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, A.

Negativizzare l'MRD pretrapianto allogenico nella AML a rischio intermedio?

No: noli tempus perdere

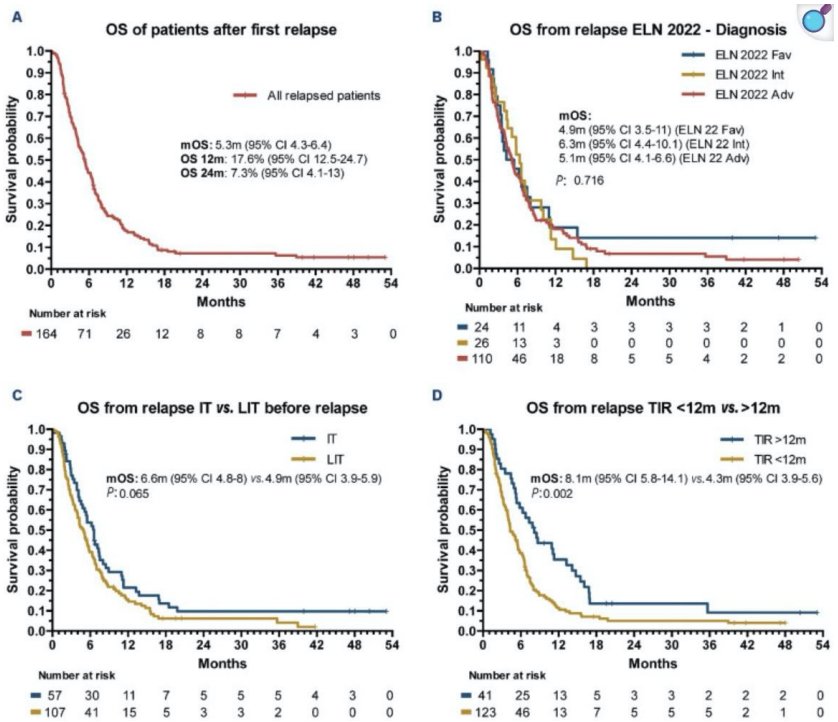
A. Rambaldi (Bergamo)

Disclosure statement

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

Outcomes and genetic dynamics of AML at first relapse

- MD Anderson Cancer Center (April 2017- October 2022)
- 875 AML
- median age 65 years (range 18-94)



Bataller A et al.: Haematologica. 2024 May 2. doi: 10.3324/haematol.2024.285057 [Epub ahead of print]

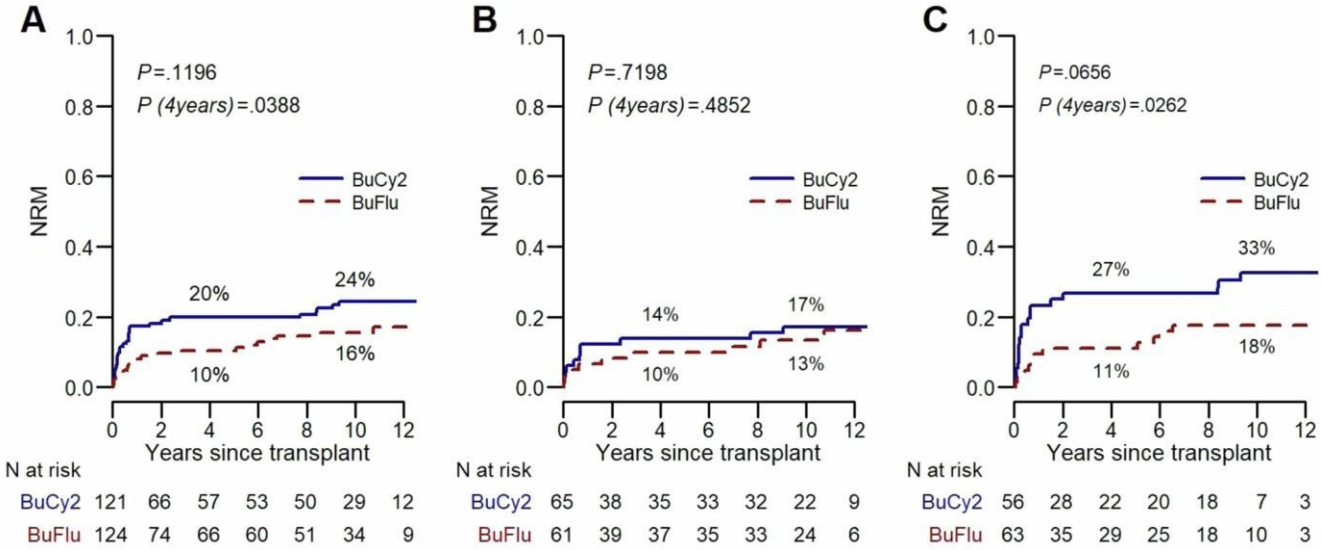
In AML AlloHSCT is the most effective consolidation treatment: estimated risk of relapse with and without transplant and estimate of incidence of non-relapse mortality following allo-SCT

2017 ELN risk stratification	Estimated risk of relapse following consolidation with			Maximal tolerated NRM prognostic scores for allo-SCT to be considered	
	MRD after cycle 2 chemotherapy	Chemotherapy alone (%)	Allo- SCT (%)	HCT-CI score	NRM risk (%)
Favorable	Negative	30	15-20	N/A (not advisable to proceed)	
	Positive	75	30-40	3-4	<30
Intermediate	Negative	55	25-30	2	<20
	Positive	75	35	3-4	<30
Adverse	N/A	>90	50	5	<35

Jan J. Cornelissen and Didier Blaise, Blood 2016;12 7(1):62 -70

Loke J, Vyas H and Craddock C (2021) Front. Oncol. 11:666091. doi: 10.3389/fonc.2021.666091

