XX Congresso della Società GITMO

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Oltre la ciclofosfamide post-trapianto: ruolo della riduzione di dose e dell'associazione con l'ATG

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Disclosures of Nicola Polverelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis			X		X	X	
Sanofi							X
Neovii							X

Outline

- From guidelines to clinical practice: positioning of PTCy vs ATG
- Limitations of standard PTCy: toxicity and unmet clinical needs
- Optimizing PTCy dosing: can we reduce dose while preserving efficacy?
- PTCy plus ATG combination: rationale and current evidence

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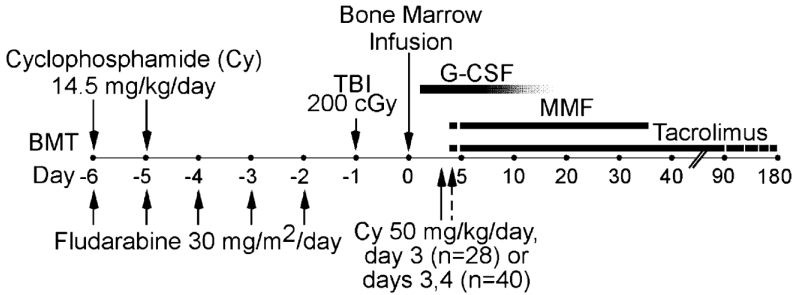
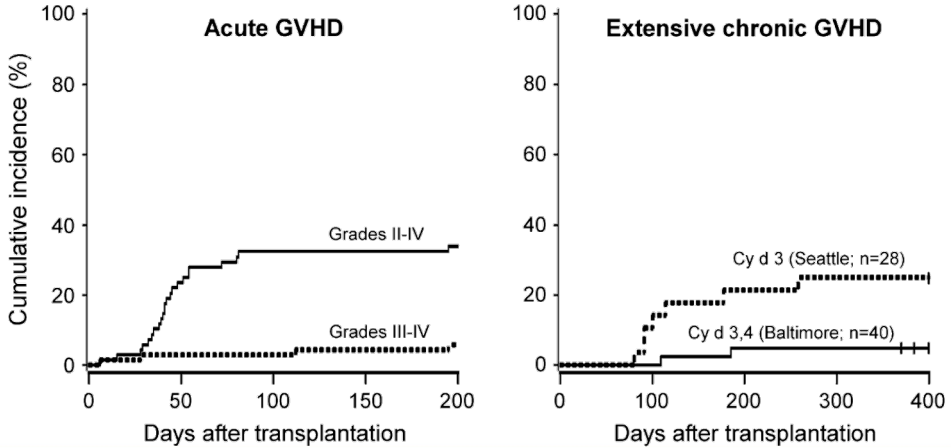
PTCy in Haploidentical Transplantation: A Pivotal Study

Two trials (Seattle and Baltimore, 1999–2006) enrolled 68 high-risk patients **ineligible** for **standard allo-HCT.**

Features	No (68)
Median age, years (range)	46 (1–71)
No. (%)	
Sex, Male (%)	42 (62%)
Diagnosis, No. (%)	
AML	27 (40%)
CR1 / CR>1 / Not in CR	12 / 13 / 2
ALL	4 (6%)
CR1 / CR>1 / Not in CR	2 / 1 / 1
MDS	1 (1%)
CML/CMML	6 (9%)
CLL/HL/NHL	26 (38%)
MM/plasmacytoma	3 (4%)
PNH	1 (1%)
No. prior treatment regimens (range)	4 (0–10)
Sensitive to prior treatment (%)	49 (77%)
Prior autologous transplant (%)	21 (31%)



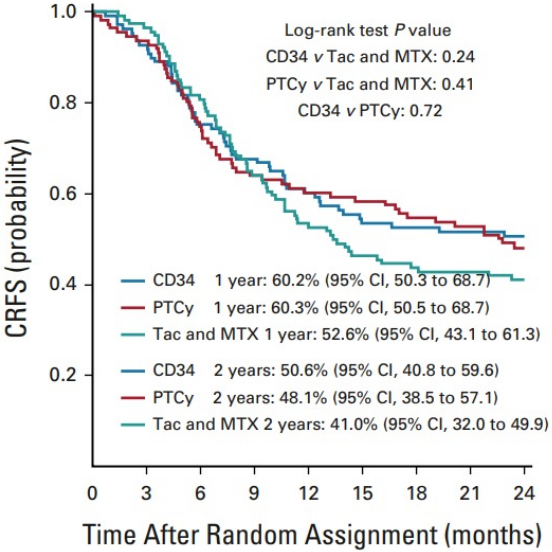


Luznik L et al. ***BBMT 2008***; 14:641-50

CNI-free cGVHD prophylaxis: the BMT CNT 1301 Study

Phase III trial (n=346 AML/MDS low blast, MAC matched donor transplant): 1:1:1 randomization to **ex vivo TCD (PB)** vs **PTCy (BM)** vs **MTX/TAC (BM)**. *Primary endpoint*: 2-year CRFS.

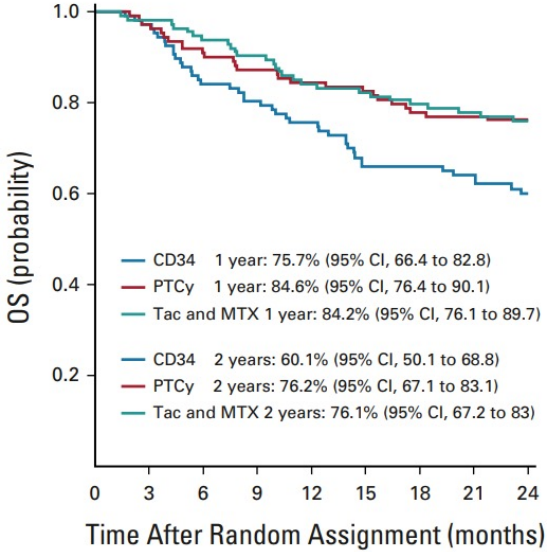
CRFS



No. at risk:

CD34	114	101	81	72	64	56	54	51	49
PTCy	114	104	83	70	66	63	59	57	47
Tac and MTX	118	110	92	73	60	52	49	48	42

OS



. at risk:

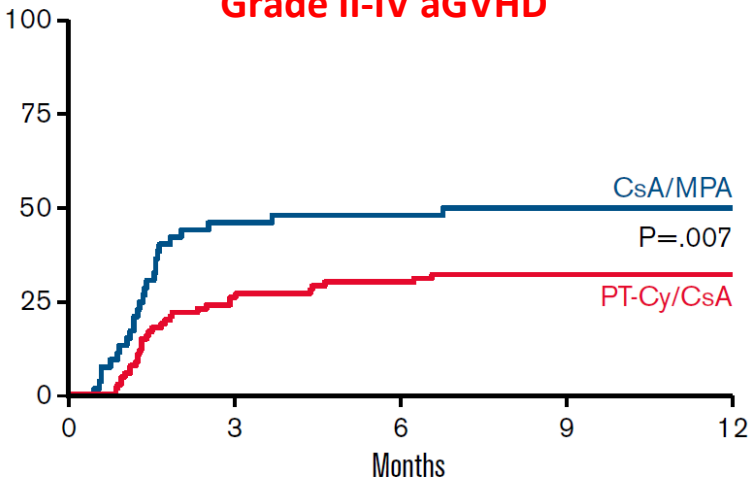
34	114	105	90	85	80	69	68	64	59
Cy	114	108	101	95	92	89	84	83	75
c and MTX	118	112	107	103	95	92	89	87	81

