Will PTCy replace ATG as GvHD prophylaxis in unrelated donor HSCT for AML? NO

Enrico Maffini, Trapianto e T.cellulari avanzate, IRCCS Bologna, Ist.Seragnoli

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NO DISCLOSURES							
NO DISCLOSURES							

L’attuale standard nella profilassi della GvHD nel trapianto da donatore non-familiare è rappresentato dalla globulina antilinfocitaria.

Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation

Olaf Penack, Monia Marchetti, Tapani Ruutu, Mahmoud Aljurf, Andrea Bacigalupo, Francesca Bonifazi, Fabio Ciceri, Jan Cornelissen, Ram Malladi, Rafael F Duarte, Sebastian Giebel, Hildegard Greinix, Ernst Holler, Anita Lawitschka, Stephan Mielke, Mohamad Mohty, Mutlu Arat, Arnon Nagler, Jakob Passweg, Hélène Schoemans, Gerard Socié, Carlos Solano, Radovan Vrhovac, Robert Zeiser, Nicolaus Kröger, Grzegorz W Basak

rATG (Thymoglobulin [Sanofi, Paris, France] or Grafalon [Neovii, St Gallen, Switzerland]) is recommended for preventing GVHD in patients undergoing matched unrelated donor allogeneic stem-cell transplantation†

The incidence and severity of chronic GVHD was reduced in clinical trials in allogeneic stem-cell transplant recipients treated with rATG or Grafalon as part of the conditioning regimen[7–9]

Penack O, et al. Lancet Haematol 2020;7:e157-167

ATG in allogeneic transplantation. Formulations and dosing (rabbit)

. **Thymoglobuline** – rabbit siera immunized with human thymocytes.

. **ATLG** (ex Fresenius, now Grafalon) – rabbit siera immunized with Jurkat T-cell leukemia cell line

. SIB: ATG-F 30 mg/kg // thymoglobuline ranging from 2.5 to 5 mg/kg.

. HLA-matched UD: ATG-F 60 mg/kg and the dose of thymoglobuline 4.5 to 7.5 mg/kg

Data from different studies are discordant because of:

. different formulations, doses, and timing used
. the heterogeneity of the studied populations,
. the hematopoietic stem cell sources
. the intensity of the conditioning regimens

Moreover:
. They have not been compared clinically in head-to-head studies.
. These different formulations do not have obvious dose equivalencies.
. There is substantial interpatient variability.

TIMiNG is Crucial

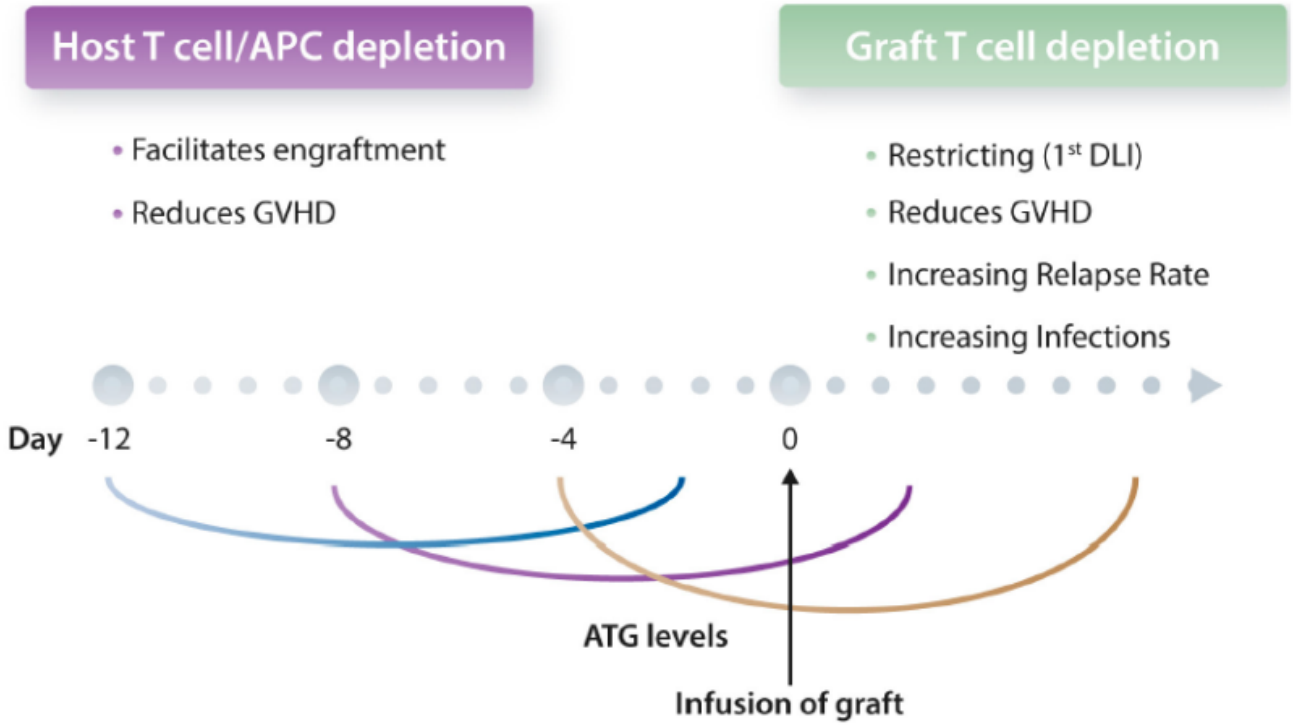


Figure 2. The dual sword of ATG, it is all about timing. APC = antigen presenting cell; ATG = anti-thymocyte globulin; DLI = donor lymphocyte infusion; GVHD = graft vs host disease.

