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

PRESENTAZIONE DEL QUESITO

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

ASU FC Azienda sanitaria universitaria Friuli Centrale

UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura

CONVEGNO EDUCAZIONALE GITMO

HOT QUESTIONS IN TRASPLANTATION AND CELLULAR THERAPIES

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

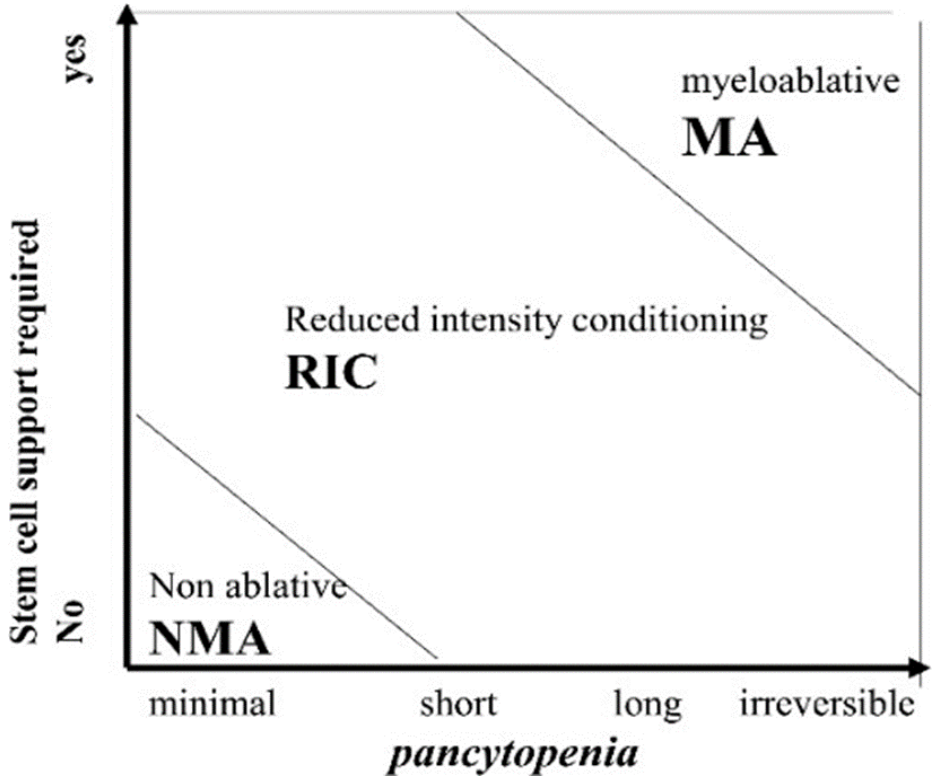
EFFECTS OF THE CONDITIONING REGIMENS

MYELOABLATIVE: to create the necessary bone marrow space to allow the engraftment

ANTI-NEOPLASTIC: to kill residual neoplastic cells of the underlying disease

IMMUNOSUPPRESSIVE: to avoid reject and Graft versus Host Disease effect (additional drugs in case of related/unrelated mismatching or other risk factors)

Reduced Intensity and Non Myeloablative Conditioning Regimens Definition



- ***Non Myeloablative*** **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:*** **all others non standard conditioning regimens**

Bacigalupo et al, BBMT 2009

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

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

Bone Marrow Transplantation (2020) 55:1114–1125
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 patients

This article has been corrected since Advance Online Publication and a correction is also printed in this issue

Alexandros Spyridonidis[1] · Myriam Labopin[2] · Bipin N. Savani[3] · Riitta Niittyvuopio[4] · Didier Blaise[5] ·

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	9.6 iv & 12 po	12.8 iv & 16 po	1
Treosulfan (g/m2)	30	36	42	1
Melphalan (mg/m2)	<140	≥140	≥200	1
Thiotepa (mg/kg)	<10	≥10	≥20	0.5
Fludarabine (mg/m2)	≤160	>160		0.5
Clofarabine (mg/m2)	≤150	>150		0.5
Cyclophosphamide (mg/kg)	<90	≥90		0.5
Carmustine (mg/m2)	≤250	280–310	≥350	0.5
Cytarabine (g/m2)	<6	≥6		0.5
Etoposide (mg/kg)	<50	≥50		0.5

SCORE :

