Μπορούμε να παρέμβουμε στη φυσική πορεία του ΣΕΛ;

Γεώργιος Μπερτσιάς

Κλινική Ρευματολογίας και Κλινικής Ανοσολογίας, ΠαΓΝΗ και
Ιατρική Σχολή Πανεπιστημίου Κρήτης

Ηράκλειο, 30-09-2023

NX-GR-BEL-PPTX-230011 Preparation date September 2023 ΙΣΧΥΣ September 2023

Δήλωση συμφερόντων

Τα τελευταία 2 έτη έχω λάβει τιμητική αμοιβή από τις εταιρείες: Lilly, AENORASIS, SOBI, GSK, AstraZeneca, Pfizer

Για τη συγκεκριμένη ομιλία έχω λάβει τιμητική αμοιβή από την GSK

Κλινική Περίπτωση

- Woman 33 years old, nulliparous
- History of hypothyroidism

- **Diagnosed with SLE** in 2011: ANA 1:320+, anti-dsDNA+, anti-Ro/SSA+, arthritis, thrombocytopenia (>70.000/mm^3), acute cutaneous lupus, hair loss/alopecia,
- In 2013, she developed kidney disease (**minimal change disease**) attributed to lupus, and she responded very well to glucocorticoids (18 months' course) and azathioprine

- 2015-2016: **repeated episodes of active rash and arthritis**, managed with short course of glucocorticoids. Azathioprine was temporarily switched to methotrexate, which was not tolerated (GI distress)

- On 02/2016 she presented with an **acute flare**:
  - Fever >38, fatigue, rash (ACLE) over the trunk and upper arms, hair loss, arthritis (wrists, MCPs, MTPs), ↑ anti-dsDNA, ↓ C3/C4, ↑ ESR/CRP
  - Treatment: HCQ 400 mg/d, azathioprine 150 mg/d
  - She received pulses IV methylprednisolone (2 grams) followed by oral prednisone (30 mg/day, gradually tapered to 7.5 mg/day after 3 months)

Κλινική Περίπτωση

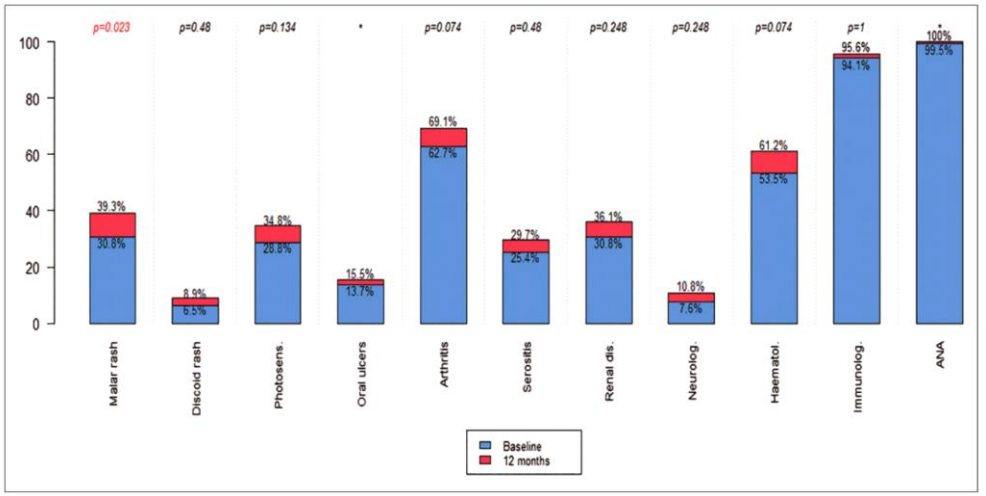
- During the next months, the patient experienced
  - 3 additional **relapses of SLE** (arthritis, fever, rash) at a prednisone dose of 7.5-10 mg/day
  - She also had lymphopenia (1000/μL), serological activity (↑ anti-dsDNA, ↓ C3/C40 and ↑ ESR/CRP
  - All flares were treated **with increases in glucocorticoids** while **ciclosporin was added to azathioprine**

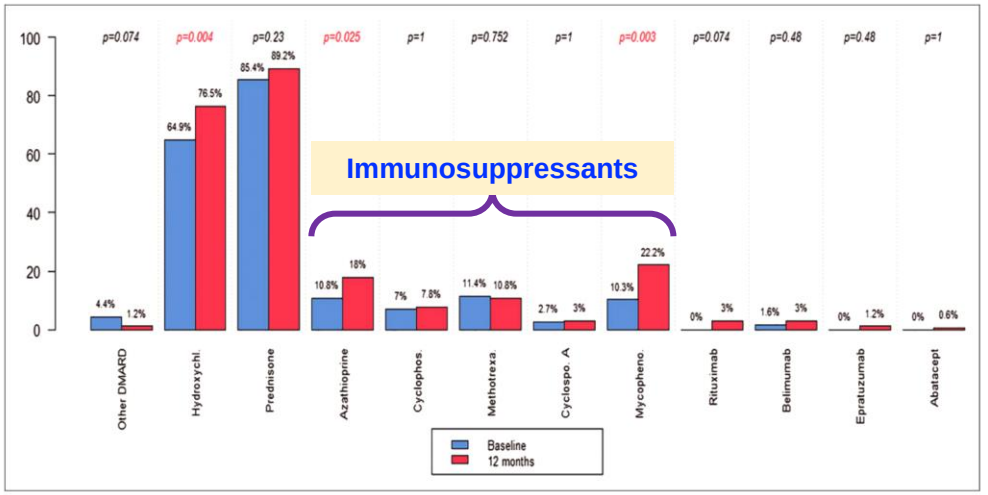
- On 06/2017:
  - While on treatment with HCQ 400 mg/day, azathioprine 150 mg/day, ciclosporin 100 mg/day, prednisolone 10 mg/day, she developed left pleurisy
  - Chest CT reveled **mild/moderate pleural effusion** (left) and mild pericardial effusion. She still had serological activity, and residual activity from skin, joints

Φυσική πορεία του ΣΕΛ κατά τα πρώτα έτη μετά τη διάγνωση

Prognosis during the first year

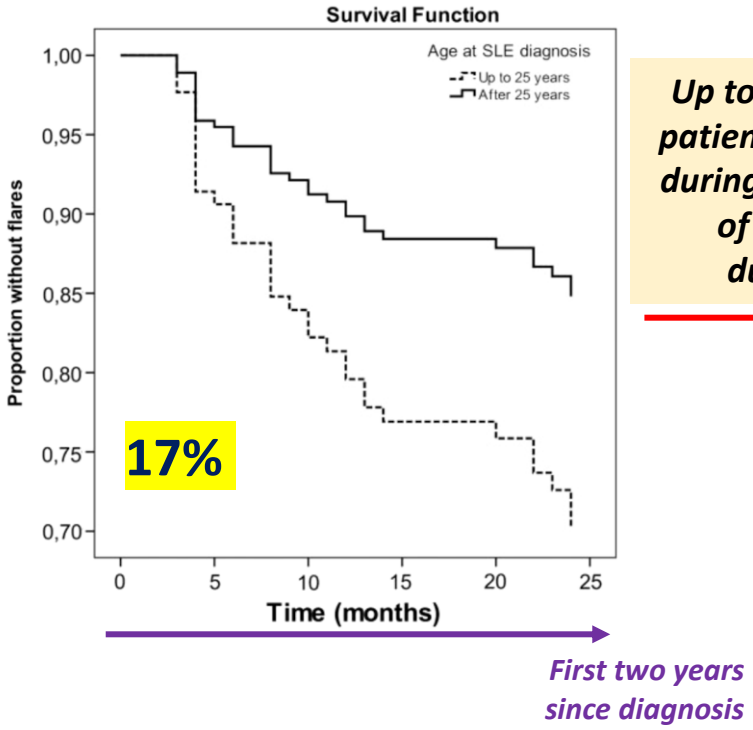
- 20-30% των ασθενών έχουν ήπια πορεία με το υπόλοιπο ποσοστό να μοιράζεται μεταξύ μετρίως σοβαρής και πολύ σοβαρής νόσου
- Accrual of **new manifestations** and organ involvement
- Increased **need for treatments** (glucocorticoids, immunosuppressants)
- **Only about 35% of patients achieves clinical remission**





Sebastiani GD, et al. *Lupus*. 2018; 27: 1479-88
Piga M, et al. Rheumatology. 2020; 59: 2272–81
Segura BT, et al. Rheumatology. 2020; 59: 524–33
Koelmeyer R, et al. Lupus Sci Med. 2020; 7: e000372

Οι υποτροπές είναι συχνές και επιδρούν αρνητικά στην πρόγνωση της νόσου



Up to 60-70% of patients will flare during 5-10 years of disease duration

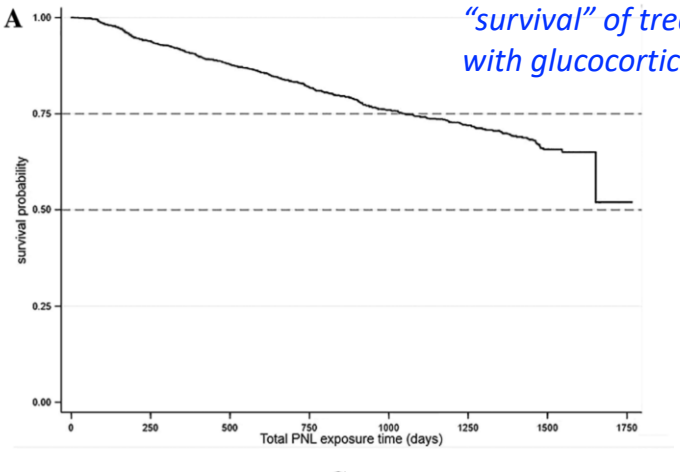
Ασθενείς «υψηλού κινδύνου» για εξάρσεις

- Younger patients
- High disease activity (SLEDAI ≥12)
- Immunological activity (↑ anti-dsDNA, ↓ C3/C4)
- Renal, CNS, hematological disease, vasculitis
- Non-use of hydroxychloroquine
- Poor adherence to treatment
- (Premature) discontinuation of immunosuppressive treatment

