XX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

ROMA, ERGIFE PALACE HOTEL, 7-8 MAGGIO 2026

Il condizionamento TBF nella leucemia acuta mieloide è uno standard? Le ragioni del NO

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Disclosures of Anna Grassi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Pfizer							X
Jazz							X
MSD							X

Agenda

- Cosa è «standard» nel trapianto
- La malattia refrattaria
- Il problema della tossicità

La difficoltà di definire uno standard

La necessità di condurre studi clinici

Is there an optimal myeloablative conditioning regimen in adult AML? (TBI-Cy vs. BU-Cy2 vs. Flu-BU4 vs.other…)

- ✓ **Busulfan is a good alternative to TBI** (in combination with Cyclophosphamide)*

  Nagler, A et al.: J Clin Oncol. 2013 Oct 1;31(28);
  Copelan E, Blood, 2013;122;
  Bredeson C., Blood, 2013;122;

- ✓ **Fludarabine is a good alternative to Cyclophosphamide** (in combination with Busulfan)

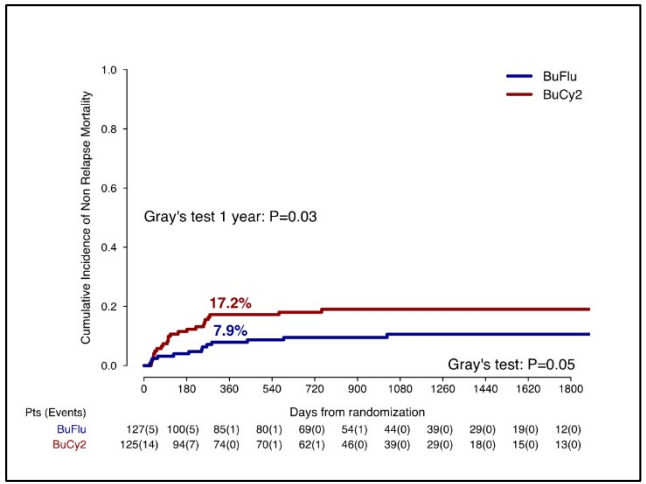
  Rambaldi A, et al.: Lancet Oncol. 2015 Nov;16(15);
  Cavallaro G et al.: Blood Cancer J. 2024 Aug 21;14(1):141;
  Ling Y, et al; Journal of Clinical Oncology 2023 Oct 10;41(29)