Low Intensity < 2.5

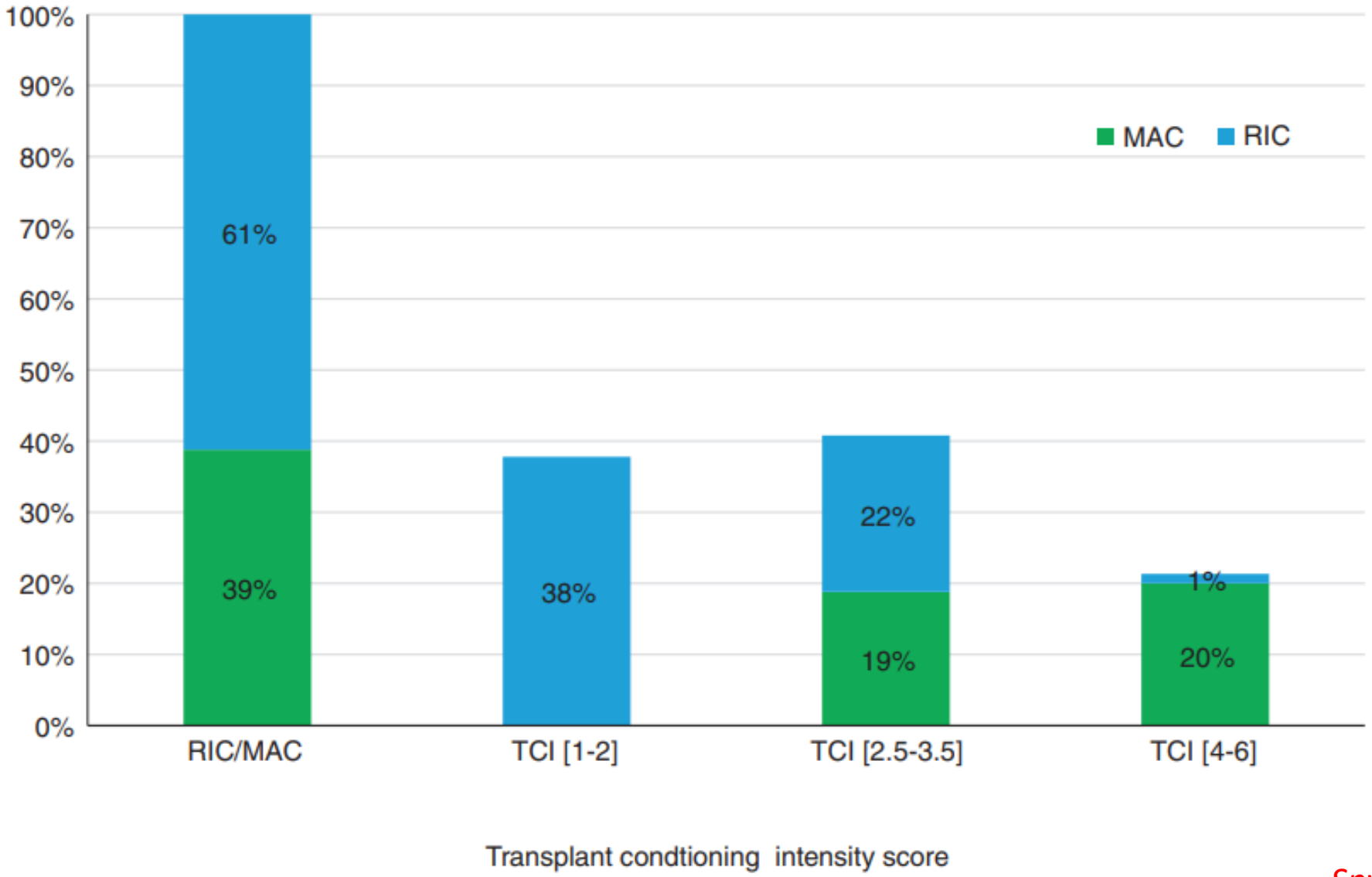
Intermediate Intensity 2.5-3.5

High Intenity >3.5

Most Conditioning Regimens = Intermediate Intensity

BETTER NRM PREDICTION

NO DIFFERENCES IN TERMS OF RELAPSE and RFS



Spyridonidis et al, 2020

45-54 years

55-65 years

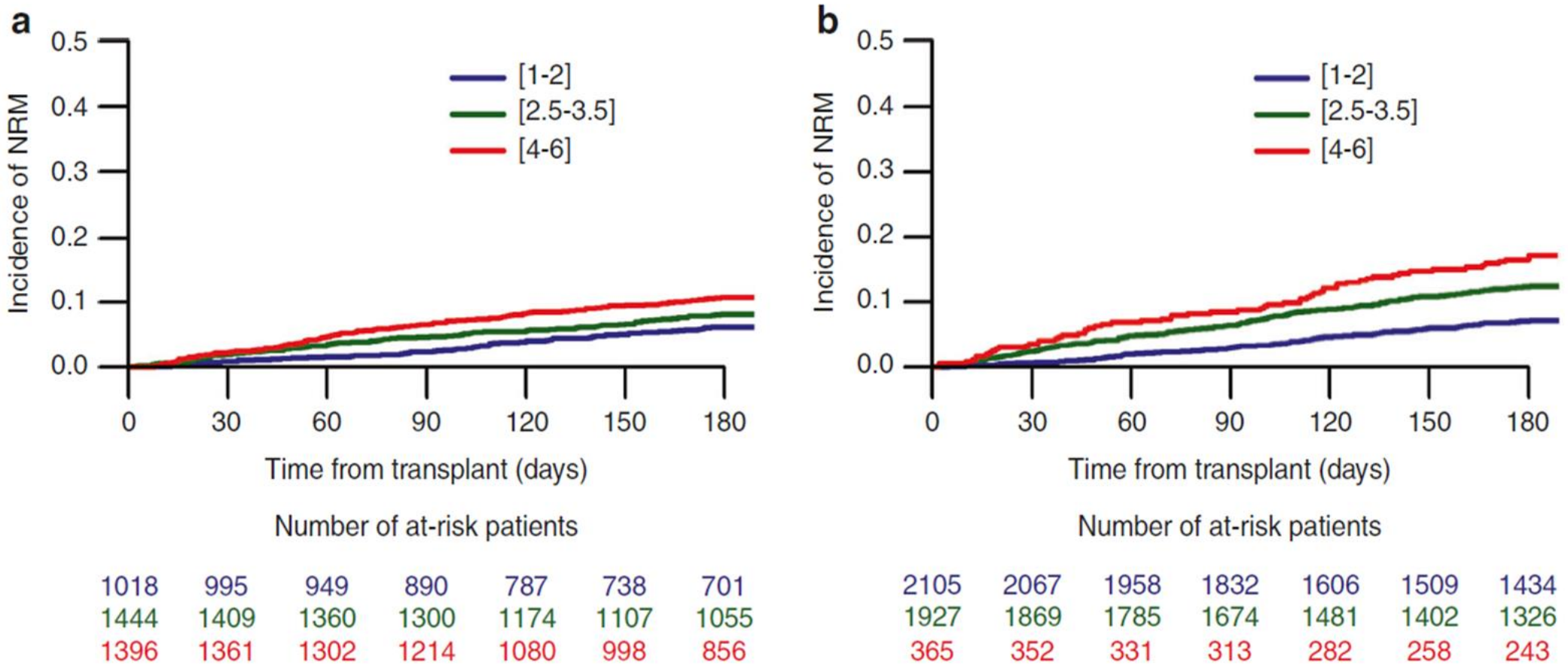
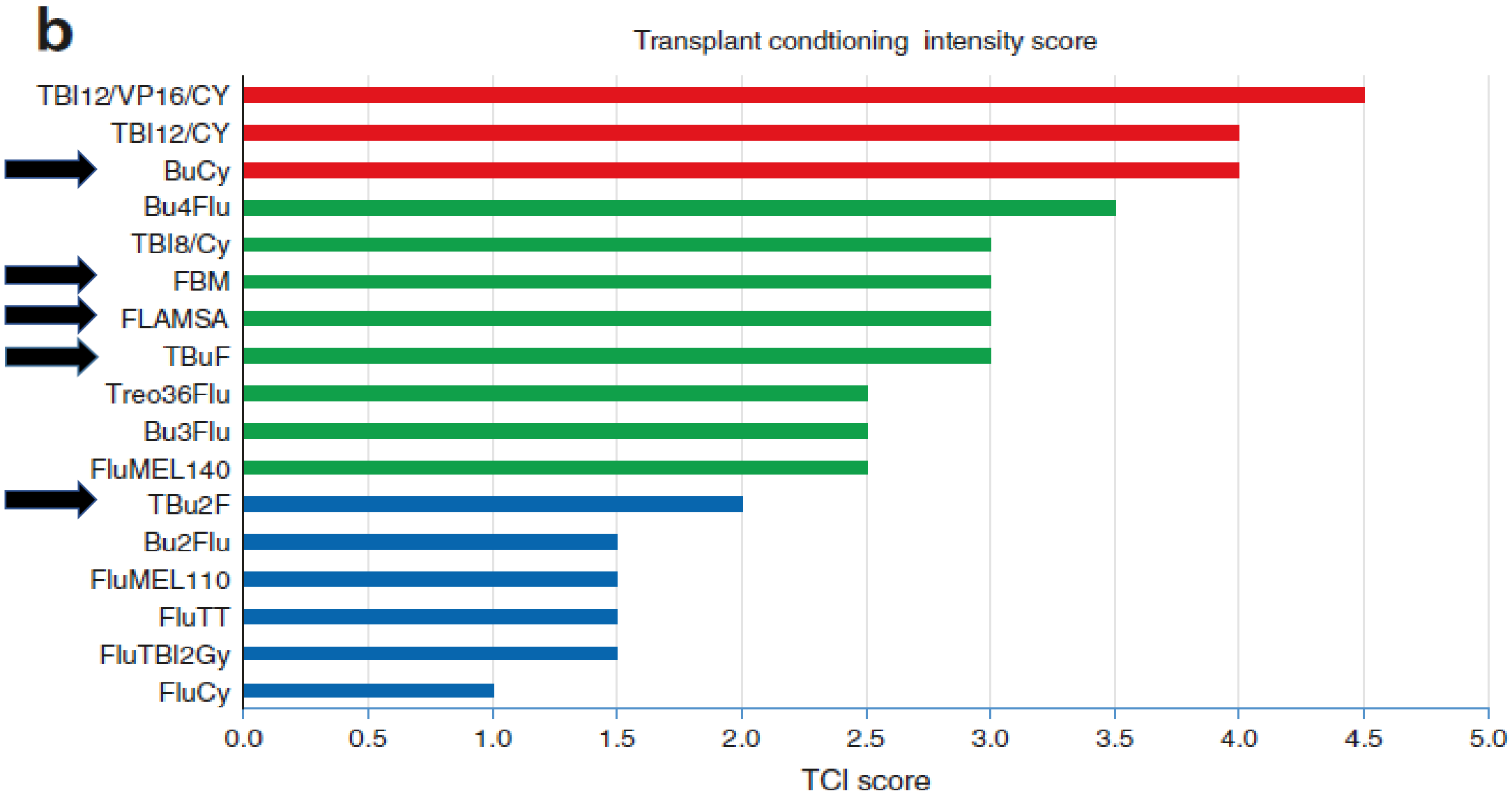


Fig. 2 Early nonrelapse mortality (NRM) according to TCI. a Early NRM in the subgroup of patients aged 45–55 years at transplant ($n = 3858$). **b** Early NRM in patients aged between 55 and 65 years ($n = 4397$).

Spyridonidis et al, 2020


b
Transplant condtioning intensity score
TBI12/VP16/CY
TBI12/CY
BuCy
Bu4Flu
TBI8/Cy
FBM
FLAMSA
TBuF
Treo36Flu
Bu3Flu
FluMEL140
TBu2F
Bu2Flu
FluMEL110
FluTT
FluTBI2Gy
FluCy
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
TCI score

CONDIZIONAMENTO AD INTENSITA' BASSA (TCI <2.5)

SINGOLO ALCHILANTE

TBI 2-Flu

Total Body irradiation 2 Gray

Fludarabina 40 mg/m2/die x 4d

Flu-Mel

Fludarabina 40 mg/m2/die x 4d

Melfalan 110 mg/mq x 1d

Treo-Flu

Treosulfano 10g/mq x3d

Fludarabina 30mg/mq/die x 5d

DOPPIO ALCHILANTE

TT-Bu2-Flu

Thiotepa 5 mg/Kg/die x 2d

Busulfano 3.2 mg/kg/die x 2d

Fludarabina 40 mg/m2/die x 4d

CONDIZIONAMENTO AD INTENSITA' INTERMEDIA (TCI 2.5 – 3.5)

TBI 12-Flu

Total Body irradiation 12 Gray

Fludarabina 40 mg/mq/die x 4d

SINGOLO ALCHILANTE

Bu4-Flu

Busulfano 3.2 mg/kg/die x 4d

Fludarabina 40 mg/m2/die x 4d

DOPPIO ALCHILANTE

TT-Bu-Flu

Thiotepa 5 mg/Kg/die x 2d

Busulfano 3.2 mg/kg/die x 4d

Fludarabina 40 mg/m2/die x 4d

Flu-Car-Mel

Fludarabina 40 mg/m2/die x 3d

Carmustina (BCNU) 300 mg/mq x 1d

Melfalan 110 mg/mq x 1d

CONDIZIONAMENTO AD INTENSITA' ALTA (TCI ≥ 4.0)

SINGOLO ALCHILAANTE

TBI 12-Cy

Total Body irradiation 12 Gray

Ciclofosfamide 60 mg/kg/die x 2 day

TBI 12-Cy-VP16

Total Body irradiation 12 Gray

Ciclofosfamide 60 mg/kg/die x 2 d

Etoposide 30-60 mg x 1d

DOPPIO ALCHILANTE

Bu4-Cy

Busulfano 3.2 mg/kg/die x 4d

Ciclofosfamide 60 mg/kg/die x 2d

Bu4-Flu-Mel

Busulfano 3.2 mg/kg/die x 4d

Fludarabina 40 mg/mq/die per 4d

Melfalan 140 mg/mq x 1d

Meccanismo di Azione Alchilanti:

Formazione di un legame covalente con il DNA tramite donazione di gruppi alchilici alle basi puriniche e conseguente crosslinking inter/intra catene>>> danno irreversibile

