Disclosure

Astra Zeneca, Gilead, Abbvie, Neovii, Novartis

GVH Actualités

Aspects thérapeutiques

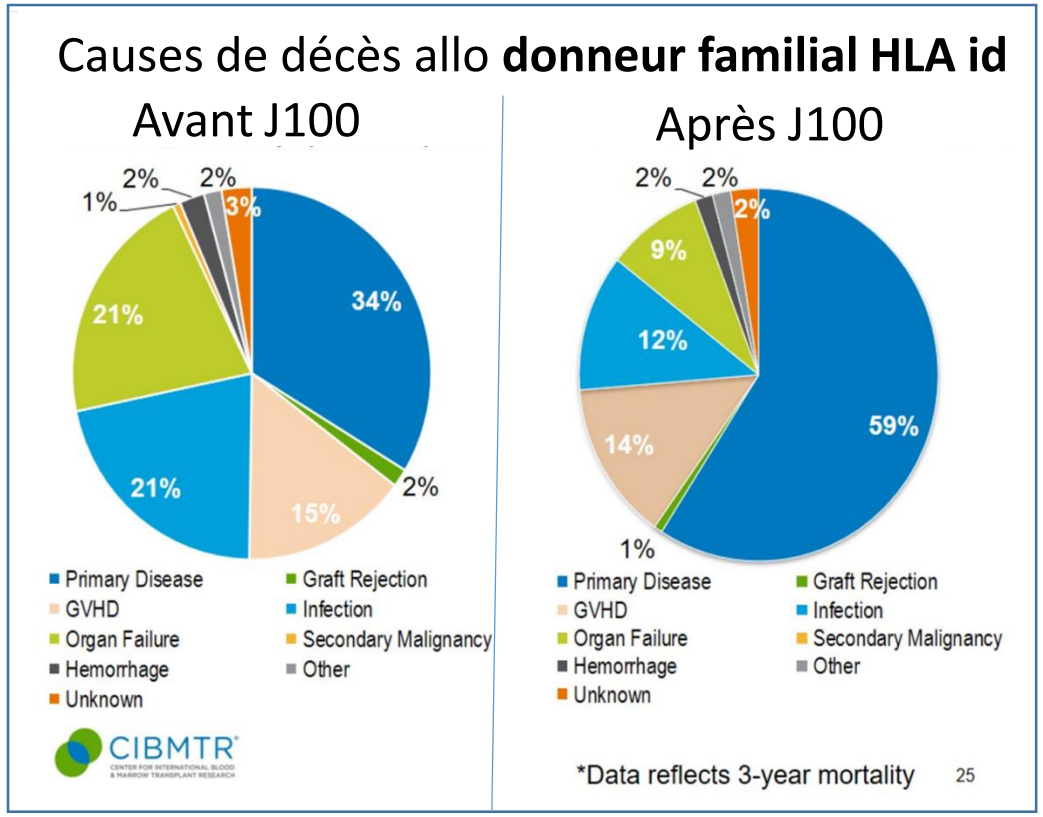
Stéphanie Nguyen

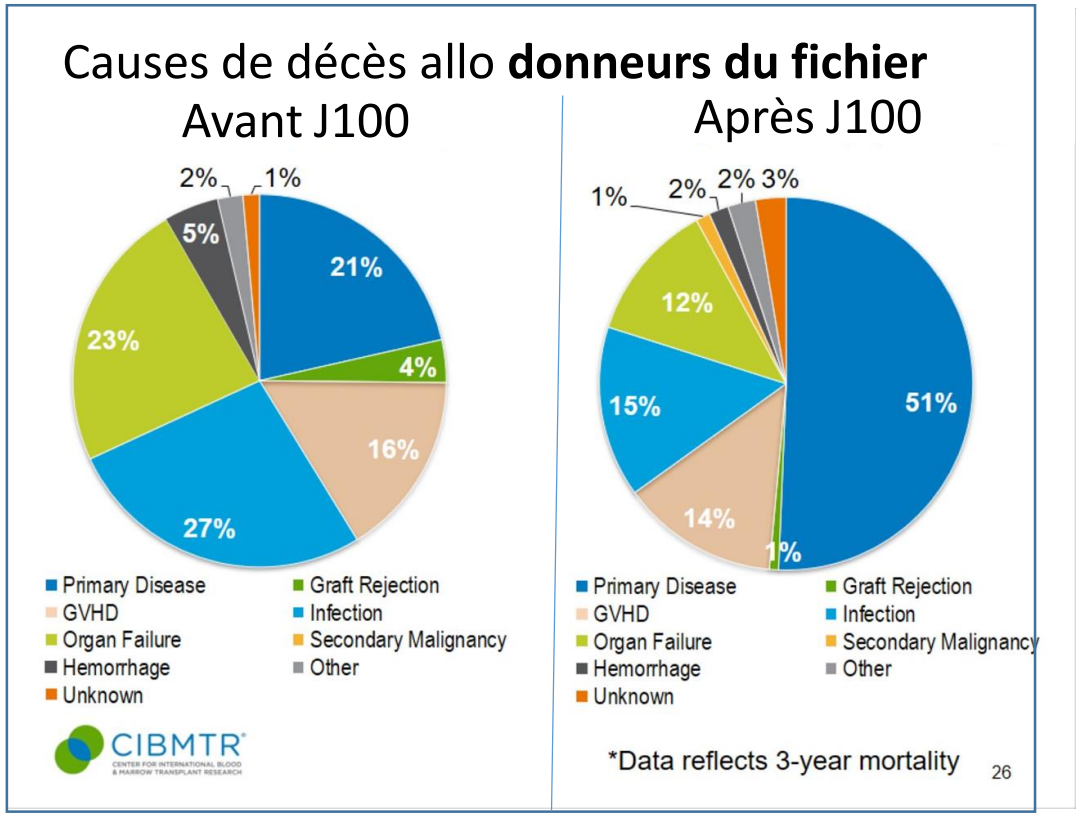
Congrès SFGM-TC, Lille

17 Novembre 2023

Causes de décès post allogreffe

CIBMTR 2016-2017





Rechute de l'hémopathie cause principale>50% des décès

Infections
15-30% décès

↔

GVH (graft vs Host)
15% causes de décès

↔

Défaillance d'organe
10-20% des décès

Guidelines prévention de la GVH Donneur HLA id

1-Association inh calcineurine (Tacro ou ciclo)+ anti-métabolites

2- SAL recommandé pour:

