RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

29 et 30 SEPTEMBRE 2022

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

IMAGE FREEPIK

Sous l'égide de :

AI2R Filière · aviesan alliance nationale pour les sciences de la vie et de la santé · CeRéMAIA · GRI · European Reference Network for rare or low prevalence complex diseases · Fédération Immunologie · Imidiate · RITA Rare Immunodeficiency AutoInflammatory AutoImmune · Société Française de Dermatologie et de Pathologie Sexuellement Transmissible · Société Française d'Immunologie · SFR société française de rhumatologie · SOFREMIP Rhumatologie & maladies inflammatoires pédiatriques · SNFEM

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Traitements intensifs par thérapies cellulaires des maladies auto-immunes

Pr Grégory Pugnet

Interniste CHU Toulouse

29 et 30 SEPTEMBRE 2022

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

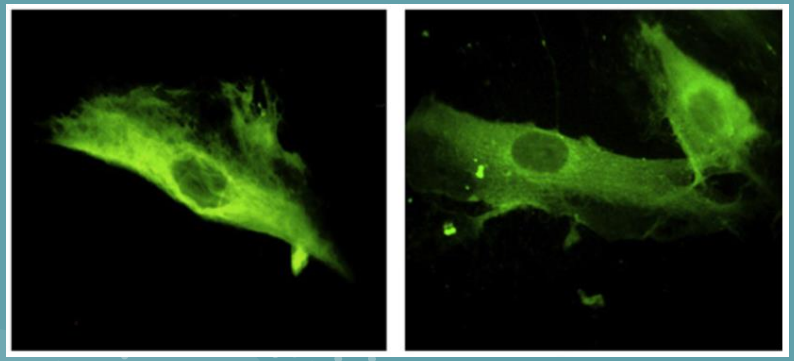
Sous l'égide de :

LIENS D'INERETS

Bords/consultant : Grifols, Boehringer, Abbvie, Alynlam, Amicus, Takeda, Pfizer

Frais de déplacements/intervenant : Abbvie, Actelion, Amicus, Boehringer, GSK, Novartis, Fresenius Kabi, Alynlam, Pfizer

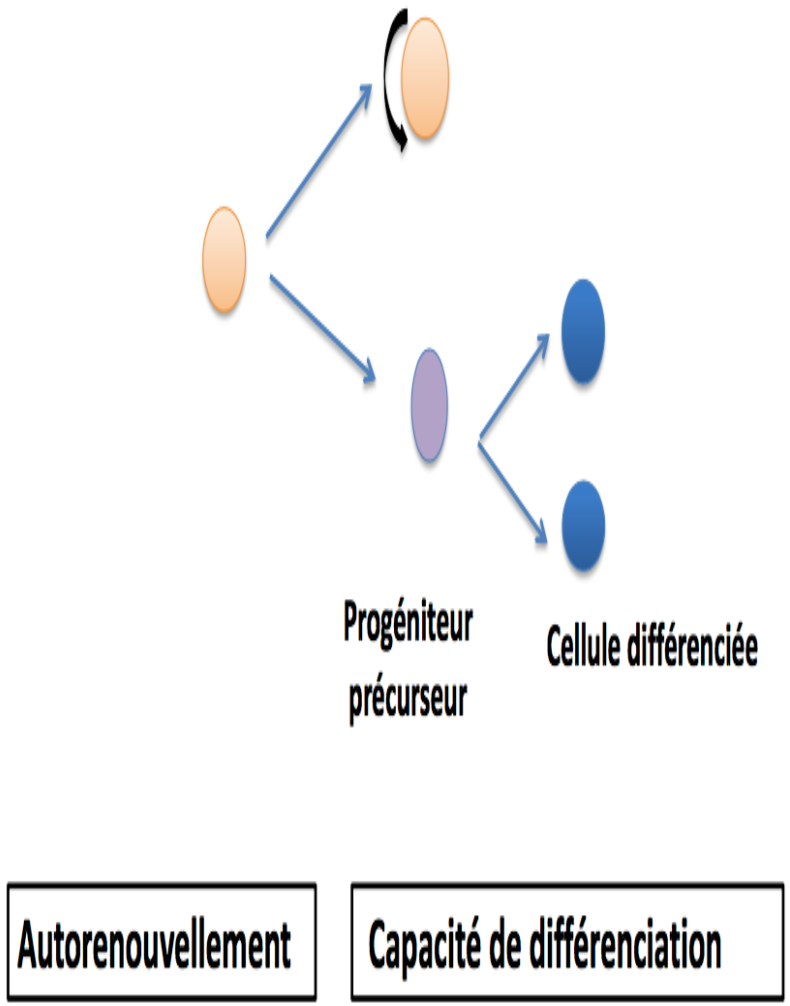
Qu’est ce que la thérapie cellulaire?



La Thérapie Cellulaire regroupe un ensemble de procédures thérapeutiques qui utilisent des greffes de cellules

Pour reconstituer un tissus lésé et par là même restaurer (à long terme) une fonction déficiente

Ou dans un but d’immunomodulation

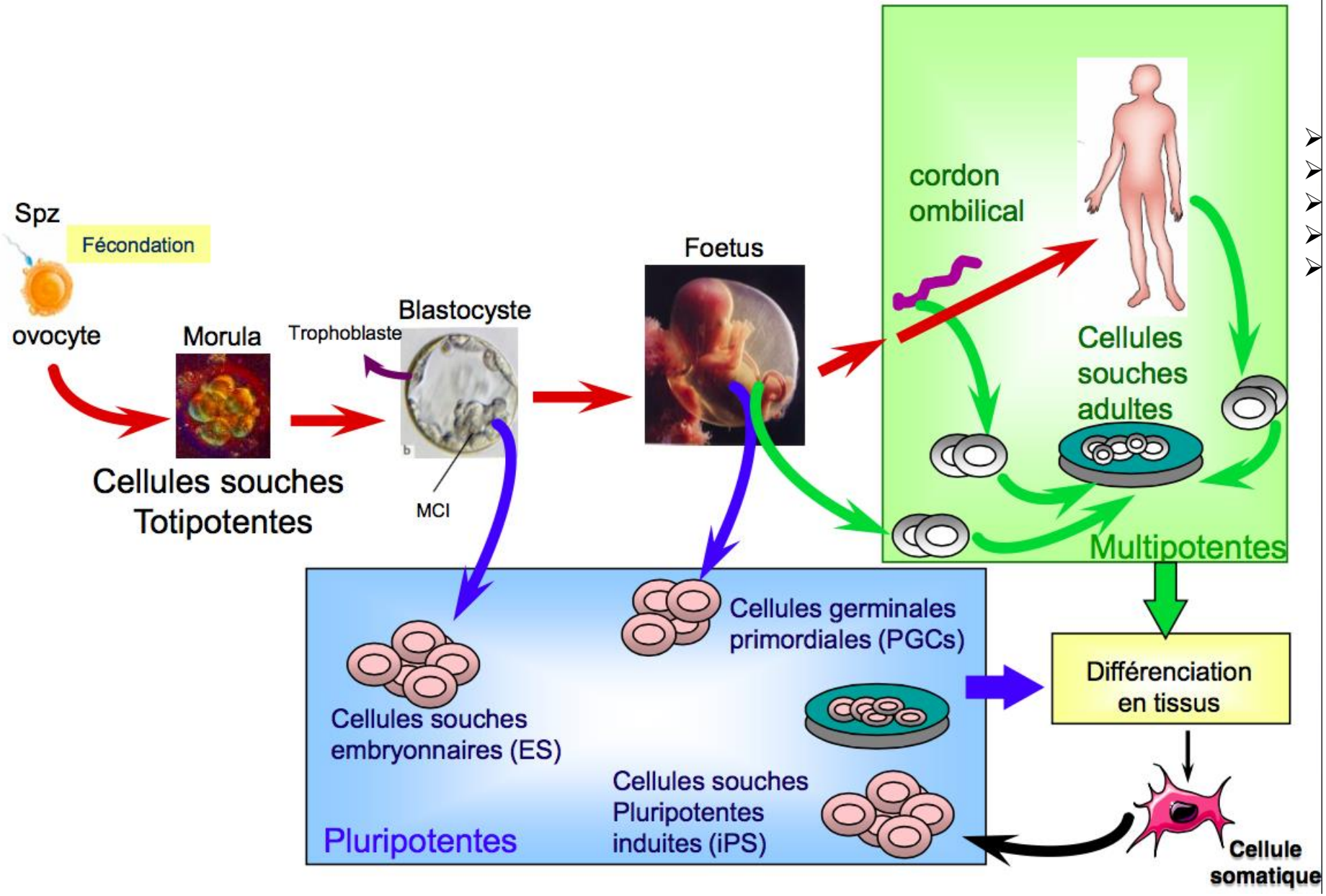


Qu'est ce qu'une cellule souche?

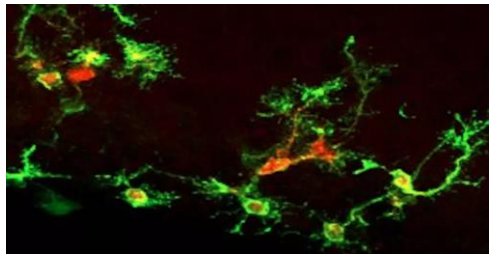
C'est une cellule qui n'est pas reconnaissable morphologiquement, mais par ses capacités fonctionnelles *in vitro* et *in vivo*

- **Auto-renouvellement**
- **Différenciation** d'une seule cellule vers plusieurs lignées
- **Fonctionnalité *in vivo*** : capacité d'une seule cellule à reconstituer au moins un tissu, à long terme

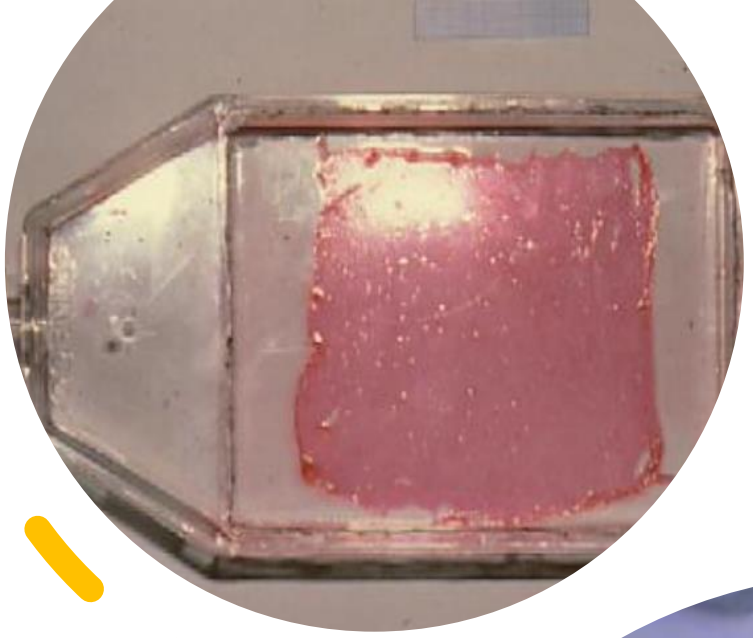
Différentes sources des cellules souches



- Cellules souches hématopoïétiques
- Cellules souches mésenchymateuses
- Cellules souches neurales
- Cellules souches de l'épiderme
- Cellules souches de la cornée



La Thérapie Cellulaire

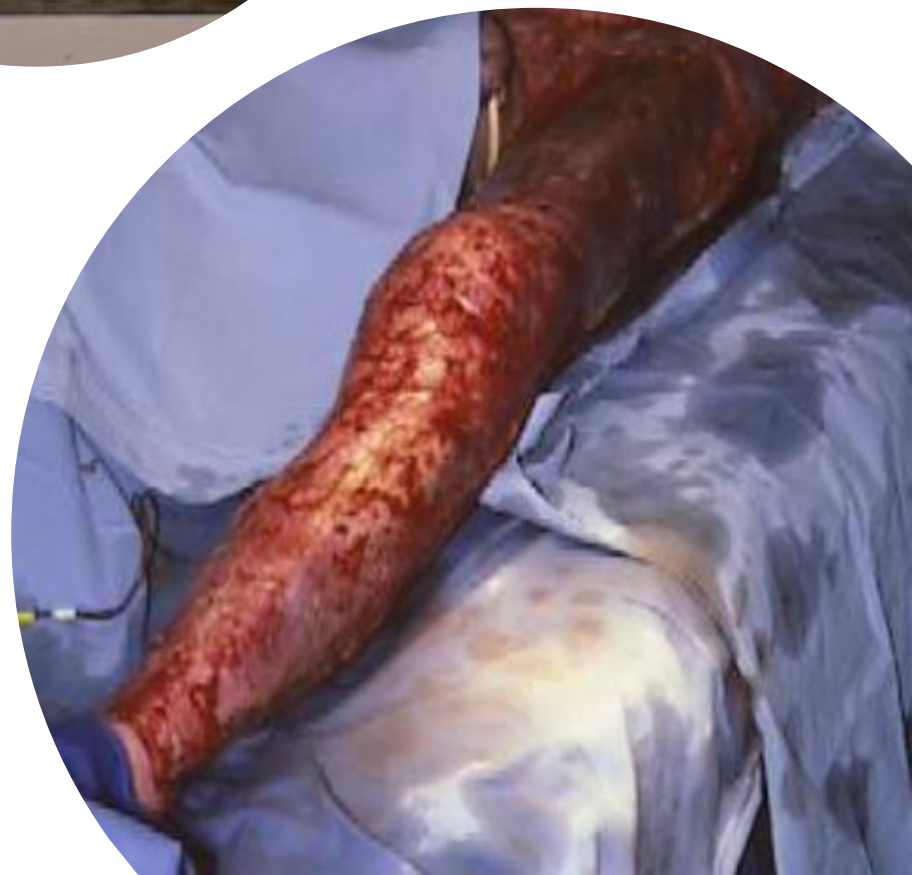


On greffe en routine des cellules souches hématopoïétiques depuis plus de 30 ans

Validation de nouvelles indications? – Nouveaux développements liés aux recherches actuelles ?

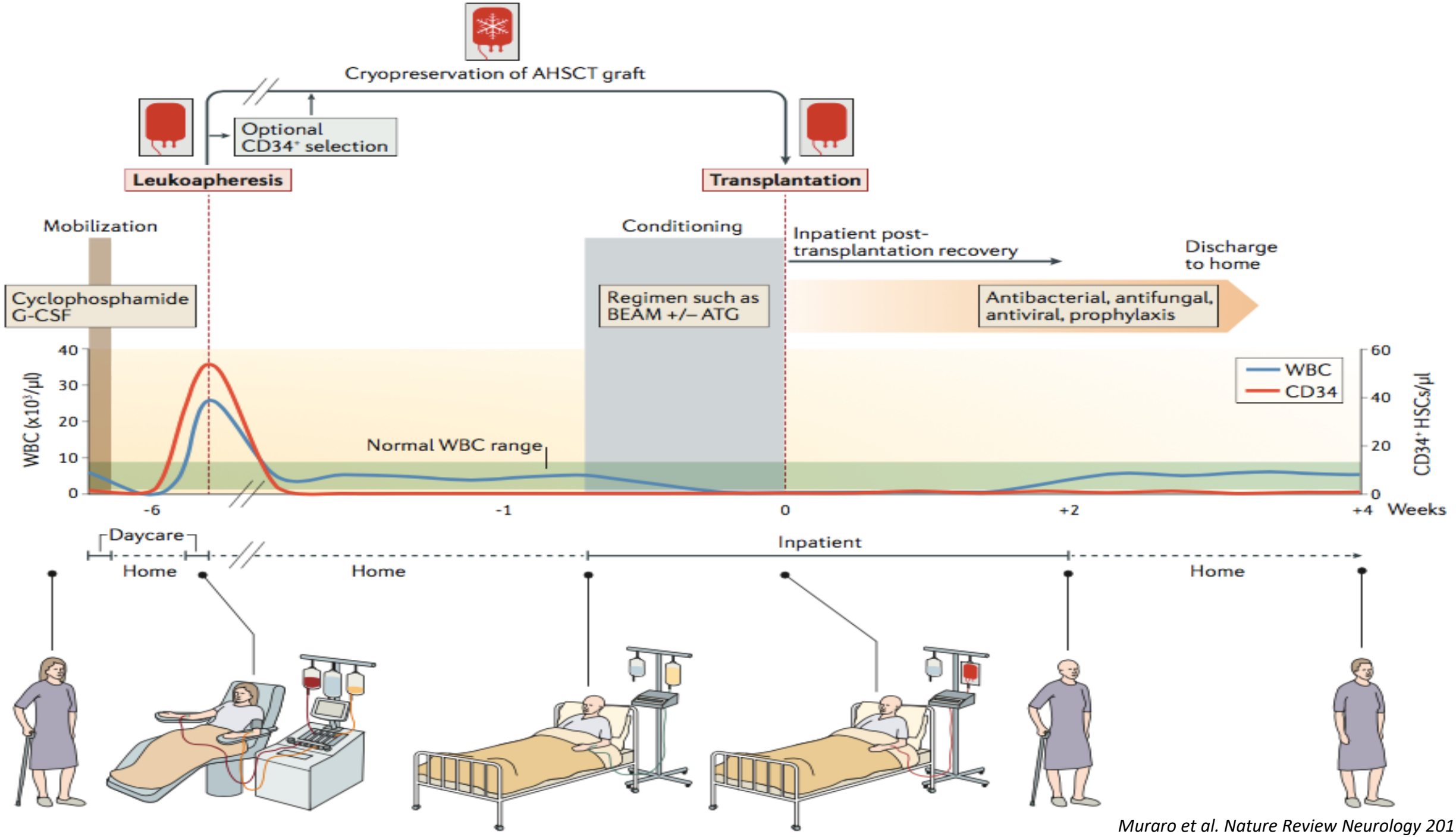
Hier | Aujourd'hui | Demain

On greffe des cellules somatiques adultes et fœtales en routine et au cours d'essais cliniques



