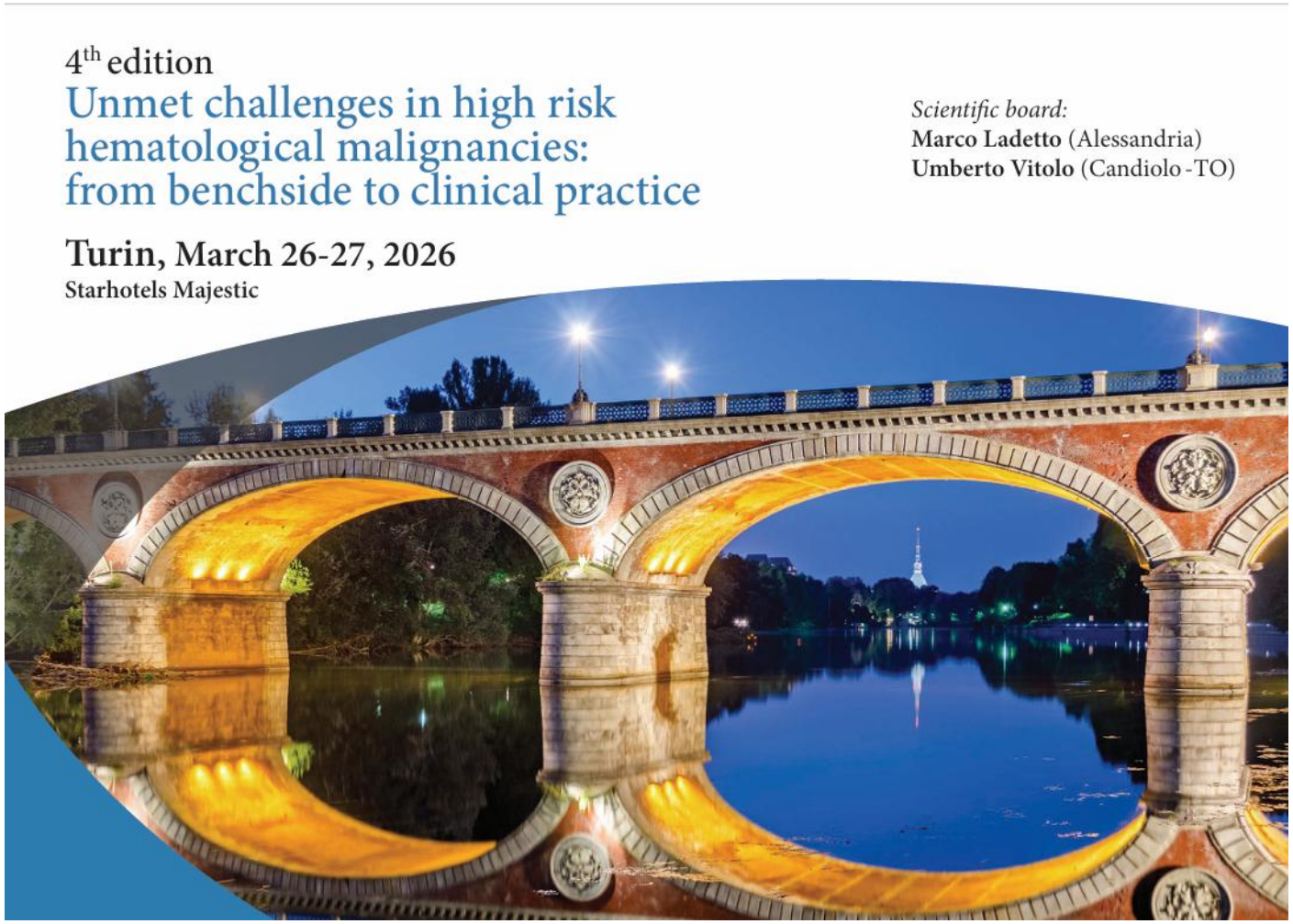


The evolving strategies in the treatment of young adults and elderly patients with ALL

Alessandro Rambaldi

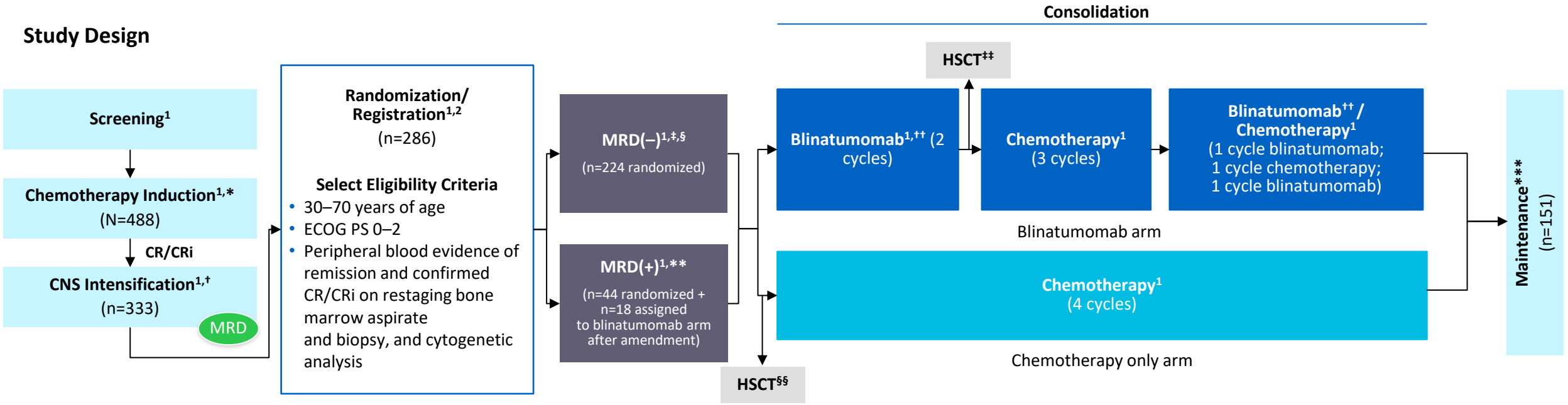
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen			✔			✔	✔
Pfizer			✔				
Novartis			✔			✔	
Kite Gilead			✔			✔	✔
Jazz			✔			✔	✔
Omeros			✔			✔	✔
Incyte			✔				
Sanofi			✔				
Pierre Fabre			✔			✔	
Italfarmaco			✔			✔	✔

Incorporating blinatumomab in the frontline treatment of BCP ALL

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



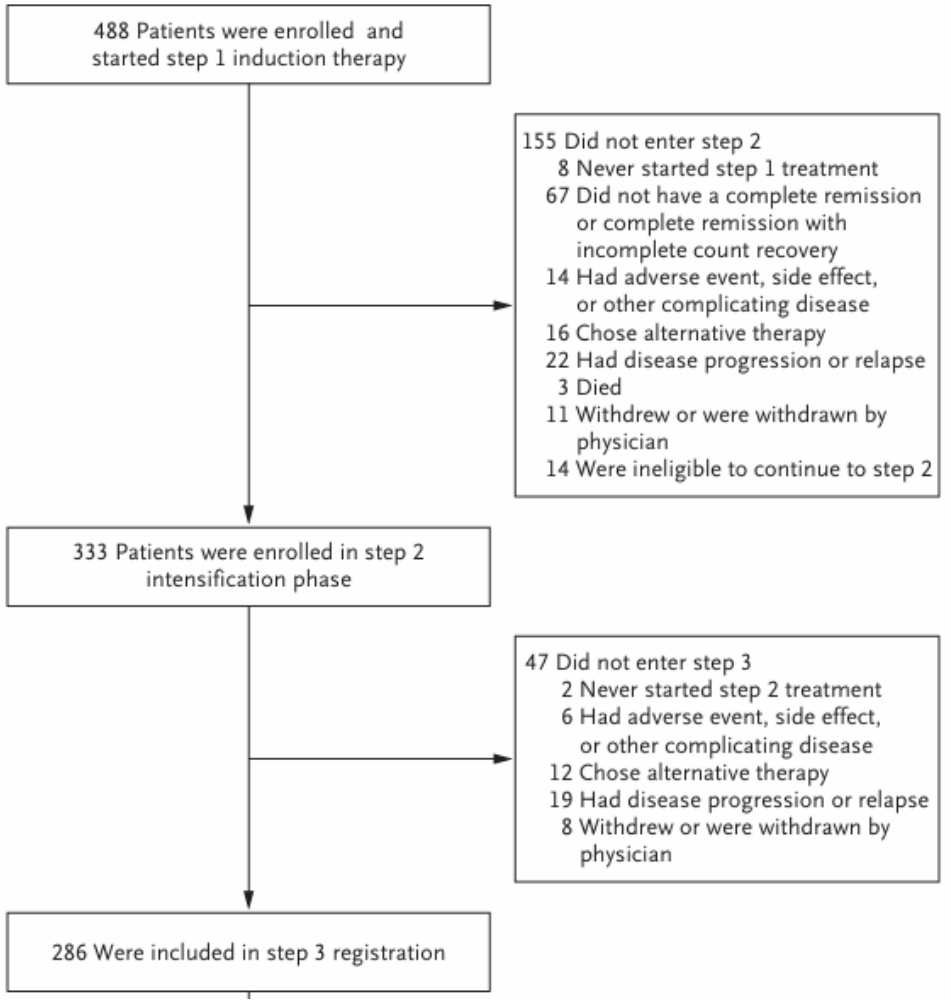
Stratification factors:[1]
- Age
- CD20 status
- Intended rituximab use
- HSCT intent

