Emerging Treatments for Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that may affect different organs or organ systems with variable severity. SLE is characterized by a fluctuating course, with periods of flares and periods of remission. Symptoms vary widely but commonly include fatigue, fever, joint pain, non-scarring alopecia, and symptoms associated with organ damage, particularly to the kidneys.

The global prevalence of SLE is estimated of approximately 3.4 million people and the newly diagnosed population is estimated to be 400.000 people annually. SLE predominantly affects women, particularly those of childbearing age. Predisposing factors trigger pathogenic mechanisms mainly driven by activation of Toll-like receptors and type I interferon signalling in the innate immune system and activation of T and B cells in the adaptive immune system.

Successful management of SLE requires an early diagnosis, vigilant monitoring for new organ involvement such as lupus nephritis, and a potentially disease modifying treatment targeting remission as defined by the '*Definition of Remission in SLE*' (DORIS) criteria. Achieving a low disease activity as defined by the '*Lupus Low Disease Activity State*' (LLDAS) can be an alternative treatment target. Although hydroxychloroquine and belimumab have already demonstrated disease modifying actions in non-renal SLE as part of standard-of-care therapy, therapies providing durable clinical responses without requiring chronic immunosuppressive drugs are still lacking. Novel therapeutic approaches include monoclonal antibodies with dual action such as ianalumab and obinutzumab and chimeric antigen receptor T cells (CAR-T cells) such as resecabtagene autoleucel; both targeting B cell receptors or proteins involved in B cell activation with the aim to provide a deep B cell depletion. Whether these investigational therapies can achieve durable drug-free responses is currently evaluated in clinical trials in patients with moderately to severely active SLE with or without lupus nephritis.

Charité Research Organisation GmbH has long-standing experience in implementing early-stage projects for new SLE drugs. In this Whitepaper, we provide an overview of novel therapeutic approaches for SLE with or without kidney disease that may potentially lead to complete remission. Another focus is laid on research into precise diagnostic tools using proteomics, individual responder assessment, and digital integration supported by artificial intelligence (AI) that are increasingly providing new insights into the pathogenetic nature of non-renal SLE and Lupus Nephritis.

Introduction

Clinical characteristics

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease affecting different organs or organ systems with variable severity resulting in heterogeneous phenotypes. SLE is caused by overreacting immune system erroneously producing antibodies that attack the body itself leading to organ damage and inflammatory reactions. Unlike other forms of lupus, SLE can affect nearly any organ and organ system in the body.

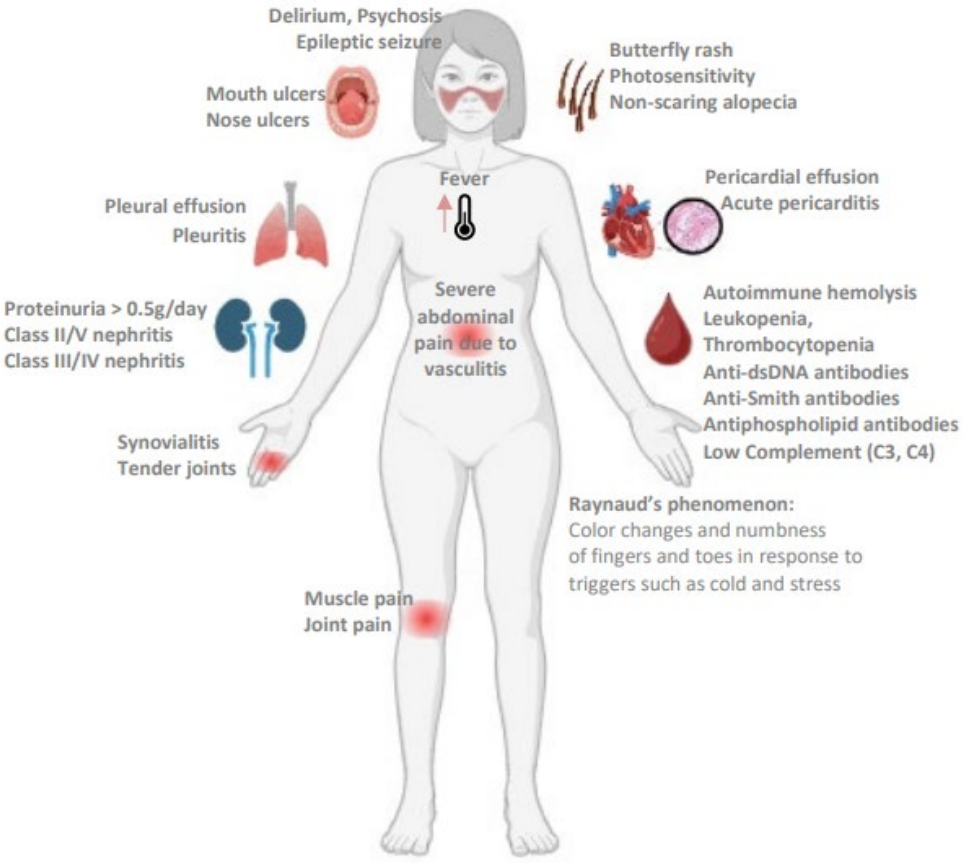


Figure 1. Common signs and symptoms of Systemic Lupus Erythematosus
Created with BioRender

SLE is a chronic disease characterized by fluctuating periods of flares, low disease activity and remission. Periods of flares often severely impair the quality of life and participation of those affected. Symptoms vary widely but commonly include fatigue, fever, joint pain, butterfly-shaped (malar) rash, and symptoms associated with organ damage, particularly to the kidneys, heart, and central nervous system. It can also lead to the destruction of cells in the hematopoietic system such as red blood cells or platelets (**Figure 1**). In 1997, the American College of Rheumatology (ACR) agreed upon 11 indexes required to define SLE: malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, serositis (pleuritis or pericarditis), renal disorder, neurological disorder, haematological syndrome, immunological evidence, and positive anti-nuclear antibodies (ANA) [Hochberg et al., 1997]. In 2019, new

classification criteria for SLE have been defined by the European League Against Rheumatism (EULAR) and the ACR namely with fever, autoimmune haemolysis, non-scarring alopecia, low complement levels of C3 and/or C4 being included, and malar rash and photosensitivity being removed [Aringer et al., 2019] (**Table 1**).

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Table 1. Classification criteria for systemic lupus erythematosus.
§Additional criteria items within the same domain will not be counted.
*Note: In an assay with at least 90% specificity against relevant disease controls.
Source: Table adopted from Aringer et al., 2019

Epidemiology

Unfortunately, epidemiological data on SLE are still lacking for about 80% of countries worldwide explaining the great variability. The first study using Bayesian hierarchical linear mixed model to estimate global, regional, and country-specific SLE incidence, prevalence, and population even in regions without SLE epidemiological data, confirmed that there are significant variations by region, race, and gender [Tian et al., 2023]: The global prevalence of SLE is estimated of approximately 3.4 million people (**Figure 2**). The global SLE incidence and newly diagnosed population were estimated to be 5.14 (1.4 to 15.13) per 100 000 person-years and 400.000 people annually, respectively. Incidence rates vary, with Poland, the USA, and Barbados showing the highest rates in a large-scale global study. SLE predominantly affects women, particularly those of childbearing age, though rates are higher and disease more severe in African-Americans and individuals of Hispanic and Asian descent. Recent research highlights a greater focus on disparities, disease burden, and new therapeutic approaches.

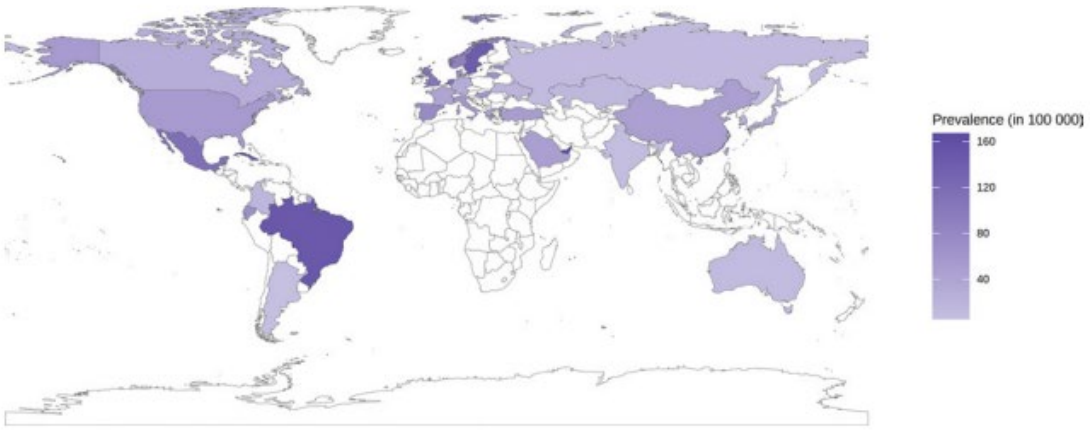


Figure 2. One-year period (physician or dermatologist diagnosed) prevalence of systemic lupus erythematosus for overall population by country.
Source: Figure adopted from Tian et al., 2023

Predisposing risk factors

Risk factors predisposing to SLE are mainly of intrinsic (genetic, epigenetic, hormonal) or extrinsic nature including environmental (UV-light and infections), habitual (smoking, alcohol abuse or high carbohydrate diet), physiological and psychological factors. SLE has a strong polygenic predisposition. Depending on the statistical method used, heritability in SLE is estimated to be large ranging from 44% to 66% across populations [Lawrence et al., 1987; Ku et al., 2015]. So far, 330 susceptibility loci could be identified by genome-wide association studies (GWASs) on ancestry-matched data sets showing genetic heterogeneity between ancestral groups [Laurynenka & Harley, 2024]: There are 225 loci found in East Asian (EAS), 106 in European (EU), 11 in African-American (AA), 18 Mixed American (MA), and 1 in Egyptian

ancestries. Unexpectedly, most of the known loci, 252 (76%) of the 330, have only been established in a single ancestry.

The researchers evaluated several pathways influenced by SLE associated genes mainly involving the regulation of immune responses including immune cell activation and differentiation, the regulation of production and response to cytokines, including type I interferon (IFN), apoptosis, the detection and removal of immune complexes and apoptotic particles, and the interactions with pathogens and microbiota, including leishmaniasis, Epstein-Barr virus infection, influenza A, SARS-CoV, and many others (**Table 2**).

Term	Overlap	Adjusted *P*-value	Odds ratio
Interleukin (IL)-12 complex	70/504	2.1E-29	7.2
IL23 complex	57/456	2.3E-21	6.2
IL35 complex	55/281	5.1E-21	6.5
B-cell receptor complex	60/566	3.5E-19	5.2
Interferon (IFN) regulatory factor 5 complex	22/59	2.7E-18	24.5
IFN-γ signaling pathway	31/97	6.2E-18	12.3
Immune system	157/1943	4.0E-17	2.5
Immune system signaling by IFNs, interleukins, prolactin, and growth hormones	46/280	6.9E-15	5.2
Cytokine signaling in the immune system	76/702	7.8E-14	3.3
Th1- and Th2-cell differentiation	25/92	1.5E-13	9.7
Cell adhesion molecules	31/148	2.0E-13	6.9
MHC protein complex	14/21	3.0E-13	51.3
Intestinal immune network for IgA production	18/48	1.5E-12	15.4
IFN-α/β signaling	20/64	1.1E-11	11.7
NF-κB complex	61/864	2.6E-11	3.3
Adaptive immune system	71/733	1.3E-10	2.9
Fc receptor complex	25/185	8.4E-10	6.4
Antigen processing and presentation	19/78	1.1E-09	8.3
Th17-cell differentiation	22/107	1.2E-09	6.7
Positive regulation of T-cell activation	23/107	7.5E-09	7.1

Table 2. Pathways influenced by genes associated with SLE
Top 20 pathways based on p-value.
Source: Table adopted from [Laurynenka & Harley, 2024]

Key pathogenic mechanisms

SLE predisposing factors trigger pathogenic mechanisms involving aberrant adaptive and innate immune responses that lead to a loss of immune self-tolerance and decreased clearance of circulating autoantigens. Multiple cell types are either overactivated or dysfunctional, including B cells/plasma cells, T cells, dendritic cells, monocytes/macrophages, natural killer cells, neutrophils, and endothelial cells. The type I IFN pathway is a major driver of aberrant responses in both, the innate and adaptive immune system in SLE pathogenesis.

Circulating autoantigens resulting from defective clearance of apoptotic cells, and abnormal responses of dendritic cells and neutrophils trigger Toll-like receptor (TLR) signalling in the innate immune system and activation of T and B cells in the adaptive immune system. TLR activation enhances generation of type I IFN by innate lymphoid cells (ILC) which directly triggers B cell activation and production of auto-antibodies. Activated autoreactive T cells stimulate B cells to produce autoantibodies against nuclear components (so called antinuclear antibodies, ANA), which form immune complexes that deposit in tissues causing inflammation and organ damage [Dai et al., 2025] (**Figure 3**).

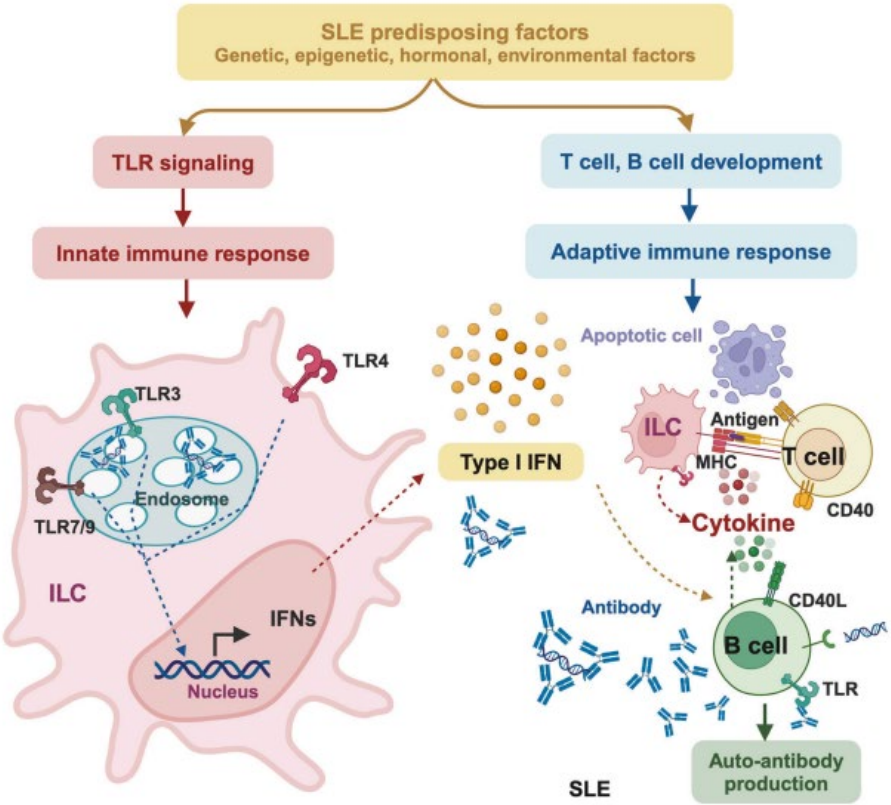


Figure 3. Pathogenic mechanisms in SLE via over-activating innate and adaptive immune responses
CD40L = CD40 Ligand, IFN = type I interferon, ILC = innate lymphoid cells, MHC = major histocompatibility complex, SLE = Systemic Lupus Erythematosus, TLR = Toll-like receptor
Source: Figure adopted from [Dai et al. 2025]

Management of SLE

Current standard-of-care therapies for SLE

The cornerstone for induction of remission is still hydroxychloroquine (HCQ) that was developed in the 1950s from chloroquine during efforts to synthesize alternatives to quinine as antimalarials. HCQ is effective mainly by interference with TLRs in both, the innate and adaptive immune system. Its accumulation in lysosomes and autophagosomes is causing an increased pH and thereby dampens major histocompatibility complex-II (MHC-II) antigen presentation and subsequent T cell activation. In addition, HCQ accumulation diminishes viral

recognition by endosomal TLRs, resulting in a decreased type I IFN production by cells of the innate immune system [in 't Veld et al., 2021].