DeWitte M, et al. HemaSphere 2021;5:6

Antirelapse effect of pretransplant exposure to rabbit antithymocyte globulin

Rosy Dabas,[1] Kareem Jamani,[1,2] Shahbal B. Kangarloo,[2] Poonam Dharmani-Khan,[1-3] Tyler S. Williamson,[1] Samar Ousia,[1,2,4] Caylib Durand,[1,2] Don Morris,[1,2] Douglas Mahoney,[1] Lynn Savoie,[1,2] Ahsan Chaudhry,[1,2] Victor H. Jimenez-Zepeda,[1,2] Faisal M. Khan,[1-3] Andrew Daly,[1,2] and Jan Storek[1,2]

[1]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [2]Alberta Health Services, Calgary, AB, Canada; [3]Alberta Public Laboratory, Calgary, AB, Canada; and [4]Faculty of Medicine, Ain Shams University, Cairo, Egypt

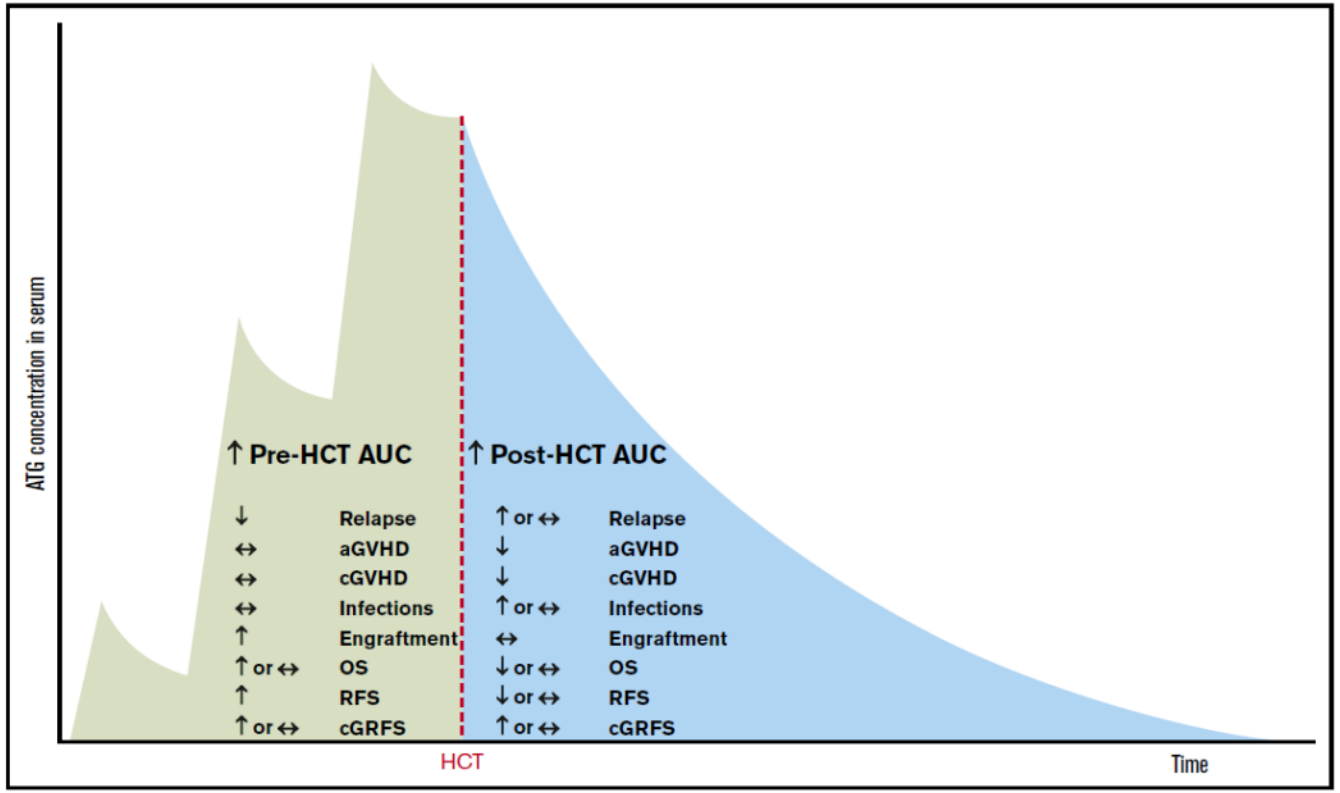
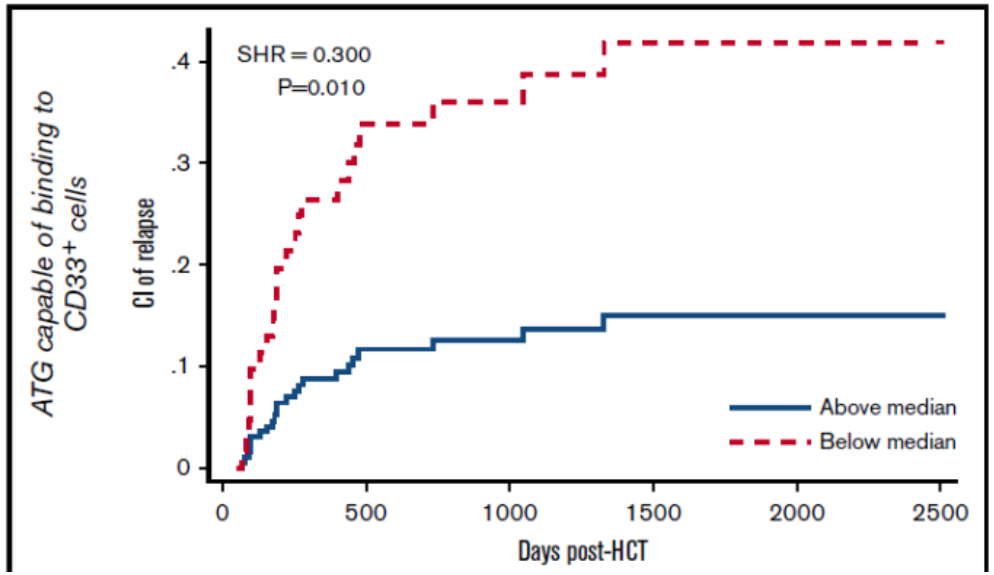
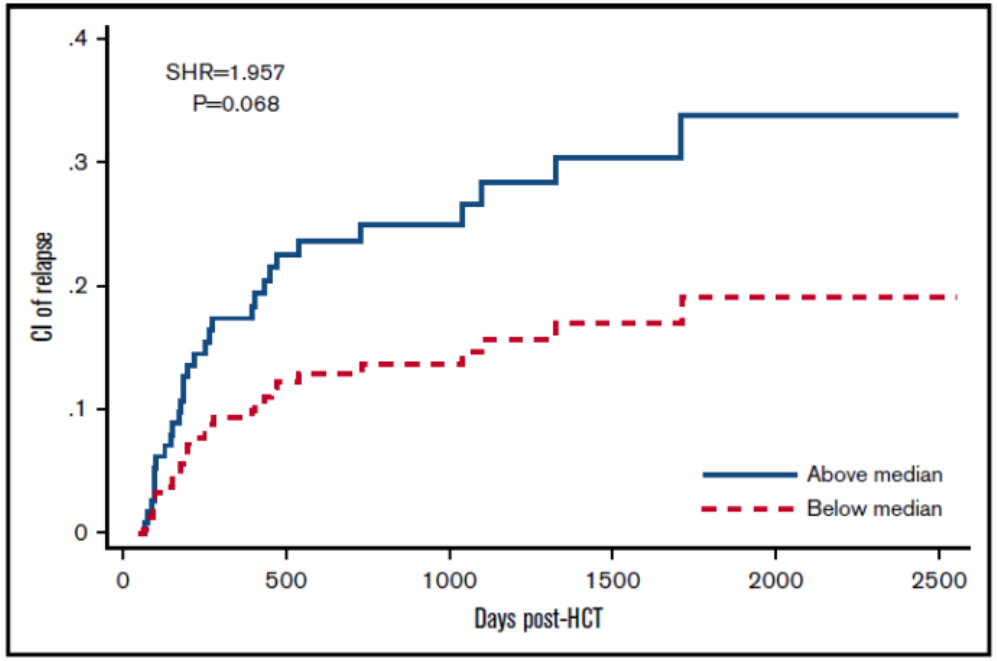