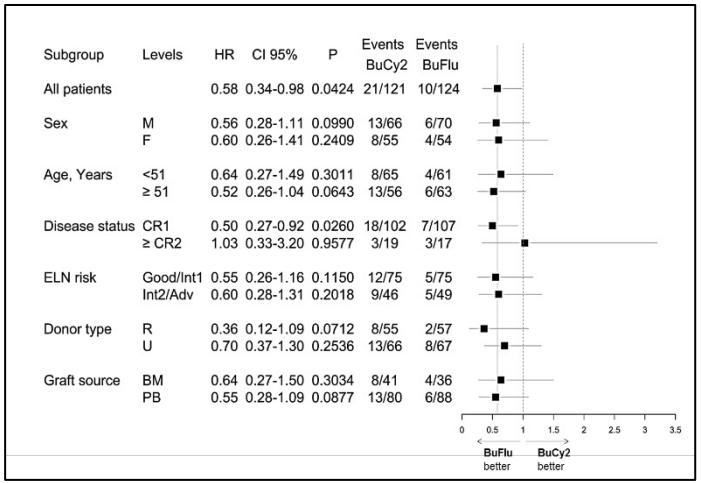
GITMO AML-R2 Trial: BuFlu vs BuCy2

Phase III, <u>randomized</u> multicenter study

252 AML

median age, 51y



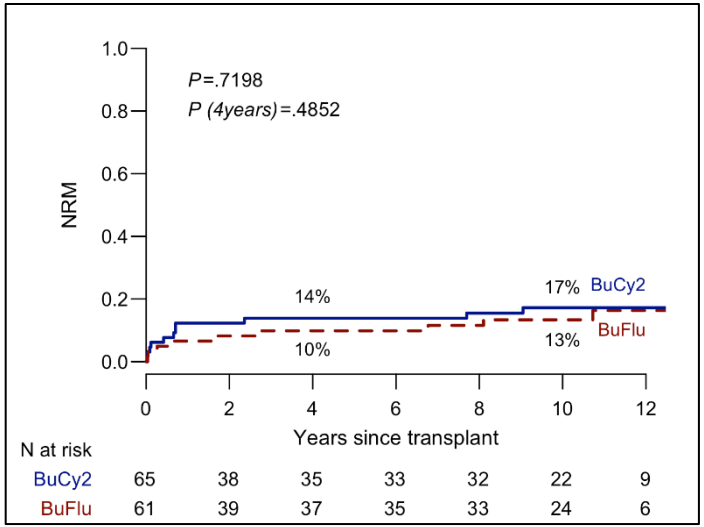


Expected 1-year NRM: 25% in BuCy2 vs 12.5% in BuFlu

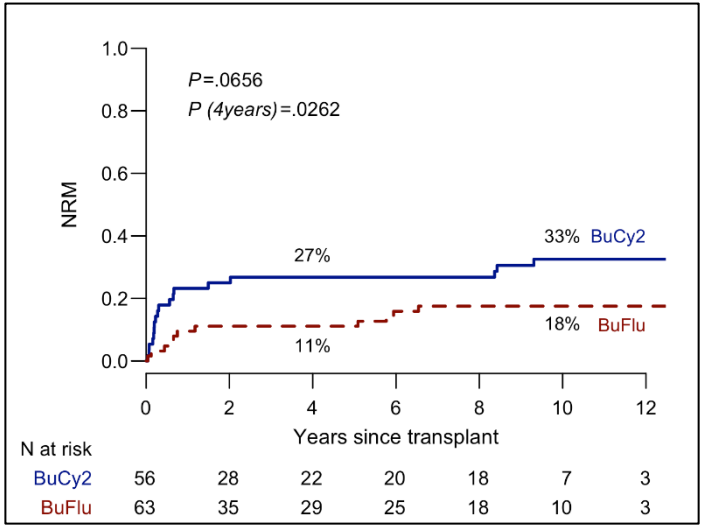
Rambaldi A, et al., Lancet Oncology, 2015

Long-term results of the GITMO AML-R2 trial
NRM

Under 51 years old

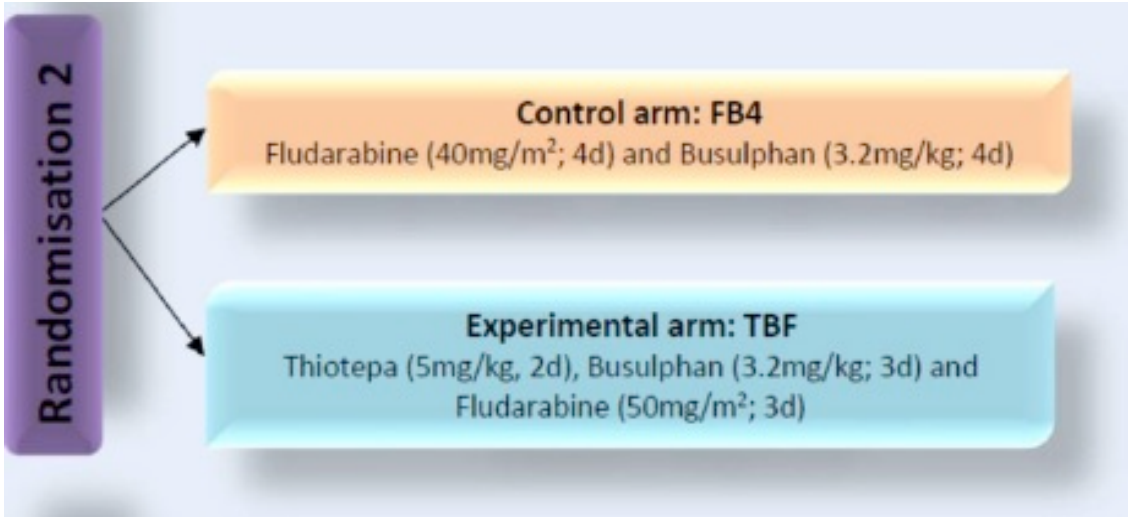


Over 51 years old



Rambaldi A, et al., Lancet Oncology, 2015
Cavallaro et al.: Blood Cancer J 2024

Addition of thiotepa to a busulphan based conditioning regimen doesn not improve survival in patients allografted for acute myeloid leukaemia and myelodysplasia: Results of the UK IMPACT COSI Trial



Charles Craddock et al., ASH Annual Meeting 2025

COSI Trial: Study design

- Prospective, randomized, multicenter UK trial
- Enrolled patients N=317: AML n=242 (CR1 205; CR2 37) and MDS n=75
- Donors: matched sibling n=52; matched unrelated n=265
- Arms: Flu/Bu (control) vs Flu/Bu + thiotepa (Thio); analyzed separately for myeloablative (MAC N=99) and reduced-intensity (RIC N=218) conditioning
- GVHD prophylaxis: ciclosporin + ATG–based
- Primary endpoint: overall survival (OS)

- Median age: 44 (MAC) vs 64 (RIC) years
- MRD assessed by flow cytometry 28 days pre-HCT; threshold 0.1%
- MAC: Flu 40mgx4 days; Bu 3.2 mg/kg ×4 days (control) vs Bu ×3 + Thio 5 mg/kg ×2 days
- RIC: Flu 30mgx5 days; Bu 3.2 mg/kg ×2 days (control) vs Bu ×2 + Thio 5 mg/kg ×1 day

Charles Craddock et al., ASH Annual Meeting 2025

COSI Trial: Results

MAC N=99

- 2-yr OS: 75% (Flu/Bu4) vs 72% (Flu/Bu3+Thio), p=0.73
- Relapse (CIR): 31% vs 11% with Thio, p<0.001
- TRM: 4% vs 22% with Thio, p<0.001
- MRD subgroups: no OS improvement in MRD– or MRD+ patients (67% (Flu/Bu4) vs 63% (Flu/Bu3+Thio) in MRD+)

RIC N=218

- 2-yr OS: 71% (Flu/Bu2) vs 69% (Flu/Bu2+Thio), p=0.87
- Relapse (CIR): 30% vs 20% with Thio, p=0.12
- TRM: 8% vs 17% with Thio, p=0.01
- MRD+ OS 41% (control) vs 56% (Thio), p=0.15

