La strategia di trattamento “Risk-adapted” e il ruolo del trapianto allogenico di cellule staminali emopoietiche nelle LAL

Federico Lussana
Dipartimento di Oncologia e Ematologia– Università di Milano
ASST Ospedale Papa Giovanni XXIII, Bergamo

Disclosures of Federico Lussana

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					✔	✔	
Amgen					✔	✔	
Clinigen						✔	
Incyte					✔		
Jazz					✔		
Pfizer					✔	✔	

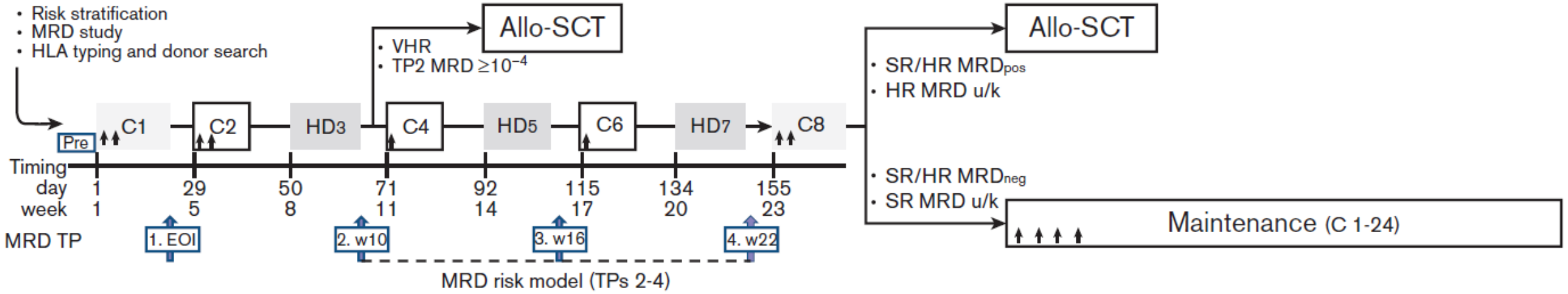
Program Overview

1. Indication for allogeneic stem cell transplantation in Ph-negative ALL

2. Is alloHSCT for Ph+ ALL in CR1 still necessary?

3. The role of alloHSCT after CAR-T cell therapy

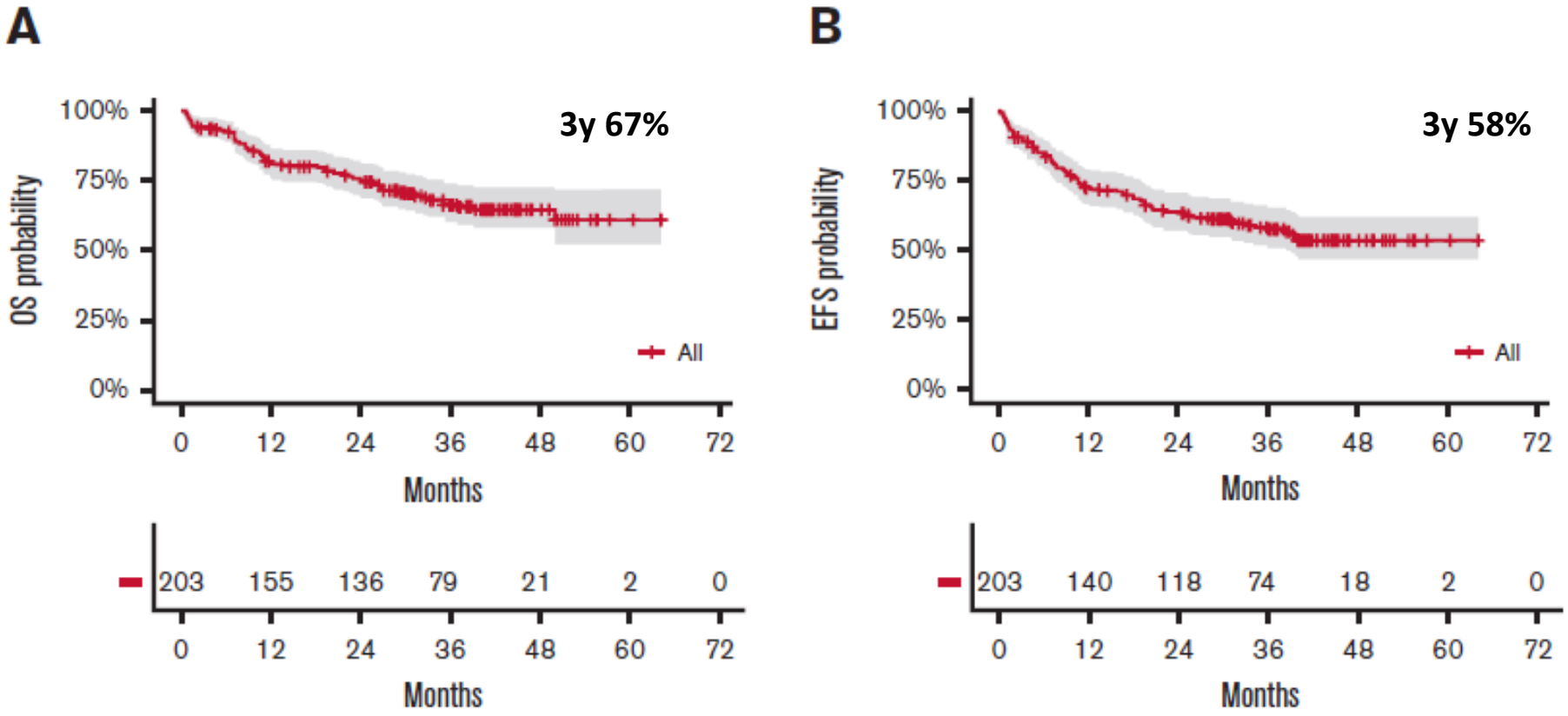
The national treatment program for adult ALL



Risk Classification	
Very high risk for early switch to alloHSCT	WBC count > 100 x 10^9 cells/L and/or highly adverse cytogenetics/genetics, MRD+ TPs 2-4
High risk	WBC count > 30 x 10^9 cells/L, a pro–B phenotype, or a late complete remission
Standard risk	No risk factors

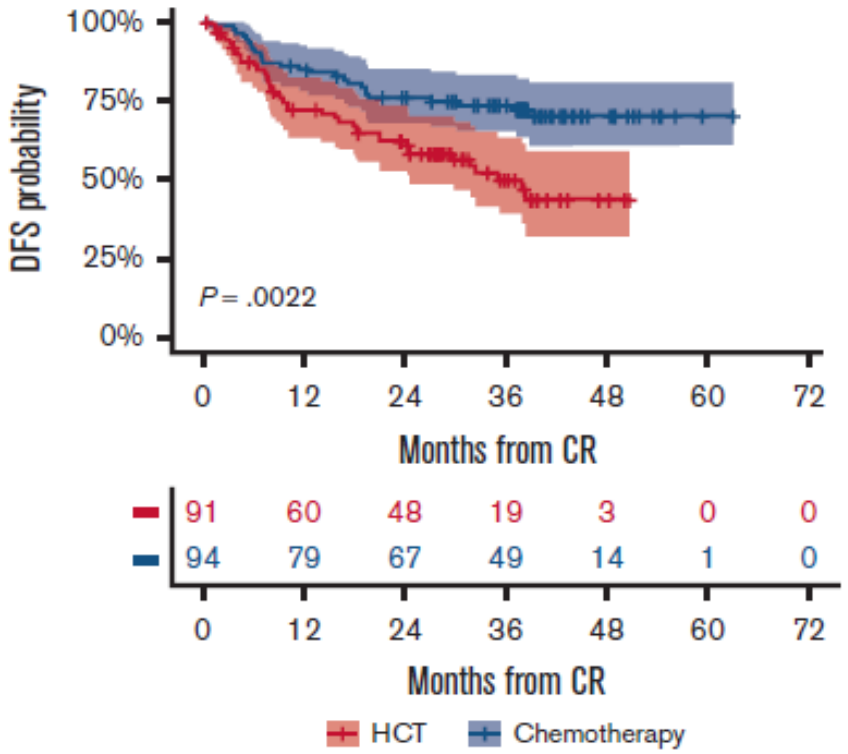
Bassan R et al: Blood Advances 22 August 2023 • Volume 7, Number 16, 4448-4461

