Autolus

Developing and Delivering a New Generation of T Cell Therapies

April 23, 2025

Investor R&D Update

Forward looking statements

These slides contain forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements are statements that are not historical facts, and in some cases can be identified by terms such as “may,” “will,” “could,” “expects,” “plans,” “anticipates,” and “believes.” These statements include, but are not limited to, statements regarding Autolus’ development of its product candidates, including the obe-cel program; the profile and potential application of obe-cel in additional disease settings; the future clinical development, efficacy, safety and therapeutic potential of the Company’s product candidates, including progress, expectations as to the reporting of data, conduct and timing and potential future clinical and preclinical activity and milestones; expectations regarding the initiation, design and reporting of data from clinical trials and preclinical studies; the extension of the pipeline beyond obe-cel; expectations regarding the regulatory approval process for any product candidates; the Company’s current and future manufacturing capabilities; and the Company’s anticipated cash runway. Any forward-looking statements are based on management’s current views and assumptions and involve risks and uncertainties that could cause actual results, performance, or events to differ materially from those expressed or implied in such statements. These risks and uncertainties include, but are not limited to, the risks that Autolus’ preclinical or clinical programs do not advance or result in approved products on a timely or cost effective basis or at all; the results of early clinical trials are not always being predictive of future results; the cost, timing and results of clinical trials; that many product candidates do not become approved drugs on a timely or cost effective basis or at all; the ability to enroll patients in clinical trials; and possible safety and efficacy concerns. For a discussion of other risks and uncertainties, and other important factors, any of which could cause Autolus’ actual results to differ from those contained in the forward-looking statements, see the section titled “Risk Factors” in Autolus' Annual Report on Form 10-K filed with the Securities and Exchange Commission, or the SEC, on March 20, 2025 as well as discussions of potential risks, uncertainties, and other important factors in Autolus’ subsequent filings with the Securities and Exchange Commission. All information in this presentation is as of the date of the presentation, and Autolus undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise, except as required by law. You should, therefore, not rely on these forward-looking statements as representing the Company’s views as of any date subsequent to the date of this presentation.

Welcome

Agenda

1. Autolus is positioned for value creation
2. Opportunity in SLE and lupus nephritis
   - Medical need and treatment landscape
   - CARLYSLE SLE P1 data
   - Pivotal study in lupus nephritis
3. Q&A Part 1
4. Opportunity in multiple sclerosis
   - Medical need and treatment landscape
   - Planned P1 MS study
5. Early-stage pipeline outlook
6. Q&A Part 2

Today's Speakers

Invited Guests

David Isenberg, MD
University College London (UCL)

Mark Freedman, MD
University of Ottawa

Management

Christian Itin, Ph.D.
Chief Executive Officer

Matthias Will, MD
Chief Development Officer

Autolus is positioned for value creation

Building on a strong foundation with obe-cel

- Highly active, fast off-rate CD19 CAR T therapy with a well managed safety profile
- First FDA-approved CAR T therapy without a REMS obligation – building on a substantial safety data base
- Established infrastructure for manufacturing and commercialization
- Commercial presence in key US centers – building to 60 centers in 2H 2025
- Expect to add UK and select EU countries in upcoming 12 months
- Year-end 2024 cash position of $588M

AUCATZYL®
obecabtagene autoleucel
suspension for IV infusion

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Obecabtagene Autoleucel in Adults with B-Cell Acute Lymphoblastic Leukemia

Roddie C, et al "Obecabtagene autoleucel in B-cell acute lymphoblastic leukemia" N Engl J Med 2024; DOI: 10.1056/NEJMoa2406526

Momentum in the AUCATZYL® U.S. launch

High level of engagement with physicians for expanding the use of AUCATZYL in adult R/R B ALL indication

38 US Treatment Centers Authorized as of April 22, 2025

Autolus™ Assist

- >85% of total U.S. medical lives covered
- Anticipated payor mix: approximately 60% commercial and 40% government/other

Anticipated New Markets

- Anticipated decision in the UK in Q2 2025; EU in 2H 2025
- Country-by-country investments and launch plans based on pricing and reimbursement assessments

PLANS FOR AUTOIMMUNE DISEASE

Expanding the obe-cel opportunity

A pipeline in a product

Obe-cel drives deep reset of the B cell compartment

Combined with a favorable tolerability profile with low levels or no high- grade CRS and ICANS

Results we have observed in clinical trials in B cell malignancies

- High MRD-negative complete remission rate in relapsed or refractory (r/r) adult and pediatric acute B cell lymphoblastic leukemia (ALL) patients (94%)[1]
- Long term outcomes indicate complete removal of all malignant B cells in r/r ALL[1,2,3]
- Experience in non-Hodgkin lymphoma indicate high metabolic complete remission rate (88% in r/r LBCL and 95% in r/r FL)[4]
- Long term outcomes in patients with LBCL[4]

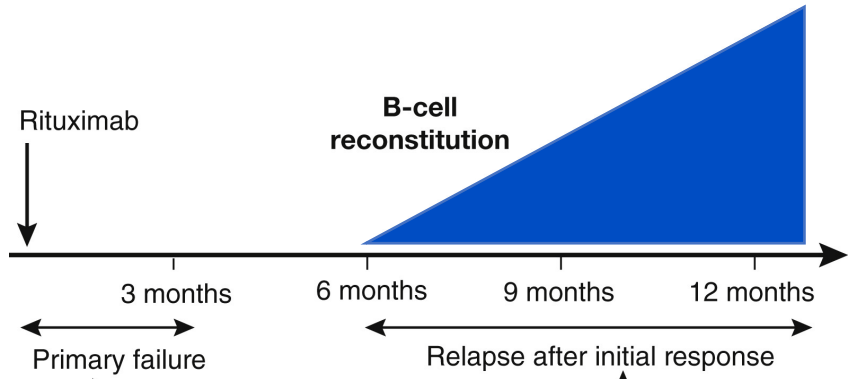
Targeted positioning of obe-cel in:

- Frontline consolidation in aggressive B cell malignancies in ALL and LBCL
  - Aim for long term outcomes, while avoiding over-treatment
- B cell mediated autoimmunity with an aim to reset the B cell compartment, and remove autoreactive antibodies and B cells
  - Aim for sustained effect with a one-time therapy

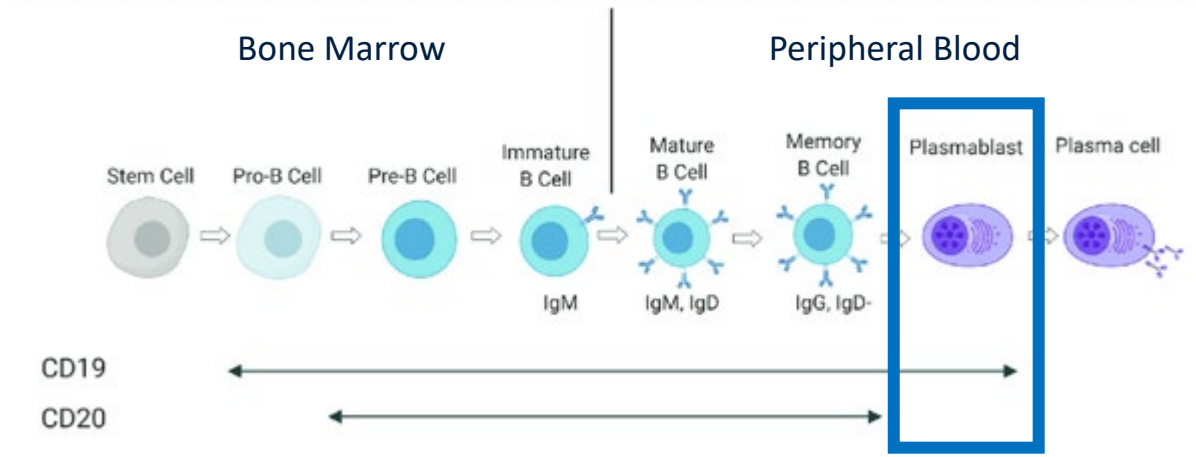
1. Roddie C, et al "Obecabtagene autoleucel in B-cell acute lymphoblastic leukemia" N Engl J Med 2024; DOI: 10.1056/NEJMoa2406526
2. Ghorashian, S., Kramer, A.M., Onuoha, S. *et al.* Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. *Nat Med* **25**, 1408–1414 (2019). https://doi.org/10.1038/s41591-019-0549-5
3. Roddie C, et al. J Clin Oncol 2023;41:16_suppl, 7000
4. Roddie et al, ASH 2023, Poster 2114

B cell targeting approaches in autoimmune disease

- B cell targeting antibody therapy showed a transient effect in a proportion of patients
  - Rituximab (CD20)
  - Belilumab (BAFF / BlyS)
  - Anifrolumab (IFNα/βR)
  - Obinatuzumab (CD20)
- Extending targeting to include all B cell stages and plasmablasts combined with a more potent approach may improve clinical outcomes
- Extending targeting to include plasma cells could impact immunization status of patients
- Landmark CD19 CAR T clinical experiment by Georg Schett[1] and Andreas Mackensen at the University of Erlangen in patients with refractory autoimmune disease indicate long term outcomes in patients who have failed SoC incl. B cell targeting therapy



Crickx, Etienne et al. Kidney International, Volume 97, Issue 5, 885 - 893



1 Mugiakakos et al,N Engl J Med 2021, Mackensen et al. Nature Medicine 2022
Bergmann et al. Ann Rheum Dis 2023, Fischbach et al. Med 2024

Inflammation and structural organ damage in autoimmunity

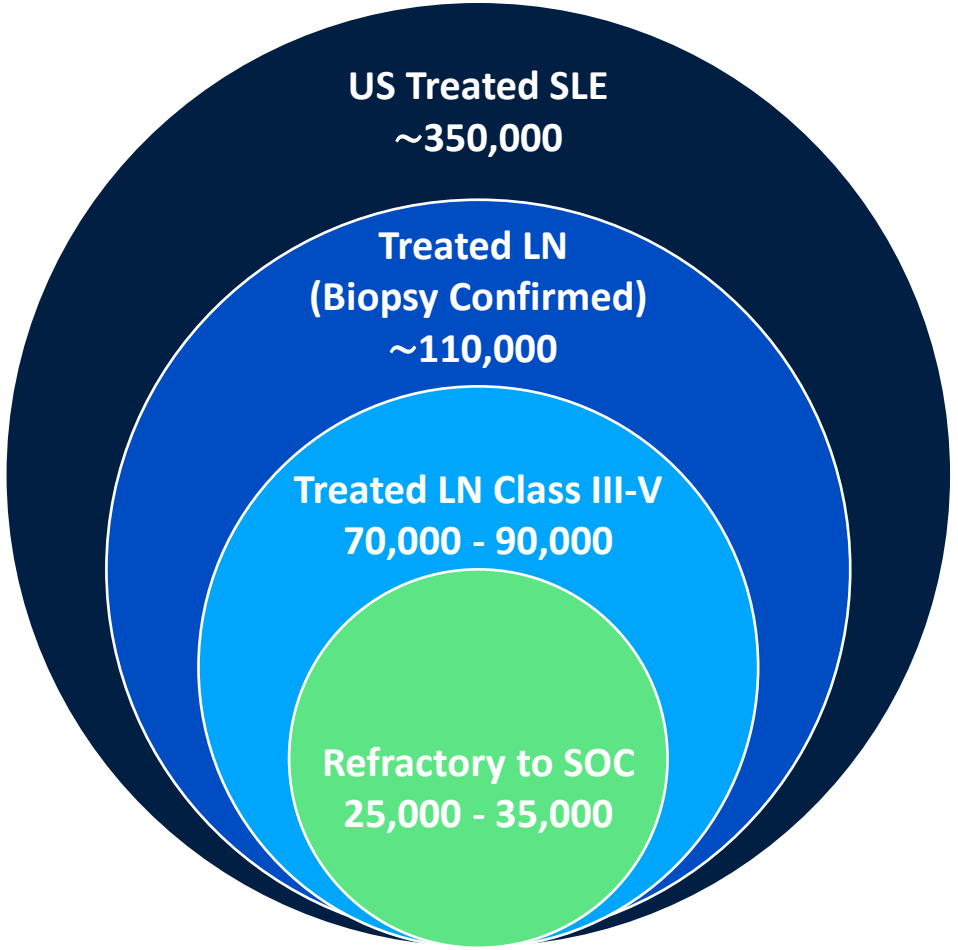
- Autoimmune disease is driven by auto-reactive antibodies redirecting the immune system onto various organs and tissues.
- With continued inflammatory process organs and tissues become damaged, fibrotic and over time can lose function.
- An anti-inflammatory approach targeting B cells and auto-antibody producing plasmablasts or plasma cells will - if successful - remove the inflammatory auto-reactive process.
- Reversibility and full recovery of a patient will largely depend on the level of tissue and organ damage and the respective organ's ability to regenerate.

CD19 CAR T therapy will be focused on severe/refractory patients.

- Key elements of patient selection:
  - Active inflammatory disease
  - Limited chronicity of disease
  - Evidence of organ involvement
  - Limited extent of organ damage
- Desired outcome:
  - Remove autoimmunity memory and antibodies
  - Stabilize impacted organ
  - Upside is improved organ function

Refractory lupus nephritis is a high unmet medical need

- Kidneys are one of the most common organs involved in SLE - 30% – 40% are lupus nephritis patients
- High disease activity is associated with inflammatory processes
- Uncontrolled inflammation leads to high chronicity due to accumulated kidney damage
- Despite treatment advances including regulatory approvals of belimumab and voclosporin the goal to sufficiently improve short and long-term outcomes in patients with LN remains unmet
- There are no treatment options for refractory patients



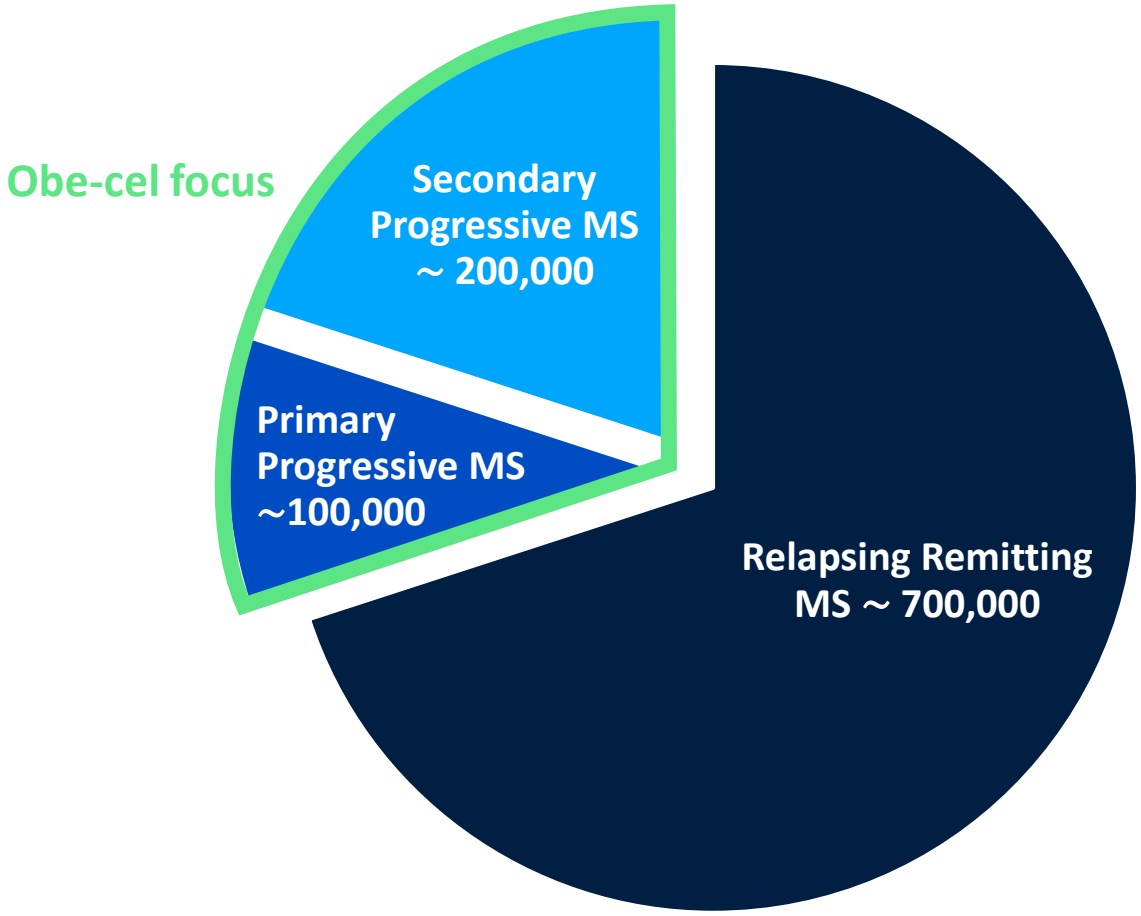
Clarivate/DRG Epidemiology, Arthritis Rheumatol. 2023 Apr;75(4):567-573, Arthritis & Rheumatology. 2017;69(10):2006-2017

Progressive multiple sclerosis is a high unmet medical need

- MS impacts approximately 1,000,000 individuals in the US[1] and there is currently no known cure

- Around 30% of patients have progressive disease and more than half of Progressive MS patients experience disability progression despite receiving disease modifying agents[2]

- Highest unmet need for patients who continue to progress despite being treated with highly effective agents for at least 6 months



1: GlobalData MS Market Forecast 2020-2030 April 2023
2:Watson, C., Thirumalai, D., Barlev, A. et al. Treatment Patterns and Unmet Need for Patients with Progressive Multiple Sclerosis in the United States: Survey Results from 2016 to 2021. Neurol Ther 12, 1961–1979 (2023). https://doi.org/10.1007/s40120-023-00532-2

David Isenberg, MD, FRCP, FAMS

University College of London

- Leading academic rheumatologist and the Emeritus Professor of Rheumatology at University College London, UK and runs UK's largest SLE clinic (> 900 patients)
- Pioneering work in autoimmune diseases, especially in systemic lupus erythematosus (SLE), vasculitis and antiphospholipid syndrome
- Fellow of the Royal College of Physicians and the Royal Academy of Medical Sciences
- Developed disease activity and damage assessment tools for lupus and led the introduction of B-cell targeted therapy for SLE (e.g. rituximab, belimumab, ianalumab and others)
- Past president of the British Society of Rheumatology (2004-2006), past chair of the British Isles Lupus Assessment Group (BILAG) and Chair of the Systemic Lupus International Collaboration Clinics (1998-2003)
- Evelyn Hess Prize from the Lupus Foundation of America (2010), the Master of the American College of Rheumatology (2016) among others
- Published so far 625 original articles, 325 reviews/chapters and 20 books, including the principal editorship of the Oxford Textbook of Rheumatology
- Serves of several editorial boards of several major journals including the Journal of Rheumatology
- Performs with the band “Lupus Dave and the Davettes” at medical events

THERAPIES FOR LUPUS – WHERE ARE WE NOW? WHERE ARE WE GOING?

Professor David Isenberg

Emeritus Professor of Rheumatology

UCL

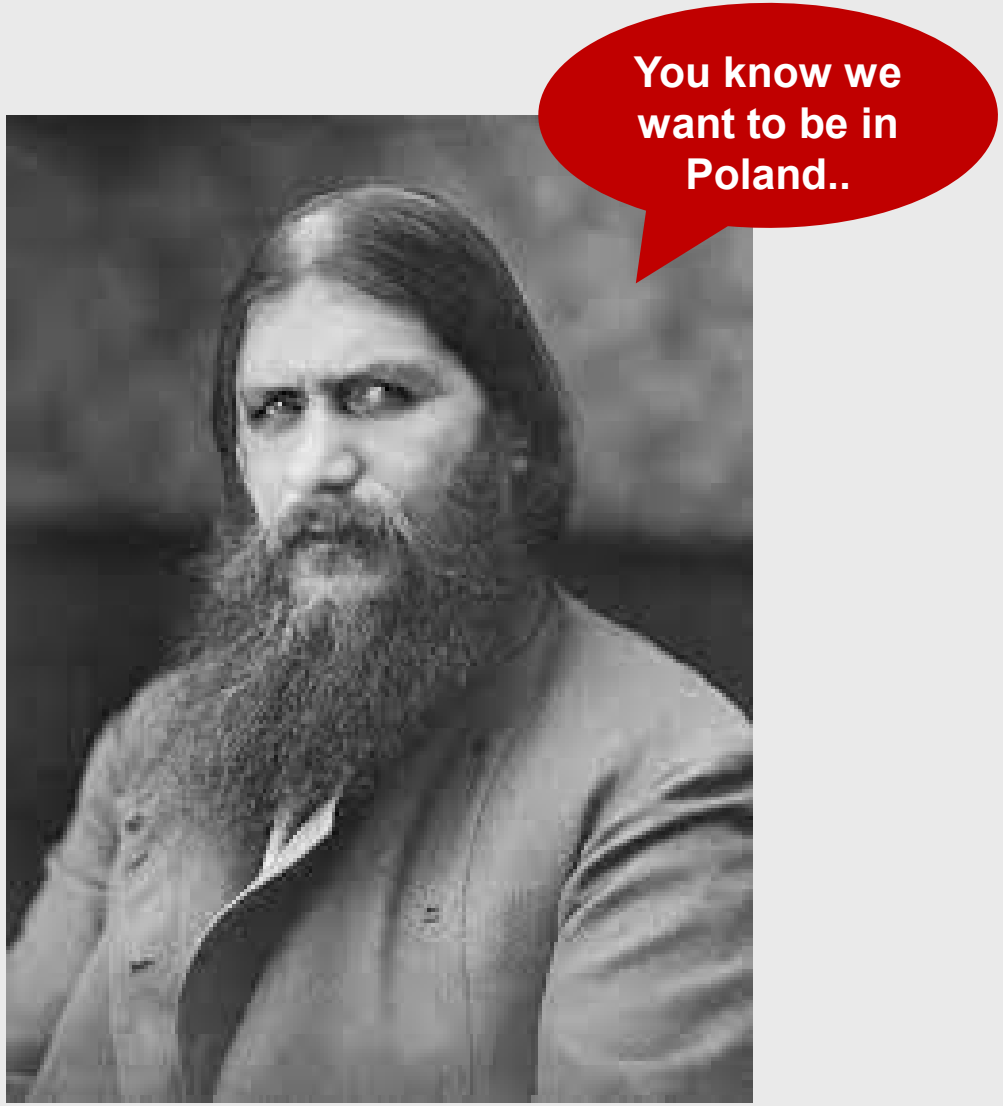
A FEW MONTHS AGO, A TRAINEE SAID TO ME…

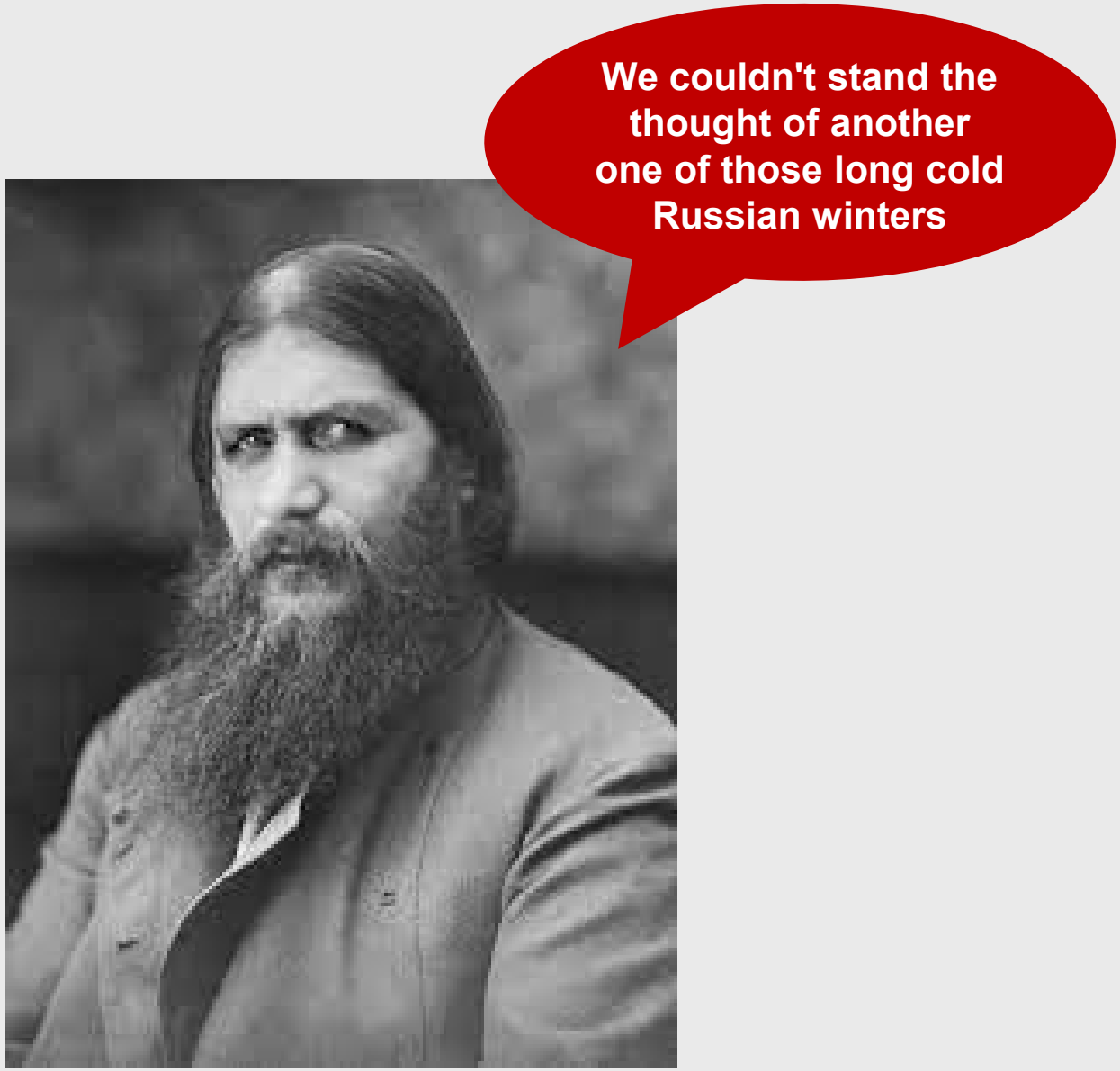
“The treatment for SLE?

I thought that was all sorted out now.”

