Post-EULAR 2021 Lupus/Sjögren

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OP0291 (2021)

SEVERITY OF LABIAL MINOR SALIVARY GLAND FOCUS SCORE AND FUTURE LYMPHOMA DEVELOPMENT IN SJÖGREN'S SYNDROME

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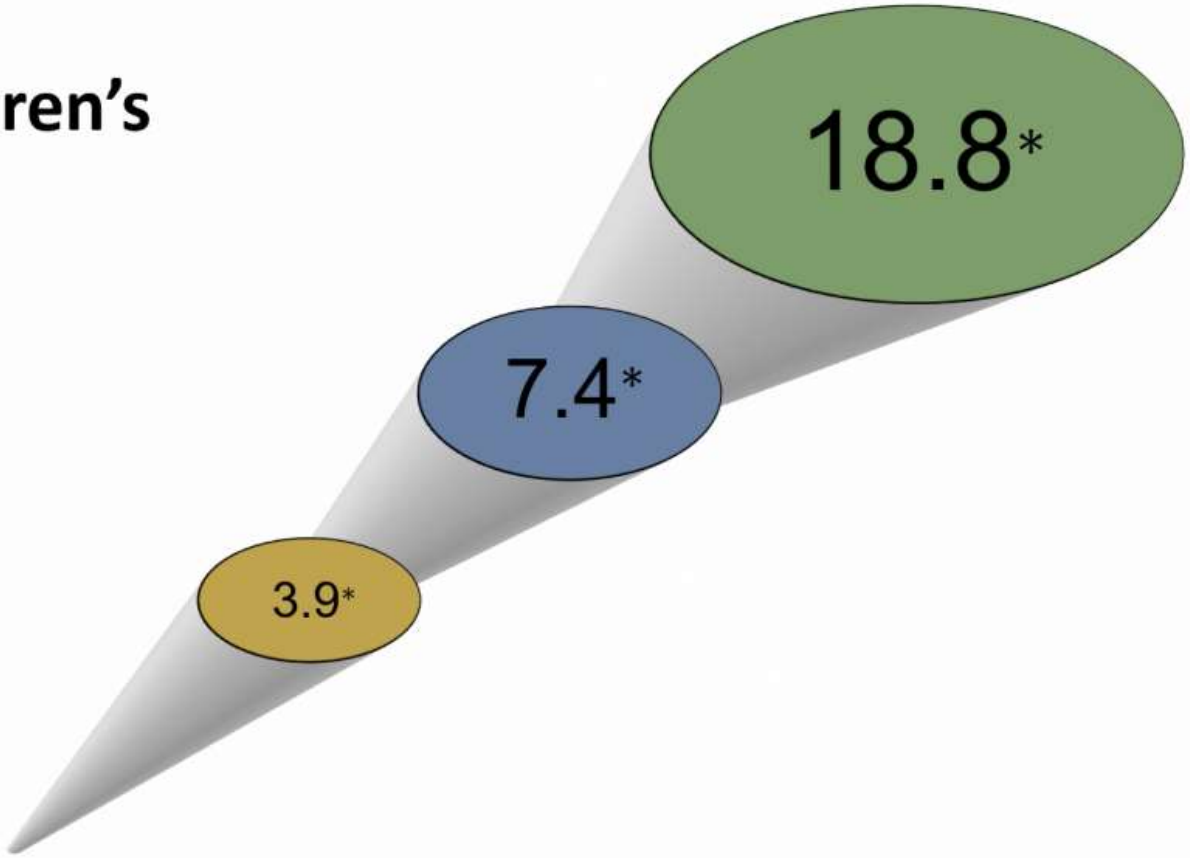
✓ Lymphoma in Autoimmune Disorders

- **Sjogren's**
- **SLE**
- **RA**



*Standardized Incidence Ratios

Zinzaras E, et al. Arch Inter Med 2005

Table 3 The currently accepted 'Focus Score' Pathologic Grading System for the diagnosis of Sjögren's syndrome.[18] A focus score of 1 or more qualifies for scoring on the ACR/EULAR criteria

Focus score	No. of lymphocytic foci per 4 mm^2
0	None or a small aggregate or infiltrate
1	One aggregate of 50 or more lymphocytes
2–11	Two to 11 aggregates (raw number)
12	Twelve aggregates or confluent infiltrate

