Il condizionamento con doppio alchilante è preferibile ai condizionamenti convenzionali nella preparazione del trapianto allogenico nelle leucemie acute?

Le ragioni del NO

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ASU FC Azienda sanitaria universitaria Friuli Centrale

UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

CONVEGNO EDUCAZIONALE GITMO

HOT QUESTIONS IN TRASPLANTATION AND CELLULAR THERAPIES

Udine
13-14 novembre 2023
Aula Polifunzionale - Ospedale di Udine

Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Disclosures

MSD, Pfizer, Jazz

Agenda

- Origine e significato del regime di condizionamento

- Donatori alternativi: il problema dell'engraftment

- La malattia refrattaria

- Il problema della tossicità

Il regime di condizionamento

Nei pazienti con patologie ematologiche maligne il regime di condizionamento ha principalmente due significati:

- Fornire una immunoablazione sufficiente da prevenire il rigetto del trapianto

- Ridurre il "tumor burden"

In origine la TBI

Nei pazienti con patologie ematologiche maligne si è utilizzata tradizionalmente la TBI , per lo più in associazione con Ciclofosfamide (TBI-CY):

- Effetto immunosoppressivo

- Attività antileucemica e antilinfomatosa

- Capacità di penetrare nei "santuari"

Regimi di condizionamento solo chemioterapici

- Si basano sui farmaci alchilanti (Busulfano, Melphalan, Thiotepa,..)

- Attivi su tutte le patologie mieloidi, sul mieloma, sulla leucemia linfoblastica ma non sul compartimento linfoide maturo per cui si usano in associazione per es con Ciclofosfamide, Fludarabina

- Introduzione del Busulfano e.v. ha comportato una riduzione della tossicità epatica e della variabilità individuale dei livelli plasmatici
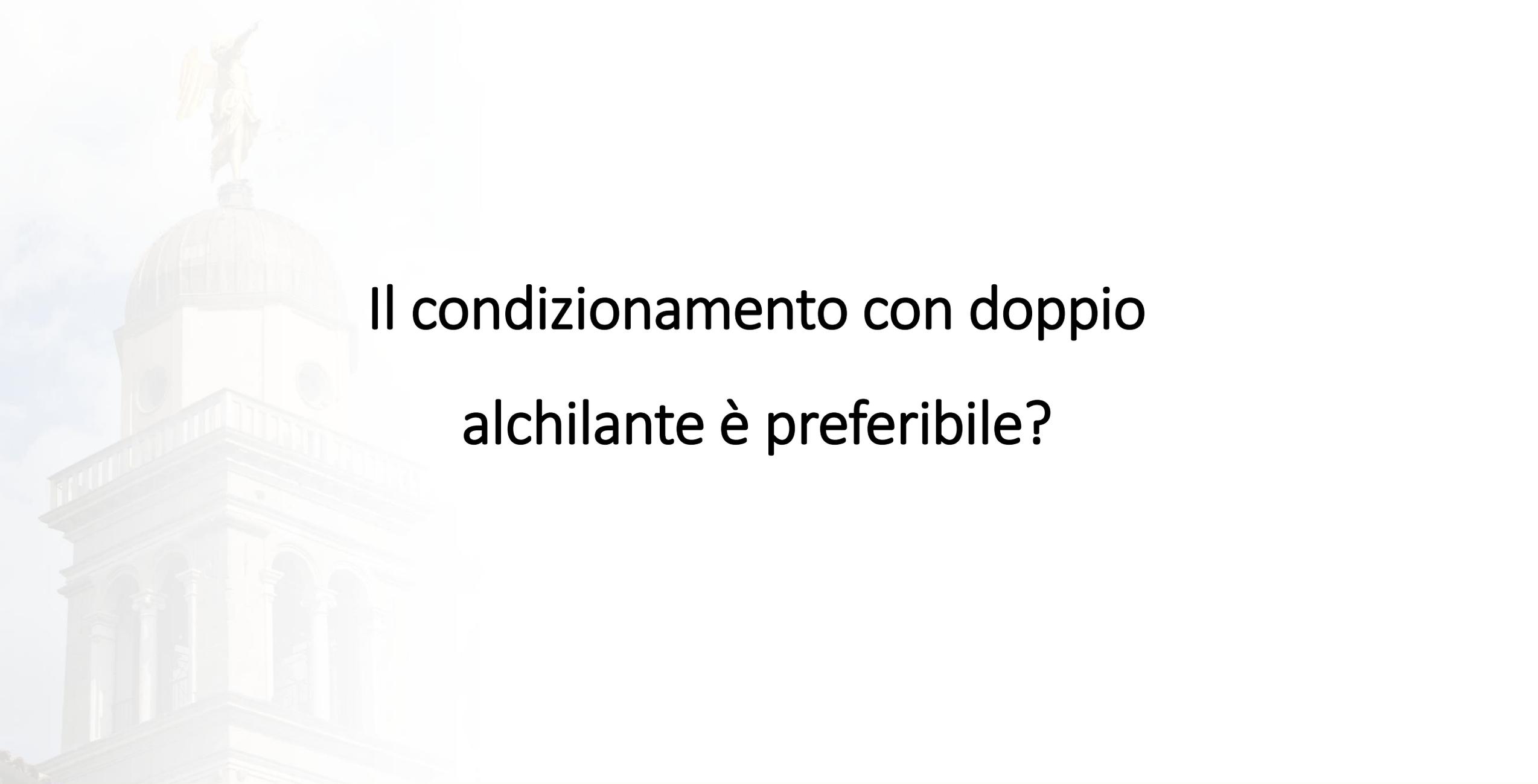
Il condizionamento con doppio alchilante è preferibile?
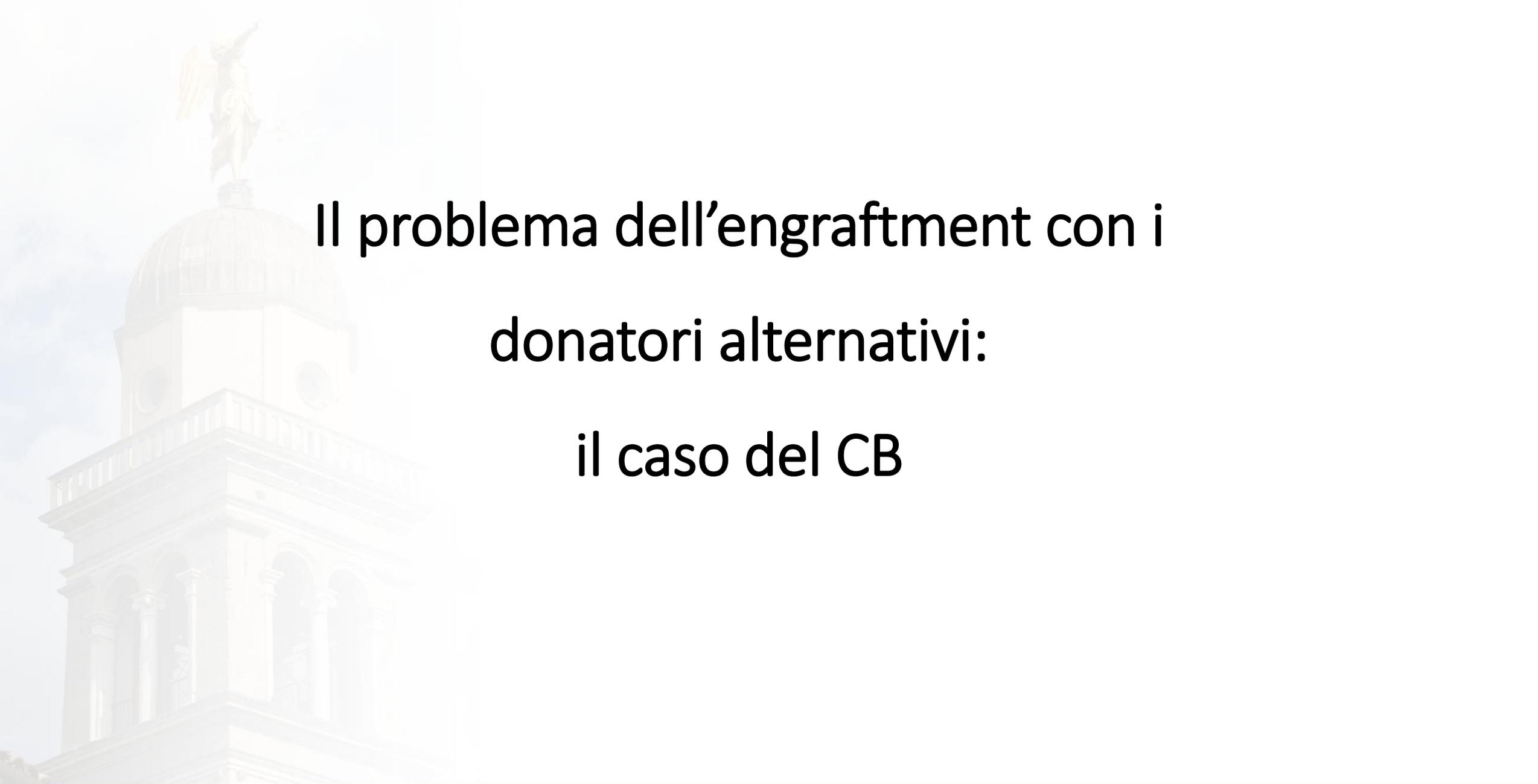
Il problema dell'engraftment con i donatori alternativi:

il caso del CB

ASTCT Guidelines for Adult and Conditioning Regimen in CB

Survival after CBT for Hematologic Malignancies with Various Conditioning Regimens

Series	Patient Characteristics	Conditioning	Survival
High-dose			
Kanda et al., 2011 [47]	n = 27	Flu 160 mg/m², TBI 1350 cGy	2-yr OS: 58%, 2-yr PFS: 52%
	Leukemias, MDS, lymphoma		
	Median age, 33 yr; range, 20–58 yr		
Barker et al., 2015 [19]	n = 56	Cy 120 mg/m², Flu 75 mg/m², TBI 1320 cGy	3-yr OS: 52%; 3-yr PFS: 50%
	Leukemias, MDS		
	Median age, 35 yr; range, 18-49 yr		
Anand et al., 2017 [48]	n = 31	Flu 160 mg/m², TBI 1350 cGy, thiotepa 10 mg/kg	3-yr OS: 57%, 3-yr PFS: 51%
	Acute leukemias, MDS, lymphoma		
	Median age, 46 yr; range, 19-65 yr		
Intermediate intensity			
Sanz et al., 2013 [45]	n = 102	Thiotepa 10 mg/kg, Bu 9.6 mg/kg i.v., Flu 150 mg/m², ATG 8 mg/kg	5-yr PFS: 34%
	Leukemias		
	Median age, 30 yr; range, 16-52 yr		
Milano et al., 2020 [50]	n = 130	Treosulfan 42 m/m², Flu 150/200 mg/m², TBI 200 cGy	3-yr OS: 66%, 3-yr PFS: 57%
	Leukemias, MDS		
	Median age, 45 yr; range, 0.6-65 yr		
Barker et al., 2020 [8]	n = 90	Cy 50 mg/kg, Flu 150 mg/m², thiotepa 10 mg/kg, TBI 400 cGy	3-yr OS: 82%, 3-yr PFS: 76%
	Acute leukemias (68%), MDS, MPD, NHL		
	Median age, 47 yr; range, 21-63 yr		
DeFilipp et al., 2020 [32]	n = 31	Flu 180 mg/m², Mel 100 mg/m², TBI 200 cGy	2-yr OS: 53%, 2-yr PFS: 47%
	Leukemias, MDS, lymphoma		
	Median age, 57 yr; range, 21-68 yr		
Kalin et al., 2019 [58]	n = 68	Flu 160 mg/m², Cy 60 mg/kg, TBI 400 cGy	1-yr OS: 61%, 1-yr PFS: 60%
	Leukemias, MDS, lymphoma, aplastic anemia		
	Median age, 57 yr; range, 20-69 yr		
Nonmyeloablative			
Fuchs et al., 2020 [22]	n = 186	Cy 50 mg/kg, Flu 200 mg/m², TBI 200 cGy	2-yr OS: 46%, 2-yr PFS: 35%
	Acute leukemias, MDS, lymphoma		
	Median age, 58 yr; range, 20-70 yr		
Peffault de Lator et al., 2018 [59]	n = 26	Cy 120 mg/kg, Flu 120 mg/m², ATG 5 mg/kg, TBI 200 cGy	2-yr OS: 84%
	Aplastic anemia		
	Median age, 16 yr; range, 9-23 yr		

Flu indicates fludarabine; Cy, cyclophosphamide; Mel, melphalan; TBI, total body irradiation; ATG, anti-thymocyte globulin.

