American College of Rheumatology 2016

Sclérodermie Systémique

Benjamin Chaigne

Sclérodermie systémique
American College of Rheumatology
2016

- 7 sessions
- 1 communication « late-breaking »
- > 200 abstracts

ACR/ARHP Annual Meeting
Washington, DC • 2016

Plan

- Physiopathologie: 2 abstracts
- Clinique : 2 abstracts
- Biomarqueurs: 2 abstracts
- Données épidémiologiques du registre PHAROS (HTAP-ScS
- Traitement
  - Essais cliniques
    - Analyses post-hoc SLS I et II: 2 abstracts
    - MMF + belimumab: 1 abstract
    - Etude SCOTT: late-breaking abstract
  - Perspectives thérapeutiques
- Conclusion

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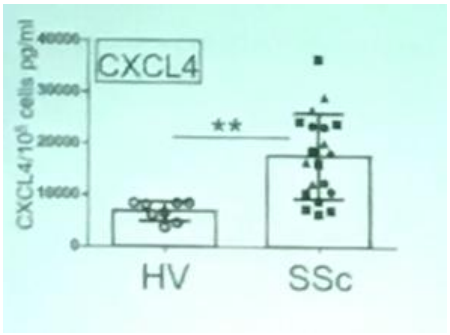
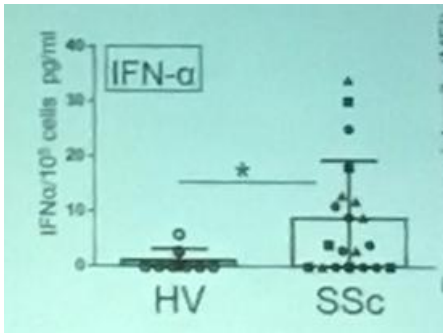
Physiopathologie

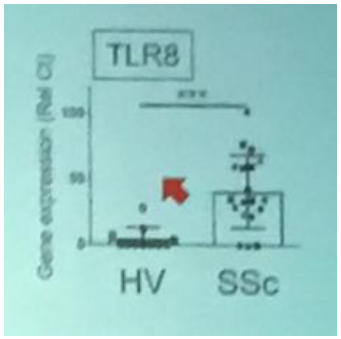
1009 - **Plasmacytoid dendritic cells are activated in systemic sclerosis (SSc) and contribute to the disease by inudcing IFNα and CXCL4**
Marie-Dominique Ah Kioon et al.

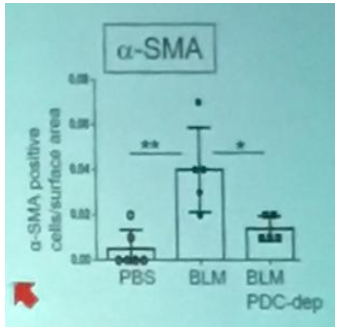
Messages clés

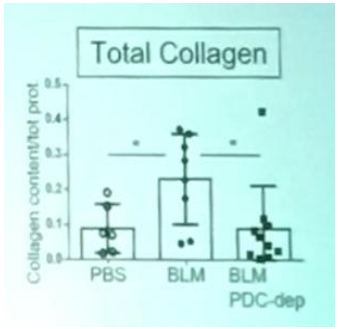
- pDC sont activées et leur suppression améliorent la fibrose
- Elles produisent CXCL4 et IFNα, régulés par PI3Kδ
- Sécrétion dépendante de TLR8
- CXCL4 potentialise la réponse IFNα par les pDC

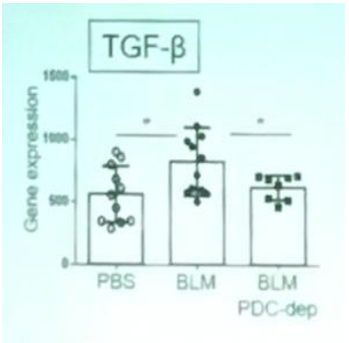








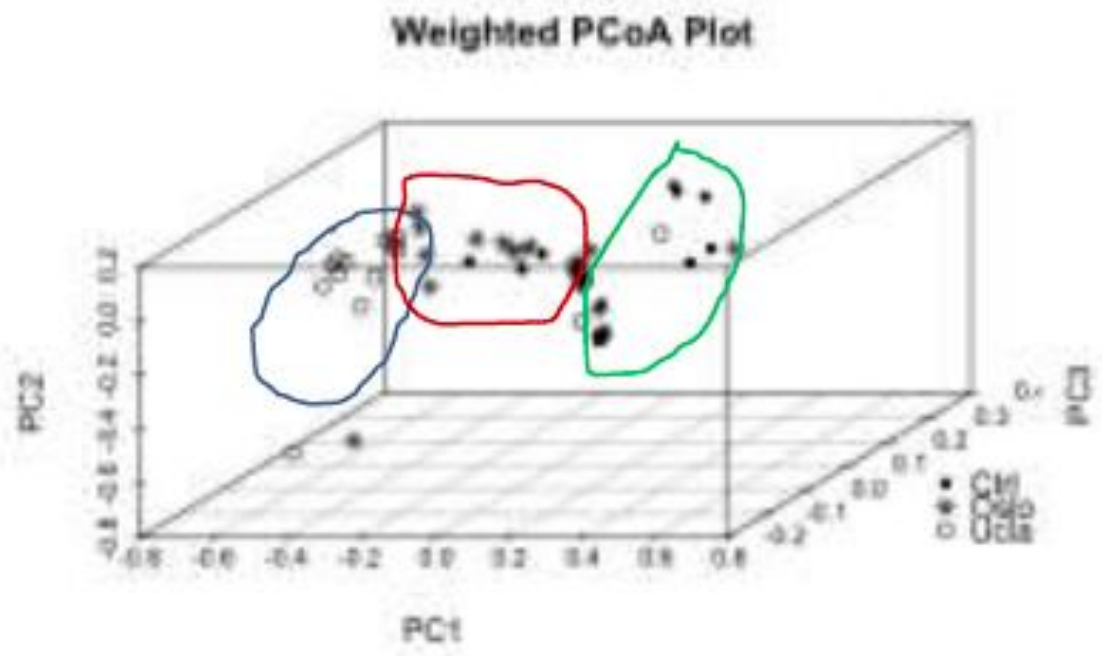




2015 – **Systemic sclerosis disease state is associated with specific alterations in gastrointestinal microbiotal in two independent cohorts**
Elizabeth Volkmann et al.

- 2 cohortes de 17 patients sclérodermiques (UCLA et Oslo) comparées à une cohorte de sujets sains (HC)

HC vs OSLO
R2= 0.126
P=0.002



HC vs UCLA
R2= 0.355
P=0.001

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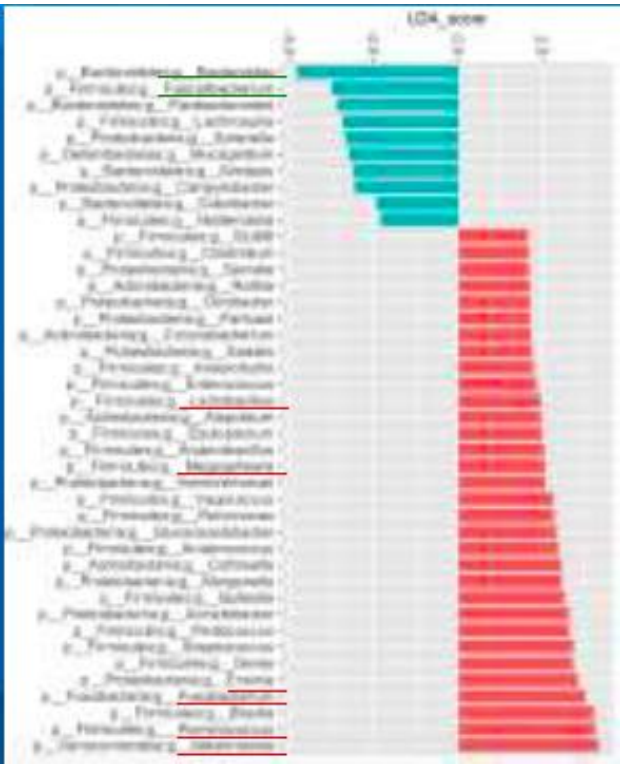
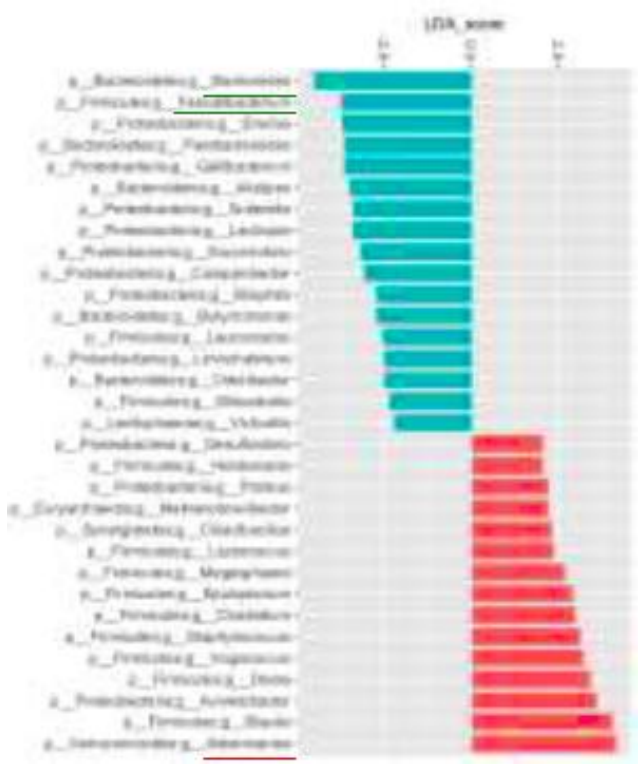
UCLA vs HC