According to EULAR 2023 update, the use of HCQ and other pharmacological interventions is directed by patient characteristics, type and severity of organ involvement, treatment-related harms, comorbidities, risk for progressive organ damage, and patient preferences [Fanouriakis et al., 2023]: Based on individual risk for flare, treatment with HCQ is recommended for all SLE patients at a target dose of 5mg/kg per day (at higher doses increased risk for retinal toxicity). Use of HCQ is recommended in women with SLE preconceptionally and throughout pregnancy as it reduces the risk of SLE flares and of poor obstetrical outcomes. More data are needed to support its benefit in pregnant women with anti-phospholipid syndrome [Andreoli et al., 2017]. Glucocorticoids (GCs), are needed to treat acute flares. In patients with moderate-to-severe disease, pulses of intravenous methylprednisolone (125–1000mg/day, for 1–3 days) can be administered. GCs have significant side effects in the long-term and should therefore be reduced to maintenance dose of maximal 5mg per day (prednisone equivalent) and withdrawn as soon as possible. In patients not responding to HCQ (alone or in combination with GCs) or patients unable to reduce GCs below doses acceptable for chronic use, addition of immunosuppressive agents such as methotrexate (MTX), azathioprine (AZT) or mycophenolate should be considered. MTX inhibits DNA synthesis in immune proliferating cells and is also effective in skin and joint manifestations. However, its use is limited by its liver and bone marrow toxicity, and it is contraindicated in pregnancy. AZT can be used as alternative to MTX in pregnancy. Treatment with HCQ plus GCs and/or immunosuppressants (standard-of-care) is able to stop flares and functions mainly for disease control, but is not effective to achieve complete remission.

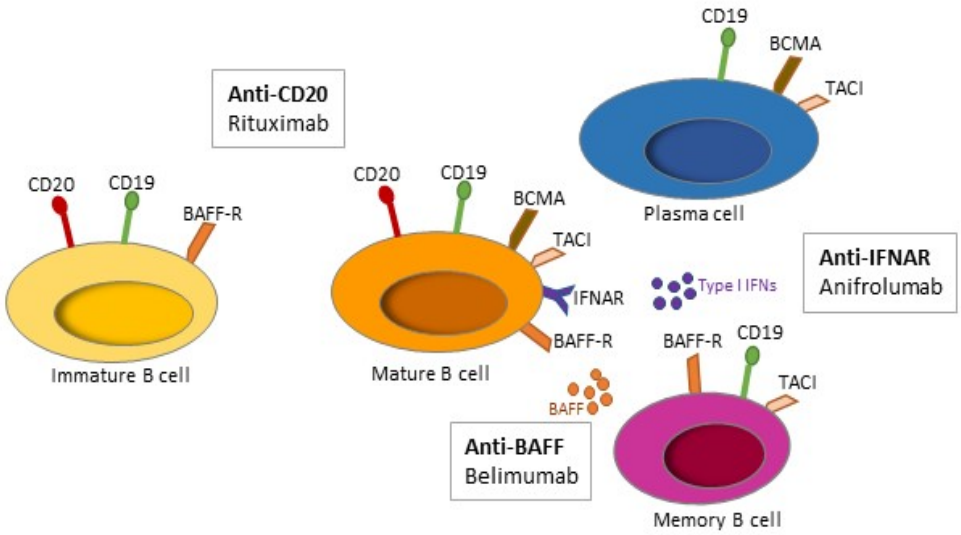


Figure 4. Mechanism of action of B cell targeting biologicals available for SLE treatment
Abbreviations: BAFF = cell activating factor belonging to the tumor necrosis factor family, BAFF-R = BAFF Receptor, BCMA = B cell maturation antigen, IFN = interferon, IFNAR= type I IFN receptor; TACI = transmembrane activator and calcium modulator and cyclophilin ligand interactor

In the last decade, novel therapies for SLE entered the market significantly improving the management of SLE including the monoclonal antibodies rituximab (anti-CD20), belimumab (anti- BAFF mAb) and anifrolumab (anti-IFNAR1) (**Figure 4**). These biologics are targeting B cell survival and proliferation or B cell activation mechanisms supposed to be involved in SLE pathogenesis. These, so-called B-cell depleter, can be added to standard-of-care in severe, therapy refractory SLE with or without kidney involvement [Fanouriakis et al., 2023].

Belimumab is a recombinant human IgG1λ monoclonal antibody that inhibits the soluble form of BAFF (B cell activating factor) that is also known as B lymphocyte stimulator (BLyS). BAFF is the natural ligand for three TNF receptor superfamily members (TNFRSFs): TNFRSF13C (BAFF-R, B cell activating factor receptor), TNFRSF13B (TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor), and TNFRSF17 (BCMA, B-cell maturation antigen) which are expressed mainly on mature B lymphocytes. Binding of BAFF to BAFF-R triggers the formation and maintenance of B cells by activation of NF-κB signaling pathways and synergistic signalling with the B cell receptor [Dostert et al., 2018]. Binding of belimumab to soluble form of BAFF is preventing its interaction with BAFF receptors, thus inhibiting B cell survival and maturation. Belumimab (Benlysta®) was the first biological drug approved in 2011 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of SLE.

Rituximab is a chimeric IgG1 monoclonal antibody that targets CD20 expressing B cells. This leads to B cell depletion through apoptosis, antibody dependent cell mediated cytotoxicity (ADCC), or antibody-dependent phagocytosis (ADP). However, the use of rituximab is off-label, as randomized studies in lupus nephritis (LN) showed no significant effects in addition to mycophenolate therapy [Rovin et al., 2012]. Nevertheless, data from a meta-analysis showed that rituximab can reduce both disease activity and glucocorticoid demand in SLE as well as proteinuria in LN [Alshaiki et al., 2018]. Based on these data, its off-label use is supported in severe, refractory disease or in cases of severe immune thrombocytopenia and in LN, especially after failure of cyclophosphamide-based therapy [Fanouriakis et al., 2023].

Anifrolumab is a fully humanized IgG1k monoclonal antibody that specifically binds to the Type I IFN receptor subunit 1 (IFNAR1) on mature B cells and prevents signalling by all type IFNs [Peng et al., 2015]. By blocking IFN signals, anifrolumab reduces inflammation, suppresses the IFN gene signature, and helps to normalize the overactivated immune system in SLE. Novel B cell depleting therapies are currently in development to further improve the management of SLE.

Management of reproductive health in women with SLE

The 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases recommends that women with SLE should plan pregnancies during periods of disease remission or low-to-moderate disease activity, ideally when the condition has been stable for at least 6 months. Key recommendations include working with a multidisciplinary medical team, ensuring all pre-pregnancy screenings

are complete, and continuing pregnancy-compatible lupus medications like HCQ and AZT throughout pregnancy. A healthy lifestyle, including folic acid supplementation, is also crucial [Sammaritano et al., 2020].

Management of active proliferative Lupus Nephritis

Patients with active proliferative LN should receive low-dose intravenous cyclophosphamide as determined in the EuroLupus trial [Houssiau et al., 2004] or mycophenolate and GCs. Alternatively, combination therapy with belimumab can be considered either with cyclophosphamide or mycophenolate or calcineurin inhibitors (especially voclosporin or tacrolimus) combined with mycophenolate [Fanouriakis et al., 2023].

Obinutuzumab (GA101) was developed by Roche and Genentech primarily for the treatment of haemato-oncologic diseases to address the need for novel therapeutics with higher activity than rituximab [Goede et al., 2015]: Obinutuzumab is a type II, glycoengineered, humanized anti-CD20 mAb. The glycoengineered Fc portion enhances the binding affinity to the FcγRIII receptor on immune effector cells, resulting in increased antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP). Since obinutuzumab does not accumulate CD20 molecules in lipid rafts, no Fc clustering in lipid rafts occurs, which leads to decreased activation of complement-dependent cytotoxicity via complement 1q.

In 2014, it has been approved as Gazyvaro® in combination with chemotherapy for the treatment of chronic lymphocytic leukemia and follicular lymphoma. Due to encouraging results obtained in randomized clinical trials, the EULAR consortium recommends B cell depletion by anti-CD19 CAR-T cells or anti-CD20 therapy such as rituximab also as potential therapeutic approach for patients with severe, therapy refractory SLE, although long-term data are pending [Fanouriakis et al., 2023]. The observation that obinutuzumab induced superior B-cell cytotoxicity to rituximab in a series of in vitro assays measuring B cell cytotoxicity in rheumatoid arthritis and SLE patient samples [Reddy et al., 2017], has prompted several phase 2 clinical trials showing efficacy of obinutuzumab in lupus nephritis (LN) [Furie et al., 2021] and in SLE patients with secondary non-depletion nonresponse to rituximab (2NDNR) occurring in about 14 % of patients due to development of neutralizing antibodies with repeated cycles of rituximab treatment [Arnold et al., 2022; Yusof et al., 2017].

Based on positive results from the phase 2 NOBILITY [Furie et al., 2022] and phase 3 REGENCY (NCT04221477) studies, the European Commission has recently approved Gazyva®/Gazyvaro® (obinutuzumab) in combination with mycophenolate mofetil (MMF) for the treatment of adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis. Key efficacy results from REGENCY demonstrated that 46.4% of patients on obinutuzumab plus standard therapy (MMF and glucocorticoids) achieved a complete renal response at week 76 compared to 33.1% patients on standard therapy alone. In addition, a statistically significant and clinically meaningful reduction of corticosteroid use and an improvement in proteinuric response and complement levels and reductions in anti-dsDNA were observed. [Furie et al., 2025] (**Figure 5**). No unexpected safety signals were identified. More serious adverse events,

mainly infections and events related to coronavirus disease 2019, occurred with obinutuzumab than with placebo.

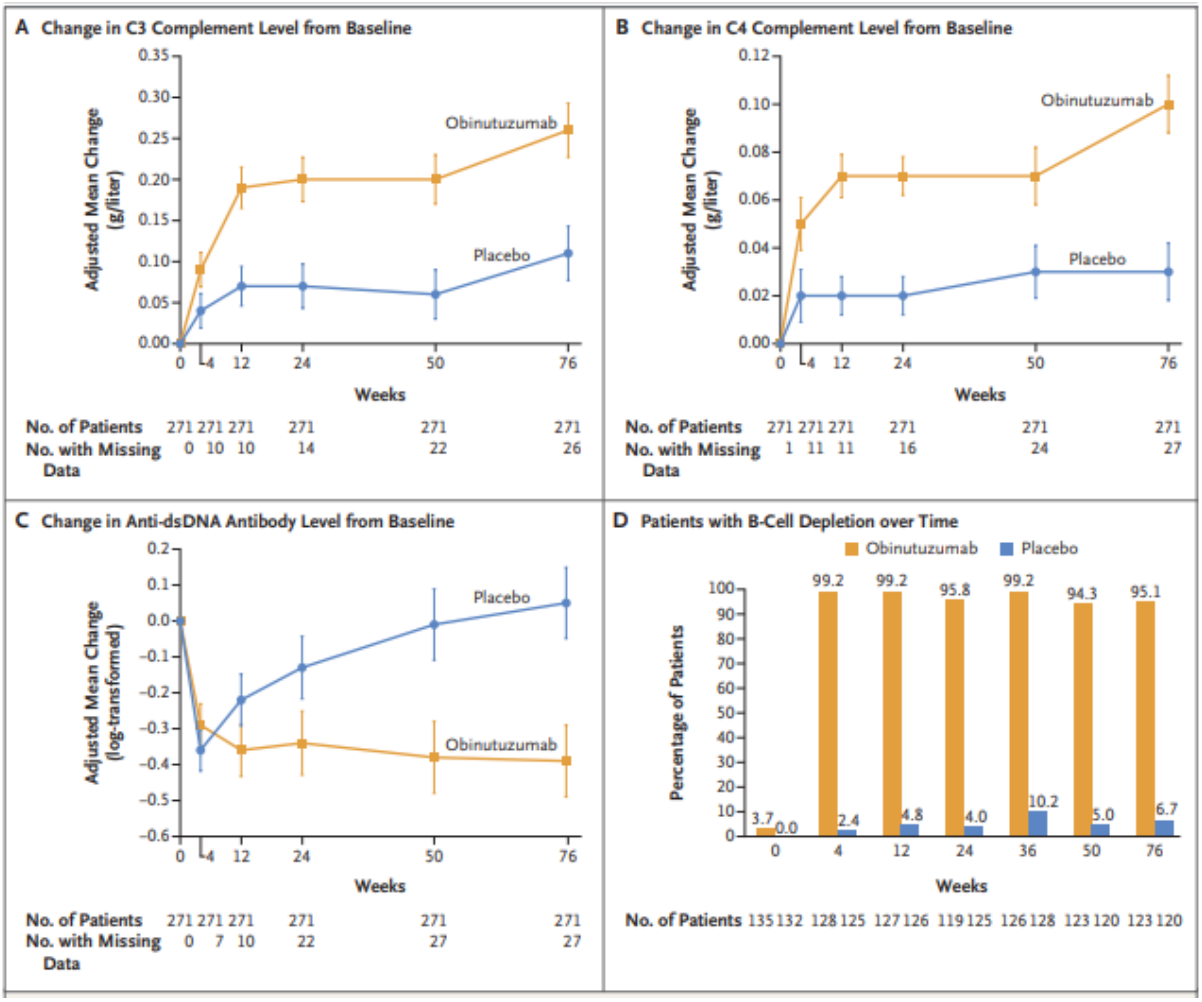


Figure 5. Serologic and pharmacodynamic analyses over time.

Panel A shows the adjusted mean change in the C3 complement level from baseline in the intention-to-treat population. Panel B shows the adjusted mean change in the C4 complement level from baseline in the intention-to-treat population. Panel C shows the adjusted mean change in anti-dsDNA antibody level from baseline (log-transformed) in the intention-to-treat population. In Panels A, B, and C, an analysis-of-covariance model was used with multiple imputation for missing data; I bars indicate the standard error. Panel D shows the percentage of patients with B-cell depletion over time (T and B natural killer cells) in the safety population. B-cell depletion was defined by an absolute CD19-positive B-cell count lower than 10 cells per cubic millimeter.