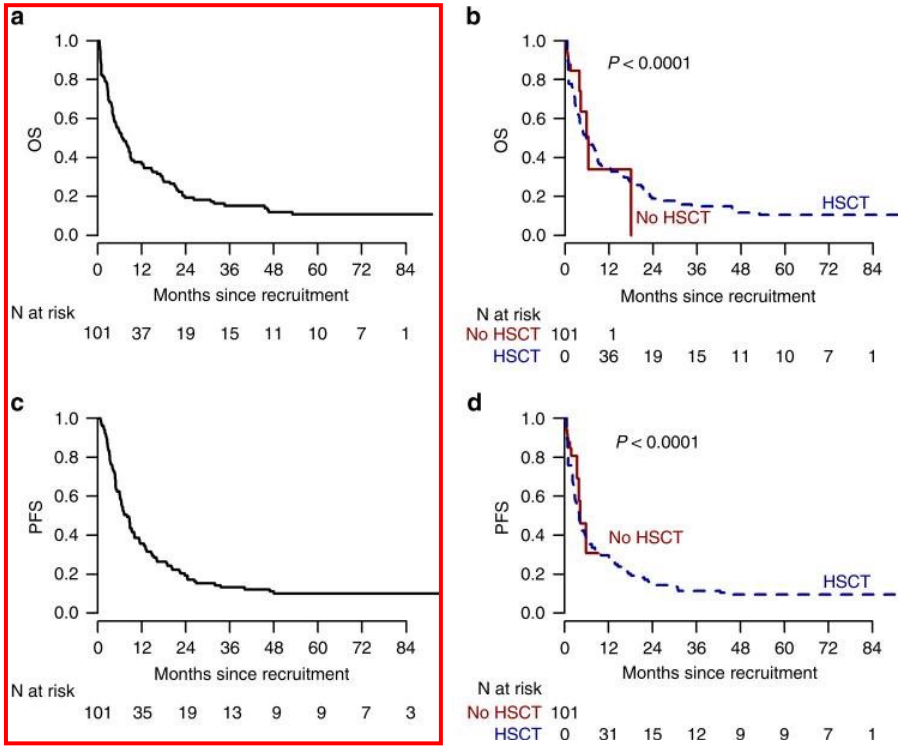
Charles Craddock et al., ASH Annual Meeting 2025

L’effetto antileucemico

il problema della malattia refrattaria

Myeloablative conditioning with TBF in active leukemia: GANDALF-01

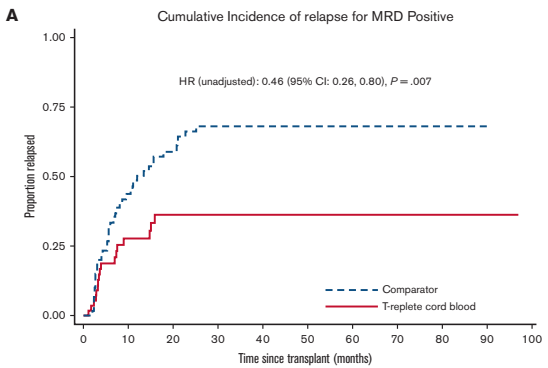
- A phase II multicenter open-label study from URD, CB and family haplo donors in R/R LA
- 101 pts, median age 54 y (19-69)
- MAC regimen including:
  - thiotepa (10 mg/kg)
  - busulfan (9.6 mg/kg)
  - fludarabine (150 mg/mq)
- 1 and 2-years OS 38% and 19%
- 1 and 2 years CIR 38% and 49%
- 1 and 2 years TRM 30% and 33%

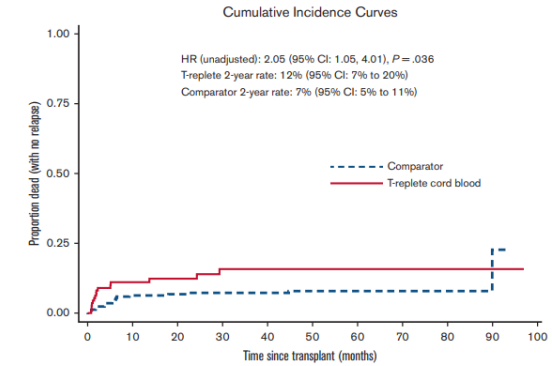


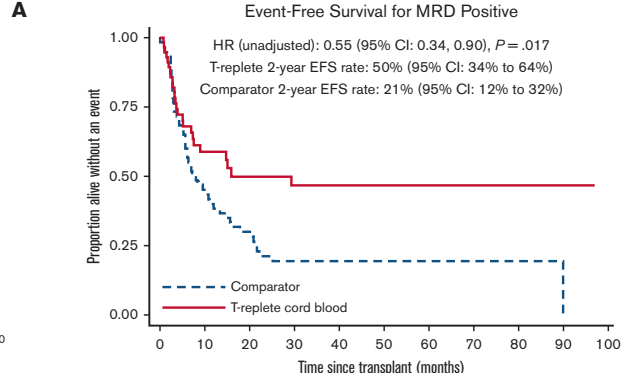
Bonifazi F, et al: Bone Marrow Transplantation, 2022

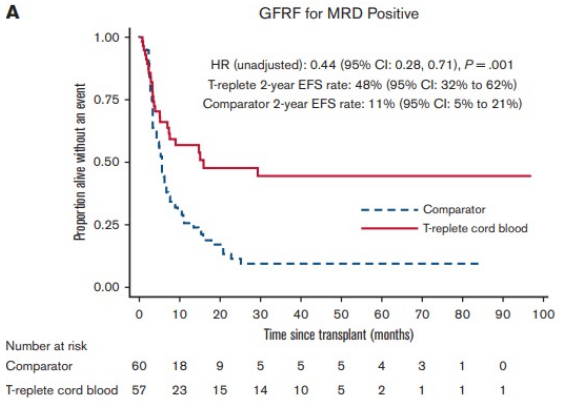
Alternative donor source for high risk AML: the case of T-replete cord blood alloSCT