Ines L, et al. *Rheumatology*. 2014; 53: 85-9
Ugarte-Gil MF, et al. *Lupus*. 2018; 27(4): 536-44
Petri M, et al. *Arthritis Rheum*. 2013; 65(8): 2143-53

More than 50% of patients remain on GC treatment after more than 4 years of follow up

- **Asia-Pacific Collaboration SLE cohort**
- **2860 patients, >19800 visits**
- **Mean follow-up: 2 years**
- **30.5% had SLEDAI-2K >4 at baseline**
- **48% developed at least one flare**
- **12% accrued new organ damage**

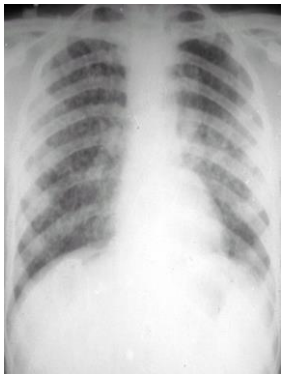


"survival" of treatment with glucocorticoids

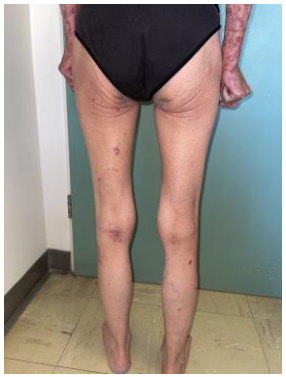
Immunosuppressives were more frequently discontinued as compared to glucocorticoids, espically in patients with moderate activity !!

Kandane-Rathnayake et al. *Arthritis Care Res*. 2022; DOI 10.1002/acr.24740

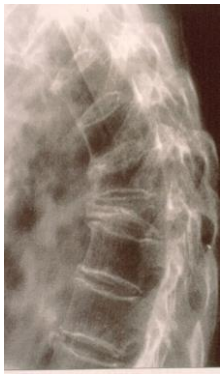
Βλάβη οργάνων & συννοσηρότητες



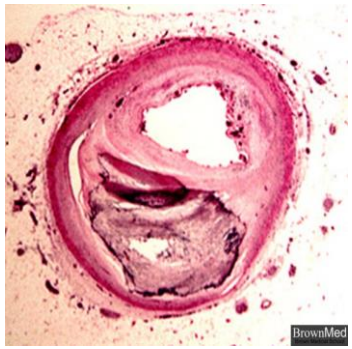
Fibrosis



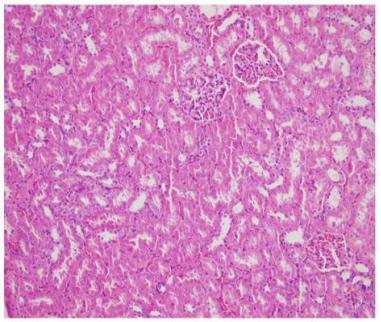
Muscle atrophy



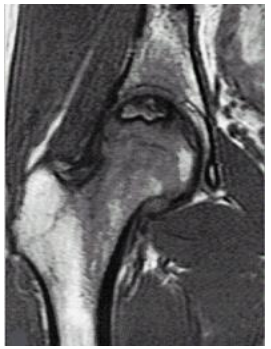
Osteoporotic fractures



Atherosclerosis (MI, CVD)



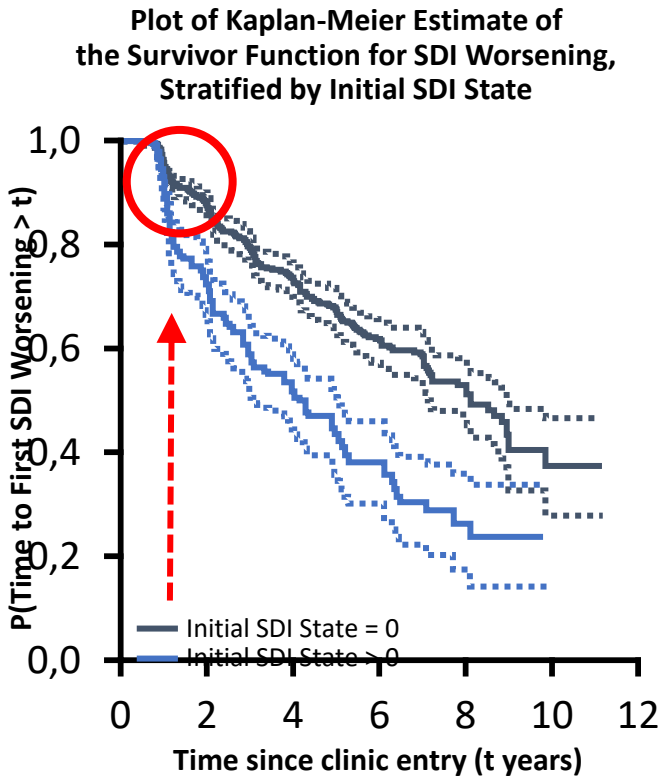
Kidney fibrosis-atrophy



Osteonecrosis

Jönsen A, *et al.* *Arthritis Care Res* 2011; **63**:1233–1237; Yurkovich M, et al. Arthritis Care Res 2014; **66**:608–616

Up to 40-50% of SLE patients accrue organ damage within 7 years since diagnosis



- **Damage develops in <u>15–20% of SLE patients within the first two years since disease diagnosis</u>**
- **Crete SLE Registry**: 32% after mean follow-up 7 years
- **Attikon SLE Registry**: 17.8% within 6 months from diagnosis
- Most frequently afflicted organs: eyes, skin (atrophy), MSK (osteop. #), neurological, cardiovascular (MI/angina) etc.

Bruce IN, et al. *Ann Rheum Dis*. 2015; 74:1706-13; Pego-Reigosa JM, et al. *Rheumatology (Oxford)*. 2016 (epub); Conti F, et al. *Lupus*. 2016; 25: 719–726; Gergianaki I, et al. *Ann Rheum Dis*. 2017; 76(12):1992-2000; Nikolopoulos D, et al. *Lupus*. 2020; 29(5): 514–522

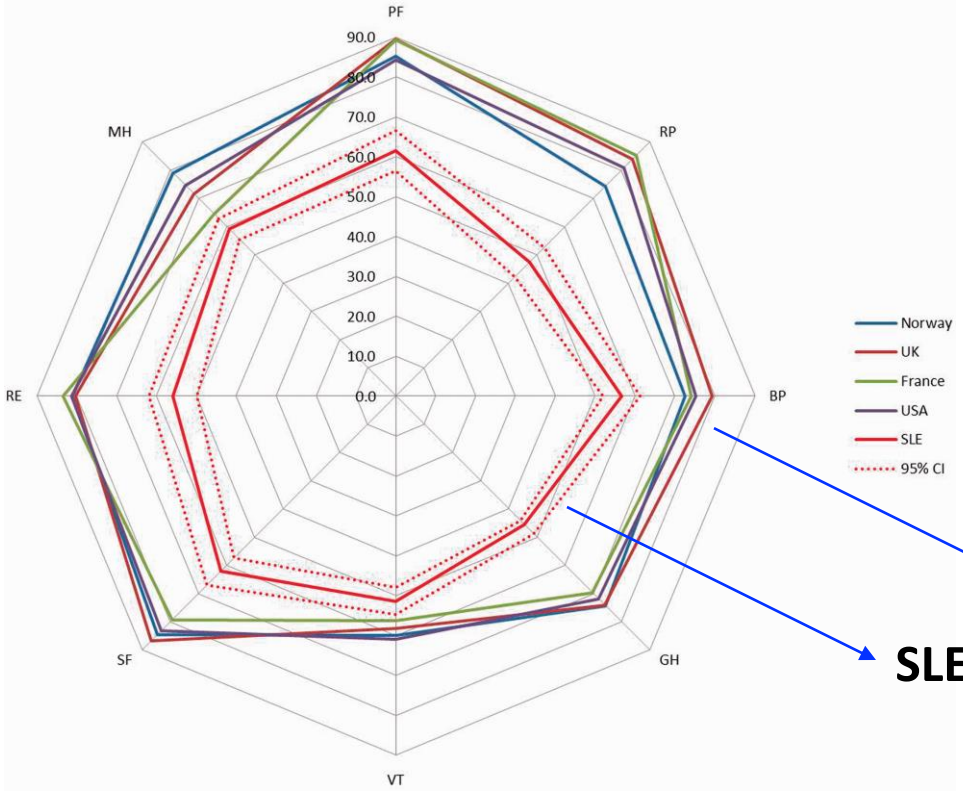
Φυσική πορεία του ΣΕΛ

1. Προσβολή νέων οργάνων
2. Αύξηση τίτλων αυτοαντισωμάτων
3. Εξάρσεις νόσου – αυξημένη ενεργότητα
4. Ανάγκη χρήσης ανοσοτροποποιητικών/ανοσοκατασταλτικών φαρμάκων
5. Μακροχρόνια χρήση γλυκοκορτικοειδών
6. Μη-αναστρέψιμη βλάβη οργάνων