Source: *Figure adopted from [Furie et al., 2025]*

Evaluation of Remission

Successful management of SLE requires an early diagnosis, vigilant monitoring for new organ involvement such as lupus nephritis (LN), potentially disease modifying treatment targeting remission as defined by the 'Definition of Remission in SLE' (DORIS) criteria [van Vollenhoven et al., 2021]: The 2021 DORIS Task Force recommended a single definition of remission in SLE,

based on clinical Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Physician Global Assessment (PGA) score, and allowed standard-of-care treatments including antimalarials, glucocorticoids and/or immunosuppressive agents or biologics (**Panel 1**).

- **Clinical SLEDAI = 0**
- **Physician Global Assessment <0.5 (0-3)**
  - Irrespective of serology
  - The patient may be on antimalarials, low-dose glucocorticoids (prednisolone ≤5mg/day), and/or stable immunosuppressants including biologics.

Panel 1. The 2021 definition of remission in SLE (DORIS criteria)
Source: van Vollenhoven et al., 2021

Alternative treatment targets can be used such as achieving a low disease activity, as defined by the 'Lupus Low Disease Activity State' (LLDAS) and approaching for patient adherence to treatment. The LLDAS defines a disease state characterized by minimal clinical activity and a daily prednisolone dose of ≤7.5 mg. It is less stringent than DORIS remission, associated with better SLE outcome, and an important endpoint in clinical trials [Franklyn et al., 2016]. Changes in SLE disease activity in 9 different organ systems can be graded using the British Isles Lupus Assessment Group (BILAG) score, each from A (very active) to E (no current or previous activity). A flare is defined as a new "A" or "B" score in at least one system, and the scoring is based on the physician's intent to treat. The more comprehensive BILAG-2004 version includes 97 clinical manifestations to determine the activity level in each domain, with a score of "A" indicating a need for escalation of therapy and a score of "B" indicating moderate activity [Isenberg et al. 2005]. Clinical composite end points often used in clinical trials are the SLE responder index 4 (SRI-4) and the BILAG-based Combined Lupus Assessment (BICLA). The SRI-4 is a composite end point encompassing a decrease ≥4 points in the SLEDAI index, the absence of new severe organ involvement (BILAG score A/B) and no disease worsening in the physician global assessment (PhGA). The BICLA is defined by the simultaneous achievement of four criteria: an improvement in all active organ systems according to the BILAG index (e.g., all A domains to B or lower, and all B domains to C or lower), no new severe (A) or moderately severe (B) activity, no worsening on the PhGA by more than 0.3 points, and no increases in restricted medications or treatment discontinuation beyond protocol-allowed limits.

Disease modifying therapies

A working definition for disease modifying therapies in SLE has been proposed as '*minimisation of disease activity with the fewest treatment-associated toxicities and slowing or preventing the progression of organ damage*' [van Vollenhoven et al., 2022]. In addition, evaluation criteria for this working definition including interim timepoints for the assessment

of the drug's disease modification potential in clinical trials and clinical practice have been proposed (**Panel 2**).

Disease Modification definition category		Interim timepoints for assessment of disease modification POTENTIAL in clinical trials (vs standard therapy alone) and clinical practice (no comparison)		Disease modification CONFIRMED
		Outcomes year 1	Outcomes years 2–5	Outcomes year >5
Extra renal	Minimising disease activity with minimal treatment-associated toxicity AND Slowing/Preventing organ damage progression	► Significant reduction in disease activity measured using a validated tool (ie, SELENA-SLEDAI, BILAG, SRI-4) ► Significant reduction in severe flare measured using a validated tool (ie, SFI or BILAG) ► Reduction in use of steroids* and/or immunosuppressants	► Sustained improvement in multiple organ domains/no worsening in multiple organ domains ► Prevention of severe flares ► Continued reduction in use of steroids* and/or immunosuppressants	No change in SDI or delayed progression
Renal	Minimising disease activity with minimal treatment-associated toxicity AND Slowing/Preventing organ damage progression	► Significant improvement in uPCR or kidney activity index via biopsy ► Significant reduction in renal flare ► Minimise eGFR decline (ie, ≤30%) ► Reduction in use of steroids* and/or immunosuppressants	► Sustained improvement in uPCR or no worsening in kidney chronicity index via biopsy ► Prevention of renal flares ► Minimise further decline in eGFR (ie, <30%) ► Continued reduction in steroids* and/or immunosuppressants	No change in SDI or delayed progression

Panel 2. Proposed matrix for application of the SLE-specific disease modification criteria

*≤7.5 mg/day per 2019 EULAR SLE treatment guidelines and LLDAS [Fanouriakis et al., 2019; Franklyn et al., 2016] ≤5mg/day per DORIS remission definition [van Vollenhoven et al., 2021]. BILAG, British Isles Lupus Assessment Group; DORIS, Definitions Of Remission In SLE; eGFR, estimated glomerular filtration rate; EULAR, European Alliance of Associations for Rheumatology; GC, glucocorticoid; LLDAS, Lupus Low Disease Activity State; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SFI, SELENA-SLEDAI Flare Index; SLEDAI, SLE Disease Activity Index; SRI-4, SLE Responder Index-4; uPCR, urinary protein-creatinine ratio.

Source: Panel adopted from van Vollenhoven et al., 2022

The most definitive criteria are slowing or preventing organ damage progression in extrarenal SLE as judged by no worsening in the SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index). In renal SLE, the most definitive criterion is showing a reduction or no worsening in key surrogates of progression to end stage kidney disease (i.e. kidney histopathology or eGFR decline). Based on the available literature, HCQ and belimumab are the only treatments for SLE that currently satisfy the proposed (preliminary) disease modification criteria including their capacity to reduce non-renal disease activity, severe flares, use of steroids/immunosuppressants and organ damage accrual up to 5 years [Askanase et al., 2024].

An overview of established therapies that are currently used in clinical practice for the treatment of SLE and LN is given in **Table 3**.

Product Class/Product	Indication	Standard Dosing Regimen	Intensified Dose Regimen
Glucocorticoids			

Product Class/Product	Indication	Standard Dosing Regimen	Intensified Dose Regimen
Methylprednisolone	Moderate to severe SLE, LN	If needed, PO/IV short term use to control active disease, taper to ≤5mg/day as quickly as possible and discontinue, if possible	Consider pulse IV (125-1000 mg/day for up to 3 days), then 0.3-0.5 mg/kg/day depending on severity; taper as quickly as possible to ≤5mg/day
Antimalarials			
Hydroxychloroquine	Mild/Moderate/ Severe Non-renal SLE and LN	Target dose of 5 mg/kg PO real body weight/day unless contraindicated. Evaluation of individual risk for flare and retinal toxicity.	
Immunosuppressants			
Azathioprine	SLE patients not responding to HCQ (alone or in combination with GC) or unable to reduce GCs	Initial 1-3 mg/kg/day oral, then 1-2 mg/kg/day PO	
Methotrexate		Off-label for non-renal SLE with arthritis: 7.5-25 mg/week PO or SC	
Mycophenolate mofetil		Off-label: Induction 2-3g/day PO, Maintenance 1-2g/day PO	
Cyclophosphamide	Organ-threatening or life-threatening SLE	Low-dose (active proliferative LN): Induction with 500 mg IV in week 0,2,4,8 and 10 (Euro-Lupus-Regimen)	High-dose (high risk for renal failure, severe autoimmune thrombocytopenia): 0.75 bis 1 g/m^2 BSA/month IV for 6 months (NIH-Regimen)
Calcineurin inhibitors			
Voclosporin (Lupkynis®)	Active LN	23.7 mg (three soft capsules 7.9 mg each) twice daily PO up to 24 weeks (must be combined with MMF) *Cave: Dose reduction in case eGFR < 60 ml/min/1.73 m^2*	
Tacrolimus	Active LN	Off-label: 0.1 bis 0.3 mg/kg/day per os (must be combined with MMF)	
Biologics			
Rituximab/ (Mabthera®)	Organ- or life-threatening SLE refractory to cyclophosphamide	Off-label: Induction by 375 g/m^2 IV weekly for 4 weeks combined with a prior injection of MP 100 mg, individual maintenance dose starting after 18 months (mostly 500 mg every 6 months)	
Anifrolumab/ (Saphnelo®)	*Add-on* therapy in moderate to severe active SLE	300 mg as IV infusion over 30 min every 4 weeks up to 3 years depending on individual patient response	
Belimumab (Benlysta®)	Refractory severe active SLE/LN	200 mg SC every 4 weeks OR 10mg/kg IV on Day 0, 14 and 28, then every 4 weeks up to a maximum of 6 months	
Obinutuzumab (Gazyva®/Gazyvaro®)	Active LN (Class III or IV, with or without concomitant Class V)	Initial infusion of 1000 mg followed by infusions of 1000 mg at Week 2, Week 24, Week 26; then every 6 months. A risk-benefit analysis should be done at Week 76 for continuation of therapy.	
Abbreviations: GC = glucocorticoid, HCQ = hydroxychloroquine, LN = Lupus Nephritis, MMF= Mycophenolate mofetil, MP = methylprednisolone, IV = intravenous, PO = per os, SC = subcutaneous, SLE = Systemic Lupus Erythematosus			

Table 3. Currently established therapies for non-renal SLE and LN

Source: EULAR 2019, EULAR 2023 update, SmPC Lupkynis®, SmPC Saphnelo®, SmPC Benlysta®, SmPC Gazyvaro®, G-BA (17.08.2023) Voclosporin (Lupusnephritis)

Emerging therapies for SLE

The goal of current therapies for SLE is to control disease activity, reduce organ damage, and decrease long-term morbidity and mortality. Therapies providing durable clinical responses without requiring chronic immunosuppressive drugs are lacking. Novel therapeutic approaches include monoclonal antibodies and chimeric antigen receptor T cells (CAR-T cells) specifically targeting B cell receptors or proteins involved in B cell activation to reach a more profound B cell depletion. Whether the so-called 'deep B cell depleter' such as ianalumab, obinutzumab or dapirolizumab as well as resecabtagene autoleucel can achieve durable drug-free responses in patients with moderately to severely active SLE and/or LN is currently evaluated in clinical trials. Management of SLE is increasingly driven by biologic innovation, dual-pathway targeting, precision diagnostics and responder assessment, and digital (AI-assisted) integration. These advances promise not only improved outcomes but also more personalized and accessible care for patients worldwide.

B cell depleting monoclonal antibodies

Novel B cell depleting monoclonal antibodies (mAbs) with dual actions such as ianalumab, obinutuzumab and obexelimab are emerging with the scope to improve disease control or finally achieve long-standing remission. Ianalumab and obinutuzumab mainly enhance antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP) to reach a deeper B cell depletion and autoantibody reduction, whereas obexelimab is intended to reduce B-cell activity and immune response without completely depleting the B cells, which could result in a favourable safety profile (less risk for reactivation of Cytomegalovirus or Epstein-Barr-virus infections). The novel B cell depleting mAbs entered already phase 3 (ianalumab and obinutuzumab) and phase 2 (obexelimab) of clinical development (**Table 4**).

Product /Product Class	Indication (EMA)	Development Phase/NTC (clinialtrials.gov)
Monoclonal antibodies targeting B cells		
Ianalumab (VAY 736)/ Anti-BAFF receptor mAb (Novartis)	SLE	Phase 3: NCT05639114 (SIRIUS-SLE 1) Recruiting, SCE APR-2029 NCT05624749 (SIRIUS-SLE 2) Recruiting, SCE: APR-2029 NCT06133972 (SIRIUS-SLE Extension) Recruiting, SCE: APR-2032
Obinutuzumab (GA101)/ Type II, glyco-engineered anti CD20 mAb (Artiva Biotherap.)	SLE	Phase 3: NCT04963296 (ALLEGORY) Active, not recruiting, SCE: MAR-2028
Obexelimab/ anti-CD19/FcγRIIb bispecific antibody (Zenas BioPharma / Amgen)	SLE	Phase 2: NCT06559163 (SunStone) Recruiting, SCE: SEP-2026
Abbreviations: BAFF = cell activating factor belonging to the tumor necrosis factor family, CD19 = cluster of differentiation 19 expressed on all B cells; CD20 = cluster of differentiation 20 expressed on B cells except on plasmablasts or plasma cells, LN = Lupus Nephritis, SLE = Systemic Lupus Erythematosus		

Table 4. Monoclonal antibodies targeting B cells in clinical development for SLE and LN
Source: ClinicalTrials.gov (latest accessed on 03-Nov-2025)

Ianalumab (VAY736) originating from collaboration of MorphoSys AG and Novartis is a novel fully human IgG1 monoclonal antibody with a dual mechanism of action: B-cell depletion by antibody-dependent cellular cytotoxicity (ADCC) and BAFF receptor blockade that interrupts BAFF-mediated signaling for B-cell maturation, proliferation, and survival. ADCC activity of ianalumab is greatly enhanced by elimination of fucose residues from the carbohydrate moiety attached to the Fc part of the antibody [Yamane-Ohnuki et al., 2004].