- Retrospective Study (consecutive patients). N=367 (CB=112)
- Compared with other cell source MR, MUD, MMUD, HD), TRCB transplant results in improved disease-free survival and relapse risk in pediatric AML/MDS
- Compared with other cell source, CB transplant cures with less GVHD and particularly improved GvHD-free, relapse-free
- Pediatric (Age 7y)
  CB 8/8 HLA









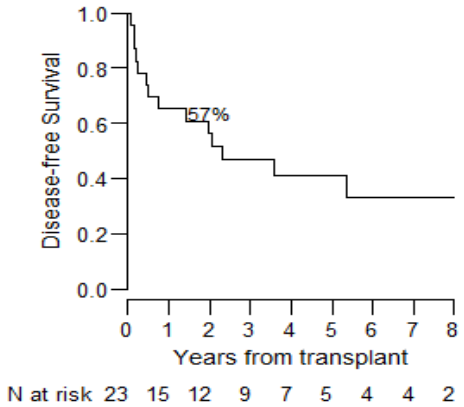
Horgan C et al.: Blood Advances 2023

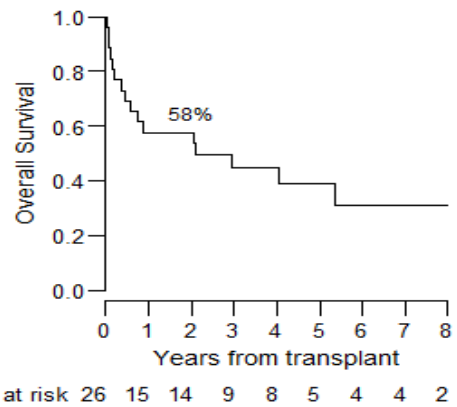
Alternative donor source for high risk AL: TBF and low dose of ATG

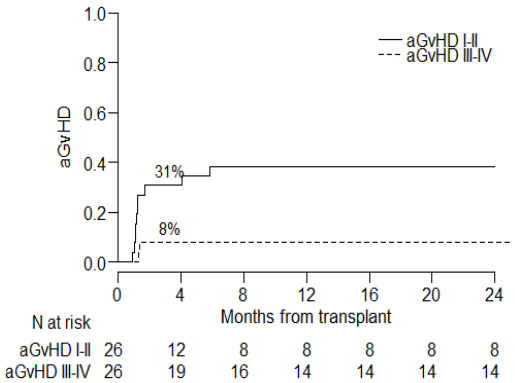
Retrospective, consecutive

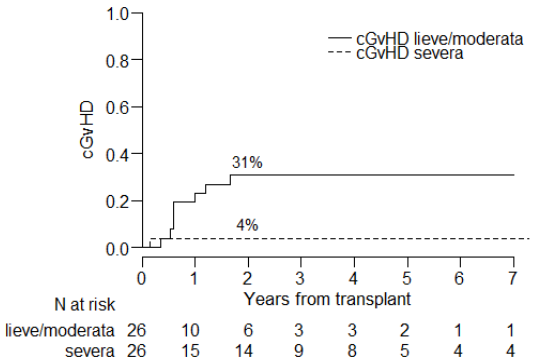
N=26 Adult High Risk Leukemia:

- 1/3 CR1 (CK ± p53)
- 1/3 ≥ CR2
- 1/3 Active Desease









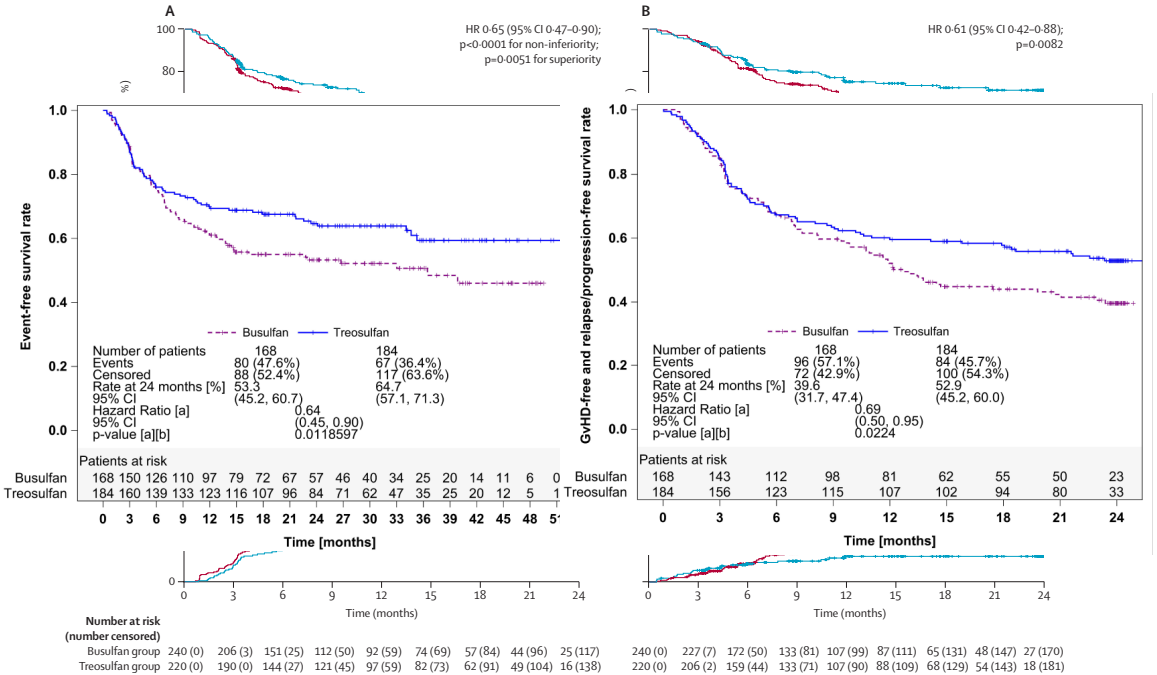
Castelli M EBMT 2025. unpublished

Scelta del condizionamento:

