Supplementary Table S1. Definitions of the treatment targets used in the current study

	Lupus Low Disease Activity State (LLDAS) [1]	**Definition of Remission in SLE (DORIS)** [2]
	All relevant criteria should be fulfilled	
Criterion 1	SLEDAI-2K [1] ≤4, with no activity in major organ systems (renal, neurological, cardiopulmonary, vasculitis, fever)	Clinical SLEDAI-2K [1] =0
Criterion 2	No new features of lupus disease activity compared with the previous assessment, defined as any new SLEDAI-2K component that was not present at the previous assessment.	n/a
Criterion 3	SELENA-SLEDAI physician global assessment ≤1 [2]	SELENA-SLEDAI physician global assessment <0.5 [2]
Criterion 4	Current prednisolone (or equivalent) dose ≤7.5 mg daily	Current prednisolone (or equivalent) dose ≤5 mg daily
Criterion 5	Standard maintenance doses of immunosuppressive drugs and approved biological agents [3]	Standard maintenance doses of immunosuppressive drugs and approved biological agents [3]

[1] SLE disease activity index-2000; [2] On a scale of 0 (no activity) to 3 (maximum activity); [3] Includes methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, rituximab and belimumab. Antimalarials are permitted.

Supplementary Table S2. Organ involvement in SLE patients (inclusion visit)

SLEDAI-2K item	N (%)
SLEDAI1 -Seizure	2 (0.6%)
SLEDAI2 -Psychosis	2 (0.6%)
SLEDAI3 -Confusion/altered mental status	0
SLEDAI4 -Optic neuritis / retinal exudate	3 (0.9%)
SLEDAI5 -Cranial neuropathy	8 (2.3%)
SLEDAI6 -Headache	0
SLEDAI7 -Cerebrovascular disease	6 (1.7%)
SLEDAI8 -Vasculitis	15 (4.3%)
SLEDAI9 -Arthritis	240 (69.4%)
SLEDAI10 -Myositis	1 (0.3%)
SLEDAI11 -Urine casts	16 (4.6%)
SLEDAI12 -Haematuria	30 (8.7%)
SLEDAI13 -Proteinuria	42 (12.1%)
SLEDAI14 -Pyuria	13 (3.8%)
SLEDAI15 -Inflammatory skin rash	185 (53.5%)
SLEDAI16 -Hair loss	76 (22.0%)
SLEDAI17 -Mucosal ulcers	11.6%
SLEDAI18 -Pleural effusion	16 (4.6%)
SLEDAI19 -Pericarditis	22 (6.4%)
SLEDAI20 -Low serum C3/C4	141 (40.8%)
SLEDAI21 -High serum anti-dsDNA	113 (32.7%)
SLEDAI22 -Fever	16 (4.6%)
SLEDAI23 -Thrombocytopenia	44 (12.7%)
SLEDAI24 -Leucopenia	26 (7.5%)

Supplementary Table S3. Risk for subsequent severe flare in LLDAS+/DORIS– compared to DORIS state (visit-by-visit analysis)

LLDAS+/DORIS– subgroup versus DORIS (reference)	**HR (95% CI) for subsequent severe flare** [1]		
Glucocorticoid dose	Basic model	Adjusted for clinical SLEDAI-2K	Adjusted for PGA
≤5 mg/day	**1.69 (1.02–2.80)** [a]	1.48 (0.82–2.68)	1.35 (0.80–2.28)
>5 mg/day	**1.97 (1.07–3.63)** [a]	1.74 (0.89–3.42)	1.65 (0.89–3.05)
Clinical SLEDAI-2K	Basic model	Adjusted for glucocorticoid dose	Adjusted for PGA
0	1.43 (0.76–2.72)	1.43 (0.75–2.71)	1.20 (0.63–2.28)
>0	**1.96 (1.19–3.28)** [b]	**1.95 (1.18–3.22)** [b]	1.58 (0.94–2.64)
PGA	Basic model	Adjusted for glucocorticoid dose	Adjusted for clinical SLEDAI-2K
<0.5	1.27 (0.37–4.29)	1.24 (0.37–4.24)	1.09 (0.31–3.84)
≥0.5	**1.82 (1.13–2.92)** [a]	**1.81 (1.13–2.91)** [a]	1.61 (0.92–2.81)