MUD= Donneurs du fichier 10/10

MRD= apparentés HLA id + CSP

Greffes à haut risque de GVH

MAC

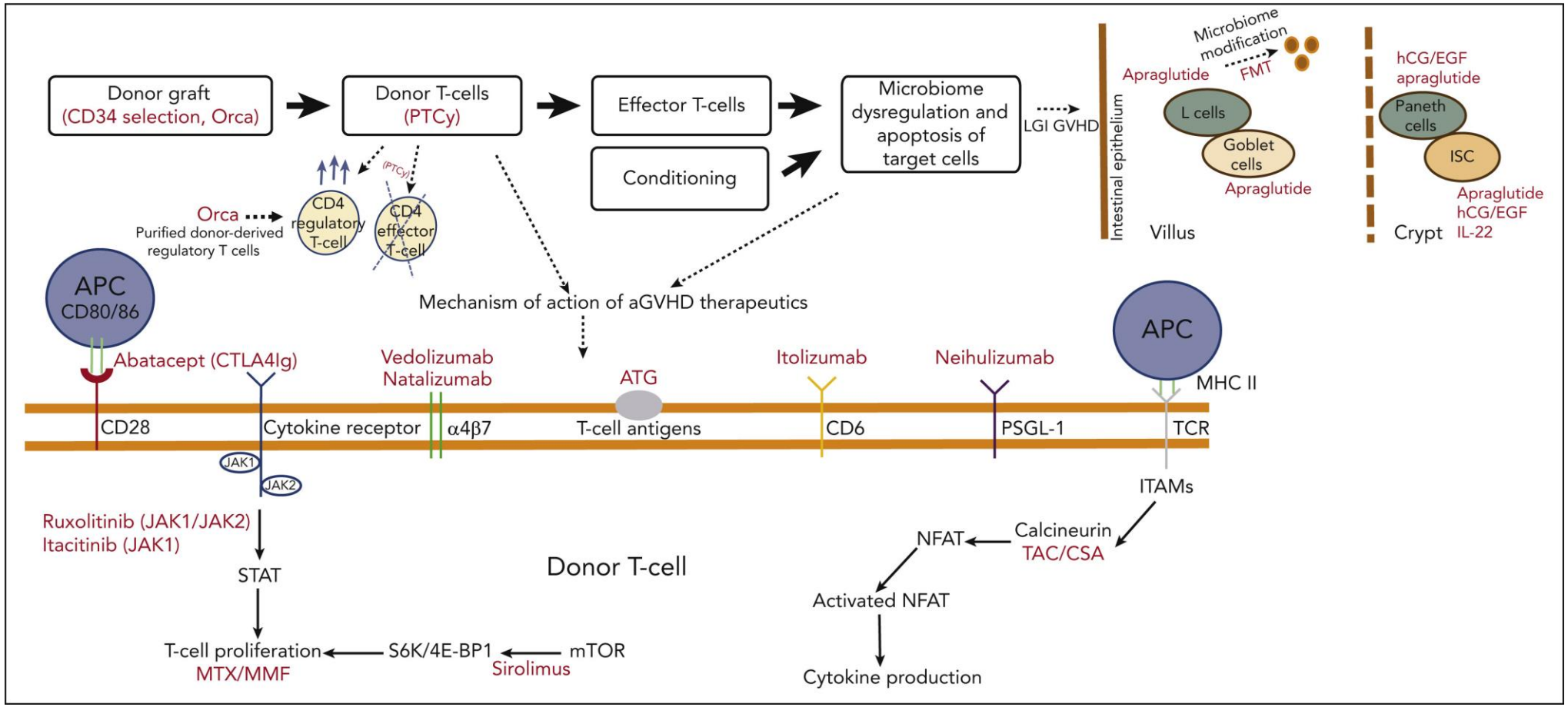
MTX

RIC

Cellcept

Guidelines EBMT
Penack, Lancet hematol 2020

Novel developments in the prophylaxis and treatment of acute GVHD



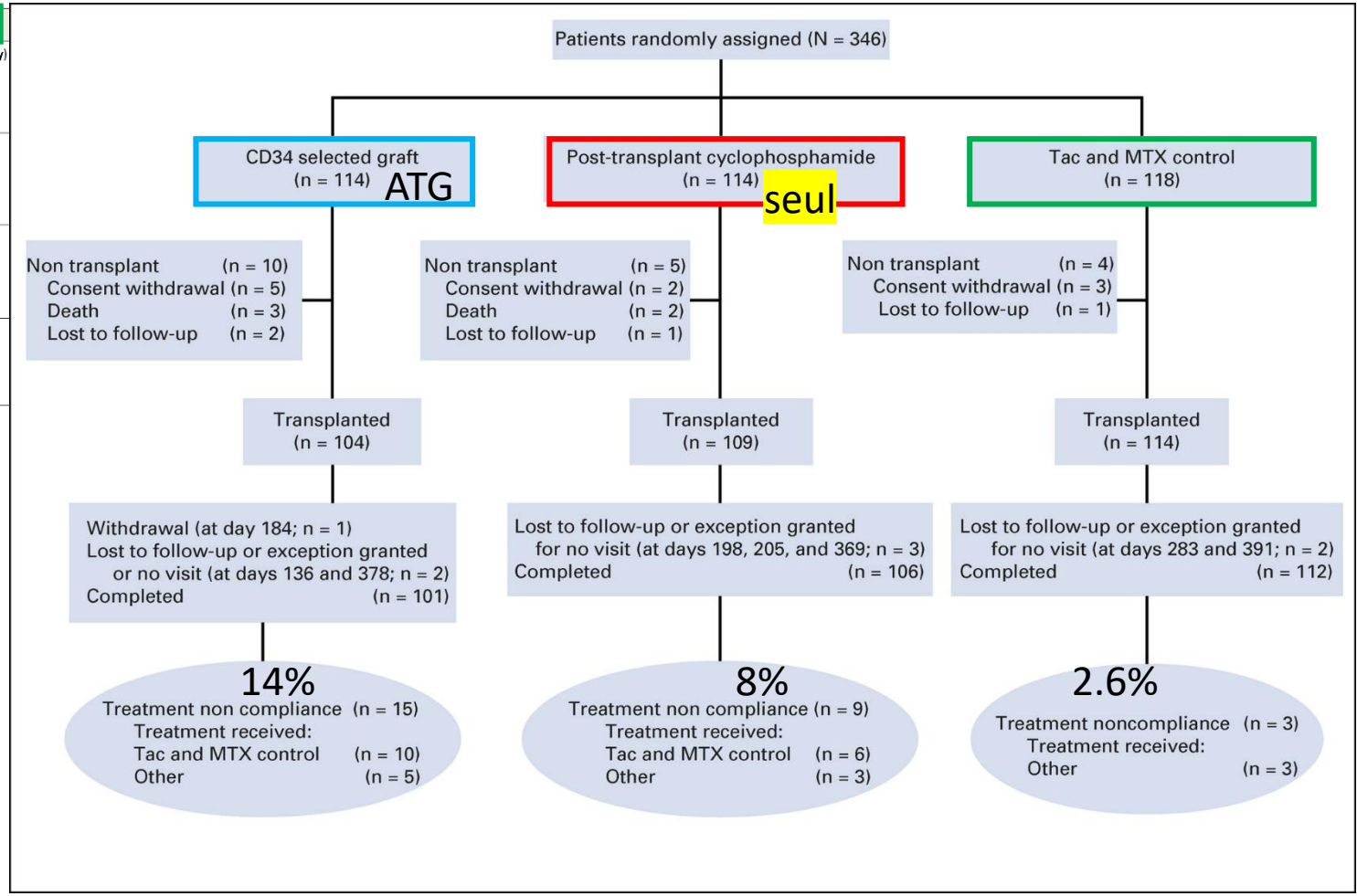
Jamy, Blood 2023 (revue)

Intérêt du Cyclophosphamide à fortes doses post transplant (Cy-PT) en prévention de la GVH dans les greffes matchées?

Phase III Randomisée: Prophylaxie GVH par CyPT vs CD34+/ATG vs Tacro-MTX dans les greffes HLA matchées avec MAC hémopathies malignes

MAC

CD34 Selection Arm (PBSC)		Post-Transplant Cy Arm (BM)		Control Arm (BM)	
A	**Total Body Irradiation (TBI)/ Cyclophosphamide/Thiotepa/rATG** • TBI (1375 cGy) • Cyclophosphamide (120 mg/kg) • Thiotepa (10 mg/kg) • rATG (5mg/kg)	C	**Busulfan[a]/Cyclophosphamide (Bu/Cy)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Cyclophosphamide (100 mg/kg)	G	**Busulfan[a]/Cyclophosphamide (Bu/Cy)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Cyclophosphamide (120 mg/kg)
B	**Busulfan[a]/Melphalan/Fludarabine/rATG** • Busulfan (9.6 mg/kg IV) • Fludarabine (125 mg/m^2) • Melphalan (140 mg/m^2) • rATG (5mg/kg)	D	**Busulfan[a]/Fludarabine (Bu/Flu)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Fludarabine (160 mg/m^2)	H	**Busulfan[a]/Fludarabine (Bu/Flu)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Fludarabine (160 mg/m^2)
		E	**Cyclophosphamide/Total Body Irradiation (Cy/TBI)** • Cyclophosphamide (100 mg/kg) • TBI (1200-1420 cGy)	I	**Cyclophosphamide/Total Body Irradiation (Cy/TBI)** • Cyclophosphamide (120 mg/kg) • TBI (1200-1420 cGy)
		F	**Total Body Irradiation/Etoposide (TBI/Etoposide)** • TBI (1200-1320 cGy) • Etoposide (60 mg/kg)	J	**Total Body Irradiation/Etoposide (TBI/Etoposide)** • TBI (1200-1320 cGy) • Etoposide (60 mg/kg)



Age 51 ans (13-66)
26 centres US+Allemagne

61.3% LAM , 20-25% LAL, 33.2% high DRI

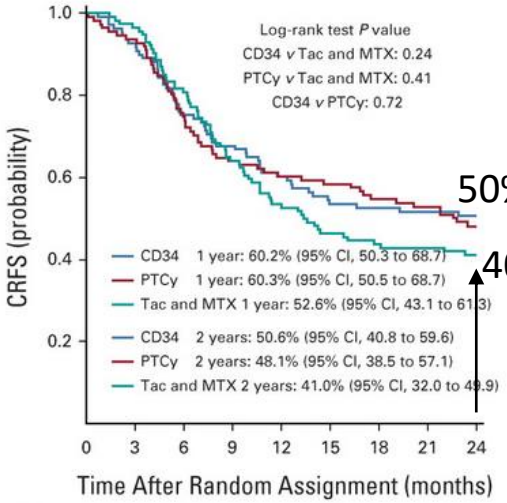
62% MUD 8/8, 38% MRD, and the median time from diagnosis to HCT was 5 months

90% MO dans les groups HDCy et Tacro MTX

Luznik jco 2022

A

CRFS=GVHc mod sev rel free survival



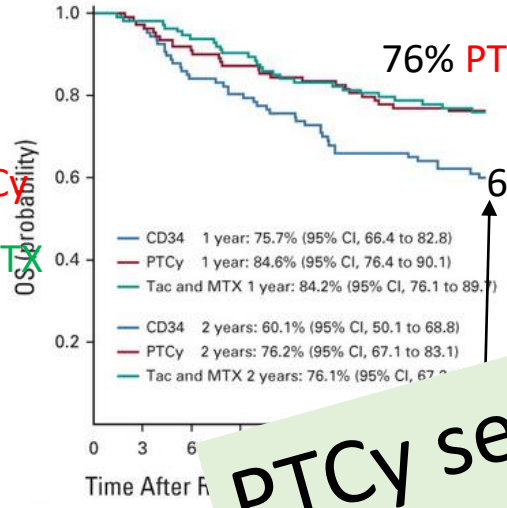
50% CD34/PTCy

40% Tacro MTX

P = .41

B

OS

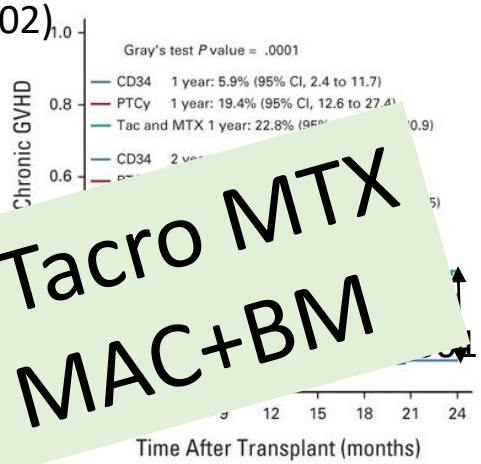


76% PTCy/Tacro MTX

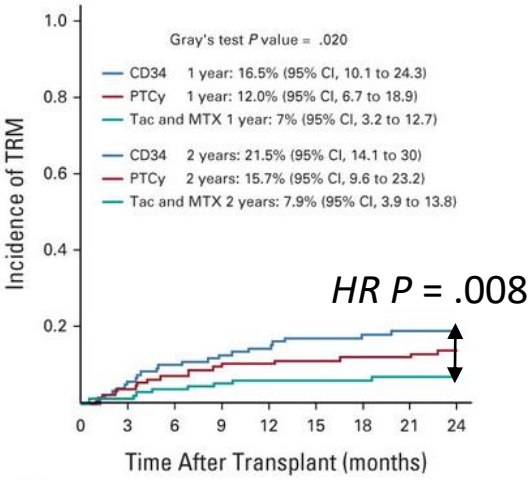
(HR *P* = .02)

60% CD34

Peu de GVHc sev mod avec CD34



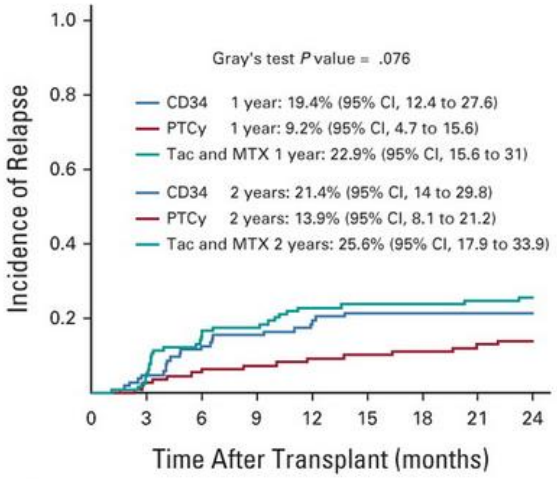
TRM élevée CD34 (infections)