L Metheny, et al; Transplantation and Cellular Therapy 2021

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%

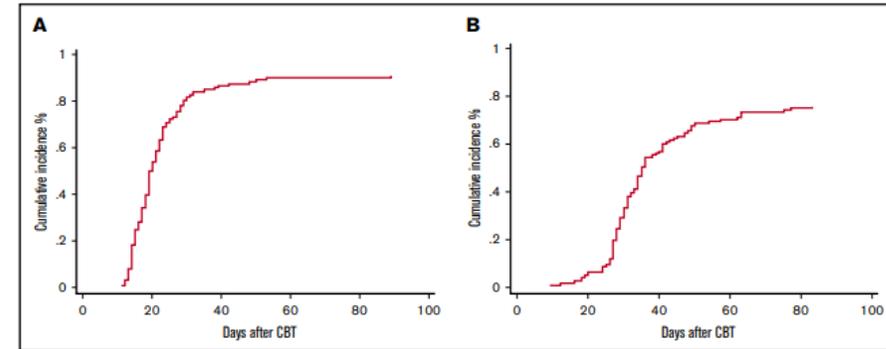- 3-years CIR and TRM 24% and 18%

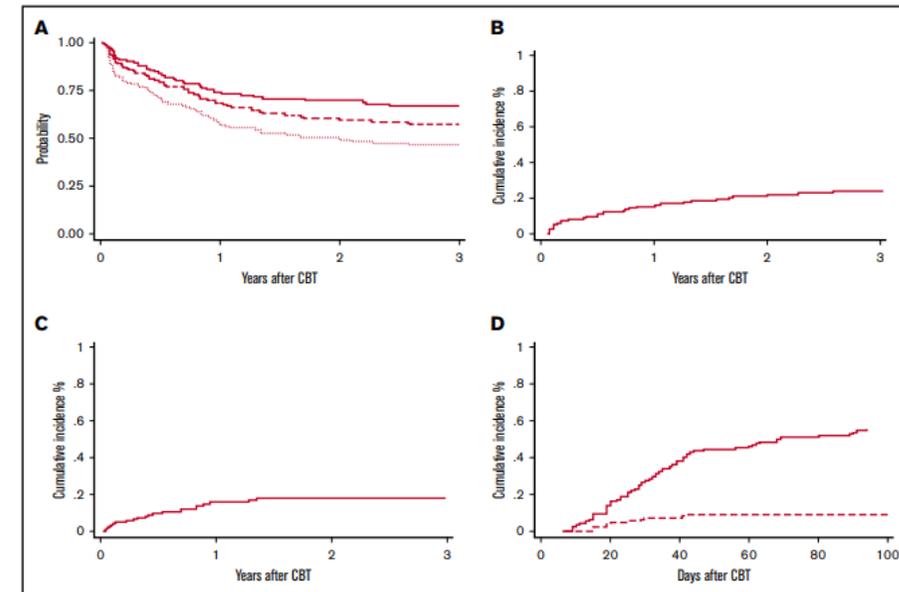Figure 1. **Cumulative incidence to day +100 in CBT recipients.** (A) Neutrophil engraftment. (B) Platelet engraftment.

Figure 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 conditioning 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
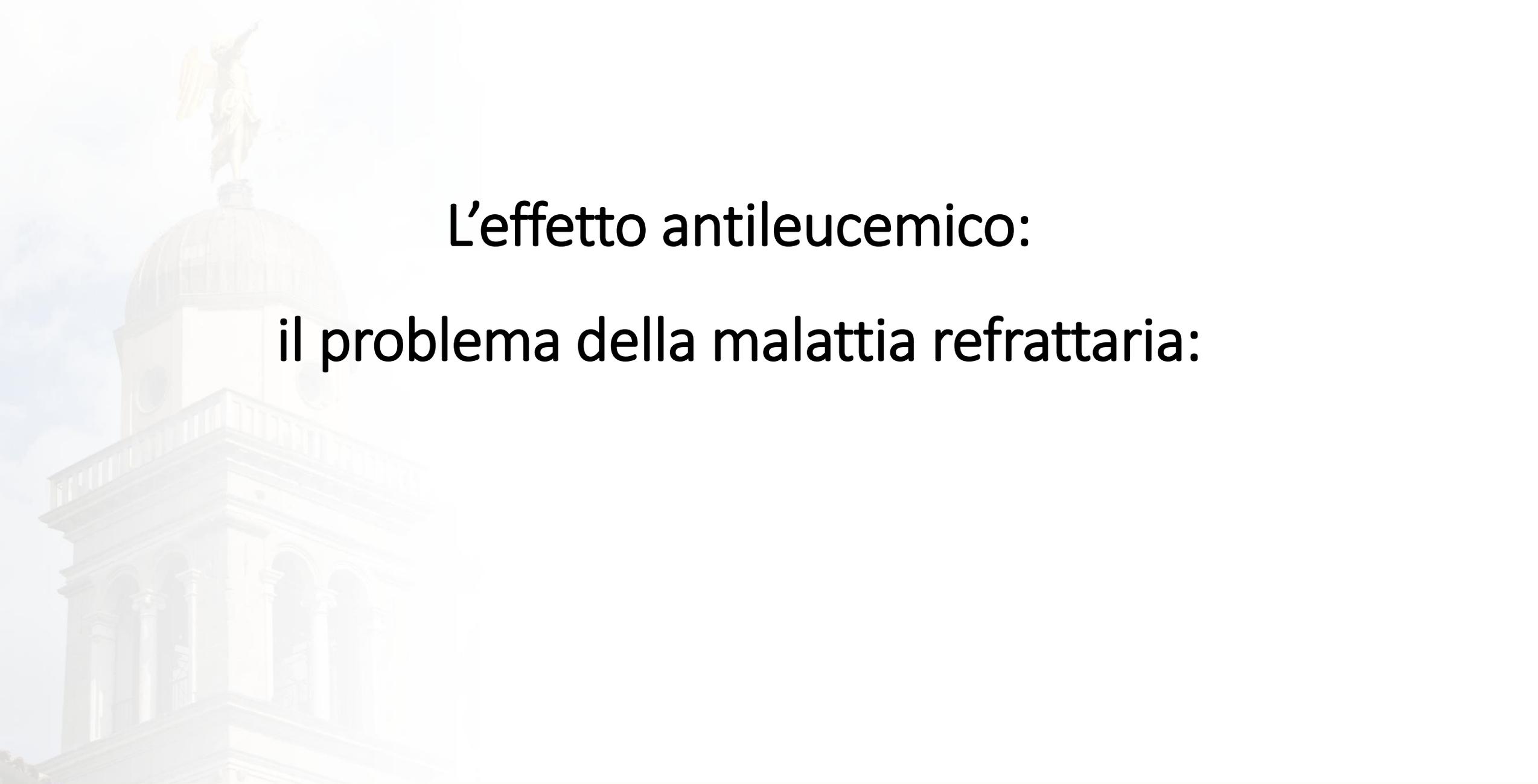
L'effetto antileucemico:

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%

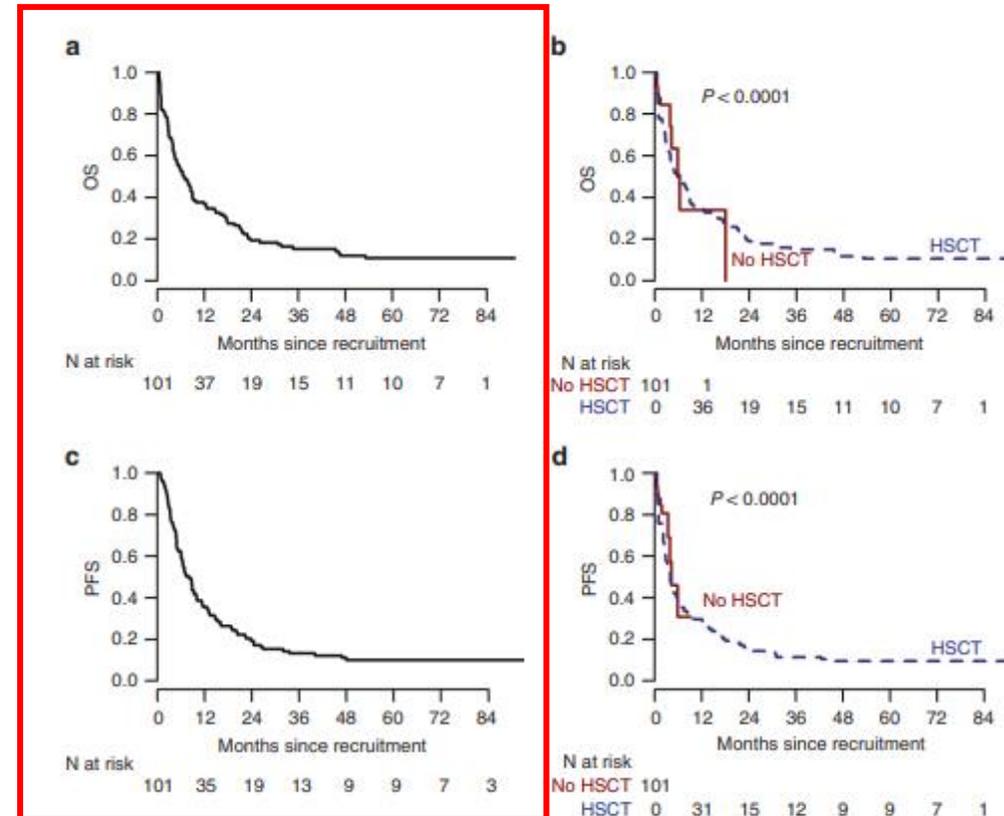- 1 and 2 years CIR 38% and 49%

- 1 and 2 years TRM 30% and 33%

Fig. 2 **Overall survival and progression-free survival of the entire study population.** Overall survival of the overall population (**a**); Simon–Makuch survival curves comparing the transplant vs not transplant cohorts (**b**). Progression-free survival of the overall population (**c**); Simon-Makuch progression-free survival curves comparing the transplant vs not transplant cohorts (**d**). OS overall survival, PFS progression-free survival.

