

Stato dell'arte: il condizionamento della leucemia acuta mieloide nell'adulto

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Corso di Formazione GITMO

Trapianto e terapie cellulari: cellule, donatori e condizionamenti

Udine, 8-9 Ottobre 2026

Aula Polifunzionale Ospedale di Udine

Disclosures of Dr. ssa Alessandra Picardi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board
MEDAC					X	
TILLIOTS					X	
KITE					X	
NOVARTIS					X	
TAKEDA						X
ALEXION						X
ASTELLAS					X	
GRIFOLS						X

Conditioning Regimen in AML

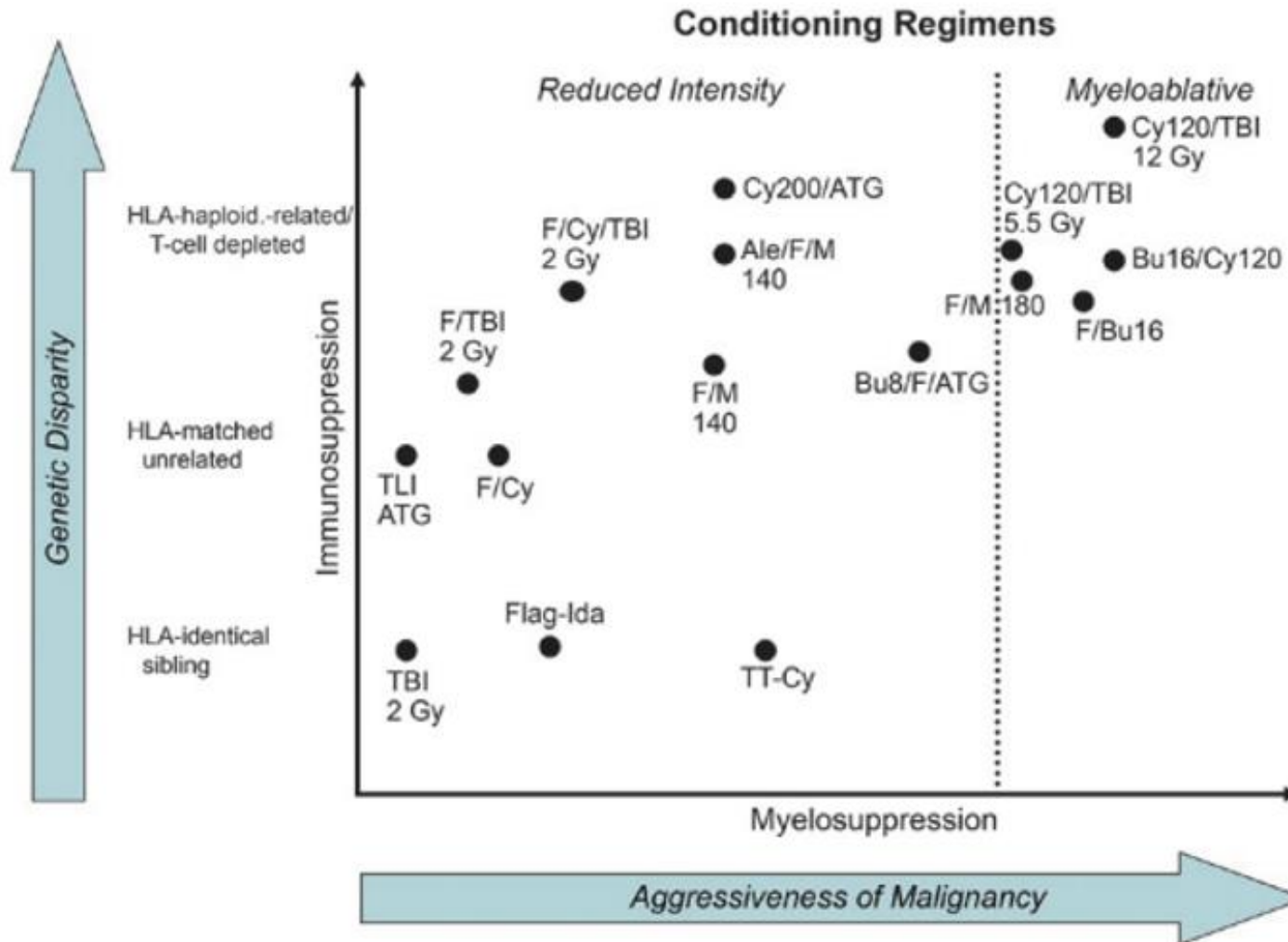
- Aims & Definition
- Determinant Factors for the choice
- Italian Recommendations : in progress

EFFECTS OF THE CONDITIONING REGIMENS

1 HSCT: Historical Perspective

7

- **MYELOID** disease
- **ANTI-NE** disease
- **IMMUNE** effect (ac risk facto



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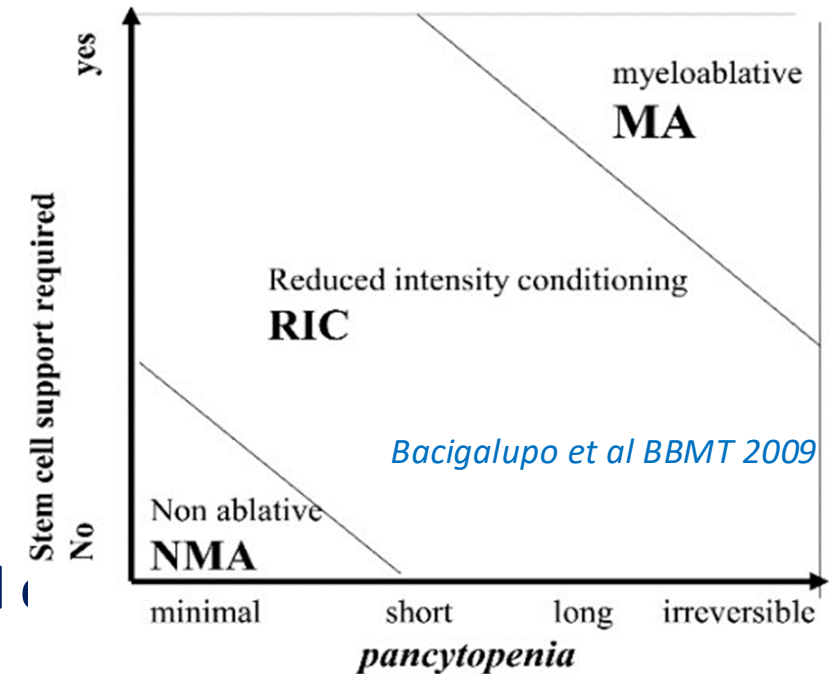
of the underlying

sus Host Disease
matching or other

Definition of Reduced Intensity and Non Myeloablative Conditioning Regimens

NMA and RIC from introduction of purine analog and dose reduction of alkylating agents or TBI

- **Non Myeloablative (NMA)** usually include
 - ☐ 2Gy TBI, Fludarabine and Cyclophosphamide
 - ☐ 2Gy TBI and Fludarabine
 - ☐ Fludarabine and CY
 - ☐ Low dose of Busulphan (3.2 mg/kg) and Fludarabine
- **Reduced Intensity (RIC):** all others non standard



NMA differs from RIC in that the former can result in only minimal cytopenias that do not require stem cell support whereas RIC require stem cell support

TCl= Transplant Conditioning Intensity

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<https://doi.org/10.1038/s41409-020-0803-y>



ARTICLE



Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia

This article has been corrected since Advance Online Publication and a correction has been published in this issue.

Alexandros Spyridonidis¹ · Myriam Labopin² · Bipin N. Savani³ · Jukka Vekemans⁴ · Didier Blaise⁵

Component	Dose level			Added points for each dose level
	Low	Intermediate	High	
TBI fractionated (Gray)	≤5	6–8	≥9	1
Busulphan (mg/kg)	≤6.4 iv & ≤8 po	12 po	12.8 iv & 16 po	1
Treosulfan (g/m ²)	30	36	42	1
Melphalan (mg/m ²)	<140	≥140	≥200	1
Thiotepa (mg/kg)	<10	≥10	≥20	0.5
Fludarabine (mg/m ²)	<160	≥160	≥200	0.5
Clofarabine (mg/m ²)	<150	≥150	≥200	0.5
Cyclophosphamide (mg/m ²)	<90	≥90	≥120	0.5
Camustine (mg/m ²)	≤250	280–300	≥350	0.5
Cytarabine (g/m ²)	<6	≥6	≥12	0.5
Etoposide (mg/kg)	<50	≥50	≥75	0.5

TBF and BUFLU = Intermediate or Low
BCUY = HIGH

SCORE :

