SCLERODERMIE: GREFFE ou PAS GREFFE?

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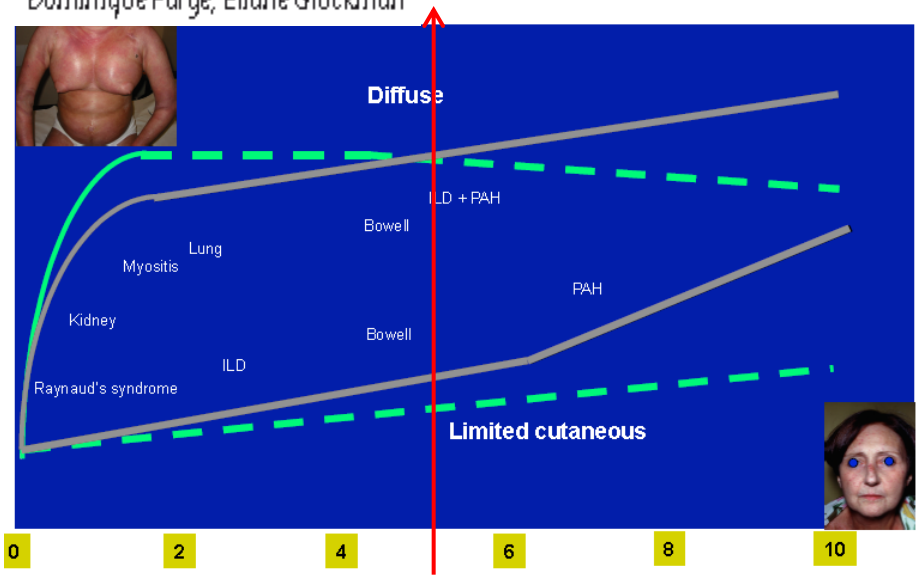
www.mathec.com

Autologous HSCT in systemic sclerosis: a step forward

www.thelancet.com Published online July 20, 2011 DOI:10.1016/S0140-6736(11)61100-8

*Dominique Farge, Eliane Gluckman



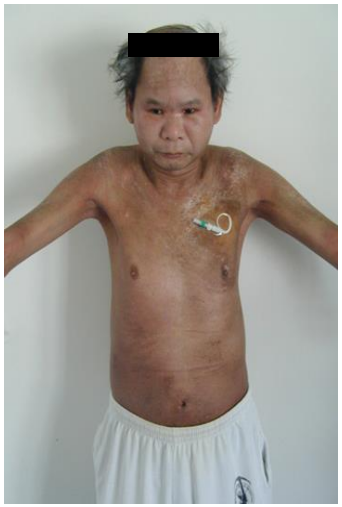
HSCT ***MSC***

@ **Prévalence 7–500 / Million**

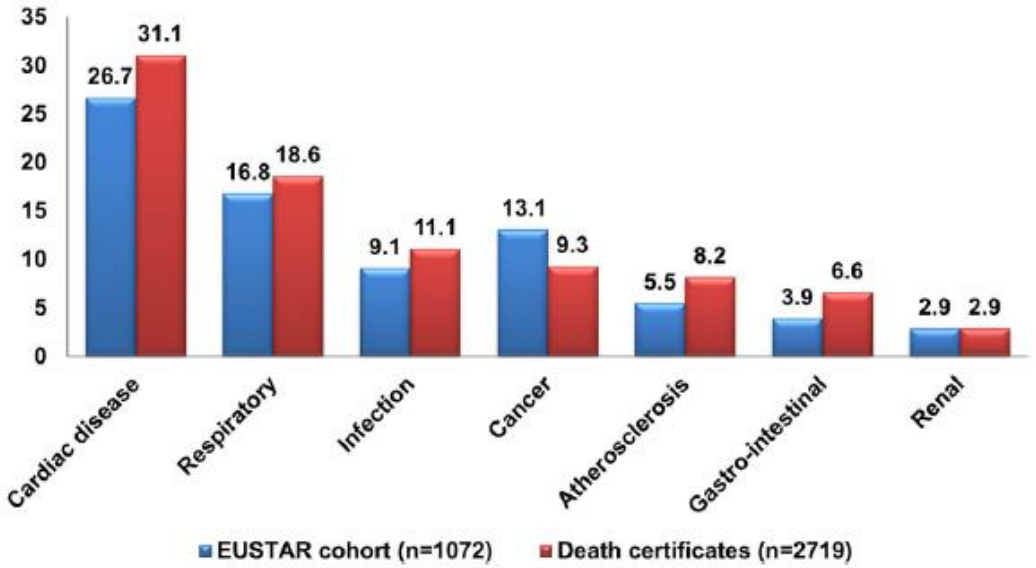
x 1.2 -1.8 femmes noires

1996--2019

Taux Mortalité (SMR)
x 3.5 / population générale



Elhai et al Ann Rheum Dis 2017



Left Ventricle Replacement Fibrosis Detected by CMR Associated With Cardiovascular Events in Systemic Sclerosis Patients

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Rica Stanciu, MD
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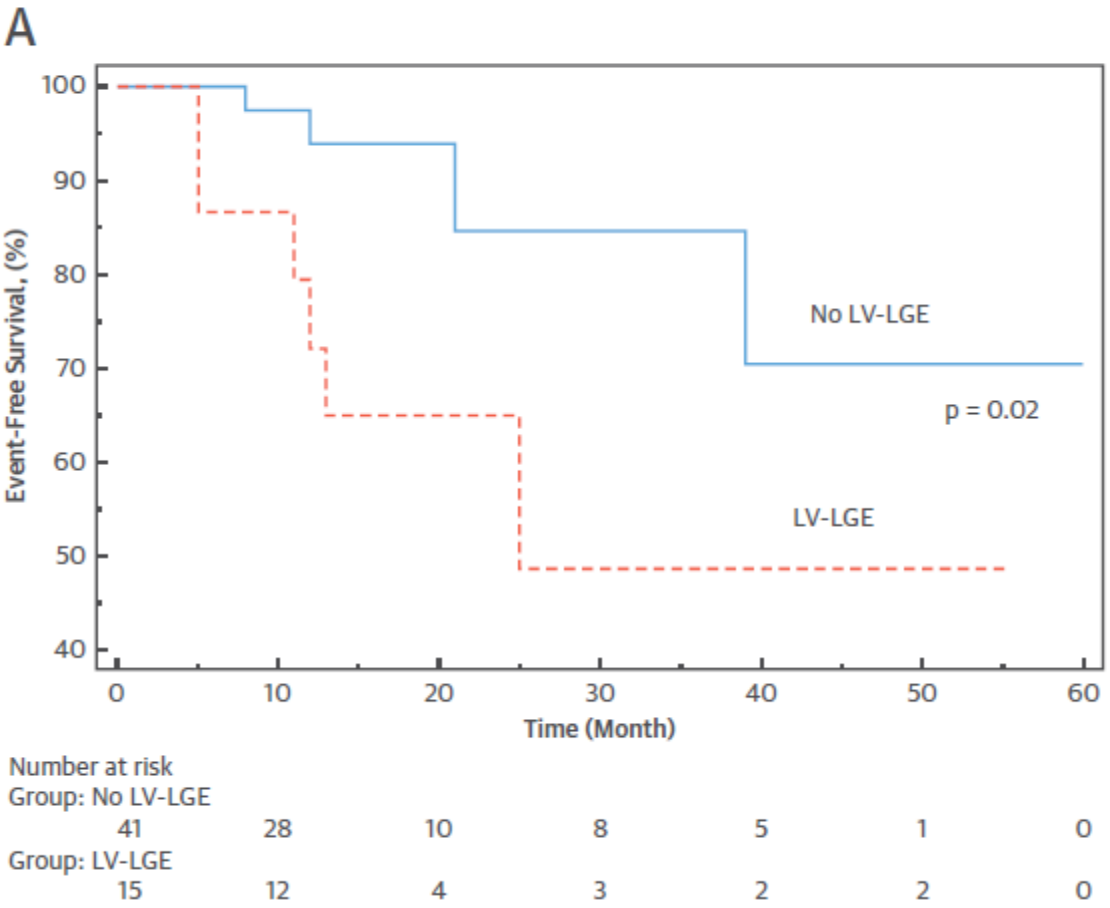
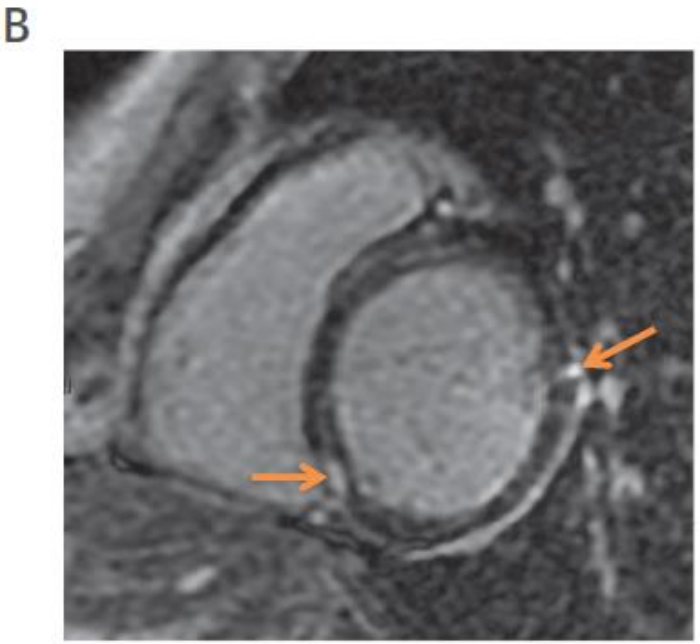
Ludivine Perdrix, MD
Pierre Boutouyrie, MD, PhD
Arshid Azarine, MD
Gilles Soulat, MD
Dominique Farge, MD, PhD

FIGURE 1 Kaplan-Meier Survival Curves for LV LGE or No-LV-LGE



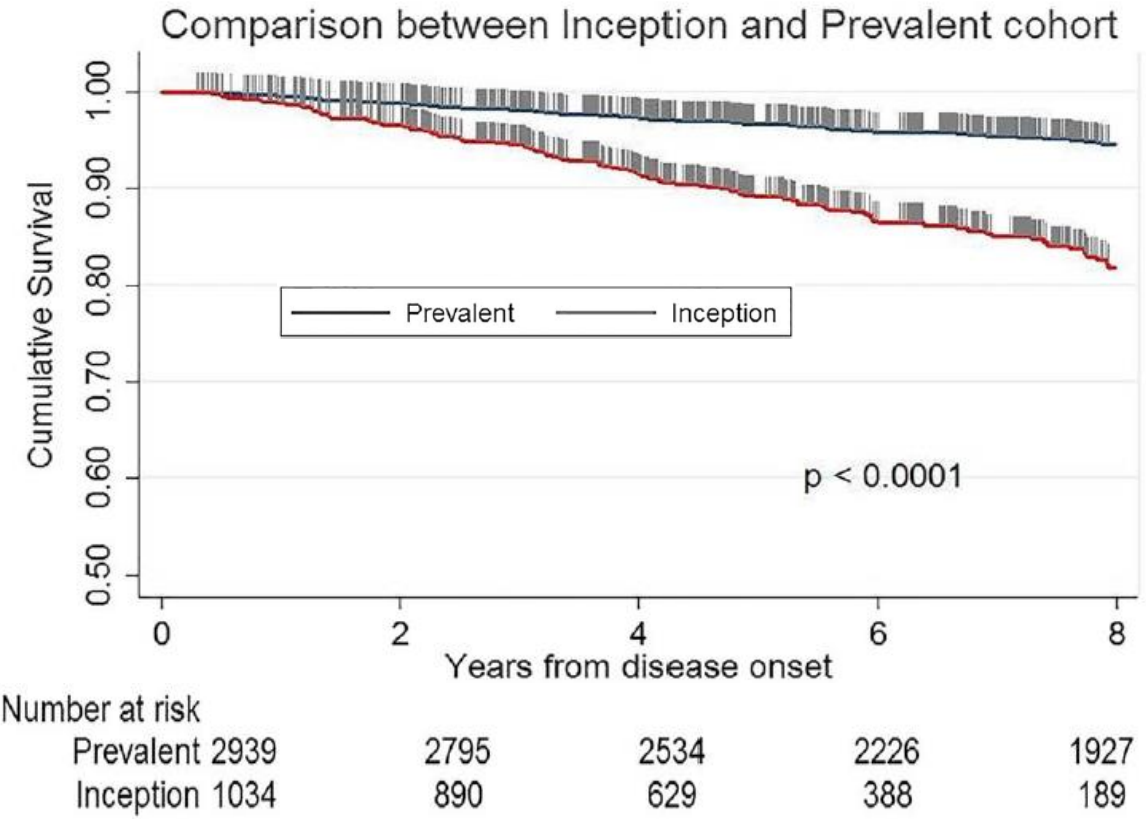


(A) Kaplan-Meier survival curves are shown of the time to event according to the presence (LV-LGE) or absence (No-LV-LGE) of left ventricular late gadolinium enhancement in CMR. **(B)** One case illustrates CMR presence of LV-LGE with a nodular pattern of focal enhancement at 2 different locations **(arrows)**. CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV = left ventricle.