Reduced quality of life (QoL) in patients with SLE

✓HRQoL is reduced in SLE patients[1-4] . Only partially related to disease activity → rather, associated with pain, fatigue and other patient-related factors

✓The extent of this reduction is **comparable to severe medical illnesses**, including AIDS, Sjogren's syndrome and RA , psoriatic arthritis, congestive heart failure, post-myocardial infarction[2,3,4]

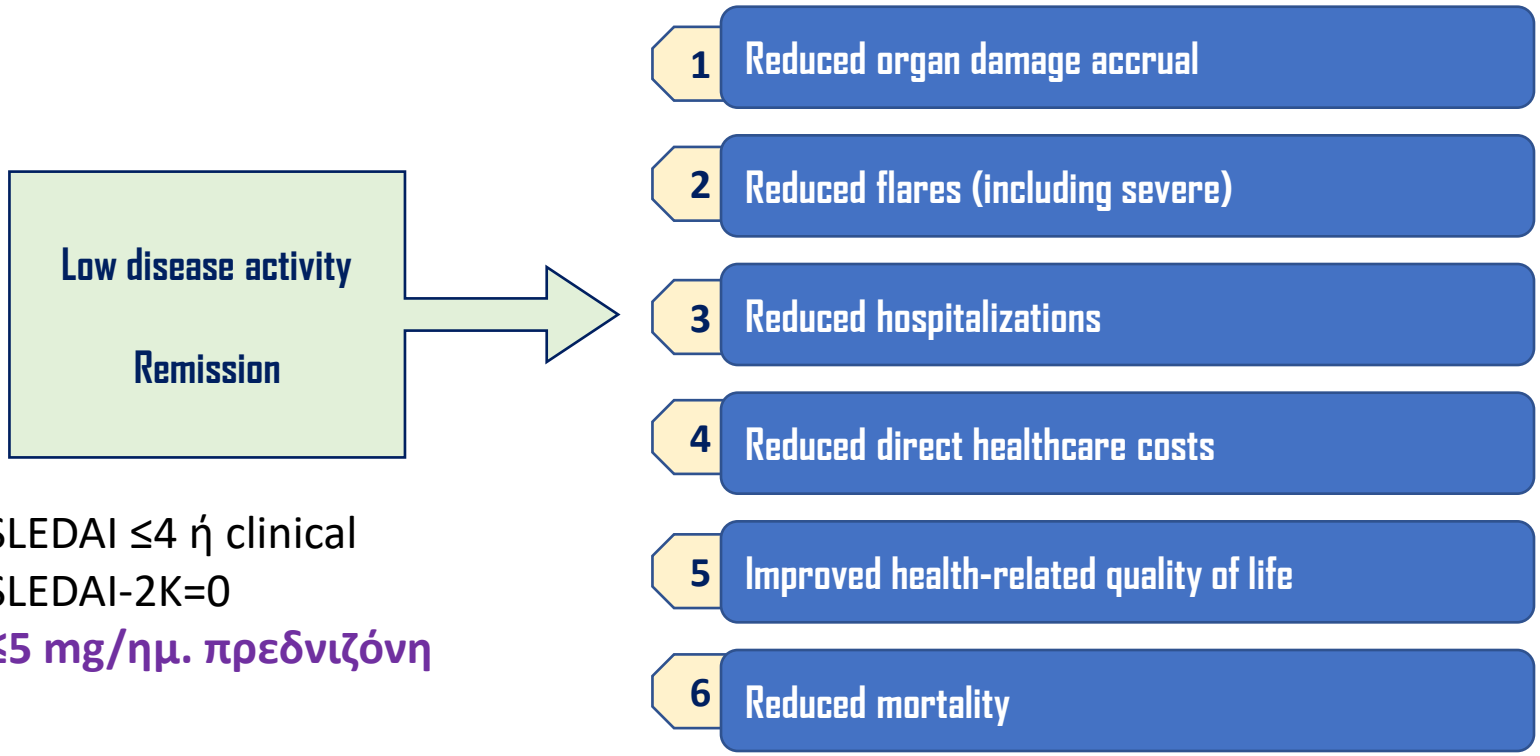


1) Kiani A, et al. *Rheumatology* 2013; **52**:1651–1657; 2) Mc Elhone, *et al. Lupus* 2006;15:633–643; 3) Thumboo J and Strand V. *Ann Acad Med Singapore* 2007; 36:115–122; 4) Jolly M. *J Rheumatol* 2005;32:1706-1708

Μπορούμε να παρέμβουμε στη φυσική πορεία του ΣΕΛ;

- ✓Στρατηγική
- ✓Φάρμακα

Attainment of theapeutic goals (remission, low disease activity) is linked to improved outcomes in patients with SLE



SLEDAI ≤4 ή clinical
SLEDAI-2K=0
≤5 mg/ημ. πρεδνιζόνη

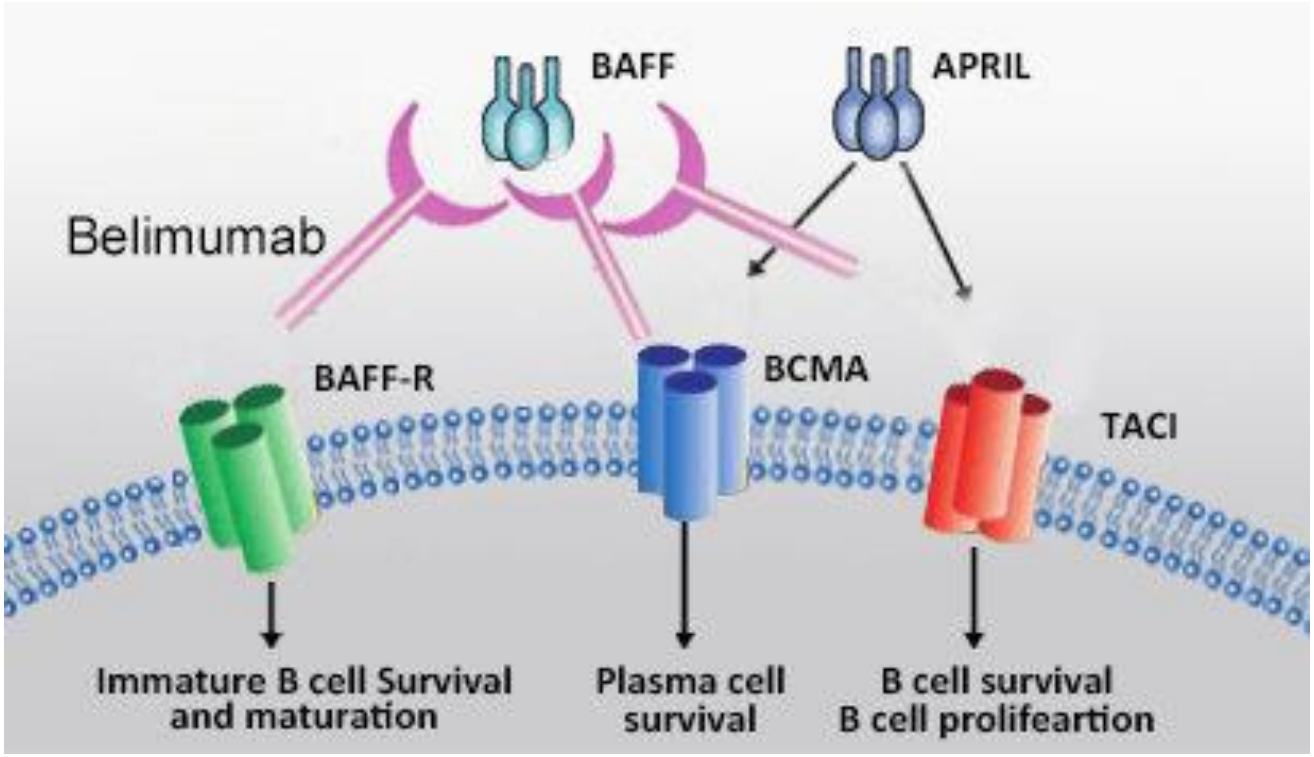
Yeo A-L, et al. *Arthritis Care Res*. 2019; doi: 10.1002/acr.24023; Zen M, et al. Ann Rheum Dis. 2015;74: 2117–2122; Zen M, et al. Ann Rheum Dis. 2017; 76: 562-565; Ugarte-Gil MF, et al. Lupus Sci Med. 2021; 8(1):e000542; Golver V, et al. Lancet Rheumatol. 2019; 1: e95–102; Golder V, et al. Lancet Rheumatol. 2019; 1: e103–10; Sharma C, et al. *Arthritis Care Res (Hoboken)*. 2020; 72: 447-51; Kandane-Rathnayake R*, et al. Lancet Rheumatol*. 2022; 4: e822–30; Petri M and Magder LS. *Arthritis Rheumatol*. 2018; 70: 1790-5

Targeted (biologic) therapies in SLE

- Tailored to the underlying pathophysiology of the disease
- Indicated as ‘add-on’ therapy especially for cases with **incomplete disease control under ‘standard-of-care’ treatment**

- **Belimumab** (anti-BAFF)
- **Anifrolumab** (anti-IFNAR)
- Rituximab, Obinutuzumab (B-cell depletion)
- Other treatments under development

