Nuove strategie di prevenzione della GvHD: personalizzazione della profilassi in base al donatore e al razionale clinico”

Massimo Martino

Direttore Ematologia e CTMO, GOM, BMM; Reggio Calabria
Presidente GITMO



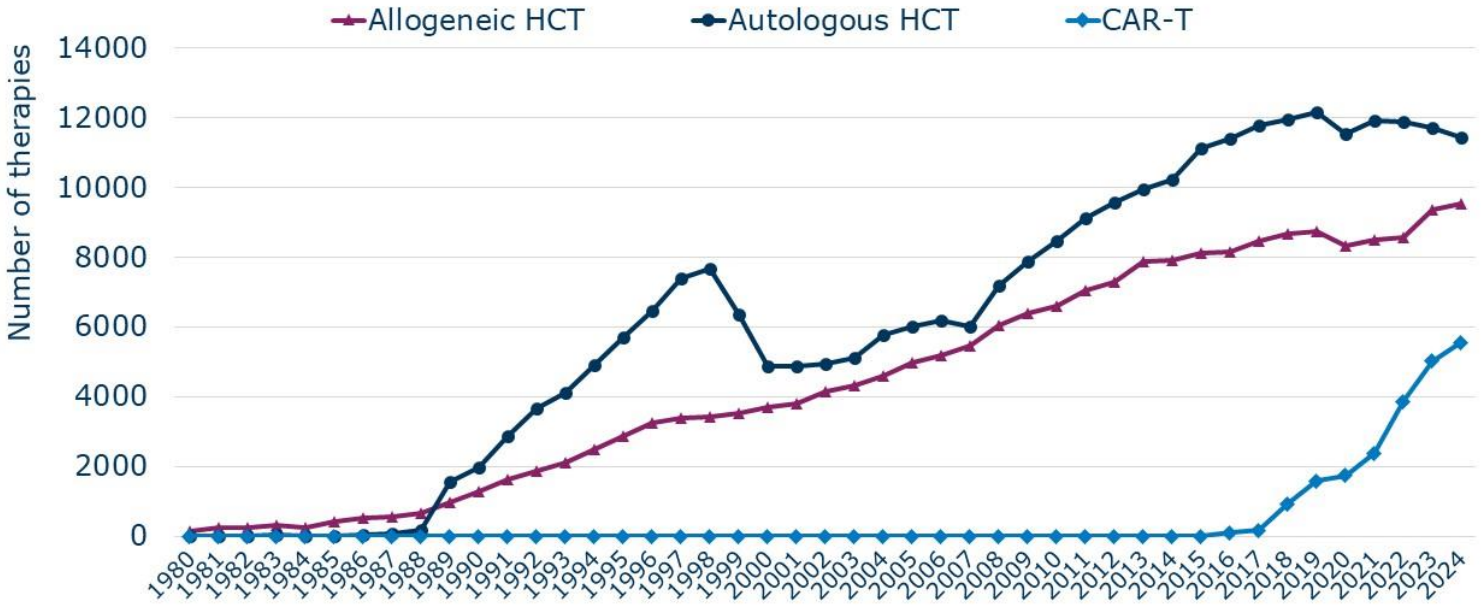
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LECCE, 12-14 ottobre 2026
HILTON GARDEN INN

Disclosures of Massimo Martino

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Medac	x				x	x	
Kite/Gilead					x	x	
BMS					x	x	
Novartis					x	x	
Jansenn					x	x	
AMGEN					x	x	
JAZZ					x		
Takeda						x	
Therakos					x		
Vertex						x	
Pfizer					x	x	
Abbvie					x		
Roche					x	x	
Astellas					x	x	
Astra Zeneca					x	x	

First cellular therapies in US, per year, 1980-2024



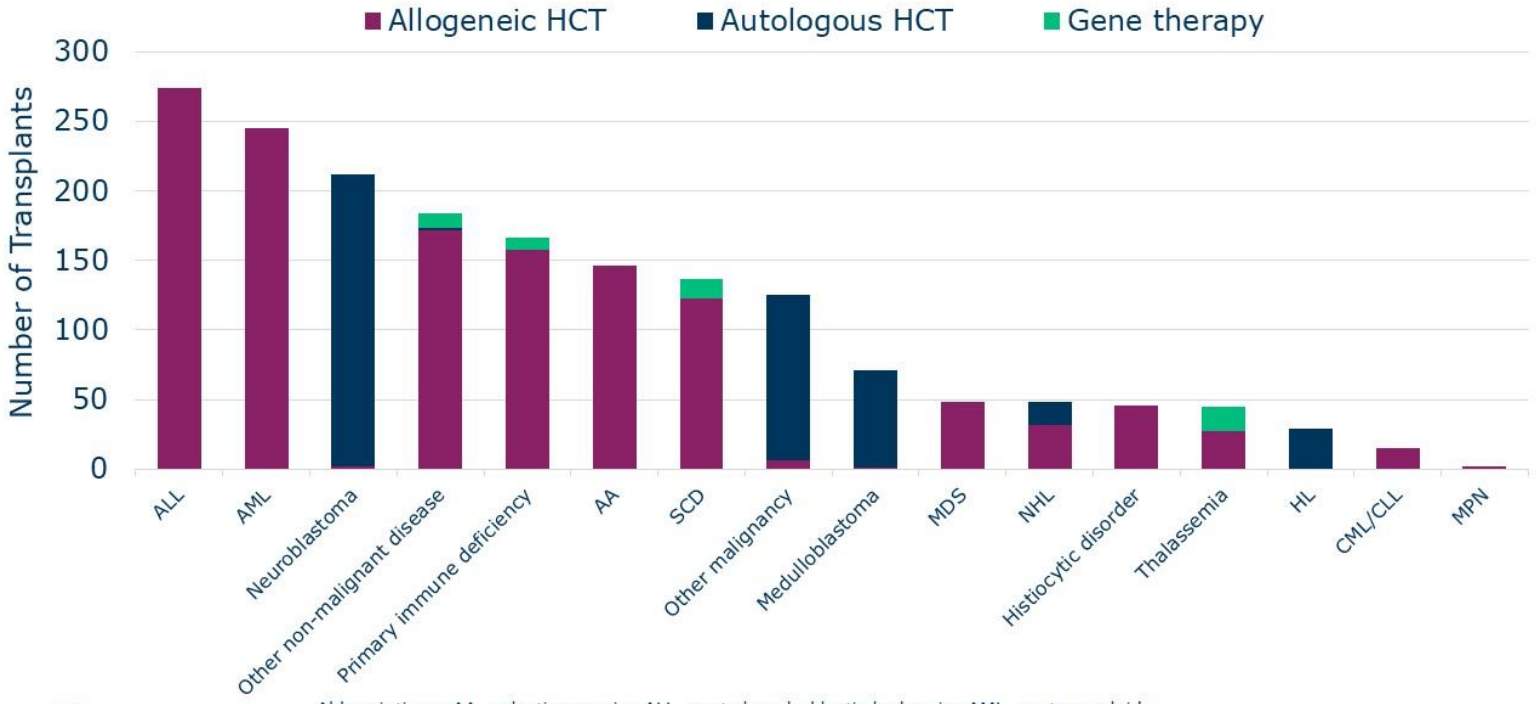
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A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Abbreviations: CAR-T, chimeric antigen receptor T cell; HCT, hematopoietic cell transplantation.

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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025**

HCTs by indication, US, pediatrics, 2024



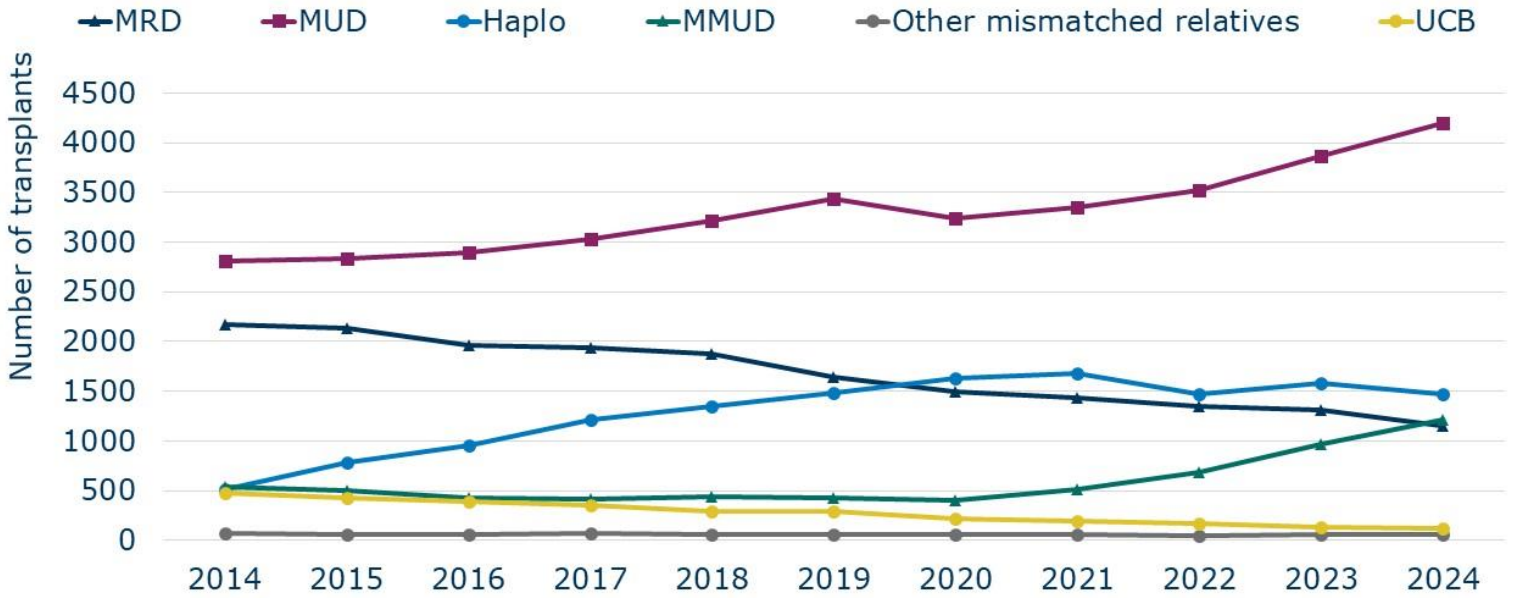
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Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML/CLL, chronic myeloid leukemia/chronic lymphocytic leukemia; HCT, hematopoietic cell transplantation; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; SCD, sickle cell disease.