Outcomes the GIMEMA 1913 study

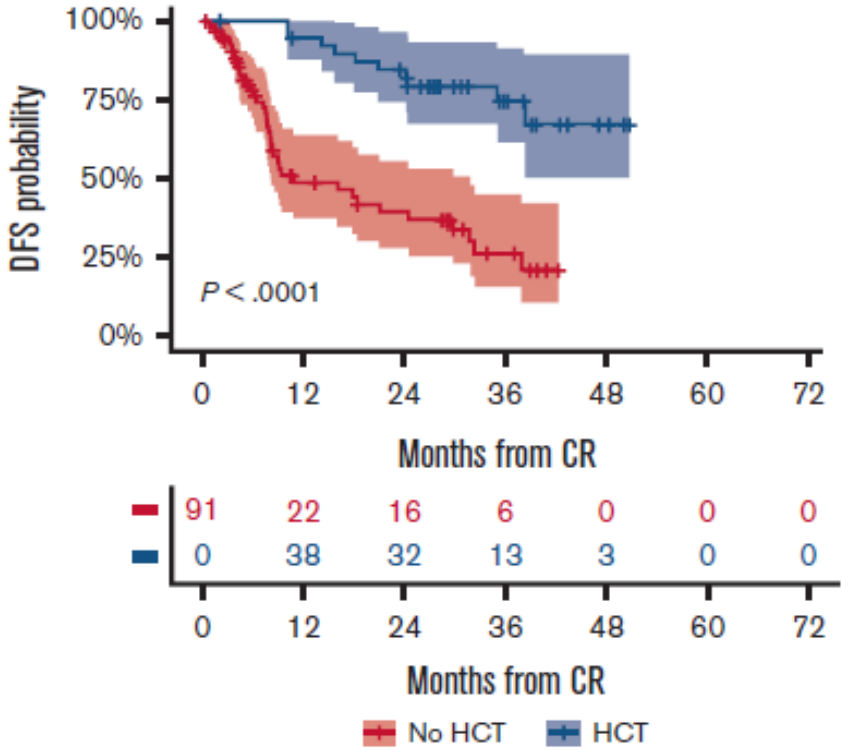


Bassan R et al: Blood Advances 22 August 2023 • Volume 7, Number 16, 4448-4461

GIMEMA 1913: Disease free survival by an ITT analysis

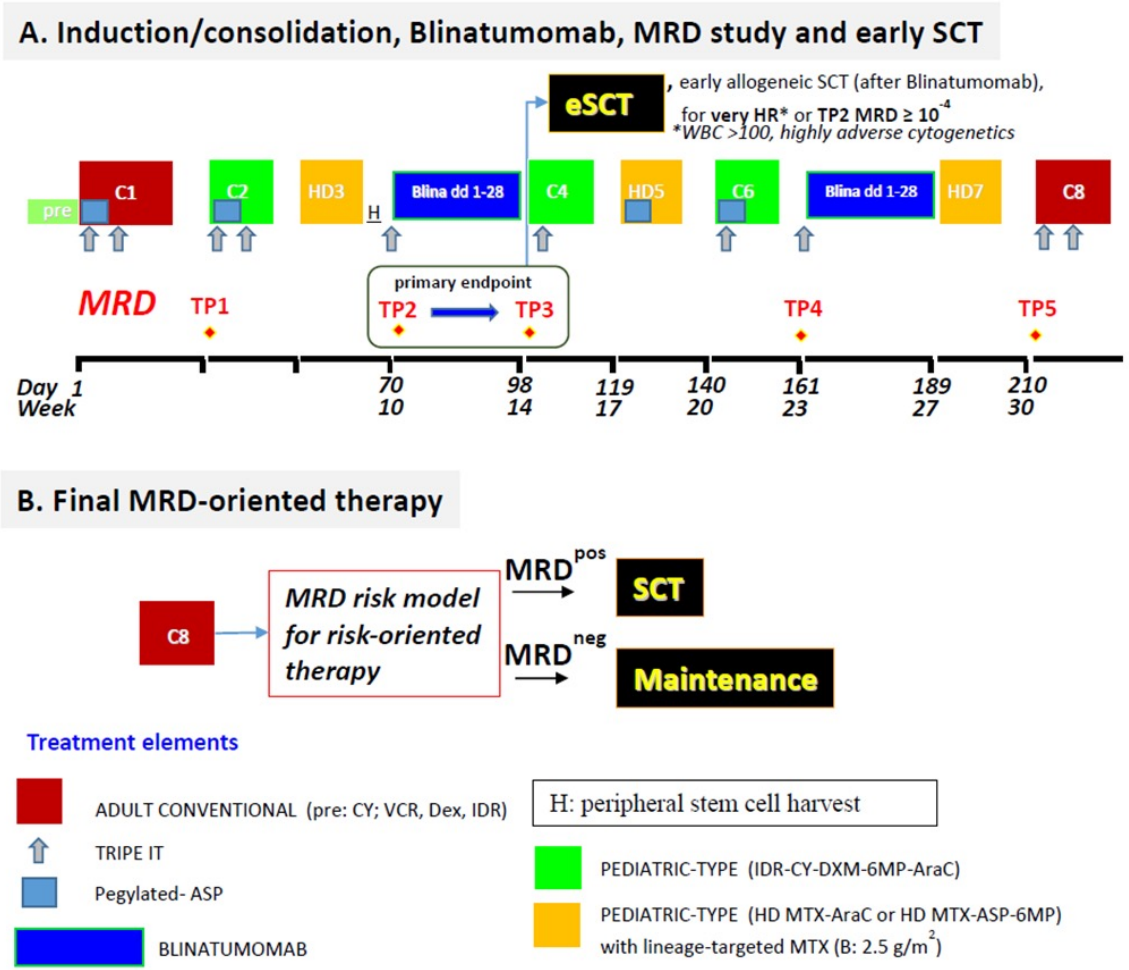


- 3-year DFS per ITT : CHT 74%, alloHSCT 50%, P = .0022

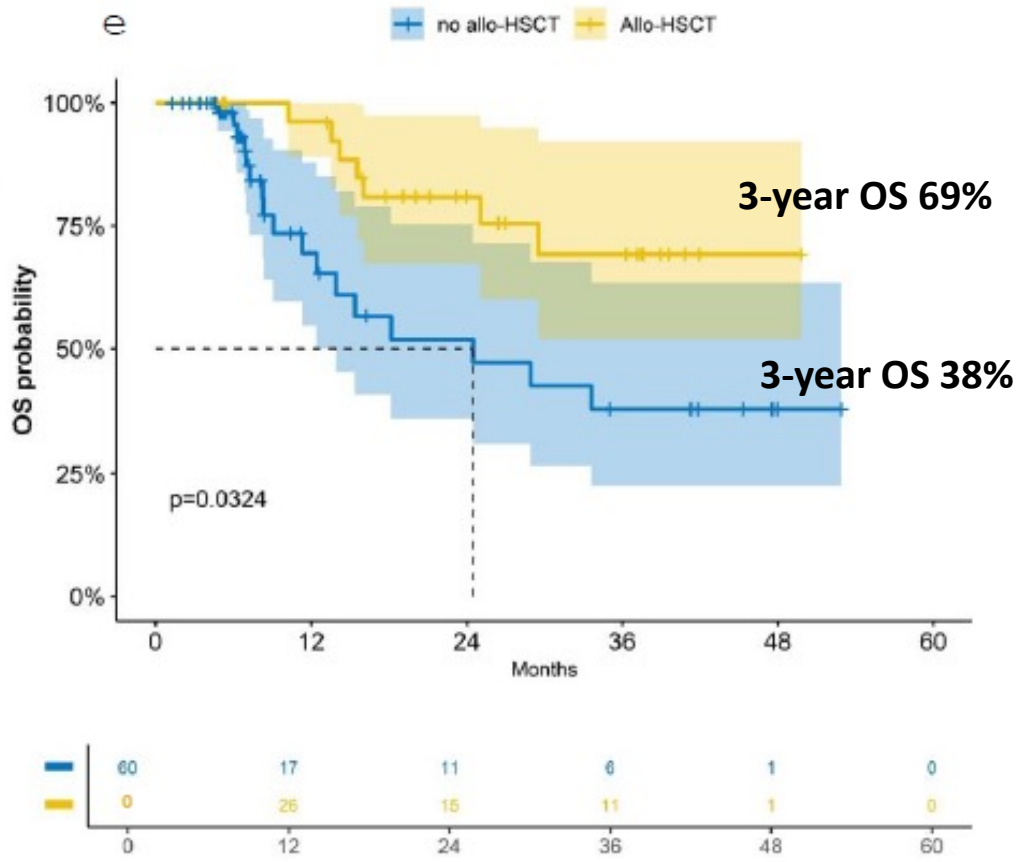


- 3-year DFS in the ITT per time-dependent alloHSCT realization: HSCT, 75% vs no HSCT, 26%, P < .0001

GIMEMA LAL 2317: time-dependent analysis of HSCT realization (in patients with ITT to HSCT)



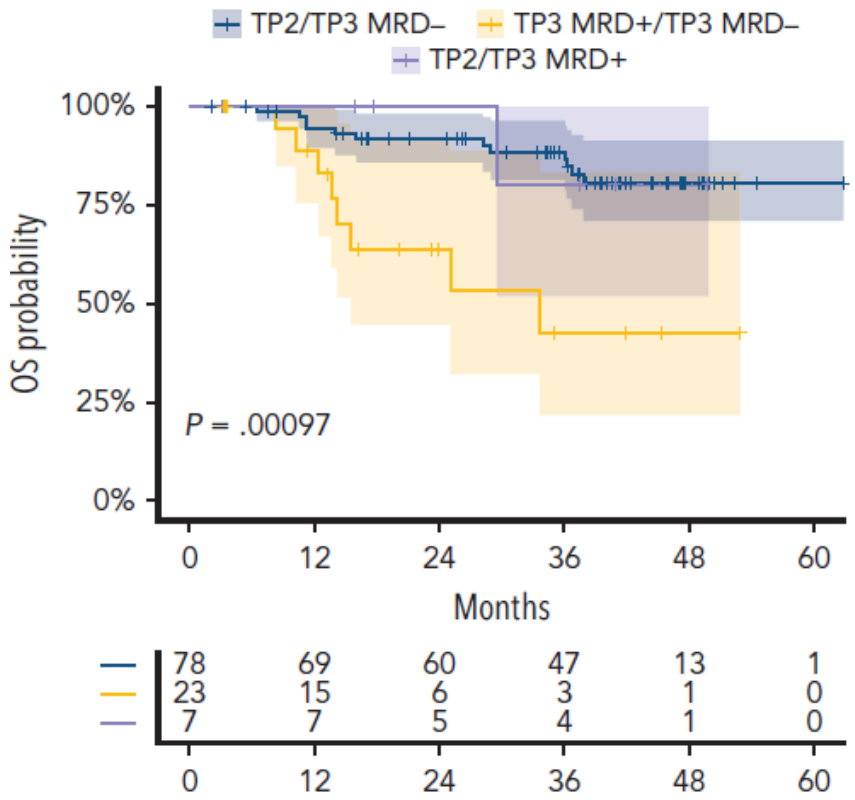
Overall population



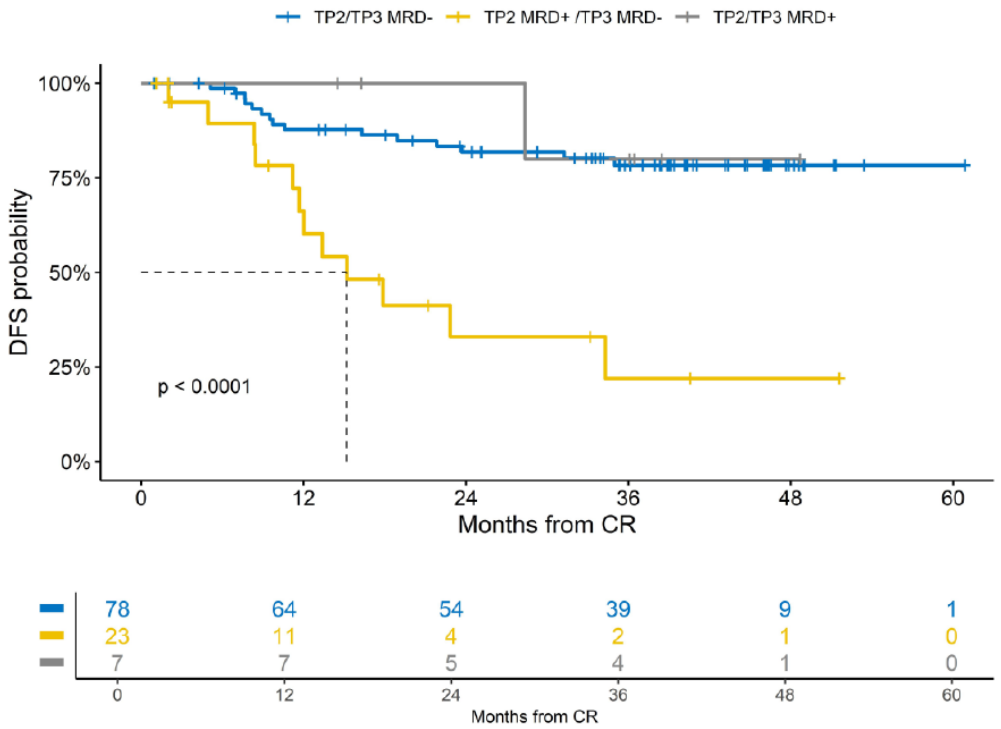
Bassan R, et al. *Blood* 2025;145:2447-2459.