[1] Multiple-failures hazard models comparing subgroups of LLDAS+/DORIS– visits (according to glucocorticoid dose, clinical SLEDAI-2K, PGA) against DORIS visits (reference); the basic model included gender, age and follow-up duration as covariates, whereas additional models adjusted also for the effects of glucocorticoid dose, clinical SLEDAI-2K or PGA; [a] $p<0.05$; [b] $p<0.01$; HR, hazard ratio; 95% CI, 95% confidence interval; PGA, SELENA-SLEDAI Physician Global Assessment; SLEDAI-2K, SLE disease activity index 2000; DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State

Supplementary Table S4. Effect of DORIS and LLDAS attainment (% of cumulative time) against the risk for organ damage accrual and severe flares

	Organ damage accrual [1]		**Severe flares** [2]	
	RR (95% CI)	Z-statistic	RR (95% CI)	Z-statistic
Model A [3]				
DORIS	0.992 (0.987–0.997)	-3.01 (p=0.003)	0.984 (0.980–0.989)	-7.16 (p<0.001)
LLDAS exclusive DORIS	0.994 (0.988–0.999)	-2.02 (p=0.044)	0.993 (0.989–0.996)	-4.05 (p<0.001)
Model B [4]				
LLDAS inclusive DORIS	0.993 (0.989–0.997)	-3.32 (p=0.001)	0.989 (0.986–0.991)	-8.86 (p<0.001)

[1] Cumulative increase in SDI during the observation period; [2] Number of severe flares during the observation period; [3] Generalized linear model (GLM; negative binomial) using both DORIS (per 1%-time unit) and LLDAS exclusive DORIS (per 1%-time unit) as predictors. Additional variables included in the model were gender, age at inclusion, disease duration, baseline SLEDAI-2K, duration of follow-up; [4] GLM using LLDAS (per 1%-time unit) as predictors. Additional variables included in the model were gender, age at inclusion, disease duration, baseline SLEDAI-2K, duration of follow-up. RR, risk ratio; 95% CI, 95% confidence interval; DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State

Supplementary Table S5. Frequency of SLE patients in remission (DORIS) and low disease activity (LLDAS) who accrued or not organ damage and severe flares

	Organ damage accrual (≥1-point increase in SDI)		**Severe flare(s)** (≥1 incident)	
	No	**Yes**	**No**	**Yes**
SLE patients in DORIS				
Ever attainment [1]	152 (70.7%)	63 (29.3%)	174 (80.9%)	41 (19.1%)
≥30% of time [2]	98 (75.4%)	32 (24.6%)	119 (91.5%)	11 (8.5%)
≥40% of time	80 (77.7%)	23 (22.3%)	97 (94.2%)	6 (5.8%)
≥50% of time	65 (81.3%)	15 (18.8%)	78 (97.5%)	2 (2.5%)
≥60% of time	45 (81.8%)	10 (18.2%)	54 (98.2%)	1 (1.8%)
≥70% of time	28 (84.8%)	5 (15.2%)	33 (100.0%)	0 (0.0%
SLE patients in LLDAS				
Ever attainment	224 (69.3%)	99 (30.7%)	235 (72.8%)	88 (27.2%)
≥30% of time	180 (70.6%)	75 (29.4%)	206 (80.8%)	49 (19.2%)
≥40% of time	160 (72.4%)	61 (27.6%)	193 (87.3%)	28 (12.7%)
≥50% of time	145 (74.4%)	50 (25.6%)	173 (88.7%)	22 (11.3%)
≥60% of time	115 (79.9%)	29 (20.1%)	135 (93.8%)	9 (6.3%)
≥70% of time	85 (85.0%)	15 (15.0%)	98 (98.0%)	2 (2.0%)

[1] Attainment on at least one visit; [2] Proportion of follow-up time in the corresponding target; DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State

Supplementary Table S6. Comparison between durable attainment of remission (DORIS) and of low disease activity (LLDAS) against the risk for organ damage accrual and severe flares

		Organ damage accrual		**Severe flare**	
Comparator group	*Reference group*	RR (95% CI)	P value	RR (95% CI)	P value
LLDAS^{+}/DORIS^{-} ≥24 months	DORIS^{+} ≥24 months	1.31 (0.82–2.11)	0.261	2.06 (1.22–3.49)	0.007
LLDAS^{+}/DORIS^{-} ≥50% time	DORIS^{+} ≥50% time	1.29 (0.83–2.00)	0.263	2.32 (1.48–3.64)	<0.001