NRM has been remarkably reduced after alloHSCT in AML…

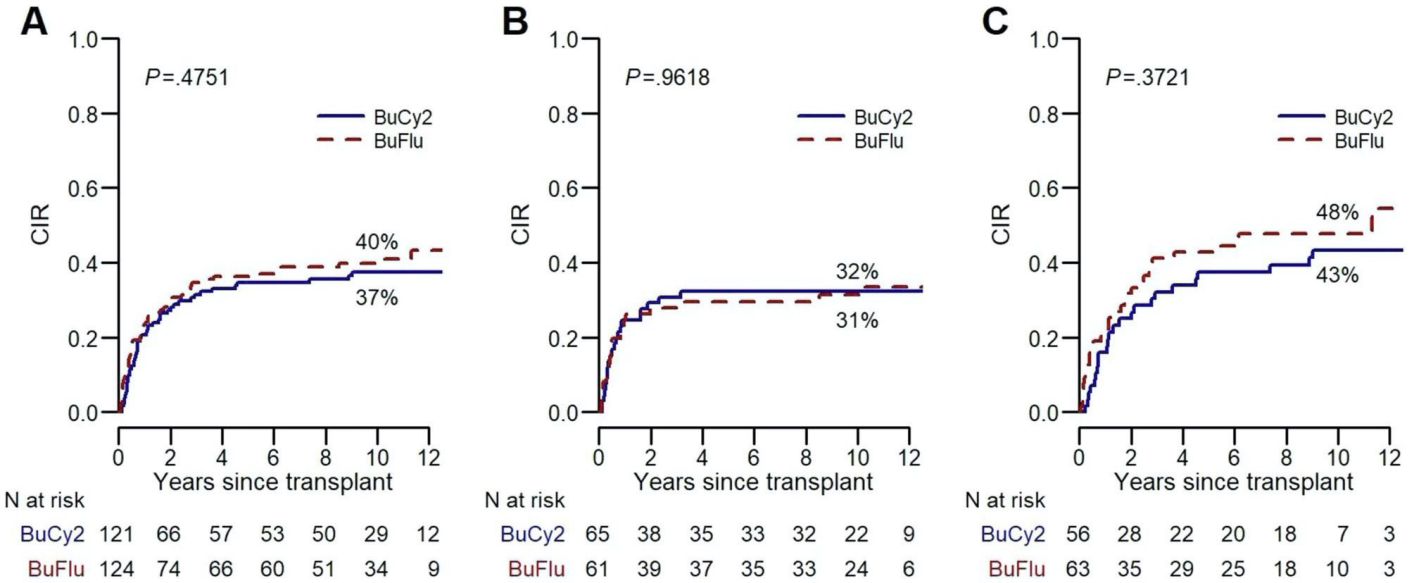


Non-relapse mortality (NRM) at year 4 and 10 after transplantation of the entire study population (**A**); Non-relapse mortality at 4 and 10 years in patients younger than 51 years (**B**); Non-relapse mortality at 4 and 10 years in patients older than 51 years (**C**).

G. Cavallaro et al BCJ Blood Cancer Journal (2024)14:141

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

… but leukemia relapse remains high



A Cumulative incidence of relapse (CIR) at 10 years in the entire study population; **B** Cumulative incidence of relapse at 10 years in patients younger than 51 years; **C** Cumulative incidence of relapse at 10 years in patients older than 51 years.

G. Cavallaro et al BCJ Blood Cancer Journal (2024)14:141

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

What should be done in each newly diagnosed AML?

- Risk definition, high-resolution HLA typing and donor search activation within 30 days
- Donor identification and selection within 60 days
- Allogeneic transplant in each intermediate/high risk AML within 90-120 days

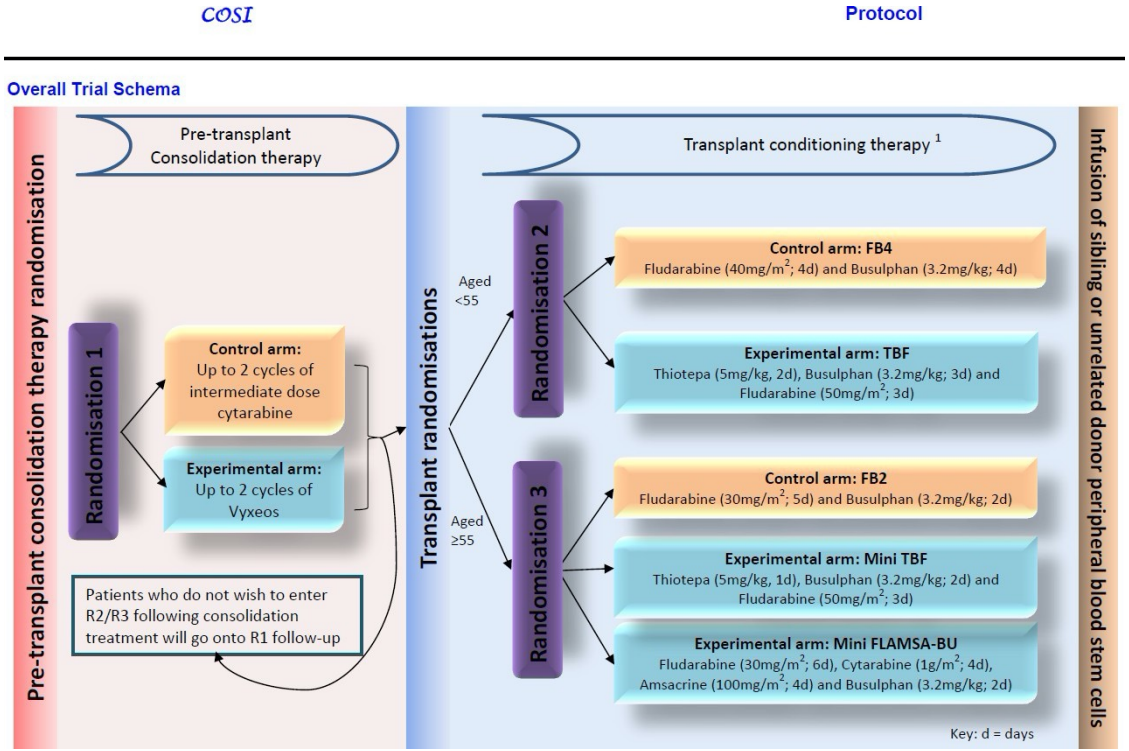
G. Cavallaro et al BCJ Blood Cancer Journal (2024)14:141

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

An International Randomised Clinical Trial of Therapeutic Interventions with the Potential to Improve Outcome in Adults with AML and High-Risk MDS Undergoing AlloHSCT (COSI Study)

Is this timing feasible? (from diagnosis to transplant)

Yes, it is!