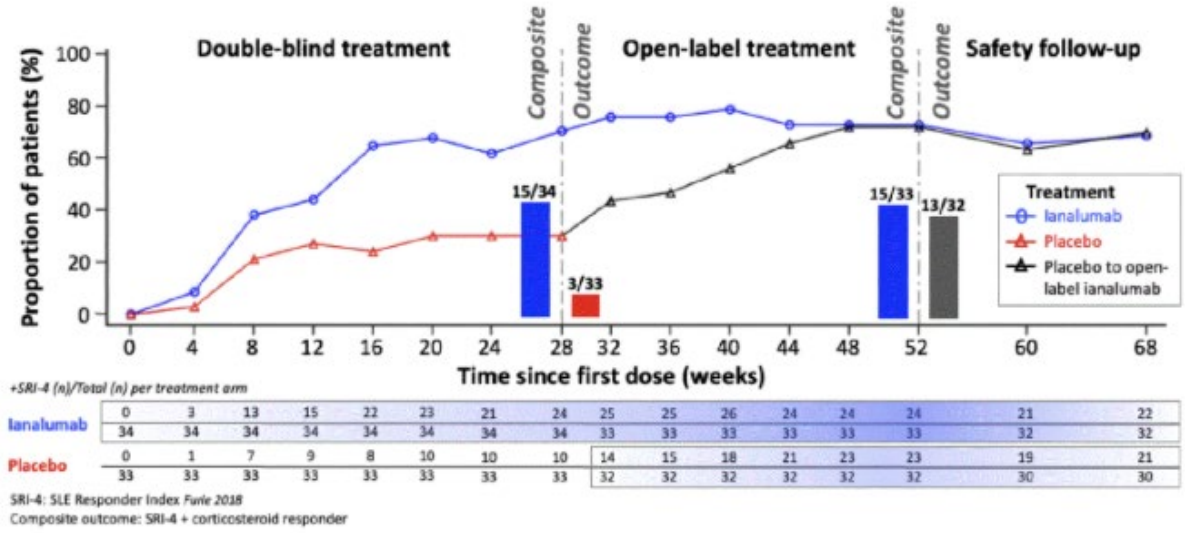


Figure 6. SRI-4 responders over time and composite SRI-4+CS responders (bar graphs)
Source: Figure adopted from Mysler et al., 2024

Ianalumab is currently in development for B-cell-driven autoimmune diseases, including Sjögren's disease, immune thrombocytopenia, and SLE. Favorable results were reported for a phase 2b trial with SLE patients receiving ianalumab 300 mg or placebo every 4 weeks and who switched at week 28 to open-label ianalumab through week 48 [Mysler et al., 2024]: Patients with ANA ≥1:80, ≥4 of 11 ACR 1997 SLE classification criteria, SLE disease activity index 2000 (SLEDAI-2K) score ≥6, and, British Isles Lupus Assessment Group-2004 (BILAG-2004) ≥1 A or ≥2 B were included. Outcomes were measured at baseline, every 4 weeks up to week 52, then week 60 and week 68. The proportion of patients treated with ianalumab or placebo achieving the primary composite endpoint criteria for SRI-4 plus corticosteroid tapering responder at week 28 was 44.1% (n/N=15/34) vs 9.1% (n/N=3/33), respectively, and at week 52 for patients switching from active treatment to open-label ianalumab or switching from placebo to ianalumab was 45.5% (n/N=15/33) vs 40.6% (n/N=13/32; **Figure 6**). Longer duration of ianalumab exposure at week 52 versus week 28, or for placebo+24 weeks, resulted in further improvement in outcomes for incidence BILAG flare, status of SRI-6, SRI-8, DORIS and LLDAS, and serum levels of complement and autoantibodies. IgG reduction from baseline (geometric mean, 95% CI) at week 52 was 0.78 (0.73-0.84). Treatment responses were maintained during the safety follow up period at week 68 without unexpected or new safety findings.

Ianalumab is now investigated in two ongoing phase 3 trials, SIRIUS-SLE1 (NCT05639114) and SIRIUS-SLE2 (NCT05624749) evaluating the efficacy, safety and tolerability of ianalumab as *add-on* therapy to standard-of-care in active SLE. In addition, a long-term extension study SIRIUS-SLE-LTE (NCT06133972) will evaluate long-term safety and tolerability of ianalumab in SLE patients who have previously completed the treatment period in one of the two SIRIUS-SLE core studies.

Obinutuzumab is a type II, glycoengineered, humanized anti-CD20 mAb. The glycoengineered Fc portion enhances the binding affinity to the FcγRIII receptor on immune effector cells, resulting in increased antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP). Obinutuzumab induced superior B-cell cytotoxicity to rituximab in a series of in vitro assays measuring B cell cytotoxicity in rheumatoid arthritis and SLE patient samples [Reddy et al., 2017]. Several phase 2 clinical trials have shown efficacy of obinutuzumab in lupus nephritis (LN) [Furie et al., 2021; Furie et al., 2022] and in SLE patients with secondary non-depletion nonresponse to rituximab (2NDNR) occurring in about 14 % of patients due to development of neutralizing antibodies with repeated cycles of rituximab treatment [Arnold et al., 2022; Yusof et al., 2017]. In December 2025, the European Commission has approved Gazyva®/Gazyvaro® (obinutuzumab) in combination with mycophenolate mofetil (MMF) for the treatment of adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis based on positive results from the phase 2 NOBILITY [Furie et al., 2022] and phase 3 REGENCY (NCT04221477) studies [Furie et al., 2025]. Obinutuzumab is currently tested in the phase 3 trial ALLEGORY (NCT04963296) in about 300 patients with active, autoantibody-positive SLE who have a high disease activity (SLEDAI-2K score>8) despite their standard-of-care therapy. The primary endpoint measure is the percentage of participants who achieve the SLE Responder-Index-4 (SRI-4) at week 52.

B cell depleting CAR-T cell therapies

Treatment of SLE with the goal of long-term remission remains challenging. CAR-T cell therapy is known to lead to long-term remission in approximately 50% of patients (who are otherwise incurable) with highly malignant B-cell lymphomas due to deep and sustained B-cell depletion. Therefore, this therapeutic approach was also considered for non-malignant B-cell-driven diseases such as SLE, especially when anti-CD20 antibodies such as rituximab show at least a transient response. The use of CAR-T cell therapies in severe forms of SLE represents a novelty in medicine and opens up new possibilities and concepts for treatment. Emerging CAR-T cell therapies for SLE are targeting specifically long-living CD19-positive and/or BCMA-positive plasmablasts that recognize autoantigens (taking over the function of antigen-presenting cells and stimulate follicular T helper cells) and can induce autoreactive T-cell responses.

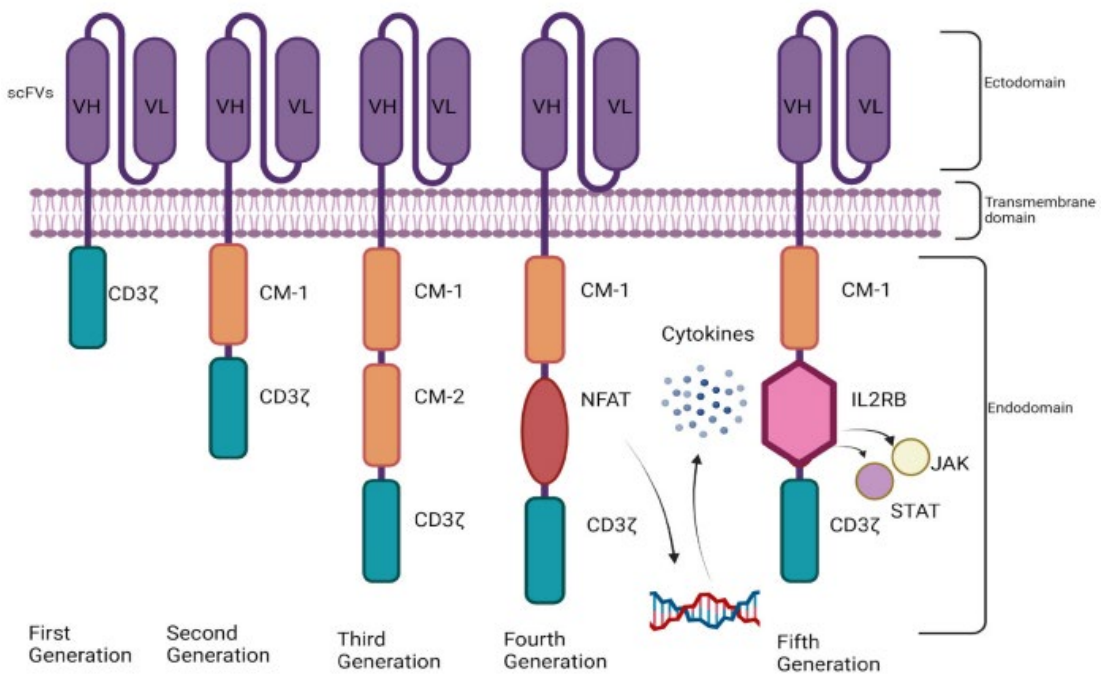


Figure 7. Overview of CAR structures from the first to the fifth generation.
Abbreviations: CAR = chimeric antigen receptor, CM = costimulatory molecule, IL-2R = interleukin receptor, ITAMs = immunoreceptor tyrosine-based activation motifs, Jak = Janus kinase, NFAT = nuclear factor of the activated T-cell, STAT = signal transducer and activator of transcription, scFv = single-chain variable fragment, TMD = transmembrane domain, VL = variable regions of the light chain, VH = variable regions of the heavy chain.
Source: Figure adopted from [Abdalhadi et al., 2024].

The key components of CARs include an ectodomain for ligand binding, a transmembrane domain, one or more cytoplasmic endodomains, and a spacer domain connecting the single-chain variable fragment (scFv) and the transmembrane domain. CAR engineering has progressed and delivered already five generations of CARs aiming to improve target specificity, T-cell persistence and safety profiles [Abdalhadi et al., 2024] (**Figure 7**): First generation CARs contain only a CD3ζ as signaling domain. Second generation CARs harbor CD3ζ and one co-stimulatory molecule (CM), allowing dual signaling pathway. Third generation CARs combine CD3ζ and several CMs that deliver multiple signaling. Fourth generation CARs incorporate a nuclear factor of the activated T-cell (NFAT)-responsive cassette that expresses cytokines playing anti-cancer activities. Fifth generation CARs include membrane receptor IL-2Rβ that provides a binding site for STAT3 and activates the JAK-STAT signaling domain resulting in synergistic activation of triple signals from CD3ζ, CMs, and cytokine-inducing JAK-STAT3/5 pathway.

Several case reports of successful anti-CD19 CAR-T cell therapy (after preconditioning with fludarabine and cyclophosphamide) for refractory SLE are supporting this innovative approach [Mackensen et al., 2022]. Single administration of CAR-T cell therapy led to drug-free clinical and serological remission (reduced antinuclear and anti-ds DNA antibodies) in several patients with severe refractory disease, while maintaining long-term remission remains difficult mainly due to limited persistence of CAR-T cells [Abdalhadi et al., 2024]. The acute side effect profile of anti-CD19 and/or BCMA-specific CAR-T cells appears to be significantly better than in hematological malignancies [Muller et al., 2024; Wang et al., 2024]. Due to the short follow-

up periods to date, no conclusions can currently be drawn about SLE-specific long-term side effects. An overview of novel CAR-T cell therapies targeting B cells which entered already phase 2 of clinical development for SLE and/or LN is given in **Table 5**.

Product /Product Class	Indication (EMA)	Development Phase/NTC (clinialtrials.gov)
Descartes-08/ mRNA-engineered autologous CAR-T cells targeting BCMA (Cartesian Therap.)	SLE	Phase 2: NCT06038474 Recruiting, SCE: NOV-2026
AZD 0120/ dual CAR- T cells targeting CD19/BMCA (AstraZeneca)	Refractory SLE	Phase 1/Phase2: NCT06897930 Recruiting, SCE: MAY-2029
Rese-cel (CABA-201)/ autologous CAR-T cells targeting CD19 (Cabaletta Bio)	SLE LN	Phase 1/Phase2: NCT06121297 (RESET-SLE) Recruiting, SCE: DEC-2027
P-CD19CD20-ALLO1/ allogenic dual CAR-T cells targeting CD19/CD20 (Genentech)	Refractory SLE	Phase 1/Phase2: NCT06984341 Not yet recruiting, SCE: NOV-2033
Meta10-19/ metabolically armed (expressing IL-10) CAR-T cells targeting CD19 (Zhejiang University)	Moderate to Severe SLE	Phase 1/Phase 2: NCT06711146 Recruiting, SCE: APR-2027
YTB323/ autologous CAR-T cells targeting CD19 (Novartis)	Refractory SLE	Phase 1/Phase2: NCT05798117 Active, not recruiting, SCE: SEP-2026
Abbreviations: BCMA = B-cell maturation antigen, CAR-T cells = chimeric antigen receptor T cells, CD19 = cluster of differentiation 19 expressed on all B cells; CD20 = cluster of differentiation 20 expressed on B cells except on plasmablasts or plasma cells, LN = Lupus Nephritis, SLE = Systemic Lupus Erythematosus		

Table 5. CAR-T cell therapies in clinical development for SLE and/or LN
Source: ClinicalTrials.gov (latest accessed on 03-Nov-2025)

Descartes-08 (Cartesian Therapeutics) is an autologous mRNA-engineered CAR-T cell therapy (rCAR-T) targeting B-cell maturation antigen (BCMA), a surface antigen expressed on plasma cells and plasmacytoid dendritic cells. These cells represent a small fraction of mature B cells which produce autoantibodies and inflammatory cytokines (e.g. type 1 IFNs) that are key pathogenic factors in SLE. Descartes-08 is designed to be dosed safely in an outpatient setting without prior chemotherapy.

In a Phase 2 clinical trial (NCT04146051) in patients with generalized myasthenia gravis, descartes-08 was observed to be well tolerated, and adverse events were transient and mostly mild, supporting outpatient administration without the need for pretreatment chemotherapy [Chahin et al., 2025]: Clinical improvements and autoantibody reductions were observed after BCMA-directed mRNA CAR-T treatment that persisted through the 1-year follow-up period. The favorable safety profile of Descartes-08 contrasts with DNA-based CAR-T cells, which carry oncogenic risk from genomic integration of CAR DNA and require lymphodepletion chemotherapy with potential hematologic toxicities. Using mRNA CAR-T cells to target BCMA can result in durable depletion of autoantibodies and clinically meaningful improvement in myasthenia gravis severity scores without severe toxicity such as agammaglobulinemia or increased risk of infection. Based on the favorable phase 2 results in myasthenia gravis patients, a further phase 2 (NCT06038474) trial is currently evaluating the safety, tolerability and manufacturing feasibility of Descartes-08 CAR- T cells in 30 patients with SLE.

Rese-cel (resecabtagene autoleucel, formerly CABA-201) from Cabaletta Bio is an autologous 4-1BB anti-CD19-CAR T cell therapy, designed to deeply and transiently deplete CD19 positive cells following a weight-based one-time infusion. This approach may enable an "immune system reset" with the potential for durable response without chronic immunosuppression.

The RESET-SLE phase 1/2trial (NCT06121297) is currently evaluating the safety and efficacy of rese-cel in two independent cohorts of non-renal SLE (ANA+ or dsDNA+, and SLEDAI-2K ≥8 despite standard-of-care) and LN (active, biopsy-confirmed class III or IV ± V LN despite standard-of-care). A single weight-based infusion of $1x10^6$ CAR T cells/kg is administered following a preconditioning regimen (fludarabine 25mg/m^2/d on Days -5, -4 and -3, and cyclophosphamide 1,000mg/m^2 on Day -3). All non-glucocorticoid immunosuppressive and antimalarial agents are stopped by Day -5.

So far, six patients, four in the non-renal SLE cohort and two in the LN cohort have been dosed with rese-cel and have completed at least 1 month of follow-up in the RESET-SLE trial and the preliminary results have been presented at EULAR 2025 [Sheikh et al., 2025]: Rese-cel has been well-tolerated with Grade 1 cytokine release syndrome (CRS) reported in 2 patients without need of tocilizumab. One LN patient experienced Grade 4 immune effector cell-associated neurotoxicity syndrome (ICANS), associated with a potential occult infection, which resolved following standard management. Clinical improvement (LLDAS and DORIS remission) has been observed in 3 out of 4 non-renal SLE patients (follow up range 1 month to 9 months). The remaining non-renal SLE patient with class V LN achieved a substantial reduction in SLEDAI-2K score (26 to 8) and significant reduction in the urinary protein-creatinine ratio (UPCR) from 1.08 to 0.52mg/mg at week 28. In the LN cohort, one patient achieved LLDAS by week 24 and the other patient had a reduction in SLEDAI (14 to 11) by week 4 (latest follow-up). Both LN cohort patients experienced a complete renal response (UPCR below 0.45mg/mg) at their latest follow up. All patients remained off all SLE-related immunosuppression, and are currently undergoing glucocorticoid taper. These initial data suggest that rese-cel may reset the immune system in SLE, allowing patients to achieve meaningful clinical responses while off of all immunosuppressive therapies and tapering corticosteroids.