Table 1. Patient characteristics

Characteristic	N (%)
No. of patients	152
Patient age, y	
Median	53
Range	18-71
Patient sex	
Male	89
Female	63
Donor age, y	
Median	31
Range	16-68
Donor sex	
Male	101
Female	51
End of follow-up for all patients, d	
Median	708
Range	53-2554
End of follow-up for surviving patients, d	
Median	1077
Range	89-2554
Underlying disease	
AML	78 (51.6)
ALL	24 (15.6)
Other acute leukemia	2 (1.3)
MDS	14 (9.1)
CML/CMML	7 (4.5)
MF	4 (2.6)
MPN	1 (0.6)
CLL/lymphoma	19 (12.4)
Other hematological malignancy	3 (1.9)
Disease risk*	
Good	79 (52.2)
Poor	73 (47.7)
Donor type†	
HLA-matched sibling	55 (35.9)
7-8/8 HLA-matched unrelated	97 (63.9)





Key Points

- Pre-HCT exposure to ATG may have an antirelapse effect, whereas post-HCT exposure may have a prorelapse effect.
- Pre-HCT exposure may have a proengraftment effect; high post-HCT exposure is associated with less GVHD and more fatal infections.

Table 2. Associations between high pre- or post-HCT ATG AUC and outcomes

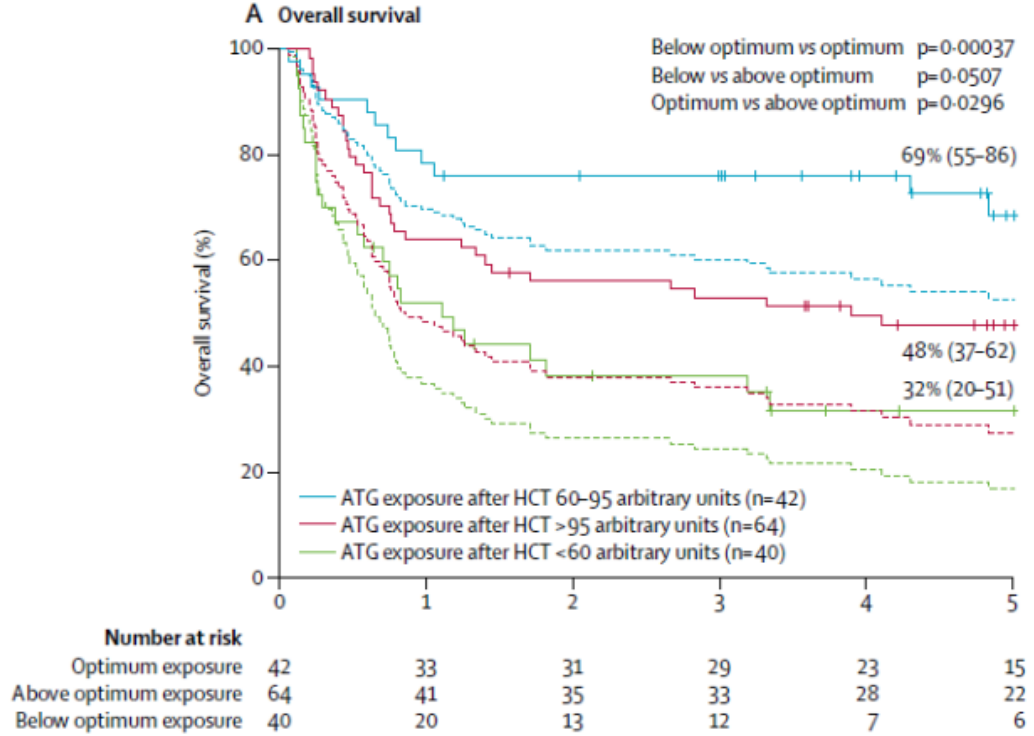
	Pre-HCT AUC					Post-HCT AUC				
Outcome	MNCs	Lymphocytes	T cells	CD4 T cells	CD33 cells*	MNCs	Lymphocytes	T cells	CD4 T cells	CD33 cells*
Relapse	↓				↓		↑	↑	↑	
aGVHD (grade 2-4)	↓					↓↓	↓↓↓	↓↓	↓↓	
cGVHD (moderate to severe; NST)						↓	↓			↓
OS	↑								↓	
RFS	↑								↓	
cGRFS	↑									↑