Chief Investigator: Professor Charles Craddock

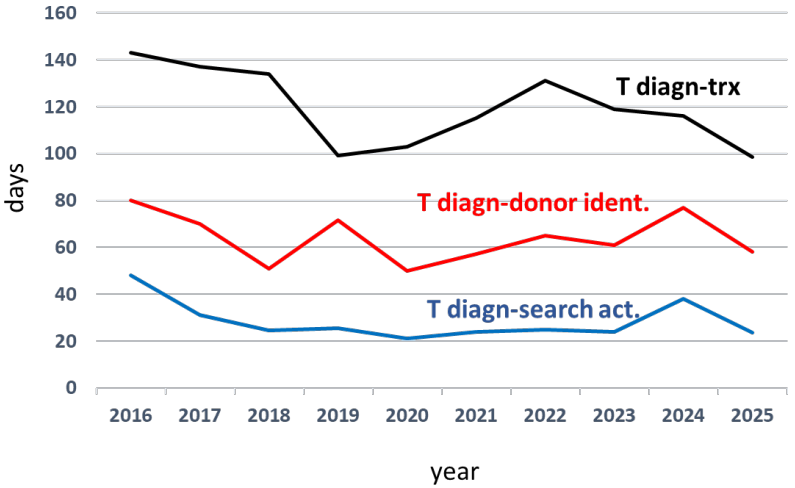
Donor search activation, identification and time to transplant in AML: Bergamo results

Period: 2016-2025

Donor search activations for AML:180

Donor identified 150 (83%) (140 UD+ 10 CB)

Transplants performed:123 (68%) (94 UD +10 CB+ 19 Haplo)

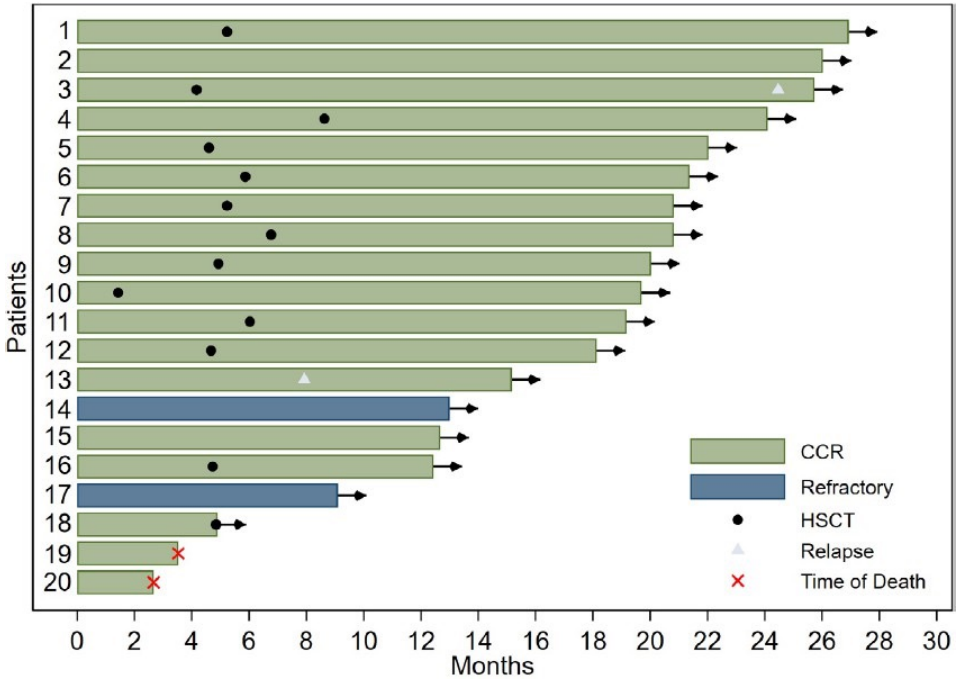


MRD is prognostically important, but what can we do to improve it before transplant?

- **Perhaps not all induction treatments are equal…**
- **Be careful before reducing the intensity of the conditioning regimen…**

Venetoclax combined with cladribine, idarubicin, cytarabine (CLIA-VEN) results in higher remission rates over conventional 7 + 3 chemotherapy without increased toxicity in newly diagnosed AML

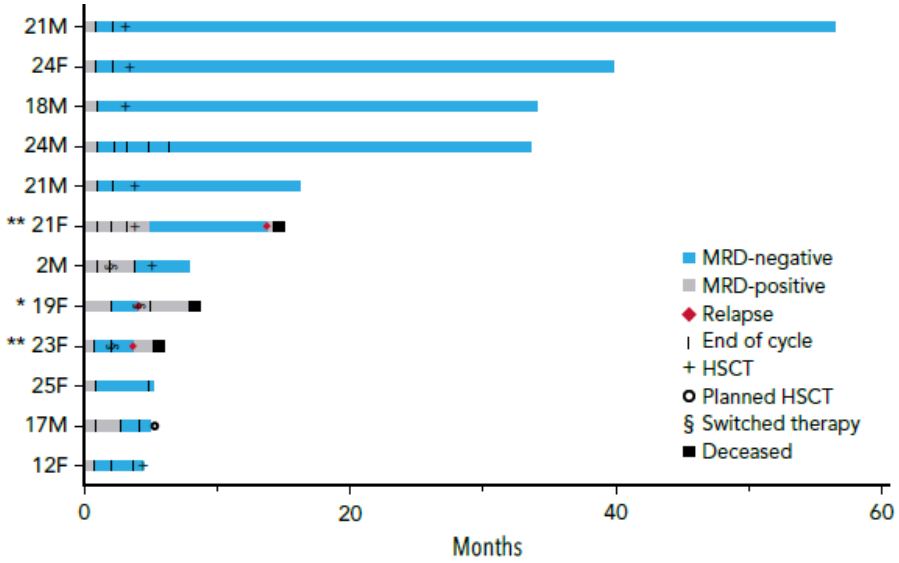
In this retrospective study: CLIA-VEN was associated with a higher cumulative incidence of composite CR (CCR) (90% vs. 54.8%; $p = 0.002$) and minimal residual disease (MRD) negative
CCR (93.8% vs. 40.9%; $p < 0.001$) at 28 days



Lee BJ et al.: Br J Haematol. 2026;208:570–578

FLAG-IDA plus venetoclax for children, adolescents, and young adults with newly diagnosed AML

- FLAG-IDA with venetoclax shows promise as frontline pediatric acute myeloid leukemia therapy.
- In 12 patients treated at MD Anderson, most achieved remission with good early survival outcomes, and many proceeded to transplant.
- Common toxicities included cytopenias, **comparable to previous regimens (??)**.