Inhibitors of B cell activation

Dapirolizumab pegol (DZP) from UCB/Biogen is a potential *first-in-class* humanized monovalent pegylated Fab antibody fragment against the CD40 ligand (CD40L) lacking an Fc domain. DZP binds CD40L, blocking CD40-CD40L interactions and CD40 activation, and has broad modulatory effects on SLE immunopathology including reducing B and T cell activation and downregulating interferon pathways [Cutcutache et al., 2023; Powlesland et al., 2024].

The results of the first DZP phase 3 trial PHOENYCS GO (NCT04294667) were presented at EULAR 2024 [Clowse et al., 2024] and EULAR 2025 [Vital et al., 2025]. PHOENYCS GO included 315 patients with moderate-to-severe SLE who received intravenous DZP 24 mg/kg plus standard-of-care medication (DZP+SOC) or placebo (PBO+SOC) every 4 weeks over a period of

48 weeks. The trial has met both, its primary endpoint (BILAG-based Composite Lupus Assessment (BICLA) response at week 48) and secondary endpoint (SRI-4 response at week 48) (**Figure 8**). Through Week 48, 11.6% versus 23.4% of patients receiving DZP+SOC versus PBO+SOC had severe BILAG flares (nominal p=0.0257; difference 11.5%). In patients with glucocorticoid dose >7.5mg/day at baseline, 72.4% versus 52.9% of patients receiving DZP+SOC versus PBO+SOC reduced their dose to ≤7.5mg/day at Week 48 (nominal p=0.0404; difference 17.1%).

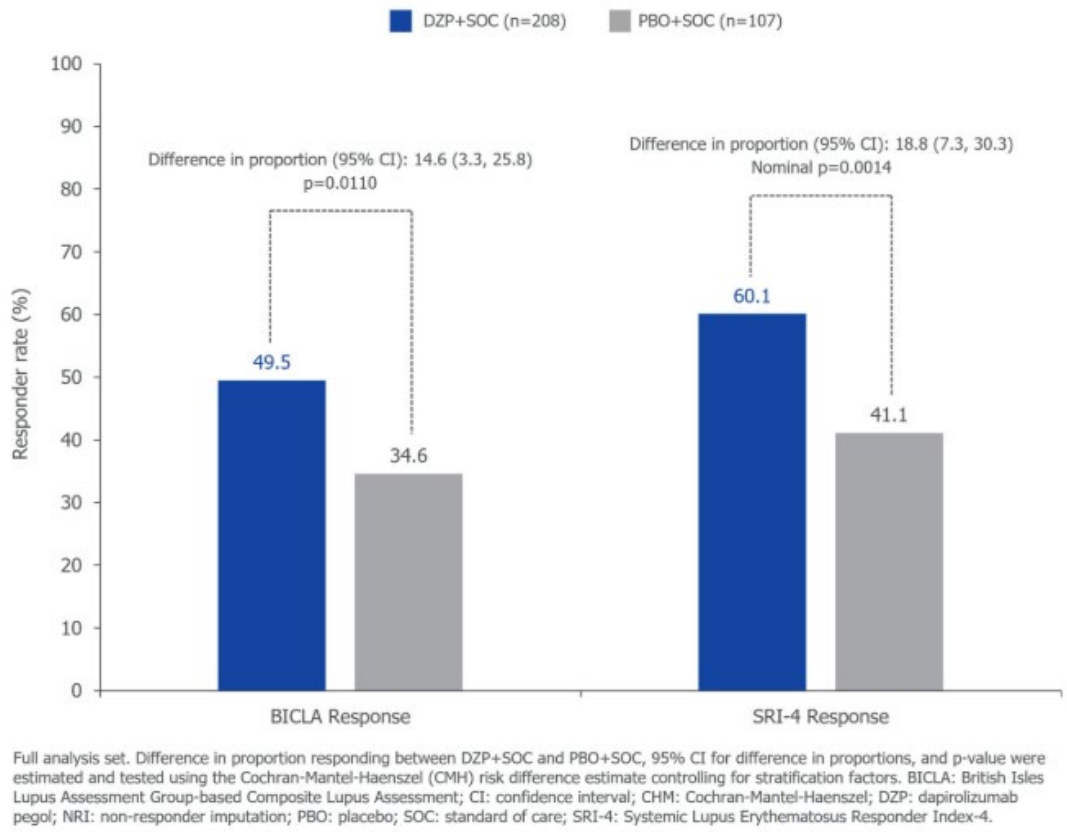
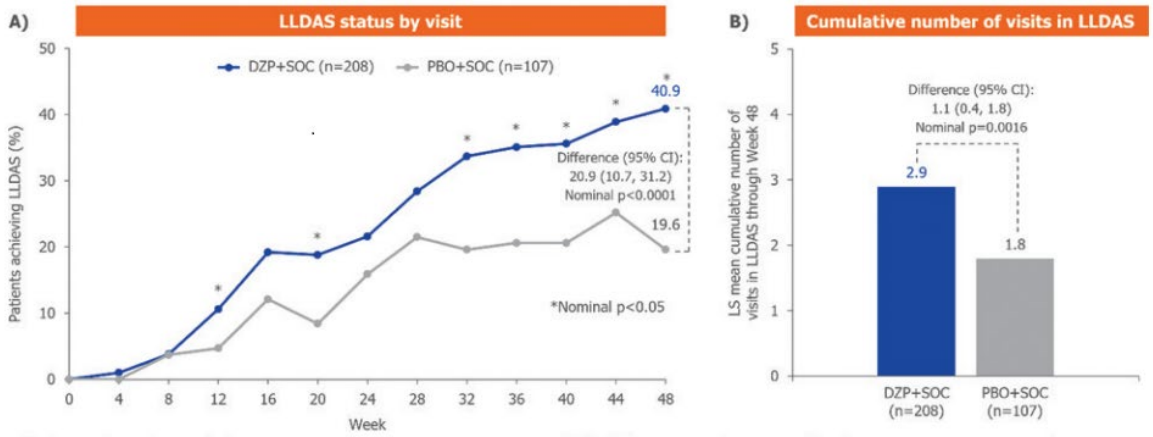


Figure 8: Achievement of BICLA response and SRI-4 response at Week 48 (NRI)
Source: Figure adopted from Vital et al., 2025

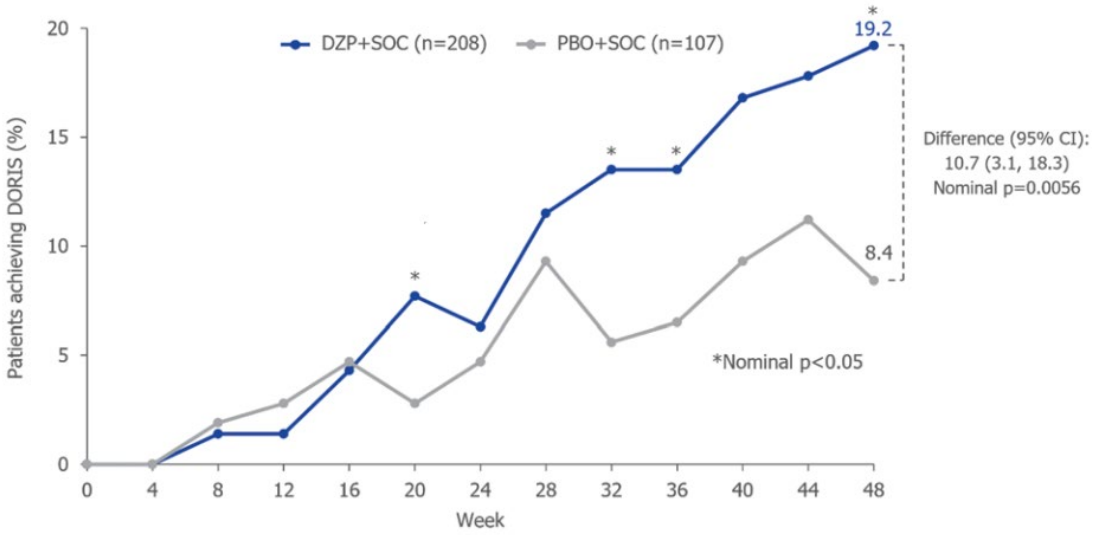
Treatment with DZP was generally well tolerated. Compared with PBO+SOC, treatment with DZP+SOC resulted in higher rates of achievement and time in the prognostically important endpoints of LLDAS and DORIS [Morand et al., 2025] (**Figure 9-10**). Alongside the significant improvements in overall SLE disease activity, improvements were also seen across additional clinical measures, including fatigue scales [Parodis et al., 2025]. Participants from the PHOENYCS GO study may continue to be followed in a long-term open-label study (NCT04976322) and a second phase 3 trial PHOENYCS FLY (NCT06617325) study is ongoing.



Full analysis set. *Nominal p<0.05 for the DZP+SOC versus PBO+SOC comparison. LLDAS requires all of the following criteria tobe met: no significant disease activity as per SLEDAI-2K and BILAG 2004; SLEDAI-2K score ≤4 with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever); no new and/or worsening disease activity defined as no SLEDAI-2K component documented as present that was not documented present at previous visit; PGA ≤33 mm and prednisone equivalent systemic dose for an SLE indcation ≤7.5 mg per day. BILAG: British Isles Lupus Assessment Group; CI: confidence interval; CNS: central nervous system; DZP: dapirolizumab pegol; LLDAS: Low Lupus Disease Activity State; LS: least squares; NRI: non-responder imputation; PBO: placebo; PGA: Physician Global Assessment; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

Figure 9: (A) Achievement of LLDAS by visit and (B) cumulative number of visits in LLDAS through week 48 (NRI)

Source: Figure adopted from Morand et al., 2025



Full analysis set. *Nominal p<0.05 for the DZP+SOC versus PBO+SOC comparison. DORIS requires all of the following criteria tobe met: clinical SLEDAI-2K score of 0 (SLEDAI-2K without serology: anti-dsDNA and C3/C4 items); PGA ≤16 mm; prednisone equivalent systemic dose for a SLE indication ≤5 mg per day at >50% of the last 28 days (>14 of the last 28 days) and the prednisone dose is ≤5 mg/day at all days in the 7 days before a visit, at the day of the visit and at the day after the visit. Anti-dsDNA: anti-double stranded DNA; CI: confidence interval; C3: complement C3; C4: complement C4; DORIS: Definition of Remission in SLE; DZP: dapirolizumab pegol; NRI: non-responder imputation; PBO: placebo; PGA: Physician Global Assessment; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2K; SOC: standard of care.

Figure10: Achievement of DORIS by visit (NRI)

Source: Figure adopted from Morand et al., 2025

A summary of investigational therapies inhibiting B cell activation which entered already phase 2 or 3 of clinical development for SLE and/or LN is given in **Table 6**.

Product/ Product Class	Indication (EMA)	Development Phase/NTC (clinialtrials.gov)
Inhibitors of B cell activation		
Dapirolizumab pegol/ potential *first-in-class* humanized monovalent pegylated Fab antibody fragment targeting CD40 ligand (CD40L) (UCB, Biogen)	SLE	Phase 3 NCT04294667 (PHOENYCS GO): Completed JUN-2024 with positive results [Vital et al., 2025; Morand et al, 2025] NCT06617325 (PHOENYCS FLY): Recruiting, SCE: MAY-2028
Iscalimab (CFZ533)/ anti-CD40 mAb (Novartis)	SLE LN	Phase 2 NCT03656562: Completed 38-APR-2025, Results posted: SR-4 responder rate for CFZ533 40% (8/20) and for placebo 30% (6/20) Phase 2 NCT03610516: Completed JUN-2023 with positive results [Shen et al., 2025]
Frexalimab/ antiCD40 mAb (Sanofi)	SLE	Phase 2 NCT05039840 (APATURA): Recruiting, SCE: OCT-2026
Orelabrutinib/ irreversible BTK inhibitor (Beijing InnoCare Pharma Tech Co Ltd)	SLE	Phase 2b NCT05688696 Recruiting, SCE: May-2026
Telitacicept/ TACI-Fc fusion protein targeting BLyS+ APRIL (RemeGen Co., Ltd.)	SLE	Phase 2 NCT06456567 (REMESLE-2) Recruiting, SCE: MAY-2027
TQB3702/ BTK inhibitor (small molecule) (Chia Tai Tianqing Pharmaceutical Group)	SLE	Phase 2 NCT06859931 Not yet recruiting, SCE: DEC-2026

Abbreviations: ADCC = antibody-dependent cellular cytotoxicity, APRIL = A proliferation inducing ligand, BDCA2 = blood dendritic cell antigen 2, BCMA = B-cell maturation antigen, BLyS = B-Lymphocyte-Stimulator, BTK = Bruton's tyrosine kinase, JAK = Janus kinase, IFN-1 = Interferon-1, IL = Interleukin, LN = Lupus Nephritis, mAb = monoclonal antibody, SLE = Systemic Lupus Erythematosus, SCE = Study Completion Expected, S1PR = Sphingosine 1 Phosphat Receptor, TCE = T cell engager, TNF = tumour necrosis factor, TYK2 = Tyrosine Kinase 2

Table 6. Inhibitors of B cell activation in development for SLE and LN

Source: ClinicalTrials.gov (latest accessed on 03-Nov-2025)

Inhibitors of JAK/STAT pathway

The Janus kinase (JAK) is a typical tyrosine kinase (TYK) that is involved in signal transduction of about 40 types of cytokines (e.g., type I and type II IFNs) and growth factors. The four different JAK isoforms (i.e., JAK1, JAK2, JAK3, and TYK2) form heterodimers or homodimers and transduce intracellular signals through combination with seven types of transcription factors referred to as signal transducers and activators of transcription (STATs). The four JAK isoforms and seven STAT transcription factors mediate intracellular signal transduction downstream of cytokine receptors, which are implicated in the pathology of autoimmune, allergic and inflammatory diseases [Tanaka et al., 2022] (**Figure 10**).