GIMEMA LAL2317: TP2 MRD+ remains a high-risk feature

OS



DFS



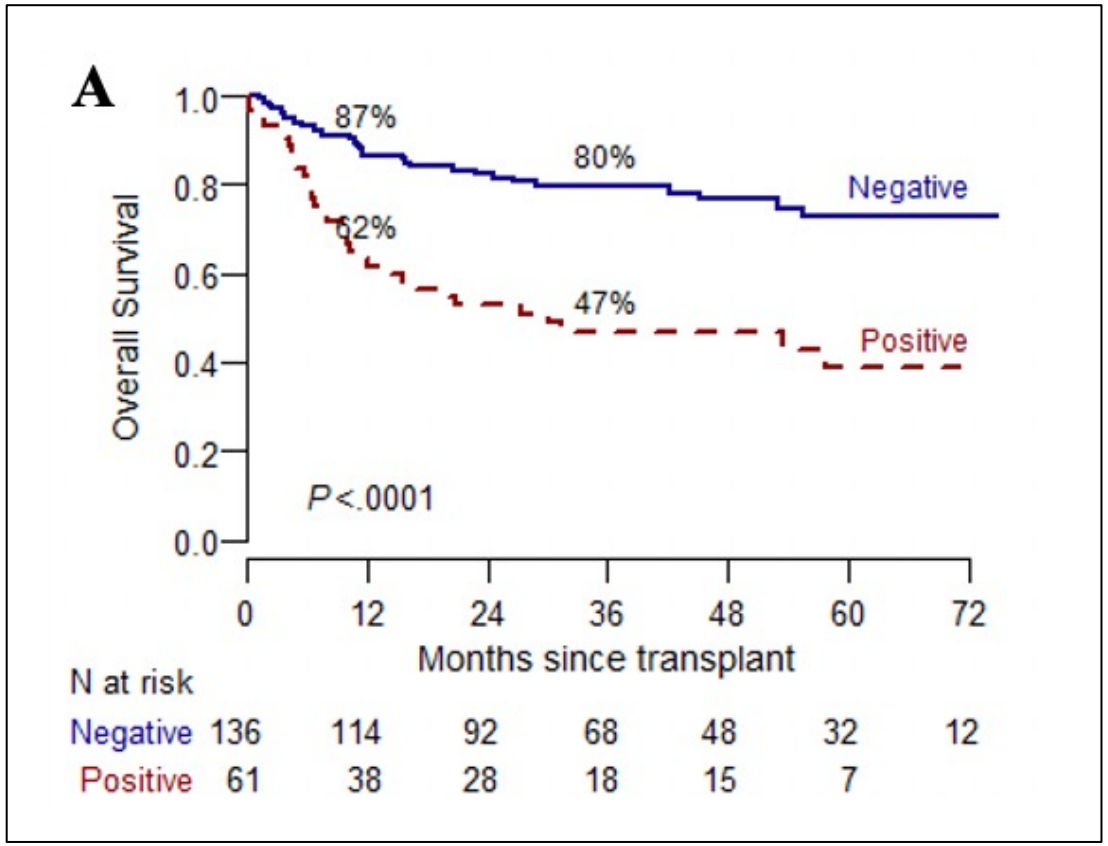
Bassan R et al, Blood. 2025 May 22;145(21):2447-2459.

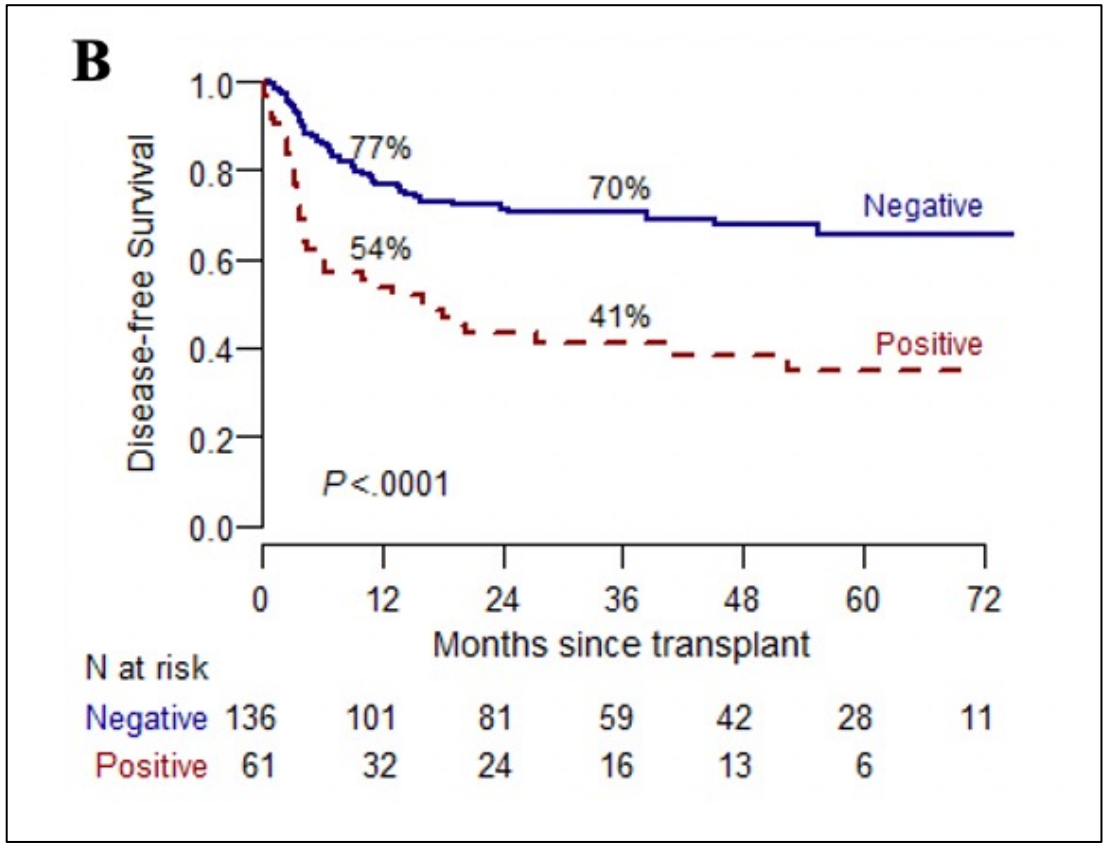
The Role of Allogeneic Stem Cell Transplantation in Ph- ALL in CR1:

whenever possible for MRD+ patients (after chemotherapy),

and/or high-risk biological profile

Main outcomes of Allografted ALL Treated with the GIMEMA LAL 1913 Protocol in the Real-Life according to MRD status at transplant

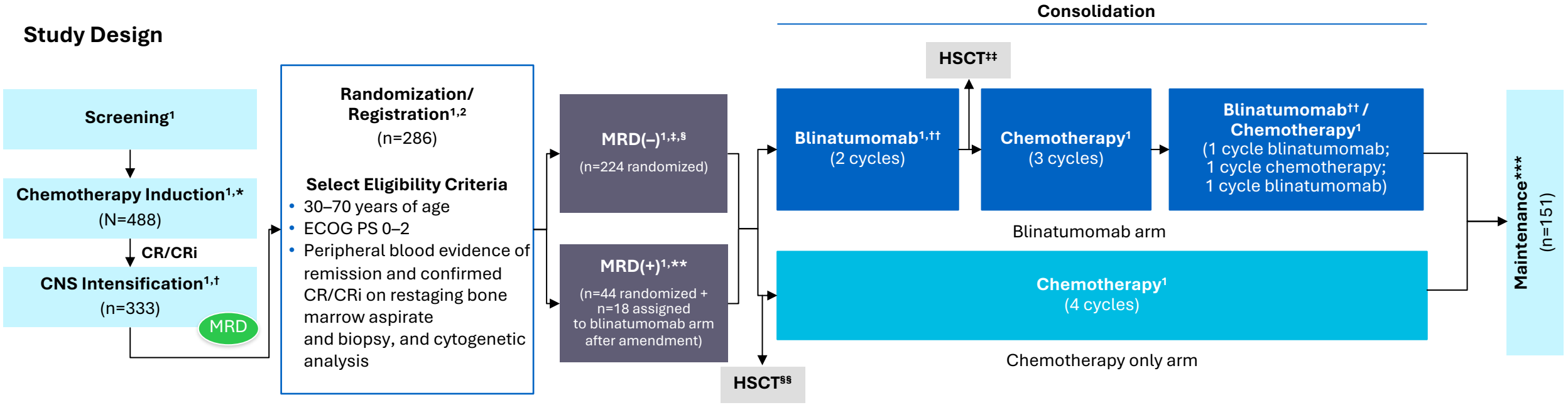




Cavallaro G,… and Lussana BMT 2025

ECOG-ACRIN E1910: A Global, Randomized, Controlled, Phase 3 Trial of Blinatumomab Alternating With Chemotherapy vs Chemotherapy Alone in Frontline Consolidation in Adult Patients With Ph(–) B-ALL

