Conditioning regimens for allogenic hematopoietic cell transplantation

SAYEH PARKHIDEH

ADULT HEMATOLOGIST ;MEDICAL ONCOLOGIST

TALEGHANI HOSPITAL

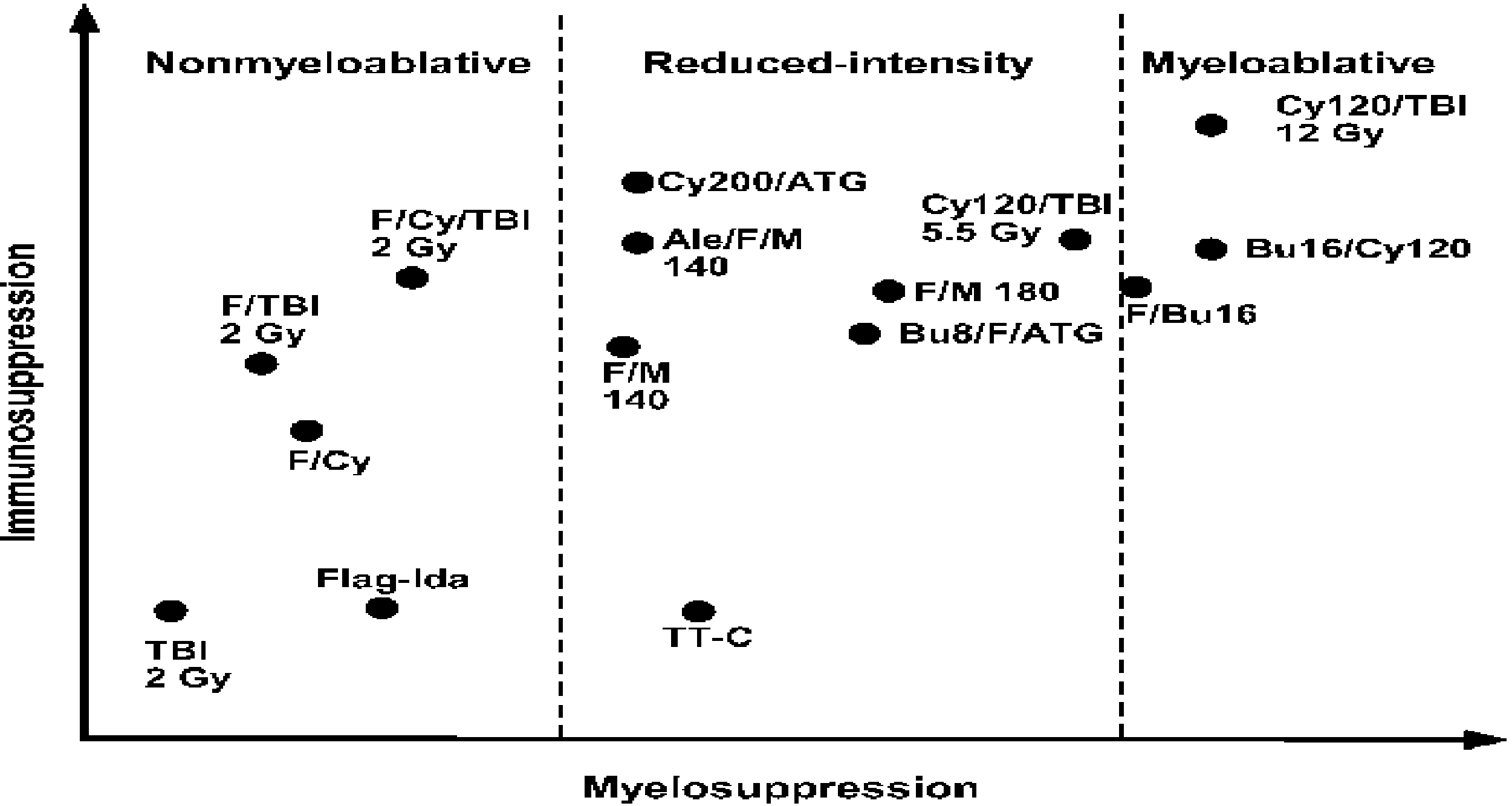
SHAHID BEHESHTI UNIVERSITY OF MEDICAL SCIENCES

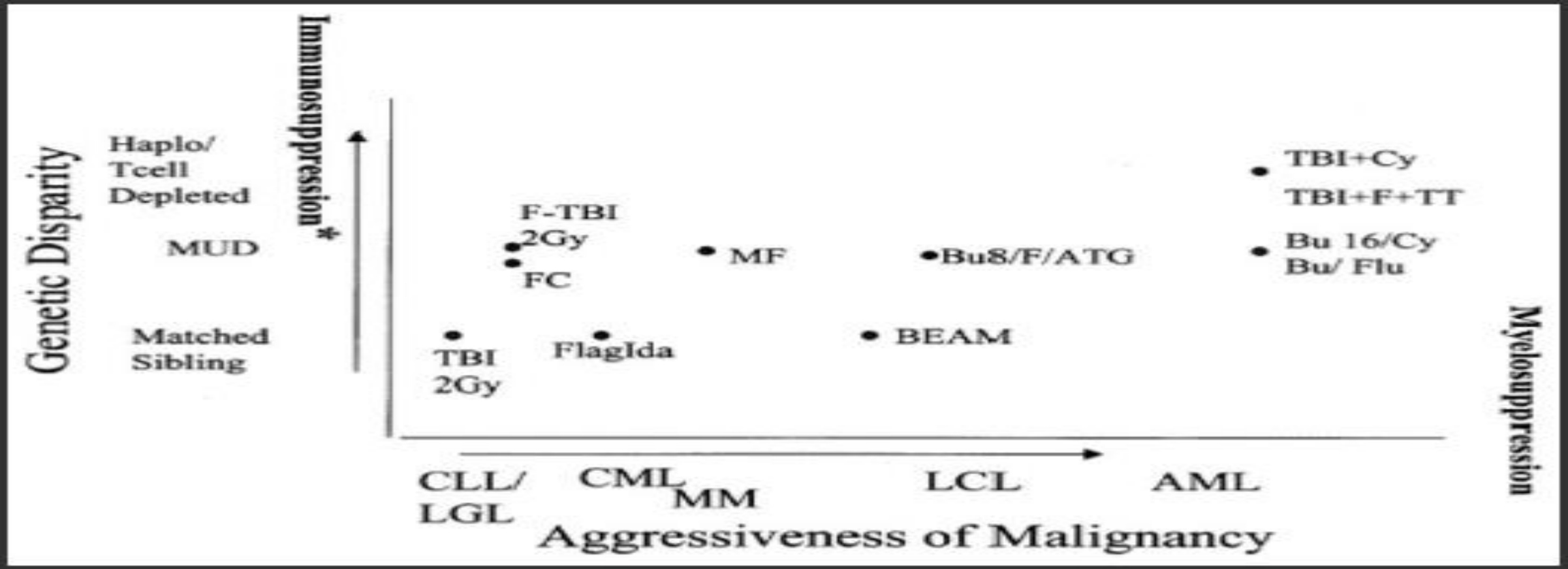
- Hematopoietic cell transplantation (HCT) is a potentially curative therapeutic approach for a variety of malignant and nonmalignant hematopoietic diseases.