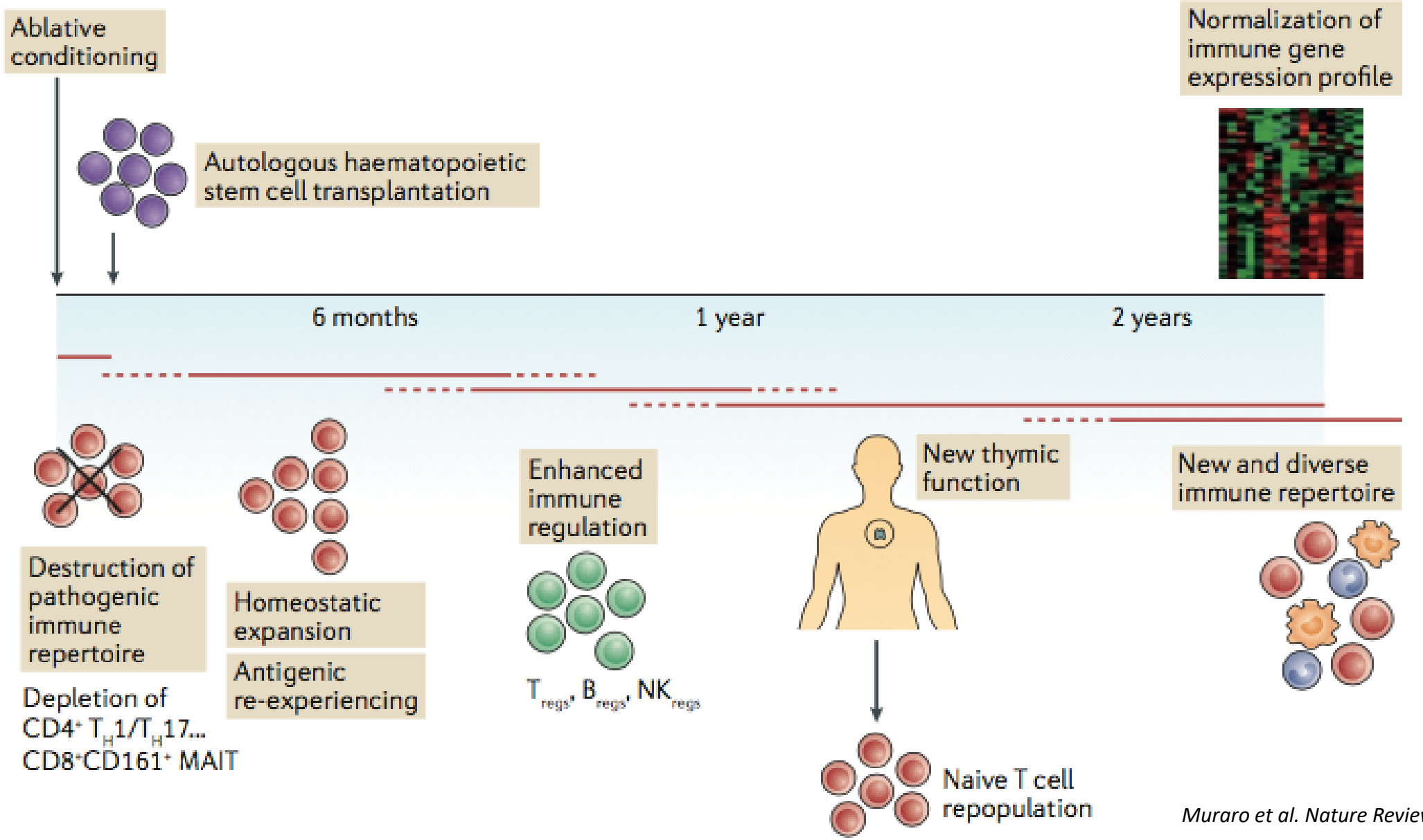
Traitements intensifs par thérapies cellulaires des maladies auto-immunes

- Intensification par greffe de cellules souches hématopoïétiques (CSH)
- « Add-on therapy » par cellules souches mésenchymateuses (CSM)
- CAR-T Cells



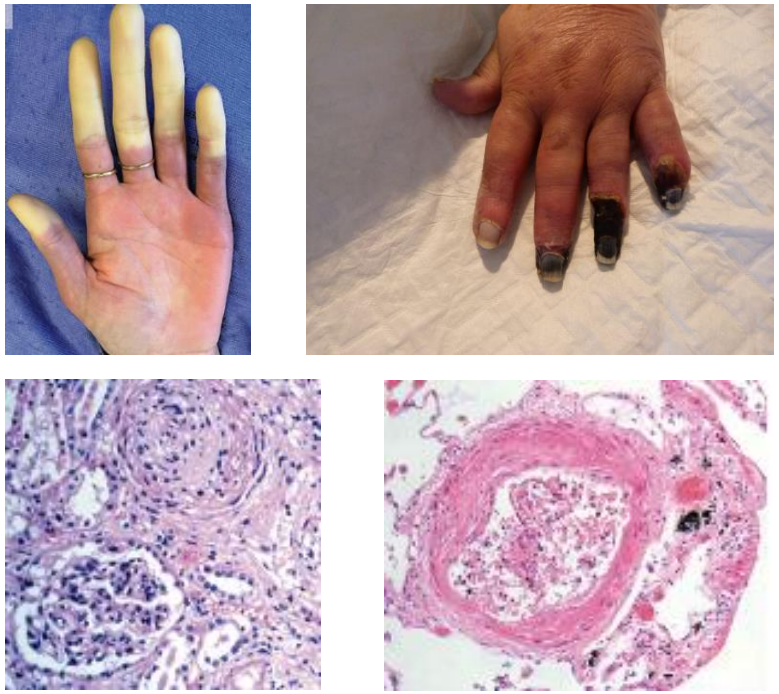
Muraro et al. Nature Review Neurology 2017

Proposed model of therapeutic mechanisms of AHSCT



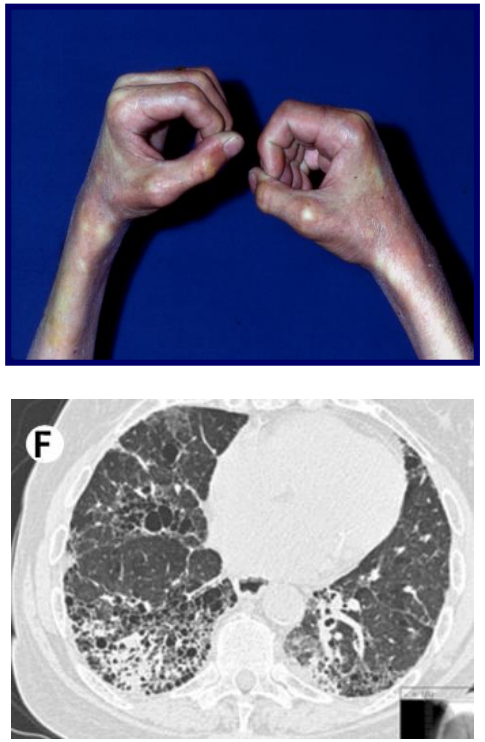
Muraro et al. Nature Review Neurology 2017

Sclérodermie Systémique



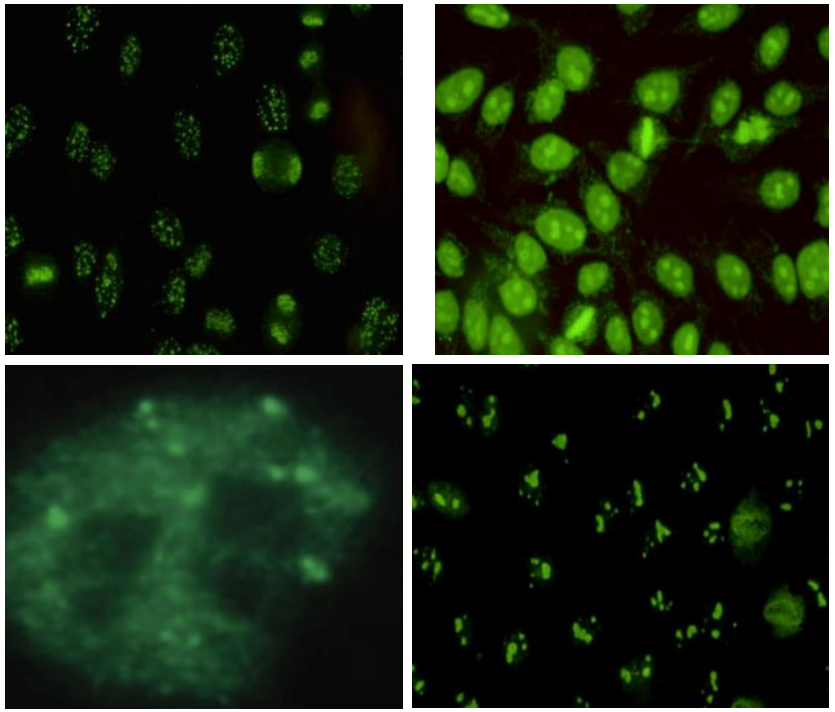
Vasculopathie

Phénomène de Raynaud
Ulcères digitaux
Crise rénale sclérodermique
HTAP



Fibrose

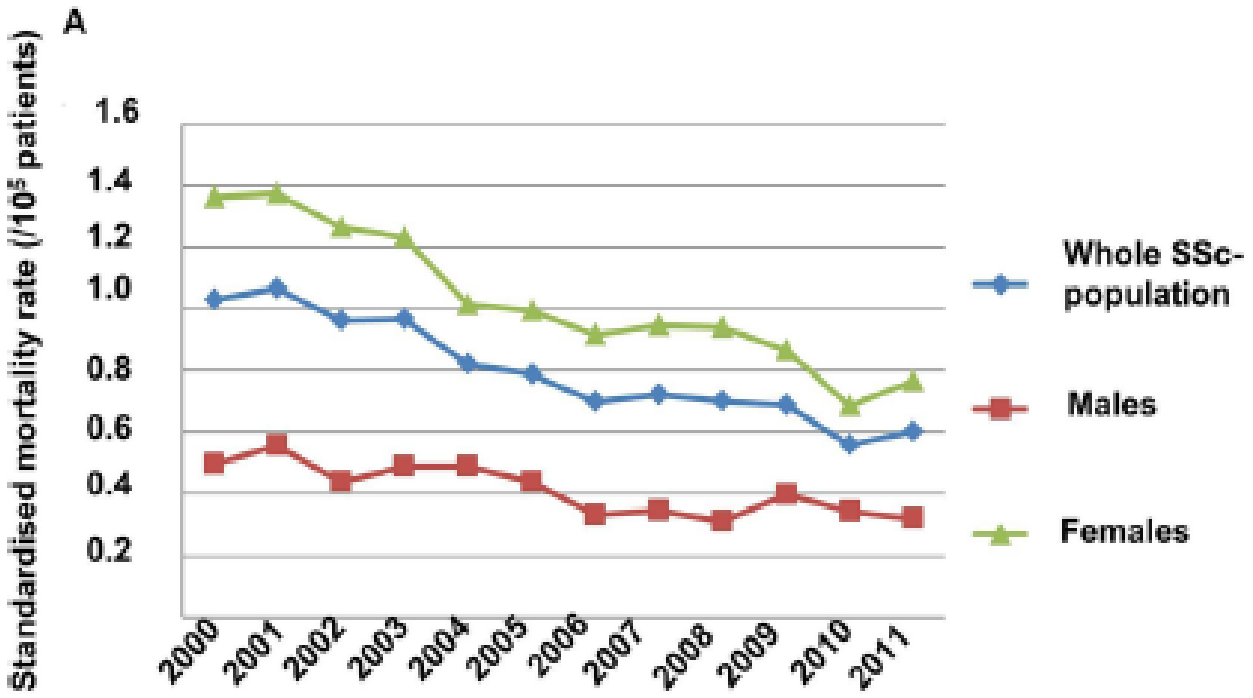
Cutanée
Poumon
Tube digestif
Coeur



Auto-immunité

Anticorps spécifiques:
-Anti-centromère
-Anti-Scl70
-Anti-RNA pol III

Sclérodermie Systémique cutanée diffuse récente rapidement évolutive: pronostic sombre



Survie à 5 ans dans SSc

No of risk factors	Total no of patients	No of patients deceased	Mortality (%)	Mortality (%) Bryan *et al*[6]
0	509	12	2.2	7.1
1	349	45	12.9	22.8
2	168	55	32.7	54.8
3	23	7	30.4	100

The table presents the number of risk factors according to the prognostic model of 5-year survival for newly diagnosed systemic sclerosis.[6] The number of patients and mortality in the current study are compared with the mortality in the original study by Bryan *et al.*[6]

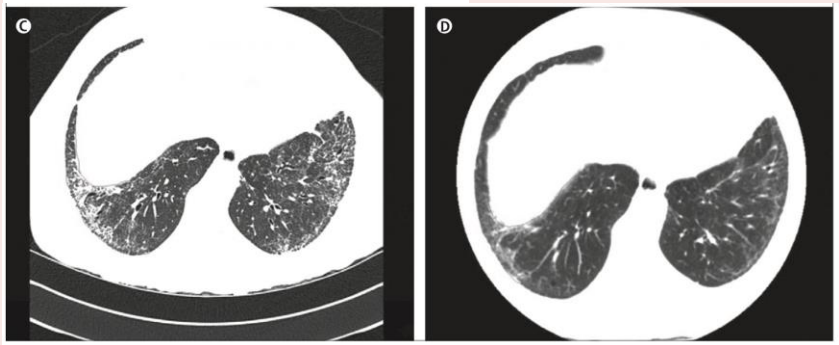
Fransen J et al Ann Rheum Dis 2011
Elhai et al Ann Rheum Dis 2017

Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial

Richard K Burt, Sanjiv J Shah, Karin Dill, Thomas Grant, Mihai Gheorghiade, James Schroeder, Robert Craig, Ikuo Hirano, Karin Marshall, Eric Ruderman, Borko Jovanovic, Francesca Milanetti, Sandeep Jain, Kristin Boyce, Amy Morgan, James Carr, Walter Barr*

Age (years)	45 (32-58)	44 (26-54)
Sex (female)	9	8
Ethnicity		
White	7	8
Hispanic	1	0
Black	2	1
Disease duration from diagnosis (months)	13·6 (2-33)	18 (6-36)
History of Raynaud's	9	9
Modified Rodnan skin score	28 (6-48)	19 (4-45)
Systemic sclerosis		
Diffuse	8	7
Limited (with lung involvement)	2	2
Gastrointestinal		
Gastrointestinal reflux disease	10	9
Patulous (gaping) oesophagus	6	5
Small bowel involvement	1	0
Lung		
Forced vital capacity	62% (53-70)	67% (43-84)
Diffusing capacity of CO_2 corrected	58% (29-82)	75% (29-111)
Involvement on high-resolution chest tomography	7	8
Non-specific interstitial pneumonia	6	8
Usual interstitial pneumonia	1	0
Bronchiectasis	1	0
Honeycombing	1	0
Nodules or micronodules	0	3
Cardiac		
Abnormal electrocardiogram	8	2
Tricuspid annular plane systolic excursion (cm)	2·24 (NA)	2·42 (NA)
Cardiac catheterisation		
Pulmonary artery systolic pressure (mm Hg)	29 (4·5)	28 (6·9)
Mean pulmonary artery pressure (mm Hg)	20 (4·0)	19 (4·8)

	Before switch to transplantation				
	Cyclophosphamide group (n=9)		Transplant group (n=10)		p value
	Baseline	1 year	Baseline	1 year	
Predicted forced vital capacity (%)					
Mean (SD)	67% (17·0)	61% (19·8)	62% (15·0)	74% (15·7)	0·004
Median (range)	78% (43–84)	69% (35–83)	62% (36–85)	82% (52–96)	--
Rate of change (%)†	--	-9%	--	15%	0·006
Predicted total lung capacity (%)					
Mean (SD)	83% (14·8)	74% (18·7)	76% (14·6)	80% (17·9)	0·005
Median (range)	89% (59–99)	69% (45–95)	73% (57–102)	72% (62–104)	--
Predicted DLCO corrected for haemoglobin (%)					
Mean (SD)	75% (27·5)	74% (37·0)	58% (21·8)	69% (18·6)	0·36
Median (range)	80% (29–111)	73% (28–120)	58% (29–94)	67% (33–90)	--
Volume diseased lung (mL)‡					
Mean (SD)	877 (240·6)	985 (277·1)	823 (268·9)	551 (277·1)	0·001
Median (range)	961 (462–1195)	858 (808–1189)	850 (359–1095)	546 (240–1118)	--
Modified Rodnan skin score					
Mean (SD)	19 (13·7)	22 (14·2)	28 (13·6)	15 (7·9)	0·0004
Median (range)	16 (6–45)	22 (3–44)	30 (6–47)	16 (2–29)	--



Lancet 2011; 378: 498–506

Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

Original Investigation Research

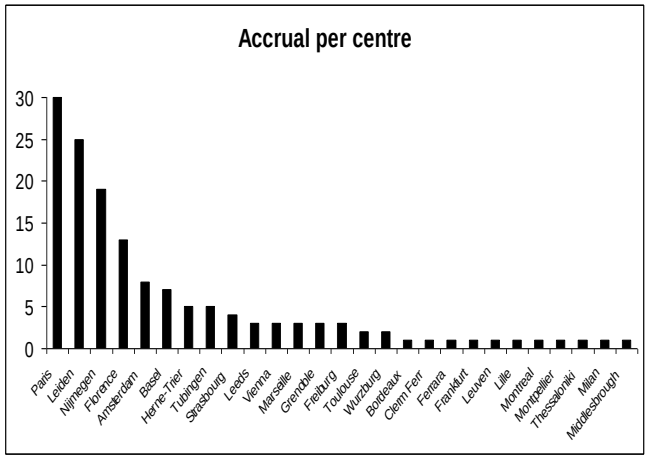
Van Laar JVL and Farge D et al

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

Table Baseline Characteristic of Study Patients

Characteristic	All Patients (N=156)	Transplant Arm (N=79)	Control Arm (N=77)
Age - yr	43.8 (11.3)	44.2 (11.1)	43.3 (11.5)
Female sex – no. (%)	92 (59.0)	43 (54.4)	49 (63.6)
Disease Duration - yr	1.4 (1.3)	1.4 (1.2)	1.5 (1.4)
Major organ involvement – no. (%)			
Lung	135 (86.5)	68 (86.1)	67 (87.0)
Kidney	5 (3.2)	3 (3.8)	2 (2.6)
Heart	13 (8.3)	6 (7.6)	7 (9.1)
None	16 (10.3)	8 (10.1)	8 (10.4)
Current or past smoker– no. (%)	84 (53.8)	41 (51.9)	43 (55.9)
Pre-trial use of cyclophosphamide – no.	34 (21.8)	17 (21.5)	17 (22.1)
Weight (kg)	68.6 (14.4)	71.5 (15.2)	65.6 (12.9)
BMI	23.8 (4.1)	24.7 (4.1)	22.9 (4.0)
Modified Rodnan skin score (mRSS)	25.3 (8.0)	24.8 (8.1)	25.8 (7.9)
Creatinine clearance (mL/min)	76.7 (25.9)	76.8 (26.1)	76.5 (26.0)
LVEF by echo	64.9 (8.5)	64.7 (8.7)	65.1 (8.3)
VC (% of predicted)	81.4 (18.4)	81.7 (19.3)	81.1 (17.6)
DLCO (% of predicted)	58.5 (14.1)	59.3 (14.3)	57.7 (14.0)
HAQ score	1.35 (0.8)	1.25 (0.74)	1.44 (0.84)

France: 49; Netherlands: 54
Allemagne: 20; Italie: 16
Suisse 7, GB: 5, Austriche:3, Belgique 1, Can1 1Grece: 1



Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis A Randomized Clinical Trial

Original Investigation Research

Van Laar JVL and Farge D et al

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

Table 2. Treatment Responses in Clinical Outcome Variables, Change in the Area Under the Time Response Curve From Baseline to 2 Years' Follow-up

