Lupus Nephritis
New Treatments and Updated Guidelines in
initial therapy for focal (class III) or diffuse (class IV) lupus nephritis

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Introduction

Prevalence lupus in general population is:

25 to 150 per **100,000** people

Lupus nephritis (LN) occurs in approximately :

40% *of patients with SLE*

and

5%–15% *of these patients progressing to ESKD within 10 years*

Introduction

- ***45000***
- ***18000***
- ***1800***

Risk factors for progressive kidney disease

Clinical parameters :

- Proteinuria (the best clinical prognostic biomarker)
- glomerular filtration rate
- complement levels
- anti-dsDNA titer
- presence of antiphospholipid antibodies

kidney biopsy classification:

activity and chronicity

the best clinical prognostic biomarker

- Proteinuria

(cutoff of 0.7–0.8 g/24 hours at 1 year is predictive of a good long-term renal prognosis)

novel biomarkers with kidney disease progression

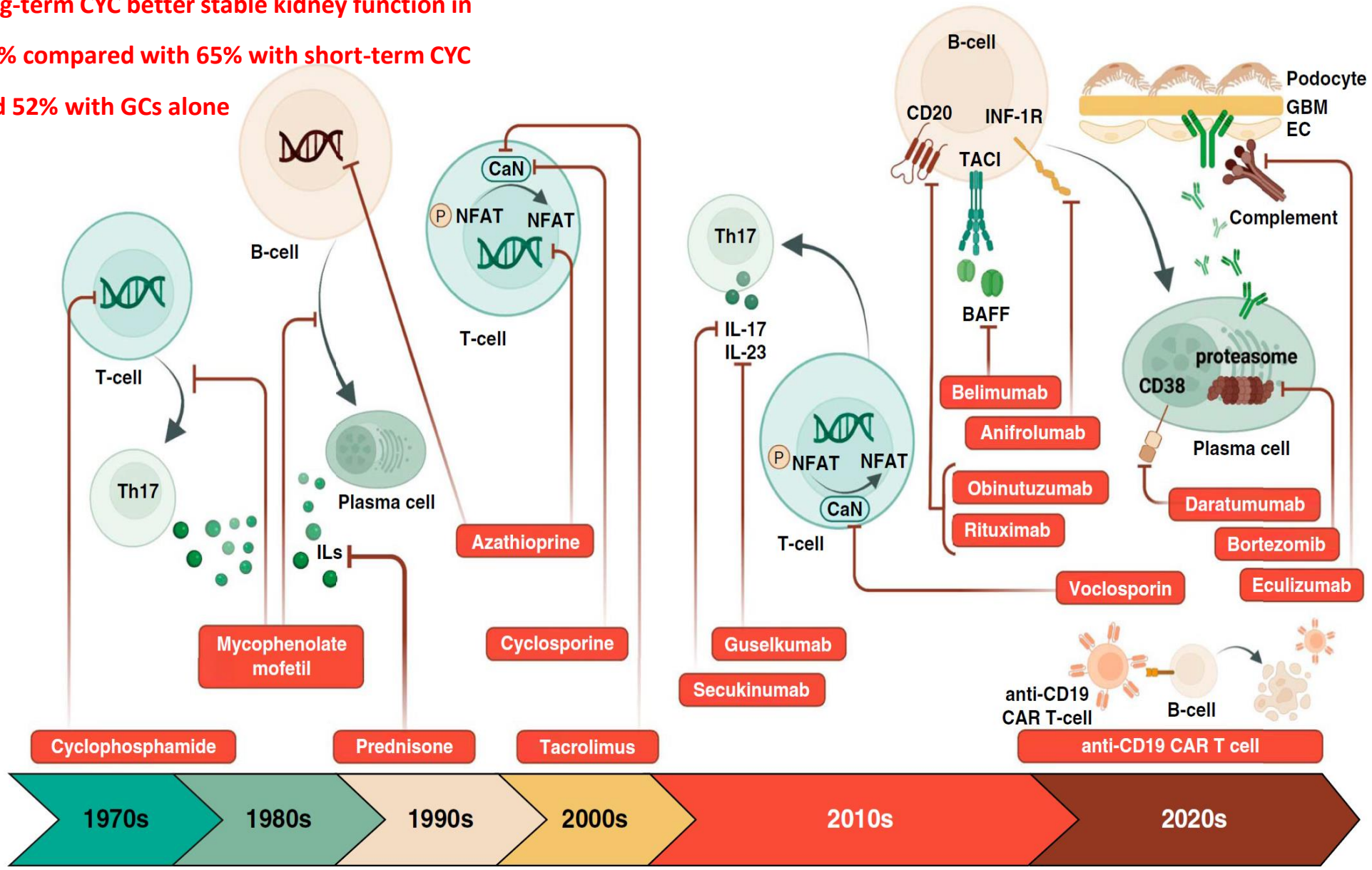
- **Anti-dsDNA and antihistone antibodies with an IgG2 isotype .**
- **Antibodies to annexin A1 and α-enolase have been associated with proliferative LN.**
- **In membranous LN, exostosin 1 and 2 antigens have been identified in approximately 30% of subjects and are associated with a better prognosis.**