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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025**

First alloHCTs in US, by donor type, 2014-2024, adults



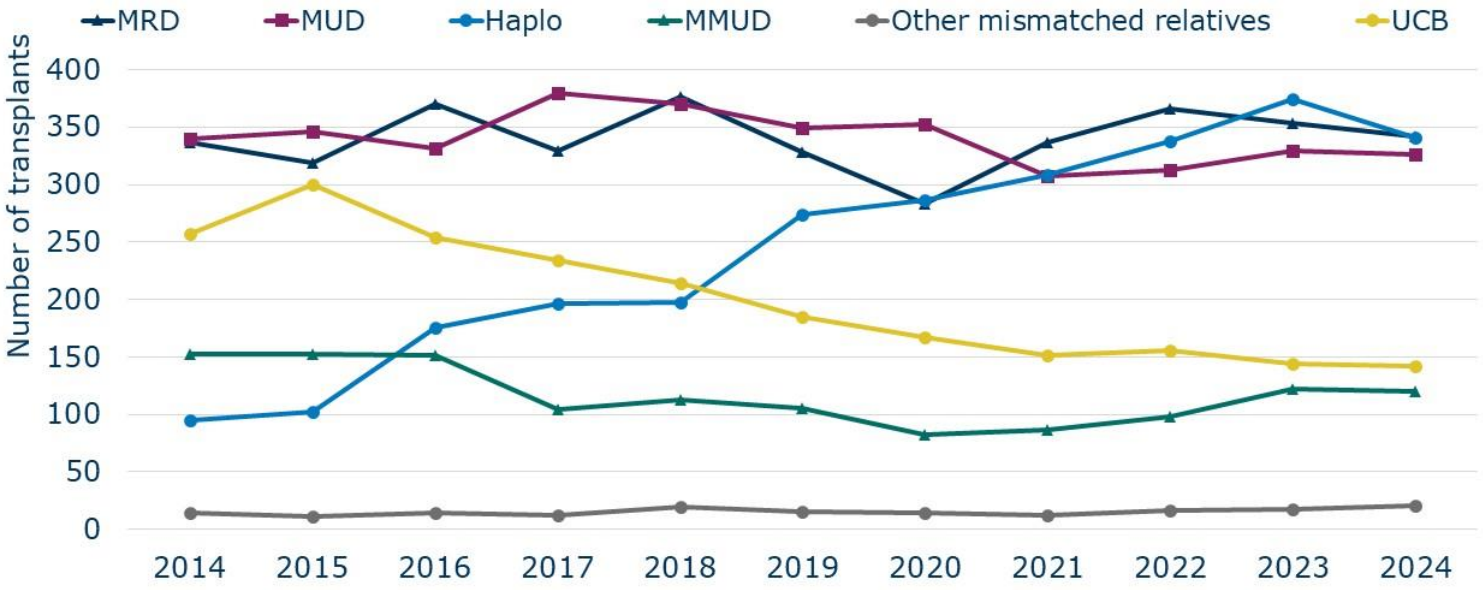
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A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; haplo, haploidentical; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; UCB, umbilical cord blood.

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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025**

First alloHCTs in US, by donor type, 2014-2024, pediatrics

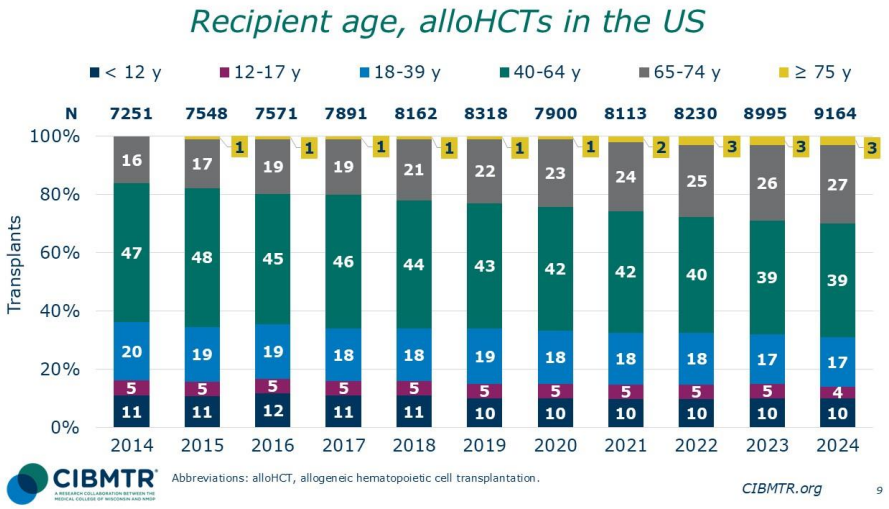


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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025**



Anno	N	< 12 a	12–17 a	18–39 a	40–64 a	65–74 a	≥ 75 a
2014	7251	798 (11%)	363 (5%)	1450 (20%)	3408 (47%)	1160 (16%)	n.d. (<1%)
2015	7548	830 (11%)	377 (5%)	1434 (19%)	3623 (48%)	1283 (17%)	75 (1%)
2016	7571	909 (12%)	379 (5%)	1438 (19%)	3407 (45%)	1438 (19%)	76 (1%)
2017	7891	868 (11%)	395 (5%)	1420 (18%)	3630 (46%)	1499 (19%)	79 (1%)
2018	8162	898 (11%)	408 (5%)	1469 (18%)	3591 (44%)	1714 (21%)	82 (1%)
2019	8318	832 (10%)	416 (5%)	1580 (19%)	3577 (43%)	1830 (22%)	83 (1%)
2020	7900	790 (10%)	395 (5%)	1422 (18%)	3318 (42%)	1817 (23%)	79 (1%)
2021	8113	811 (10%)	406 (5%)	1460 (18%)	3407 (42%)	1947 (24%)	162 (2%)
2022	8230	823 (10%)	412 (5%)	1481 (18%)	3292 (40%)	2058 (25%)	247 (3%)
2023	8995	900 (10%)	450 (5%)	1529 (17%)	3508 (39%)	2339 (26%)	270 (3%)
2024	9164	916 (10%)	367 (4%)	1558 (17%)	3574 (39%)	2474 (27%)	275 (3%)

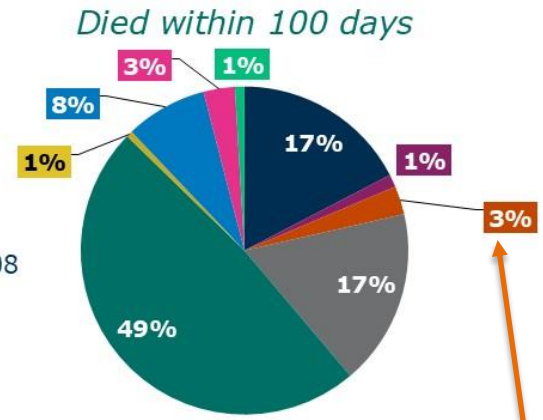
Considerando insieme le due fasce sotto i 18 anni, i trapianti pediatrici sono rimasti stabili in numero assoluto (circa 1160 nel 2014, circa 1280 nel 2024). Il loro peso sul totale è però sceso dal 16% al 14%. La crescita complessiva viene quasi tutta dagli over 65, passati da circa 1160 a circa 2750 trapianti l'anno.

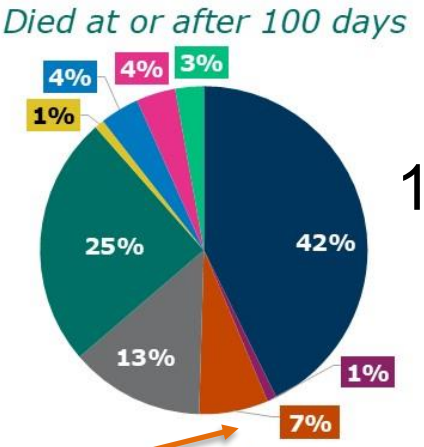
Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025 - modificato**

Causes of death after alloHCT, pediatrics, US, 2020-2024, all donor sources

5,1%

Age < 18 years
Total transplants = 6308





12,5%

■ Primary disease ■ Graft rejection ■ GVHD ■ Hemorrhage ■ Infection
■ Secondary malignancy ■ Organ failure ■ Other ■ Not reported

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Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; GVHD, graft-versus-host disease.

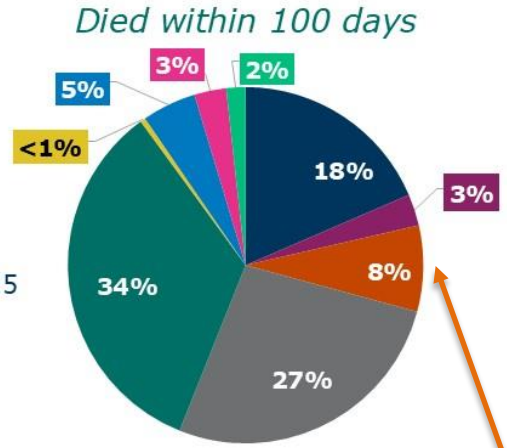
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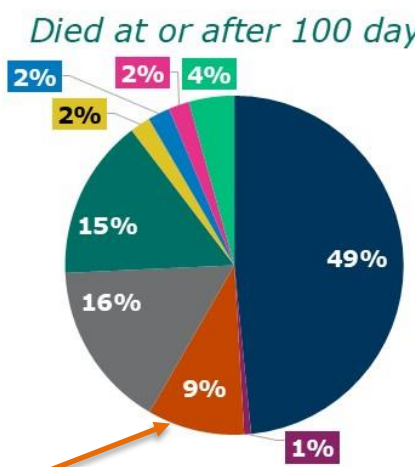
Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025**

Causes of death after alloHCT, adults, US, 2020-2024, all donor sources

7,9%

Age ≥ 18 years
Total transplants = 37655





26,6%

Primary disease | Graft rejection | GVHD | Hemorrhage | Infection
Secondary malignancy | Organ failure | Other | Not reported