Luznik L et al. ***JCO 2022***; 40:356-68

PTCy in 8/8 matched transplantation: HOVON NL2128 study

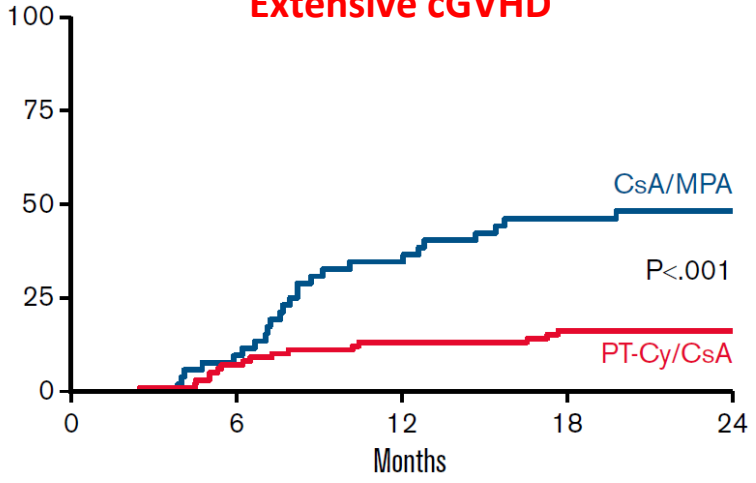
Phase III randomized trial enrolling 151 high-risk patients receiving NMA conditioning randomized 2:1 to **PTCy/CSA (short course)** vs **CSA/MMF**. *Primary endpoint:* non severe GVHD* within 180 days

Grade II-IV aGVHD



At risk:				
CsA/MPA	52	25	20	19	19
PT-Cy/CsA	99	66	59	53	51

Extensive cGVHD



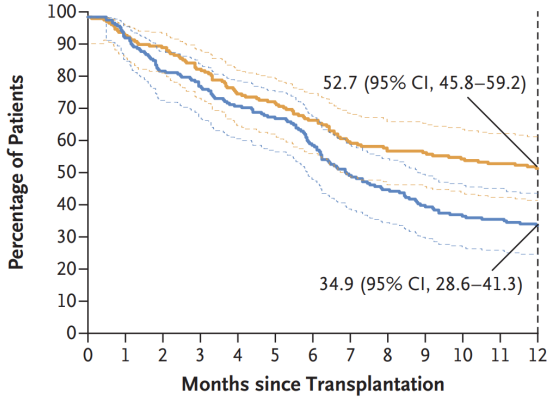
At risk:				
CsA/MPA	52	36	21	15	13
PT-Cy/CsA	99	75	59	52	46

*defined as grade I or grade II aGVHD without gastrointestinal involvement, and cGVHD not requiring systemic treatment)

PTCy in 8/8 or 7/8 matched transplantation: a practice-changing study

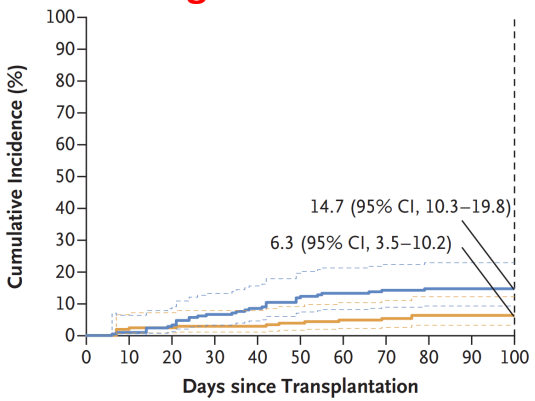
Phase III randomized trial enrolling 431 onco-hematological patients receiving RIC randomized 1:1 to **PTCy/TAC/MMF** vs **MTX/TAC**. *Primary endpoint: 1y* GRFS

GRFS



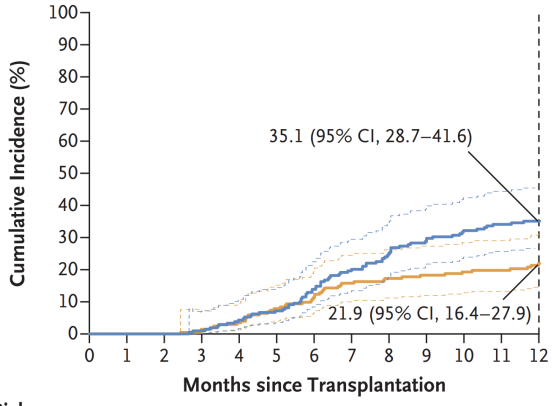
No. at Risk													
Experimental prophylaxis	214	197	187	172	155	149	138	123	117	116	112	109	24
Standard prophylaxis	217	199	174	164	150	142	125	106	97	87	80	78	14

g3-4 aGVHD



No. at Risk													
Experimental prophylaxis	208	203	199	195	192	190	186	185	181	179	176		
Standard prophylaxis	212	209	204	193	187	178	174	172	170	170	169		

Mod-severe cGVHD



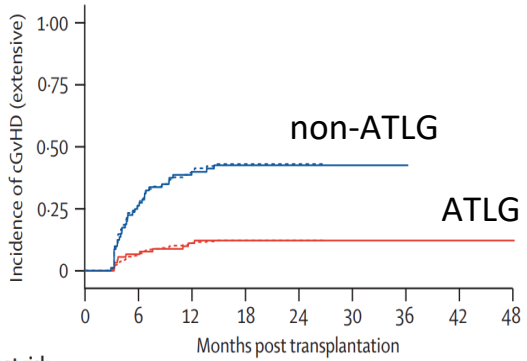
No. at Risk													
Experimental prophylaxis	208	200	195	186	175	164	154	139	131	127	123	121	30
Standard prophylaxis	212	207	198	193	179	169	148	129	116	105	94	88	17

OS, **DFS** and **transplant-related deaths** were **similar** among the two groups

Role of AT(L)G in the prevention of GVHD

Product: **ATLG** (60mg/Kg)
Setting: AL/MDS/CML/MPN
Transplant year: 2003-2007
Setting: MUD

Ext cGVHD

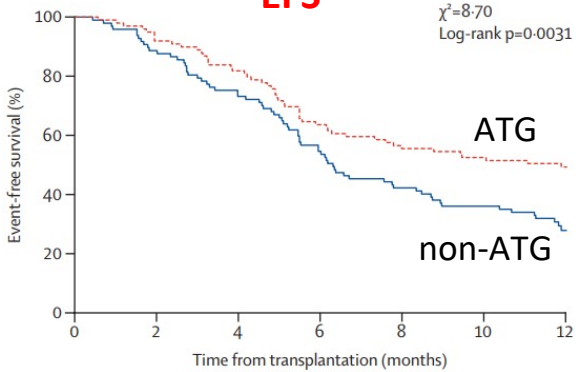


Number at risk

ATG-F	90	70	54	43	28	14	13	4	2
Control	80	43	26	17	8	4	1	0	0

Product: **ATG** (4,5mg/Kg)
Setting: AL/MDS/CML/others
Transplant year: 2010-2013
Setting: MUD/MMUD