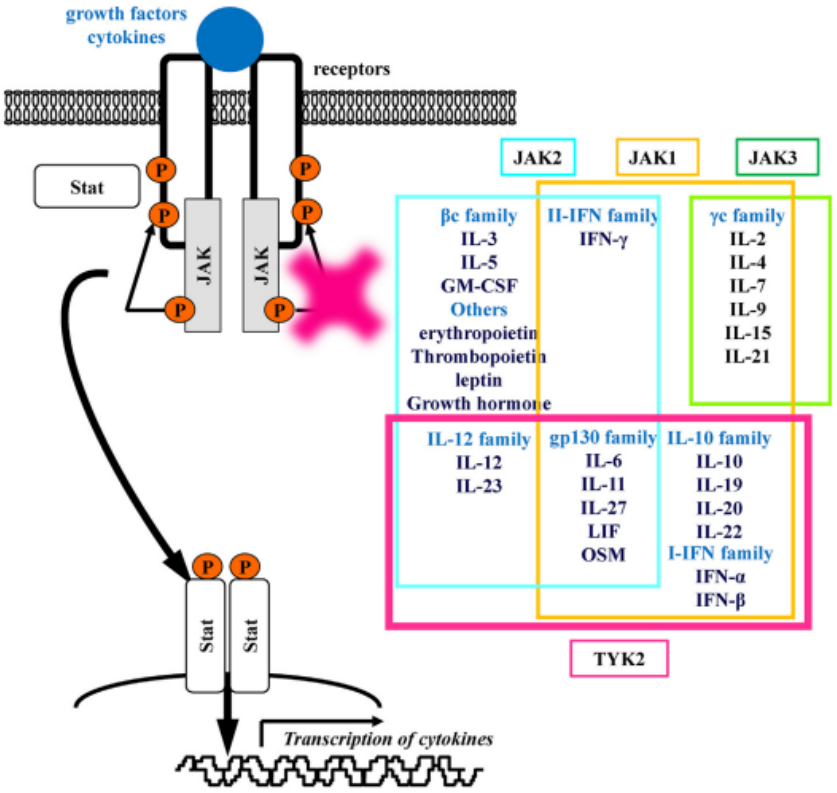


Figure 11. JAK/STAT signaling pathway
Source: Figure adopted from Tanaka et al., 2022

Development of targeted small-molecule therapies such as JAK inhibitors, with varied selective inhibitory profiles, has already been proven as beneficial in the management of several inflammatory and autoimmune disorders, as for example the development of deucravacitinib and upadacitinib. However, no JAK inhibitor has been approved for the treatment of SLE up to date. Deucravacitinib and upadacitinib have recently entered phase 3 of clinical development for SLE as both have delivered promising phase 2 results in the treatment of patients with moderately to severely active SLE. Deucravacitinib (Sotyktu®) has been already approved (EMA 2023) for treatment of moderate to severe plaque psoriasis. Upadacitinib (Rinvoq®) has been approved (EMA 2019, FDA 2019) as extended-release tablet formulation for rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis and

several other autoimmune conditions. These approvals are generally for patients whose disease is moderate-to-severe and has not responded adequately to other treatments, with age restrictions varying by indication.

Deucravacitinib is a highly selective allosteric inhibitor of the tyrosine kinase 2 (TYK2). Instead of competing with adenosin triphosphate (ATP) at the catalytic domain of the enzyme, deucravacitinib binds to regulatory pseudokinase domain of TYK2. This allosteric binding event locks the TYK2 enzyme into an inactive conformation preventing it from activating and phosphorylating downstream signaling proteins. TYK2 is an intracellular signaling molecule which is part of the JAK family plays a critical role in mediating inflammatory signals through type I IFN, interleukin (IL)-12/IL-23, gp130 family and the IL-10 family. In contrast to JAK-inhibitors, deucravacitinib leaves IL-2 signaling and proliferation of regulatory T cells intact. The targeted effect provides a selective anti-inflammatory action while minimizing broad immunosuppression [Catlett et al., 2021; Tanaka et al., 2022; Zhang et al., 2023] (**Figure 11**).

Deucravacitinib demonstrated positive outcomes in the phase 2 PAISLEY Study (NCT03252587) in which it met the primary endpoint SRI-4 at week 32, as well as the secondary endpoints at week 48 including SRI-4, BICLA, LLDAS, CLASI-50, and change from baseline in active (tender and swollen) joint count. The most common adverse events had been nasopharyngitis, upper respiratory tract infections, headache, and acne [Morand et al., 2022]. Based on the positive results of phase 2 the company has initiated two phase 3 trials with identical study designs (POETYK-SLE 1 and POETYK-SLE 2) in adult patients investigating efficacy and safety with moderate to severe SLE.

Upadacitinib is an orally administered selective Janus kinase 1 (JAK1) inhibitor that blocks the JAK1 enzyme's ATP-binding site by acting as an ATP-competitive inhibitor. By competing with ATP, it prevents the enzyme from binding nucleotide, which stops the kinase from phosphorylating downstream proteins necessary for the JAK1/JAK-STAT signaling pathway thereby reducing proinflammatory cytokines including type I and type II IFNs [Tanaka et al., 2022] (**Figure 11**). The drug is generally administered once daily and has a half-life of 9 hours.

Positive results were reported for the phase 2 SLEek study (NCT03978520), a 48-week clinical trial in adults with moderately to severely active SLE. Upadacitinib 30 mg alone or in combination with elsubrutinib 60mg (high dose combination group) demonstrated significant improvements in SLE disease activity and reduced flares through 48 weeks. The primary endpoint of SRI-4 and glucocorticoid dose tapering (≤10mg QD) at week 24 was achieved by 54.8% (p=0.028) of patients in the upadacitinib monotherapy group and 48.5% (p=0.081) of patients in the high dose combination group, compared with 37.3% of patients in the placebo group. In both active dosing groups, no safety signals have been identified beyond those previously reported for these classes of drugs [Merrill et al., 2024]. Elsubrutinib (also known as ABBV-105) is an orally administered selective Bruton's tyrosine kinase (BTK) inhibitor which is hypothesized to inhibit activation of B cells and immune complex-driven activation of neutrophils and dendritic cells [Goess et al., 2019].

Building on these promising Phase 2 results, the currently running phase 3 'SELECT-SLE' trial (NCT05843643) is designed to assess the effectiveness and safety of upadacitinib in patients with moderately to severely active SLE. After a 42-day screening period, participants will undergo a 52-week placebo-controlled treatment period, followed by an optional 52-week re-randomized double-blind extension treatment period. Subjects that had been receiving the upadacitinib and demonstrate low disease activity, will receive modified doses in a blinded fashion, and those that have not experienced a decrease in disease activity, will continue the initial blinded upadacitinib dose. Subjects that had been on placebo, will be transitioned to blinded upadacitinib. JAK inhibitors which are currently in phase 2 or3 of clinical development for SLE are summarised in **Table 7**.

Product/ Product Class	Indication (EMA)	Development Phase/NTC (clinialtrials.gov)
Upadacitinib/ selective JAK1 inhibitor (AbbVie)	SLE	Phase 3: NCT05843643 (SELECT-SLE): Recruiting, SCE: OCT-2027
Deucravacitinib/ selective TYK2 inhibitor (Bristol Myers Squibb)	SLE	Phase 3: NCT05617677 (POETYK-SLE-1): Recruiting, SCE: DEC-2027 NCT05620407 (POETYK-SLE-2): Recruiting, SCE: DEC-2027
ESK-001 / selective TYK2 Inhibitor (Alumis)	SLE	Phase 2b NCT05966480 (LUMUS): Active, not recruiting, SCE: SEP-2027
GLPG3667/ATP competitive TYK2 inhibitor (Galapagos NV)	SLE	Phase 2 NCT05856448 (GALACELA): Active, not recruiting. SCE: MAR-2026
Abbreviations: JAK1 = Janus kinase 1, SLE = Systemic Lupus Erythematosus, TYK2 = Tyrosine kinase 2		

Table 7. JAK-inhibitors in development for SLE

Source: ClinicalTrials.gov (latest accessed on 03-Nov-2025)

Other novel immunomodulating therapies for SLE

Further novel immuno-modulating SLE drug candidates include small molecules and monoclonal antibodies that mostly inhibit parts of the overactivated immune system in SLE including complement factors or Toll-like receptors (TLRs). More advanced novel drug projects that entered already phase 3 of clinical development include cenerimod modulating sphingosine 1 phosphate (S1P1) receptors and the monoclonal antibody litifilimab targeting blood dendritic cell antigen 2 (BDCA2) on plasmacytoid dendritic cells, and the available results of both will be discussed in some more detail in the following.

Cenerimod from Idorsia Pharmaceuticals is a potential *first-in-class* oral sphingosine-1-phosphate 1 (S1P1) receptor modulator, which plays a crucial role in regulating the exit of lymphocytes (T and B cells) from lymphoid organs into the bloodstream. Cenerimod traps these lymphocytes within the lymph nodes. Therefore, it reduces the number of circulating

lymphocytes that can contribute to the autoimmune inflammatory process in SLE without causing the severe immunosuppression associated with some of the therapies.

Cenerimod has been extensively investigated from preclinical to finally phase 3. The phase 1 already showed a sustained reduction in circulating lymphocyte counts which was reversible after discontinuation of the drug. The encouraging results confirmed the mode of action and the desired safety profile [Juif et al., 2017]. The phase 2 proof-of-concept CARE study (NCT03742037) showed that treatment with 4mg cenerimod led to a significant reduction in disease activity (measured by a modified SLEDAI-2K score) and anti-dsDNA antibodies suggesting clinical improvement [Hermann et al., 2019]. A further phase 2b study did not meet the overall primary endpoint, however it confirmed the 4mg as the most beneficial dose in particular in the group with high interferon-1-gene expression [Askanase et al., 2025].

The phase 3 program OPUS (Oral S1P1Receptor ModUlator in SLE) consists of two multicenter, randomized, double-blind, placebo-controlled, parallel group studies OPUS-1 (NCT05648500) and OPUS-2 (NCT05672576). The trials are actively running to prove efficacy and safety of the 4mg dosage as an *add-on* therapy on top of standard-of-care treatment in patients with moderate to severe SLE.

Litifilimab (BIIBO59) from Biogen is a potential *first-in-class* humanized IgG1 monoclonal antibody targeting blood dendritic cell antigen 2 (BDCA2) that is a C-type lectin receptor exclusively expressed on plasmacytoid dendritic cells that are crucial in the immune system due to their ability to produce large amounts of type I IFNs in response to viral infections. However, in autoimmune diseases like SLE, these plasmacytoid dendritic cells can become dysregulated and produce excessive type I IFNs, contributing to disease pathology. BDCA2 inhibitors such as lifitilimab reduce this overactive immune response by targeting the BDCA2 receptor, thereby blunting the production of interferons and other inflammatory cytokines [Pellerin et al., 2015, Furie et al., 2022].

The efficacy and safety of litifilimab is currently evaluated in two phase 3 trials TOPAZ-1 (NCT04895241) and TOPAZ-2 (NCT04961567) in patients with active SLE receiving non-biologic standard-of-care for SLE. The primary endpoint is the SRI-4 response at week 52. In a third phase 3 trial, called AMETHYST (NCT05531565), litifilimab injections are currently evaluated for its efficacy to improve symptoms in patients with active Cutaneous Lupus Erythematosus (CLE).

Based on a thorough review of clinical trial projects currently published on ClinicalTrials.gov and the publicly available literature, further immuno-modulating SLE drug candidates which entered already phase 2 or 3 of clinical development are summarised according to their mode of action in the following **Table 8**.

Product/ Product Class	Indication (EMA)	Development Phase/NTC (clinialtrials.gov)
Complement factor inhibitors		
Iptacopan/ oral, complement B inhibitor (Novartis)	Active LN Class III-IV, +/- V	Phase 2 NCT05268289 Recruiting, SCE: SEP-2028
Ravulizumab/ complement 5 targeting mAb (Alexion Pharmaceuticals Ltd)	LN, IgA nephropathy	Phase 2 NCT04564339 (SANCTUARY): Active, not recruiting, SCE: MAY-2026
Toll-like receptor inhibitors		
Afimetoran/ TLR 7/8 inhibitor (BMS)	SLE	Phase 2 NCT04895696 Active, not recruiting, SCE: APR-2029
Enpatoran/ *first-in-class* oral TLR7/8 inhibitor (Merck KGaA)	SLE, CLE	Phase 2 NCT05162586 (WILLOW): Completed Nov-2024 with positive results [Morand et al., EULAR 2025]
Others		
Cenerimod/ S1P1 receptor modulator trapping lymphocytes (T and B cells) within lymph nodes (Idorsia)	SLE	Phase 3 NCT05648500 (OPUS-1): Recruiting, SCE: MAY-2027 NCT05672576 (OPUS-2): Recruiting, SCE: May-2027
Litifilimab/ mAb targeting BDCA2 on plasmacytoid dendritic cells thereby inhibiting their production of IFN-1 (Biogen)	SLE CLE	Phase 3 NCT04895241 (TOPAZ-1): Recruiting, SCE: MAR-2027 NCT04961567 (TOPAZ-2): Recruiting, SCE: MAR-2027 Phase 3 NCT05531565 (AMETHYST): Recruiting, SCE: DEC-2027
Nipocalimab/ FcRn mAb reducing auto-antibodies (Janssen)	SLE LN	Phase 2: NCT04882878 Completed DEC-2024, no results posted NCT04883619: Not yet recruiting, Study start estimated JAN-2026
Felzartamab/ anti-CD38 mAb (Hi-Bio, A Biogen Company)	SLE	Phase 1 / Phase 2: NCT06064929: Recruiting, SCE: JAN-2026
Abbreviations: BDCA2 = blood dendritic cell antigen 2, CLE = Cutaneous Lupus Erythematosus, IFN-1 = Interferon-1, LN = Lupus Nephritis, mAb = monoclonal antibody, SCE = Study Completion Expected, SLE = Systemic Lupus Erythematosus, S1PR = Sphingosin 1 Phosphat Receptor		

Table 8. Other novel immunomodulating drugs in development for SLE, CLE and LN

Source: ClinicalTrials.gov (latest accessed on 03-Nov-2025)

Precision Medicine and Biomarkers for SLE

Achieving long-term remission in SLE is still demanding and limited by the heterogeneity and fluctuating nature of this autoimmune disorder and the lack of validated prognostic biomarkers. Precise diagnostic tools using proteomics, individual responder assessment, and digital integration supported by artificial intelligence (AI) are increasingly providing new insights into the pathogenetic nature of non-renal SLE and lupus nephritis. These advances promise not only improved outcomes but also more personalized and accessible care for patients worldwide. Therefore, big efforts are currently made to use biomarkers for personalizing SLE treatment, especially in therapy refractory cases. This was also emphasized by valuable research contributions presented at EULAR 2025, two of them are discussed in the following.

Immune Mapping of Lupus Nephritis

As treatment responses in lupus nephritis (LN) are still inadequately low, a better understanding of its pathogenesis may improve clinical management. A spatially-resolved kidney proteomic approach combined with immune mapping was presented by Professor Andrea Fava (Johns Hopkins University, Division of Rheumatology, Baltimore, MD, USA) and collaborators to identify specific immune structures in distinct subtypes of LN [Lee et al., 2025]: The researchers used a serial immunohistochemistry workflow, followed by imaging and de-staining cycles. Image processing was performed using HALO (Indica Labs), including *AI-assisted* tissue classification. The analyses of 29 kidney biopsies of LN identified 12,371 cellular aggregates. Most (97%) aggregates were small (<30 cells), however medium and large aggregates included 33.7% of immune cells (**Figure 12**): Glomerular aggregates were numerically increased in proliferative and mixed classes. These were small and primarily composed of CD68+ myeloid cells. Glomerular aggregates rich in CD68+ cells negatively correlated with UPCR (urine-protein-creatinine-ratio), while aggregates rich in lymphocytes negatively correlated with chronicity. In contrast, tubulointerstitial aggregate density was similar across all subtypes of LN and negatively correlated with glomerular filtration rate (GFR). Significant heterogeneity in aggregate composition revealed 10 aggregate subtypes. Small aggregates tended to be restricted to 1-2 cell types each, while medium and large aggregates included mixed proportions of CD4+ T, CD8+ T, B, dendritic, myeloid, and plasma cells, suggesting germinal center-like structures.