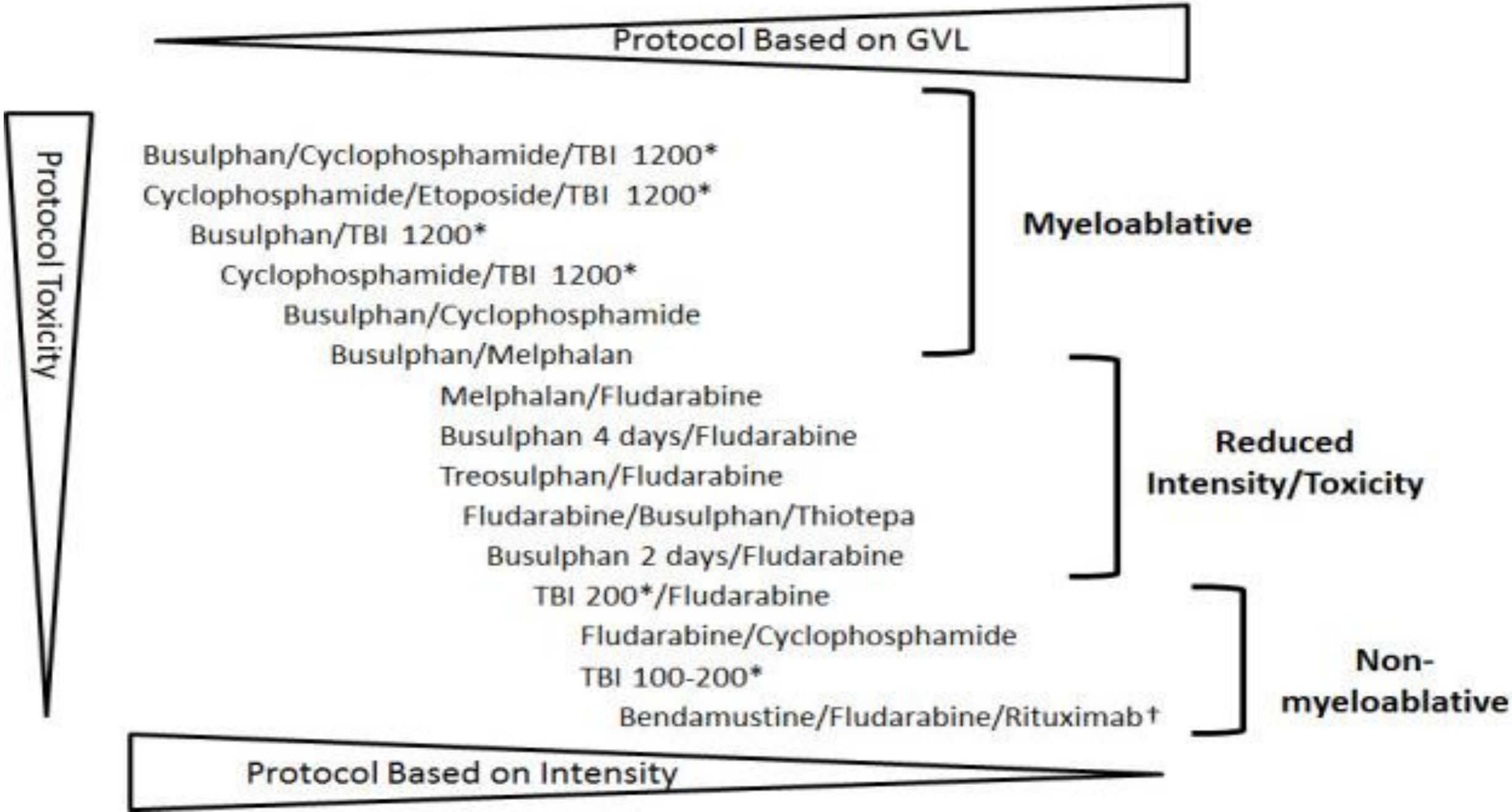
- When HCT is performed in patients with malignant disorders, preparative or conditioning regimens are administered as part of the procedure to achieve 2 goals

1-provide sufficient immune ablation to prevent graft rejection

2-reduce the tumor burden.


Nonmyeloablative
Reduced-intensity
Myeloablative
Immunosuppression
Myelosuppression
Cy120/TBI
12 Gy
Cy200/ATG
Cy120/TBI
5.5 Gy
Ale/F/M
140
Bu16/Cy120
F/Cy/TBI
2 Gy
F/M 180
F/Bu16
F/TBI
2 Gy
Bu8/F/ATG
F/M
140
F/Cy
Flag-Ida
TBI
2 Gy
TT-C


Genetic Disparity
Haplo/
Tcell
Depleted
MUD
Matched
Sibling
Immunosuppression*
F-TBI
2Gy
FC
MF
Bu8/F/ATG
TBI+Cy
TBI+F+TT
Bu 16/Cy
Bu/ Flu
TBI
2Gy
FlagIda
BEAM
Myelosuppression
CLL/
LGL
CML
MM
LCL
AML
Aggressiveness of Malignancy


Protocol Based on GVL
Protocol Toxicity
Busulphan/Cyclophosphamide/TBI 1200*
Cyclophosphamide/Etoposide/TBI 1200*
Busulphan/TBI 1200*
Cyclophosphamide/TBI 1200*
Busulphan/Cyclophosphamide
Busulphan/Melphalan
Melphalan/Fludarabine
Busulphan 4 days/Fludarabine
Treosulphan/Fludarabine
Fludarabine/Busulphan/Thiotepa
Busulphan 2 days/Fludarabine
TBI 200*/Fludarabine
Fludarabine/Cyclophosphamide
TBI 100-200*
Bendamustine/Fludarabine/Rituximab†
Myeloablative
Reduced Intensity/Toxicity
Non-myeloablative
Protocol Based on Intensity

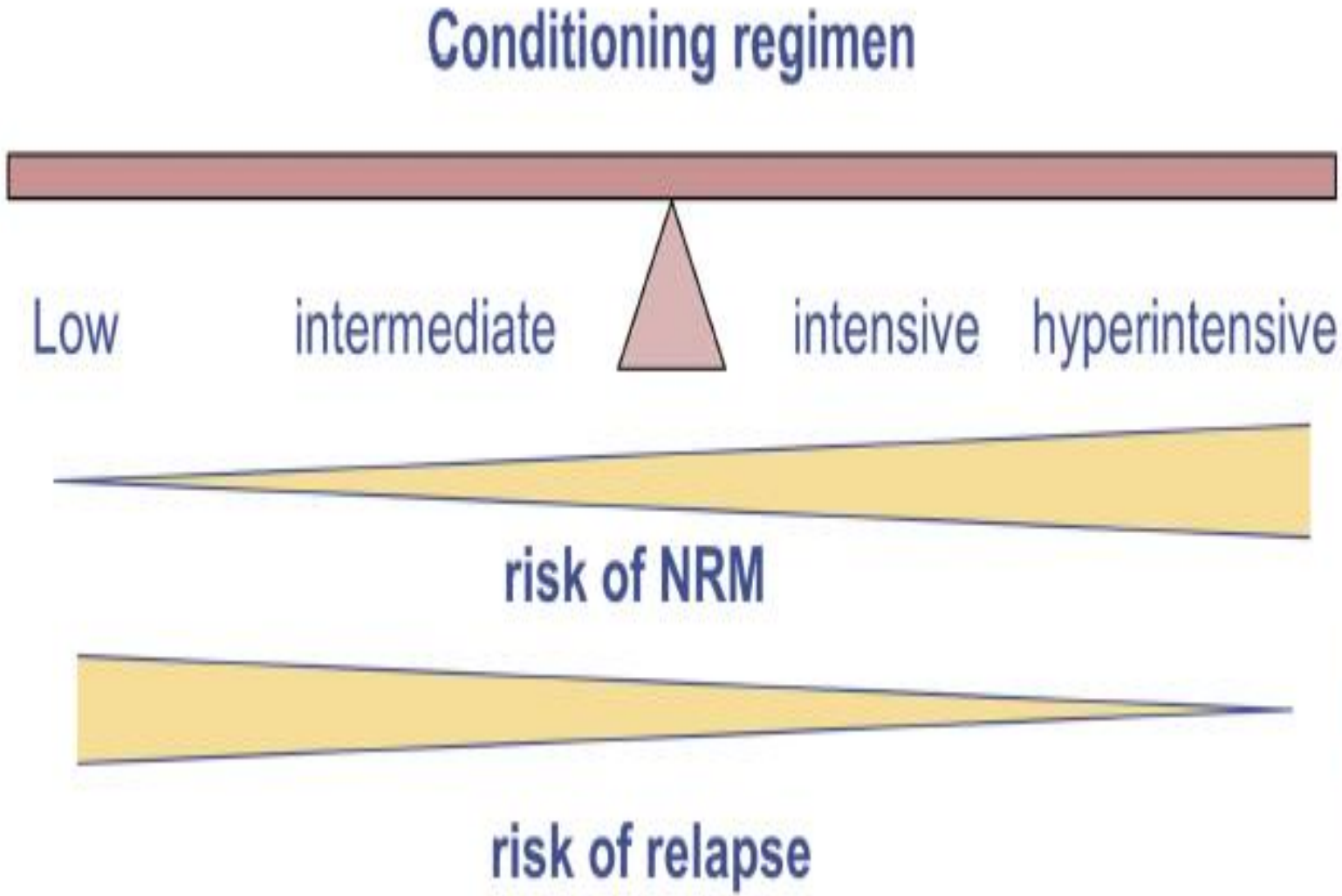
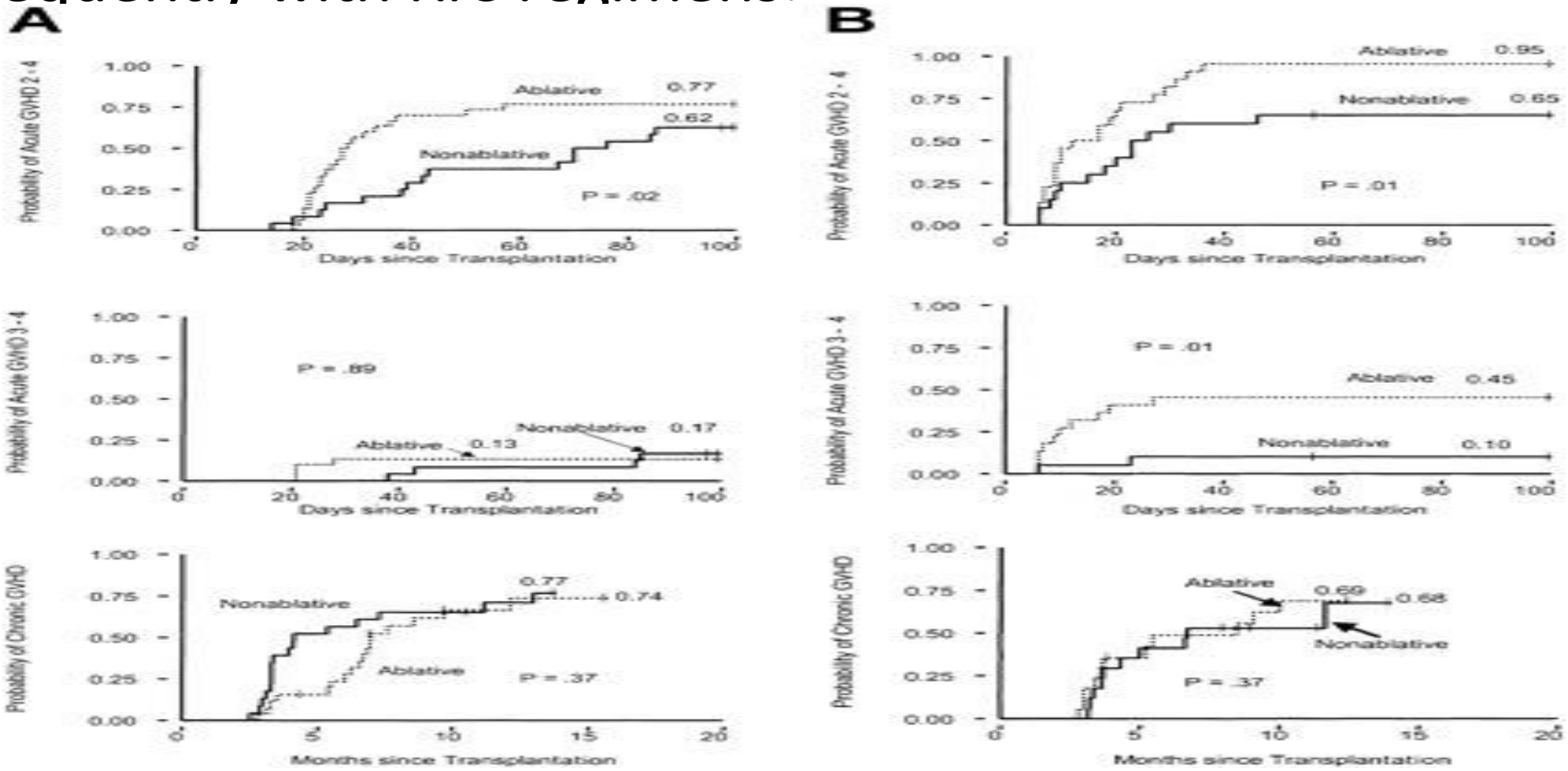