Oral surgery 2019

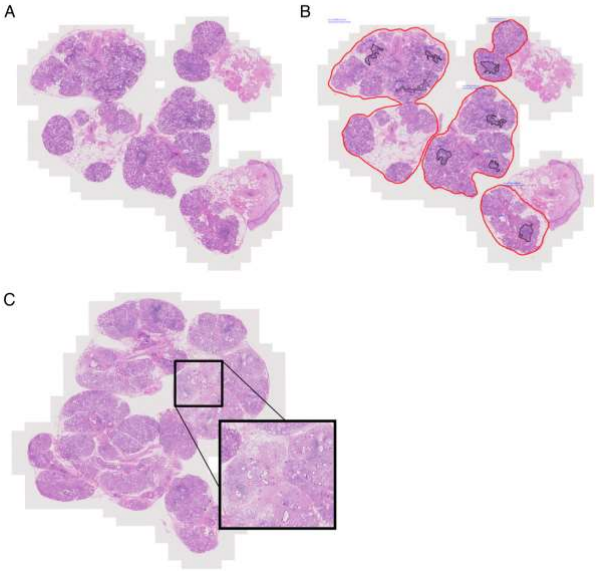
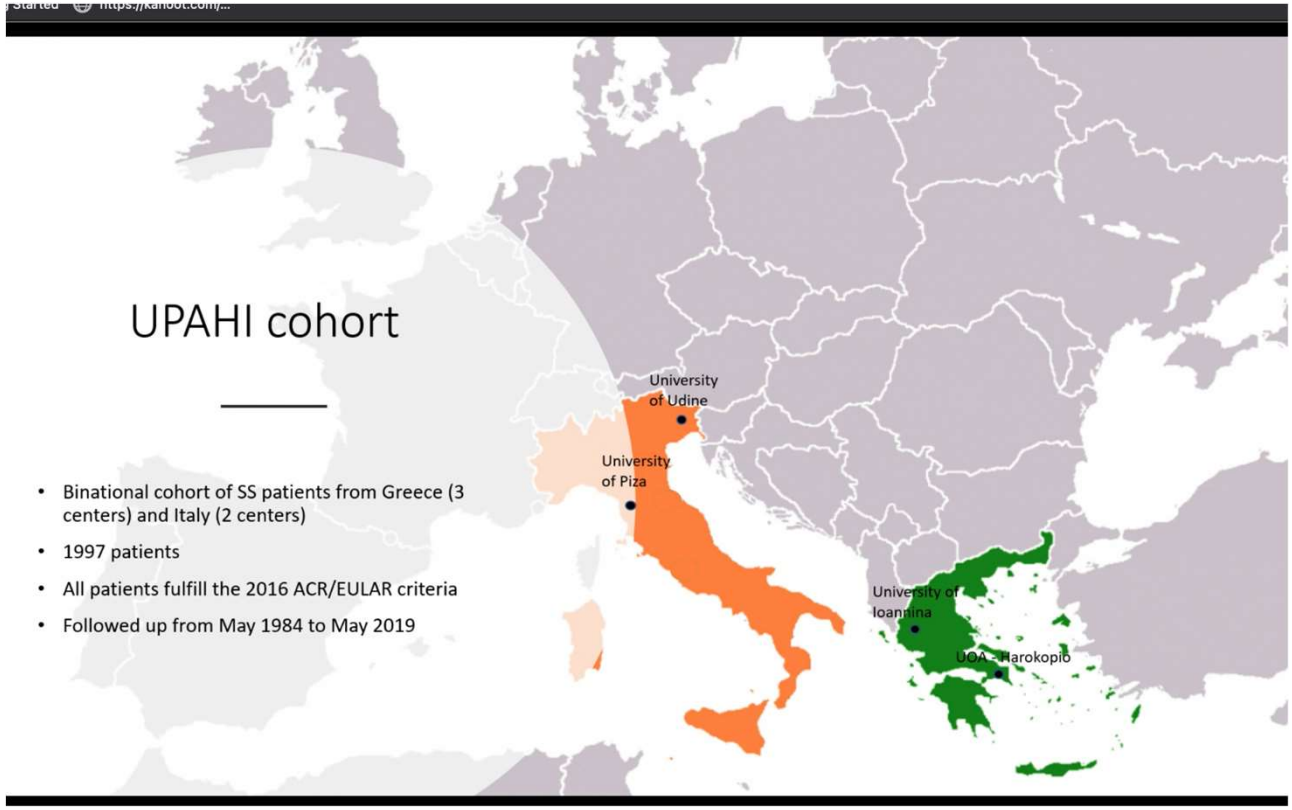
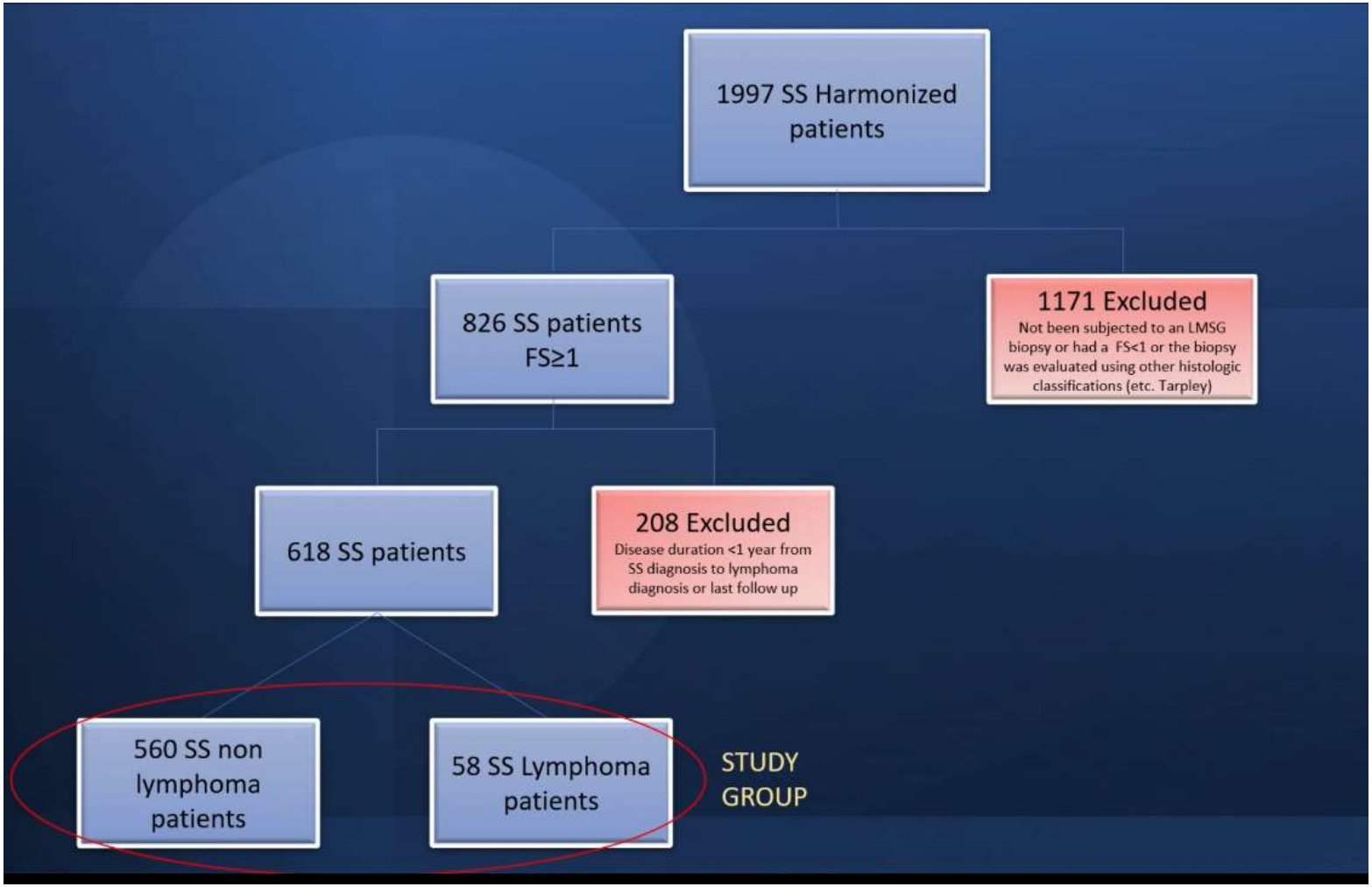