Current Practice and Review of Updated Guidelines

long-term CYC better stable kidney function in

85% compared with 65% with short-term CYC

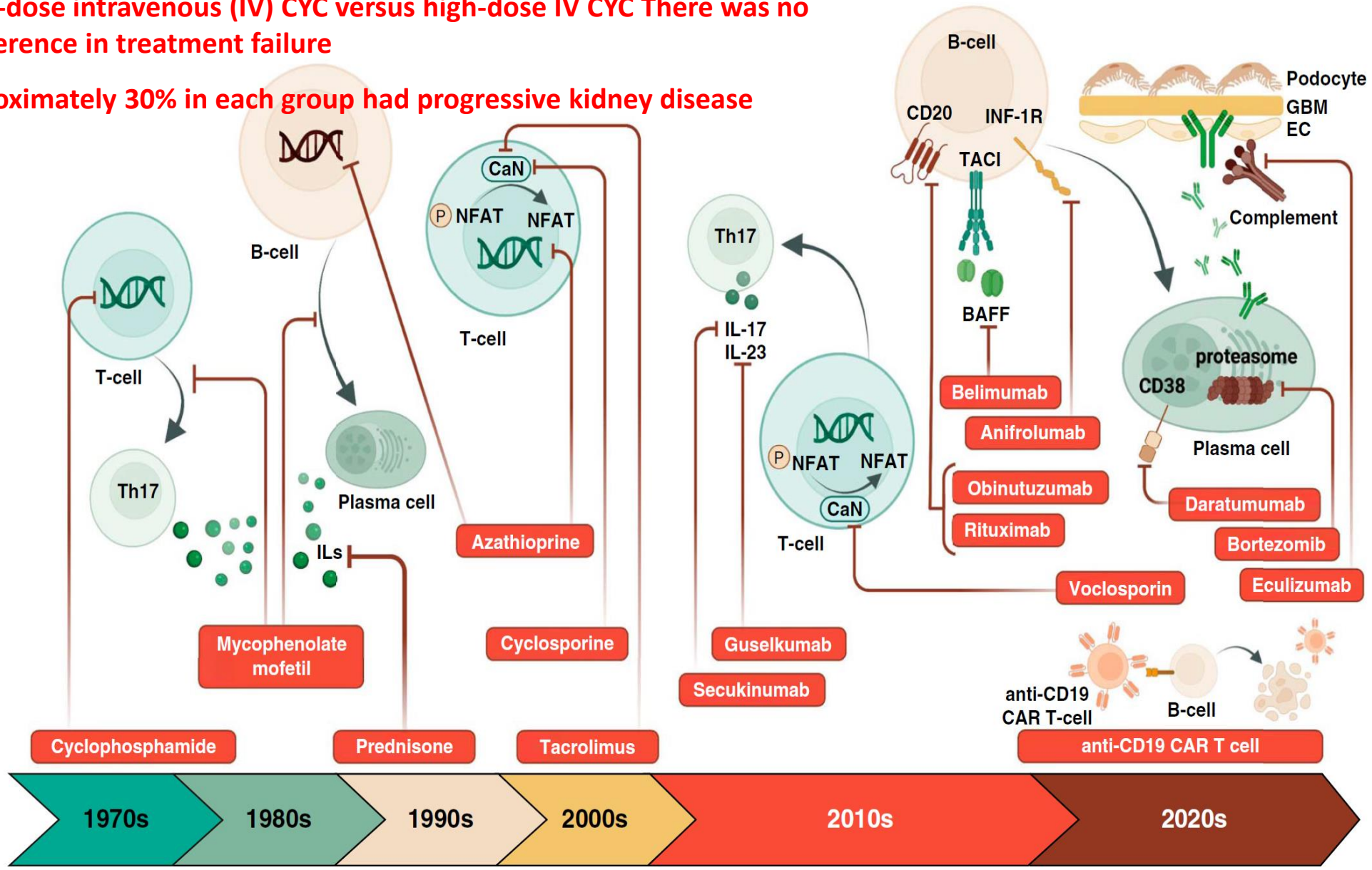
and 52% with GCs alone



Current Practice and Review of Updated Guidelines

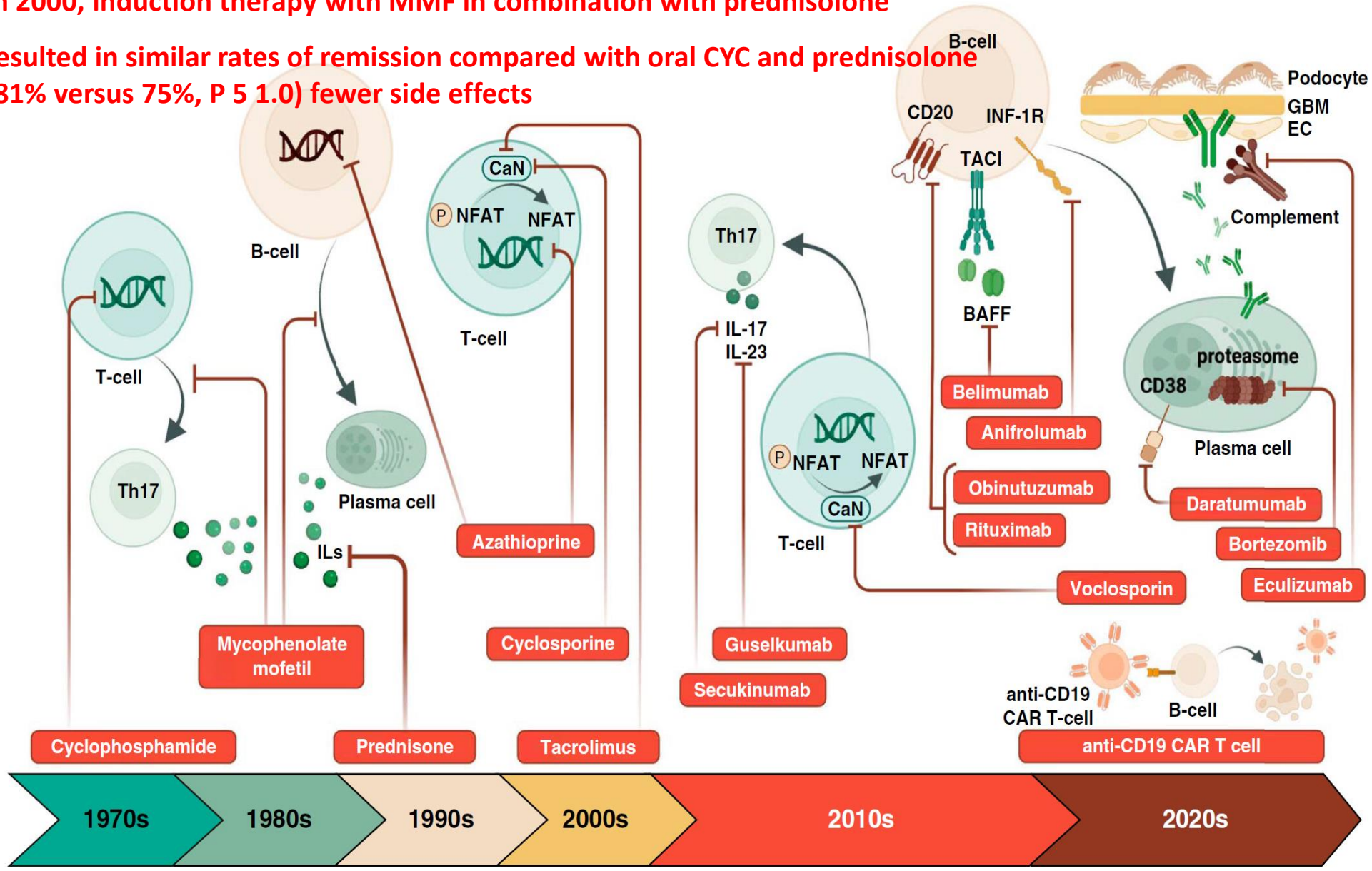
low-dose intravenous (IV) CYC versus high-dose IV CYC There was no difference in treatment failure

pproximately 30% in each group had progressive kidney disease



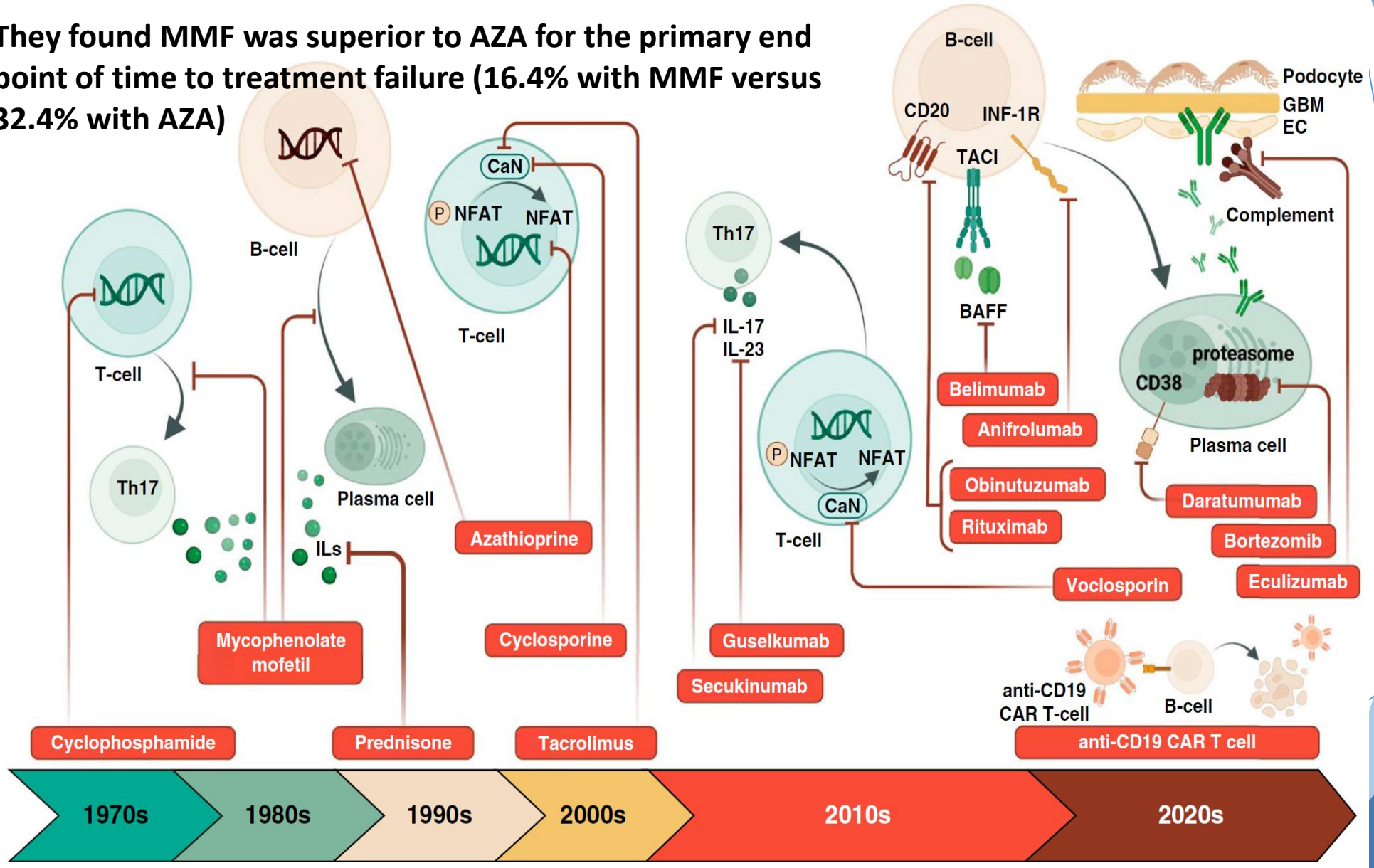
Current Practice and Review of Updated Guidelines

- In 2000, induction therapy with MMF in combination with prednisolone
- resulted in similar rates of remission compared with oral CYC and prednisolone (81% versus 75%, P 5 1.0) fewer side effects



Current Practice and Review of Updated Guidelines

- MMF comparewith AZA for maintenance therapy
- They found MMF was superior to AZA for the primary end point of time to treatment failure (16.4% with MMF versus 32.4% with AZA)