Low Intensity < 2.5

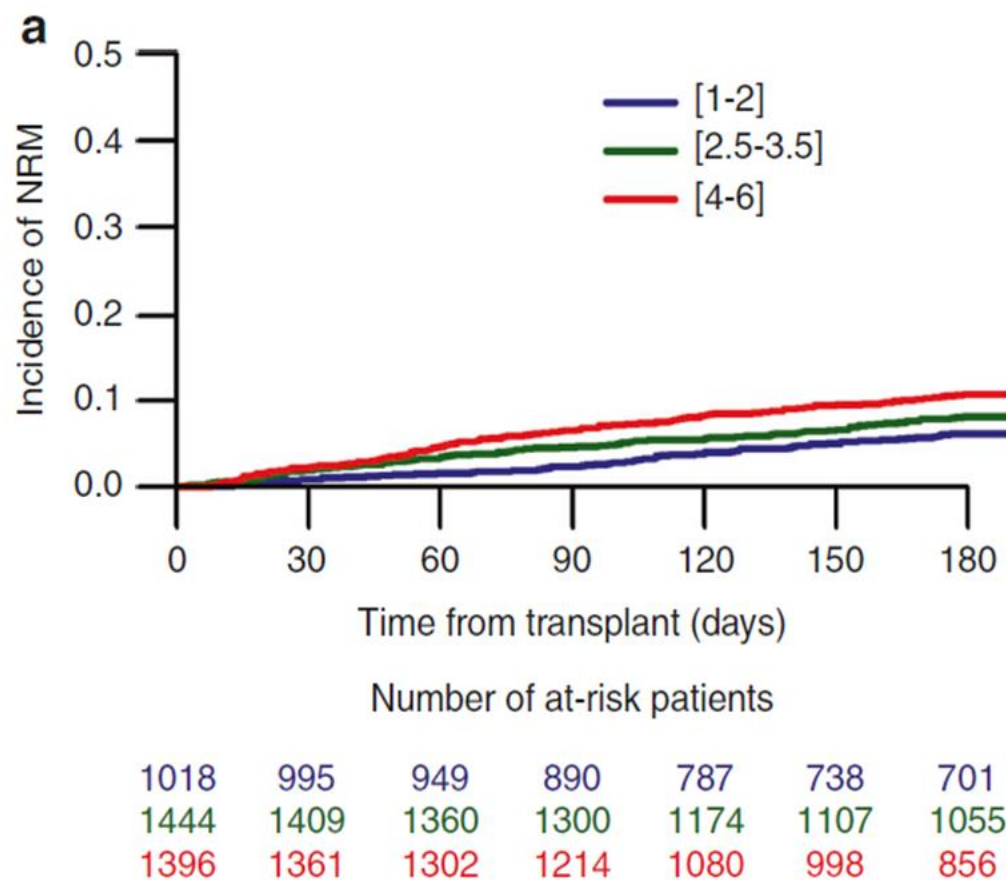
Intermediate Intensity 2.5-3.5

High Intensity >3.5



BETTER Relapse and 100/180 days NRM
PREDICTION versus RIC/MAC

45-54 years



55-65 years

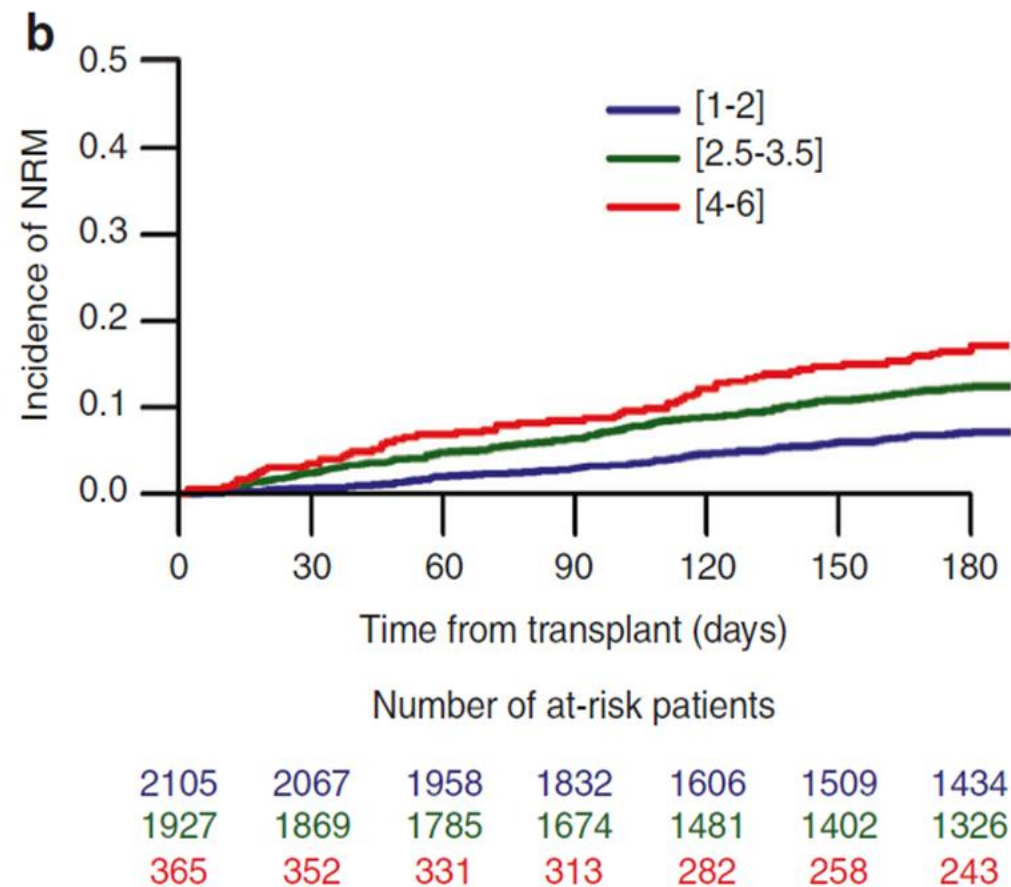


Fig. 2 Early nonrelapse mortality (NRM) according to TCL. **a** Early NRM in the subgroup of patients aged 45–55 years at transplant ($n = 3858$). **b** Early NRM in patients aged between 55 and 65 years ($n = 4397$).

Determinant Factors for the choice of Transplant Conditioning Intensity

- Age
- HCT-I
- Frailty – Fitness
- Previous Therapy

Determinant Factors for the choice

- Age $> 55 - 60$ years

- Disease Status

≥ 3 or ≥ 5

- HCT-I or CCI

- Frailty – Fitness

- Previous Therapy

Innovative Concepts

[Charlson Comorbidity Index](#) predicts the risk of death and 10-year survival for patients with multiple concurrent comorbidities, adding 1 point for every decade of life starting at age 50 or 60 whereas HCT-I adds 1 point > 40 years

CCI High score ≥ 5

Predictive Impact on Frailty Score

Multivariable Logistics Regression Analysis		
Age		
Older >60 years (vs. younger ≤60)	0.60 (0.29–1.27)	0.183
Baseline Diagnosis		
Acute leukemia (vs. others)	2.55 (1.15–5.65)	0.021
Karnofsky Performance Status		
60–80% (vs. 90–100%)	6.69 (3.17–14.11)	<0.001
HCT-CI Score		
>3 (vs. 0–3)	2.44 (1.09–5.42)	0.029

Table 6. HCT Frailty Scale for Outcome Prediction in Younger and Older Adults.

	Univariate Regression Analysis			Multivariable Analysis
Age Group	HCT Frailty Scale	HR (95% CI)	<i>P</i> value	Interaction <i>P</i> value
Overall Survival				
Patients aged 60 or younger	Frail (vs. Fit)	5.08 (1.91–13.55)	0.001	0.794
	Pre-Frail (vs. Fit)	2.52 (1.01–6.29)	0.047	
Patients older than 60	Frail (vs. Fit)	3.86 (1.55–9.60)	0.004	
	Pre-Frail (vs. Fit)	1.63 (0.71–3.72)	0.246	
Non-Relapse Mortality				
Patients aged 60 or younger	Frail (vs. Fit)	2.86 (1.28–6.40)	0.010	0.841
	Pre-Frail (vs. Fit)	1.73 (0.85–3.49)	0.130	
Patients older than 60	Frail (vs. Fit)	2.97 (1.33–6.63)	0.008	
	Pre-Frail (vs. Fit)	1.39 (0.70–2.79)	0.347	

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Conditioning Regimen in AML

- Aims & Definition
- Determinant Factors for the choice
- Italian Recommendations with the aim to identify the conditioning regimens according to intensity (TCI) and underlying disease: in progress

Comparator = BuCy/Intervento TBICy

ARTICLE



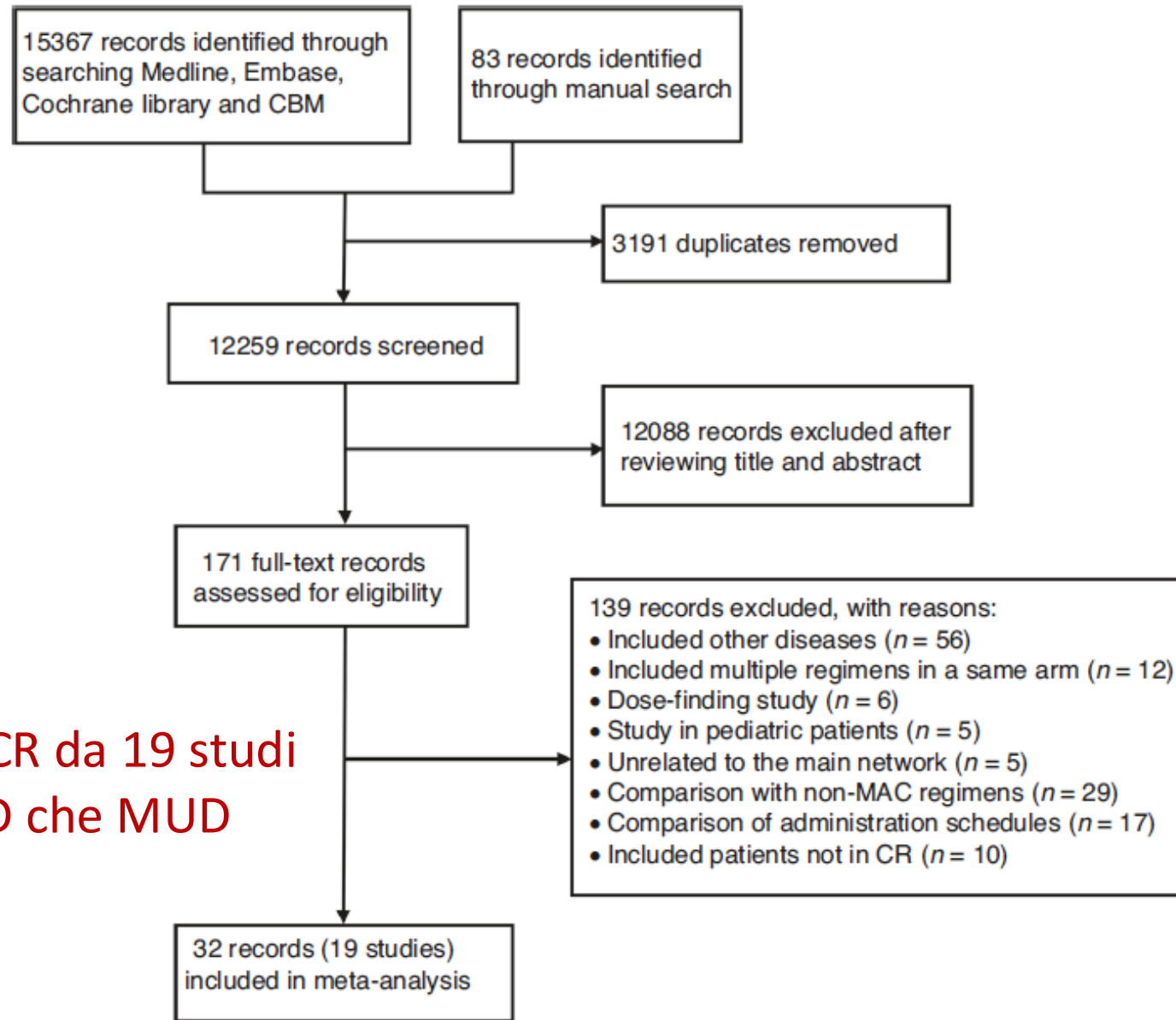
Myeloablative conditioning regimens in adult patients with acute myeloid leukemia undergoing allogeneic hematopoietic stem cell transplantation in complete remission: a systematic review and network meta-analysis

High TCI
> 3.5

Chengxin Luo^{1,2,5}, Guixian Wu^{1,2,5}, Xiangtao Huang^{1,2}, Yaqun Ding^{1,2}, Yarui Huang^{1,2}, Qiuyue Song³, Yu Hou^{1,2}, Jieping Chen^{1,2}✉, Xi Li⁴✉ and Shuangnian Xu^{1,2} ✉

The optimal myeloablative conditioning (MAC) regimens in adult patients with acute myeloid leukemia (AML) undergoing allogeneic hemopoietic stem cell transplantation (allo-HSCT) in complete remission (CR) remain unclear. We performed a systematic review and network meta-analysis to compare the effects of different MAC regimens. Bayesian network meta-analysis was performed using WinBUGS version 1.4.3. 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. Pooled hazard ratios (HRs) with the associated 95% credibility interval (95% CrI) are obtained for all comparisons. We included 19 eligible studies, involving 8104 AML patients and 9 MAC regimens. Compared with Bu/Cy, 3-day busulfan plus fludarabine and thiotepe (Bu3/Flu/TT) is associated with significantly better overall survival (HR, 0.70; 95% CrI, 0.51 to 0.96) and lower risk of relapse (HR, 0.59; 95% CrI, 0.35 to 0.98). Bu3/Flu/TT is also associated with superior overall survival than Cy/TBI (cyclophosphamide plus total body irradiation), and lower risk of relapse than Bu4/Flu (4-day busulfan plus fludarabine). These results suggest that thiotepe-based new MAC regimen Bu3/Flu/TT is associated with improved outcomes in AML patients undergoing allo-HSCT in CR and worth further investigation.