OSLOvs HC

UCLA vs OLSO



2015 – **Systemic sclerosis disease state is associated with specific alterations in gastrointestinal microbiotal in two independent cohorts**
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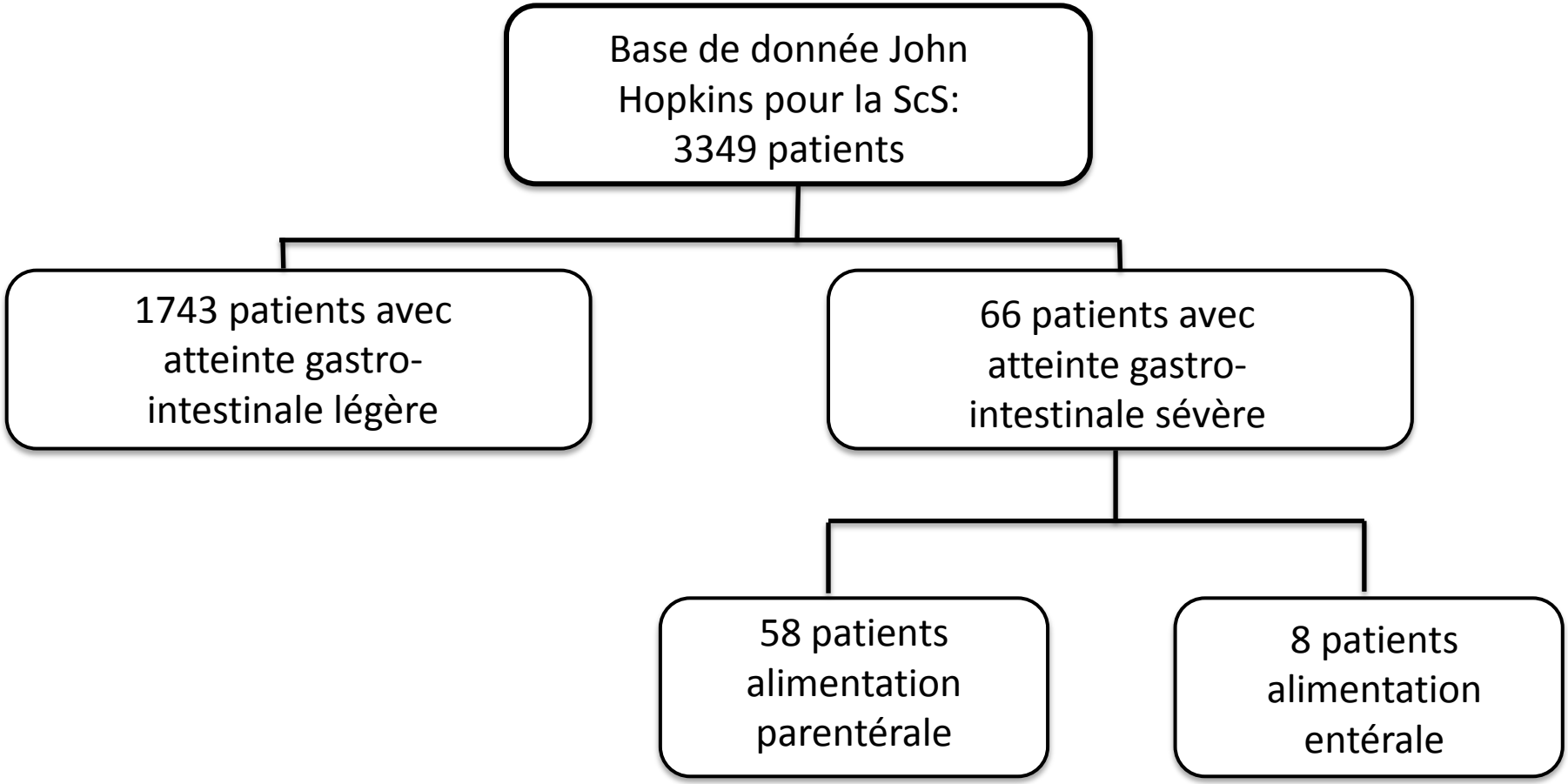
- **Eléments du microbiote associés à ScS:**
  - Augmentés
    - *Fusobacterium* (UCLA)
    - *Akkermansia* (UCLA)
    - *Ruminococcus* (UCLA)
    - *Lactobacillus* (UCLA Oslo)
  - Diminués
    - *Bacteroides* (UCLA Oslo)
    - *Faecalibacterium* (UCLA)

Clinique

3249– **Improvement in cough and cough-related quality of life in participants undergoing treatment for SSc-related Interstitial lung disease**
Elizabeth Volkmann et al.

- Patients de l'étude SLS-II:
  - 61% ont toux dite « fréquente »
    - Toux fréquente = « la plupart et plusieurs jours par semaine »
  - Groupe de patients avec toux fréquente:
    - DLCO plus basse
    - Plus de fibrose et d'ILD
    - 77% RGO (vs 59% dans le groupe sans toux fréquente)
    - Pas de différence de qualité de vie
    - 42% disparition de toux à 2 ans
    - Pas de facteur retrouvé en multivarié sur résolution de la toux

974 – **Diffuse scleroderma, male sex, and myopathy are associated with severe gastrointestinal dysmotility in scleroderma**
Zsuzsanna McMahan et al.



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Zsuzsanna McMahan et al.

Analyse multivariée entre atteinte gastro-intestinale sévère et caractéristiques basales

Variable	OR	95% CI	p-value
Age	0.99	0.96 - 1.01	0.351
Disease duration	1.00	1.00 - 1.00	0.549
Male	2.72	1.35 - 5.50	0.005
Diffuse	2.84	1.31 - 6.18	0.008
White	0.72	0.34 - 1.52	0.393
Myopathy	3.24	1.47 - 7.15	0.004

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Tableau. Analyse multivariée entre atteinte sévère et caractéristiques basales

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Biomarqueurs

3250 – **Serum MCP-1 levels predict long-term progression of ILD in SSc**
Minghua Wu et al.

- **Objectif:**

Evaluer la valeur prédictive des taux sériques CCL-2 IL-10 et IL-6 dans la progression et la survie liée à PID (CVF)

- **Canadian SSc Research Group:** n=171 patients

Characteristics		Canadian Cohort SSC (n=171)
Female gender		142 (83%)
Age at first study visit, mean ±SD years		53.1 ±11.9
Diffuse cutaneous involvement		66 (39%)
Disease duration, mean ±SD years		2.2 ±1.2
Ethnicity	White	159 (93%)
	Black	3 (2%)
	Latino	2 (1%)
Antibodies	Anti-centromere antibody	46 (27%)
	Anti-topo I antibody	32 (19%)
	Anti-RNA polymerase III antibody	19 (11%)
	Anti-U1 RNP antibody	8 (5%)
Immunosuppression		49 (29%)

3250 – **Serum MCP-1 levels predict long-term progression of ILD in SSc**
Minghua Wu et al.

Longitudinal analysis: Predictive significance of baseline cytokine levels for progression of FVC%*

Cytokines/ Chemokines	Interaction term between baseline FVC and follow up *b*	95% CI	*P* -value
CCL-2	**-0.58**	**(-1.14; 0.03)**	**0.038**
IL-10	-0.06	(-0.75; 0.63)	0.859
IL-6	-0.58	(-1.21; 0.04)	0.068

* Adjusted for age at enrollment, gender

3250 – **Serum MCP-1 levels predict long-term progression of ILD in SSc**
Minghua Wu et al.

Multivariable longitudinal analysis of predictive significance of CCL-2 for the decline in FVC%*

Cytokine	*b*	95% CI	*P*-value
Time: CCL2	-0.55	(-1.08; -0.01)	0.046
Time	1.96	(-1.21; 5.13)	0.225
CCL-2	-3.42	(-7.21; 0.37)	0.077
Diffuse	-1.76	(-8.03; 4.52)	0.583
Immunosuppression	-7.09	(-13.56; -0.62)	0.032
Topo I	-10.42	(-17.24; -3.59)	0.003
CRP	-0.18	(-0.36; 0.01)	0.064

* Adjusted for age at enrollment, gender.

3250 – **Serum MCP-1 levels predict long-term progression of ILD in SSc**
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- Higher serum CCL-2 levels was associated with poorer survival:

  ---HR: 3.89, 95% CI(0.23; 7.55), p=0.037

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SUMMARY

- CCL-2 have predictive significance for rate of change in FVC% over time.
- Serum CCL-2 levels were predictive of faster decline in FVC%; while IL10, IL-6 levels were not predictive decline in FVC% over time by multivariable analysis.
- Higher CCL-2 level was associated with poorer survival.

3245 – **Surfactant protein D and Krebs von Den Lungen-6 predict severity of SSc related ILD in two independent cohorts**
Volkmann Elizabeth and al.

- Objectif: déterminer si les dosages de KL-6 et SPD circulant peuvent prédire l'évolution de la PID dans les cohortes SLS I et SLS II

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MAIN FINDINGS

- KL-6 and SP-D both associated with extent of ILD at baseline in SLS II cohort
- KL-6 also associated with extent of ILD at baseline in SLS I cohort
- Low KL6 at baseline associated with improvements in DLCO and radiographic extent of ILD in SLS II cohort

Données épidémiologiques

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3246 – **Predictors of long-term outcomes in SSc-associated pulmonary hypertension from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry**
Kathleen Kolstad and al.

- Registre multicentrique 2006
- Suivi prospectif de patients SSc
- Incidence des PAH
  - Group 1 PAH Patients
    - KT (mPAP > ou = 25; PCWP < ou = 15)
    - FVS > 65%
    - Pas d'ILD radiographique
- 165 patients inclus (90% femme, 60 ans âge moyen)

3246 – **Predictors of long-term outcomes in SSc-associated pulmonary hypertension from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry**

Kathleen Kolstad and al.