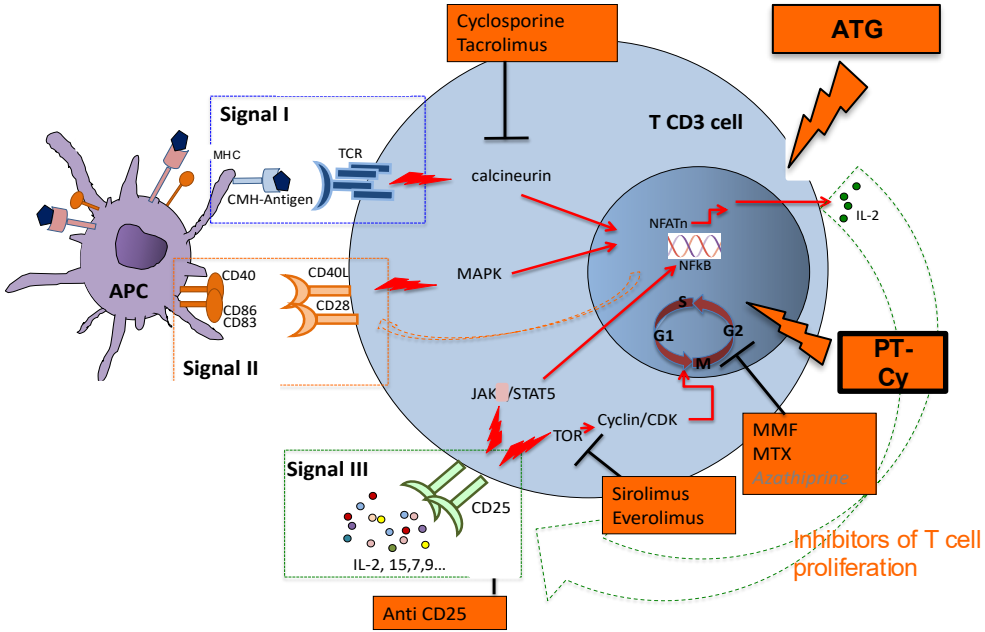
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Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; GVHD, graft-versus-host disease.

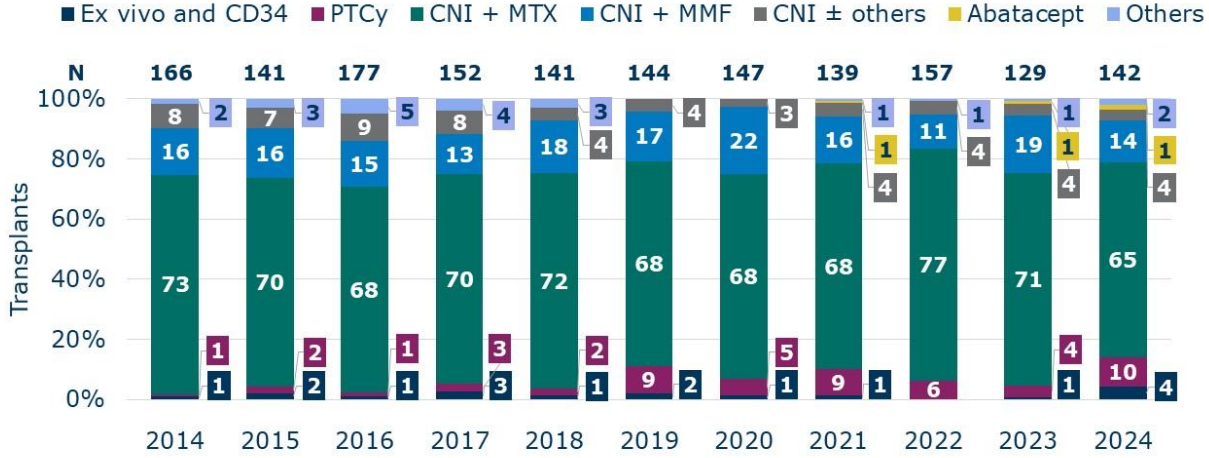
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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025**

Prevention of GvHD: therapeutic targets



GVHD prophylaxis of MRD HCTs, US, 2014-2024, pediatrics, malignant diseases



CNI-based prophylaxis remains the standard; PTCy is emerging only slowly

65–77%
CNI + MTX
Dominant every year; lowest share of the decade in 2024 (65%)

11–22%
CNI + MMF
Main alternative; peaked in 2019–2020, 14% in 2024

1% → 10%
PTCy
Negligible until 2018; 4–10% since 2019, highest in 2024

Take-home: ex vivo/CD34 selection (1–4%) and abatacept (~1% since 2021) remain niche. Unlike adult practice, the shift to PTCy in pediatric MRD transplants is modest, reflecting good MRD outcomes in children, late-effect concerns and limited pediatric data.

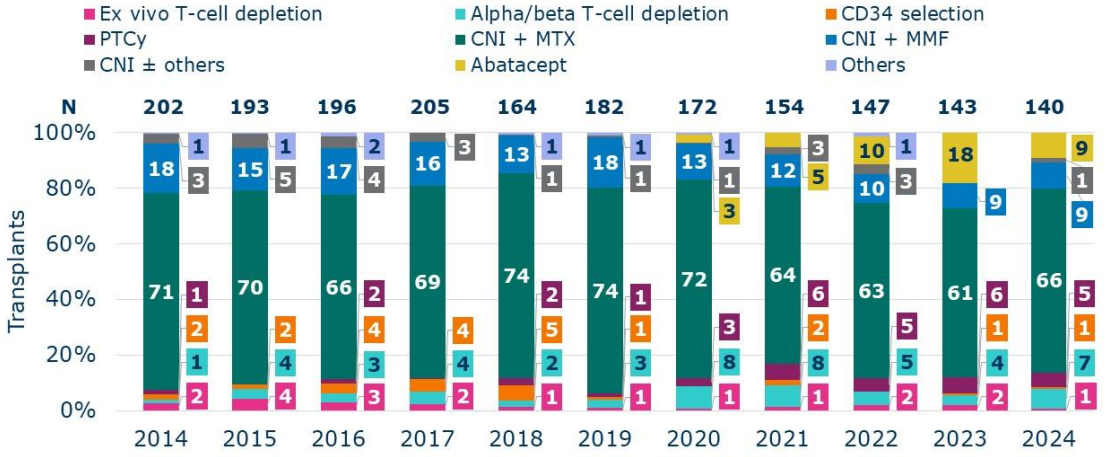
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A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Abbreviations: CNI, calcineurin inhibitor; ex vivo and CD34, ex vivo T cell depletion and CD34-selected grafts; HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; MRD, matched related donor; MTX, methotrexate; PTCy, post-transplant cyclophosphamide.

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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025 – modified**

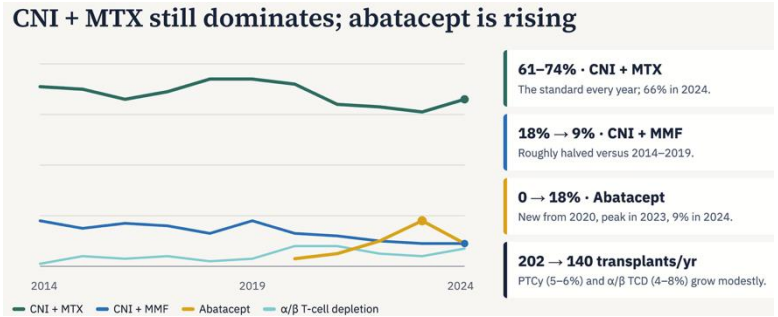
GVHD prophylaxis of MUD HCTs, US, 2014-2024, pediatrics, malignant diseases



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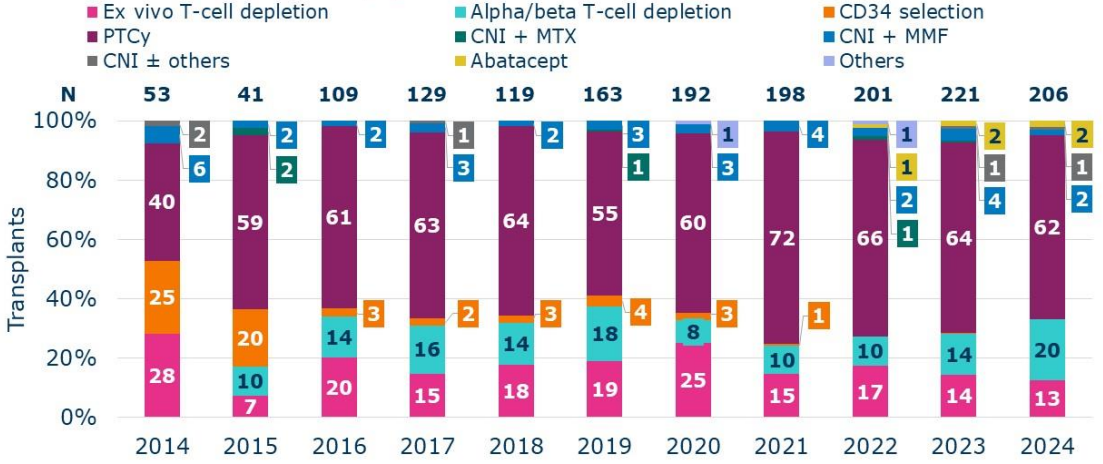
Abbreviations: CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; MMF, mycophenolate mofetil; MTX, methotrexate; MUD, matched unrelated donor; PTCy, post-transplant cyclophosphamide.

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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025 – modified**

GVHD prophylaxis of haplo HCTs, US, 2014-2024, pediatrics, malignant diseases



PTCy dominates

40% in 2014 → 55–72% since 2015; 62% in 2024

α/β depletion rising

From 0% to ~20% of haplo HCTs in 2023–2024

CD34 selection gone

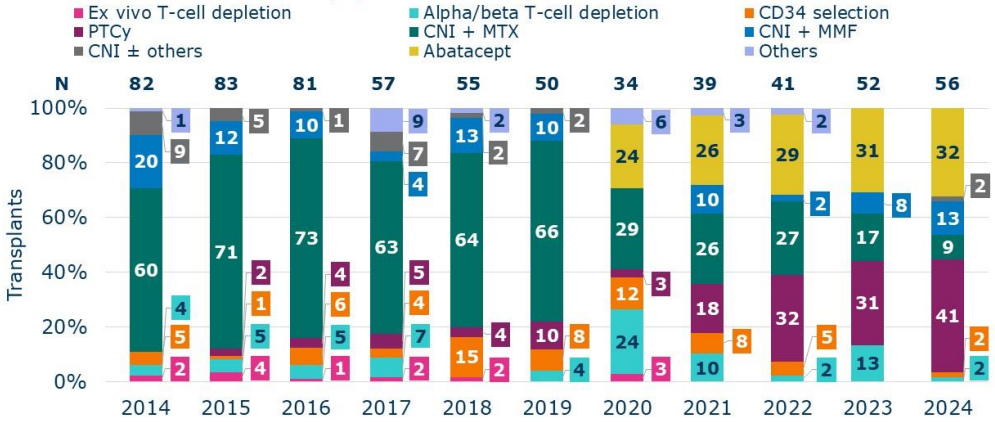
25% in 2014, ≤4% by 2016, absent after 2019

Abbreviations: CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; haplo, haploidentical donor; HCT, hematopoietic cell transplantation; MMF, mycophenolate mofetil; MTX, methotrexate; PTCy, post-transplant cyclophosphamide.