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

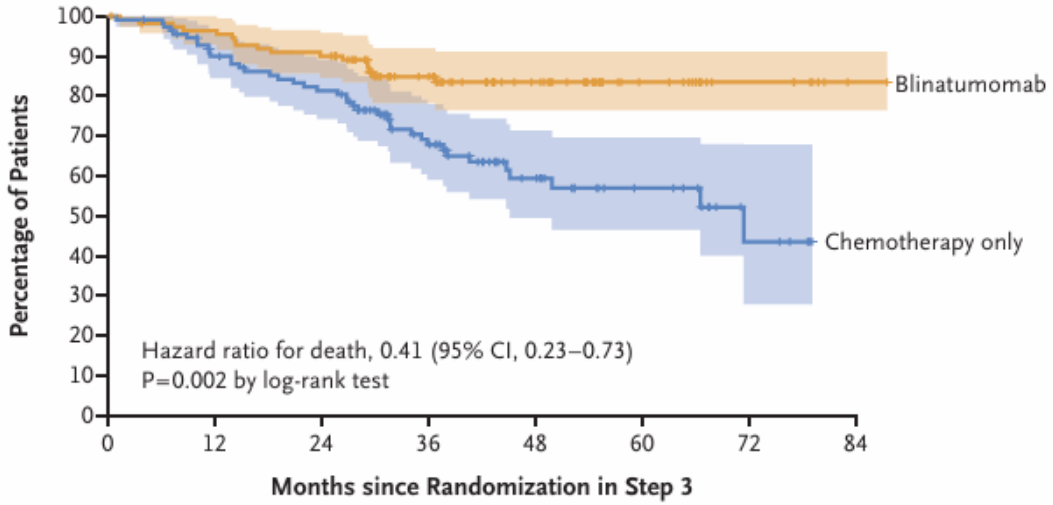
ECOG-ACRIN E1910: A Global, Randomized, Controlled, Phase 3 Trial of Blinatumomab Alternating With Chemotherapy vs Chemotherapy Alone in Frontline Consolidation in Adult Patients With Ph(–) B-ALL



1. Litzow MR, et al. *N Engl J Med*. 2024;391:320-333.

Blinatumomab for MRD-Negative Adult ALL Patients with Newly Diagnosed Ph– B-ALL: The ECOG-ACRIN E1910 Study

A Overall Survival among Patients with MRD-Negative Status

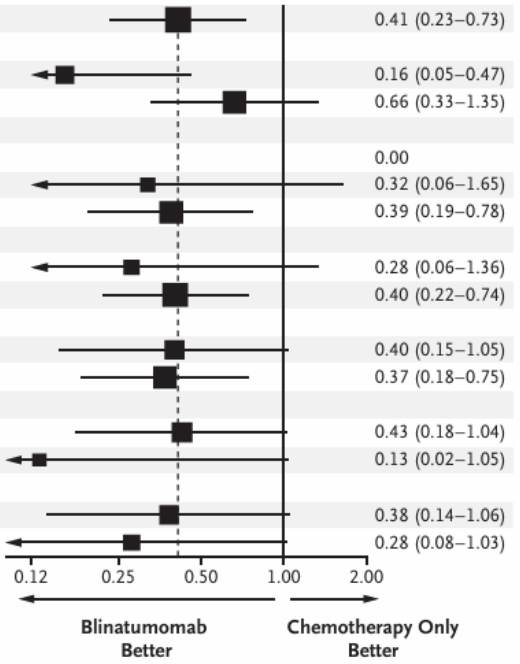


No. at Risk

Blinatumomab	112	106	99	65	41	19	8	1
Chemotherapy only	112	96	85	53	28	15	5	0

B Subgroup Analysis

Subgroup	Blinatumomab	Chemotherapy Only	Hazard Ratio for Death (95% CI)
	no. of deaths/total no.		
All MRD-negative patients	17/112	40/112	0.41 (0.23–0.73)
Age			
<55 yr	4/66	21/65	0.16 (0.05–0.47)
≥55 yr	13/46	19/47	0.66 (0.33–1.35)
Combined molecular risk			
Favorable	0/19	6/28	0.00
Intermediate	2/22	5/19	0.32 (0.06–1.65)
Unfavorable	12/50	24/45	0.39 (0.19–0.78)
BCR::ABL1–like genotype			
BCR::ABL1–like	2/16	7/15	0.28 (0.06–1.36)
Not *BCR::ABL1*–like	15/96	33/97	0.40 (0.22–0.74)
Transplantation intended			
Yes	6/36	13/35	0.40 (0.15–1.05)
No	11/76	27/77	0.37 (0.18–0.75)
CD20 status			
Positive	7/45	16/46	0.43 (0.18–1.04)
Negative	1/26	7/26	0.13 (0.02–1.05)
Rituximab use			
Yes	5/33	14/36	0.38 (0.14–1.06)
No	3/38	9/36	0.28 (0.08–1.03)



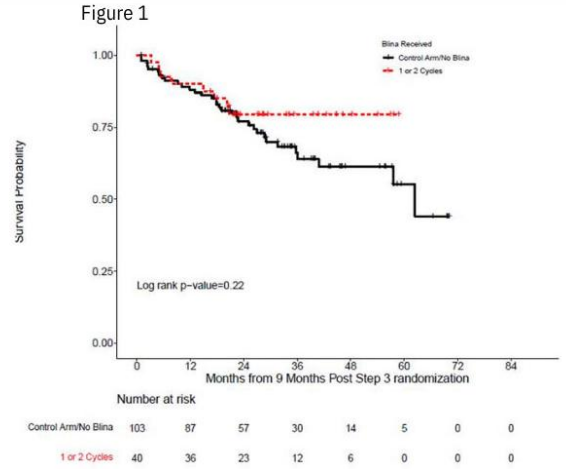
Litzow MR et al.: N Engl J Med 2024;391:320-33

When should blinatumomab be incorporated?

- Only 224 of the original 488 enrolled patients “made it” to randomization
- More than half (264 patients) did not undergo randomization, most commonly due to refractory or relapsed disease.
- This suggests that some adults with B-ALL have inherently chemotherapy-resistant leukemia and would benefit from early exposure to blinatumomab, perhaps subverting impending treatment failure.
- Studies are underway investigating blinatumomab as part of earlier induction therapy

Outcomes of Consolidation Therapy By Number of Cycles of Blinatumomab Received In the ECOG-ACRIN E1910 Randomized Phase NCTN Trial

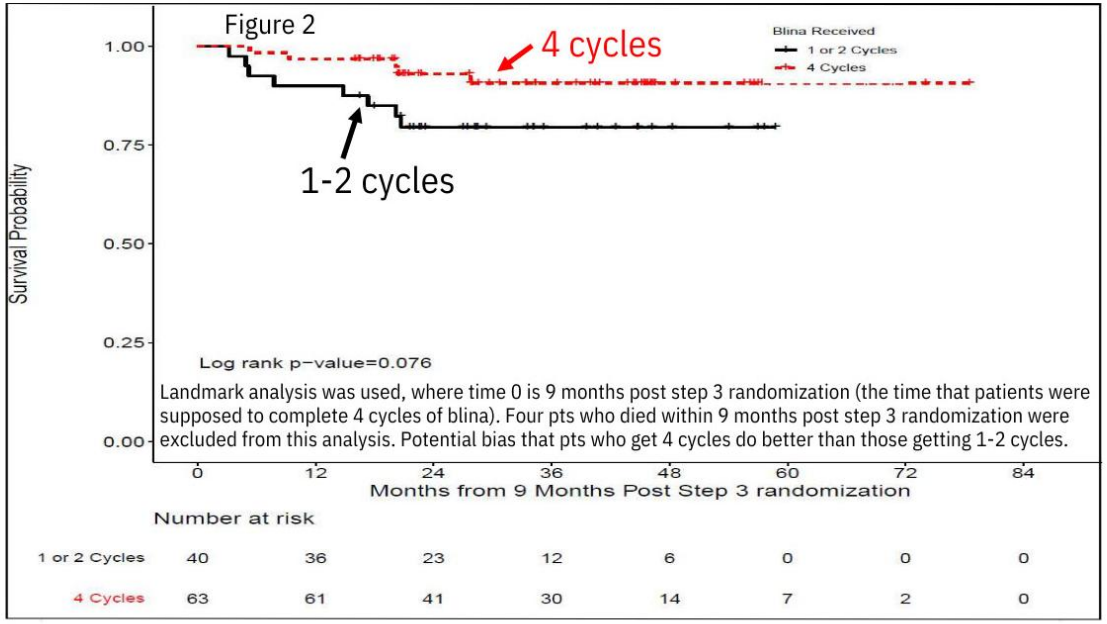
Figure 1



1 -2 cycles
Vs
control

Landmark analysis was used, where time 0 is 9 months post step 3 randomization (the time that patients were supposed to complete 4 cycles of blina). Four pts who died within 9 months post step 3 randomization were excluded from this analysis.