THE BORDER – RUSSIA/POLAND

A PEASANT FAMILY STORY

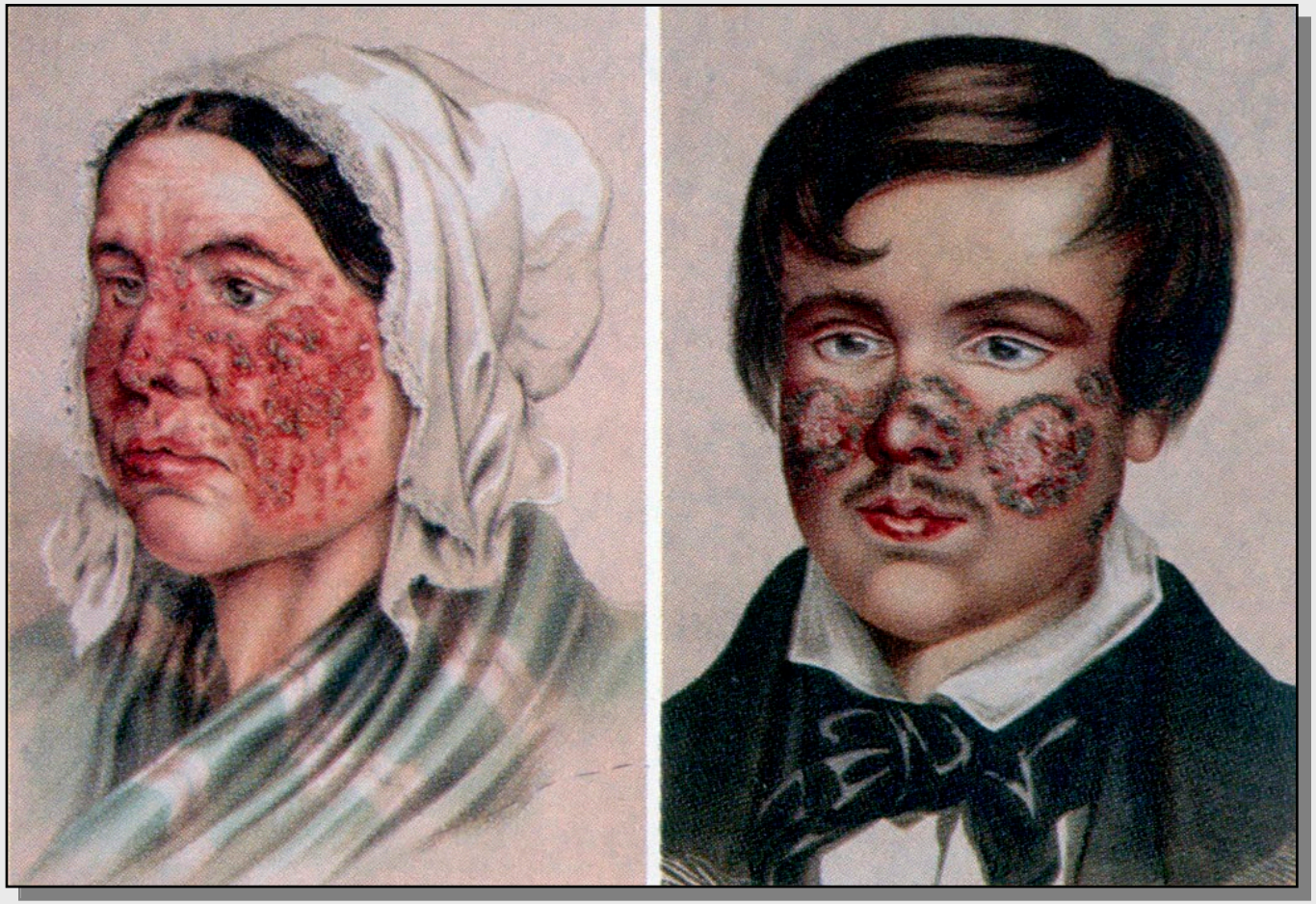

You know we want to be in Poland..


We couldn't stand the thought of another one of those long cold Russian winters

SO THE MORAL OF THE STORY IS….

PERCEPTION

History of Lupus



The UCL Lupus Clinic 1978-2025

Cohort = 920 ; Details of the first 800 – clinical (1)

Sex ratio	F : M	= 736 : 64
Disease duration		= 14.1 yr (SD=10)
Ethnicities	Caucasian	= 448 (56%)
	Afro-Caribbean	= 176 (22%)
	Asian	= 106 (13%)
	Chinese	= 42 (5%)
	Others	= 26 (3%)

The UCL Lupus Clinic 1978-2025

Cohort (n= the first 800); Details – clinical (2)

	%		%
Rash	54	Arthritis	90
Photosensitivity	35	Serositis	36
Alopecia	25	Renal	30
Oral ulcers	27.5	CNS	20

SLE – OUTCOMES

UCL – cohort

- Since 1978 – over 920 patients under long term review
- Deaths n = 170 (19%)

Mean age of death = 54.8 yrs [SD = 18.3] – range 17 - 95

Main causes of death = infection/vascular/cancer/active disease including renal

SLE – OUTCOMES

1950s – 4 yr survival ≃ 50%

2025 – 15 yr survival ≃ 85%

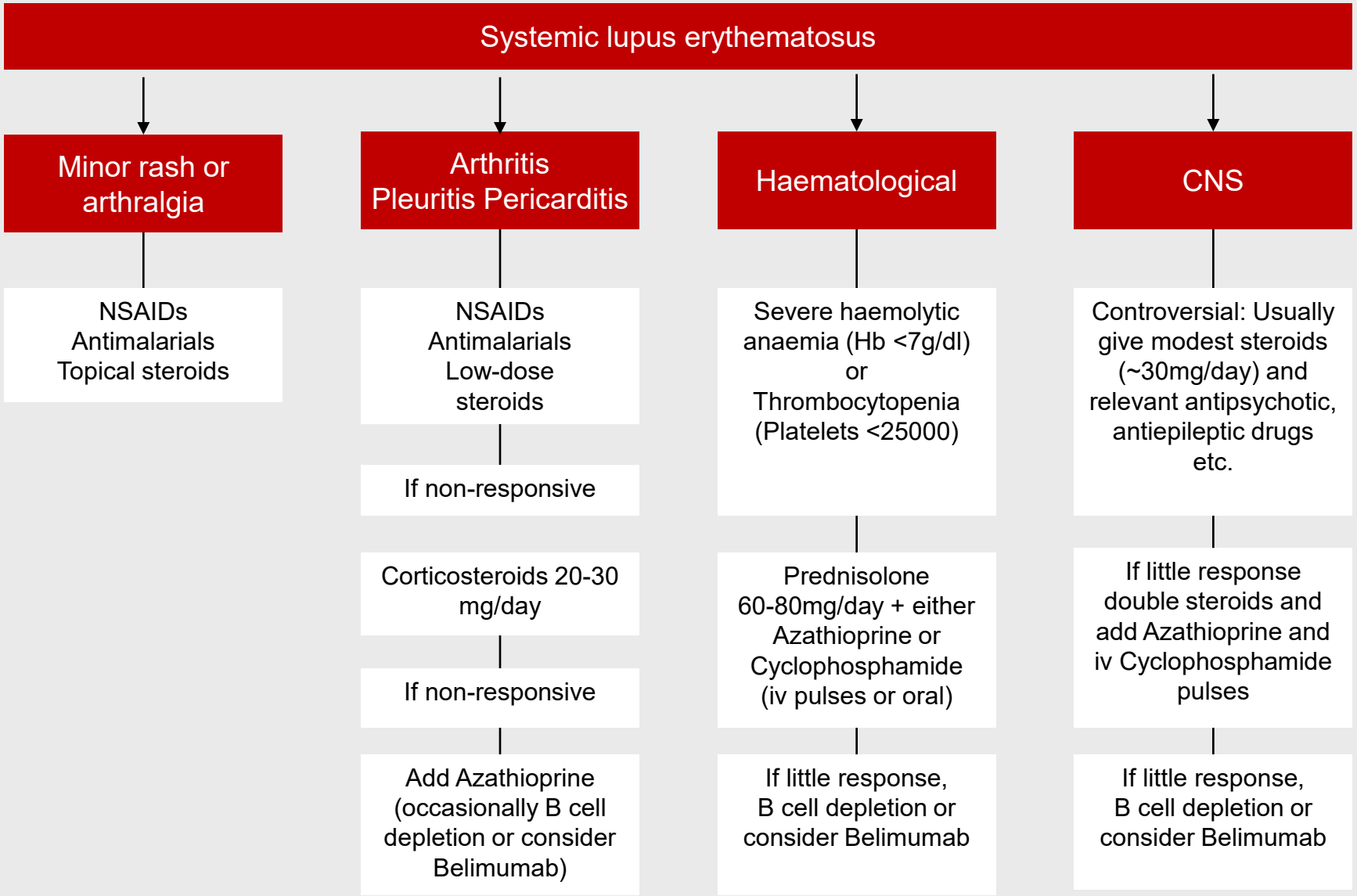
AND LET'S NOT FORGET

MORBIDITY

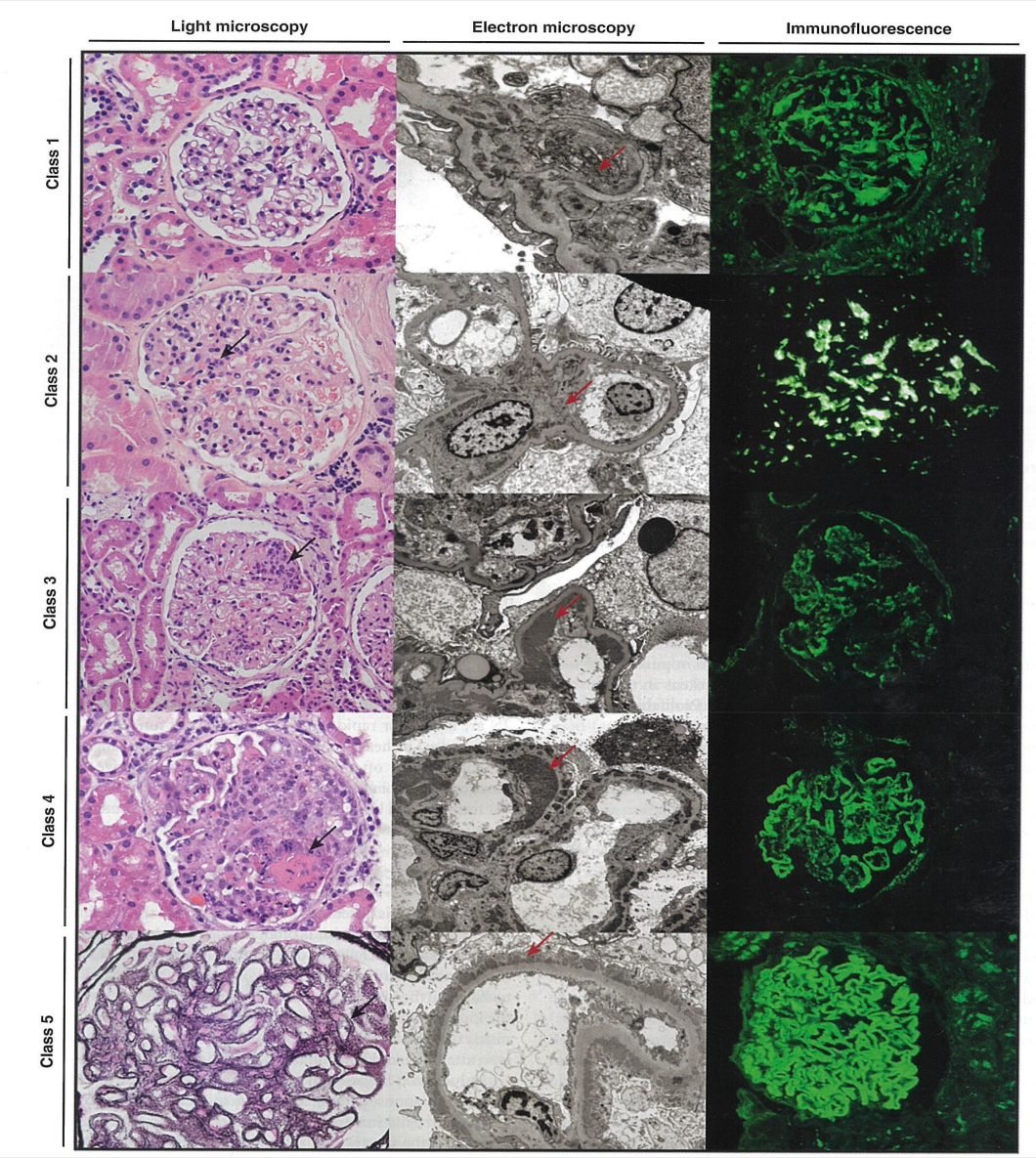
INCREASED RISK OF:

- CVS events
- Infection
- Osteoporosis
- Infertility
- Hypertension
- Other steroid side-effects e.g. cataracts

Systemic Lupus Erythematosus



LUPUS RENAL HISTOLOGY



CURRENT THERAPY FOR LUPUS NEPHRITIS

- **Conventionally Prednisolone is given together with:**

Mycophenolate/

Cyclophosphamide

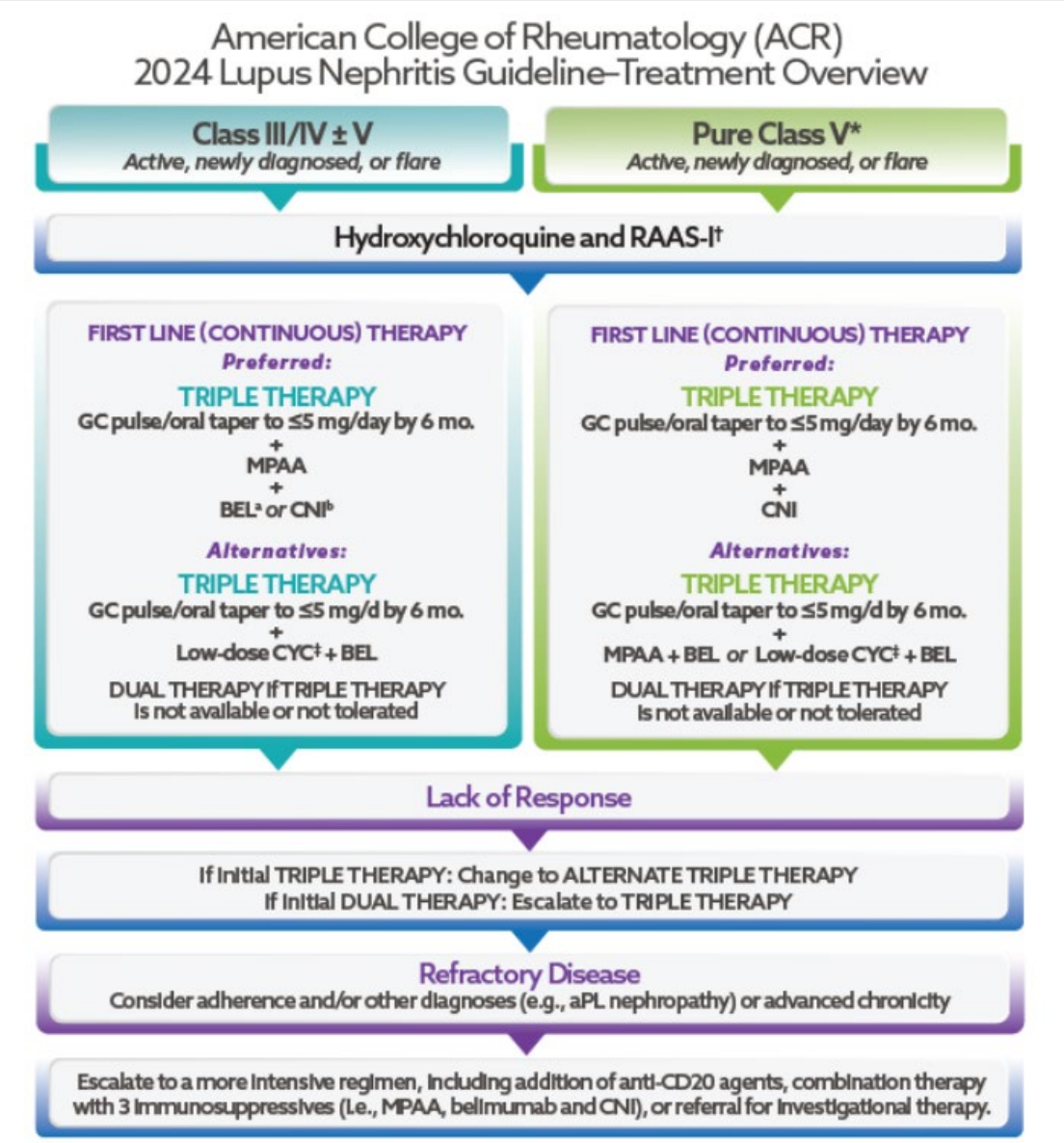
Or if the patient is pregnant

Azathioprine

- **In addition, tight control of BP and the use of Hydroxychloroquine are important.**

- **If the above approach does not work, consider Rituximab / Benlysta/ Voclosporin**

Treatment Guidelines in Lupus Nephritis



- ACR 2024 guidelines recommend triple therapy for class III/IV ± V LN:
- Hydroxychloroquine and RAAS backbone with

1. Glucocorticoid pulse and taper to 5 mg/d by M6
2. Mycophenolate (MPAA)
3. B-cell targeting agents (e.g. Belimumab) or calcineurin inhibitors (CNI)

- Patients who fail to respond are given an alternative triple therapy

- There is no recommended approach for refractory patients having failed B-cell targeting agents and CNI

40-YEAR FOLLOW-UP OF A LUPUS NEPHRITIS (UCL) COHORT

KEY FACTS

- From 1975-2015, 219 lupus nephritis pts (91% F) were followed up:
  - The five-year mortality rates decreased from 24.1% (1975-84) to approximately 5% currently.
  - Progression to end-stage renal failure occurred in 38 patients (17.4%).
  - A decrease in incidence among Caucasians but increased in African and Asian patients.
  - The outcome in LN has not changed significantly in the past thirty years.

Gisca et al. Rheumatology 2021; 60: 814-22.

Assessing Outcome in Lupus Nephritis – 40-year cohort study [1]

	1975 – 1985	1986 – 1995	1996 – 2005	2006 - 2015
n =	29	50	92	48
Age at SLE diagnosis [yr]	28	23	23	26
Age at LN diagnosis [yr]	29	26	26	29
End-stage renal disease within 5 yr of LN	3%	4%	7%	4%
Mortality	24%	4%	4%	3%
Age at death [yr]	42	42	50	33

Gisca, Duarte, Farinha, Isenberg. Rheumatology 2021; 60: 1814

Assessing Outcome in Lupus Nephritis – 40-year cohort study [2]

CONCLUSION

Despite the changes in treatment of lupus nephritis in the past 20 years, we have reached a plateau in 5-year mortality and progression to end-stage renal disease rates; suggesting that new therapeutic and management approaches….are needed to improve outcomes…

Incidence, Prevalence and Mortality of Lupus Nephritis:

A…Four Decades Study Using The Lupus Midwest Network [1]

- Patient with incident LN [1976 - 2018] in Olmstead County Minnesota [n = 72]
- Estimated prevalence ↑ from 168/100,000 [1985] to 212/100,000 [2015]
- **LN patients had** a standardized mortality ratio of 6.33 [95% CI, 3.81 – 9.89] with **no improvement in mortality gap in the last 4 decades**
- At 10 yrs, survival was 70%; 13% of LN patients had end-stage renal disease.

Hocaoglu et al. A & R 2023; 75: 567-73.

Incidence, Prevalence and Mortality of Lupus Nephritis:

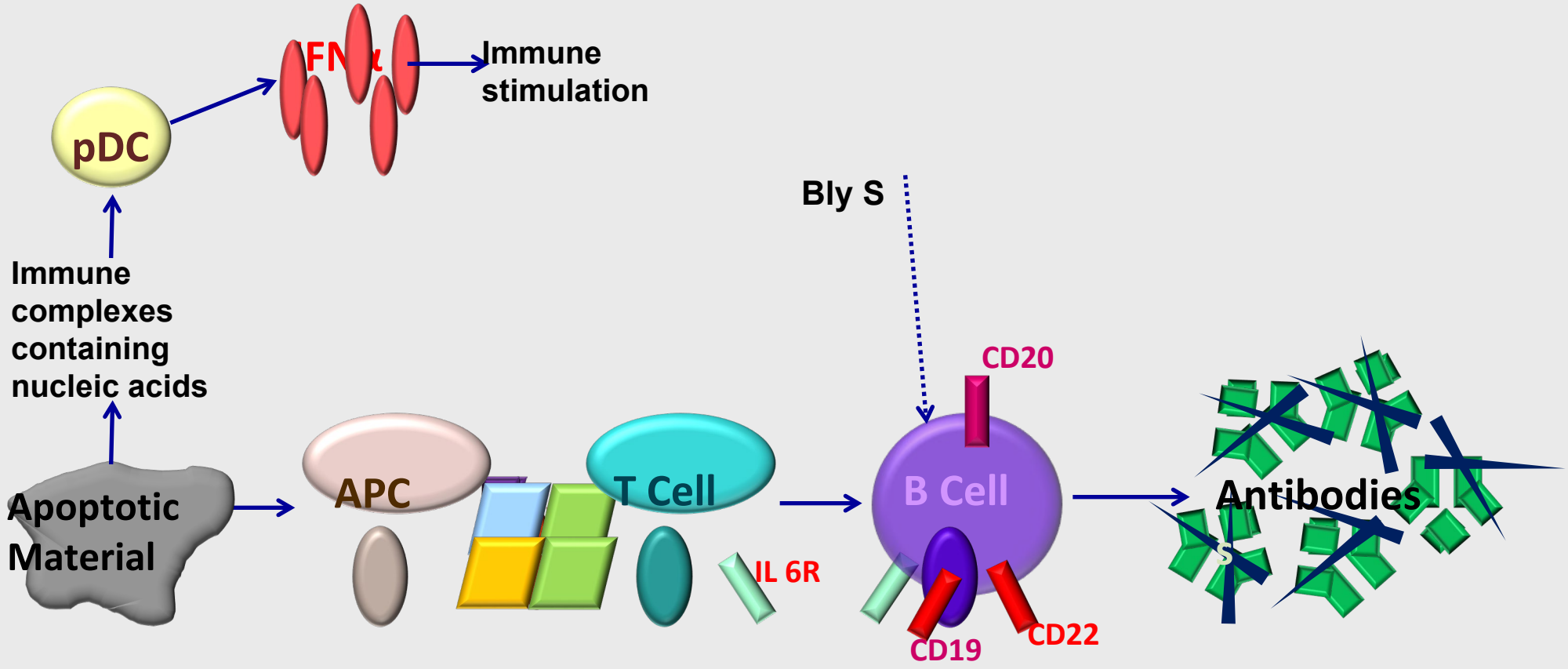
A…Four Decades Study Using The Lupus Midwest Network [2]

CONCLUSION

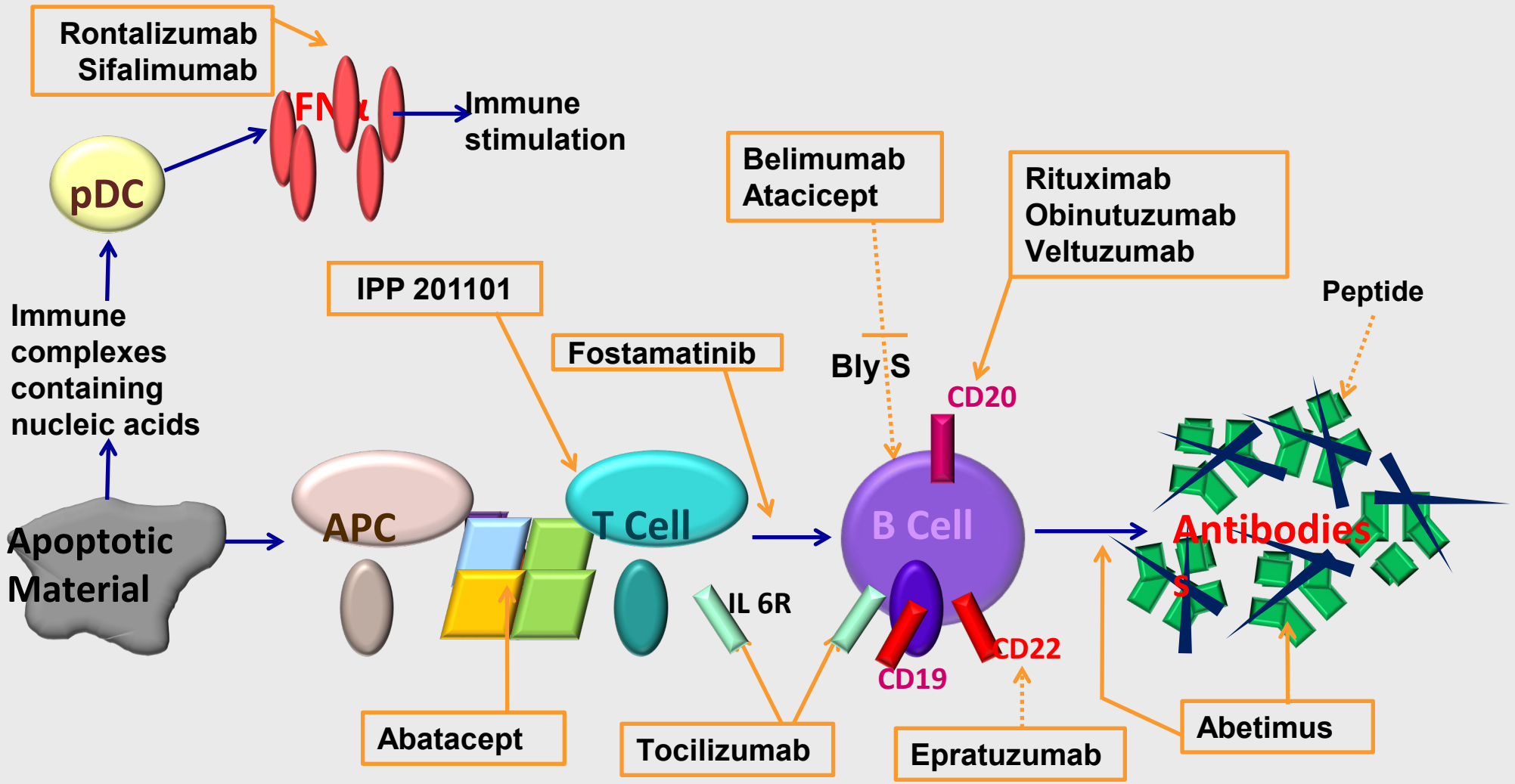
The incidence and prevalence of LN….increased in the last 4 decades.

LN patients have poor outcomes with high rates of end-stage renal disease and mortality rates 6 times that of the general population.

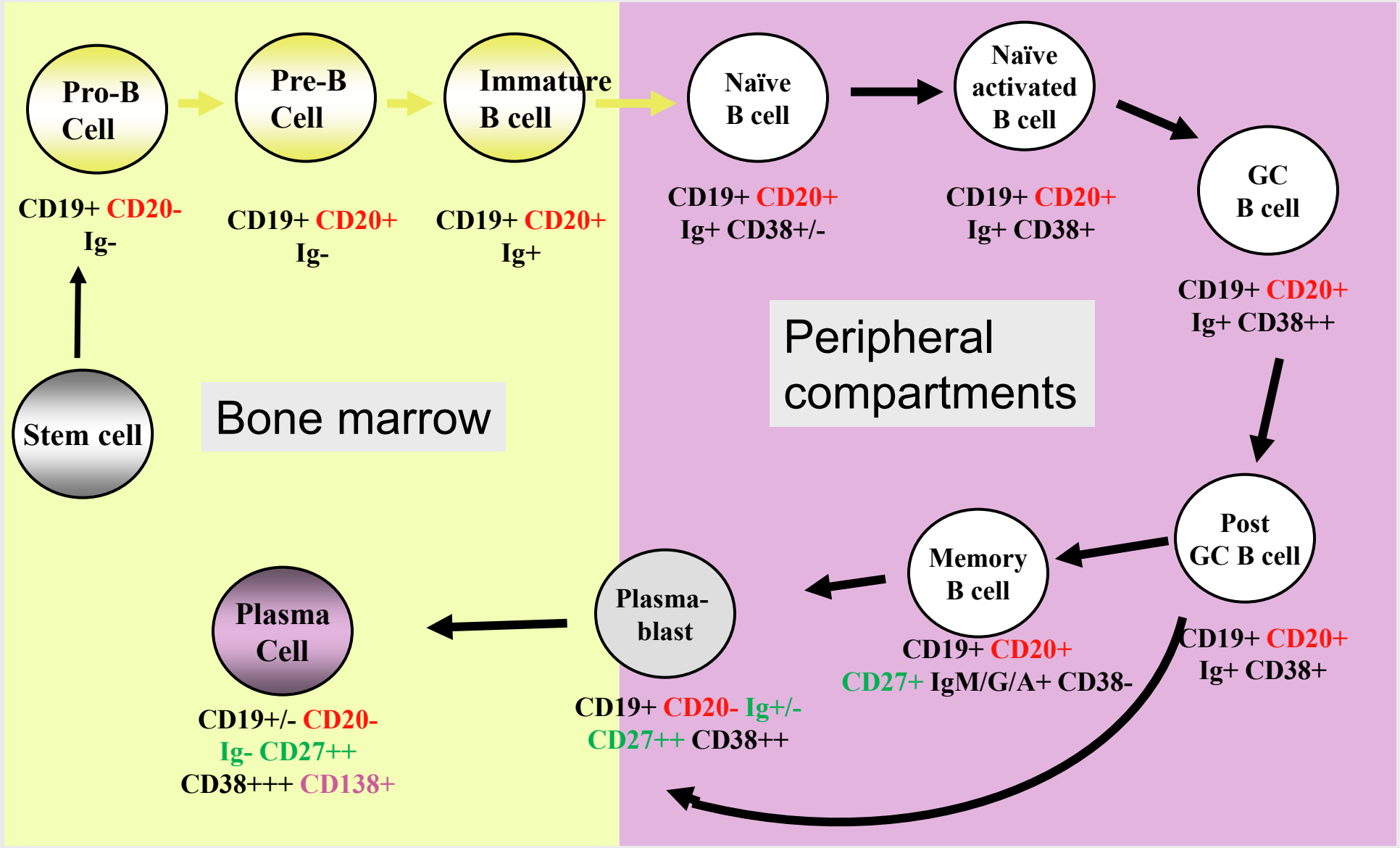
Target pathway for SLE therapies



Some targeted therapies for SLE



B CELL DEVELOPMENT



When to Use B-cell targeting agents in SLE

1. When everything else has failed.

2. Before using anything at all!

Long Term Follow up on the first 50 Patients Treated with B Cell Depletion

The UCL Experience

Regime used [with very few exceptions]

Day 1	-	1g rituximab IV
	-	250 mg methylprednisolone IV
Day 2	-	750 mg cyclophosphamide
Day 14	-	repeat day 1
Day 15	-	repeat day 2

b. **STOP** - prior immunosuppressive drugs until CD19 counts return to normal.