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Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025 – modified**

GVHD prophylaxis of MMUD HCTs, US, 2014-2024, pediatrics, malignant diseases



Abbreviations: CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; MMF, mycophenolate mofetil; MMUD, mismatched unrelated donor; MTX, methotrexate; PTCy, post-transplant cyclophosphamide.

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CNI + MTX: sharp decline

~60–73% of transplants in 2014–2019; a small minority by 2024

PTCy: now most common

Rare before 2018; ~40% of transplants in 2024

Abatacept: rapid uptake

Appears around 2020; ~25–32% in recent years

Volume: dip, then recovery

~80/year (2014–16) → 34 (2020) → 52–56 (2023–24)

Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. **Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025 – modified**

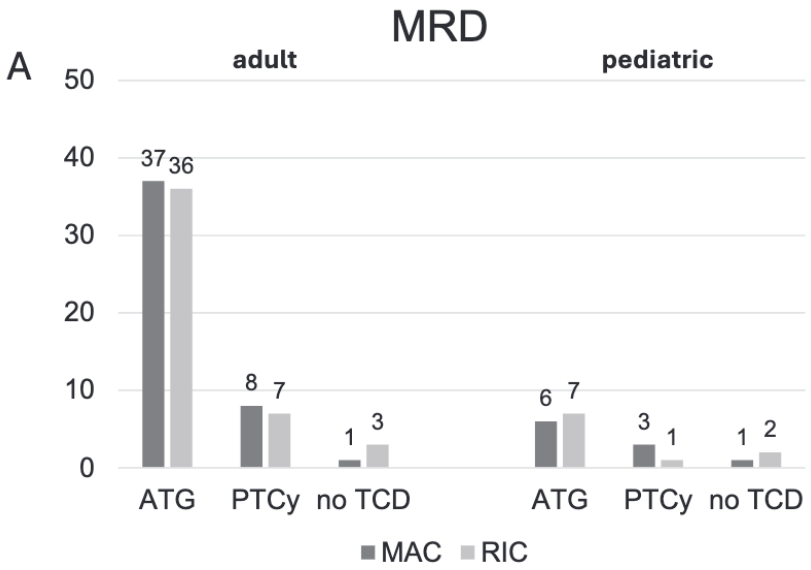
Trends in GVHD Epidemiology, Prophylaxis and Management: The Gruppo Italiano per il Trapianto di Midollo Osseo, Cellule Staminali Emopoietiche e Terapia Cellulare (GITMO) GVHD24 Study

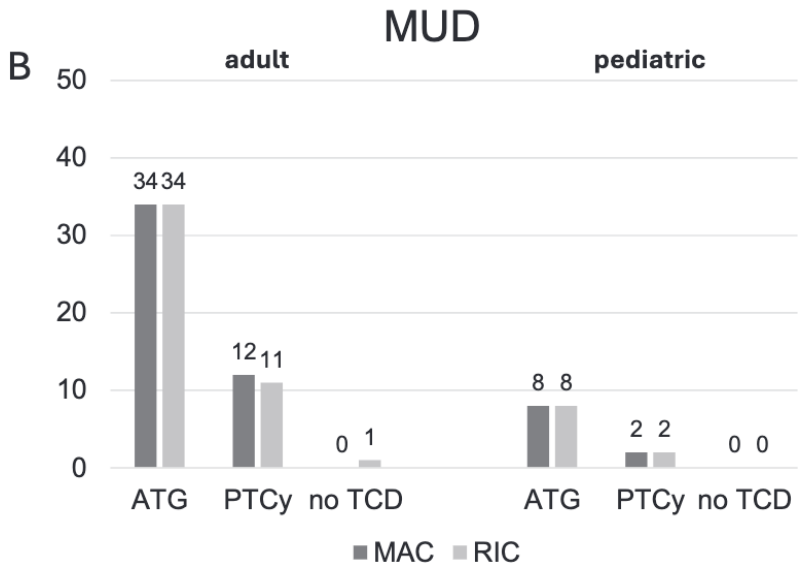
A total of 62 GITMO-affiliated centers performed allo-HSCT in 2023 and were invited to participate; 56 centers (90.3%) provided complete data, covering 93.0% of national transplant activity

Features	Adult *N* (%)	Pediatric *N* (%)	*p*
Number of transplant	1604 (86.1)	258 (13.9)	—
Diseases			$p<0.001$
Acute leukemias	1002 (62.5)	129 (50.0)	
Myelodysplastic syndromes	191 (11.9)	24 (9.3)	
Myeloproliferative neoplasms	147 (9.2)	5 (1.9)	
Lymphoproliferative disorders	178 (11.1)	11 (4.3)	
Multiple myeloma and PCD	20 (1.2)	0 (0)	
Nonmalignant disorders	42 (2.6)	79 (30.6)	
Other indications	24 (1.5)	10 (3.9)	
Conditioning intensity			$p<0.001$
Myeloablative	885 (55.2)	188 (72.9)	
Reduced intensity	719 (44.8)	70 (27.1)	
Stem cell source			$p<0.001$
Peripheral blood	1471 (91.7)	118 (45.7)	
Bone marrow	124 (7.7)	137 (53.1)	
Cord blood	9 (0.6%)	3 (1.2)	
Donor type			$p=0.003$
MRD	293 (18.3)	55 (21.3)	
MUD	599 (37.3)	69 (26.7)	
MMUD	244 (15.2)	37 (14.3)	
Haploidentical	468 (29.2)	97 (37.7)	

Polverelli N, ……., Martino M..Am J Hematol. 2026 Feb;101(2):350-355.

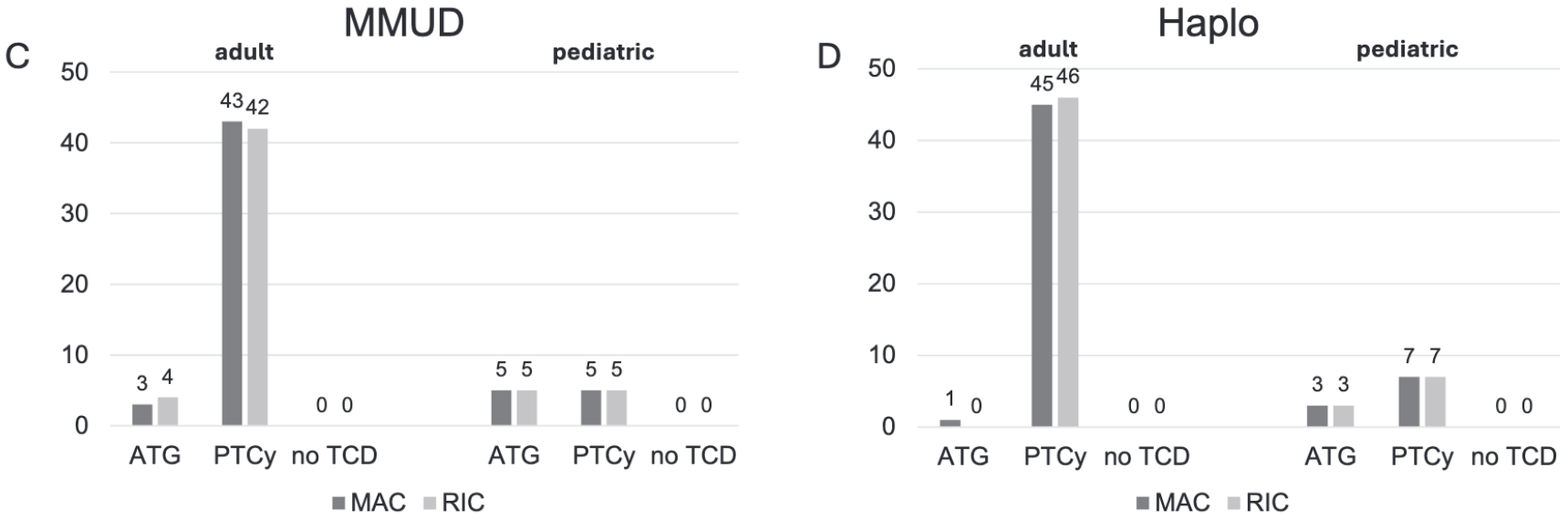
GVHD prophylaxis strategies by donor type and transplant center





Polverelli N, ……., Martino M..Am J Hematol. 2026 Feb;101(2):350-355.

GVHD prophylaxis strategies by donor type and transplant center



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

Polverelli N, ……., Martino M..Am J Hematol. 2026 Feb;101(2):350-355.

Setting	Adulti	Pediatrici*	Evidenza clinica
Donatore familiare compatibile / non consanguineo compatibile	CNI + metotrexato (MTX) dopo condizionamento mieloablativo; CNI + micofenolato mofetile (MMF) se condizionamento non mieloablativo, controindicazione a MTX o necessità di attecchimento rapido.	Familiare compatibile: generalmente CNI da solo; non consanguineo compatibile: CNI + MTX/MMF.	Le linee guida GITMO/SNLG 2024 raccomandano MTX nel mieloablativo e MMF nel non mieloablativo o quando MTX è controindicato. Sistema Nazionale Linee Guida (ISS) 2024
Graft periferico adulto, donatore compatibile	Considerare globulina anti-timocitaria (ATG) aggiunta al backbone, soprattutto da donatore non consanguineo; nell'adulto è raccomandata anche con donatore familiare e cellule periferiche.	Evitare routinariamente ATG nel familiare compatibile, soprattutto se graft midollare.	ATG è raccomandata nel donatore non consanguineo compatibile e, nell'adulto, nel familiare compatibile con cellule periferiche. Sistema Nazionale Linee Guida (ISS) 2024
Donatore aploidentico o incompatibile	Ciclofosfamide post-trapianto (PTCy) + tacrolimus + MMF è la piattaforma di riferimento; non usare PTCy isolata con graft periferico.	PTCy-based o deplezione T ex vivo secondo esperienza del centro.	PTCy è consolidata nell'aploidentico; nel trial randomizzato BMT CTN 1703, PTCy/tacrolimus/MMF ha ridotto GVHD severa e migliorato la sopravvivenza libera da GVHD/recidiva rispetto a tacrolimus/MTX. Nature reviews. Disease primers 2023
Cordone ombelicale	CNI + MMF; evitare MTX e ATG; PTCy ancora sperimentale.	Stesso principio.	MTX ritarda l'attecchimento, ATG non è raccomandata e PTCy resta sperimentale nel trapianto da cordone. Transplantation and Cellular Therapy 2021

*Le raccomandazioni pediatriche GITMO/SNLG si riferiscono a neoplasie ematologiche; per immunodeficienze e patologie non maligne servono protocolli specifici.