(KDIGO) Kidney Disease: Improving Global Outcomes 2011

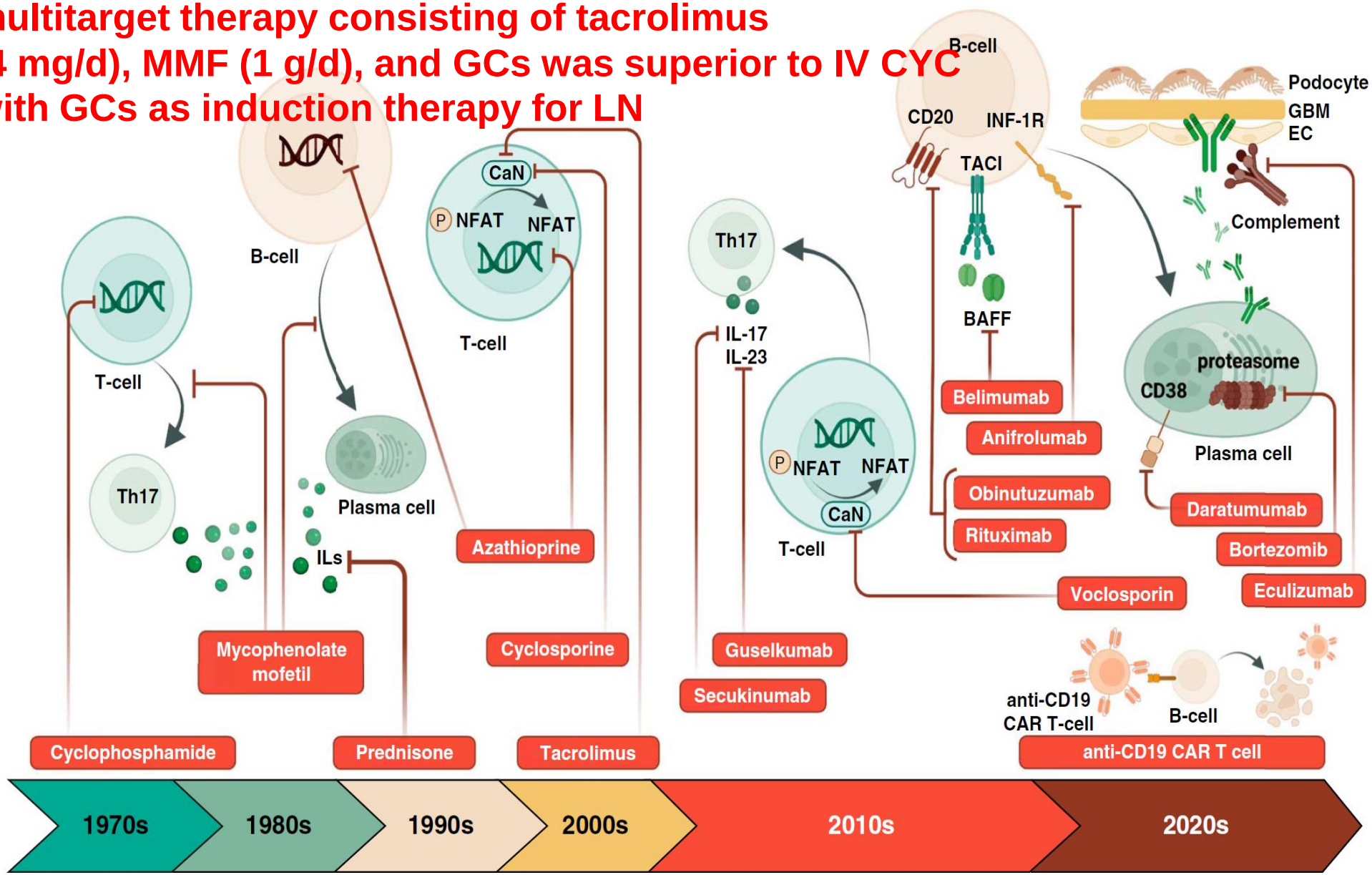
- recommended first-line induction therapy for LN classes III and IV with either

  CYC or mycophenolate

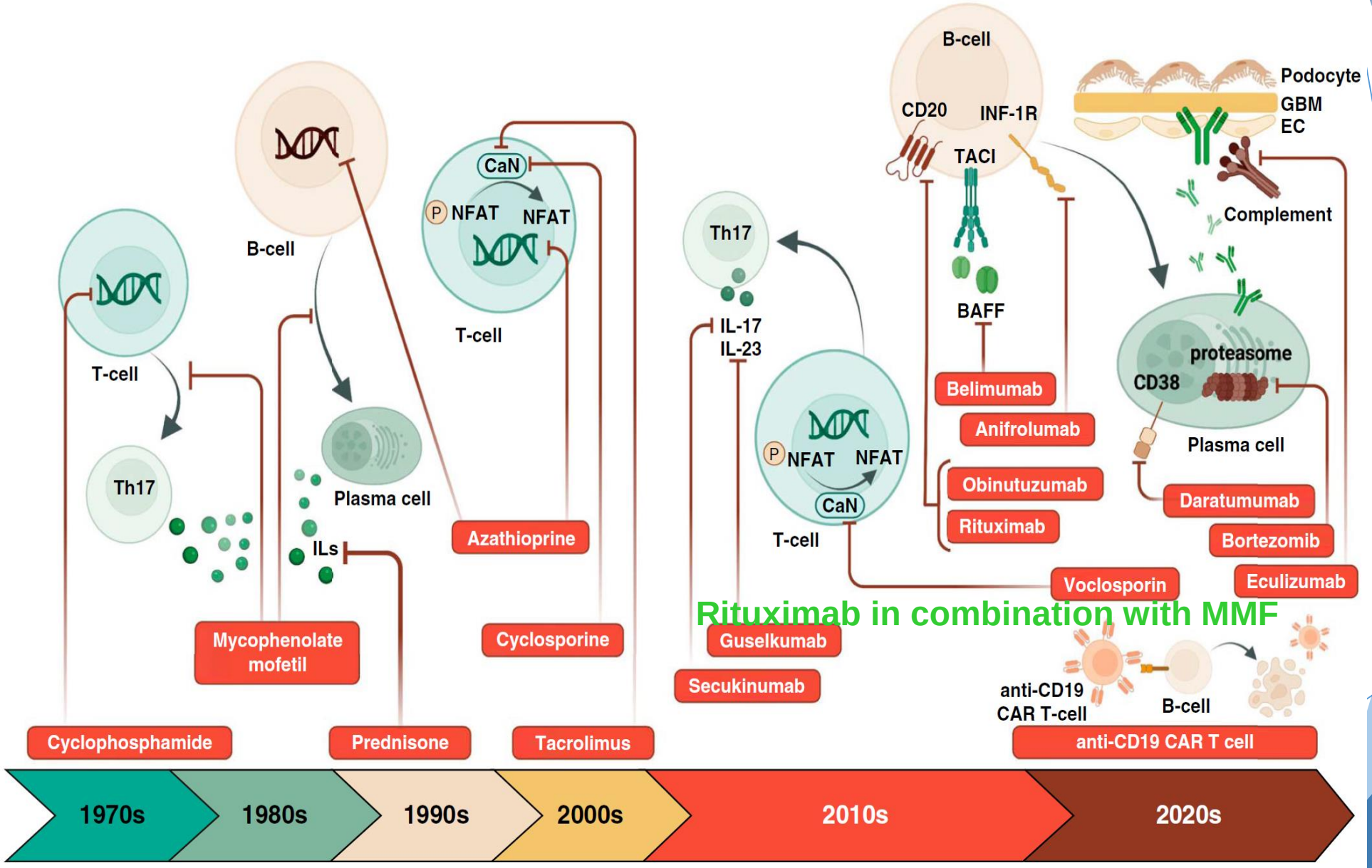
- maintenance therapy with AZA or MMF and low-dose oral corticosteroids (category 1B recommendation).