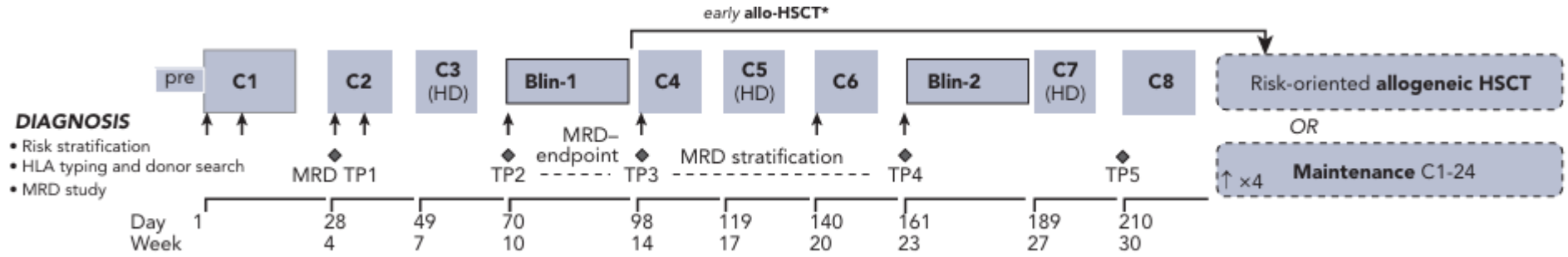
Figure 2

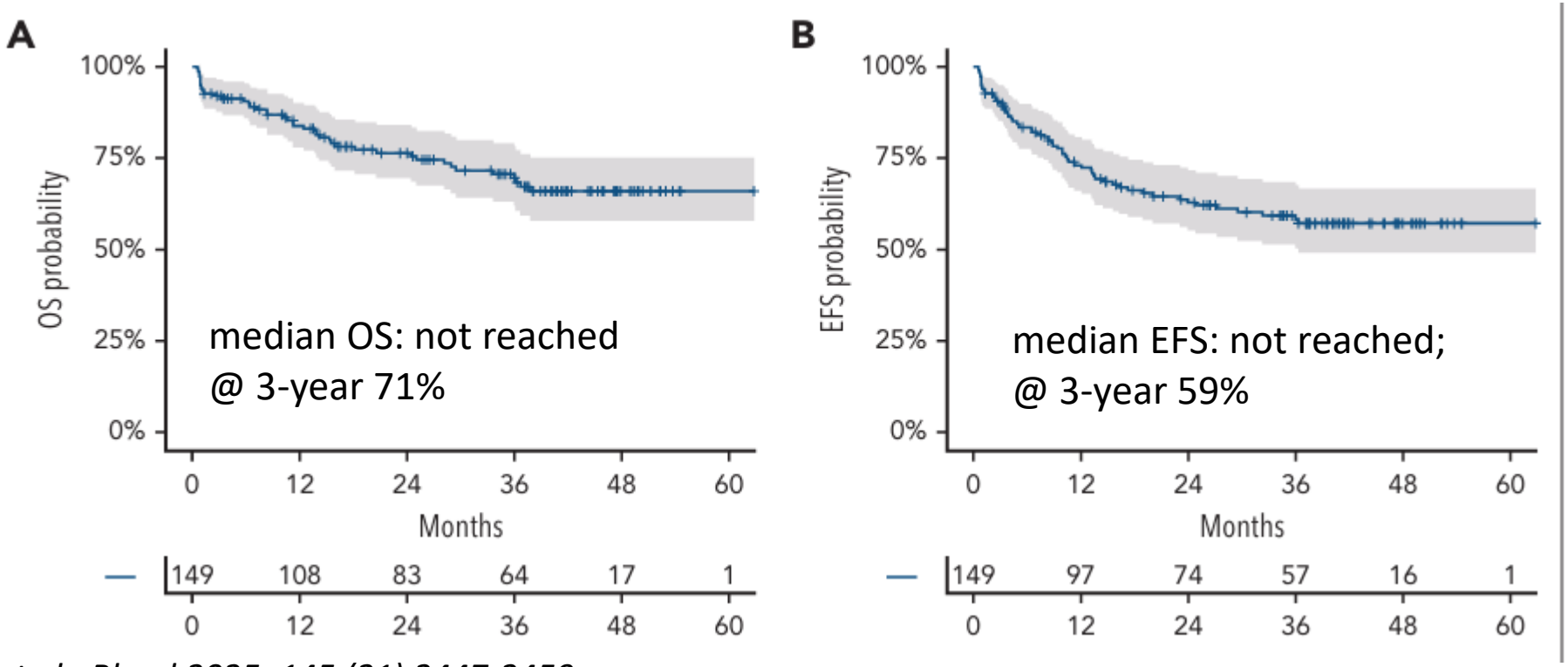


Luger SM et al.: Blood, 2023 *Blood* (2023) 142 (Supplement 1): 2877.https://doi.org/10.1182/blood-2023-189648

Up-front blinatumomab improves MRD clearance and outcome in adult Ph– B-lineage ALL: the GIMEMA LAL2317 phase 2 study

median age, 41 years (range, 18-65)



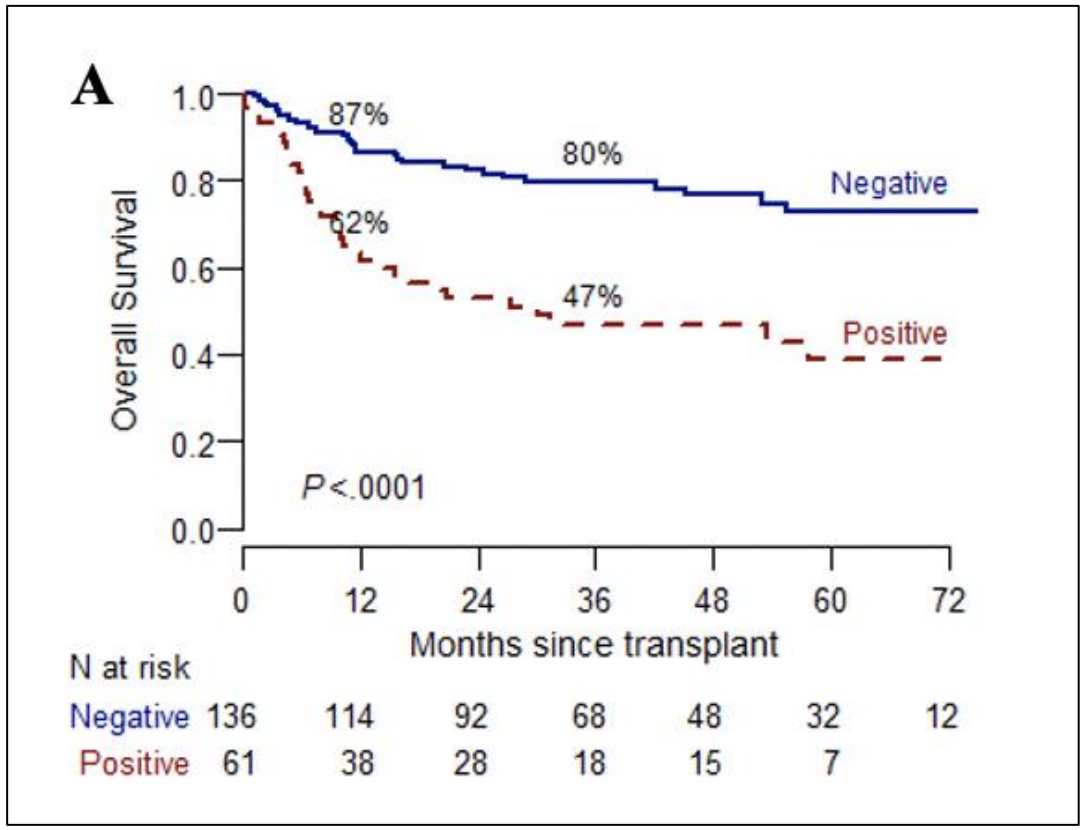


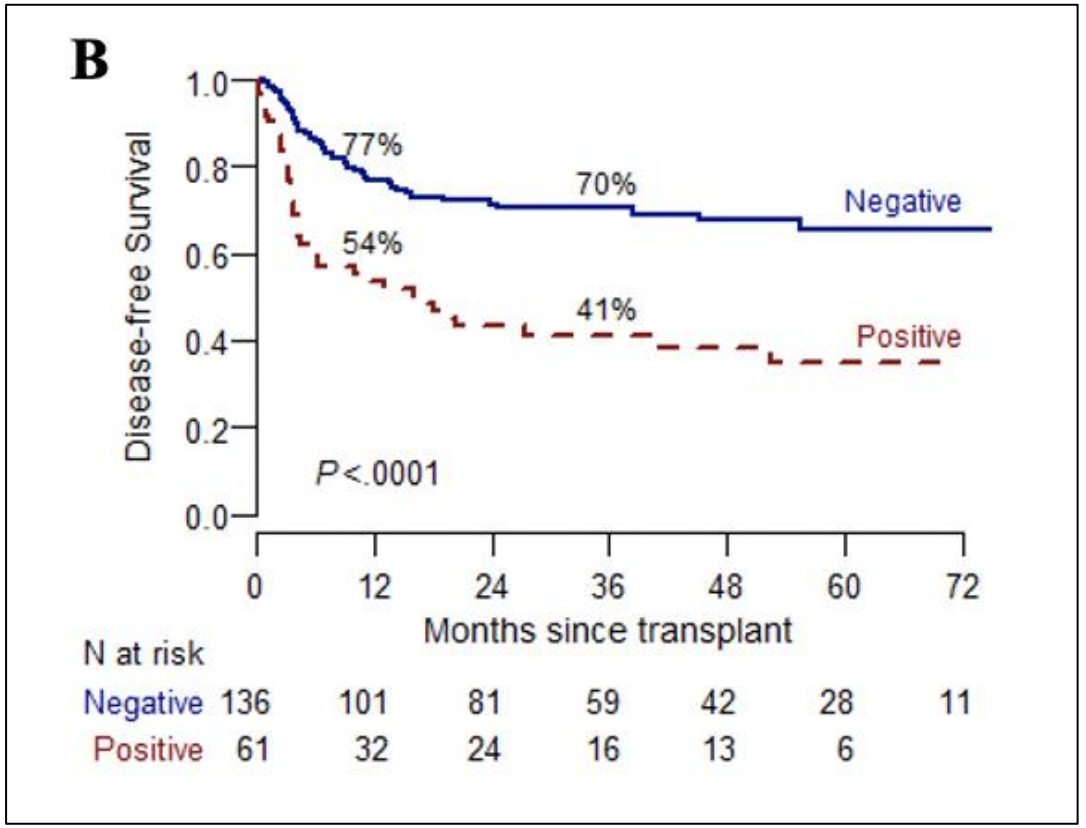
Bassan R et al.: Blood 2025; 145 (21) 2447-2459.

Is transplant (always) the good equalizer?

(Should we transplant an MRD+ patient in CR1?)