Profilassi e terapia della Graft Versus Host Disease (GVHD) acuta e cronica *Sistema Nazionale Linee Guida (ISS)* GITMO-Gruppo Italiano per il Trapianto di Midollo Osseo cellule staminali...2024
Malard F, Holler E, Sandmaier BM, Huang H, Mohty M. Acute graft-versus-host disease. Nat Rev Dis Primers. 2023 Jun 8;9(1):27. doi: 10.1038/s41572-023-00438-1. PMID: 37291149.
Ponce DM, Politikos I, Alousi A, Carpenter PA, Milano F, MacMillan ML, Barker JN, Horwitz ME; American Society for Transplantation and Cellular Therapy Cord Blood Special Interest Group. Guidelines for the Prevention and Management of Graft-versus-Host Disease after Cord Blood Transplantation. Transplant Cell Ther. 2021 Jul;27(7):540-544. doi: 10.1016/j.jtct.2021.03.012. PMID: 34210500.

CNI + antimetabolita restano la base

Raccomandazione (invariata rispetto al 2020)	Cat.
In MRD e MUD: inibitore della calcineurina (CNI) + antimetabolita	1
Ciclosporina o tacrolimus equivalenti; la CsA è lo standard in Europa	1
Metotrexato come antimetabolita nel condizionamento mieloablativo	1
MMF al posto di MTX se controindicato o serve attecchimento rapido (es. aspergillosi)	2A
MMF come antimetabolita nel condizionamento non mieloablativo o RIC	2A
rATG (Thymoglobulin o Grafalon) nel trapianto da MUD	1
rATG nel trapianto da MRD con cellule staminali periferiche	2B

Penack O et al. Lancet Haematol 2024;11:e147–59 · Panel 1

PTCy o rATG? Dipende dal donatore

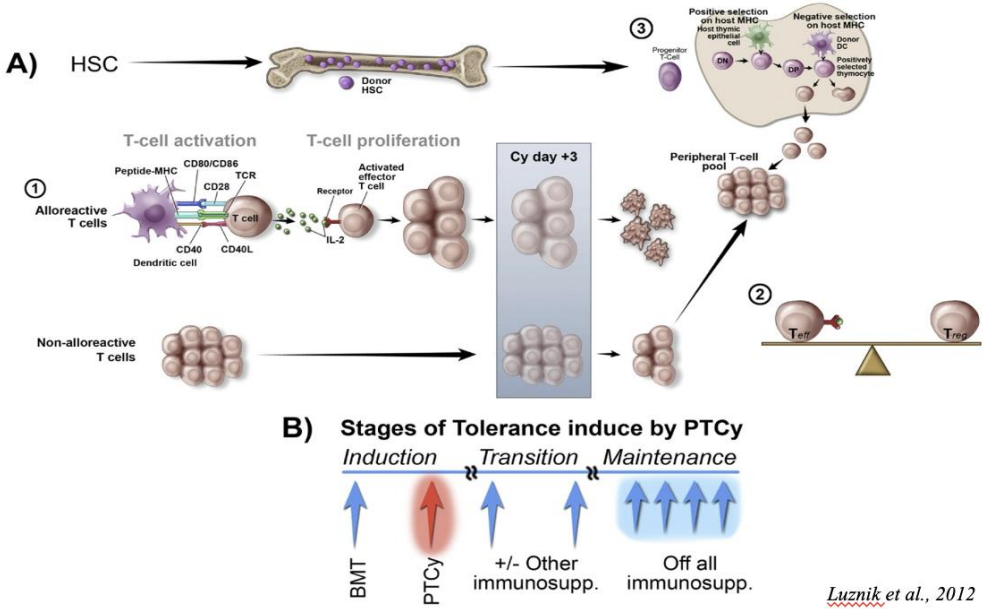
Donatore	Raccomandazione	Cat.
Familiare HLA-identico (MRD)	PTCy non va preferita in generale alla rATG; la rATG resta raccomandata (PBSC: cat. 2B)	2A
Non correlato compatibile (MUD)	Profilassi con rATG o PTCy, preferita a una profilassi senza nessuna delle due	1
Non correlato, 1 mismatch (MMUD)	rATG o PTCy, preferite a nessuna delle due; nessuna superiore all'altra	2A

PTCy + rATG insieme? Evidenze non sufficienti per raccomandarlo: nel registro EBMT (LMA, MUD) nessuna differenza in GVHD, NRM, recidiva e sopravvivenza.

Penack O et al. Lancet Haematol 2024;11:e147–59 · Panel 1

Haplo-identical hematopoietic stem cell transplantation

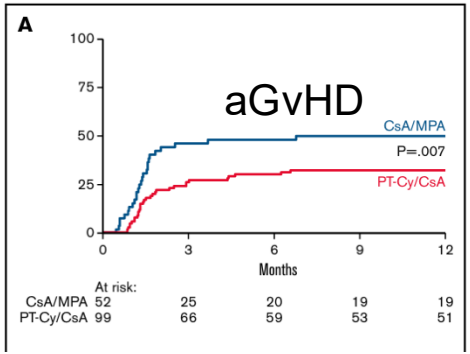
3. High-dose cyclophosphamide based GvHD prophylaxis

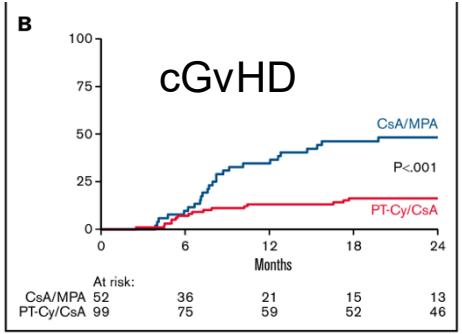


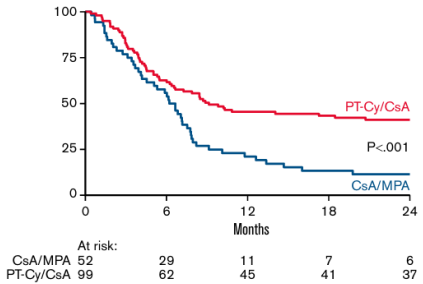
La PTCy elimina in modo mirato i linfociti T alloreattivi appena attivati e risparmia staminali, cellule T di memoria non alloreattive e Treg. È questo che rende fattibile e sicuro il trapianto aploidentico.

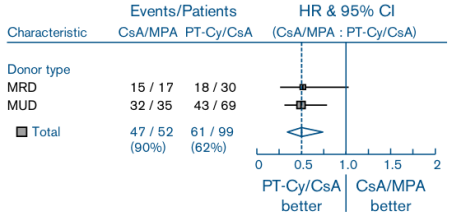
PTCy for matched related and unrelated donors?

Posttransplant cyclophosphamide for prevention of graft-versus-host disease: results of the prospective randomized HOVON-96 trial







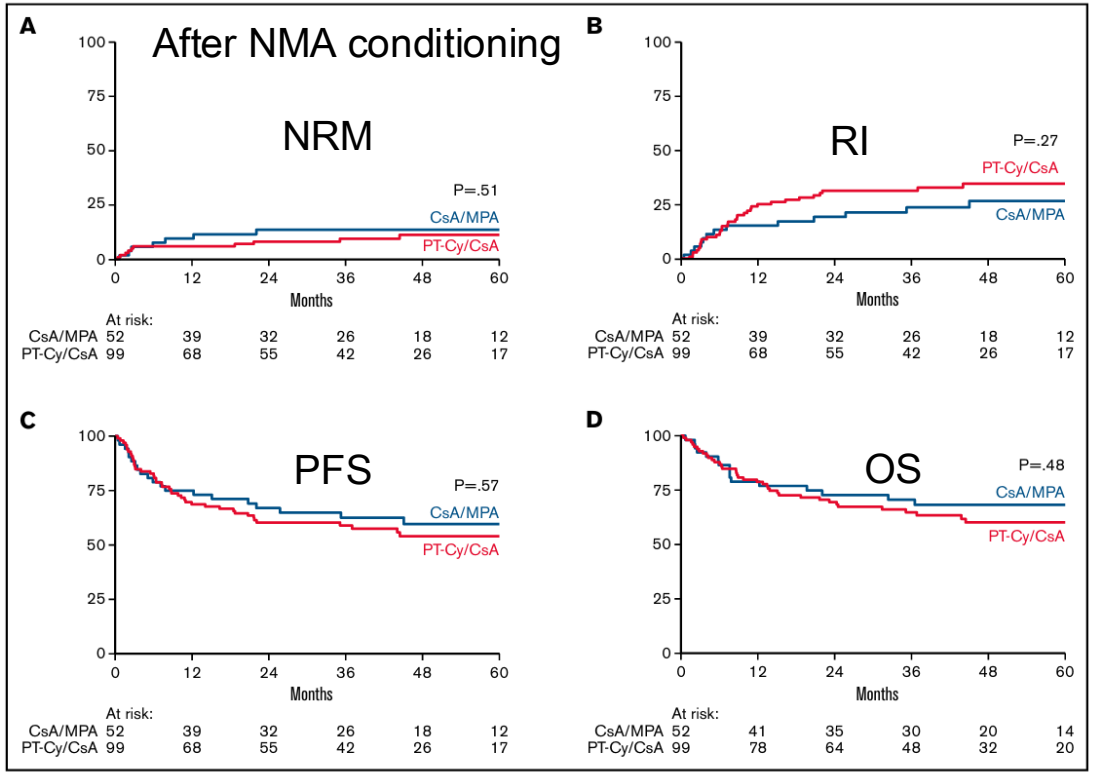


GVHD-free, relapse-free survival (GRFS)

PT-Cy combined with a short course of CsA after NMA matched alloHSCT significantly improves GRFS due to a significant reduction in severe acute and chronic GVHD.