Figure 1. The balance between risk for non-relapse mortality and risk for relapse when choosing conditioning intensity.

The known complications of Allo-HSCT such as pancytopenia, mucositis and organ damage occur less frequently with RIC regimens.



Dose intensity for conditioning in allogeneic hematopoietic cell transplantation: can we recommend “when and for whom” in 2021?

Factors which may be helpful in the dec process: balance between the risk of re and non-relapse mortality

Table 4. **Risk factors influencing treatment failure (relapse or NRM) after allogeneic HSCT.**

Disease-specific factors	
Advanced disease status	relapse > NRM
Unfavorable cytogenetics/molecular genetics	relapse > NRM
Susceptibility to GVL-effect	relapse > NRM
Patient-specific risk factors	
Age	NRM > relapse
Performance status	NRM > relapse
Comorbidities	NRM > relapse
Transplant-specific risk factors	
MRD positivity	relapse > NRM
HLA disparity	NRM > relapse
CMV incompatibility	NRM > relapse
Center effect (JACIE accredited)	NRM > relapse

NRM, non-relapse mortality; HSCT, hematopoietic stem cell transplantation; GVL, graft-*versus*-leukemia effect; MRD, measurable residual disease; CMV, cytomegalovirus; JACIE, Joint Accreditation Committee ISCT-Europe & EBMT.

Toxicity-reduced myeloablative conditioning *versus* myeloablative conditioning

- Another attempt to reduce intensity and toxicity without losing myeloablative intensity of the conditioning regimen was made by replacing cyclophosphamide with **FLUDARABINE**

- Another option to maintain myeloablation, according to the given definition, and immunosuppression but also to reduce non-hematologic toxicity was investigated by replacing busulfan by the **alkylator** **treosulfan**

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journal homepage: www.bbmt.org

Intravenous Busulfan Compared with Treosulfan-Based Conditioning for Allogeneic Stem Cell Transplantation in Acute Myeloid Leukemia: A Study on Behalf of the Acute Leukemia Working Party of European Society for Blood and Marrow Transplantation

Avichai Shimoni [1,*], Myriam Labopin [2], Bipin Savani [3], Rose-Marie Hamladji [4], Dietrich Beelen [5], Ghulam Mufti [6], Gerard Socié [7], Jeremy Delage [8], Didier Blaise [9], Patrice Chevallier [10], Edouard Forcade [11], Eric Deconinck [12], Mohamad Mohty [13], Arnon Nagler [1,2]

Treosulfan is a prodrug of a bifunctional alkylating agent produced in vivo in a nonenzymatic reaction

It does not require enzymatic activation or hepatic metabolism

In the SCT setting treatment with treosulfan
results in rapid, profound, and stable myelosuppression
because of its dual effect on committed and noncommitted stem cells

Treosulfan exhibits strong immunosuppressive
characteristics with low proinflammatory cytokine release
. This facilitates stem cell engraftment and associates with
a lower risk of graft-versus-host disease (GVHD)

Table 1 Comparative properties of alkylating agents

From: Treosulfan-based conditioning before hematopoietic SCT: more than a BU look-alike

Properties	*BU*	*Treosulfan*	*Melphalan*	*Cytoxan*	*BCNU*
Immunosuppression					
In vitro	–[26]	+++[25]	–	++[81]	–
In vivo	–[84]	+++[30]	–[83]	++[82]	–
Distribution	Liver, lung, brain, kidney[84]	Kidneys[23]	Kidneys+spontaneus chemical degradation[83]	Kidney, hepatic bioactivation[85]	Hydrolysis+hepatic[85]
Liver toxicity and VOD	+++[86]	+[41]	–[85]	+++[85]	+++[85]
Pneumonitis	++[87, 88, 89]	–	–	+	+++[85]
Hemorrhagic cystitis	+[87, 88, 89]	–	–	+++[85]	–
Convulsion	+++[87, 88, 89]	+[43]	–	–	CNS toxicity ++[85] Non-convulsion
Mucositis	++	++[41, 43]	+++[83, 90]	–	+
Cardiotoxicity	–	–	–	++[85]	–
BM suppression	+++[91]	+++	+++	++	+++

Abbreviations: CNS=central nervous system; VOD=veno-occlusive disease.

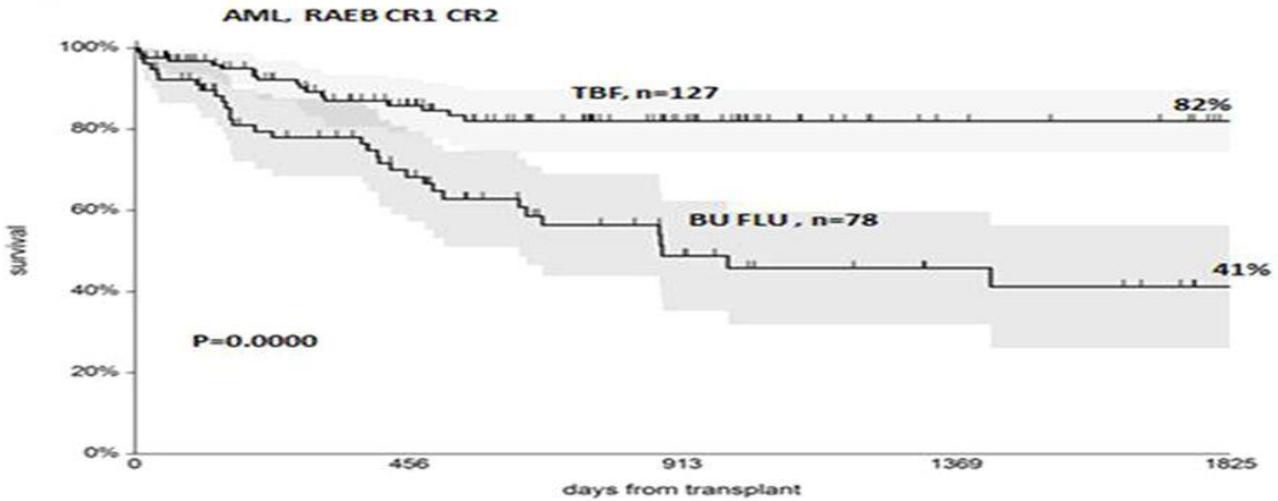
Back to article page ›

Busulfan Fludarabine (BU-FLU) Compared to Thiotepa Busulfan Fludarabine (TBF) for Allogeneic Transplants in Acute Myeloid Leukemia (AML) or Refractory Anemia with Excess Blasts (RAEB) in Remission