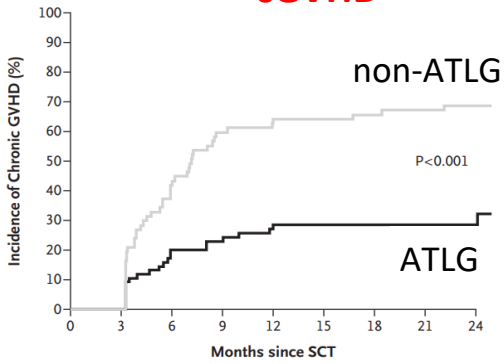
EFS



97	87	73	55	42	36	19
99	94	82	64	54	53	44

Product: **ATLG** (30mg/Kg)
Setting: AML/ALL
Transplant year: 2006-2012
Setting: MRD

cGVHD



No. at Risk

ATG	83	78	55	46	42	40	38	38	25
Non-ATG	72	68	34	23	21	20	18	17	9

No statistically significant **difference in relapse** incidence with the inclusion of AT(L)G compared with standard GVHD prophylaxis

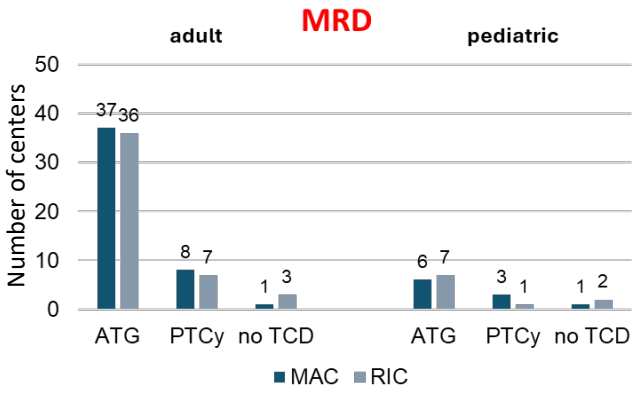
Finke J et al. ***Lancet Oncol 2009***; 10: 855–64; Finke J et al. ***Lancet Haematol 2017***; 4: e293–301; Walker I et al. ***Lancet Oncol 2016***; 17: 164–73; Kroger N et al. ***NEJM 2016***; 374:43-53

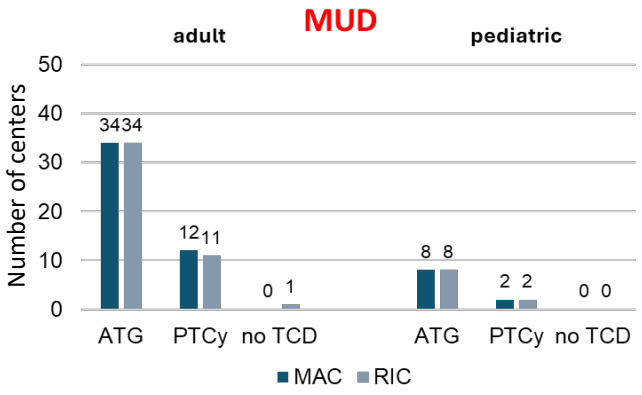
The current EBMT 2024 recommendations on GVHD prophylaxis

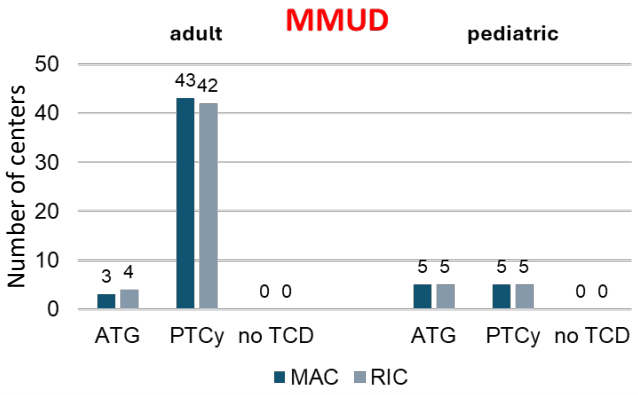
	MRD	MUD	MMUD	MMRD
Recommendations	PTCy should not be preferred to rATG	PTCy or rATG should be preferred over prophylaxis without either agent	PTCy or rATG should be preferred over prophylaxis without either agent	Not covered
Grading	NCCN 2A	NCCN 1	NCCN 2A	-

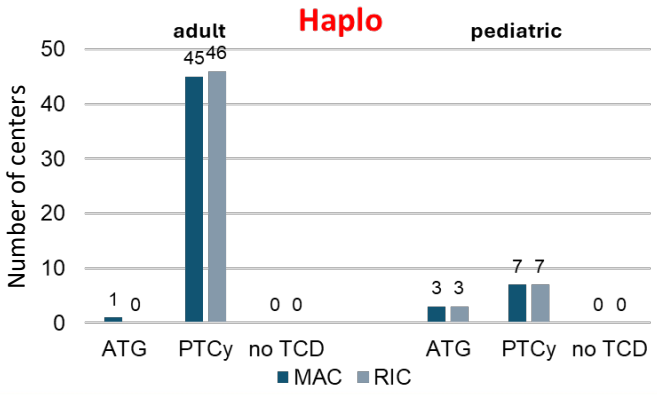
Penack O et al. ***Lancet Haematology 2024***; 11: e147-e159

GVHD prophylaxis in contemporary Italian transplant practice

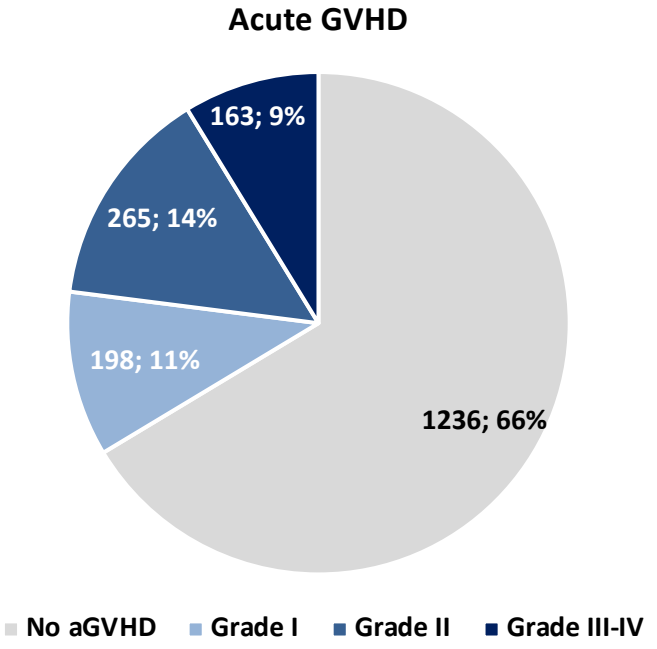


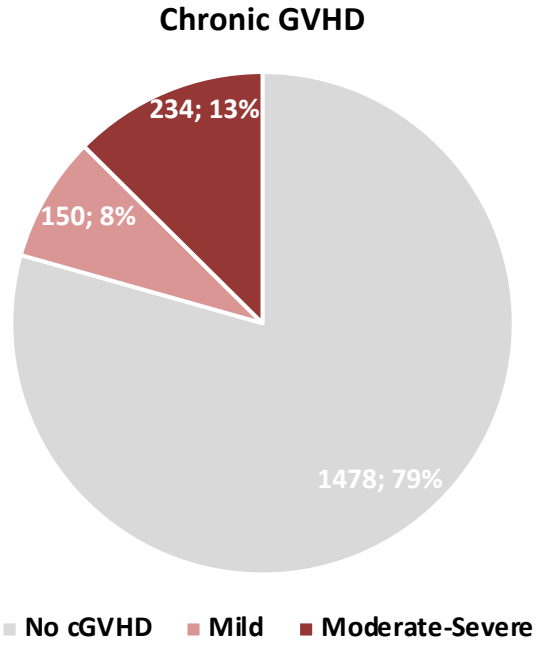






Epidemiology of Acute and Chronic GVHD: GITMO GVHD24 survey





Data on 1862 transplants (**93.0% of 2023 Italian transplant activity**) performed in 56 GITMO Centers (90.3%)