F Bonifazi, et al; Bone Marrow Transplantation 2022

Sequential treatment (FLAMSA-RIC) in active leukemia

- A phase II multicenter open-label study from URD, MRD 10/10 or 9/10 in R/R LA

- 103 pts, median age 52 y (18-68)

- FLAMSA-RIC regimen including:
    - fludarabine, HD Arac, Amsacrine

    - TBI, Cyclophosphamide, ATG

- 1 and 2-years OS 54% and 40%

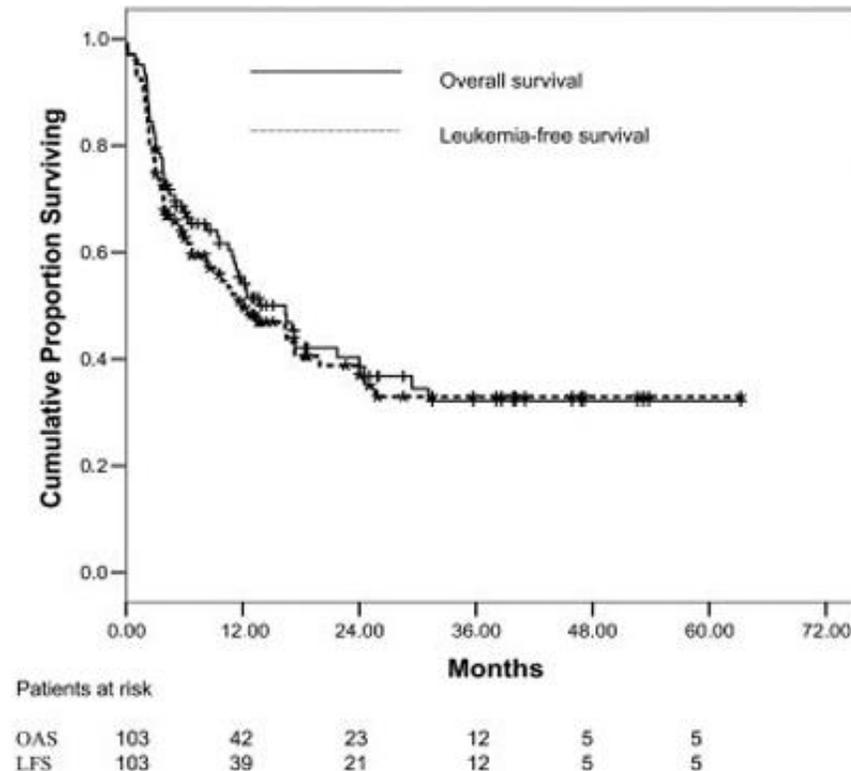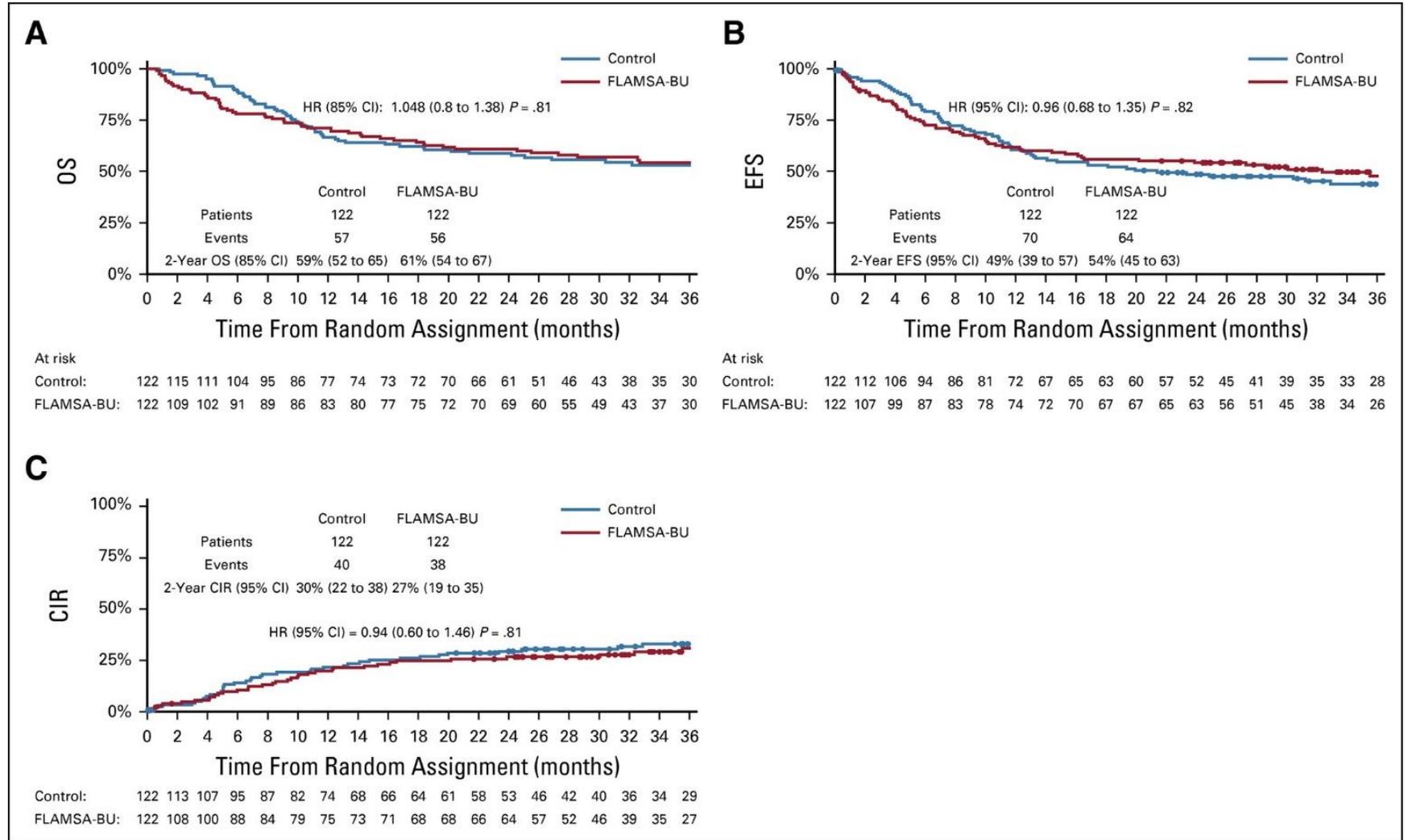- 1 and 2 years LFS 51% and 45%

- 1 and 2 years TRM 17% and 22%

Figure 1. Overall survival and leukemia-free survival.