Table 1 Clinical characteristics of the 2 groups

		BU-FLU	TBF	P values
Number		78	127	
Recipient's age		54 (18-67)	53 (17-70)	0.5
Year of Transplant		2014 (08-17)	2015 (10-17)	0.07
CR1 , n (%)		66 (85%)	90 (71%)	
CR2, n (%)		12 (15%)	37 (29%)	0.2
Donor type :	HLA ident. Sibling	30(38%)	15(12%)	
	Family mismatched	3(4%)	91(72%)	
	Unrelated donor	45(58%)	21(16%)	0.0000
Stem cell soure	BM	26(33%)	112(88%)	
	PB	52(67%)	13(10%)	
	CB	0	2 (2%)	0.0000
TRM		25% (16-38%)	9% (5-17%)	0.007
RRD		33% (18-50%)	9% (6-20%)	0.008
Survival		41% (26-56%)	82% (74- 90%)	0.000
Median follow up days		481 (8-2625)	551 (2-2277)	0.5

Figure 1: Overall Survival Curve



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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 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] · Charles Craddock[6] · Gerard Socié[7] · Uwe Platzbecker[8] · Dietrich Beelen[9] · Noel Milpied[10] · Jan J. Cornelissen[11] · Arnold Ganser[12] · Anne Huynh[13] · Laimonas Griskevicius[14] · Sebastian Giebel[15] · Mahmoud Aljurf[16] · Eolia Brissot[2] · Florent Malard[2] · Jordi Esteve[17] · Zinaida Peric[18] · Frédéric Baron[19] · Annalisa Ruggeri[20] · Christoph Schmid[21] · Maria Gilleece[22] · Norbert-Claude Gorin[2] · Francesco Lanza[23] · Roni Shouval[24] · Jurjen Versluis[12] · Gesine Bug[25] · Yngvar Fløisand[26] · Fabio Ciceri[27] · Jamie Sanz[28] · Ali Bazarbachi[29] · Arnon Nagler[30] · Mohamad Mohty[2]

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Abstract

To address limitations of the currently used reduced-intensity/myeloablative conditioning (RIC/MAC) classification scheme we aimed to develop a tool that can capture more standardized the conditioning intensity of allogeneic hematopoietic cell transplantation (HCT). We assigned intensity weight scores for frequently used conditioning regimen components and used their sum to generate the transplant conditioning intensity (TCI) score. We retrospectively tested the impact of TCI on 8255 adult (45–65 years) acute myeloid leukemia patients who underwent HCT in first complete remission. A Cox model for early

- **Novel drugs** (e.g., thiotepa and optimized forms of drugs e.g., treosulfan) with reduced nonhematological toxicity are frequently used now a days and their different toxicity profiles are not considered in the current RIC/MAC classification scheme.
- **RIC/MAC operational rules ignore the additional intensity of purine analogs** used for immunoablation (e.g., fludarabine, clofarabine) or of disease-specific drugs used to achieve reduction in relapse risk (e.g., cytarabine, etoposide), and thus important prognostic information is lost

The TCI score ranged from 1 to 6 (median 2.5) with a median of 2 (range, 1–5.5) in the RIC group and 4 (range, 2.5–6) in the MAC group ($p < 0.001$)

Table 1 Intensity weighted scores for common components included in transplantation conditioning regimens.

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

iv intravenously, *po* per os, *TBI* total body irradiation.

NRM nonrelapse mortality. Others see Table 2.

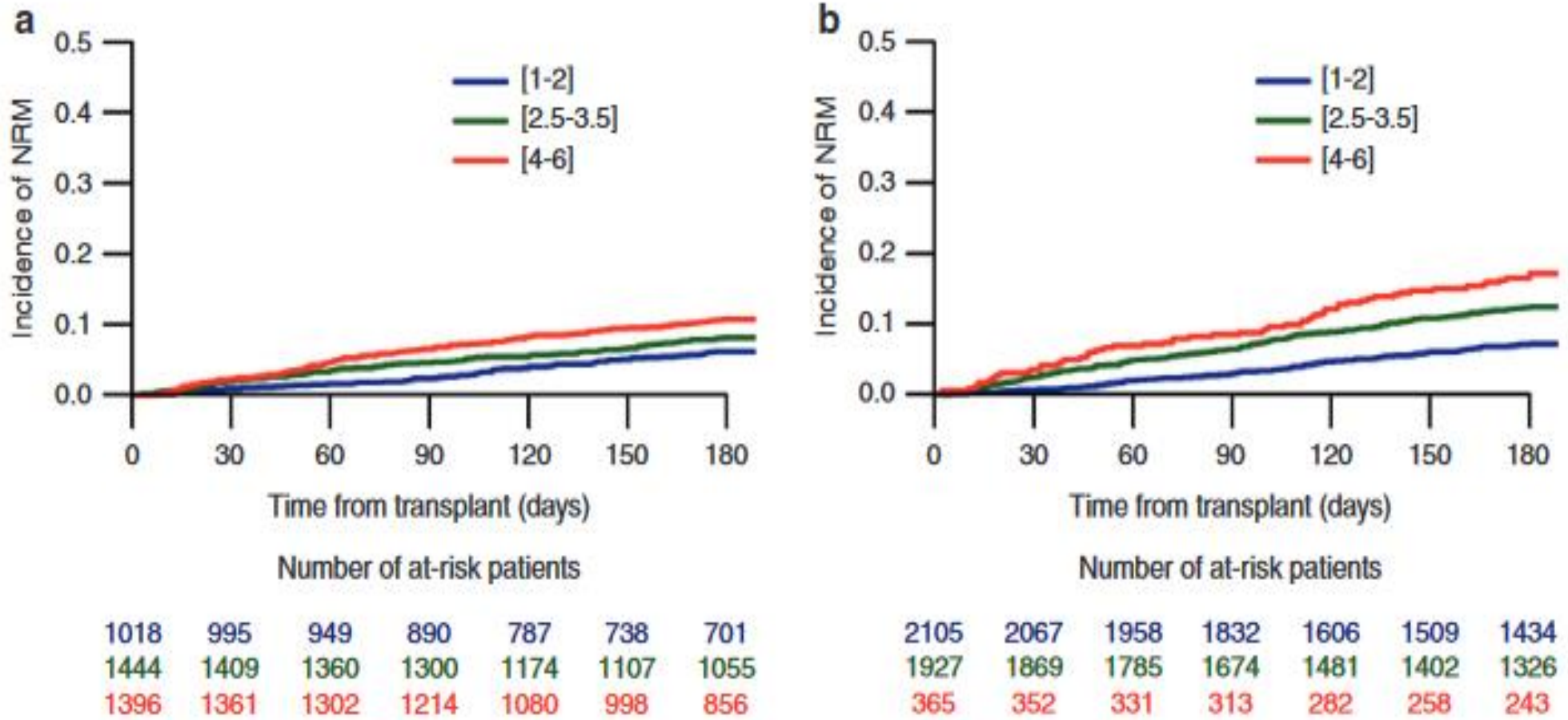


Fig. 2 Early nonrelapse mortality (NRM) according to TCI. a Early NRM in the subgroup of patients aged 45–55 years at transplant ($n = 3858$). **b** Early NRM in patients aged between 55 and 65 years ($n = 4397$).

Clinical Trial > J Clin Oncol. 2021 Mar 1;39(7):768-778. doi: 10.1200/JCO.20.02308.
Epub 2020 Dec 29.

Augmented Reduced-Intensity Regimen Does Not Improve Postallogeneic Transplant Outcomes in Acute Myeloid Leukemia

Charles Craddock [1 2], Aimee Jackson [2], Justin Loke [1], Shamyla Siddique [2], Andrea Hodgkinson [2], John Mason [2], Georgia Andrew [3], Sandeep Nagra [1], Ram Malladi [4], Andrew Peniket [5], Maria Gilleece [6], Rahuman Salim [7], Eleni Tholouli [8], Victoria Potter [9], Charles Crawley [4], Keith Wheatley [2], Rachel Protheroe [10], Paresh Vyas [5], Ann Hunter [11], Anne Parker [12], Keith Wilson [13], Jiri Pavlu [14], Jenny Byrne [15], Richard Dillon [16], Naeem Khan [3], Nicholas McCarthy [3], Sylvie D Freeman [3]