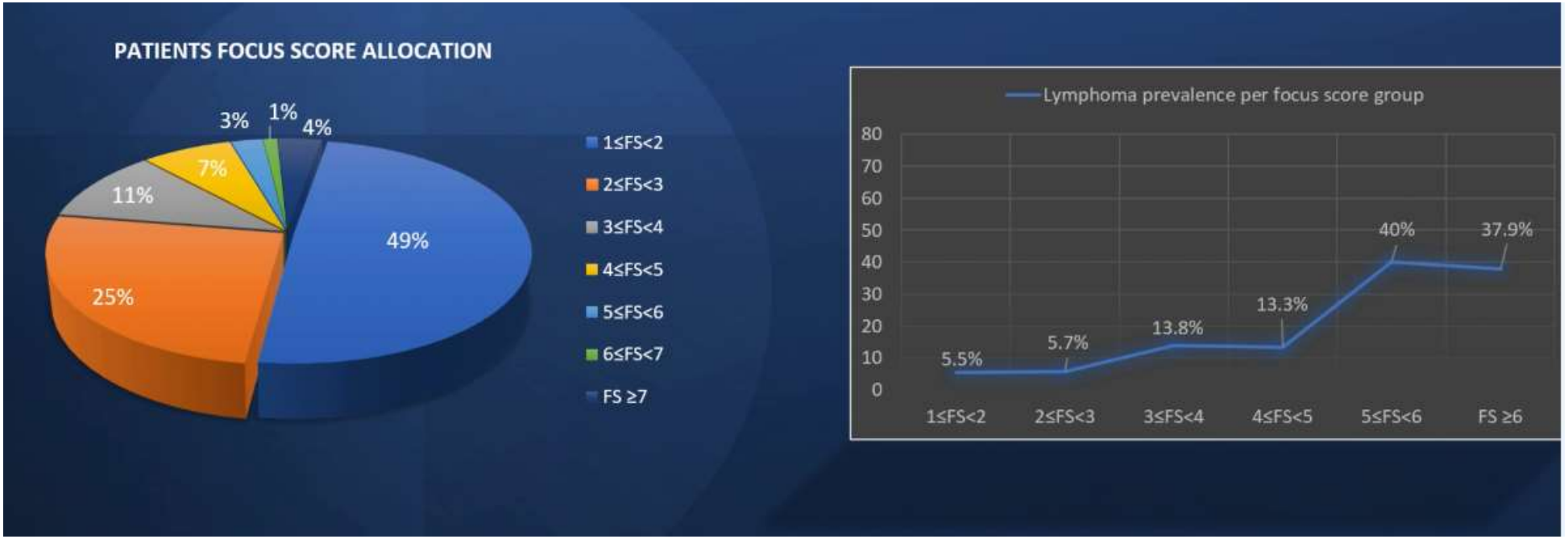
Figure 2 (A) Microphotograph illustrating salivary gland biopsy obtained from a patient with primary Sjögren's syndrome, stained with H&E. (B) Image analysis applied to macrosection showing delineation of glandular tissue in *red*. Focus score is calculated by counting the number of foci, whose area is delineated within the *black lines*, dividing by the whole glandular surface area in mm^2 and multiplying by 4 to give the number of foci per 4 mm^2 over the whole glandular area. In this example, the glandular surface delineated includes interspersed atrophic areas but excludes any attached epithelial or connective tissue. The measured glandular area is 20.89 mm^2 and there are 8 foci giving a focus score of 1.53. (C) Microphotograph illustrating salivary gland biopsy obtained from a patient with diagnosis of primary Sjögren's syndrome that presents a large area of fibrosis and parenchymal atrophy, alongside areas of focal lymphocytic sialadenitis (original magnification ×20).

Ann Rheum Dis 2016

- **Objectives:** To investigate an association of focus score grading with lymphoma development and time to lymphoma occurrence
- Suche nach einem Focus score cut-off mit prognostischer Bedeutung


UPAHI cohort
• Binational cohort of SS patients from Greece (3 centers) and Italy (2 centers)
• 1997 patients
• All patients fulfill the 2016 ACR/EULAR criteria
• Followed up from May 1984 to May 2019
University of Udine
University of Piza
University of Ioannina
UOA - Harokopio


1997 SS Harmonized patients
826 SS patients FS≥1
1171 Excluded
Not been subjected to an LMSG biopsy or had a FS<1 or the biopsy was evaluated using other histologic classifications (etc. Tarpley)
618 SS patients
208 Excluded
Disease duration <1 year from SS diagnosis to lymphoma diagnosis or last follow up
560 SS non lymphoma patients
58 SS Lymphoma patients
STUDY GROUP


PATIENTS FOCUS SCORE ALLOCATION
49%
25%
11%
7%
3%
1%
4%
1≤FS<2
2≤FS<3
3≤FS<4
4≤FS<5
5≤FS<6
6≤FS<7
FS ≥7
Lymphoma prevalence per focus score group
80
70
60
50
40
30
20
10
0
5.5%
5.7%
13.8%
13.3%
40%
37.9%
1≤FS<2
2≤FS<3
3≤FS<4
4≤FS<5
5≤FS<6
FS ≥6

Focus score as a continuous variable correlated independently with lymphoma development

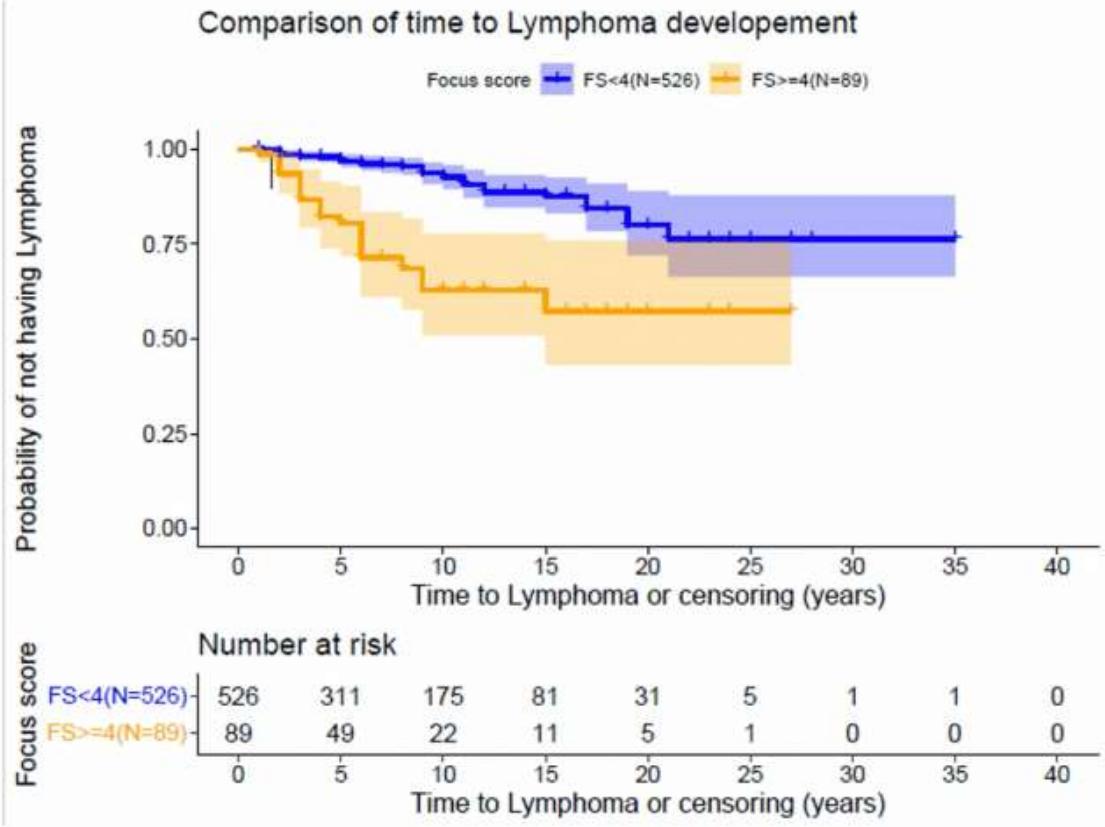
FCBF-based multivariable logistic regression analysis results with lymphoma as an outcome in 618 SS patients with FS≥1.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Cryoglobulinemia	1.73	5.928	0.021 **	1.457	24.558
SGE	1.577	5.078	0.008 **	1.849	13.975
Focus Score	0.27	1.316	0.049 **	1.034	1.677
Lymphadenopathy	0.739	2.239	0.29	0.661	7.713
Age at SS diagnosis	-0.033,	0.967	0.146	0.935	1.0
Autoimmune thyroiditis	-0.046	0.995	0.701	0.323	3.081
Dry mouth	0.387	0.995	0.654	0.258	9.679