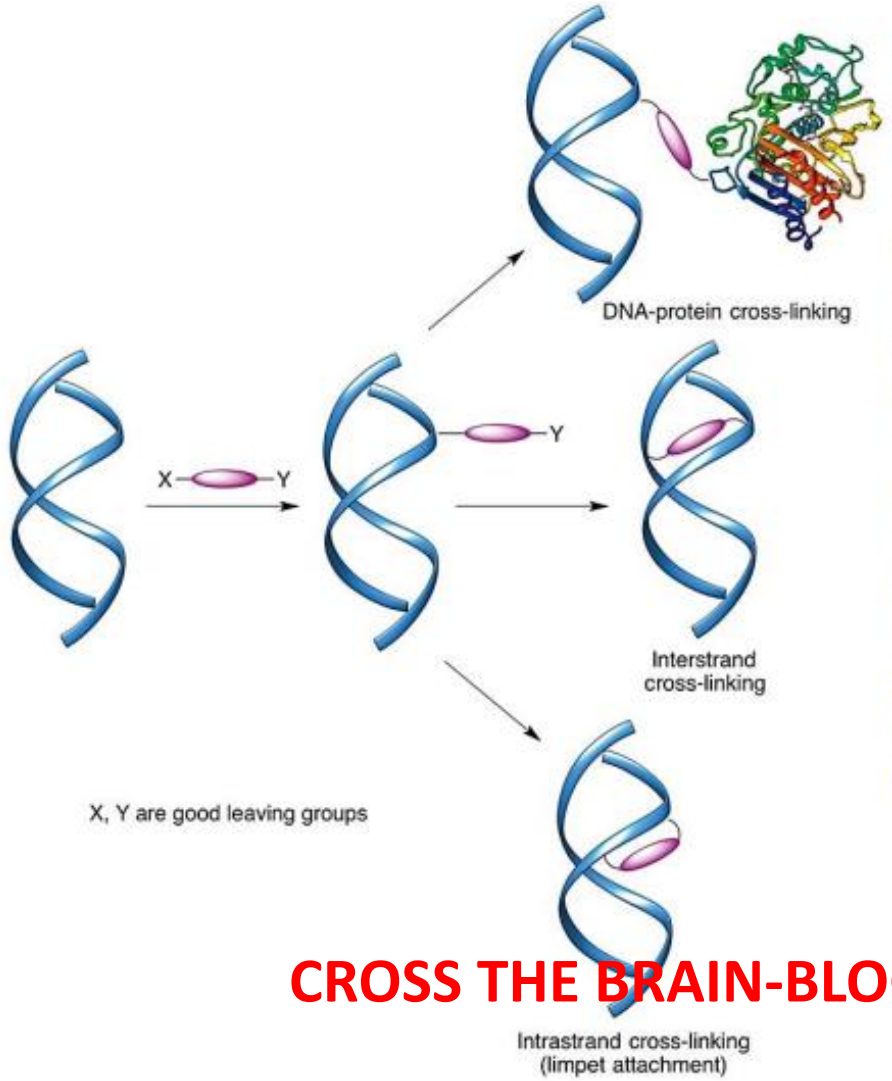
Classificazione FARMACI ANTITUMORALI

(codice ATC*: L01-farmaci antineoplastici)

L01A: Agenti alchilanti	L01AA (Analoghi della mostarda azotata): Melfalan, Ciclofosfamide, Ifosfamide, Clorambucile, L01AB (Alchilsulfonati): Busulfano. L01AC (Etilenimine): Tiotepa. L01AD (Nitrosouree): Fotemustina. L01AX (altre sostanze alchilanti): Dacarbazina, Temozolomide, Pipobromano.
L01B: Antimetaboliti	L01BA (analoghi dell'acido folico): Pemetrexed, Metotrexato, Raltitrexed. L01BB (analoghi della purina): Fludarabina, Cladribina, Mercaptopurina, Tioguanina. L01BC (analoghi della pirimidina): Citarabina, Fluorouracile, Gemcitabina, Tegafur uracile, Capecitabina.
L01D: Antibiotici citotossici e sostanze correlate	L01DA (actinomicine): Dactinomicina L01DB (antracicline e sostanze correlate):
Strutture varie	Derivati dell'idrazina Uree e uretani Altri

* ATC: Classificazione Anatomica Terapeutica Chimica delle specialità medicinali

Agenti alchilanti: composti capaci di legare covelentemente un gruppo alchilco ad una biomolecola in codizioni fisiologiche (soluzione acquosa pH 7.4, 37°C);
Agenti alchilanti il DNA, interagiscono con le cellule in ogni fase del ciclo, (> G1, S)

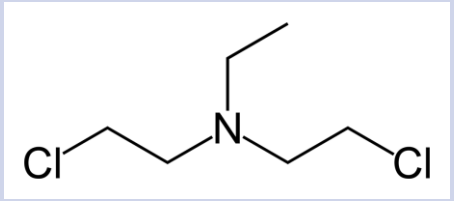
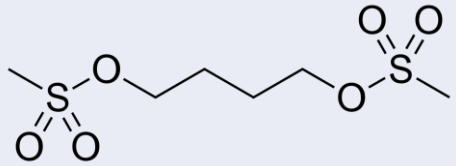


L'alchilazione

- ⊠ replicazione DNA e trascrizione dell'RNA dal DNA modificato.
- induce frammentazione del DNA per reazioni idrolitiche;
- ⊠ l'azione degli enzimi preposti alla riparazione del DNA quando questi tentano di rimuovere le basi alchilate;
- induce forme di accoppiamento anomale tra nucleotidi (HB tra basi);
- da alchilanti bidentati (più citotossici) formano ponti intrastrand;
- genera crosslinking tra DNA e proteine associate o tra strands complementari (interstrands) impedendo la separazione durante la replicazione o traduzione;

CROSS THE BRAIN-BLOOD BARRIER AND ARE RADIOMIMETIC AGENTS

AGENTI ALCHILANTI

CLASSE FARMACOLOGICA	FARMACO	TOSSICITA'
MOSTARDE AZOTATE: 	**Melfalan**	Nausea e vomito persistenti, mucosite.
	Ciclofosfamide, Ifosfamide	Cistite emorragica, epatotossicità, nefrotossicità, mucosite, cardiotossicità.
	Bendamustina, etc.	Epatotossicità, mucosite, nausea e vomito.
NITROSOUREE:	**Carmustina (BCNU) etc.**	Neurotossicità (atassia, stati allucinatori), polmonite interstiziale.
ETILENIMMINE:	**Tiotepa etc.**	Epatotossicità, tossicità cutanea, neurotossicità (encefalopatia).
ALCHILSOLFONATI: 	**Busulfano**	Epatotossicità/VOD, neurotossicità (convulsioni), mucosite, iperpigmentazione cutanea.
	Treosulfano	**XXXXXXXX**
TRIAZENI:	**Dacarbazina, Procarbazina etc.**	Nausea, vomito, tossicità cutanea, epatossicità, dolori nella sede di iniezione.
COMPLESSI DI COORDINAZIONE DEL PLATINO:	**CisPlatino, CarboPlatino, OxaliPlatino etc.**	Nausea e vomito, ototossicità, tossicità renale (minore per Oxa), neuropatia.

TREOSULFAN

- Pro-drug of a bifunctional alkylating agent with cytotoxic activity towards hematopoietic precursor cells.

- Activity due to spontaneous conversion to a intermediate mono epoxide and L-dioxybutane

- The de g in DNA, v c + antileu

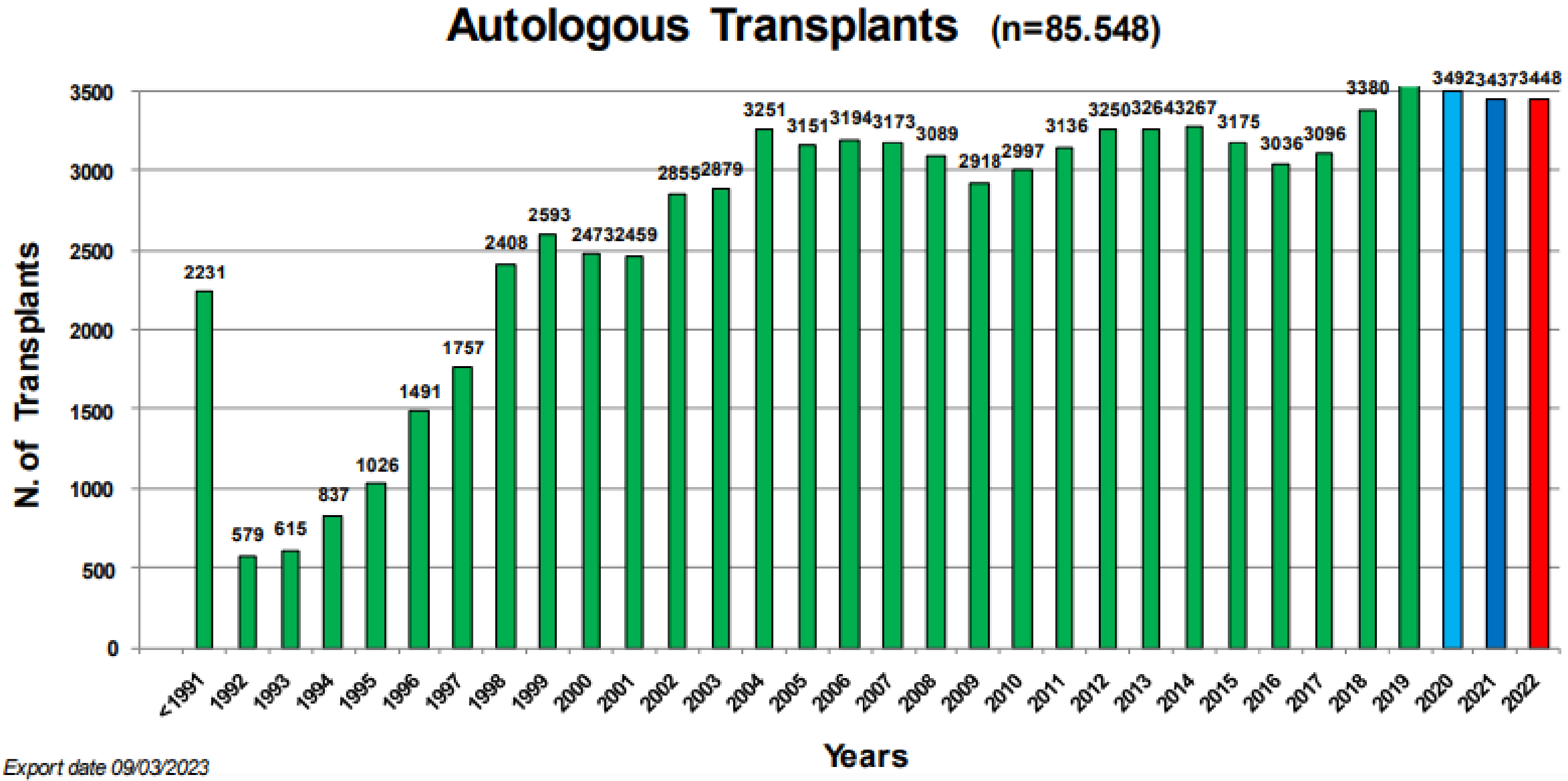
PHASE III TRIAL: FT10 vs TB2 in AML or MDS with HCT-I >2 or age > 50