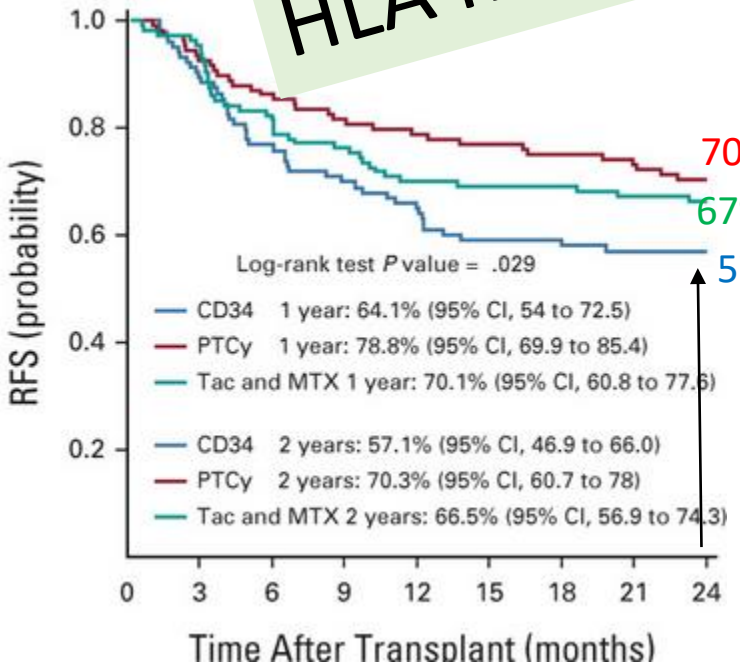


HR P = .008

PTCy seul = Tacro MTX

HLA match MAC+BM

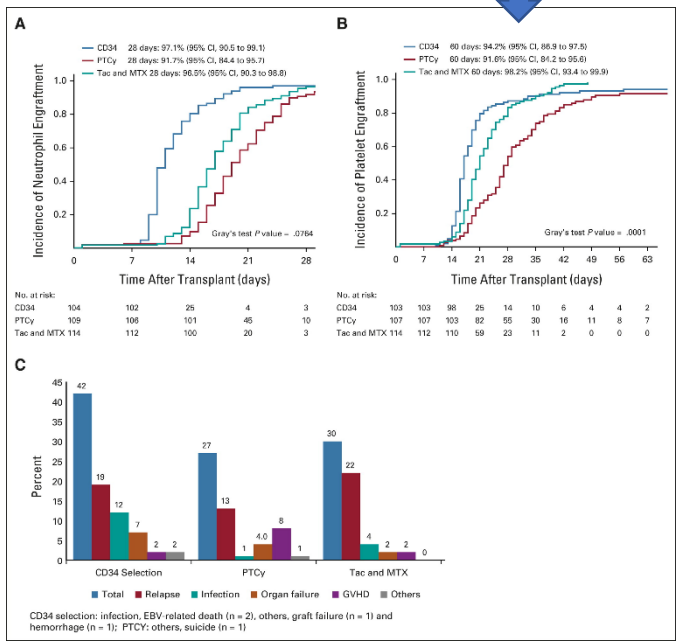




70% PTCy

67% Tacro/MTX

57% CD34



Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis vs Tacro MTX greffes matchées (BMT-CTN) Phase 3 rando

50% LAM 30% MDS 9% LAL

67% URD 8/8
30% MRD 8/8
3% MMUD 7/8

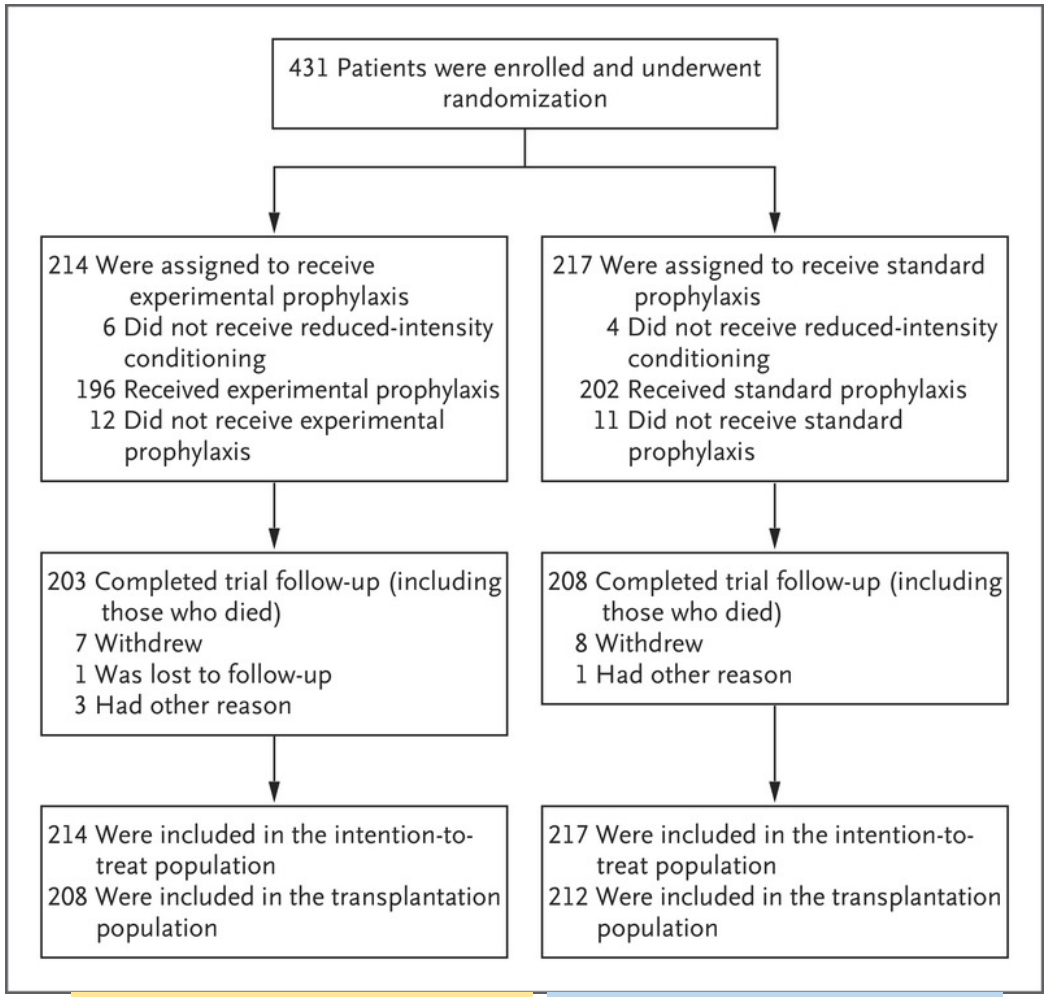
RIC

Fluda + Bu, MEL, TBI2Gy, CPM

Greffon de **CSP**

Objectif primaire GRFS 1 an

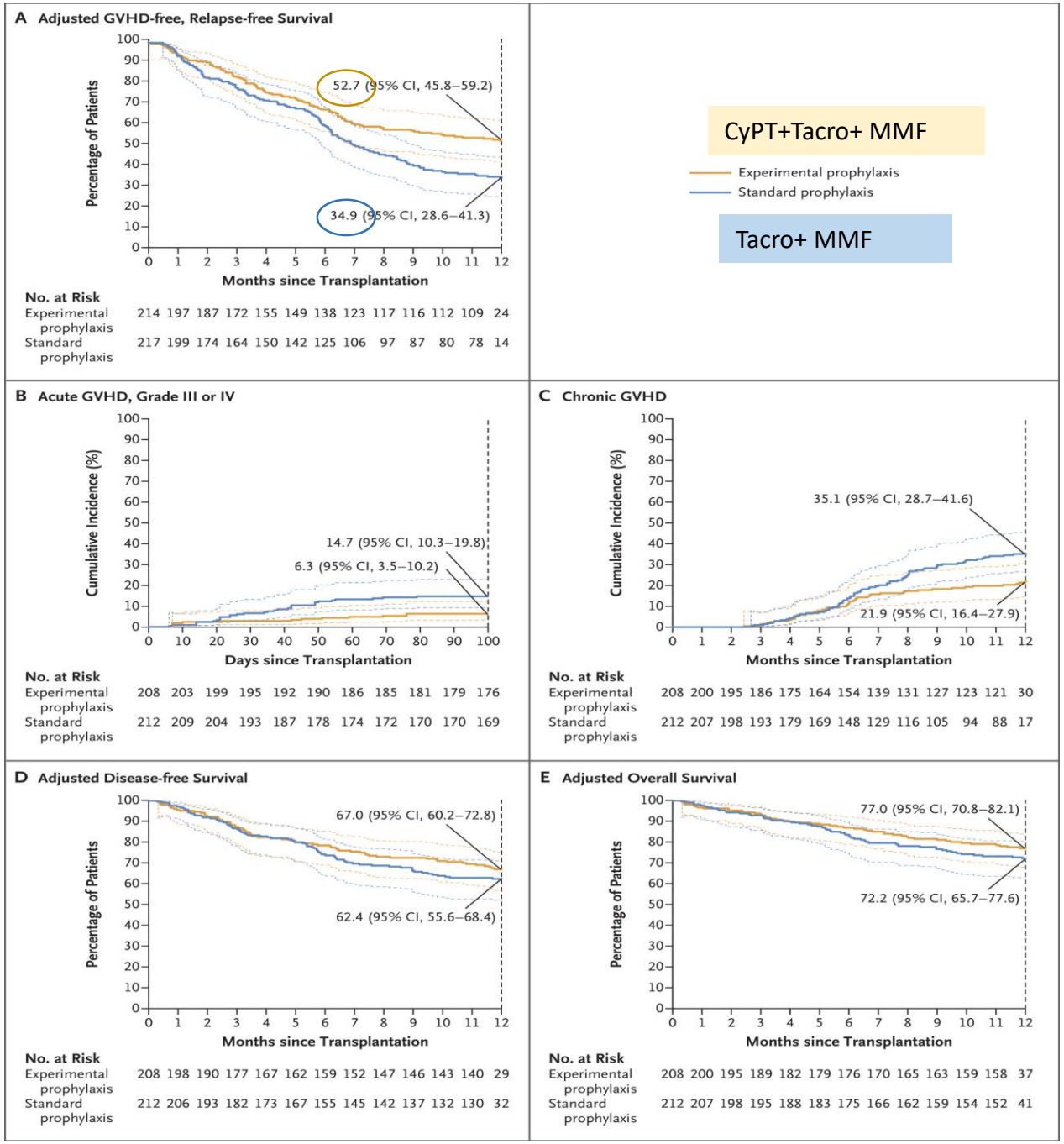
Follow up med 1 an après rando
2 ans inclusions
juin 2019-juin 2021
37 centres US



HD-CyPT 50mg/Kg J3J4 + Tacro M3-M6 MMF J35

Tacro M3-M6 + MTX J1 J3 J6 J11 (15/10/10/10)

Javier Bolaños-Meade, NEJM 2023



CyPT+Tacro+ MMF > Tacro+ MMF

Mais pas de SAL alors que le greffon est des CSP et qu'il y a une majorité de MUD