Early Mortality in a Multinational Systemic Sclerosis Inception Cohort

Yanjie Hao,[1] Marie Hudson,[2] Murray Baron,[2] Patricia Carreira,[3] Wendy Stevens,[4] Candice Rabusa,[4] Solene Tatibouet,[5] Loreto Carmona,[6] Beatriz E. Joven,[3] Molla Huq,[7] Susanna Proudman,[8] Mandana Nikpour,[7] the Canadian Scleroderma Research Group, and the Australian Scleroderma Interest Group

Arthritis Rheum 2018



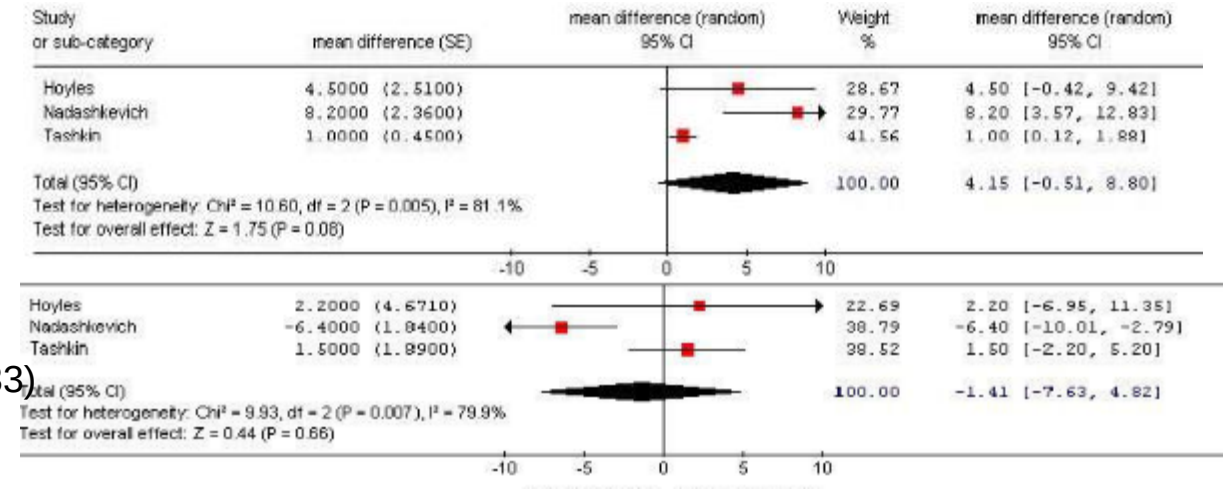
13% death after 3 yrs FU (IQR: 1.0-5.1yrs)

POOLED SMR : 4.06 (95% CI: 3.39-4.85)

Variable	Combined inception cohort		Combined prevalent cohort	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male sex	2.28 (1.42–3.65)	0.001	1.72 (1.27–2.33)	0.001
Age at disease onset, years†	1.05 (1.03–1.07)	0.000	1.05 (1.04–1.06)	<0.0001
Diffuse disease subtype	1.83 (1.14–2.92)	0.002	1.40 (1.07–1.83)	0.013
Disease duration at recruitment, years	0.59 (0.47–0.74)	<0.0001	0.71 (0.68–0.74)	<0.0001
Anticentromere antibody‡	–	–	0.71 (0.53–0.94)	0.019
Anti–Scl-70 antibody‡	–	–	0.95 (0.67–1.35)	0.774
PAH	2.35 (1.29–4.29)	0.006	2.50 (1.83–3.42)	<0.0001
ILD‡	–	–	1.31 (1.01–1.70)	0.040
Myocardial involvement	0.99 (0.44–2.23)	0.977	1.18 (0.83–1.69)	0.363
Renal crisis	1.87 (1.01–3.48)	0.048	1.33 (0.86–2.07)	0.205
IHD and/or CVD	1.54 (0.86–2.76)	0.145	1.28 (0.96–1.72)	0.094
Malignancy‡	–	–	0.97 (0.72–1.30)	0.832

FVC : mean change
2.83% (95% CI:0.35; 5.31)

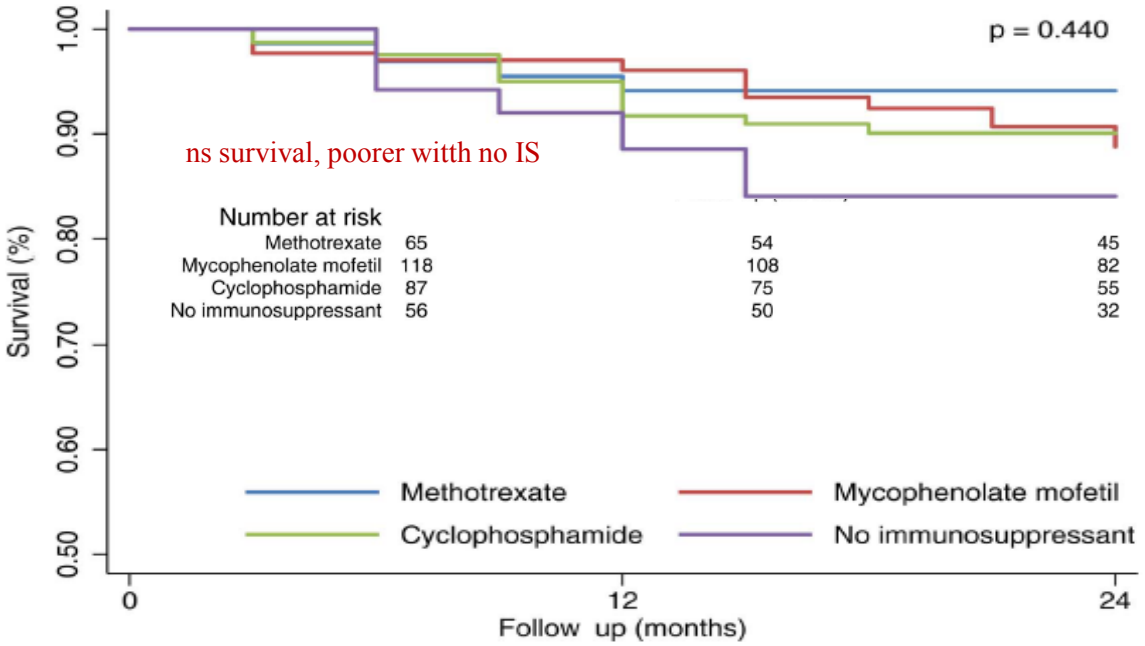
DLCO : mean change
4.56% (95% CI :-0.21; 9.33)



Nanini Athr Res Ther 2008

ESOS Study
Early Diffuse cutaneous SSc
326 pts 50 centers;

Herrick AL, *et al. Ann Rheum Dis* 2016;**0**:1–12.



https://www.mathec.com/soignants/recommandations-de-bonnes-pratiques/

Phases I-II

1997 Special Report : **Blood and marrow stem cell transplants in auto-immune disease: a consensus report written on behalf of the European League against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT)** **Tyndall** A, Gratwohl A.- BMT

2002 **Autologous bone marrow transplantation in the treatment of refractory systemic sclerosis: early results from a French multicentre phase I-II study.** Farge D et al., Br J Haematol.

2004 **Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry.** Farge D et al. Ann Rheum Dis.

2008 **Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis.** Vonk MC et al, Ann Rheum Dis.

Phases II-III

2011 **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.** Burt RK et al, Lancet.

2014 **Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial.** van Laar JM and Farge D, et al JAMA.

2018 **Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma.clinical trial** Sullivan et al NEJM.

Recommandations

2012 **Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation.** Snowden JA et al, BMT **GRADE 1 EVIDENCE**

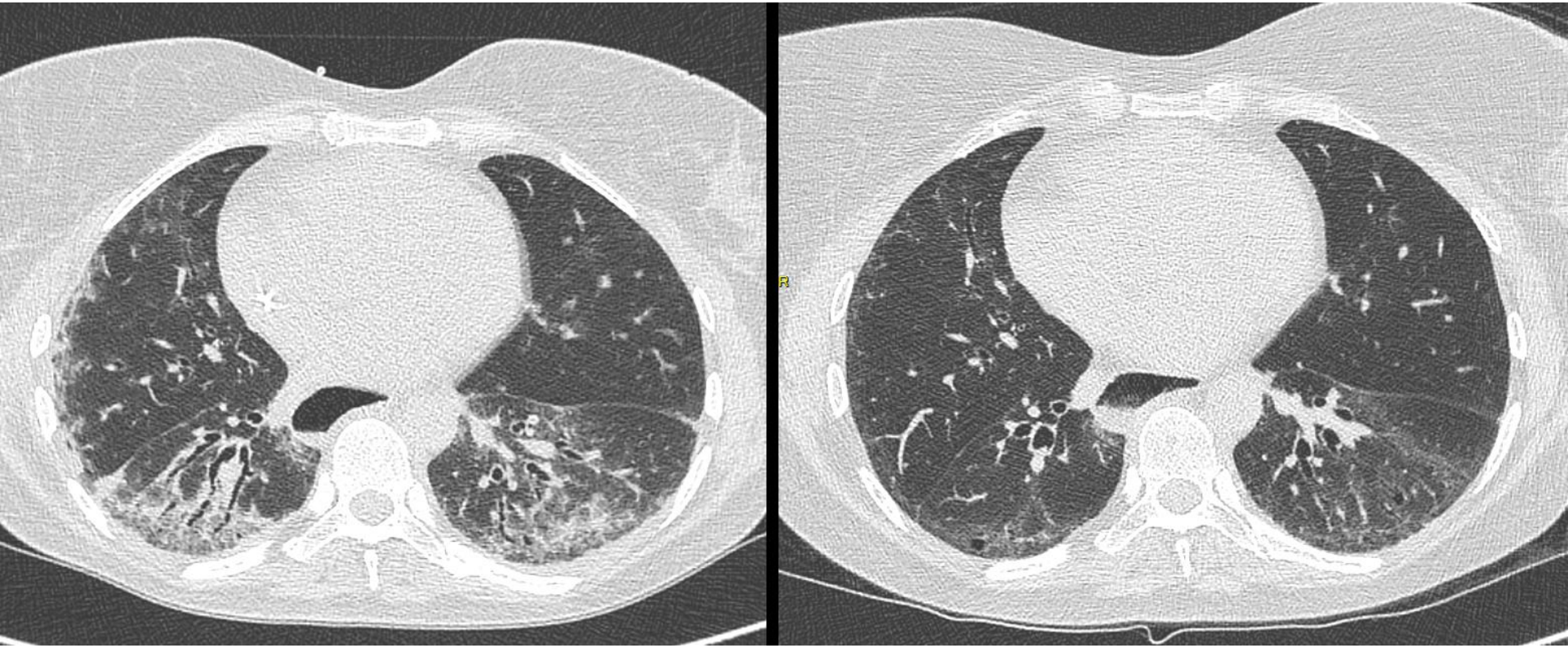
2015 **SCT for severe autoimmune diseases: consensus guidelines of the European Society for Blood and Marrow Transplantation for immune monitoring and biobanking.** Alexander T, BMT