Main outcomes of allo-SCT in adult Ph- B-ALL treated with the GIMEMA LAL 1913 Protocol in the Italian Real-Life

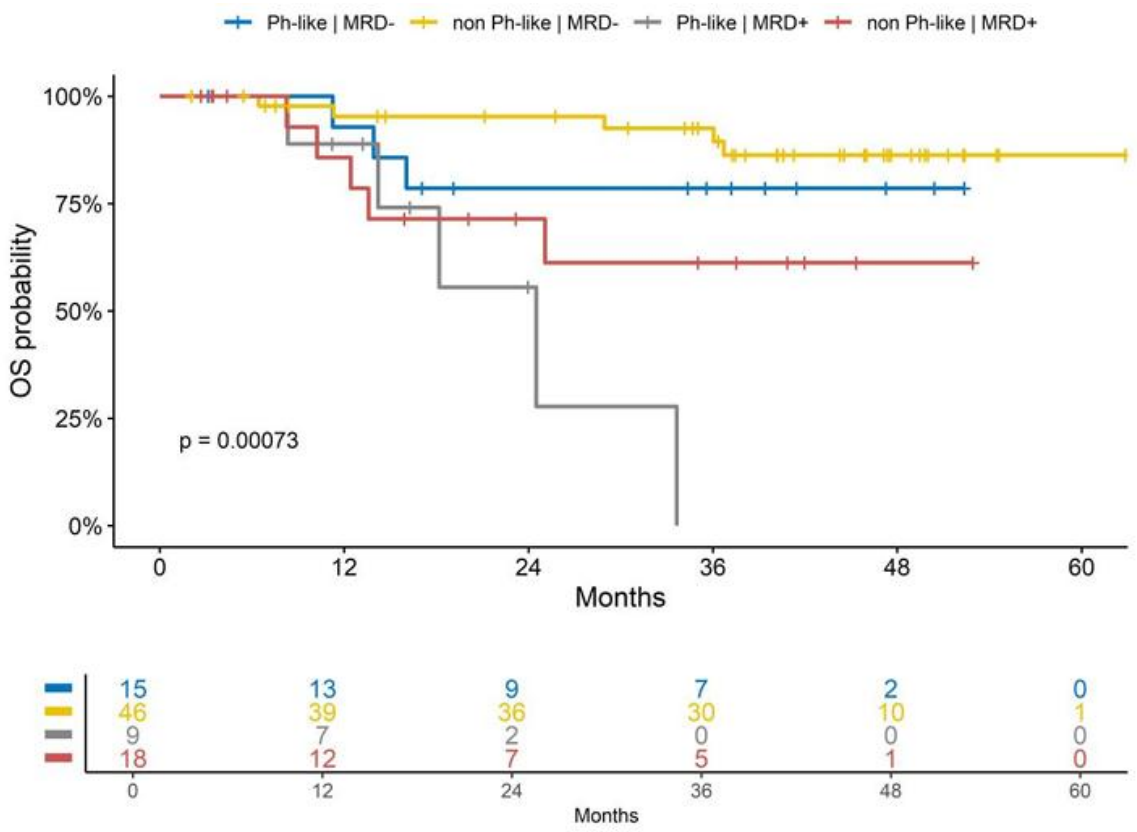


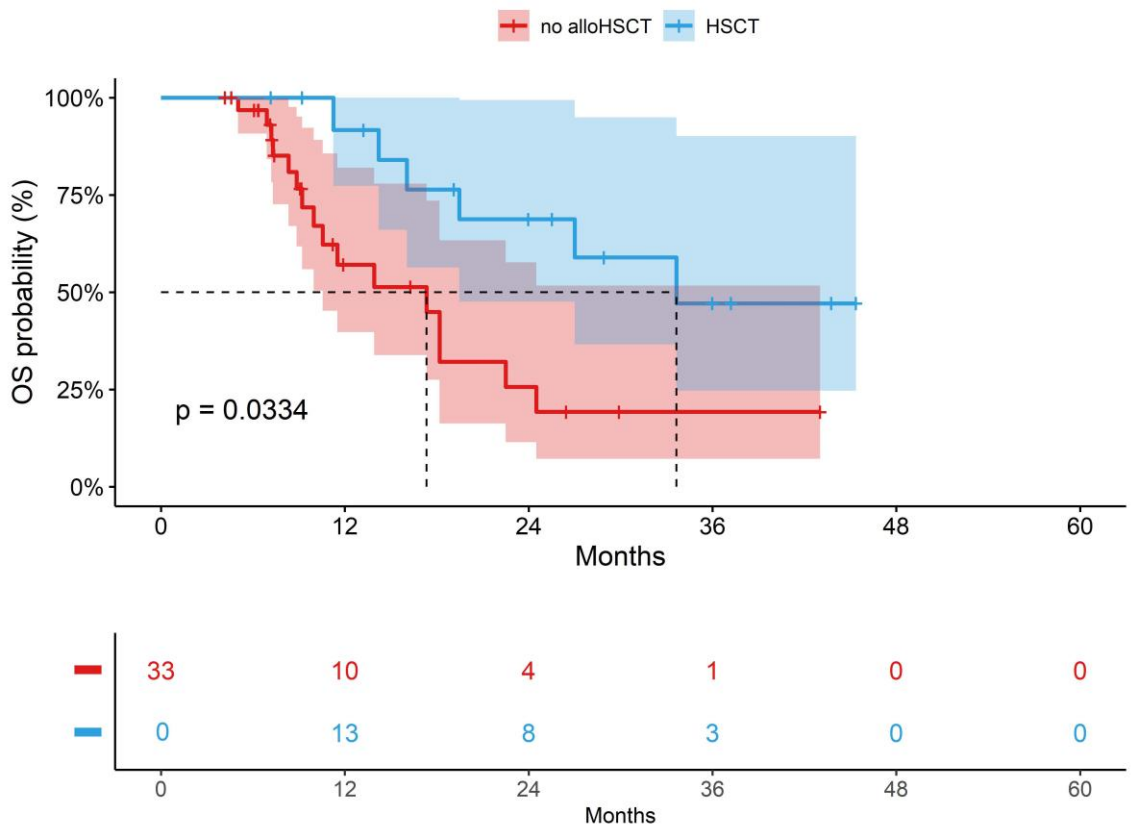


- Higher risk of disease relapse and a worse OS in patients with pre-transplant MRD positivity

Cavallaro G et al.: Bone Marrow Transplant. 2025 Sep;60(9):1228-1235. doi: 10.1038/s41409-025-02632-z. Epub 2025 Jun 2.

Overall Survival in Ph-like patients



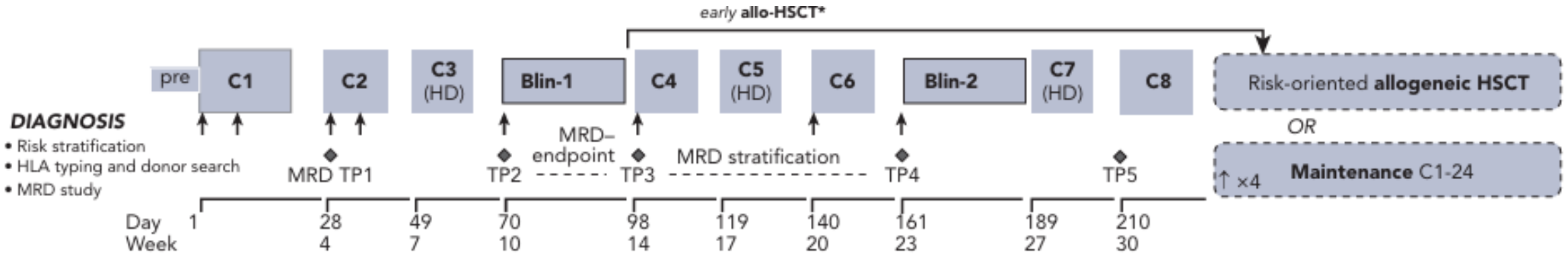


Bassan R et al.: Blood 2025; 145 (21) 2447-2459.

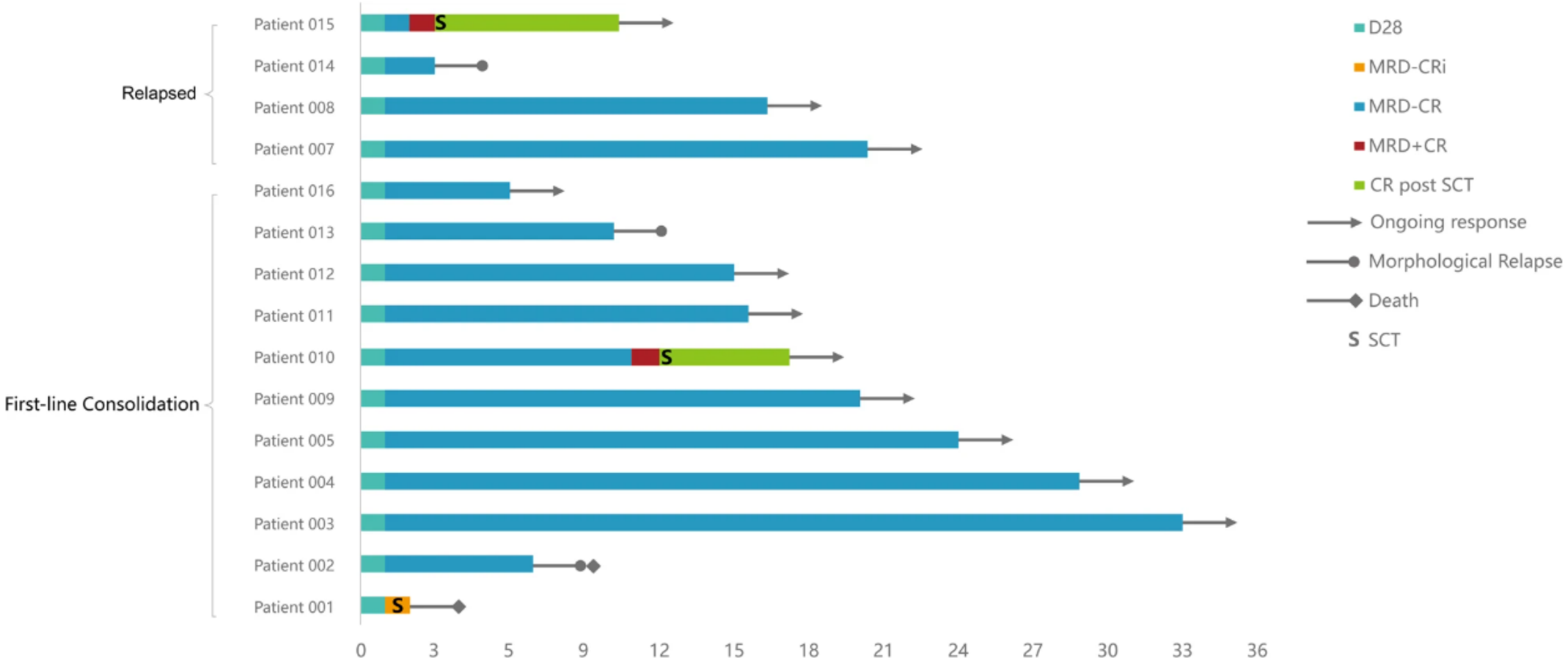
Lussana F et al, in preparation

Should we consider a change in the current place in therapy of alloHSCT ?