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

18-70 ans
allo hémopathie maligne à risque rechute
NMA
greffon CSP, MUD, MRD
rando 2:1

n=99
CyPT+Ciclo
jusqu'à J70 en l'absence de GVH

>

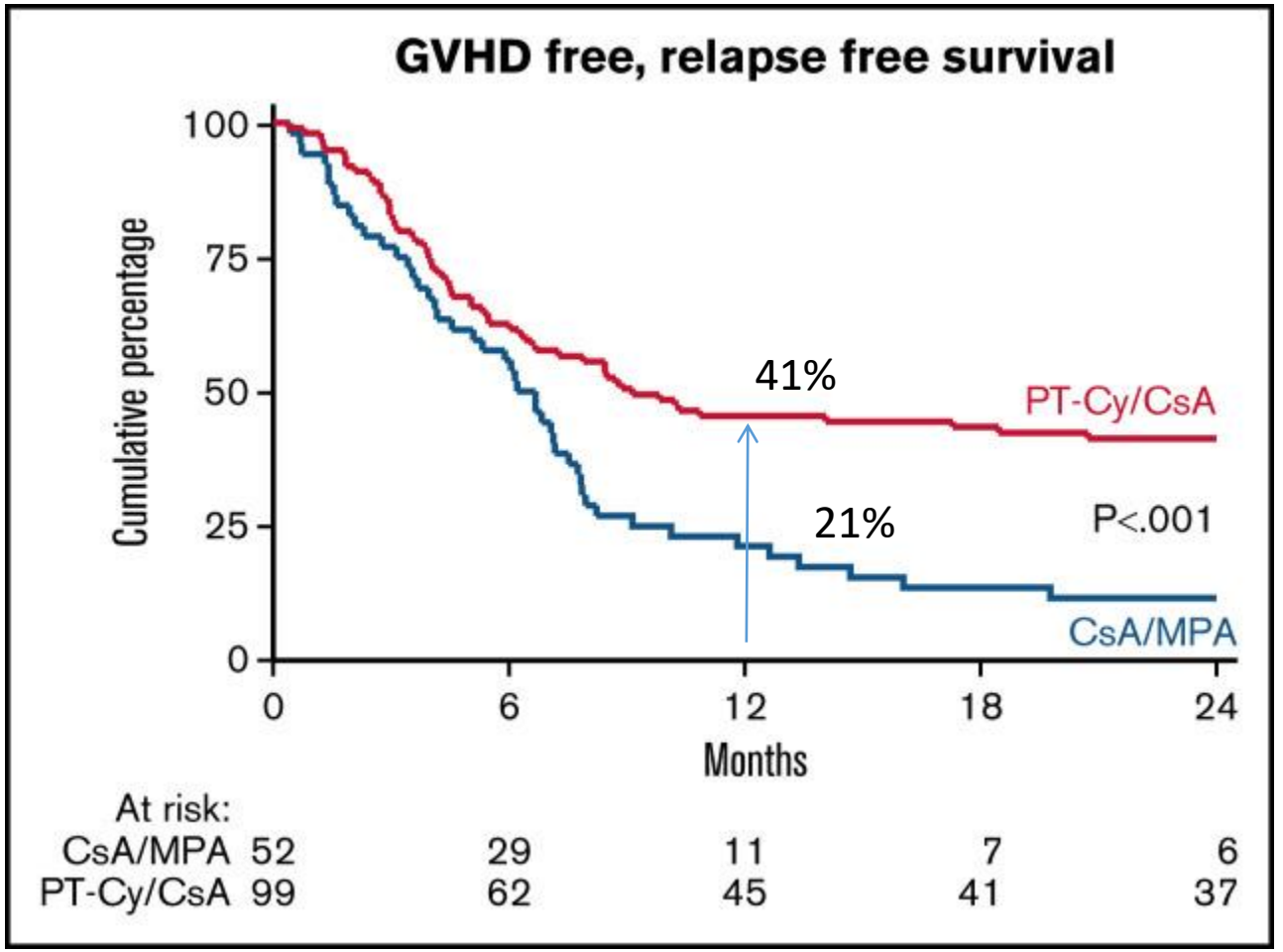
n=50
ciclo+MPA (acide mycophénolique)
jusqu'à J90+

GVHa II-IV 30%

GVHc ext 16%

GVHaII-IV 48%

GVHc ext 48%



Broers Blood Adv 2022

Cy- PT fait pareil que ciclo/tacro +MTX dans des greffes matchées de MO en MAC, SANS SAL

Cy- PT+ ciclo/tacro+MMF fait mieux que ciclo/tacro +MTX ou MMF dans des greffes matchées de CSP en RIC/NMA, SANS SAL

Nouvelles RECO de L'EBMT (à paraître)

Greffe MUD sans SAL: privilégier CyPT

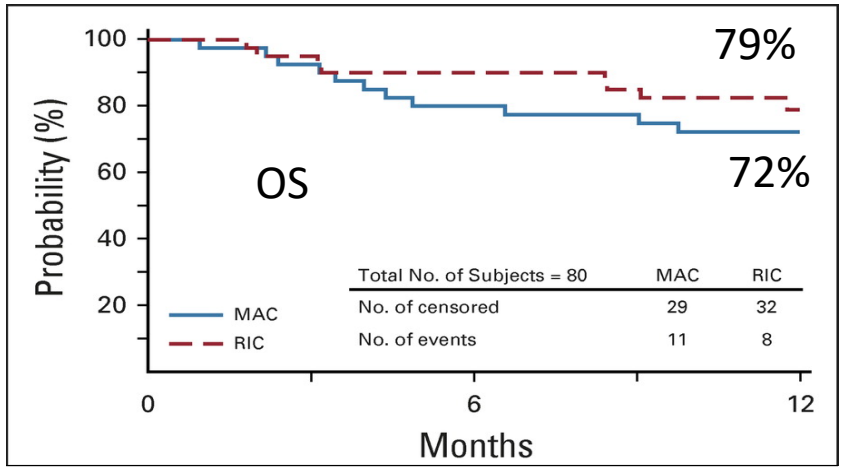
Greffes MRD avec SAL: pas d'argument pour remplacer SAL par CyPT

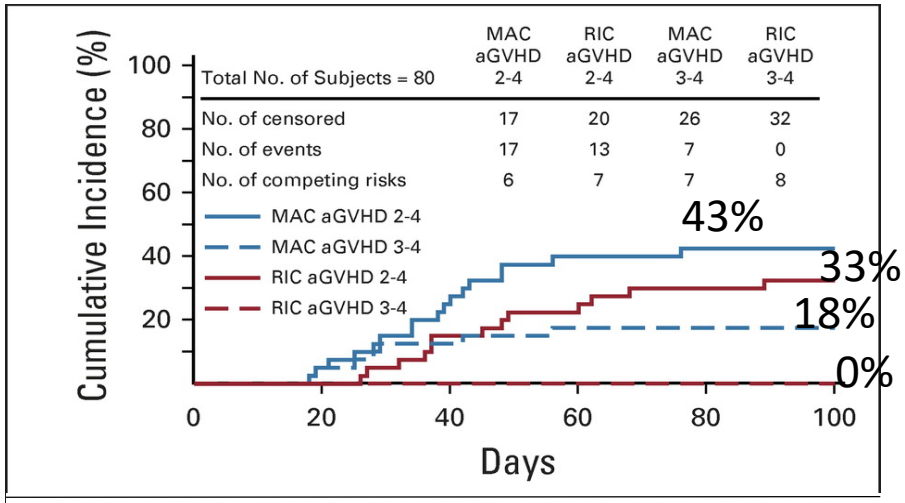
Greffes MUD avec SAL: CyPT en alternative du SAL est une possibilité

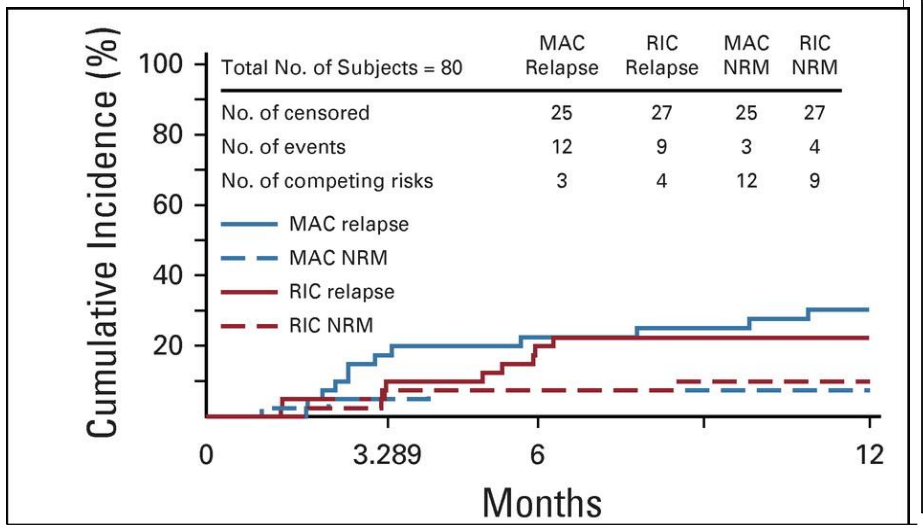
Quid des greffes MMUD?