2017 **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** Farge D, BMT

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) Grégory Pugnet, Bull Cancer

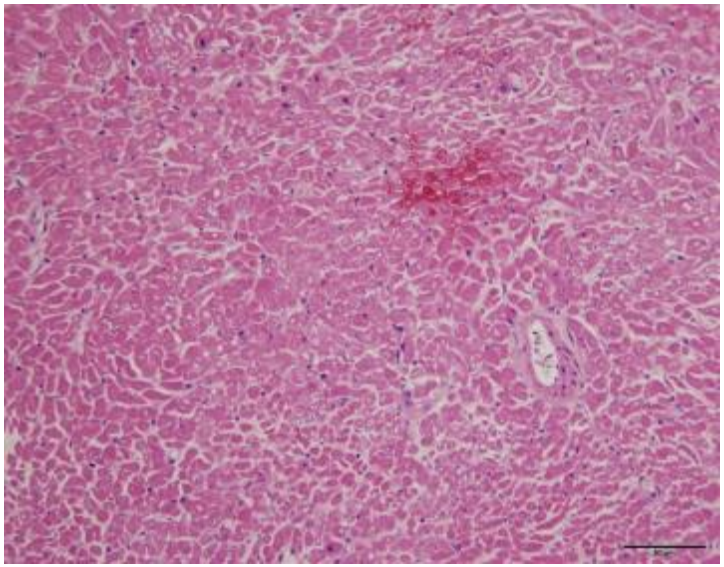
Protocole National de Diagnostic et de Soins 2017 Sclérodermie Systémique

YES



St Louis Hospital MATHEC before and 6 years after HSCT April 2018

Despite normal MRI and cardiac evaluation:

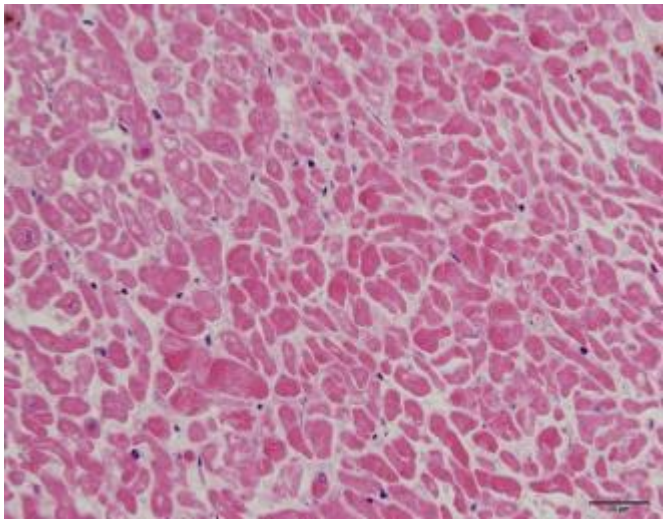


diffuse interstitial oedema
no evidence of fibrosis nor inflammatory infiltrate (x 20)

ACUTE CYCLO CARDIOTOXICITY

Martin et al BMT 2017

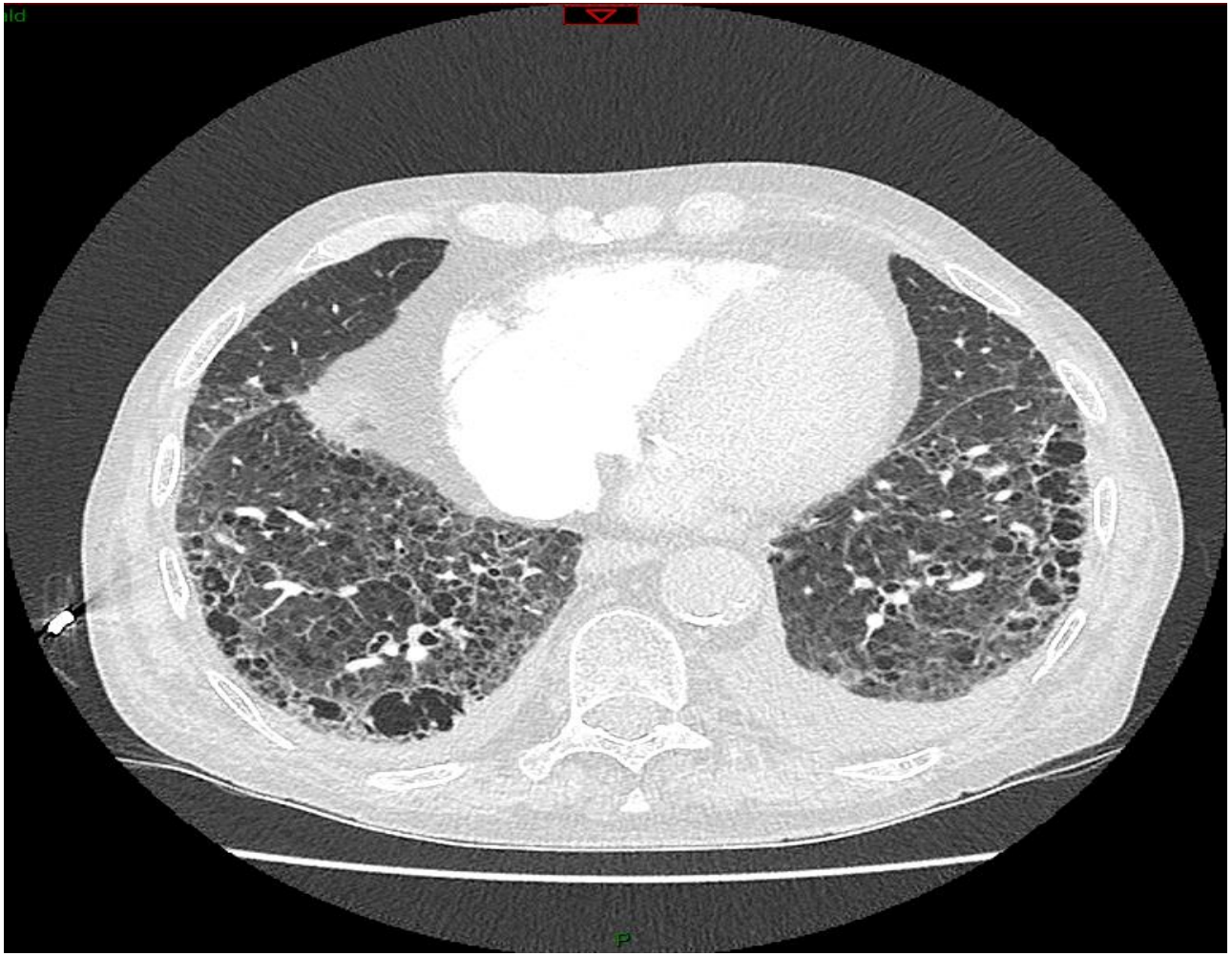
within 3 wks after iv CYCLO toxic endothelial damage

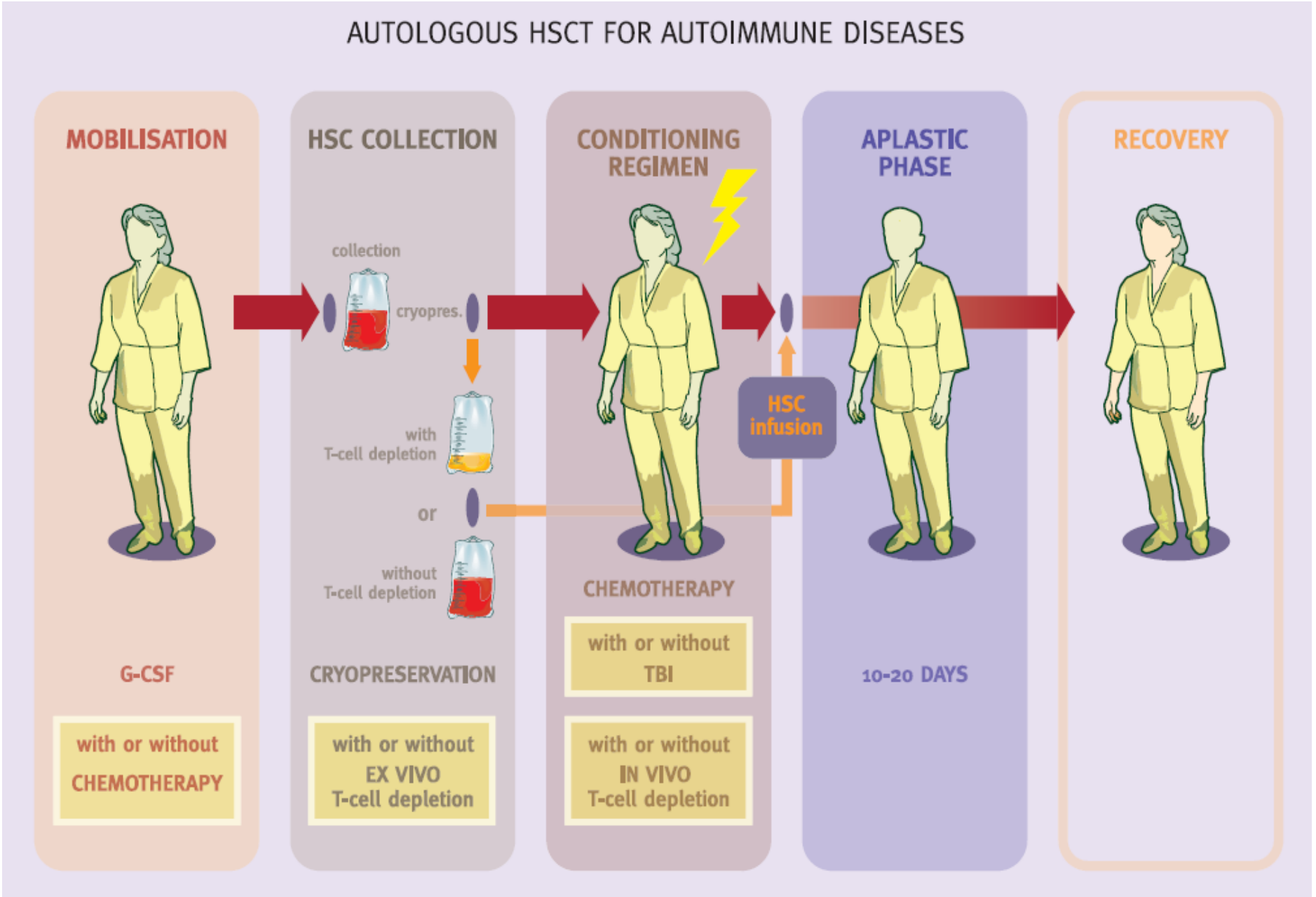


Diffuse ischemic myocardial necrosis:
nuclear extravasation or pycnosis, hyperstaining by eosin.
Intracellular oedema and diffuse interstitial oedema (X40).