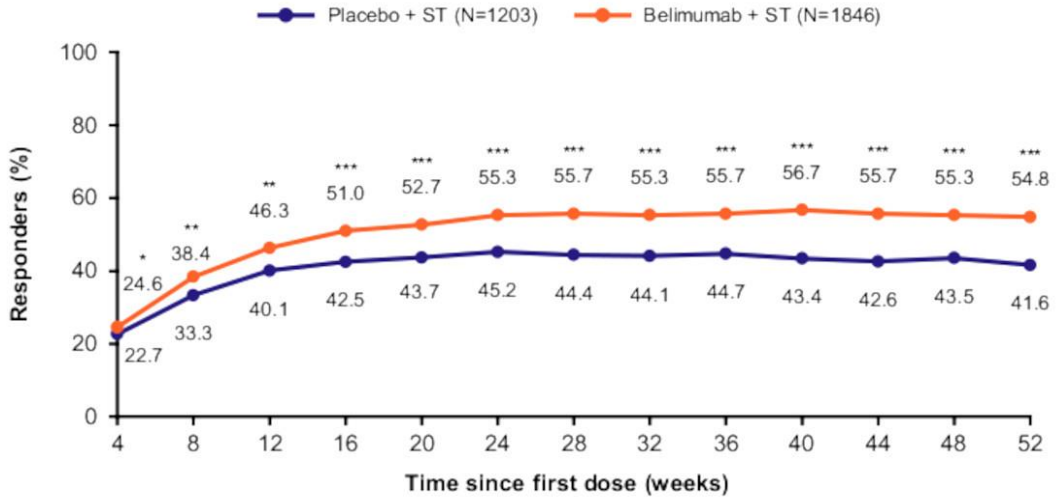
Belimumab (anti-BAFF mAb)



Αθροιστικά δεδομένα αποτελεσματικότητας από τις τυχαιοποιημένες κλινικές δοκιμές

(n=1217 SoC, n=1869 BEL+SoC)

Figure 2. SRI-4 response over 52 weeks in the overall population



Number of patients with SRI-4 response

	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo + ST	273	400	482	511	526	544	534	530	538	522	513	523	501
Belimumab + ST	454	709	855	942	972	1020	1028	1021	1029	1046	1028	1020	1011
OR (95% CI) vs placebo	1.11 (0.93, 1.32)	1.25 (1.07, 1.46)	1.30 (1.11, 1.51)	1.40 (1.20, 1.63)	1.44 (1.24, 1.68)	1.50 (1.29, 1.74)	1.56 (1.34, 1.81)	1.57 (1.35, 1.83)	1.54 (1.33, 1.80)	1.71 (1.46, 1.99)	1.69 (1.45, 1.96)	1.60 (1.38, 1.87)	1.70 (1.46, 1.98)

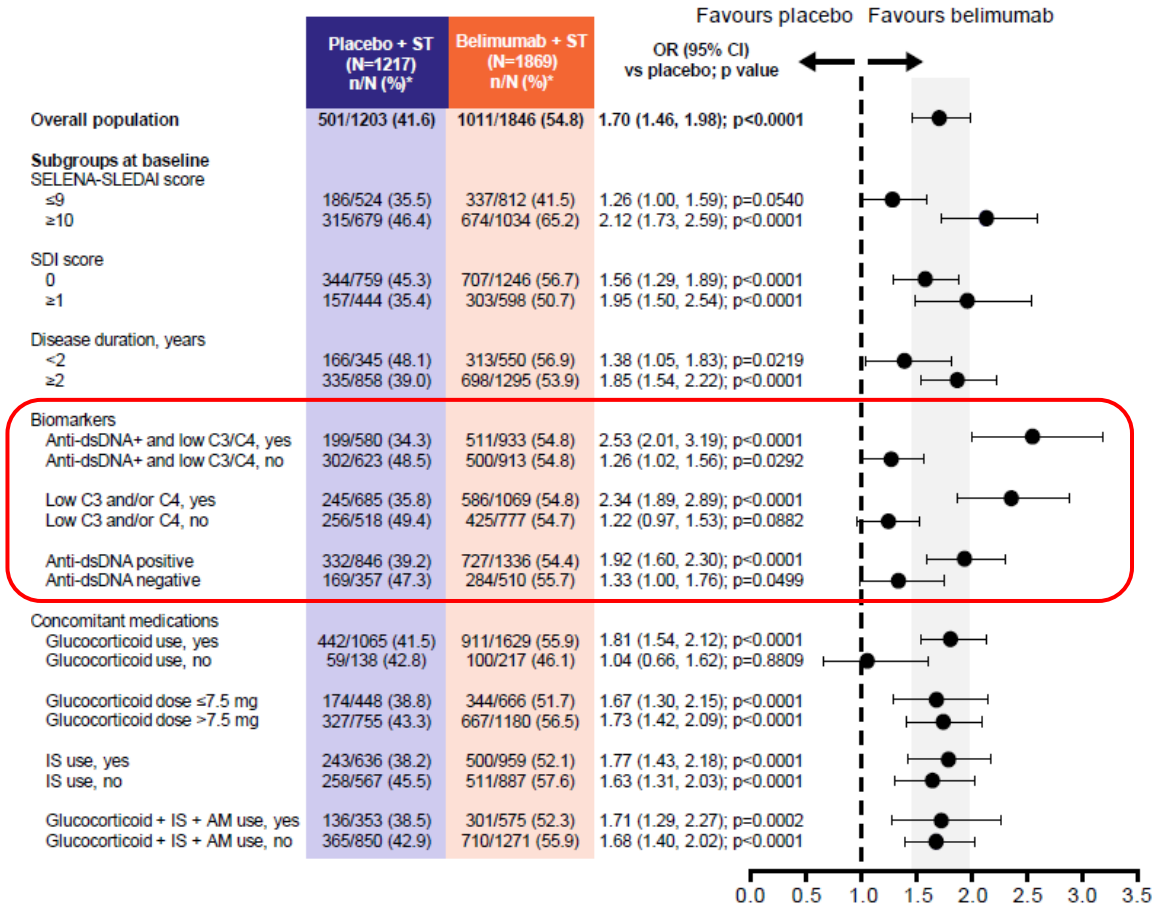
*p=0.2701; **p<0.01, ***p<0.0001.

Patients receiving belimumab were 52% more likely to experience sustained SRI-4 response (maintained through Week 52)

(hazard ratio [95% CI]: 1.52 [1.36, 1.69]; p<0.0001)

Petri M, et al. *Ann Rheum Dis.* 2022; 81 (Suppl 1): 323; DOI: 10.1136/annrheumdis-2022-eular.1807

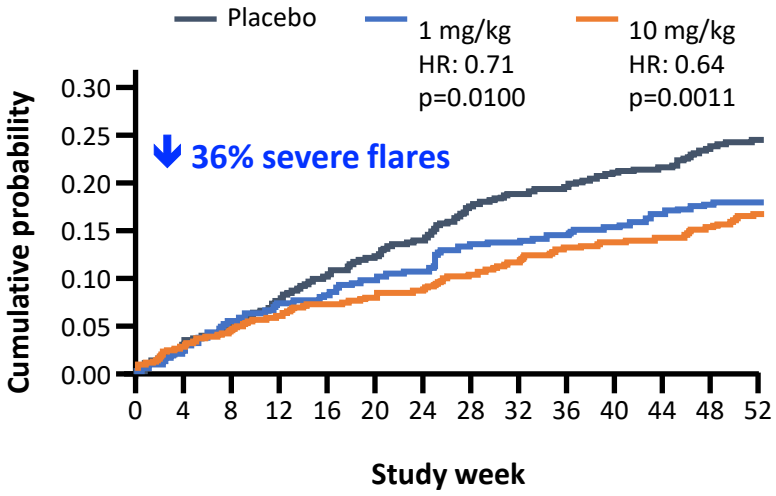
Αθροιστικά δεδομένα αποτελεσματικότητας από τις τυχαιοποιημένες κλινικές δοκιμές (n=1217 SoC, n=1869 BEL+SoC)



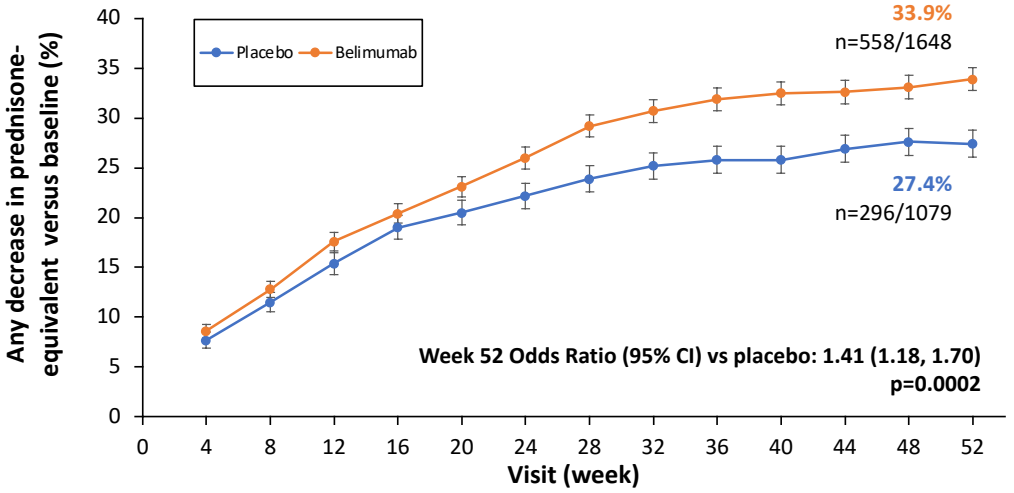
Petri M, et al. *Ann Rheum Dis.* 2022; 81 (Suppl 1): 323; DOI: 10.1136/annrheumdis-2022-eular.1807