CONTINUE - hydroxychloroquine & steroids (10 mg→15mg).

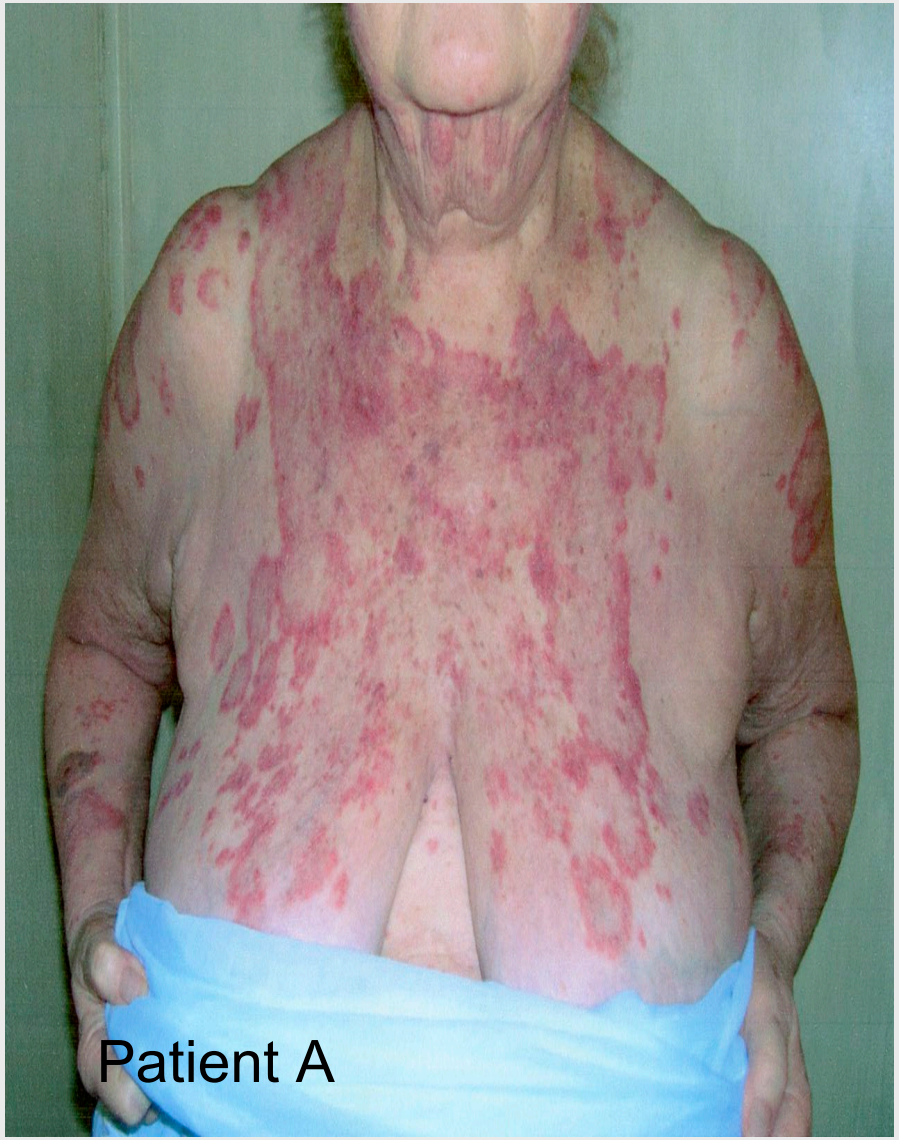
Lu et al Arthritis Care Res , 2009, 61, 482

Results

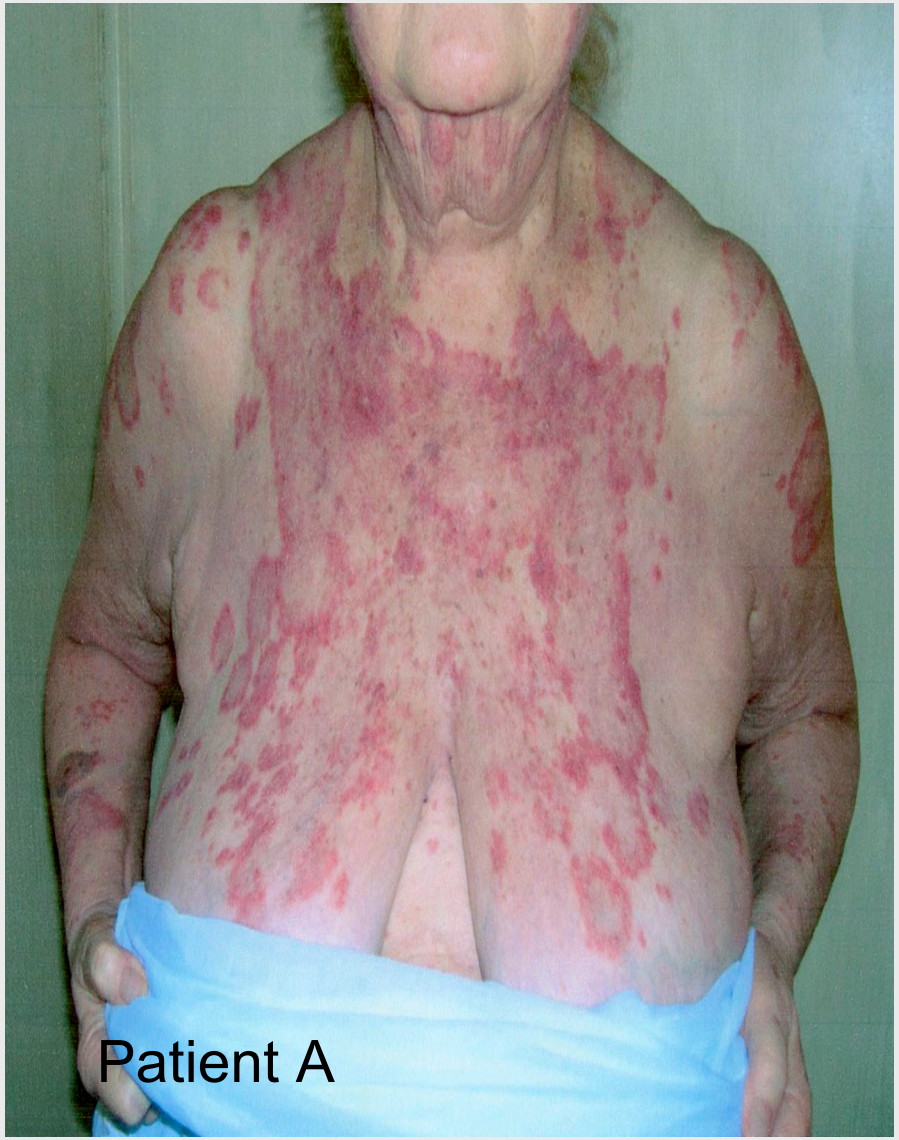
Clinical outcome at 6 months: BILAG

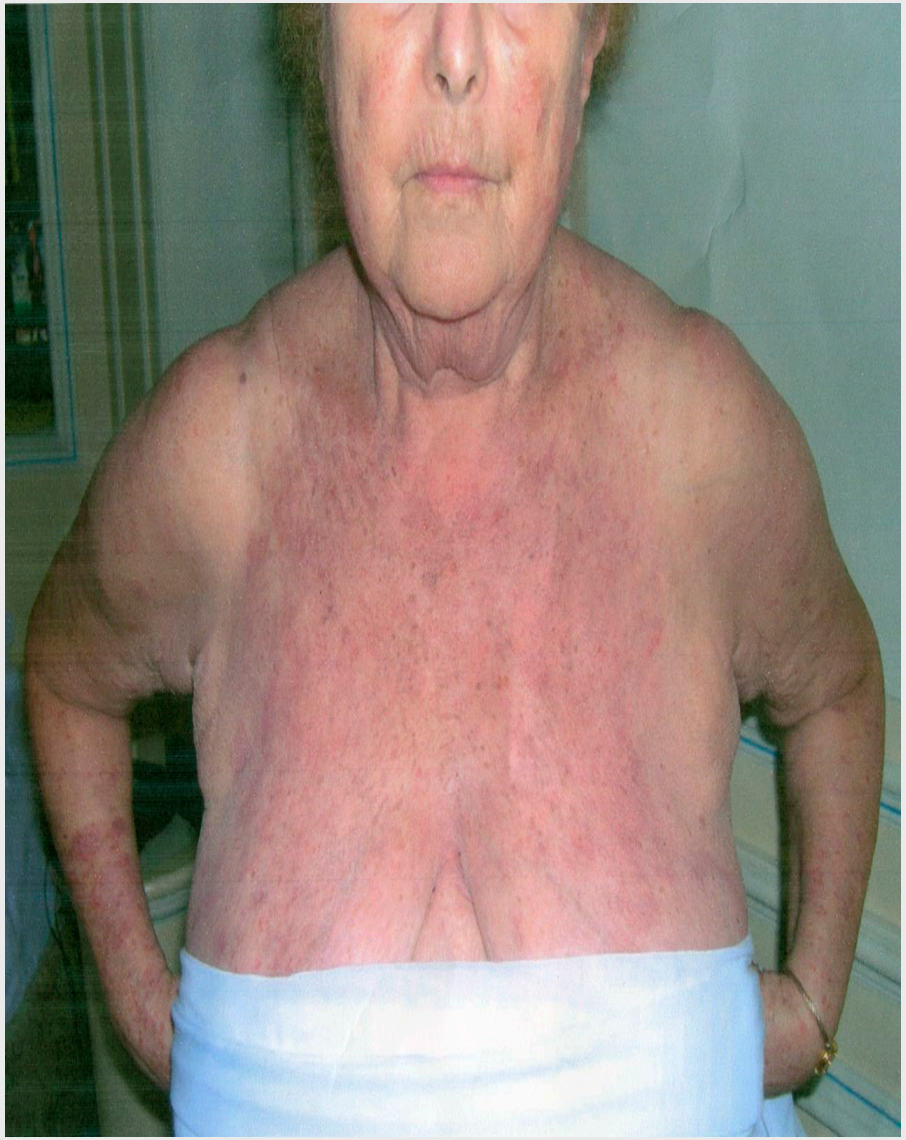
Full Remission	**n = 19 (42%)**
Partial remission	**n = 21 (47%)**
No improvement	**n = 5 (11%)**

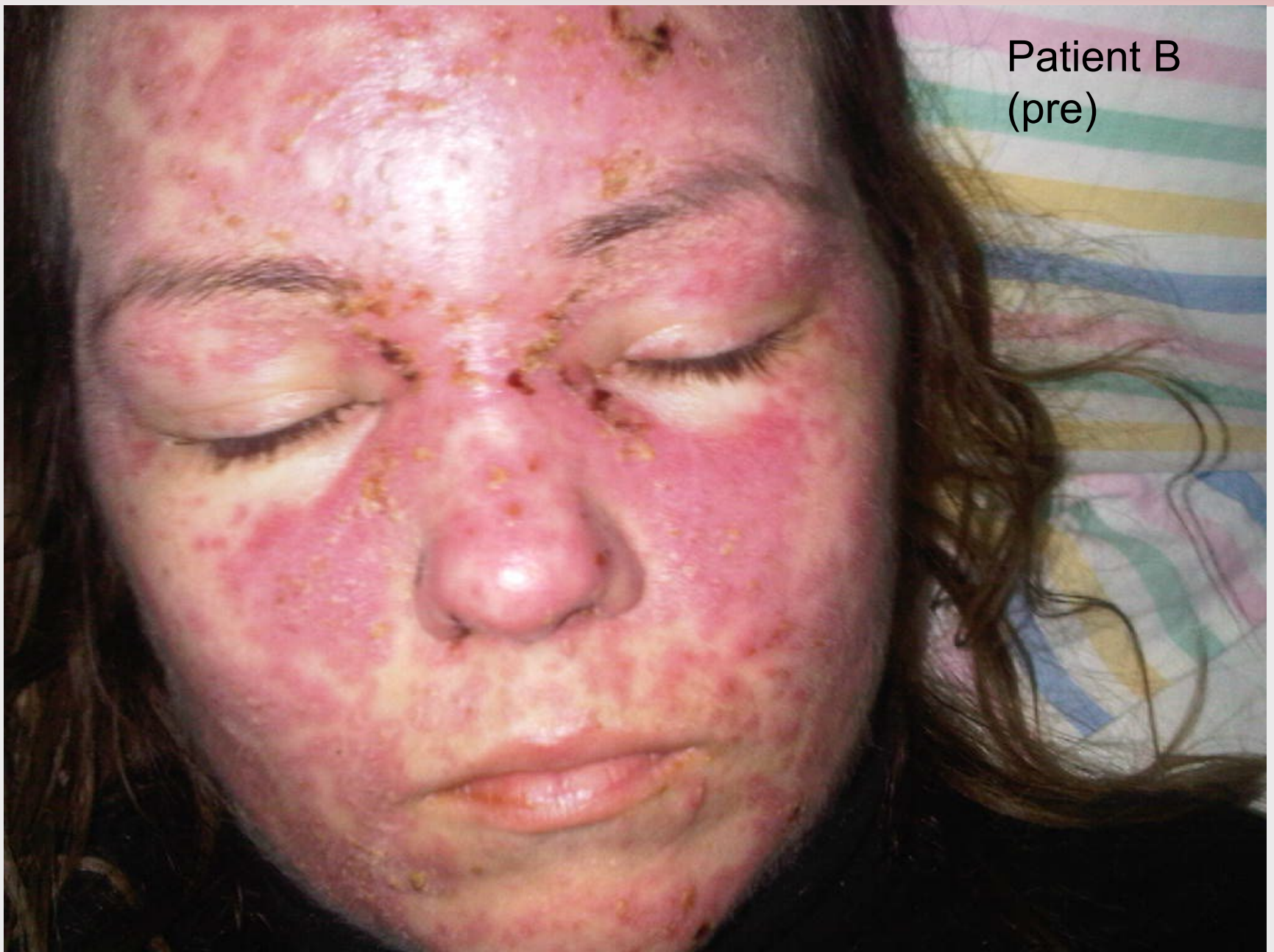
Severe Sub-acute Cutaneous Lupus – Before B cell Depletion

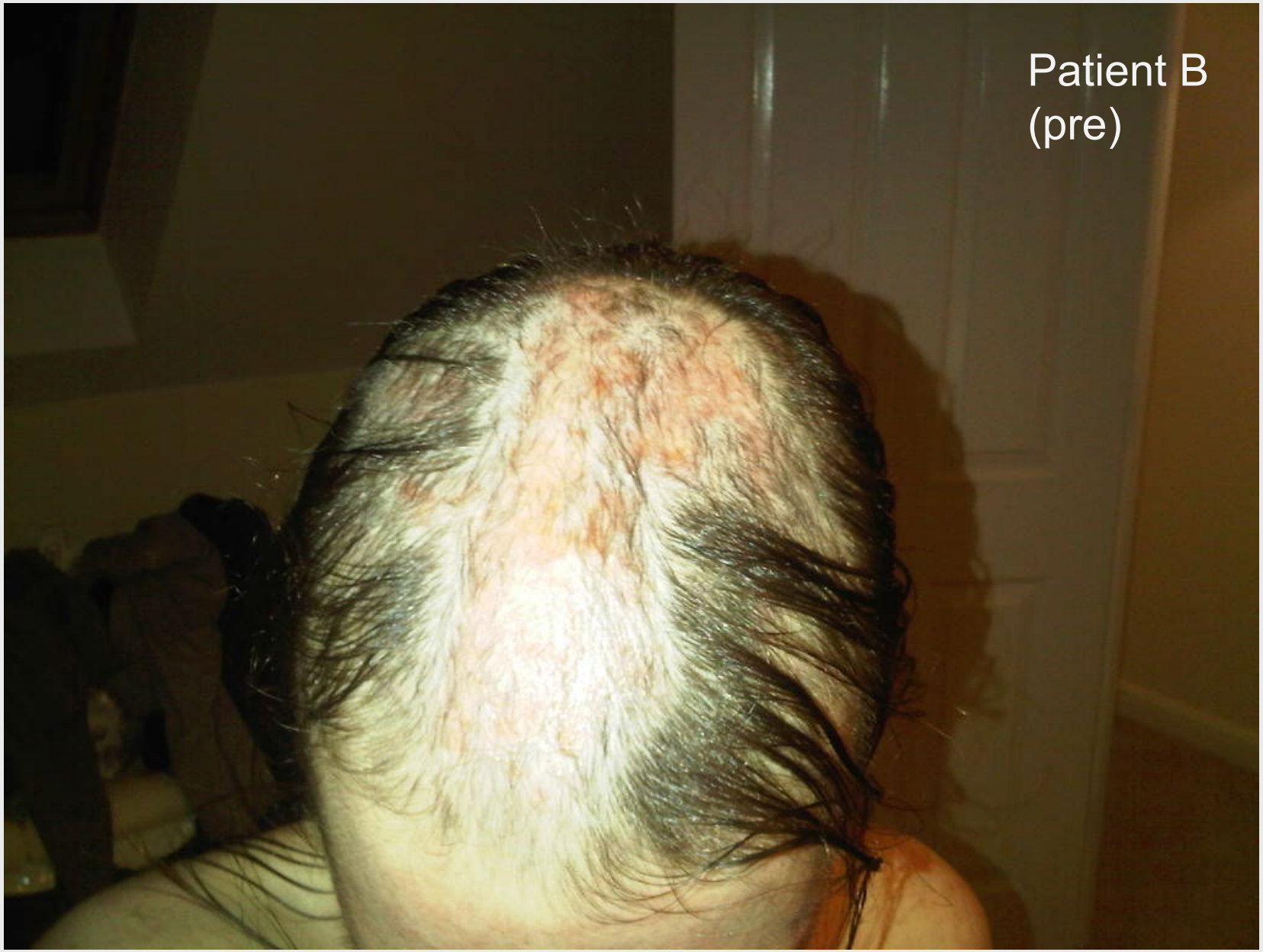


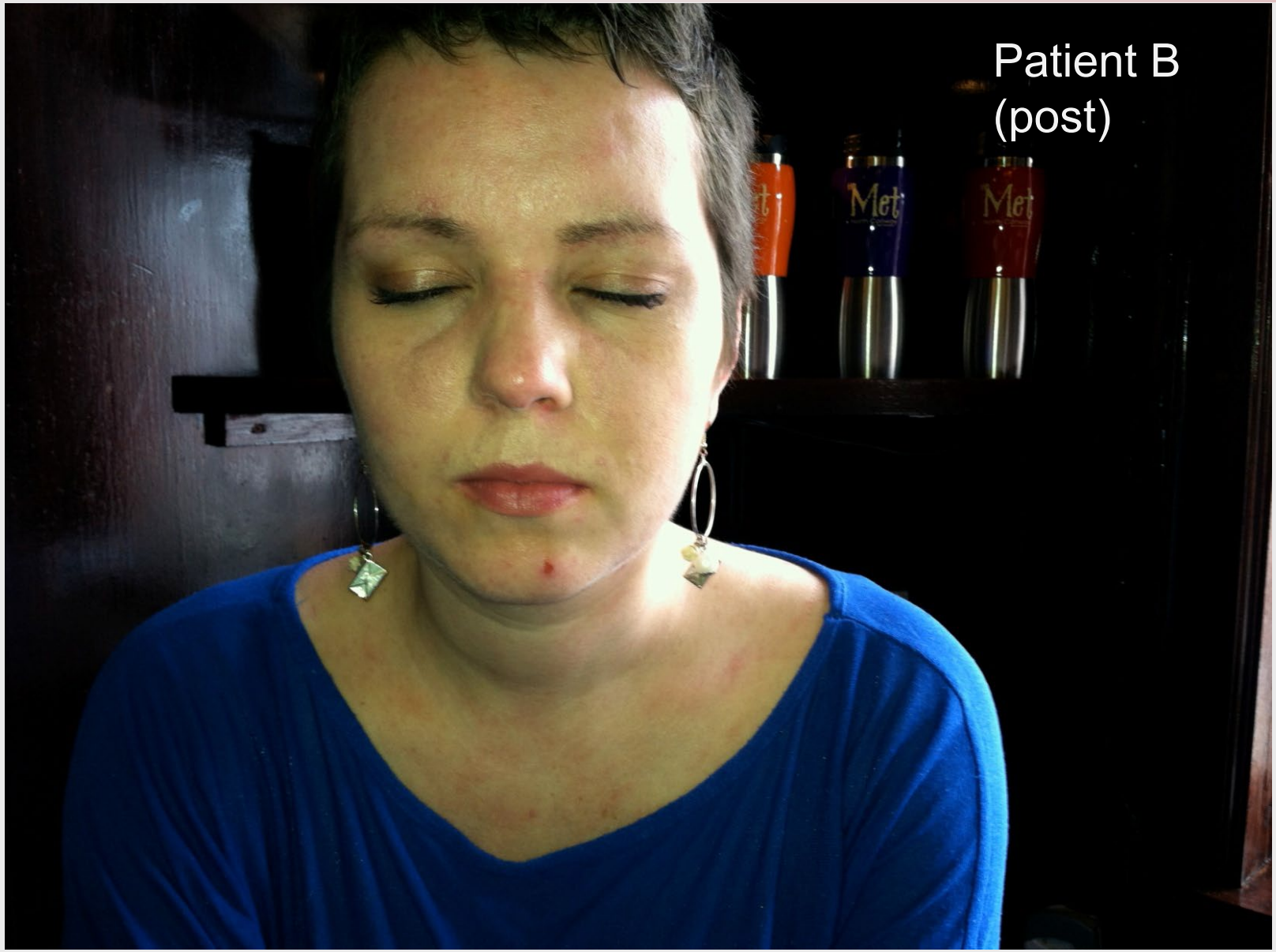
Severe Sub-acute cutaneous Lupus Treated with B cell Depletion – Before and 1 Month Afterwards



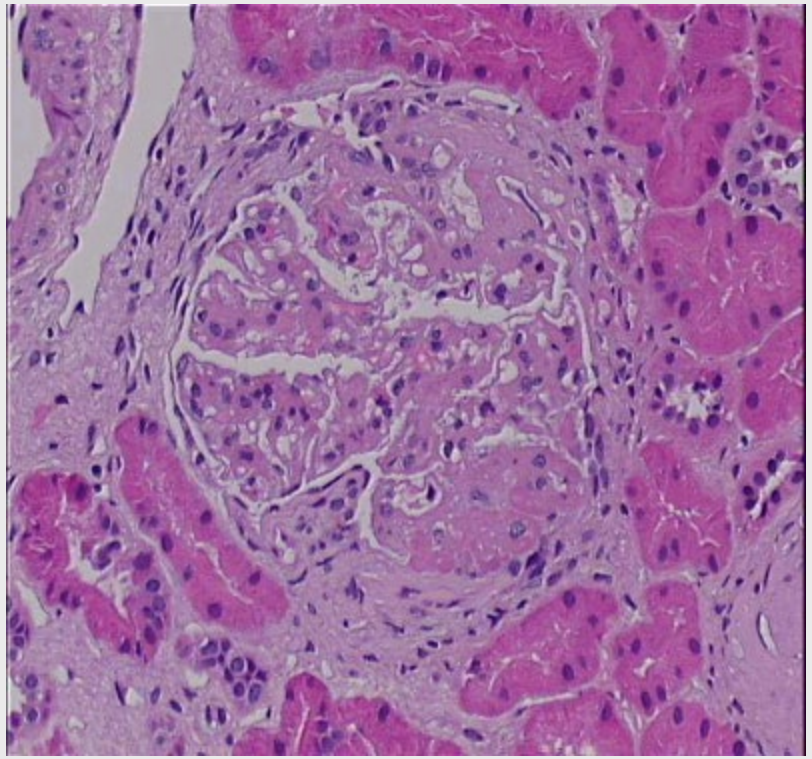



Patient B
(pre)

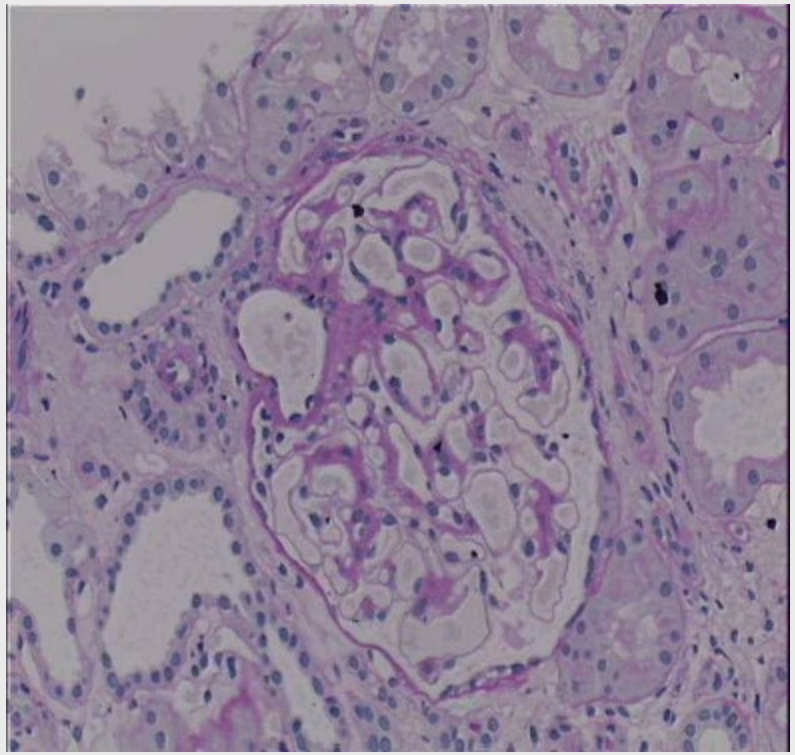

Patient B
(pre)


Patient B
(post)

Renal biopsy appearance – Patient C



Before



After

With thanks to Professor Ronald Van Vollenhoven

BUT there were some important positives…

Secondary serological endpoints

- Significant reduction in anti-dsDNA antibodies and ↑ in C3 and C4 at week 52 and 78

Exploratory endpoints – 78 weeks	Placebo	Rituximab	p
At least 50% reduction in proteinuria	54.2%	70.8%	0.04
CR or PR proteinuria	56.9%	73.6%	0.04
Black patients overall response 52 weeks	45%	70%	ns
Black patients overall response 78 weeks	35%	60%	ns
Started CyP prior to week 52	11%	0%	0.006
Started CyP prior to week 78	15.3%	2.8%	0.02
Average daily dose pred week 16-52	12.8±6.5	10.9±4.1	0.05