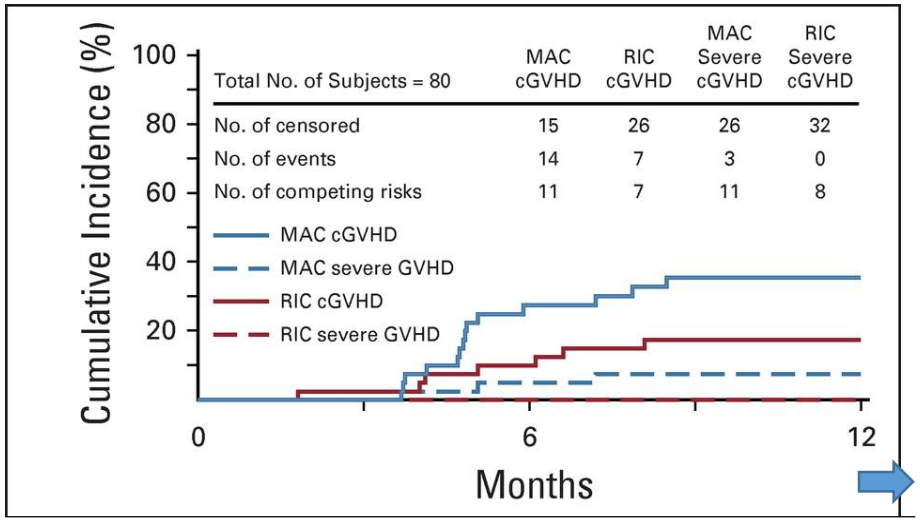
PT-Cy dans les MMUD

Bronwen E. Shaw, JCO 2021









Phase 2 prospective Cy-PT MMUD (39% 4 à 6/8 match)
End point: OS 1 an>65%
N=80 pts dans 11 centres US, sponsor NMDP
LAM (46%), LAL (21%), LNH ou LH (20%)
51 ans med (18-70)

CDT MAC standart ou Bu Flu/ RIC: Baltimore

Greffon: moelle

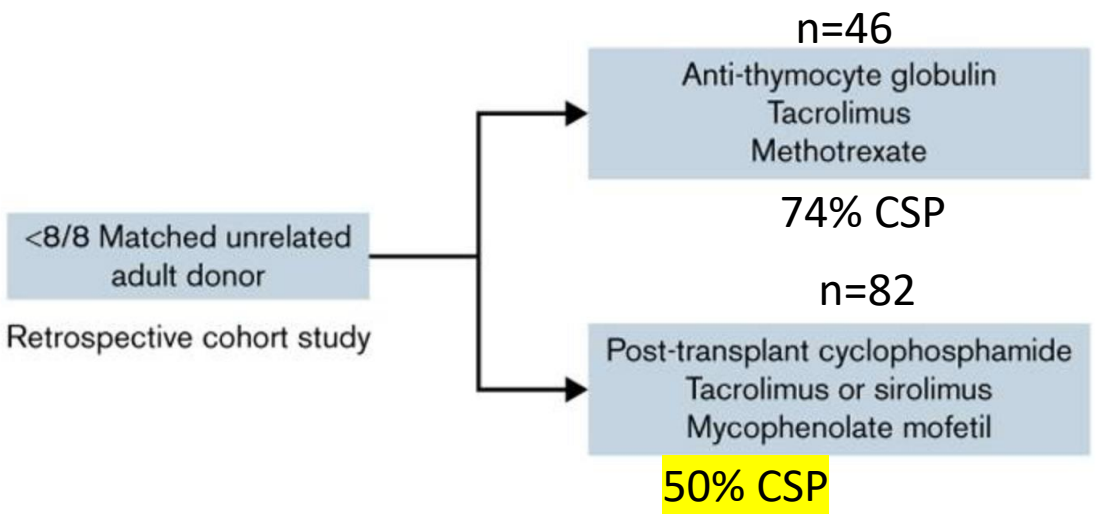
PT-Cy J+3J+4
Sirolimus+ MMF J+5

48% minorités ethniques

GRFS 1 an: 38% MAC, 55% RIC

Pour info, endpoint alter gref GRFS 2 ans 30% MMUD 9/10

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



CyPT>SAL

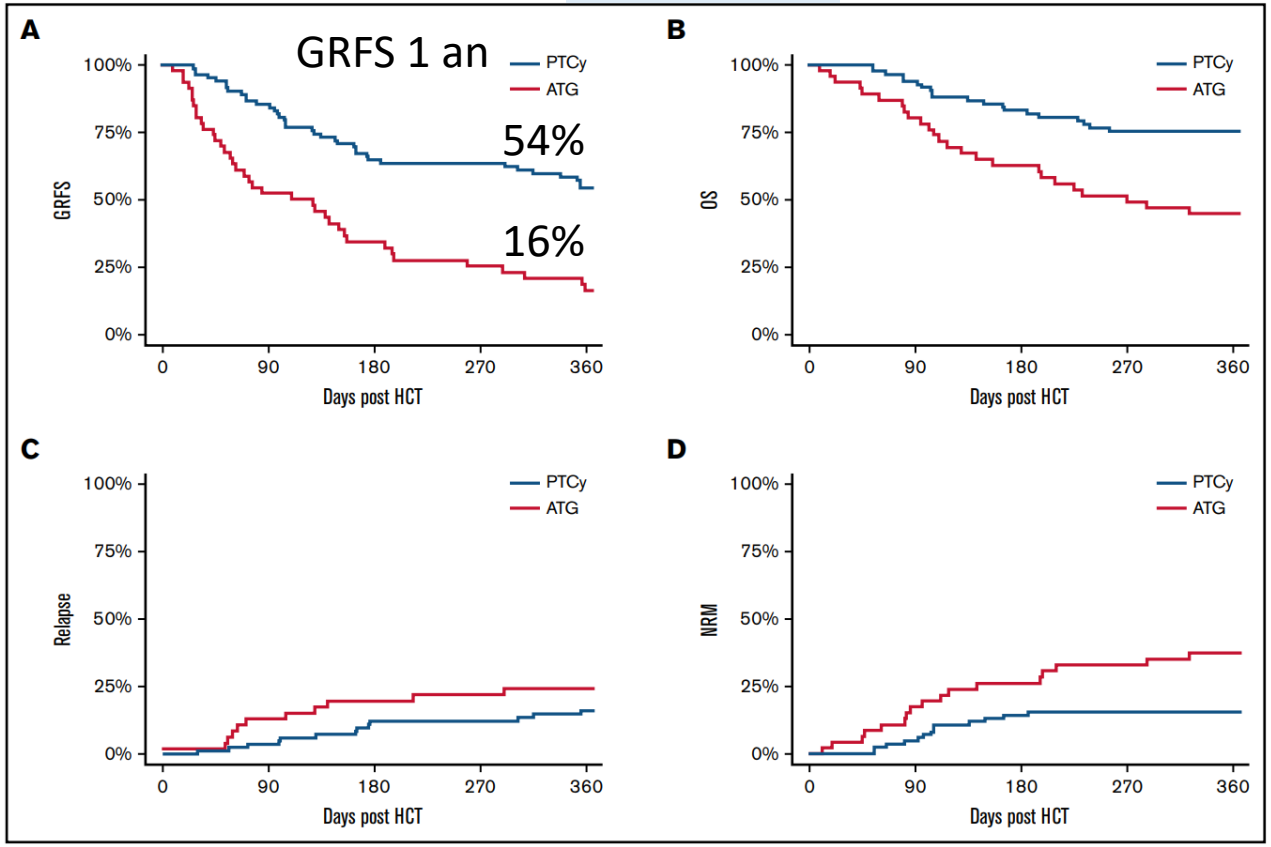


Figure 1. GRFS, OS, relapse, and RFS in both cohorts. GRFS (A), OS (B), cumulative incidence of relapse (C), and cumulative incidence of death without relapse (D).

Nouvelles reco EBMT

dans les MMUD: SAL ou CyPT

Gimenez, Blood adv 2022

Nouvelles reco EBMT

Chez l'adulte GVHa ref corticoides: RUXOLUTINIB recommandé

Chez l'adulte GVHc ref corticoides: RUXOLUTINIB recommandé
BELUMOSUDIL: option thérapeutique potentielle
IBRUTINIB: option thérapeutique potentielle

Prévention GVH

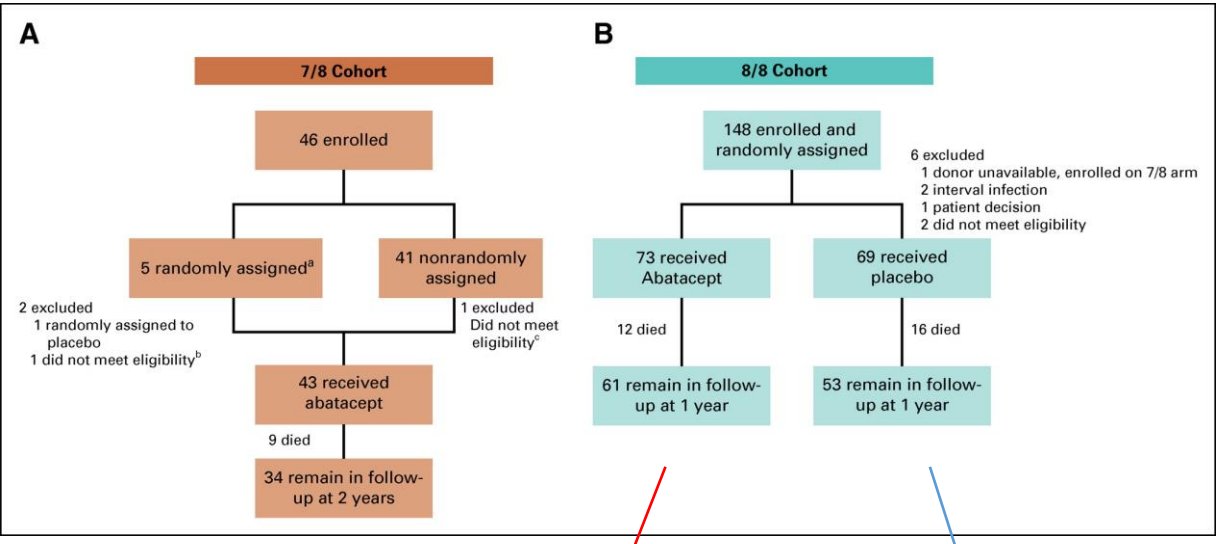
MRD: SAL recommandé, CyPT est une option thérapeutique potentielle

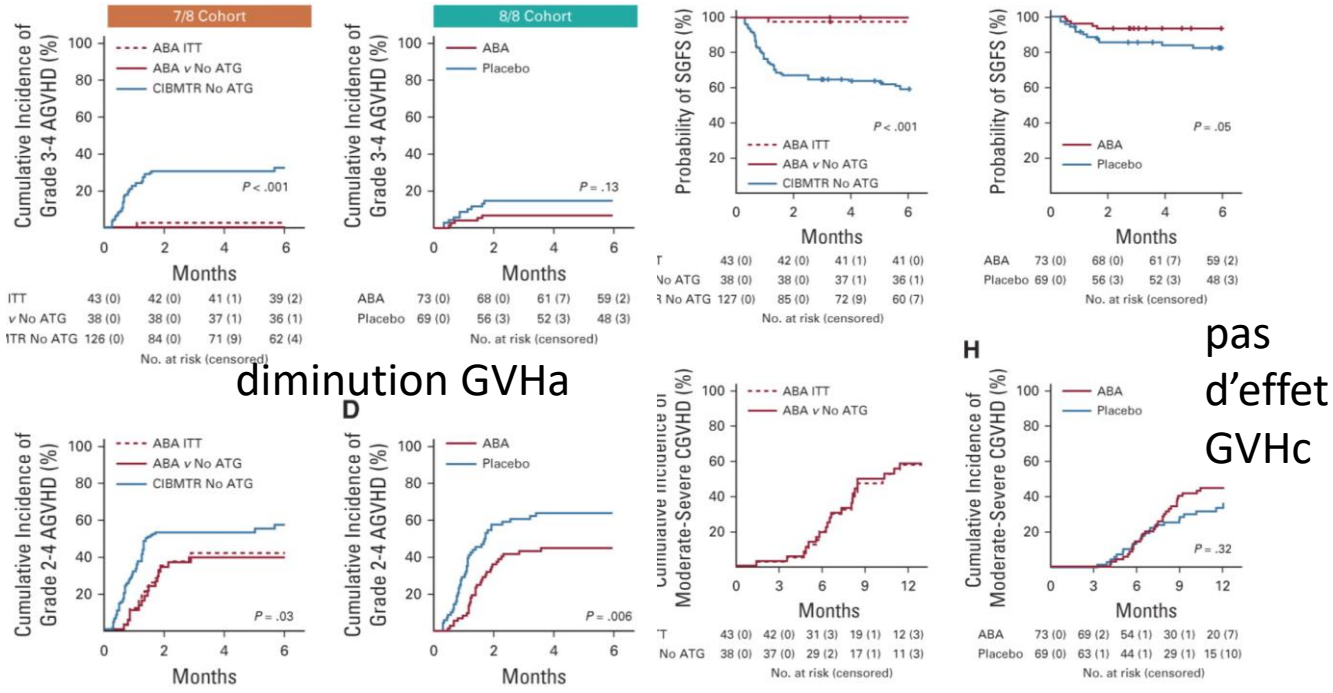
MUD: SAL ou CyPT recommandé

MMUD: SAL ou CyPT recommandé

Phase II Trial of Costimulation Blockade With Abatacept for Prevention of Acute GVHD