Broers AEC, et al. Blood Adv. 2022 Jun 14;6(11):3378-3385..

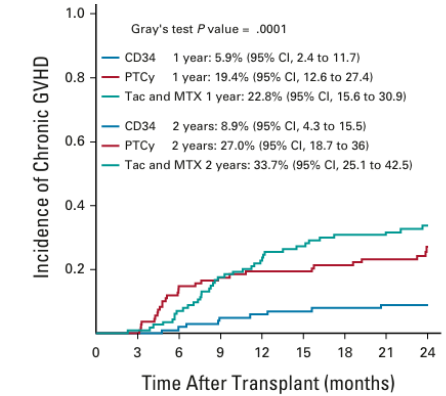
Posttransplant cyclophosphamide for prevention of graft-versus-host disease: results of the prospective randomized HOVON-96 trial

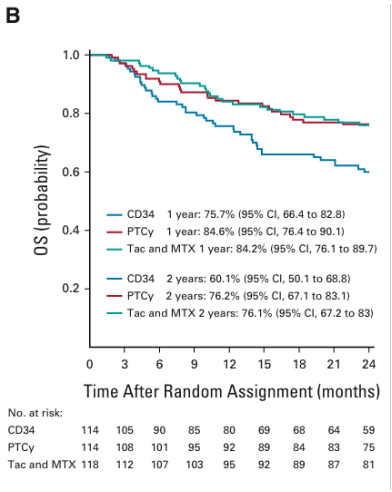


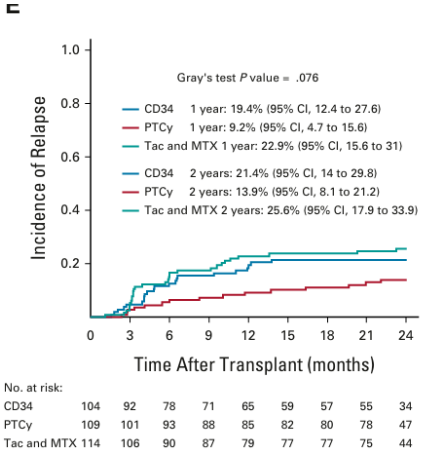
Broers AEC, et al. Blood Adv. 2022 Jun 14;6(11):3378-3385..

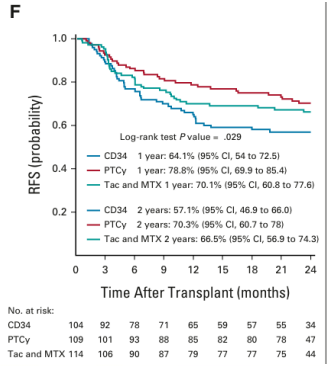
Randomized Phase III BMT CTN Trial of Calcineurin Inhibitor–Free Chronic Graft-Versus-Host Disease Interventions in Myeloablative Hematopoietic Cell Transplantation for Hematologic Malignancies

- phase III trial
- acute leukemia or myelodysplasia
- HLA-matched donor to receive
- CD34-selected peripheral blood stem cell, PTCy after a bone marrow (BM) graft, or tacrolimus and methotrexate after BM graft (control).
- The primary end point was cGVHD (moderate or severe) or relapse-free survival (CRFS)









CD34 selection resulted in lower rates of chronic GVHD but was associated with worse survival compared with the other interventions.

Post-transplant cyclophosphamide without CNI was not superior to tacrolimus and methotrexate with BM in relation to chronic GVHD and survival

Luznik L, et al. J Clin Oncol. 2022

ORIGINAL ARTICLE

Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis

- Adults ≥18 y with hematologic cancers in remission or controlled
- First allogeneic HSCT, peripheral-blood graft
- Reduced-intensity or nonmyeloablative conditioning
- Donor: 6/6 matched sibling, or 8/8 or 7/8 matched unrelated

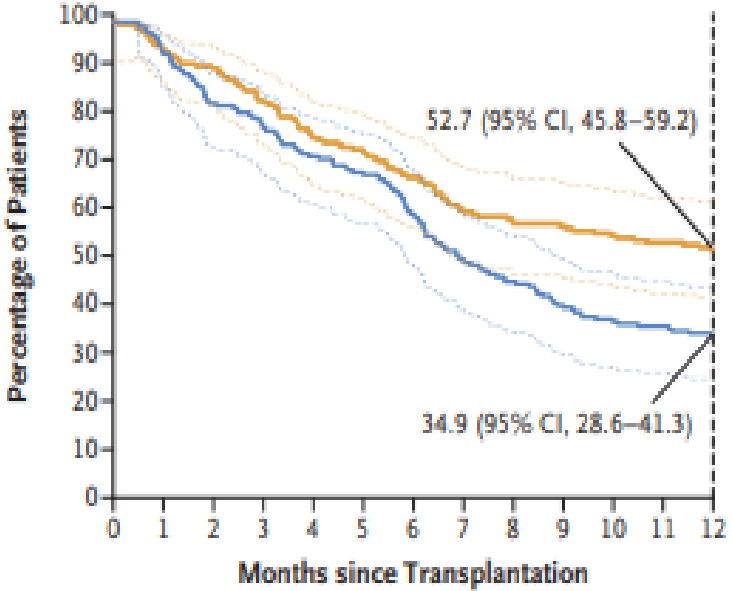
Primary end point: 1-year GVHD-free, relapse-free survival (GRFS)

Phase 3, multicenter: 37 US centers		
Drug	**Experimental: PTCy–Tac–MMF**	**Standard: Tac–MTX**
Cyclophosphamide	50 mg/kg/day on days +3 and +4, with mesna and hydration	—
Tacrolimus	From day +5; taper from day 90, stop by day 180	From day −3; taper from day 90, stop by day 180
Mycophenolate	15 mg/kg/dose (max 1 g three times daily), days 5–35	—
Methotrexate	—	15 mg/m² day 1; 10 mg/m² days 3, 6 and 11

Conditioning: Flu/Bu, Flu/Mel, Flu/Cy, Flu/TBI 200 cGy, or Flu/Cy/TBI. Target CD34+ dose 2–10 × 10^6/kg. Supportive care per institution.

Bolaños-Meade et al. N Engl J Med 2023;388:2338-48

A Adjusted GVHD-free, Relapse-free Survival



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

PRIMARY END POINT

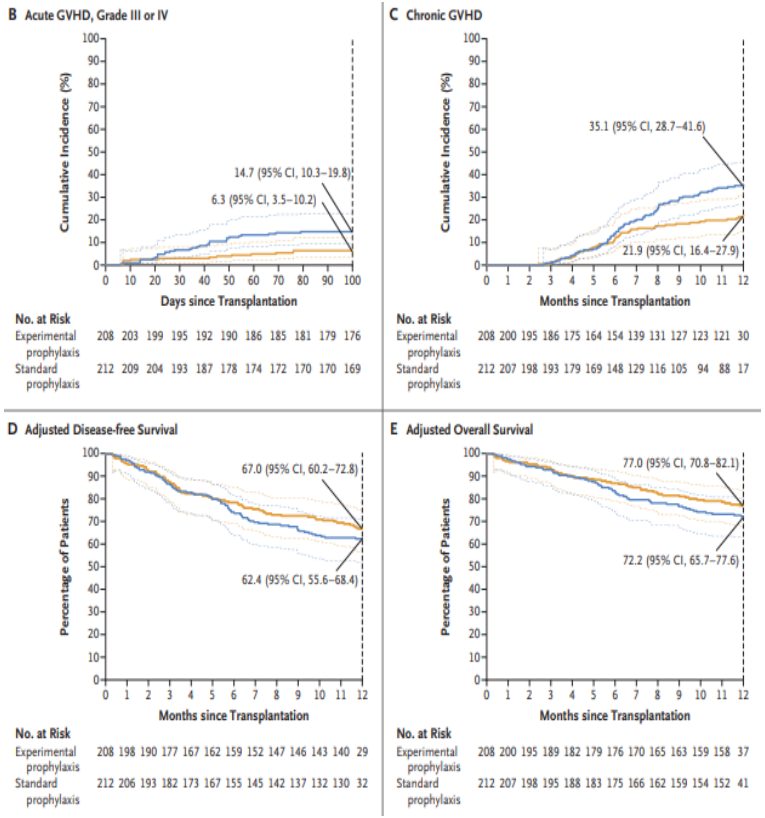
PTCy improved 1-year GRFS by about 18 points

52.7%
PTCy–Tac–MMF
95% CI 45.8–59.2 · 98 events

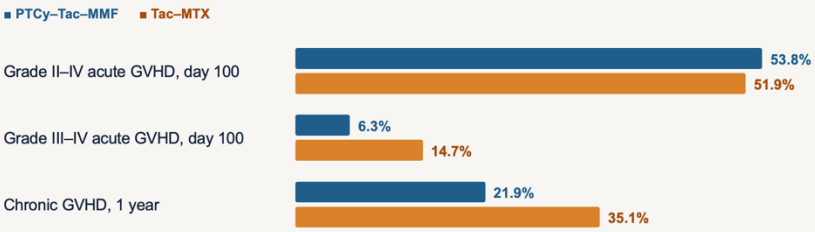
34.9%
Tac–MTX
95% CI 28.6–41.3 · 135 events

Adjusted HR for GVHD, relapse or death **0.64** (95% CI 0.49–0.83), **P = 0.001**

Bolaños-Meade et al. N Engl J Med 2023;388:2338-48



Less severe acute and less chronic GVHD



Moderate or severe chronic GVHD: 14 vs 35 patients (severe: 3 vs 11).

Bolaños-Meade et al. N Engl J Med 2023;388:2338-48

At 1 year, % (95% CI)	PTCy–Tac–MMF	Tac–MTX
Overall survival	77.0 (70.8–82.1)	72.2 (65.7–77.6)
Disease-free survival	67.0 (60.2–72.8)	62.4 (55.6–68.4)
Relapse or progression	20.8 (15.5–26.7)	20.2 (15.0–25.9)
Transplant-related death	12.3 (8.2–17.2)	17.2 (12.4–22.6)
Immunosuppression-free survival	50.0 (42.8–57.2)	39.7 (32.9–46.8)

HR for relapse 0.98 (0.64–1.52)

Cumulative incidence, %	PTCy–Tac–MMF	Tac–MTX
Neutrophil recovery, day 28	90.3	93.4
Platelets >20,000/μL, day 100	90.3	92.8
Grade 2 infection, 1 year	33.7	20.5
Grade 3 infection, 1 year	12.2	13.3
CMV reactivation, day 100	7.3	7.1

No trade-off in relapse or survival

Bolaños-Meade et al. N Engl J Med 2023;388:2338-48

Limitations

Narrow population

Adults, HLA-matched donors, reduced-intensity conditioning only; myeloablative and pediatric settings untested.