C Schmid, et al; Blood 2006

The FIGARO trial: intensified FLAMSA-Bu regimen vs. conventional fludarabine-based RIC regimen

Phase II, **randomized**, multicenter study

244 AML

median age, 59

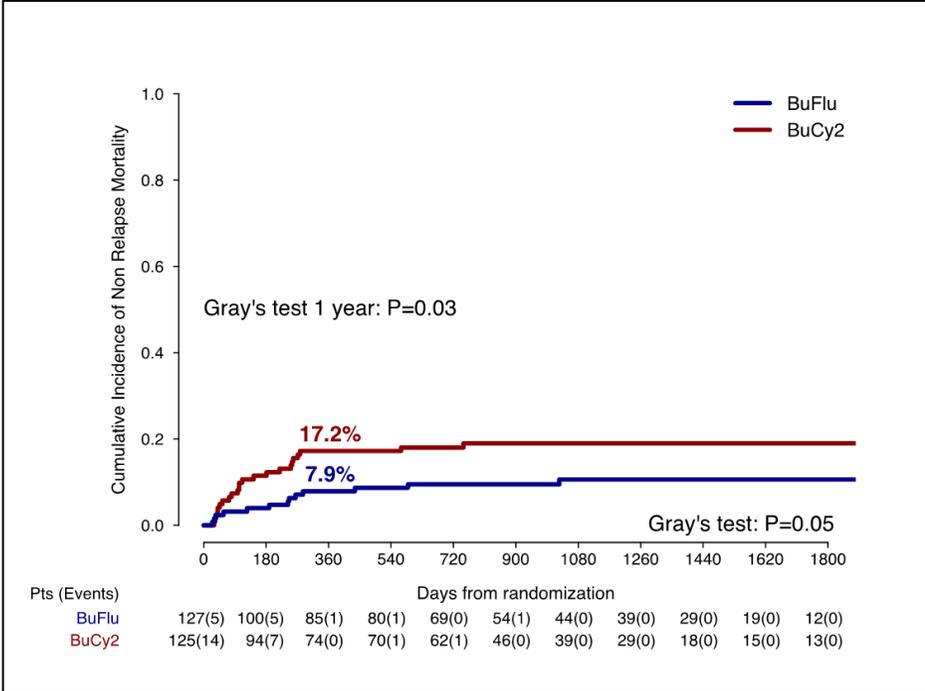*Craddock C et al.: Journal of Clinical Oncology 2020*

Scelta del condizionamento:

il problema della tossicità

AML-R2 Trial: Primary endpoint 1-year NRM

Phase III, randomized, multicenter study
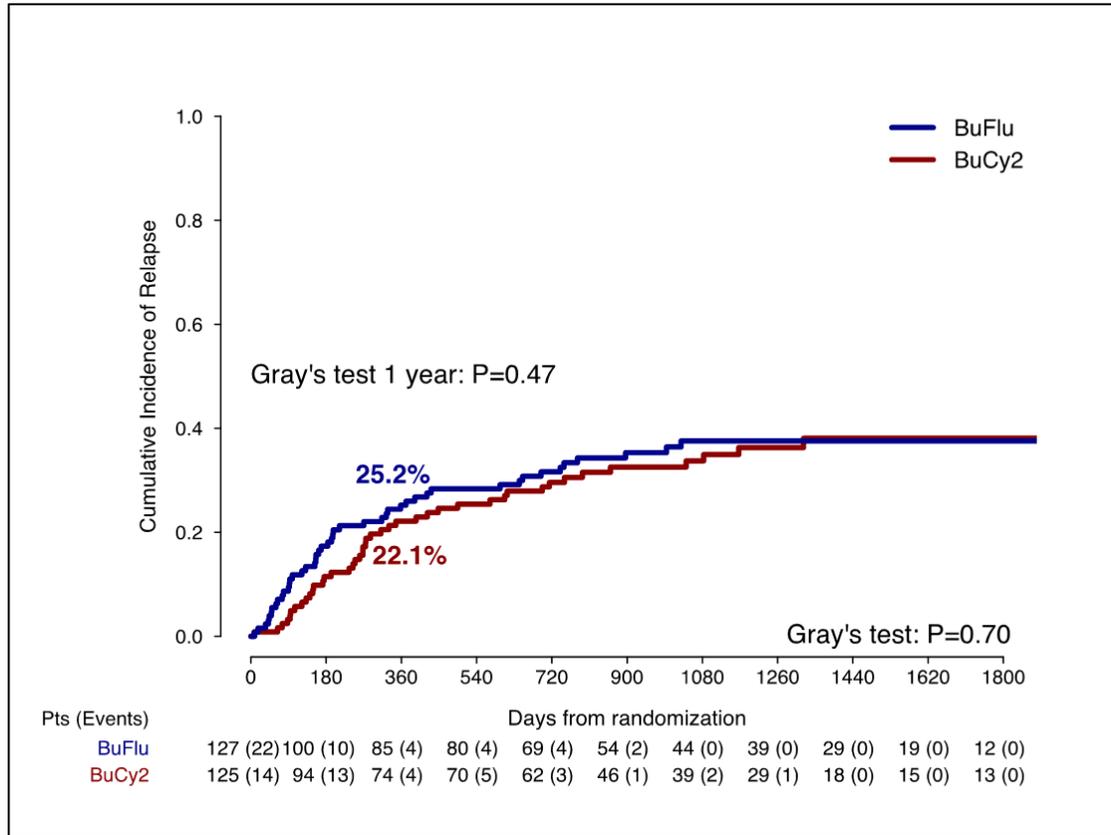
252 AML

median age, 51y

Gray's test 1 year: P=0.03

17.2%

7.9%

Gray's test: P=0.05

Pts (Events)										
BuFlu	127(5)	100(5)	85(1)	80(1)	69(0)	54(1)	44(0)	39(0)	29(0)	19(0)	12(0)
BuCy2	125(14)	94(7)	74(0)	70(1)	62(1)	46(0)	39(0)	29(0)	18(0)	15(0)	13(0)

Subgroup	Levels	HR	CI 95%	P	Events BuCy2	Events BuFlu
All patients		0.58	0.34-0.98	0.0424	21/121	10/124
Sex	M	0.56	0.28-1.11	0.0990	13/66	6/70
	F	0.60	0.26-1.41	0.2409	8/55	4/54
Age, Years	<51	0.64	0.27-1.49	0.3011	8/65	4/61
	≥ 51	0.52	0.26-1.04	0.0643	13/56	6/63
Disease status	CR1	0.50	0.27-0.92	0.0260	18/102	7/107
	≥ CR2	1.03	0.33-3.20	0.9577	3/19	3/17
ELN risk	Good/Int1	0.55	0.26-1.16	0.1150	12/75	5/75
	Int2/Adv	0.60	0.28-1.31	0.2018	9/46	5/49
Donor type	R	0.36	0.12-1.09	0.0712	8/55	2/57
	U	0.70	0.37-1.30	0.2536	13/66	8/67
Graft source	BM	0.64	0.27-1.50	0.3034	8/41	4/36
	PB	0.55	0.28-1.09	0.0877	13/80	6/88