Watkins, JCO 2021





diminution GVHa

pas d'effet GVHc

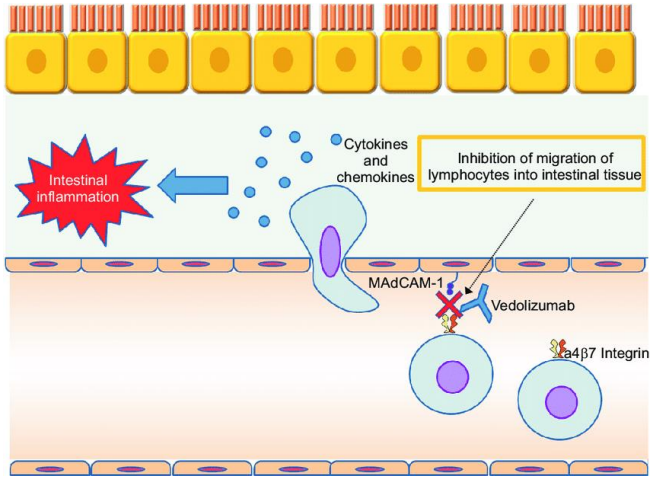
CNI/MTX + abatacept
10 mg/kg/dose
J-1, +5, +14, +28

CNI/MTX + placebo

MAC, 60-50% CSP, Pas d'ATG

In December 2021, abatacept in combination with a calcineurin inhibitor and methotrexate was approved by the FDA for the prophylaxis of acute GVHD among patients undergoing allogeneic transplant from a matched or 1-allele mismatched unrelated donor

Vedolizumab for Prophylaxis of Lower Gastrointestinal (GI) Acute Graft-Versus-Host Disease (aGvHD) after Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) from Unrelated Donors: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study (GRAPHITE)



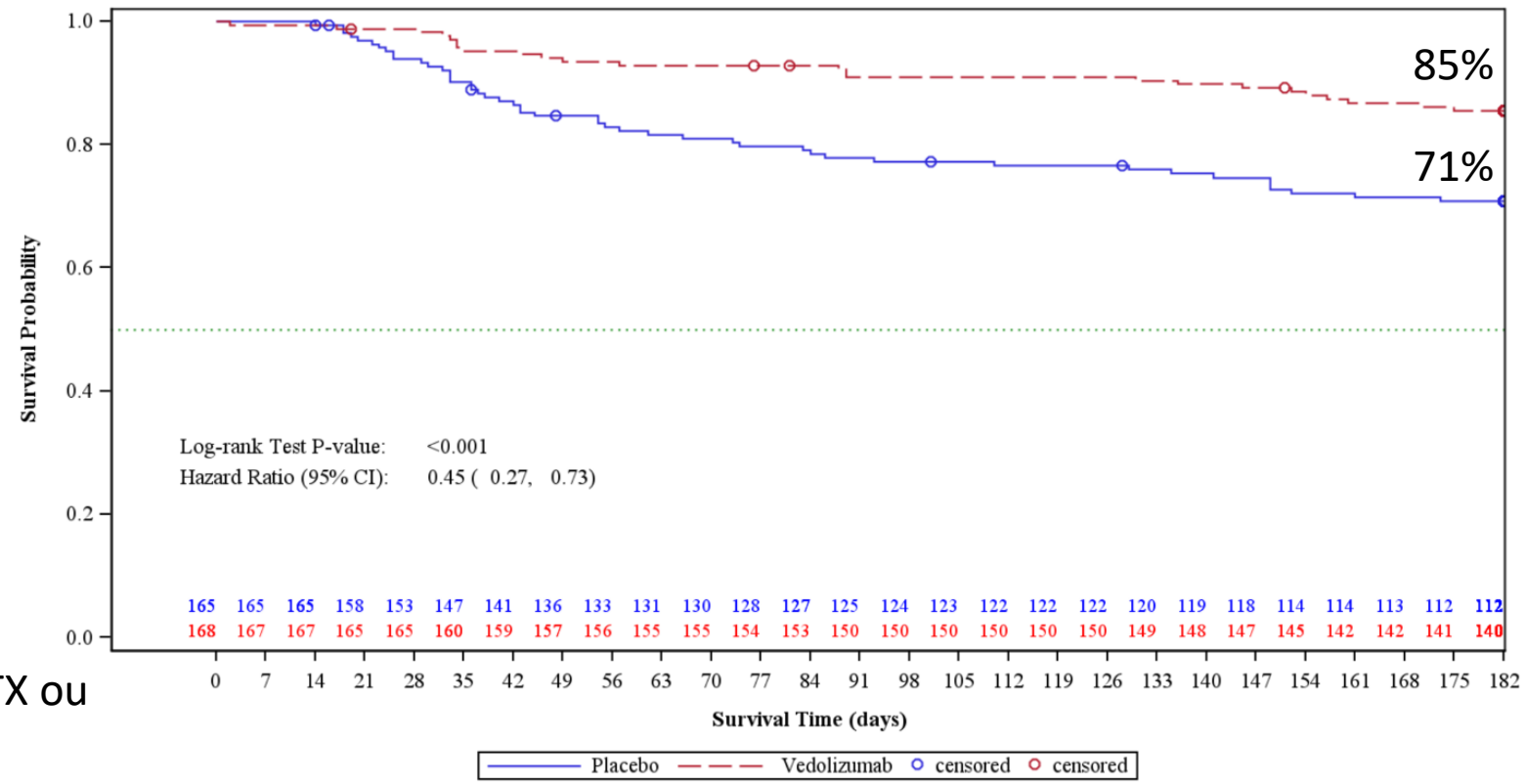
Vedolizumab Ac anti α4β7 integrin exprimés sur lympho essentiel pour trafficking GI

n=168
vedo+CNI+ MTX ou MMF

n=165
Placebo+CNI+ MTX ou MMF

7/8 ou 8/8 MUD, RIC/MAC

Figure. Primary endpoint: Lower gastrointestinal aGvHD free Survival by Days+180 (red line: vedolizumab arm; blue line: placebo arm)



Chen; Tandem Meetings: Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR, fev 2023

Traitements curateurs GVHaigue

1ere ligne GVHa 2-4: Corticoides à fortes doses

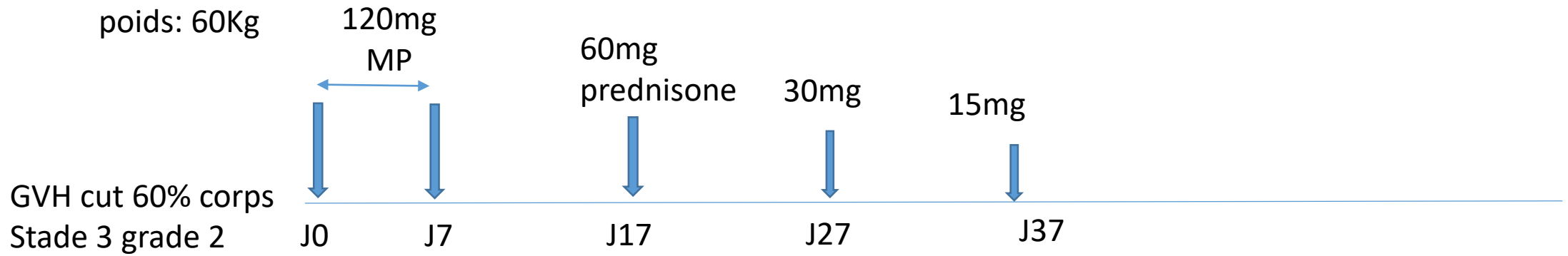
2mg/Kg methylprednisolone ou 2-2.5mg/Kg prednisone
GVH grade 2 cutanée ou dig haut: 1mg/Kg