Baseline Clinical Characteristics	
Limited Cutaneous Disease	71%
Anti-Centromere Positive	70%
Time from first Raynaud's symptom	Median 11.5 years (0.3-54.4)
Time from first non Raynaud's symptom	Median 8.5 (0-43.2)
Creatinine	Median 0.9 (0.4-3.1)
NYHA Functional Class	1 (16%) 2 (44%) 3 (36%) 4 (4.43%)
6 Minute Walk Distance (6MWD)	Mean 348.1 meters (137.7)
Pulmonary Function Test Results	
FVC/DLCO	Median 2.1 (1.0 to 6.1)
Forced Vital Capacity % Predicted	Median 82.3 (65-142)
DLCO % Predicted	Median 40.1 (13-97.1)
Echocardiogram Results	
Right Ventricular Systolic Pressure	Median 55.5 mmHg (15-123)
Pericardial effusion	49%
Right Heart Catheterization Results	
Mean Pulmonary Artery Pressure	Median 35 mmHg (25-70)
Pulmonary Capillary Wedge Pressure	Median 10 mmHg (1-15)
Pulmonary Vascular Resistance	Median 4.8 WU (1.7-26.96)
Cardiac Output	Median 5.1 (1.5-83)

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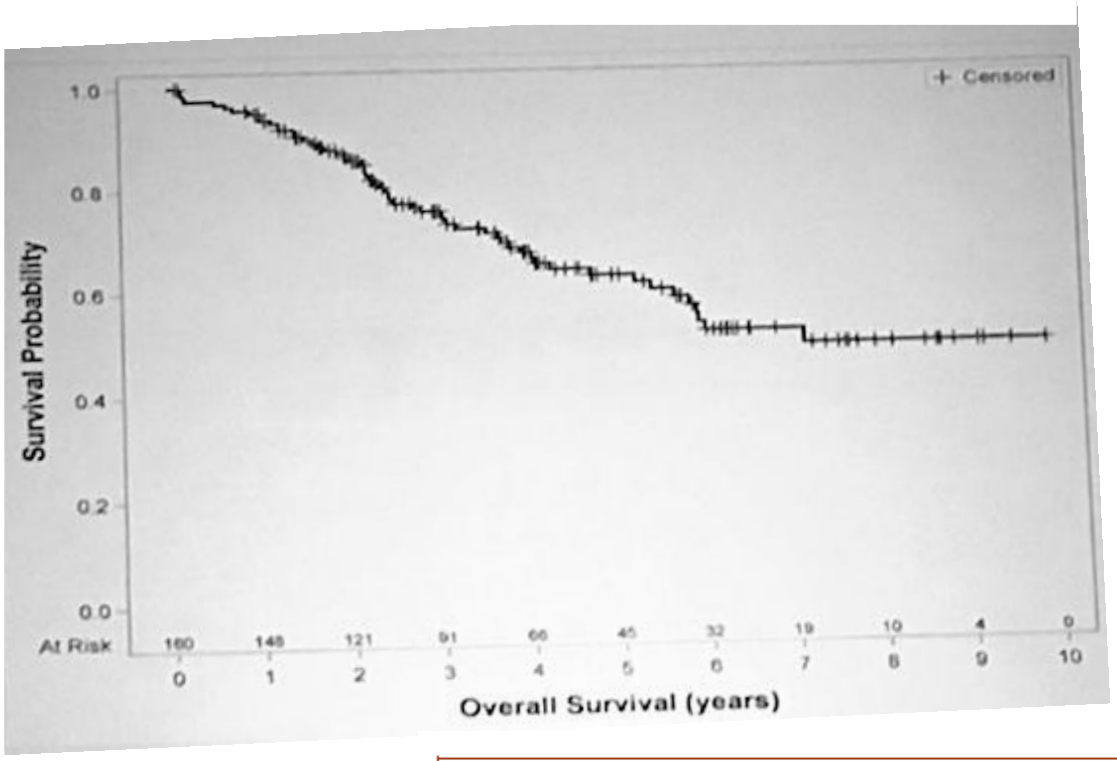

Cumulative survival Rates
1 year 95%
3 years 75%
5 years 63%
8 years 49%

Predictors of Overall Survival			
	Hazard Ratio	95% CI	P-Value
Baseline 6MWD (10 meter increase)	0.97	0.94-0.99)	0.01
% Predicted DLCO (10% increase)	0.75	0.60-0.94	0.01

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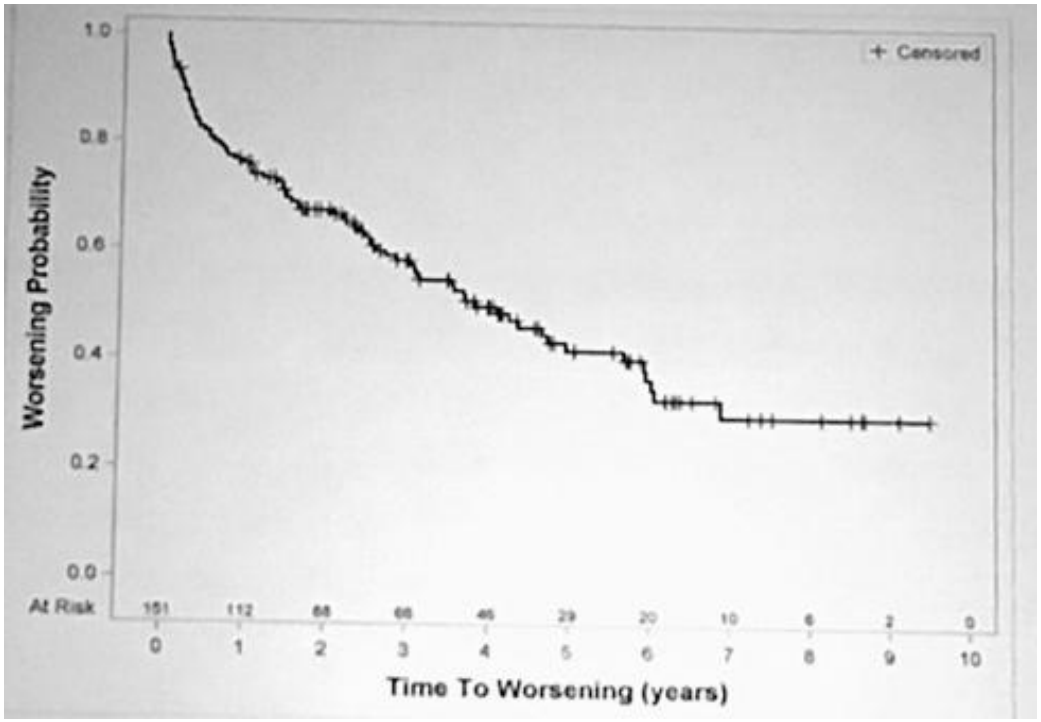

Percent free from clinical worsening

1 year 76%

3 years 58%

5 years 42%

8 years 30%

Predictors of Clinical Worsening			
	Hazard Ratio	95% CI	P-Value
Pulmonary Vascular Resistance (PVR) >4.76 WU	3.25	1.97-5.36	<0.0001
6MWD (10 meter increase)	0.98	0.96-0.99	0.009

Traitement

824 – **Mycophenolate vs placebo for the treatment of SSc- related ILD**
Elizabeth Volkmann and al.

3248 – **Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post-hoc analyses from the SLS I and II**
Rajaie Namas and al.

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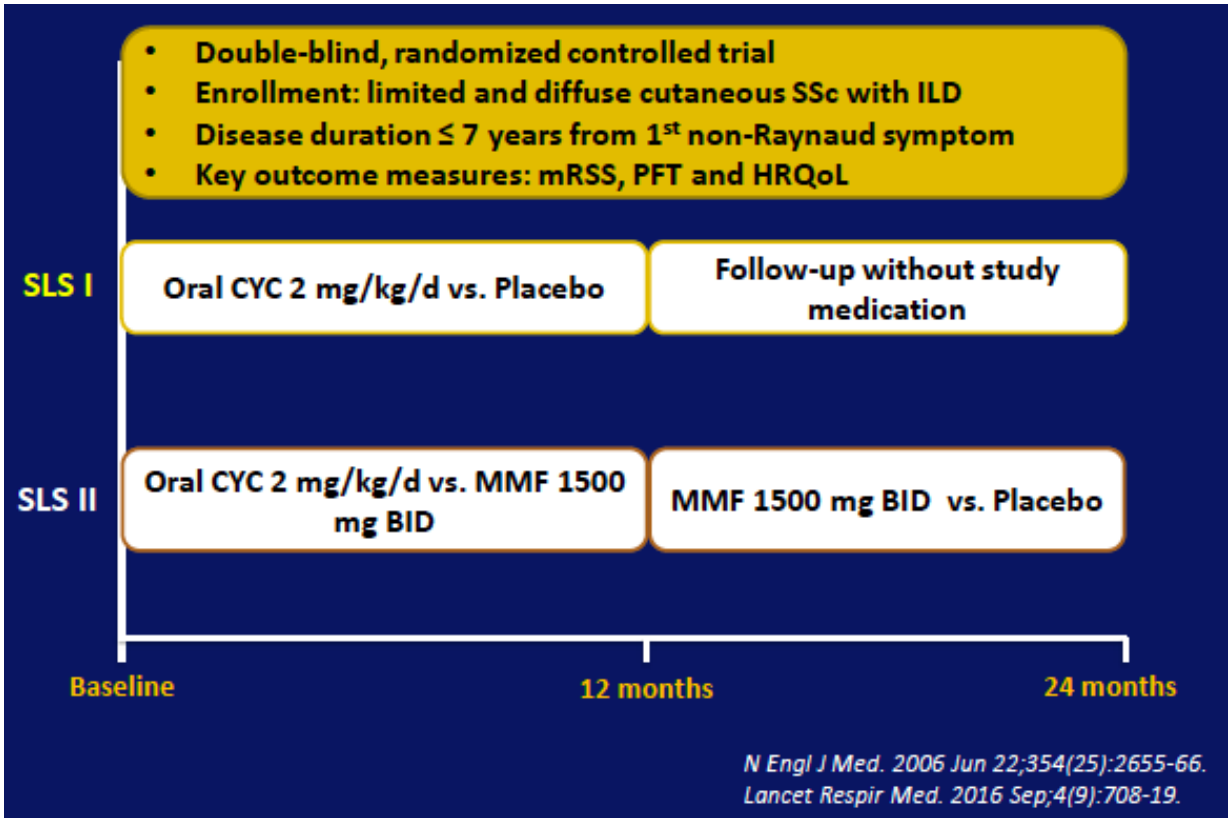