*** The strongest potentially independent variables identified by the FCBF algorithm to construct the logistic regression model, after analysing initially the following features included in the unified dataset: Gender, Age at SS, Dry mouth, Dry eyes, Anti-Ro, Anti-La, ANA, Focus Score, history of SGE, history of generalized Lymphadenopathy, Rheumatoid Factor, monoclonal gammopathy, Low C4(<20), Arthralgia-myalgia, Arthritis, Raynaud, Palpable purpura, Myositis, PNS-vasculitic, CNS involvement, Liver involvement – autoimmune hepatitis, Liver involvement- PBC, Lung involvement – interstitial disease, Lung involvement – small airway disease, Interstitial renal disease, Kidney involvement -GN-biopsy, Autoimmune thyroiditis, Cryoglobulinemia.**

****< 0.05 (95% confidence interval): final independent lymphoma associated factors**

Kaplan Meier analysis: Time to lymphoma diagnosis between patients with FS<4 compared to patients with FS≥4



Patienten mit Focus score >=4

- Häufiger
  - Speicheldrüsen Schwellung (46% vs 27%) p= 0.0004
  - Lymphadenopathie 24 % vs 13 %
  - ANA , RF, Anti-SSA abs, Cryoglobuline, monoklonale Ig
  - Häufiger Lymphome 26% vs 7%
- Seltener
  - Autoimmune Thyroiditis 19% vs 38%

FS< 4

FCBF-based multivariable logistic regression analysis results with lymphoma as an outcome in low Focus Score group.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Cryoglobulinemia	1.325	3.92	0.147	0.69	23.134
SGE	3.92	5.213	0.02 **	1.541	17.779
Lymphadenopathy	0.788	2.32	0.35	0.493	11.281
Age at SS diagnosis	-0.037	0.964	0.236	0.92	1.01
Gender	0.4	1.603	0.748	0.149	20.147
Autoimmune thyroiditis	0.008	1.051	0.736	0.283	3.956

**< 0.05 (95% confidence interval): final independent lymphoma associated factors

SGE

FS≥ 4

FCBF-based multivariable logistic regression analysis results with lymphoma as outcome in high Focus Score group.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Cryoglobulinemia	0.917	2.571	0.421	0.288	24.681
Low serum C4	1.306	3.836	0.147	0.701	21.575
Rheumatoid Factor	1.027	2.877	0.282	0.484	17.654
Salivary gland enlargement	0.815	2.34	0.345	0.47	11.777
Focus score	0.333	1.409	0.035**	1.104	1.803
Monoclonal gammopathy	0.298	1.399	0.779	0.142	15.134
Raynaud's phenomenon	0.517	1.75	0.561	0.321	9.746

**< 0.05 (95% confidence interval): final independent lymphoma associated factors

Focus score

Conclusions

- FS was proven an independent lymphoma associated risk factor as a continuous variable
- FS is inversely correlated with the time interval from SS to lymphoma diagnosis
- The FS threshold of 4 maximizes the difference in the time interval from SS diagnosis to lymphoma diagnosis defining high and low FS subgroups suggesting essentially a follow up strategy for early lymphoma diagnosis that can be applied in all SS patients

POS0744 (2021)

A NEGATIVE INTERFERON BIOMARKER CD169 / SIGLEC-1 RULES OUT SYSTEMIC LUPUS ERYTHEMATOSUS

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SIGLEC-1 wird durch Interferon typ I induziert

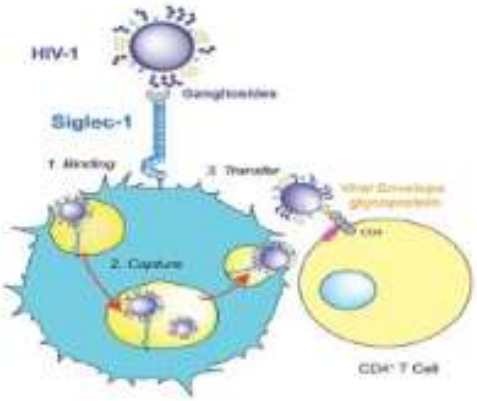

Figure 2: Showing an example of a blood monocyte expressing SIGLEC1: sialic acid-binding immunoglobulin-like lectin 1
→ Type I interferon induced and regulated adhesion molecule [1]

SIGLEC-1 als diagnostischer Marker für SLE

Diagnostisches Potential von Siglec-1

- Retrospektiv
- 232 Patienten (Charite) zwischen 2015-2020
- 2 Gruppen: SLE Patienten und Patienten mit SLE mimic
- 76 (32%) SLE

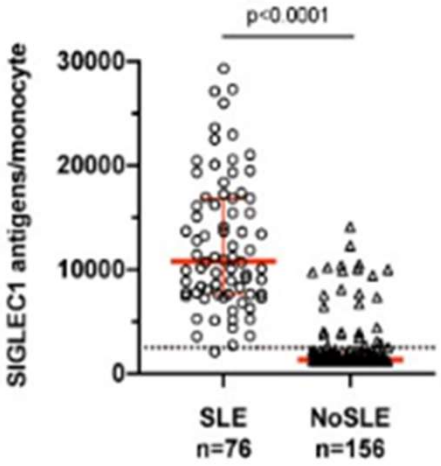

Figure 3: Showing SIGLEC1 values in SLE vs. Non-SLE mimicking condition group

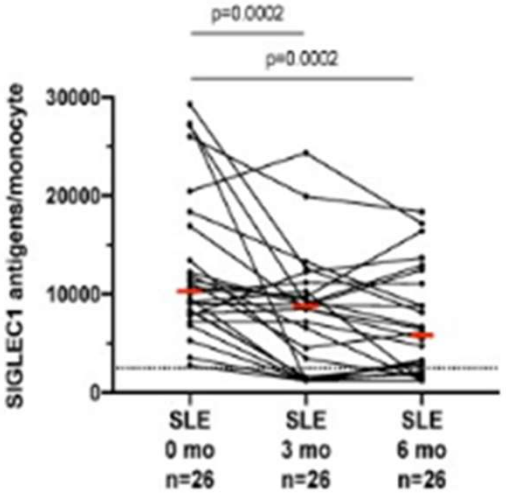

Figure 4: Showing Follow-up values of SIGLEC1 in the SLE group after 3 and six months

