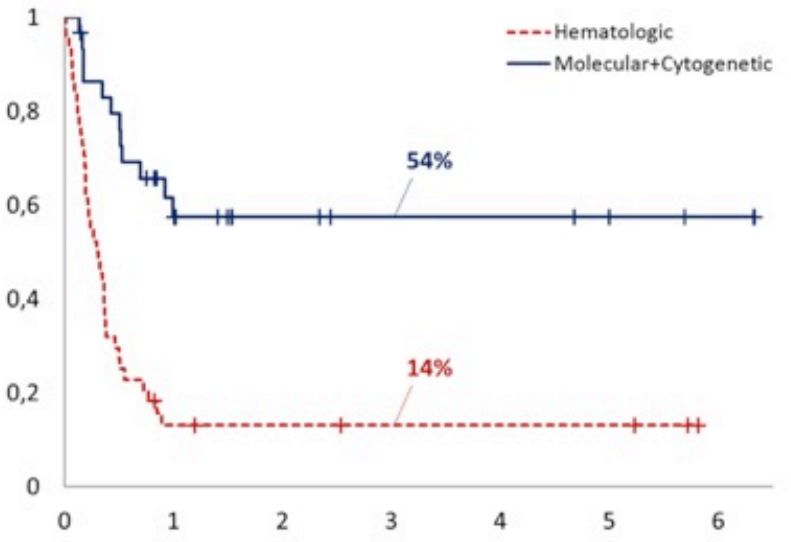


Bednarski J.J. et al *Blood* 2022

Clinical outcome after the sequential Infusion of Donor Lymphocyte Infusion and Cytokine-Induced Killer Cells



N at risk (events)													
Hematologic	44	(28)	15	(3)	9	(1)	6	(0)	6	(1)	5	(1)	0
Molec+Cytog	30	(8)	19	(0)	12	(1)	6	(0)	5	(0)	3	(0)	2



N at risk (events)													
Hematologic	44	(38)	5	(0)	4	(0)	3	(0)	3	(0)	3	(0)	0
Molec+Cytog	30	(12)	14	(0)	8	(0)	5	(0)	5	(0)	3	(0)	2

Introna M., Lussana F . Et al. : Biology of Blood and Marrow Transplantation 2017

Split Dual-CAR CIK for the targeting of R/R AML

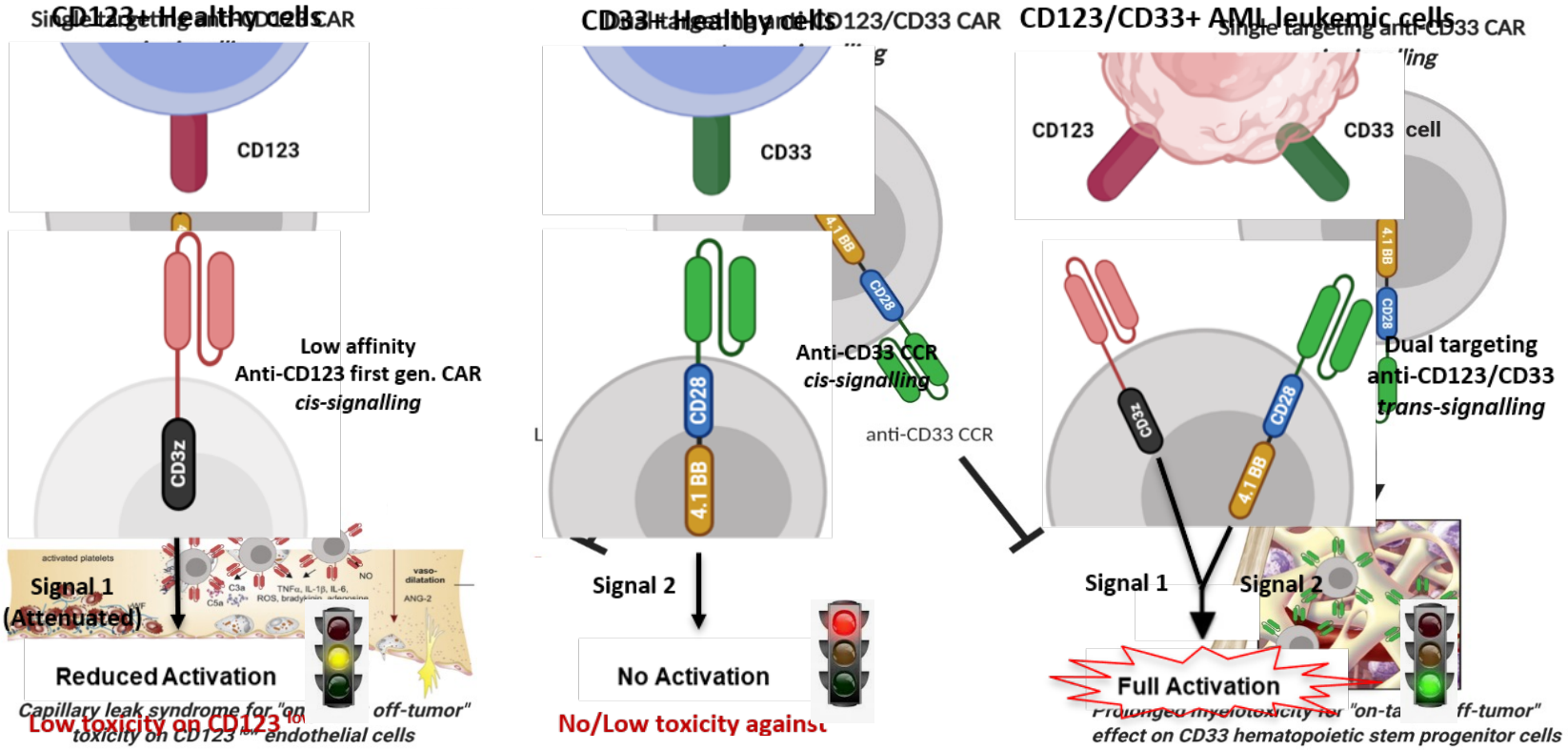
AML

Target selection

CAR design

Gene engineering

Manufacturing



By courtesy of S. Tettamanti and A. Biondi