Study Design



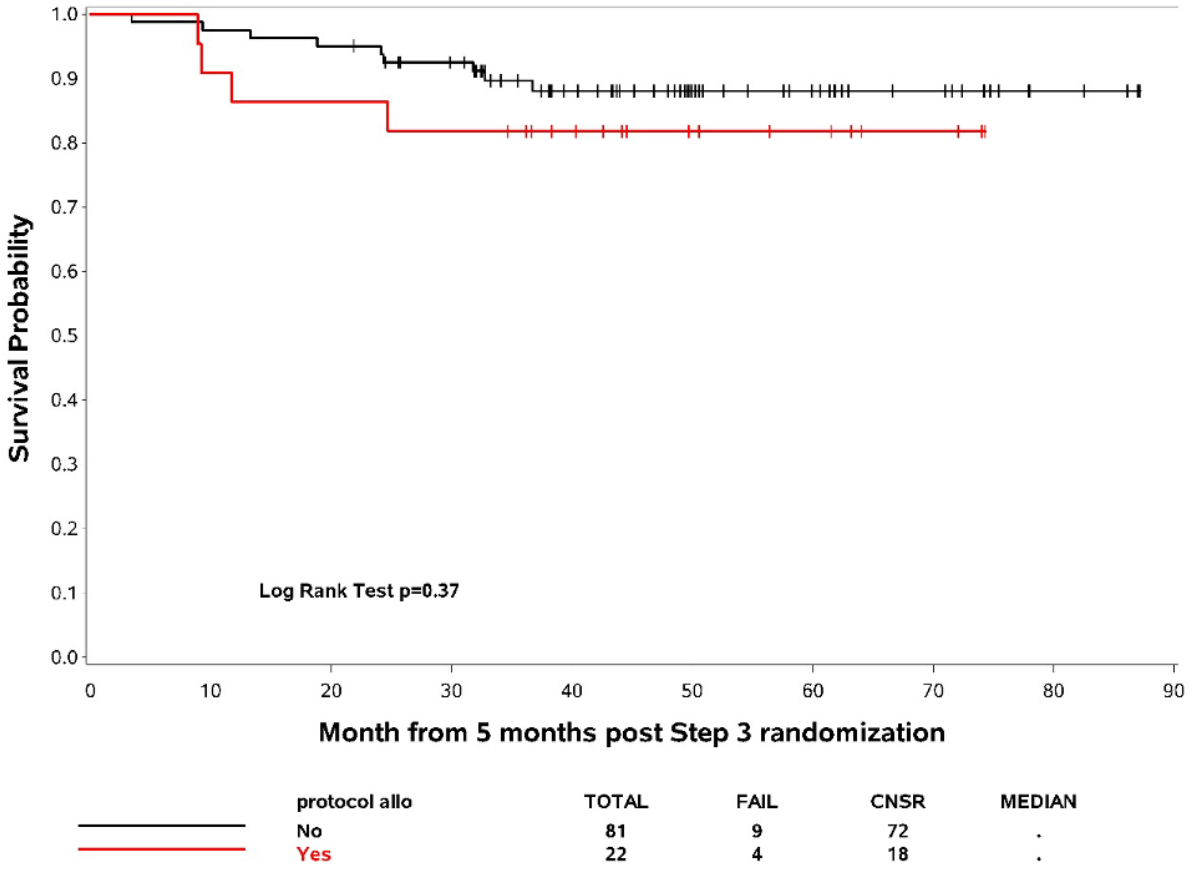
Stratification factors:[1]
- Age
- CD20 status
- Intended rituximab use
- HSCT intent

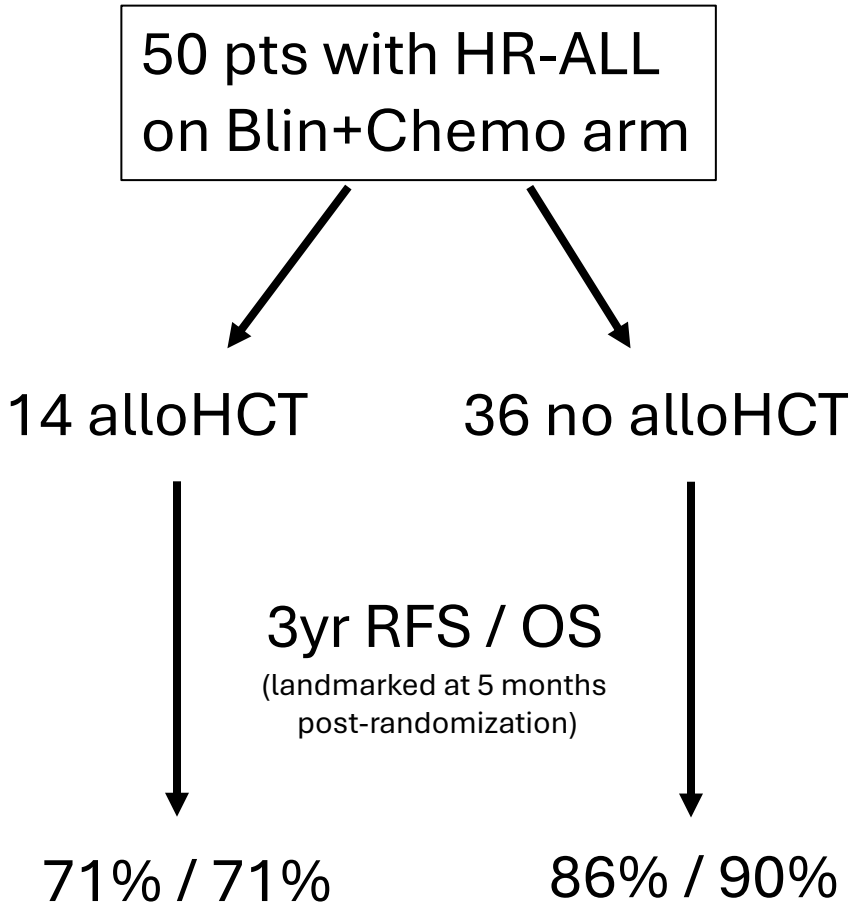
Primary endpoint:[1]
- OS in patients who were MRD(–)

Select secondary endpoint:[1]
- RFS in patients who were MRD(–)

1. Litzow MR, et al. *N Engl J Med*. 2024;391:320-333. **2.** Litzow MR, et al. *N Engl J Med*. 2024;391(protocol):320-333.Aptos

ECOG-ACRIN E1910 phase 3 Trial: No benefit of alloHSCT in MRD-negative patients



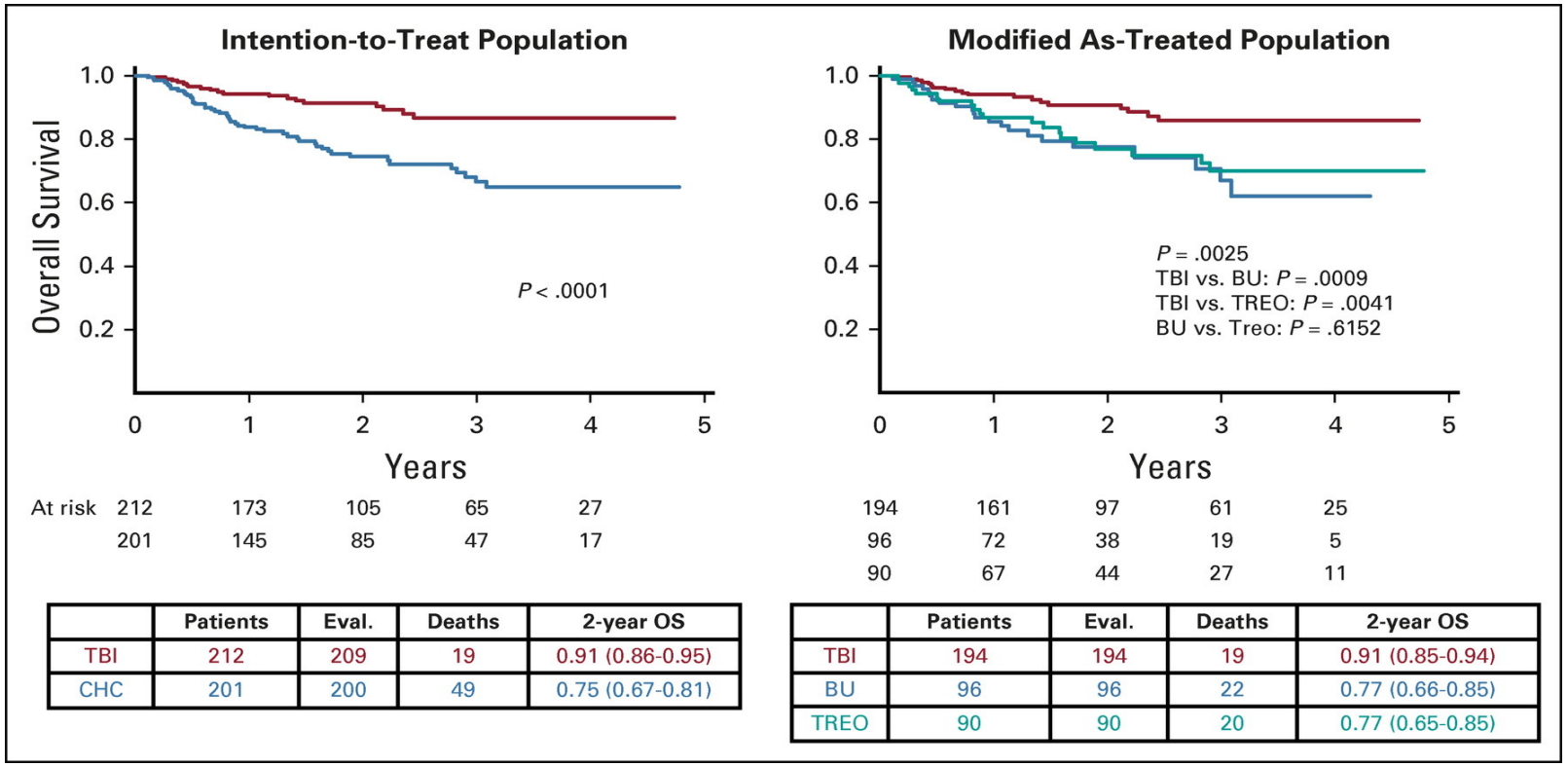


The receipt of allo-HCT had no effect on 3yr-OS and 3yrs-RFS in MRD neg

Liedtke M, et al. ASH 2024; Abstract 779 and oral presentation.