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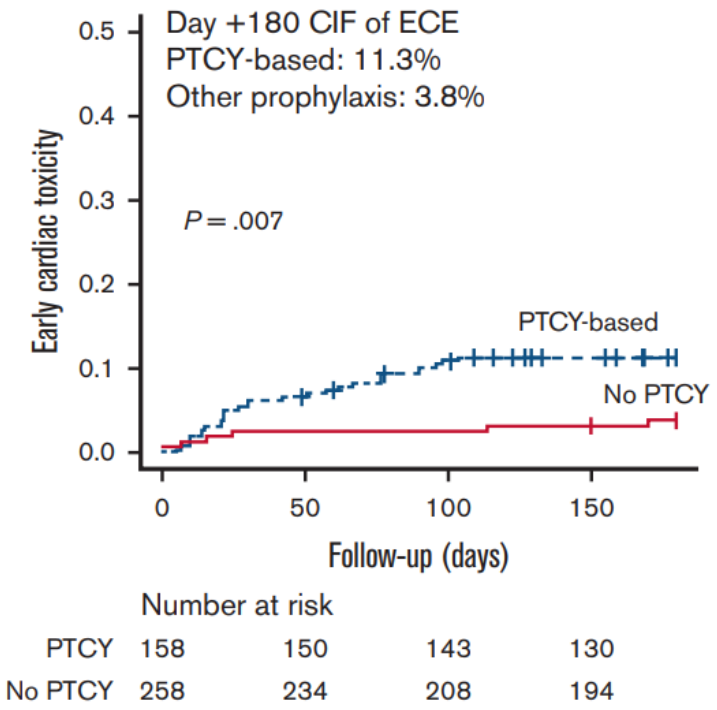
Infectious risk in patients receiving PTCy-based prophylaxis

PTCy effectively **suppresses allo-reactive T cells**, but this benefit comes at the cost of **delayed engraftment and immune reconstitution** and a **higher risk of infections**

Study	Setting	Years	N	Comparison	Bacteria	BSI	CMV	100d-IRM
Goldsmith (2021)	Multicenter CIBMTR	2012-2017	2765	Haplo-PTCy MRD-PTCy Sib-CNI	-	-	42% 37% 23% (*p<0.001*)	-
Chang (2019)	Single center USA	2011-2018	187	Haplo-PTCy Matched (Tac/MTX)	40.9% 41.5%	20% 9.2% (*p=0.06*)	59.1% 23.8% (*p<0.01*)	8.9% 1.4% (*p=0.03*)

Mikulska M et al. ***Blood Reviews 2023***; 62:101092; Goldsmith SR et al. ***Blood 2021***;137(23):3291–305; Chang G et al. ***J Blood Med 2019***;10:135–43

The impact of PTCy on cardiac toxicity



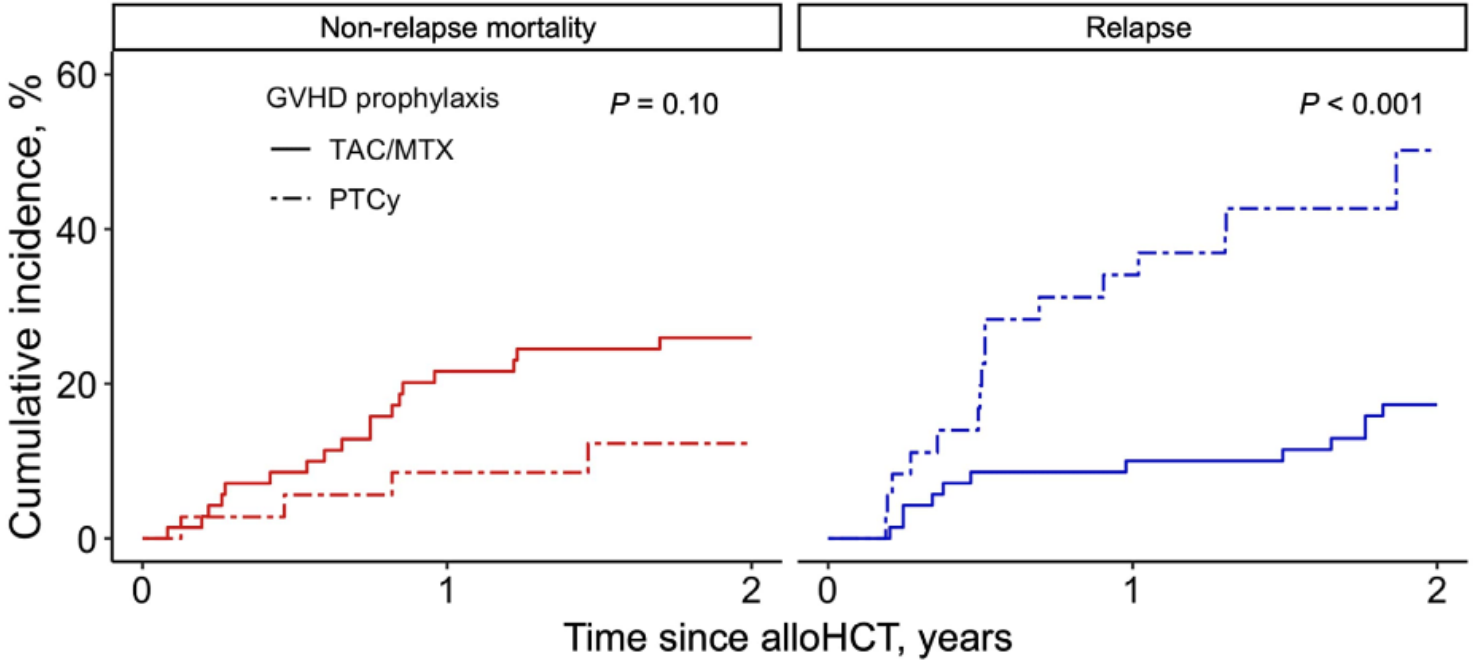
Variable	HR (95% CI)	P Value
PTCy without TBI	3.79 (1.05–13.60)	.041
TBI without PTCy	6.00 (1.24–34.07)	.027
PTCy with TBI	6.98 (2.01–24.24)	.002
Prior history of cardiac disease	5.28 (2.63–10.60)	<.001
Prior treatment with CY	1.66 (0.78–3.52)	.190

History of HTN showed a trend toward a **higher incidence** of cardiac events: HR 1.94 (CI95%: 0.94-4.03, 0.073)

Perez-Valencia AI et al. ***Blood Adv 2022***;7(10):2018–2031

Can the risk of relapse be affected by PTCy?

In **107 Mayo Clinic patients** with **high-risk myeloid neoplasms** undergoing **RIC/NMA allo-HCT**, **PTCy** independently predicted **relapse** (HR 6.7, 95% CI 2.63–17.09; p<0.001).