Variable	AUC, Mean (SD)		Difference (95% CI)	*P* Value
	HSCT Group (n = 67)[a]	Control Group (n = 64)[a]		
Weight, kg	-0.7 (9.5)	-0.8 (9.6)	0.2 (-3.5 to 3.1)	.91
Modified Rodnan skin score	-19.9 (10.2)	-8.8 (12.0)	11.1 (7.3 to 15.0)	<.001
Creatinine clearance, mL/min[b]	-12.1 (29.7)	-1.2 (24.1)	10.9 (1.5 to 20.3)	.02
LVEF, % by cardiac echocardiography	2.2 (14.7)	-1.9 (13.8)	0.3 (-4.7 to 5.2)	.91
Forced vital capacity, % predicted	6.3 (18.3)	-2.8 (17.2)	-9.1 (-14.7 to -2.5)	.004
Total lung capacity, % predicted	5.1 (17.5)	-1.3 (13.9)	-6.4 (-11.9 to -0.9)	.02
Residual volume, % predicted	-4.8 (33.7)	-2.1 (26.9)	2.7 (-7.9 to 13.2)	.62
DLCO, % predicted	-4.7 (13.7)	-4.1 (17.6)	0.6 (-4.9 to 6.0)	.84
HAQ-DI	-0.58 (1.14)	-0.19 (0.79)	0.39 (0.51 to 0.73)	.02
SF-36 score				
Physical component	10.1 (15.8)	4.0 (11.2)	-6.1 (-10.9 to -1.4)	.01
Mental component	3.1 (16.0)	3.4 (17.1)	0.3 (-5.41 to 6.07)	.91
EQ-5D				
Index-based utility score	0.31 (0.50)	0.03 (0.44)	-0.29 (-0.45 to -0.12)	<.001
VAS score	16.9 (44.5)	10.2 (39.7)	-6.7 (-21.33 to 7.87)	.36

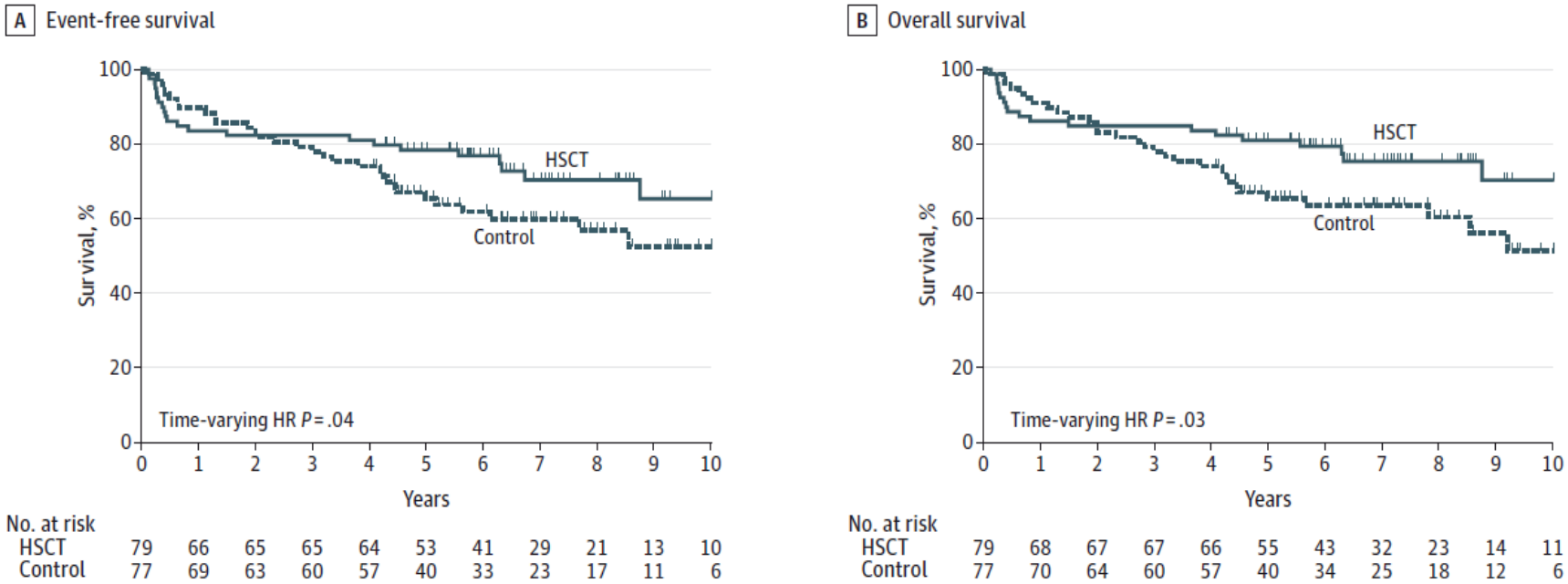
Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis A Randomized Clinical Trial

Original Investigation Research

Van Laar JVL and Farge D et al

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

Figure 2. Event-Free and Overall Survival During 10-Year Follow-up



10% TRM in ASTIS: 15 yrs recruitement

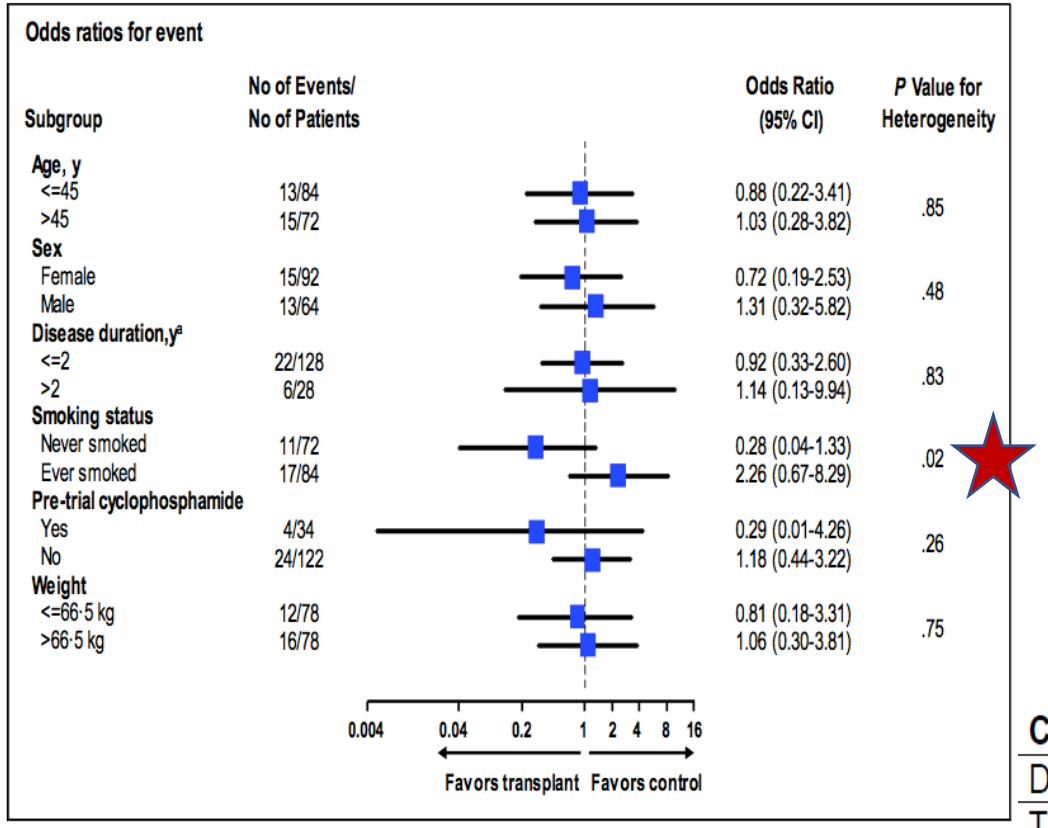
Hazard ratios (HRs) and 95% CIs were calculated by Cox regression. Hazard ratios were time-varying. The hazard (slope of the survival curve) in the hematopoietic stem cell transplantation (HSCT) group is initially high because of treatment-related mortality but gradually improves. At 1-year follow-up, the HR already favors the HSCT group, which leads to the crossing of the survival curves at 2 years' follow-up. A, Three-month follow-up: HR, 2.01 (95% CI, 0.74-5.49); *P* = .17; 6-month follow-up: HR, 1.35 (95% CI, 0.62-2.96); *P* = .45; 1-year follow-up: HR, 0.52 (95% CI, 0.28-0.96); *P* = .04; 2-year follow-up: HR, 0.35 (95% CI, 0.16-0.74); *P* = .006; 3- through 10-year follow-up: HR, 0.34 (95% CI, 0.16-0.74); *P* = .006. B, Three-month follow-up: HR, 2.40 (95% CI, 0.75-7.67); *P* = .14; 6-month follow-up: HR, 1.50 (95% CI, 0.61-3.68); *P* = .38; 1-year follow-up: HR, 0.48 (95% CI, 0.25-0.91; *P* = .02; 2-year follow-up: HR, 0.29 (95% CI, 0.13-0.65); *P* = .002; 3- through 10-year follow-up: HR, 0.29 (95% CI, 0.13-0.64); *P* = .002.

Mobilisation: CY 4g /m2 G-CSF (10µg/kg/day) + CD34+ selection
Conditionnement CY 200 mg/kg (J1-J4) + SAL (7.5mg/k sur 3 J)

© MATHEC® 10/2018

ASTIS CAUSES OF DEATH PLEASE READ THE ANNEX !!

JAMA. 2014;311(24):2490-2498.



Survival, days[b]	Survival after Transplant, days	Cause of Death	Autopsy	Relationship to Treatment[c]
153	11	progressive heart failure after HSCT, related to underlying SSc and treatment	not done	probably related
131	35	hemodynamic shock during ATG administration followed by ARDS, mesenteric ischemia, ATN and subsequently MOF	extensive fibrosis and pleural thickening, dilated cardiomyopathy, peripheral (but not coronary) atherosclerosis and ATN	definitely related
87	5	shock and subsequently ARDS	not done	definitely related
144	46	hemodynamic shock, EBV reactivation, PTLD, ATN, ARDS and subsequently MOF	malignant lymphoma in spleen and lymph nodes	definitely related

Cause of Death	Transplant Group (n=19)[a]	Control Group (n=30)
Disease progression	9 (47.4)	19 (63.3)
Treatment-related	8 (42.1)	0
Cardiovascular	0	4 (13.3)
Cerebrovascular	1 (5.3)	0
Hemato-oncological malignancy	1 (5.3)	5 (16.7)
Other[b]	0	2 (6.7)

ORIGINAL ARTICLE

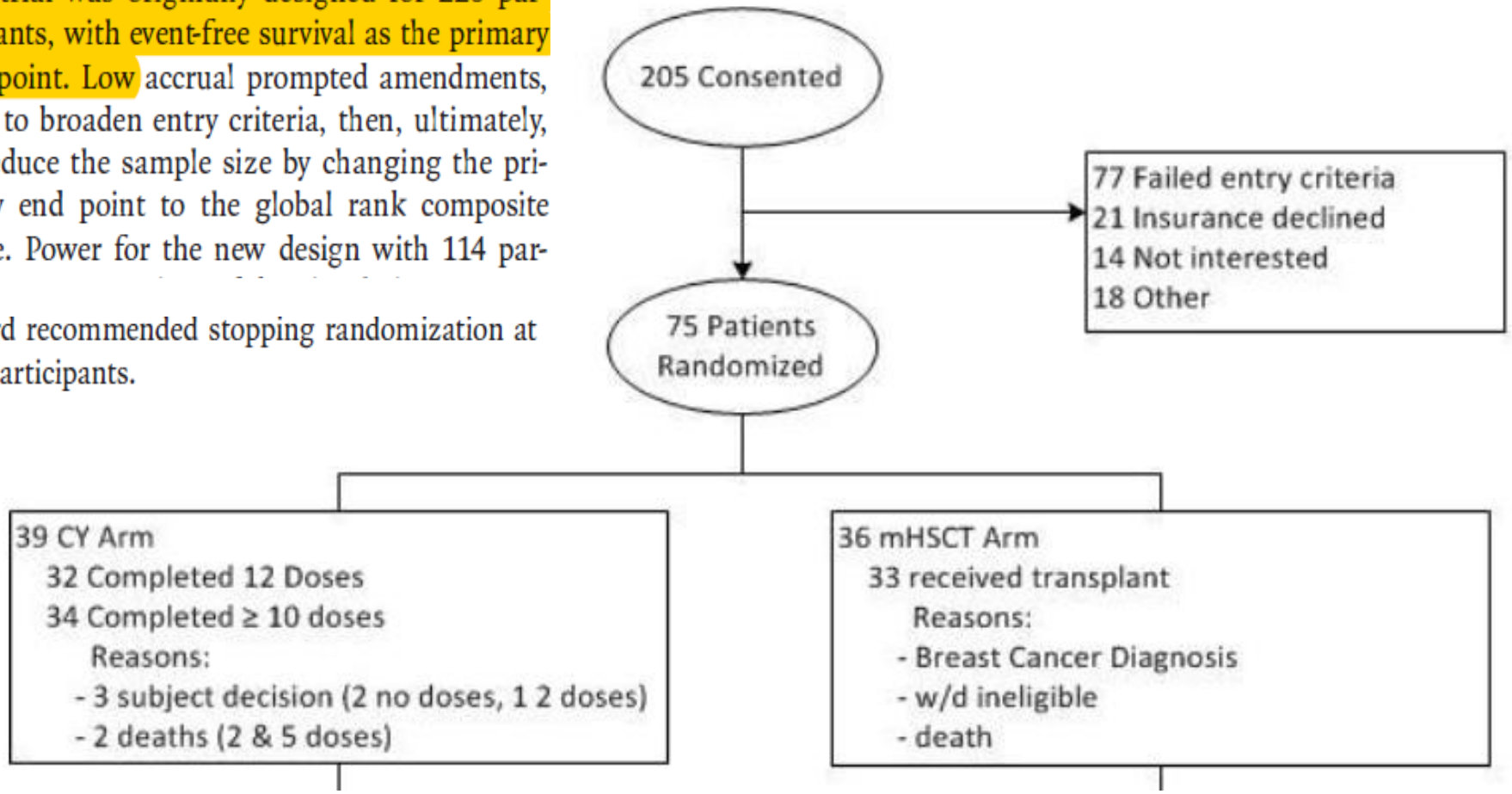
N Engl J Med 2018;378:35-47.
DOI: 10.1056/NEJMoa1703327

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

STATISTICAL ANALYSIS

The trial was originally designed for 226 participants, with event-free survival as the primary end point. Low accrual prompted amendments, first to broaden entry criteria, then, ultimately, to reduce the sample size by changing the primary end point to the global rank composite score. Power for the new design with 114 par-

board recommended stopping randomization at 75 participants.



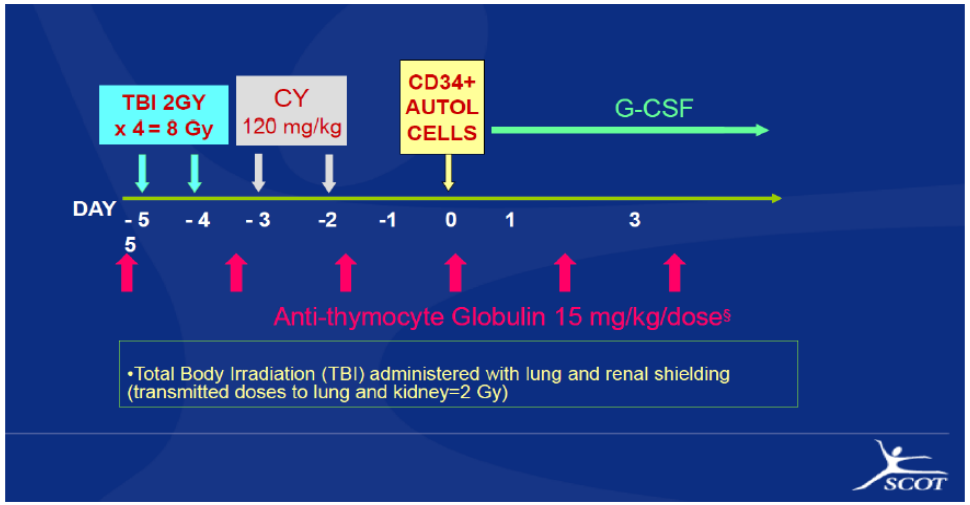
ORIGINAL ARTICLE

N Engl J Med 2018;378:35-47.
DOI: 10.1056/NEJMoa1703327

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

Table 1. Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Transplantation (N=36)	Cyclophosphamide (N=39)	Total (N=75)
Mean age — yr	44.9±10.9	46.9±10.4	45.9±10.6
Female sex — no. (%)	19 (53)	29 (74)	48 (64)
Race — no. (%)†			
White	29 (81)	31 (79)	60 (80)
Black	2 (6)	4 (10)	6 (8)
Other	5 (14)	4 (10)	9 (12)
Smoking status — no. (%)			
Current or former smoker	14 (39)	10 (26)	24 (32)
Never smoked	22 (61)	29 (74)	51 (68)
Mean duration of scleroderma before randomization — mo	25.1±12.9	29.0±16.0	27.1±14.6
DMARD use in previous 6 mo — no. (%)	26 (72)	25 (64)	51 (68)
Previous use of cyclophosphamide — no. (%)	8 (22)	17 (44)	25 (33)
Lung involvement — no. (%)	36 (100)	37 (95)	73 (97)
Mean modified Rodnan skin score‡	28.5±8.7	30.8±10.5	29.7±9.7
Mean FVC — % of predicted value	74.5±14.8	73.8±17.0	74.1±15.9
Mean DLco — % of predicted value	53.9±7.6	52.7±8.2	53.3±7.9
Mean left ventricular ejection fraction — %§	61.0±6.1	59.9±4.3	60.4±5.2
Mean creatinine clearance — ml/min	122.8±41.7	124.9±54.3	123.9±48.3
Mean ESR — mm/hr¶	29.8±26.5	32.2±24.9	31.1±25.4
Mean SF-36 physical component score‖	29.5±9.2	28.9±9.5	29.2±9.3
Mean SF-36 mental component score‖	44.7±10.7	44.6±9.9	44.6±10.2
Mean HAQ-DI score**	1.2±0.6	1.4±0.9	1.3±0.8



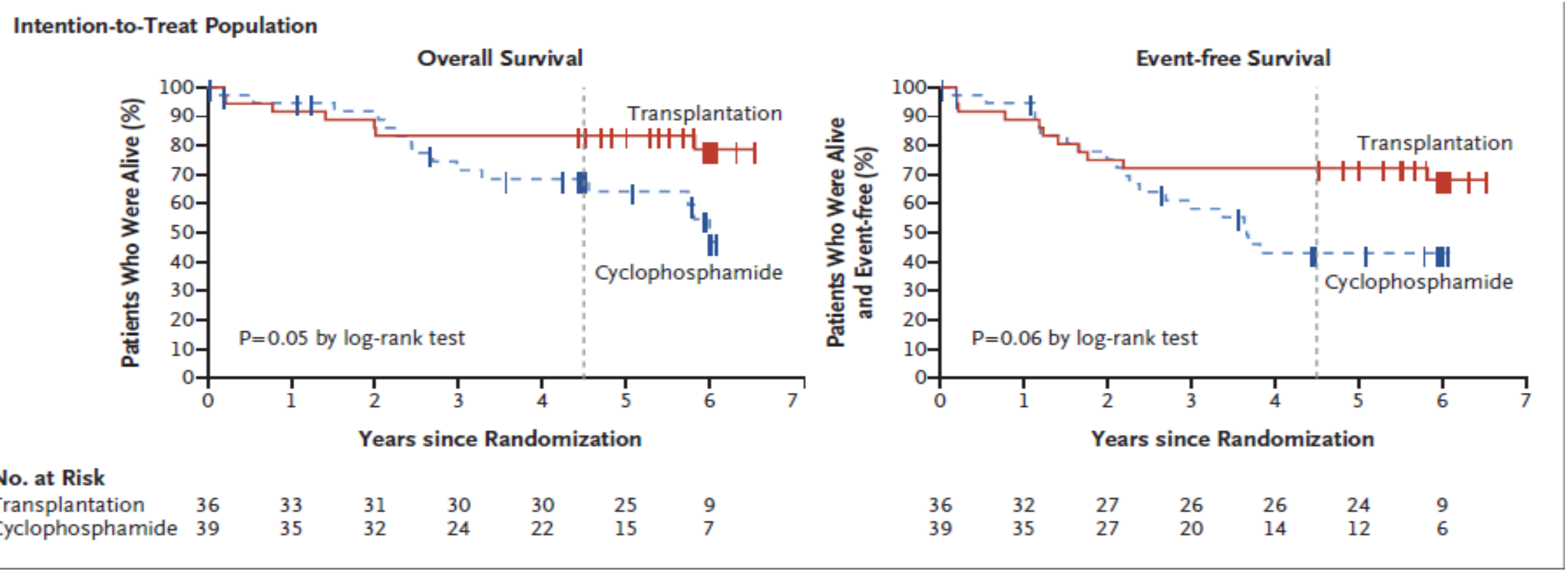
	Hierarchy of component outcomes					Pairwise Comparisons						
						Subject						
Subject	Mortality	EFS Failure	FVC	HAQ-DI	mRSS	1	2	3	4	5	6	GRCS
1	Dead (2 mo)					.	0	-1	-1	-1	-1	-4
2	Dead (50 mo)					0	.	-1	-1	-1	-1	-4
3	Alive	Yes (renal)	↓>10%	No Δ	↓>25%	1	1	.	-1	-1	-1	-1
4	Alive	Yes (lung)	↓>10%	↓>0.4	No Δ	1	1	1	.	-1	-1	1
5	Alive	No	No Δ	No Δ	↓>25%	1	1	1	1	.	-1	3
6	Alive	No	↑>10%	↓>0.4	No Δ	1	1	1	1	1	.	5

The GRCS is an analytic tool that accounts for multiple disease manifestations simultaneously but does not measure clinical disease activity or severity; it reflects how participants compare to one another based on a hierarchy of ordered outcomes. To compute the GRCS, each subject is first compared to every other subject and assigned a "pairwise comparison score" of 1 (better off), 0 (no different), or -1 (worse off). The table provides an example of how 6 hypothetical subjects would be scored.