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

A Rambaldi, et al., Lancet Oncology, 2015

Secondary endpoints: CIR and LFS

Cumulative incidence of relapse

Leukemia free survival

A Rambaldi, et al., Lancet Oncology, 2015
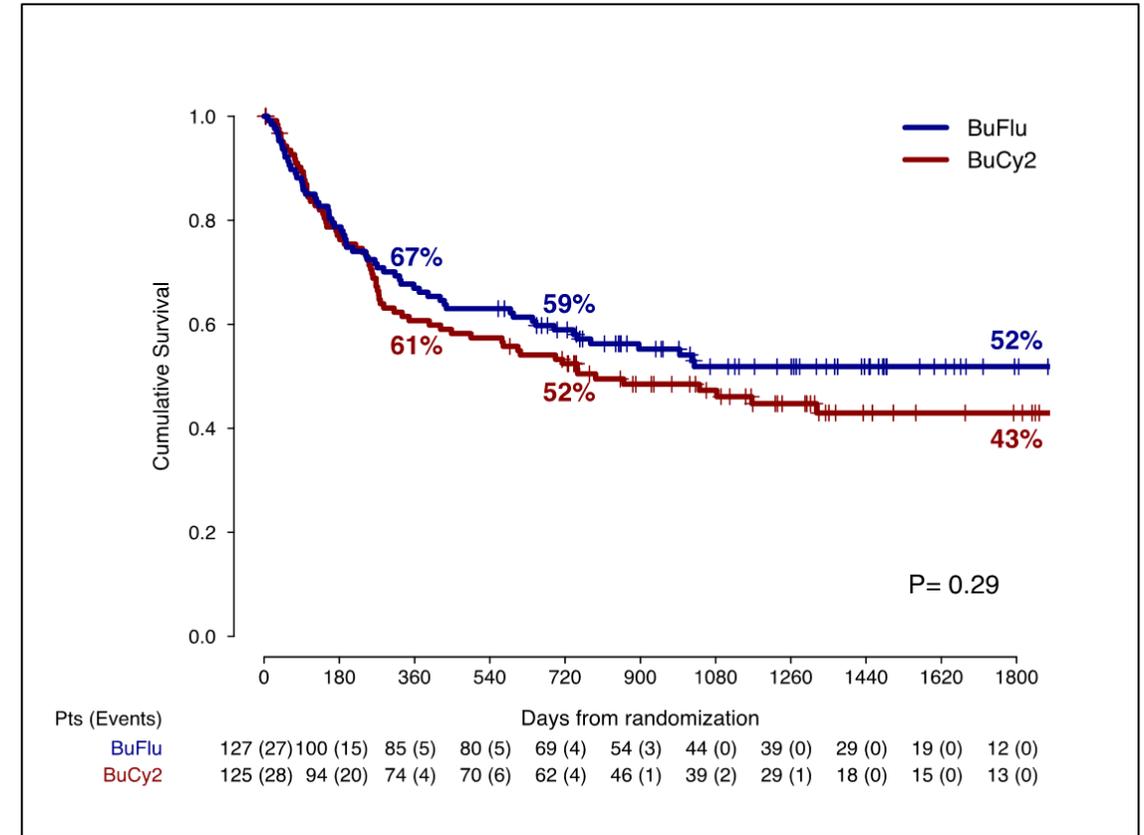
Long-term results of the GITMO AML-R2 trial: NRM
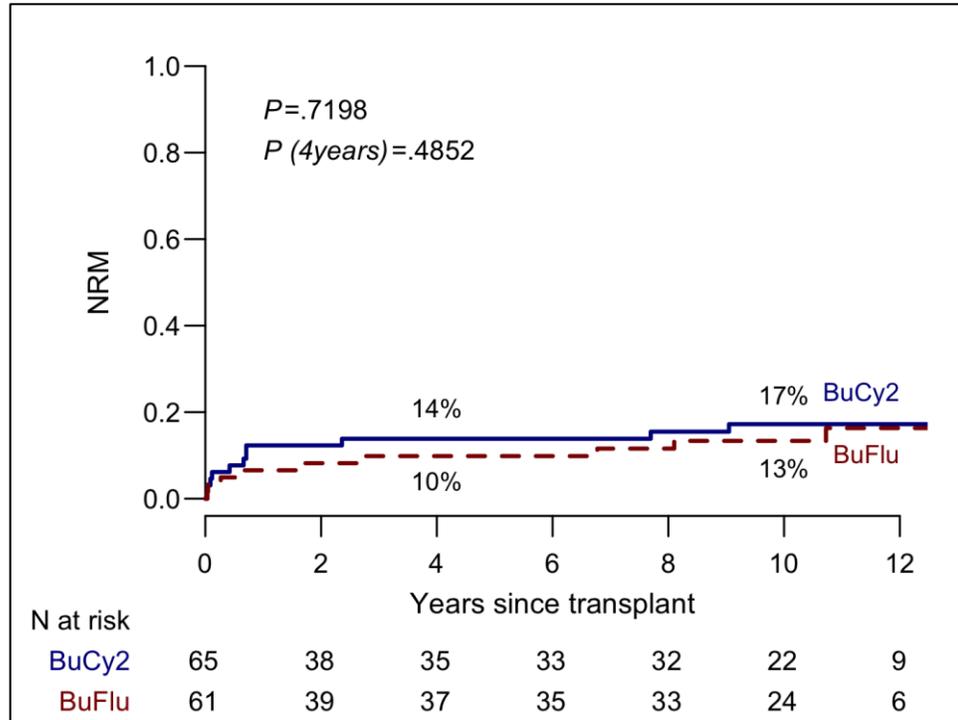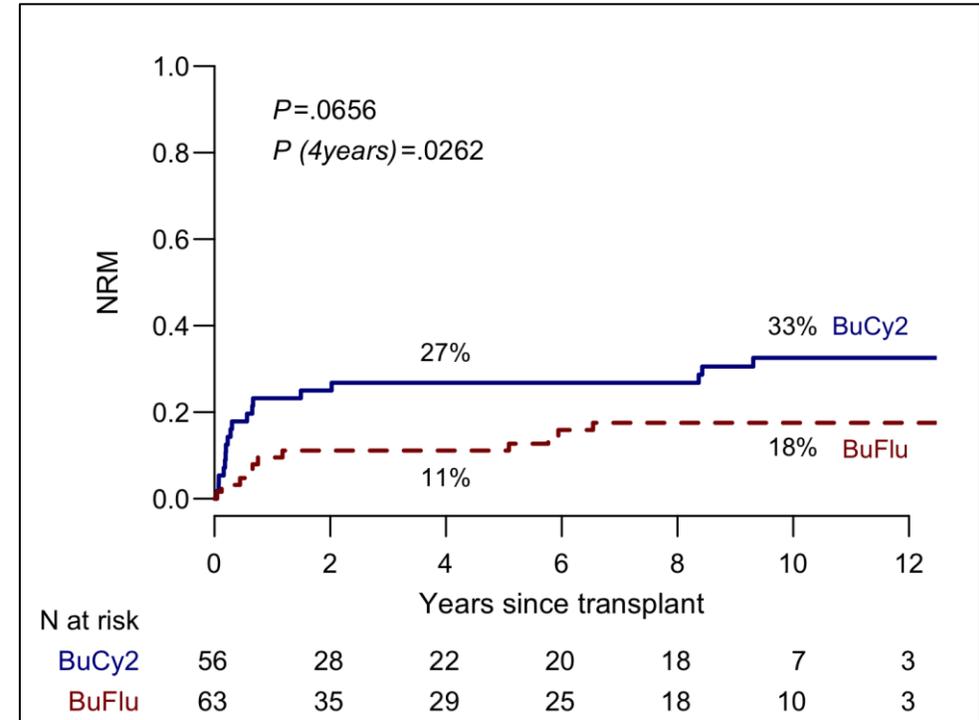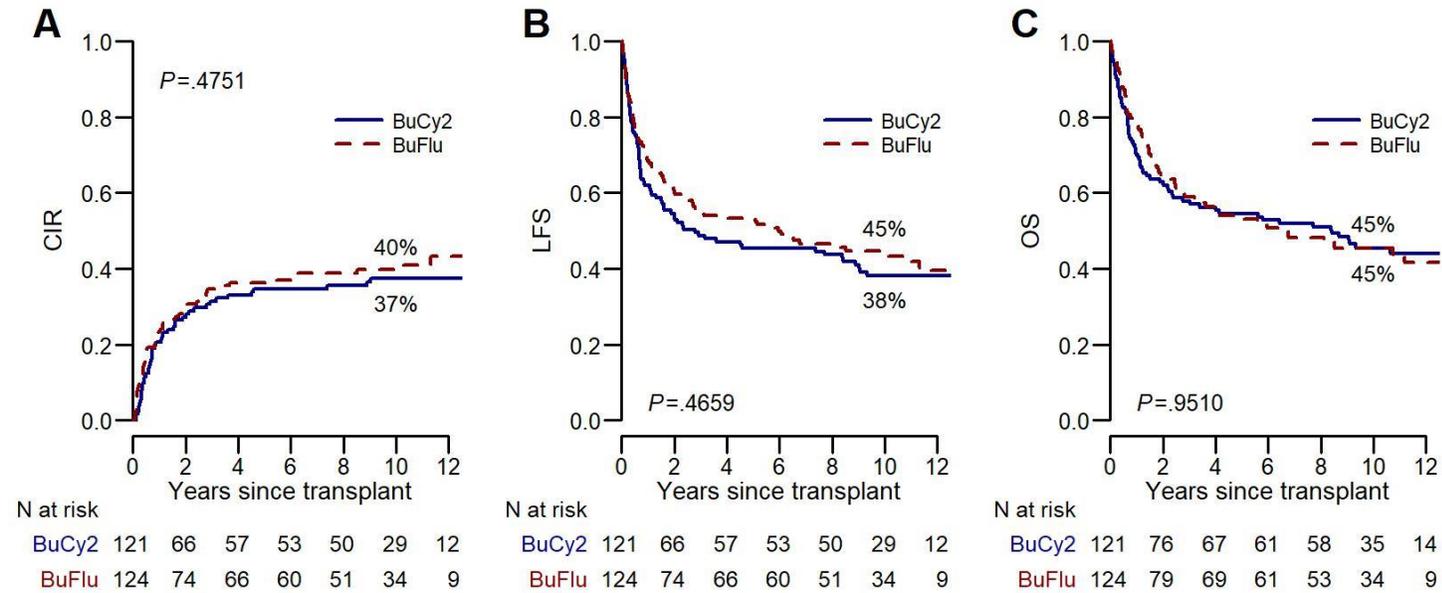