The role of conditioning regimen

ALL SCT Ped FORUM: TBI vs CHEMO



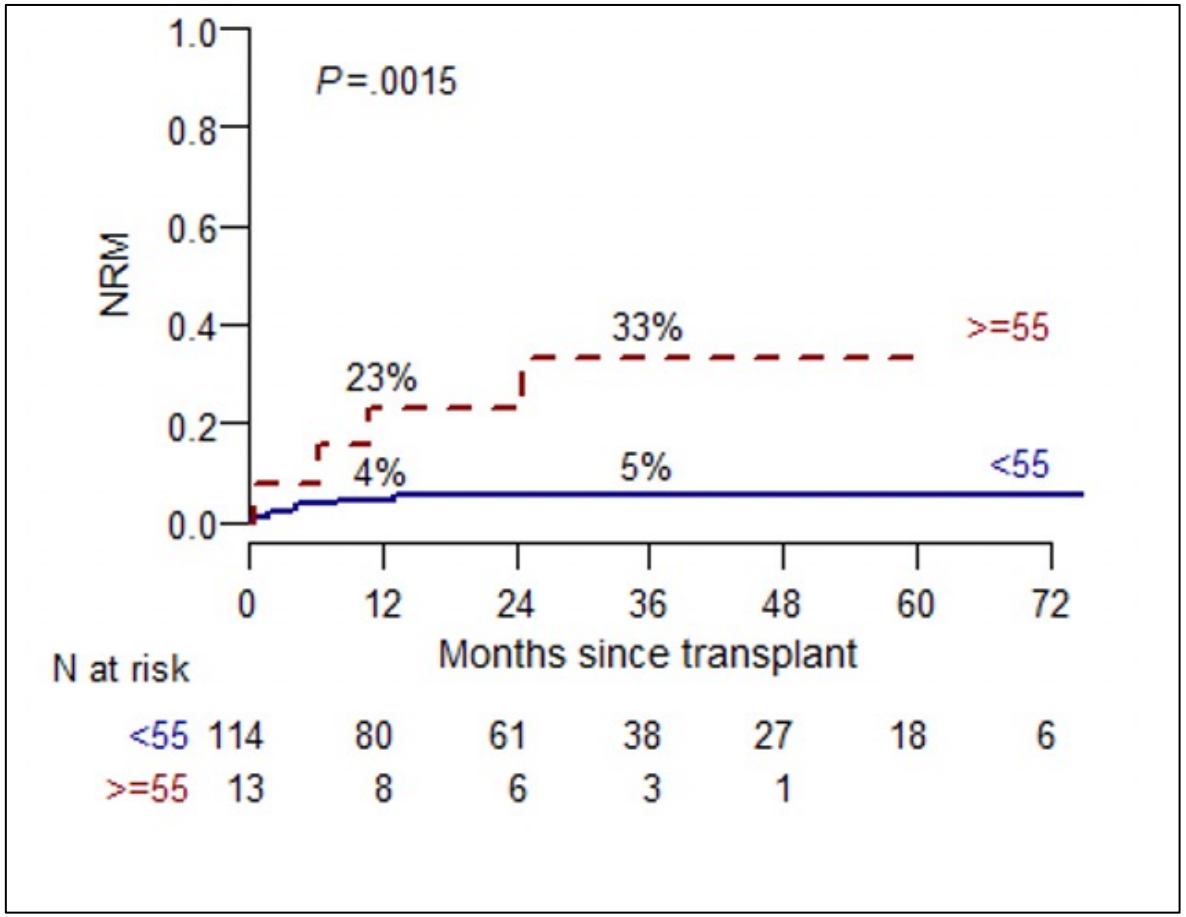
	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

	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

NRM in patients receiving TBI according to age

- Patients aged ≥ 55 years receiving TBI had a significantly higher NRM compared to the younger population (33% vs 5%,p= .0015)



Cavallaro G,... and Lussana BMT 2025

Personal opinion
(Hematology HPG 23 Bergamo)

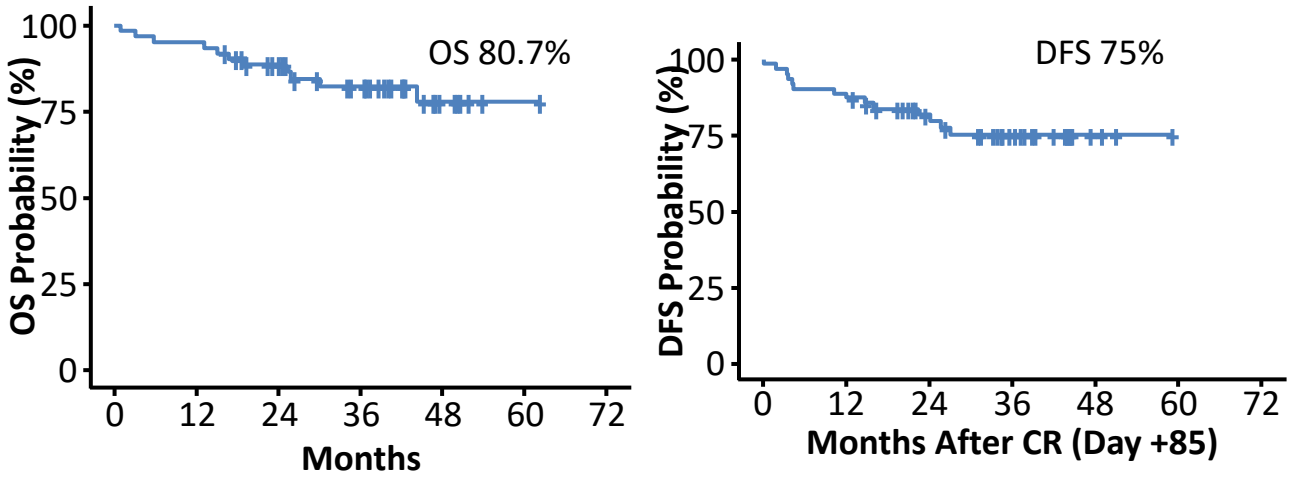
- TBI (12 Gy or 8 Gy)-based conditioning should be used whenever possible (up to the age of 55 years)

- Fludarabine (dosage 160mg/m^2) can safely replace cyclophosphamide in the conditioning

The role of alloHSCT in the setting of Ph+ ALL and TKI in combination with blinatumomab

Efficacy of a chemo-free induction-consolidation strategy in Ph+ ALL

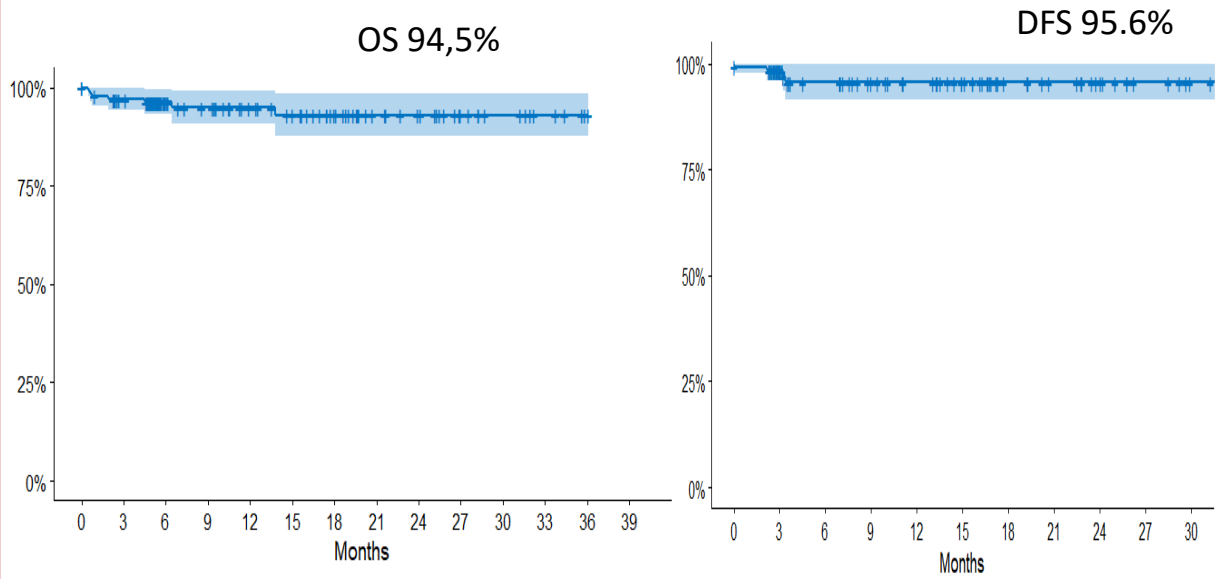
GIMEMA D-ALBA trial



- Median FU: 53 months
- Primary endpoint: MRD negativity after 2 Blinatumomab cycles

Foà R et al. NEJM 2020 &. *J Clin Oncol.* **2024**;42:881-885.