INDICATION AS LOW INTENSITY CONDITIONING REGIMEN IN AML AND MDS AND HIGH INTENSITY IN NON NEOPLASTIC DISEASES

- Immunosuppressive effects due to its toxicity on:
  - primitive and differentiated progenitor cells
  - T and NK cells
  - reduction in cellularity of primary and secondary lymphatic organs
  - preclusive effect on the "cytokine storm" involved in GvHD) and VOD

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

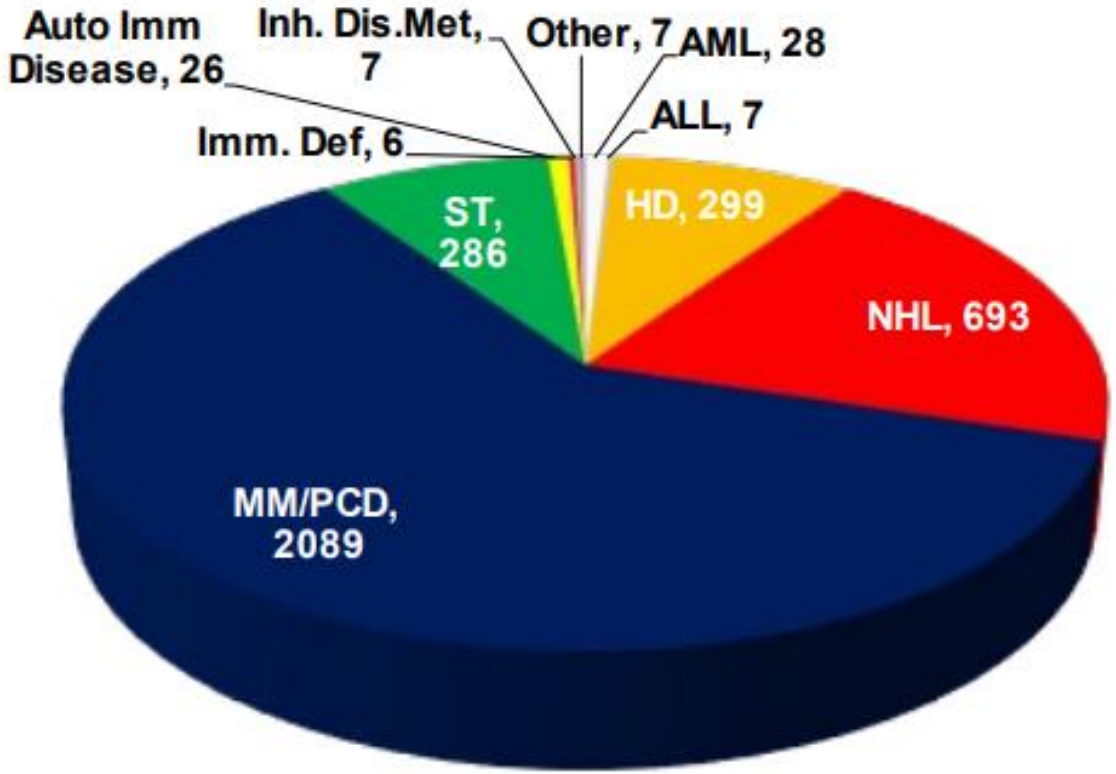
GITMO ACTIVITY 2022



Export date 09/03/2023

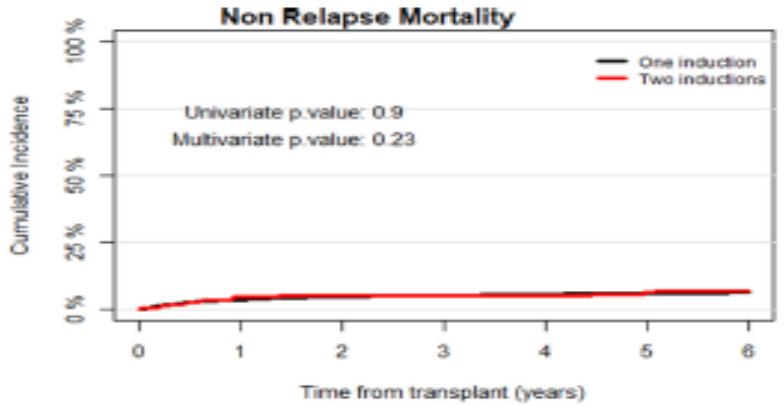
GITMO ACTIVITY 2022

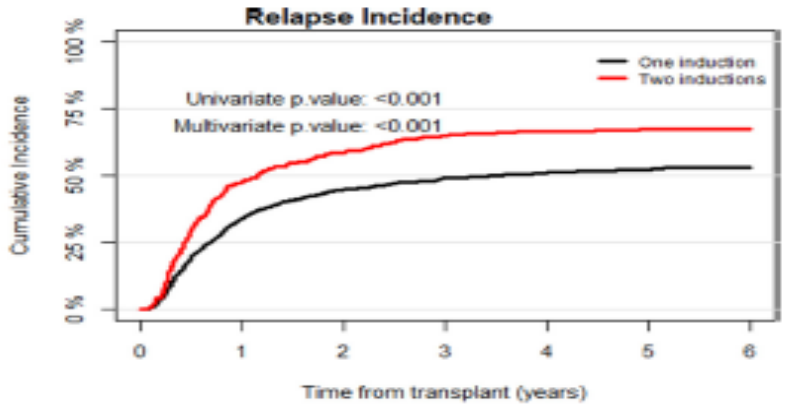
Autologous Transplants - Indications 2022

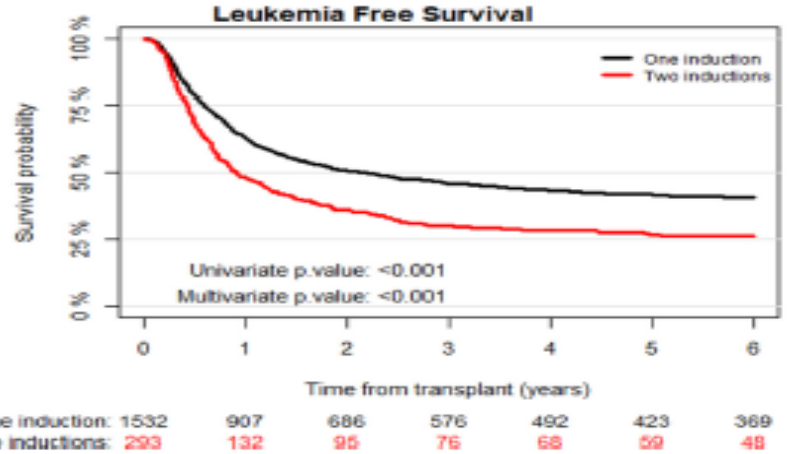


Export date 09/03/2023

CONDITIONING REGIMEN FOR ASCT IN ACUTE LEUKEMIA







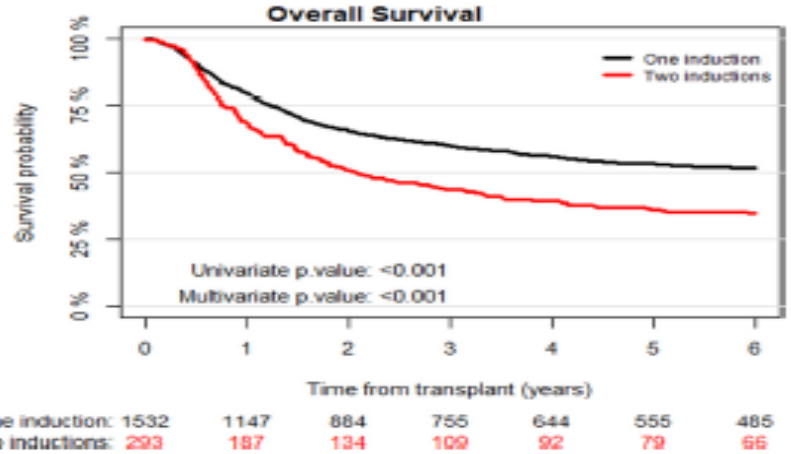


FIGURE 1 Autologous transplantation outcome – Non-relapse mortality (NRM), relapse incidence (RI), leukemia-free survival (LFS) and overall survival (OS) in patients with AML with one and two induction courses.