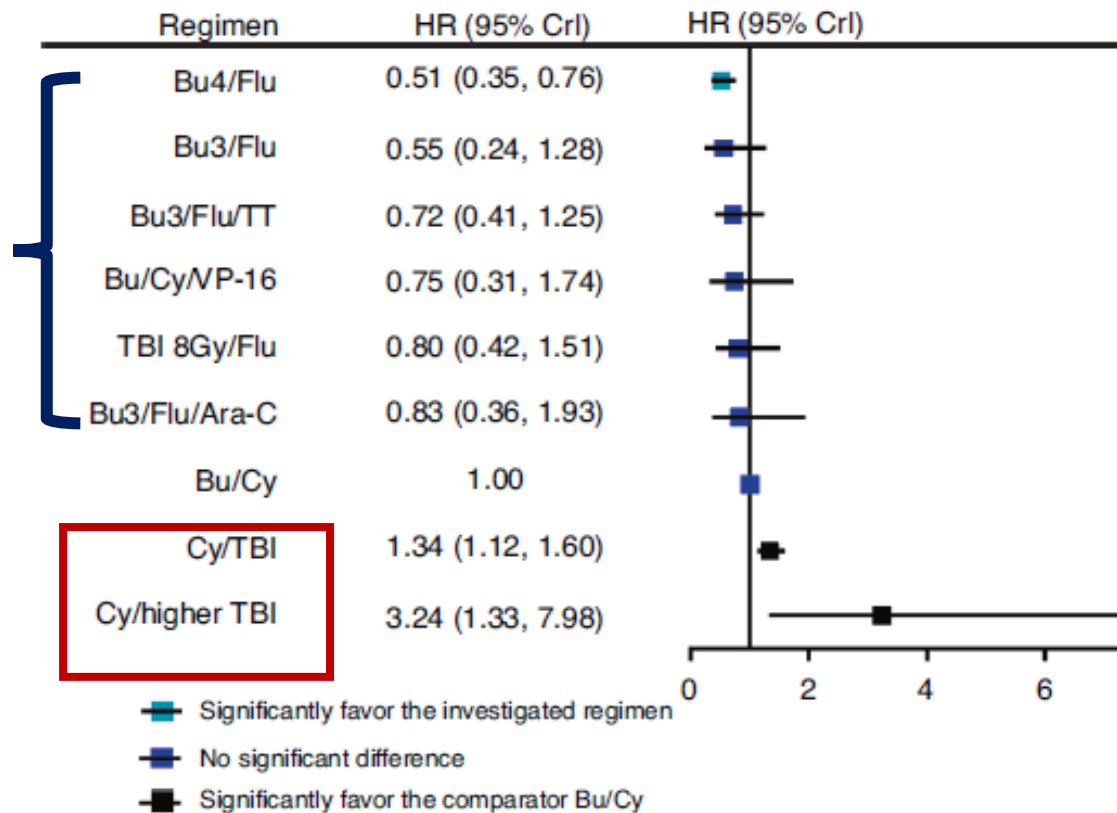
Ottobre 2026



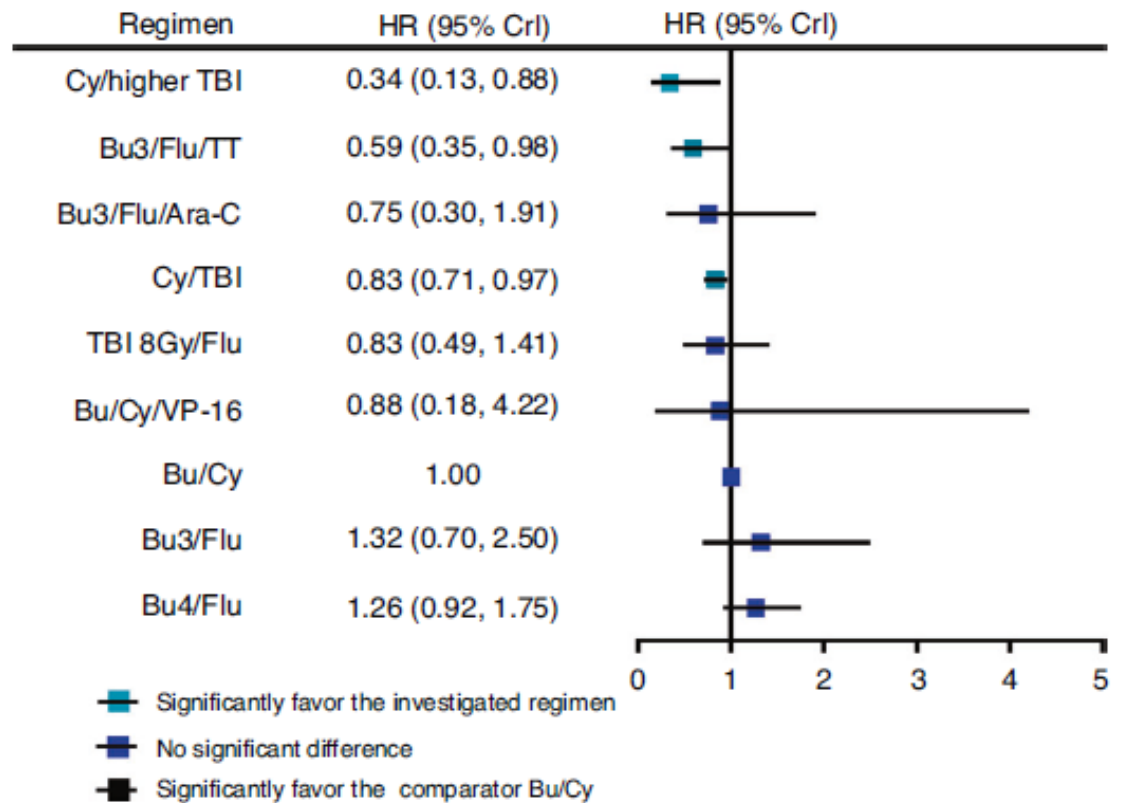
8104 pts adulti in CR da 19 studi
(6 RCT) sia MSD che MUD

Luo C et al, BMT 2023

NRM



CI of RELAPSE



- Compared with Bu/Cy, TBI 8 Gy/Flu are **Intermediate TCI**
- BuCy versus TBI Cy: Better or Similar OS in 1 RCT (2013) and 2 Registry Clinical Trials (CIBMTR 2023 and EBMT 2013)

Luo C et al, BMT 2023

Udine, 8-9 Ottobre 2026

Conclusions

BuCY vs TBI based in AML, as High TCI

BuCy is better than high dose of TBI/CY in terms of OS and NRM

- Rizzo et al Blood 2009: 28.874 allogeneic HSCT>>>development of new solid cancers at twice the rate expected based on general population rates in adults, with the risk increasing over time , achieving 3-fold among patients followed for 15 years or more after transplantation. Among patients irradiated at ages under 30 years, the relative risk of non-SCC was 9 times that of non-irradiated patients
- Specific subgroups or clinical scenarios (e.g., dendritic cell leukemia) might benefit from TBI (as an option).
- Clinical trials: Young patients at very high risk might warrant specific studies that include TBI-based regimens.

BuCy vs Treo based, as TreoFluMel or TTF

Treo 14 + 2nd alkylating agent = high TCI in almost of cases

- No direct comparison, however, a meta-analysis and three recent retrospective studies have demonstrated a 2-year NRM of <10% and a 2-year GRFS of >50% (Greco 2021), despite the high-risk population analyzed.

The Question : is necessary a High Transplant Conditioning Intensity?

TBI, particularly in the context of haploidentical transplantation.

- The panel should recommend a prospective evaluation of this regimen (and other combinations involving treosulfan paired with other alkylating agents), especially for patients at high risk of relapse — also assessing the economic impact.

Validation of the transplant conditioning intensity (TCI) index for allogeneic hematopoietic cell transplantation

Alexandros Spyridonidis¹, Myriam Labopin², Tobias Gedde-Dahl³, Arnold Ganzer⁴, Matthias Stelljes⁵, Charles Craddock⁶,

AML= 4060 allogeneic HSCT

2018 -2021

Age: 55 -75

low = 1934, 48%; intermediate n = 1948, 48%, high n = 178, 4%, according TCI score

Table 3. Multivariable analysis for early NRM, NRM, REL.

		NRM day 100		NRM day 180		NRM		REL	
		HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
TCI	Low (Ref)	1		1		1		1	
	Intermediate	1.95 (1.42–2.69)	<0.0001	1.62 (1.26–2.08)	0.0001	1.44 (1.20–1.74)	0.0001	0.66 (0.57–0.78)	<0.0001
	High	4.00 (2.20–7.28)	<0.0001	2.86 (1.76–4.64)	<0.0001	1.87 (1.25–2.80)	0.003	0.79 (0.55–1.13)	0.20
	High vs Intermed.	2.05 (1.17–3.57)	0.012	1.76 (1.12–2.78)	0.015	1.3 (0.88–1.91)	0.19	1.19 (0.83–1.7)	0.34
Age	per 10 years	1.76 (1.31–2.37)	0.0002	1.66 (1.31–2.11)	<0.0001	1.65 (1.38–1.97)	<0.0001	0.95 (0.82–1.11)	0.53
HCT-CI	0 (Ref)	1		1		1		1	
	1–2	1.15 (0.81–1.62)	0.43	1.07 (0.82–1.42)	0.61	1.33 (1.09–1.62)	0.006	0.99 (0.83–1.18)	0.94
	≥3	1.49 (1.07–2.09)	0.019	1.41 (1.08–1.83)	0.011	1.38 (1.12–1.69)	0.002	1.05 (0.88–1.24)	0.59
KPS	≤80	1.65 (1.23–2.21)	0.0008	1.53 (1.22–1.94)	0.0003	1.46 (1.22–1.75)	<0.0001	1.02 (0.87–1.2)	0.77

No significant differences between high and Int TCI in terms of Relapse suggesting that the index allows the identification of “reduced toxicity regimens”, regardless the relapse

Impact of conditioning regimen on outcomes of young AML patients (< 40 years) undergoing HCT in complete remission, with transplant conditioning intensity score of 3.5-4.0. A study from the acute leukemia working party of the European Society for Blood and Marrow Transplantation