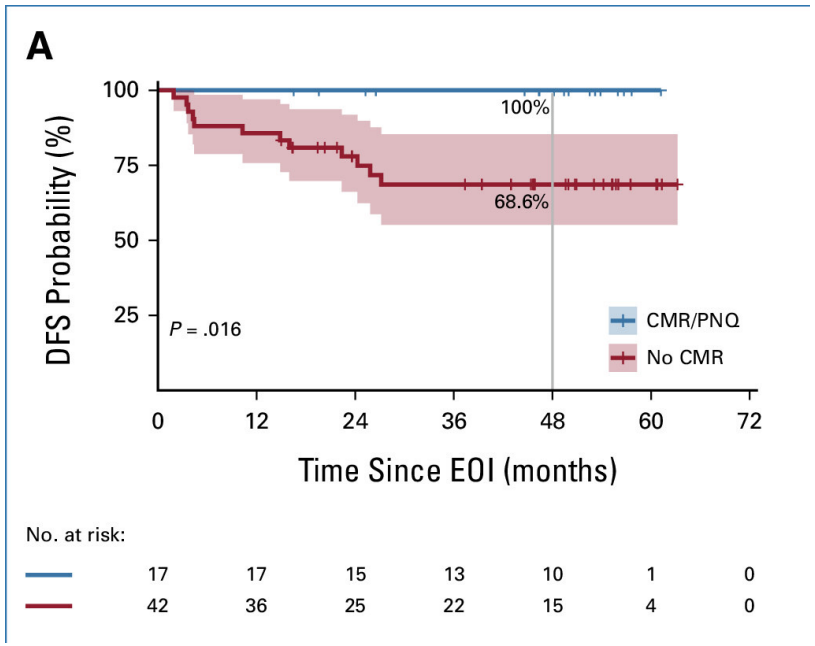
GIMEMA ALL 2820 trial

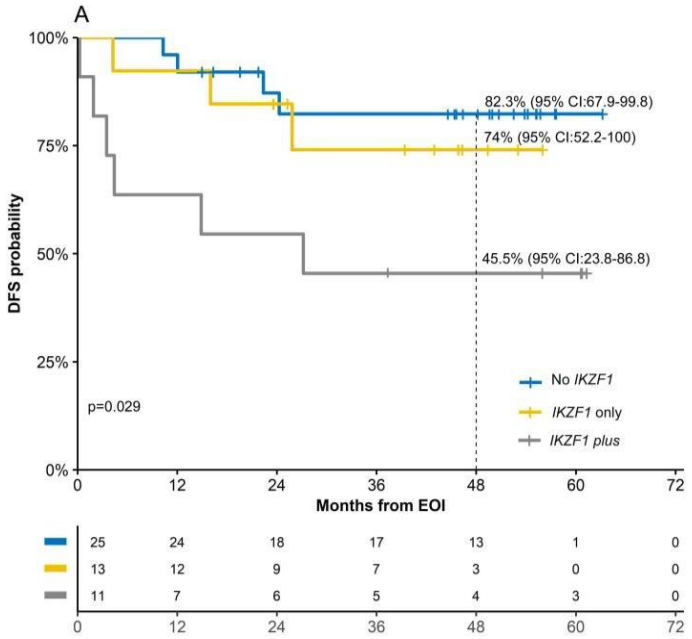


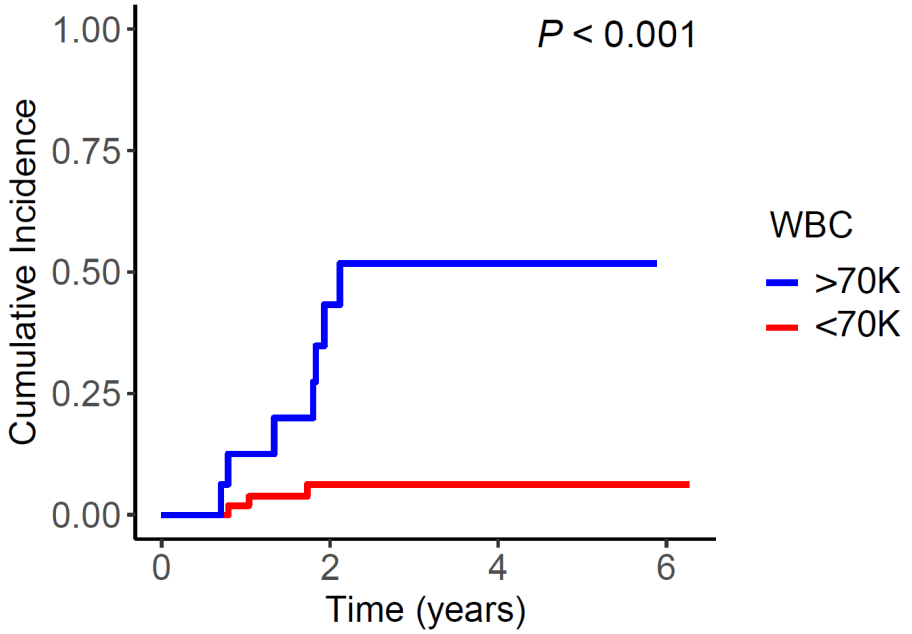
- Median FU: 8.5 months
- Primary endpoint: MRD negativity after 2 Blinatumomab cycles

Chiaretti et al, abs 835, ASH 2024

Special concerns for patients receiving chemo-free strategies





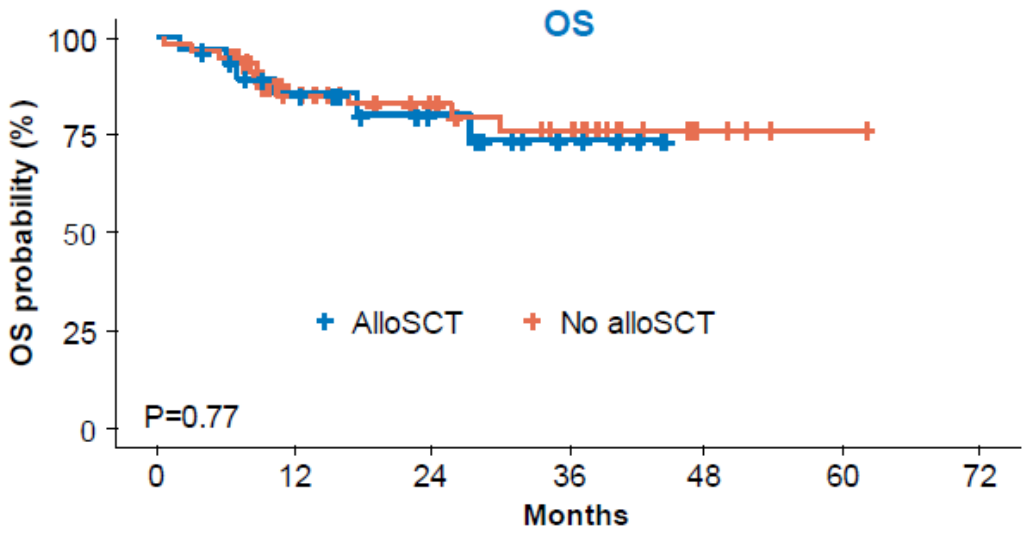


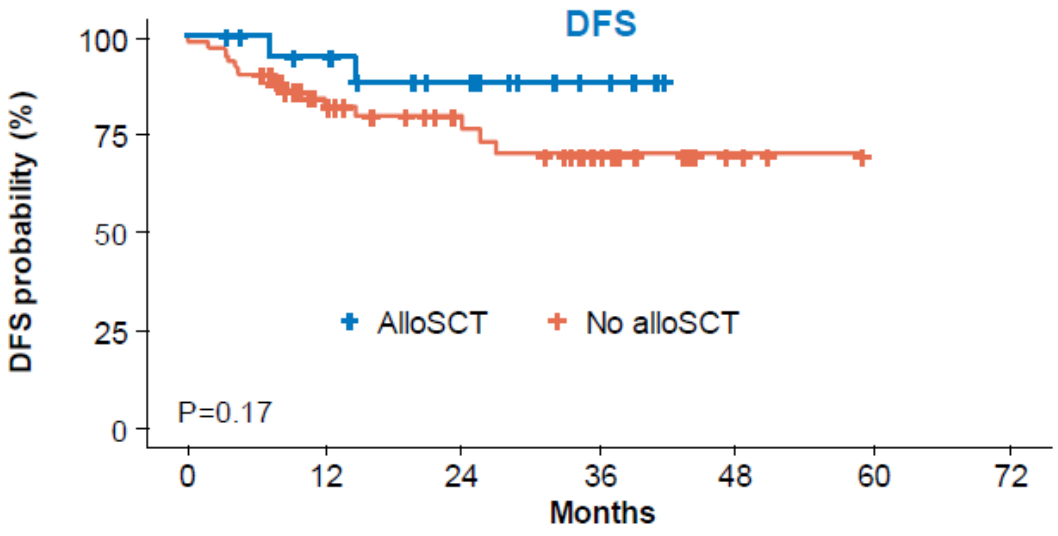
- MRD
- *IKZF1*^{plus}
- WBC >70K

Foà R et al. NEJM 2020 &. *J Clin Oncol.* **2024**;42:881-885; Kantarjian H et al, JCO 2024

The role of transplant in the D-ALBA Trial

(median [range] follow-up: 40 [0.9–62.5] months)

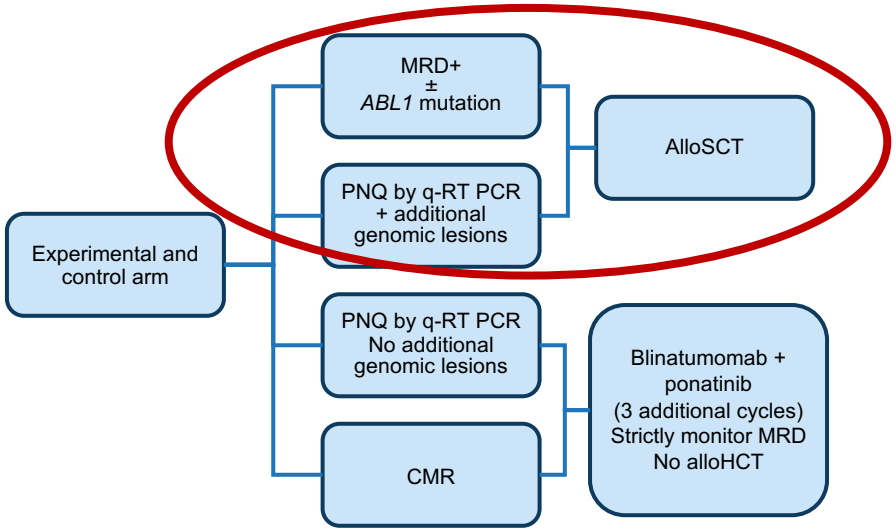




24 (46%) patients underwent alloHSCT, out of these 6 were in second CHR
Enrichment in MRD+ cases within allografted patients;
TRM: 12.5% in 1st CHR and 13% overall

Foà R, et al. J Clin Oncol 2024; Chiaretti S et al. Poster presented at EHA 2022 Abstract P353

GIMEMA ALL 2820 trial: the biologically-driven allo-SCT allocation reduced the rate of transplant



	N=16
Age, median (range)	49 (27-67)
>65 years	1 (27)
Gender: M/F (%)	13/3 (50/50)
WBC, median (range)	23 (2-207)
p190	10
p210, p190/210	5, 1
IKZF1^{plus}	9

Reasons for transplant

- MRD persistence (n=7)
- *IKZF1*^{plus} (n=9)
- Both (n=5)

So far, no relapses nor transplant-related deaths

Adapted from Chiaretti S, et al. ASH 2023; Abstract 4249;

The role of alloHSCT Beyond CR1?