il problema della tossicità

Treosulfan or busulfan plus fludarabine as conditioning for older patients with AML or MDS: a randomised, non-inferiority, phase 3 trial

- A phase III Randomized multicenter study Treo (10 x 3) vs. BuFlu2
- Subgroup analysis in 352 pts, median age 59 y (31-70)
- 2-years EFS 65% and 53%
- GRFS 53% and 40%



Beelen DW et al.: Lancet Haematol 2020

Stolzel F et al.: Haematologica 2026

Conclusions

- The superiority of newer conditioning regimens (i.e. two alkylating agents) remains to be demonstrated by well designed clinical trials
- Lowering NRM is the starting point for planning innovative post-transplant therapies -> **Disease relapse is the true unmet clinical need**
- It is probably reasonable intensify the conditioning regimen, whenever possible, in pre-transplant MRD positive patients. Post-transplant MRD can be even more important and can guide early post-transplant interventions
- The outcome of high-risk AML such as those with mutant TP53 with either 17p– and/or CK and primary refractory AML remains poor. Incorporating new agents before, during and after the conditioning regimen or change source of stem cell is a possible solution but needs further investigation.

- Il «GruppoTrapianti" dell'Ospedale Papa Giovanni XXIII di Bergamo: Prof. Rambaldi, Prof. Lussana, Dr.ssa Algarotti, Dr.ssa Micò, Dr.ssa Rambaldi, Dr.ssa Rizzuto., Dr.ssa Finazzi, Dr.Cavallaro, Marta, Davide, Giada, Federica, Teresa, Edoardo, Cecilia.
- Il Laboratorio Paolo Belli e il Laboratorio Lanzani
- I medici, gli infermieri dell'Ematologia, i pazienti trapiantati e le loro famiglie

Grazie!

Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Caratteristiche dei pazienti della coorte recente (ATG-G 15 mg/kg dal G-6)

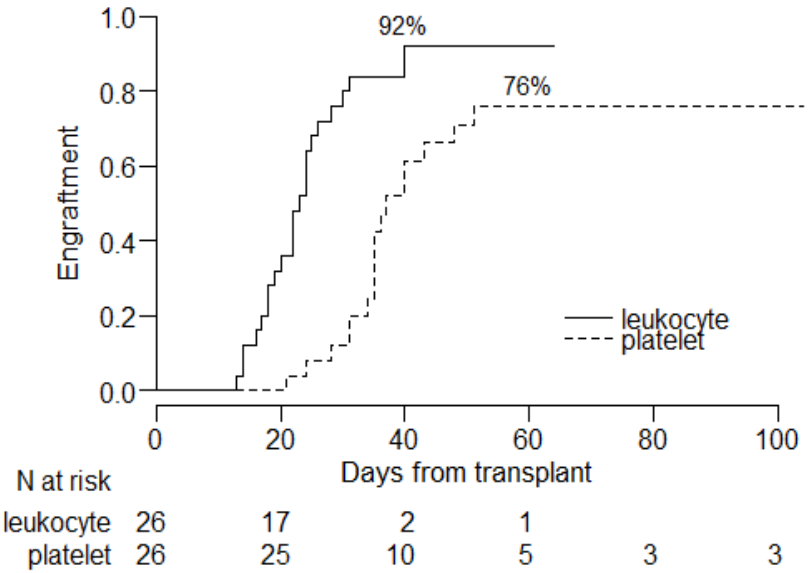
Caratteristiche	N= 26
Età mediana, anni (range)	53 (22-71)
Peso mediano, kg (range)	73 (41-98)
Gruppo etnico – no. (%)	
Caucasici	22 (85)
Africani	3 (11)
Asiatici	1 (4)
Diagnosi – no. (%)	
Leucemia Mieloide Acuta (AML)	20 (77)
Leucemia Linfoblastica Acuta (ALL)	4 (15)
Leucemia Neutrofilica Cronica	1 (4)
Leucemia a cellule T positiva per HTLV-1	1 (4)
Stato di malattia pre- HSCT – no. (%)	
CR1	10 (38)
CR2 *	9 (35)
Malattia Attiva	7 (27)
Sorror pre-trapianto ≥3	13 (50%)
Tempo mediano dalla diagnosi al trapianto in pz in CR1	4,6 (2,5 - 5,7)

Caratteristiche ad alto rischio dei pazienti trapiantati in CR1 – no. (%)	N = 10
Caratteristiche a rischio sfavorevole sec. ELN 2022	4 (40)
Caratteristiche a rischio intermedio sec. ELN 2022	4 (40)
Caratteristiche a rischio sfavorevole sec. GIMEMA	2 (20)

*Tra i pazienti in ≥ CR2: 1 paziente HSCT3; 4 pazienti HSCT2.