THE REAL RISK

NO





Saccardi R, Gualandi F, Autoimmunity, 2008

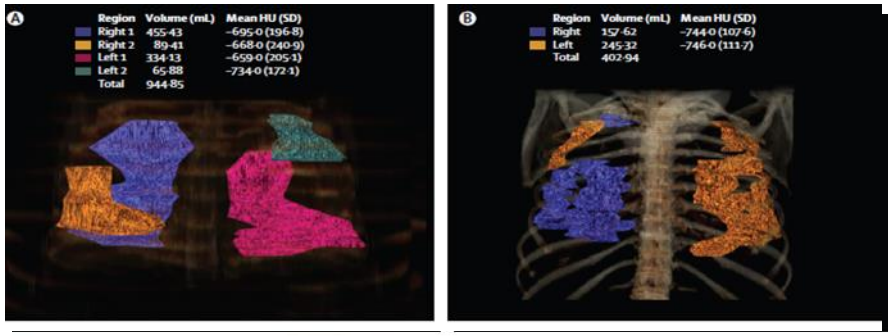
Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial

Lancet 2011; 378: 498–506

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)	..



Cardiac involvement and treatment-related mortality after non-myeloablative haemopoietic stem-cell transplantation with unselected autologous peripheral blood for patients with systemic sclerosis: a retrospective analysis

www.thelancet.com Published online January 28, 2013

N = 90 pts : 5 %TRM

Richard K Burt, Maria Carolina Oliveira, Sanjiv J Shah, Daniela A Moraes, Belinda Simoes, Mihai Gheorghiade, James Schroeder, Eric Ruderman, Dominique Farge, Z Jessie Chai, Zora Marjanovic, Sandeep Jain, Amy Morgan, Francesca Milanetti, Xiaoqiang Han, Borko Jovanovic, Irene B Helenowski, Julio Voltarelli*

1 The main outcome was treatment-related mortality

thickness by modified Rodnan skin score and pulmonary function by forced vital capacity, total lung capacity, and diffusing capacity of carbon monoxide (DLCO; percentage predicted and corrected for haemoglobin). We administered quality of life questionnaires (short form [SF]-36) for the last 30 consecutive patients from

2

one site (Northwestern University). We defined relapse as any of the following criteria: increase from best improvement of skin score by 25% or decline in forced vital capacity by 10%, renal crisis, start of total parenteral nutrition, or restarting of immune suppressive or modulating medication.

3

	Normal echocardiogram or electrocardiograph or female sex	Abnormal echocardiogram or electrocardiograph or male sex	p value*
DLCO			
Group: echocardiogram	Normal 71·3% (3·1)	Abnormal 56·7% (3·8)†	0·0045
Group: electrocardiograph	Normal 73·3% (4·6)	Abnormal 62·0% (3·0)‡	0·045
Group: sex	Female 66·3% (2·8)	Male 64·5% (4·9)	0·75
FVC			
Group: echocardiogram	Normal 70·8% (3·2)	Abnormal 68·4% (2·4)	0·58
Group: electrocardiograph	Normal 73·6% (4·6)	Abnormal 68·2% (2·1)	0·28
Group: sex	Female 66·1% (2·5)	Male 66·3% (3·1)	0·95
Total lung capacity			
Group: echocardiogram	Normal 80·3% (3·4)	Abnormal 78·8% (2·3)	0·70
Group: electrocardiogram	Normal 81·9% (4·4)	Abnormal 78·7% (2·1)	0·51
Group: sex	Female 75·8% (2·4)	Male 75·2% (3·0)	0·80
mRSS			
Group: echocardiogram	Normal 16·1 (1·7)	Abnormal 18·2 (1·3)	0·33
Group: electrocardiograph	Normal 16·1 (2·4)	Abnormal 17·8 (1·1)	0·51
Group: sex	Female 17·0 (1·4)	Male 16·4 (2·1)	0·77

Response to treatment: 25% ↑ mRSS and/or≥10% ↑ DLCO or FVC at month 12

SSC PATIENT selection : EKG, cardiac echo with TAPSE, 24h Holter, MRI ,right heart catheter with fluid challenge= update the 2004 EBMT guidelines

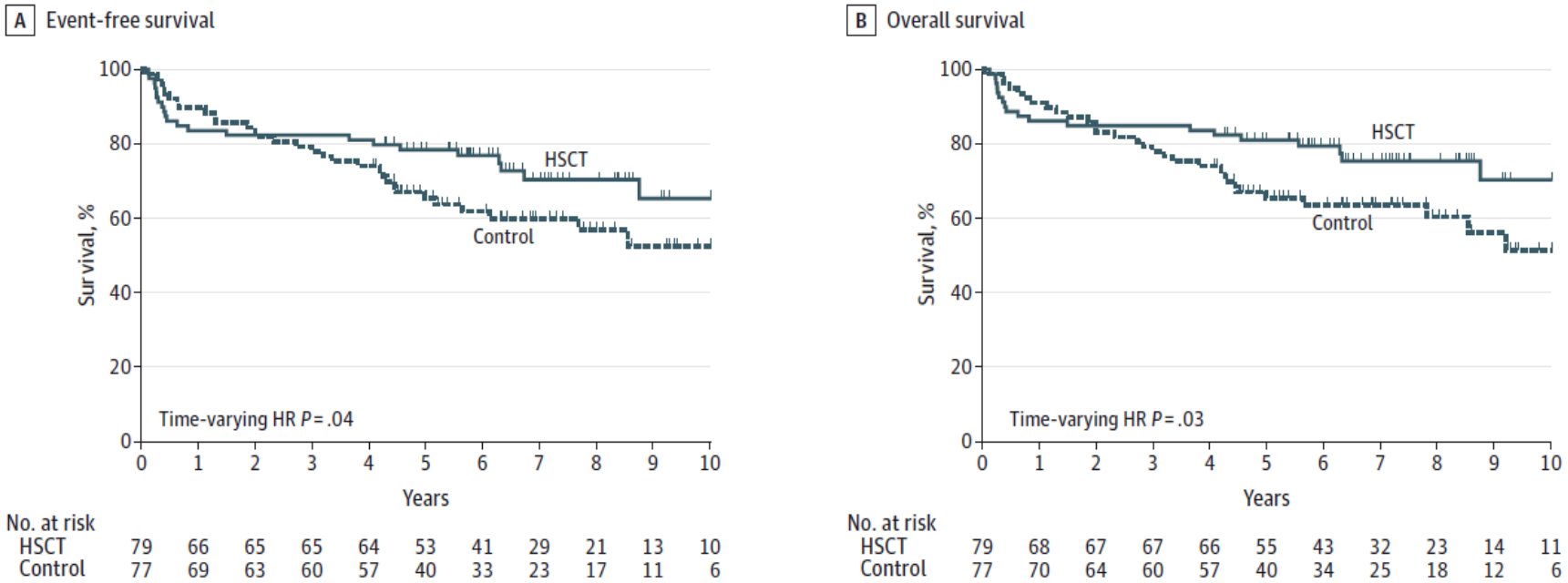
Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis A Randomized Clinical Trial

Original Investigation Research

Van Laar JVL and Farge D et al

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

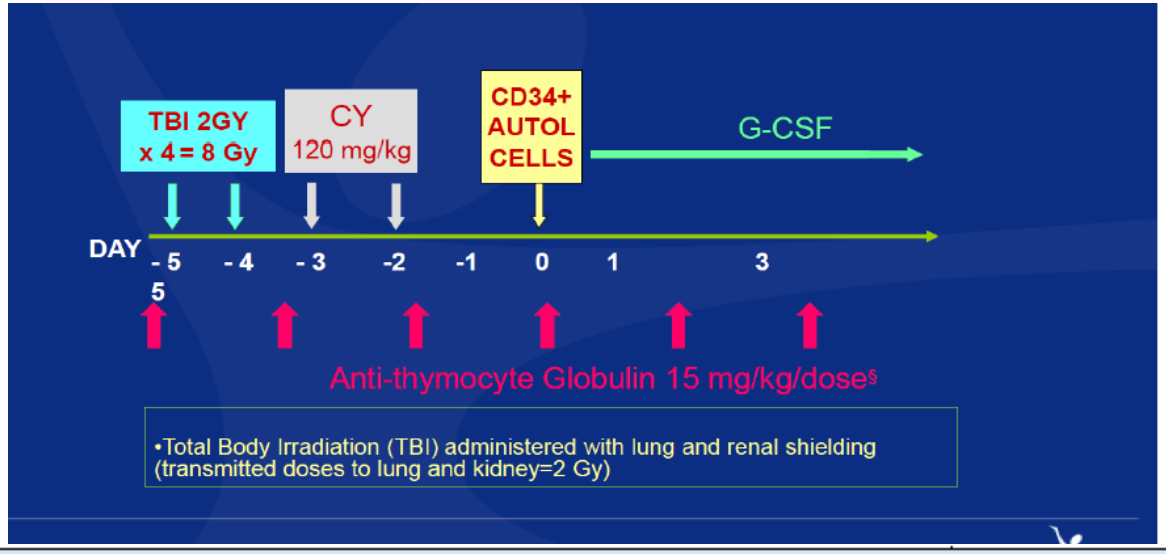
Figure 2. Event-Free and Overall Survival During 10-Year Follow-up



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)



	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

COMBINING MORTALITY AND LONGITUDINAL MEASURES IN CLINICAL TRIALS

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

SCOT US trial Sullivan K. et al NEJM 2018

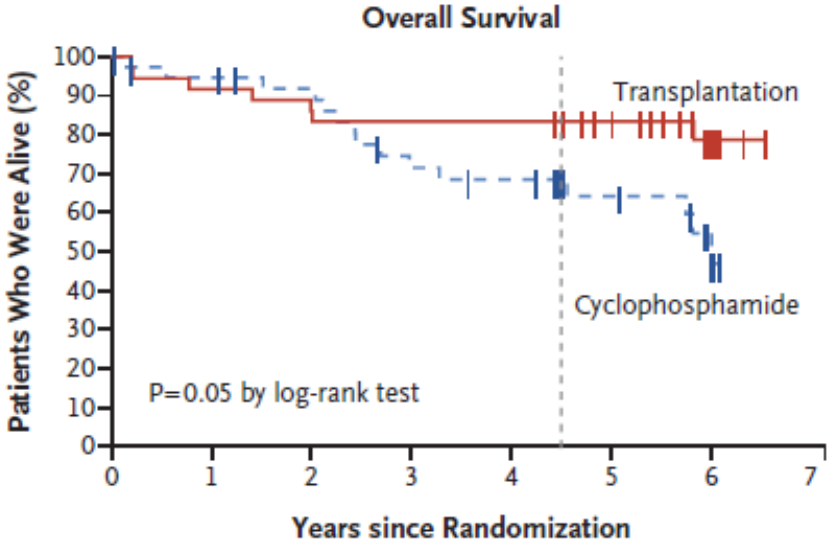
STATISTICAL ANALYSIS

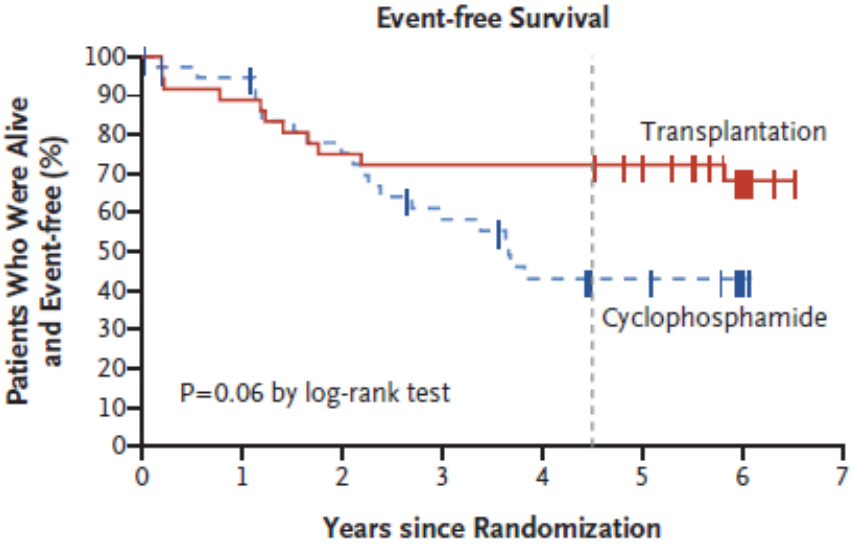
The trial was originally designed for 226 participants, with event-free survival as the primary end point. Low accrual prompted amendments, first to broaden entry criteria, then, ultimately, to reduce the sample size by changing the primary end point to the global rank composite score. Power for the new design with 114 participants per board recommended stopping randomization at 75 participants.