Allogeneic Transplant Remains Goal of Remission Beyond CR1

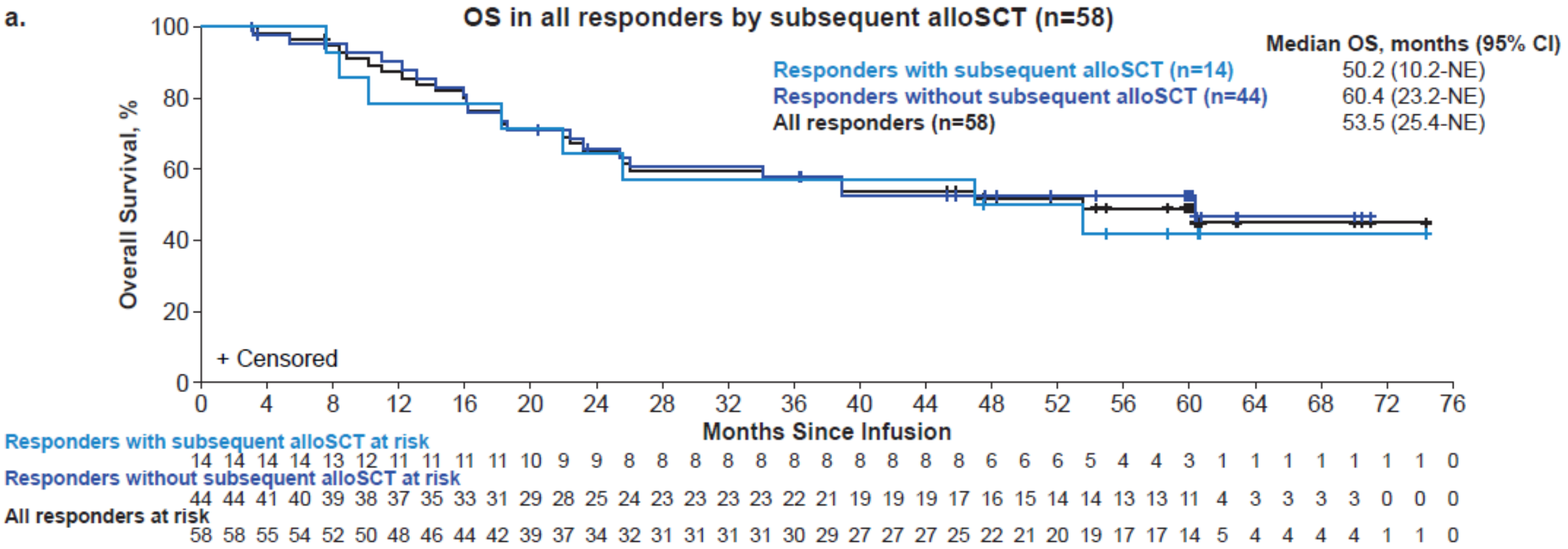
- CR rates with new immune targeting approaches significantly better
  - High rates of undetectable MRD with the immune targeting strategies
- However, with possible exception of CAR-T therapy, none of these approaches are curative in the relapsed setting
- Antibodies based therapies **should** be used as a bridge to allogeneic transplant

Which patients benefit most from alloHSCT after CAR-T?

Sequential alloHSCT after CAR-T cell therapy

Study	Patients enrolled/transplanted (%)	Ref
Zuma 3	78/14 (18%)	*Shah BD Lancet 2021; 398: 491–502*
Rocca Consortium	189/30 (16%)	*Roloff GW et al.: J Clin Oncol 43:558-566, 2024*
Felix	99/18 (18%)	*Roddie C et al.: N Engl J Med 2024;391:2219-30*
Eliana	79/17 (21%)	*Laetsch TW et al.: J Clin Oncol* 41:1664-1669, 2022
RWE CIBMTR	786/196 (25%)	*John S et al.: Blood Advances 2025*

Overall Survival in ZUMA-3 by Subsequent AlloSCT

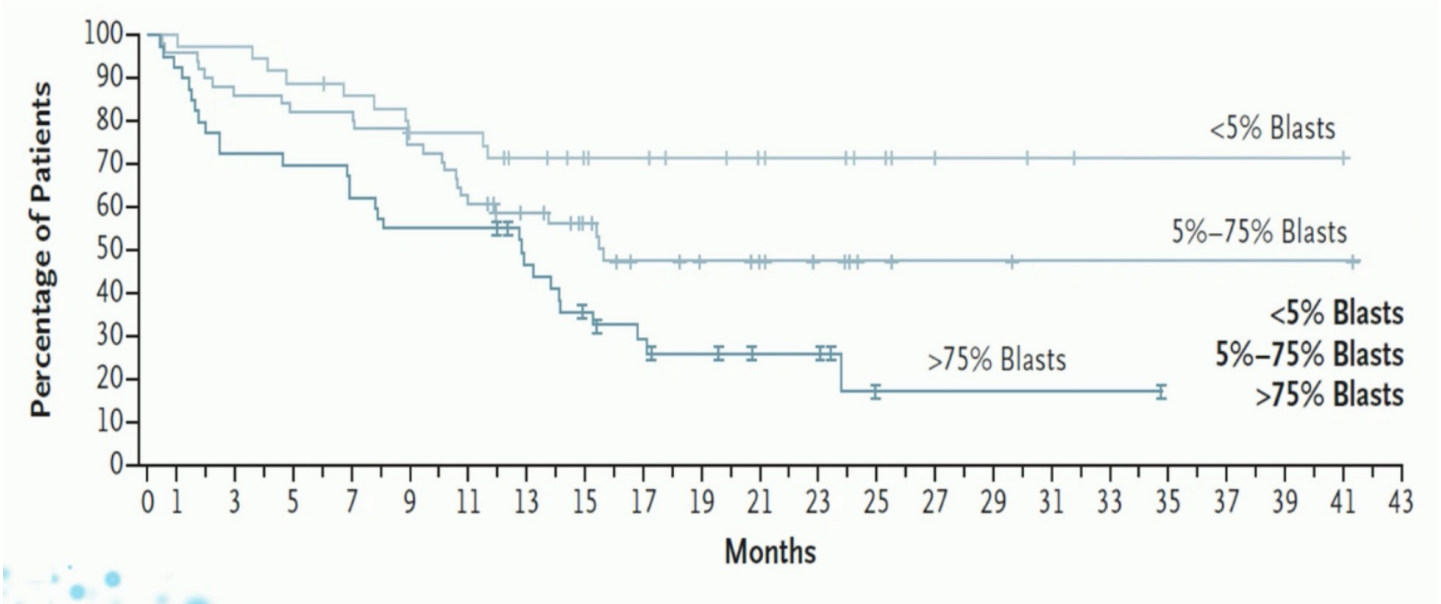


Shah, B.D., Cassaday, R.D., Park, J.H. et al. Leukemia 2025; Oluwole et al. EHA 2025 (Abstract PF374; poster presentation)

Can specific subsets of patients achieve durable remission without transplantation?

Pre-infusion factors impacting relapse following CD19 CAR T cells

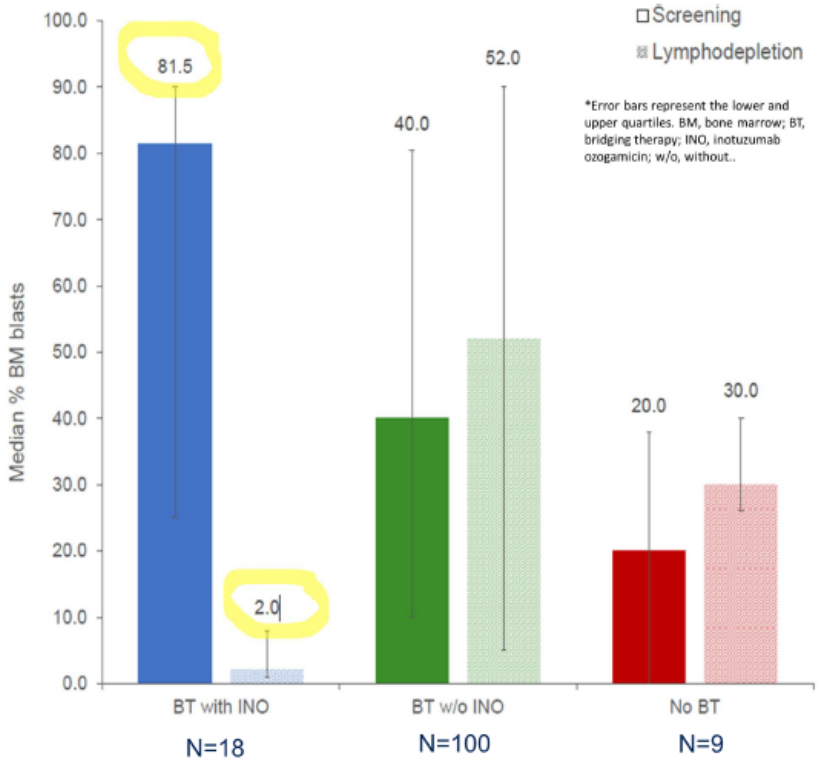
- **High pre-infusion leukemia burden**
- Extramedullary disease
- Blinatumomab non-response
- KMT2A rearrangement
- CD19/ 28ζ CAR construct



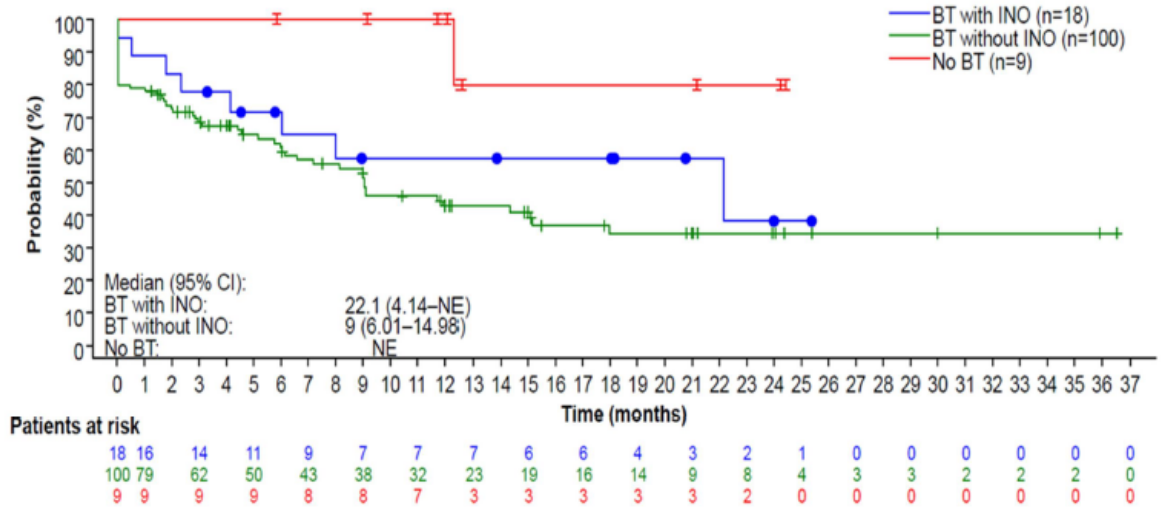
- Lamble AJ et al., Blood Advances2022; Myers RM et al, Blood 2023; Shah NN et al. J Clin Oncol 2021; Schultz LM, et al. J Clin Oncol. 2022 ; Kadauke S J Clin Oncol 2021; Roddie C et al. NEJMs 2024

Can we reduce leukemic burden with good bridging therapy?