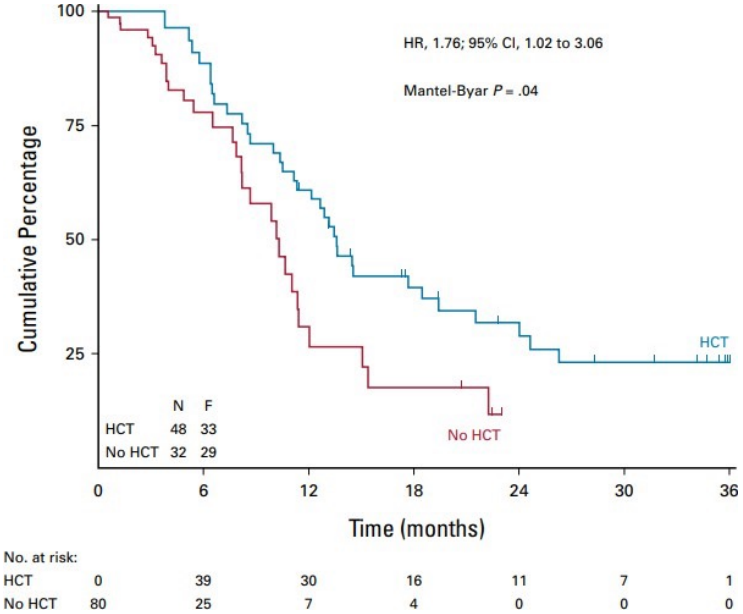
Reeja R et al.: Blood 20 NOVEMBER 2025 | VOLUME 146, NUMBER 21 2611

What about patients who will never get into a meaningful MRD negative remission

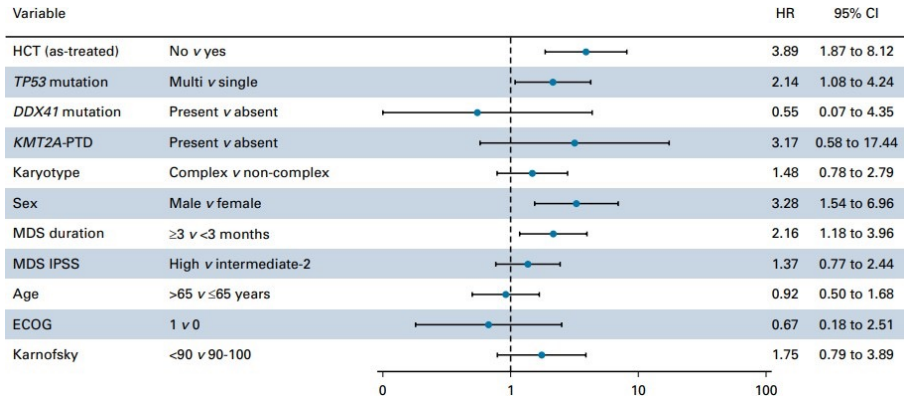
AlloHSCT for TP53-mutated MDS/AML: utility or futility?

AlloHSCT improves Overall Survival of patients with mutated TP53

OS in Patients WithTP53 mutations With HCT as Time-Dependent Covariate

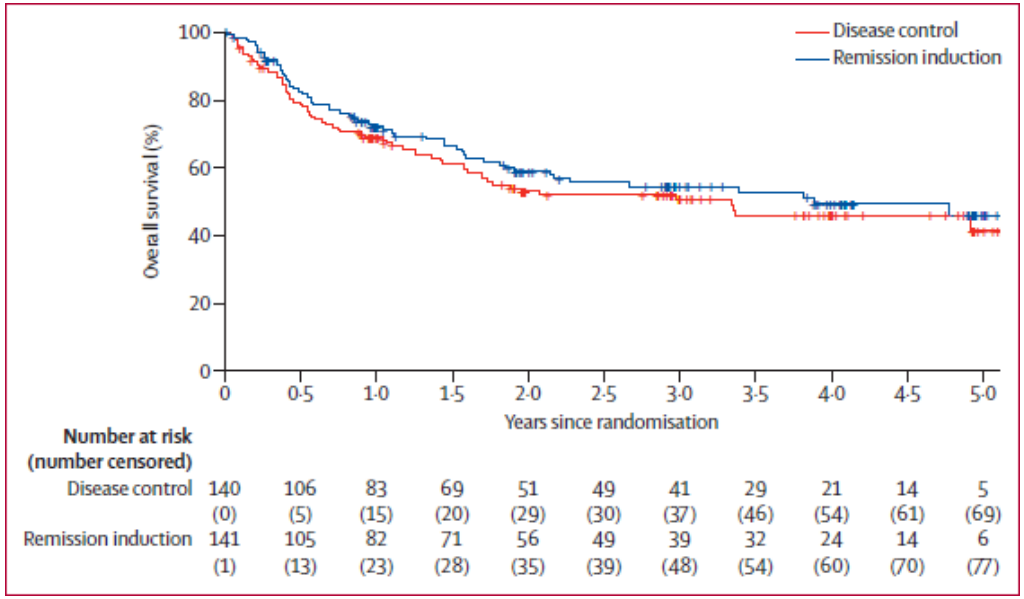


Forest plot of subgroup analyses in patients with mutated TP53



Versluis J. et al.: J Clin Oncol 41:4497-4510, 2023 DOI https://doi.org/10.1200/JCO.23.00866