Death from any cause — no. (%)			
By 54 mo	6 (17)	11 (28)	0.28
By 48 mo	6 (17)	11 (28)	0.28
Treatment-related death — no. (%)§			
By 54 mo	1 (3)	0	0.48
By 48 mo	1 (3)	0	0.48

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

C Intention-to-Treat Population





No. at Risk

Transplantation	36	33	31	30	30	25	9
Cyclophosphamide	39	35	32	24	22	15	7

	36	32	27	26	26	24	9
	39	35	27	20	14	12	6

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.

CONTRA- INDICATIONS or EXCLUSION to AHSCT

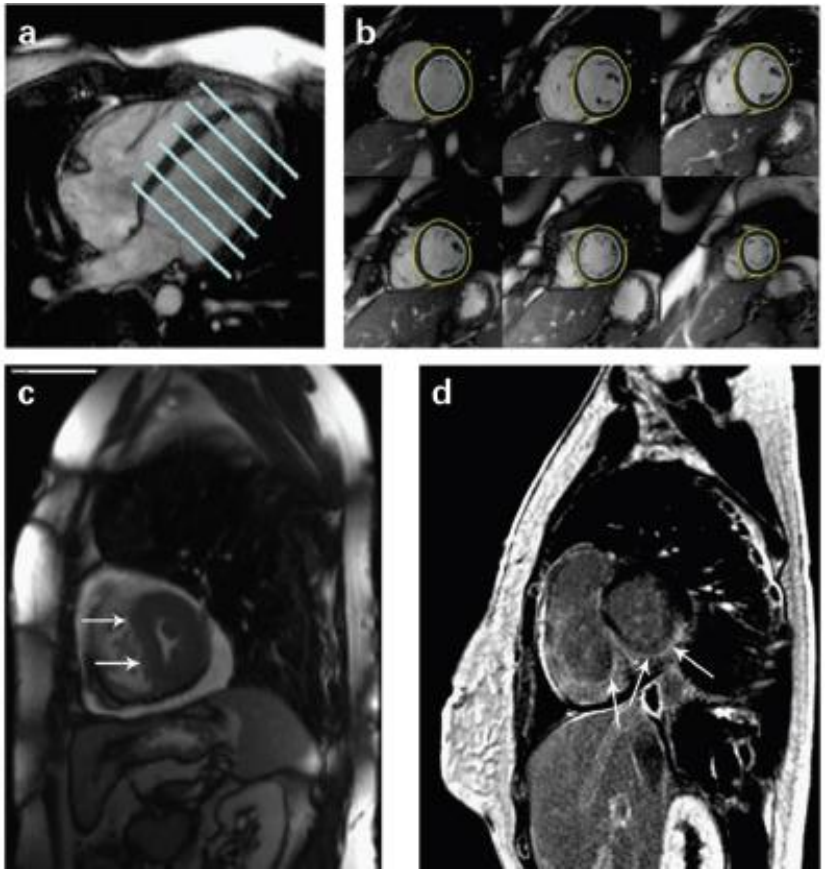
Age	**> 65 years**
Pregnancy	Pregnancy or unadequate contraception throughout investigation
Psychiatric	Psychiatric disease including alcohol or drug abuse
Consent	Inability to provide informed consent for treatment
Liver function	Liver function test abnormalities (i.e. 2-fold transaminases or bilirubin, cirrhosis)
Neoplasms	Concurrent neoplasms or myelodysplasia or haematological disorders
Infection	Active acute or chronic infection, including HIV, HTLV-1,2, hepatitis B and C, active cancer or major side effects of previous cancer treatment
Heart	LVEF <45% or impaired RV or LV function, significant atherosclerotic or valvular heart disease, pericardial effusion with haemodynamic consequences atrial or ventricular arrhythmia or 2nd or 3rd degree heart block.
LUNG	Any significant SSc or non-SSc related respiratory disease with respiratory failure (PaO_2 <8.0 kPa), interstitial lung disease with FVC <65% or **DLCO-SB < 65 %** extensive disease on HRCT, mean PAP≥25mmHg **Smoking**
Renal	Any definite SSc renal crisis in the previous 6 months or non-scleroderma related renal disease defined as creatinine clearance<40 ml/min

Snowden J, et al. BMT 2012 ; Farge D and Burt R et al BMT 2017; Pugnet G et al Bull Cancer. 2017

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



Intial screening

- Obtain medical records
- Speak with referring MD or complete questionnaire to confirm the presence of either dcSSc or lcSSc plus lung involvement

Appropriate candidate?

Yes

Invite for initial evaluation

- Lab testing: Cell blood count, Liver function tests, Basic chemistry panel, ANA, SCI-70, anti-polymerase III antibody, BNP (or NTproBNP)
- Pulmonary fuction testing
- High-resolution chest CT
- Electrocardiography
- Echocardiogram with doppler and tissue doppler plus dobutamine stress
- Cardiac MRI with contrast
- Cardiac catheterization with fluid challenge
- Holter monitor if history of palpitations or abnormal ECG
- Endoscopy if anemia or history of GAVE

No

Excluded From HSCT

Any cardiac exclusion criteria for HSCT?

Yes

- Baseline (resting) PASP > 40 mmHg or mPAP > 25 mmHg
- PASP > 45 mmHg or mPAP > 30 mmHg after fluid challenge
- Decrease or lack of augmentation of CO after fluid challenge
- Pulmonary vascular resistance > 3 Wood units
- D-sign of septal bounce on cardiac MRI
- LVEF < 45%
- Unrevascularized severe coronary artery disease
- Untreated severe arrhythmia
- Cardiac tamponade
- Constrictive pericarditis

No

Proceed with HSCT

THE NISCC 1 STUDY 2018

? effectiveness of AHSCT for early severe or rapidly progressive SSc as performed by different study protocols used in various EBMT centres

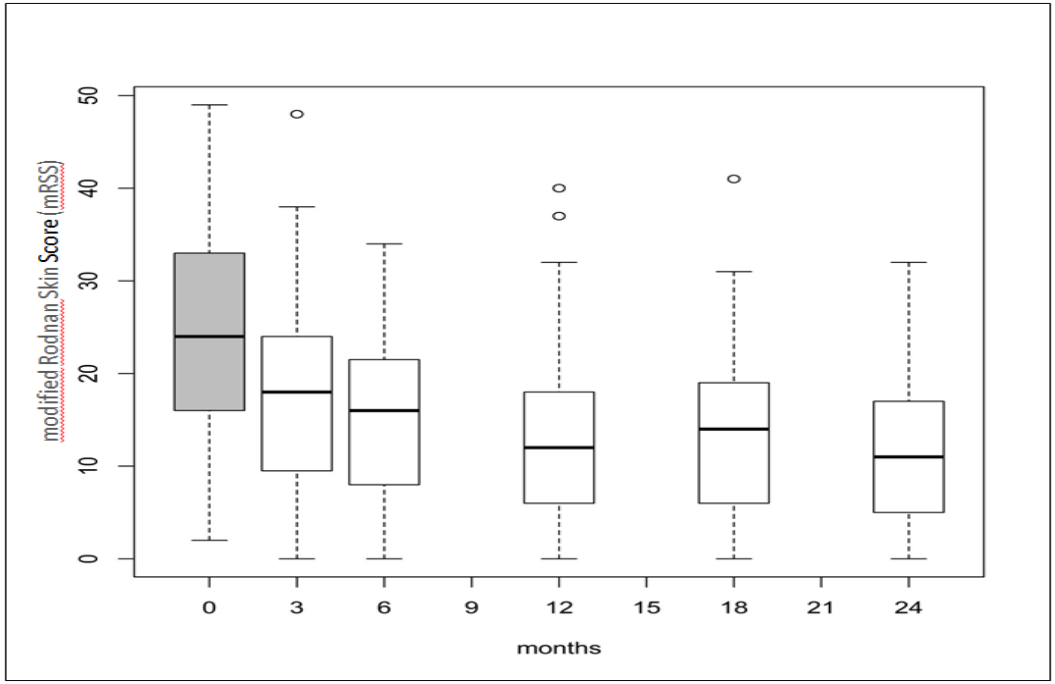
- **80 pts recruited**
  24 months follow up

Primary endpoint: PFS = survival since Baseline (1st day of mobilisation) without progression of SSc.

Secondary endpoints

Safety
Overall Survival
Response to treatment
Improvement in QOL
100-day TRM
Non Relapse Mortality (NRM)
Relapse incidence (RI)

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)



ClinicalTrials.gov Identifier: NCT02516124

ACTUALITES

des CRMR Maladies Auto-Immunes Systémiques Rares,
Université Paris Descarte, Paris, France

• 15 au 17 février 2018

5th Systemic sclerosis world congress,
Bordeaux, France

• 18 au 31 mars 2018

44th Annual meeting of the

AGENDA

R.C.P. MATHEC

Descriptif

La RCP est une réunion de concertation pluridisciplinaire réunissant différents spécialistes des maladies auto-immunes et auto-inflammatoire (interniste, neurologue, rhumatologue, hématologue, etc.) dans le but de discuter des différentes stratégies thérapeutiques qui s'offrent aux patients MAI. La décision du traitement le plus adéquat aux patients souffrant de MAI est prise de façon collégiale par ce groupe d'experts.

La présentation d'un patient au cours d'une RCP se fait via un formulaire qui doit être complété et retourné à l'adresse mail indiqué dans le formulaire au maximum la veille de la RCP. Les formulaires des patients qui seront présentés sont ensuite envoyés à tous les participants afin que chacun puisse avoir toutes les informations nécessaires à disposition pour discuter du cas.

Cette réunion a lieu tous les premiers mercredi du mois à 14h30. Un rappel de la réunion est effectué 8 jours et 3 jours avant la date de la réunion afin de pouvoir laisser le temps aux médecins spécialistes de remplir et de retourner le formulaire de présentation du patient.

Tous les intervenants, de tout horizon, désireux de participer à cette réunion sont les bienvenus.

Formulaire

Nous vous remercions de télécharger et de compléter ce formulaire pour chaque patient dont vous souhaitez que la situation soit examinée à la RCP « Thérapie cellulaire et MAI ».

Merci de nous faire parvenir le formulaire 8 à 3 jours avant la date prévue de la RCP par e-mail à l'adresse elodie.lemadre@aphp.fr , joignable au Tél : 01.42.38.50.93, ou par fax au 01.42.49.94.78 afin que nous puissions le diffuser à tous les participants.