Few mismatched donors

Only 3.5% had 7/8 unrelated donors; ATG was excluded by design.

Short follow-up

1-year horizon misses late relapse and late chronic GVHD; longer follow-up is ongoing.

Bolaños-Meade et al. N Engl J Med 2023;388:2338-48

Graft-versus-Host Disease Prophylaxis with Cyclophosphamide and Cyclosporin

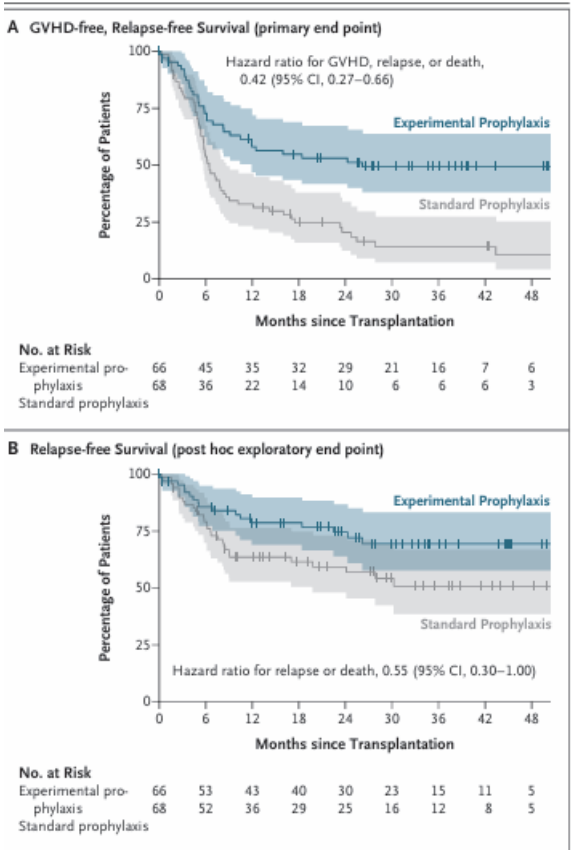
Authors: David J. Curtis, M.B., B.S., Ph.D. , Sushrut S. Patil, M.B., B.S., M.D., John Reynolds, Ph.D., Duncan Purtill, M.B., B.S., Clinton Lewis, M.D., David S. Ritchie, M.B., Ch.B., Ph.D., David J. Gottlieb, M.B., B.S., M.D., +12 , for the Australasian Leukaemia and Lymphoma Group* Author Info & Affiliations

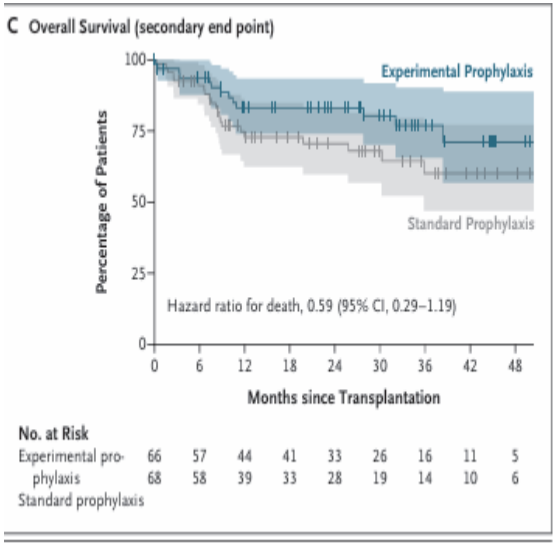
BM12 CAST: Study Design

Item	Details
Study type	Phase 3, randomized, open-label, multicenter (Australasian Leukaemia and Lymphoma Group)
Population	Adults (21–70 years) with AML, ALL or MDS
Donor	HLA-matched related (sibling) donor
Conditioning	Myeloablative or reduced-intensity
Randomized patients	134: 66 experimental, 68 standard
Experimental arm	IV cyclophosphamide 50 mg/kg on days +3 and +4, then oral cyclosporin from day +5 for 90 days
Standard arm	Oral cyclosporin from day −1 for 90 days + IV methotrexate 15 mg/m² on day +1 and 10 mg/m² on days +3, +6 and +11
Primary endpoint	GVHD-free, relapse-free survival (GRFS)
Secondary endpoints	Grade III–IV acute GVHD, moderate-to-severe chronic GVHD, immunosuppression-free survival at 12 months, relapse, overall survival, quality of life
Median follow-up	36 months

Curtis DJ, Patil SS, Reynolds J, et al. *Graft-versus-Host Disease Prophylaxis with Cyclophosphamide and Cyclosporin.* **N Engl J Med** 2025.

PTCy as GvHD prophylaxis in HLA-ident Sibling HSCT





Endpoint primario (GRFS): a 3 anni 49% con il regime sperimentale contro 14% con quello standard (HR per GVHD, recidiva o morte 0,42; IC 95% 0,27–0,66). La GRFS mediana è stata di 26,2 contro 6,4 mesi (P < .001)

OS: 2 anni 83% con ciclofosfamide/ciclosporina vs 71% con ciclosporina/metotrexato (HR 0,59; IC 95% 0,29–1,19), quindi non statisticamente significativa

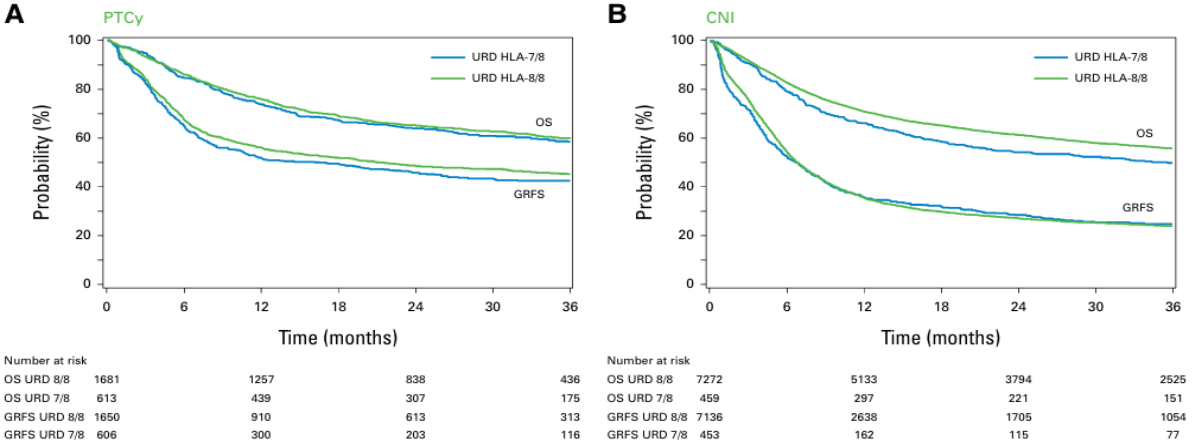
Curtis DJ, Patil SS, Reynolds J, et al. *Graft-versus-Host Disease Prophylaxis with Cyclophosphamide and Cyclosporin.* **N Engl J Med** 2025.

PTCy for mismatched unrelated donors (MMUD)?

Post-Transplant Cyclophosphamide–Based Graft-Versus-Host Disease Prophylaxis Attenuates Disparity in Outcomes Between Use of Matched or Mismatched Unrelated Donors

Brian C. Shaffer, MD, MS[1]; Mahasweta Gooptu, MD[2]; Todd E. DeFor, MS[3]; Martin Maiers, MS[3]; Javier Bolaños-Meade, MD[4]; Ramzi Abboud, MD[5]; Adrienne D. Briggs, MD[6]; Farhad Khimani, MBBS[7]; Dipenkumar Modi, MD[8]; Richard Newcomb, MD[9]; Elizabeth J. Shpall, MD[10]; Caitrin Bupp, MPH[3]; Stephen R. Spellman, MBS[3]; Heather E. Stefanski, MD, PhD[3]; Bronwen E. Shaw, MD, PhD[11]; Jeffery J. Auletta, MD[3,12]; Steven M. Devine, MD[3]; Antonio M. Jimenez Jimenez, MD, MSc[13]; and Monzr M. Al Malki, MD[14]

Characteristic	PTCy URD 8/8	CNI URD 8/8	PTCy URD 7/8	CNI URD 7/8	Total
No. of patients	1,681	7,272	613	459	10,025
Patient age, years, median (range)	62.0 (18.0-82.2)	60.6 (18.0-82.7)	57.9 (18.0-78.8)	58.2 (18.1-81.4)	60.7 (18.0-82.7)
Donor age, years, median (range)	27.6 (18.0-60.9)	26.8 (18.0-66.5)	28.8 (18.0-61.2)	28.3 (18.0-61.4)	27.1 (18.0-66.5)
AML	909 (54.1)	3,937 (54.1)	330 (53.8)	243 (52.9)	5,419 (54.1)
ALL	250 (14.9)	1,209 (16.6)	128 (20.9)	93 (20.3)	1,680 (16.8)
MDS	522 (31.1)	2,126 (29.2)	155 (25.3)	123 (26.8)	2,926 (29.2)



Retrospective, registry-based cohort study (CIBMTR)

Shaffer BC, Gooptu M, DeFor TE, et al.. J Clin Oncol. 2024

Comparison	Endpoint	HR (95% CI)	p	Interpretation
MMUD + PTCy vs MUD + PTCy	OS	0.96 (0.82–1.11)	0.60	No difference
MMUD + PTCy vs MUD + PTCy	GRFS	0.90 (0.79–1.02)	0.10	No difference
MUD + PTCy vs MUD + CNI	OS	0.88 (0.80–0.96)	0.004	Better survival with PTCy
MUD + PTCy vs MUD + CNI	GRFS	0.61 (0.57–0.66)	<0.0001	Better GRFS with PTCy
MMUD + PTCy vs MUD + CNI	GRFS	0.68 (0.60–0.76)	<0.0001	Better GRFS with PTCy, even with a mismatched donor
Ancestry subgroups	OS/GRFS	—	—	PTCy benefit independent of patient ancestry

with PTCy, OS and GRFS are similar for 7/8 MMUD and 8/8 MUD. This expands access to HCT for patients of every ancestry, especially those without a fully matched donor.