Cavallaro et al.: EBMT 2023 Oral Communication

# Long term results of GITMO AML-R2 trial

- NRM reduction was not counterbalanced by increased disease relapse rate, even at a very long follow-up

Cavallaro et al.: EBMT 2023 Oral Communication

# Busulfan-Fludarabine in haploidentical setting

- **Randomized** phase 3 trial of BuFlu vs BuCy in haploidentical transplant

- 386 pts (n=194 BuFlu, n=192 BuCy)

- 1-year TRM (primary endpoint) 7,2% in BuFlu vs 14.1% in BuCy (p=0.041)

- 5-years relapse rate 17,9% in BuFlu vs 14,2% in BuCy

- Outcomes superimposable to GITMO AML-R2 trial

Y Ling, et al; Journal of Clinical Oncology 2023
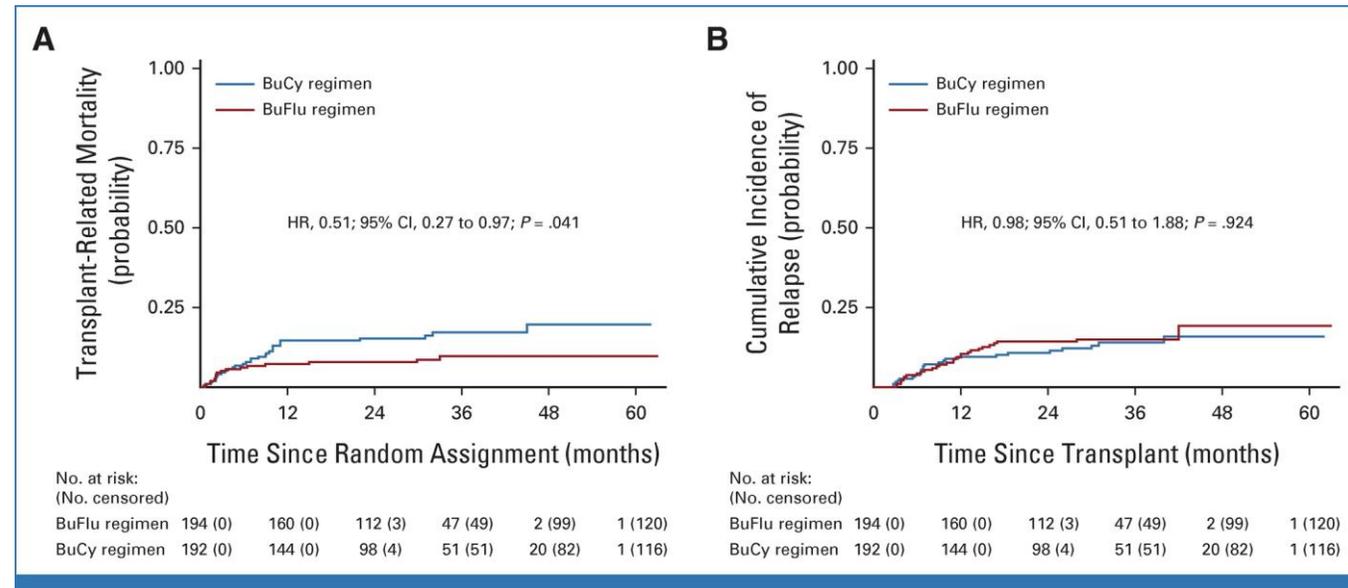
An International Randomised Clinical Trial of Therapeutic Interventions with the Potential to Improve Outcome in Adults with Acute Myeloid Leukaemia and High-Risk Myelodysplasia Undergoing Allogeneic Stem Cell Transplantation (the COSI trial)
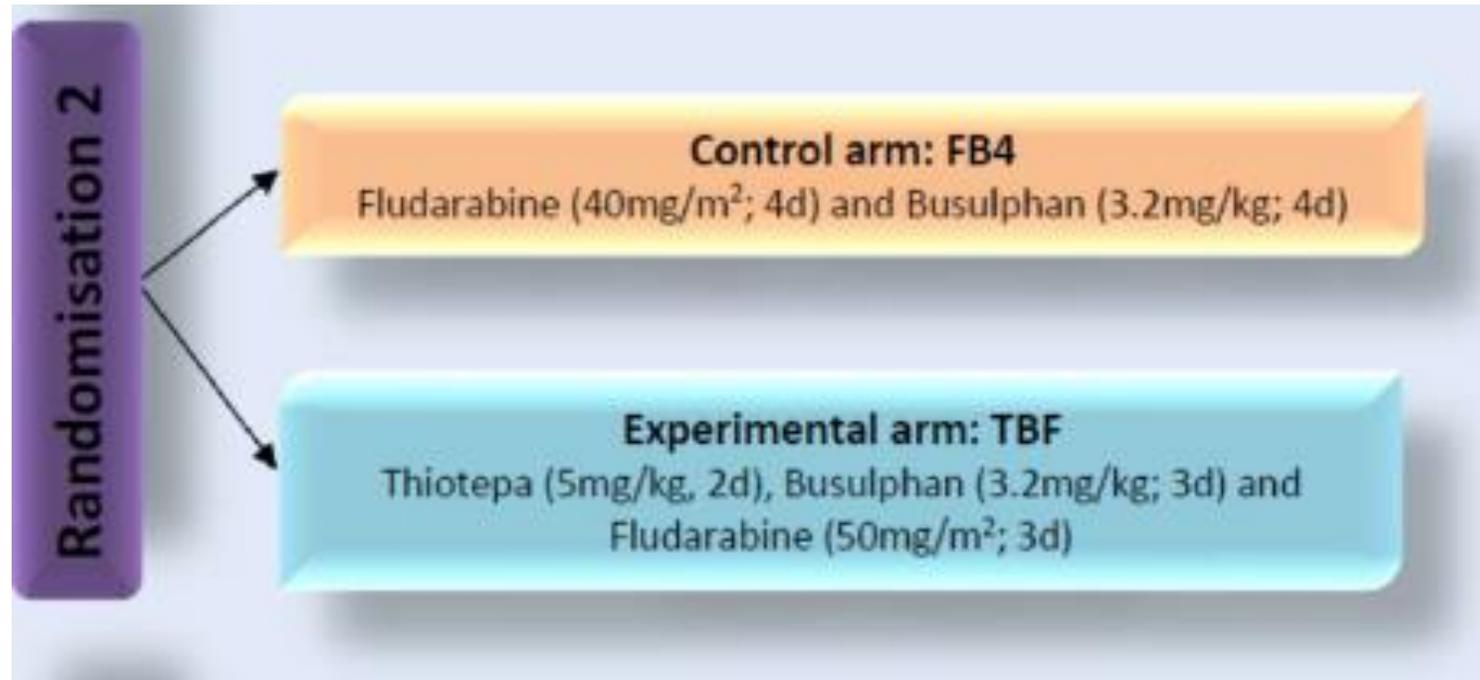
- **Chief Investigator: Professor Charles Craddock**
- **Sponsor: University of Birmingham**
- **EudraCT number: 2017-004801-42**
- **ClinicalTrials.gov number: NCT04217278**