Risultati: pazienti trapiantati con ATG-G 15 mg/kg

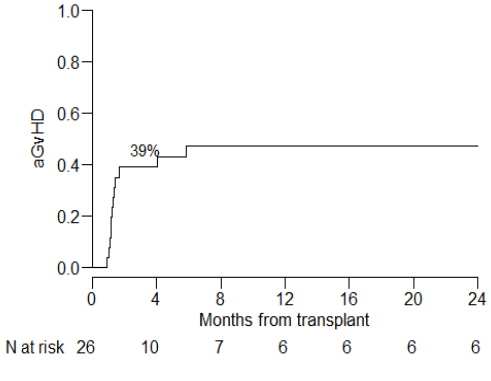
Attecchimento:

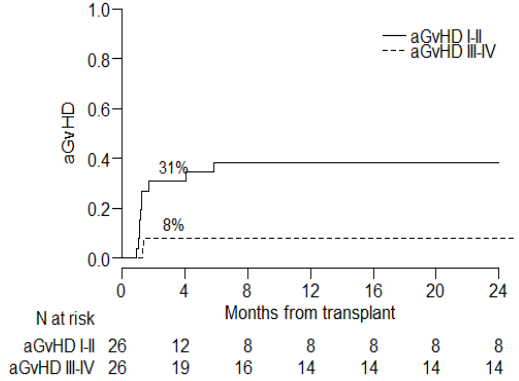


- **23 pazienti (89%) hanno ottenuto l'attecchimento leucocitario ad una mediana di 22 giorni (range 13-54) dal trapianto.**
- **20 pazienti (77%) hanno raggiunto l'attecchimento piastrinico con una mediana di 35,5 giorni (range 21–189).**
- **Tre pazienti (11%) sono deceduti senza raggiungere l'attecchimento leucocitario rispettivamente ai giorni +11, +31 e +35 post-trapianto.**

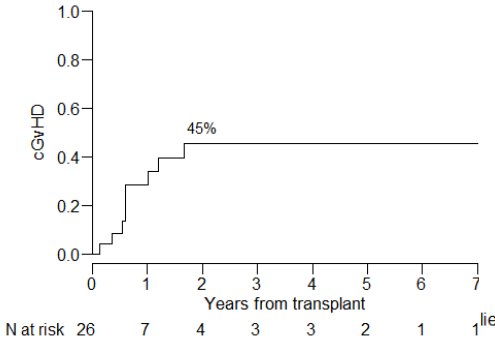
Risultati: pazienti trapiantati con ATG-G 15 mg/kg

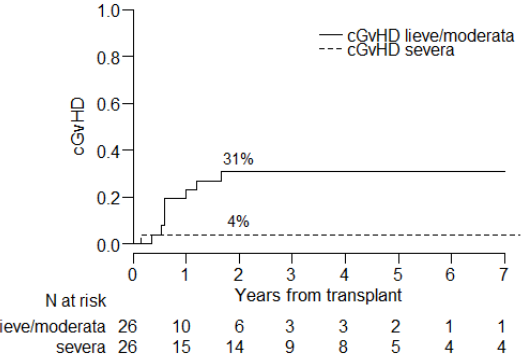
GvHD acuta:





GvHD cronica:



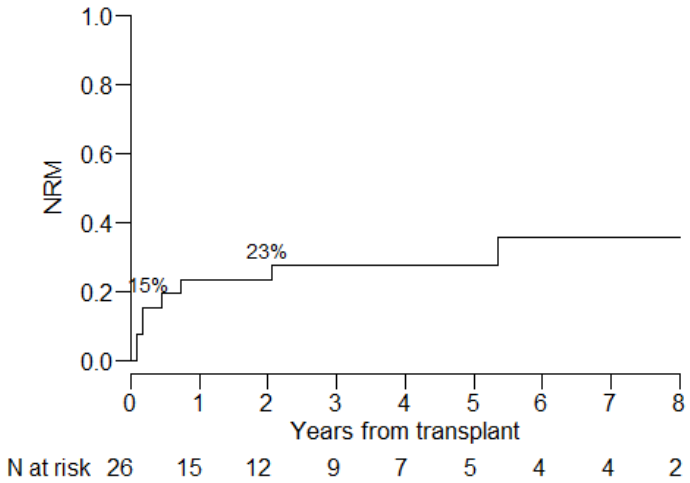


- 12 pazienti **(46%)** hanno sviluppato aGvHD a una mediana di **38 giorni** (range, 27-175) post trapianto.
- Nessuno di grado IV.
- Incidenza di **aGvHD a 100 giorni: 39%** (aGvHD **grado III-IV: 8%**).

- 9 pazienti **(35%)** hanno sviluppato cGvHD a una mediana di **219 giorni** (range, 51-436) post trapianto.
- 1 paziente di grado severo.
- Incidenza di **cGvHD a 2 anni: 45%** (cGvHD **severa: 4%**).

Risultati: pazienti trapiantati con ATG-G 15 mg/kg

Non Relapse Mortality:



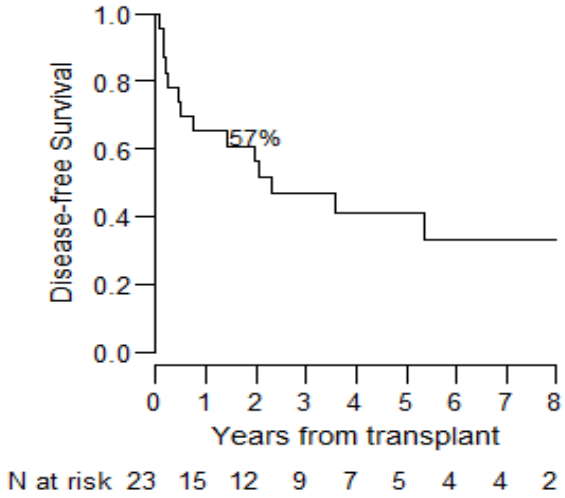
* 5 pazienti deceduti per infezione (in 3 casi fungina),

NRM a **100 giorni** post trapianto**: 15%,** a **2 anni: 23%**.