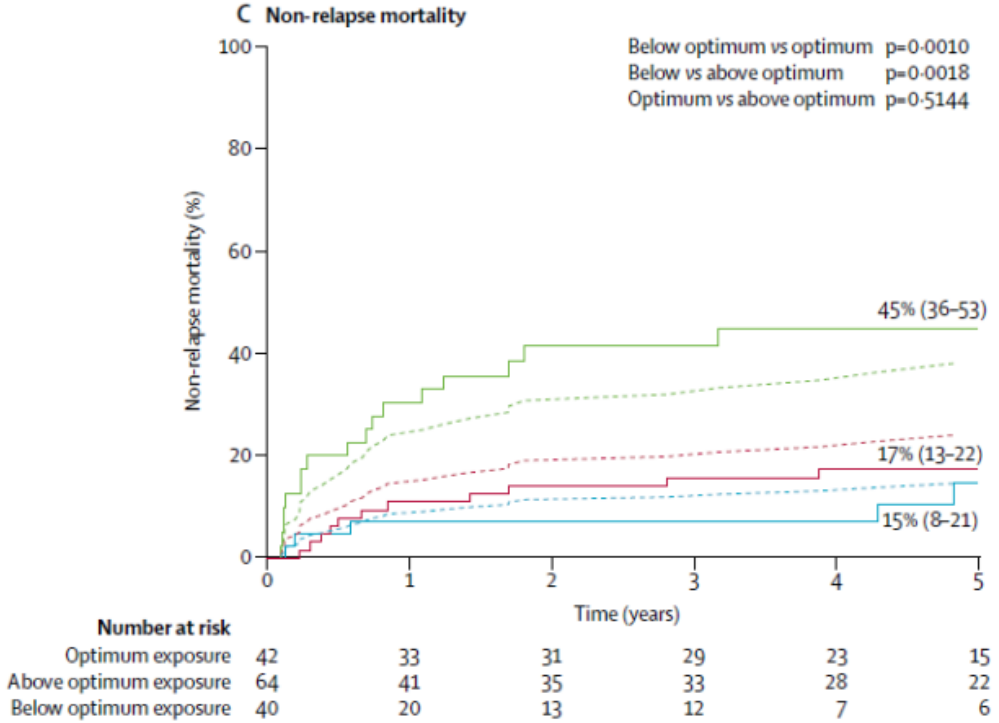
Dabas R, et al. Blood Adv 2019;3(9):1394-1405

Association between anti-thymocyte globulin exposure and survival outcomes in adult unrelated haemopoietic cell transplantation: a multicentre, retrospective, pharmacodynamic cohort analysis

Admiraal R, et al. Lancet Haematol 2017;4:e183-191

Rick Admiraal, Stefan Nierkens, Moniek A de Witte, Eefke J Petersen, Ger-jan Fleurke, Luka Verrest, Svetlana V Belitser, Robbert G M Bredius, Reinier A P Raymakers, Catherijne A J Knibbe, Monique C Minnema, Charlotte van Kesteren, Jurgen Kuball, Jaap J Boelens**

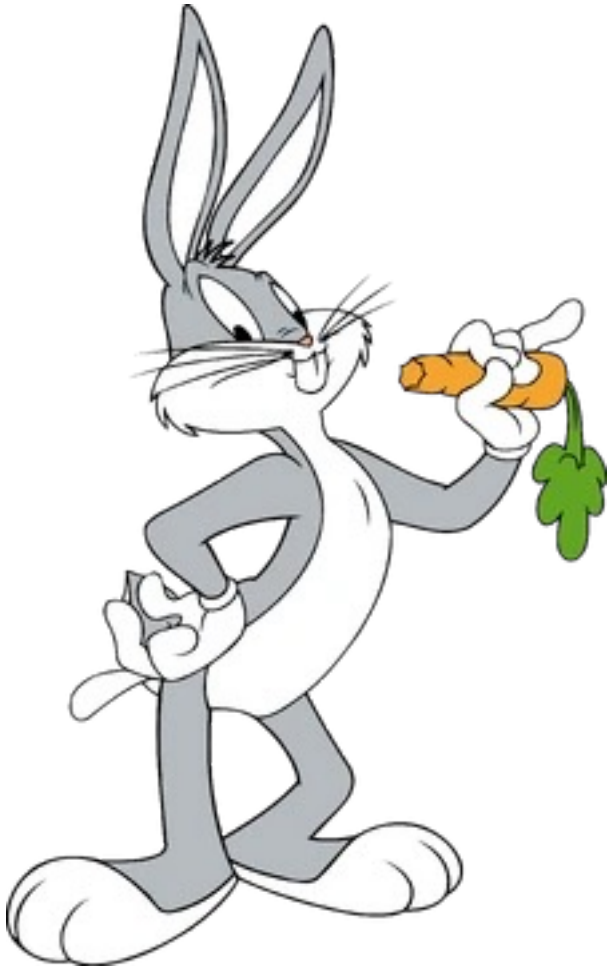




Individualized approach ATG-dosing?

- it is possible that the effect and outcomes with ATG are dependent on lymphocyte count at the time of infusion → it is likely that an individualized approach to ATG dosing and timing could be beneficial ….. BUT

- For each HCT setting, the ideal AUC *before* HCT and the ideal AUC *after* HCT need to be established, using a standardized, universally accepted assay for measuring anti-thymocyte globulin concentrations for the calculation of the AUC



PT-CY vs. ATG among HLA-matched unrelated donor transplant. What's up?

Not that much..

Post-transplant cyclophosphamide versus antithymocyte globulin in patients with acute myeloid leukemia in first complete remission undergoing allogeneic stem cell transplantation from 10/10 HLA-matched unrelated donors

Eolia Brissot[1,2*], Myriam Labopin[3], Ian Moiseev[4], J. J. Cornelissen[5], Ellen Meijer[6], Gwendolyn Van Gorkom[7], Montserrat Rovira[8], Fabio Ciceri[9,10], Laimonas Griskevicius[11], Didier Blaise[12], Edouard Forcade[13], Martin Mistrik[14], Stephan Mielke[15], Claude Eric Bulabois[16], Riitta Niittyvuopio[17], Eric Deconinck[18], Annalisa Ruggeri[9,10], Jaime Sanz[19,20], Alexandros Spyridonidis[21], Bipin Savani[22], Sebastian Giebel[23], Arnon Nagler[24] and Mohamad Mohty[1,2]

Table 2 Cumulative incidence of GVHD

	180-day acute GVHD II–IV	180-day acute GVHD III–IV	2-year chronic GVHD	2-year ext. chronic GVHD
PTCY	28.8% [22.2–35.7]	8.8% [5.1–13.7]	31.4% [23.3–39.8]	18.5% [12–26.1]
ATG	29.2% [26.8–31.6]	9% [7.6–10.6]	33.6% [31–36.2]	13.1% [11.2–15]
***p* value**	0.68	0.89	0.43	0.11

Abbreviations: *ATG* antithymocyte globulin, *Ext* extensive, *GVHD* graft-versus host disease, *PTCY* post-transplantation cyclophosphamide

Table 4 Two-year survival outcomes

	Relapse	NRM	LFS	OS	GRFS
PTCY	25.2% [18–32.9]	15.2% [9.7–21.8]	59.7% [50.6–67.6]	62.7% [53.4–70.7]	41.6% [33–50]
ATG	23.7% [21.4–26]	16.7% [14.8–18.8]	59.6% [56.8–62.2]	64.8% [62.1–67.4]	49.3% [46.6–52.1]
***p* value**	0.6	0.6	0.97	0.95	0.2