COMBINING MORTALITY AND LONGITUDINAL MEASURES IN CLINICAL TRIALS

Statist. Med. **18**, 1341–1354 (1999)

SCOT US trial Sullivan K. et al NEJM 2018



A 72 mois : TRM : 6% ASCT vs 0% cyclo
Survie Globale: 86% ASCT vs 51% cyclo

TBI 8 Gy + Cyclo 120 mg/kg + hATG 90 mg/kg(Lung + Kidney shielding: 2 Gy) CD34+ AHSCT
Vs cyclophosphamide 750 mg/m^2 x 12 mo. (n=39)

Autologous HSCT is efficacious, but can we make it safer?

Richard K. Burt and Dominique Farge

NATURE REVIEWS | RHEUMATOLOGY
doi:10.1038/nrrheum.2018.34
Published online DD Mon 2018

Trial	Patients treated with HSCT (*n*)	Regimen	End points	HSCT-related deaths	Incidence of cancer	Overall survival
ASSIST	10	Non-myeloablative • CYC 200 mg/kg • rATG 6.5 mg/kg	Clinical improvement (mRSS or FVC) ($P = 0.00001$)	0%	0% (0 of 10)	100% (2 years)
ASSIST regimen	89	Non-myeloablative • CYC 200 mg/kg • rATG either 6.5 mg/kg or 4.5 mg/kg	• OS = 78% • RFS = 70% • mRSS ($P = 0.0003$) • FVC ($P = 0.004$)	6%	0% (0 of 89)	78% (5 years)
ASTIS	75	Non-myeloablative • CYC 200 mg/kg • rATG 7.5 mg/kg	• EFS ($P = 0.006$) • mRSS ($P < 0.001$) • FVC ($P = 0.004$)	10%	1.3% (1 of 75)	• 82% (5 years) • OS ($P = 0.002$)
SCOT	33	Myeloabaltive • TBI 800 cGy • CYC 120 mg/kg • eATG 90 mg/kg	EFS (2005–2010) • ITT ($P = 0.06$) • PP ($P = 0.02$) GRCS (after 2010) • ITT ($P = 0.01$) • mRSS (ITT, $P = 0.05$; PP, $P = 0.01$) • FVC (ITT, $P = 0.3$; PP, $P = 0.5$)	6%	9% (3 of 33)	• 86% (54 months) • 54 months OS ($P = 0.28$) • 72 months OS ($P = 0.02$)

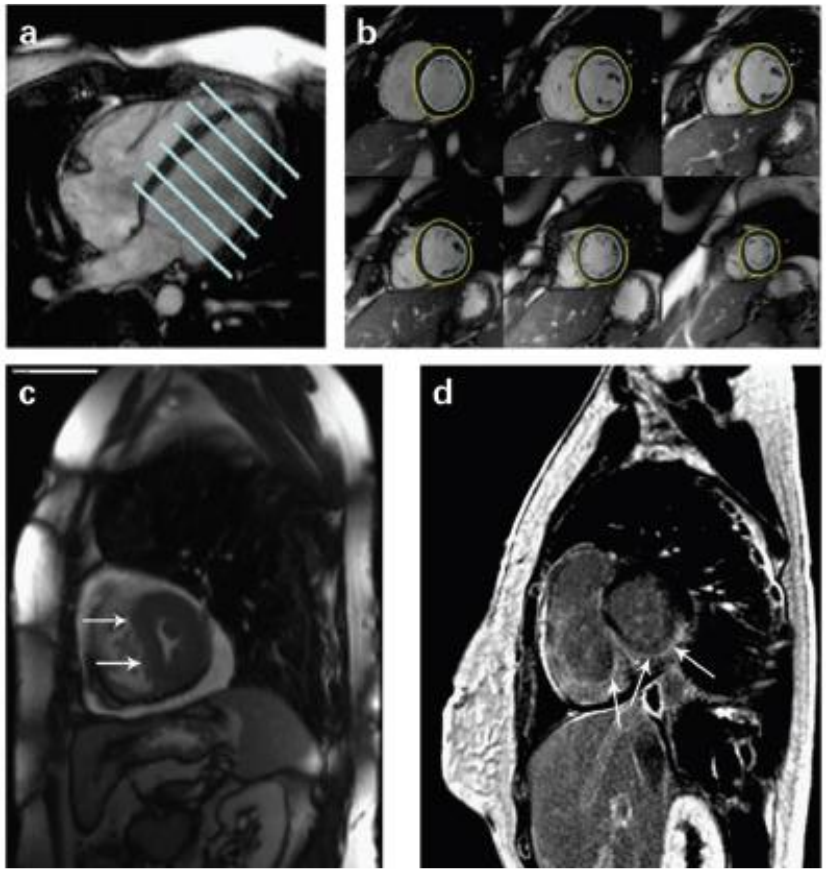
CYC, cyclophosphamide; EFS, event-free survival; eATG, equine anti-thymocyte globulin; FVC, forced vital capacity; GRCS, global rank composite score; HSCT, haematopoietic stem cell transplantation; ITT, intention to treat; mRSS, modified Rodnan skin score; OS, overall survival; PP, per protocol; rATG, rabbit anti-thymocyte globulin; RFS, relapse-free survival; TBI, total body irradiation.

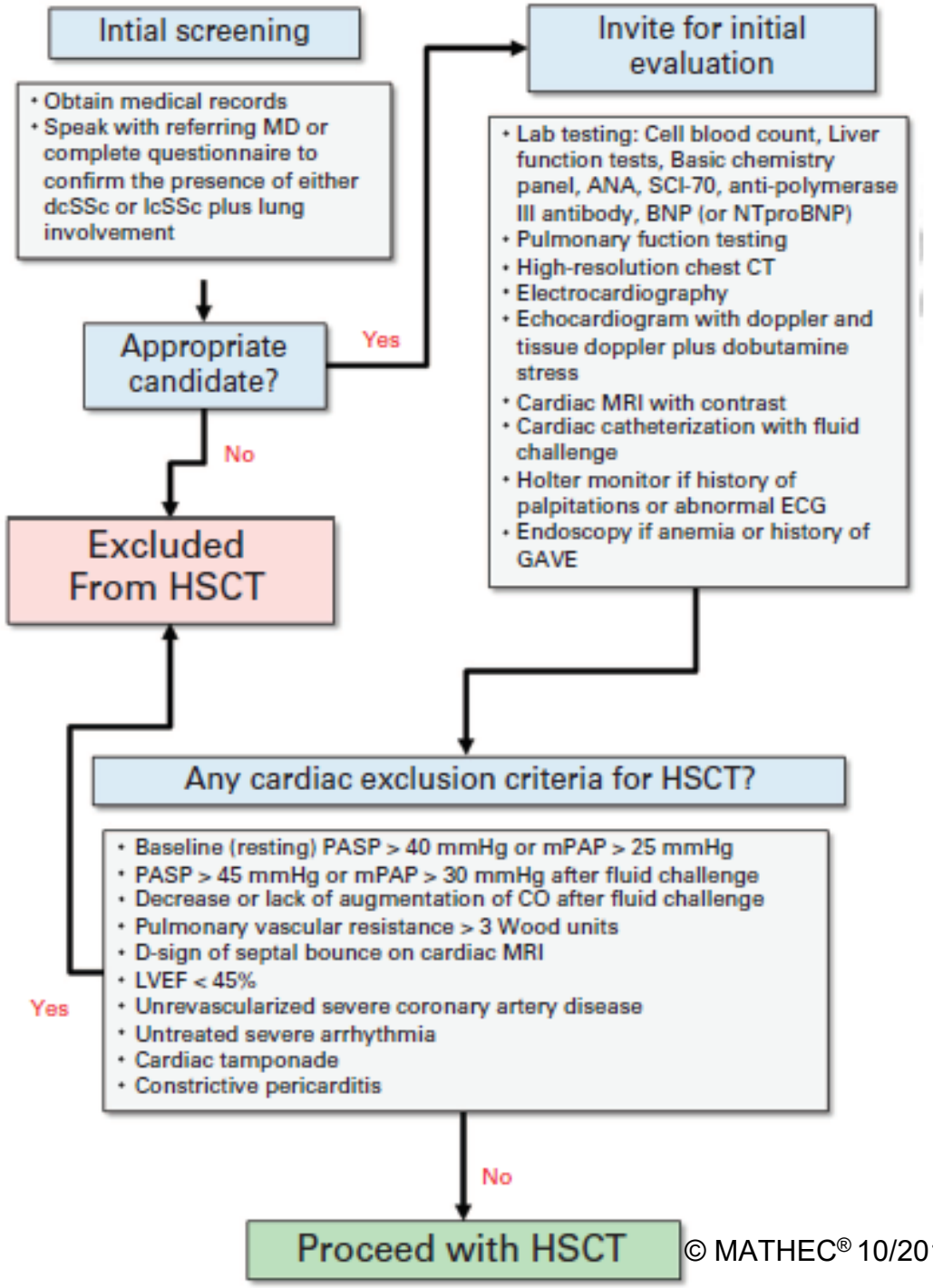
© MATHEC® 10/2018

Cardiopulmonary assessment of patients with systemic sclerosis for hematopoietic stem cell transplantation: recommendations from the European Society for Blood and Marrow Transplantation Autoimmune Diseases Working Party and collaborating partners

Bone Marrow Transplantation (2017)

ADWP EBMT , BRASIL AND CHICAGO





© MATHEC® 10/2018

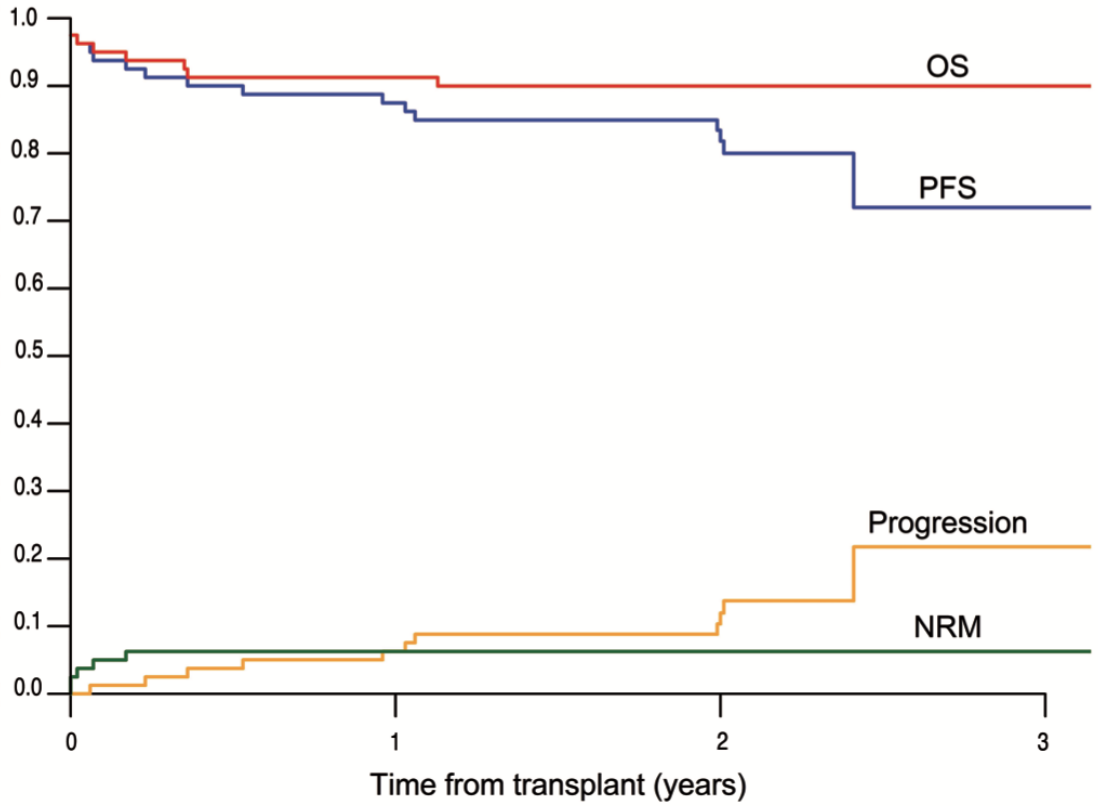
Autologous stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional study from the European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party

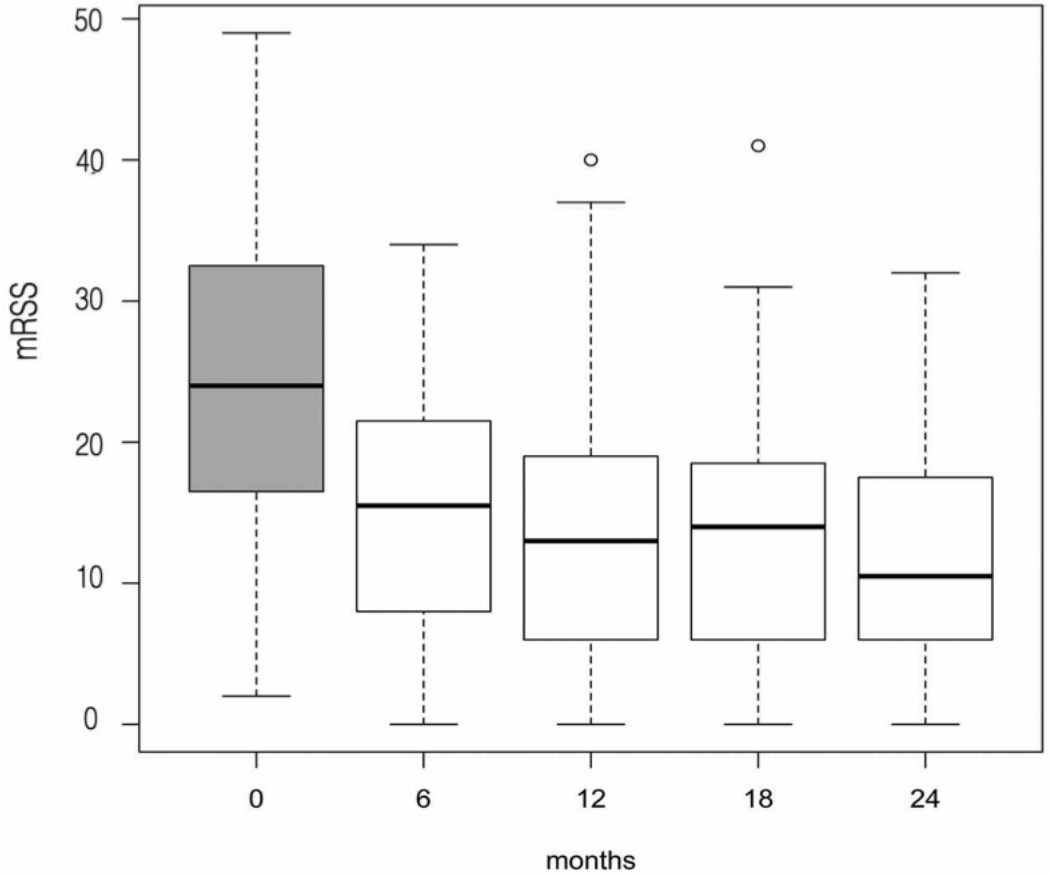
Ferrata Storti Foundation

Joerg Henes,[1] Maria Carolina Oliveira,[2] Myriam Labopin,[3] Manuela Badoglio,[4] Hans Ulrich Scherer,[5] Nicoletta Del Papa,[6] Thomas Daikeler,[7] Marc Schmalzing,[8] Roland Schroers,[9] Thierry Martin,[10] Gregory Pugnet,[11] Belinda Simoes,[12] David Michonneau,[13] Erik W.A. Marijt,[14] Bruno Lioure,[15] Jacques Olivier Bay,[16] John A Snowden,[17] Montserrat Rovira,[18] Anne Huynh,[19] Francesco Onida,[20] Lothar Kanz,[21] Zora Marjanovic[22] and Dominique Farge[23] for the NISSC1 members

Haematologica 2021
Volume 106(2):1-9

Response : 83.7 % (95% CI: 75.3 - 91.5),
RI 26.4 % (95% CI: 16.9 – 38.6)
PFS 69.6 % (95% CI: 59 - 80.1)
OS 90.2 % (95% CI: 83.7 - 96.6).
100d 2yrs NRM 6.2 % (95% CI: 2.3-13)





Sclérodermie Systémique:
Greffe de CSH autologue recommandation de grade A

Indications et suivi des autogreffes de cellules souches hématopoïétiques dans les maladies auto-immunes et auto-inflammatoires : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

Bulletin du CANCER

Grégory Pugnet[1], Christina Castilla-Llorente[2], Mathieu Puyade[3], Louis Terriou[4], Manuela Badoglio[5], Christophe Deligny[6], Perrine Guillaume-Jugnot[7], Céline Labeyrie[8], Ilham Benzidia[9], Hélène Faivre[9], Pauline Lansiaux[9], Zora Marjanovic[10], Jean-Henri Bourhis[2], Catherine Faucher[11], Sabine Furst[11], Anne Huynh[12], Thierry Martin[13], Patrick Vermersch[14], Ibrahim Yakoub-Agha[15], Dominique Farge[9]