Remission induction versus immediate AlloHSCT for patients with relapsed or poor responsive AML(ASAP): a randomised, open-label, phase 3, non-inferiority trial



Number at risk (number censored)											
Disease control	140	106	83	69	51	49	41	29	21	14	5
	(0)	(5)	(15)	(20)	(29)	(30)	(37)	(46)	(54)	(61)	(69)
Remission induction	141	105	82	71	56	49	39	32	24	14	6
	(1)	(13)	(23)	(28)	(35)	(39)	(48)	(54)	(60)	(70)	(77)

Stelljes M et al.: Lancet Haematol 2024; 11: e324–35

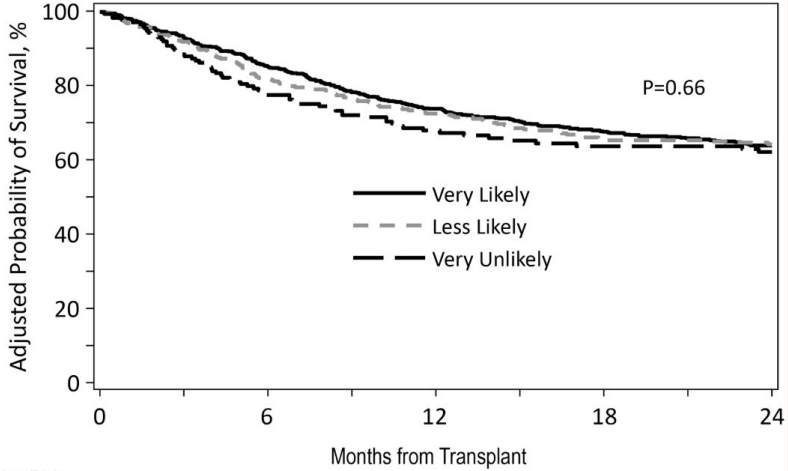
Time to transplant matters!

(more than MRD before transplant and HLA match)

Primary Results From Blood and Marrow Transplant Clinical Trials Network 1702: Clinical Transplant-Related Long-Term Outcomes of Alternative Donor Allogeneic Transplantation

Aim and key hypothesis

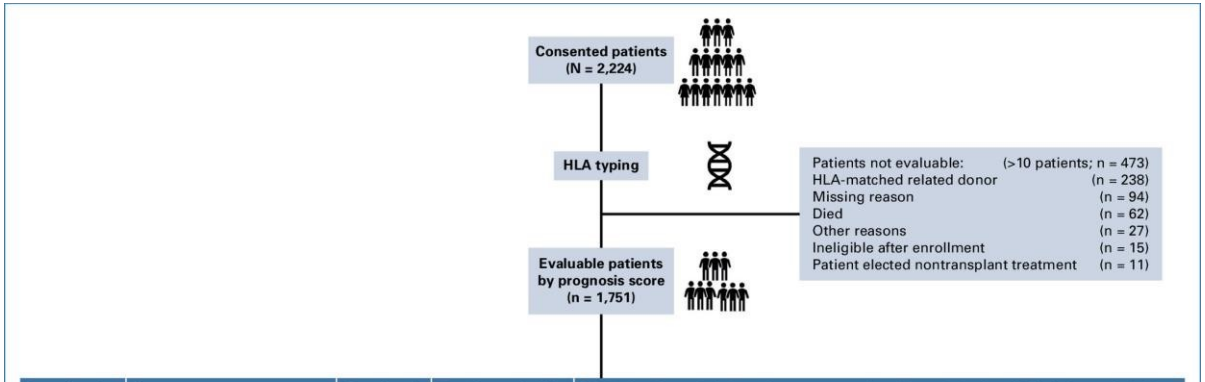
- The likelihood of finding a human leukocyte antigen (HLA)–matched unrelated donor (MUD) for hematopoietic cell transplantation can be predicted using a donor search prognosis score.
- Patients without a MUD may use alternative donors (haploidentical related, mismatched unrelated, or umbilical cord blood).
- The primary end point was 2-year survival from evaluability and compared between those Very Likely (>90%) and Very Unlikely (<10%) to find a MUD.



N at Risk					
Very Likely	668	564	481	391	303
Less Likely	340	278	244	182	126
Very Unlikely	170	130	112	86	70

Lee SJ et al.: Journal of Clinical Oncology 43:3369-3380; 2025

Looking for the Best Allogeneic Donor and the BMT CTN 1702 Study: Noli Tempus Perdere



Donor Search Prognosis	Strategy	Transplanted patients	Time from evaluability to transplant, months median(min-max)	Multivariate Cox model of transplant outcomes, adjusted for a priori selected clinical characteristics, by donor search prognosis						
				Relapse	TRM	DFS	OS	Grade 2 to 4 GVHD	Grade 3 to 4 GVHD	Any chronic GVHD
Very likely n = 958	Search for HLA-matched URD with intention to do 8/8 MUD HCT	n = 668	3.3 (0.1-39.7)	1 Overall $P = .66$	1 Overall $P = .89$	1 Overall $P = .24$	1 Overall $P = .66$	1 Overall $P = .93$	1 Overall $P = .38$	1 Overall $P = .42$
Very unlikely n = 276	Direct to alternative donor source without a prolonged URD search	n = 170	3.3 (0.5-35.4)	1.40 $P = .047$	1.06 $P = .78$	1.25 $P = .10$	1.15 $P = .36$	0.95 $P = .71$	1.13 $P = .65$	0.92 $P = .59$
Less likely n = 517	Observational study of search and transplant practice according to the usual center practice	n = 340	3.4 (0.1-42.6)	1.15 $P = .32$	1.09 $P = .64$	1.11 $P = .33$	1.03 $P = .78$	0.97 $P = .80$	1.33 $P = .16$	0.85 $P = .19$

Rambaldi A.: Journal of Clinical Oncology 43:3331-3333; 2025

A golden rule to reduce the risk of relapse after transplant

buy time to give the donor immune system a chance to tackle leukemia outgrowth

Maintenance therapy with oral decitabine plus cedazuridine after alloHSCT for MDS