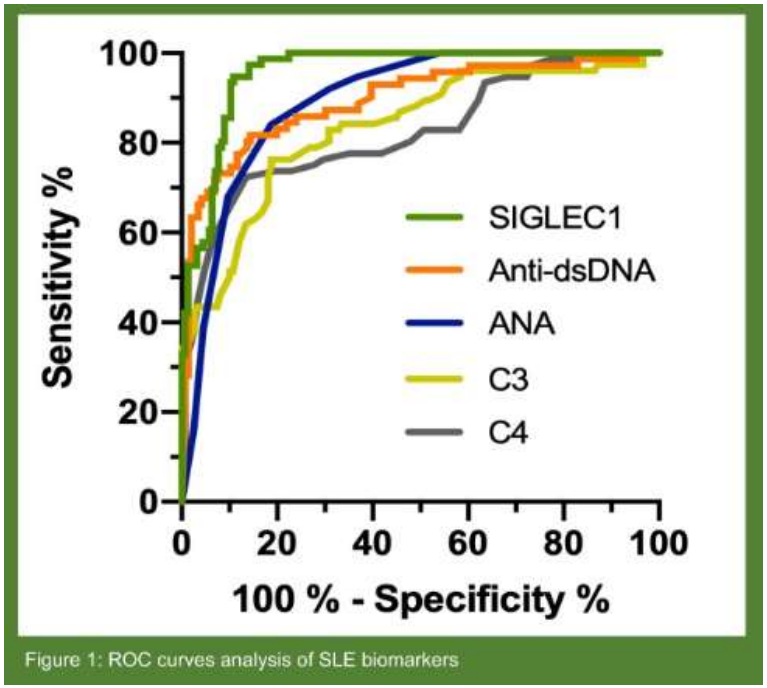

Figure 1: ROC curves analysis of SLE biomarkers

Typ 1 Interferon Aktivität ist entscheidend bei SLE Diagnosestellung
aber retrospektiv, Abgrenzung gegen andere Typ I Interferon assoziierte Erkrankungen?

OP0129 (2021)

- **BELIMUMAB AFTER RITUXIMAB SIGNIFICANTLY REDUCED IGG ANTI-DSDNA ANTIBODY LEVELS AND PROLONGED TIME TO SEVERE FLARE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS**
- **M. Shipa[1], A. Embleton-Thirsk[2], M. Parvaz[1], L. Santos Ribeiro[1], P. Muller[2], K. Chowdhury[2], D. Isenberg[1], C. Doré[2], C. Gordon[3], M. Ehrenstein[1]**
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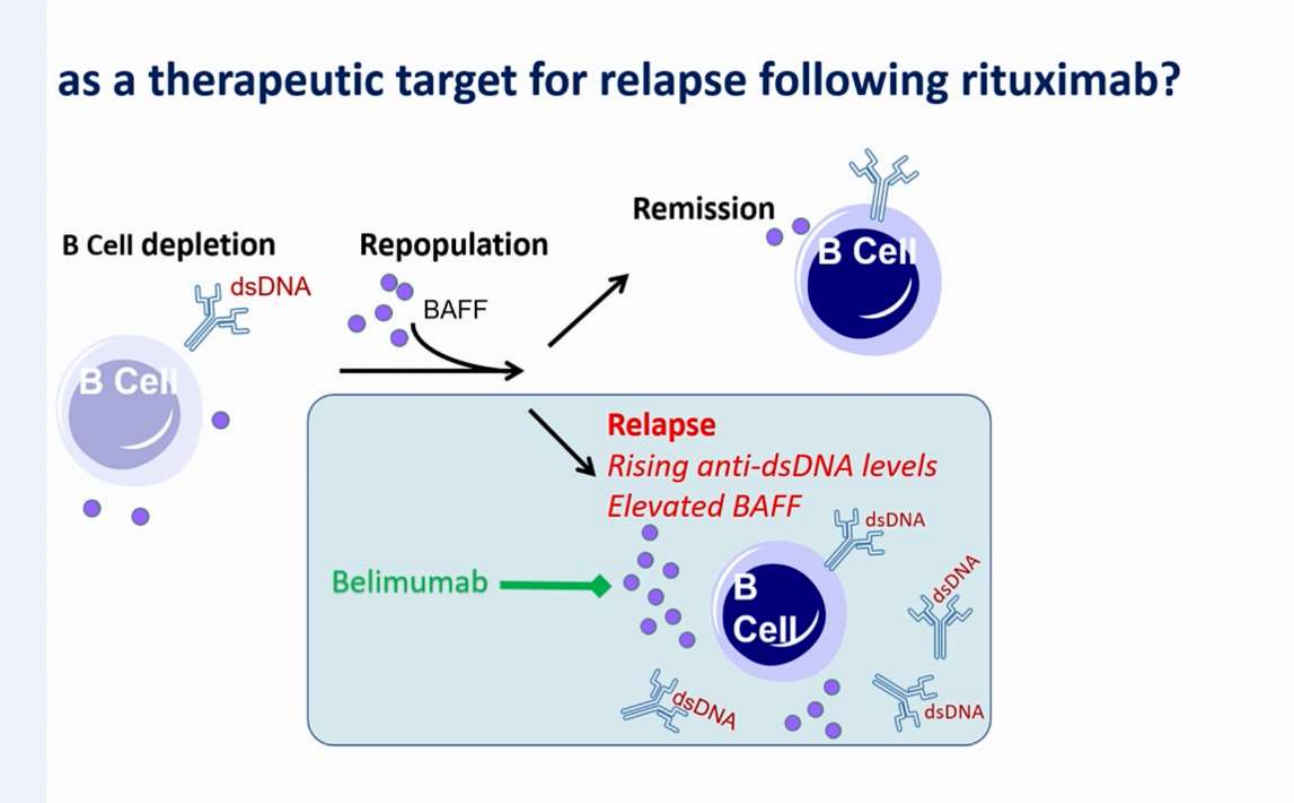
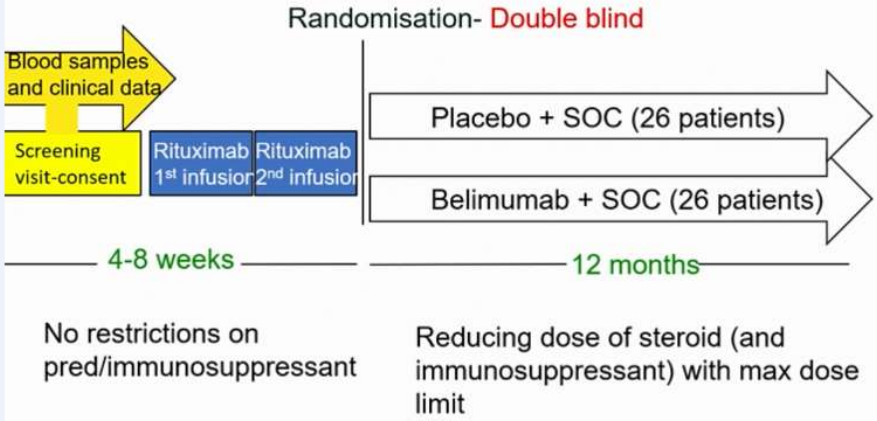
BAFF Inhibition