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Table 1. Baseline characteristics of SLS I placebo and SLS II MMF participants

	Placebo (n= 79)	MMF (n= 69)
	Mean(SD)/(%)	Mean(SD)/(%)
Age	48.1 (12.4)	52.6 (9.7)
Female	65%	70%
SSc Duration (years)	3.1 (1.8)	2.6 (1.7)
Diffuse SSc	57%	62%
FVC % Predicted	68.6 (13.0)	66.5 (8.3)
DLCO % Predicted	46.2 (13.3)	54.0 (11.1)
MRSS	14.0 (10.5)	15.3 (10.4)

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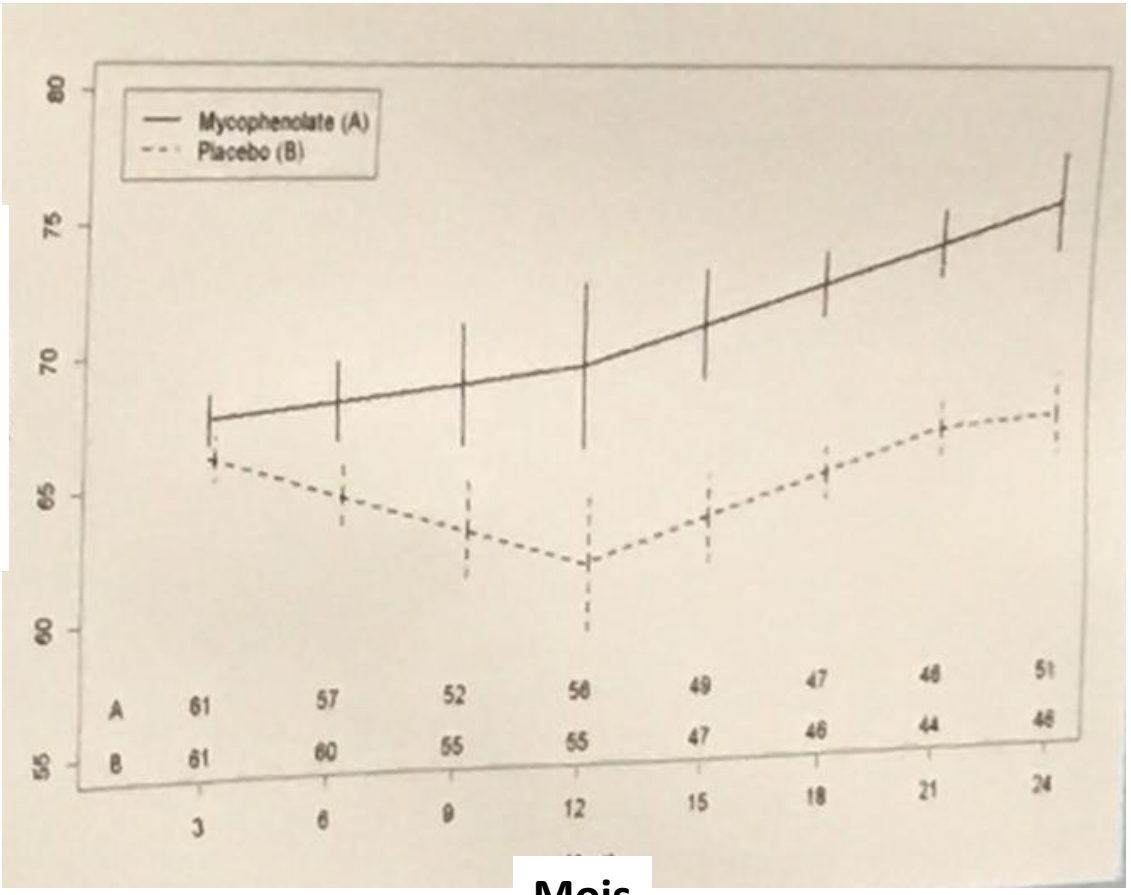

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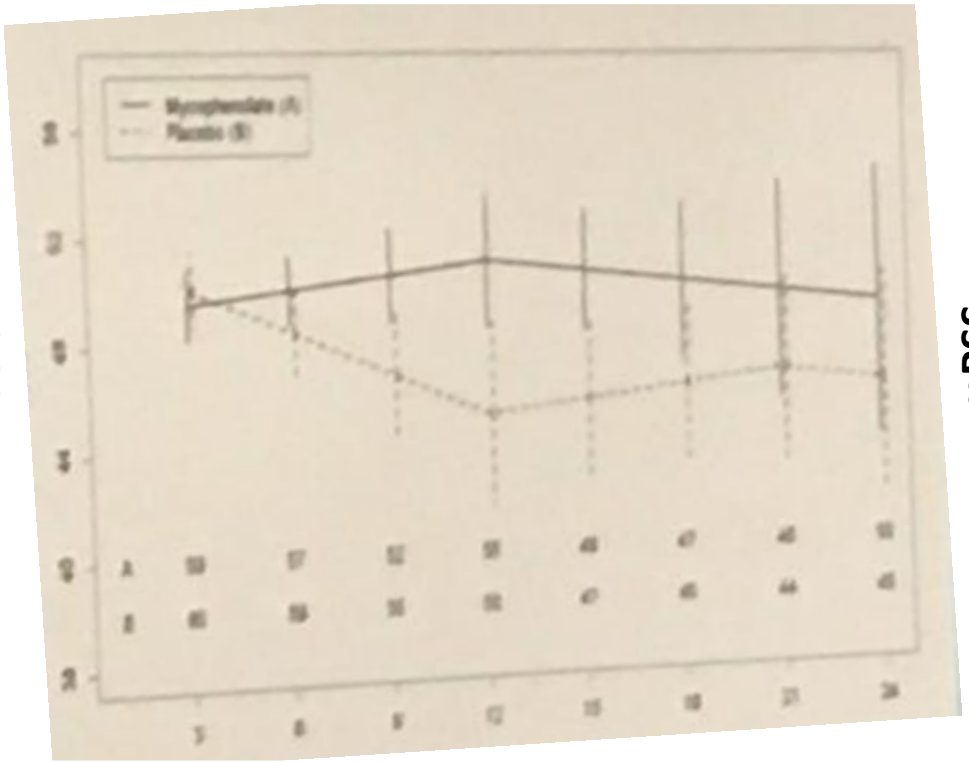
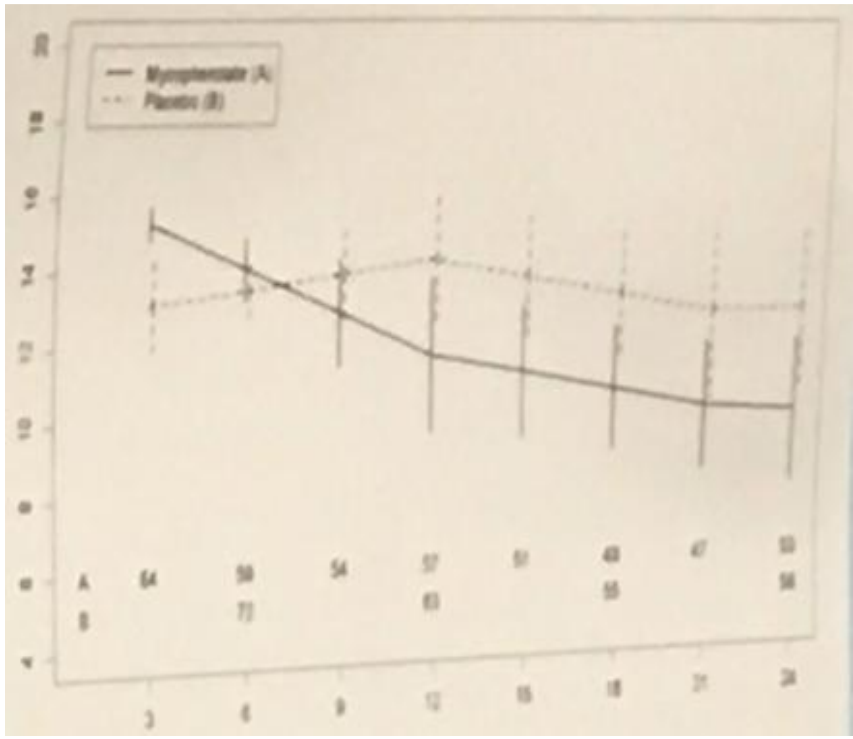
DLCO %



Mois

mRSS



Mois

3248 – **Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post-hoc analyses from the SLS I and II**

Rajaie Namas and al.

	SLS-I and SLS-II (N= 300)	SLS-I (N= 158)	SLS-II (N= 142)	p value SLS-I vs. II
Age, year, Mean±SD	50.3 ±11.3	48.5 ±12.3	52.3 ±9.7	**0.004**
Gender (Female/Male),%	72%/28%	70%/30%	74%/26%	0.48
Diffuse /limited, %	59%/41%	59%/41%	59%/41%	0.85
Disease duration, year, Mean±SD	2.9 ±2.0	3.2 ±2.1	2.6 ±1.8	**0.01**
Disease duration ≤24 months,n (%)	123, 41%	53, 33%	70, 50%	**0.003**
mRSS, Mean±SD	14.7 ±10.7	14.8 ±10.9	14.7 ±10.5	0.89
mRSS in dcSSc, Mean±SD	20.9 ±9.6	21.1 ±9.9	20.8 ±9.4	0.85
FVC % predicted, Mean±SD	67.4 ±10.8	68.1 ±12.1	66.5 ±9.1	0.21
DLCO% predicted, Mean±SD	50.1 ±13.4	46.6 ±12.9	54.0 ±12.7	**<0.001**

3248 – **Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post-hoc analyses from the SLS I and II**

Rajaie Namas and al.