Current Practice and Review of Updated Guidelines

multitarget therapy consisting of tacrolimus (4 mg/d), MMF (1 g/d), and GCs was superior to IV CYC with GCs as induction therapy for LN



Current Practice and Review of Updated Guidelines



the KDIGO glomerular disease guidelines(2021)

- recommend that in patients with active class III or IV LN, either low-dose IV CYC or MMF in conjunction with GCs is used for induction therapy. Recognizing that lower dose GCs may be as effective as higher-dose GCs moderate, or reduced dose schemes (discussed below).
- For maintenance, KDIGO now recommends MMF over AZA

the KDIGO glomerular disease guidelines(2021)

Also recommended :

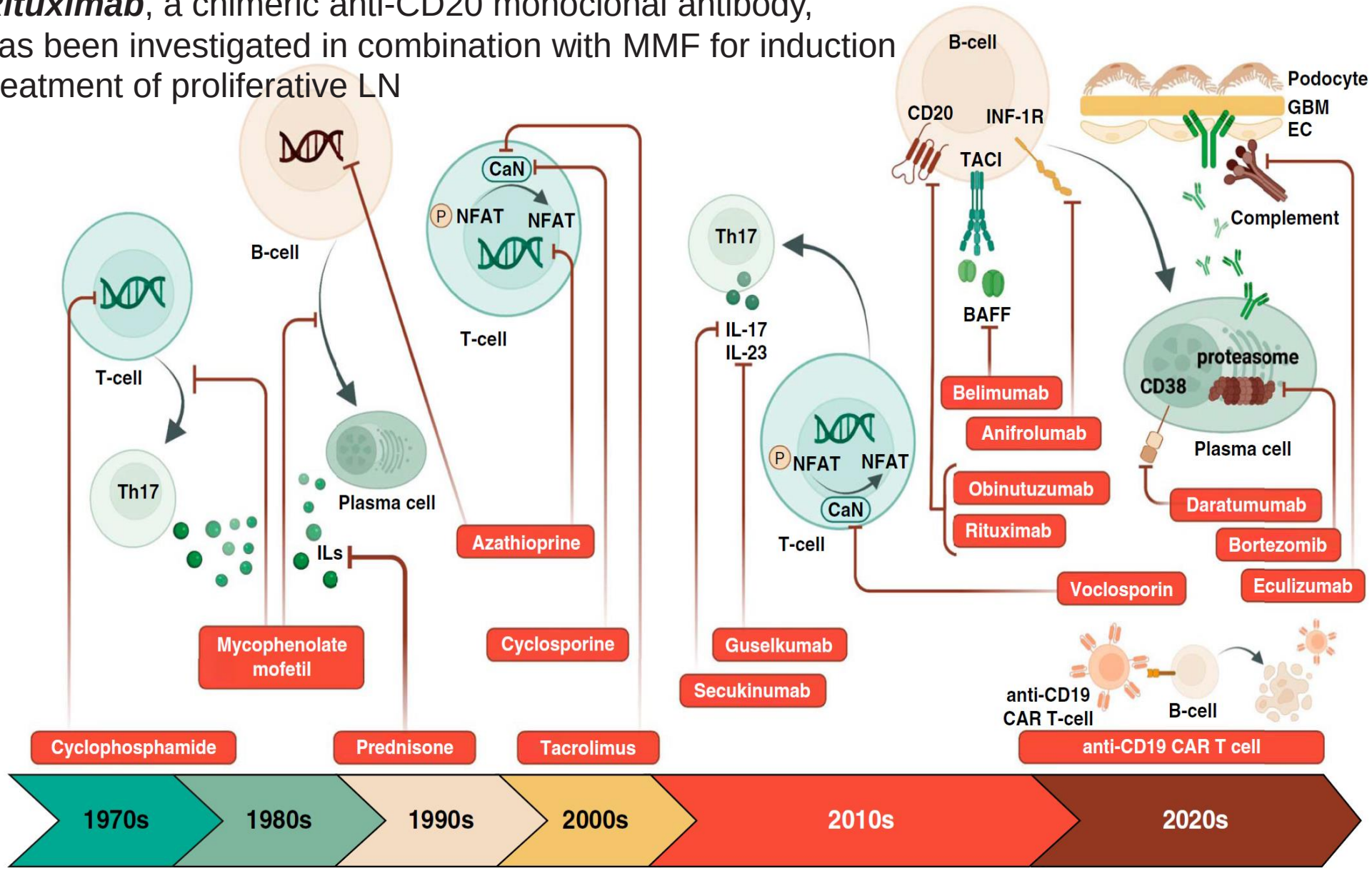
- renin–angiotensin system blockade

  for all patients and immunosuppressive therapy for those with nephrotic syndrome, extra renal manifestations of SLE, or complications of proteinuria, such as thrombosis, edema, or dyslipidemia

- All classes of LN are additionally managed with hydroxychloroquine per clinical practice guidelines

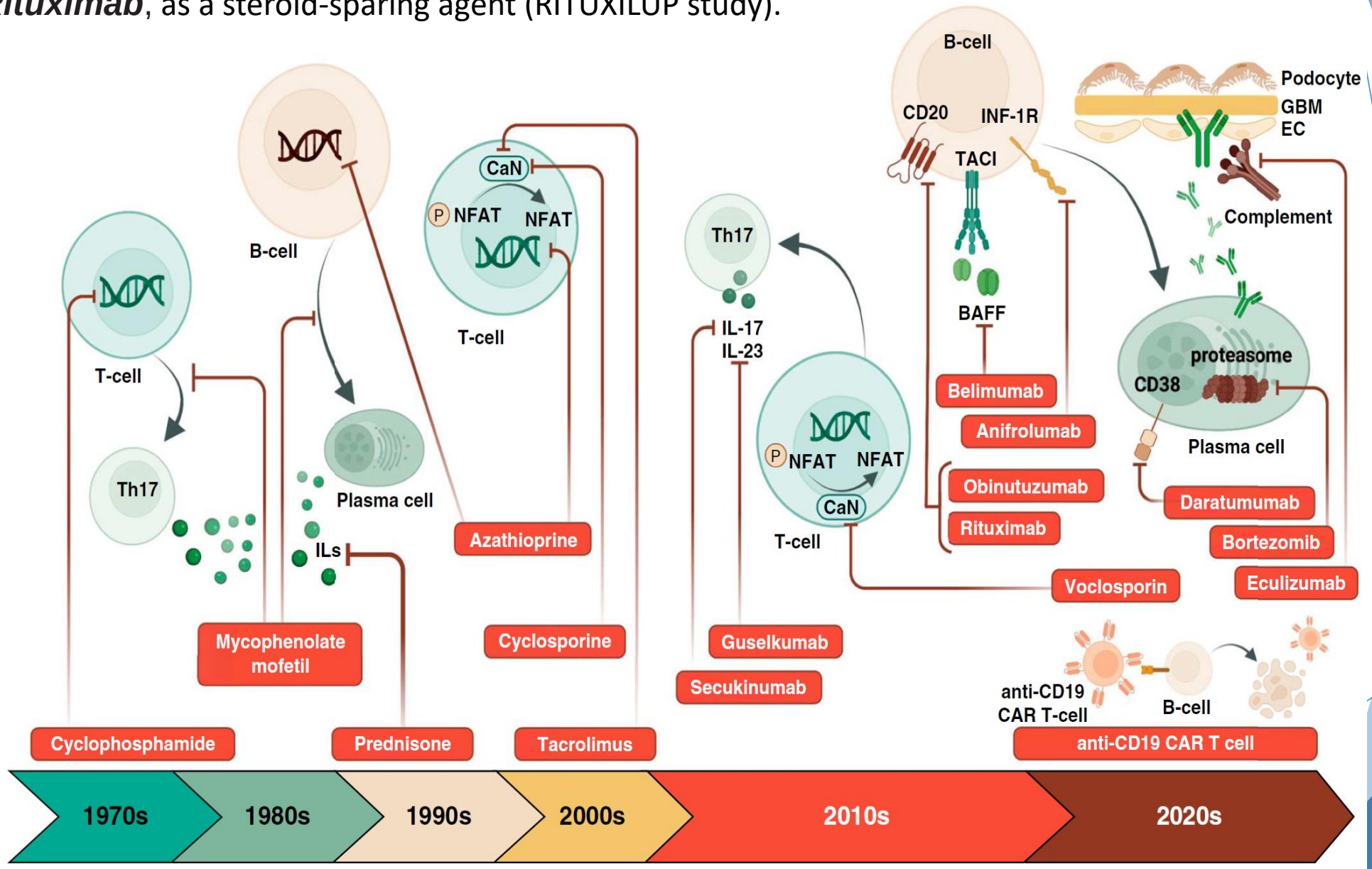
Current Practice and Review of Updated Guidelines

Rituximab, a chimeric anti-CD20 monoclonal antibody, has been investigated in combination with MMF for induction treatment of proliferative LN