Bull Cancer 2017; 104S: S169–S180

en ligne sur / on line on
www.em-consulte.com/revue/bulcan
www.sciencedirect.com

Update of EULAR recommendations for the treatment of systemic sclerosis

Otylia Kowal-Bielecka,[1] Jaap Fransen,[2] Jerome Avouac,[3] Mike Becker,[4,5]

SPECIAL REPORT

SCT for severe autoimmune diseases: consensus guidelines of the European Group for Blood and Marrow Transplantation for immune monitoring and biobanking

T Alexander[1], A Bondanza[2], PA Muraro[3], R Greco[2], R Saccardi[4], T Daikeler[5], M Kazmi[6], C Hawkey[7], BP Simoes[8], K Leblanc[9], WE Fibbe[10],

Protocole National de Diagnostic et de Soins

Sclérodermie Systémique

Sclérodermie Systémique cutanée diffuse récente rapidement évolutive: AHSCT recommandations

- Age: entre 18 et 65 ans (cas pédiatriques)
- Sclérodermie systémique cutanée diffuse ou limité avec une durée de la maladie depuis le 1er signe hors Raynaud
  - ≤ 2 ans avec mRSS ≥ 20 et atteinte du tronc
    - VS ≥ 25
    - Hb < 11 sans autre cause retrouvée
  - ≤ 5 ans avec mRSS ≥ 15
    - Atteinte viscérale significative ou s'aggravant défini par
      - Atteinte pulmonaire: DLCO et/ou CVF ≤ 80% et atteinte interstitielle
      - Atteinte rénale: HTA, anomalies urinaires, MAT, IR modérée
      - Atteinte cardiaque: FA, flutter, BAV, IC congestive réversible
  - ≤ 5 ans mRSS < 14 et avec atteinte pulmonaire sévère évolutive
    - Altération de la CVF de 10 % et/ou de la DLCO de 15 %

Contre-indications communes à l'autogreffe de CSH pour MAI

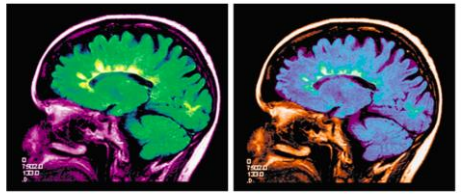
Les recommandations sont :

- âge > 65 ans ;
- tabagisme actif ou sevré depuis moins de 3 mois ;
- grossesse ou absence de contraception adaptée pendant toute la procédure et au moins trois ans après la greffe ;
- affection(s) concomitante(s) sévère(s) :

Hachulla E. et al. Orphan J Rare Dis 2021
PNDS Sclérodermie Systémique HAS 2020
Farge D. et al. Bone Marrow Transpl 2017
Pugnet G. et al. Bulletin du cancer 2017
Snowden et al. Bone Marrow Transpl 2012

La sclérose en plaques en France

science & médecine Le Monde



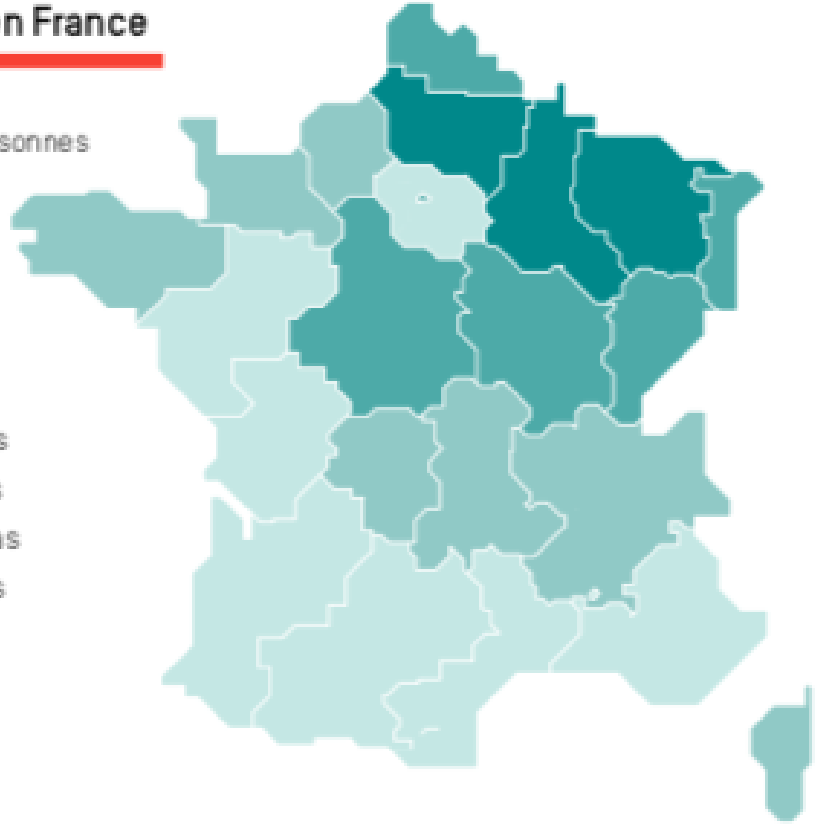
La greffe contre **la sclérose en plaques**

Profils des malades

2,3	**millions** de malades dans **le monde**
120 000	**personnes** touchées en **France**
3/4	des personnes malades sont des **femmes**
5 000	**diagnostiqués** en France par an
entre 25 et 35	**ans** C'est l'âge moyen de début de la maladie

Prévalence en France

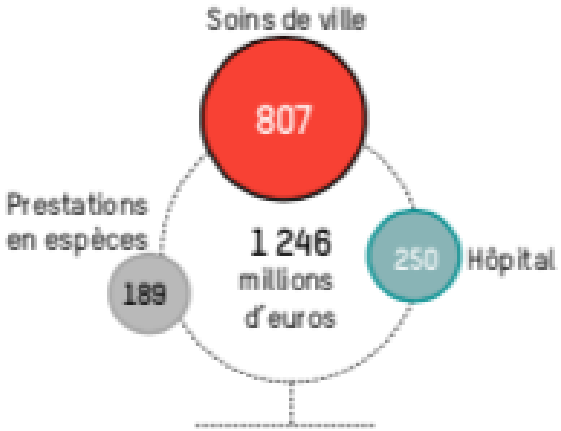
Nombre de cas pour 100 000 personnes



- Moins de 85 cas
- de 85 à 100 cas
- de 100 à 115 cas
- Plus de 115 cas

Dépenses en 2016

pour l'Assurance-maladie, attribuées à la prise en charge de la sclérose en plaques



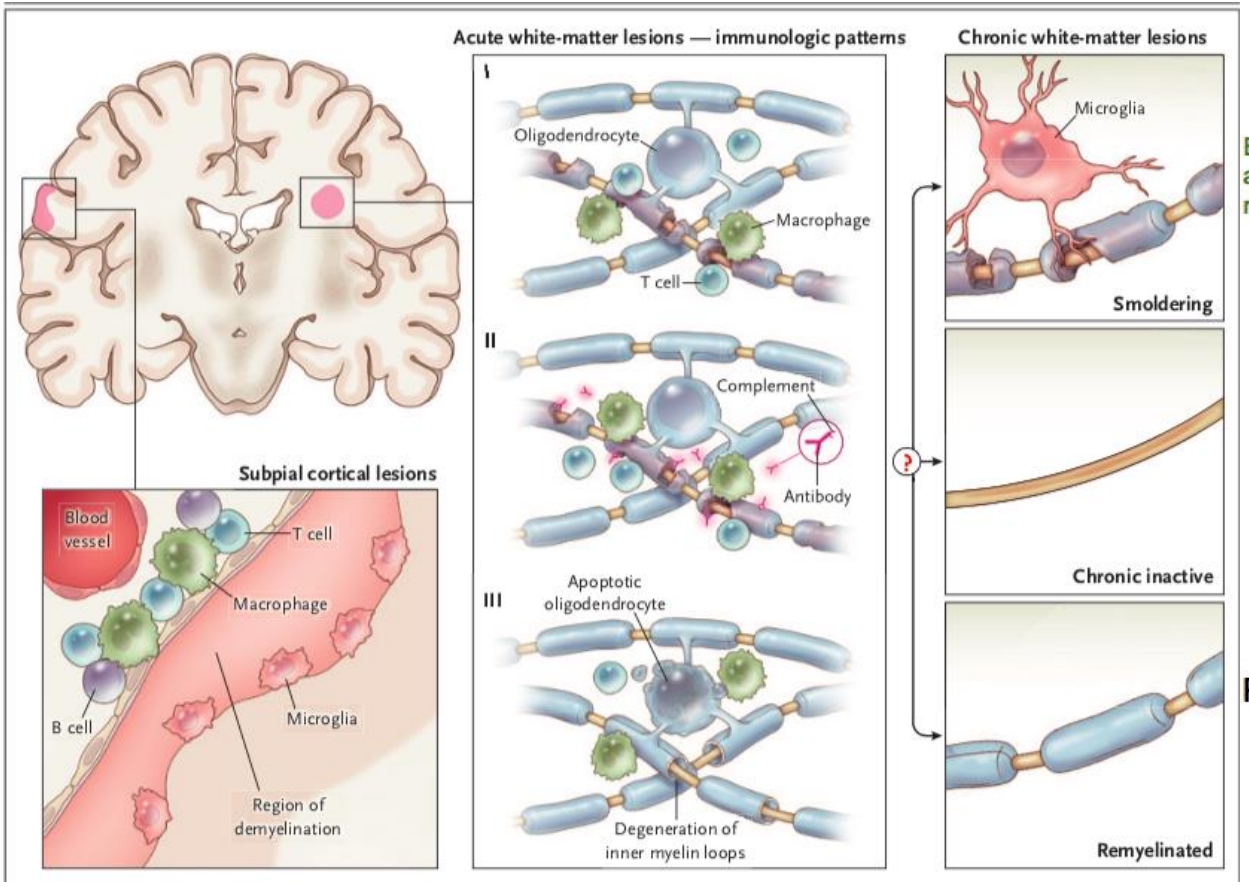
11 150 euros

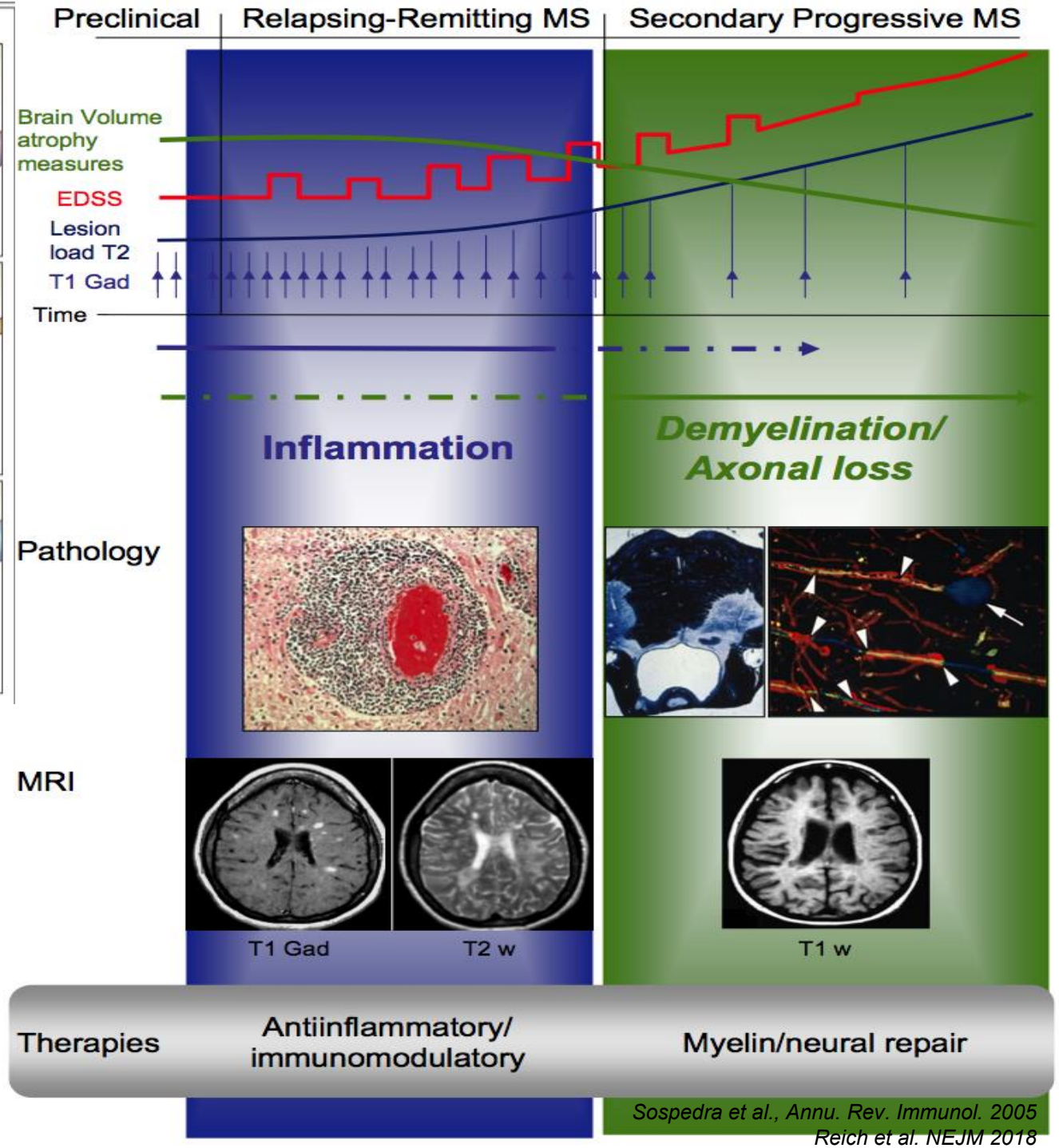
C'est la dépense annuelle moyenne remboursée par patient (régime général + mutuelle)

Première cause de handicap sévère non traumatique du sujet jeune

Copyright MATHEC

Le Monde mercredi 13 Février 2019



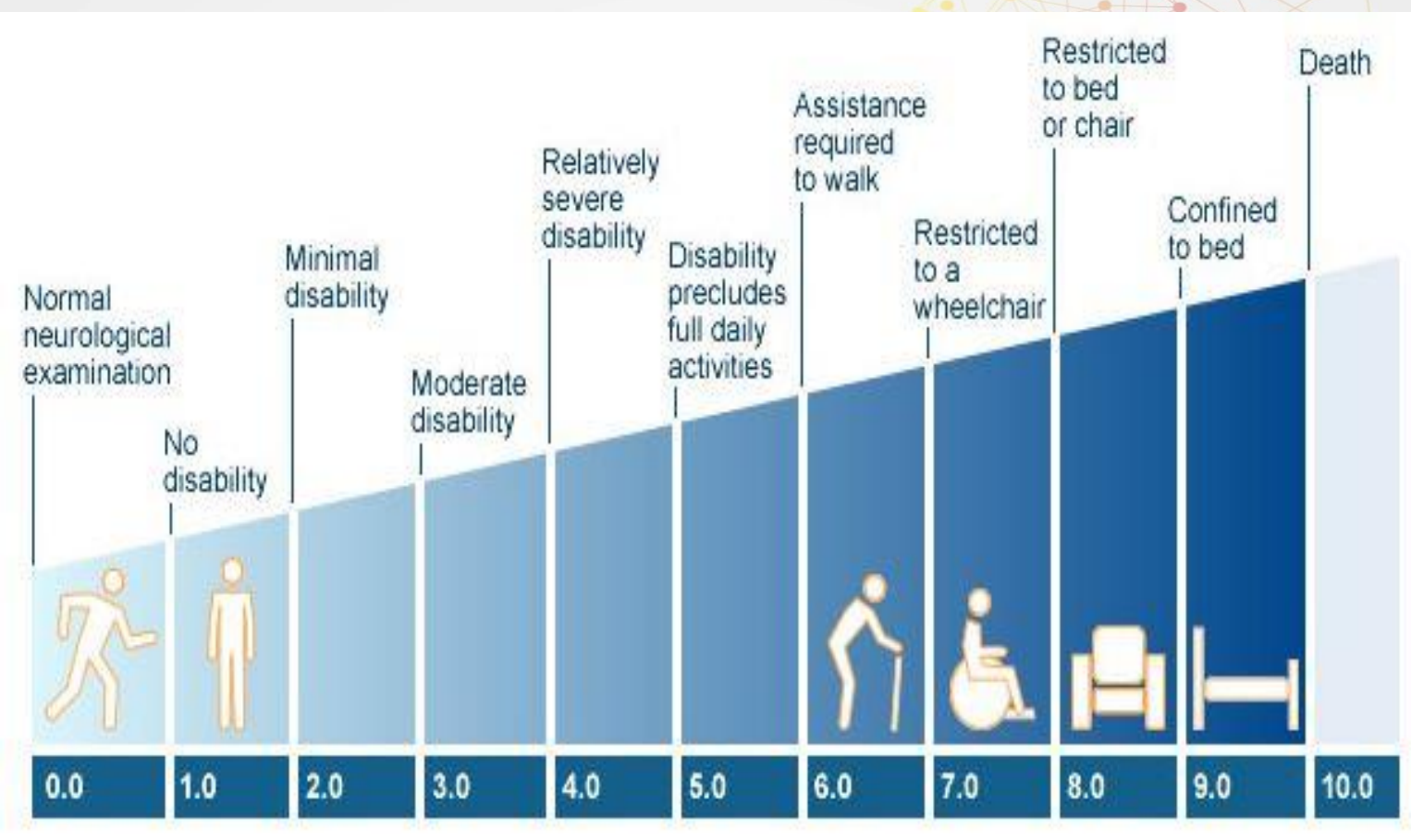


- Complex genetic background
- Multiple environmental risk factors
- Autoimmune inflammation
- Demyelination, axonal damage, glial proliferation
- CD4+ T cell-mediated autoimmune disease

Sospedra et al., Annu. Rev. Immunol. 2005
Reich et al. NEJM 2018

Copyright MATHEC

MULTIPLE SCLEROSIS – A TWO PHASES DISEASE



"Flares"
- IV steroids
- *plasmapheresis*

"Auxiliary"
- regular physical activity
- sun exposure,
- Vit D3 adjustment
- healthy nutrition
- Vit supplementation

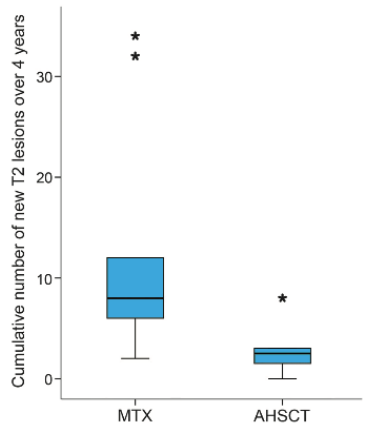
First line treatment
- glatiramer-acetate
- interferon-b
- fingolimod
- fumaric acid
- teriflunomide