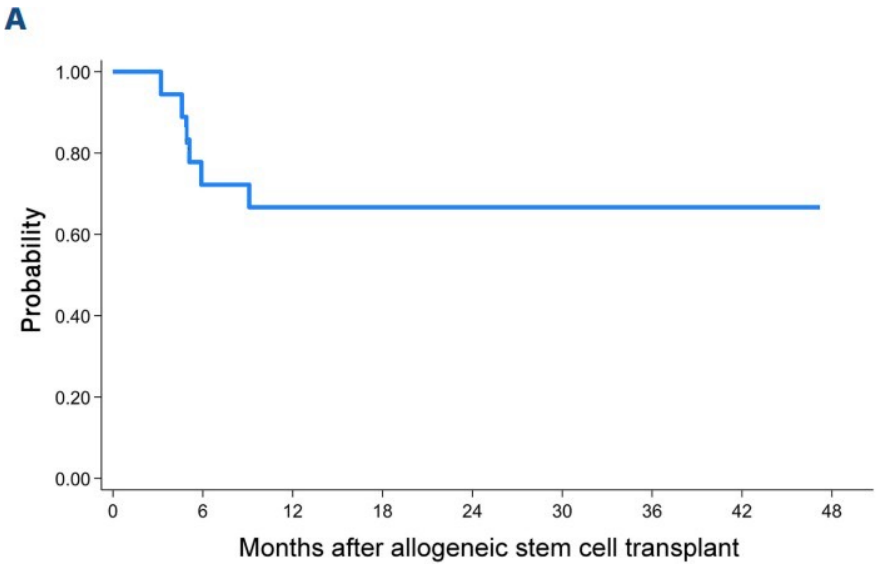
Baseline characteristics	Values
Age in years, median (range)	62.5 (28-76)
Sex, N (%) Male Female	 12 (66.6) 6 (33.3)
TP53 mutated, N (%)	8 (44)
BM blast count % at diagnosis, median (range)	5 (2-15)
IPPS-R, high and very high risk, N (%)	9 (50)
Pre-HSCT BM blast count %, median (range)	2 (1-4)
Stem cell source, N (%) Bone marrow Peripheral blood stem cells	 1 (5) 17 (95)
Conditioning regime, N (%) Fludarabine/melphalan-based Busulfan-based Fludarabine-TBI	 3 (17) 14 (78) 1 (5)
Donor type, N (%) Matched unrelated donor Matched sibling Haploidentical	 10 (56) 7 (39) 1 (5)

- Oral decitabine 35 mg - cedazudirine 100 mg
- maintenance start within 180 days post-HSCT
- Patients included were in CR, defined as <5% BM blasts and MRD- by Flow Cytometry
- No active GVHD and active infection at time of maintenance initiation

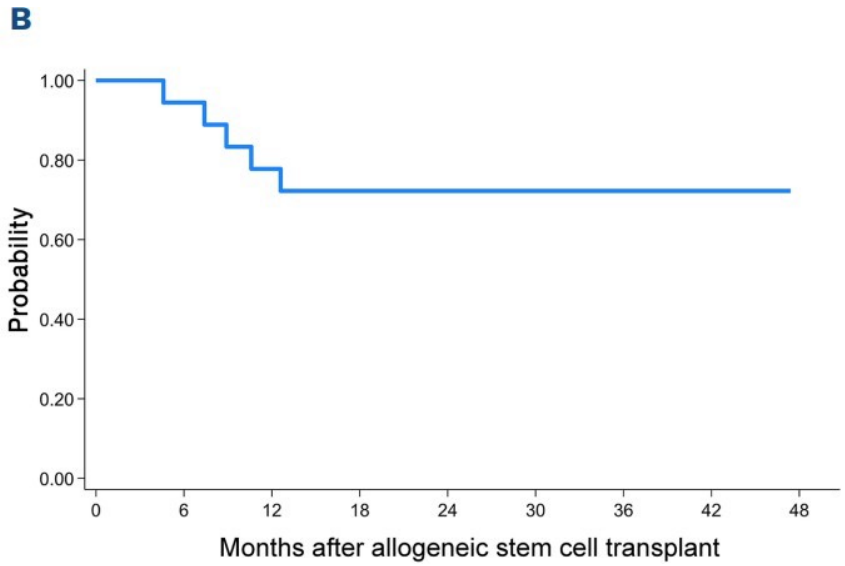
Smallbone P et al.: Haematologica Vol. 110 No. 8 (2025): August, 2025 https://doi.org/10.3324/haematol.2024.287177

Maintenance therapy with oral decitabine plus cedazuridine after alloHSCT for MDS

Progression-free survival



Overall survival



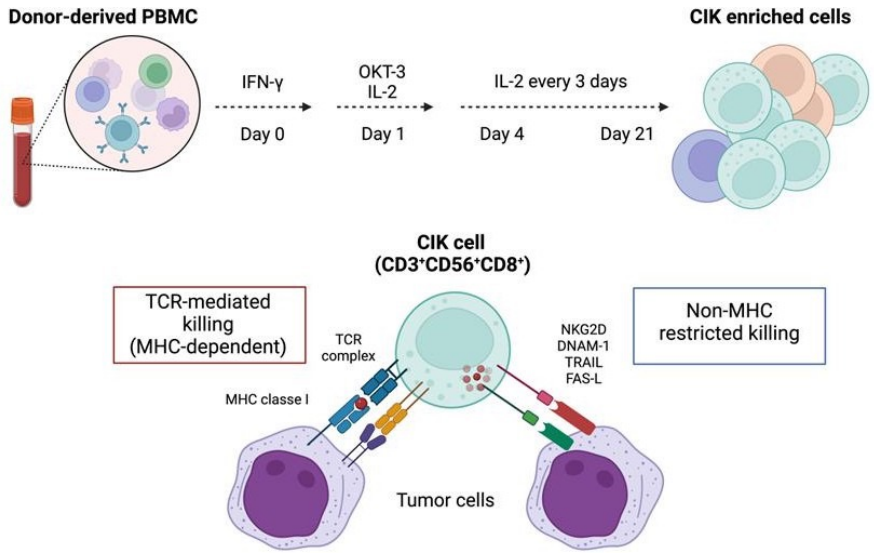
Smallbone P et al.: Haematologica Vol. 110 No. 8 (2025): August, 2025 https://doi.org/10.3324/haematol.2024.287177