CONDITIONING REGIMEN FOR ASCT IN ACUTE LEUKEMIA

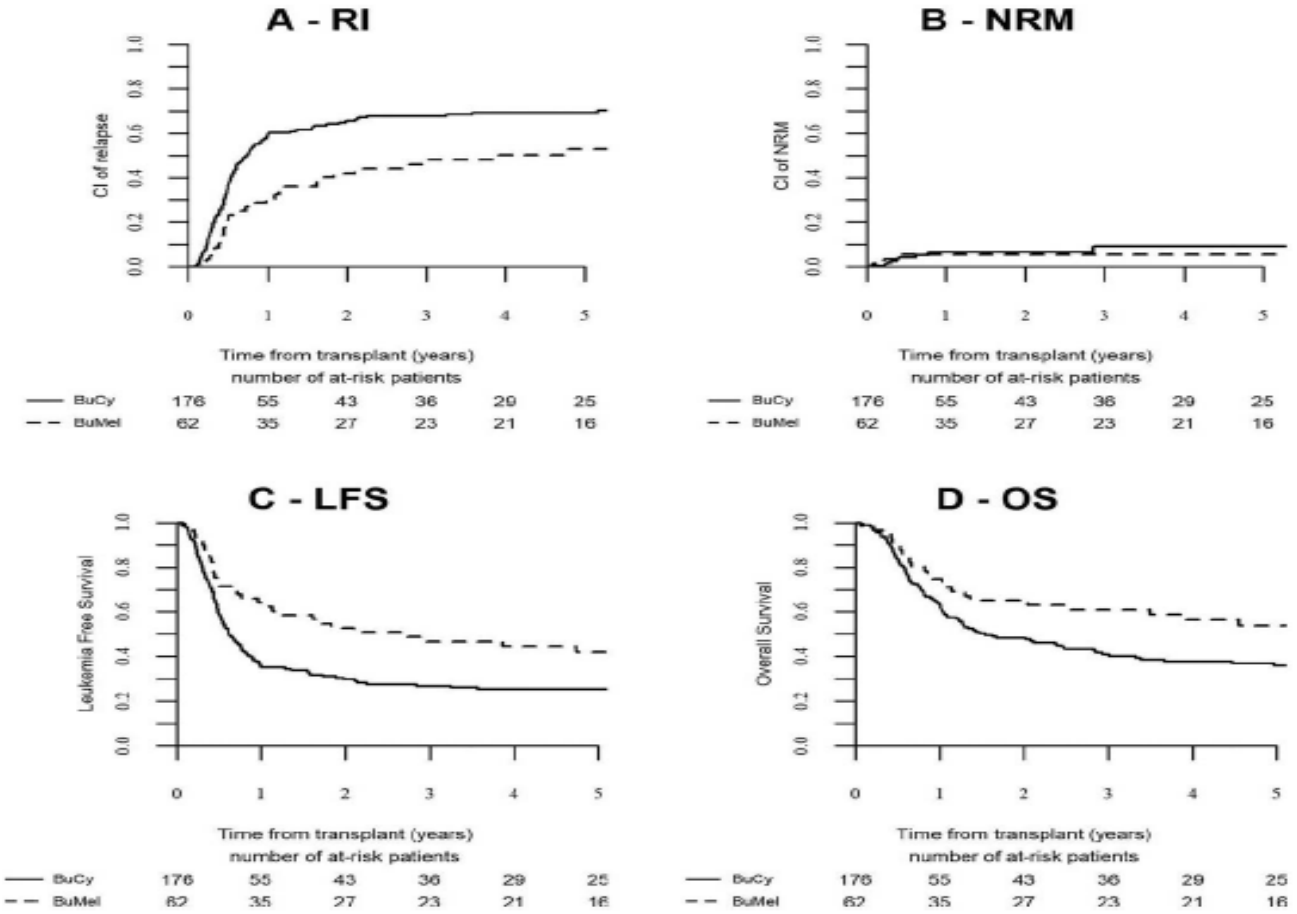


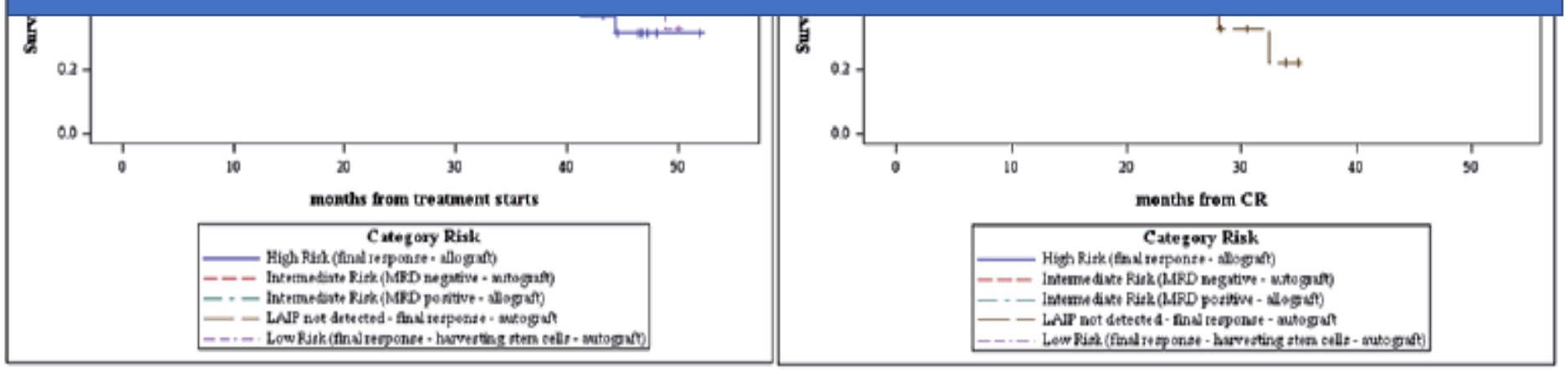
FIGURE 1 Outcome of AML patients autografted in first remission with BUCY or BUMEL as pretransplant regimen. Poor risk group defined by cytogenetics and/or the presence of a FLT3-ITD mutation. (A) Relapse incidence, (B) Non relapse mortality, (C) Leukemia free survival, (D) Overall survival

B003

RISK-ADAPTED, MRD-DIRECTED THERAPY FOR YOUNG ADULTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA: RESULTS OF THE AML1310 TRIAL OF THE GIMEMA GROUP

Intermediated risk-AML: similar OS and DFS between MRD pos and neg pts who received auto or allo, respectively

CONDITIONING REGIMEN: BU-CY



Venditti et al SIE 2017

Thiotepa-based high-dose therapy for autologous stem cell transplantation in lymphoma: a retrospective study from the EBMT

L Sellner[1], A Boumendil[2], H Finel[2], S Choquet[3], G de Rosa[4], F Falzetti[5], R Scime[6], G Kobbe[7], F Ferrara[8], A Delmer[9], H Sayer[10], S Amorim[11], R Bouabdallah[12], J Finke[13], G Salles[14], I Yakoub-Agha[15], E Faber[16], E Nicolas-Virelizier[17], L Facchini[18], D Vallisa[19], E Zuffa[20], A Sureda[2,21] and P Dreger[1,2] on behalf of the EBMT Lymphoma Working Party

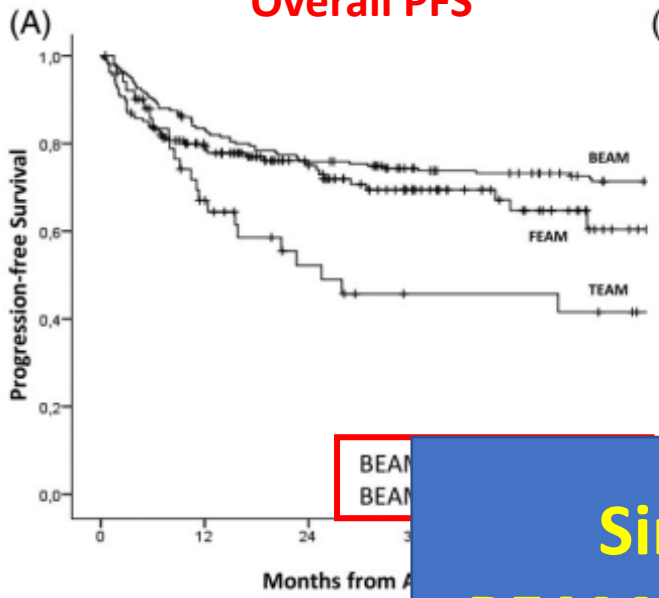
Clinical information about thiotepa-based autologous stem cell transplantation (auto-SCT) outside the primary central nervous system lymphoma (PCNSL) field is sparse. In this registry-based retrospective study, we evaluated potential risks and benefits of thiotepa-based preparative regimens compared with BEAM (carmustine, etoposide, cytarabine, melphalan) in auto-SCT for diffuse large B-cell lymphoma (DLBCL, excluding PCNSL), follicular lymphoma (FL) or Hodgkin lymphoma (HL). A total of 14 544 patients (589 thiotepa and 13 955 BEAM) met the eligibility criteria, and 535 thiotepa- and 1031 BEAM-treated patients were matched in a 1:2 ratio for final comparison. No significant differences between thiotepa and BEAM groups for any survival end point were identified in the whole sample or disease entity subsets. For a more detailed analysis, 47 TEAM (thiotepa, etoposide, cytarabine, melphalan)-treated patients were compared with 75 matched BEAM patients with additional collection of toxicity data. Again, there were no significant differences between the two groups for any survival end point. In addition, the frequency of common infectious and non-infectious complications including secondary malignancies was comparable between TEAM and BEAM. These results indicate that thiotepa-based high-dose therapy might be a valuable alternative to BEAM in DLBCL, HL and FL. Further evaluation by prospective clinical trials is warranted.

Bone Marrow Transplantation (2016) **51,** 212–218; doi:10.1038/bmt.2015.273; published online 16 November 2015

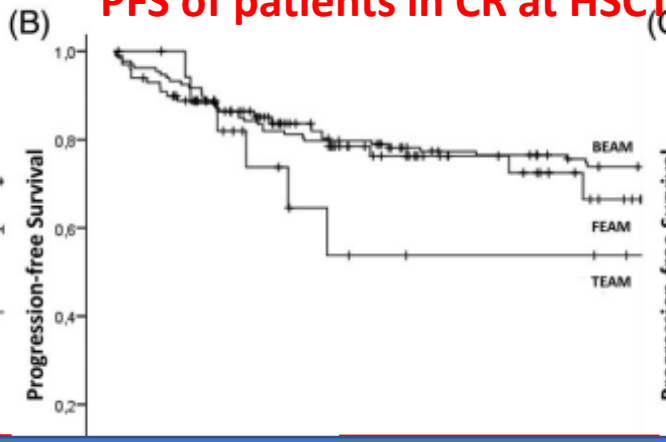
BEAM conditioning regimen ensures better progression-free survival compared with TEAM but not with FEAM in lymphoma patients undergoing autologous stem cell transplant