Belimumab helps to stabilize SLE and reduce the need for glucocorticoids

Prevention of flares

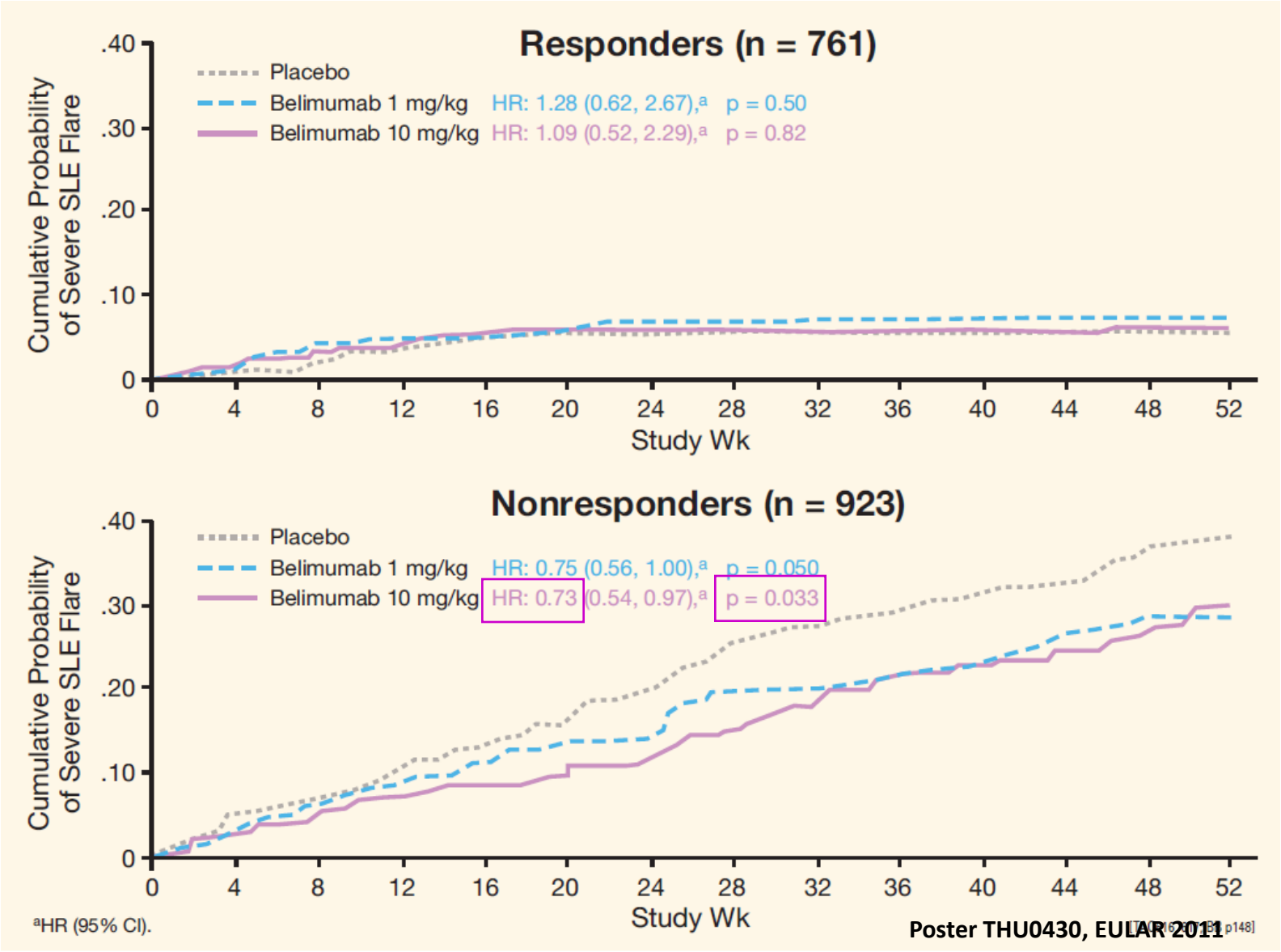


Reduction of glucocorticoids



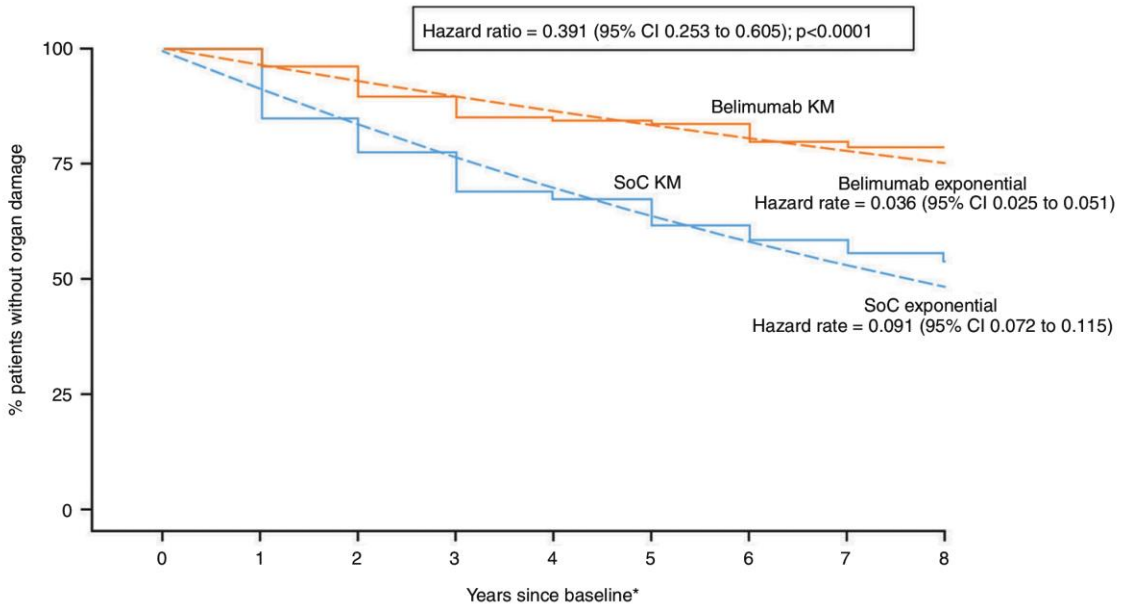
The risk for increasing the dose of GC was significantly lower in belimumab- vs. placebo-treated patients (HR 0.65; 0.52, 0.81, p=0.0001)

Belimumab reduces the risk for severe flare irrespective of improvement in disease activity



Poster THU0430, EULAR 2011

Πρόληψη ανάπτυξης βλάβης σε όργανα-στόχους σε ασθενείς ΣΕΛ υπό θεραπεία με belimumab



Total number of patients at risk at each time point

Belimumab	179	166	137	121	112	88	65	31	0
SoC	179	135	111	83	71	57	44	30	28

Figure 3 Difference in time to organ damage progression in patients with ≥1 year of follow-up.*Years are 48 weeks in length. KM, Kaplan-Meier; SLE, systemic lupus erythematosus; SoC, standard of care.

- **Data from the BLISS trials were compared against 'historical controls'** (propensity matching applied)
- **Patients treated with belimumab were 61% less likely to progress to a higher SDI score** over any given year of follow-up, compared with patients treated with SoC alone

Jrowitz MB, et al. *Ann Rheum Dis*. 2019;78:372–9
enhoven R, et al. *Rheumatology*. 2020; 59: 281-91
Jrowitz M, et al. *Lupus Sci Med*. 2020; 7: e000412