Generalized linear model (negative binomial) including gender, age at inclusion, duration of follow-up as covariates; outcomes included the cumulative: a) increase in SDI, and b) sever flares during the follow-up period; RR, risk ratio; 95% CI, 95% confidence interval; DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State

Supplementary Table S7. Operational characteristics of different cut-offs of time exposure (percentage of total observation period) in each treatment target against organ damage accrual in SLE patients with active moderate-to-severe disease

	Frequency[1]	GLM model fit[2]		Classification metrics[3]		
		AIC	BIC	Sensitivity	Specificity	Sum
DORIS						
≥30%	37.6%	721.44	729.14	0.4242	0.6832	1.1074
≥40%	29.9%	714.21	721.91	0.3463	0.7723	1.1186
≥50% *	23.3%	714.09	721.79	0.2814	0.8515	1.1329
≥60%	15.8%	712.53	720.24	0.1948	0.9010	1.0958
≥70%	9.5%	713.96	721.66	0.1212	0.9505	1.0717
LLDAS						
≥30%	73.3%	723.61	731.32	0.7403	0.2772	1.0175
≥40%	63.2%	720.08	727.79	0.6580	0.4158	1.0739
≥50%	55.7%	716.14	723.84	0.5931	0.5248	1.1178
≥60% *	41.7%	701.90	709.61	0.4848	0.7327	1.2175
≥70%	29.0%	701.37	709.08	0.3636	0.8515	1.2151

[1] Proportion (%) of cohort who meet each definition; [2] Information criteria (Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC] obtained from the generalized linear model (GLM) treating organ damage accrual as dependent variable and each target cut-off as predictor; [3] Obtained from 2×2 contingency tables of favourable outcome (free or not of new organ damage) by each target cut-off. Asterisk (*) denotes the selected target cut-off based on optimal combination of feasibility (frequency), model fit and combined sensitivity and specificity. DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State

Supplementary Table S8. Operational characteristics of different cut-offs of exposure (months of sustained attainment) in each treatment target against organ damage accrual in SLE patients with active moderate-to-severe disease

	Frequency[1]	GLM model fit [2]		Classification metrics [3]		
		AIC	BIC	Sensitivity	Specificity	Sum
DORIS						
≥9 months	39.3%	686.08	693.62	0.4208	0.6634	1.0842
≥12 months	35.8%	687.09	694.63	0.3846	0.6931	1.0777
≥18 months	27.7%	682.91	690.45	0.3077	0.7822	1.0899
≥24 months *	20.2%	680.25	687.79	0.2353	0.8614	1.0967
≥30 months	15.3%	684.00	691.55	0.1719	0.8812	1.0531
≥36 months	10.9%	679.98	687.52	0.1312	0.9307	1.0619
LLDAS						
≥12 months	66.4%	689.34	696.88	0.6847	0.3861	1.0708
≥15 months	62.3%	688.19	695.73	0.6471	0.4356	1.0827
≥18 months	56.1%	682.90	690.44	0.5928	0.5149	1.1076
≥24 months	45.5%	683.66	691.20	0.4887	0.6238	1.1125
≥30 months	35.8%	684.23	691.77	0.3937	0.7228	1.1164
≥36 months *	28.0%	678.91	686.46	0.3213	0.8119	1.1331
≥42 months	19.3%	683.24	690.78	0.2262	0.8812	1.1074

[1] Proportion (%) of cohort who meet each definition; [2] Information criteria (Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC] obtained from the generalized linear model (GLM) treating organ damage accrual as dependent variable and each target cut-off as predictor; [3] Obtained from 2×2 contingency tables of favourable outcome (free or not of new organ damage) by each target cut-off. Asterisk (*) denotes the selected target cut-off based on optimal combination of feasibility (frequency), model fit and combined sensitivity and specificity. DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State

Supplementary Table S9. Sustained attainment of DORIS ≥24 months and LLDAS ≥36 months is associated with significant reduction in the risk for adverse events in patients with SLE

Adverse event	Incidence rate ratio [2] (95% CI)	P value
All adverse events		
DORIS ≥24 months *vs*. <24 months	0.79 (0.71–0.85)	<0.001
LLDAS ≥36 months *vs*. <36 months	0.89 (0.85–0.93)	<0.001
Serious adverse events but not fatal		
DORIS ≥24 months *vs*. <24 months	0.61 (0.44–0.84)	0.003
LLDAS ≥36 months *vs*. <36 months	0.67 (0.54–0.83)	<0.001
Serious adverse events requiring hospitalization		
DORIS ≥24 months *vs*. <24 months	0.66 (0.49–0.88)	0.005
LLDAS ≥36 months *vs*. <36 months	0.70 (0.56–0.87)	0.002
Death		
DORIS ≥24 months *vs*. <24 months	– [2]	–
LLDAS ≥36 months *vs*. <36 months	0.20 (0.02–2.53)	0.212