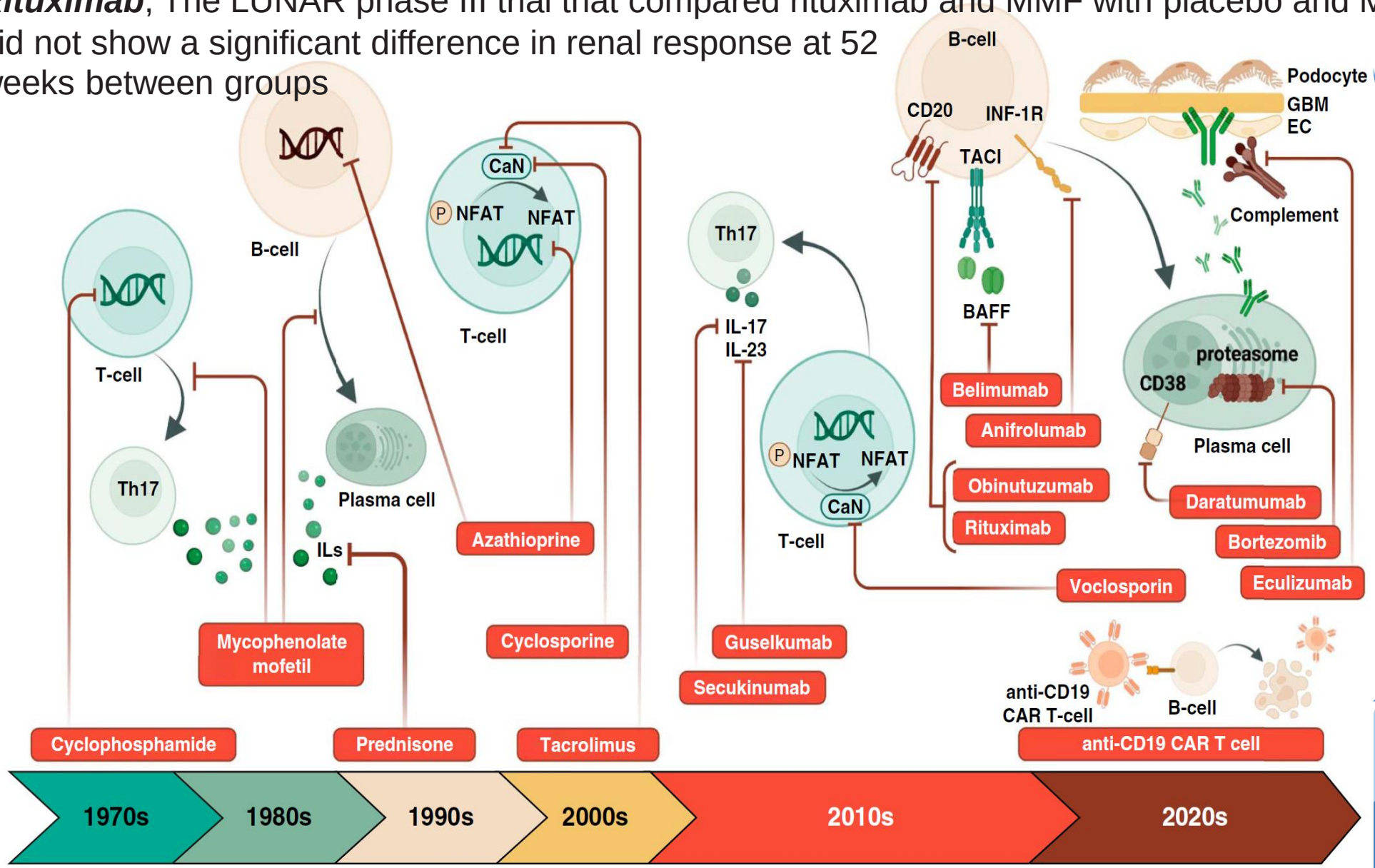
Current Practice and Review of Updated Guidelines

Rituximab, as a steroid-sparing agent (RITUXILUP study).



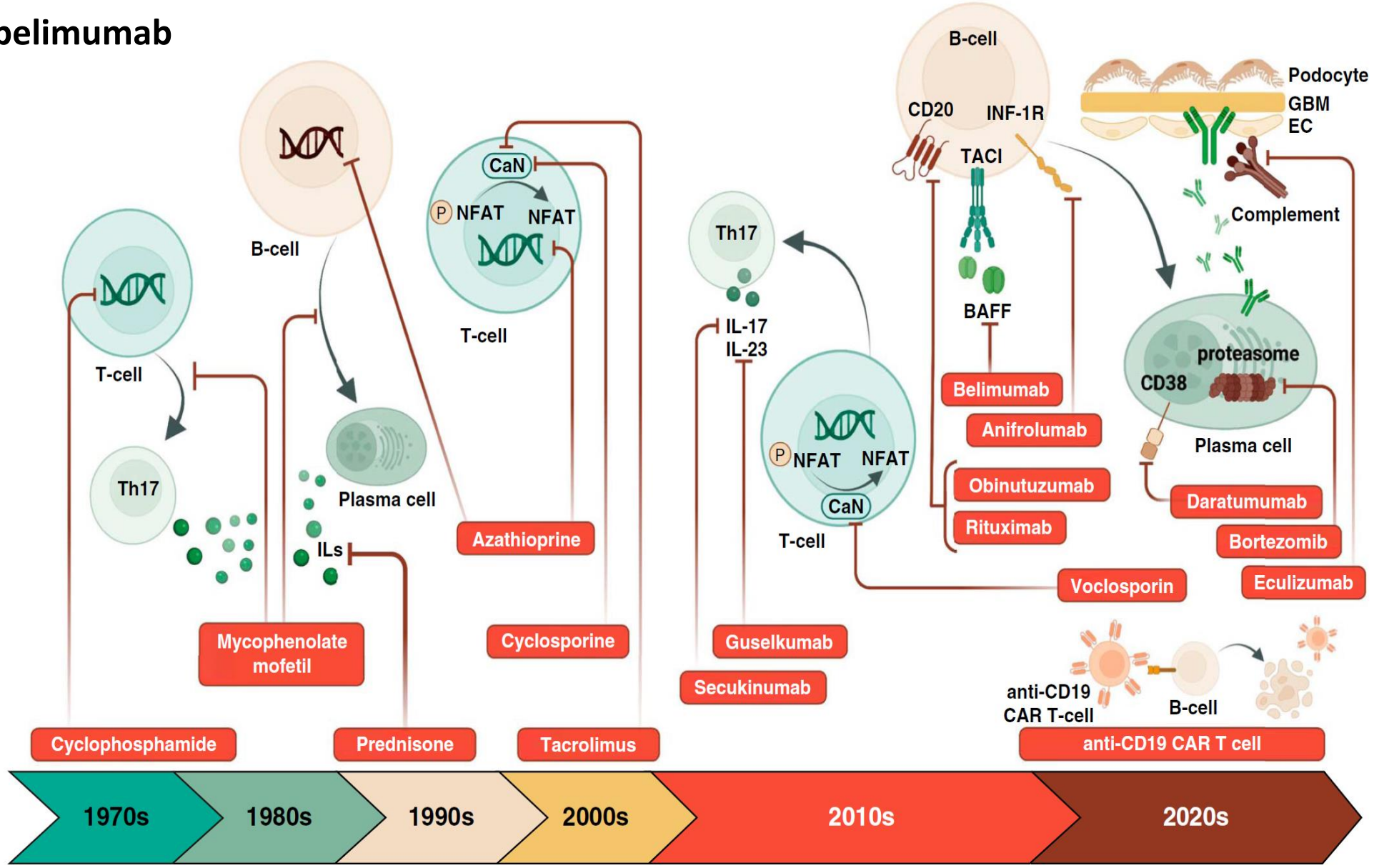
Current Practice and Review of Updated Guidelines

Rituximab, The LUNAR phase III trial that compared rituximab and MMF with placebo and MMF and did not show a significant difference in renal response at 52 weeks between groups