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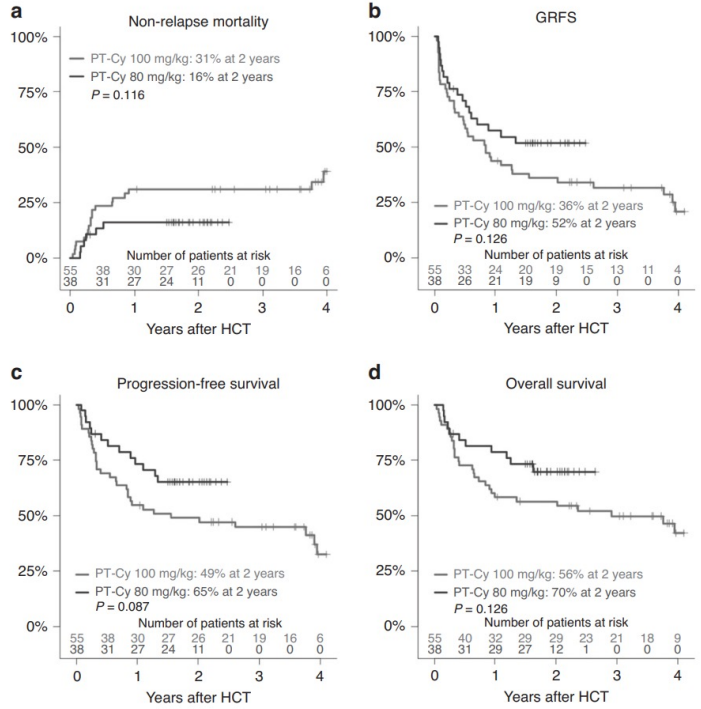
Reduced-dose PTCy for MAC/RIC PBSC-haplo transplants

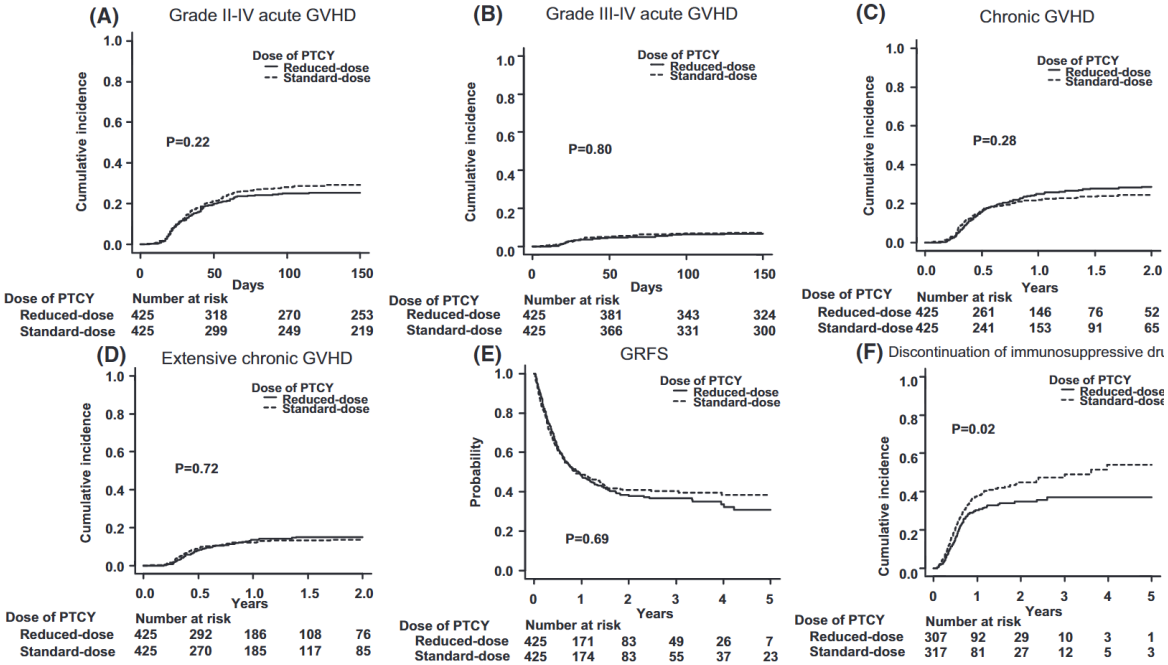
Retrospective study on **93 patients** who received a PBSC-haplo transplant at 3 European Centers

Parameter	PT-Cy 80 mg/kg (n=38)	PT-Cy 100 mg/kg (n=55)	p-value
Age, median (range)	69 (63–77)	68 (65–75)	0.19
Male (%)	50	67	0.15
AML (%)	11 (29)	19 (34)	0.25
CR at transplant (%)	19 (50)	27 (49)	1
High/very high DRI (%)	10 (26)	28 (51)	**0.06**
HCT-CI ≥3 (%)	16 (42)	26 (47)	0.78
Prior cardiac event (%)	6 (16)	10 (18)	0.98
Conditioning regimen			0.16
NMA TBI-based (%)	24 (63)	38 (69)	
TBF (%)	11 (29)	8 (15)	
Sequential (%)	3 (8)	9 (16)	
GVHD prophylaxis			
Cyclosporine + MMF (%)	100	100	1
ATG (%)	19 (50)	15 (27)	**0.04**



Comparison of different PTCy doses by propensity score matching

Japanese registry study including **1507 haplo transplant** recipients (2010–2011) treated with **PTCy 100 or 80 mg/kg**



Long-term transplant **outcomes** were similar between the two groups in terms of **OS**, **NRM,** and **relapse**.

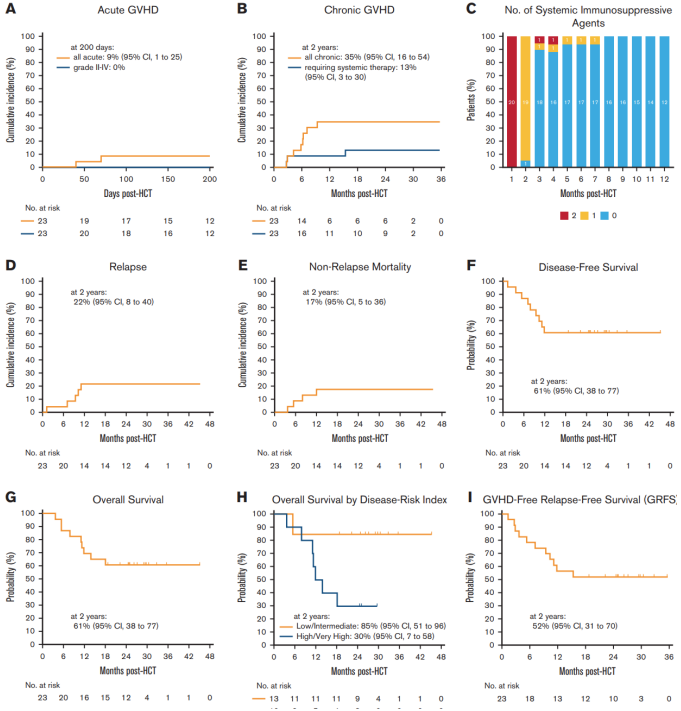
However, **faster neutrophil engraftment** and **lower rates of bacterial infections** were observed with the lower PTCy dose

The PS was calculated using the following variables: age, disease risk, HCT-CI, conditioning regimen intensity and PS

Intermediate-dose PTCy for MAC haplo BM transplants

Phase 1/2 NIH trial to reduce PTCY dose with primary endpoint grade III-IV aGVHD

Parameter	PTCy 50 mg/kg d+3/+4	PTCy 25 mg/kg d+3/+4	PTCy 25 mg/kg d+4
N (patients)	5	23	7
aGVHD grade II–IV	9%	0%	↑
cGVHD	~27%	13%	↑
ANC Engraftment	19 days	14 days	ND
Immune recovery	Slower	Faster	ND
Relapse (2y)	~18%	22%	ND
NRM (2y)	~18%	17%	ND
GRFS (2y)	~45%	52%	ND