Enrico Maffini ¹✉, Maud Ngoya ², Mohamed Houhou², Malek Benakli ³, Babak Bahar⁴, Mahmoud Aljurf ⁵, Khalid Halahleh ⁶,

BuCY and TBI based = high TCI = 4
VS
TBF and BU4FLU = intermediate TCI = 3.5

The optimal myeloablative conditioning regimen for adolescents and young adults with acute myeloid leukaemia (AML) is currently unknown. In this retrospective analysis conducted on AML patients aged 18-40 years, in complete remission (CR), who received an allogeneic hematopoietic cell transplantation (HCT) we compared outcomes of different conditioning regimens. A total of 4323 patients, with median age of 30.9 years, transplanted from 2010 to 2022, received one of four regimens: high-dose total body irradiation (TBI)-based ($n = 1031$), thiotepa-busulfan (Bu)-fludarabine (Flu) (TBF) $n = 219$, Bu-Flu ($n = 1100$), and Bu-cyclophosphamide (Cy) ($n = 1973$). Prolonged OS and PFS for Bu-Flu (hazard ratio [HR] 0.73, 95% CI 0.57–0.92, $p = 0.008$; HR 0.78, 95% CI 0.64–0.94, $p = 0.01$), and TBF (HR 0.59, 95% CI 0.38–0.92, $p = 0.02$; HR 0.67, 95% CI 0.47–0.94, $p = 0.02$), respectively, as well as less RI for both Bu-Flu (HR 0.77, 95% CI 0.63–0.95, $p = 0.01$), and TBF (HR 0.68, 95% CI 0.47–0.99, $p = 0.046$). In conclusion, young adult AML patients seem to benefit from high dose TBI-free regimens, in terms of survival and toxicity, with four major myeloablative regimens. TBF and Bu-Flu were associated with better clinical outcomes, partly reflecting the general improvement in supportive therapies and patient selection introduced in recent years. Prospective clinical trials are warranted.

Bone Marrow Transplantation: <https://doi.org/10.1038/s41409-026-02991-1>

Table 3. Multivariate analysis of clinical outcomes after HCT (Part 1).

		PFS		OS		RI		NRM		GRFS	p value
		Estimation (95% CI)	p value	Estimation (95% CI)	p value	Estimation (95% CI)	p value	Estimation (95% CI)	p value	Estimation (95% CI)	
Conditioning	TBI	1		1		1		1		1	
	Bu-Cy	0.95 (0.82–1.1)	0.49	0.87 (0.72–1.04)	0.12	0.96 (0.81–1.12)	0.59	0.98 (0.72–1.34)	0.92	0.98 (0.85–1.12)	0.72
	Bu-Flu	0.78 (0.64–0.94)	0.01	0.73 (0.57–0.92)	0.008	1.44 (1.12–1.76)	0.01	0.84 (0.56–1.25)	0.39	0.88 (0.74–1.04)	0.13
	TBF	0.67 (0.47–0.94)	0.02	0.59 (0.38–0.92)	0.02	0.68 (0.47–0.99)	0.046	0.64 (0.3–1.38)	0.25	0.70 (0.52–0.94)	0.02
Year of HCT (per 5 y)		0.94 (0.85–1.04)	0.22	0.89 (0.79–1)	0.055	1.04 (0.93–1.16)	0.53	0.69 (0.56–0.84)	<0.001	1.01 (0.93–1.01)	0.83
Age at HCT (per 2 y)		1.01 (0.99–1.03)	0.4	1.03 (1.01–1.05)	0.01	0.99 (0.97–1.01)	0.39	1.07 (1.03–1.11)	0.002	1.01 (0.99–1.03)	0.22
Cytogenetic risk	Fav/Inter	1		1		1		1		1	
	Adverse	1.94 (1.65–2.27)	<0.001	2.25 (1.87–2.72)	<0.001	2.11 (1.77–2.51)	<0.001	1.38 (0.97–1.98)	0.07	1.22 (1.07–1.38)	0.003
	NA/failed	1.16 (1–1.35)	0.048	1.42 (1.19–1.7)	<0.001	1.23 (1.04–1.45)	0.02	0.99 (0.73–1.34)	0.96	1.55 (1.36–1.78)	0.001
F to M combination	No	1		1		1		1		1	
	Yes	0.86 (0.73–1.02)	0.08	0.89 (0.74–1.08)	0.24	0.86 (0.72–1.04)	0.11	0.87 (0.62–1.22)	0.42	0.96 (0.85–1.1)	0.57
CMV status patient	Negative	1		1		1		1		1	
	Positive	1.07 (0.94–1.22)	0.32	1.13 (0.96–1.32)	0.14	1.03 (0.89–1.19)	0.7	1.23 (0.93–1.63)	0.14	1.03 (0.92–1.15)	0.57
Karnofsky	< 90	1		1		1		1		1	
	≥ 90	0.79 (0.66–0.94)	0.007	0.69 (0.57–0.85)	<0.001	0.85 (0.7–1.04)	0.11	0.66 (0.47–0.92)	0.01	0.85 (0.73–0.98)	0.03
In vivo TCD	No	1		1		1		1		1	
	Yes	1.19 (1.02–1.39)	0.02	1.09 (0.9–1.31)	0.37	1.27 (1.07–1.5)	0.006	1.01 (0.74–1.38)	0.94	0.83 (0.73–0.94)	0.005
Type of donor	MRD	1		1		1		1		1	
	MUD	0.91 (0.78–1.06)	0.24	1.02 (0.84–1.22)	0.87	0.79 (0.66–0.93)	0.005	1.46 (1.06–2.02)	0.02	1.0 (0.87–1.13)	0.94
Disease status	CR1	1		1		1		1		1	
	CR2	1.37 (1.19–1.58)	<0.001	1.46 (1.24–1.72)	<0.001	1.31 (1.11–1.55)	<0.001	1.53 (1.16–2.02)	0.003	1.21 (1.07–1.36)	0.002

NRM non-relapse mortality, PFS leukemia-free survival, OS overall survival, RI relapse incidence, F female, M male, CMV cytomegalovirus, y years, TBI total body irradiation, HCT hematopoietic cell transplant, Fav Favorable, Inter Intermediate, TCD T-cell depletion, MRD matched related donor, MUD matched unrelated donor, CR complete remission, GRFS graft-versus-host disease-free, relapse-free survival.

Comparison of fludarabine–melphalan and fludarabine–treosulfan as conditioning prior to allogeneic hematopoietic cell transplantation—a registry study on behalf of the EBMT Acute Leukemia Working Party

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In recent years considerable variations in conditioning protocols for allogeneic hematopoietic cell transplantation (allo-HCT) protocols have been introduced for higher efficacy, lower toxicity, and better outcomes. To overcome the limitations of the classical definition of reduced intensity and myeloablative conditioning, a transplantation conditioning intensity (TCI) score had been developed. In this study, we compared outcome after two frequently used single alkylator-based conditioning protocols from the intermediate TCI score category, fludarabine/melphalan 140 mg/m² (FluMel) and fludarabine/treosulfan 42 g/m² (FluTreo) for patients with acute myeloid leukemia (AML) in complete remission (CR). This retrospective analysis from the registry of the Acute Leukemia Working Party (ALWP) of the European Society of Bone Marrow Transplantation (EBMT) database included 1427 adult patients (median age 58.2 years) receiving either Flu/Mel ($n = 1005$) or Flu/Treo ($n = 422$). Both groups showed similar 3-year overall survival (OS) (54% vs 51.2%, p value 0.49) for patients conditioned with FluMel and FluTreo, respectively. However, patients treated with FluMel showed a reduced 3-year relapse incidence (32.4% vs. 40.4%, p value < 0.001) and slightly increased non-relapse mortality (NRM) (25.7% vs. 20.2%, p value = 0.06) compared to patients treated with FluTreo. Our data may serve as a basis for further studies examining the role of additional agents/ intensifications in conditioning prior to allo-HCT.

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**Intermediate
TCI ≤ 3.5
TF14 (n=422) vs
FluMel (n=1005)**

TF = TREO 14 >>> TCI 3.5 vs FluMel140 >>> TCI 2.5

Table 3. Multivariate analysis of outcome variables.

	Relapse		NRM		LFS		OS		GRFS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
FluTreo vs FluMel	1.46 (1.15–1.85)	0.002	0.66 (0.47–0.93)	0.018	1.1 (0.91–1.33)	0.31	0.9 (0.73–1.11)	0.31	1.14 (0.93–1.4)	0.21
Age (per 10 years)	1 (0.9–1.11)	0.99	1.57 (1.34–1.83)	<0.0001	1.16 (1.06–1.27)	0.001	1.21 (1.1–1.33)	<0.0001	1.1 (1.01–1.19)	0.029
Year of allo-HCT	0.96 (0.92–0.99)	0.012	0.98 (0.94–1.03)	0.51	0.97 (0.95–1)	0.078	0.98 (0.95–1.01)	0.27	1 (0.97–1.03)	0.98
secAML	0.94 (0.72–1.24)	0.68	1.14 (0.84–1.56)	0.4	1.04 (0.84–1.29)	0.69	1.12 (0.9–1.4)	0.32	1.06 (0.87–1.3)	0.55
adverse cytogenetics	2.8 (2.18–3.6)	<0.0001	1.46 (0.97–2.19)	0.068	2.2 (1.77–2.74)	0.0001	2.08 (1.65–2.64)	<0.0001	2 (1.62–2.47)	<0.0001
CR2 + vs CR	1.26 (0.98–1.6)	0.067	1.4 (1.06–1.84)	0.017	1.34 (1.11–1.62)	0.002	1.32 (1.08–1.61)	0.006	1.24 (1.04–1.49)	0.018
Donor reference =MSD	1		1		1		1		1	
MUD 10/10	0.98 (0.77–1.24)	0.85	2.03 (1.49–2.76)	<0.0001	1.37 (1.13–1.66)	0.002	1.45 (1.18–1.79)	0.0004	1.23 (1.02–1.49)	0.028
MUD 9/10	1.12 (0.78–1.59)	0.54	4.63 (3.17–6.76)	<0.0001	2.2 (1.7–2.85)	<0.0001	2.62 (2–3.43)	<0.0001	2.21 (1.71–2.84)	<0.0001
Female to male	0.95 (0.71–1.27)	0.74	1.88 (1.4–2.53)	<0.0001	1.36 (1.1–1.68)	0.004	1.39 (1.11–1.75)	0.004	1.29 (1.05–1.58)	0.014
KPS ≥ 90	0.92 (0.72–1.19)	0.54	0.7 (0.52–0.93)	0.015	0.77 (0.63–0.93)	0.006	0.72 (0.59–0.88)	0.001	0.85 (0.7–1.03)	0.094
Pat. CMV pos	1.11 (0.88–1.4)	0.37	1.22 (0.91–1.63)	0.18	1.16 (0.96–1.4)	0.12	1.11 (0.91–1.36)	0.31	1.11 (0.92–1.32)	0.27
Don. CMV pos	0.98 (0.79–1.22)	0.87	0.99 (0.76–1.29)	0.93	1.03 (0.86–1.22)	0.78	1 (0.83–1.21)	0.98	0.97 (0.82–1.14)	0.72
in vivo TCD	1.07 (0.79–1.46)	0.66	0.63 (0.43–0.92)	0.017	0.85 (0.67–1.09)	0.21	0.83 (0.63–1.08)	0.16	0.66 (0.52–0.83)	0.0005
Frailty		0.65		0.085		0.88		0.26		0.14