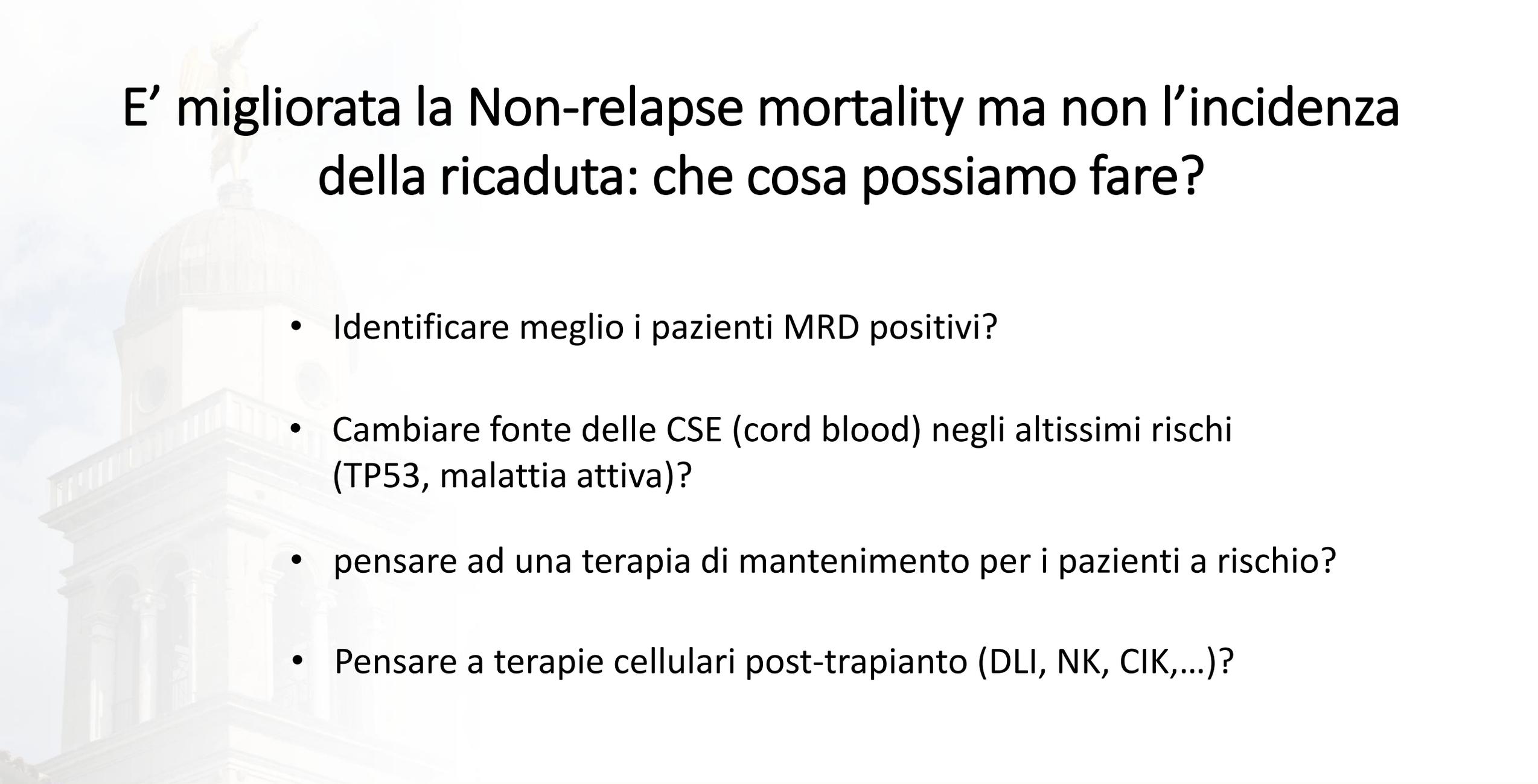
E' migliorata la Non-relapse mortality ma non l'incidenza della ricaduta: che cosa possiamo fare?

- Identificare meglio i pazienti MRD positivi?

- Cambiare fonte delle CSE (cord blood) negli altissimi rischi (TP53, malattia attiva)?

- pensare ad una terapia di mantenimento per i pazienti a rischio?

- Pensare a terapie cellulari post-trapianto (DLI, NK, CIK,…)?

Conclusions-1

- Allogeneic transplantation of hematopoietic cells is an effective treatment of many hematological diseases (particularly leukemia) even in advanced stage

- Disease relapse is the leading cause of treatment failure

- Allogeneic transplantation of hematopoietic cells provide a platform for immunotherapy

Conclusions-2

- Type and intensity of conditioning regimen should be carefully selected to minimize the tumor burden while keeping TRM as low as possible

- Numerous pharmacological and cellular therapies are now available to interact on this platform

- The right combination of all these elements could lead to the elimination of all cancer cells or to the establishment of a durable immune control

Grazie!