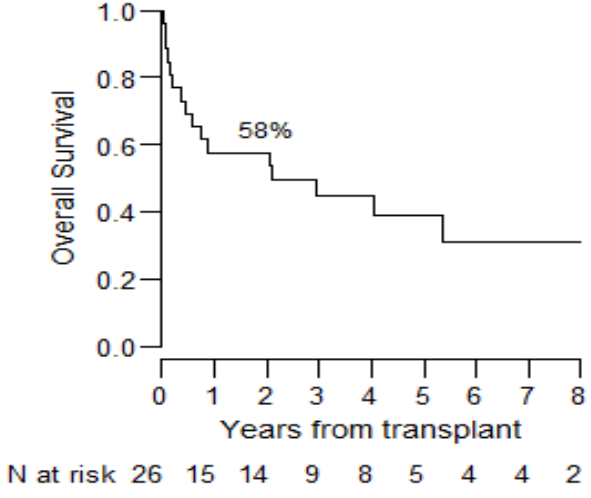
Infezioni:

20 pazienti (77%) hanno sviluppato almeno un'infezione post trapianto: **11 riattivazioni di CMV**, 7 cistiti da BK virus, 4 polmoniti (di cui 3 fungine), 4 infezioni batteriche, 2 da EBV, 2 da SARS-CoV-2 e 1 caso di encefalite erpetica.

Disease Free Survival:



Overall Survival:



- 6 pazienti (**23%**) sono **ricaduti** a una mediana di 345 (range, 59-837) giorni post trapianto. 1 paziente ha sviluppato una **Secondary Graft Failure** ed è stato sottoposto un altro trapianto. E' ricaduto al giorno +1313.
- Al follow-up più recente, 10 pazienti (**38%) vivi**, con un follow-up mediano di 4,4 anni (range 2,0–9,8).
- La **DFS** e la **OS a 2 anni** sono rispettivamente del **57% e 58%.**

Treosulfan-based conditioning in CB

- Double arm phase 2 multicenter trial of Treo-Flu-TBI in CB
- 130 pts, median age 45 y (0,6-65)
- Cumulative Incidence of recovery
  - ANC 91% median 19 days
  - PLT 75% median 31 days
- Primary GF: 5%
- Secondary GF 0%
- 3-years OS and DFS 66% and 57%
- 3-years CIR and TRM 24% and 18%

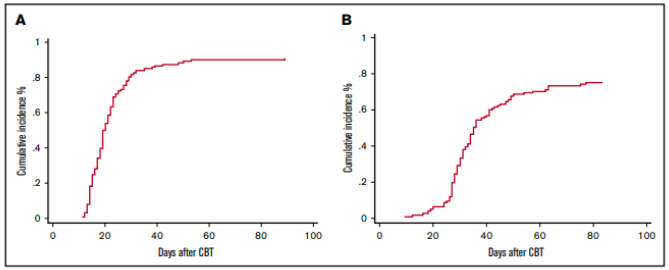
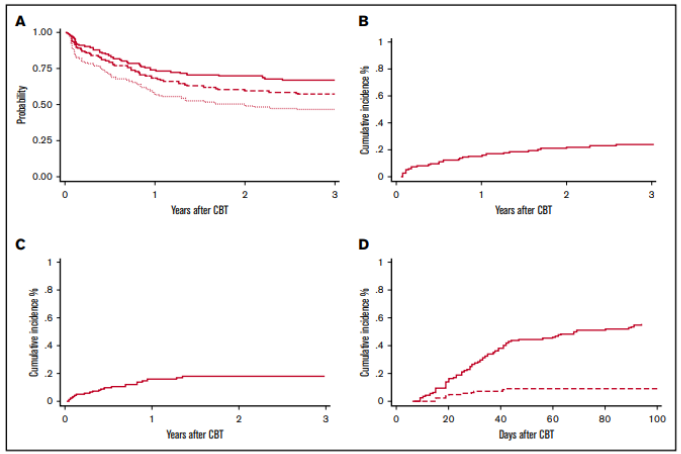


Figure 1. Cumulative incidence to day +100 in CBT recipients. (A) Neutrophil engraftment. (B) Platelet engraftment.



igure 2. Survival and other outcomes for CBT recipients. (A) OS (solid red line), RFS (dashed red line), and GRFS (dotted red line) at 3 years after a TREO-based onditioning regimen. Cumulative incidence of overall relapse (B) and TRM (C) at 3 years after a TREO-based conditioning regimen, and of grade II-IV (solid red line) and III-IV dashed red line) aGVHD to day +100 (D).