	SLS-I Placebo group		SLS-I CYC group		SLS-I and SLS-II CYC		SLS-II Pooled data (CYC+ MMF)	
	N	(Mean±SD)	N	(Mean±SD)	N	(Mean±SD)	N	(Mean±SD)
Baseline	46	20.4 (9.4)	49	21.6 (10.3)	132	21.1 (9.7)	83	20.8 (9.4)
6 month	43	-2.6 (5.7) †	45	-2.7 (6.4)†	114	-2.6 (6.4)†	69	-2.4 (6.4)†
12 month	37	-1.7 (6.9) †	43	-5.3 (7.4) *†	109	-5.4 (6.5)*†	66	-5.5 (5.9) *†
18 month	33	-3.4 (6.2)†	36	-6.9 (7.4) *†	94	-6.6 (7.3)*†	58	-6.4 (7.3) *†
24 month	34	-3.9 (5.9)†	32	-7.2 (7.3) *†	94	-7.1 (8.1)*†	62	-7.0 (8.6) *†

Negative score denotes improvement

†p< 0.05 for for mRSS at follow up vs. baseline within each group

*p< 0.05 for SLS-II pooled and SLS-I CYC groups compared to SLS-I Placebo group

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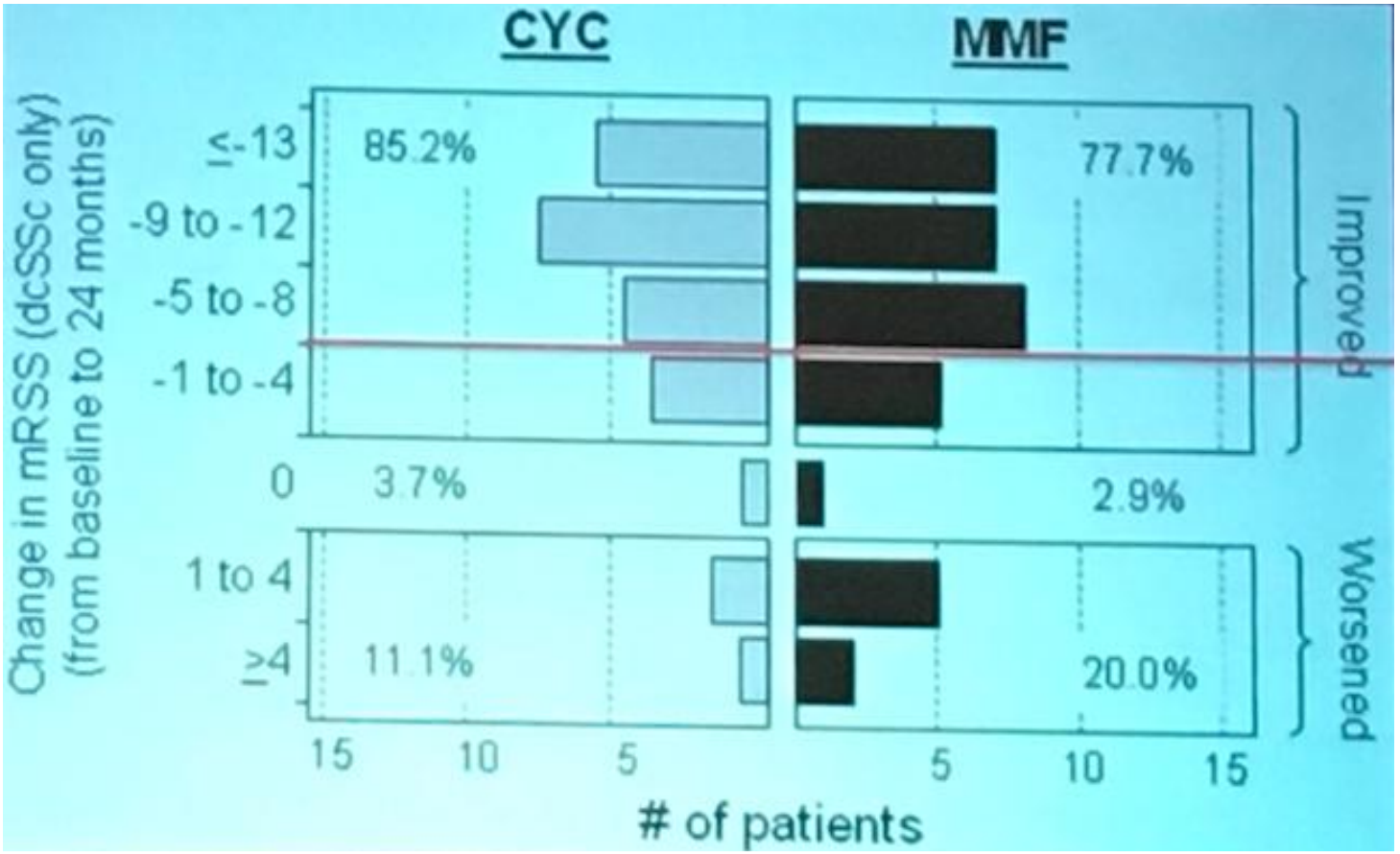
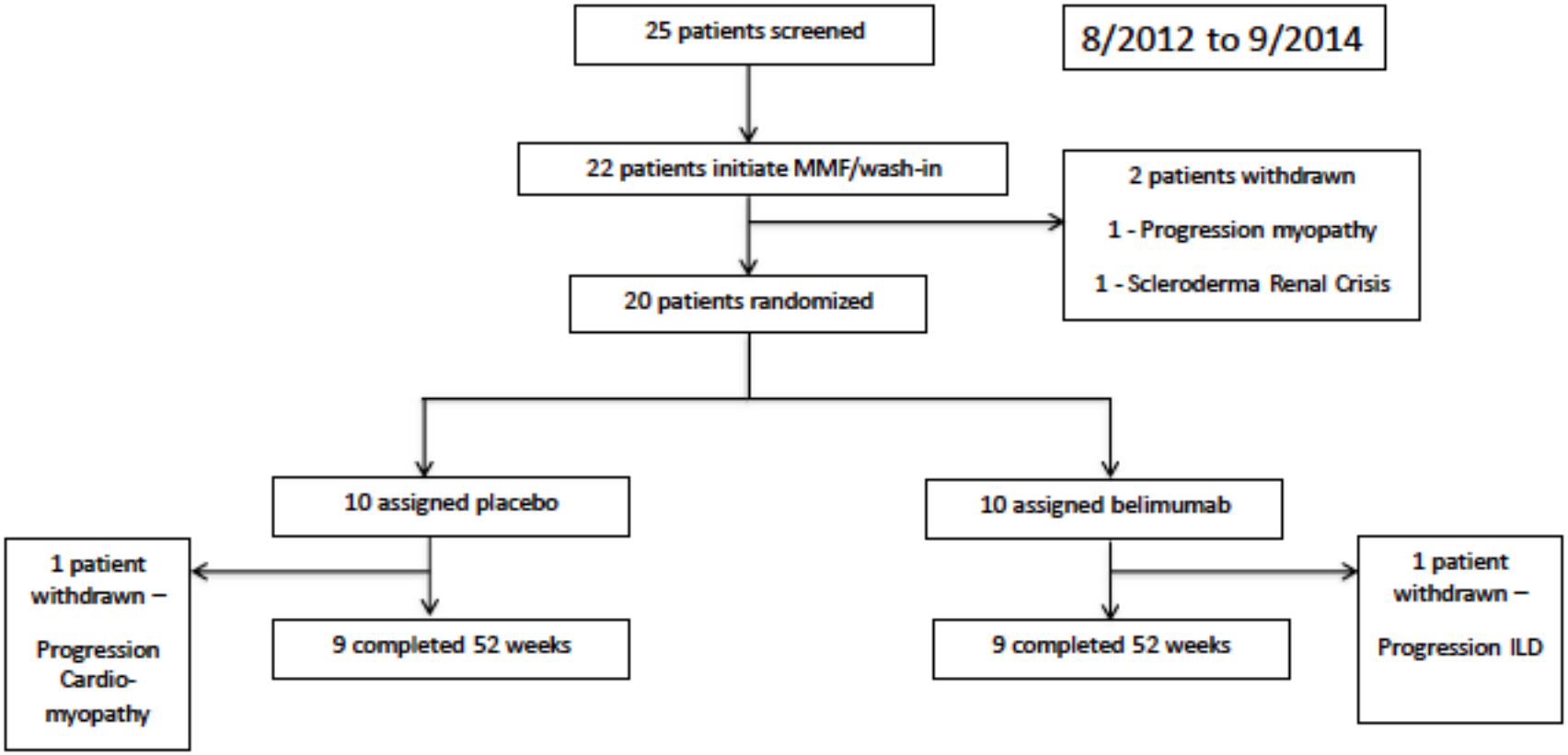


MCID

CYC n = 27

MMF n = 35

3247 – Safety and **efficacy of belimumab with background mycophenolate for early diffuse SSc: a randomized, placebo controlled, pilot trial**
Jessica Gordon et al.