Relapse remains the issue

Study (Author, Year)	Relapse Rate	Median Follow up	95% CI	Regimen/Context Notes
Gavriilaki et al., 2025	25.3%	36 months	na	
Berning P et al., 2024	21%	36 months	15–27	FluTreo vs TBI/Flu (8 Gy); comparable outcomes
Gagelmann N et al., 2024	20%	12 months	14–29	Myelofibrosis; Busulfan vs Treosulfan dose intensity
Robin M et al., 2024	20%	36 months	14–29	Myelofibrosis; Treosulfan vs Busulfan (EBMT registry)
Pasic I et al., 2024	15.6%	24 months	7.1–29.4	MDS; Treosulfan vs Busulfan (propensity-matched)
Finke J et al., 2022	36%	36 months	25–52	TTT (Thiotepa–Flu–Treosulfan); 2nd transplant, high risk
Shimoni A et al., 2021	25%	60 months	21–30	MDS; Treosulfan vs other RIC/MAC (EBMT)
Lazzari L et al., 2021	44.5%	144 months	34.9–53.6	Treosulfan-based; very long follow-up
Beelen DW et al., 2020	24.1%	24 months	17.8–31.3	RCT: Treosulfan/Flu vs Busulfan/Flu in elderly AML/MDS
Wedge E et al., 2020	14.8%	36 months	5.8–27.8	MDS; FluTreo
Gavriilaki (FT14) 2025	25.3%	Overall (median FU 16.3 mo)	na	FT14 (Flu 150 mg/m ² + Treo 42 g/m ²); mixed AML/MDS/MF cohort

MEDIAN 2-YRS RELAPSE RATE = 20-25%

A phase II multicenter prospective study to evaluate the safety and efficacy of myeloablative-dose treosulfan plus fludarabine (FT14) conditioning regimen in allogeneic hematopoietic stem cell transplantation for AML patients aged 40–65 in first complete remission

Daniele Avenoso ^{1,15}, Vera Radici^{1,15}, Alessandro Leoni¹, Cristina Skert², Massimo Martino ³, Nicola Mordini ⁴, Francesco Saraceni ⁵, Attilio Olivieri ⁵, Fabio Ciceri ⁶, Cristina Tecchio ⁷, Alessandra Picardi ⁸, Giorgia Saporiti⁹, Francesca Patriarca¹⁰, Paola Bresciani¹¹, Chiara Nozzoli¹², Denise Maravalle¹³, Nicola Polverelli ¹⁴, Gabriele Magliano¹, Enrico Morello¹, Mirko Farina ¹, Simona Bernardi ¹, Federica Re ¹, Luca Garuffo¹, Simone Maifredi¹, Silvia Zanon¹, Rachele De Domenico¹, Michele Malagola ¹ and Domenico Russo¹✉

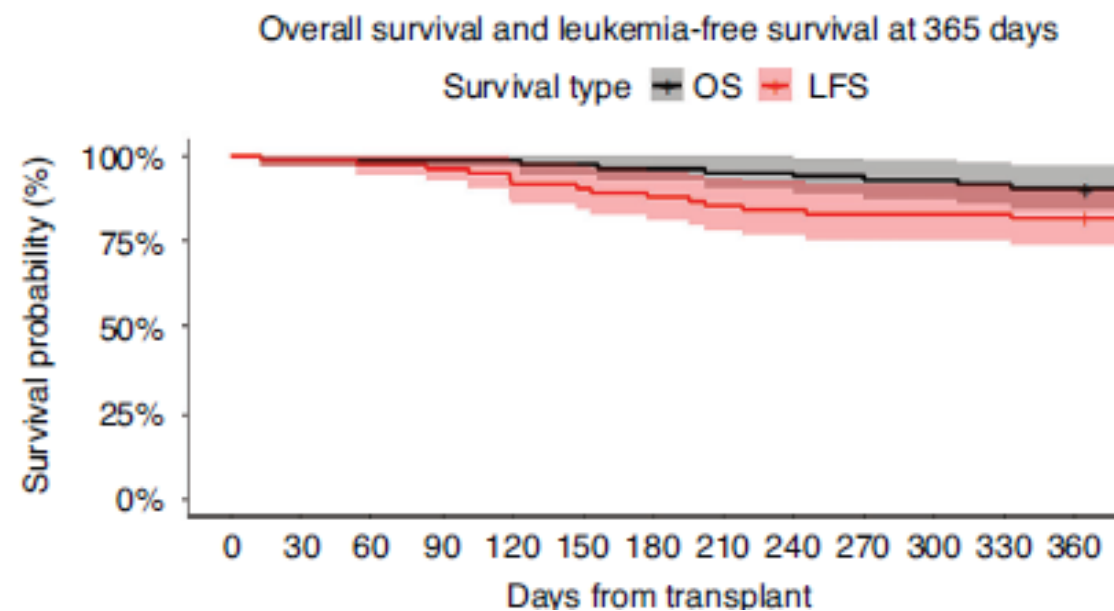
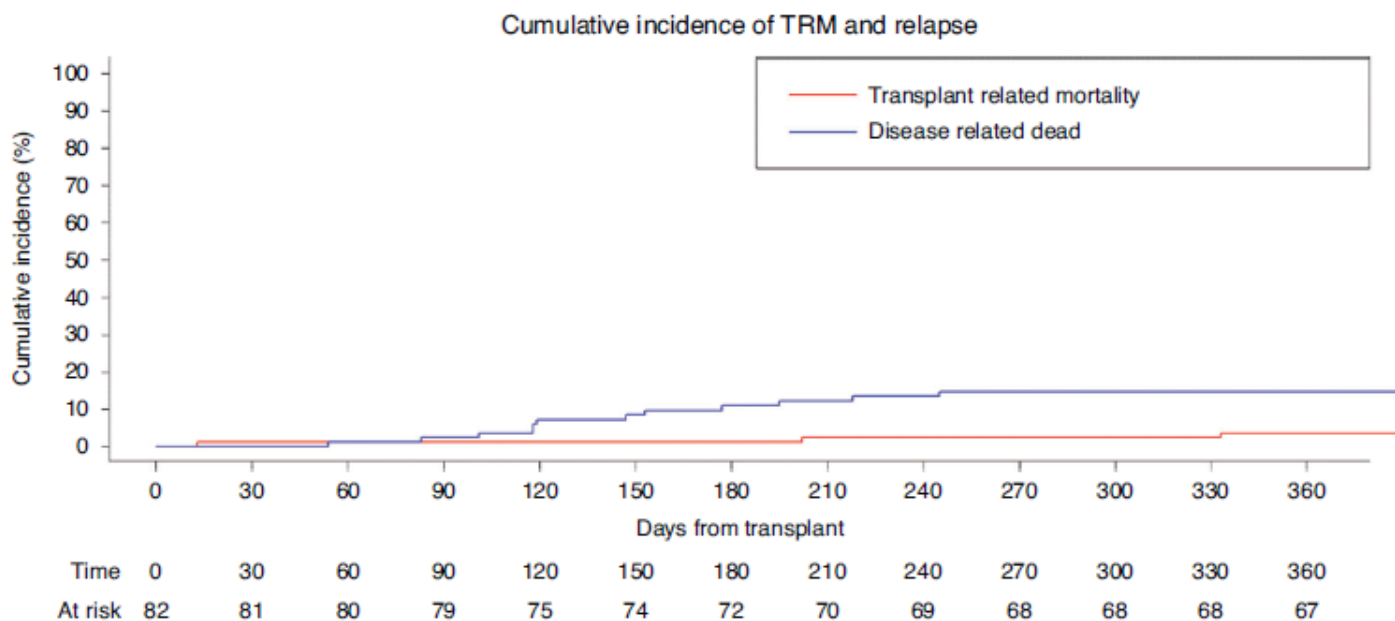
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Evidences supporting the use of myeloablative-dose Treosulfan combined with Fludarabine remain largely retrospective, with outdated prospective studies available. In this phase II multicenter prospective trial, we evaluated the safety and efficacy of FT14 conditioning regimen in patients with acute myeloid leukemia undergoing allogeneic stem cell transplantation in first complete remission. (EudraCT Number: 2021-006515-28; Clinical trial number NCT07232953). The study was designed to provide a non-inferior alternative to standard busulfan-containing regimens, which would enable effective transplantation while minimizing toxicity. The primary objective was 1-year Leukemia-free survival (LFS). In total, 82 patients were enrolled in the study with a median follow up of 19.7 months; donor used were matched sibling in 22, matched unrelated 52 and mismatched unrelated in 8 cases, respectively. LFS at 180-day and 365-day were 87.8% and 81.7%, respectively. Cumulative incidence of relapse at 1 year after allo-HSCT was 14.9% with mean time to relapse of 5.6 months. Also, FT14 regimen provided an excellent safety with nearly absent NRM, no cases of septic death, and no cases of primary graft failure. Our study supports the use of FT14 as effective myeloablative conditioning regimen for AML patients aged 40–65 y in first complete remission, especially in patients for whom busulfan based conditioning

**Intermediate
TCI ≤ 3.5**

**Primary Aim:
1yr-LFS
compared to FB4
(65%)**

**Non-inferiority
trial, assuming a
lower toxicity of
FT14**



1-yr LFS = 81% vs 65 % of FB4

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

Charles Craddock, Graham McIlroy, Hannah Vincent, Gabrielle Smith, Sarah Johnson, Rebecca Collings, Rebecca Faville, Vitor Jesus, Victoria Potter, Eleni Thelouli, Rachel Protheroe, Andrew Clark, Keith Wilson, Alexander Martin, Charles Crawley, Amy Publicover, Andrew Peniket, Anjum Khan, Jiri Pavlu, Patrick Medd, Jenny Byrne, Ronjon Chakraverty, Wendy Ingram, Andrea Bacigalupo, Alessandro Rambaldi, Aimee Jackson, Sylvie Freeman