Télécharger notre calendrier 2017 des RCP au format pdf

Calendrier annuel des RCP

✔ Mercredi 4 Janvier 2017 14h30 – 16h30

✔ Mercredi 1er Février 2017 14h30 – 16h00

✔ Mercredi 1er Mars 2017 14h30 – 16h00

✔ Mercredi 5 Avril 2017 14h30 – 16h00

✔ Mercredi 3 Mai 2017 14h30 – 16h00

✔ Mercredi 7 Juin 2017 14h30 – 16h00

✔ Mercredi 5 Juillet 2017 14h30 – 16h00

Pas de RCP au mois d'Aout

✔ Mercredi 6 Septembre 2017 14h30 – 16h00

✔ Mercredi 20 Septembre 2017 14h30 – 16h00

✔ Mercredi 4 Octobre 2017 14h30 – 16h00

✔ Mercredi 18 Octobre 2017 14h30 – 16h00

✔ Mercredi 8 Novembre 2017 14h30 – 16h00

✔ Mercredi 22 Novembre 2017 14h30 – 16h00

✔ Mercredi 6 Décembre 2017 14h30 – 16h00

✔ Mercredi 20 Décembre 2017 14h30 – 16h00

Connexion téléphonique

Participants :

1. Composer le numéro d'appel local du pays où vous vous situez (voir ci-dessous), pour la France c'est le 01 70 72 15 89

2. Puis entrer sur votre clavier téléphonique le code PIN Participant 110513 suivi de la touche #

3. Vous rejoignez la conférence audio

Nous vous remercions de télécharger les numéros d'accès par pays

Les compte-rendus des RCP MATHEC sont disponibles dans l'espace membre

HOW TO MAKE HSCT for SSc SAFER

1 CONDITIONING LESS TOXIC

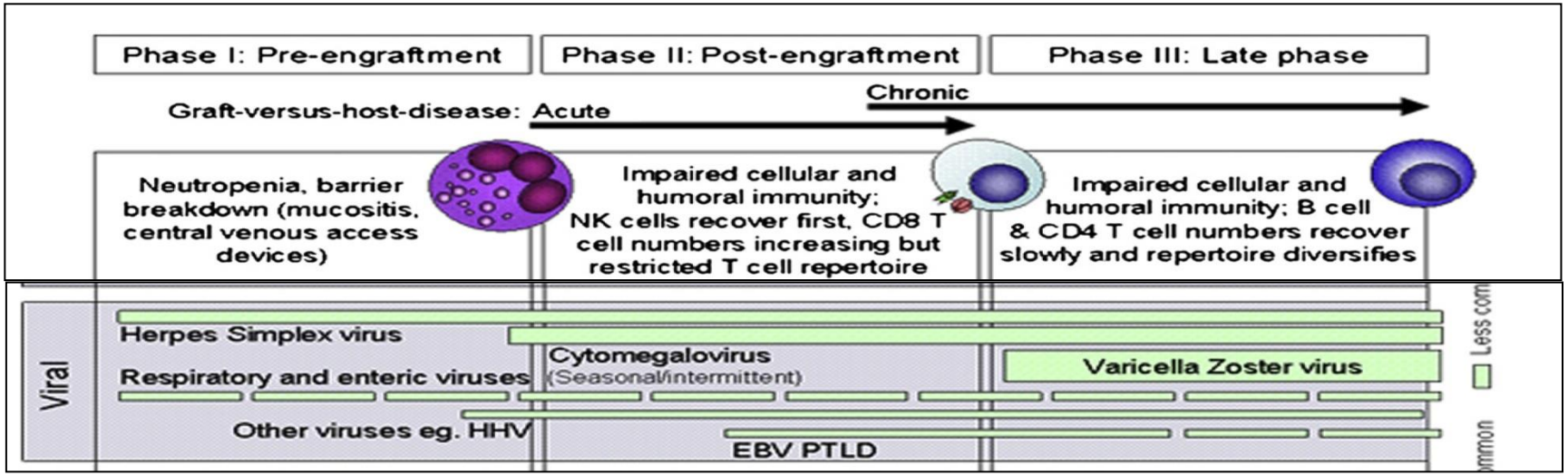
	D-5	D-4	D-3	D-2	D-1
Fludarabine dose (mg/m^2)	30	30	30		
Cytoxan (mg/m^2)		60	60		
RATG (mg/m^2)	0,5	1,5	1,5	1,5	1,5
Steroids (mg/Kg/D)	1	1	1	1	1

A regimen for bad heart function defined :PAPs > 45 mmHg (M/F) and mean PAPs > 30 mmHg (M/F)

Septal D sign :

	D-5	D-4	D-3	D-2	D-1
Fludarabine dose (mg/m^2)	30	30	30	30	
Cytoxan (mg/m^2)				60	
RATG (mg/m^2)	0,5	1,5	1,5	1,5	1,5
Steroids (mg/Kg/D)	1	1	1	1	1

«RATG»protocole **RATG dose at 0.5 mg/Kg/D at D-5,** then1.5 mg/Kg/D for other days + steroids dose at 1 mg/Kg/D at D-5, D-4, D-3, D-2 and D-1.



EBV-DNA q PCR
every 15 days
for 3 mths.
+
Close clinical monitoring

HSV

CMV

HHV6

VZV

EBV

Respiratory viruses

Adenovirus

BK/JK

HBV/HCV

0 1 2 3 4 5 6

months after HSCT

QUELS PATIENTS et COMMENT GREFFER SSc en 2019 ?

1.Tout pt avec atteinte viscérale précoce
+ SSc précoce progressive: candidat potentiel

EUSTAR non greffés : suivi court et long terme

EBMT + ASTIS+ ASSIST + SCOT++

CY vs placebo / vs MMF *Tashkin NEJM 2006 AmJ RespCCm 2007*

=>: ESOS vs NISSC early vs late response

controlled trials. However, the benefits of cyclophosphamide in scleroderma-related interstitial lung disease came at the expense of a high degree of adverse effects, and an analysis of data from a 2 year study revealed the loss of cyclophosphamide-related benefits 1 year after treatment was stopped.

Because the benefit-to-risk ratio of cyclophosphamide for scleroderma-related interstitial lung disease is somewhat inconclusive, researchers have been actively pursuing the study

Lancet Respir Med 2016; 4:708–19

2. SELECTION PATIENT +++

Pas trop tôt ..mais pas trop tard avant 5 ans

Meilleur dépistage précoce atteinte organe **FAI2R**

Eliminer contre-indication

3. RCP MATHEC

4. EQUIPE DE GREFFE : CENTRE EXPERT

5 . MOBILISATION ET CONDITIONNEMENT moins toxiques

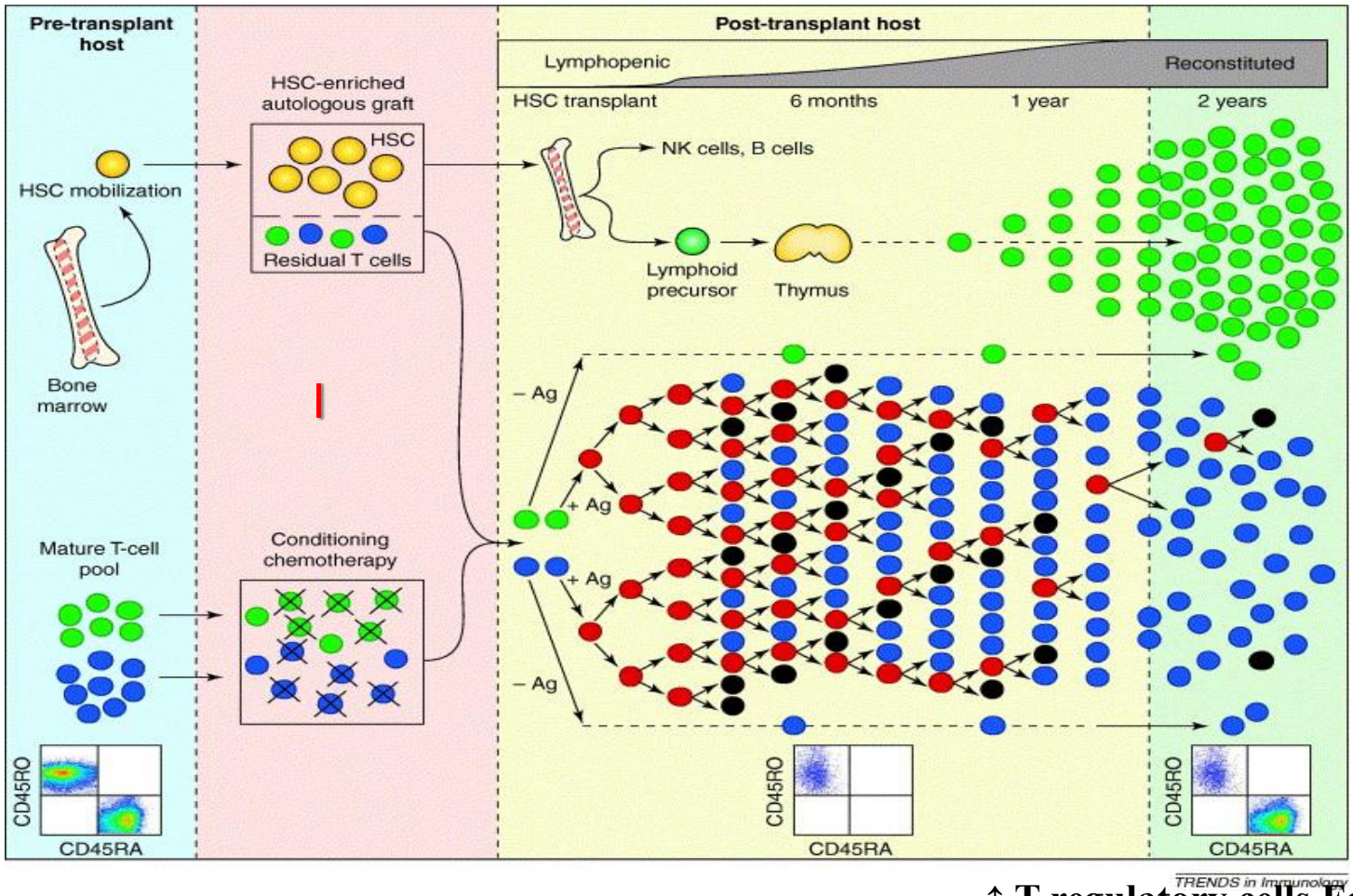
6. RESPECT DES BONNES PRATIQUES: ACCREDITATION JACIE/ SFGM-TC + PNMR 1, 2, 3

Immune reconstitution after AHSCT: renewal of the immune repertoire

Type I : replacement of mature T/B memory repertoire with **naïve, non-pathogenic cells**

Type II : reinstatement of Immune Regulation ↑ **nb and/or function of regulatory cells**

immunophenotyping, TREC (Thymic output), **CDR3 spectratyping / nucleotide sequencing**



Naïve

Memory

Senescent

Farge Arthritis Rhum 2008 (n = 7), Barault BMT2013 (n = 7), Michel BMT 2016 (n=7), Farge Hemato Oncol 2017 (n=12), Coelho Blood Advances 2018