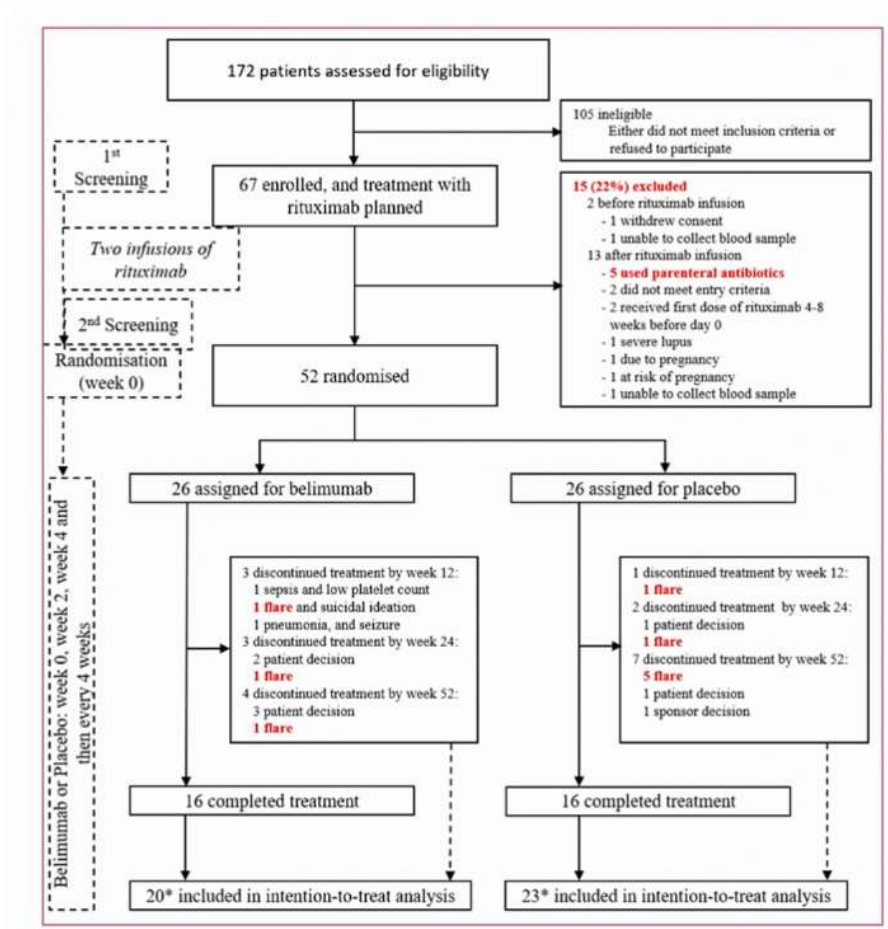
Trial design- 52 patients recruited

BEAT Lupus



No restrictions on pred/immunosuppressant

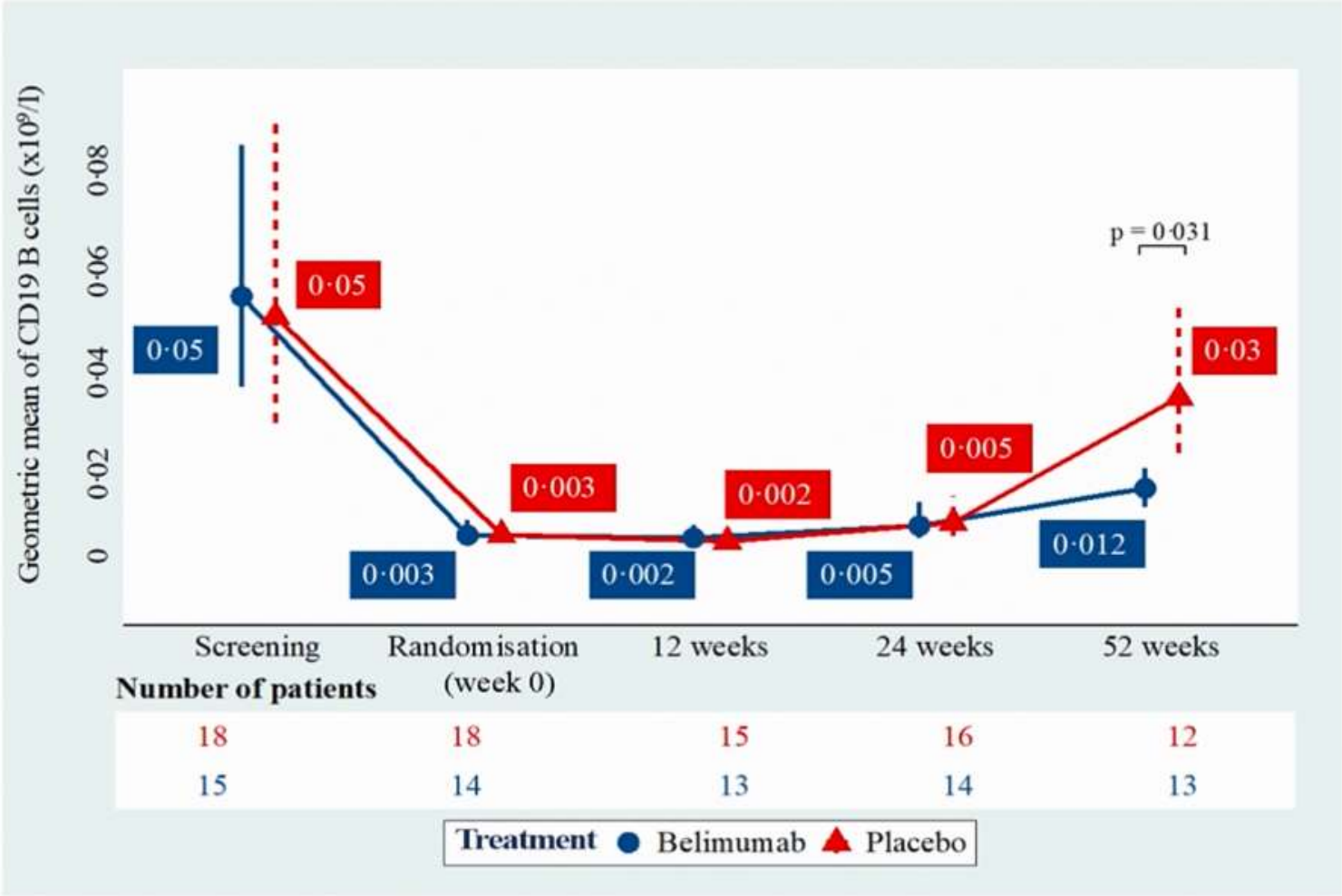
Reducing dose of steroid (and immunosuppressant) with max dose limit