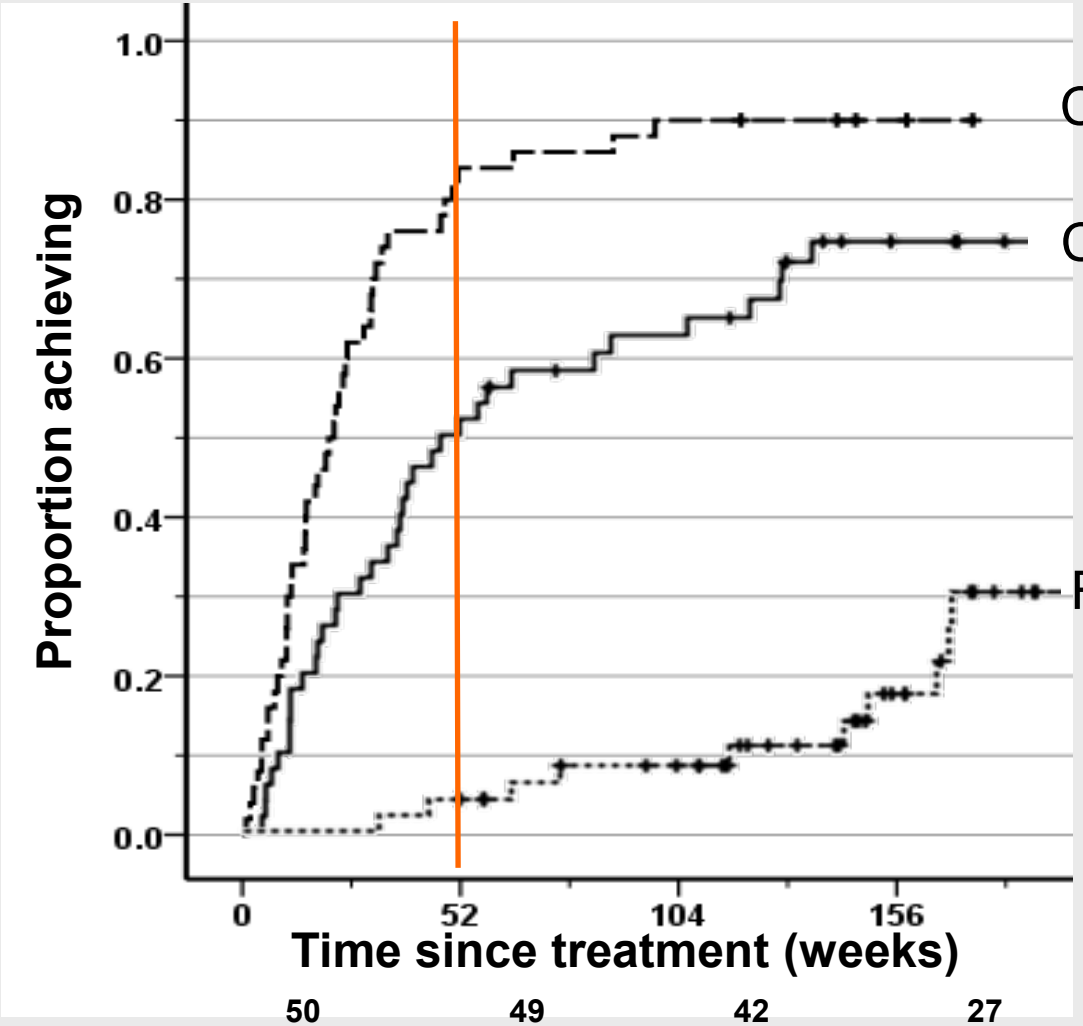
- No new safety signals

Treatment regime - Rituxilup

- Steroid avoiding regime
- Used in all new and relapsing lupus who are not already on steroids and who do not have cerebral lupus
- Very low toxicity
- Established as our first line treatment protocol

Condon et al. Annals Rheum Dis. 2013; 72:1280-6

Time to remission and relapse newly diagnosed LN patients

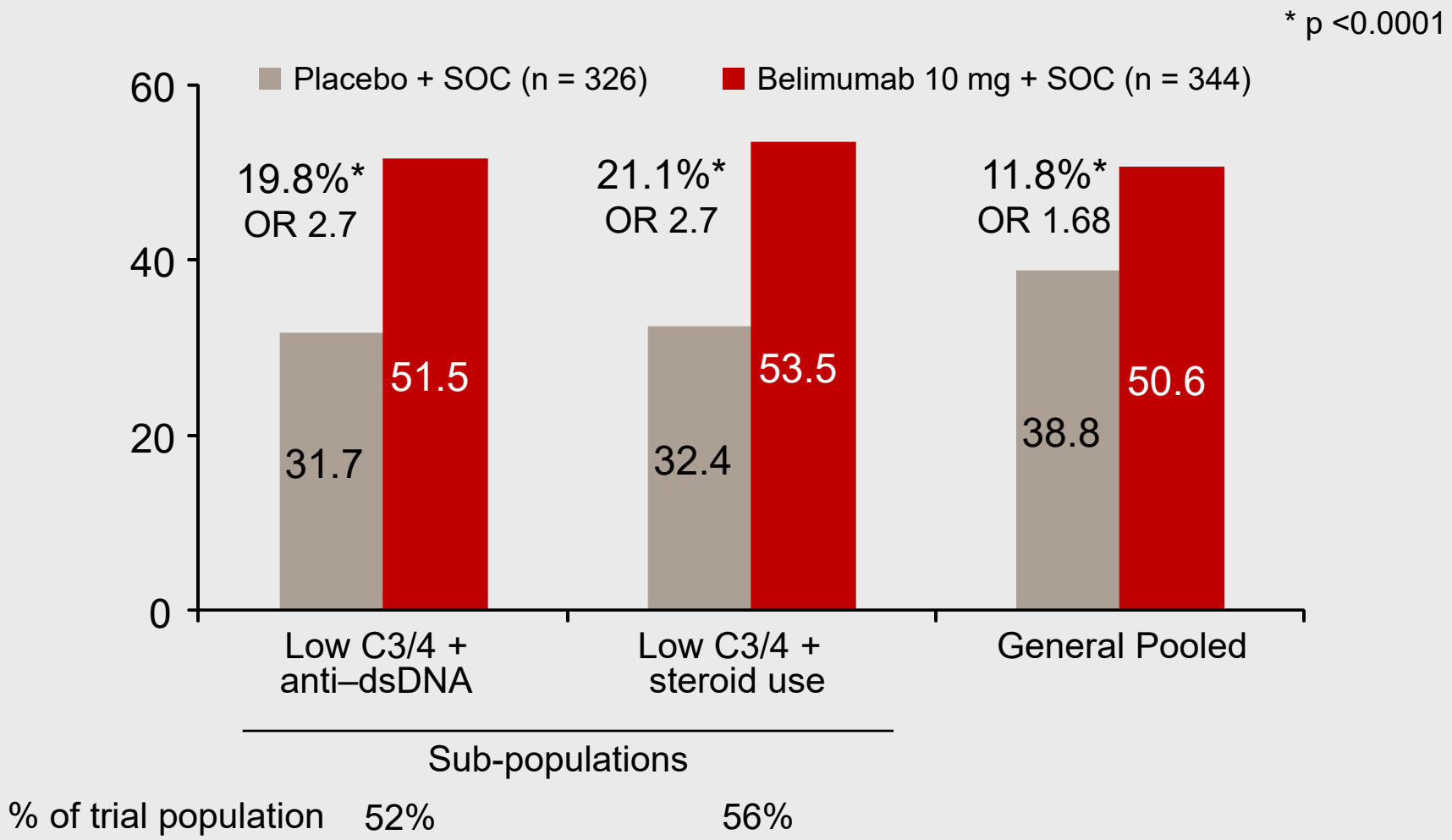


In CR:

- 12 wks 9 (18%)
- 26 wks 16 (32%)
- 52 wks 26 (52%)

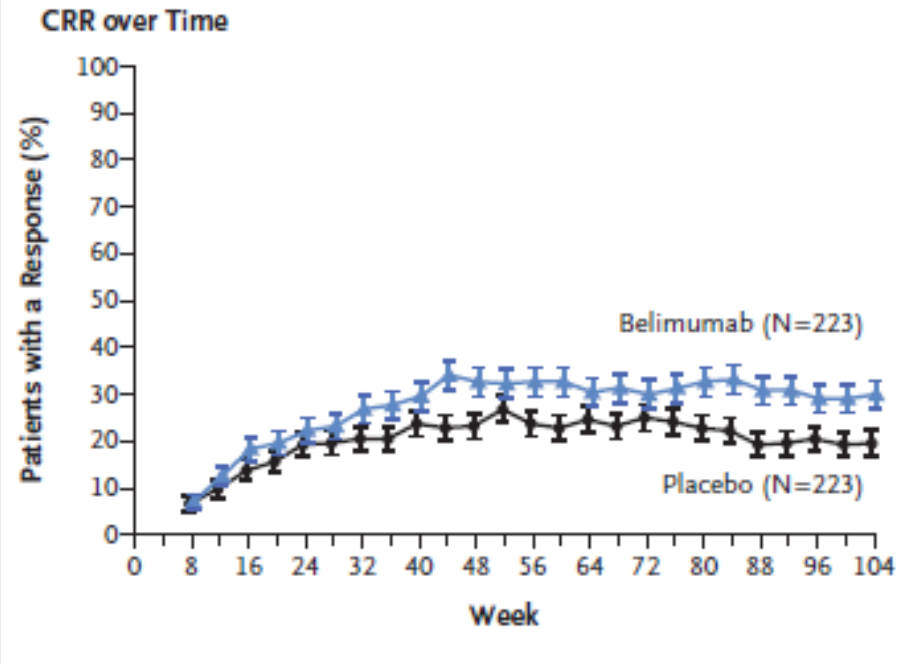
Condon et al. Annals Rheum Dis. 2013; 72:1280-6

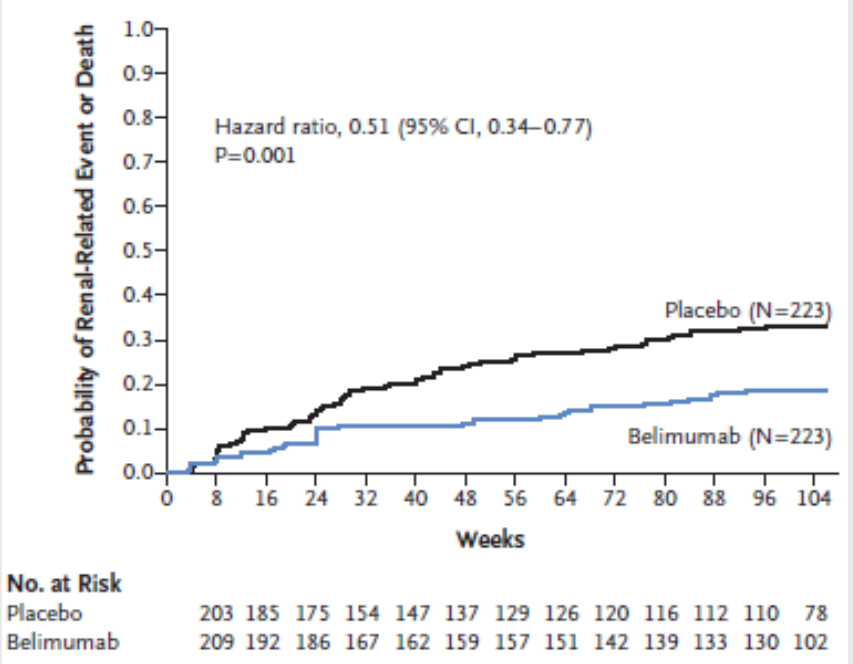
Belimumab trial subpopulation analysis: SRI Response Rate at Week 52 based on Combination of Baseline Disease Characteristics



Moran et al NEJM 2020; 382: 211-21

Belimumab+SOC vs SOC achieving a 30% CRR @ wk 104





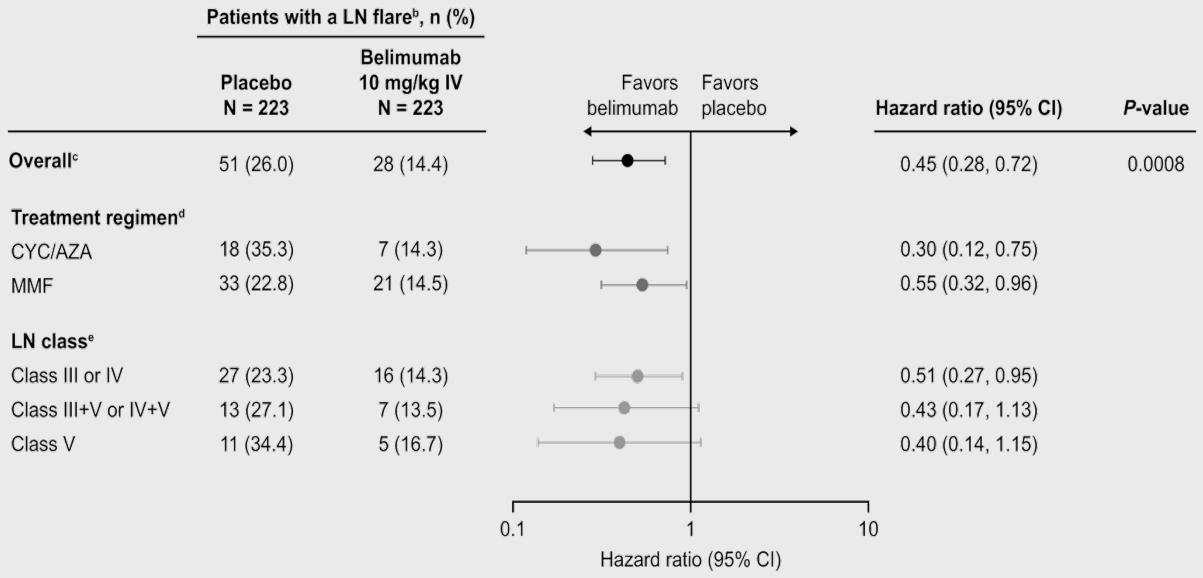
Event	Belimumab (N=223)	Placebo (N=223)
	no.	
Any event	35	63
Death from any cause	1	2
Progression to ESKD	0	1
Doubling of creatinine level from baseline	1	1
Increased proteinuria, impaired kidney function, or both	17	39
Treatment failure related to kidney event	16	20

Furie et al NEJM 2020

BLISS-LN

Improvement in eGFR and Reduction of Renal Flares

BLISS-LN post hoc analysis	Placebo (n=223)	BEL (n=223)	OR (95% CI)	P
30%↓ eGFR-sustained	25 (11.2%)	8 (3.6%)	0.29 (0.13- 0.68)	0.004
40%↓ eGFR-sustained	15 (6.7)	4 (1.8)	0.25 (0.08- 0.78)	0.018

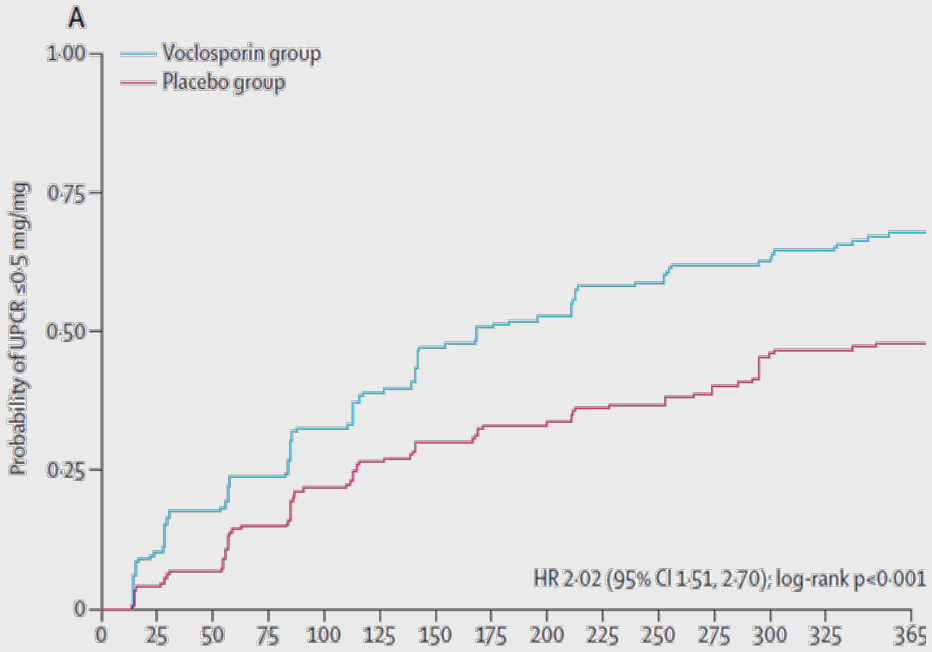


Rovin B et al., KI, 2022

Voclosporin v Benlysta (for Lupus nephritis)

Resolution of Proteinuria

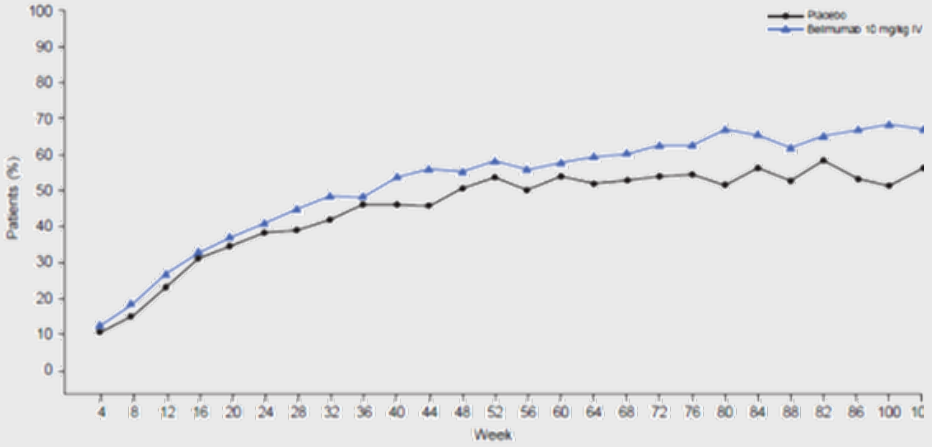
AURORA 1



Time to UPCR ≤ 0.5

CRR 41% vs 23%

BLISS-LN



Patients with proteinuria shift from ≥ 0.5 to <0.5.

Rovin et al Lancet 2021

Furie et al NEJM 2020

BIOLOGICS/OTHER NEW MOLECULES IN SLE – WHERE ARE WE NOW? – 4 -

New approaches for achieving B-cell depletion:

1. CD20 directed bispecifics, e.g. mosunetuzumab (no data yet)
2. Obinutuzumab [fully humanized anti-CD20]
3. Combination therapy e.g. rituximab plus Benlysta
4. CAR T-cell therapy

GAZYVA (OBINUTUZUMAB)

- **REGENCY showed that Gazyva helped more patients achieve a complete renal response when added to standard of care**

- **The phase III study met both primary and key secondary endpoints: CRR 46.4% vs 33.1%**

- **NB: Only Benlysta is approved for the treatment of nephritis.**

Furie et al NEJM 2025

HOT NEWS – REGENCY Phase III Trial Of Obinutuzumab

	Obinutuzumab (n = 135)	Placebo (n = 136)	Difference (95% CI)	P Value
Week 76				
CRR	46.4%	33.1%	13.4%	0.02
CRR w/PT*	42.7%	30.9%	11.9%	0.04

* with prednisone taper to <7.5 mg weeks 64 and 76

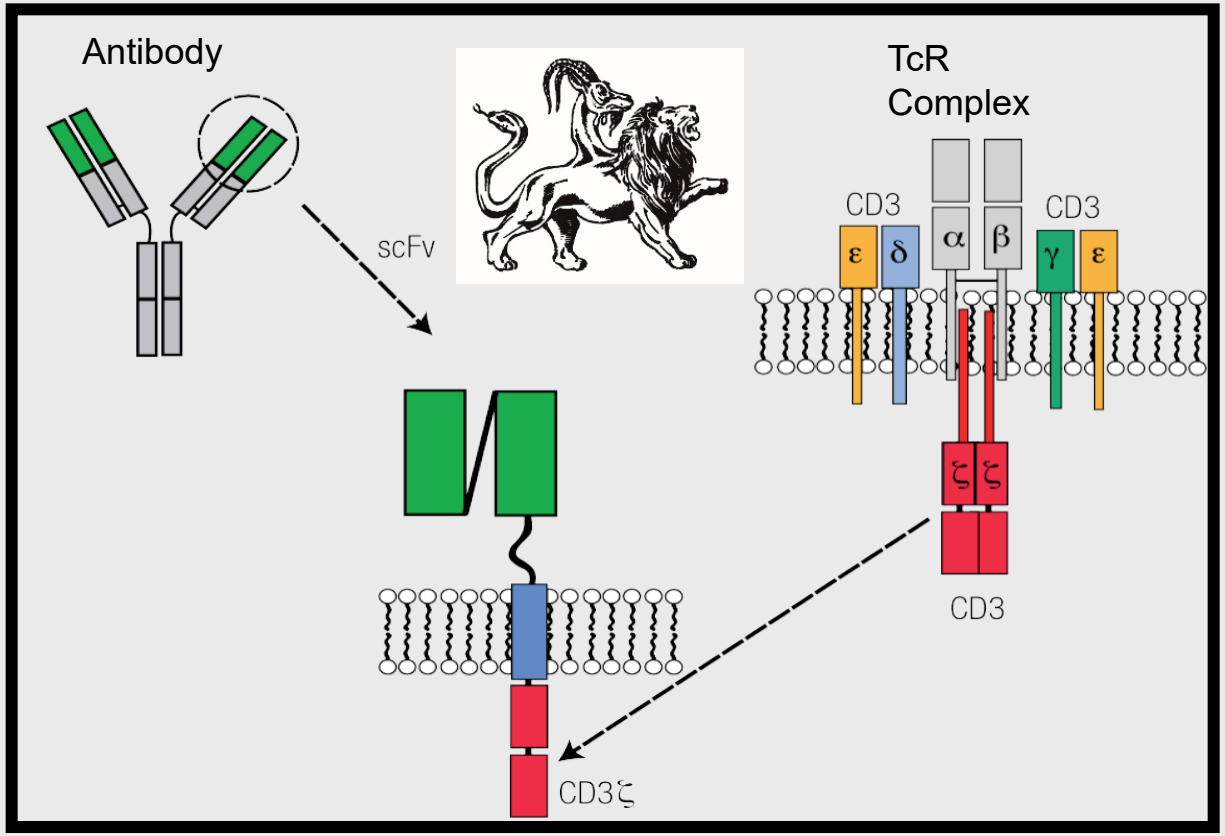
Furie et al. NEJM 2025

BIOLOGICS/OTHER NEW MOLECULES IN SLE – WHERE ARE WE NOW? -

Combination therapies Rituximab + Benlysta

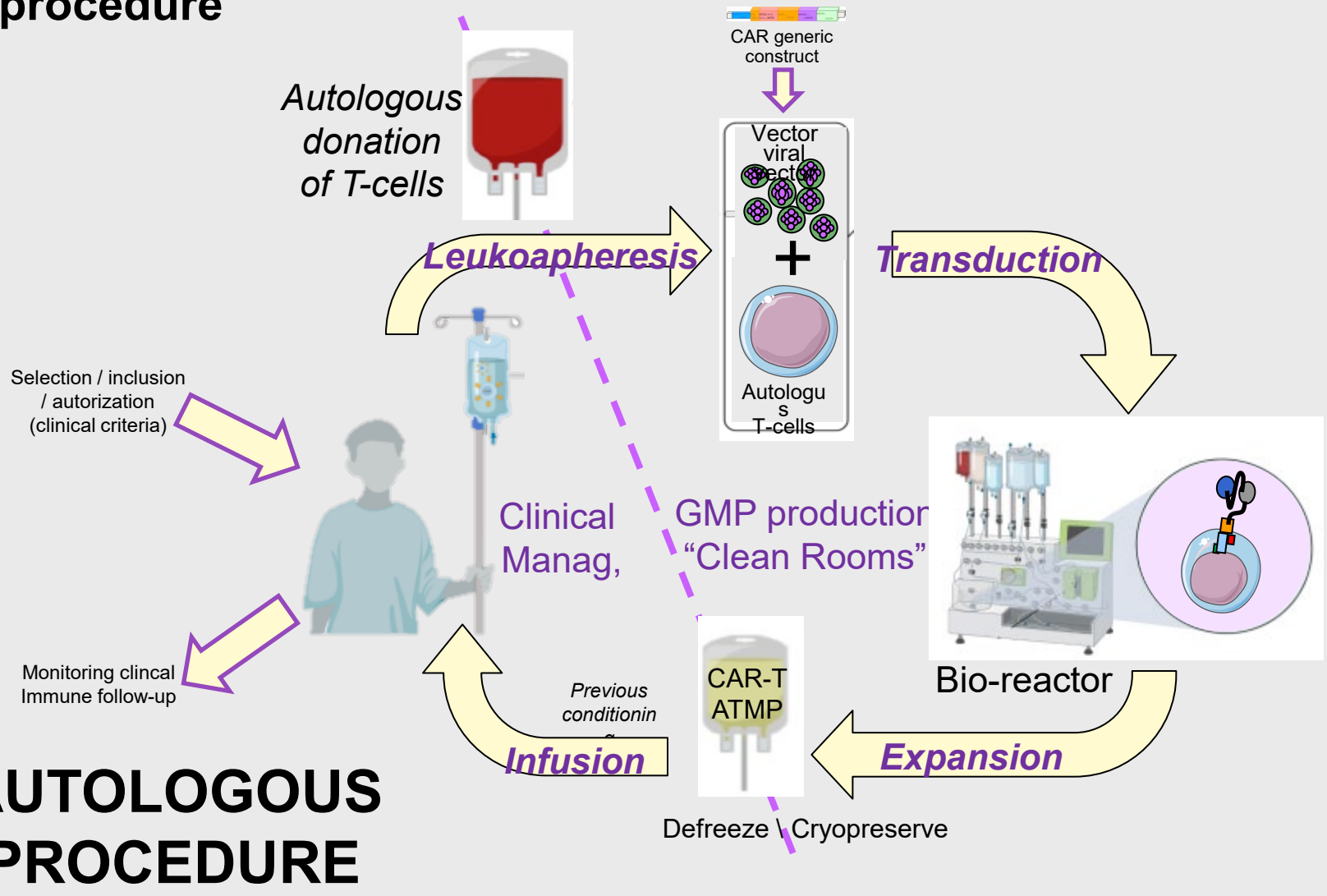
BEAT-LUPUS	CALIBRATE	BLISS-BELIEVE
Renal + Non-Renal (n = 52)	Renal (n = 42)	Non-Renal (n = 292)
Phase IIb	Phase III safety study	Phase III – 3 arm study
Met serological primary endpoint [↓ dsDNA] ↓ flare frequency	No difference between the arms	No difference between the arms

CAR = Chimeric Antigen Receptor



Sònia Guedán Carrió y Anna Boronat Barado
Chapter 6. Monografías SEI – Elsevier. “Inmunoterapia antitumoral con linfocitos genéticamente modificados (CAR): una realidad con futuro”

CAR-T procedure (drug)