Primary endpoint: difference in median change in mRSS from baseline to 52 semaines

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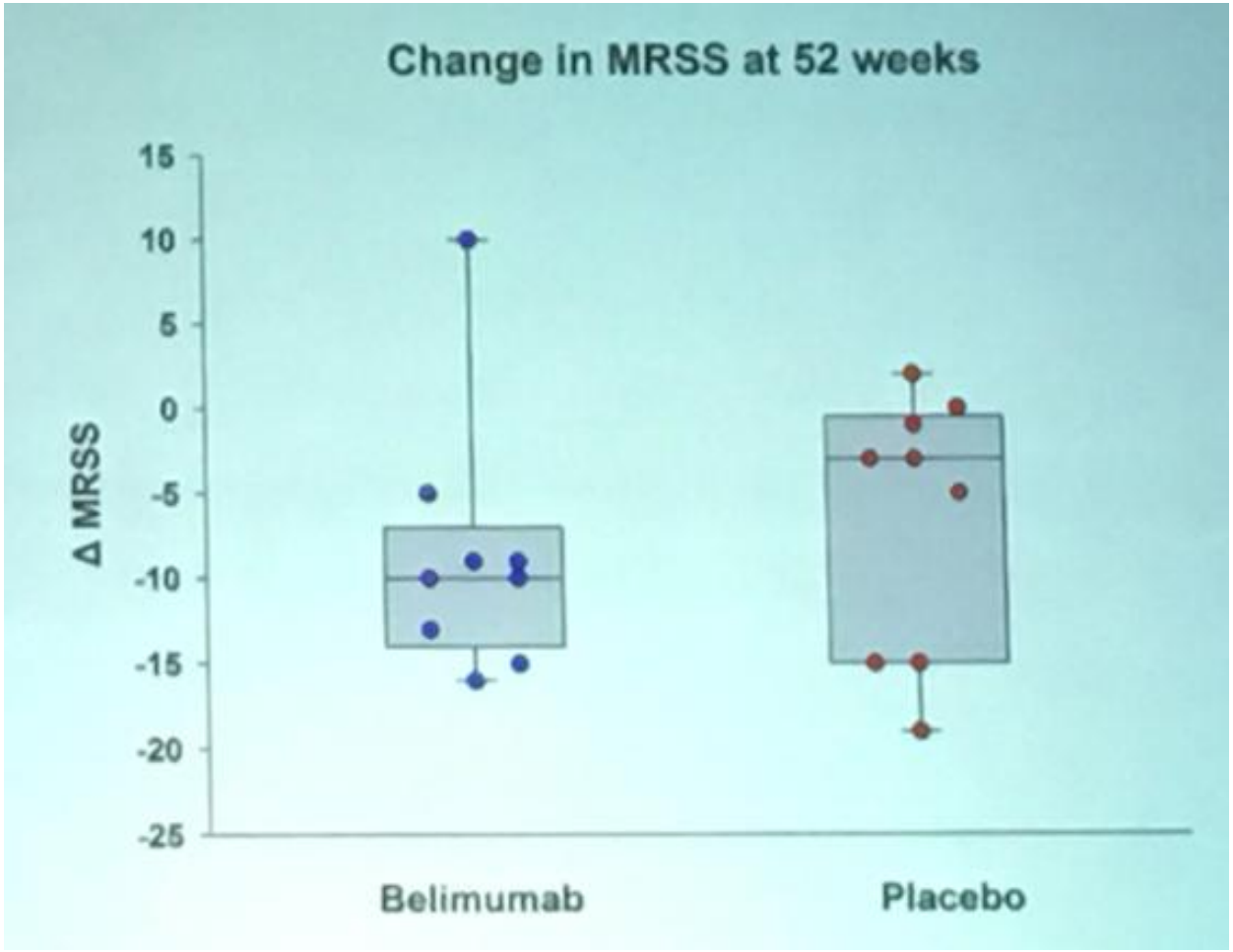

Median [IQR] change of MRSS:

- Placebo: -3.0 [-15,-1]
- Belimumab: -10 [-13, -9]
- P = 0.411

6L – **Myeloablative autologous transplantation of CD34^{+}-selected hematopoietic stem celles (HSCT) vs monthly intravenous cyclophosphamide (CYC) for severe SSc with internal organ involvement: outcomes of a randomized North American clinical trial**
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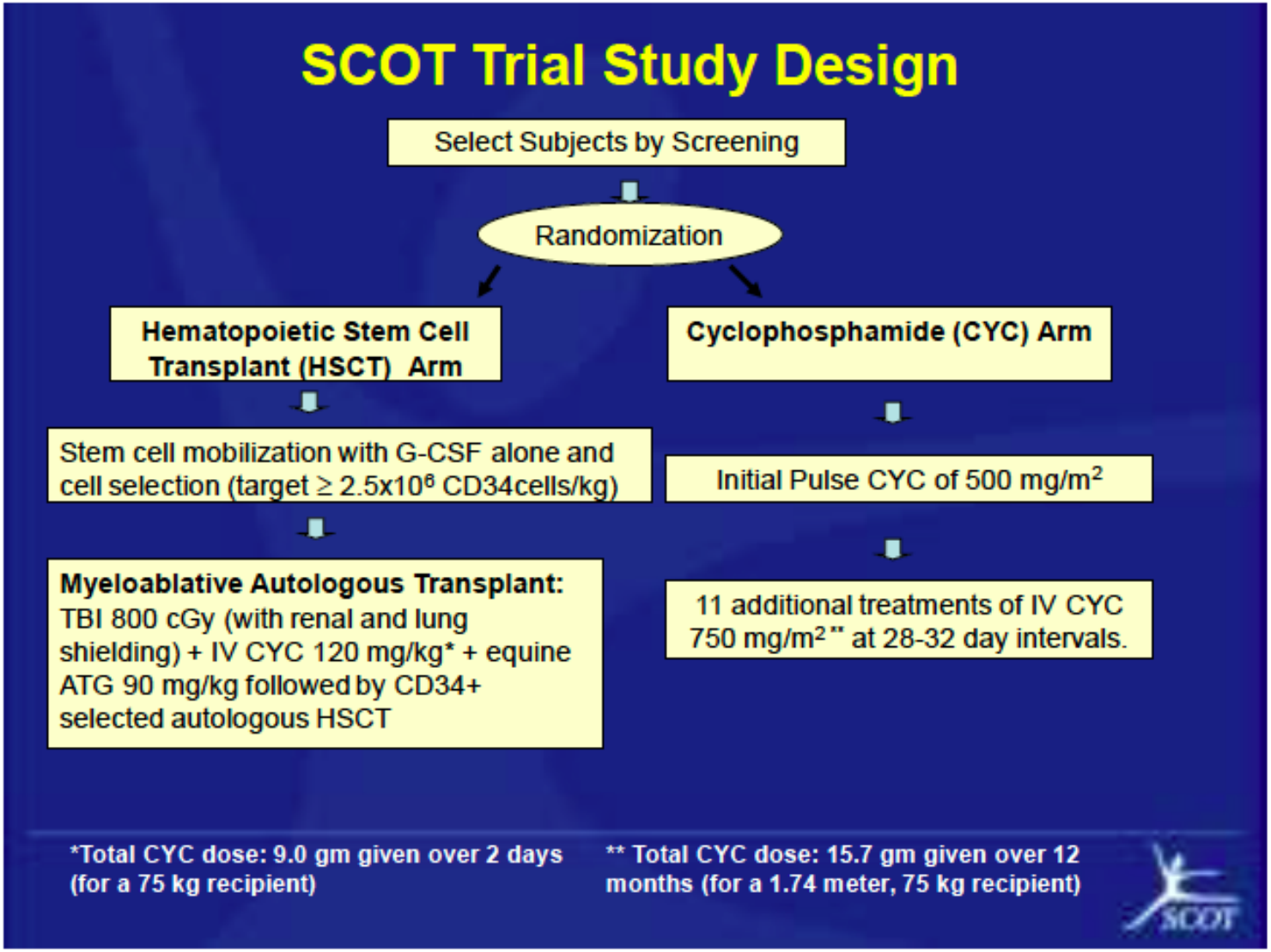

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Keith Sullivan et al.

	Transplant N=36	Cyclophosphamide N=39
Age, mean (SD) year	45 (11)	47 (10)
Female	19 **(53%)**	29 **(74%)**
Race n		
White	29 (81%)	31 (80%)
Black or African American	2 (6%)	4 (10%)
Asian	2 (6%)	1 (3%)
Other	3 (8%)	3 (8%)
Smoking Status n		
Ever	14 (39%)	10 (26)
Never	22 **(61%)**	29 **(74%)**
Duration Scleroderma, mean (SD) mo	25 (13)	29 (16)
Lung Involvement, n	36 (100%)	37 (95%)
Modified Rodnan Skin Score, mean (SD)	29 (9)	31 (11)
DLCO (% Predicted), mean (SD)	54 (8)	53 (8)