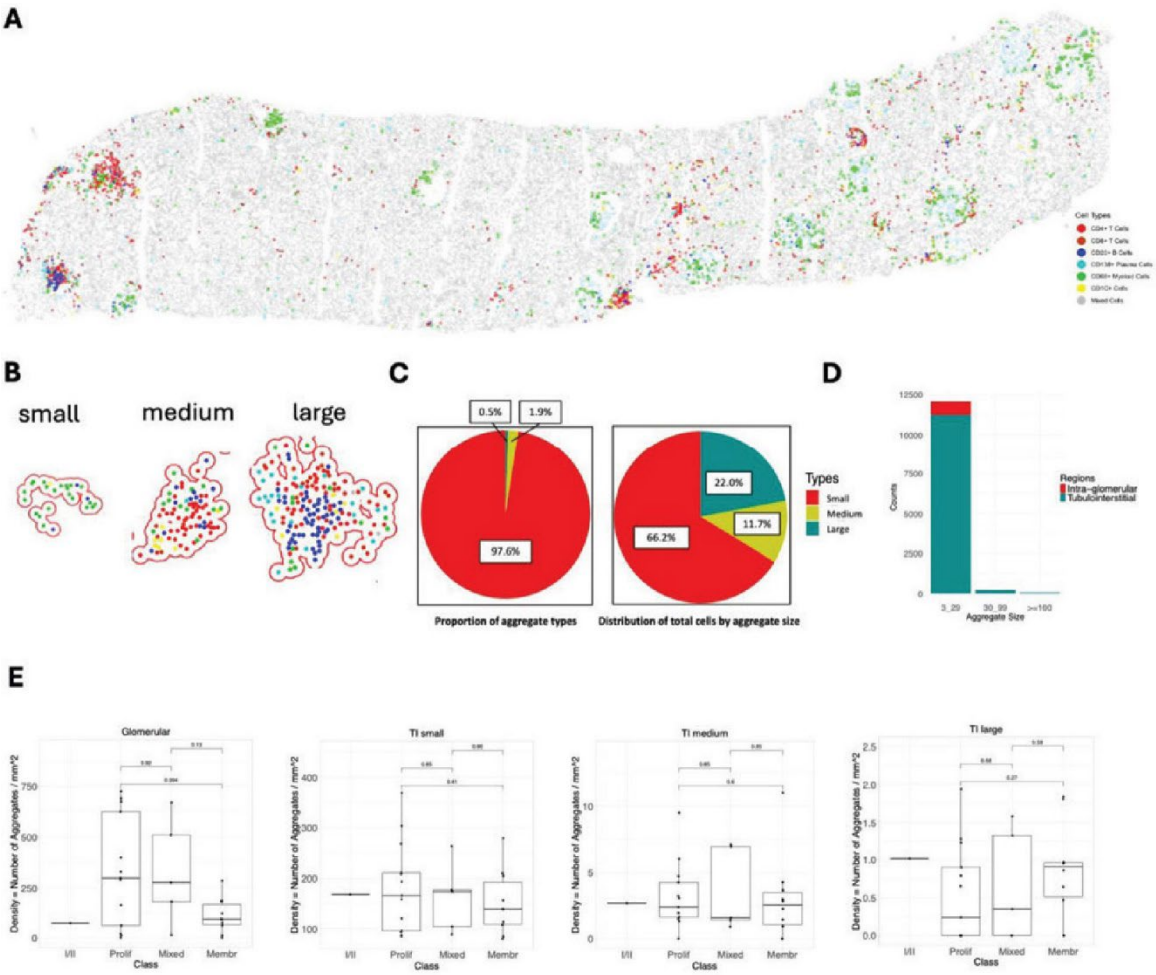


Figure 12. Demographics of intrarenal immune cell aggregates.

Digitalized biopsy showing an example of the distribution of immune cells in LN. (B) Examples of intrarenal immune cell aggregates of different sizes. (C) Distribution of aggregates by size and by total cells. (D) Distribution of aggregates by size and region. (E) Density of aggregate types according to size and class.

Source: Figure adopted from Lee et al., 2025

Heatmap analyses revealed that tubulointerstitial inflammation appeared similar in membranous and proliferative LN, but specific immune structures correlated with distinct clinical and pathological features. Thus, AI-driven spatial mapping in LN may be a useful tool for targeted interventions (**Figure 13**).

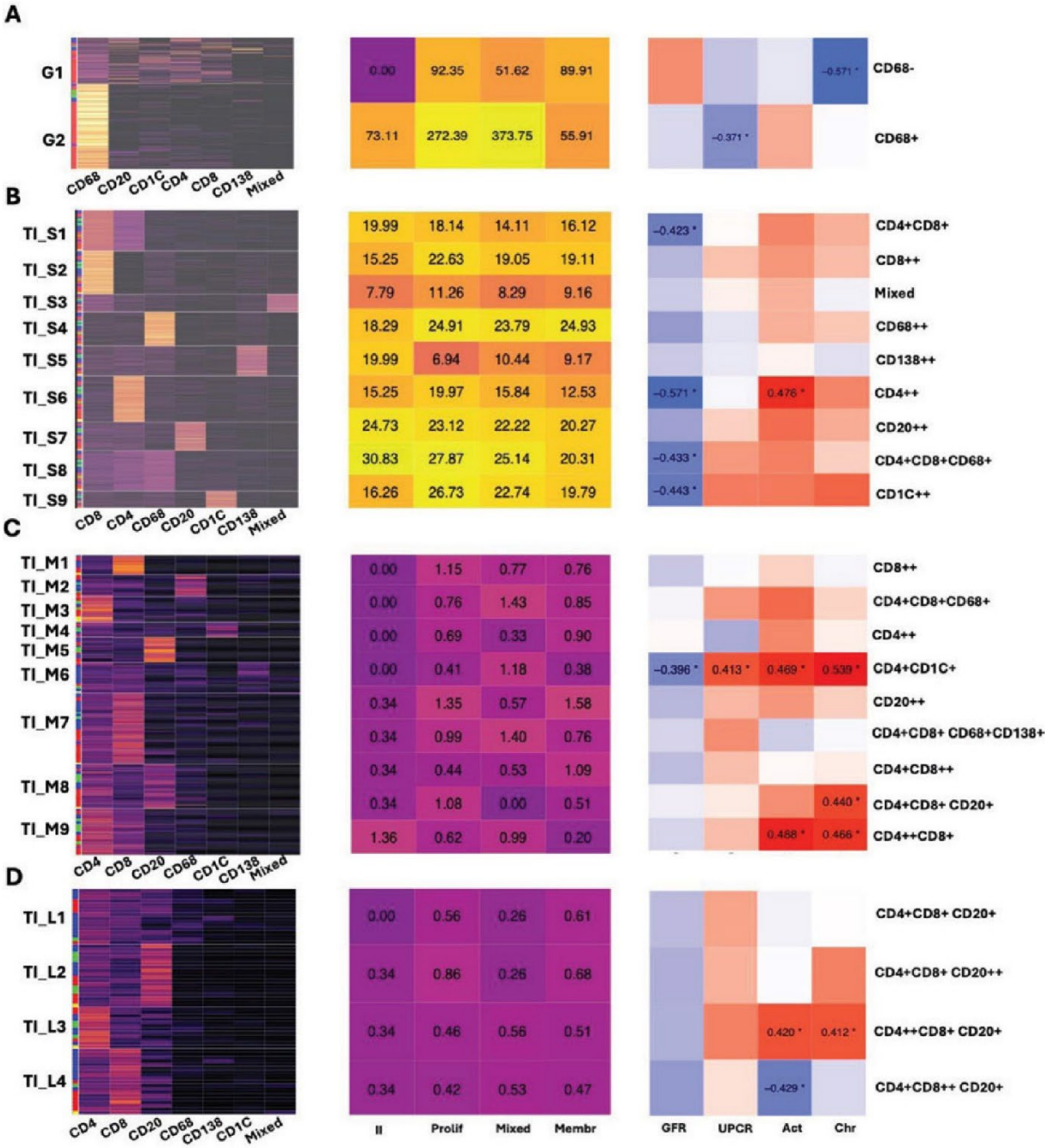


Figure 13. Correlation between aggregate subtypes and clinical features.

Heatmaps on the left displaying the subtypes of immune cell aggregates. The proportion of immune cell types in each aggregate was used for K-means clustering to determine aggregate subtypes. The column annotation rows of the heatmaps represent LN classes, red: proliferative; green: mixed, blue: pure membranous; yellow: ISN class II. Heatmaps in the middle show the average density of different aggregates, measured as the average number of aggregates per mm². Heatmaps on the right showing the correlation matrices between the aggregate subtypes and clinical features. Clinical features, including GFR, urinary protein-creatinine ratio (UPCR), and NIH activity and chronicity indices, were correlated with each aggregate subtype using Pearson's correlation coefficient. Correlation coefficients with statistical significance are shown and marked with asterisks. (A) Glomerular small aggregate (B) Tubulointerstitial small aggregate (C) Tubulointerstitial medium aggregate (D) Tubulointerstitial large aggregate. Act: NIH activity index; Chr: NIH chronicity index

Source: Figure adopted from Lee et al., 2025

Identification of RITUXIMAB Super-Responders

Treatment with rituximab may still be considered in case of refractory SLE disease, although its efficacy is variable depending on the depth of B cell depletion and rate of repopulation [EULAR 2023 update]. Individual patient characteristics such as complement levels and FcγR genotype are supposed to influence treatment response to rituximab. Plasmablast repopulation ≤0.0008 x 10^9/L at 6 months after first rituximab treatment was found to be associated with longer treatment response [Md Yusof et al., 2017]. The results of a single center observational study, including rituximab-treated SLE patients who followed an on-demand retreatment strategy for 20 years, were reported at EULAR 2025 [Patel et al., 2025] (**Figure 14**). Based on survival curve, patients with more than 3 years of relapse free survival after a first rituximab cycle were defined as 'rituximab super-responders'. This occurred in 23/114 patients (20%) with median duration of response of 263 weeks.

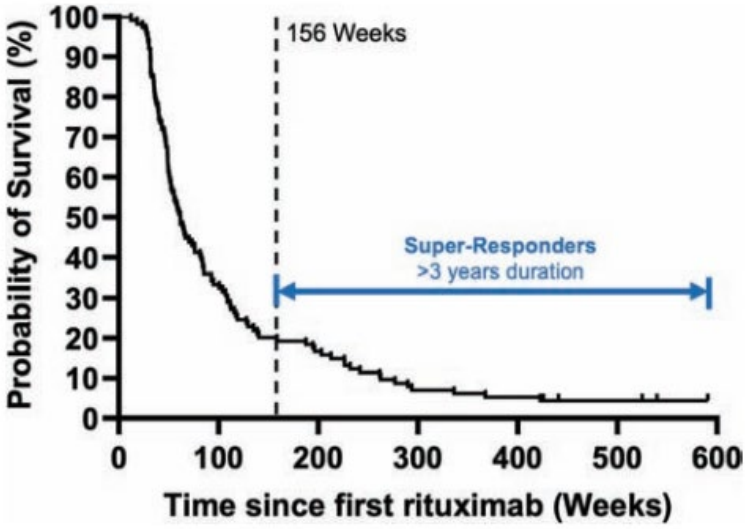


Figure 14. Kaplan-Meier plot of relapse-free survival after a first cycle of rituximab.
Source: Figure adopted from Patel et al., 2025

One in five RTX-treated patients had >3 years response to their first cycle, and 1 in 12 had sustained, immunosuppressant-free remission. Sustained suppression of plasmablasts was observed at 3 years: median 0.0008 x 10^9/L (interquartile range: 0.0005, 0.0034). RTX-super-response was associated with patient characteristics typically denoting disease severity (early disease, non-European ancestry and APS), as well as marked suppression of plasmablast repopulation. No other factors (age, gender, anti-dsDNA+, low C3/C4, number of antibodies, concomitant immunosuppressant, disease activity score, and active BILAG A/B in 5 most frequent domains) were predictive. The authors concluded that given their safety and low cost, anti-CD20 monoclonal antibodies in early poor-prognosis SLE may be preferable to intensive therapy in refractory disease. Thus, identification of "rituximab super-responders" in SLE suggests that biomarker-guided therapy could optimize outcomes and reduce treatment burden.

Concluding Remarks

- The scope of current SLE therapies is to control disease activity, reduce organ damage, and decrease long-term morbidity and mortality. The cornerstone for induction of remission is still hydroxychloroquine (HCQ) that is effective to reduce non-renal disease activity, severe flares, use of steroids/immunosuppressants and organ damage. Treatment with HCQ plus glucocorticoids and/or immunosuppressants (standard-of-care) is able to stop flares and functions mainly for disease control, but (with the exception of rare cases) is not effective to achieve complete remission.
- Clinically significant improvements in SLE outcomes have been demonstrated with monoclonal antibodies such as rituximab (anti-CD20), belimumab (anti- BAFF) and anifrolumab (anti-IFNAR1) which are targeting B cell survival and proliferation or B cell activation. According to EULAR 2023, these, so-called B-cell depleter, are recommended in addition to standard-of-care in severe, therapy refractory SLE with or without kidney involvement. However, therapies providing durable clinical responses without requiring chronic immunosuppressive drugs are still lacking.
- Novel therapeutic approaches aiming to provide a more profound B cell depletion include monoclonal antibodies with dual actions (such as ianalumab and obinutuzumab) or specifically targeting B cell activation (such as dapirolizumab pegol). A deeper B cell depletion can also be achieved with chimeric antigen receptor T cells (CAR-T cells) targeting B cell (CD19 and/or CD20) receptors (such as rese-cel) or proteins like BCMA involved in B cell activation (such as descartes-08). Whether the deeper B cell depletion observed with these investigational therapies is able to induce durable drug-free responses is currently evaluated in clinical trials in patients with moderately to severely active SLE with or without lupus nephritis.
- Achieving long-term remission in SLE is still demanding and limited by the heterogeneity and fluctuating nature of this autoimmune disorder and the lack of validated prognostic biomarkers. Precise diagnostic tools using proteomics, individual responder assessment, and digital integration supported by artificial intelligence (AI) are increasingly providing new insights into the pathogenetic nature of non-renal SLE and lupus nephritis. These advances promise not only improved outcomes but also more personalized and accessible care for patients worldwide.