Current Practice and Review of Updated Guidelines

belimumab



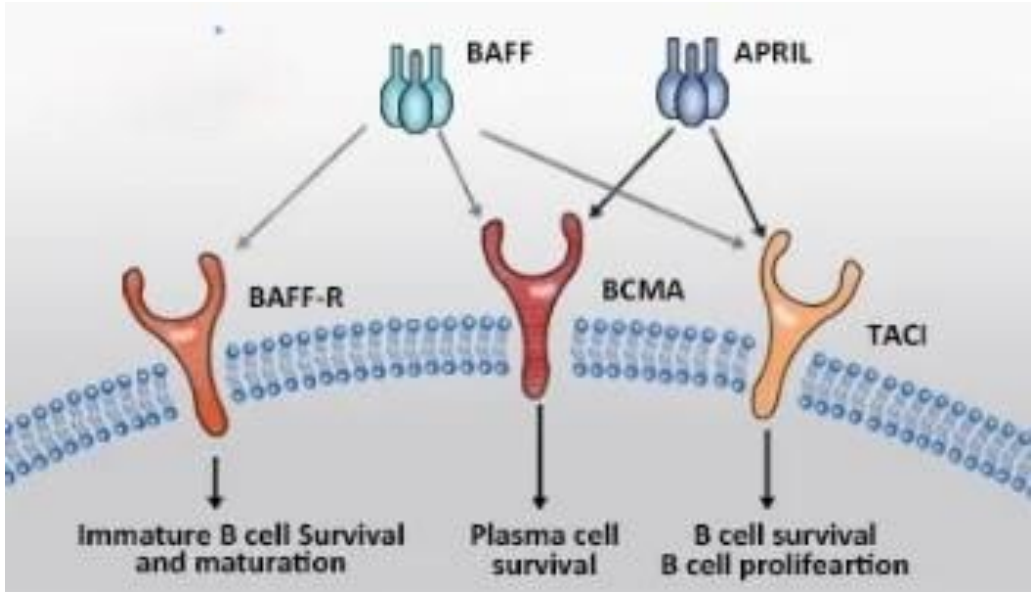
New to Practice

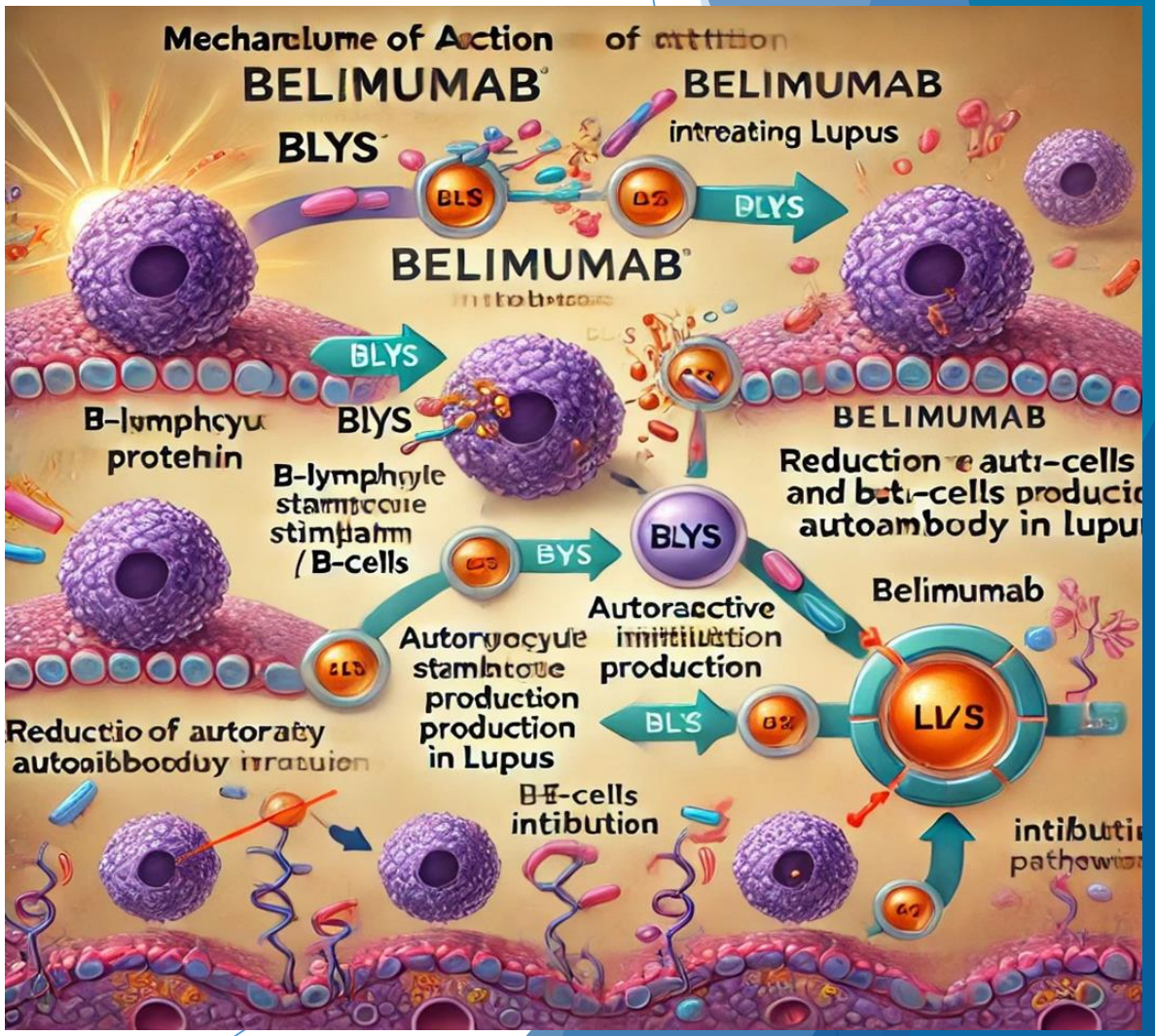
- ***Belimumab***
- **is a fully human monoclonal antibody that inhibits soluble B lymphocyte stimulator protein.**
- ***Baff (BLYS) is TNF family and need for***

B cell survive and maturation

Produced by:

Monocyte,macrophage,dendertic cell, neutrophphil





Belimumab International Study in Lupus Nephritis (BLISS-LN)

active class III or IV (class V) or pure class V LN

randomized to receive IV belimumab 10 mg/kg every two weeks 6 dose or placebo on a background of SOC therapy

primary
efficacy renal response with belimumab than placebo at week 104 (43% versus 32%; P 5 0.03)

secondary
end point of a complete renal response (CRR; 30% versus 20%; P 5 0.02).

the risk of subsequent lupus flares was reduced (14%versus 26%),
and the risk **renal-related event or death was nearly 50% lower with belimumab compared with standard therapy alone (hazard ratio, 0.51; 95% confidence interval [CI], 0.34 to 0.77; P 5 0.001)**

Usefulness of belimumab in adult patients with systemic lupus erythematosus evaluated using single indexes: a meta-analysis and systematic review

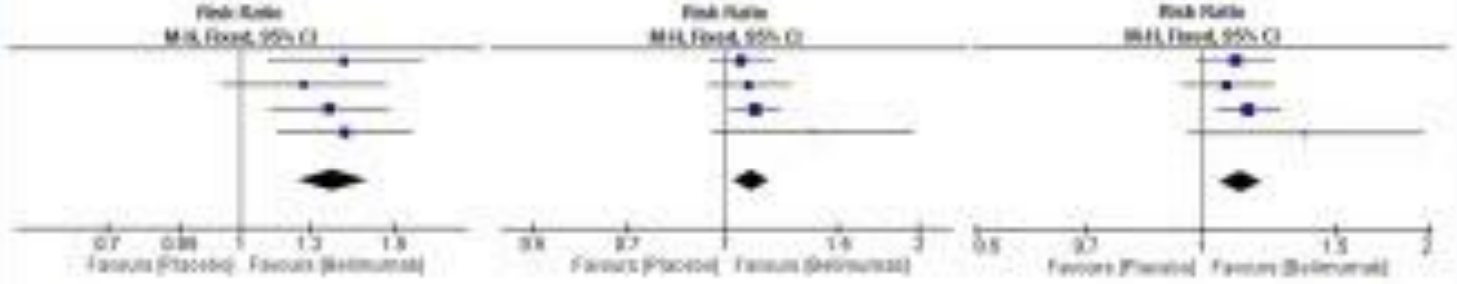
12 Reports
8 Clinical trials

8197 patients with SLE

Belimumab + Standard of care	VS	Placebo + Standard of care
IV 10mg/kg		
SC 200mg		

Primary efficacy outcome

Secondary efficacy outcome



Addition of belimumab to standard of care in adult patients with SLE is effective when evaluated using various single indexes recommended in clinical guidelines.

Voclosporin

- a single amino acid substitution cause increased calcineurin binding
- lower incidence of new-onset diabetes compared with tacrolimus
- less risk of hypertension
- Less risk of nephrotoxicity
- lower doses required to produce calcineurin inhibition
- does not affect systemic MPA exposure
- In addition to its immunosuppressive effects, voclosporin also exerts hemodynamic and direct podocyte anti protein uric effects, leading to a rapid reduction in proteinuria especially in class **v**

Ongoing Clinical Trials

- **The NOBILITY: 2phase**

  Obinutuzumab, a fully humanized anti-CD20 antibody that more potently depletes B cells, demonstrated higher renal response rates when added to SOC comparedwith SOC alone

- **The REGENCY trial:3phase**

  evaluate obinutuzumab in active proliferative LN (class III or IV +/- class V)

- **The AURORA-2**

  long-term safety and tolerability of the combination of voclosporin, MMF, and low-dose GCs