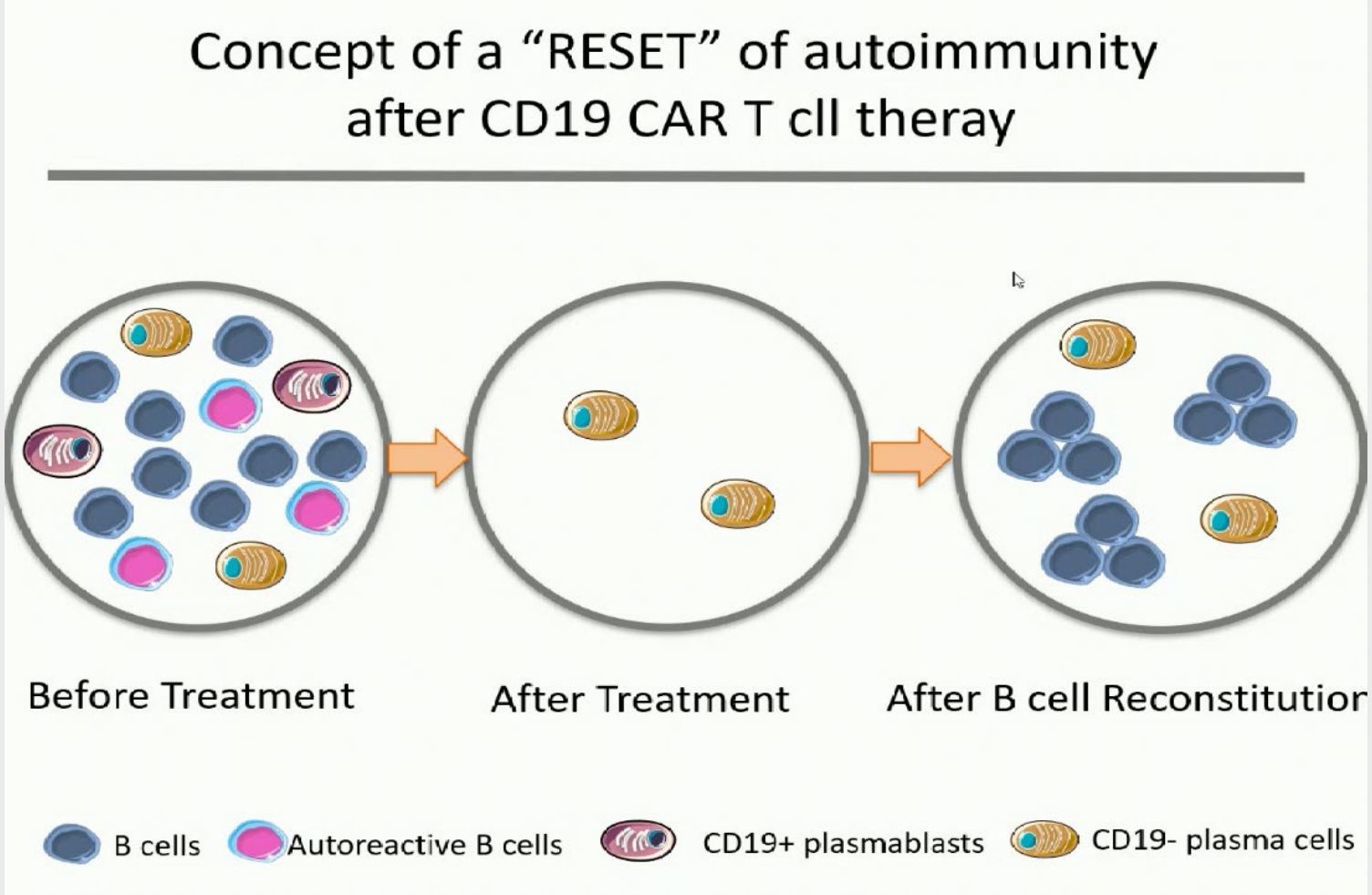
AUTOLOGOUS PROCEDURE

Emerging CAR T Lupus data in early clinical experience

	Erlangen	Cabaletta	Kyverna	Novartis	BMS
Product	Various	Rese-cel	KYV-101	Rapca-cel	BMS-986353
n	19 SLE	4 SLE & 2 LN	6 LN	11 LN	11 SLE
Baseline LN Disease	-	**Class III –V**	**Class II-V**	**Class III –V**	-
CRS	**Yes (Gr 1 & 2)**	**Yes (Gr 1 & 2)**	**Yes (Gr 1 & 2)**	**Yes (Gr 1 & 2)**	**Yes (Gr 1 & 2)**
ICANS	No	**Yes* (Gr 4)**	**Yes (Gr 1)**	**Yes (Gr 2)**	**Yes (Gr 3)**
Efficacy	100% DORIS at month 6. No relapse (median follow up 18months)	3/4 DORIS and 1/2 complete renal responses	SLEDAI-2k improved	SLEDAI 2K down to <10 for all pts	median 10-point reduction in SLEDAI-2K
Study	NCT06347718	NCT06121297	NCT05938725	NCT05798117	NCT05869955
Data	EHA/EBMT 7th CAR T Meeting 2024	March 2025	Nov 2024	Dec 2024	ACR 2024

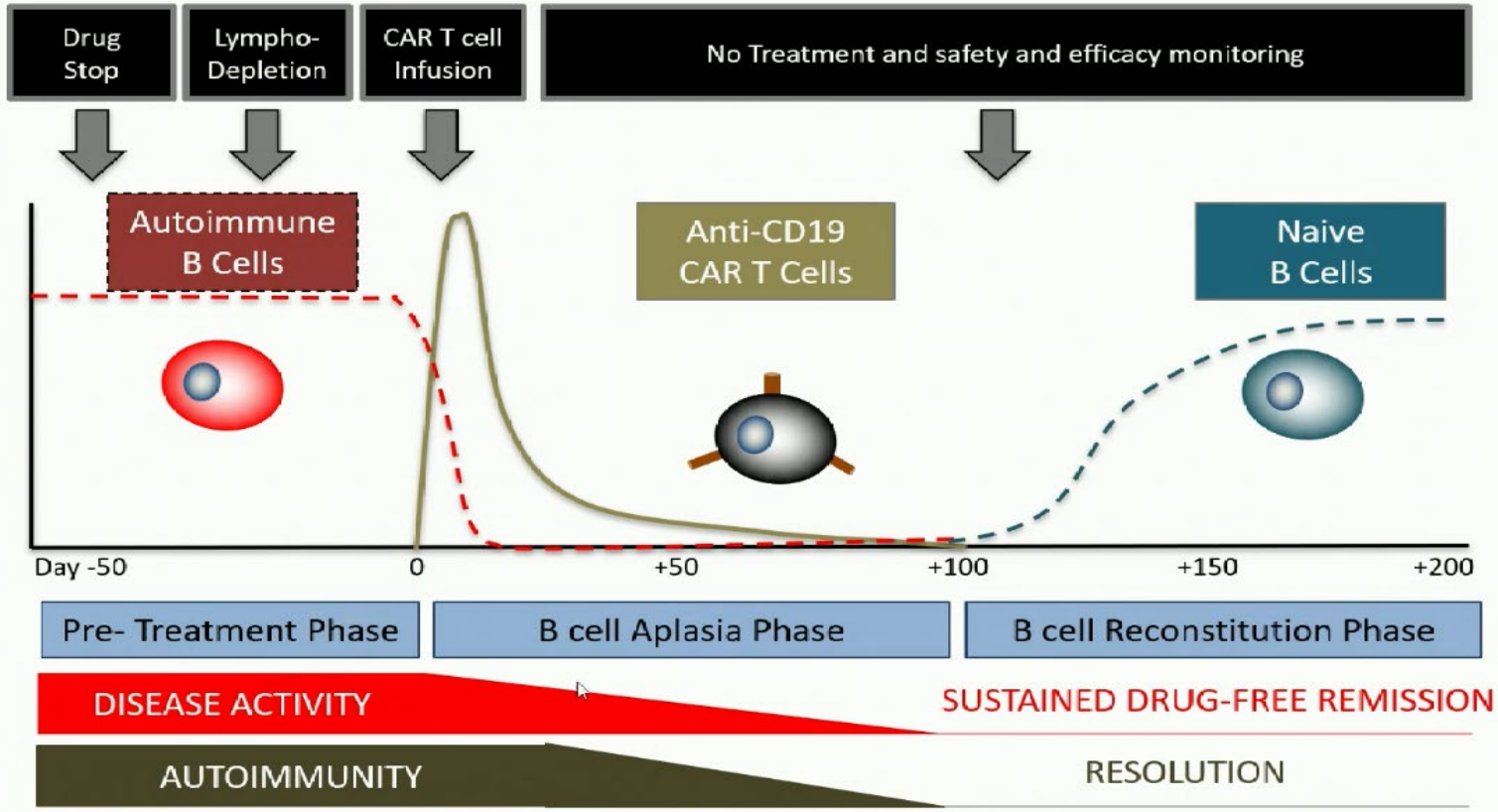
* A case of grade 3 ICANS was also observed in Cabaletta's Scleroderma Phase 1 trial

- Reported CAR T observations from small cohorts, largest from Schett's
- Included LN subjects had mostly NIH class II-III disease, some class V addition
- CRS G2 was observed with all tested CAR T constructs in few cases
- ICANS was reported for each cohort (up to G4) except for the Erlangen cohort



G Schett;EULAR May 2023

Wrap it up!



G Schett;EULAR May 2023

CD19 CAR T cell therapy for SLE: an exciting advancement ….

- Currently administered at specialty centers, path to outpatient administration to be further validated
- Data from well designed clinical trials required to properly assess
- Current evaluation in refractory patients without treatment alternatives, best use preventing end organ damage may be early on
- Long term follow up for larger patient cohorts relevant to determine long term clinical and cost benefit

UNMET/ONGOING NEEDS IN SLE

- Earlier diagnosis of commencement of treatment.
- Try to minimize the use of long-term steroids.
- Patients need to be referred to specialist centres
- How to manage patients who are poorly compliant.
- How to manage patients with very aggressive disease responding inadequately to steroids/immunosuppressives/biologics.

WHAT WOULD I BE LOOKING FOR IN A NEW AGENT TO TREAT LUPUS/LUPUS NEPHRITIS

- **Is it more effective than currently available therapies?**
- **Is it safe?**
- **How much does it cost [and how does the cost compare to the cost of currently available therapies?]**

CONCLUSIONS (1)

- **Although the outcome for SLE patients is better in 2025 than in the 1950s, major problems of morbidity and mortality remain.**

- **Based upon a better understanding of the immunopathology, we are now producing B-cell targeting therapies addressing precisely those cells or pathways likely to be responsible for SLE.**

CONCLUSIONS (2)

- We have clearly reached the limits with conventional therapies [steroids, Azathioprine, MMF etc].

- To improve long-term outlook we have to move to the earlier and possibly combined use of biologics or CAR T therapy.

- The future is bright – we just have to get there.

Autolus

Initial results from the Phase 1 trial of obe-cel in patients with severe lupus and organ manifestation

CARLYSLE Study

David Isenberg, MD FRCP FAMS
University College London

Ongoing Phase 1 CARLYSLE: *Obe-cel CD-19 CAR T in severe refractory systemic lupus erythematosus (SLE)*

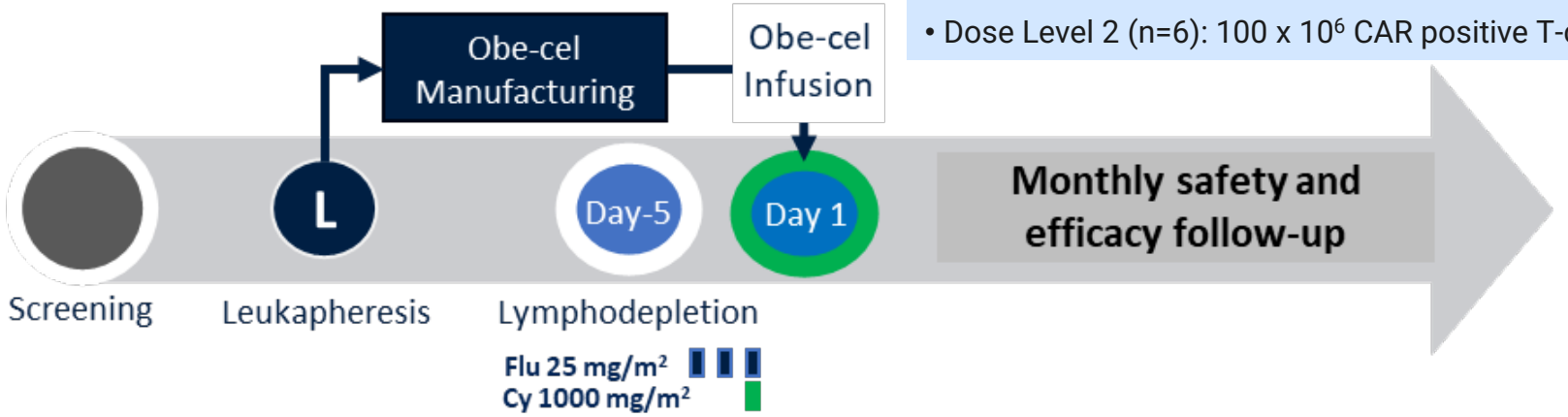
Key Inclusion Criteria

- Diagnosis of SLE based on (EULAR)/ (ACR) 2019 classification
- Positive (ANA) (≥ 1:80), or anti-dsDNA (≥ 30 IU/mL) or anti-Smith (> ULN), anti-histone or anti-chromatin (> ULN)
- Severe, refractory SLE **with organ involvement**

Key Exclusion Criteria

- Recurrent or active, severe or unstable neuropsychiatric lupus
- Any acute, severe lupus-related flare that needs immediate treatment
- Significant, likely irreversible organ damage related to SLE (e.g., end-stage renal disease)
- Diagnosis of another non-SLE autoimmune disease (e.g. polymyositis, dermatomyositis)

- Dose Level 1 (n=6): 50 x 10^6 CAR positive T-cells
- Dose Level 2 (n=6): 100 x 10^6 CAR positive T-cells



Summary of findings from first dose cohort (n=6) at $50x10^6$ cells

Baseline Characteristics

- **Six patients aged 19-50 years, (5 female and 1 male)**
- **Disease history of 3 and 23 years with SLEDAI-2K scores at screening ranging from 15 to 28**
- **All patients had lupus nephritis class III/IV with 4/6 patients having also class V components:**
  - Serum creatinine was elevated in 4/6 patients (ranging from 69-222 µmol/l)
  - Baseline eGFR was reduced in 4/6 patients (ranging from 47-161 ml/min/SA)
  - Baseline UPCR was elevated in all patients (ranging from 0.49 to 4.0 mg/mg (normal range <0.13))
- **Other manifestations**
  - 2/6 also had musculoskeletal manifestations
  - 4/6 of patients also had dermal manifestations
- **Prior therapies**
  - All patients had failed prior B-cell modifying agents, none of them as immediate last therapy prior to obe-cel
  - 3/6 patients had failed prior calcineurin inhibitor (CNI)

Data cut off 17 March 2025

Summary of safety profile, key events

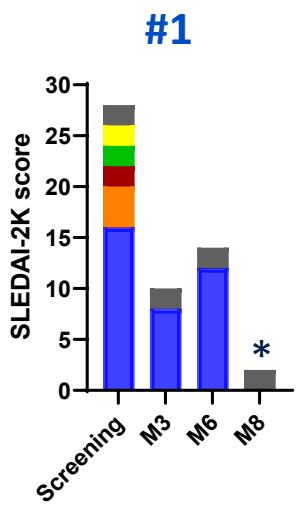
Highest grade of treatment-emergent adverse event observed by patient:							
TEAE, Grade	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**	**Patients, n (%)**
CRS	-	-	1	-	1	1	3 (50%)
ICANS	-	-	-	-	-	-	0 (0%)
Neutropenia	3	3	4	4	3	3	6 (100%)
Anemia	-	-	3	3	1	3	4 (67%)
Thrombocytopenia	-	-	-	3	-	-	1 (17%)
Infection	2	2	3	3	1	2	6 (100%)

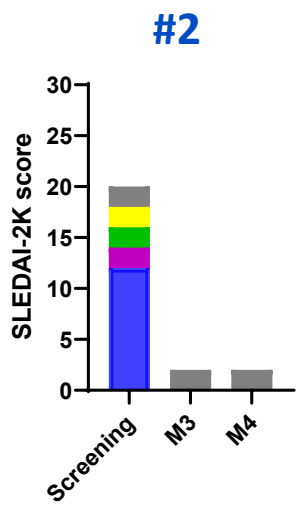
- **No high-grade CRS, No ICANS observed, No DLTs observed**
- Transient hypertension, including G3, due to abnormal kidney function prior to start of therapy according to PI's judgement nor pre-existing hypertension (3/6)

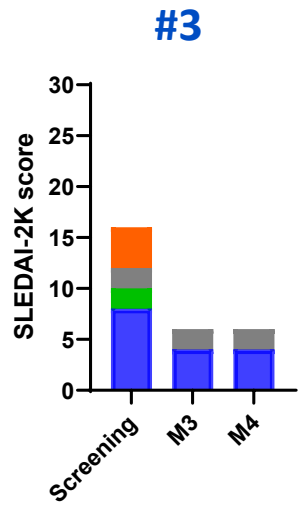
10+ point drop by M3 in SLEDAI-2K scores

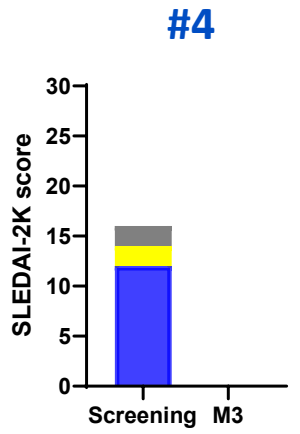
No immunosuppressive drugs except for maintenance doses of prednisone; tapering in all patients ongoing.

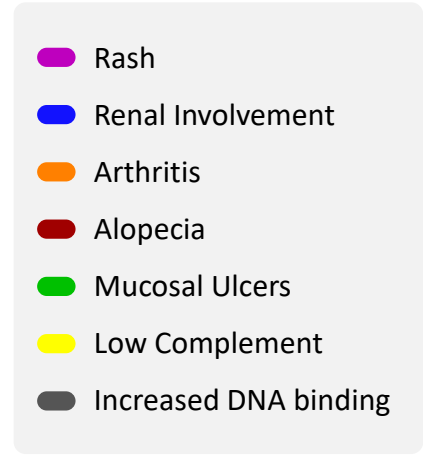
M3+ follow up



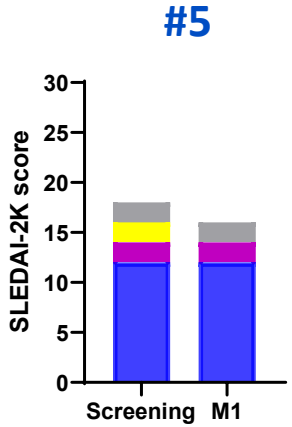


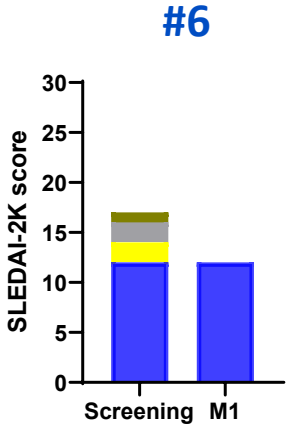






M1 follow up





- All patients benefited significantly from obe-cel
- Skin: rash, alopecia and mucosal ulcers resolved by M3
- Musculoskeletal: Arthritis resolved by M1
- Complement normalized in all patients by M1

*Kidney biopsy on month 7 showed no disease activity

Three out of six patients with complete renal response within 3 months

	UPCR (normal range <0.13mg/mg)		Serum creatinine (normal range 45-92umol/L)		eGFR (normal range >90ml/min/SA)		
	D-30	Last FU	D-30	Last FU	D-30	Last FU	
1	4	0.42 (M8)	222	348	57	34	
2	0.49	**0.27** (M3)	69	80	161	**149**	CRR at M3
3	1.32	1.87 (M3)	124	127	56	54	
4	2.08	**0.13** (M3)	123	92	47	**62**	CRR at M3
5	2.26	**0.40** (M1)	100	119	107	**85**	CRR at M1
6	0.91	3.37 ** (M1)	132	165	50	47	

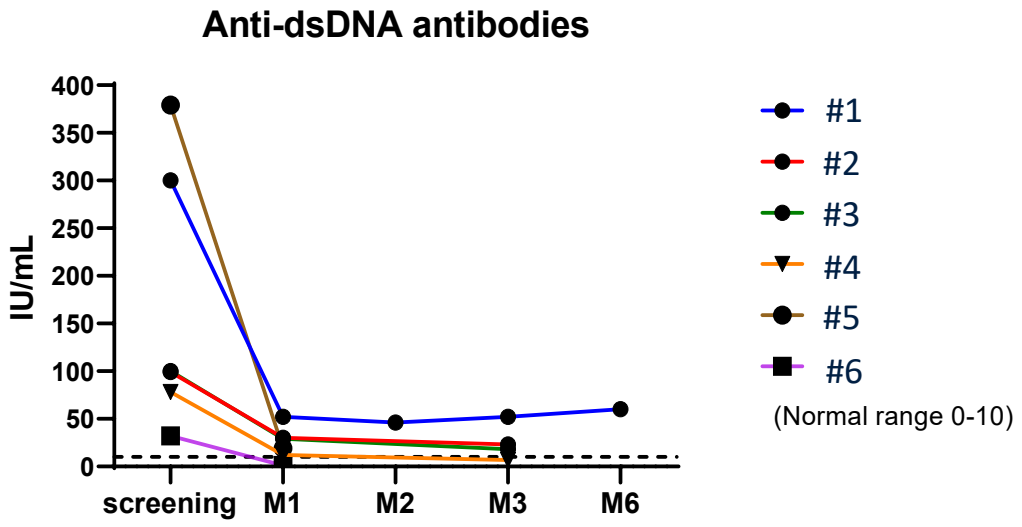
Transient worsening of renal function due to hypertension and inflammatory response not due to LN per PI's judgment
** UPCR increase caused by urinary tract infection observed on Day 27

Short Term Efficacy Outcomes – Anti-dsDNA antibodies & complement

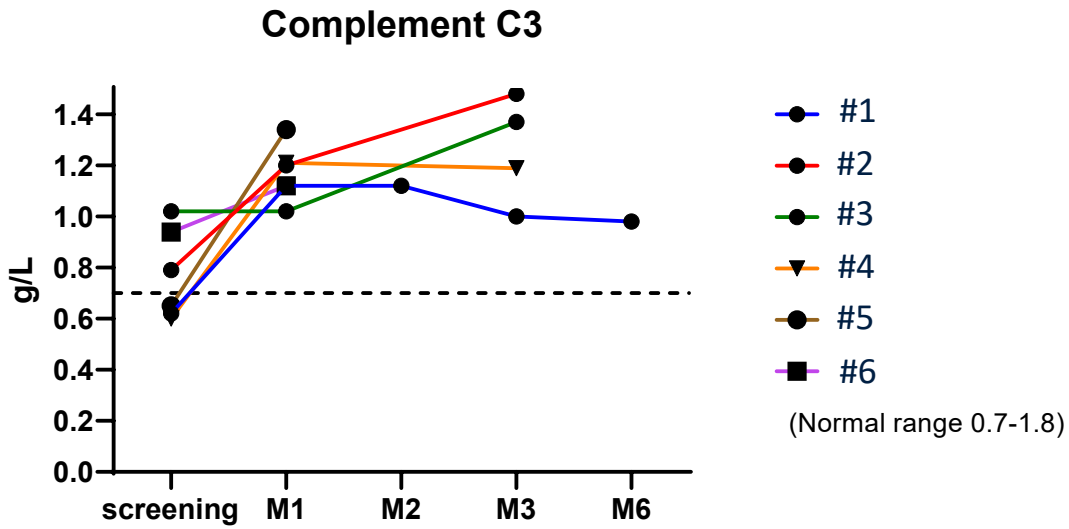
Improvement in serology was observed starting from M1 post infusion (anti-dsDNA decrease to ULN and complement normalization)

- Complement C3 normalized by M1 for all patients
- Anti-dsDNA improved for all by M1, normalized in 2 patients

Anti-dsDNA antibodies



Complement C3



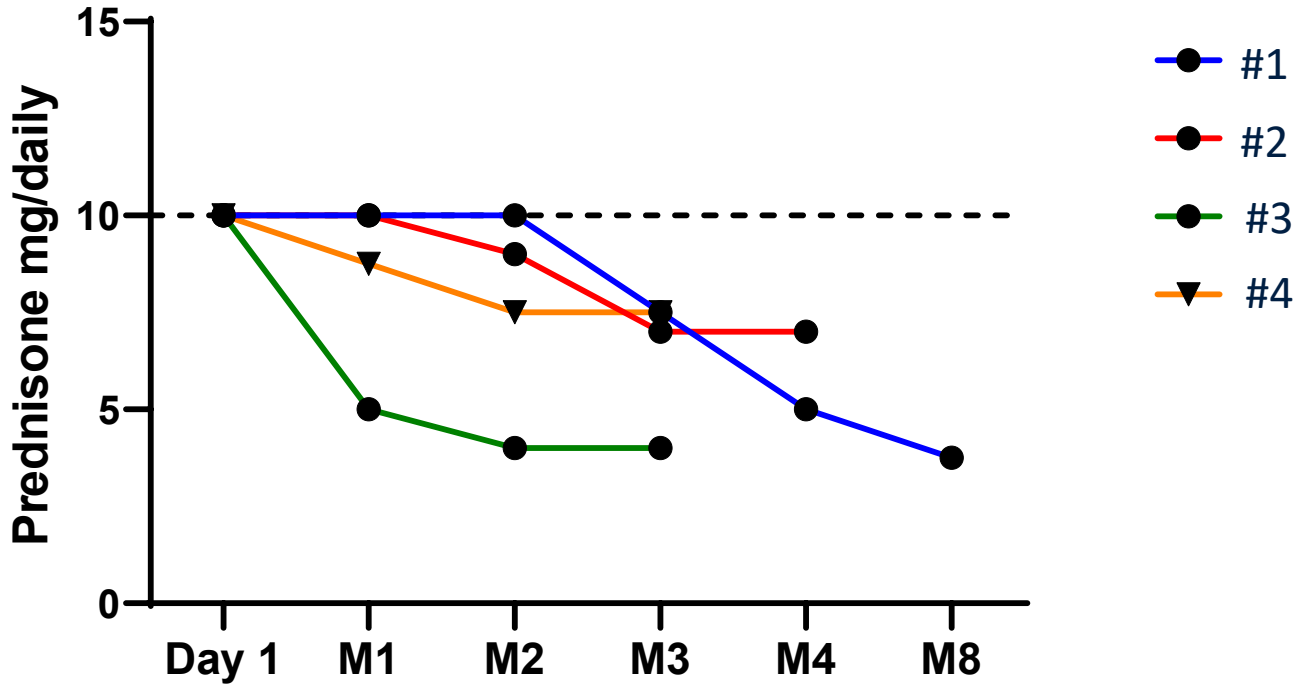
Steroids tapering post obe-cel infusion in all patients post M1

- All patients received bridging therapy with a median steroid dose of 15mg/daily (range
- 5-500mg/daily)

- Following obe-cel infusion, steroids tapering below 10mg/daily occurred for all patients (no more than 10mg/daily is permitted post obe-cel infusion)

- No additional SLE medications have been administered to any of the patients

Steroids tapering post infusion

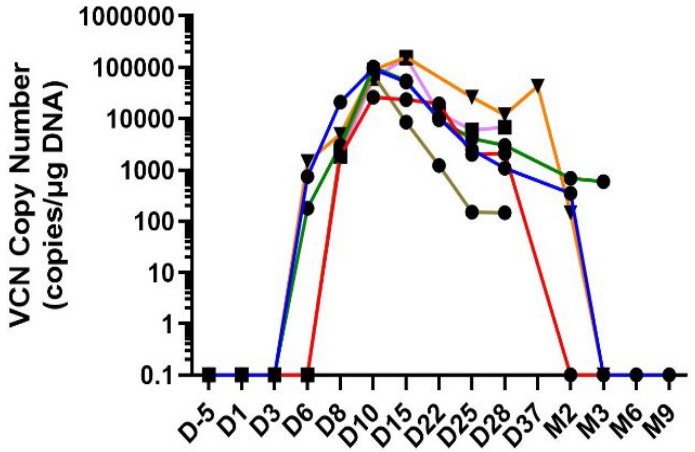


Median dose is reported
Note: Patient 007 and 008 reached 4weeks FU at data cut-off 17Mar25. They are receiving since day 1 10mg qd