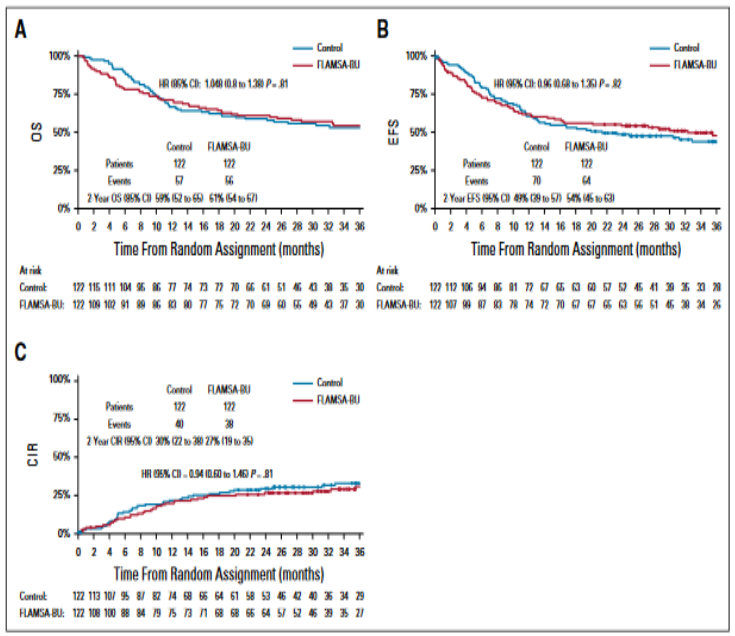
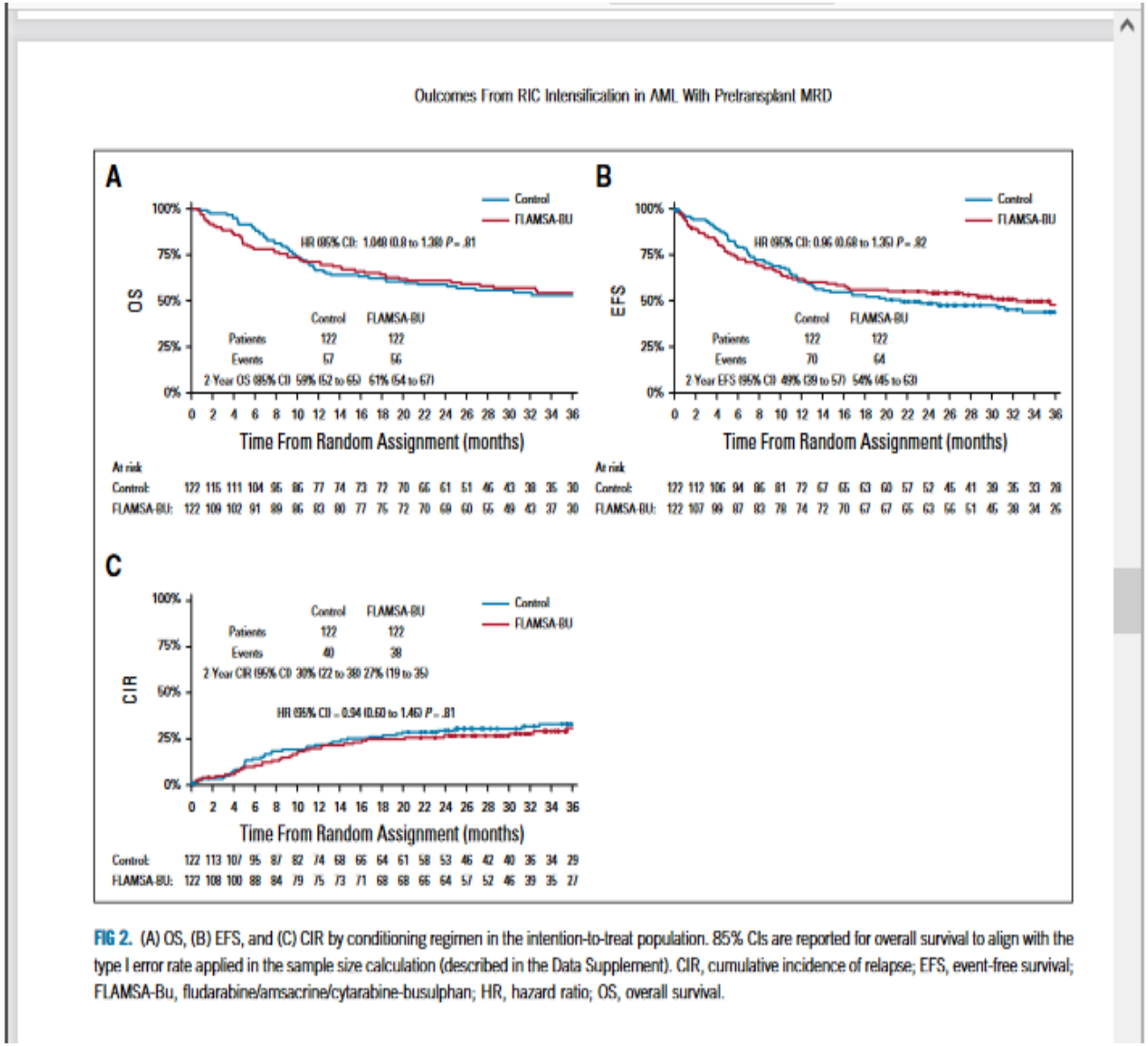


FIG 2. (A) OS, (B) EFS, and (C) CIR by conditioning regimen in the intention-to-treat population. 85% CIs are reported for overall survival to align with the type I error rate applied in the sample size calculation (described in the Data Supplement). CIR, cumulative incidence of relapse; EFS, event-free survival; FLAMSA-Bu, fludarabine/amsacrine/cytarabine-busulphan; HR, hazard ratio; OS, overall survival.


Outcomes From RIC Intensification in AML With Pretransplant MRD
FIG 2. (A) OS, (B) EFS, and (C) CIR by conditioning regimen in the intention-to-treat population. 85% CIs are reported for overall survival to align with the type I error rate applied in the sample size calculation (described in the Data Supplement). CIR, cumulative incidence of relapse; EFS, event-free survival; FLAMSA-Bu, fludarabine/amsacrine/cytarabine-busulphan; HR, hazard ratio; OS, overall survival.

Treatment of cGvHD in 2020 is unsatisfactory

To say the least

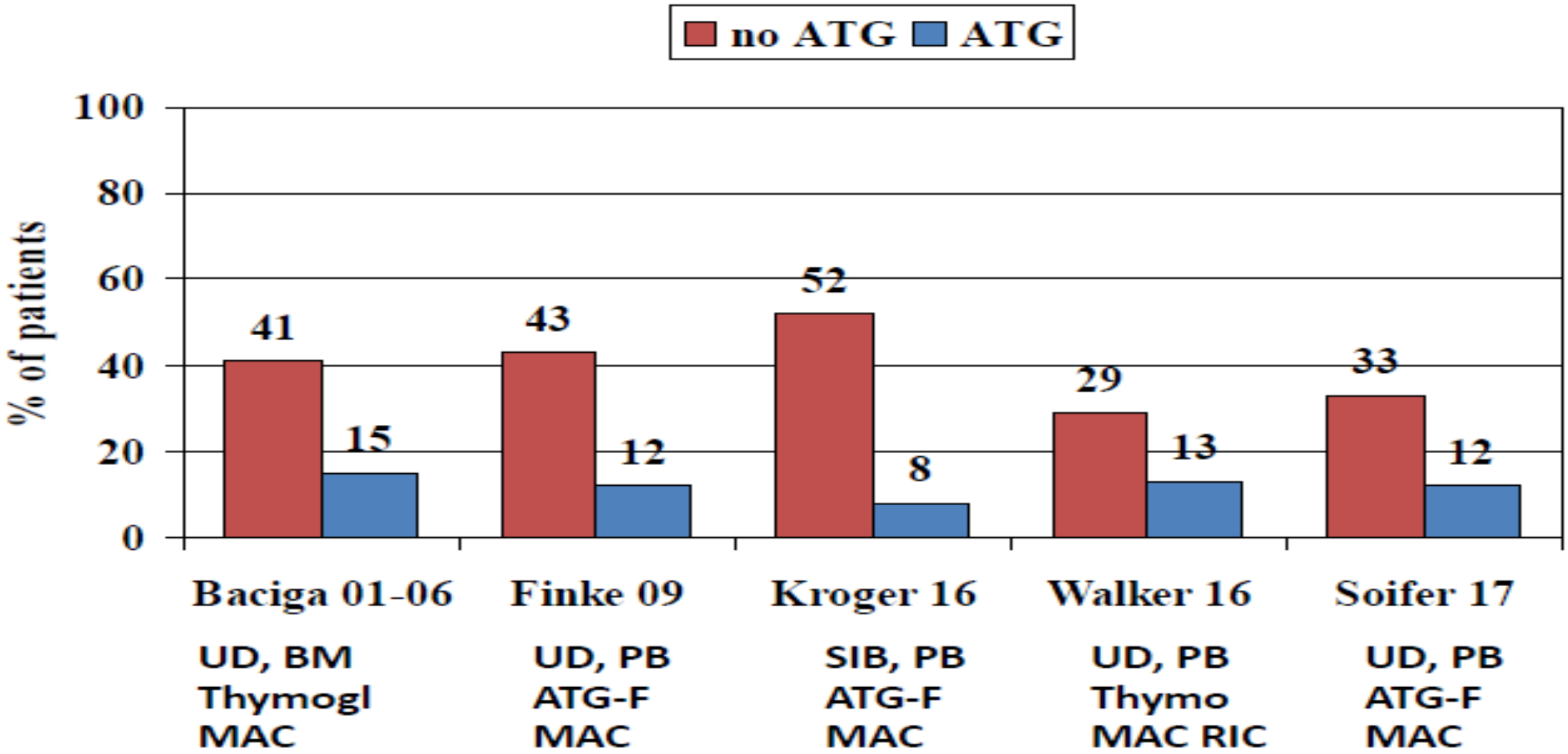
WHY SHOULD WE USE ATG?