How to change the national treatment program for adult ALL?



CAR-T cells for MRD positive adult B cell ALL: a phase I clinical study

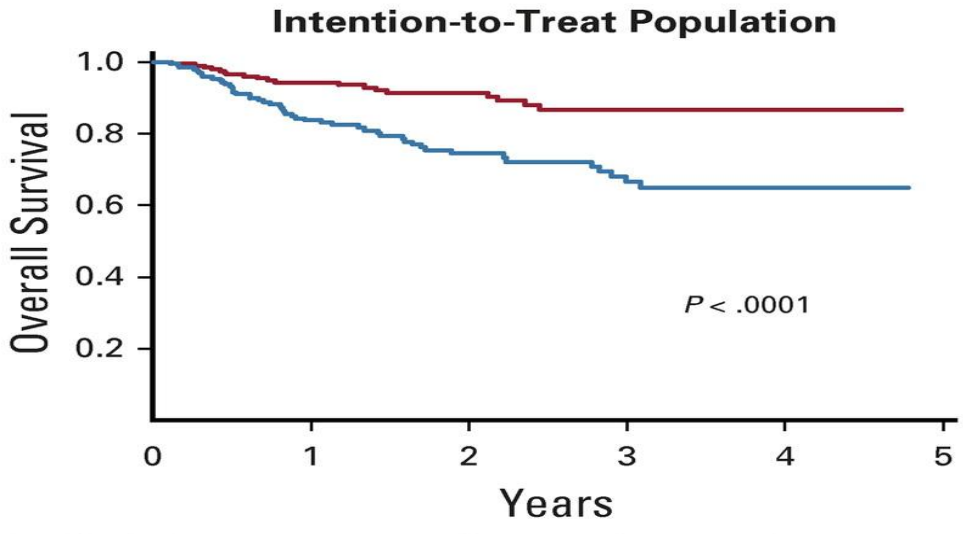


The bar chart shows the clinical response and follow-up of patients during CAR-T therapy. Each bar represents an individual patient and the study number.

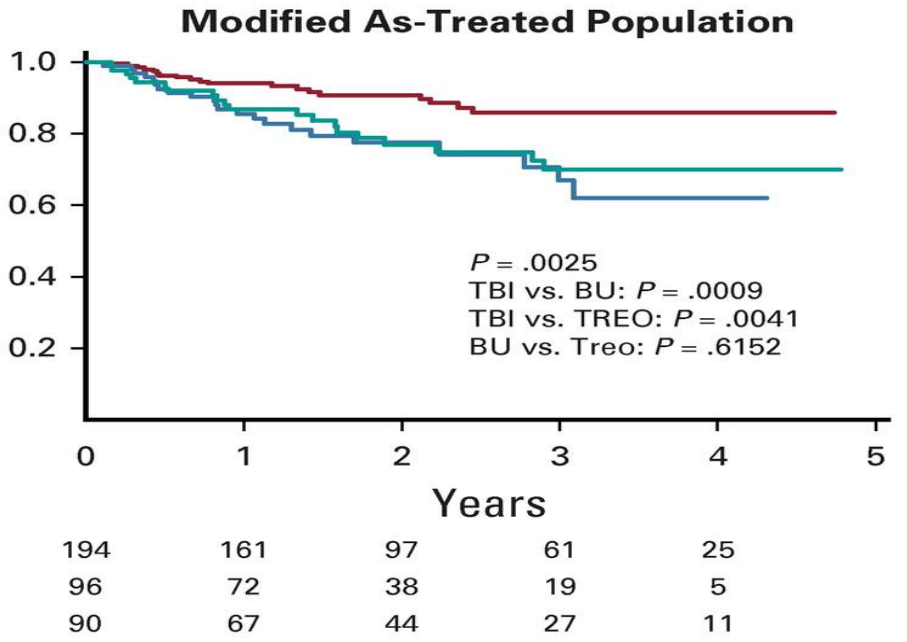
Niu J et al.: Blood Cancer Journal volume 13, Article number: 44 (2023)

How should we do an AlloHSCT ?

AlloHSCT in pediatric patients: the FORUM trial (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)