172 patients assessed for eligibility
105 ineligible
Either did not meet inclusion criteria or refused to participate
1st Screening
67 enrolled, and treatment with rituximab planned
15 (22%) excluded
2 before rituximab infusion
- 1 withdrew consent
- 1 unable to collect blood sample
13 after rituximab infusion
- 5 used parenteral antibiotics
- 2 did not meet entry criteria
- 2 received first dose of rituximab 4-8 weeks before day 0
- 1 severe lupus
- 1 due to pregnancy
- 1 at risk of pregnancy
- 1 unable to collect blood sample
Two infusions of rituximab
2nd Screening
Randomisation (week 0)
52 randomised
Belimumab or Placebo: week 0, week 2, week 4 and then every 4 weeks
26 assigned for belimumab
26 assigned for placebo
3 discontinued treatment by week 12:
1 sepsis and low platelet count
1 flare and suicidal ideation
1 pneumonia, and seizure
3 discontinued treatment by week 24:
2 patient decision
1 flare
4 discontinued treatment by week 52:
3 patient decision
1 flare
1 discontinued treatment by week 12:
1 flare
2 discontinued treatment by week 24:
1 patient decision
1 flare
7 discontinued treatment by week 52:
5 flare
1 patient decision
1 sponsor decision
16 completed treatment
16 completed treatment
20* included in intention-to-treat analysis
23* included in intention-to-treat analysis

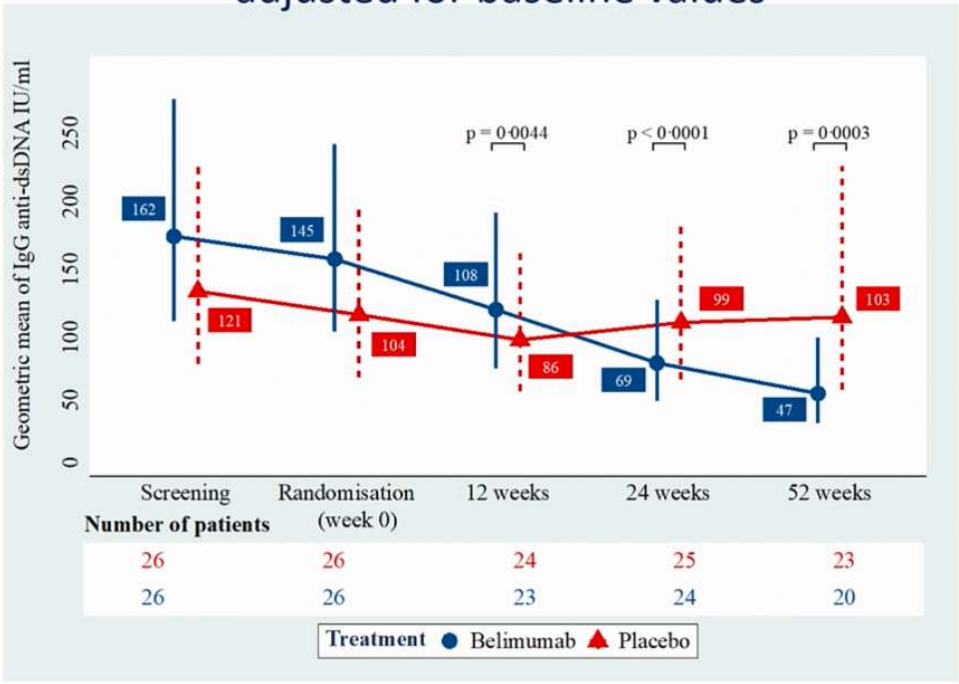
	Placebo (n = 26)	Belimumab (n = 26)
Age, years[a]	41 (10·6)	38 (11·4)
Sex – no. of patients (%)		
Male	*3 (12%)*	*5 (19%)*
Female	*23 (88%)*	*21 (81%)*
Ethnicity – no. of patients (%)		
White	*17 (65·4%)*	*13 (50%)*
Black	*3 (12%)*	*3 (12%)*
South Asian	*2 (7·7%)*	*4 (15·4%)*
Chinese	*1 (3.8%)*	*2 (7·7%)*
Other	*3 (11·5%)*	*4 (15·4%)*
Disease duration from screening, years	9·2 (7·4)	11·8 (8·8)
Time between screening and randomisation, days	*44·3 (9·5)*	*41·5 (9·1)*
Previous Rituximab – no. of patients (%)	8 (30·8%)	6 (23·1%)
Previous Rituximab within 2 years from screening – no. of patients (%)	3 (11·5%)	4 (15·4%)
Concomitant Immunosuppressant at randomisation – no. of patients (%)		
Mycophenolate	*15 (57·7%)*	*19 (73·1%)*
Azathioprine	*2 (7·7%)*	*2 (7·7%)*
Methotrexate	*1 (3·8%)*	*2 (7·7%)*
Not on any Immunosuppressant	*6 (23·1%)*	*2 (7·7%)*
Concomitant hydroxychloroquine at randomisation– no. of patients (%)	20 (76·9%)	17 (65·4%)
Average daily prednisolone dose at screening, mg/day[a]	14·9 (9·8)	13·3 (9.0)
Average daily prednisolone dose at randomisation, mg/day[a]	12·5 (6·7)	12·9 (7·7)
Patients taking prednisolone at randomisation, no. of patients (%)	24 (92·3%)	22 (84·6%)
Patients taking ≥ 7.5 mg/day prednisolone at randomisation, no. of patients (%)	18 (69·2%)	15 (57·7%)
Patients taking ≥ 10 mg/day prednisolone at randomisation, no. of patients (%)	16 (61·5%)	13 (50%)
Organ involvement (either BILAG A/B) at screening – no. of patients (%)		
Constitutional	*2 (7.7%)*	*3 (12%)*
Cardiorespiratory	*6 (23·1%)*	*4 (15%)*
Mucocutaneous	*14 (53·8%)*	*13 (50%)*
Musculoskeletal	*9 (34·6%)*	*11 (42·3%)*
Neuro-psychiatric	*1 (3·8%)*	*0 (0%)*
Ophthalmic	*0 (0%)*	*1 (3·8%)*
Gastro-intestinal	*0 (0%)*	*0 (0%)*
Renal	*10 (38·5%)*	*10 (38·5%)*
Haematological	*0 (0%)*	*1 (3·8%)*
BILAG score at randomisation – no. of patients (%)		
≥ 1 BILAG A	*8 (30.7%)*	*6 (23%)*
≥ 1 BILAG A or 2 BILAG B	*9 (34.6%)*	*13 (50%)*
≥ 1 BILAG B	*20 (77%)*	*23 (88.4%)*
Positive anti-dsDNA IgG antibody at screening – no. of patients (%)	23 (88·5%)	24 (92·3%)
Low Complement C3 at screening – no. of patients (%)	13 (50%)	11 (42·3%)