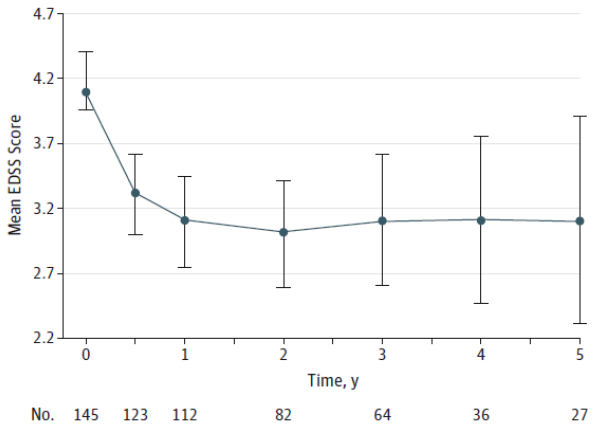
Second line treatment
- fingolimod
- natalizumab (α-VLA4)
- ocrelizumab (anti-CD20)
- *cladribine*
- *α-CD25*
- *laquinimode……..*

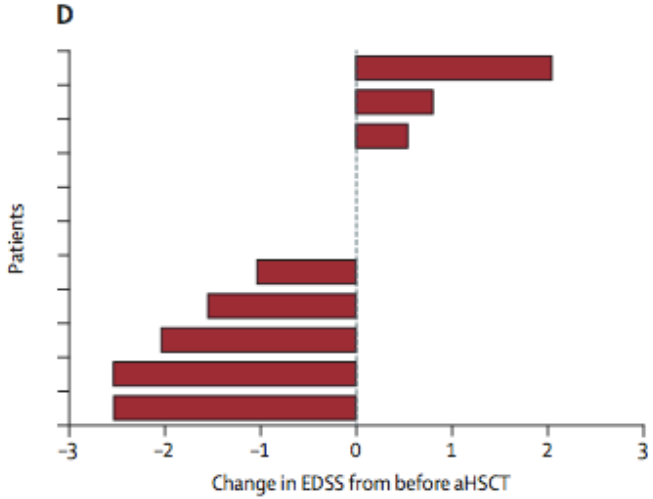
Second/third line treatment
- mitoxantrone
- Rituximab (anti-CD20)
- alemtuzumab (α-CD52)
- *Autologous HSCT*
- MMF, Cyclophosphamide

Copyright MATHEC

La sclérose en plaques: phase II AHSCT







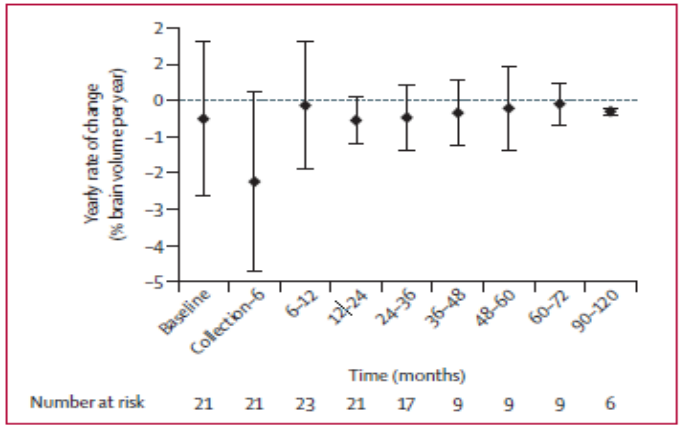
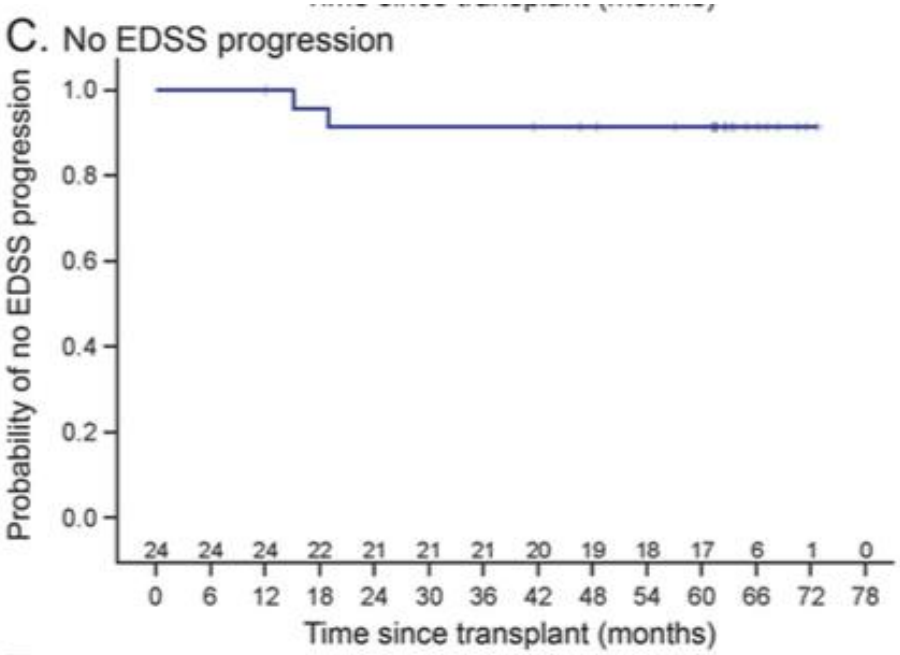
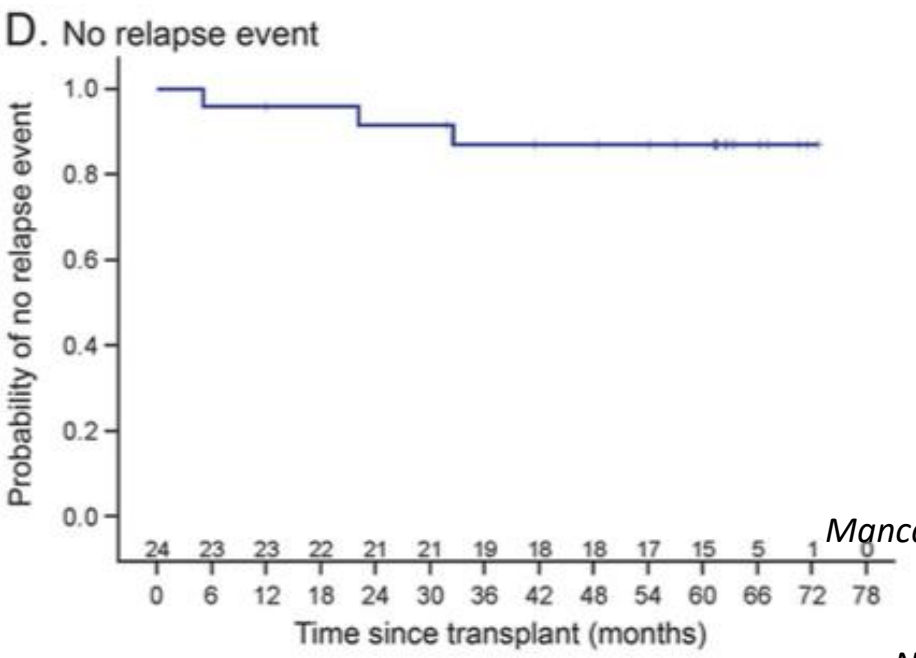


Figure 4: **Yearly rate of change in brain volume before and after autologous haemopoietic stem-cell transplantation**





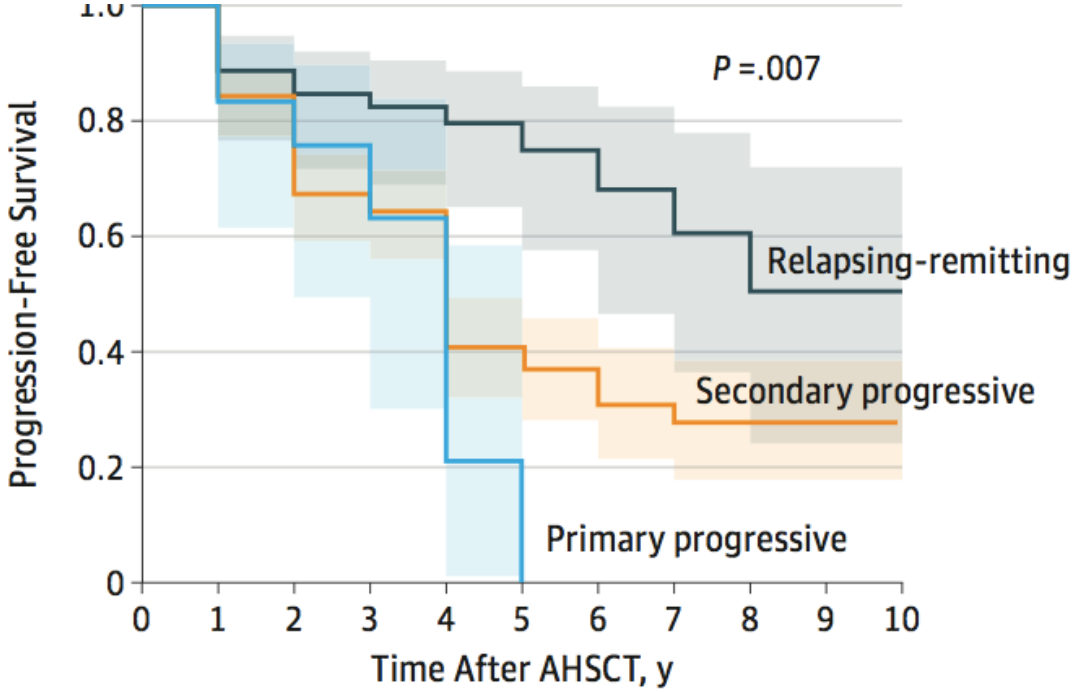
Mancardi et al. Neurology 2015
Burt R. et al. JAMA 2015
Atkins et al. Lancet 2016
Nash et al. Neurology 2017

Copyright MATHEC

JAMA Neurology | Original Investigation

Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis

Paolo A. Muraro, MD; Marcelo Pasquini, MD; Harold L. Atkins, MD; James D. Bowen, MD; Dominique Farge, MD; Athanasios Fassas, MD; Mark S. Freedman, MD; George E. Georges, MD; Francesca Gualandi, MD; Nelson Hamerschlak, MD; Eva Havrdova, MD; Vassilios K. Kimiskidis, MD; Tomas Kozak, MD; Giovanni L. Mancardi, MD; Luca Massacesi, MD; Daniela A. Moraes, MD; Richard A. Nash, MD; Steven Pavletic, MD; Jian Ouyang, MD; Montserrat Rovira, MD; Albert Saiz, MD; Belinda Simoes, MD; Marek Trněný, MD; Lin Zhu, MD; Manuela Badoglio, MSc; Xiaobo Zhong, MS; Maria Pia Sormani, PhD; Riccardo Saccardi, MD; for the Multiple Sclerosis–Autologous Hematopoietic Stem Cell Transplantation (MS-AHSCT) Long-term Outcomes Study Group



No. at risk

Relapsing-remitting	53	53	44	38	29	17	11	9	6	4	1
Secondary progressive	162	162	121	90	71	32	18	10	4	2	1
Primary progressive	24	24	11	6	3	1					

Copyright MATHEC

NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs

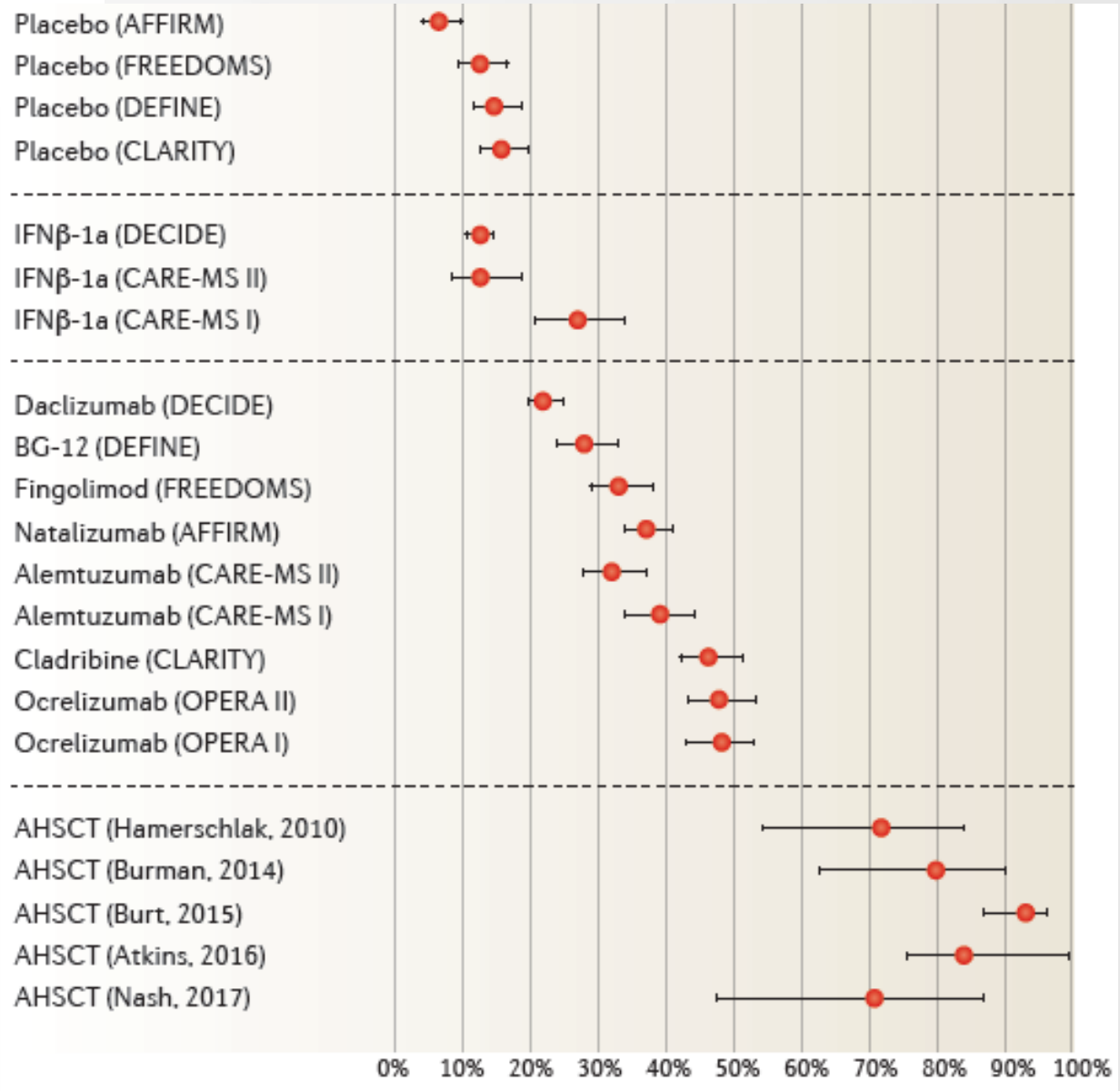
Maria Pia Sormani, Paolo A Muraro, Riccardo Saccardi and Gianluigi Mancardi