Adverse events during follow-up were classified according to the CTCAE system. [1] Obtained from generalized linear model adjusting for the effects of age, gender, age and disease duration; [2] Cannot be estimated; DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State

Supplementary Table S10. Estimates of cumulative organ damage accrual and severe flares across the three patient clusters

	Organ damage accrual (delta-SDI per patient-year)				
	Crude estimates		Adjusted estimates[1]		
Cluster	Mean (SEM)	ANOVA	Mean (SEM)	95% CI	Wald test
1	0.086 (0.028)		0.095 (0.026)	0.043–0.146	
2	0.136 (0.022)	p=0.297	0.136 (0.019)	0.099–0.173	p=0.325
3	0.110 (0.017)		0.103 (0.021)	0.062–0.144	
	Severe flares (no. events per patient-year)				
	Crude estimates		Adjusted estimates[1]		
Cluster	Mean (SEM)	ANOVA	Mean (SEM)	95% CI	Wald test
1	0.220 (0.044)		0.184 (0.039)	0.107–0.260	
2	0.149 (0.022)	p<0.001	0.155 (0.028)	0.100–0.210	p<0.001 [2]
3	0.352 (0.030)		0.371 (0.031)	0.311–0.431	

[1] Generalized linear model adjusting for the effects of sex, age and duration of follow-up; [2] post-hoc pairwise Sidak test revealed significant difference between Cluster 3 and Cluster 2 (p<0.001) and between Cluster 3 and Cluster 1 (p=0.001); SEM, standard error of the mean; ANOVA, analysis of variance

Supplementary Table S11. Accrued organ damage in the study sample of SLE patients with active moderate-to-severe disease

	Cluster 1	Cluster 2	Cluster 3	All patients	
	n	n	n	n	
1. Cataract	3	7	7	17	10.5%
2. Retinal change or optic atrophy	0	2	2	4	2.5%
3. Cognitive impairment or major psychosis	1	4	5	10	6.2%
4. Seizures requiring therapy for ≥6 months	0	1	1	2	1.2%
5. Cerebrovascular Accident	1	3	3	7	4.3%
6. Cranial/Peripheral Neuropathy (excluding optic)	1	4	5	10	6.2%
7. Transverse Myelitis	0	2	0	2	1.2%
8. Estimated or Measured GFR <50%	1	3	0	4	2.5%
9. Proteinuria ≥3.5 g/24 hours	1	1	0	2	1.2%
10. End-stage renal disease	0	0	0	0	0.0%
11. Pulmonary Hypertension	1	1	1	3	1.9%
12. Pulmonary Fibrosis (clinical or radiographic)	0	1	1	2	1.2%
13. Shrinking Lung (radiographic)	0	0	0	0	0.0%
14. Pleural Fibrosis (radiographic)	0	0	0	0	0.0%
15. Pulmonary Infarction (radiographic)	0	1	0	1	0.6%
16. Angina or Coronary Artery Bypass	0	2	1	3	1.9%
17. Myocardial Infarction	1	2	0	3	1.9%
18. Cardiomyopathy (left ventricular dysfunction)	0	1	2	3	1.9%
19. Valvular disease (murmur >3/6)	1	6	2	9	5.6%
20. Pericarditis for ≥6 months or pericardiectomy	0	2	1	3	1.9%
21. Claudication for ≥6 months	1	1	0	2	1.2%
22. Minor tssue loss - peripheral vasc. disease	1	0	0	1	0.6%
23. Significant tssue loss - peripheral vasc. disease	0	0	0	0	0.0%
24. Venous Thrombosis with complications	1	0	1	2	1.2%
25. Infarction or resection of bowel/GI, spleen	3	3	2	8	4.9%
26. Mesenteric Insufficiency	0	0	0	0	0.0%
27. Chronic Peritonitis	0	0	0	0	0.0%
28. Stricture or Upper GI tract surgery	0	1	0	1	0.6%
29. Chronic Pancreatitis	0	0	0	0	0.0%
30. Muscle Atrophy or Weakness	1	5	2	8	4.9%
31. Deforming or erosive arthritis	1	1	2	4	2.5%
32. Osteoporosis with fracture or vertebral collapse	1	4	4	9	5.6%
33. Avascular Necrosis	0	0	2	2	1.2%
34. Osteomyelitis	0	1	0	1	0.6%
35. Tendon rupture	1	3	4	8	4.9%
36. Scarring Chronic Alopecia	1	1	3	5	3.1%
37. Scarring of panniculum (not scalp, pulp space)	0	1	2	3	1.9%
38. Skin ulceration (excl. thrombosis) ≥6 months	0	1	0	1	0.6%
39. Premature Gonadal Failure	1	2	1	4	2.5%
40. Diabetes (regardless of therapy)	1	4	4	9	5.6%
41. Malignancy (except dysplasia)	2	2	5	9	5.6%