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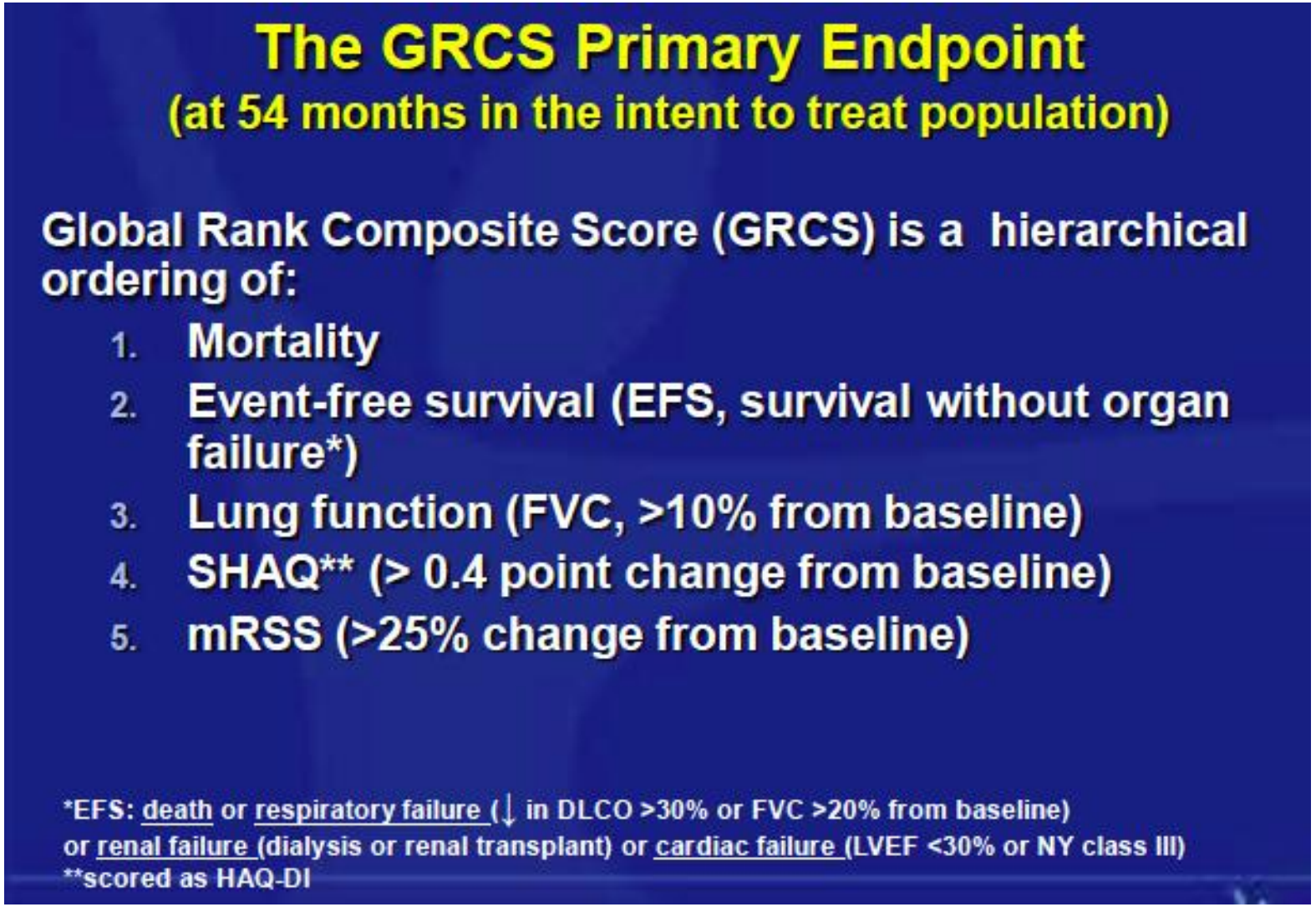

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		Transplant (N=36)	Cyclophosphamide (N=39)	p-value
Primary Endpoint:				
GRCS at Month 54	Median (min, max)	17 (-58, 52)	- 6 (-58, 52)	**0.013**
Secondary Endpoints:				
GRCS at Month 48	Median (min, max)	20 (-58, 55)	- 8 (-58, 55)	0.008
EFS at Months 48 & 54	n (%) failure	10 (28%)	20 (51%)	0.059
Mortality (all causes) at Months 48 & 54	n (%) deaths	6 (17%)	11 (28%)	0.28

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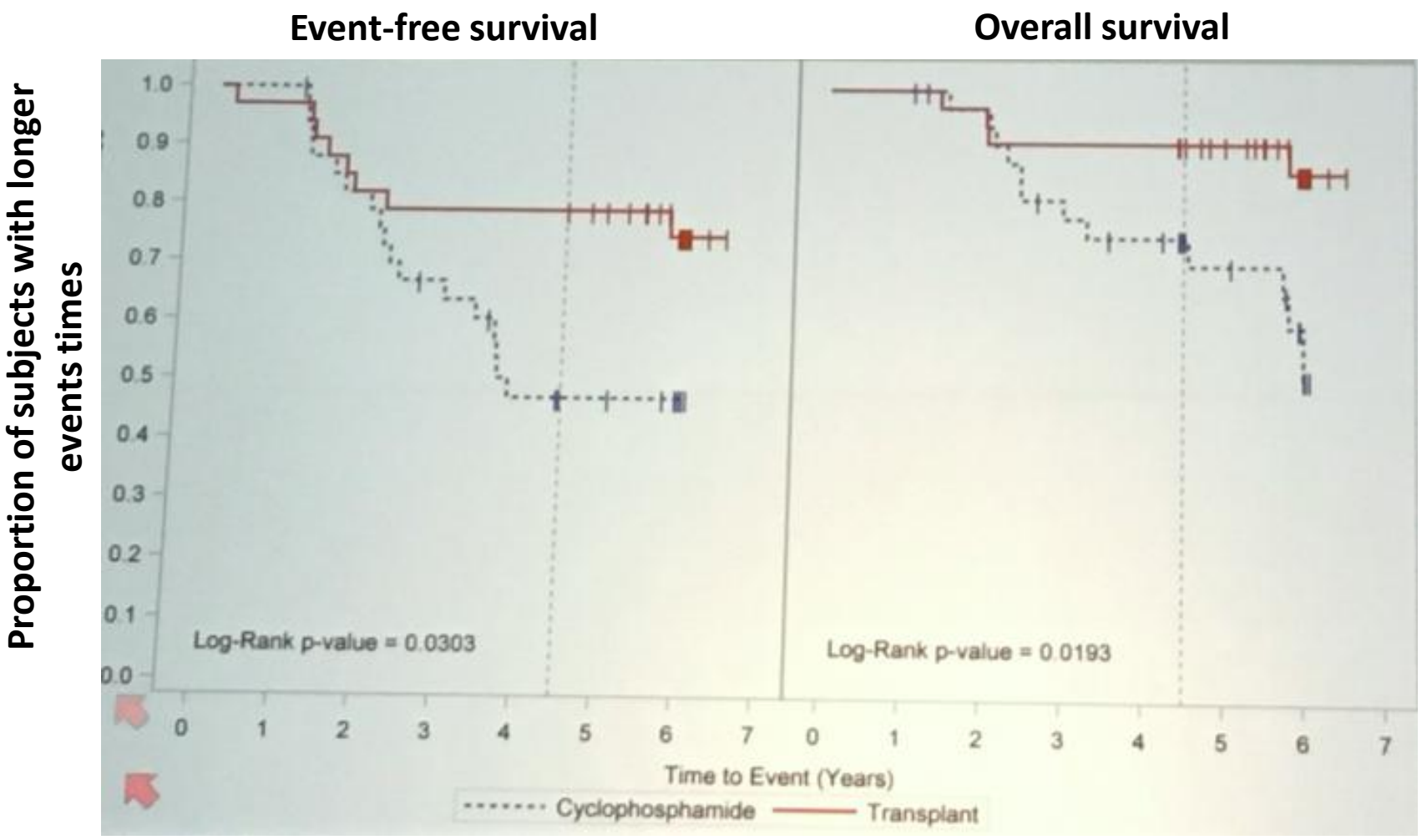

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Secondary Efficacy Endpoints in the Treated Population*

		Transplant	Cyclophosphamide	p-value
PP (all treated)	n	33	34	
GRCS Month 54	Median (min, max)	16 (-56, 46)	- 11 (-56, 46)	0.004
GRCS Month 48	Median (min, max)	17 (-56, 49)	- 13 (-56, 49)	0.003
EFS Month 48 & 54	Failure, n	7 (21%)	17 (50%)	0.021
Mortality (all causes) Month 48 & 54	Deaths, n	3 (9%)	8 (24%)	0.19

Abbreviations: EFS, Event-free Survival; GRCS, Global Rank Composite Score;
*PP, Per Protocol (Treated) Population: those transplanted or given ≥ 9 doses cyclophosphamide.

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Secondary Disease Progression Events
(month 54 in the treated population)

	HSCT (N=33)	CYC (N=34)	P - value
Initiated DMARDs, n	3 (9%)	15 (44%)	0.001
Pulmonary artery hypertension, n	0	5 (15%)	0.022
Congestive heart failure*, n	0	4 (12%)	0.042

Abbreviations: CYC, cyclophosphamide; DMARDS, Disease Modifying Anti-Rheumatic Drugs; HSCT, Hematopoietic Stem Cell Transplant

* Requiring Treatment

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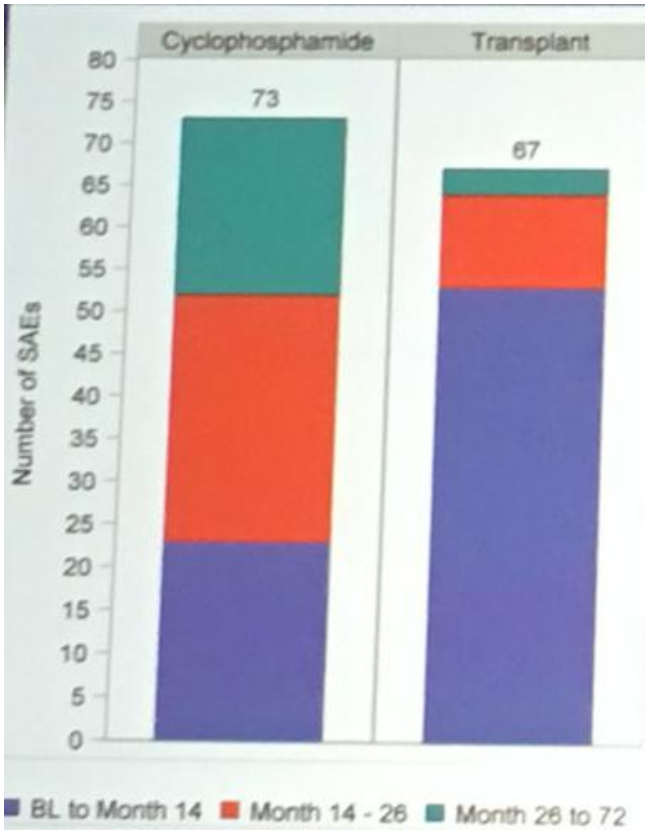
Serious Adverse Events (M72)