F Milano, et al; Blood Advances 2020

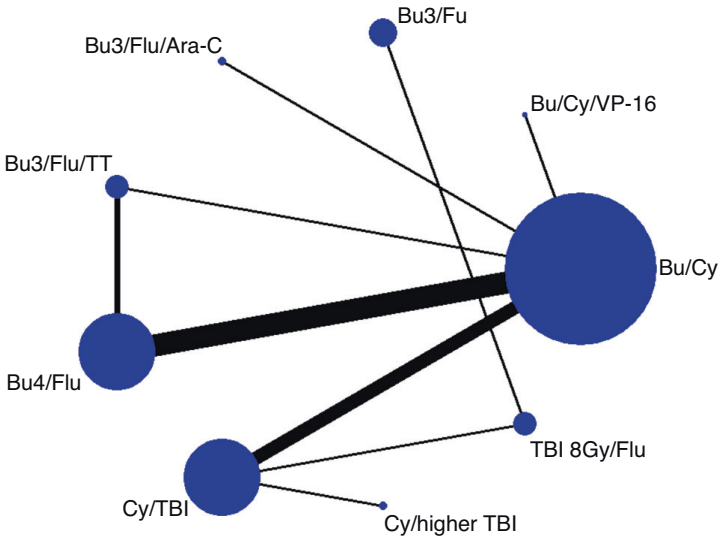
Myeloablative conditioning regimens in adult patients with AML undergoing AlloHSCT in CR: a systematic review and network meta-analysis

» A systematic review to compare the effects of different MAC regimens.

» A Bayesian network meta-analysis was performed

» The commonly used MAC regimen Bu/Cy (4-day busulfan for total 16 mg/kg orally or 12.8 mg/kg intravenously, plus 2-day cyclophosphamide for total 120 mg/kg intravenously) is chosen as the common comparator

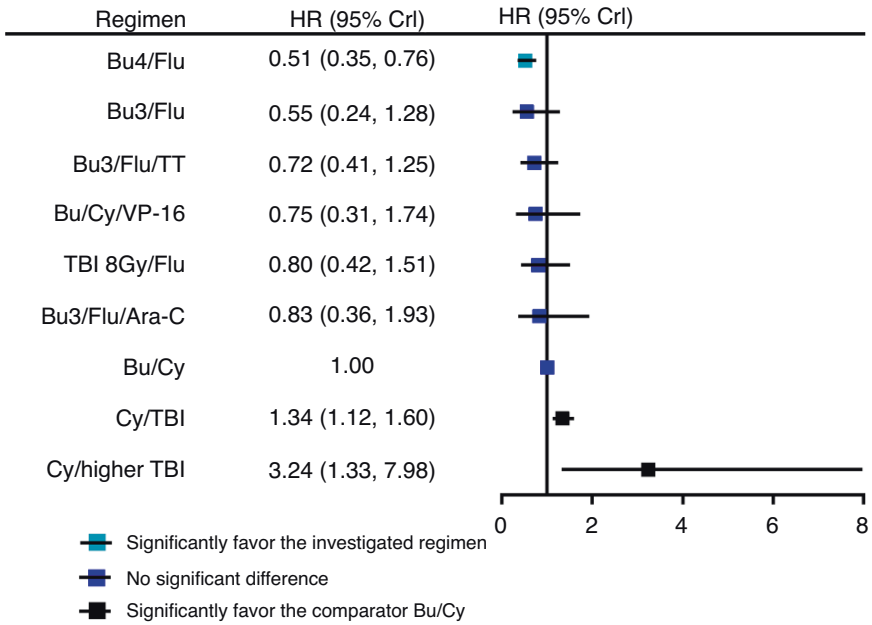
The network plot depicting all direct comparisons for overall survival



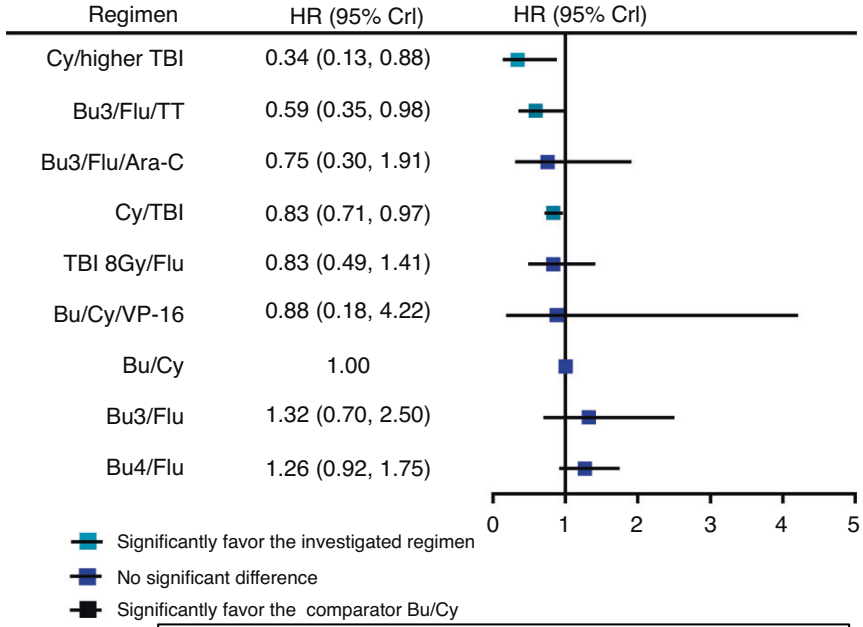
Luo C et al.: Bone Marrow Transplantation (2023)

Myeloablative conditioning regimens in adult patients with AML undergoing AlloHSCT in CR: a systematic review and network meta-analysis

Forest plot with HR and 95% CrI for non-relapse mortality



Forest plot with HR and 95% CrI for cumulative incidence of relapse



Luo C et al.: Bone Marrow Transplantation 2023