Author and contact:
Claudia Werner, MD, PhD
Charité Research Organisation GmbH
Charitéplatz 1, 10117 Berlin
claudia.werner@charite-research.org

References

Abdalhadi HM, Chatham WW, Alduraibi FK. CAR-T-Cell Therapy for Systemic Lupus Erythematosus: A Comprehensive Overview. Int. J. Mol. Sci. 2024, 25, 10511. https://doi.org/10.3390/ ijms251910511

Alshaiki F, Obaid E, Almuallim A, Taha R, El-Haddad H, Almoallim H. Outcomes of rituximab therapy in refractory lupus: a meta-analysis. Eur J Rheumatol 2018, 5(2):118–126. https:// doi.org/10.5152/eurjrheum.2018.17096

Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2017;76:476–85.

Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M et al. 2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:1151–1159. doi:10.1136/annrheumdis-2018-214819

Arnold J, Dass S, Twigg S, et al. Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab. Rheumatology (Oxford) 2022;61(12):4905–09.

Askanase AD, D'Cruz D, Kalunian K, Merrill JT, Navarra SV et al. Cenerimod, a sphingosine-1-phosphate receptor modulator, versus placebo in patients with moderate to severe systemic lupus erythematosus, CARE phase 2 trial. LANCET 2025 (7,1) e21-e32, https://doi.org/10.1016/ S2665-9913(24)00246-7

Askanase AD, Furie RA, Dall'Era M, et al. Disease-modifying therapies in systemic lupus erythematosus for extrarenal manifestations. Lupus Science & Medicine 2024;11:e001124. doi:10.1136/ lupus-2023-001124

Catlett IM, Hu Y, Gao L, Banerjee S, Gordon K, Krueger JG: Molecular and clinical effects of selective tyrosine kinase 2 inhibition with deucravacitinib in psoriasis. J Allergy Clin Immunol. 2021 Nov 10. pii: S0091-6749(21)01690-0. doi: 10.1016/j.jaci.2021.11.001. (PubMed ID 34767869)

Chahin N, Sahagian G, Feinberg MH, Stewart CA, Jewell CM et al. Durability of Response to B-Cell Maturation Antigen-Directed mRNA Cell Therapy in Myasthenia Gravis. Annals of Clinical and Translational Neurology, 2025; 0:1–9 https://doi.org/10.1002/acn3.70167

Clowse M, Isenberg D, Merrill J, Dörner T, Petri M, Vital E, Morand E, Jimenez T, Brookes S, Gaiha-Rohrbach J, Martin C, Nelde A, Stach C. Dapirolizumab Pegol Demonstrated Significant Improvement in Systemic Lupus Erythematosus Disease Activity: Efficacy and Safety Results of a Phase 3 Trial [abstract]. *Arthritis Rheumatol.* 2024; 76 (suppl 9).

Cutcutache I, Powlesland A, Skelton A, Sun Y, Page M, Stojan G, Lipsky P, Skowera A, Stach C. Dapirolizumab Pegol Impacts Important Immunologic Pathways in SLE: Pharmacodynamic Analysis of B Cell and Type I Interferon Pathways from a Phase 2b Trial [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9).

Dai X, Fan Y and Zhao X. Systemic lupus erythematosus: updated insights on the pathogenesis, diagnosis, prevention and therapeutics. Signal Transduction and Targeted Therapy (2025) 10:102.

Dostert C, Grusdat M, Letellier E, and Brenner D. (2019). The TNF Family of Ligands and Receptors: Communication Modules in the Immune System and Beyond. Physiol. Rev. 99, 115–160. doi:10.1152/physrev.00045.2017.

Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus Ann Rheum Dis 2019;78:736–745.

Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis 2024;83:15–29.

Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a lupus low disease activity state (LLDAS). Ann Rheum Dis 2016;75:1615–21.

Furie RA, van Vollenhoven RF, Kalunian K, M.D., Sandra Navarra, M.D., Juanita Romero-Diaz, M.D., Victoria P. Werth, M.Det al Trial of Anti-BDCA2 Antibody Litifilimab for SLE. NEJM (2022); 387: 894-904.

Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2022 Jan;81(1):100-07.

Furie RA, Rovin BH, Garg JP, Santiago MB, Aroca-Martínez G, Zuta Santillán AE et al. Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis. N Engl J Med. 2025 Feb;392:1471-83.

Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2021. doi:10.1136/annrheumdis-2021-220920.

G-BA (17.08.2023): Bundesministerium für Gesundheit. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) – Voclosporin (Lupusnephritis) Fundstelle: BAnz AT 25.09.2023 B3

Goede V, Klein Ch, Stilgenbauer S. Obinutuzumab (GA101) for the Treatment of Chronic Lymphocytic Leukemia and Other B-Cell Non-Hodgkin's Lymphomas: A Glycoengineered Type II CD20 Antibody. Oncol Res Treat 2015;38:185–192.

Goess C, Harris CM, Murdock S, et al. ABBV-105, a selective and irreversible inhibitor of Bruton's tyrosine kinase, is efficacious in multiple preclinical models of inflammation. Mod Rheumatol 2019;29:510–22.

Hermann V, Batalov A, Smakotina S, Juif P-E, Cornelisse P. First Use of Cenerimod, a selective S1P1 receptor modulator, for the treatment of SLE: a double-blind, randomised, placebo-controlled, proof-of-concept study. Lupus Science & Medicine 2019;6:e000354

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 40, 1725 (1997).

Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004; 50(12):3934–394

Isenberg DA, Rahman A, Allen E, Farewell V, Akil M et al. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology 2005;44:902–906.

Juif P-E, Baldoni D, Reyes M, et al. Pharmacokinetics, pharmacodynamics, tolerability, and food effect of Cenerimod, a selective $S1P_1$ receptor modulator in healthy subjects. Int J Mol Sci 2017;18:E2636

Kreuzaler M, Rauch M, Salzer U, Birmelin J, Rizzi M, Grimbacher B, Plebani A, Lougaris V, Quinti I, Thon V, Litzman J, Schlesier M, Warnatz K, Thiel J, Rolink AG, Eibel H (January 2012). "Soluble BAFF levels inversely correlate with peripheral B cell numbers and the expression of BAFF receptors". Journal of Immunology. 188 (1): 497–503. doi:10.4049/jimmunol.1102321C. Y.

Kuo CF, Grainge MJ, Valdes AM, See L-C, LuoS-F et al. Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. JAMA Intern. Med. 175, 1518–1526 (2015).

in 't Veld AE, Jansen MAA, Ciere LCA, Moerland M. Hydroxychloroquine effects on TLR signalling: Underexposed but unneglectable in COVID-19. Journal of Immunology Research Volume 2021, Article ID 6659410, 7 pages.

Laurynenka V and Harley JB (2024) The 330 risk loci known for systemic lupus erythematosus (SLE): a review. Front. Lupus 2:1398035. doi: 10.3389/flupu.2024.1398035

Lawrence JS, Martins CL, Drake GL. A family survey of lupus erythematosus, 1: heritability. J Rheumatol. 1987;14(5):913-921.

Lee CY, Marlin MC, Yang X, Morkotinis V, Celia AU et al. POSO317 THE IMMUNE MAP OF LUPUS NEPHRITIS: A SPATIALLY-RESOLVED KIDNEY PROTEOMIC APPROACH. Annals of the Rheumatic Diseases, Vol. 84, Suppl. 1, June 2025, pp 576-577. h

Mackay F and Schneider P. 2009. Cracking the BAFF code. Nat. Rev. Immunol.9: 491–502.

Mackensen A, Muller F, Mougiakakos D, Boltz S, Wilhelm A, Aigner M, Volkl S, Simon D, Kleyer A, Munoz L et al (2022) Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nat Med 28:2124–2132.

Merrill JT, Tanaka Y, D'Cruz D, et al. Efficacy and safety of upadacitinib or elsubrutinib alone or in combination for patients with systemic lupus erythematosus: a phase 2 randomized controlled trial. Arthritis Rheumatol 2024;76:1518–29.

Md Yusof MY, Shaw D, El-Sherbiny YE, Dunn E, Rawstron AC et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Ann Rheum Dis. 2017 Nov;76(11):1829-1836.

Morand E, Pike M, Merill J, van Vollenhoven R, Werth V et al. EFFICACY AND SAFETY OF DEUCRAVACITINIB, AN ORAL, SELECTIVE, ALLOSTERIC TYK2 INHIBITOR, IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. DOI: 10.1136/annrheumdis-2022-eular.5020a

Morand E, Carter L, Dall'Era M, Petri M, Vital E et al. ACHIEVEMENT OF LOW DISEASE ACTIVITY AND REMISSION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH DAPIROLIZUMAB PEGOL: 48-WEEK RESULTS FROM A PHASE 3 TRIAL. [abstract]. *Arthritis Rheumatol.* 2025; 77 (suppl 9). https://acrabstracts.org/abstract/achievement-of-low-disease-activity-and-remission-in-patients-with-systemic-lupus-erythematosus-treated-with-dapirolizumab-pegol-48-week-results-from-a-phase-3-trial/. Accessed November 4, 2025.

Morand E**,** Dall'Era M, Sanchez-Guerrero J, Pearson D, Werth VP et al. RANDOMISED, PLACEBO-CONTROLLED PHASE II STUDY OF ORAL ENPATORAN, A FIRST-IN-CLASS TOLL-LIKE RECEPTOR 7/8 INHIBITOR, IN SYSTEMIC LUPUS ERYTHEMATOSUS. https://doi.org/10.1016/j.ard.2025.05.391

Muller F, Taubmann J, Bucci L, Wilhelm A, Bergmann C, Volkl S, Aigner M, Rothe T, Minopoulou I, Tur C et al (2024) CD19 CAR T-cell therapy in autoimmune disease—A case series with follow-up. N Engl J Med 390:687–700.

Mysler E, Ignatenko S, Gordienko A, Cortés-Hernández J, Agmon-Levin N, et al. Safety and Efficacy of Subcutaneous Ianalumab (VAY736) for up to 68 Weeks in Patients with Systemic Lupus Erythematosus: Results from Phase 2 Study [abstract]. *Arthritis Rheumatol.* 2024; 76 (suppl 9). https://acrabstracts.org/abstract/safety-and-efficacy-of-subcutaneous-ianalumab-vay736-for-up-to-68-weeks-in-patients-with-systemic-lupus-erythematosus-results-from-phase-2-study/. Accessed October 7, 2025

Parodis I, Gordon C, Merrill J et al. IMPROVEMENT OF FATIGUE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH DAPIROLIZUMAB PEGOL: 48-WEEK RESULTS FROM A PHASE 3 TRIAL. Annals of the Rheumatic Diseases, Vol. 84, Suppl. 1, June 2025, pages 1227-1229.

Patel J, Emery P, Vital EM, MD Yusof MY. POS0325 RITUXIMAB SUPER-RESPONDERS: CHARACTERISTICS OF PATIENTS WITH MORE THAN 3 YEARS RESPONSE TO A SINGLE CYCLE OF TREATMENT. Ann Rheum Dis, Vol. 84, Suppl. 1, June 2025, pp 584-585.

Pellerin A, Otero K, Czerkowicz JM, Kerns HM, Shapiro RI et al. Anti-BDCA2 monoclonal antibody inhibits plasmacytoid dendritic cell activation through Fc-dependent and Fc-independent mechanisms. EMBO Molecular Medicine (2015) Vol 7, No 4. Pp 464-476.

Peng L, Oganesyan V, Wu H, Dall'Acqua WF, Damschroder MM. Molecular basis for antagonistic activity of anifrolumab, an anti-interferon-a receptor 1 antibody. MAbs 2015;7:428–39.

Powlesland AS, Cutcutache I, Skelton A, Shock A, Page M et al. DAPIROLIZUMAB PEGOL IMPACTS IMPORTANT IMMUNOLOGIC PATHWAYS IN SYSTEMIC LUPUS ERYTHEMATOSUS: PHARMACODYNAMIC ANALYSIS OF T CELL AND ANTIGEN PRESENTING CELL PATHWAYS FROM A PHASE 2B TRIAL. Annals Rheum Dis 2024;83 (suppl 1):261. https://doi.org/10.1136/annrheumdis-2024-eular.192

Reddy V, Klein C, Isenberg DA, et al. Obinutuzumab induces superior B-cell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. Rheumatology (Oxford) 2017;56(7):1227–37.

Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, Appel G, LUNAR Investigator Group (2012) Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the LupusNephritis Assessmentwith Rituximab study. Arthritis Rheum64(4):1215–1226.

Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Care & Research 2020; 72: 461–488.

Scherlinger M, Kolios A.G.A, Kyttaris VC and Tsokos GC. Advances in the treatment of systemic lupus erythematosus. Nature Reviews Drug Discovery (2025

Sheikh S., Derebail V, Grover N, Gulati G, Abed M et al. (2025) RESET-SLE: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), a Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Non-Renal SLE and Lupus Nephritis [abstract]. *Arthritis Rheumatol.* 2025; 77 (suppl 9). https://acrabstracts.org/abstract/reset-sle-clinical-trial-evaluating-rese-cel-resecabtagene-autoleucel-a-fully-human-autologous-4-1bb-cd19-car-t-cell-therapy-in-non-renal-sle-and-lupus-nephritis/. Accessed November 4, 2025.

Tanaka Y. Systemic lupus erythematosus. Best Practice & Research Clinical Rheumatology 2022;36:101814.

Tian J, Zhang D, Yao X, Huang Y, Lu Q. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. Ann Rheum Dis 2023;82:351–356.

van Vollenhoven RF, Bertsias G, Doria A, et al. DORIS definition of remission in SLE: final recommendations from an international task force. Lupus Sci Med 2021;8:e000538.

van Vollenhoven R, Askanase AD, Bomback AS, et al. Conceptual framework for defining disease modification in systemic lupus erythematosus: a call for formal criteria. Lupus Sci Med 2022;9:e000634. 10.1136/lupus-2021-000634

Vital EM, Clowse MEB, Isenberg D, Merrill J, Dörner T et al. DAPIROLIZUMAB PEGOL DEMONSTRATED SIGNIFICANT IMPROVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY: EFFICACY AND SAFETY RESULTS OF A PHASE 3 TRIAL. Ann Rheum Dis Vol. 84, Suppl. 1, JUNE 2025, pp 1900-902.

Wang W, He S, Zhang W, Zhang H, DeStefano VM, Wada M, Pinz K, Deener G, Shah D, Hagag N et al (2024) BCMA-CD19 compound CAR T cells for systemic lupus erythematosus: a phase 1 open-label clinical trial. Ann Rheum Dis. 2024 Sep 30;83(10):1304-1314. doi: 10.1136/ard-2024-225785.

Yamane-Ohnuki N, Kinoshita S, Inoue-Urakubo M, et al. Establishment of FUT8 knockout Chinese hamster ovary cells: an ideal host cell line for producing completely defucosylated antibodies with enhanced antibody-dependent cellular cytotoxicity. Biotechnol Bioeng 2004;87:614–22.

Yusof MYM, Shaw D, El-Sherbiny YM et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. *Ann Rheum Dis* 2017;76:1829–36.

Zhang K, Ye K, Tang H, Qi Z, Wang T et al. Development and Therapeutic Implications of Tyrosine Kinase 2 Inhibitors. J. Med. Chem. 2023, 66 (7), 4378−4416.