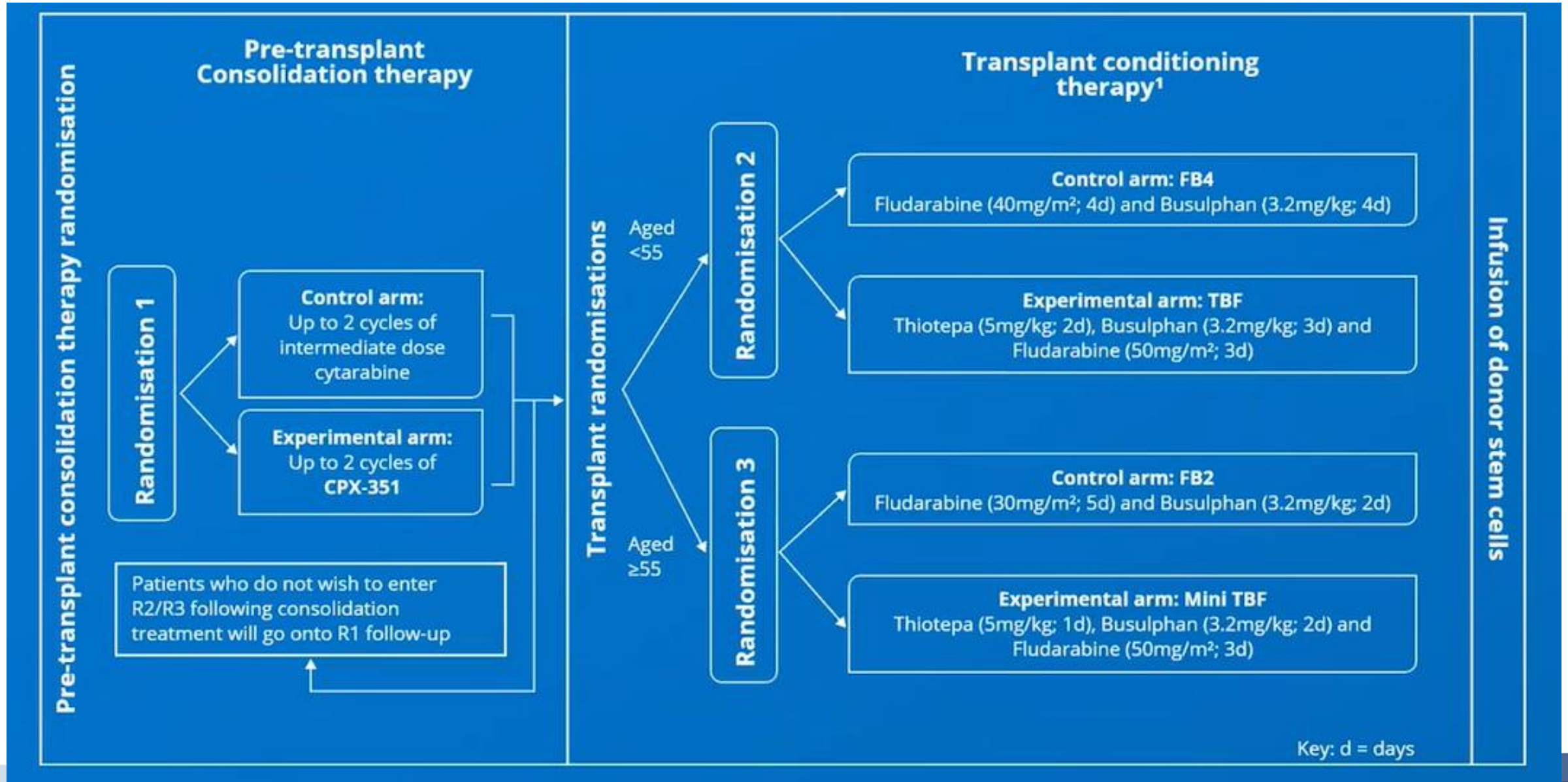
post-ASH 2026

Udine, 8-9 Ottobre 2026

Aula Polifunzionale Ospedale di Udine

COSI TRIAL

Craddock et al. post-ASH 2026



COSI TRIAL

Craddock et al. post-ASH 2026

R2 - Patients aged between 18 – 54 years
- Suitable for MAC allo-SCT

R3 - Patients aged ≥ 55 years (or < 55 with
comorbidities precluding MAC allo-SCT)
- Suitable for RIC allo-SCT

Patients with a morphologically documented diagnosis of AML or MDS who are clinically indicated to receive a MAC or RIC allograft with one the following disease characteristics:

- **AML**
 - CR1 or 2
 - Must have received ≥ 2 courses intensive chemotherapy prior to SCT
- **MDS**
 - Advanced or high risk MDS including intermediate or high risk CMML (e.g. CPSS int-2 or high risk), who have $< 10\%$ blasts at the time of randomisation
- HLA-matched sibling or suitable unrelated donor a ($<$ single allele mismatch at HLA-A, -B, -C, DR β 1, DQB1)
 - ECOG performance of 0, 1 or 2

Udine, 8-9 Ottobre 2020

R3 = Low Intensity TBF vs BU2FLU

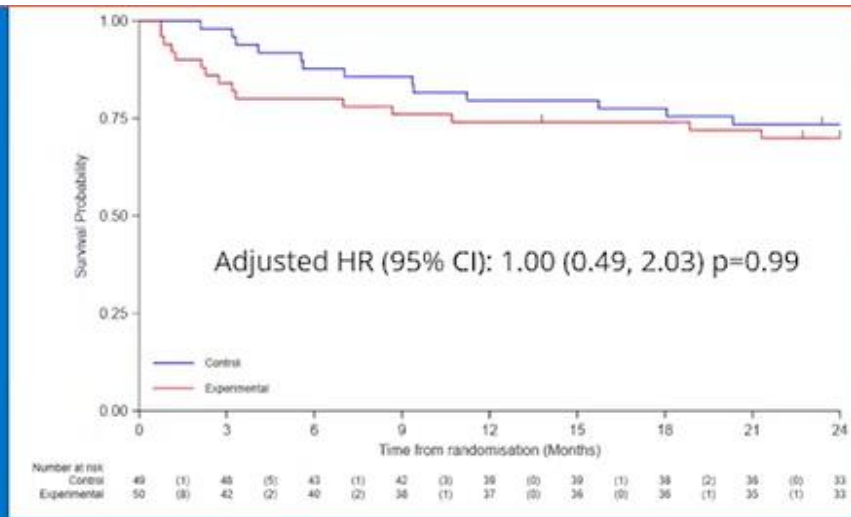
	Control (110)	Experimental (108)	Overall (218)
Underlying Disease (N (%))			
AML	78 (70.9)	79 (73.1)	157 (72.0)
MDS	32 (29.1)	29 (26.9)	61 (28.0)
Central Review Risk Stratification (N (%))			
AML			
Favourable	15 (13.6)	14 (13.0)	29 (13.3)
Intermediate	31 (28.2)	30 (27.8)	61 (28.0)
Adverse	32 (29.1)	35 (32.4)	67 (30.7)
MDS	32 (29.1)	29 (26.9)	61 (28.0)
AML Disease Status (N (%))			
CR1	68 (87.2)	68 (86.1)	136 (86.6)
CR2	10 (12.8)	11 (13.9)	21 (13.4)
Donor Type (N (%))			
Matched - Sibling	19 (17.3)	16 (14.8)	35 (16.1)
Matched - Unrelated	91 (82.7)	92 (85.2)	183 (83.9)
Sex (N (%))			
Male	77 (70.0)	72 (66.7)	149 (68.3)
Female	33 (30.0)	36 (33.3)	69 (31.7)
Age (Years)			
N	110	108	218
Median	64.0	64.0	64.0
Range	31.0, 74.0	46.0, 75.0	31.0, 75.0
MRD Pre-Transplant Status (N (%))			
MRD <0.1%	50 (45.5)	64 (59.3)	114 (52.3)
MRD ≥0.1%	31 (28.2)	18 (16.7)	49 (22.5)
Not Assessable	29 (26.4)	26 (24.1)	55 (25.2)

R2 = Intermediate Int TBF vs BU4FLU

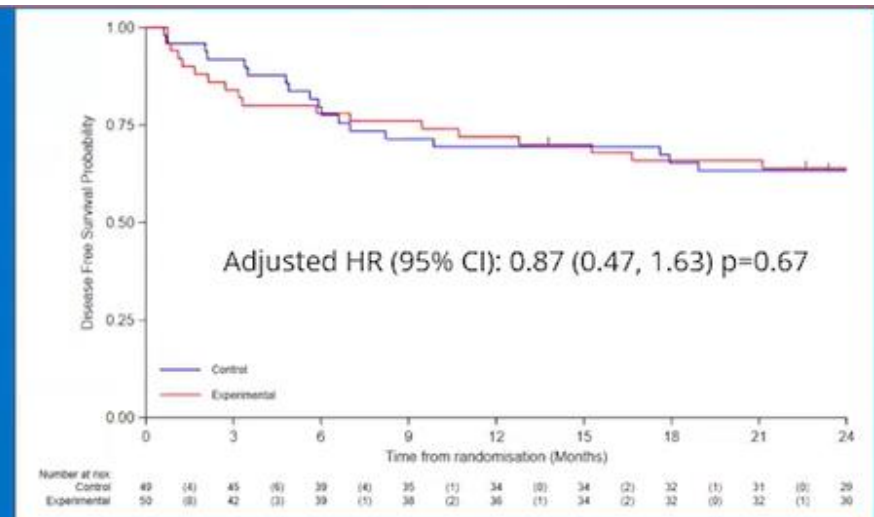
	Control (49)	Experimental (50)	Overall (99)
Underlying Disease (N (%))			
AML	42 (85.7)	43 (86.0)	85 (85.9)
MDS	7 (14.3)	7 (14.0)	14 (14.1)
Central Review Risk Stratification (N (%))			
AML			
Favourable	8 (16.3)	6 (12.0)	14 (14.1)
Intermediate	16 (32.7)	16 (32.0)	32 (32.3)
Adverse	18 (36.7)	21 (42.0)	39 (39.4)
MDS	7 (14.3)	7 (14.0)	14 (14.1)
AML Disease Status (N (%))			
CR1	33 (78.6)	36 (83.7)	69 (81.2)
CR2	9 (21.4)	7 (16.3)	16 (18.8)
Donor Type (N (%))			
Matched - Sibling	8 (16.3)	9 (18.0)	17 (17.2)
Matched - Unrelated	41 (83.7)	41 (82.0)	82 (82.8)
Sex (N (%))			
Male	25 (51.0)	22 (44.0)	47 (47.5)
Female	24 (49.0)	28 (56.0)	52 (52.5)
Age (Years)			
N	49	50	99
Median	43.0	46.5	44.0
Range	20.0, 54.0	21.0, 54.0	20.0, 54.0
MRD Pre-Transplant Status (N (%))			
MRD <0.1%	32 (65.3)	30 (60.0)	62 (62.6)
MRD ≥0.1%	9 (18.4)	8 (16.0)	17 (17.2)
Not Assessable	8 (16.3)	12 (24.0)	20 (20.2)