1. Hign incidence of chronic GvHD
   especially with PBSC without ATG

2. Less than 20% achieve a CR

3. 80% of patients have cGvHD «life-long»

% with EXT chronic GvHD in 5 randomized ATG trials: 922 pts



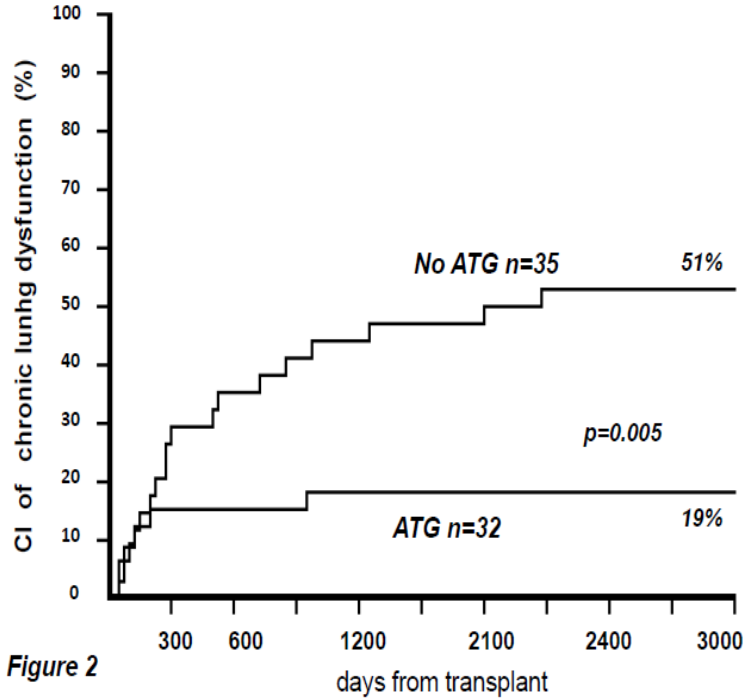


Figure 2

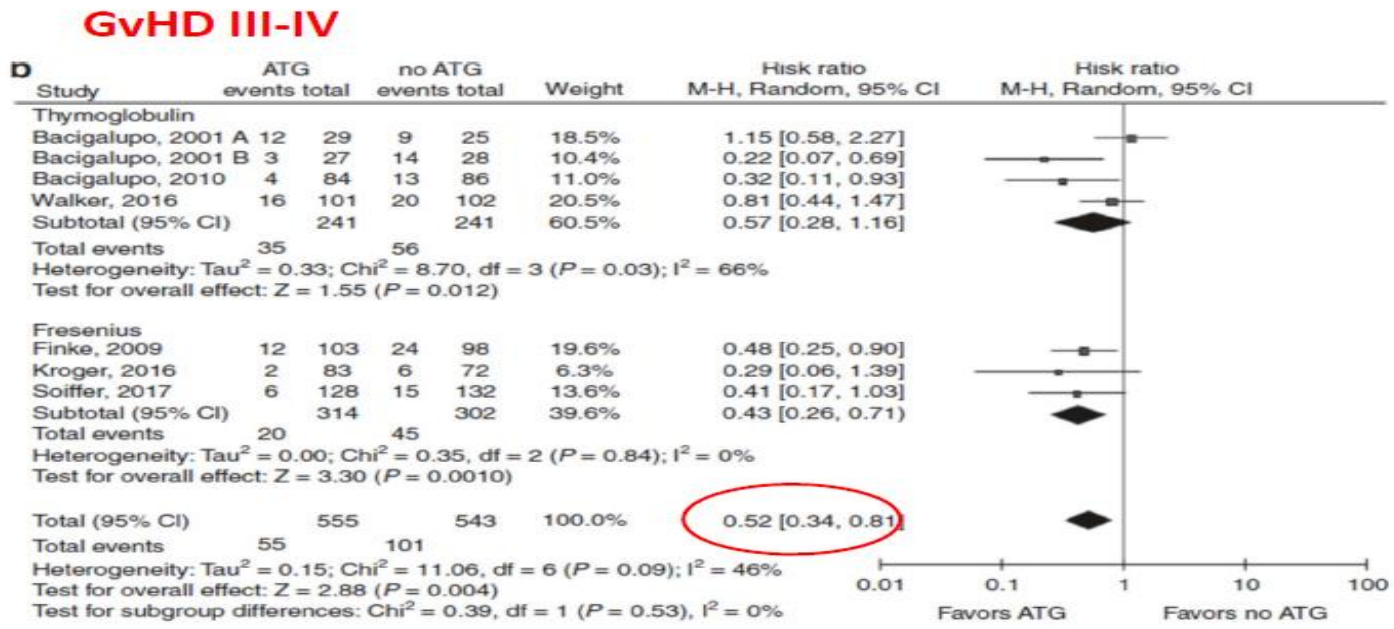


Table 1. Summary of 3 randomized trials

	GITMO[6,7]		Finke[8,9]		Kröger[10]		Total			
	ATG	noATG	ATG	noATG	ATG	noATG	ATG	noATG	RR	*P*
Patients, n	56	53	103	98	83	72	242	223	–	–
aGVHD II-IV, %	50%	70%	33%	51%	11%	18%	31%	46%	1.47	.001
aGVHD III-IV, %	23%	43%	11%	24%	2%	8%	12%	25%	2.08	.0003
cGVHD, %	37%	60%	26%	50%	22%	46%	28%	52%	1.83	.00001
ext cGVHD, %	15%	41%	12%	45%	5%	24%	11%	37%	3.43	.00001
NRM, %	39%	47%	19%	33%	14%	12%	24%	31%	1.27	.1
Relapse, %	23%	21%	33%	28%	32%	25%	29%	25%	0.84	.2
Survival, %	55%	56%	55%	43%	74%	77%	61%	59%	1.04	.6

ext, extensive; GITMO, Italian Cooperative Transplant Group; NRM, non-relapse mortality; RR, relative risk of patients not receiving ATG as compared with ATG.

ORIGINAL ARTICLE

Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease

Nicolaus Kröger, M.D., Carlos Solano, M.D., Christine Wolschke, M.D., Giuseppe Bandini, M.D., Francesca Patriarca, M.D., Massimo Pini, M.D., Arnon Nagler, M.D., Carmine Selleri, M.D., Antonio Risitano, M.D., Ph.D., Giuseppe Messina, M.D., Wolfgang Bethge, M.D., Jaime Pérez de Oteiza, M.D., Rafael Duarte, M.D., Angelo Michele Carella, M.D., Michele Cimminiello, M.D., Stefano Guidi, M.D., Jürgen Finke, M.D., Nicola Mordini, M.D., Christelle Ferra, M.D., Jorge Sierra, M.D., Ph.D., Domenico Russo, M.D., Mario Petrini, M.D., Giuseppe Milone, M.D., Fabio Benedetti, M.D., Marion Heinzelmann, Domenico Pastore, M.D., Manuel Jurado, M.D., Elisabetta Terruzzi, M.D., Franco Narni, M.D., Andreas Völp, Ph.D., Francis Ayuk, M.D., Tapani Ruutu, M.D., and Francesca Bonifazi, M.D.