High CAR T peak expansion and deep B cell aplasia

CAR-T Persistence

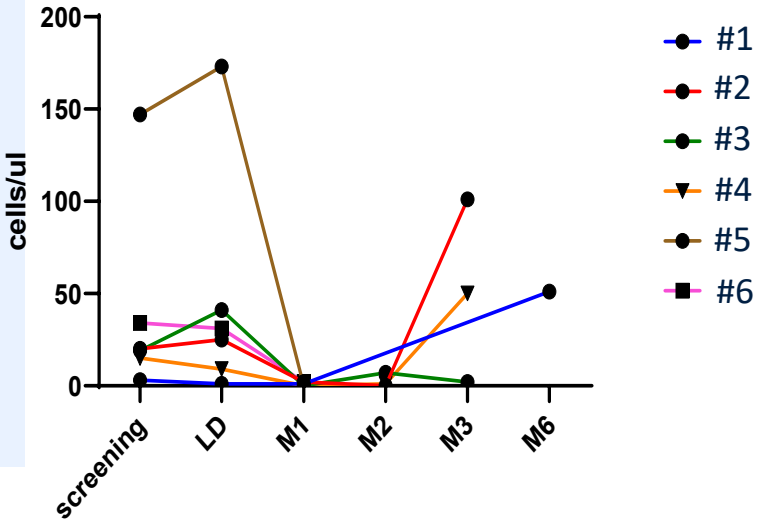
CAR T C_{max} similar to observations in heme indications and persistence between M2 and M3 for 3/6 of patients



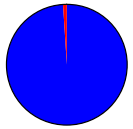
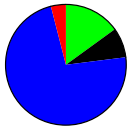
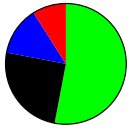
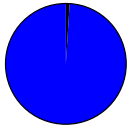
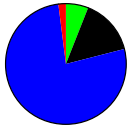
*Samples with 0 VCN are shown as 0.1 due to the log scale

B-cell Aplasia

B-cell recovery observed between M2 and M6 in 3/4 patients



B cells upon recovery display primarily a naïve phenotype in all 3 pts

Patient	Day -5	M3	M6	M9
#1	No baseline sample/data available			
#2				
#3				
#4				
#5				
#6				

- At baseline, memory B-cells represent up to 90% of B-cell population
- B-cel reconstitution occurs as early as M3
- Reconstituted B-cells are ≥90% naïve B-cells
- Double negative (CD27-, IgD-) Memory B-cells are mostly eliminated
- Early findings suggest a reset of B-cell population post obe-cel

Conclusions from CARLYSLE study to date

- **Patient population studied**
  - Patients had exhausted prior therapy options, all had B-cell depleting agent exposure, 2 also BAFF inhibitors, 3/6 also calcineurin inhibitors
  - Lupus nephritis: 5/6 patients had a class IV disease, 4/6 had also a class V component
  - Kidney function was significantly impaired (<60 ml/min/SA) in 4/6 patients
- **Safety**
  - No DLTs observed in first 6 patients dosed at $50x10^6$ cells
  - CRS only grade 1 (fever) observed in 3/6 patients
  - No ICANS
  - Transient neutropenia in all, anemia in 3/6 and thrombocytopenia in 1/6 patients
  - Transient hypertension, including G3, occurred in 5/6 patients
- **Efficacy**
  - All patients benefited from obe-cel treatment including three patients with a CRR (all by M3)
  - Complement normalized first, and in all patients
  - Musculoskeletal and dermal manifestations resolved in all patients by M3

PLANS FOR AUTOIMMUNE DISEASE

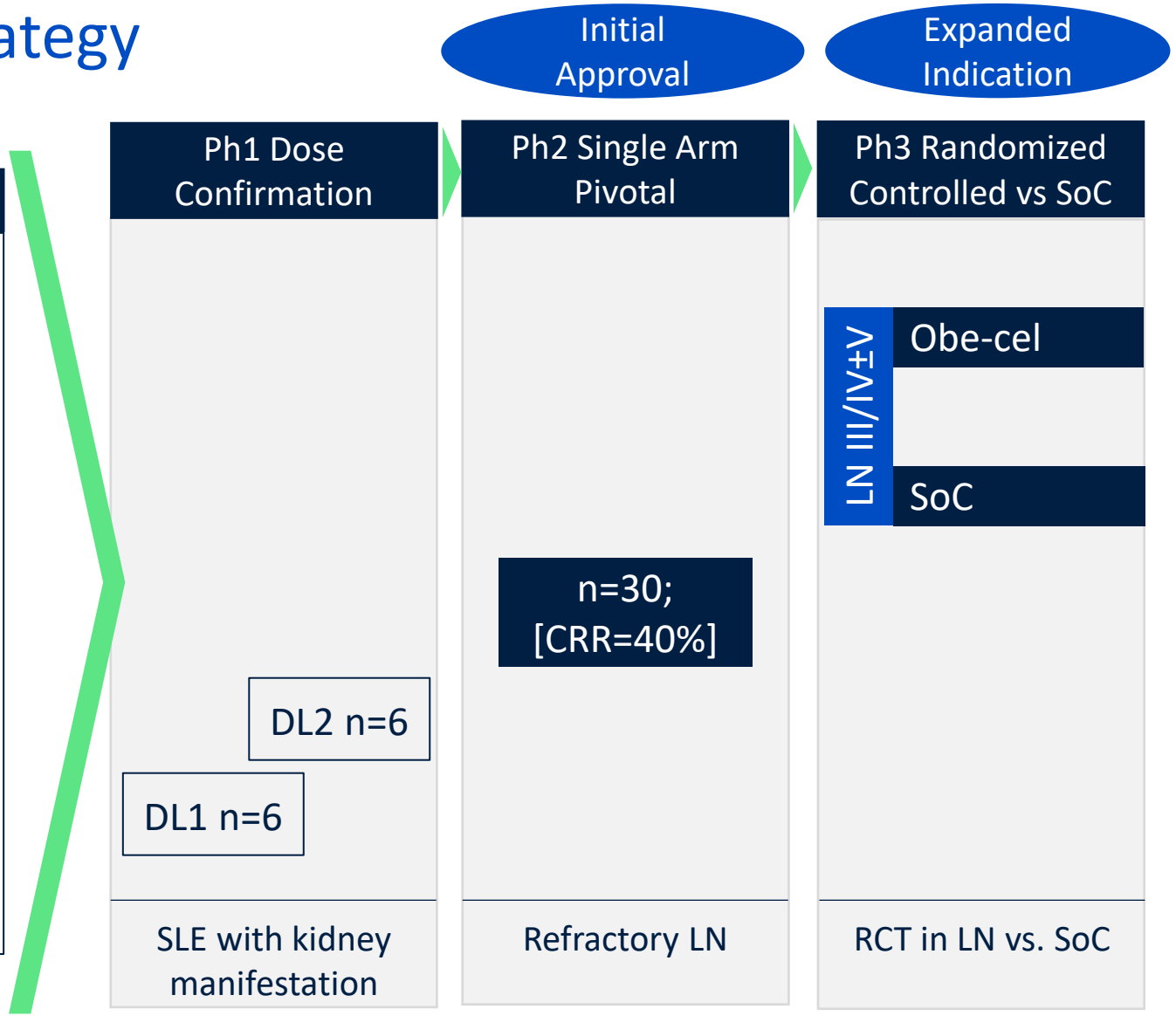
Development path in lupus nephritis (LN)

Lupus nephritis development strategy

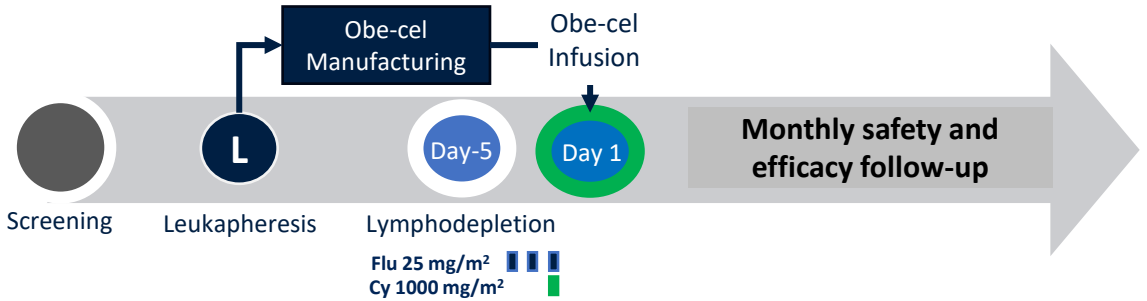
Leveraging a fast to market strategy

Development Rationale

- LN is assessed by quantitative lab- parameter based endpoints (CRR) vs. SLE with a composite endpoint depending on clinical assessments
- Current guidelines require for Class III/IV LN triple therapy including B-cell modifier or CNI, without any treatment options for those being refractory to both
- Lack of SOC for refractory LN opens the possibility to single arm trial path for initial approval
- Outcome of refractory LN single arm trial serves as good predictor for RCT in earlier LN vs. SOC



Pivotal phase 2 study in severe refractory, active lupus nephritis



Trial design	Single arm, open-label, multi-centre, phase 2
Sample size	30 patients
Patient population	• 12-65 years of age, body weight ≥ 40kg • Diagnosis of SLE based on (EULAR)/ (ACR) 2019 classification • Positive (ANA) (≥ 1:80), or anti-dsDNA (≥ 30 IU/mL) or anti-Smith (> ULN), anti-histone or anti-chromatin (> ULN) • Severe, refractory LN (ongoing active class III, IV or V (only in combination with III or IV) • Prior immunosuppressive and biologic therapies
Treatment	50 x 10^6 CAR positive T-cells following Flu/Cy lymphodepletion
Endpoints	Primary: Complete Renal Response at 6 months Key Secondary: DORIS at 6 months
Timing	• **First patient enrolled by YE 2025** • **Anticipated enrolment window: 24 months** • **One year follow up**

FDA interactions support registrational potential based on a single arm study in high-risk patients

- Collaborative approach with the FDA in reviewing IND intending to preserve registrational potential
- Defined patient population with a clear unmet medical need:
  - Eligibility will be reviewed by independent committee (rheumatologist, nephrologist, pathologist):
  - Definition of refractoriness for inclusion:
    - failure of B-cell targeting agent **and**
    - CNI where available in jurisdictions, or intolerance to those agents
- Alignment of Complete Renal Response as primary endpoint
- IND cleared in February 2025

Autolus

Questions?

Mark Freedman, HBSc, MSc, MD, CSPQ, FAAN, FRCPC

University of Ottawa

- Professor of Medicine (Neurology) at the University of Ottawa and Director of the Multiple Sclerosis Research Unit with 35 years of clinical experience
- Senior Scientist at the Ottawa Hospital Research Institute with extensive research in molecular neurochemistry, cellular immunology and neuroimmunology related to MS
- Research focused on cell-based therapies and biomarkers for MS: lead investigator in Canadian BMT study in MS and of the Canadian Mesenchymal Stem Cell Transplantation in MS study (MESCAMS) and co-director of the International Mesenchymal Stem Cell Transplantation in MS study Group
- Principal investigator in >100 clinical trials for new treatments for MS
- Led all versions of the Canadian Treatment Optimization Recommendations
- Serves on multiple editorial boards including the Multiple Sclerosis Journal and Multiple Sclerosis and Related Disorders
- Published more than 400 papers and 550 research abstracts
- Past-president of the Canadian Network of MS Clinics and recent past-president of the Americas Committee for Treatment and Research in MS (ACTRIMS)
- Aspired to be a race car driver but was precluded by his size (they sent him away saying they would need the “jaws of life” to extract him from the car.)

PLANS FOR AUTOIMMUNE DISEASE

Multiple Sclerosis

Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Multiple Sclerosis:

Current Understanding and Treatment Approaches

Mark S. Freedman MSc MD FANA FAAN FRCPC

Professor of Medicine (Neurology)
University of Ottawa

Sr. Scientist, The Ottawa Hospital Research Institute

Objectives:

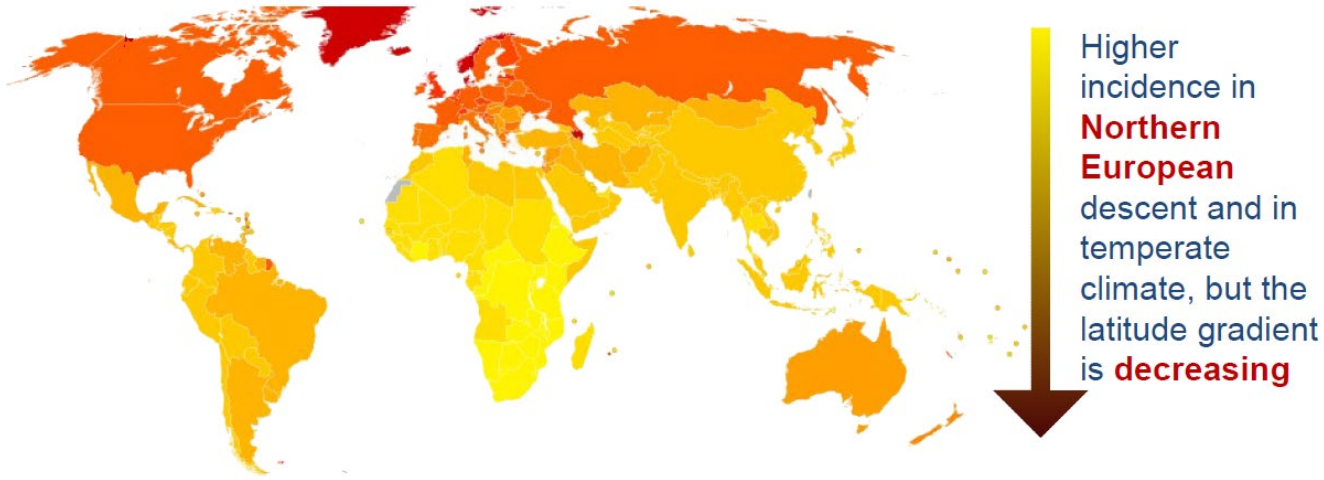
- Review of some basics
- Diagnosis
- MS Classification
- Therapeutic approaches and results
- Monitoring for treatment response
- Unmet needs for treating progressive disease
- Possible role for CAR T cell therapy

Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Fundamentals of the Disease

MS: Global Distribution

- The most common demyelinating disease with a heterogeneous prevalence worldwide[1]
  - Affects > 2 million people
- The global median prevalence of MS has increased from 30/100,000 in 2008 to 33/100,000 in 2013[1]



Region	Prevalence[1]
North America	140/100,000
Europe	108/100,000
East Asia	2.2/100,000
sub-Saharan Africa	2.1/100,000

Canada has one of the highest rates of MS in the world, with an estimated 100,000 (1 in 340) Canadians living with the disease[2]

1. Leray E, et al. Rev Neurol (Paris). 2016;172(1):3-13.
2. About MS. https://mssociety.ca/about-ms. Accessed April 20, 2018

Epidemiology of Multiple Sclerosis (MS)

- Typically, the disease becomes clinically apparent between the ages of 20 and 40 years[1]
  - Mean age at onset is 31 years (range 5-67 years)[2]
    - 3–10% of all MS cases have their first manifestations in childhood or adolescence[3]
- Women are 2-3 times more likely than men to have MS, but men have worse outcomes[4]
- No difference in mortality between MS patients and controls in the first 20 years of the disease[1]
  - The overall life expectancy is reduced by 6-7 years in MS patients[1]

1. Leray E, et al. Rev Neurol (Paris). 2016;172(1):3-13.
2. Waldman A, et al. Lancet Neurol. 2014;13:936–48
3. Gilmour H, et al. Statistics Canada, Catalogue no. 82-003-X . January 2018 Health Reports;29(1):3-8.
4. Confavreux C, et al. N Engl J Med. 2000 Nov 16;343(20):1430-8

Multiple Sclerosis

- An inflammatory demyelinating disease of the central nervous system (CNS)
- The pathologic hallmark:
  - Focal areas of myelin loss within the CNS
- Demyelination is accompanied by:
  - Variable gliosis
  - Inflammation
  - Relative axonal preservation
- Demyelinated lesions are commonly found in:
  - CNS white matter
  - Cortical gray matter

Trapp BD, et al. The Neuroscientist. 1999;5(1):48-57
Popescu BF, Continuum (Minneap Minn). 2013;19(4 Multiple Sclerosis):901-21.

Pathological Drivers of Progression in MS

Peripherally Initiated

Adaptive Immune Cells

B cell T cell T cell-B cell interaction

Centrally Driven

Innate Immune Cells

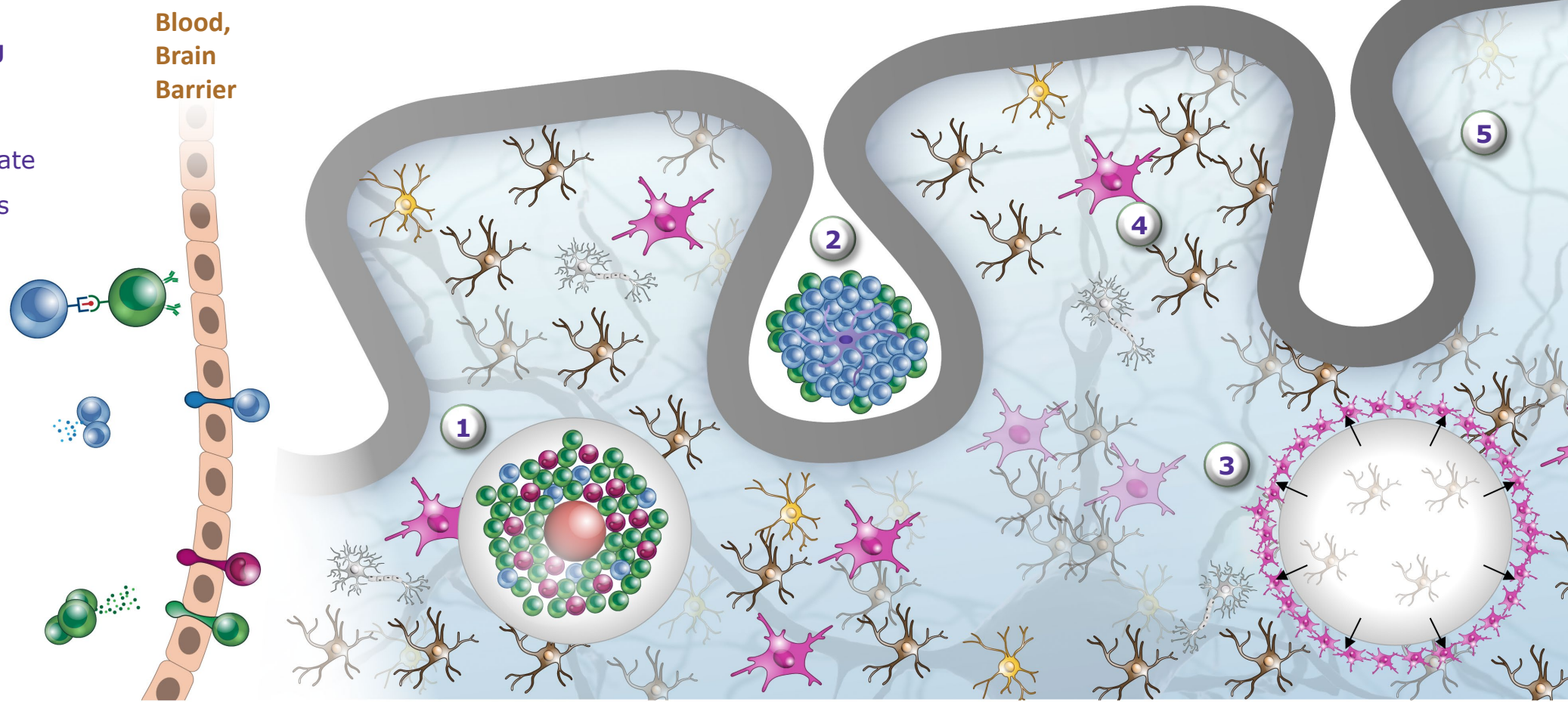
Macrophage Microglia Dendritic cell

Glia & Neurons

Astrocyte Oligodendrocyte Neurons

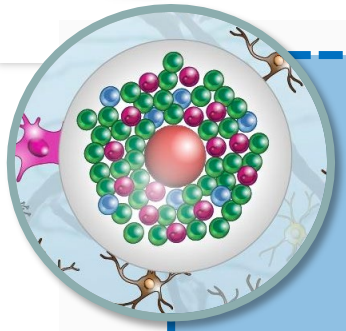
Pathologies underlying MS progression[1]

1. Focal MS lesions
2. Meningeal B-cell aggregate
3. Slowly expanding lesions
4. Diffuse gliosis
5. Age-related atrophy



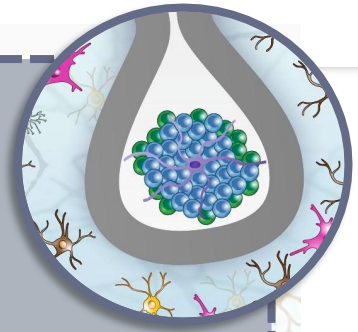
Hauser SL and Cree BAC. *Am J Med*, 133(12), Treatment of Multiple Sclerosis: A Review, 1380-1390

Pathologies Underlying MS Progression[1]



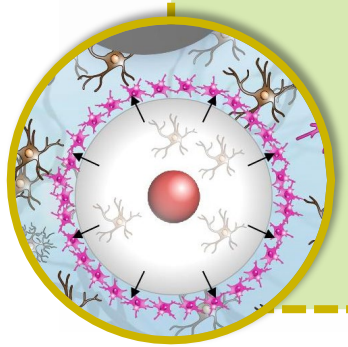
White matter lesions are characterised by:

- Presence of peripheral B cells, T cells, and macrophages[2–4]
- Gadolinium-enhancement on MRI which indicates blood–brain barrier disruption[1]



Meningeal B-cell-rich aggregates are:

- Persistent follicular-like structures that allow for a complex immune response in the grey matter[5,6]
- Associated with aggressive clinical disease, rapid disability progression, and younger death[5,6]

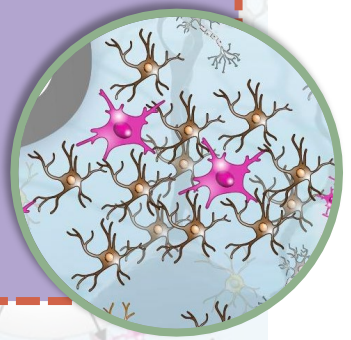


Slowly expanding lesions are:

- Characterised by a rim of activated microglia[1,7]
- Activated by B cells
- Detected longitudinally on standard MRI scans[7,8]
- Linked to long-term disability progression and a higher rate of brain atrophy[8]
- Observed in 83% of early RRMS patients[9]

Reactive microglia and astrocytes (gliosis) are characterised by:

- Increased inflammatory cytokine production[2]
- Decreased myelin density and increased axonal damage[1]
- PET imaging with specific radiotracers[10]

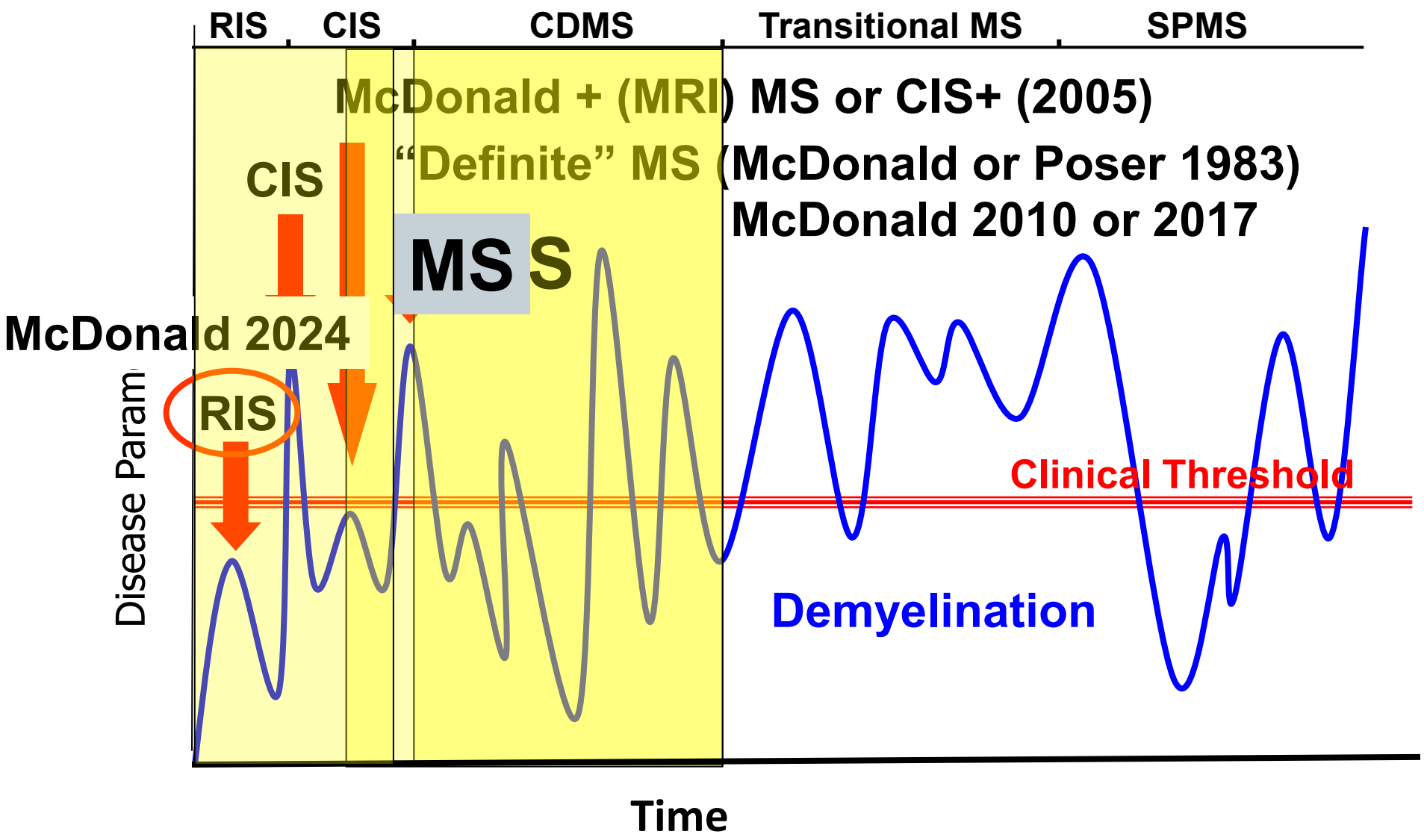


1. Hauser SL, Cree BAC. Am J Med 2020;133:1380–90; 2. Dendrou CA et al. Nat Rev Immunol 2015;15:545–58; 3. van Langelaar J et al. Front. Immunol 2020;11:760; 4. Baker D et al. EBioMedicine 2017;16:41–50;
5. Serafini B et al. Brain Pathol 2004;14:164–74; 6. Howell OW et al. Brain 2011;134:2755–71; 7. Elliott C et al. Brain 2019;142:2787–99; 8. Preziosa P et al. Neurol Neuroimmunol Neuroinflamm 2022;9:e1139;
9. Arnold DL et al. Mult Scler 2021;27:1681–1683; 10. Liu Y et al. Eur J Nucl Med Mol Imaging 2022;49:1275–1287.