Abbreviations: *ATG* antithymocyte globulin, *GRFS* GVHD-free, relapse-free survival, *LFS* leukemia-free survival, *OS* overall survival, *NRM* non-relapse mortality, *PTCY* posttransplantation cyclophosphamide

Table 1 Baseline characteristics of patients

N	ATG	PTCY
	1452	174
Follow-up		
Median time (IQR) mo	33.2 (17.6–52.7)	20.5 (6.9–32.6)
Age at allo-HSCT		
Median (range) [IQR]	56 (18.1–77.5) [44.3–62.6]	46 (18–74.2) [34.7–59.3]
Year allo-HSCT		
Median (range) [IQR]	2014 (2010–2017)	2016 (2010–2017)
Time diagnosis to allo-HSCT		
Median (range) [IQR]	5.4 (1.5–17.7) [4.4–6.6]	4.7 (1.8–17.9) [3.8–7.7]
AML		
De novo	1206 (83.06%)	161 (92.53%)
secAML	246 (16.94%)	13 (7.47%)
Cytogenetics (MRC)		
Good	59 (4.06%)	4 (2.3%)
Interm	740 (50.96%)	80 (45.98%)
Poor	291 (20.04%)	35 (20.11%)
NA/failed	362 (24.93%)	55 (31.61%)
Conditioning regimen		
MAC	687 (47.31%)	76 (43.68%)
RIC	765 (52.69%)	98 (56.32%)
Gaft cell type		
BM	143 (9.85%)	18 (10.34%)
PBSC	1309 (90.15%)	156 (89.66%)

Phase 2 trial (NCT02876679) comparing the efficacy of post-transplantation cyclophosphamide (PTCy) versus anti-T-lymphocyte globulin (ATG) for GVHD prophylaxis in patients who received matched sibling donor or a 10/10 MUD HSCT following fludarabine-busulfan RIC.

. Primary endpoint was GRFS 12 months after HCT.
. 80 patients were randomly assigned to PTCy (n=43) or ATG (n=37).
. Conditioning was RIC
. Patients who received matched sibling donor or a 10/10 matched-unrelated donor.
. Overall survival was also similar between groups (78·9% [95% CI 63·4–88·4] in the PTCy group and 80·4% [95% CI 63·1–90·2] in the ATG group, p=0·93)
. Cumulative incidence at 6 months of grade 2–4 , grade 3–4 acute GVHD and chronic GVHD were also similar.

Brissot E, et al. 47th EBMT, 2021

Table 1
Characteristics

	MUD			MSD		
	Tac/MTX/ATG(N = 306)	PTCy(N = 246)	*P* Value	Tac/MTX(N = 272)	PTCy(N = 140)	*P* Value
Age (y), median (range)						
Recipient	53 (18-79)	61 (18-77)	<.001	54 (18-74)	60 (23-72)	<.001
Donor	29 (18-59)	29 (18-60)	.9	52 (12-74)	56 (19-69)	.003
Gender (donor/recipient)						
Female/Male	41 (13)	37 (15)	.7	77 (28)	37 (26)	.2
Others	265 (87)	208 (85)		195 (72)	103 (74)	
Missing	0	1		0	0	
Race/Ethnicity			<.001			.002
White, non-Hispanic	220 (72)	203 (82)		131 (48)	95 (68)	
Black, non-Hispanic	3 (1)	7 (3)		15 (5)	4 (3)	
Hispanic or Latino	37 (12)	19 (8)		69 (25)	22 (16)	
Other/unknown	46 (15)	17 (7)		57 (20)	19 (13)	
Disease			<.001			<.001
Myeloid	180 (59)	221 (90)		174 (64)	119 (85)	
Lymphoid	126 (41)	25 (10)		98 (36)	21 (15)	
Disease			<.001			<.001
AML/MDS	158 (52)	184 (75)		152 (56)	98 (70)	
ALL	63 (21)	10 (4)		51 (19)	6 (4)	
Chronic lymphoid malignancies*	63 (21)	15 (6)		38 (14)	15 (11)	
Chronic myeloid malignancies†	22 (7)	37 (15)		22 (8)‡	21 (15)	
Graft						
Peripheral blood	195 (64)	190 (77)	.001	260 (96)	139 (99)	.04
Bone marrow	111 (36)	56 (23)		12 (4)	1 (1)	
Conditioning intensity			.3			.02
Myeloablative	196 (64)	148 (60)		172 (63)	104 (74)	
Reduced-intensity	110 (36)	98 (40)		100 (37)	36 (26)	
MAC regimens						
Bu/Flu ± other	185 (94)	148 (0)	.002	160 (93)	104 (100)	.003
TBI-MAC	11 (6)	0 (0)		12 (7)	0 (0)	

Post-Transplantation Cyclophosphamide Versus Tacrolimus and Methotrexate Graft-Versus-Host Disease Prophylaxis for HLA-Matched Donor Transplantation

Rohtesh S. Mehta*, Rima M. Saliba, Gabriela Rondon, Gheath Al-Atrash, Qaiser Bashir, Chitra M. Hosing, Partow Kebriaei, Issa Khouri, Yago Nieto, Betul Oran, Uday R. Popat, Muzaffar H. Qazilbash, Jeremy Ramdial, Samer A. Srour, Richard E. Champlin, Katayoun Rezvani, Elizabeth J. Shpall, Amin M. Alousi

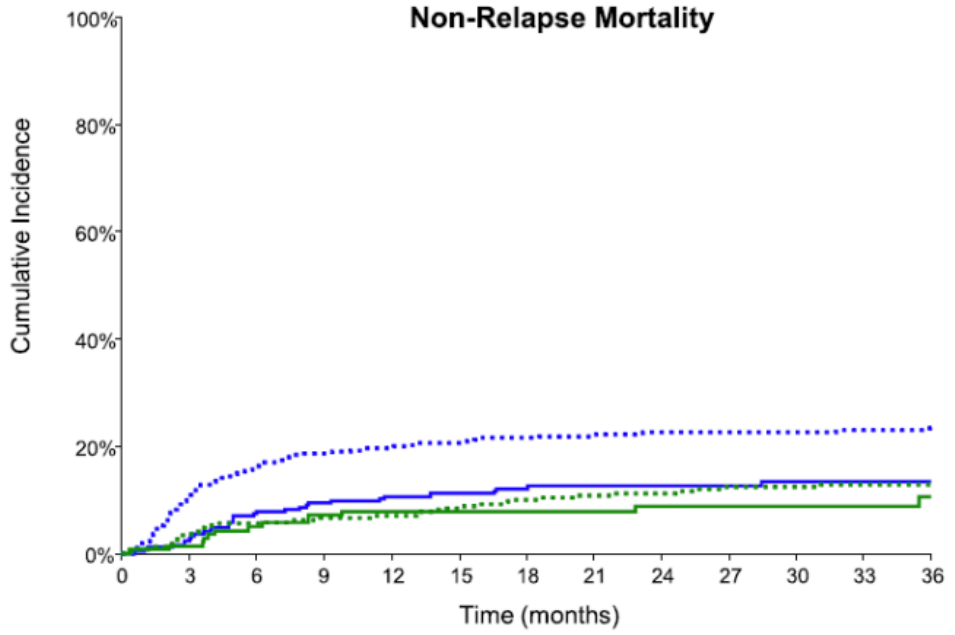
Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas

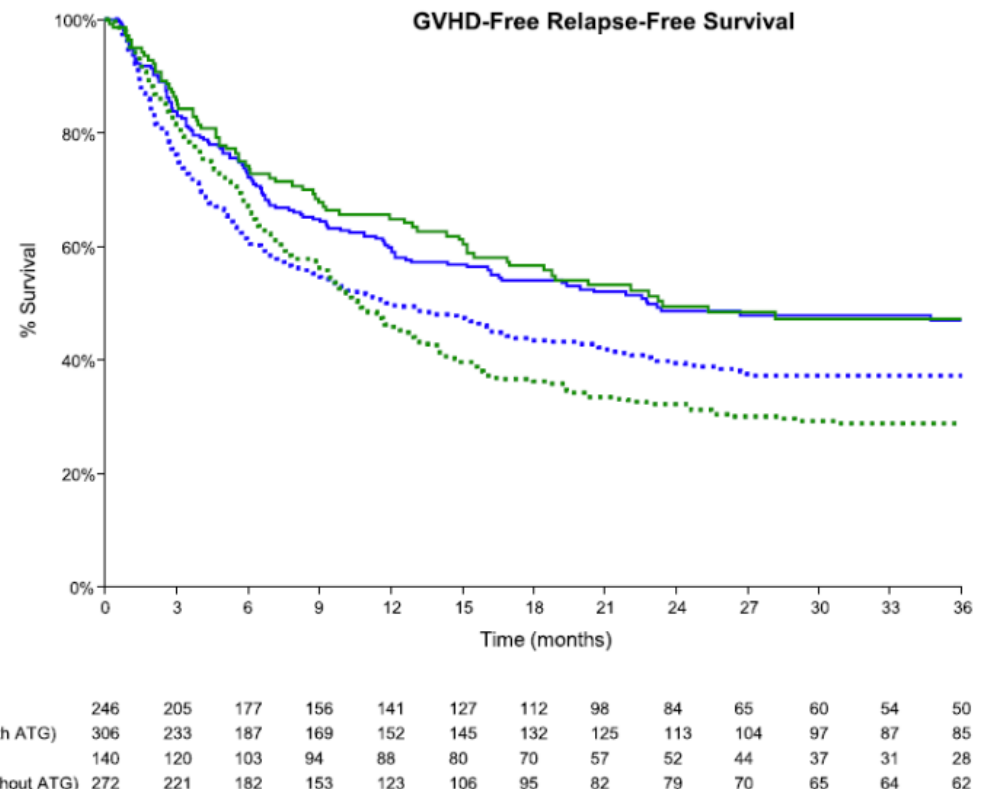
Retrospective Single-Center study

. ATG Thymoglobuline dosage 4 mg/kg in 3 days ((-3 to -1).

. PT-CY 50 mg/kg IV on days 3 and 4

Mehta RS, et al. BBMT 2022;28:695e1-10





PTCy was associated with a lower risk of viral infections, viral infection-related deaths, lower NRM, better PFS and GRFS in the MUD cohort.

Mehta RS, et al. BBMT 2022;28:695e1-10

Dose adjusted ATG might be the preferred choice to date in fully matched MUD donors, while PTCy appears to be superior when 9/10 MUD donors are used ?

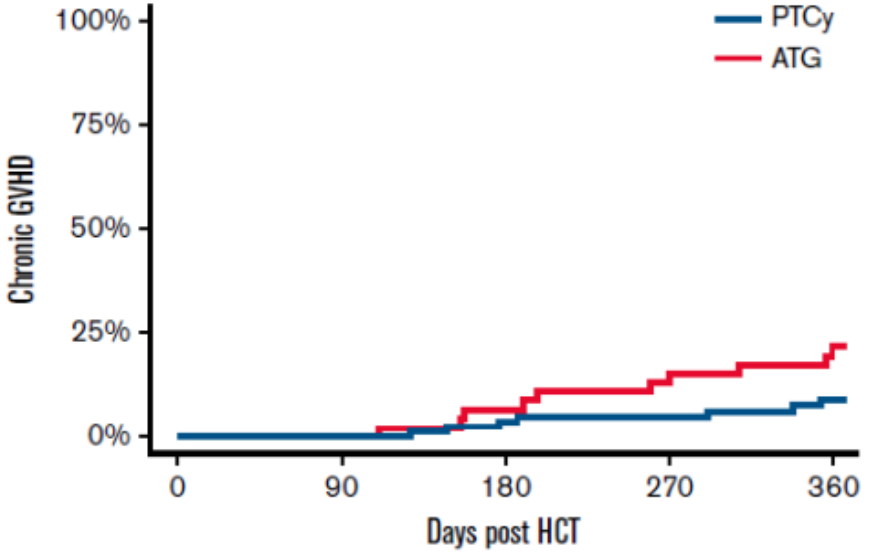
Maybe

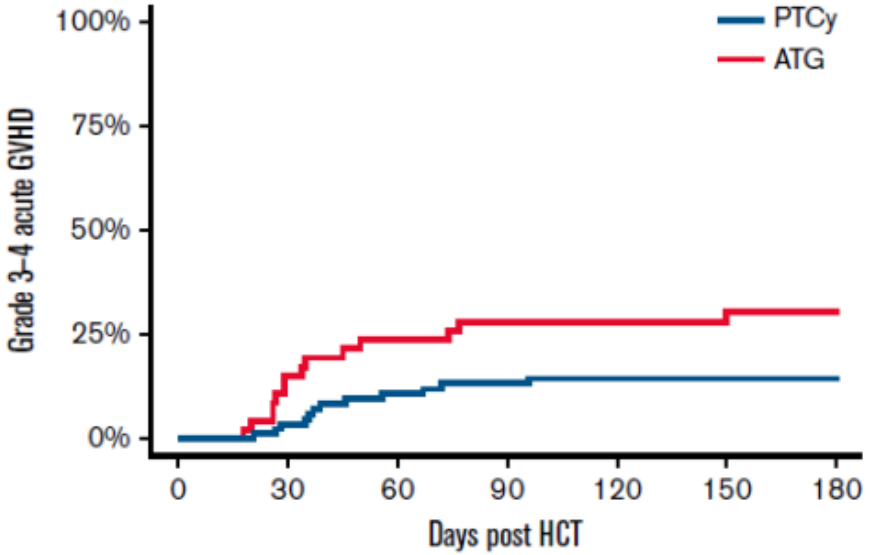
Improved GRFS after posttransplant cyclophosphamide-based vs ATG-based HLA-mismatched unrelated donor transplant