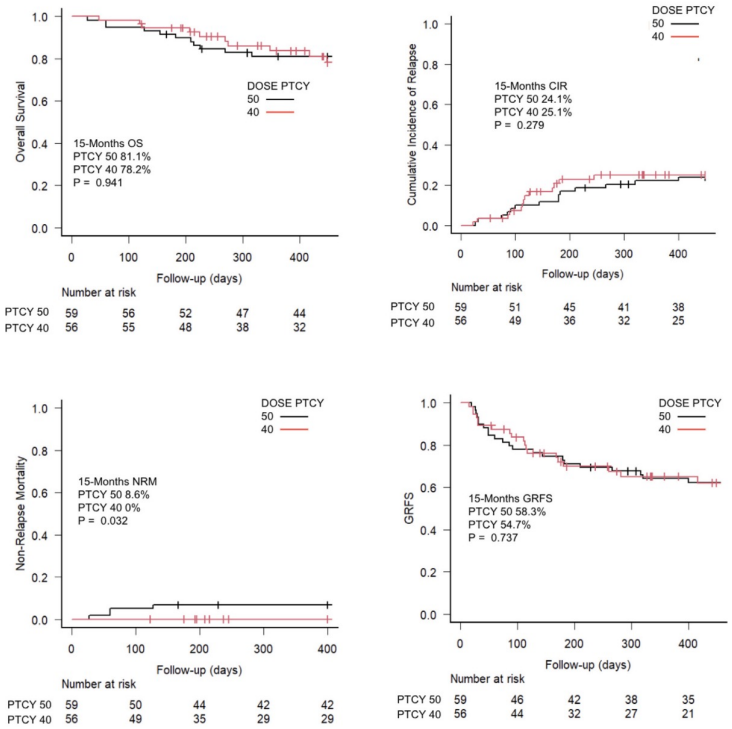


Hyder MA et al. ***Blood Adv 2025***; 9:2553-69

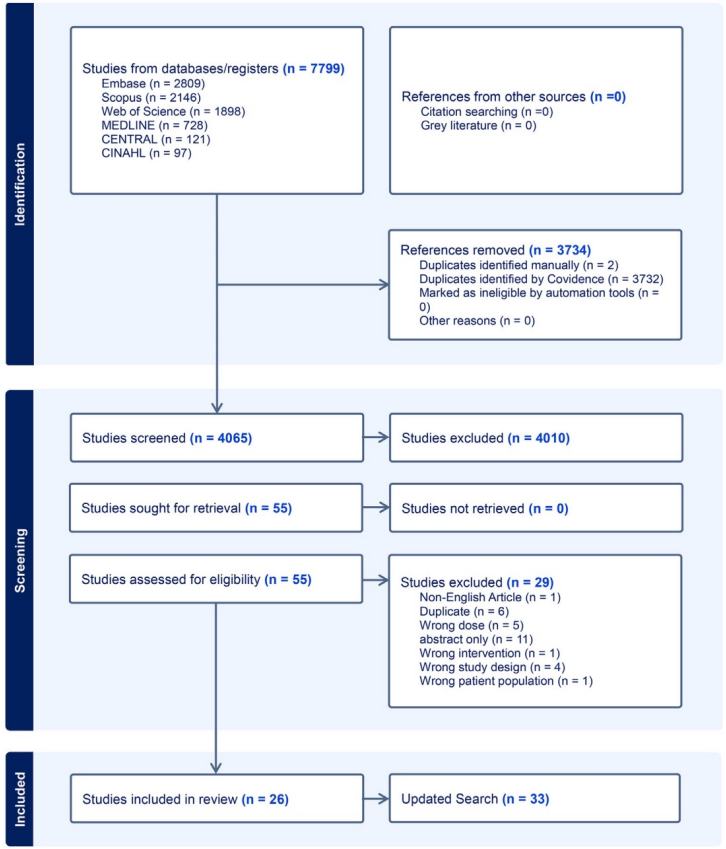
Reducing PTCy dose is matched transplant is feasible

Spanish retrospective study on **115 patients** who underwent transplant with **10/10 HLA-matched donors** with **PTCy**

Parameter	PTCy 40 (N=56)	PTCy 50 (N=59)	p value
Age, median (range)	57 (18–74)	55 (23–70)	.515
Age >65 (%)	23.2	22.0	.647
Male (%)	64.3	62.7	.861
AML (%)	41.1	33.9	.637
Hypertension (%)	37.5	27.1	.460
Diabetes (%)	17.9	8.5	.354
Cardiac history (%)	8.9	6.8	.792
KPS <90% (%)	21.4	32.2	.193
HCT-CI >3 (%)	25.0	32.2	.429
Myeloablative (%)	41.1	47.5	.491
MUD donor (%)	53.6	67.8	–
CD34+ dose (×10⁶/kg)	6.6	6.01	**.019**
Letermovir (%)	**83.6**	**19.6**	**<.001**
G-CSF (%)	**88.9**	**0**	**<.001**
Follow-up (months)	**14.6**	**34.9**	**<.001**



Review of the available studies on dose reduced PTCy in haplo



👉 **1. Feasibility**

Low-dose PTCy is feasible and likely maintains efficacy for aGVHD prevention

👉 **2. Uncertainty**

Impact on cGVHD, infections and survival remains unclear

👉 **3. Heterogeneity problem**

“Low-dose” is not a defined entity

👉 **4. Future**

Need for randomized trials and patient selection

Shafqat A et al. ***TCT 2026***; 32: 320-336

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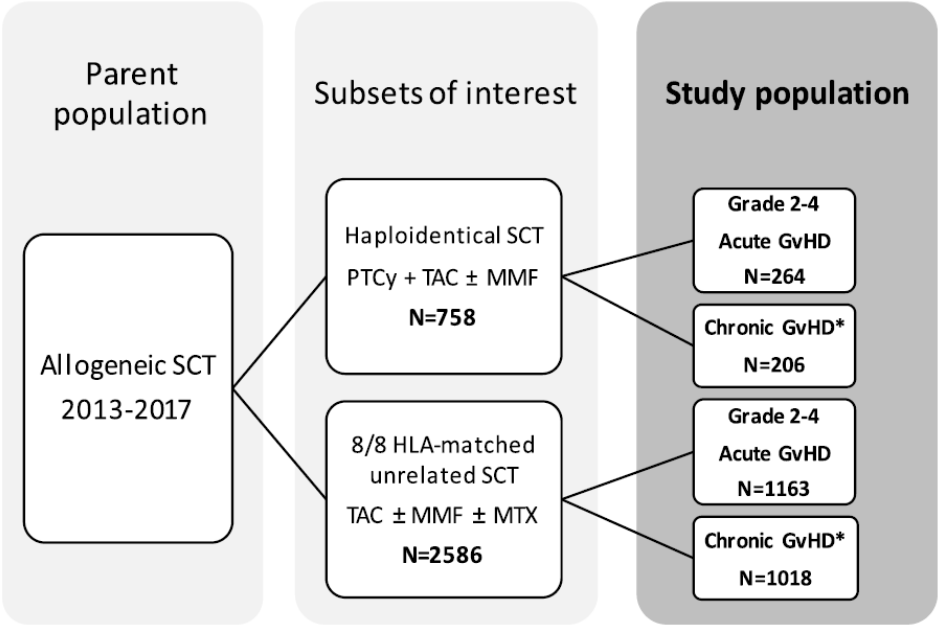
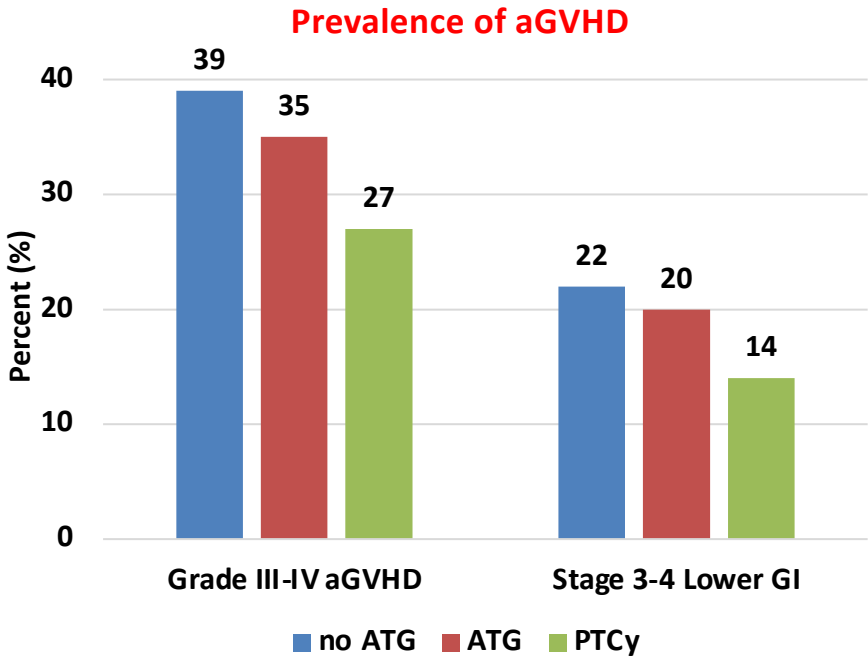
Combining PTCy with ATG may be complementary