Characteristics	BEAM ($n = 200$)	FEAM ($n = 162$)	TEAM ($n = 52$)	p
Median age (range)	47 (15–69)	49 (15–69)	42 (23–66)	NS
Sex M/F	118/82	100/62	28/24	NS
Diagnosis (%)				NS
HL	55 (27.5)	45 (27.8)	24 (46.2)	
B-NHL	123 (61.5)	93 (57.4)	24 (46.2)	
T-NHL	22 (11)	24 (14.8)	4 (7.7)	
Median number of previous treatments (range)	2 (1–5)	2 (1–6)	2 (1–5)	NS
Timing of transplant (%)				NS
After first-line	30 (15)	42 (25.9)	3 (5.8)	
After first salvage treatment	130 (65)	83 (51.2)	31 (60)	
≥3 prior lines	40 (20)	37 (22.9)	18 (34.2)	
Disease status al transplant (%)				.001
CR	133 (66.5)	100 (61.7)	19 (36.5)	
1° CR	*24*	*31*	*13*	
≥2° CR	*119*	*69*	*6*	
PR	58 (29)	59 (36.4)	29 (55.8)	
SD/PD	9 (4.5)	3 (1.9)	4 (7.7)	
PS by Karnofsky scale (%)				NS
≥80%	182 (91)	148 (91.4)	52 (100)	
<80%	18 (9)	14 (8.6)	0 (0)	
Median CD34+ infused cells x 10◦6/kg (range)	4.8 (2.2–28.5)	4.7 (2.2–17.9)	6.18 (3.5–13)	NS

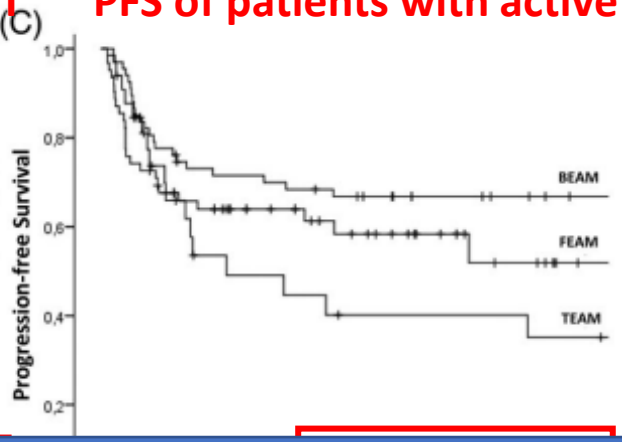
Overall PFS



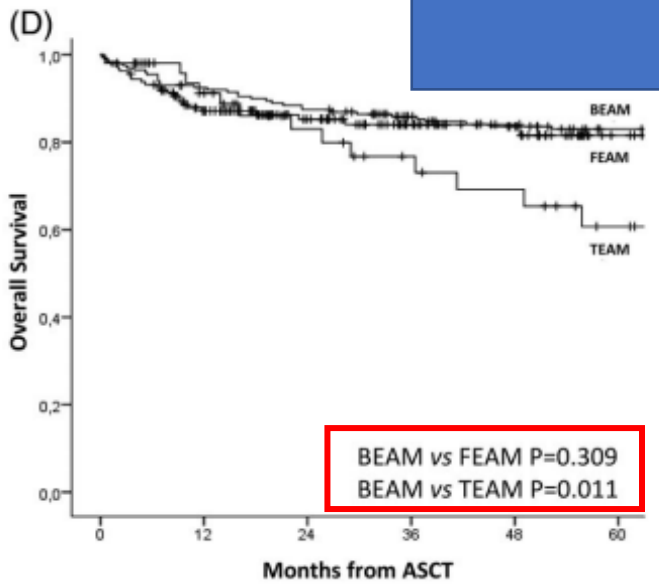
PFS of patients in CR at HSCT

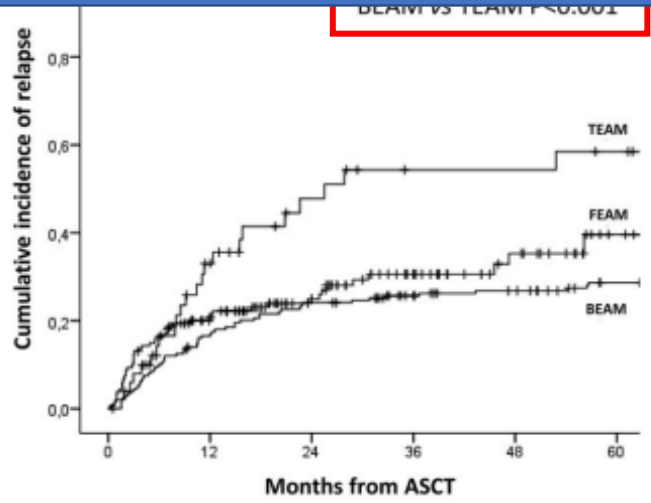


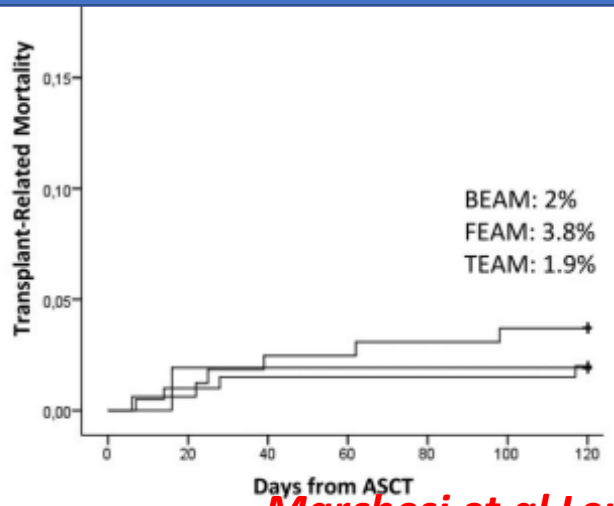
PFS of patients with active disease at HSCT



Similar resuts between BEAM and FEAM
BEAM significant better of TEAM except for NRM







Marchesi et al Leukemia and Lymphoma, 2020

CONDIZIONAMENTO AD INTENSITA' ALTA (TCI ≥ 4.0)

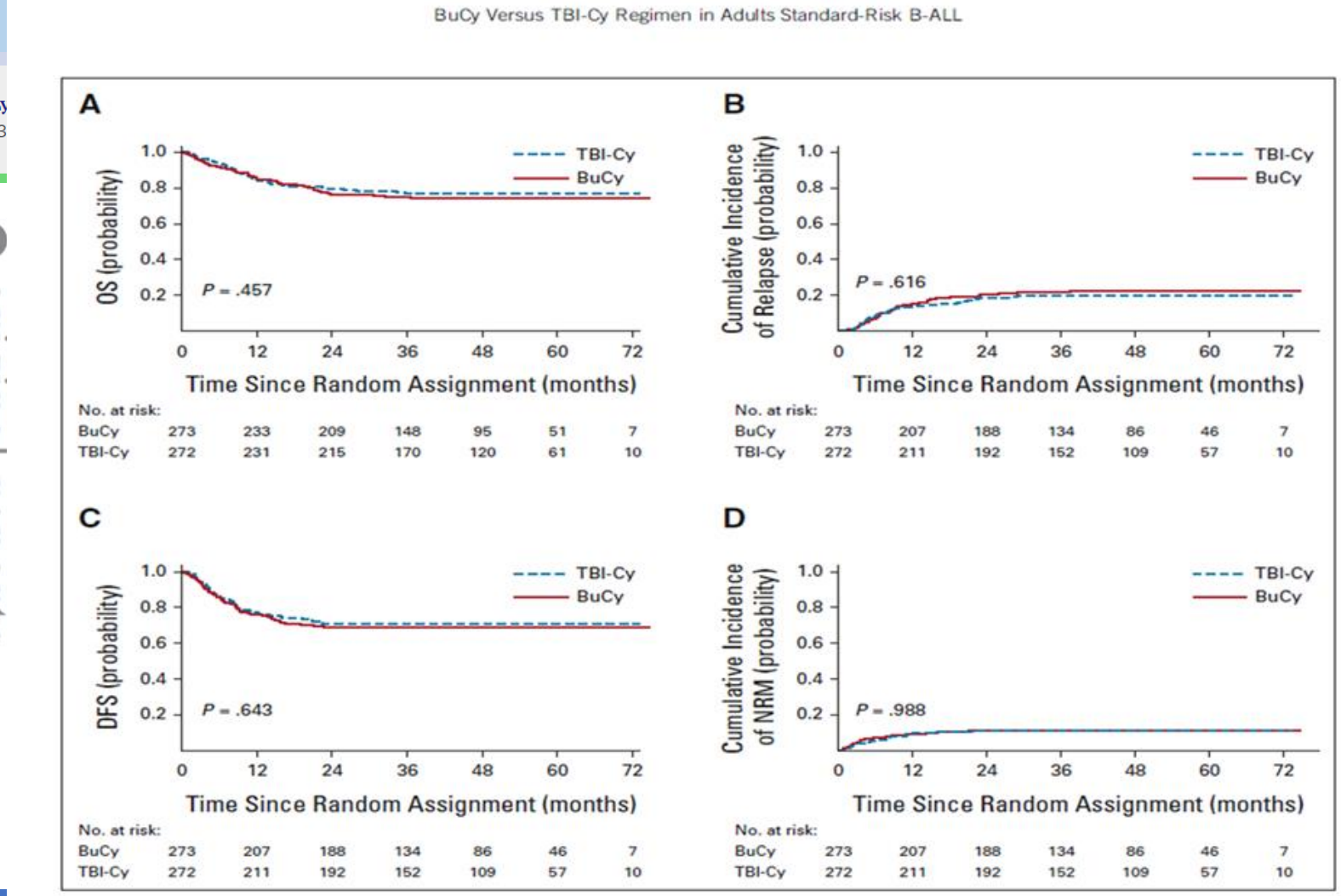


FIG 2. Outcomes of allogeneic-hematopoietic stem-cell transplantation with BuCy or TBI-Cy conditioning regimens: (A) survival by conditioning regimens, (B) cumulative incidence of disease relapse by conditioning regimens, (C) DFS by conditioning regimens, and (D) cumulative incidence of NRM by conditioning regimens. BuCy, busulfan plus cyclophosphamide; DFS, disease-free survival; NRM, nonrelapse mortality; OS, overall survival; TBI-Cy, total body irradiation plus cyclophosphamide.