Antonio Jimenez Jimenez,[1] Krishna Komanduri,[1] Samantha Brown,[2] Trent Wang,[1] Denise Pereira,[1] Mark Goodman,[1] Amer Beitinjaneh,[1] Lazaros Lekakis,[1] Stephanie Chinapen,[3] Sean Devlin,[2] Doris Ponce,[3,4] Craig Sauter,[3,4] Miguel-Angel Perales,[3,4] and Brian C. Shaffer[3,4]

Table 1. Demographic characteristics of the study cohort

Characteristic	Total (n = 128)	ATG (n = 46)	PTCy (n = 82)
Transplant center			
MSKCC	51 (40%)	13 (28%)	38 (46%)
UM SCCC	77 (60%)	33 (72%)	44 (54%)
Age, median (range), y	60 (21-75)	55 (21-72)	60 (21-75)
HLA matching			
<7/8	26 (20%)	1 (2.2%)	25 (30.5%)
7/8	102 (80%)	45 (98%)	57 (70%)
Myeloablative intensity	60 (47%)	26 (57%)	34 (41%)
Disease status			
Complete response	93 (73%)	30 (65%)	63 (77%)
Partial response	11 (9%)	7 (15%)	4 (5%)
Stable disease	10 (8%)	1 (2%)	9 (11%)
No remission	14 (11%)	8 (17%)	6 (7%)
Regimen			
Busulfan based	43 (34%)	18 (39%)	25 (31%)
Fludarabine/Cy/TBI-200	27 (21%)	5 (11%)	22 (27%)
Melphalan based	44 (34%)	16 (35%)	28 (34%)
TBI based	14 (11%)	7 (15%)	7 (9%)
HCT comorbidity index			
0-2	51 (40%)	13 (28%)	38 (46%)
≥3	77 (60%)	33 (72%)	44 (54%)
Graft source			
BM	53 (41%)	12 (26%)	41 (50%)
PB	75 (59%)	34 (74%)	41 (50%)





Then..What’s cooking?

GvHD Prophylaxis in Unrelated Donor HCT: Randomized Trial Comparing PTCY Versus ATG (GRAPPA) # NCT 05153226 - Phase 3 randomized study

- . Est.enrollement: 540 pts
- . Est. primary completion: Aug 2025
- - UD donors matched or partially matched (with not more than one allele or antigen mismatch)
- - Myeloid Neoplasms (including both disease in remission and in progression)
- - Source: PBSC

- Arm A: ATG Grafalon 10 mg/kg i.v. d-3, d-2, d-1
- Arm B: Cyclophosphamide 50 mg/kg (AIBW) i.v. d+3, d+4 post transplant

- Primary endpoints:
- Overall survival from HCT

- Relapse- and Immunosuppression-free Survival

Allogeneic Hematopoietic Cell Transplantation From HLA-matched Donor After Flu-Mel-PTCy Versus Flu-Mel-ATG Reduced-intensity Conditioning (HLA)

 # NCT03852407 - Pick-a-winner phase 2 randomized study - Belgian Hematology Society (BHS)

. Est.enrollement: 114 pts

. Est. primary completion: 2033

- HLA-matched related & unrelated donors

- All hematological Neoplasms (including both disease in remission and in progression)

- Source: PBSC

Arm A: FM + ATG Thymoglobuline 2.5 mg/kg i.v. on d-2, d-1

Arm B: FM + Cyclophosphamide 50 mg/kg i.v. d+3, d+4 post transplant

Primary endpoints:

1. Two-year cGRFS

What else?