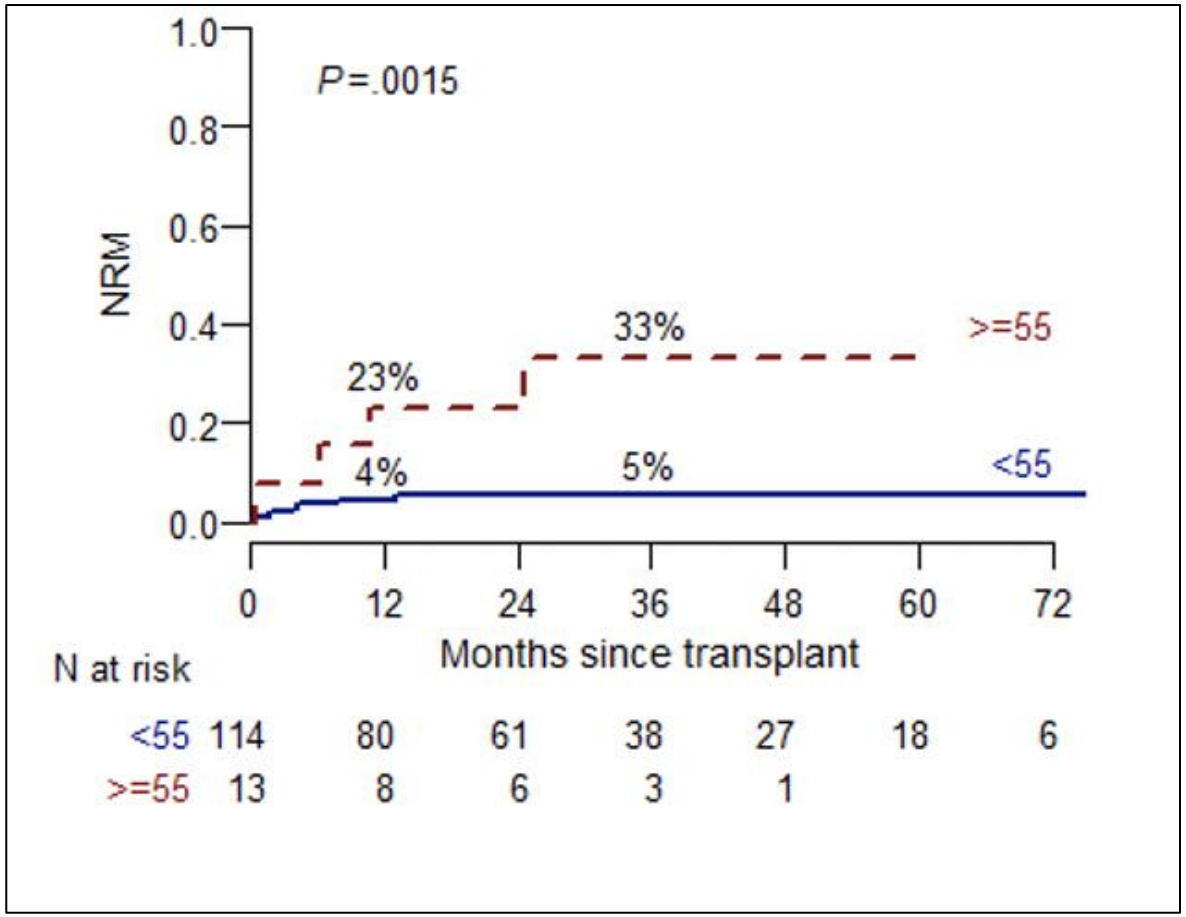


	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

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

NRM in adult ALL patients receiving TBI

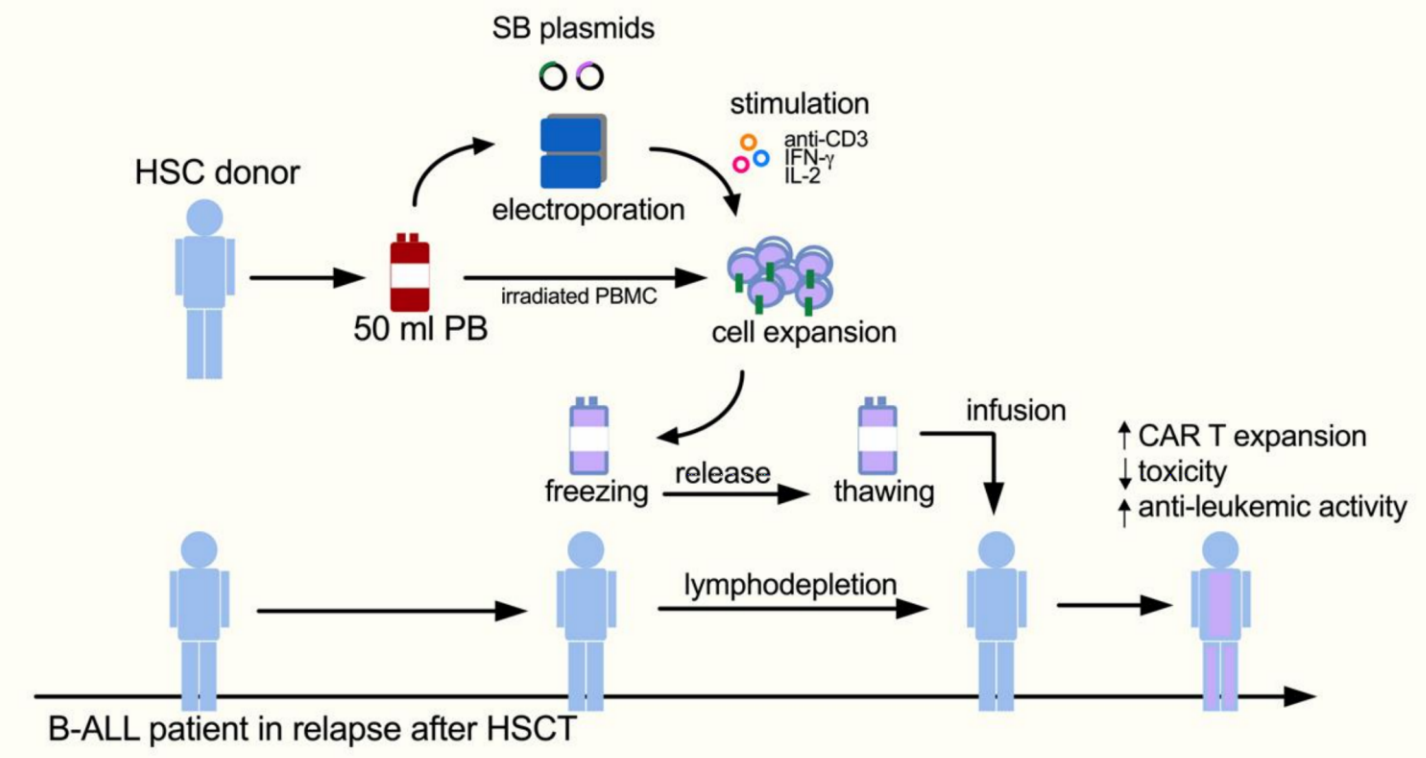
- Patients aged ≥ 55 years receiving TBI had a significantly higher NRM compared to the younger population (33% vs 5%,p= .0015)



Cavallaro G et al.: Bone Marrow Transplant. 2025 Sep;60(9):1228-1235. doi: 10.1038/s41409-025-02632-z. Epub 2025 Jun 2.

DONOR-DERIVED CARCIK-CD19 CELLS ENGINEERED WITH SB TRANSPOSON IN B-ALL RELAPSED AFTER ALLO-SCT

36 adult and pediatric patients enrolled at 2 sites



Safety

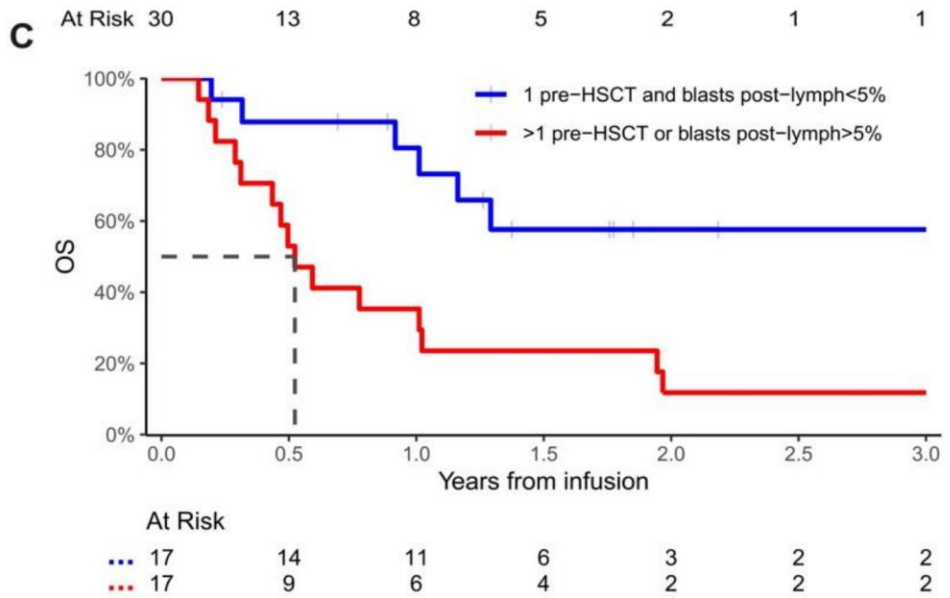
- **CRS:** Grade 1-2 = 41%, Grade 3+ = 0%
- **ICANS:** Grade 1-2 = 3%; Grade 3+ = 0%
- **GVHD:** 0%

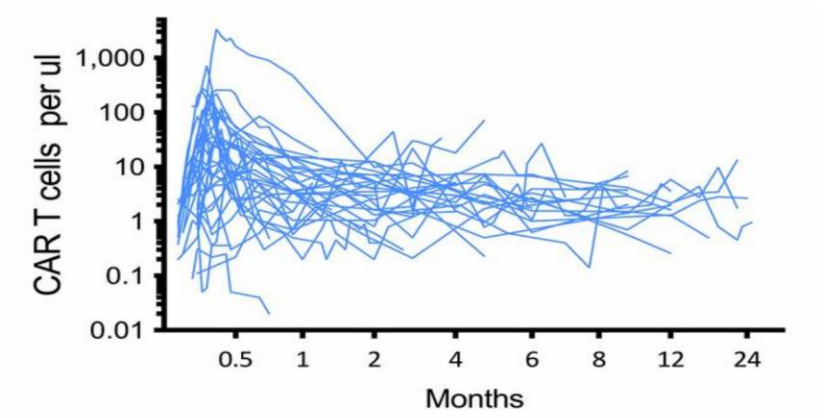
Magnani CF et al., J Clin Invest. 2020;130(11):6021-6033
Lussana F et al., Blood Cancer J. 2025;15(1):54.

DONOR-DERIVED CARCIK-CD19 CELLS ENGINEERED WITH SB TRANSPOSON IN B-ALL RELAPSED AFTER ALLO-SCT

Efficacy

- Median follow-up 2.2 years
- 30/36 reached CR (83%)
- 86% were MRD-negative
  - 12 patients (33%) did not experience a relapse
  - 3 patients (25%) underwent a second alloHSCT
  - 6 patients (17%) are still disease-free without additional therapies (1 with CAR-T circulating after 40 months)
  - 3 died in CR



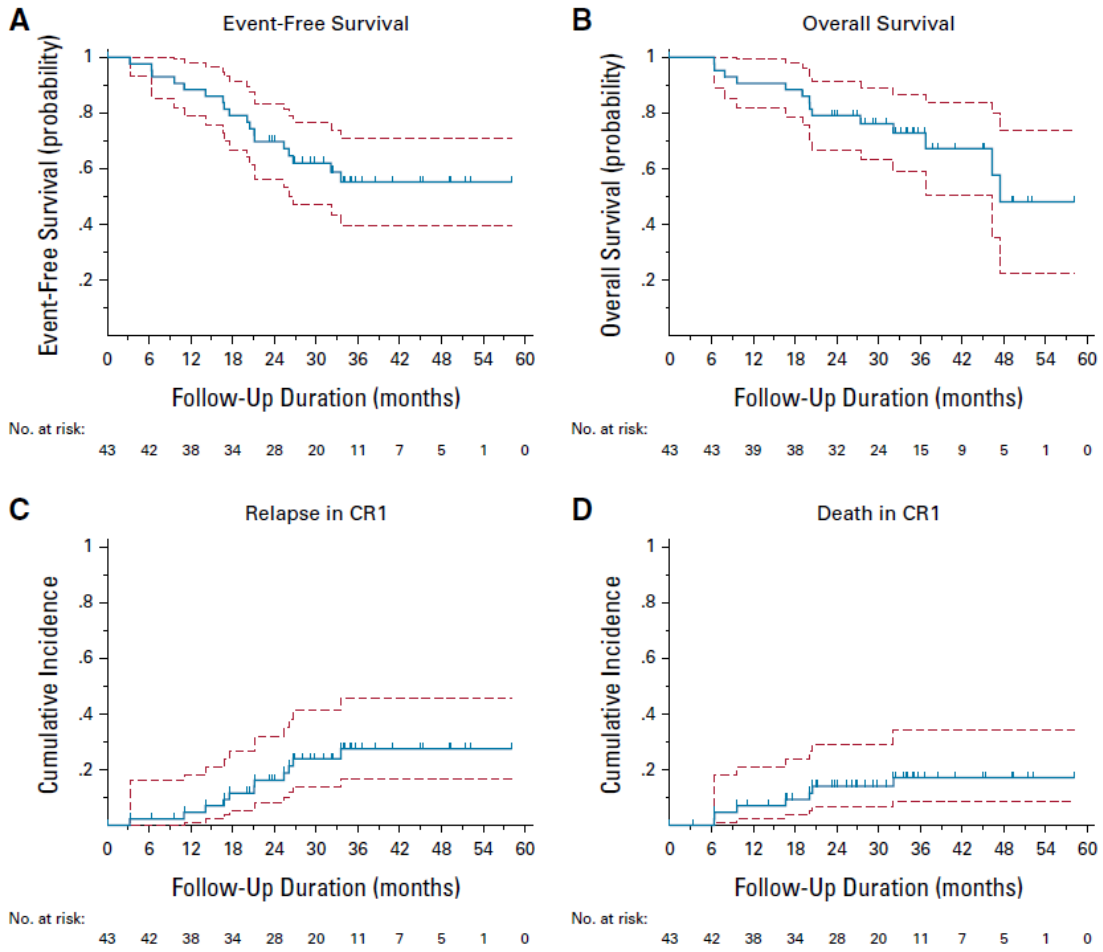


Magnani CF et al., J Clin Invest. 2020;130(11):6021-6033
Lussana F et al., Blood Cancer J. 2025;15(1):54.