CIBMTR study evaluating the impact of different **GVHD prophylaxis** strategies on **GVHD manifestations**

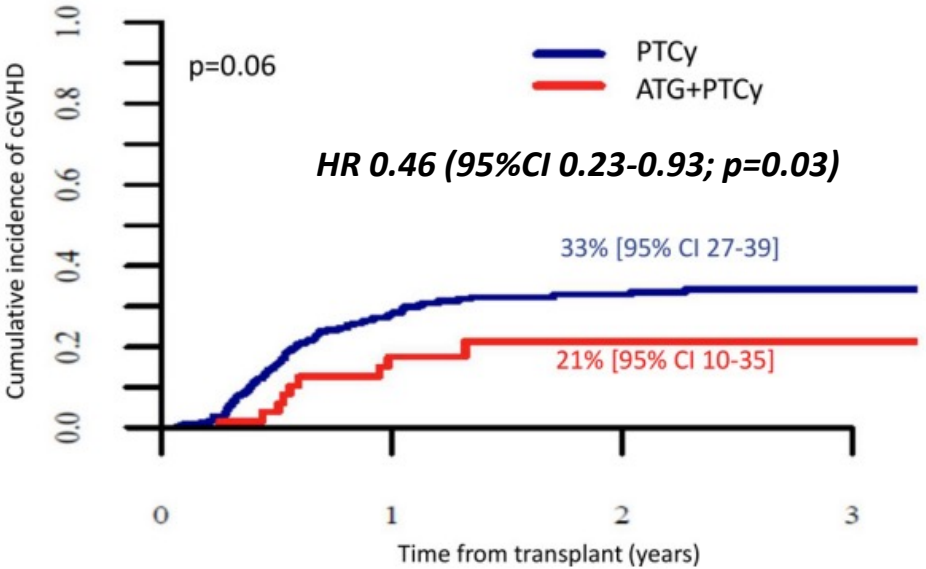




PTCy + ATG vs PTCy alone in haploidentical transplantation for AML

Characteristic	PTCy (N = 374)	ATG+PTCy (N = 67)	P Value
Patient age, yr, median	56 (18–75)	56 (26–74)	.40
Sex, females, n (%)	150 (40)	34 (51)	.10
Secondary AML, n (%)	80 (21)	10 (15)	.23
Unfavorable cytogenetics, n (%)	89 (24)	17 (25)	
KPS <90, n (%)	80 (21)	11 (16)	.35
Months from dx to allo-HCT	5 (2–24)	4.6 (2–23)	.03
ATG total dose, mg/kg, n (%)			
2.5	–	22	
5	–	28	
7.5–10	–	10	
40	–	1	
Missing	–	6	
Conditioning regimen, n (%)			.54
MAC	160 (43)	26 (39)	
RIC	214 (57)	41 (61)	
Follow-up, mo, median (range)	19 (9–36)	15 (4–36)	.59

An ALWP study on **441 adult patients** with **AML in CR1** submitted to **haplo-transplant** from 2011 to 2019

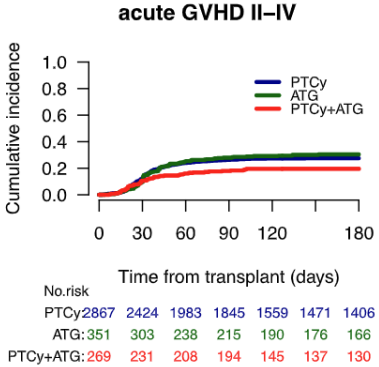


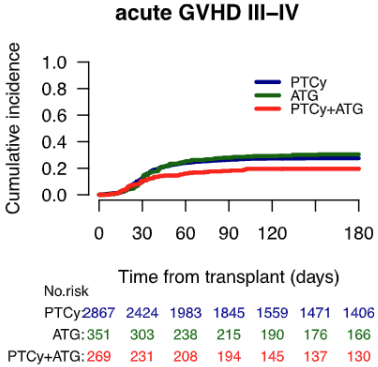
No between-group differences in the other outcomes seen

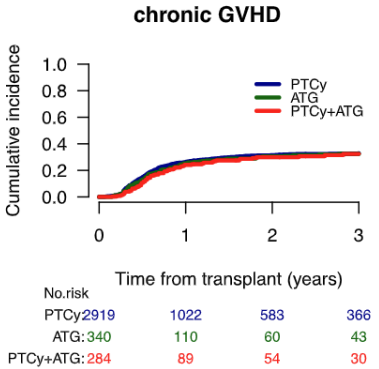
PTCy vs ATG vs combination in haploidentical transplantation for AML

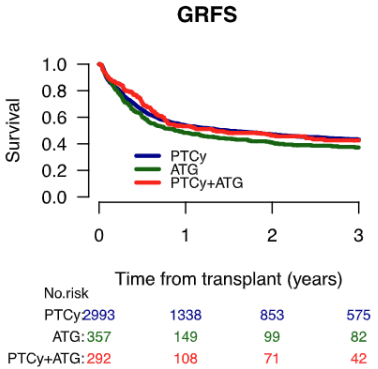
An ALWP study on **441 adult patients** with **AML in CR** submitted to **haplo-transplant** from 2007 to 2021

Features	PTCy (n=2999)	ATG (n=358)	PTCy + ATG (n=292)	p
Year of transplant	2018	2015	2018	<.0001
Donor age, years	36.5	37.5	36.4	.76
Donor sex				.1
Male	1861 (62.2%)	213 (59.8%)	197 (67.7%)	
Donor CMV				.22
Positive	1858 (63.4%)	216 (64.7%)	168 (58.5%)	
Conditioning intensity				.005
MAC	1448 (48.3%)	205 (57.3%)	139 (47.6%)	
RIC	1551 (51.7%)	153 (42.7%)	153 (52.4%)	
Stem cell source				
BM	925 (30.9%)	157 (43.9%)	55 (18.8%)	<.001
PB	2074 (69.1%)	201 (56.1%)	237 (81.2%)	