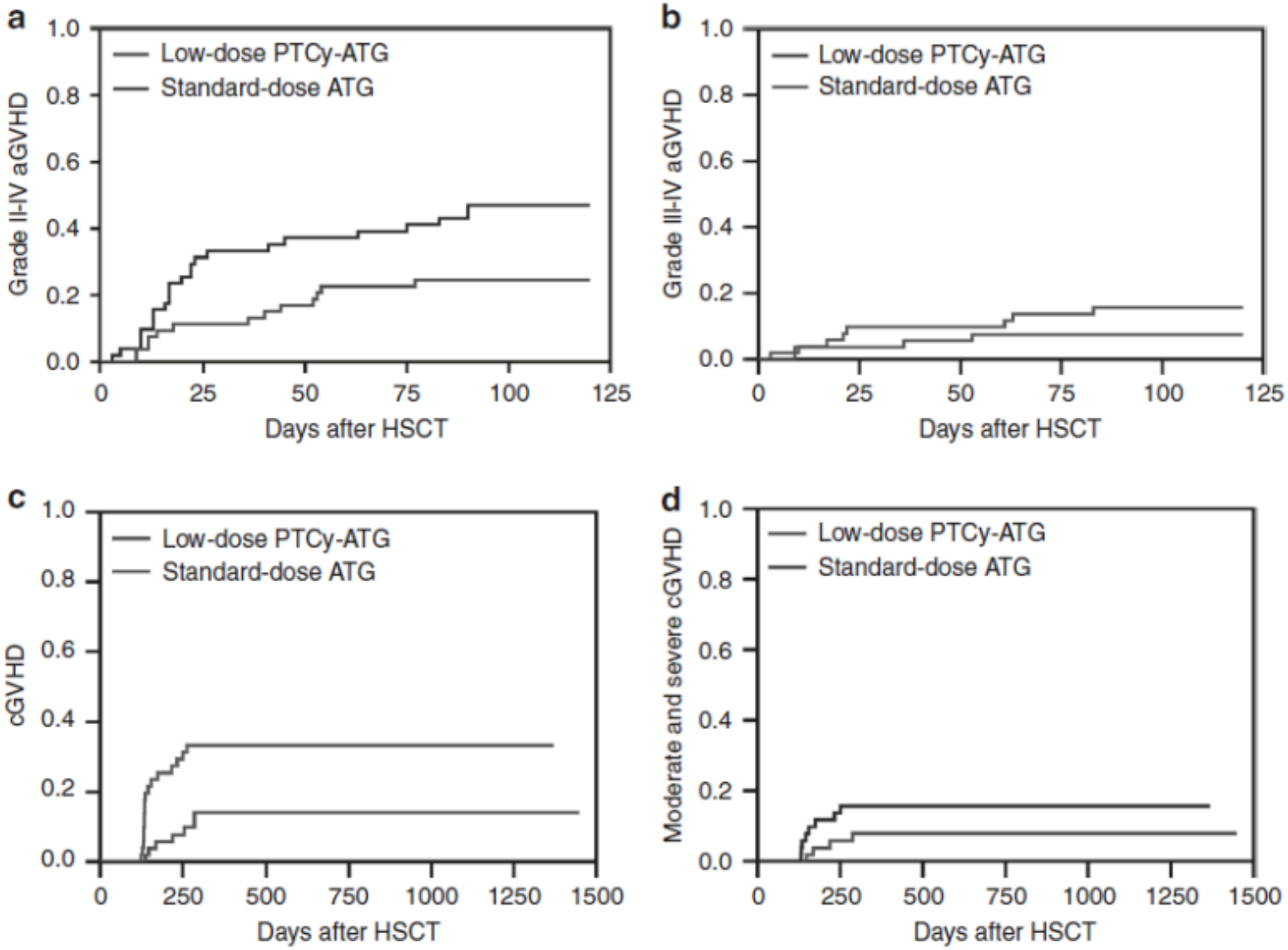
ARTICLE OPEN

Check for updates

Low-dose post-transplant cyclophosphamide with low-dose antithymocyte globulin for prevention of graft-versus-host disease in first complete remission undergoing 10/10 HLA-matched unrelated donor peripheral blood stem cell transplants: a multicentre, randomized controlled trial

Yingling Zu[1,2], Zhen Li[1], Ruirui Gui[1], Yanyan Liu[1], Yanli Zhang[1], Fengkuan Yu[1], Huifang Zhao[1], Yuewen Fu[1], Xinrong Zhan[3], Zhongliang Wang[3], Pengtao Xing[3], Xianjing Wang[4], Huili Wang[4], Jian Zhou[1]✉ and Yongping Song[1,5]✉

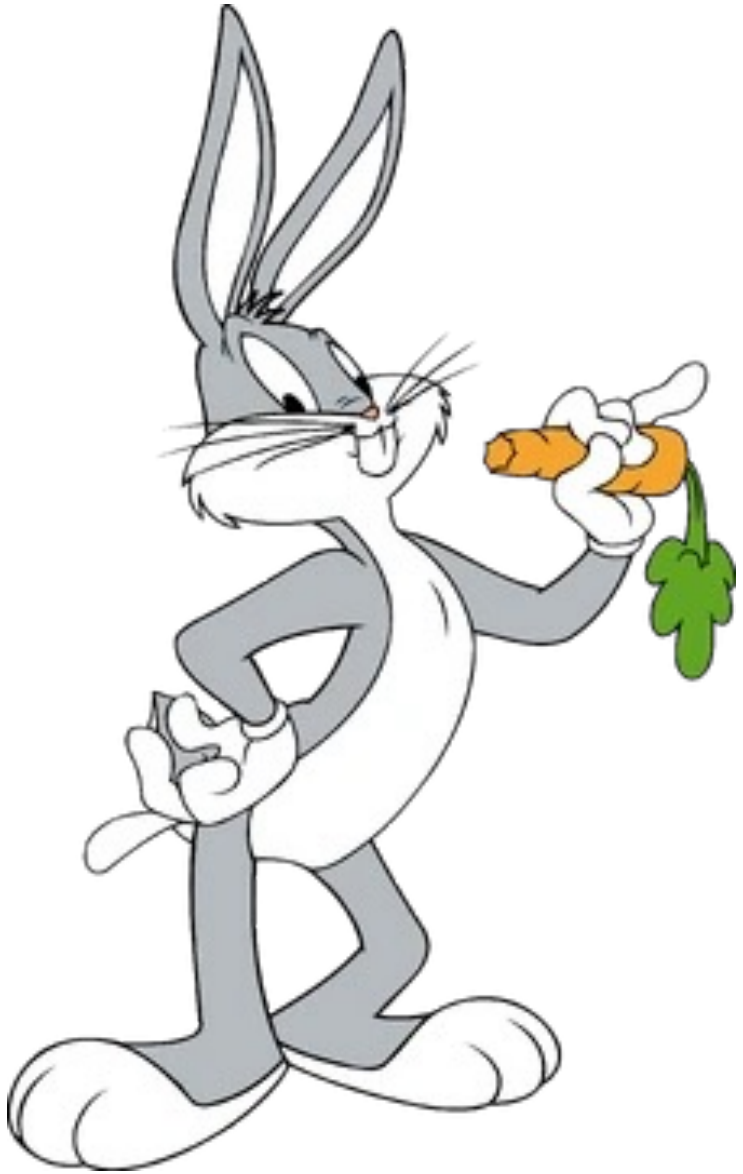
- Low-dose PTCy (20 mg/kg on day +3 and +4) and low dose ATG (6 mg/kg), was evaluated in patients with hematological malignancies undergoing 10/10 HLA MUD-PBSCT in first remission
- Multicenter study, 104 patients were randomly assigned one-to-one to low-dose PTCy-ATG (n = 53) or standard-dose ATG (10 mg/kg, n = 51).


a
Low-dose PTCy-ATG
Standard-dose ATG
Grade II-IV aGVHD
Days after HSCT
b
Low-dose PTCy-ATG
Standard-dose ATG
Grade III-IV aGVHD
Days after HSCT
c
Low-dose PTCy-ATG
Standard-dose ATG
cGVHD
Days after HSCT
d
Low-dose PTCy-ATG
Standard-dose ATG
Moderate and severe cGVHD
Days after HSCT

Despite more than 30 years of intensive research and clinical experience, the story of ATG in allogeneic-HSCT is still fascinating …

To stop this story from continuing for another 30 years, we need to introduce more harmonized, but also personalized, transplantation care.

Grazie per l’attenzione



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Istituto L.A. Seragnoli, Bologna.