The treatment for the older patients

First-Line Inotuzumab Ozogamicin in Older Patients With BP-ALL

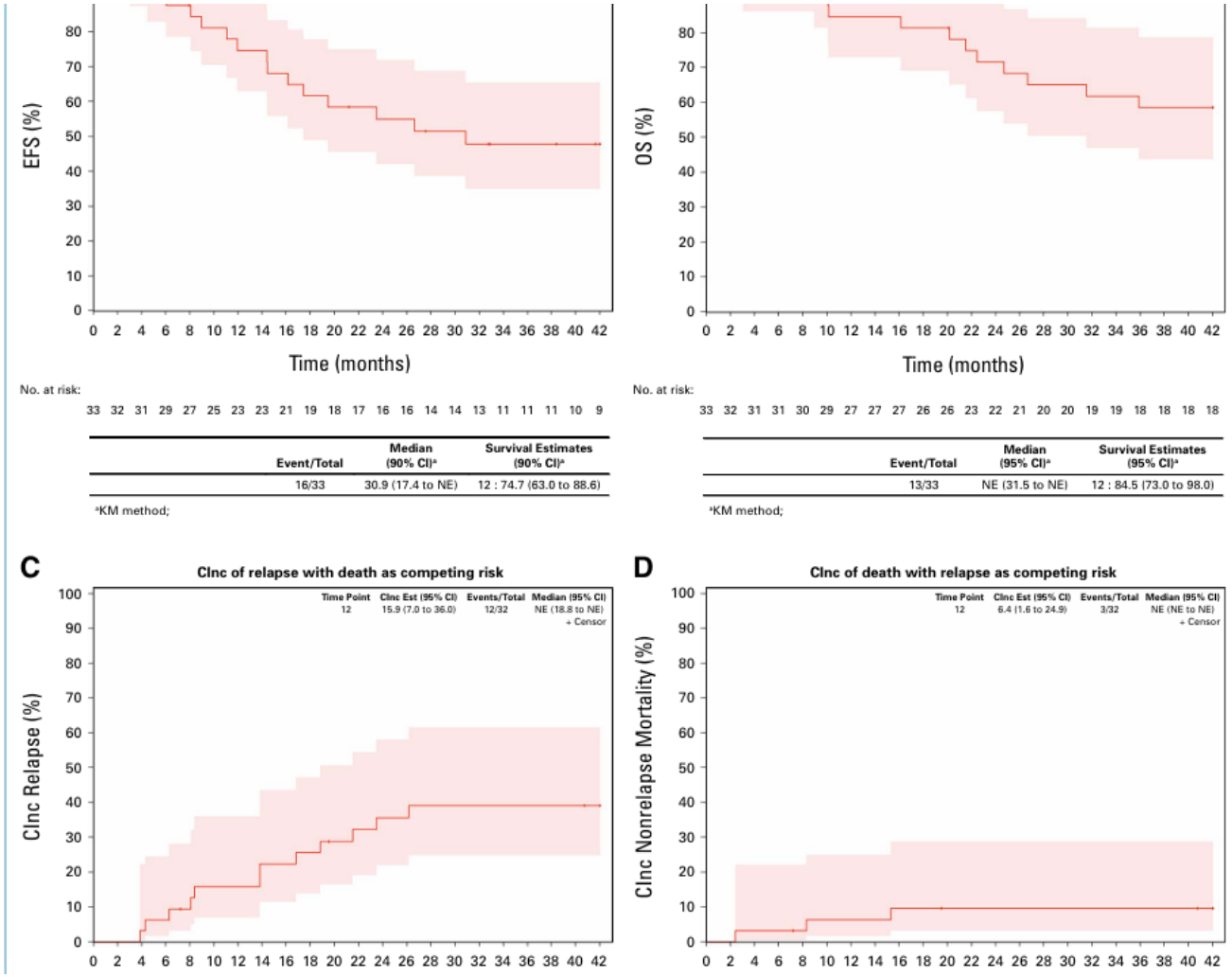
- 43 BP-ALL with a median age of 64 years (range, 56-80), two cycles of inotuzumab ozogamicin induction therapy.
- All patients achieved complete remission (CR/CR with incomplete hematologic recovery).
- (53%) and (71%) patients had no evidence of molecularly assessed MRD (minimum 10^{-4} threshold) after 2nd and 3rd inductions, respectively.
- After a median follow-up of 2.7 years, EFS at one (primary endpoint) and 3 years was 88% and 55% while overall survival (OS) was 91% and 73%, respectively.



Stelljes M et al.: J Clin Oncol. 2024 Jan 20;42(3):273-282

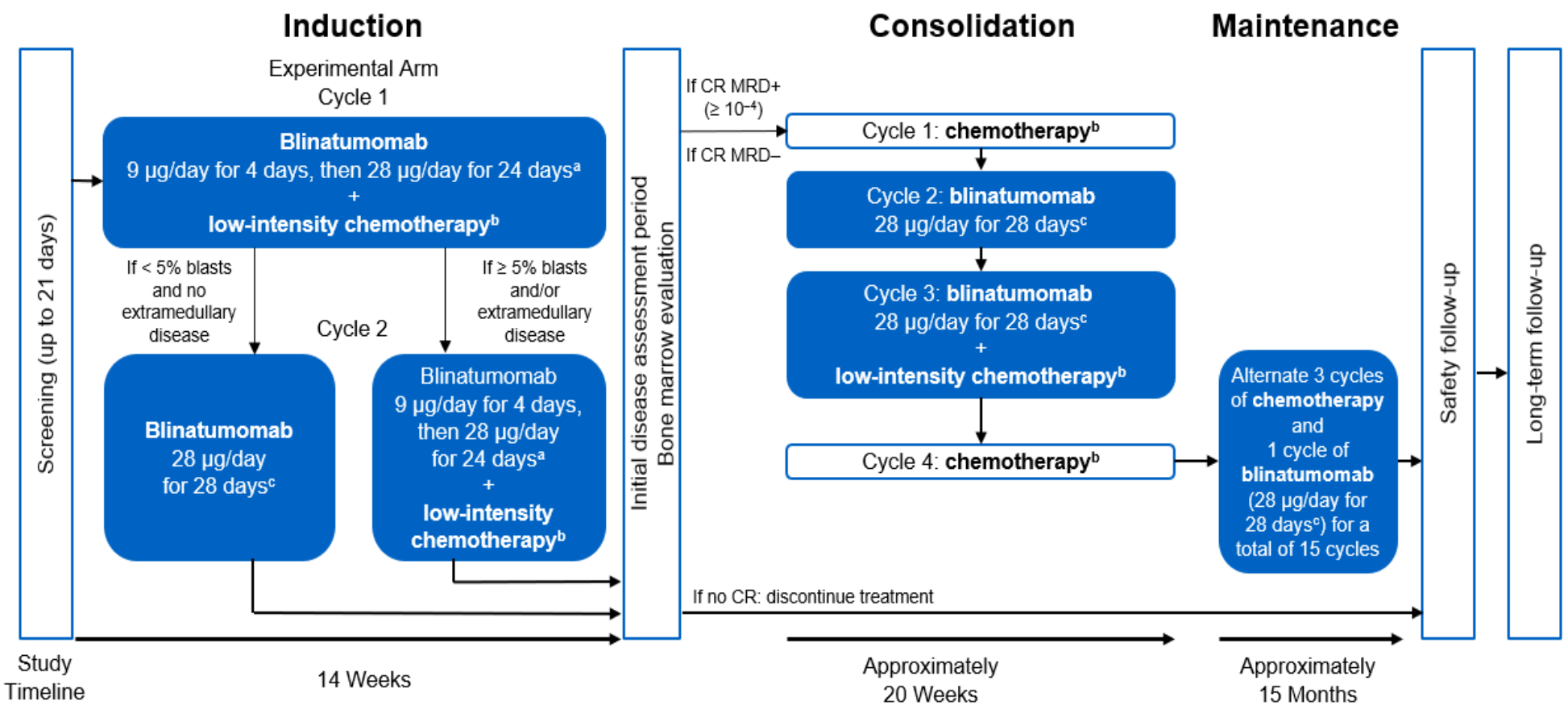
Inotuzumab Ozogamicin Then Blinatumomab for Older Adults With Newly Diagnosed B-Cell ALL: Alliance Study A041703 Cohort 1 Results

At a median follow-up of 30 months, the 1-year EFS and overall survival were 75% and 85%, respectively



Wieduwilt MJ et al Journal of Clinical Oncology 2025 DOI https://doi.org/10.1200/JCO-25-00307

Blinatumomab Alternating With Low-Intensity Chemotherapy (CT) Treatment for Older Adults With Newly Diagnosed Philadelphia (Ph)-Negative BCP-ALL: the Phase 3 Randomized Controlled Golden Gate Study



Endpoints

Primary

- **Safety run-in: safety and tolerability**
- **Phase 3: EFS, OS**

Key secondary

- Safety run-in: CR, MRD, RFS
- Phase 3: CR, MRD, RFS, safety, global health status