ABSTRACT

BACKGROUND

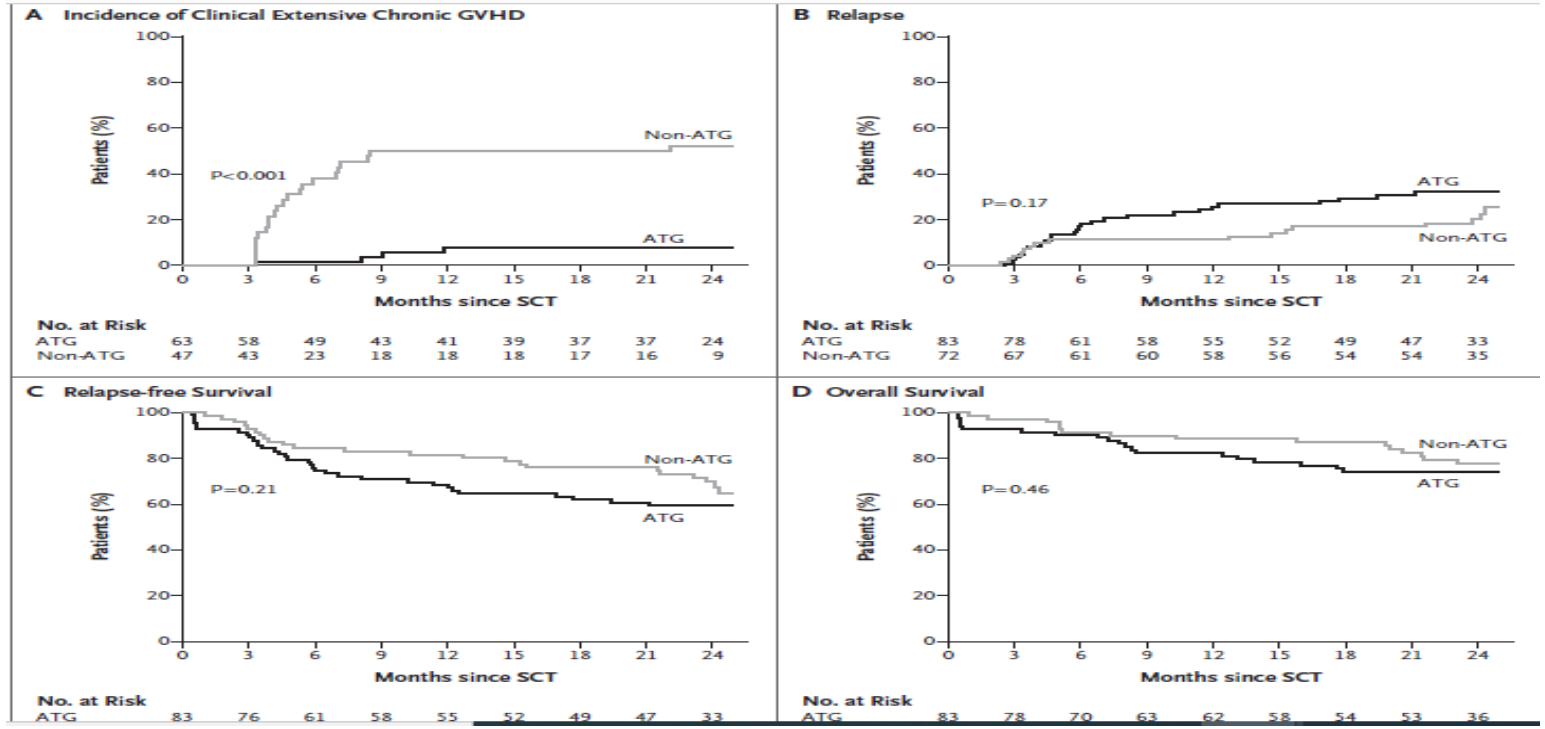
Chronic graft-versus-host disease (GVHD) is the leading cause of later illness and dea after allogeneic hematopoietic stem-cell transplantation. We hypothesized that the incl sion of antihuman T-lymphocyte immune globulin (ATG) in a myeloablative conditionir regimen for patients with acute leukemia would result in a significant reduction i chronic GVHD 2 years after allogeneic peripheral-blood stem-cell transplantation from a HLA-identical sibling.

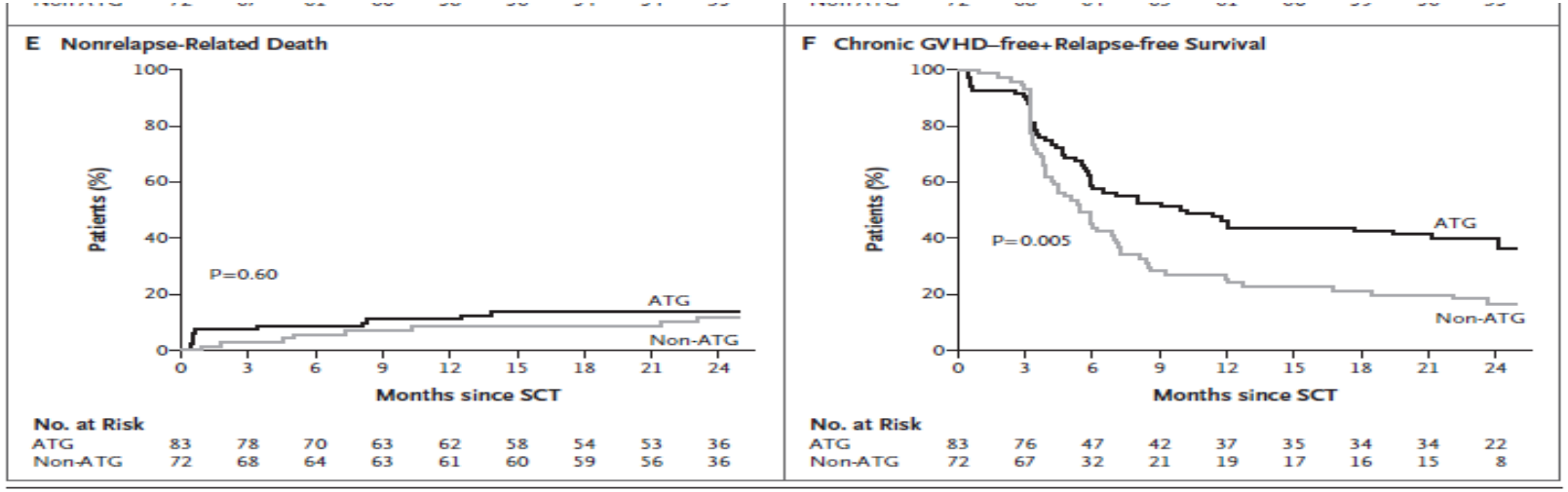
METHODS

We conducted a prospective, multicenter, open-label, randomized phase 3 study of ATG a part of a conditioning regimen. A total of 168 patients were enrolled at 27 centers. Patien were randomly assigned in a 1:1 ratio to receive ATG or not receive ATG, with stratificatic according to center and risk of disease.

RESULTS

After a median follow-up of 24 months, the cumulative incidence of chronic GVHD wa 32.2% (95% confidence interval [CI], 22.1 to 46.7) in the ATG group and 68.7% (95% C 58.4 to 80.7) in the non-ATG group (P<0.001). The rate of 2-year relapse-free survival wa





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https://doi.org/10.1038/s41409-020-0792-x

ARTICLE

Rabbit ATG/ATLG in preventing graft-versus-host disease after allogeneic stem cell transplantation: consensus-based recommendations by an international expert panel

Francesca Bonifazi[1] · Marie-Thérèse Rubio[2] · Andrea Bacigalupo[3,4] · Jaap Jan Boelens[5] · Jürgen Finke[6] · Hildegard Greinix[7] · Mohamad Mohty[8] · Arnon Nagler[9] · Jakob Passweg[10] · Alessandro Rambaldi[11] · Gérard Socie[12] · Carlos Solano[13] · Irwin Walker[14] · Giovanni Barosi[15] · Nicolaus Kröger[16]

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Dose of ATG

1. Less chronic GvHD
2. Increased likelihood of being off immunosuppressive therapy one year post-transplant
3. Less acute GvHD
4. Survival not impaired
5. No increased risk of relapse
6. Less rejection
7. Improved survival in BMF patients
8. Easy to use
9. Flexibility in diverse regimens
10. Combined prophylaxsis (with PT-CY)

Table 2 Final recommendations.

From: Rabbit ATG/ATLG in preventing graft-versus-host disease after allogeneic stem cell transplantation: consensus-based recommendations by an international expert panel

Conditioning regimen	Stem cell source	Donor	Recommendation	Agreement among experts
MALIGNANT DISEASES				
Myeloablative	Bone marrow/peripheral blood	Unrelated	Recommended	Full
Myeloablative	Peripheral blood	HLA-identical sibling	Recommended	Partial
RIC/NMA	Bone marrow/peripheral blood	HLA-identical sibling/matched or mismatched unrelated	Partially recommended	Partial
Any conditioning plus post-transplant cyclophosphamide	Bone marrow/peripheral blood	Haploidentical	Undecidable	Full
Any conditioning without post-transplant cyclophosphamide)	Bone marrow/peripheral blood	Haploidentical	Advised to follow the conditioning published protocols	Full
Any conditioning	Cord blood transplant	Cord blood	Undecidable	Full
NON-MALIGNANT DISEASES				
Any conditioning	Any stem cell source		Recommended	Full

RIC reduced intensity conditioning, *NMA* nonmyeloablative conditioning.

Biology of Blood and Marrow Transplantation
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Conditioning Regimen of 5-Day Decitabine Administration for Allogeneic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome and Myeloproliferative Neoplasms

Yi-Geng Cao, Yi He, Su-Dong Zhang, Zi-Xian Liu, Wei-Hua Zhai, Qiao-Ling Ma, Ai-Ming Pang, Jia-Ling Wei, Dong-Ling Yang, Yong Huang, Si-Zhou Feng, Er-Lie Jiang*, Ming-Zhe Han

Center of Hematopoietic Stem Cell Transplantation, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

A myeloablative conditioning regimen consisting of 20 mg/m2 Dec (on days -9 to -5), 30 mg/ideal m2Flu (days -6 to -4), 3.2 mg/ideal kg Bu (days -9 to -7), 40 mg/ideal kg Cy (days -3 to -2), and 2 g/ideal m2Ara-c (days -9 to -7) was used.