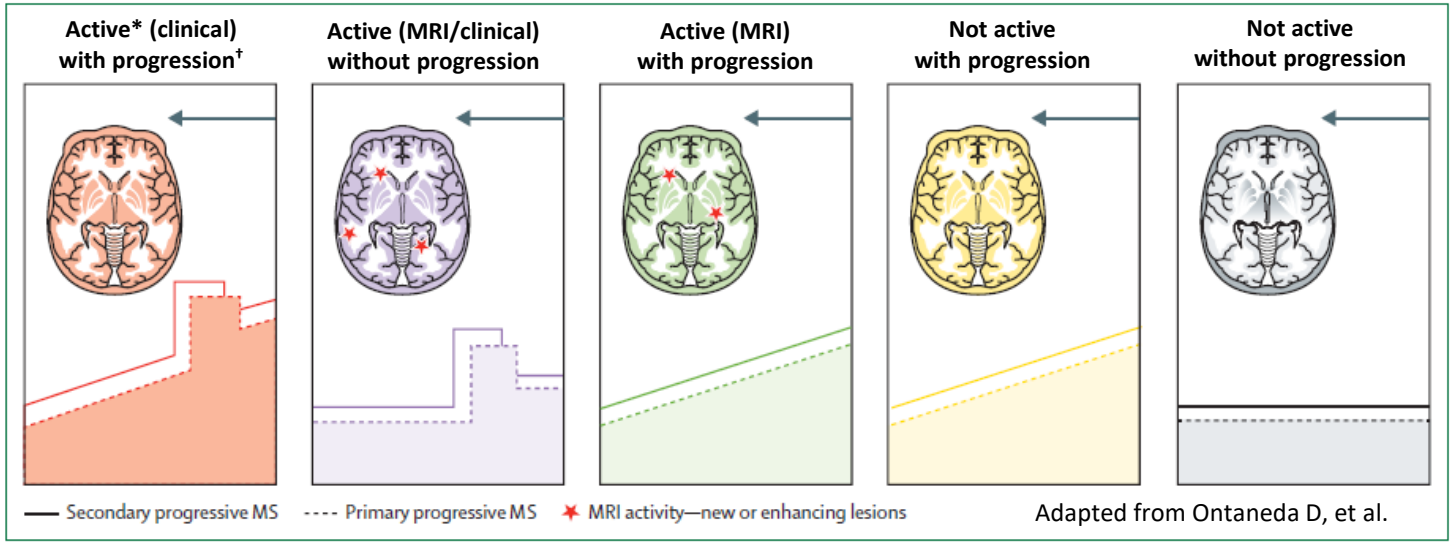
Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Diagnosing the Disease

Evolving Diagnostic Criteria



MS: New Nosology

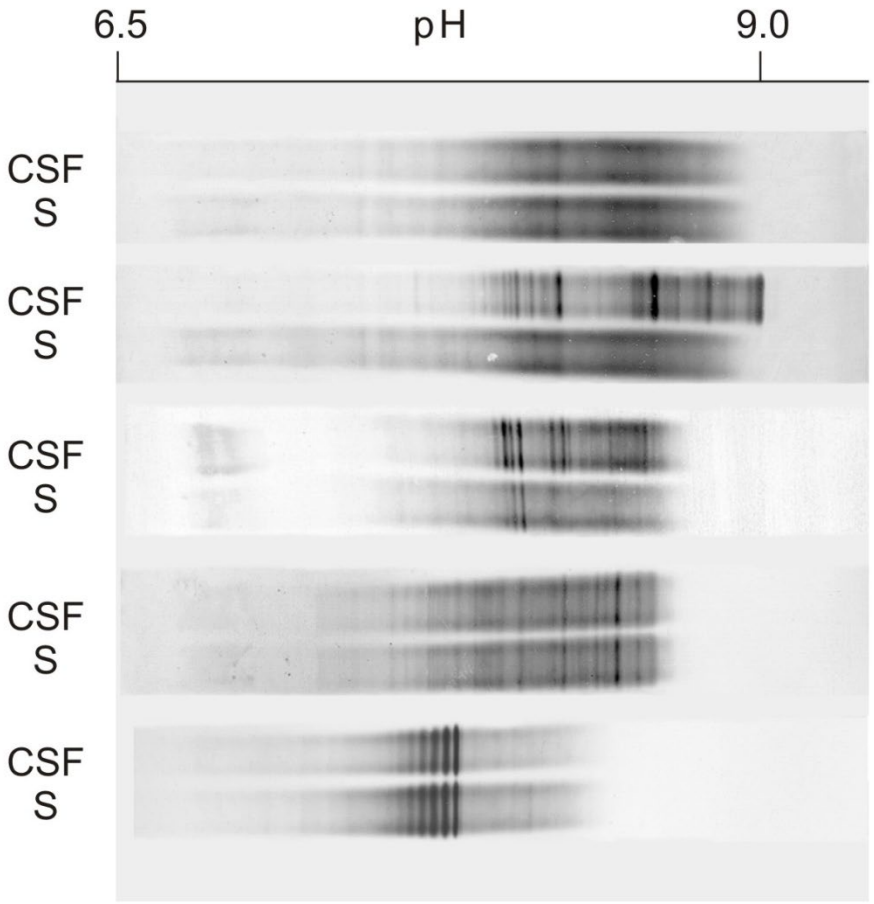
Subtype	Modifications
Radiologically isolated syndrome	• Incidental imaging findings without clinical signs or symptoms • May increase risk of developing clinical MS
Clinically isolated syndrome	• Not active • Active (transitioning to MS)
Relapsing-remitting MS (RRMS) (65–70% of patients with MS)	• Not active • Active
Primary progressive MS (PPMS) (10–15% of patients with MS)	
Secondary progressive MS (SPMS) (up to 75% progression from RRMS)	

Lublin FD, et al. Neurology. 2014;83:278–286.

Diagnosing MS: Paraclinical Testing

- Paraclinical testing to:
  - Help exclude other possible diagnoses mimicking MS
  - Look for changes compatible with MS
    - MRI
    - Evoked potentials
    - CSF

CSF Oligoclonal Bands in MS: Preferred Test is IEF-Immunoblotting

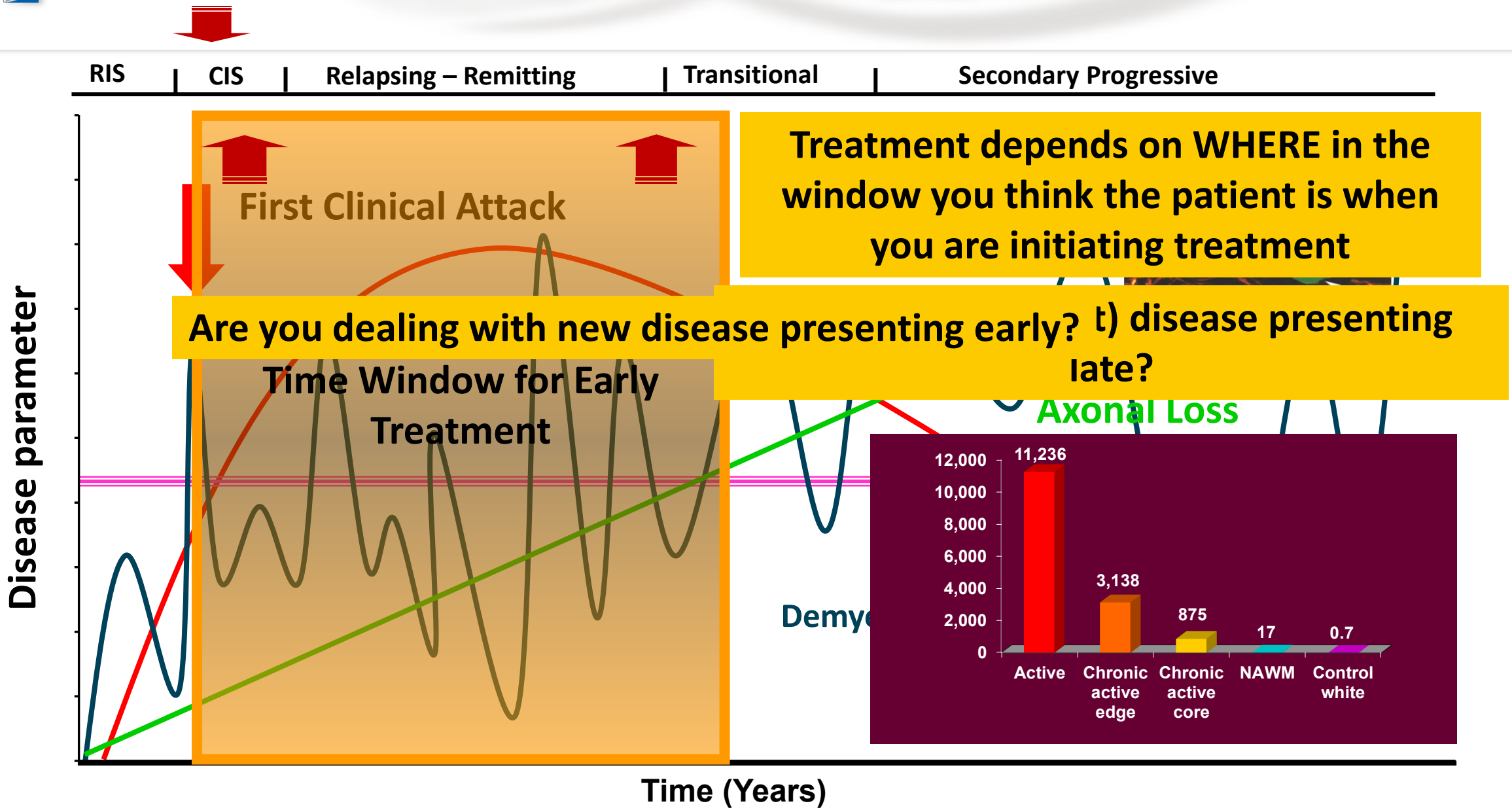


Indicates MS

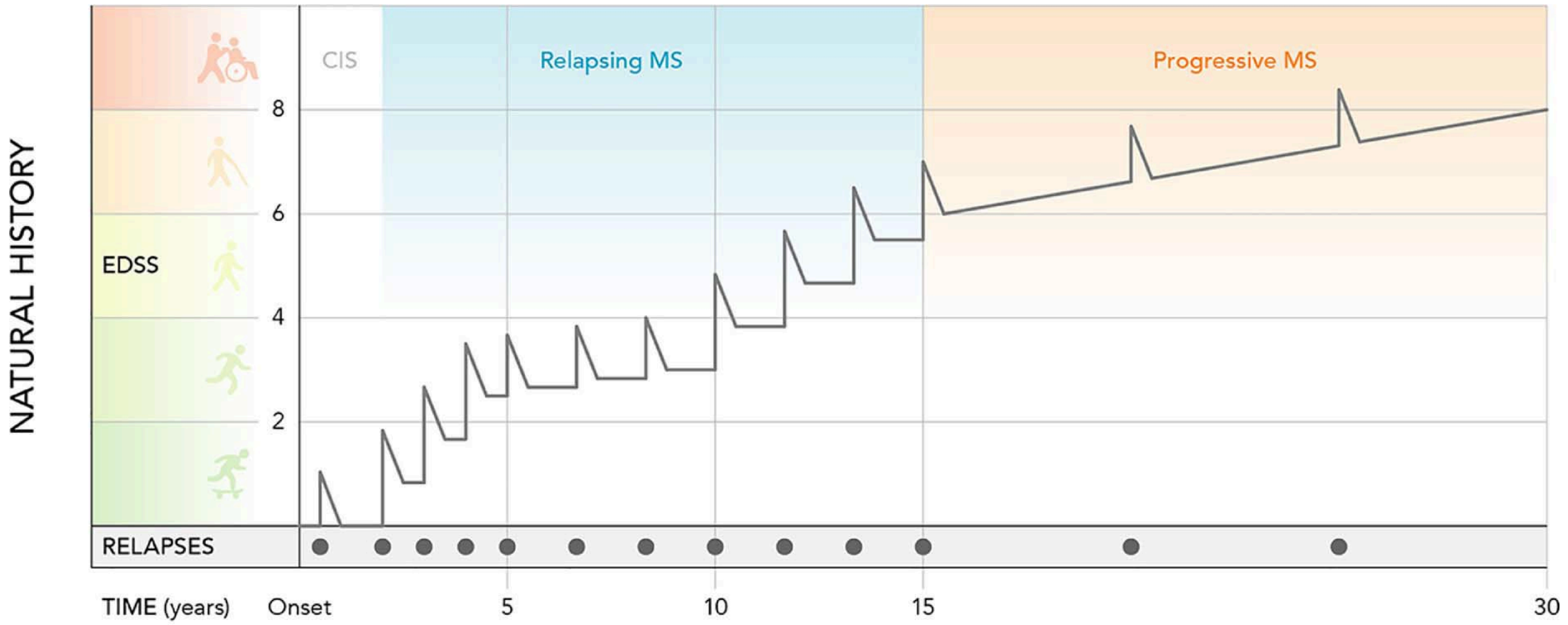
Type 1	**No Bands**
Type 2	**OCB in CSF NOT serum**
Type 3	**OCB in CSF & Non-specific bands**
Type 4	**Non-specific bands**
Type 5	**MCB**

Freedman MS et al. *Arch Neurol* 2005; 62:865-870

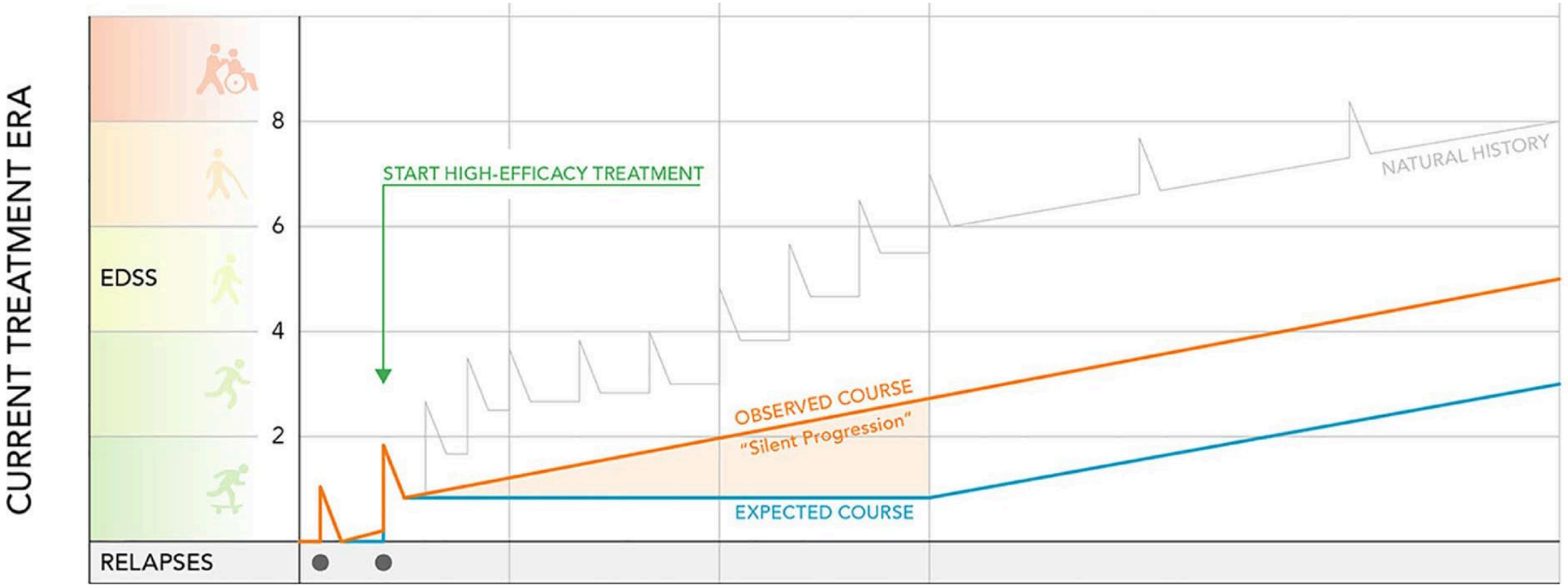
MS: Pathological vs. Clinical Course of Disease



The Natural History of MS



The *New* Natural History of MS



Historical Perception of MS

Stage 1
Inflammation; relapses

Stage 2
Neurodegeneration; disability accumulation

Peripherally initiated acute inflammation mediated by B and T lymphocytes

↓

Acute focal inflammatory lesions

↓

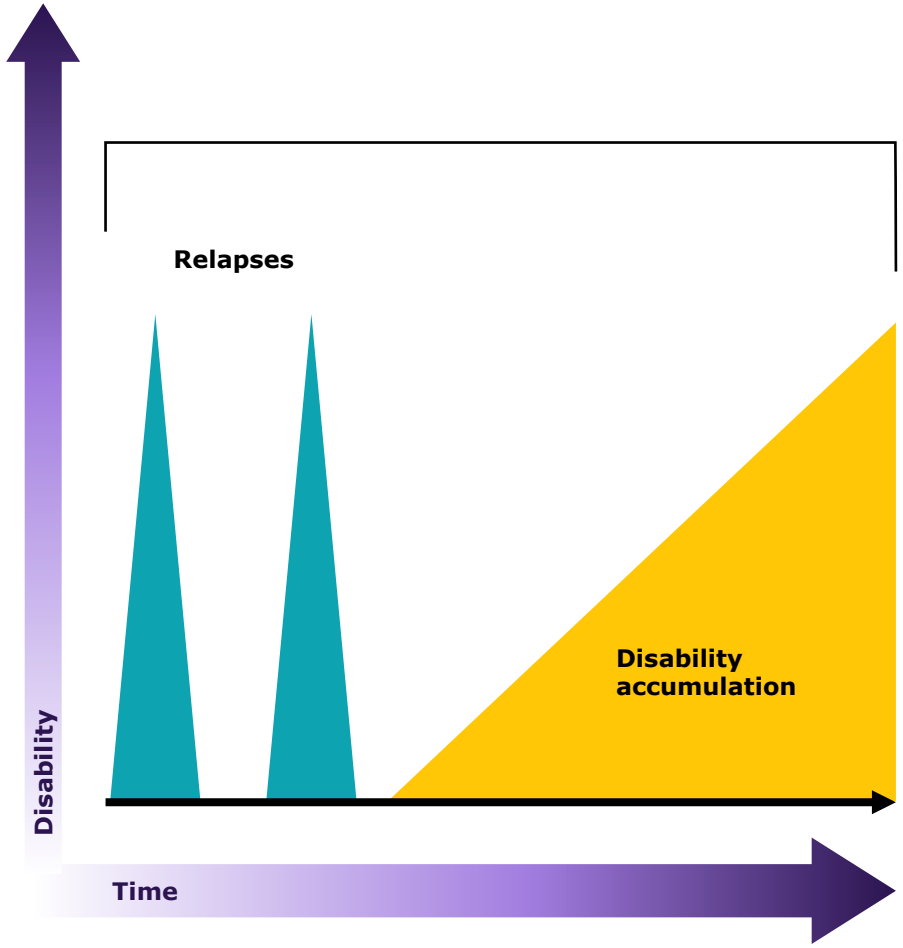
Acute relapses

↓

Progressive diffuse neurodegeneration

↓

Disability accumulation



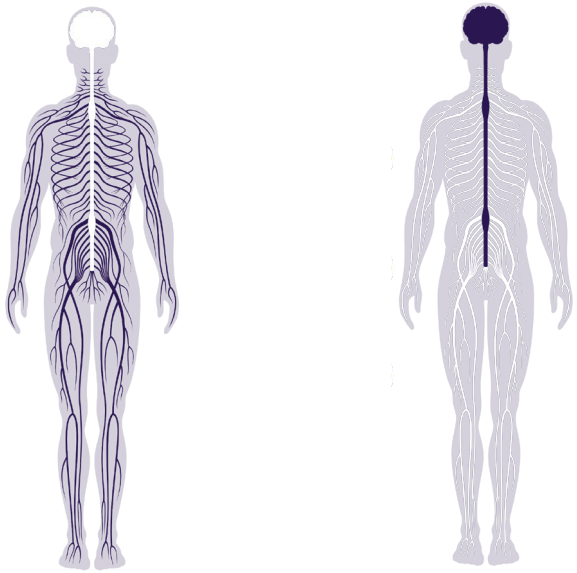
1. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:1-18; 2. Leray E, et al. Brain. 2010;133(Pt 7):1900–13; 3. Kamm C, et al. Eur Neurol. 2014;72(3–4):132–41; 4. Lublin FD, Reingold SC. Neurology. 1996;46(4):907–11; 5. Hauser SL, Cree BAC. Am J Med. 2020;133(12):1380–90.

Emerging MS Paradigm views MS as a Single Biological disease driven by TWO Parallel Inflammatory Pathways[1-6]

Emerging paradigm: Two parallel processes

Peripherally-initiated inflammation

CNS-compartmentalized inflammation



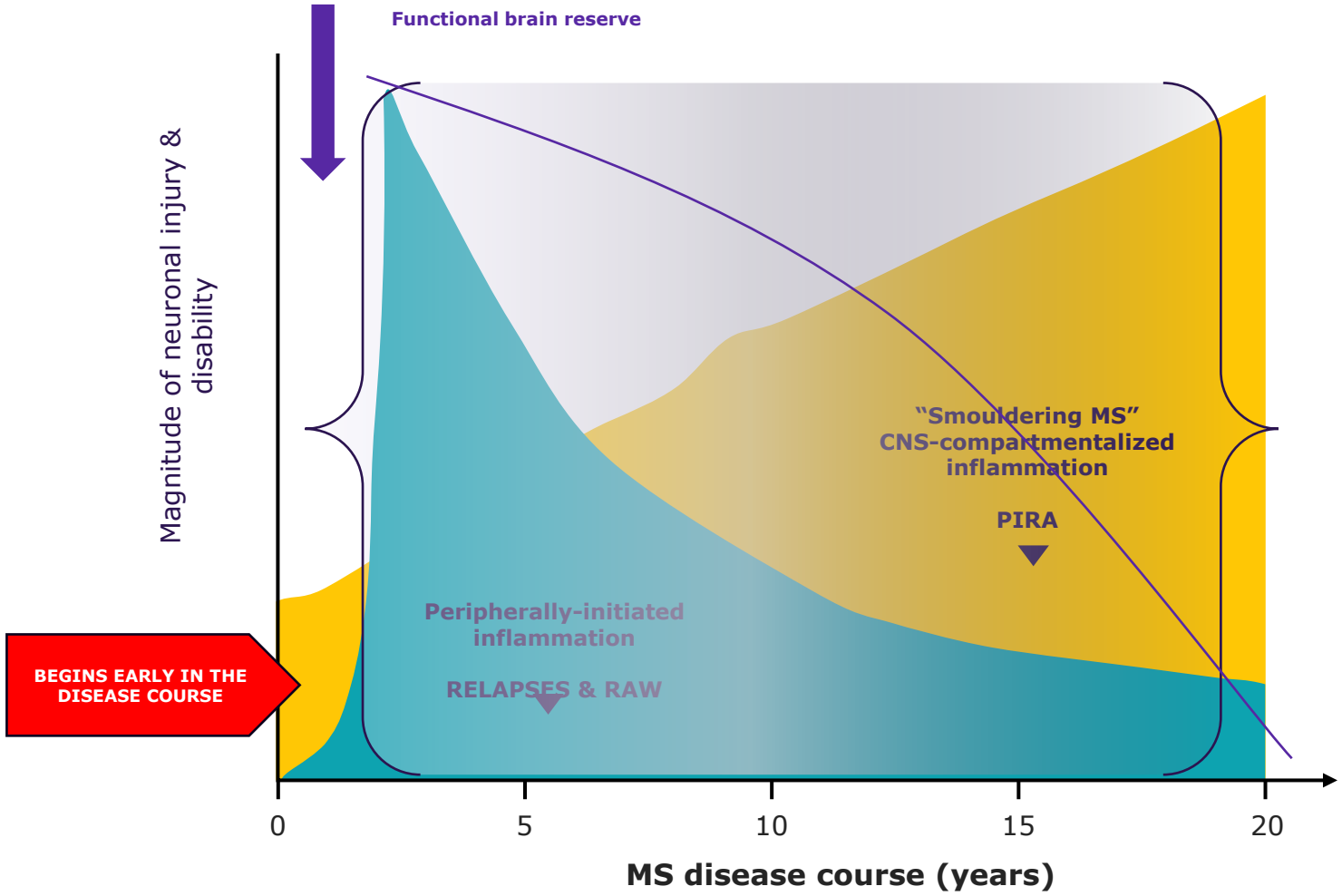
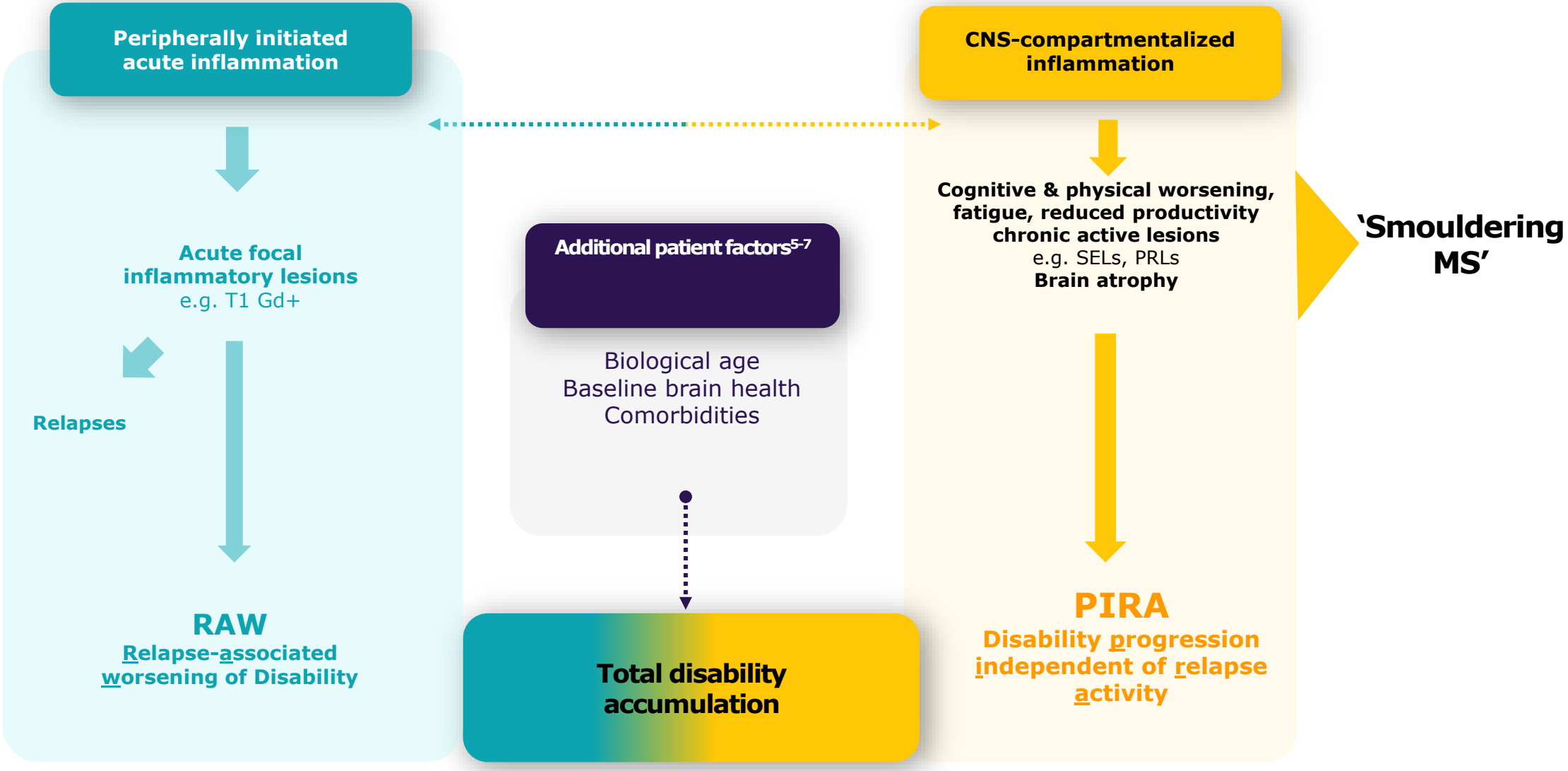


Figure adapted from Bar-Or A. The immunology of multiple sclerosis. Semin Neurol 2008;28:29–45. ©Georg Thieme Verlag KG.