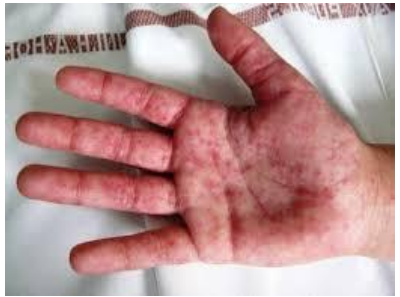
7 jours minimum

Si GVH dig: rajouter cortico non absorbés
Si GVH cut ajouter cortico topiques

1933: traitement PAR avec extraits glandes surrénales. Découverte cortisol

En cas de résolution : diminution 10% dose initiale en 4 semaines environ



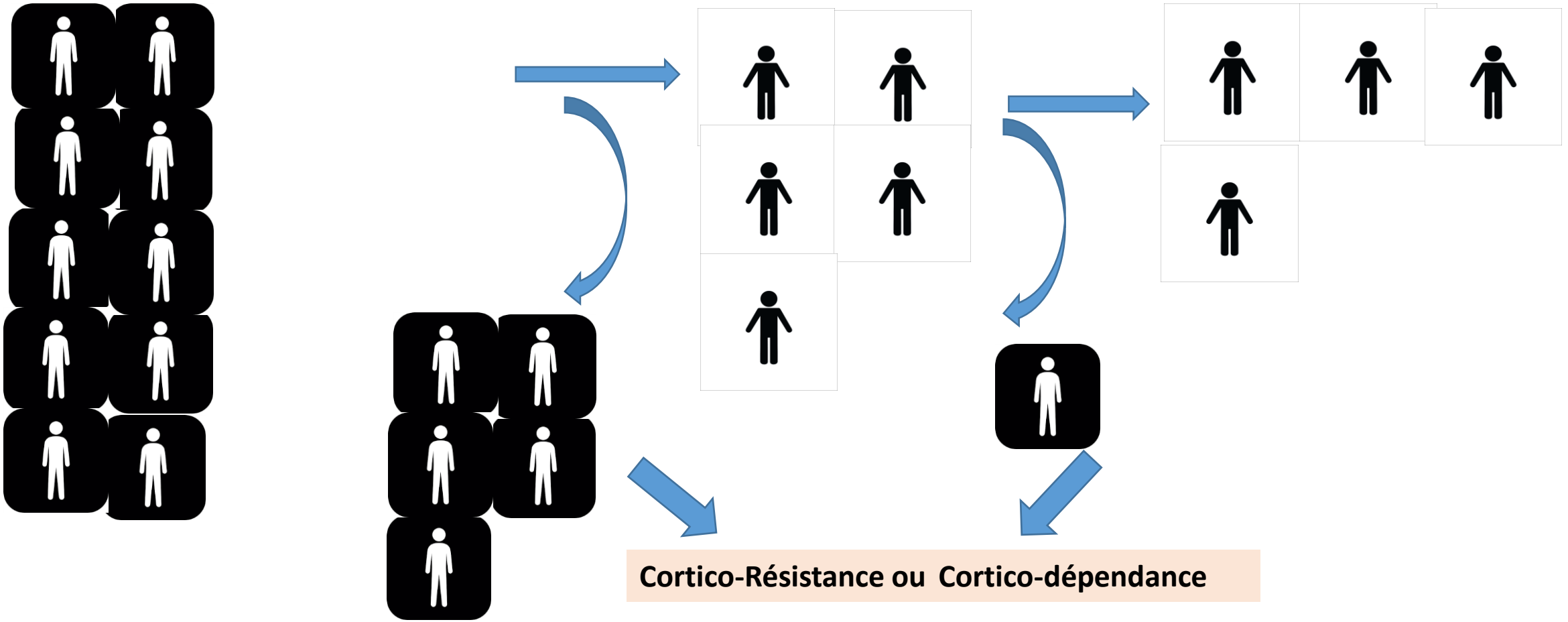


Guidelines EBMT, Penack, Lancet hematol 2020

N=10 GVHa

N=5 réponses complètes aux corticoides

N=3 à 4 réponses durables après cortico



Cortico-Résistance ou Cortico-dépendance

- Progression après 3 jours
- Persistance GVH III-IV après 7 jours
- Persistance GVH II-IV après 14 jours

Murray et al. GVHD, The european Blood and Marrow Transplantation Textbook for nurses, 2018, p221-51; D'après Zeiser EBMT 2022

A second-line treatment for acute GVHD is recommended if corticosteroid resistance or dependence occurs	100	2C	This recommendation is based on standard practice and expert opinion
There is no standard second-line treatment for acute GVHD. Current practice is to prescribe one of the following drugs: alemtuzumab, α1-antitripsin, basiliximab, cellular therapies (eg, mesenchymal cells and regulatory T-cells) daclizumab, extracorporeal photopheresis, faecal microbiota transplantation, JAK inhibitors (eg, ruxulotinib which is FDA approved), mycophenolate mofetil, methotrexate, pentostatin, rATG, sirolimus, or vedolizumab; for second-line treatment of acute GVHD, centres should follow their institutional guidelines, and patients should be treated in clinical trials when possible	100	2A	Not enough data exist from well designed studies available to be able to compare the efficacy of different second-line options

Guidelines EBMT
Penack, Lancet hematol 2020

REACH Program

Acute SR-GVHD-Completed and Published Studies

REACH1
- Single-cohort Ph 2 trial (US only)
- Ruxolitinib in combination with corticosteroids for the treatment of Grade II-IV **SR-aGVHD**

REACH2
- Ph 3, randomized, open-label, multicenter trial (ex-US)
- Ruxolitinib vs BAT in Grade II-IV **SR/D-aGVHD** after allo-SCT

REACH3
- Ph 3, randomized, open-label, multicenter trial (Global)
- Ruxolitinib vs BAT in moderate to severe **SR/D-cGVHD** after allo-SCT

Ruxo= standart de 2de ligne GVHa ou cortico R/dep

AMM

Prix France début 2024

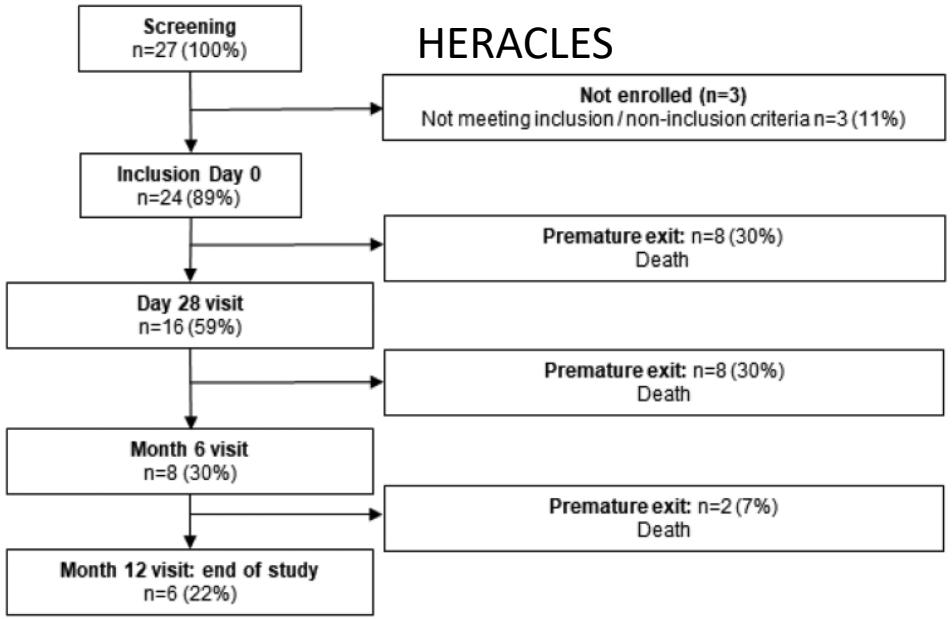
Studies in Pediatric Patients

REACH4
- Ph 1/2, single-cohort trial (ex-US)
- Ruxolitinib in combination with corticosteroids in Grade II-IV **aGVHD** after allo-SCT
- **Recruitment Completed**

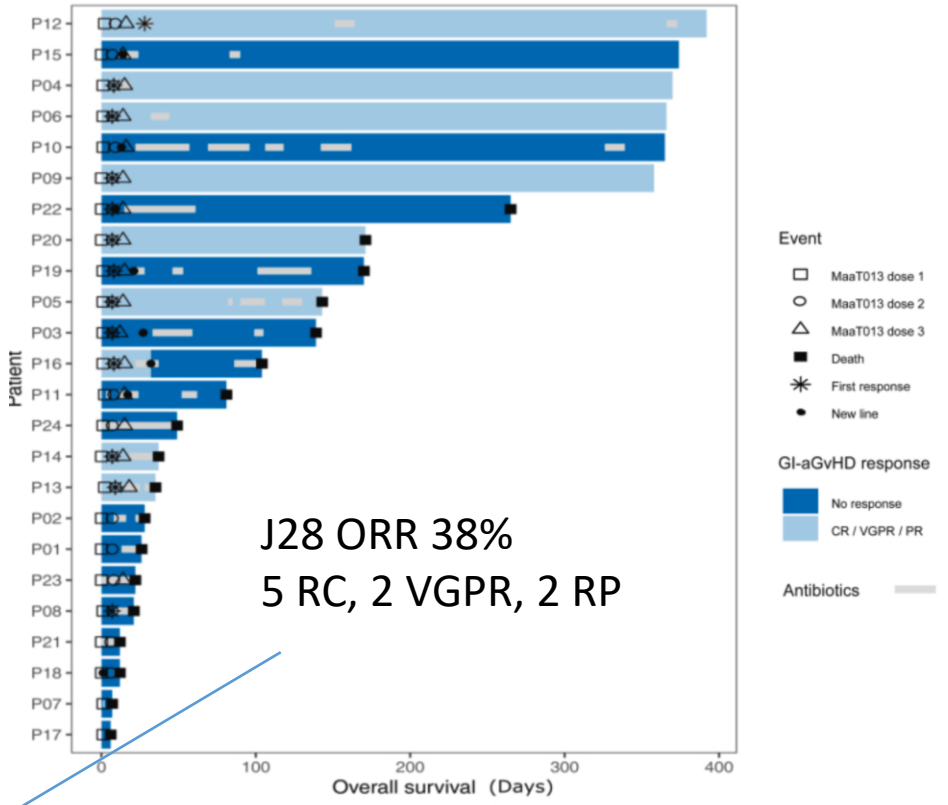
REACH5
- Ph 2, single-cohort trial (ex-US)
- Ruxolitinib in combination to corticosteroids in moderate to severe **cGVHD** after allo-SCT

REACH 1: Jagasia M, et al. *Blood*. 2020;135(20):1739-1749; REACH 2: Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810; Reach 3: Zeiser R, et al. ASH 2020. Abstract 77. 2.
REACH 4: Locatelli F, et al. EBMT 2021. Poster P063; REACH5: Locatelli F, et al. EBMT 2021. Poster P070

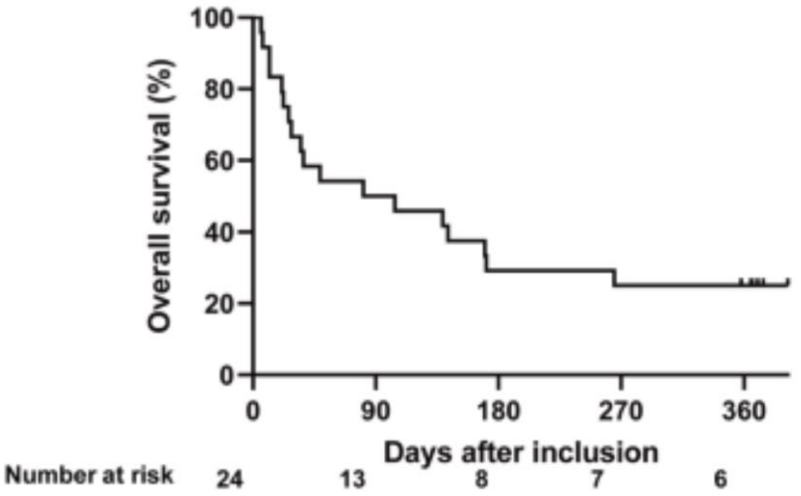
Pooled allogeneic faecal microbiota MaaT013 for steroid-resistant gastrointestinal acute graft-versus-host disease: a single-arm, multicentre phase 2 trial