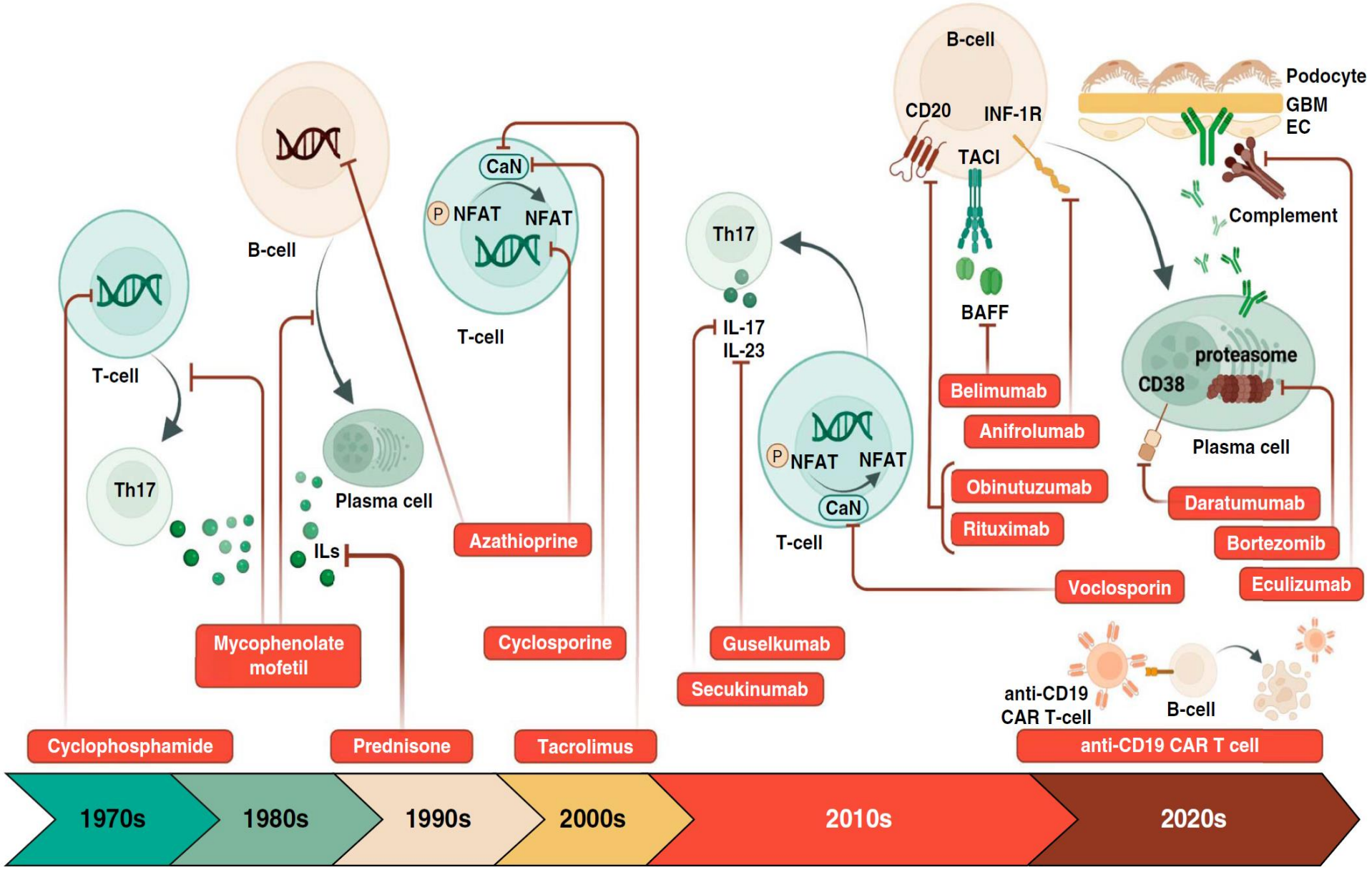
- **Novel** therapies directed at T cells include secukinumab monoclonal antibody against IL-17A, and guselkumab, monoclonal antibody against IL-23, both proinflammatory T-cell cytokines.

- **TULIP-LN** trial evaluated anifrolumab (anti IFN-1 receptor ab) for the treatment of active LN and included a lower-dose (“basic”) regimen,intensified dosing

- The complement system: (ravulizumab)targeting C5; (iptacopan) an oral inhibitorof Factor B and (ALXN2050) an oralinhibitor of Factor D (

Drug	Mechanism	Status
Obinutuzumab	Anti-CD20	Completed phase 2 (NCT02550652); Enrolling phase 3 (NCT04221477)
Secukinumab	Anti-IL17A	Enrolling phase 3 (NCT04181762)
Guselkumab	Anti-IL23	Enrolling phase 2 (NCT04376827)
Anifrolumab	Anti-IFN	Completed phase 2 (NCT02547922); Enrolling phase 3 for LN (INCT05138133)
Ravulizumab	C5 inhibitor	Enrolling phase 2 (NCT04564339)
Iptacopan	Factor B inhibitor	Enrolling phase 2 (NCT05268289)
ALXN2050	Factor D inhibitor	Enrolling phase 2 (NCT05097989)
KZR-616	Immunoproteasome inhibitor	Active phase 1b/2 for SLE with and without LN (NCT03393013)

Current Practice and Review of Updated Guidelines



KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

- 1- Intravenous cyclophosphamide can be used as the initial therapy for active Class III and Class IV LN in patients who may have **difficulty adhering to an oral regimen**.
- 2 - An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at **high risk of infertility**, such as patients who have a moderate-to-high prior cyclophosphamide exposure.
- 3 - Initial therapy with an immunosuppressive regimen that includes a CNI (voclosporin, tacrolimus, or cyclosporine) may be preferred in patients with **relatively preserved kidney function and nephrotic range proteinuria** likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.
- 4 - A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be preferred in patients with repeated kidney flares or at **high-risk for progression to kidney failure** due to severe chronic kidney disease.

Risk factors for progressive kidney disease

Clinical parameters :

- Proteinuria (the best clinical prognostic biomarker)
- glomerular filtration rate
- complement levels
- anti-dsDNA titer
- presence of antiphospholipid antibodies

kidney biopsy classification:

activity and chronicity

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

- 5 - Other therapies, such as azathioprine or leflunomide combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative LN in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with **inferior efficacy**, including **increased rate of disease flares** and/or increased incidence of drug toxicities.
- 6 - Newer biologic and non-biologic therapies are under development and may offer future options for the treatment of active LN.
- 7 - Rituximab may be considered for patients with persistent disease activity or inadequate response to initial standard-of-care therapy.

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

- **Maintenance therapy for Class III and Class IV lupus nephritis:**

  We recommend that after completion of initial therapy, patients should be placed on MPAA for maintenance .

- **The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be >36 months**.

Cost-Effectiveness

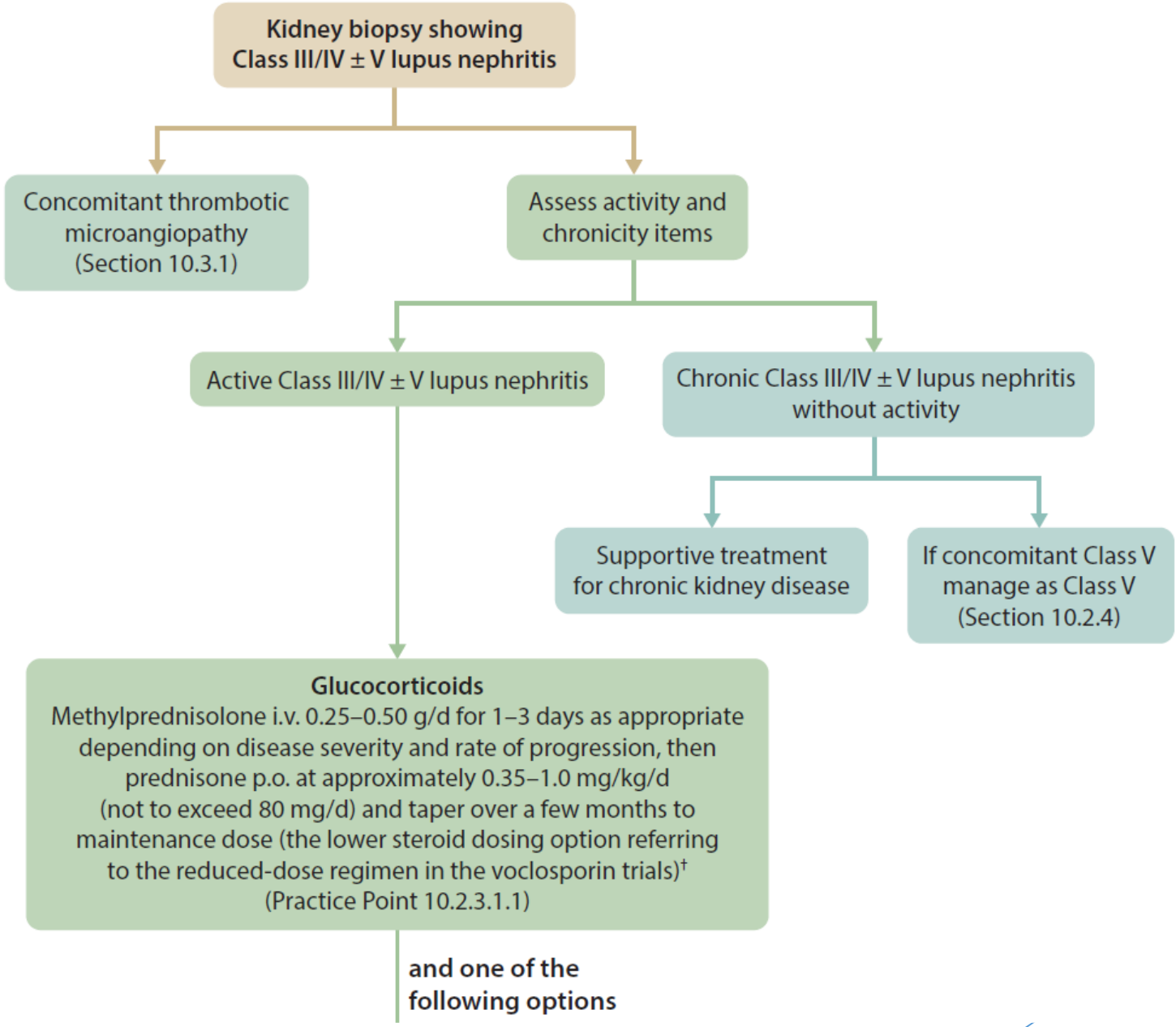
- **incremental cost-effectiveness ratio of MMF compared with AZA was $6454 per quality-adjusted life year (QALY).**
- **A 2016 study from India showed that the cost of MMF therapy was seven times as high as CYC-AZA therapy.**
- **cost-effectiveness ratio of approximately $95,000/QALY for belimumab and approximately $150,000/QALY for voclosporin**
- ***QALY*= Quality of life X Years Lived**
- ***ICER* (Incremental cost- effectiveness) = cost of new –cost of old/QALY new – QALY OLD**
- **COST EFFECTIVE if ICER < WILLINGNESS**
- ***WILLINGNESS to PAY* = 1 TO 3 X GDP PER CAPITAL**
- ***WILLINGNESS to PAY in IRAN = 4500 TO 13500 $***