R2: Patient Outcomes According to Conditioning Regimen: FB4 versus TBF

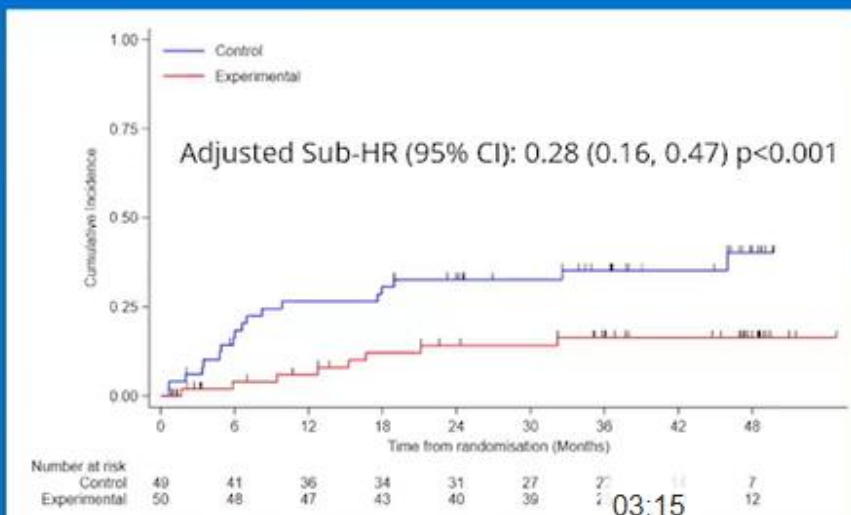
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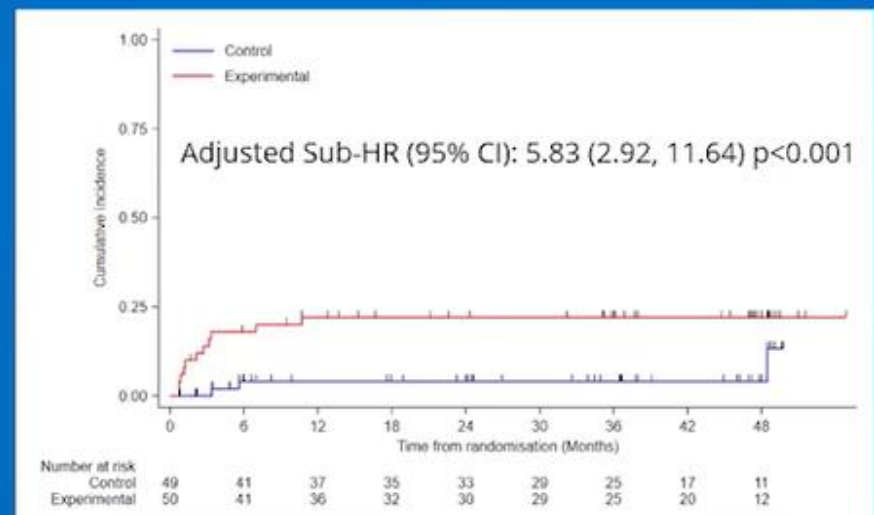
DFS



CIR



NRM



Udine, 8-9 Ottobre 2026

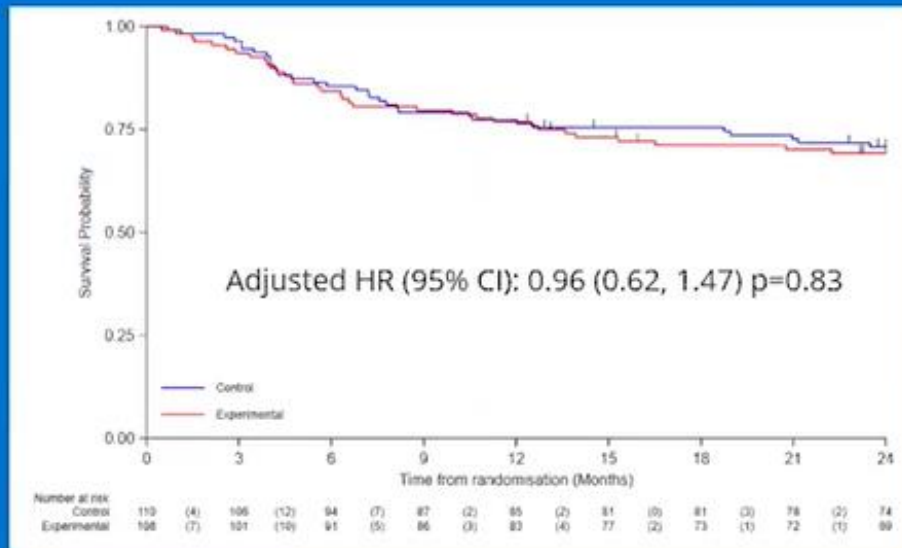
Corso di Formazione **GITMO** Trapianto e terapie cellulari: cellule, donatori e condizionamenti

Aula Polifunzionale Ospedale di Udine

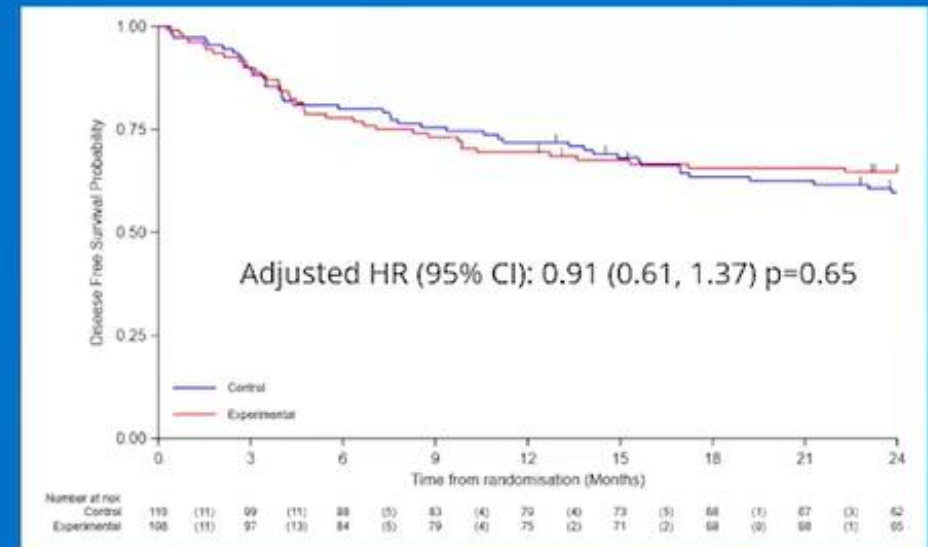
R3: Overall Results

Low TCI

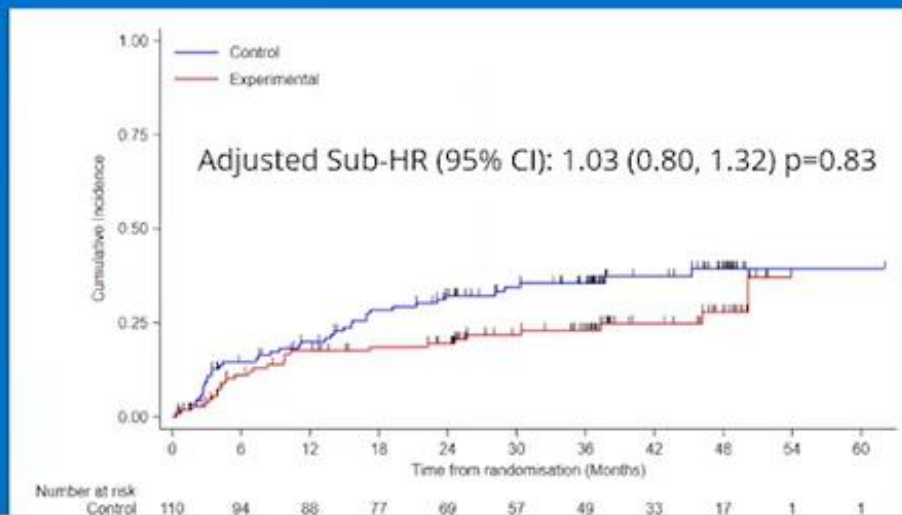
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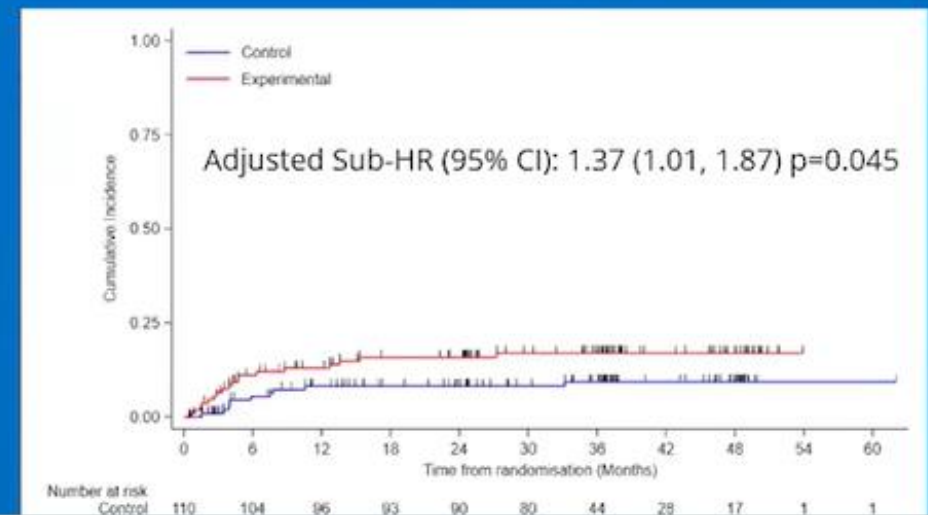
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CIR