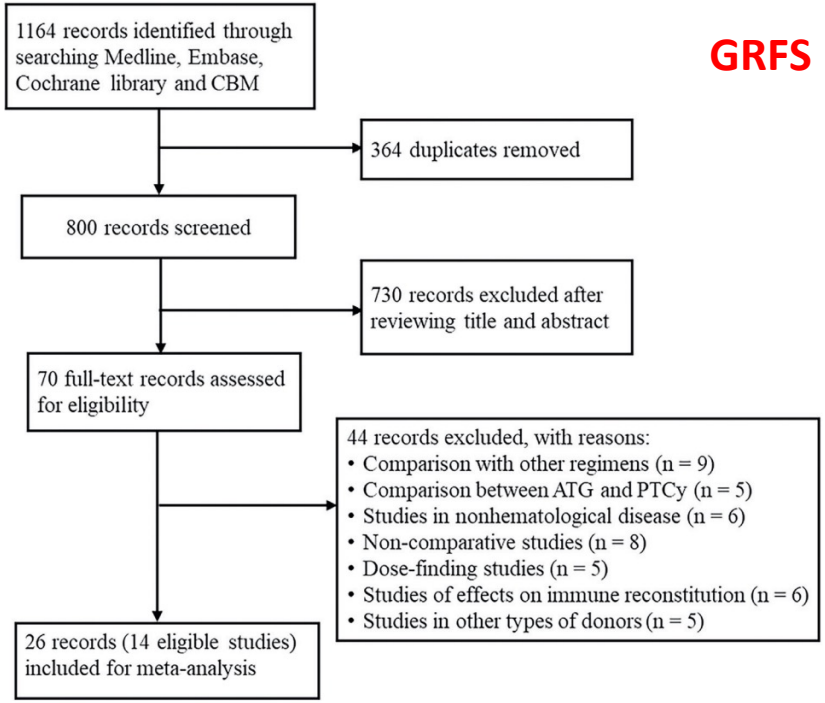




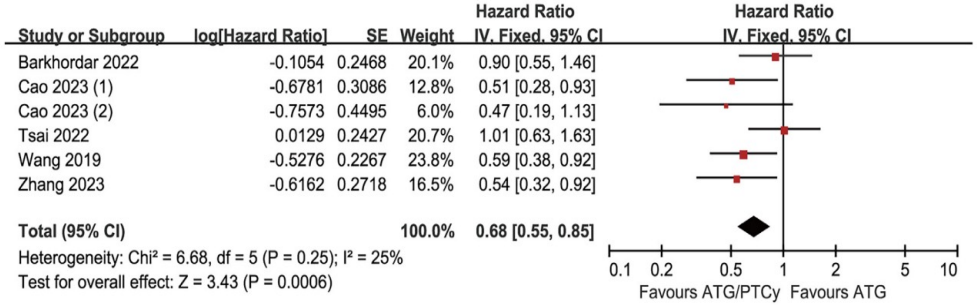


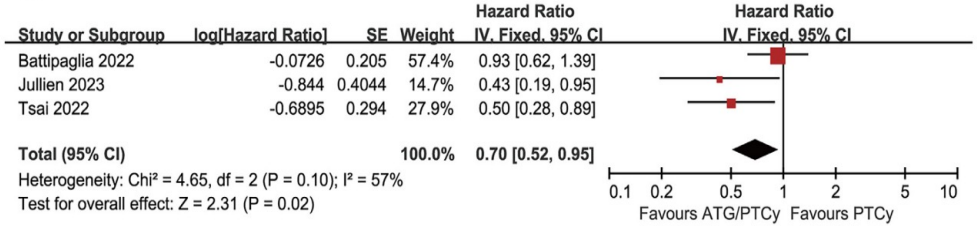


Meta-analysis of studies on combination of ATG and PTCy



GRFS





Meta-analysis results suggest that **ATG + PTCy** is associated with significantly **lower rates of grade II–IV acute GVHD**, with **similar relapse** risk and **improved overall survival and GRFS**.

Conclusions

🧬 **PTCy is a cornerstone** of modern GVHD prophylaxis, widely adopted across transplant settings, while ATG still plays a major role in current Italian practice, particularly in MUD and MRD.

⚠️ However, **standard PTCy is not optimal**, with delayed immune reconstitution leading to increased infections, along with cardiotoxicity concerns and a possible impact on relapse in high-risk disease

⚙️ **Dose optimization is feasible**: reduced-dose PTCy may preserve efficacy and improve engraftment and toxicity profile, although it remains not standardized

🔗 **Combination strategies (PTCy + ATG)** are biologically sound and associated with reduced GVHD and encouraging signals in GRFS and survival

❓ **Key gaps remain**, including optimal dose, product and schedule, patient selection, and the long-term impact on chronic GVHD, relapse, and immune recovery, with evidence still mainly retrospective

🚀 **Future direction**: moving beyond a one-size-fits-all approach toward personalized, biology-driven prophylaxis, shifting from GVHD prevention to immune modulation

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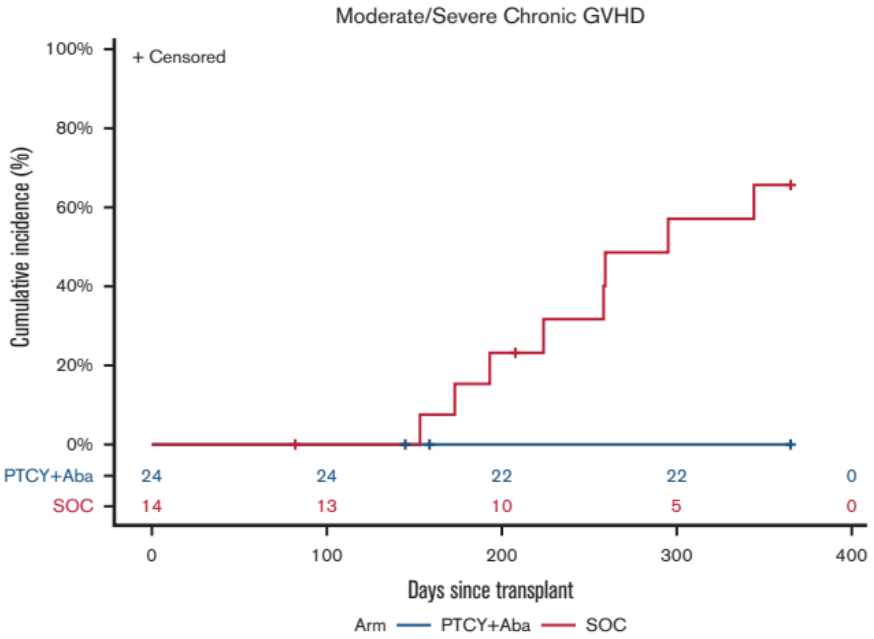
Back up

PTCy plus Aba in 8/8 matched donor

Phase II randomized trial on 43 patients with heamtological malignancies TAC/MTX vs PTCy+Aba as GVHD prophylaxis in 8/8 MUD/MRD. *Primary endpoint*: moderate-severe GVHD

Variable	PTCy + Aba (n=25)	SOC (n=15)
Sex, Male (%)	14	11
Age (mean ± SD), years	48 (±15.5)	47 (±16.5)
Disease		
ALL/AML	17	12
MDS/MPN	8	2
Lymphoma	0	1
Disease status		
CR	17	14
SD	8	1
Conditioning		
TBI/Cy	6	4
Flu/Bu4	13	6
Flu/Mel	6	5
Donor		
MRD/MUD	8/17	6/9



No differences on aGVHD and other transplant-related outcomes

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