Supplementary Table S12. Use of lupus treatments according to actively involved organs/domains (analysis of all visits)

	Antimalarials			Leflunomide			Methotrexate			Ciclosporin			Azathioprine			Mycophenolate			CYC			IVIG		Rituximab			Belimumab		
SLEDAI items	N			N			N			N			N			N			N			N		N			N		
Neurological	44	67.7%	*	0	0.0%		11	16.9%		0	0.0%		11	16.9%		10	15.4%		14	21.5%	***	0	0.0%	5	7.7%		5	7.7%	
Vasculitis	44	74.6%		0	0.0%		7	11.9%	*	17	28.8%	***	10	16.9%		8	13.6%		0	0.0%		2	3.4%	3	5.1%		13	22.0%	**
Arthritis	1137	80.9%		95	6.8%	***	498	35.4%	***	30	2.1%	***	286	20.3%	**	100	7.1%	***	49	3.5%		4	0.3%	77	5.5%	**	159	11.3%	
Myositis	8	57.1%	*	0	0.0%		1	7.1%		1	7.1%		2	14.3%		6	42.9%	**	1	7.1%		0	0.0%	0	0.0%		2	14.3%	
Renal	194	78.5%		1	0.4%	**	11	4.5%	***	11	4.5%		49	19.8%		96	38.9%	***	38	15.4%	***	0	0.0%	12	4.9%		10	4.0%	***
Rash	842	82.1%		53	5.2%	*	292	28.5%	***	36	3.5%		240	23.4%		96	9.4%	***	41	4.0%		2	0.2%	53	5.2%		112	10.9%	
Hair loss	354	84.5%	*	16	3.8%		99	23.6%		19	4.5%		128	30.5%	***	33	7.9%	***	11	2.6%		3	0.7%	19	4.5%		60	14.3%	
Ulcers	195	83.0%		10	4.3%		70	29.8%		7	3.0%		53	22.6%		10	4.3%	***	6	2.6%		0	0.0%	9	3.8%		39	16.6%	*
Serositis	51	76.1%		1	1.5%		10	14.9%		1	1.5%		15	22.4%		9	13.4%		5	7.5%		0	0.0%	0	0.0%		9	13.4%	
Low C3/C4	550	74.9%	***	4	0.5%	***	104	14.2%	***	41	5.6%	**	171	23.3%		160	21.8%	***	29	4.0%		4	0.5%	29	4.0%		129	17.6%	***
Anti-DNA	512	78.6%		6	0.9%	***	82	12.6%	***	25	3.8%		141	21.7%		161	24.7%	***	24	3.7%		3	0.5%	22	3.4%		126	19.4%	***
Fever	24	70.6%		0	0.0%		9	26.5%		1	2.9%		7	20.6%		2	5.9%		0	0.0%		0	0.0%	1	2.9%		5	14.7%	
Thromb/penia	139	78.5%		2	1.1%	*	25	14.1%	**	17	9.6%	***	38	21.5%		31	17.5%		17	9.6%	**	6	3.4%	18	10.2%	***	14	7.9%	
Leukopenia	113	80.1%		1	0.7%	*	24	17.0%	*	14	9.9%	***	37	26.2%		18	12.8%		4	2.8%		0	0.0%	8	5.7%		25	17.7%	*

For each SLEDAI-2K item(s), data represent the number (%) of visit where each treatment was used. Asterisks denote statistically significant differences as compared to the use of each medication in visits without the particular SLEDAI-2K item(s) (*p<0.05; **p<0.01; ***p<0.001). CYC, cyclophosphamide; IVIG, intravenous immunoglobulin

References

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