Effect of Belimumab on Preventing *de novo* Renal Lupus Flares

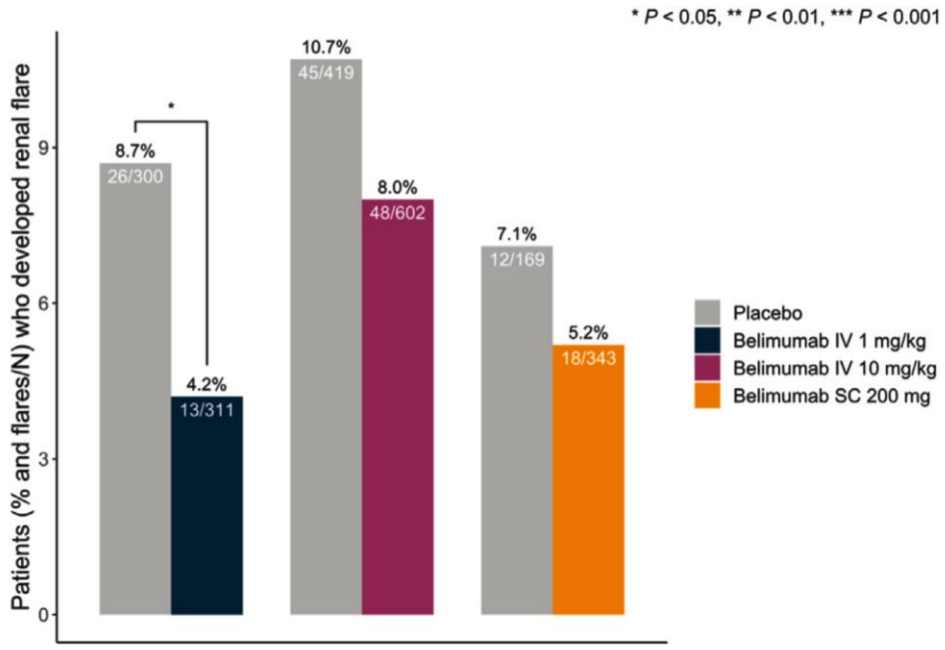


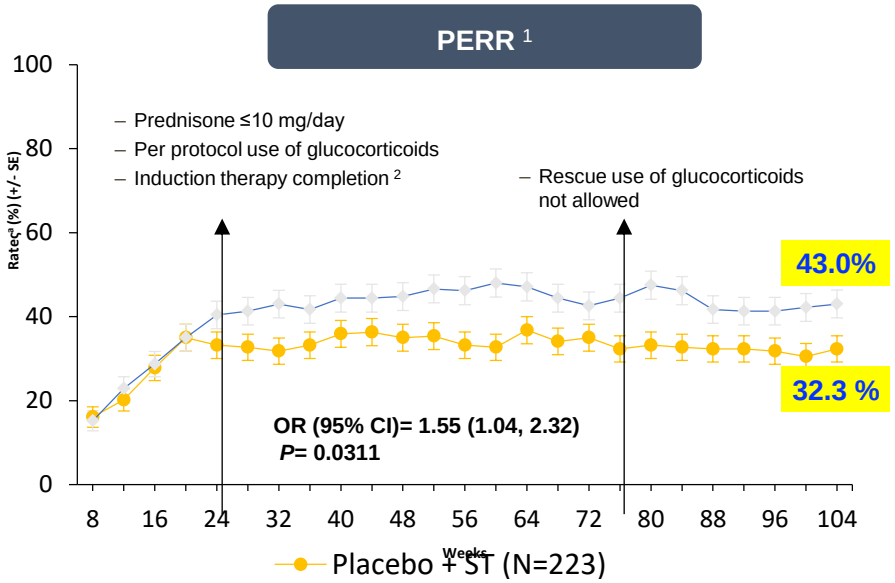
Figure 1. Renal flares in patient subgroups across belimumab dosage forms. Bars depicting proportions of patients who developed at least 1 *de novo* renal flare during follow-up in patient subgroups exposed to belimumab treatment of different dosage forms compared with patients from the same studies treated with placebo. IV, intravenous; SC, subcutaneous.

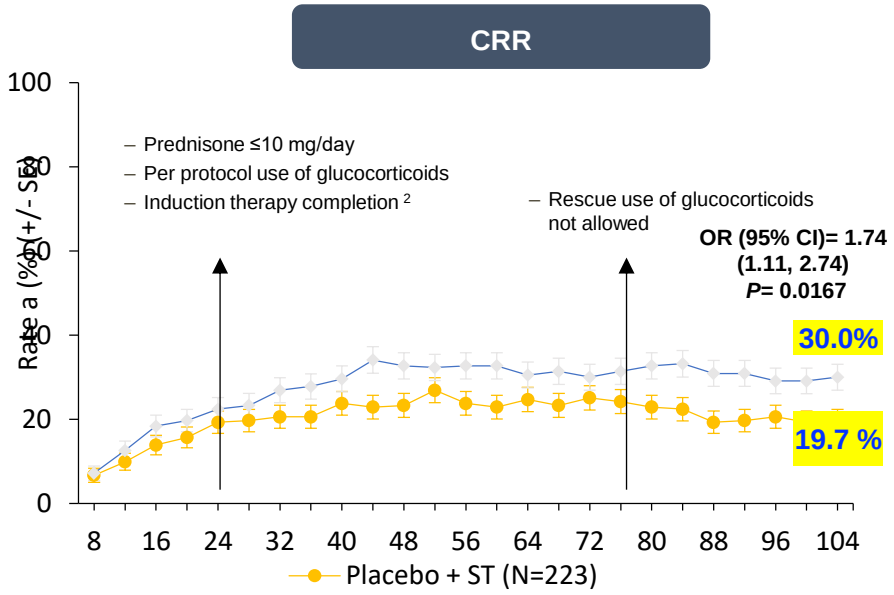
Kidney Int Rep (2023) 8, 1822–1830; https://doi.org/10.1016/j.ekir.2023.06.021

Μελέτη BLISS-LN: αποτελεσματικότητα του belimumab (add-on) στη ενεργό νεφρίτιδα λύκου

55% greater odds to meet the primary endpoint of renal response

74% greater odds to achieve complete renal response



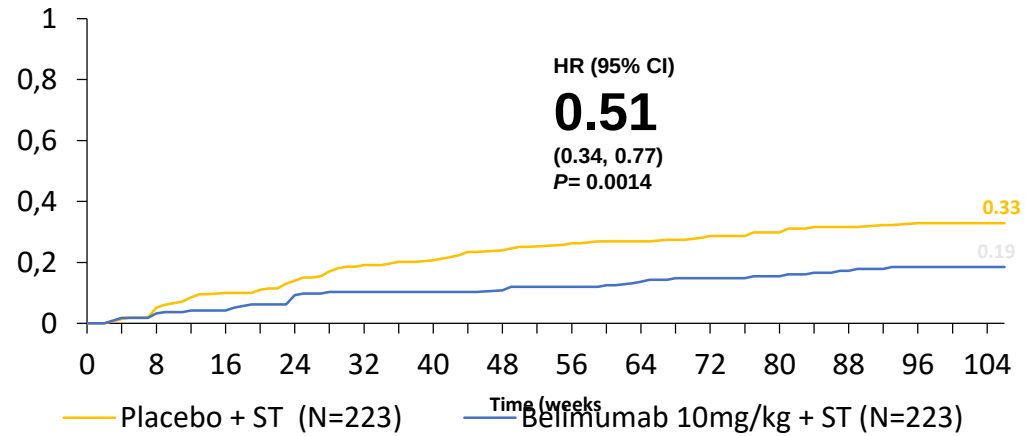


[a]Defined by response at the Week 100 visit that was confirmed by a repeat measurement at the Week 104 visit. PERR = uPCR ≤0.7; and eGFR ≥60mL/min/1.73m^2 or no more than 20% below pre-flare value; and not a treatment failure (no rescue therapy)

CI= confidence interval; IPD= investigational product discontinuation; IV= intravenous; mITT= modified intention to treat; NR= non responders; OR= odds ratio; PERR= primary efficacy renal response; ST= standard therapy; TF= treatment failure; WD= withdrawn

Furie R, et al.,. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180. PMID: 32937045

49% lower odds for renal adverse event or death in LN patients treated with belimumab versus SoC



No. patients at risk

Placebo + ST	203	185	175	154	147	137	129	126	120	116	112	110	78
Belimumab + ST	209	192	186	167	162	159	157	151	142	139	133	130	102

	Placebo + ST N=223	Belimumab 10mg/kg + ST N=223
Events [a], n	**63**	**35**
Renal worsening[b]	39	17
Treatment failure due to renal disease[c]	20	16
Doubling of serum creatinine	1	1
ESRD	1	0
Patient death	2	1

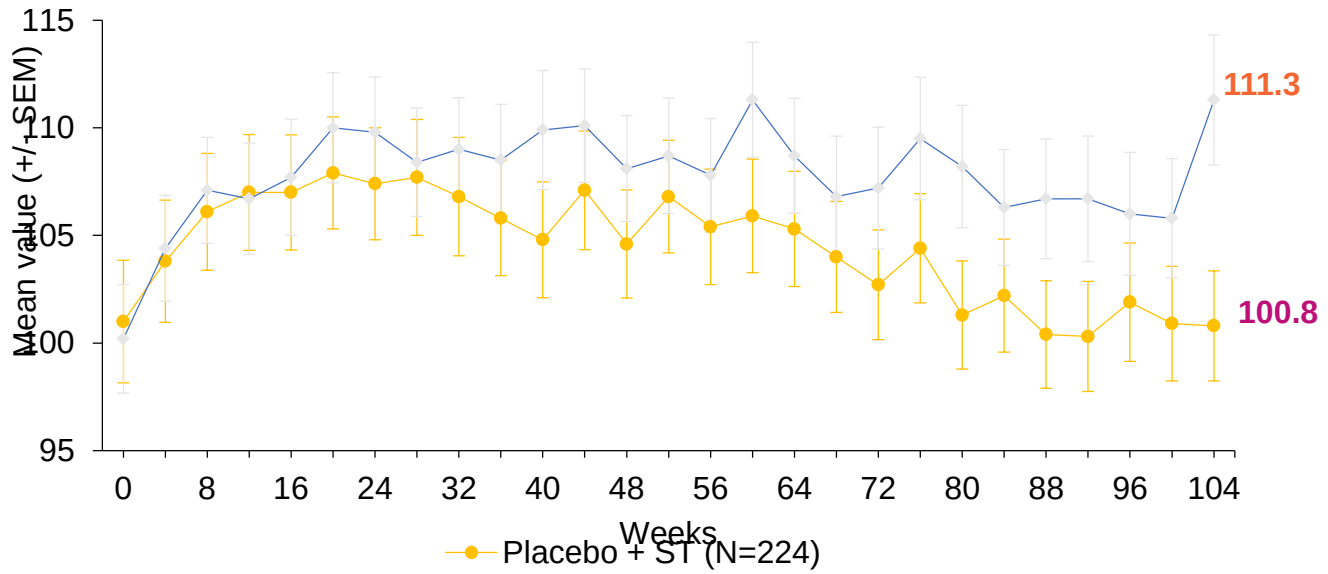
[a]First event for each patient with an event; [b]Defined by increased proteinuria (a reproducible increase in uPCR to >1g if the baseline value was <0.2g, to >2g if the baseline value was 0.2-1g, or more than twice the value at baseline if the baseline value was >1g), or impaired renal function (a reproducible decrease in GFR of >20%, accompanied by proteinuria >1g), and/or cellular [RBC/WBC] casts); [c]Based on adjudication of treatment failures; [d]Renal-related event is defined at any one of the following: end stage renal disease, doubling of serum creatinine, renal worsening from Baseline (increased proteinuria [reproducible increase in uPCR to >1g if baseline value <0.2g to >2g. if baseline value was 0.2-1g, or more than twice the baseline value if baseline value was >1g] and/or impaired renal function [reproducible decrease in GFR of >20%, accompanied by proteinuria >1g and/or cellular casts]), or renal disease related treatment failure