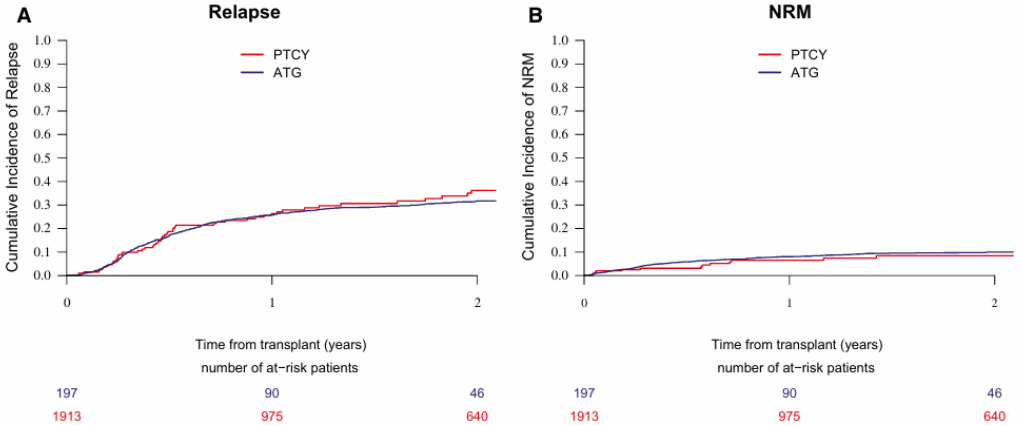
Shaffer BC, Gooptu M, DeFor TE, et al.. J Clin Oncol. 2024

ATLG/ATG vs PTCy?

ATG vs PTCY in AML and HLA-ident Sibling HSCT (EBMT)

TABLE 1. Patient, Disease, and Transplantation Characteristics

Characteristic	ATG (n = 1913)	PTCY (n = 197)	*P*
Age at allo-HCT, y, median (range)	54 (18-72)	47 (18-74)	<.01
Sex			.55
Men	1012 (53)	88 (55)	
Women	893 (47)	88 (45)	
Female donor into male recipient	456 (24)	51 (26)	.55
Secondary AML	318 (17)	31 (16)	.75
Cytogenetic risk			.51
Good	67 (3)	8 (4)	
Intermediate	869 (45)	87 (44)	
Poor	347 (19)	29 (15)	
NA/Failed	630 (33)	73 (37)	



Battipaglia et al Cancer 2021

ATG vs PTCY in AML and HLA-ident Sibling HSCT (EBMT)

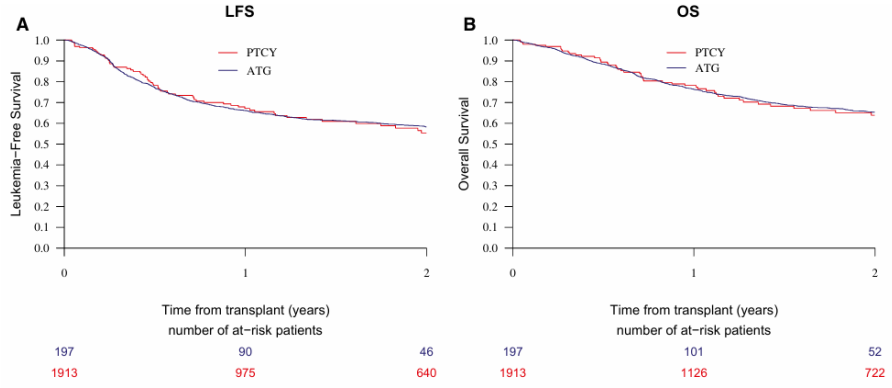
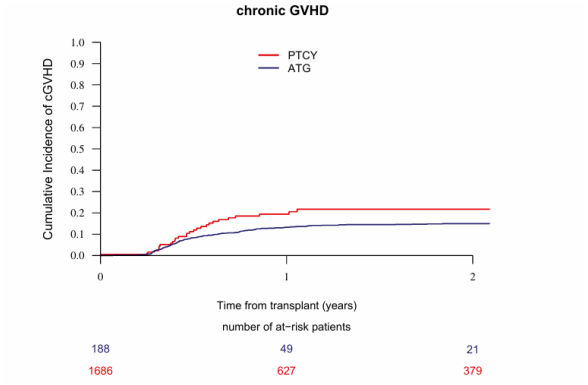


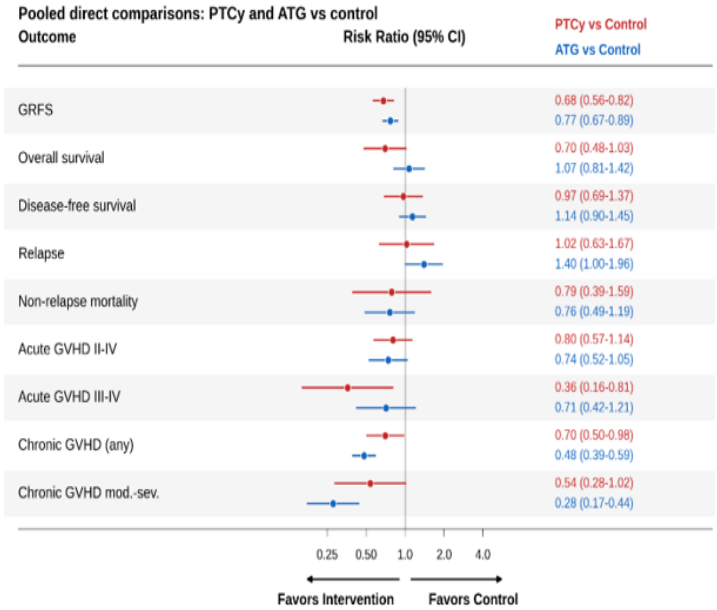
TABLE 3. Multivariate Analysis

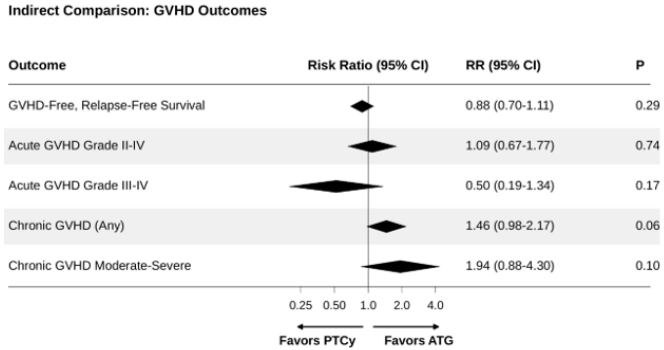
ATG vs PTCY	HR (95% CI)	*P*
LFS	1.00 (0.77-1.31)	.99
OS	0.97 (0.72-1.32)	.86
GRFS	0.85 (0.67-1.03)	.16
RI	0.97 (0.72-1.31)	.85
NRM	1.15 (0.63-2.11)	.65
Grade II-IV acute GVHD	0.96 (0.66-1.41)	.84
Grade III/IV acute GVHD	0.82 (0.43-1.58)	.56
Chronic GVHD, all grades	0.71 (0.52-0.97)	<.04
Extensive chronic GVHD	0.60 (0.38-0.93)	<.03



Battipaglia et al Cancer 2021

A network meta-analysis of randomized trials to determine optimal GVHD prophylaxis in matched sibling donor transplantation





Key message

PTCy mainly reduced severe (grade III–IV) acute GVHD vs conventional prophylaxis (RR 0.36). ATG mainly reduced chronic GVHD: any grade RR 0.48, moderate-severe RR 0.28.

Both strategies improved GVHD-free, relapse-free survival vs conventional prophylaxis (PTCy RR 0.68; ATG RR 0.77).

Neither approach significantly changed OS, DFS or NRM. PTCy showed a non-significant trend toward better OS (RR 0.70, 0.48–1.03).

PTCy had no effect (RR 1.02). ATG showed a borderline signal toward increased relapse (RR 1.40, 1.00–1.96).

No significant differences. Trends favored PTCy for severe aGVHD (RR 0.50, p=0.17) and ATG for cGVHD (any: RR 1.46, p=0.06; moderate-severe: RR 1.94, p=0.10).

In MSD transplantation, choose PTCy or ATG based on the patient's risk of acute vs chronic GVHD and relapse. A head-to-head randomized trial is needed.

Nessuna differenza è risultata significativa

Bentolila et al. *Transplantation and Cellular Therapy* (JTCT), 2026

Comparison of immune reconstitution between anti-T-lymphocyte globulin and posttransplant cyclophosphamide as acute graft-*versus*-host disease prophylaxis in allogeneic myeloablative peripheral blood stem cell transplantation

Radwan Massoud, Nico Gagelmann, Ulrike Fritzsche-Friedland, Gaby Zeck, Silke Heidenreich, Christine Wolschke, Francis Ayuk, Maximilian Christopeit and Nicolaus Kröger

Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Ferrata Storti Foundation

Haematologica 2022
Volume 107(4):857-867

	N (%)	N(%)	p
Number of patients	476 (100)	123 (100)	
Leukocytes engraftment median days (range)	12 (8-36)	16 (12-27)	**<0.001**
Platelet engraftment median days (range)	15 (8-99)	21 (9-99)	**0.024**
CMV reactivation [15 in ATG 54 in PTCY missing]	214 (46)	60 (50)	NS
EBV reactivation [34 in ATG missing, 4 in PTCY missing]	131 (33)	19 (16)	**<0.001**
Overall incidence of infection by day 100	344 (75)	109 (91)	**<0.001**
NRM at 3 years	16%	30%	**0.006**
Relapse incidence	34%	29%	NS
DFS at 3 years	50%	42%	NS
OS at 3 years	65%	58%	NS
Moderate/severe cGVHD Relapse free survival	40%	27%	NS

Legend: NS= statistically non-significant, NRM= Non relapse Mortality, OS= Overall survival, DFS= disease free survival, cGVHD= Chronic graft versus host disease

CD8, NK, NKT, gamma/delta T cells faster after ATG and CD4 after PTCy
Moderate /severe cGvHD after ATG vs PTCy: 38% vs 44%, p=0.005

Summary

1. Post-transplant Cyclophosphmide can be recommended for all donor sources to prevent acute and chronic GvHD

2. However it is not clear whether it should be preferred to ATG/ATLG as GvHD prophylaxis

Current clinical research is focussed on:

a) optimal dosing of PTCy to reduce toxicity and prevent GvHD

b) find optimal combination partner for different donor source (including ATG/ATLG plus PTCy combination)