Ongoing Randomized clinical trials

- **Safety and Efficacy of Venetoclax in Combination With Azacitidine Versus Standard of Care After AlloHSCT in AML (VIALE-T, NCT04161885)**
  - Randomized, Open Label Phase 3 Study in **AML** who received alloHCT within the past 60 days

- **Randomised Study of Oral Azacitidine vs Placebo Maintenance in AML or MDS After Allo-HSCT (AMADEUS, NCT04173533)**
  - A Double-Blind, Phase III, Randomised Study to Compare the Efficacy and Safety of Oral Azacitidine (CC-486) Versus Placebo in Subjects With **AML or MDS** as Maintenance After Allogeneic Haematopoietic Stem Cell Transplantation

Allogeneic cytokine-induced killer (CIK) cells enhance GvL hampering GvHD effect

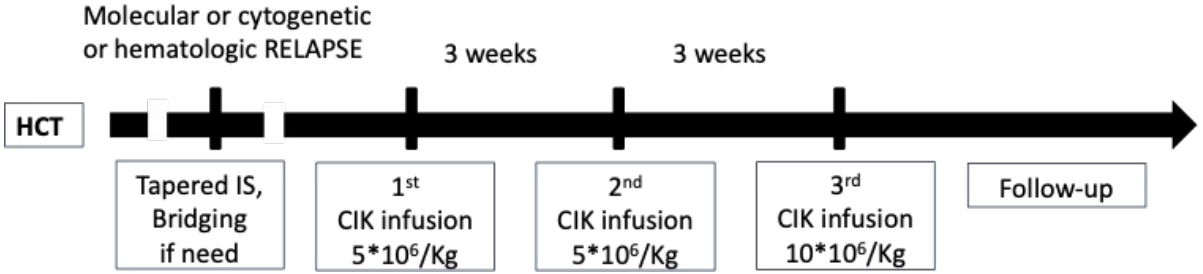


	N (%)
Age	61.9 (54.1-65.3)
Sex (M)	16 (57.1)
Disease AML MF ALL MDS	 21 (75) 5 (17.9) 1 (3.6) 1 (3.6)
Donor type (haploidentical)	19 (67.9)
Time from HCT to relapse (months)	5.3 (2.8-19.4)
Bridging therapy	9 (32.1)
Status of disease at CIK infusion Active disease RC MRD+ / MC FC / RC MRD -	 5 (17.9) 17 (60.7) 6 (21.4)
DLI pre-CIK	6 (21.4)
Concomitant therapy with CIK	7 (25)

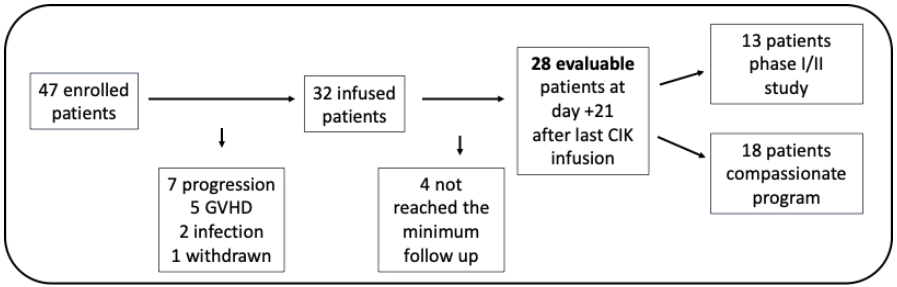
1 Introna M, et al. Bone Marrow Transplant. 2006; 2 Pievani et al, Blood, 2011; 3 Linn et al. Journal of Biomed and Biotech 2010; 4 Sangiolo et al. Journal of Cancer 2011; 5 Introna et al, Haematologica 2007; 6 Rambaldi A (2015) Leukemia 29(1):1-10; 7 Introna M (2017) Biol Blood Marrow Transplant. 23(12):2070-8; 8 Golay J etal.: Cytotherapy. 2018 Aug;20(8):1077-1088 ; 9 Magnani C et al.: Journal of Clinical Investigation 2020

Allogeneic CIK cells to enhance GvL hampering GvHD effect: background and patients characteristics

- Phase I/II trial using haplo or HLA-mismatched donor-derived CIK cells for post-HCT relapse (NCT03821519)



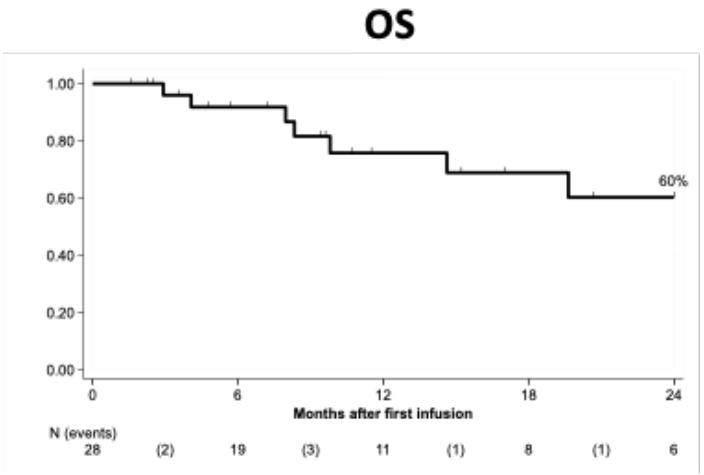
- The primary endpoint was the incidence of acute grade II-IV GvHD at day +100 after the last infusion of CIK cells