CI= confidence interval; ESRD= end-stage renal disease; GFR= glomerular filtration rate; HR= hazards ratio; ST= standard therapy; uPCR= urinary protein:creatinine ratio

Furie R, et al.,. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180. PMID: 32937045

Σταθεροποίηση του ρυθμού σπειραματικής διήθησης κατά τη διάρκεια θεραπείας με belimumab (+SoC) στη νεφρίτιδα ΣΕΛ

Average GFR was higher in belimumab-treated Lupus Nephritis patients



- Furie R, et al.,. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180. PMID: 32937045 appendix
- BSA= blood serum albumin; eGFR= estimated glomerular filtration ratio; IV= intravenous; SE= standard error; ST= standard therapy

Arthritis Care & Research
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DOI 10.1002/acr.23788

American College of Rheumatology
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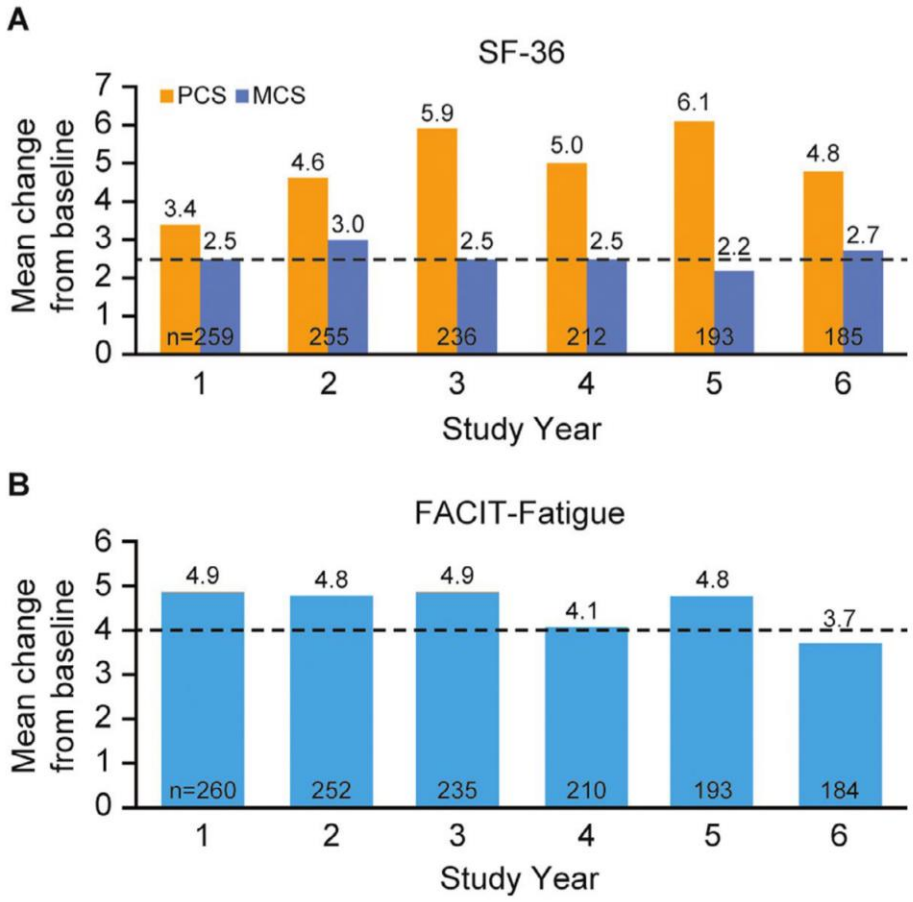
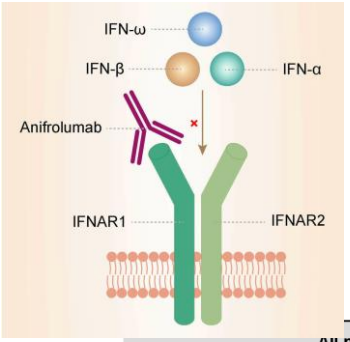
Long-Term Impact of Belimumab on Health-Related Quality of Life and Fatigue in Patients With Systemic Lupus Erythematosus: Six Years of Treatment





Anifrolumab (anti-IFNAR mAb) στο ΣΕΛ

Μελέτες TULIP-1 & -2

- 52% υπό κορτικοειδή ≥10 mg/day
- 48% υπό ανοσοκατασταλτικό
- 70% με SLEDAI-2K ≥10; 59% ανοσολογικά ενεργοί
- 28% με CLASI-I ≥10; 41% με TJC/SJC ≥6

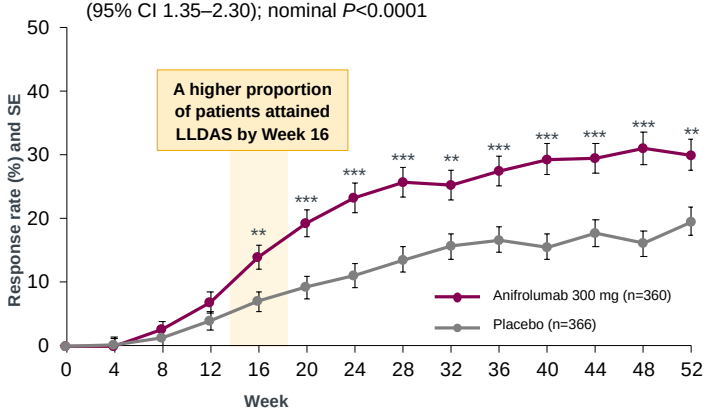
Σύνολο ασθενών | Ασθενείς με υψηλή IFNα

	All patients			IFNGS-high		
	Placebo (n=366)	Anifrolumab 300 mg (n=360)	Difference (95% CI), nominal p value*	Placebo (n=302)	Anifrolumab 300 mg (n=298)	Difference (95% CI), nominal p value*
End point	n/N (%)		Percentage points	n/N (%)		Percentage points
BICLA response, week 52	112/366 (30.8)	171/360 (47.5)	16.6 (9.7 to 23.6),<0.001	88/302 (29.4)	142/298 (47.6)	18.2 (10.5 to 25.8),<0.001
SRI(4) response, week 52	147/366 (40.1)	188/360 (52.2)	12.1 (4.9 to 19.3),<0.001	118/302 (39.0)	160/298 (53.7)	14.7 (6.8 to 22.6),<0.001
Sustained GC taper, weeks 40–52†	59/185 (31.8)	96/190 (50.5)	18.7 (8.9 to 28.4),<0.001	48/160 (30.1)	86/168 (51.2)	21.1 (10.7 to 31.5),<0.001
≥50% reduction in CLASI-A score, week 12‡	24/94 (24.9)	49/107 (46.0)	21.0 (8.1 to 34.0), 0.001	23/81 (27.9)	47/93 (50.5)	22.6 (8.4 to 36.9), 0.002
≥50% reduction in active (swollen and tender) joints, week 52§	71/190 (36.8)	81/164 (49.4)	12.6 (2.4 to 22.9), 0.016	61/157 (38.4)	64/129 (49.7)	11.3 (−0.2 to 22.8), 0.054
Annualised flare rate through week 52¶	0.67	0.51	0.75 (0.60 to 0.95), 0.017	0.77	0.54	0.70 (0.54 to 0.90), 0.005
FACIT-F response, week 52**	97/366 (26.5)	124/360 (34.3)	7.8 (1.0 to 14.5), NA	78/302 (25.9)	102/298 (34.1)	8.2 (0.8 to 15.6), 0.030
SF-36 MCS response, week 52††	75/366 (20.3)	96/360 (26.5)	6.1 (−0.1 to 12.4), NA	57/302 (18.7)	81/298 (26.9)	8.2 (1.4 to 15.0), 0.018
SF-36 PCS response, week 52‡‡	95/366 (26.1)	118/360 (32.8)	6.7 (0.0 to 13.5), NA	77/302 (25.7)	98/298 (33.0)	7.3 (−0.1 to 14.6), 0.053

Front Immunol. 2022; 13: 980079.
Ann Rheum Dis. 2022; 81:951–961

Επίτευξη χαμηλής ενεργότητας και μείωση υποτροπών υπό αγωγή με anifrolumab

Time to first LLDAS:[a] HR: 1.76
(95% CI 1.35–2.30); nominal *P*<0.0001

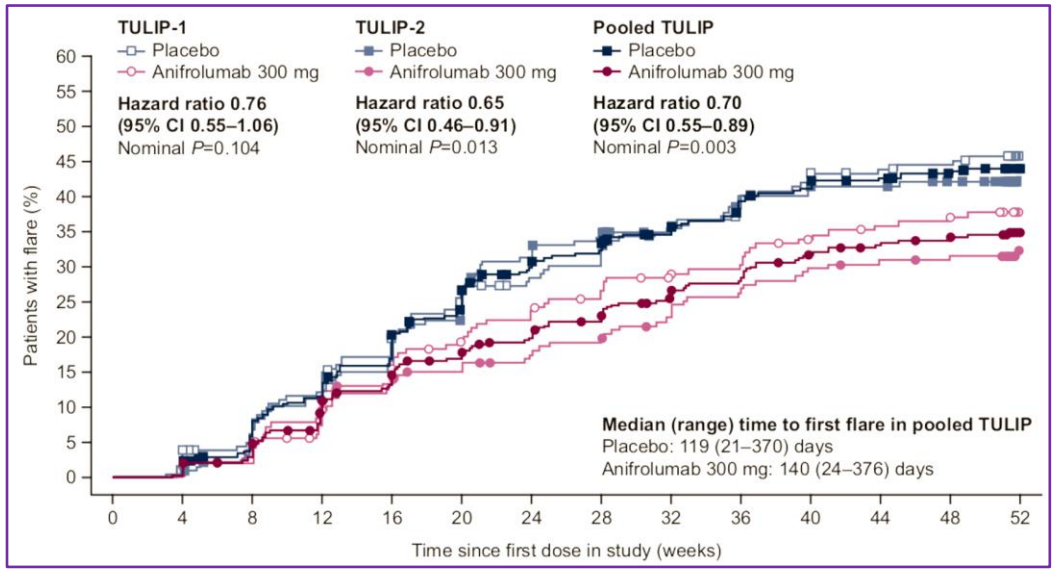


LLDAS attainment at Week 52:[b]
Odds ratio: 1.8 (95% CI 1.3–2.5)
nominal *P*=0.0011