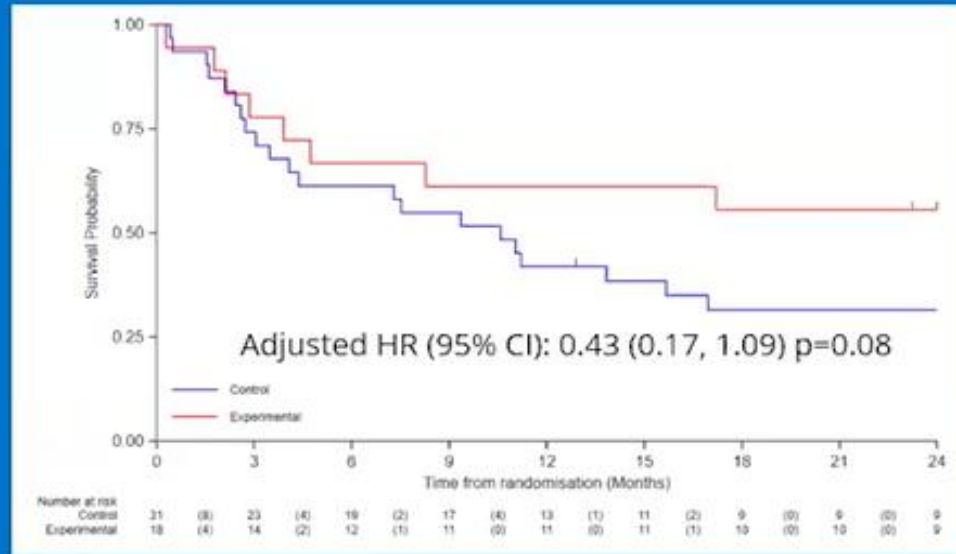
NRM



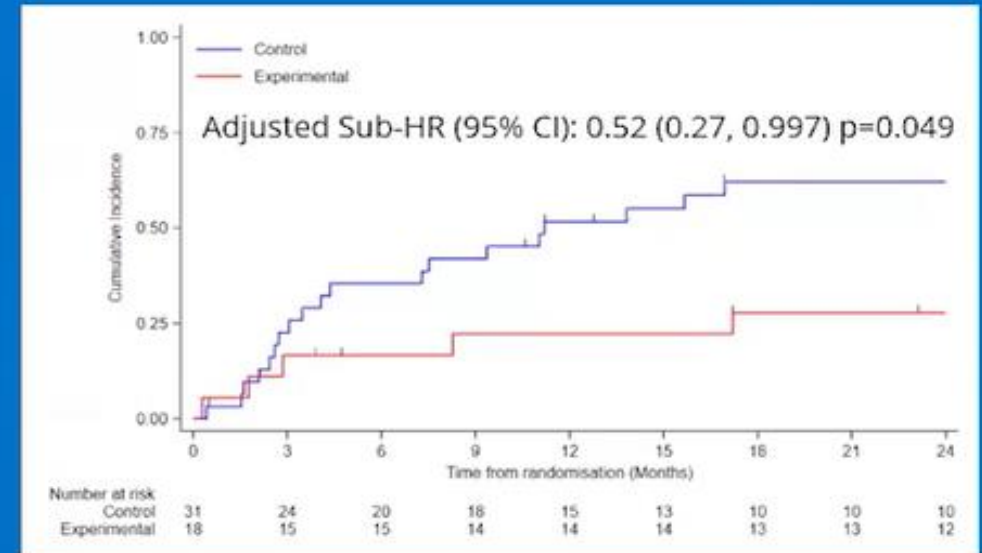
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R3: Patient Outcomes According to Pre-Transplant MRD Status $\geq 0.1\%$ Patients

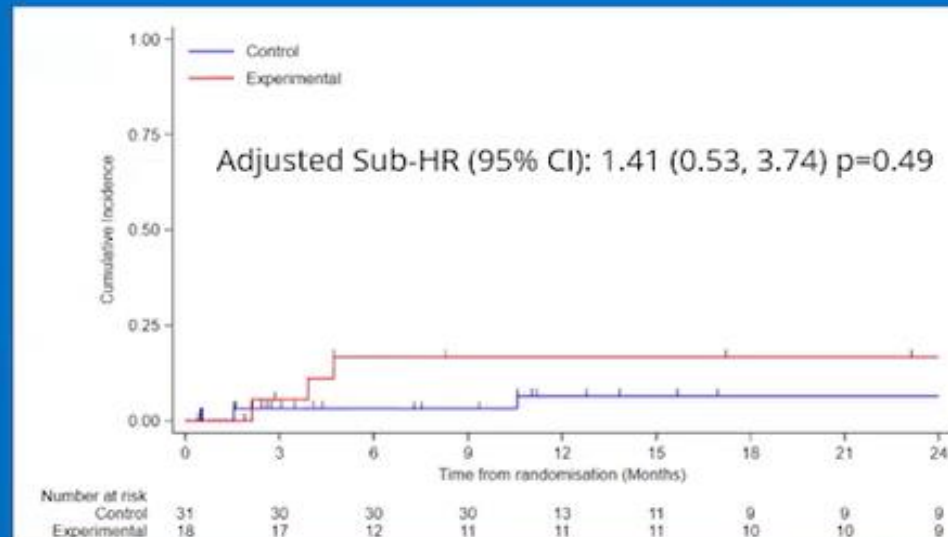
DFS



CIR



NRM



COSI Trial Conclusions

- Intermediate Intensity of TBF regimen vs BU4FLU seems consistently reduce the risk of disease relapse, however the benefit may be offset by a concomitant increase in NRM
- Low Intensity of TBF regimen is effective for reducing relapse risk in MRD+ AML and supporting a policy of HSCT without additional chemotherapy cycles

No RCT: Intermediate TCI TBF versus TTF

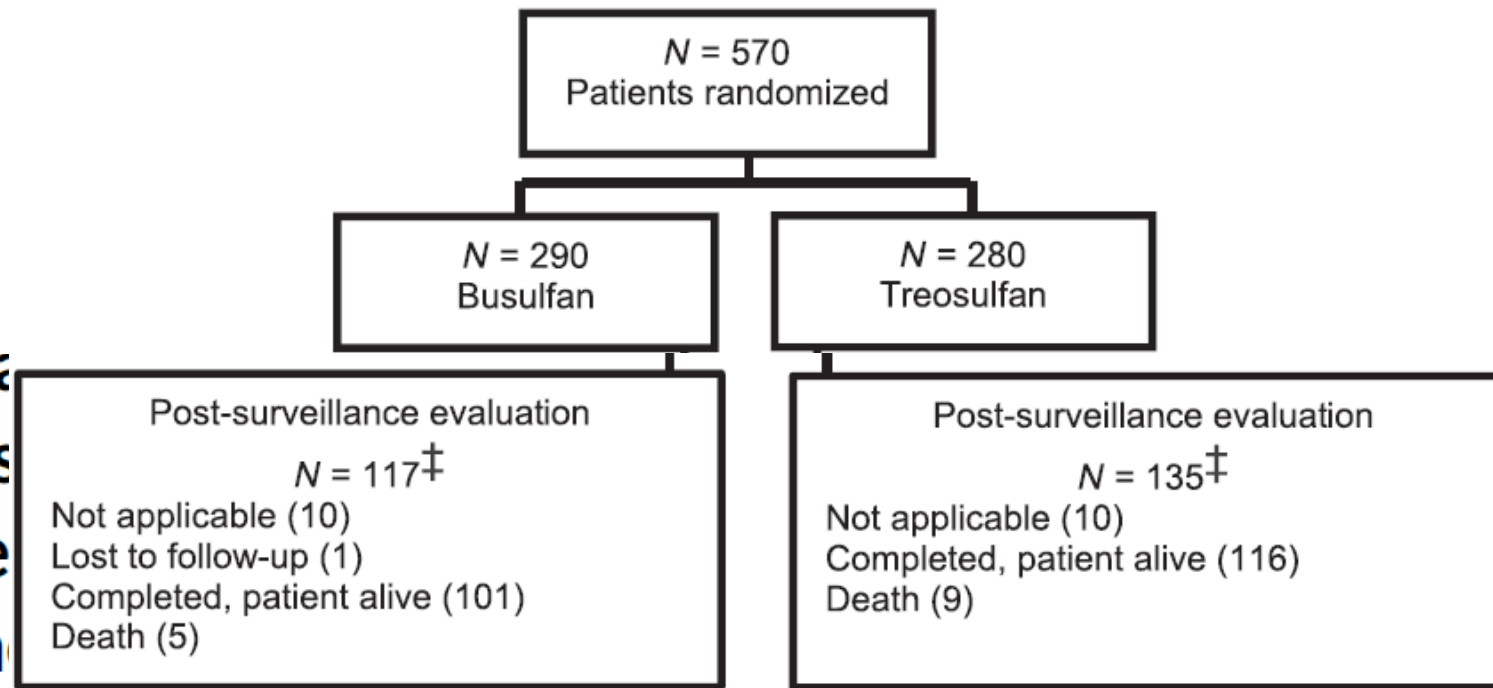
RCT Beelen BU2FLU vs TF10 Matched Donor

Received: 8 April 2025

DOI: 10.1002/ajh.

RESEARCH

Treosulfan
improves
outcome
syndrome
trial



aplastic
nized

Dietrich W. Beelen¹ | Matthias Stelljes² | Péter Reményi³ |

obre 2026

	BusulfanN = 283	TreosulfanN = 268	p-value
Median follow-up of those surviving ^a , months (range)	29.4 (3.0, 54.3)	29.7 (3.0, 52.1)	
Event-free survival			
Patients with event, n (%)	137 (48.4)	97 (36.2)	
Death ^b , n (%)	56 (19.8)	35 (13.1)	
Relapse/progression ^b , n (%)	72 (25.4)	61 (22.8)	
Primary graft failure ^b , n (%)	1 (0.4)	1 (0.4)	
Secondary graft failure ^b , n (%)	8 (2.8)	0 (0.0)	
Event-free survival at 24 months ^c , % (95% CI)	51.2 (45.0, 57.0)	65.7 (59.5, 71.2)	
Event-free survival at 36 months ^c , % (95% CI)	49.7 (43.3, 55.7)	59.5 (52.2, 66.1)	.0000001*,** .0005787*,***
Overall survival			
Patients with event, n (%)	112 (39.6)	81 (30.2)	
Overall survival at 24 months ^c , % (95% CI)	60.2 (54.0, 65.8)	72.7 (66.8, 77.8)	
Overall survival at 36 months ^c , % (95% CI)	57.8 (51.5, 64.1)	68.8 (62.8, 74.8)	
Nonrelapse mortality			
Patients with event, n (%)	56 (19.8)	35 (13.1)	
Cumulative nonrelapse mortality incidence at 24 months, % (95% CI)	20.4 (15.5, 25.2)	12.0 (8.0, 15.7)	
Cumulative nonrelapse mortality incidence at 36 months, % (95% CI)	21.0 (16.1, 26.0)	14.2 (9.5, 18.9)	.0343 [†]
Graft failure, (95% CI)			
Patients with event, n (%)	9 (3.2)	1 (0.4)	
Cumulative incidence at 36 months, % (95% CI)	3.2 (1.1, 5.3)	0.4 (0.0, 1.1)	.0392 [†]

NO DIFFERENCE IN TERMS OF RELAPSE
AML: Low TCI TREOFLU vs TBF= no evidence

Udine, 8-9 Ottobre 2026

HOW TO SELECT THE CONDITIONING REGIMEN IN AML ?

- **Low Intensity (TCI < 2.5):** HCT-I ≥ 5 + pre-Frail/Frail +/- Age > 60 years
TF10 should be preferred in frail patients with matched donor and TBF in high relapse risk,
BuFlu is a valid alternative

TTF10: in case of mismatched donor (to be confirmed)

CyFluTBI2 (Old, haplo)

- **Intermediate Intensity (2.5-3.5) :** HCT-I= 3-4 + Fit/pre-frail + Age 40-60
TBF or BU4FLU – TF14

TTF or FluMel also in case of mismatched donor (to be confirmed)

- ~~• **High Intensity >3.5 – HCT-I <3 + Fit + Age < 40 (40-50, case by case)**~~

~~**BuCy or Treo based (to be confirmed)**~~

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SIFO Arturo Cavalieri

SIF: Solo partecipazione, no revisore

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- Domenico Pastore
- Raffella Greco
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- Romano Danesi (SIF – Farmacologo)



Metodologa: Dott.ssa Monia Marchetti

Metodologo : Dott. Jacopo Olivieri

HOW TO SELECT THE CONDITIONING REGIMEN IN AML ?

- Intermediate TCI seems to be the gold standard for adult AML patients in hematological CR, according their fitness/frailty (consider elderly)
- Combination of double alkylating agents seem to be protective in terms of relapse both as Intermediate and Low TCI in AML
- Further Prospective Clinical Trial are necessary to confirm the role of new agents and their combination