Population

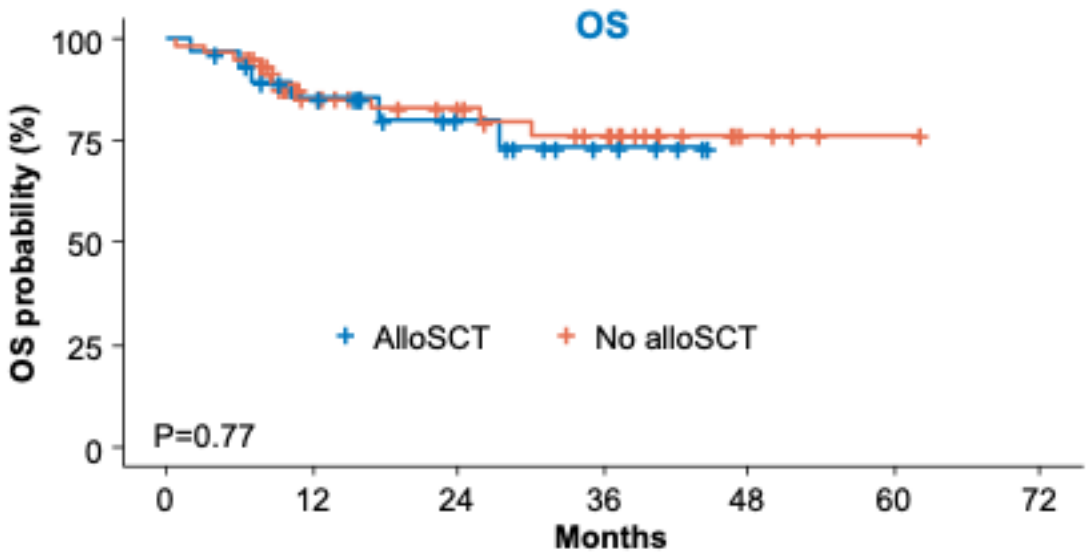
- **Adults ≥55 years and 40 to <55 years with at least 1 of comorbidities***
- **Newly diagnosed Ph– B-ALL**
- Simple size: **284 pts**

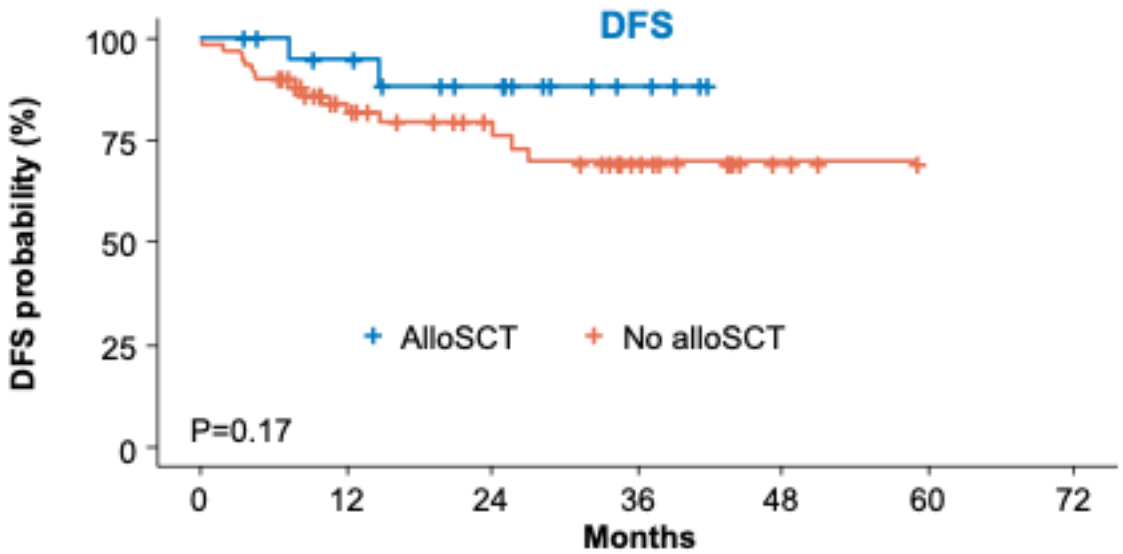
- *Jabbour, e et al.: Blood (2022) 140 (Supplement 1): 6134–6136.*

What about the “lucky patients” with a Ph+ ALL? Moving on from the incredible recent past to the future!

OS and DFS of allografted and non-allografted patients

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





- After blinatumomab treatment, 29 patients continued treatment with a TKI (72% with dasatinib)
- **46% of patients underwent alloSCT**; out of these, 6 were in second CHR

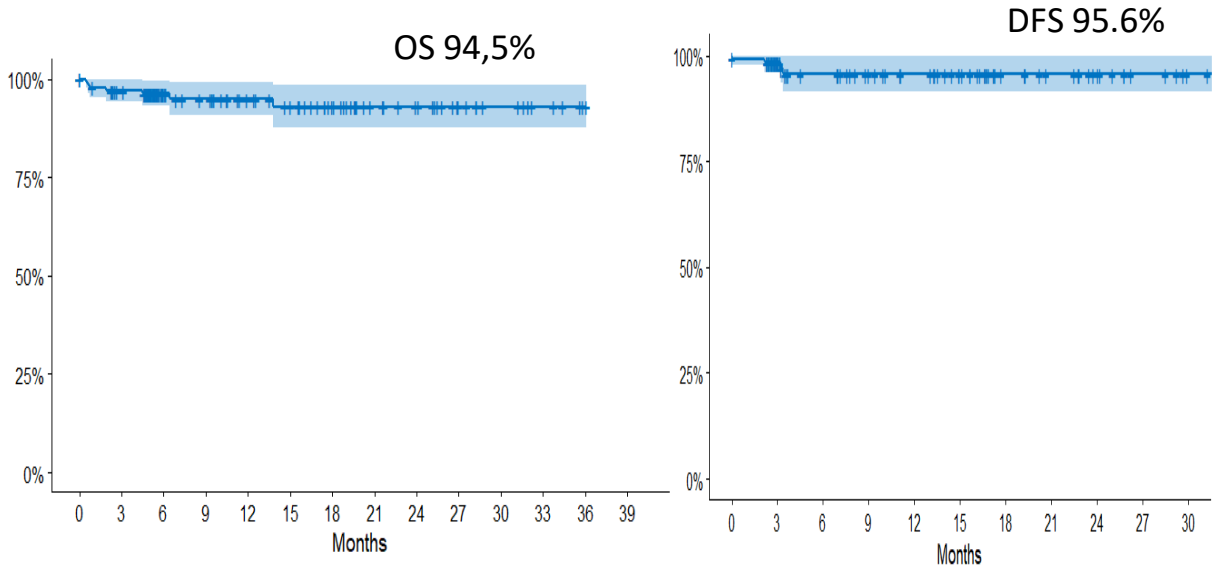
- Relapse was seen in 9 patients
  - 4 were hematologic relapses, 4 CNS, and 1 nodal relapse
  - Median time to relapse was 4.4 months (1.9–25.8)
- 6 deaths were reported in first CHR, of which 3 occurred after alloSCT

GIMEMA D-ALBA trial. Median age 54 (24–82)

Foà R, et al. J Clin Oncol 2024;42:881–5; Chiaretti S, et al. Poster presented at: European Hematology Association (EHA); June 9–12, 2022; Vienna, Austria. Abstract P353.

The GIMEMA 2820 clinical trial: OS, DFS, and response rates in the experimental arm

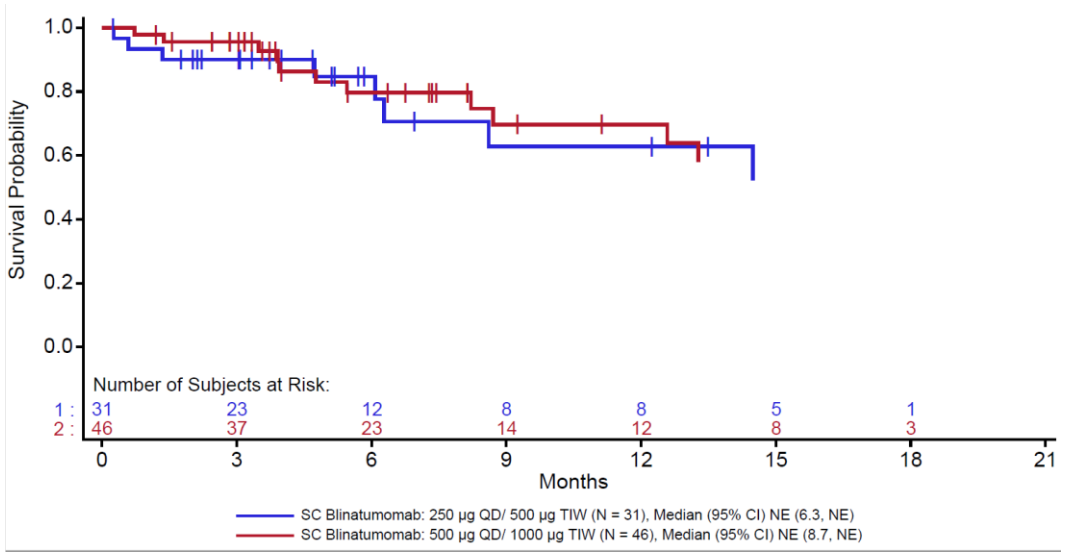
GIMEMA ALL 2820 trial



- Patients elected to AlloHSCT: about 20%

Chiaretti et al, abs 835, ASH 2024

Combining a TKI to subcutaneous blinatumomab



Jabbour E, Lussana F et al. Lancet Haematol 2025

Conclusions

- In Ph negative adult ALL, pediatric inspired chemotherapy programs with the addition of front-line blinatumomab led to a significant improvement in the outcome of adult
- Patients at high risk of relapse due to molecular or cytogenetics adverse features and lack of early MRD clearance should be referred to alloHSCT as soon as possible since transplant remains a curative treatment option for chemo-resistant patients
- The achievement of molecular remission before transplant is recommended. Post transplant immunotherapy may represent another important treatment option
- For older patients the primary goal is to avoid unnecessary toxicity and to offer immunotherapy as soon as possible
- In patients timely selected to transplant, the NRM has declined