Anifrolumab 300 mg
30.0% (108/360)

Placebo
19.6% (72/366)

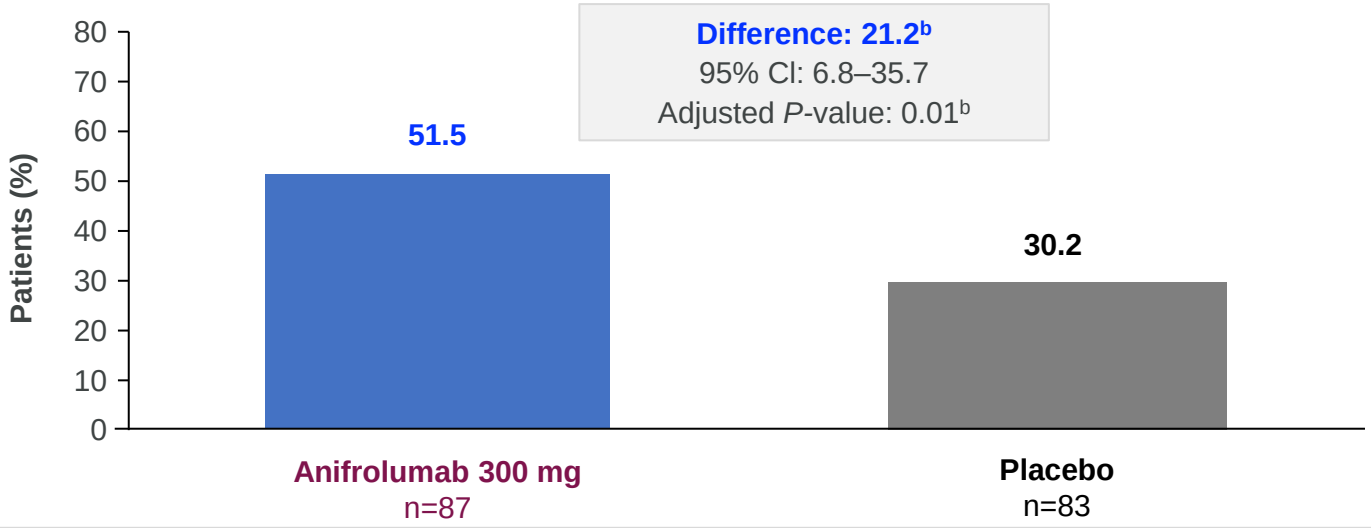
Annual flare rate:
0.43 (anifrolumab)
versus
0.63 (placebo)



Lupus. 2021; 30(8): 1254-1263

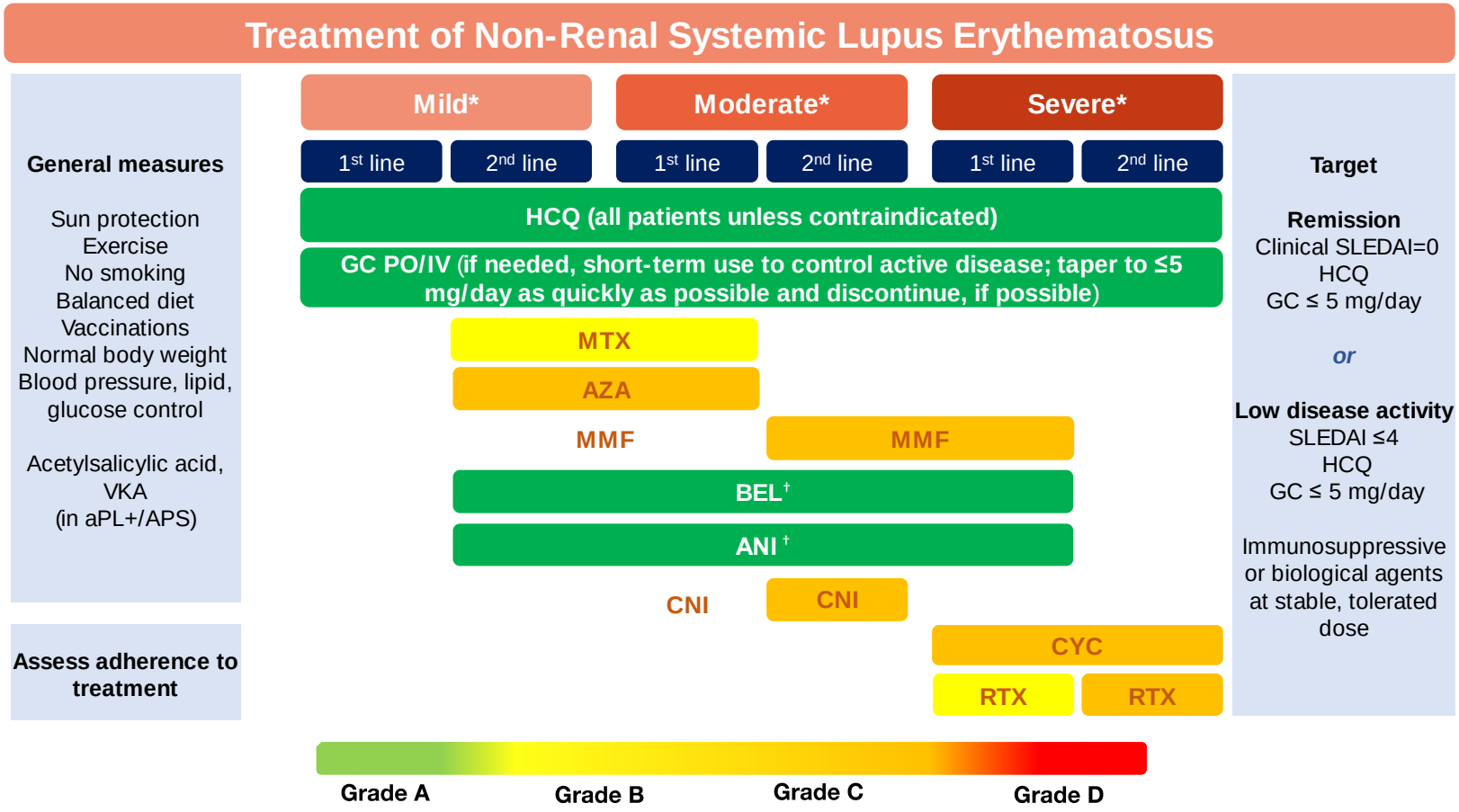
Sustained Glucocorticoid Dosage Reduction with Anifrolumab

Patients With a Sustained Dosage Reduction to ≤7.5 mg/day From W40–52[a]



CI, confidence interval; W, week. *P*-values were adjusted with the use of a weighted Holm procedure.
[a]Among patients receiving ≥10 mg/day of prednisone or equivalent at baseline; [b]Significant following multiplicity, using a stratified Cochran–Mantel–Haenszel method. *P*-values adjusted per weighted Holm procedure.
Morand EF, et al. *N Engl J Med*. 2020;382:211–21.

2023 Update of the EULAR SLE recommendations



"In patients not responding to hydroxychloroquine (alone or in combination with glucocorticoids) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents (for example methotrexate [1b/B], azathioprine 2b/C] or mycophenolate [2a/B]) and/or biologic agents (for example, belimumab [1a/A] or anifrolumab [1a/A]) should be considered."

Who might be the (best) candidates for treatment with biological agents?

- Patients with high clinical burden (ie, multiple involved organs, high disease activity or severity)
- Serologically active patients
- Patients requiring chronic treatment with glucocorticoids (inability to reduce <7.5 mg/day after 3-6 months)
- Early disease (i.e., within the first 2 since diagnosis/onset)
- Younger patients

Συμπεράσματα

- Η φυσική πορεία του ΣΕΛ συχνά περιπλέκεται με αρνητικές εκβάσεις τόσο για την ίδια τη νόσο όσο και τους ασθενείς
- Η βελτίωση της πρόγνωσης είναι εφικτή μέσω επίτευξης χαμηλής κλινικής ενεργότητας ή ύφεσης με χαμηλή δόση γλυκοκορτικοειδών (≤5 mg/ημ. πρεδνιζόνη)
- Νεότεροι βιολογικοί παράγοντες όπως το belimumab και το anifrolumab βοηθούν σημαντικά στην παραπάνω προσπάθεια
- Αυξανόμενα δεδομένα ευνοϊκού προφίλ ασφάλειας και αποτελεσματικότητας των βιολογικών παραγόντων δημιουργούν προϋποθέσεις για αλλαγή του «θεραπευτικού παραδείγματος» στο ΣΕΛ με την πρώιμη χρήση τους