Zhang, 2022

CONDIZIONAMENTO AD INTENSITA' ALTA (TCI ≥ 4.0)

SINGOLO ALCHILANTE

TBI 12-Cy

Total Body irradiation 12 Gray

Ciclofosfamide 60 mg/kg/die x 2 day

TBI 12-Cy-VP16

Total Body irradiation 12 Gray

Ciclofosfamide 60 mg/kg/die x 2 d

Etoposide 30-60 mg x 1d

DOPPIO ALCHILANTE

Bu4-Cy

Busulfano 3.2 mg/kg/die x 4d

Ciclofosfamide 60 mg/kg/die x 2d

Bu4-Flu-Mel

Busulfano 3.2 mg/kg/die x 4d

Fludarabina 40 mg/mq/die per 4d

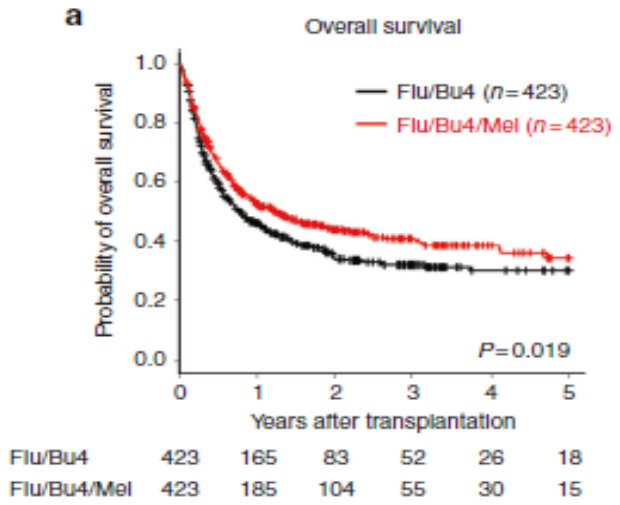
Melfalan 140 mg/mq x 1d

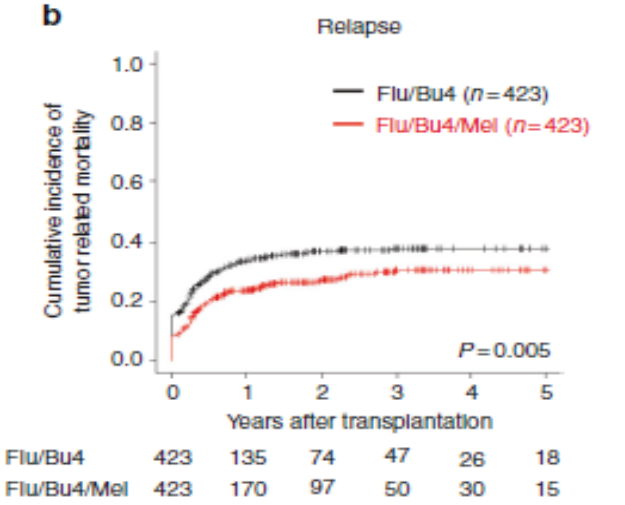
CONDIZIONAMENTO AD INTENSITA' ALTA (TCI ≥ 4.0)

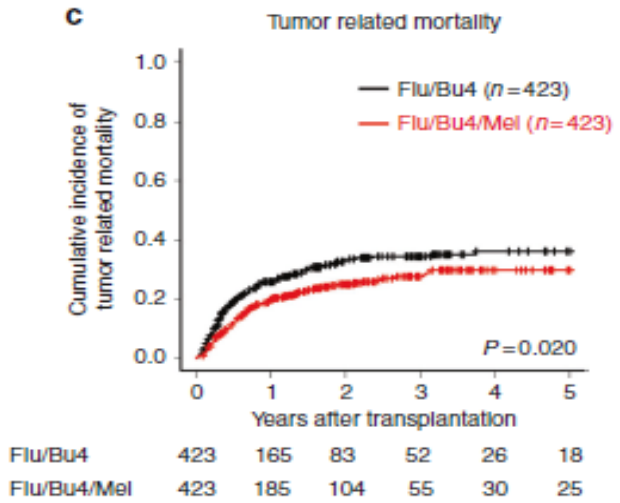
SIN ANTE

Tota e x 4d
Ciclofo die x 2d

Tota e x 4d
Ciclof e x 4d
E x 1d







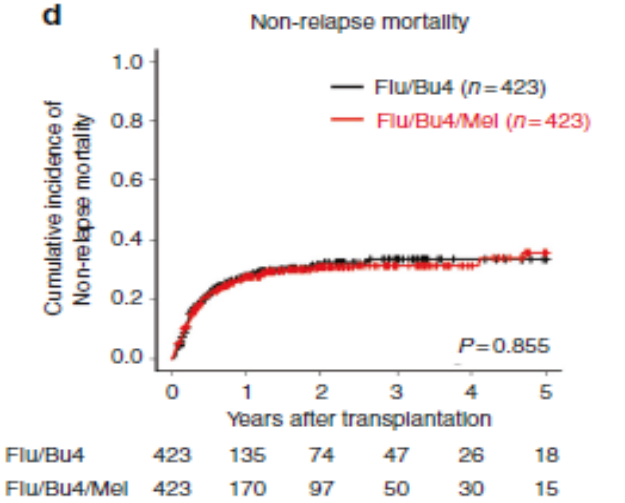


Fig. 3 Transplant outcomes in a propensity score-matched cohort. **a** Overall survival, **b** cumulative incidence of relapse, **c** cumulative incidence of relapse associated mortality, and **d** cumulative incidence of non-relapse mortality. Numbers at bottom of the figure represent the number at risk for each group. Flu/Bu4/Mel addition of melphalan to fludarabine and a myeloablative dose of busulfan, Flu/Bu4 fludarabine plus a myeloablative dose of busulfan.

CONDIZIONAMENTO AD INTENSITA' INTERMEDIA (TCI 2.5 – 3.5)

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASTCT
American Society for Transplantation and Cellular Therapy

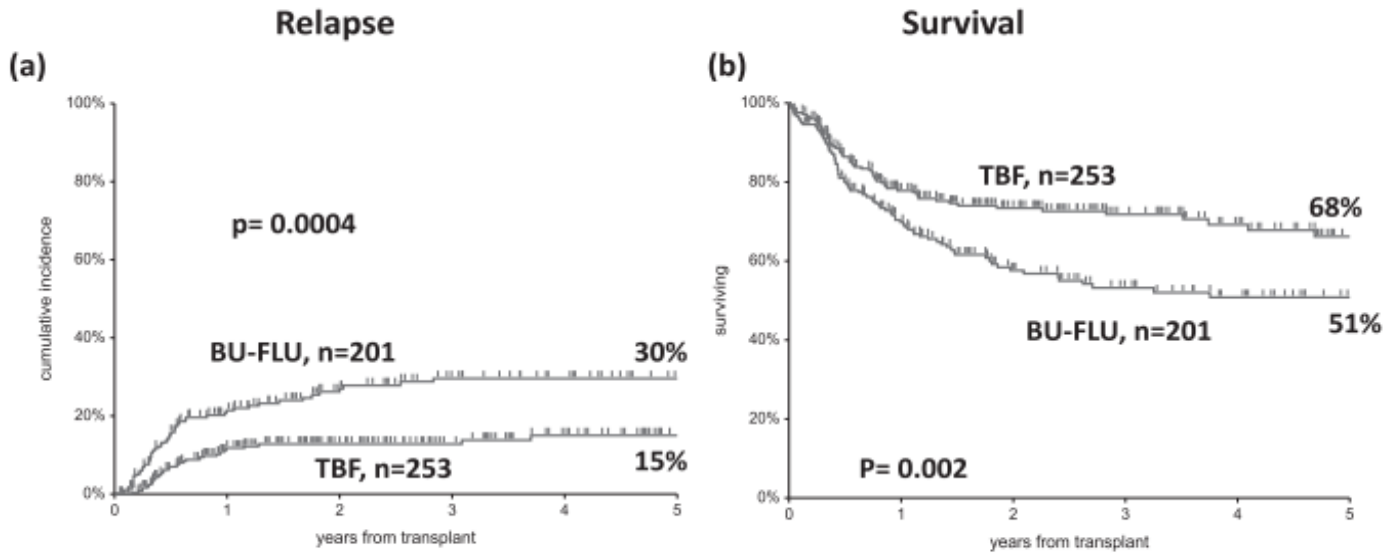


Figure 1. Cumulative incidence of relapse (a) and survival (b) for patients, with AML receiving TBF or BUFLU.