↑ **T regulatory cells Foxp3**

↑ **naive B cells after HSCT**

↑ **$CD4^+CD25^{high}FoxP3$** ↑**regulatory T cells**

↑ **$CD8^+FoxP3$** ↑ ↑ **suppressive function**

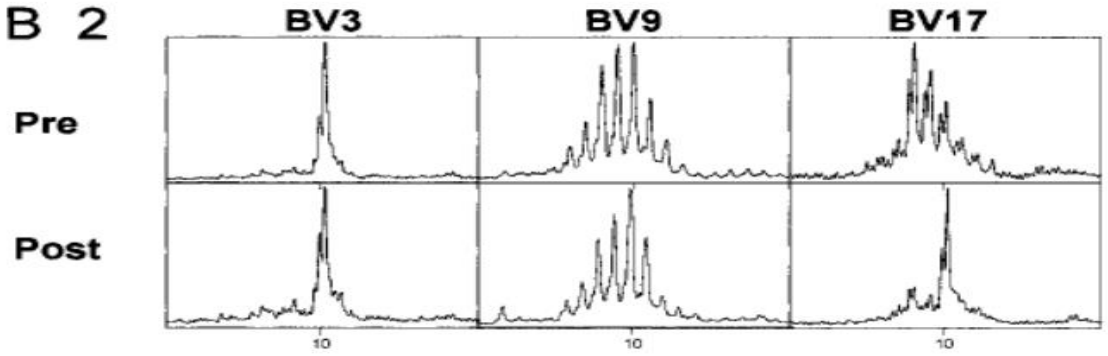
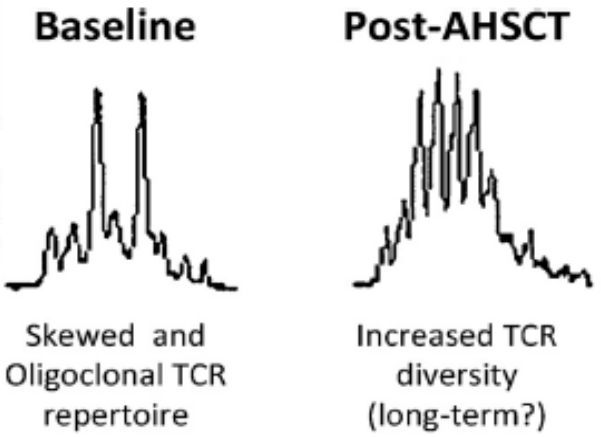


Figure 2. T cell receptor (TCR) β-chain spectratyping. Shown is the third complementarity-determining region size distribution of selected BV families before (Pre) and 12 months after (Post) hematopoietic



Sustained altered T cell homeostasis and abnormal Repertoire *Persistence of underlying disease mechanism after HSCT? Maintenance immunosuppression ?*

Farge Arthr Rheum 2005

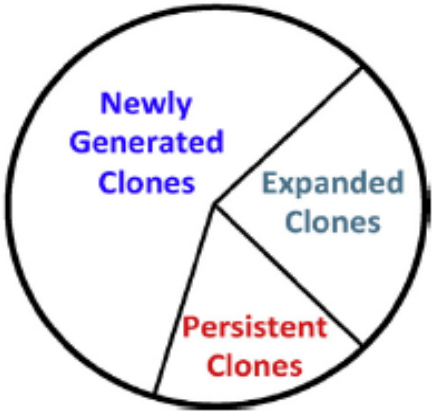


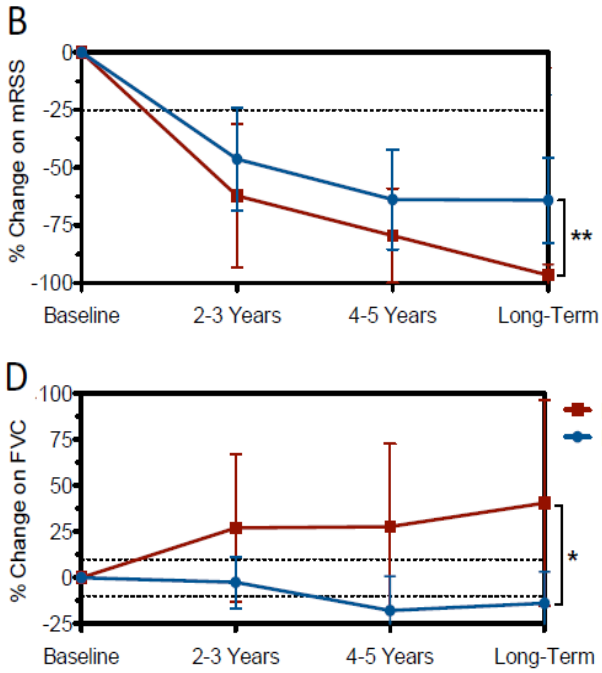
Fig. 3. AHSCT increases the TCR repertoire. The transplantation changes the skewed and oligoclonally expanded TCR repertoire observed in the patients with autoimmune disease to a higher diversified repertoire post-AHSCT (upper level). The renewal is due to the predominant presence of newly generated T-cell clones not present before treatment post-graft, but residual clones that increased during the immune reconstitution homeostatic proliferation as well persistent clones that did not change their levels are also present (lower level).

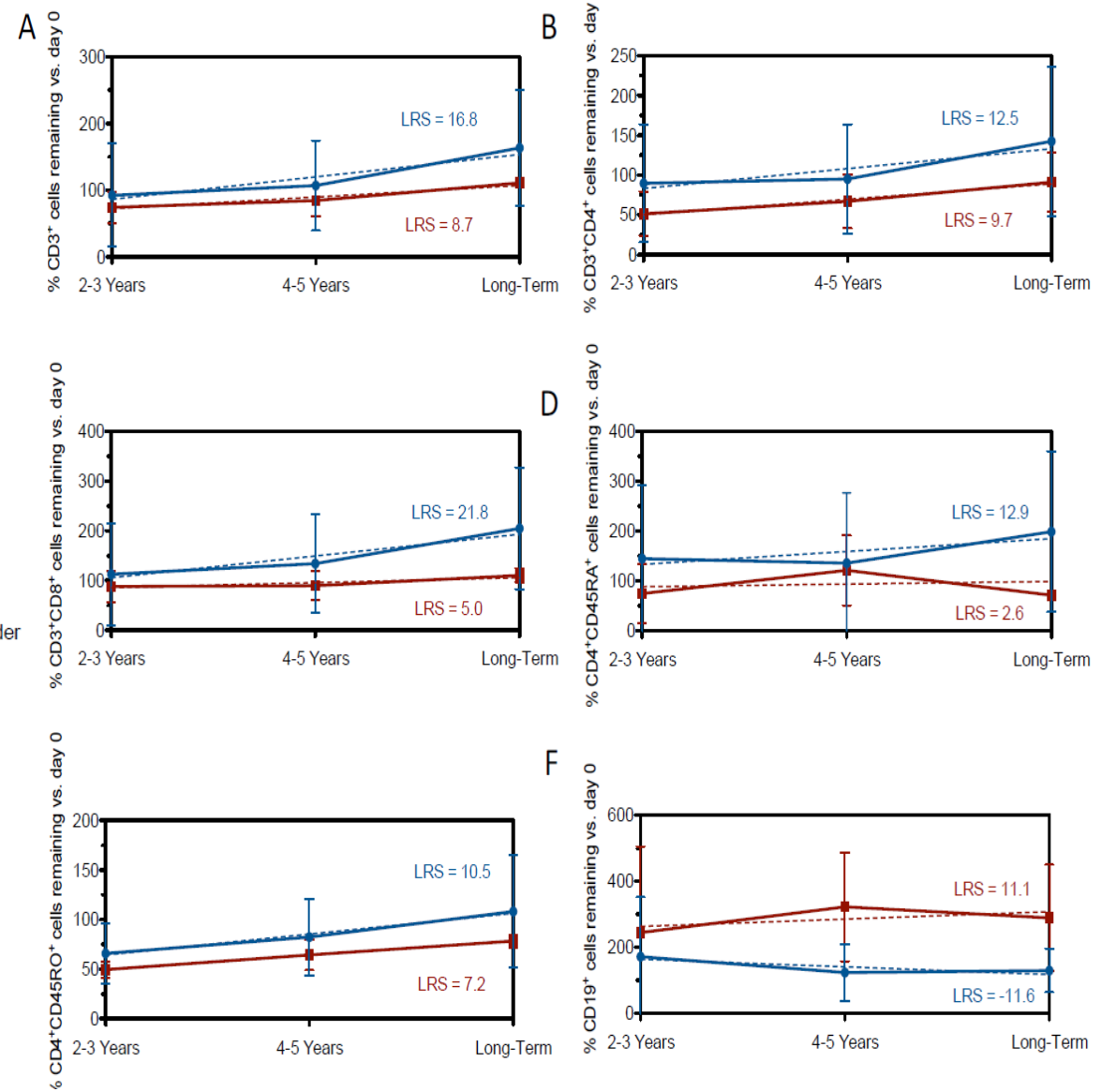
Arruda L et al
Current research in translational medicine 2016

Long-term immune reconstitution and T-cell repertoire analysis after autologous HSCT in systemic sclerosis patients

Farge et al. Journal of Hematology & Oncology (2017) 10:21

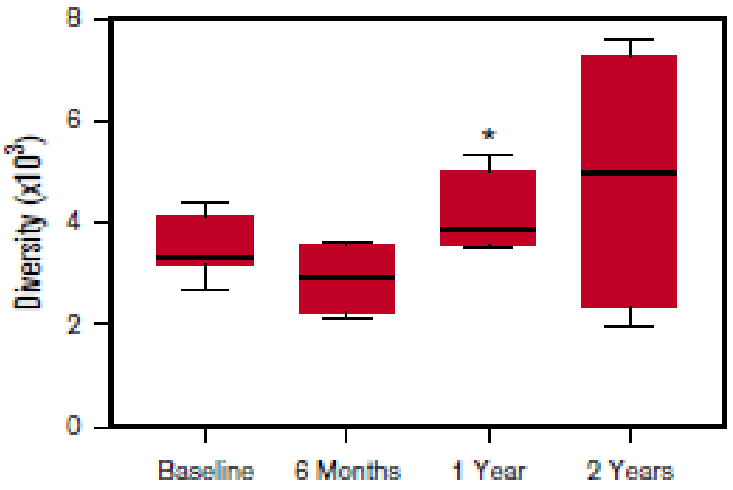
Long-term mRSS fall > 25% more pronounced in those improving FVC% > 10% (*P*=0.026
Pretransplant B cell clonal expansion + faster T-cells IR after aHSCT in non-responders /relapsing

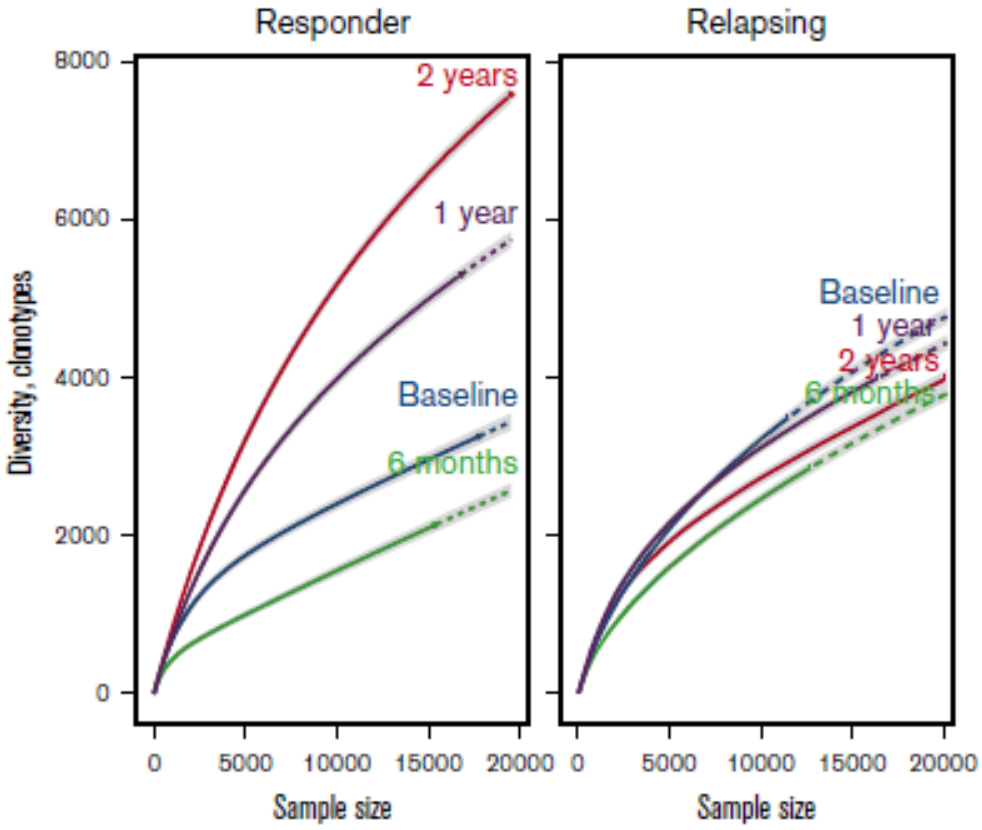




Analysis of T-cell clonotypes using TCR sequencing

Superiority of TCR diversity after AHSCT
and low clonotype overlap
in responder group