GVHa dig basse 3-4 cortico-R
TMF en 2de ligne
MaaT013: pool de 3 à 8 donneurs voie rectale



J28 ORR 38%
5 RC, 2 VGPR, 2 RP



Selles: aug richesse , bacteries productrices de butyrate chez répondeurs

n=52 patients hors protoc, ORR 58%

Malard, eClinicalMedicine 2023

Phase 2 clinical trial evaluating abatacept in patients with steroid-refractory chronic graft-versus-host disease

39 patients with SR-cGVHD treated with median 3 prior lines of therapy

↓

Abatacept 10mg/kg IV q2 weeks
Doses 1-3

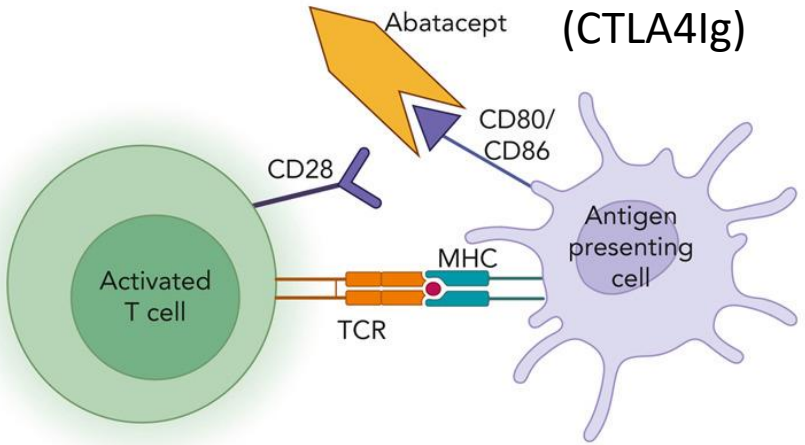
↓ 1 month

Abatacept 10mg/kg IV q4 weeks
Doses 4-6

↓ 1 month

possibilité 6 doses mensuelles sup (max 12 doses)

Clinical response assessed per NIH cGVHD Consensus Criteria



ORR 58% **CR 0%** **PR 58%**

25% median reduction in prednisone dose in responders

3 drogues approuvées FDA GVHc

Ibrutinib
ORR 67% CR 21% PR 45%
+50% reduc prednisone

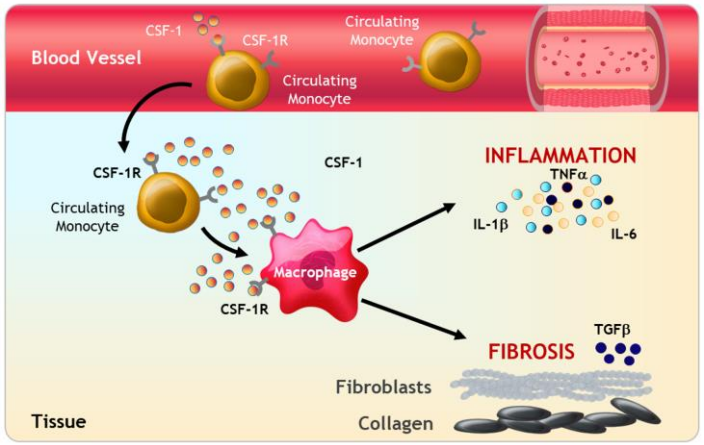
Ruxolutinib
best ORR 76% CR 12% PR 64%

Belumosudil
best ORR 74% CR 6% PR 68%
54% med reduc prednisone

Created with BioRender.com

Koshi, Blood 2023

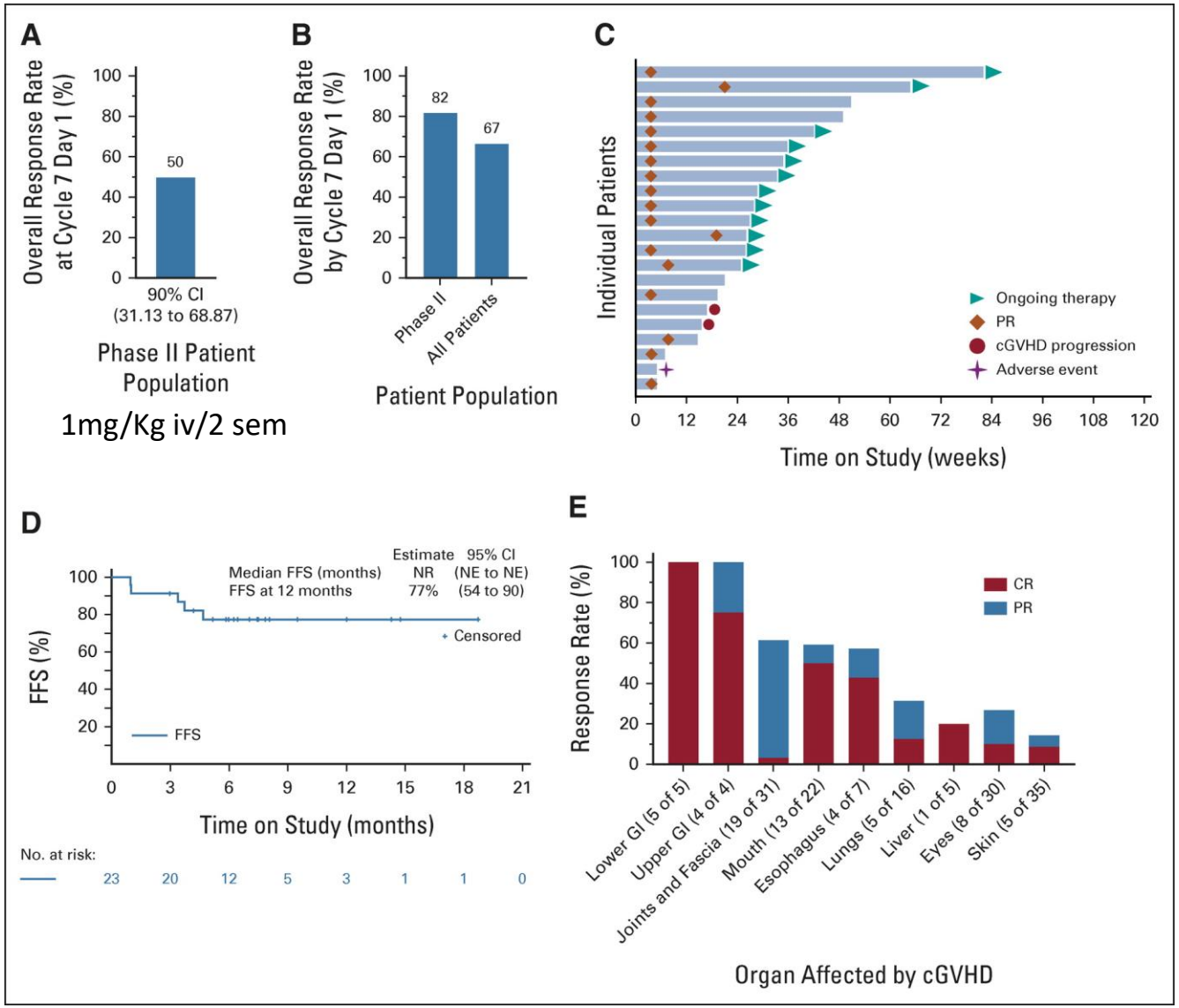
Axatilimab for Chronic GVHD After Failure of at Least Two Prior Systemic Therapies: Results of a Phase I/II Study



Syndax, Adapted from MacDonald, KP; Blood. 2017

	n=40
Time from cGVHD diagnosis to first dose, years, median (range)	3.2 (0.11-15.62)
NIH cGVHD severity, No. (%)	
Moderate	6 (15.0)
Severe	34 (85.0)
Organ involvement	
Median number of organs involved, No. (range)	4 (1-9)
Patients with ≥ 4 organs involved, No. (%)	26 (65)

Objectif ORR 60%



Kitko, JCO 2023

CONCLUSION

La GVH reste un problème majeur post allo

La plupart des études rando ne comportent pas de SAL

Prévention:

ATG reste valable pour les MRD

Pour les MUD : CyPT est une alternative au SAL

Pour les MMUD: CyPT > SAL

Abatacept semble être une drogue prometteuse

Curatif: GVHa cortico R reste problématique

Ruxo reste le traitement de reference en 2de ligne GVHa/c

Intérêt TMF dans les GVH dig cortico R

nouvelles drogues dans la GVHc

Investigational agent	Donor type	Study arm	Control arm	aGVHD (grade 3-4), %	Relapse, %	OS, %	Composite end point, %
RIC							
PTCy (BMT CTN 1703)	MRD/MUD (8/8)	PTCy/TAC/MMF (n = 214)	TAC/MTX (n = 217)	6.3 vs 14.7*	21 vs 20	76.8 vs 72.6	GRFS: 52.7 vs 34.9*
PTCy (HOVON 96)	MRD/MUD (8/8)	PTCy/CSA (n = 99)	CSA/MMF (n = 52)	6 vs 16	32 vs 24	71 vs 65	GRFS: 45 vs 21*
Vedolizumab	MUD (7/8 or 8/8)	Vedo/CNI/MTX or MMF (n = 168)	CNI/MTX or MMF (n = 165)	—	—	—	85.5 vs 70.9* Lower intestinal aGVHD-free survival
Sirolimus	MUD (7/8 or 8/8)	Siro/MMF/CSA (n = 91)	CSA/MMF (n = 77)	2 vs 8	19 vs 21	86 vs 70*	—
MAC							
Abatacept	MUD (8/8)	Aba/CNI/MTX (n = 73)	CNI/MTX (n = 69)	6.8 vs 14.8	21.5 vs 23.6	74.3 vs 64	SGFS: 93.2 vs 82*
Abatacept	MUD (7/8)	Aba/CNI/MTX (n = 43)	CNI/MTX (n = 127)†	2.3 vs 30.2*	9.3 vs 21.4	73.6 vs 45.3*	SGFS: 97.7 vs 58.75*
PTCy	MUD (7/8 or 8/8)	PTCy/TAC/MMF (n = 125)	—	4	25	80	GRFS: 57
Vedolizumab	MUD (7/8 or 8/8)	Vedo/CNI/MTX or MMF (n = 168)	CNI/MTX or MMF (n = 165)	—	—	—	85.5 vs 70.9* Lower intestinal aGVHD-free survival

Dashes denote that the results are not yet available. Aba, abatacept; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; GRFS, GVHD/relapse or progression-free survival; HOVON, Dutch-Belgian Cooperative Trial Group for Hemato-Oncology; MAC, myeloablative conditioning; SGFS, severe aGVHD-free survival; Siro, sirolimus; Vedo, vedolizumab.

*Statistically significant.

†CIBMTR cohort.

Jamy, Blood 2023 (revue)