	Cyclophosphamide	Transplant
% Patients	51	74
Taux (patient/an)	0.52	0.38



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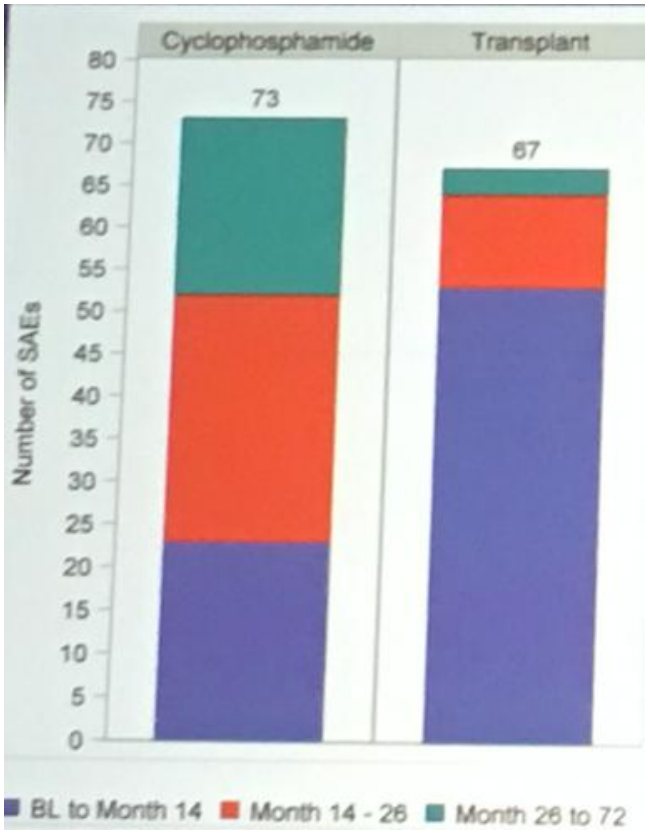
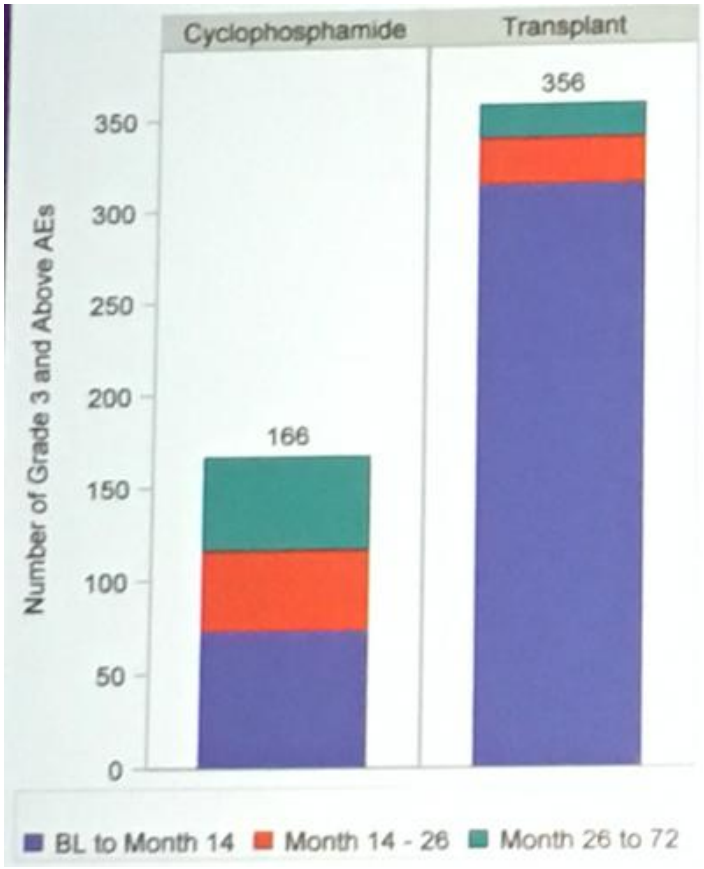
Serious Adverse Events (M72)

	Cyclophosphamide	Transplant
% Patients	51	74
Taux (patient/an)	0.52	0.38



> ou + Grade 3 AE (M72)

	Cyclophosphamide	Transplant
% Patients	84	100
Taux (patient/mois)	1.2	2



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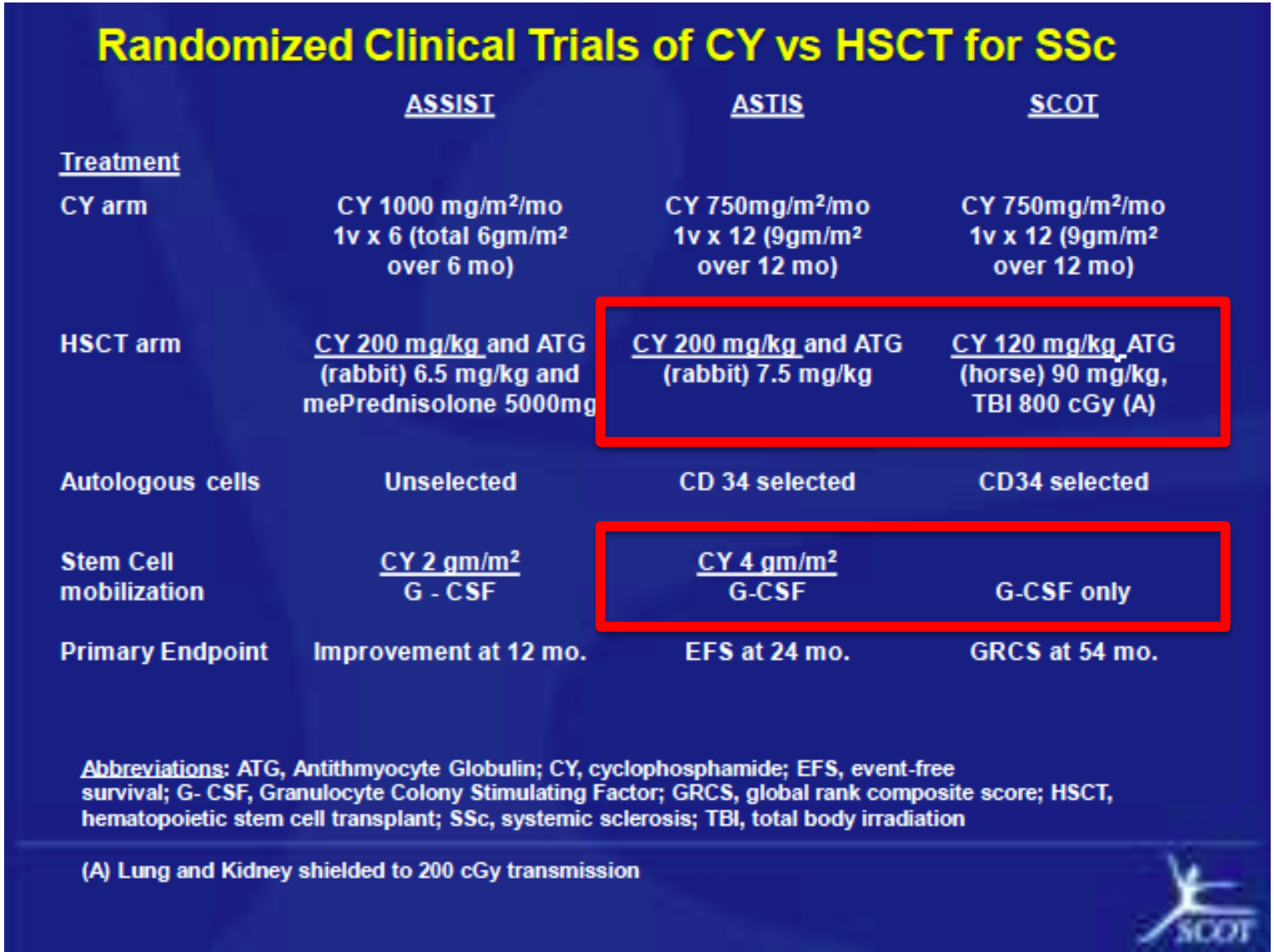

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	ASTIS	SCOT
Transplant Mortality at 54 mo.	10 %	3 %
Post Transplant DMARDs use	22 % at 24 mo.	9 % at 54 mo.

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Conclusions

- Compared to 12 months of IV CYC, myeloablative autologous HSCT has superior long-term outcomes. We found the GRCS to be a useful measure of scleroderma outcome.
- While there are risks with HSCT, these appear warranted given the success of the intervention and the underlying disease.
- Compared to published results with nonmyeloablative HSCT*, we note lower rates of transplant-related mortality and post-transplant initiation of DMARDs.
- The SCOT trial supports myeloablative HSCT as a significant advance in SSc. Early referral for transplant consultation will allow patients to make informed decisions.

Perspectives thérapeutiques

ACR/ARHP Annual Meeting
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Perspectives thérapeutiques

- **Anti-IL6R**
- **Apremilast**
- **ß1 integrin activation**
- **ß3 integrin blockade**
- **Calpain 9/S2**
- **ERK antagonists**
- **pDC depletion**
- **Inhibiteur de DPP4**
- **Inhibiteur du récepteur de sérotonine**
- **PPAR activation**
- **TLR 7/9 antagonists**

Conclusion

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- ACR 2016 et Sclérodermie Systémique:
  - Des avancées expérimentales
  - Des biomarqueurs nécessitant confirmation avant utilisation en pratique clinique de routine
  - Des avancées thérapeutiques:
    - Evidence-based medicine
    - Nombreux essais négatifs
    - Essai SCOT
    - Nombreuses perspectives thérapeutiques