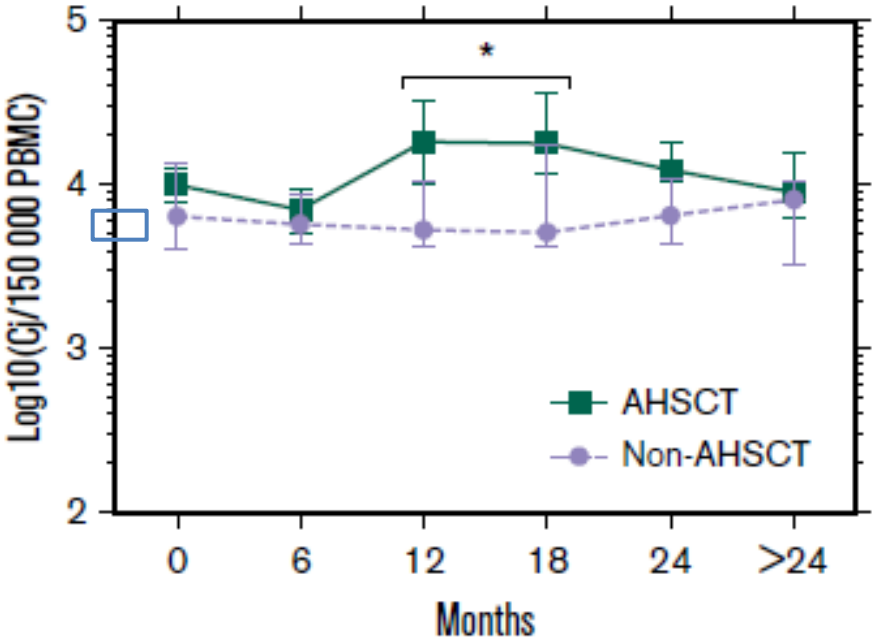


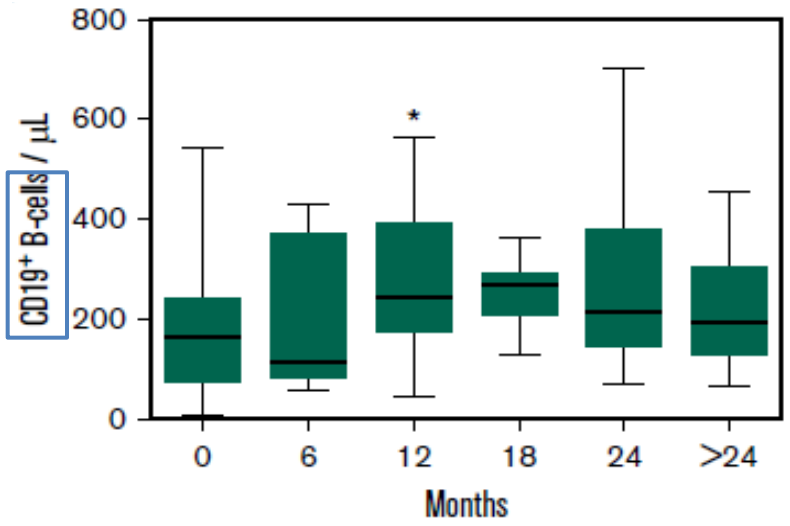


Arrruda Lc et al Blood Adv. 2018

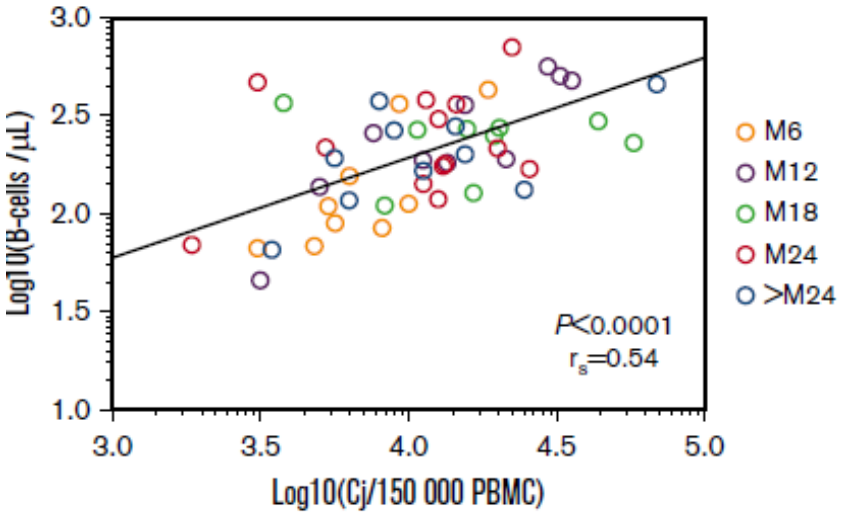
Analysis of newly-generated Naive B-cells

Increase of naive B-Cells and total B-Cells after AHSCT



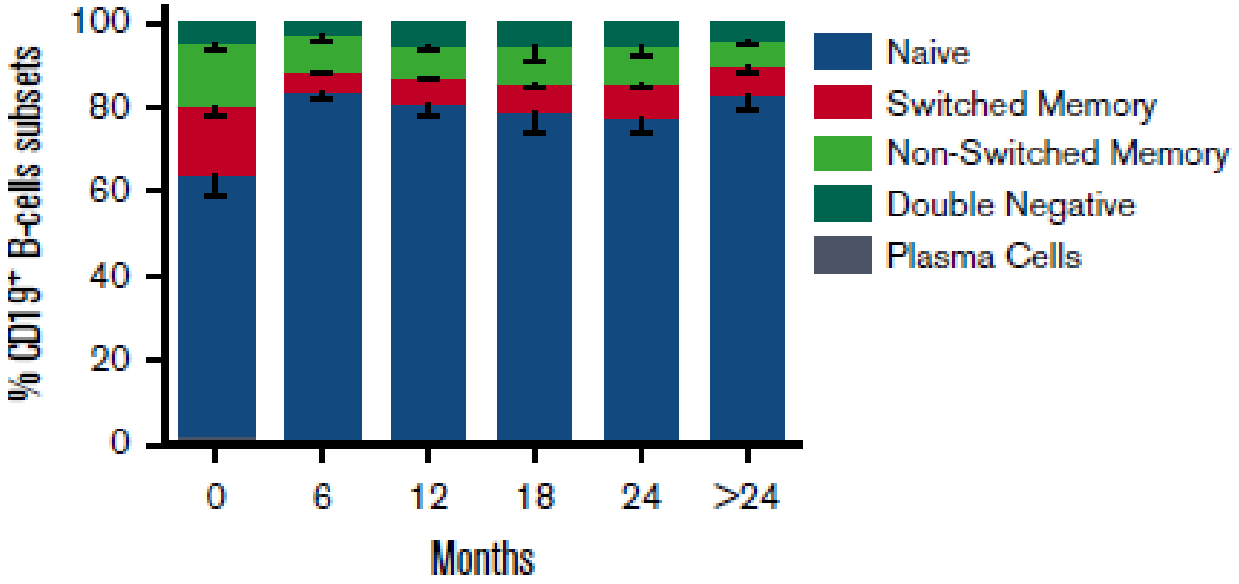


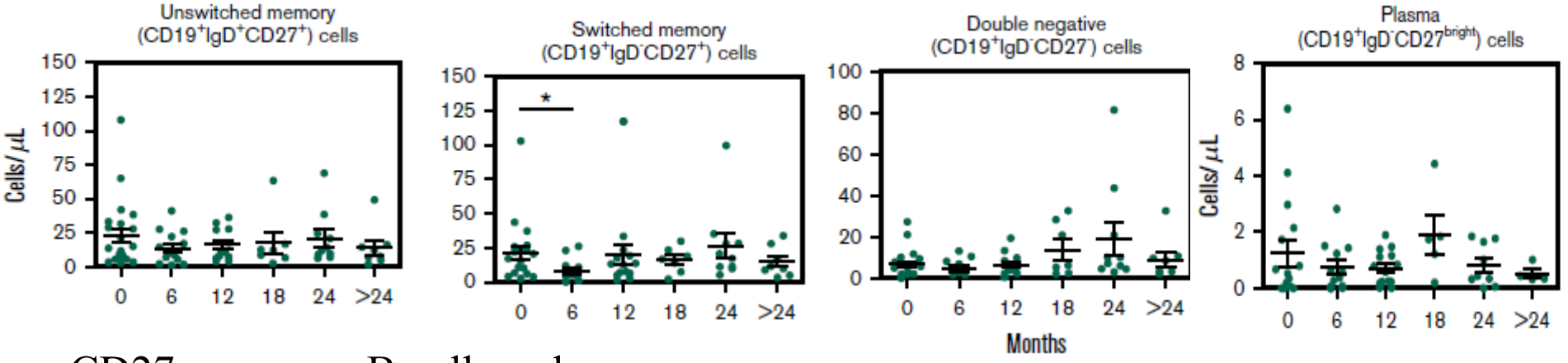
Increase of total B-cell (cjKREC)



Analysis of B-cells différenciation : from naive to memory B-cells

Number of memory B-cell (CD27+) and plasma cells are not modulated by AHSCT





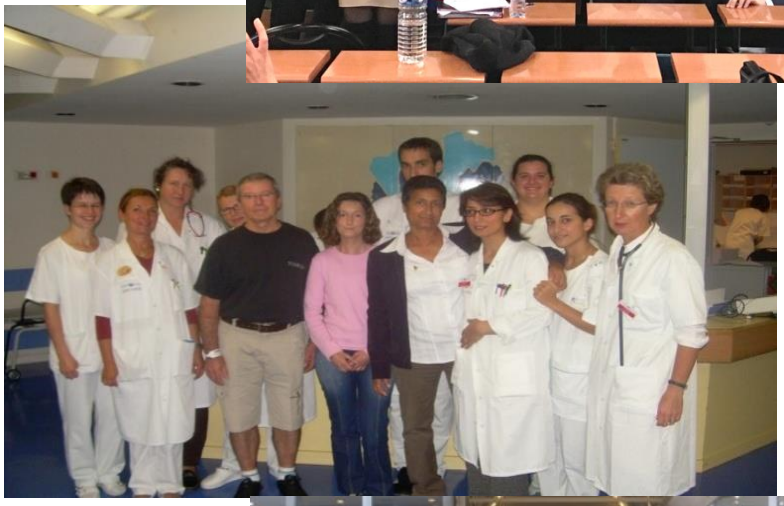
CD27 : memory B-cell marker

MATHEC
Maladies Auto Immunes & Thérapie Cellulaire

www.mathec.com

Allo MATHEC : 06 24 81 03 91

eurocord



PARIS DIDEROT
Saint Louis iuh

Groupe Hospitalier Universitaire
SAINT-LOUIS
LARIBOISIERE
FERNAND-WIDAL

SFGM TC
Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

centre de référence maladies rares

fai2r

EBMT
European Society for Blood and Marrow Transplantation

Pr E Gluckman
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M badoglio
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A Tobias
ADWP members