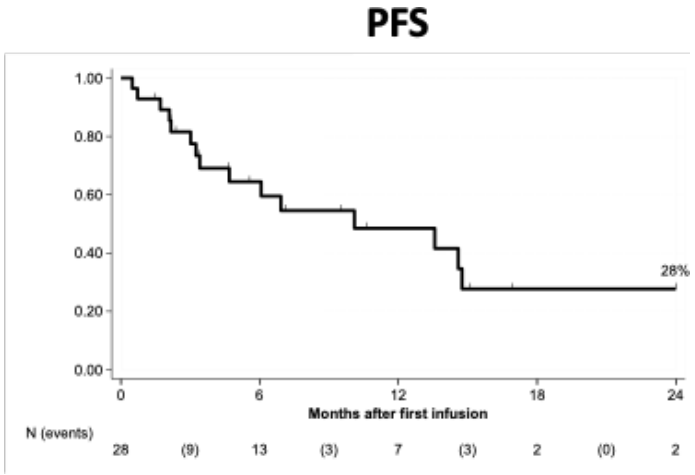


Rambaldi B et al. ASH 2025

Outcomes

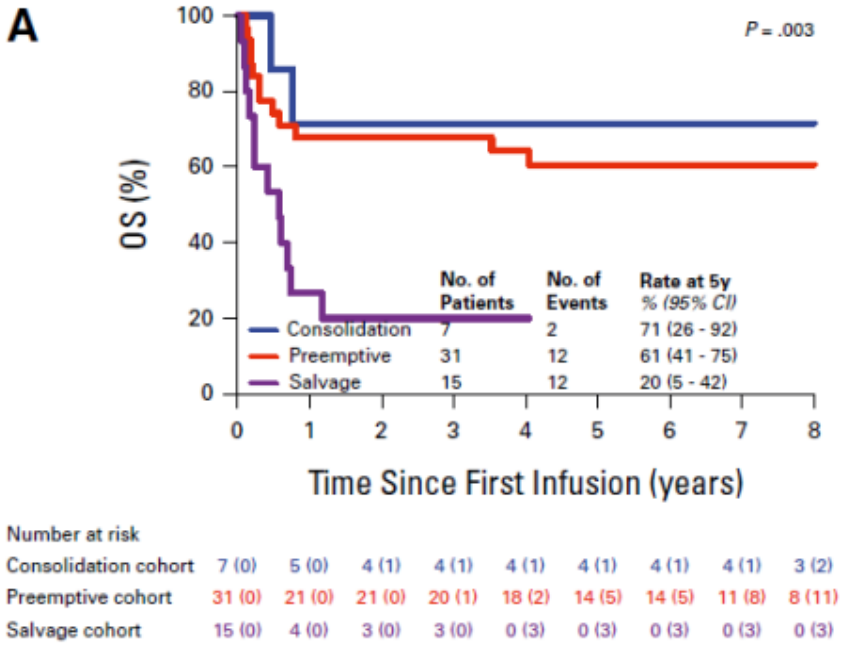
- No additional acute GvHD was reported. One patient developed mild chronic GvHD
- Starting from the first CIK infusion, the median follow-up is 9.6 months (IQR 4.6-20.1), with a median overall survival (OS) and progression-free survival (PFS) of 31.2 months (IQR 14.6-not reached) and 10.1 months (IQR 3.2-not reached), respectively.





Rambaldi B et al ASH 2025; Abstr #4154

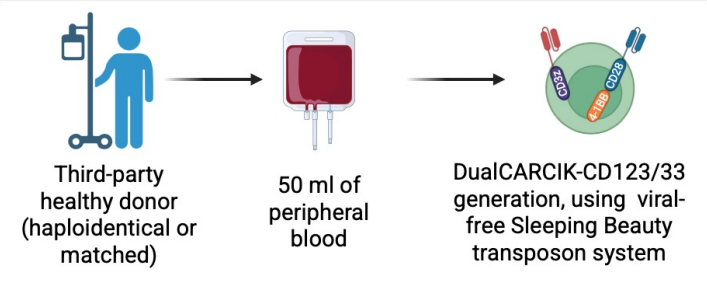
Immunotherapy First-in-Human Study of IL15–Activated Cytokine-Induced Killer Cells After Allogeneic HCT Shows Durable Remission and Serotherapy-Associated Immune Reconstitution in Leukemia



Rettinger et et al.: Journal of Clinical Oncology 2026

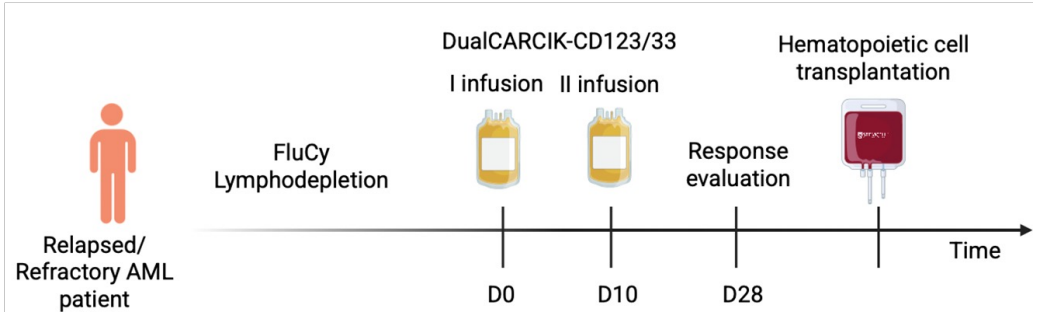
First-in-Human Anti-CD123/CD33 Chimeric Antigen Receptor Cytokine-Induced Killer (DualCARCIK-CD123/33) Cells for AML

Manufactory



Clinical Trial

A phase I/II single-arm, clinical trial to evaluate the safety, efficacy and feasibility of DualCARCIK-CD123/33 cells for R/R AML



Rambaldi B, Ottaviano G, Lucchini G and Tettamanti S

Conclusions

- MRD evaluation before transplant has a prognostic value but modest therapeutic impact on how to perform the transplant
- Time to transplant is crucial to improve the results no matter the donor HLA match
- Post-Transplant treatment with well tolerated drugs would be paramount if supported by ongoing clinical trials
- Post transplant treatment with donor derived lymphocytes or CAR-T cells would be equally welcome but feasibility, safety and efficacy of this approach remains to be demonstrated

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