Mult Scler. 2017 Feb;23(2):201-204

No Evidence of Disease Activity

New goal in RR MS management

1. No relapse
2. No ▲disability progression
3. No new or active lesions on MRI

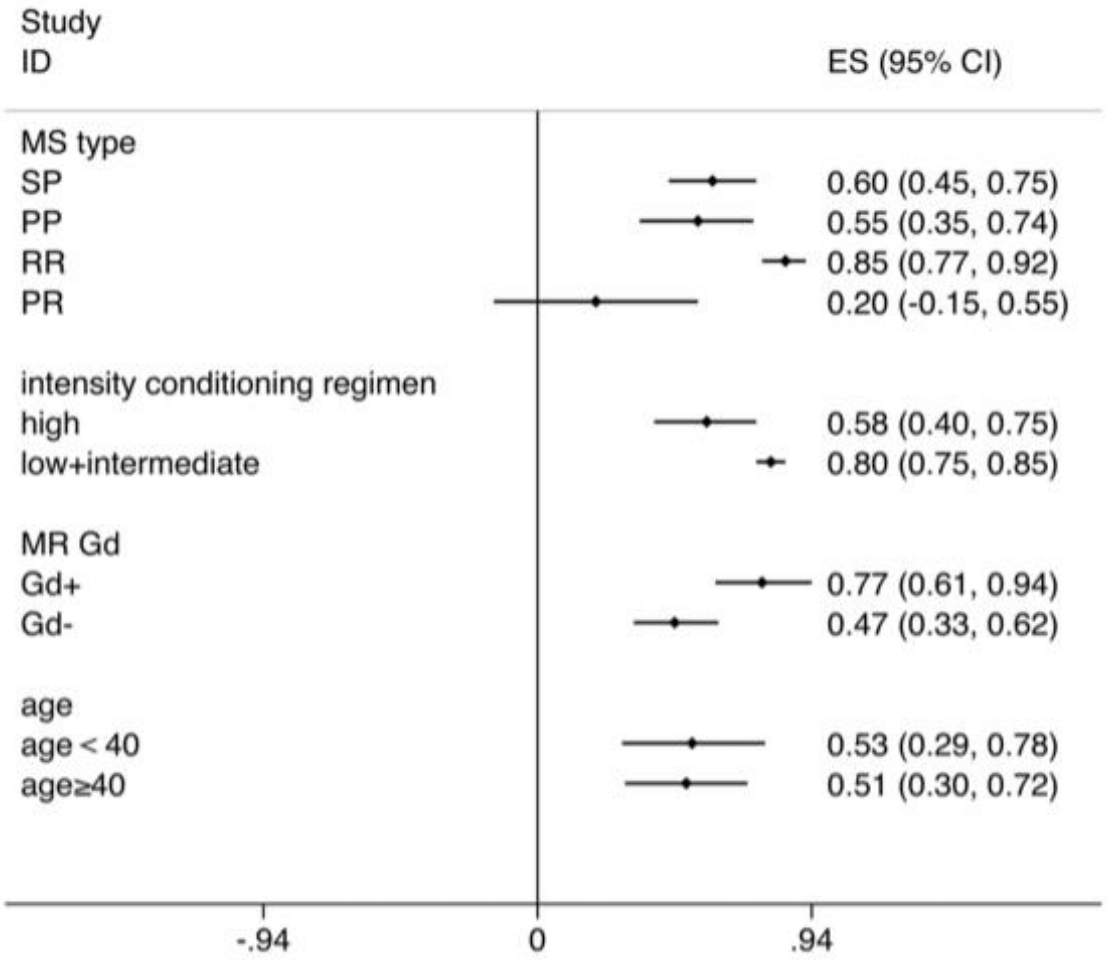


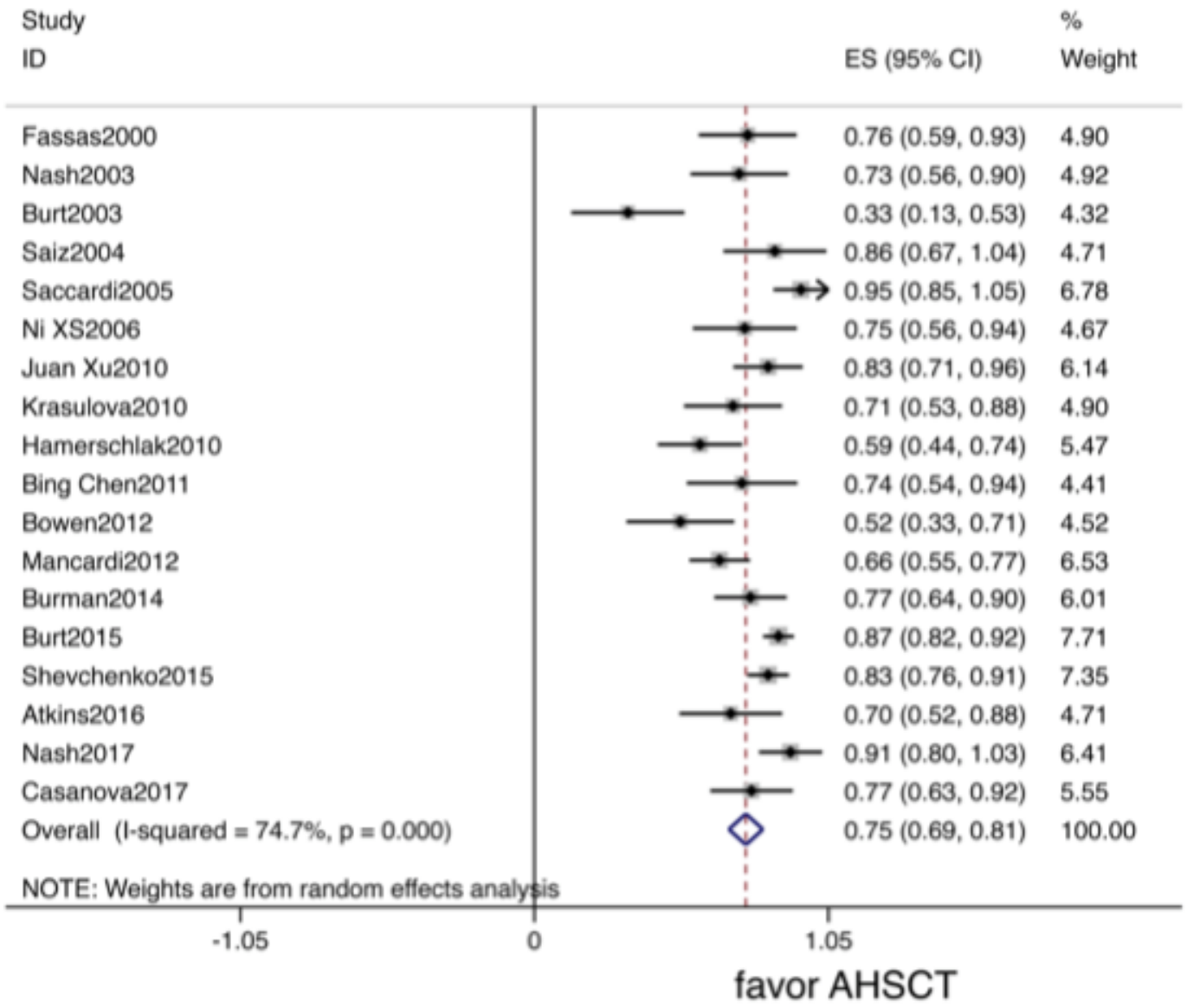
Copyright MATHEC

Muraro et al. Nature Review Neurology 2017

Efficacy and safety of autologous hematopoietic stem-cell transplantation in multiple sclerosis: a systematic review and meta-analysis

Fangfang Ge[1] · Hong Lin[1] · Zhuyi Li[1] · Ting Chang[1]

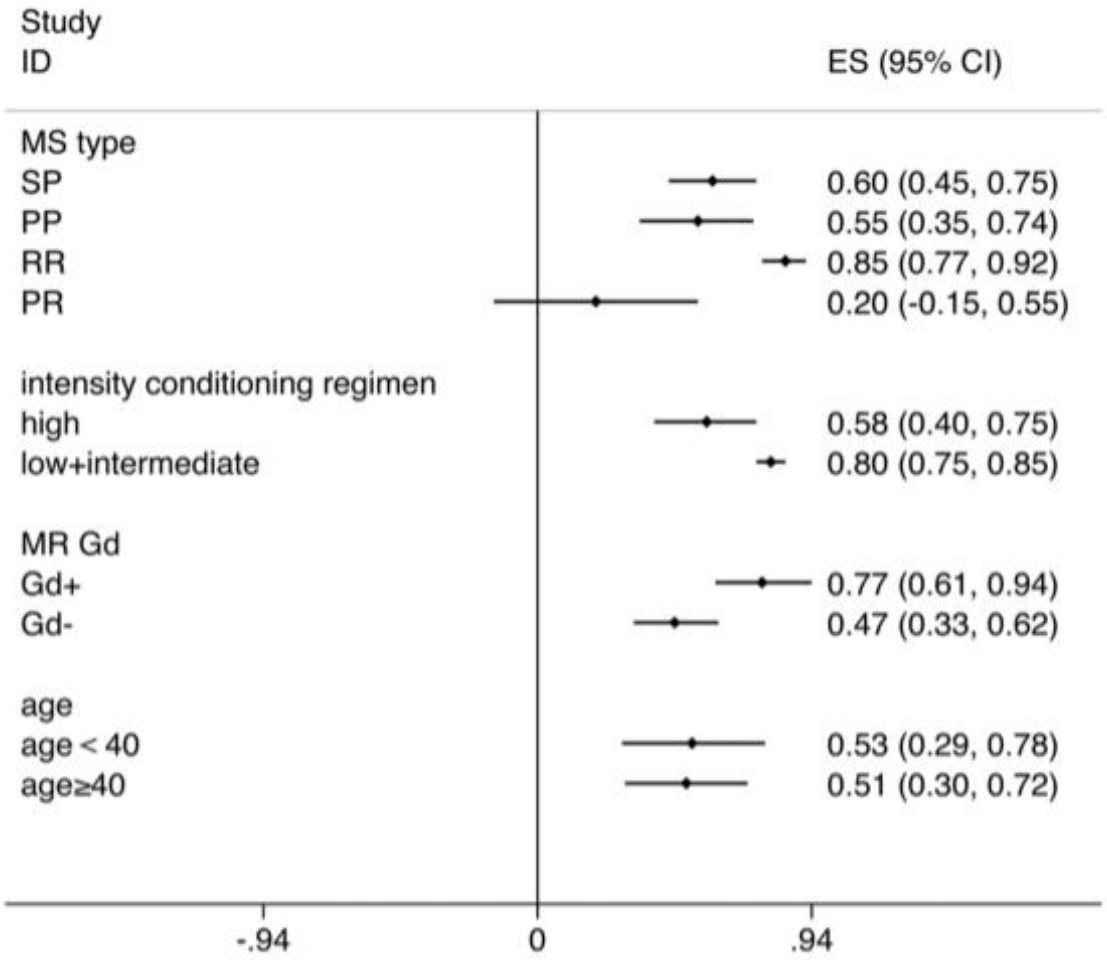




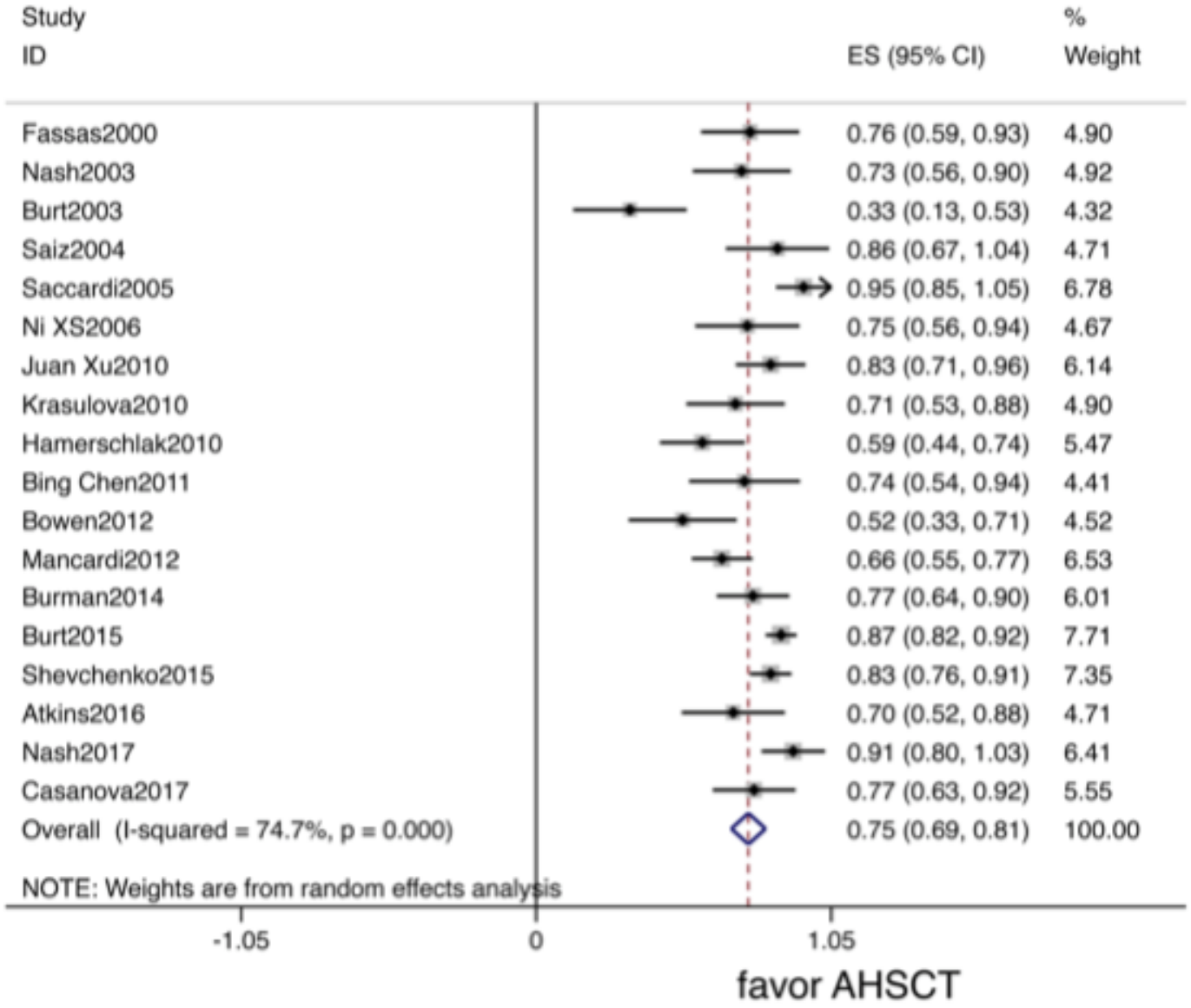
Ge et al. Neurol Sci 2018

Efficacy and safety of autologous hematopoietic stem-cell transplantation in multiple sclerosis: a systematic review and meta-analysis

Fangfang Ge[1] · Hong Lin[1] · Zhuyi Li[1] · Ting Chang[1]



TRM = 1.34%



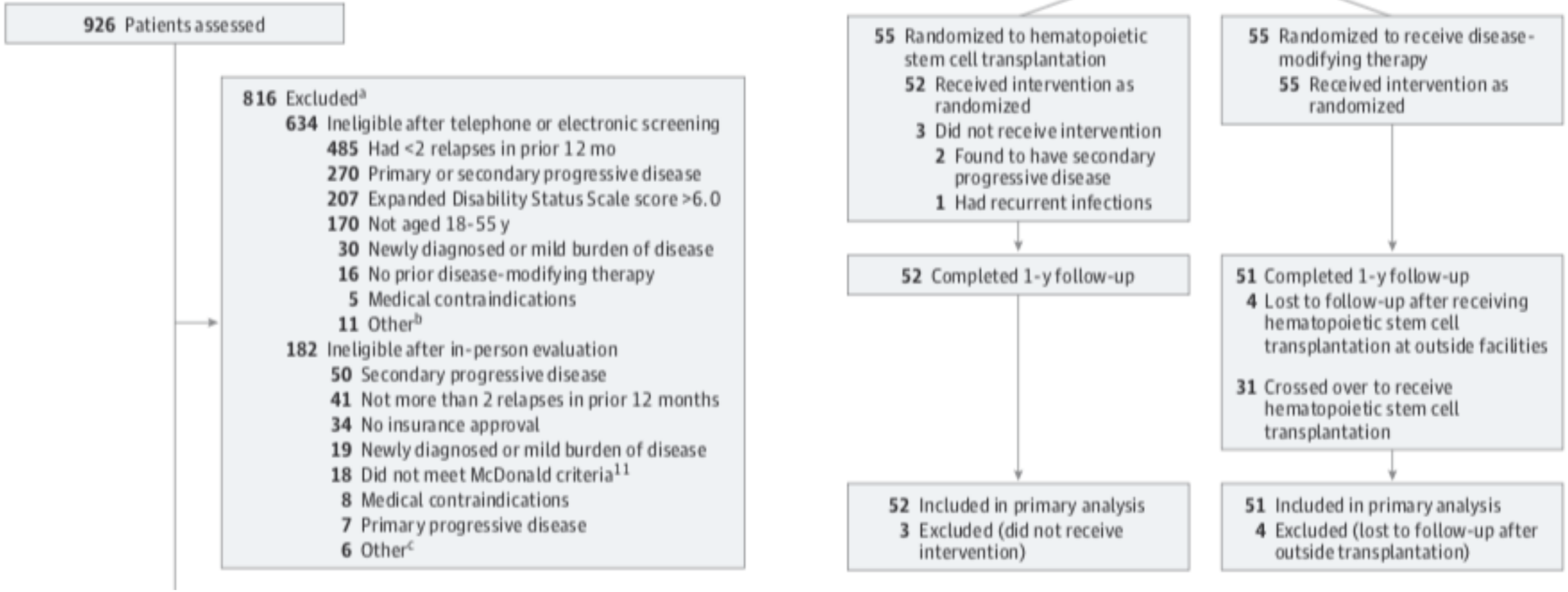
Ge et al. Neurol Sci 2018

JAMA | Preliminary Communication

Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis

A Randomized Clinical Trial

Richard K. Burt, MD; Roumen Balabanov, MD; Joachim Burman, MD; Basil Sharrack, MD; John A. Snowden, MD; Maria Carolina Oliveira, MD;



JAMA | Preliminary Communication

Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis

A Randomized Clinical Trial

Richard K. Burt, MD; Roumen Balabanov, MD; Joachim Burman, MD; Basil Sharrack, MD; John A. Snowden, MD; Maria Carolina Oliveira, MD;

Characteristics	Hematopoietic Stem Cell Transplantation (n = 55)	Disease-Modifying Therapy (n = 55)
Sex, No. (%)		
Men	21 (38)	16 (34)
Women	34 (62)	39 (66)
Age, y		
Mean (SD)	35.6 (8.4)	35.6 (8.2)
Median (range)	34 (18-54)	36 (19-52)
Duration of disease, mo		
Mean (SD)	63.1 (44.8)	84.8 (61.2)
Median (range)	56 (9-168)	65 (8-255)
Prior immune modulation/suppression history, No.		
Corticosteroids	53	54
Glatiramer acetate	30	28
Interferon beta-1a (Rebif)	17	27
Interferon beta-1a (Avonex)	20	23
Dimethyl fumarate	12	12
Interferon beta-1b	15	11
Natalizumab	7	11
Intravenous immunoglobulin	3	3
Fingolimod	6	3
Teriflunomide	1	1
Plasmapheresis	0	1
Azathioprine	1	1
Methotrexate	1	0
No. of different immune modulation/suppression treatments before hematopoietic stem cell transplantation		
Mean (SD)	3.2 (1.1)	3.2 (1.2)
Median (range)	3 (1-7)	3 (1-7)

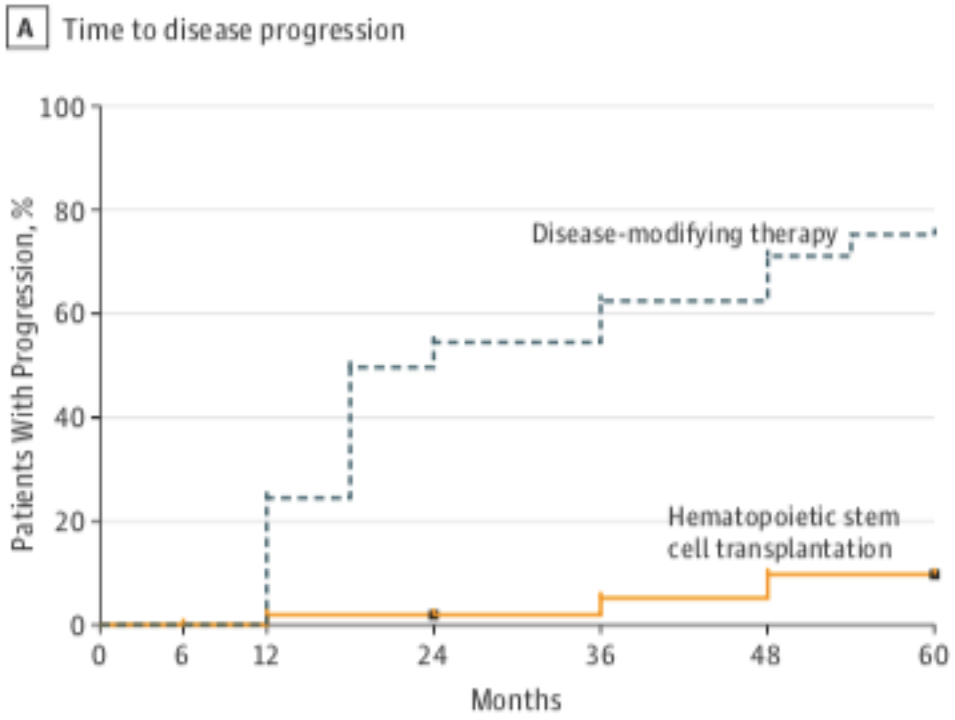
JAMA | Preliminary Communication

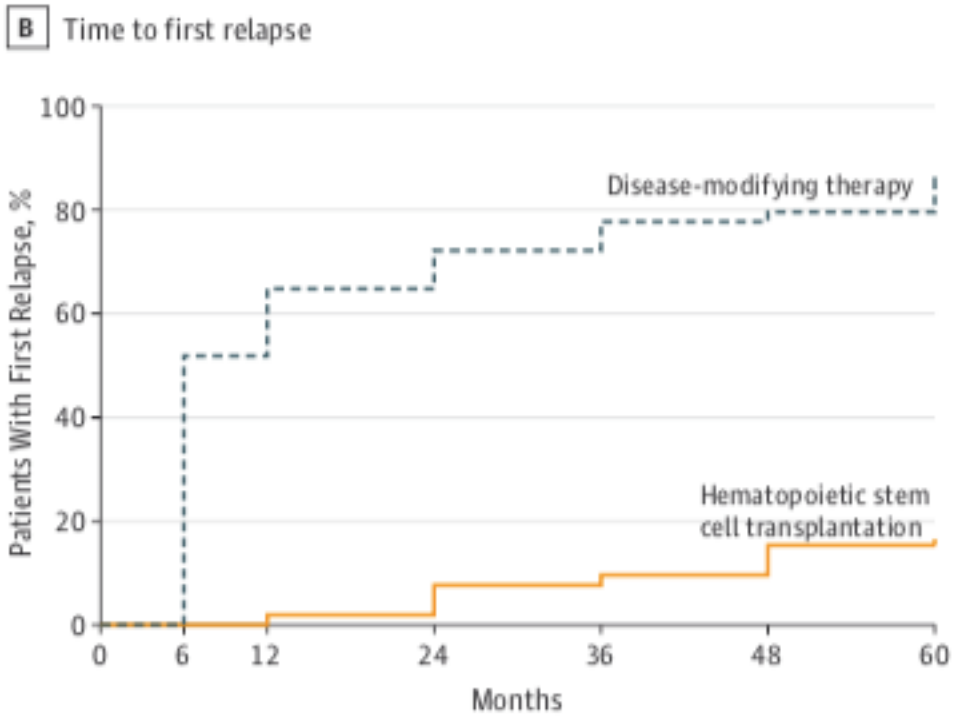
Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis

A Randomized Clinical Trial

Richard K. Burt, MD; Roumen Balabanov, MD; Joachim Burman, MD; Basil Sharrack, MD; John A. Snowden, MD; Maria Carolina Oliveira, MD;

Transplant Related Mortality =0





No. at risk

Hematopoietic stem cell transplantation	52	52	51	51	50	49	48	53	53	52	49	48	45	45
Disease-modifying therapy	54	54	43	30	26	24	23	55	26	18	15	12	11	9

JAMA | Preliminary Communication

Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis

A Randomized Clinical Trial

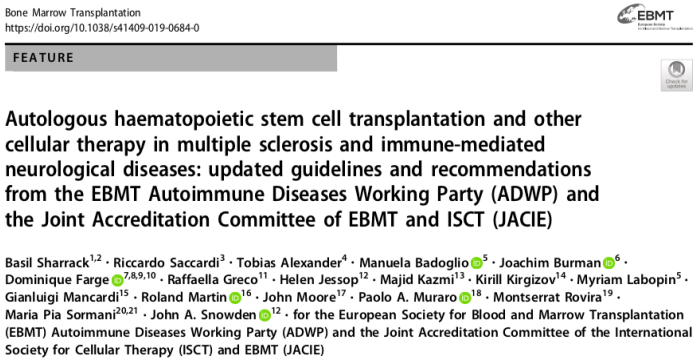
Richard K. Burt, MD; Roumen Balabanov, MD; Joachim Burman, MD; Basil Sharrack, MD; John A. Snowden, MD; Maria Carolina Oliveira, MD;

HSCT group NCI common toxicity criteria#	Number of patients with Grade 3 @
Febrile neutropenia (culture negative)	13
Metabolism abnormalities	
Hypophosphatemia	17
Hypokalemia	13
Hyperglycemia	5
Hypocalcemia	1
Hyponatremia	1
Hypomagnesemia	1
Hypermagnesemia	1
Cardiovascular	
Hypertension	3
Atrial fibrillation	1
Tachycardia	1
Syncope	1

Liver	
Elevated transaminases	5
Infection	
Urinary tract infection - *Escherichia coli*	1
Pneumonia (culture negative)	1
Clostridium difficile diarrhea	1
Rectal surveillance culture- vancomycin resistant enterococcus	1
Other	
Engraftment bone pain	1
Serum sickness	1
Seizure	1
Hematuria	1
Epistaxis	1

The rate of infection per patient per year was 0.19 in the HSCT group and 0.23 in the DMT group.

Quels patients SEP sont candidats?



Bone Marrow Transplantation
https://doi.org/10.1038/s41409-019-0684-0

FEATURE

Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE)

Basil Sharrack[1,2] · Riccardo Saccardi[3] · Tobias Alexander[4] · Manuela Badoglio[5] · Joachim Burman[6] · Dominique Farge[7,8,9,10] · Raffaella Greco[11] · Helen Jessop[12] · Majid Kazmi[13] · Kirill Kirgizov[14] · Myriam Labopin[5] · Gianluigi Mancardi[15] · Roland Martin[16] · John Moore[17] · Paolo A. Muraro[18] · Montserrat Rovira[19] · Maria Pia Sormani[20,21] · John A. Snowden[12] · for the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and EBMT (JACIE)

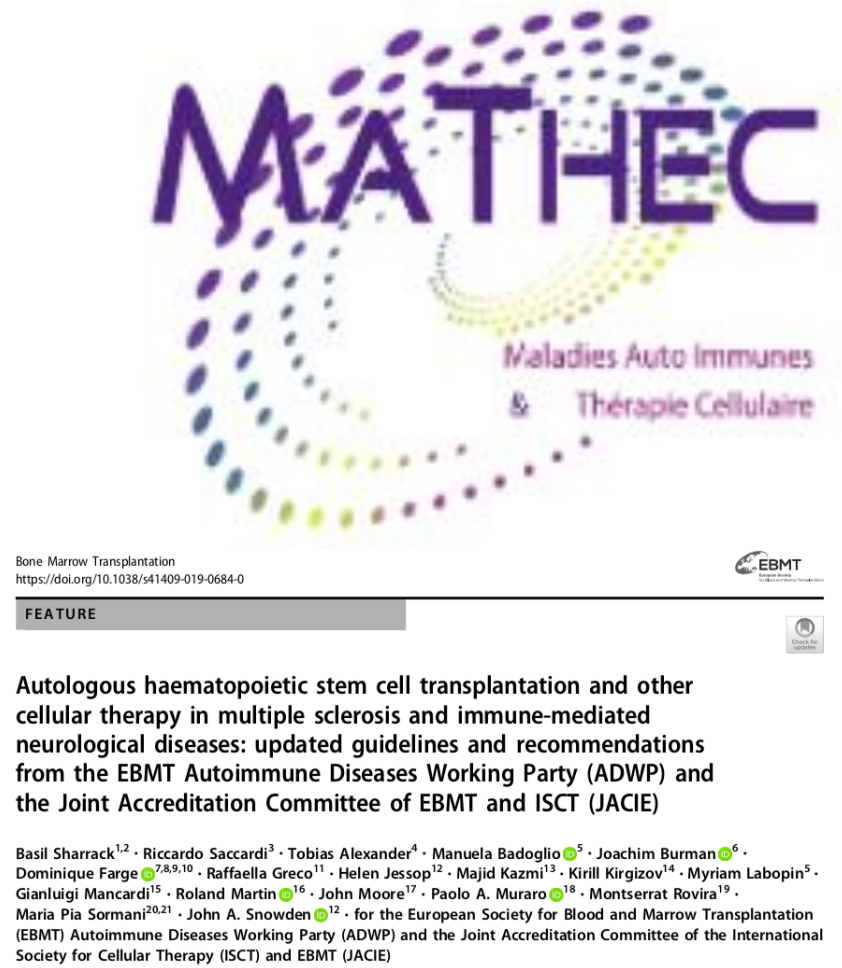
PATIENT SEP McDonald 2010, âgé de < 60 ans avec un score EDSS irréversible ≤ 6.0 qui présente une **ACTIVITE INFLAMMATOIRE**

1) SEP -RR :

- Sous traitement de 2nde ligne bien conduit depuis au moins 6 mois,
- Au moins 1 poussée significative sur le plan clinique
- Augmentation d'un score EDSS de Kurtzke de ≥ 1 point , aboutissant à un score fonctionnel coté à plus de 2 pour le paramètre le plus affecté
- Au moins une prise de gadolinium sur une IRM de moins de 3 mois.

Zephir et al. Bul du cancer 2019

Quels patients SEP sont candidats?



PATIENT SEP McDonald 2010, âgé de < 60 ans avec un score EDSS irréversible ≤ 6.0 qui présente une **ACTIVITE INFLAMMATOIRE**

2) SEP -P :

- Sous traitement bien conduit de plus de 6 mois,
- Durée de phase progressive de moins de 5 ans,
- Au moins 1 poussée significative sur le plan clinique
- Au moins une prise de gadolinium sur une IRM de moins de 3 mois ou une nouvelle lésion T2 significative sur une IRM de moins de 3 mois comparée à une IRM de référence de moins de 1 an.

Zephir et al. Bul du cancer 2019

Autologous haematopoietic stem cell transplantation for neurological diseases

Joachim Burman,[1] Andreas Tolf,[1] Hans Hägglund,[2] Håkan Askmark[1]

Burman J, *et al*. *J Neurol Neurosurg Psychiatry* 2018;**89**:147–155.

Table 2 Summary of reports of HSCT for CIDP

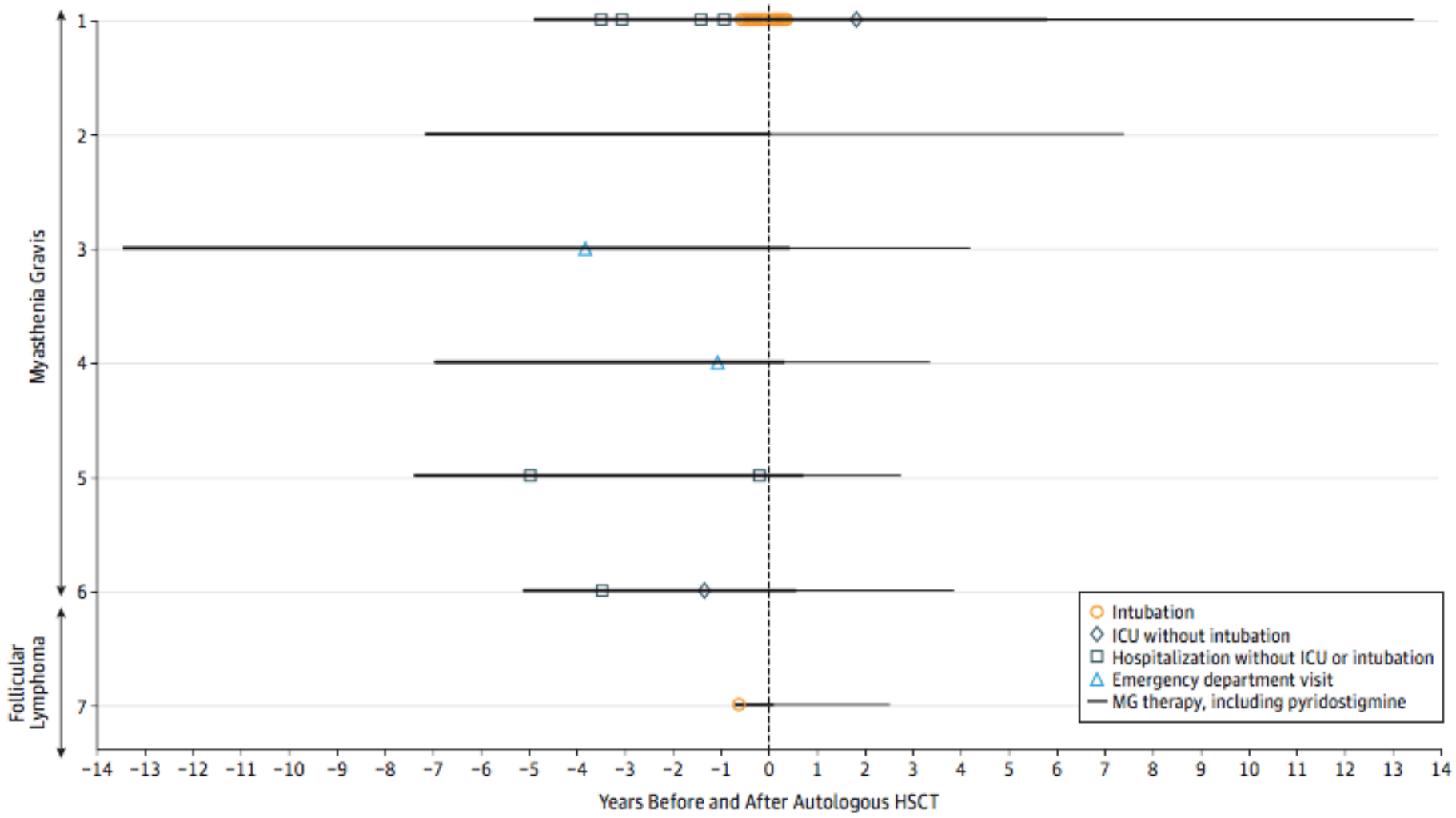
	n	Age at onset	Gender	Disease duration (months)	Conditioning	Clinical outcome	Duration of follow-up (months)	Relapse (months after HSCT)
Vermeulen *et al*[31 78]	1	38	M	120	BEAM	Good recovery, but still on prednisone 5 mg/day and relapse after 5 years	>60	60
Kamat *et al*[82]	2	42	M	24	Cy+ATG	Unable to walk to ambulant	18	None
		72	M	120	Cy+ATG	Stabilised	3	None
Oyama *et al*[79]	1	32	F	30	Cy+ATG	Rankin functional score from 4 to 1	22	None
Barreira *et al*[81]	1	24	M	144	Cy+ATG	Short transient response	2	1
Mahdi-Rogers *et al*[80]	3	29	F	252	Cy+ATG	MRC sum score 39–48–29	26	18
		58	F	156	Cy+ATG	MRC sum score 58–62	6	None
		72	M	72	Cy+ATG	MRC sum score 46–34	19	None
Axelson *et al*[84]	1	56	M	11	Cy	INCAT score from 10 to 2	101	25
				36	Cy+ATG	INCAT score from 6 to 2		None
Press *et al*[83]	11	16–67	10 M, 1 F	11–228	CY+ATG (7)	Median INCAT score from 6 to 1	6–101	23
					BEAM (3)			14
					Melphalan (1)			14
Bregante *et al*[85]	1	24	M	7	Thiotepa+Cy+G-CSF	Wheelchair users to ambulant for 6 months to unable to walk	60	6
					Fludarabin+Cy+TBI*	Unable to walk to ambulant		None

Copyright MATHEC

Original Investigation

Myasthenia Gravis Treated With Autologous Hematopoietic Stem Cell Transplantation

Figure. Emergency Department Visits and Hospitalizations Before and After Autologous Hematopoietic Stem Cell Transplant (HSCT)



Copyright MATHEC

Bryant et al. JAMA 2016

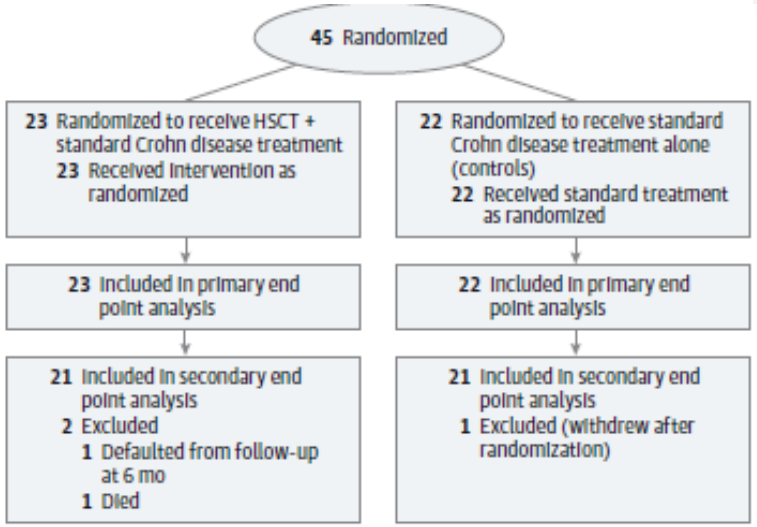
Original Investigation

Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease

A Randomized Clinical Trial

Christopher J. Hawkey, FMedSci; Matthieu Allez, PhD; Miranda M. Clark, BSc(Hons); Myriam Labopin, MD; James O. Lindsay, PhD; Elena Ricart, PhD; Gerhard Rogler, PhD; Montserrat Rovira, MD; Jack Satsangi, DPhil; Silvio Danese, PhD; Nigel Russell, MD; John Gribben, MD; Peter Johnson, MD; Jerome Larghero, MD; Catherine Thieblemont, PhD; Sandro Ardizzone, MD; Daan Dierickx, PhD; Adalberto Ibatici, MD; Timothy Littlewood, MD; Francesco Onida, MD; Urs Schanz, MD; Severine Vermeire, PhD; Jean-Frederic Colombel, MD; Jean-Paul Jouet, MD; Elizabeth Clark, MSc; Riccardo Saccardi, MD; Alan Tyndall, FRACP; Simon Travis, DPhil; Dominique Farge, PhD

JAMA. 2015;314(23):2524-2534.



RESULTS Twenty-three patients underwent HSCT and 22 received standard treatment (controls). There were no statistically significant between-group differences in proportions of patients achieving sustained disease remission, CDAI less than 150 in the last 3 months, or freedom from active disease; there was a statistically significant difference among patients able to discontinue active treatment in the last 3 months. There were 76 serious adverse events in patients undergoing HSCT vs 38 in controls; 1 patient undergoing HSCT died.

	No. (%)			
	HSCT	Control	Difference (95% CI), %	*P* Value
Sustained disease remission	2 (8.7)	1 (4.5)	4.2 (−14.2 to 22.6)	.60
Secondary outcomes				
No active treatment	14 (60.9)	5 (22.7)	38.1 (9.3 to 59.3)	.01
CDAI <150	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.052
Free of active disease	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.054

RCP Nationale MATHEC

- **MATHEC** est une association labélisée Centre de Référence des Maladies Auto-immunes Systémiques Rares au sein de la filière **FAI2R**, qui s'appuie sur un réseau d'experts de différents centres accrédités

- **RCP MATHEC** crée en 2007 sous l'égide de la **SFGM**

  - Les modalités de connexion sont sur https://www.mathec.com
  - Elle a lieu les 1er et le 3ème mercredis de chaque mois
  - Une fiche de RCP est téléchargeable et doit être transmise 48H avant la RCP
  - Un partage d'écran devrait permettre l'analyse des TDM et IRM par les participants
  - Un compte rendu est envoyé

Copyright MATHEC

ADWP - Number of HSCT: 3448

EBMT Registry – November 2020

▶ **MULTIPLE SCLEROSIS**	**1694**
▶ **CONNECTIVE TISSUE**	**865**
SSc	685
SLE	119
PM-DM	19
Sjogren	5
Antiphosph. Syndrome	6
Other/Unknown	*31*
▶ **ARTHRITIS**	**194**
Rheumatoid arthritis	82
Juvenile chronic arthritis :	
**Systemic JIA*	64
**Other JIA*	19
**Polyarticular JIA*	17
Psoriatic arthritis	3
Other	*8*
▶ **INFLAMMATORY BOWEL**	**256**
Crohn's disease	210
Ulcerative colitis	4
Other	*42*

▶ **HAEMATOLOGICAL**	**136**
ITP	37
AIHA	32
Evans'	26
Other	41
▶ **VASCULITIS**	**63**
Wegener's	14
Behcet's	13
Takayasu	3
Polyarteritis	4
Churg-Strauss	2
Other/Unknown	27
▶ **OTHER NEUROLOGICAL**	**134**
NMO	26
CIDP	61
Myasthenia gravis	10
Other/Unknown	37
▶ **INSULIN DEPENDENT DIABETES**	**20**
▶ **OTHER**	**86**

En conclusion

- Soins courant pour SSc et SEP sévères (reco grade A)
- Importance du screening exhaustif des patients candidats
- Discussion collégiale RCP puis RCP MATHEC
- Indication d'exception dans autres MAI sévères et réfractaires
- PNDS

Merci pour votre attention