[a] *Mean (SD)*

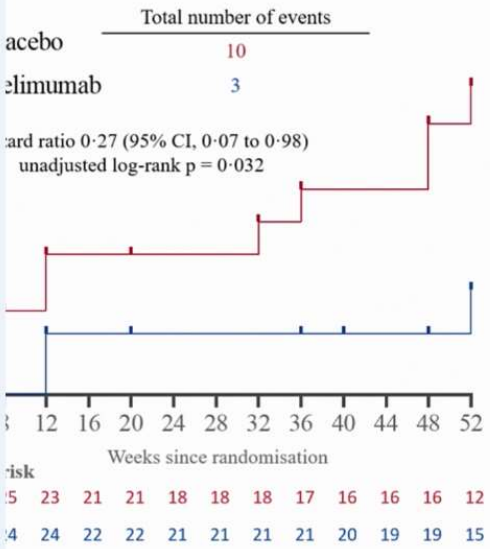
Belimumab delays B cell repopulation after rituximab (substudy)



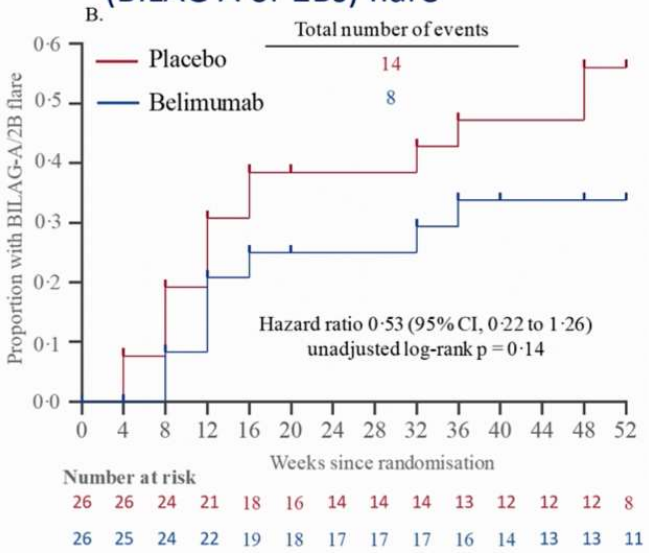
endpoint: serum IgG anti-dsDNA antibody level at 52 weeks adjusted for baseline values

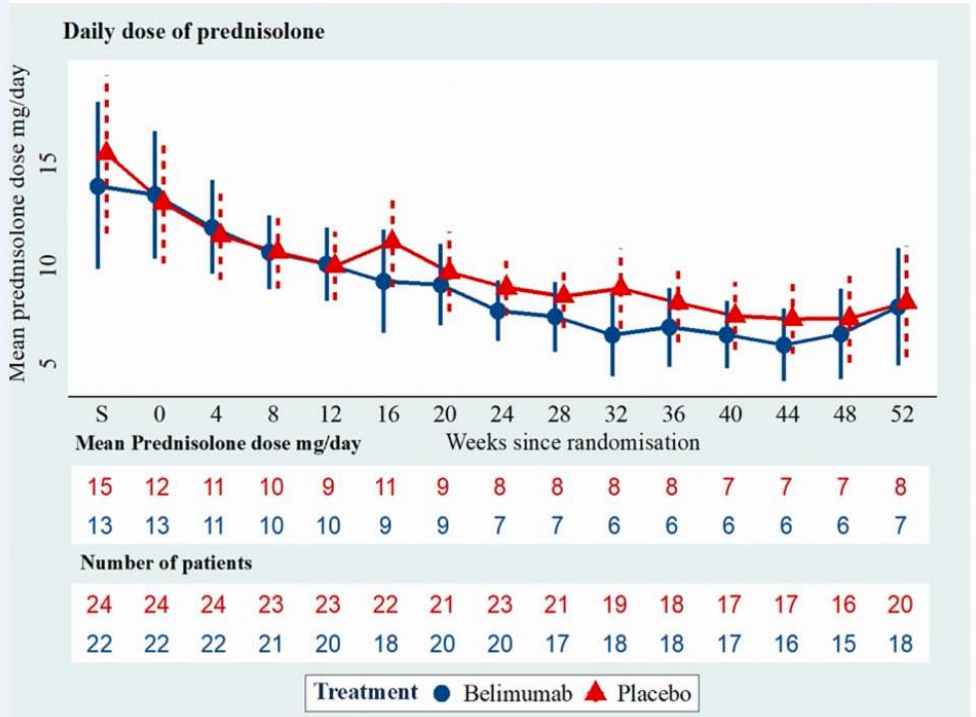


first severe (BILAG A) flare

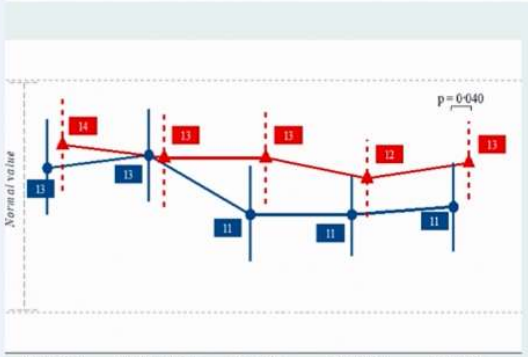


Time to first moderate or severe (BILAG A or 2Bs) flare




Daily dose of prednisolone
Mean prednisolone dose mg/day
5
10
15
S 0 4 8 12 16 20 24 28 32 36 40 44 48 52
Mean Prednisolone dose mg/day
Weeks since randomisation
15 12 11 10 9 11 9 8 8 8 8 7 7 7 8
13 13 11 10 10 9 9 7 7 6 6 6 6 6 7
Number of patients
24 24 24 23 23 22 21 23 21 19 18 17 17 16 20
22 22 22 21 20 18 20 20 17 18 18 17 16 15 18
Treatment Belimumab Placebo

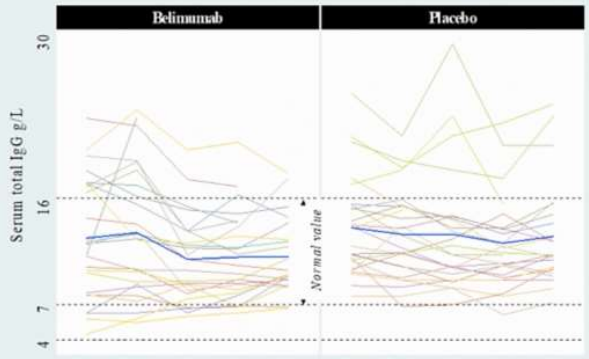
Serum total IgG levels



Screening	Randomisation (week 0)	12 weeks	24 weeks	52 weeks
umber of patients				
26	26	25	26	23
26	26	24	24	21

Treatment ● Belimumab ▲ Placebo

B.



	Scr.	Rand. (week 0)	12 weeks	24 weeks	52 weeks
No. of patients with IgG < 7 g/L (Total)	4 (26)	3 (26)	4 (24)	4 (24)	2 (21)
No. of patients with IgG < 7 g/L (Total)	0 (26)	1 (26)	1 (25)	2 (26)	0 (23)

Zusammenfassung

- RTX gefolgt von Belimumab
  - Prolongierte B-Zell Depletion
  - Längere Suppression von anti DNA-abs
  - Weniger relapses
- Unklar
  - Sek Hypogammaglobulinämie
  - RTX retreatment
- Protektive Immunität SARS-COV-2?