To monitor the effects of the Dec treatment on T cell (CD3+) and NK cell (CD3CD16+56+) responses after allografting, peripheral blood mononuclear cells (PBMCs) were analyzed by flow cytometry at days +14, +28, +42, +60, +90, +180, +280, and +360

Overall, this new regimen was associated with a low relapse rate, low incidence and severity of GVHD, and satisfactory survival in allo-HSCT recipients with MDS and MDS/MPN

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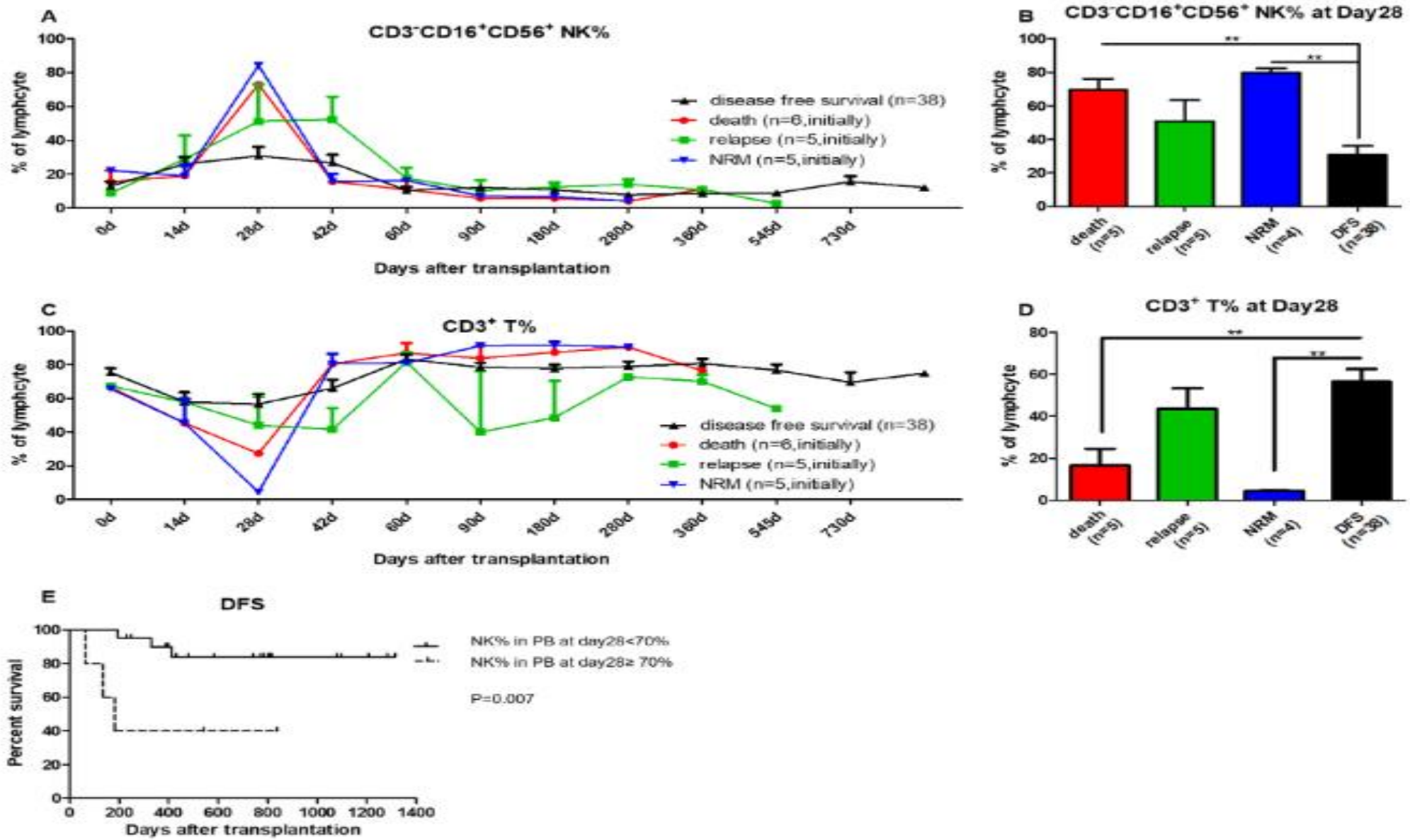


Figure 3. (A–D) Frequency of T cells and NK cells in the peripheral blood at stated time points after allo-HCT. Data are expressed as mean ± SE. $^{**}P < .01$. (E) DFS of patients with different proportions of NK cells in peripheral blood at day 28 after conditioning with decitabine at a median follow-up of 522 days after allo-HCT.

Box 2

Commonly used HLA-haploidentical alloBMT platforms

Myeloablative conditioning and T-cell depletion with 'megadose' $CD34^+$ cell allografts[50]

- TBI (8 Gy) on pretransplantation day 9
- Thiotepa (5 mg/kg/day) on pretransplantation days 8 and 7
- Fludarabine (40 mg/m^2/day) on pretransplantation days 7 to 3
- Rabbit antithymocyte globulin (5 or 6 mg/kg/day) on pretransplantation
  5 to 2
- $CD34^+$ selected PBSC allograft on day 0

Myeloablative conditioning and *in vivo* T-cell modulation using the GIAC protocol[19,87,96]

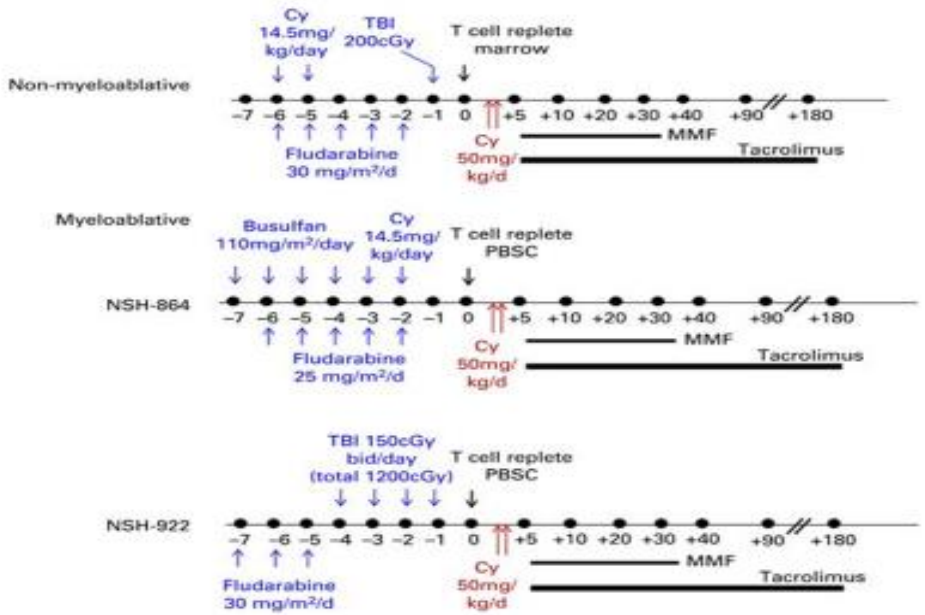
- Cytarabine (4 g/m^2/day) on pretransplantation days 10 and 9
- MMF from pretransplantation day 9 to post-transplantation day 60
- Ciclosporin-A from pretransplantation day 9 to post-transplantation day 180–300
- Busulfan (oral, 4 mg/kg/day; IV, 3.2 mg/kg/day) on pretransplantation days 8, 7 and 6
- Cyclophosphamide (1.8 g/m^2/day) on pretransplantation days 5 and 4
- Rabbit antithymocyte globulin (1.5 or 2.5 mg/kg/day) on pretransplantation days 5 to 2
- Semustine (250 mg/m^2) on pretransplantation day 3

GCSF-stimulated T-cell-replete PBSC and bone-marrow allografts on day 0

Methotrexate (15 mg/m^2) on post-transplantation day 1

Methotrexate (10 mg/m^2/day) on post-transplantation days 3, 6 and 11

option for patients who lack an HLA-identical sibling donor



Conditioning regimens For T-replete haploidentical donor transplantation used at Northside hospital.

Table 2

Relative advantages and disadvantages of each approach to haploBMT

Clinical outcome	T-cell depletion	GIAC protocol	PTCy
Engraftment	2–3	**1**	**2–3**
Acute GVHD	**1**	**3**	**2**
Chronic GVHD	**1–2**	**3**	**1–2**
Infection/deaths from infection	**3**	**2**	**1**
Nonrelapse mortality	**3**	**2**	**1**
Relapse	**2–3**	**1**	**2–3**

1 indicates most favourable; 2, intermediate; 3, least favourable. When more definitive ratings are unclear, a range is shown with the probable rating indicated in bold. Ratings take into account the findings of the available published studies (Table 1), but are unable to account for many factors that influence outcomes, such as differences between studies in patient characteristics or the malignant disease types, features or pretransplantation remission status.

Abbreviations: GVHD, graft-versus-host disease; haploBMT, human leukocyte antigen-haploidentical allogeneic blood or bone-marrow transplantation; PTCy, post-transplantation cyclophosphamide.

THE TAKE-HOME MESSAGE

- The answer to “when and for whom” with respect to HSCT conditioning intensity is complex, individualized, and constantly evolving.
- critical individual balance between the risk of NRM and the risk of relapse must be inclluded in a personalized medicine approach.

- **Toxicity-reduced myeloablative conditioning**

- ***CONSIDER APPROPRIATE DOSE OF ATG IN MATCHED SIBILING MAC***