CONDIZIONAMENTO AD INTENSITA' BASSA (TCI <2.5)

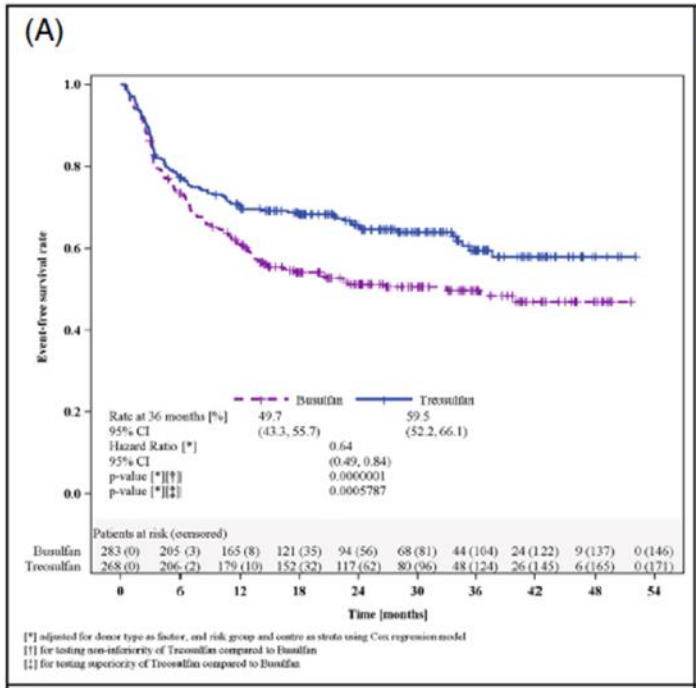
SINGO ANTE

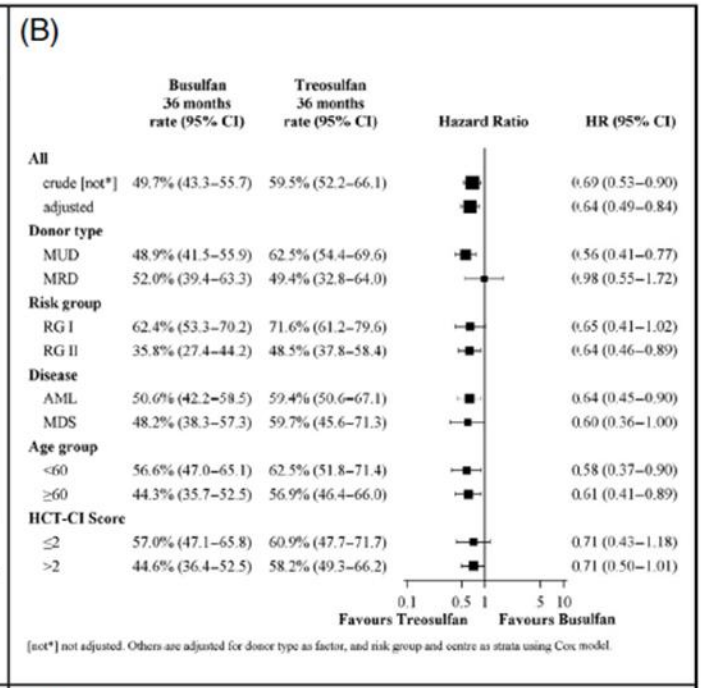
Total
Fludar

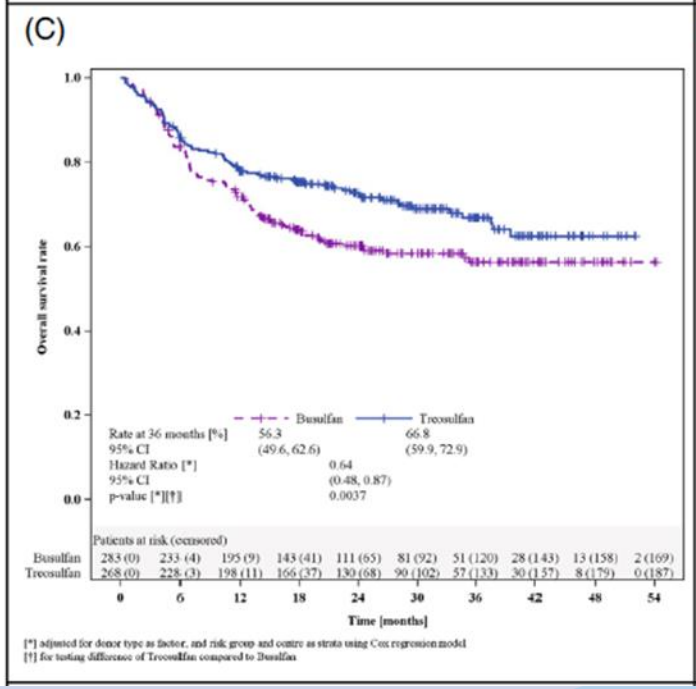
Fludar
Mel

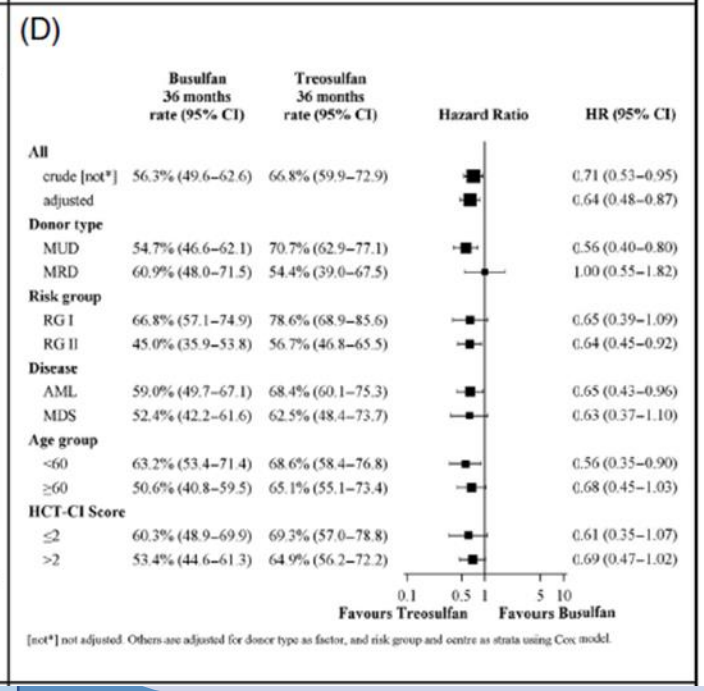
Tre
Fludar

e x 2d
die x 2d
die x 4d









CONCLUSIONS

- Currently, **High and Intermediate** Intensity Conditioning Regimens are often based on the Combination of Double Alchylating Agent
- Haplo-identical Transplant based on **PT-CY** >>>warning for the use of high dose of CY in the conditioning regimen
- Most papers **show positive effect of Double Alchylating Agent on the relapse rate** associated to increased NRM, in some analysis
- Many Retrospective Registry Analysis compared to few prospective randomized clinical trials >>> **need of prospective trials**
- The arrival of **new drugs** could impove results in terms of relapse and NRM

TERAPIA DI CONDIZIONAMENTO NEL TRAPIANTO ALLOGENICO

Combinazione di agenti citotossici/radiazioni ionizzanti che determinano mielotossicità acuta con conseguente pancitopenia nelle 2-3 settimane successive all'infusione.
La reinfusione delle CSE del donatore è indispensabile per il recupero di una normale ematopoiesi e per lo sviluppo della sorveglianza immunitaria contro la neoplasia ematologica che si vuole eradicare.

OBIETTIVI:

- Eliminazione del compartimento di cellule staminali totipotenti malate del paziente.
- Creazione dello spazio necessario alle cellule progenitrici del donatore sano per il ripopolamento midollare.
- Immunosoppressione per superare la barriera immunologica dell'ospite ed evitare il rigetto.

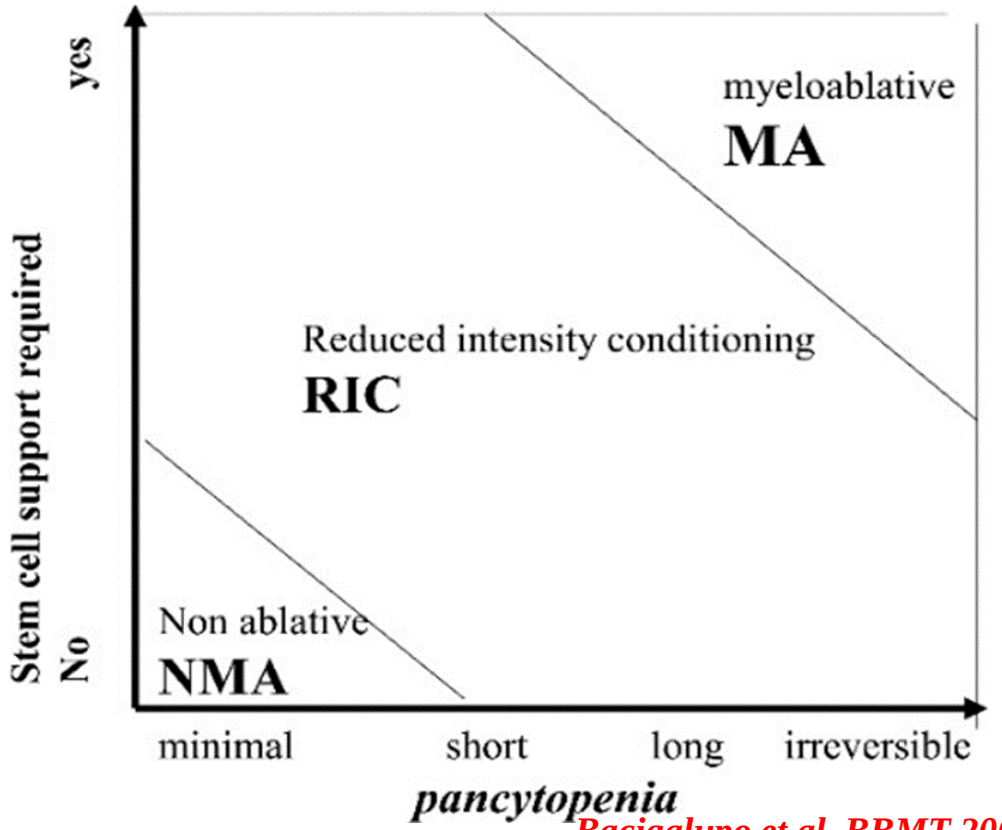
REGIMI DI CONDIZIONAMENTO: DEFINIZIONI

- Survey GITMO: oltre 40 schemi diversi e pochi studi randomizzati.
- Variano secondo il tipo di patologia, lo stato di malattia ed i risultati del workup e il performance status del paziente pre-trapianto.

➢[1]Mieloablativo (Myeloablative Conditioning, MAC), cioè capaci di distruggere completamente il midollo del ricevente.

➢NON Mieloablativo (NMA) che induce una moderata citopenia transitoria, dotato di minore tossicità globale e possibilità di ricostituzione midollare autologa.

➢A ridotta intensità (Reduced Intensity Conditioning, RIC) basati sull'impiego di agenti immunosoppressivi e mielotossici a dosi diverse dai precedenti. La differenza rispetto al NON mieloablativo consiste nella necessità di infusione di cellule staminali ematopoietiche.



Bacigalupo et al, BBMT 2009