On FELIX, IO was most effective at reducing BM blasts (82% to 2%)



IO BT may improve EFS curve for high-risk patients (>75% blasts)



Park et al. EHA 2025 and ASH 2024

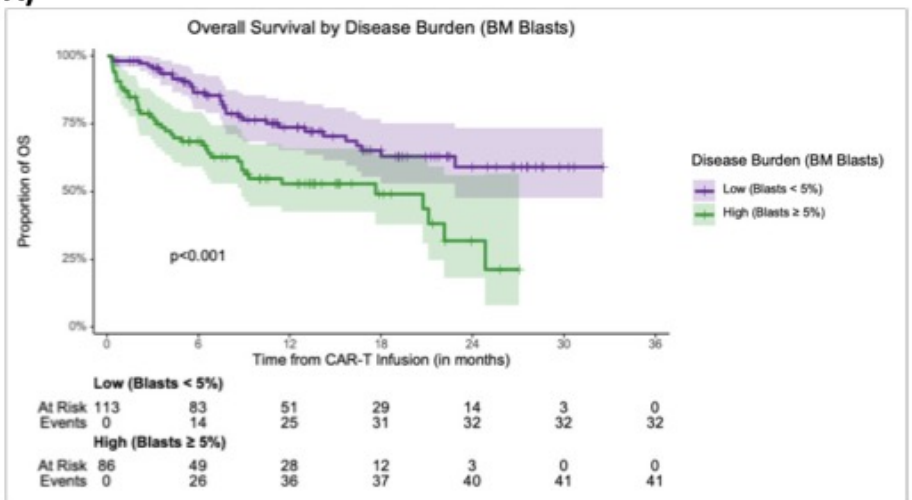
CAR HEMATOTOX independently predicts outcomes after CD19 CAR-T therapy for ALL

Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1	High: ≥ 2		

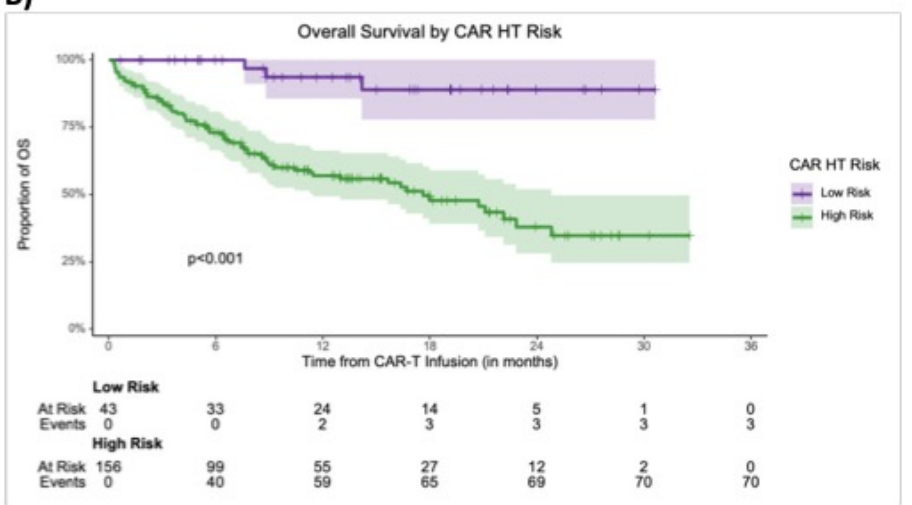
Key points

- CAR HEMATOTOX identifies a subset of ALL CAR patients with low toxicity and excellent outcomes, independent of disease burden
- In a smaller investigational cohort, HT low patients had higher CAR expansion than HT high patients for a given disease burden.

A)



B)



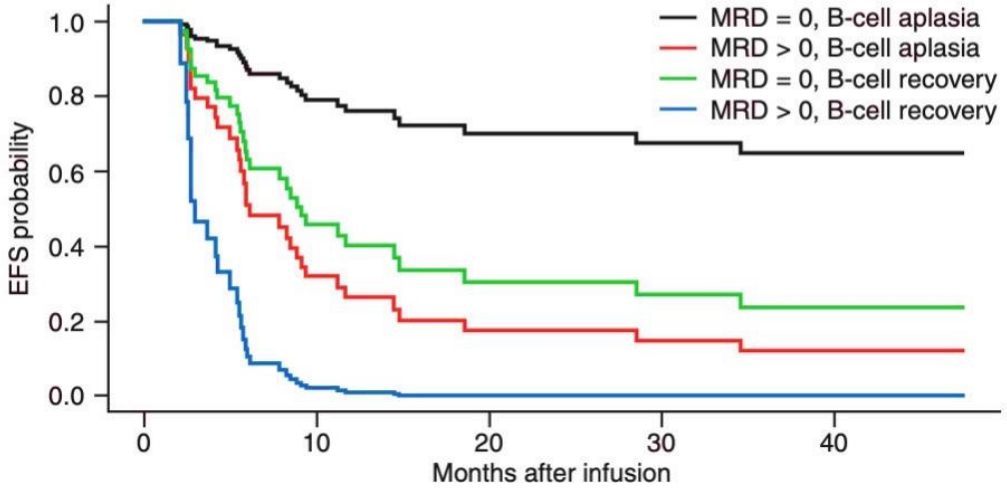
Valtis YK et al on behalf of the ROCCA Consortium Blood Advances 2025 in press

Factors relevant to predict duration of remission and outcome

A

	HR (95% CI)	P
Day 28 NGS-MRD status		
MRD = 0	—	—
MRD > 0	4.87 (2.18–10.8)	<0.001
B-cell recovery	3.33 (1.44–7.69)	0.005

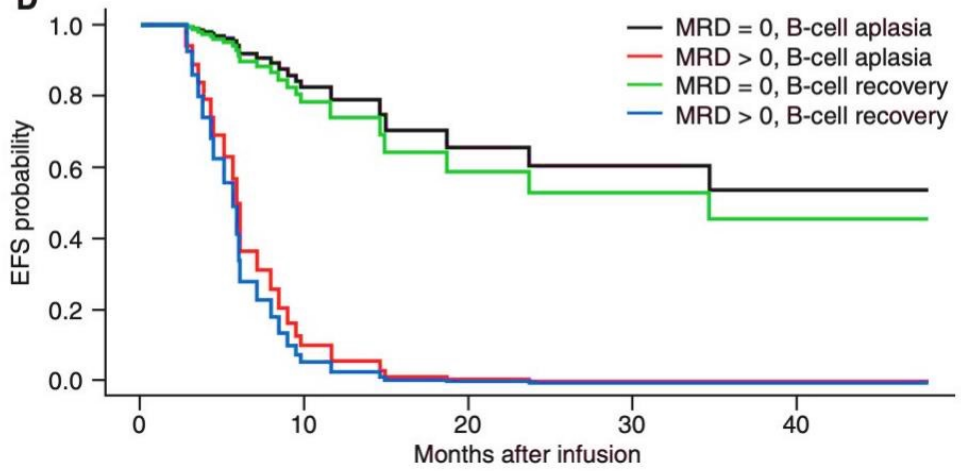
B



C

	HR (95% CI)	P
Month 3 NGS-MRD status		
MRD = 0	—	—
MRD > 0	12.0 (2.87–50.0)	<0.001
B-cell recovery	1.27 (0.33–4.79)	0.7

D



- Pts who lose B-cell aplasia <6 months or develop NGS-MRD>0 on BM are at high risk of relapse

Pulsipher et al. Blood Cancer Discovery 2022

Role of alloHSCT consolidation after CD19 CAR-T cells therapy

YES

- MRD+ CR post-CAR-T
- Early (<6 months) loss of B cell aplasia
- High tumor burden pre LD chemo

Maybe

- Presence of EMD
- Blinatumomab non-response
- KMT2A rearrangement
- No prior slloHSCT

PROBABLY NOT

- Routinely for all patients

Conclusions

- For Ph negative ALL, accurate definition of high-risk patients at diagnosis and during treatment is essential to candidate patients for transplant consolidation

- All efforts should be made to eradicate MRD before alloHSCT to increase the chance of achieving a cure

- In the coming years alloHSCT in CR1 for Ph+ ALL is likely to be applied based on a risk-adapted approach:
  - AlloHSCT in CR1 should be considered in younger and fit patients with a high leukemic burden at diagnosis, high-risk genetic features (e.g. complex karyotype, IKZF1+), or failing to achieve early molecular responses

- For some patients, CAR-T cells therapy may be a stand-alone definitive therapy:
  - Identifying patients who can be safely observed without alloHSCT after CAR-T is critical

ACKNOWLEDGMENTS

The Hematology and Transplant Team
Alessandro Rambaldi
Giuseppe Gritti
Silvia Ferrari
Anna Grassi
Alessandra Algarotti
Benedetta Rambaldi
Giuliana Rizzuto
Maria Chiara Finazzi
Marta Castelli
Gianluca Cavallaro
Davide Murgia

The Molecular Lab Paolo Belli, Bergamo

Cristian Meli
Anna Salvi
Manuela Tosi
Roberta Cavagna
Clara Belotti
Silvia Salmoiraghi
Orietta Spinelli

Cell Therapy Lab Gilberto Lanzani, Bergamo
Martino Introna
Josee Golay
Elisa Gotti
Silvia Panna
Irene Cattaneo
Olga Pedrini
Chiara Capelli

Ospedale di Bergamo
Regione Lombardia
ASST Papa Giovanni XXIII

Cell Therapy Lab Stefano Verri, IRCCS San Gerardo Monza
Giuseppe Gaipa
Chiara Magnani
Daniela Belotti
Giada Matera
Stefania Cesana
Valentina Colombo
Michele Quaroni

Fondazioni Tettamanti, Monza and Clinica Pediatrica Università di Milano Bicocca
Andrea Biondi
Adriana Balduzzi
Giovanna Lucchini
Sarah Tettamanti
Giuseppe Dastoli
Chiara Buracchi
Grazia Fazio
Giovanni Cazzaniga

Fondazione IRCCS San Gerardo dei Tintori