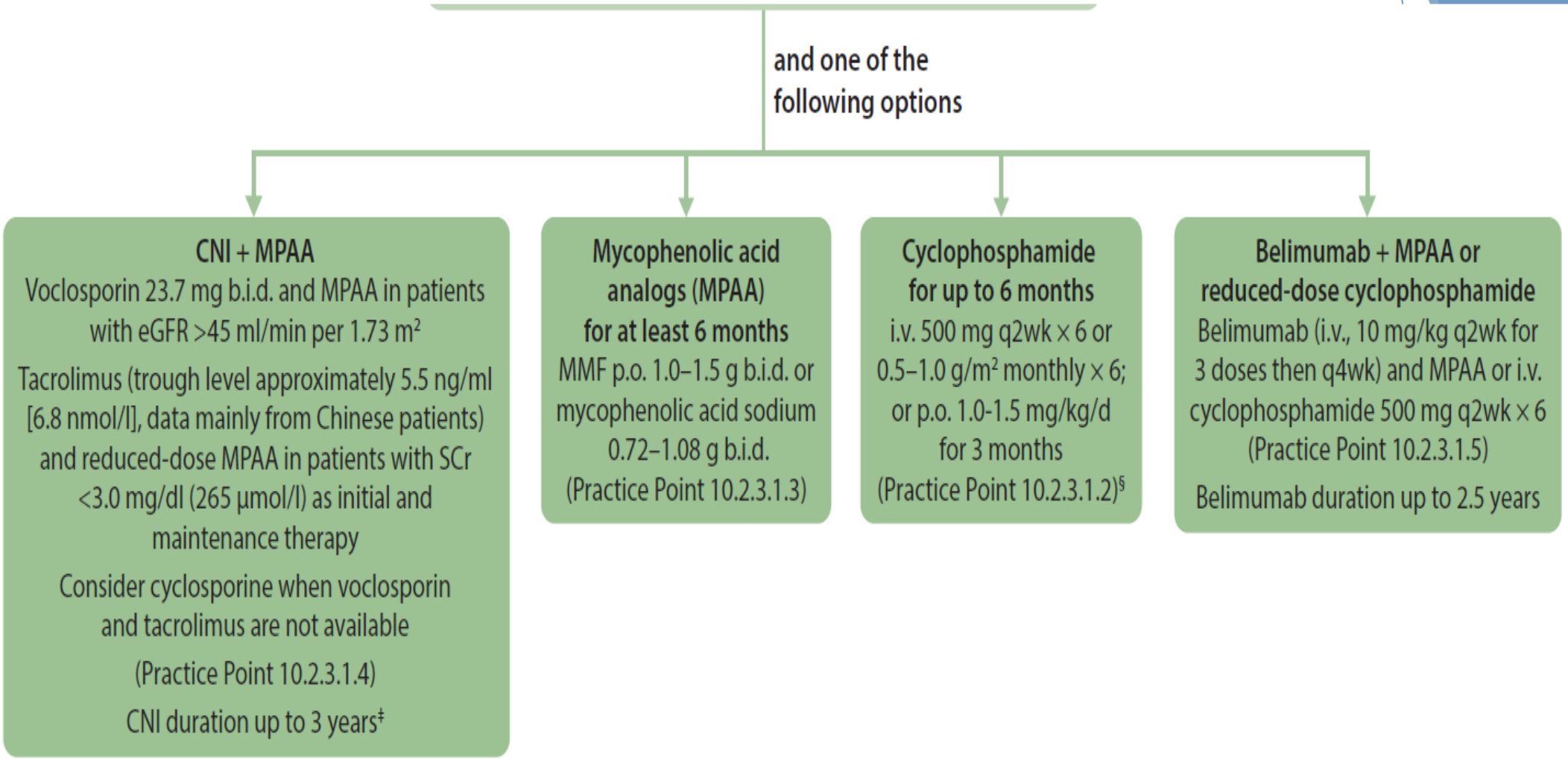
Maintenance immunosuppressive regimens in patients with lupus nephritis

Maintenance immuno-suppressive regimens	Low-dose glucocorticoids AND					
	Mycophenolic acid analogs	Azathioprine	Belimumab and mycophenolic acid analogs or azathioprine	CNI and mycophenolic acid analogs	CNI (such as voclosporin, tacrolimus or cyclosporine)	Mizoribine
Comments	Preferred treatment based on high-certainty evidence; lower flare rate than azathioprine maintenance	Low medication cost; safe in pregnancy	Efficacy and safety of belimumab demonstrated in BLISS-LN (104-wk) and open-label extension trials (28-wk) [Practice Point 10.2.3.2.5]	Efficacy and safety of voclosporin demonstrated in AURORA 1 (52-wk) and AURORA 2 continuation trials (2-yr); efficacy and safety of tacrolimus demonstrated in 'Multitarget Therapy' trial in Chinese patients in which tacrolimus and reduced-dose MPAA were given for 24 months [Practice Point 10.2.3.2.5]	Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin	Experience mostly in Japanese patients

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy


Kidney biopsy showing Class III/IV ± V lupus nephritis
Concomitant thrombotic microangiopathy (Section 10.3.1)
Assess activity and chronicity items
Active Class III/IV ± V lupus nephritis
Chronic Class III/IV ± V lupus nephritis without activity
Supportive treatment for chronic kidney disease
If concomitant Class V manage as Class V (Section 10.2.4)
Glucocorticoids
Methylprednisolone i.v. 0.25–0.50 g/d for 1–3 days as appropriate depending on disease severity and rate of progression, then prednisone p.o. at approximately 0.35–1.0 mg/kg/d (not to exceed 80 mg/d) and taper over a few months to maintenance dose (the lower steroid dosing option referring to the reduced-dose regimen in the voclosporin trials)†
(Practice Point 10.2.3.1.1)
and one of the following options


and one of the following options
CNI + MPAA
Voclosporin 23.7 mg b.i.d. and MPAA in patients with eGFR >45 ml/min per 1.73 m²
Tacrolimus (trough level approximately 5.5 ng/ml [6.8 nmol/l], data mainly from Chinese patients) and reduced-dose MPAA in patients with SCr <3.0 mg/dl (265 µmol/l) as initial and maintenance therapy
Consider cyclosporine when voclosporin and tacrolimus are not available
(Practice Point 10.2.3.1.4)
CNI duration up to 3 years‡
Mycophenolic acid analogs (MPAA) for at least 6 months
MMF p.o. 1.0–1.5 g b.i.d. or mycophenolic acid sodium 0.72–1.08 g b.i.d.
(Practice Point 10.2.3.1.3)
Cyclophosphamide for up to 6 months
i.v. 500 mg q2wk × 6 or 0.5–1.0 g/m² monthly × 6; or p.o. 1.0-1.5 mg/kg/d for 3 months
(Practice Point 10.2.3.1.2)§
Belimumab + MPAA or reduced-dose cyclophosphamide
Belimumab (i.v., 10 mg/kg q2wk for 3 doses then q4wk) and MPAA or i.v. cyclophosphamide 500 mg q2wk × 6
(Practice Point 10.2.3.1.5)
Belimumab duration up to 2.5 years

Initial therapy of active Class III/IV lupus nephritis

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any *one* of the following:

i. mycophenolic acid analogs (MPAAs) *(1B)*; or

ii. low-dose intravenous cyclophosphamide *(1B)*; or

iii. belimumab and either MPAA or low-dose intravenous cyclophosphamide *(1B)*; or

iv. MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m^2) *(1B)*.