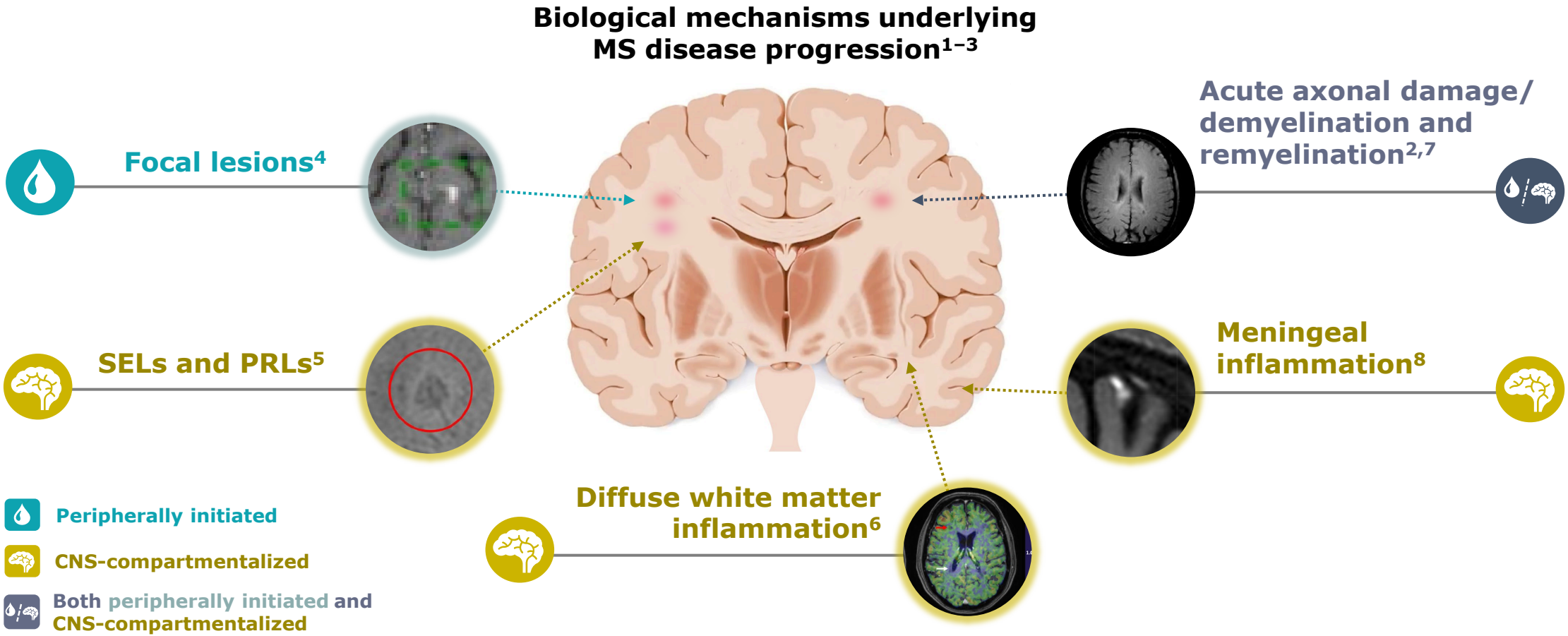
1. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:1-18; 2. Kappos L, et al. JAMA Neurol. 2020;77:1132–40; 3. Vollmer T, et al. Neurol Clin Pract. 2021;11:342–51; 4. Lublin F, et al. Brain. 2022;145:3147–61; 5. Baker D, et al. EBioMedicine. 2017;16:41–50; 6. Bar-Or A. Semin Neurol. 2008;28:29–45.

Peripherally Initiated and CNS-compartmentalized Inflammation Contribute to Pathologies Underlying Disability Accumulation[1-4]



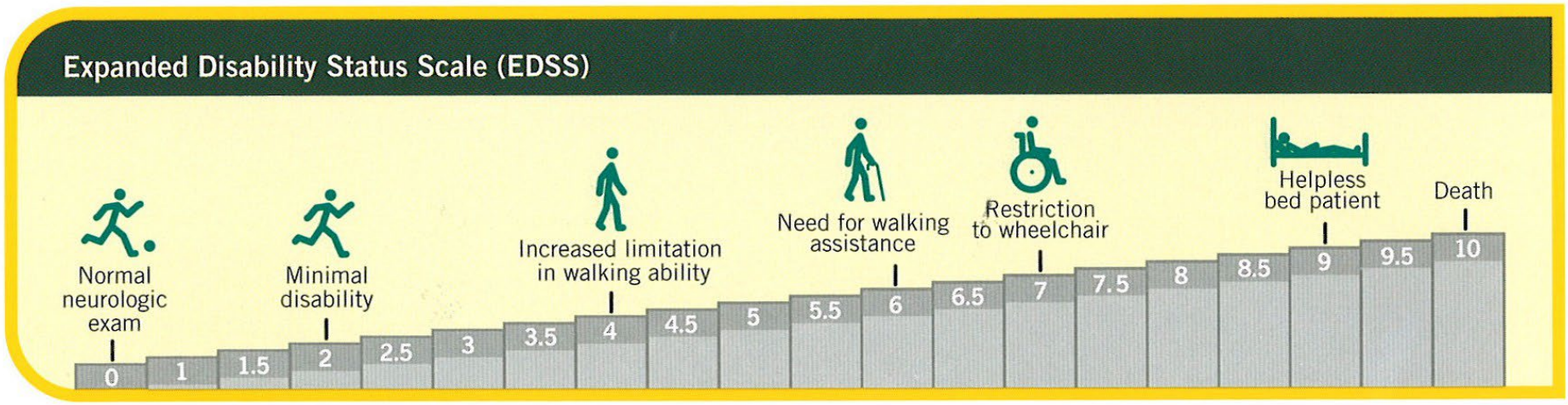
1. Hauser SL, Cree BAC. Am J Med. 2020;133:1380–90; 2. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:1–18; 3. Bayas A, et al. Mult Scler Relat Disord. 2022;68:104166; 4. Piehl F. J Intern Med. 2021;289(6):771-791; 5. Lublin F, et al. Brain. 2022;145:3147–61; 6. Scalfari A, et al. Neurology. 2011;77:1246–52; 7. Marrie RA. Nat Rev Neurol. 2017;13:375–82.

Need to Target BOTH Peripheral and CNS-Compartmentalized Inflammation?



1. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:17562864211066751; 2. Hauser SL, Cree BAC. Am J Med. 2020;133(12):1380–90; 3. Kuhlmann T, et al. Lancet Neurol. 2023;22(1):78–88; 4. Piehl F. J Intern Med. 2021;289(6):771–91; 5. Calvi A, et al. Mult Scler. 2023;29(3):352–62; 6. Airas L, et al. Front Neurol. 2018;9:181;
7. Mallik S, et al. J Neurol Neurosurg Psychiatry. 2014;85(12):1396–404; 8. Absinta M, et al. Neurology. 2015;85(1):18–28.

EDSS: Disability Scale for MS



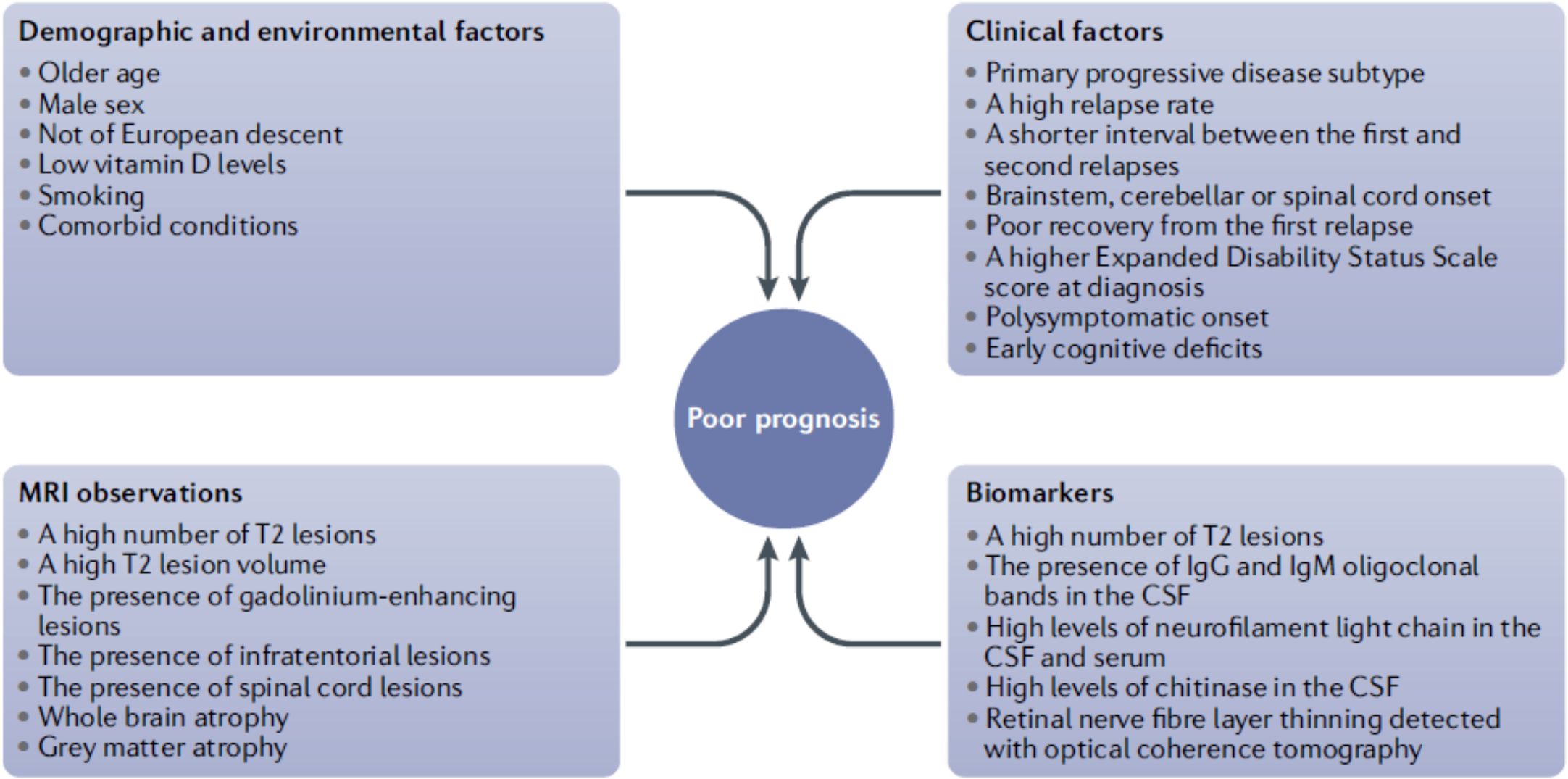
EDSS = Composite of several Functional Subscores (KFS)

- Visual
- Brainstem
- Pyramidal
- Cerebellar
- Sensory
- Bowel/Bladder
- Mental

Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Disease Modifying Treatment

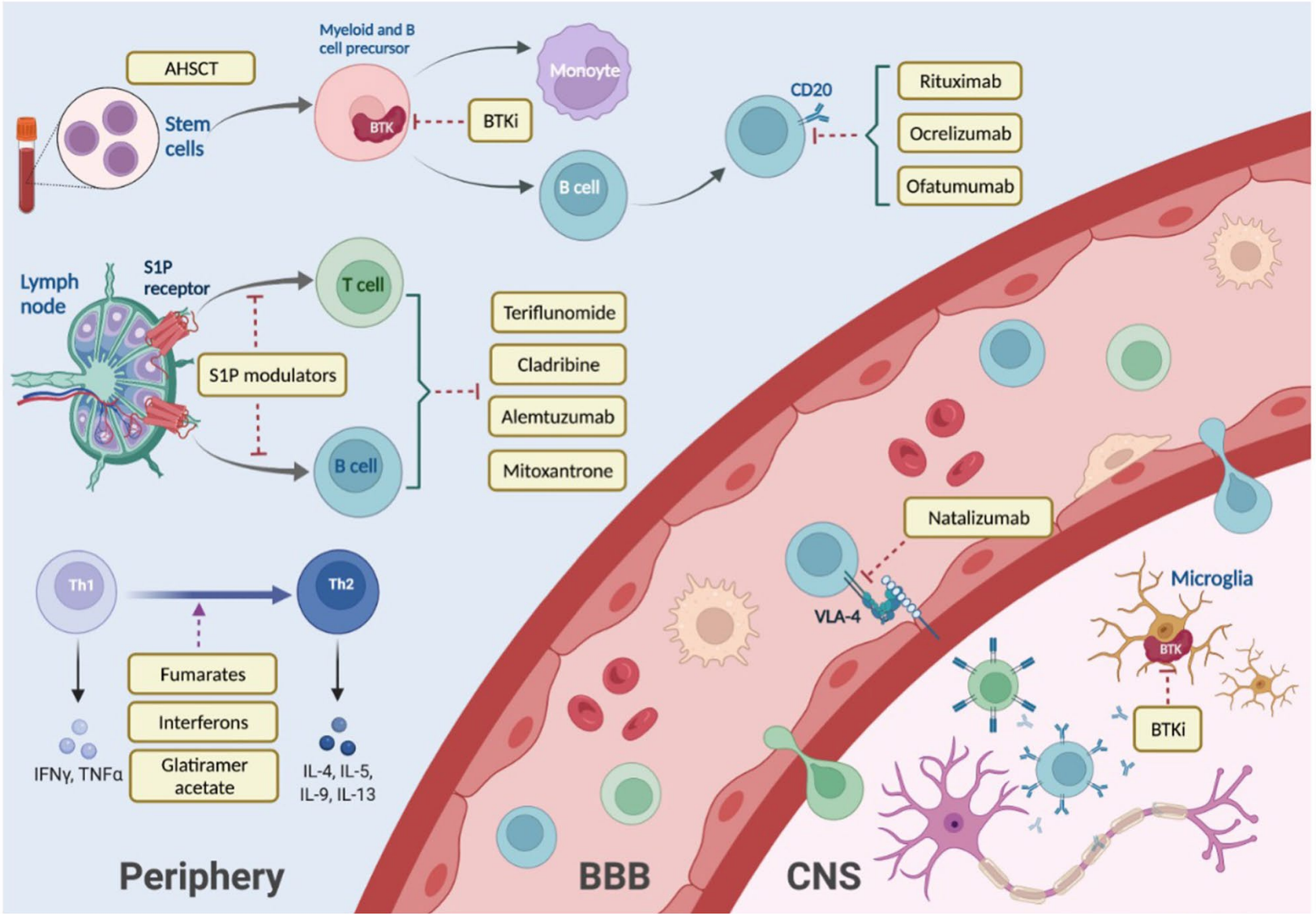
Predictors of a Poor Prognosis in Multiple Sclerosis



Rotstein D & X Montalban Nat Rev Neurol 2019;15:287-300

Disease Modifying Medications vs. MoA

- It is not known which MoA will work in any given patient
- Choice of Tx (modest vs. higher efficacy) depends on perception of risk for early progression vs. safety
- Monitoring for Tx response vital to reduce Tx inertia



Yang J et al. Front Neurol doi: 10.3389/fneur.2022.824926

Disease Modifying Medications: Categories

Immunomodulators

Interferon-β
GA
DMF
Teriflunomide

Pros

- Safety
- Long term experience

Cons

- Modest efficacy
- Many injectable

Anti-Cell Trafficking Agents

Fingolimod
Natalizumab
Ozanimod
Ponesimod
Siponimod (SPMS only)

Pros

- Greater efficacy
- Onset of action quick
- Well tolerated

Cons

- Opportunistic infections (PML)
- Cells still in body
- Rebound disease
- Long term safety unclear

Cell Depleting Therapies

Alemtuzumab
Cladribine Tablets
Ocrelizumab
Ofatumumab
Teriflunomide
Mitoxantrone
Cyclophosphamide
AHSCT (BMT)

Pros

- Definitive in depleting disease causing cells
- Some are IRT
- No rebound disease

Cons

- Opportunistic infections
- Secondary autoimmunity (alemtuzumab)
- Most cumbersome

Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Monitoring for Treatment Response

Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Biomarkers

MRI

MRI for Monitoring

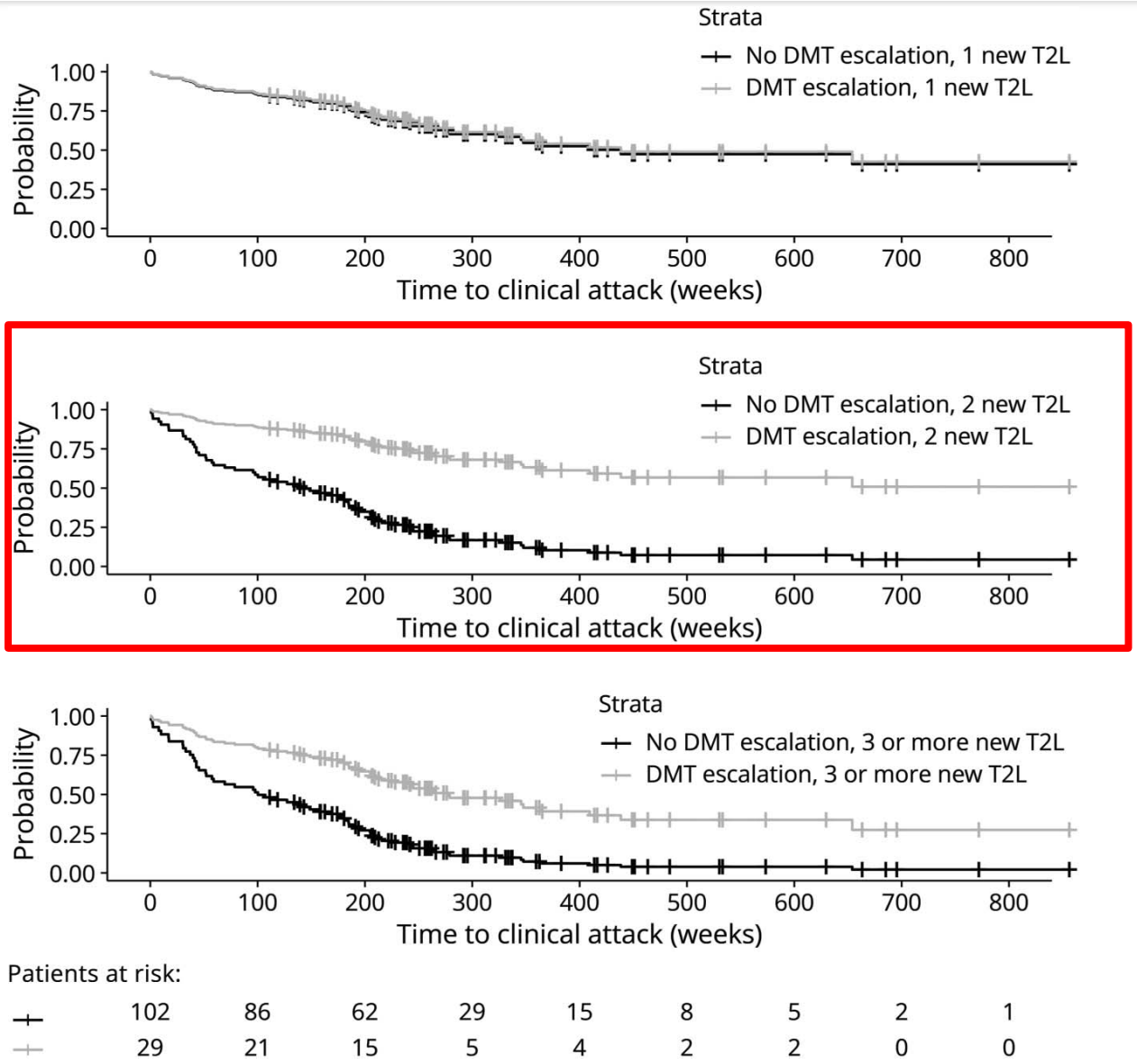
- MRI parameters
  - Brain
  - Spinal cord
  - Use of contrast
  - Sequences and metrics (eg. T1, T2, T2*Epi, volumetrics)
- Frequency
- Evaluation
  - Manual
  - Computer driven

MRI for Monitoring

- MRI parameters
  - Brain
  - Spinal cord
  - Use of contrast
  - Sequences and metrics (eg. T1, T2, T2*Epi, volumetrics)
- Frequency
- Evaluation
  - Manual
  - Computer driven

Change in DMT based on MRI Monitoring

- Danish registry
- Initial Tx with moderate efficacy agent
- Clinically stable for ≥1 year
- MRI at baseline, 3 and 6 months and then q 6 months
- Probability of being relapse free at 4 years vs. lesion development



Bsteh G et al. Neurol 2024;103:e209752.doi:10.1212/WNL.0000000000209752

MRI for Monitoring Disease Progression

- No single metric proven useful
- Brain atrophy (inverse of brain volume)
  - Gray matter atrophy vs. white matter atrophy
  - Cortical atrophy
  - Spinal cord atrophy
- Slowly expanding lesions (SEL)
- Paramagnetic rim lesions (PRLs)
- PET

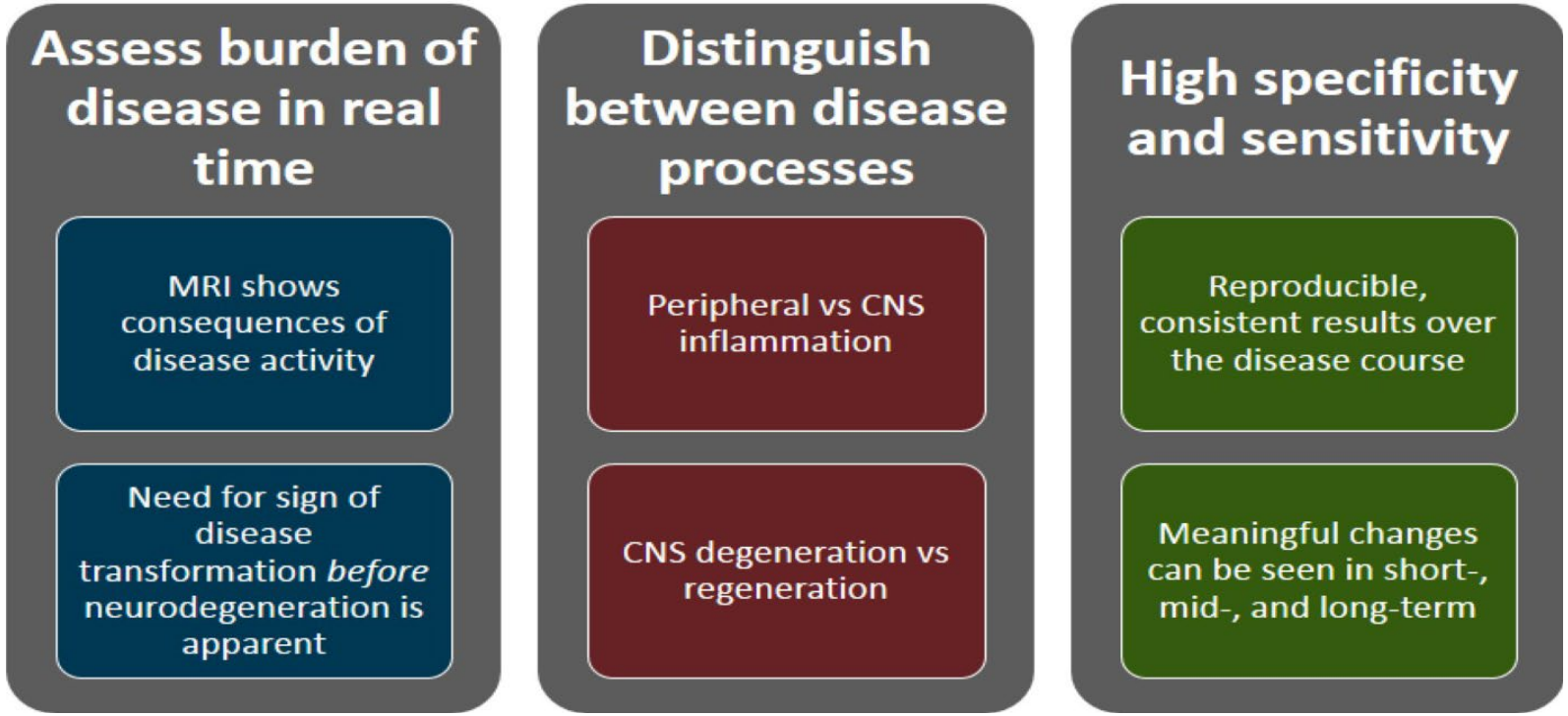
Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Biomarkers

Fluid Biomarkers

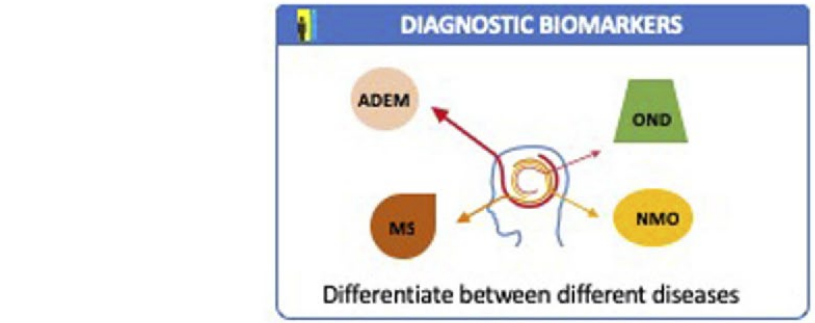
What Makes an Ideal Biomarker?

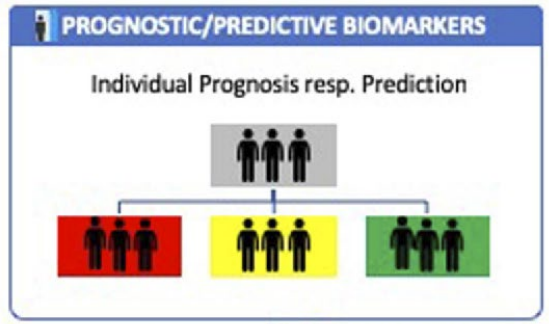
- Biological rationale
- Clinical relevance
- Practicality
- Correlation with disease activity/progression
- Correlation with treatment effects

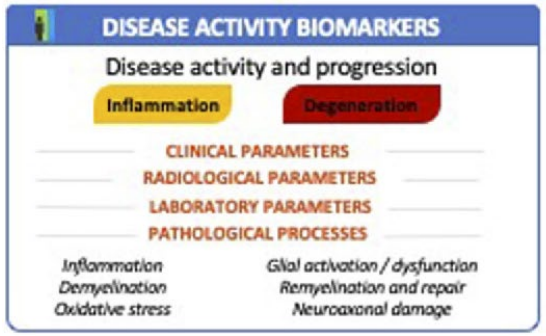


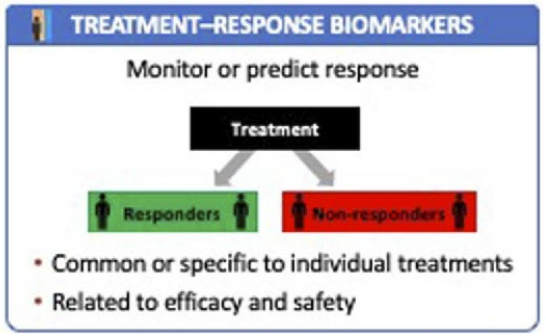
Role of a Biomarker

- **Diagnostic**
  - Used to confirm diagnosis
  - Measures a “surrogate”
- **Prognostic/Predictive**
  - Indicates disease trajectory in a given individual
- **Disease Activity Biomarkers**
  - Measures inflammatory/neurodegenerative disease components
- **Treatment Response Biomarkers**
  - Differentiate patients regarding their outcome related to efficacy and side effects (treatment responders and non-responders as well as patients with and without adverse drug reactions)









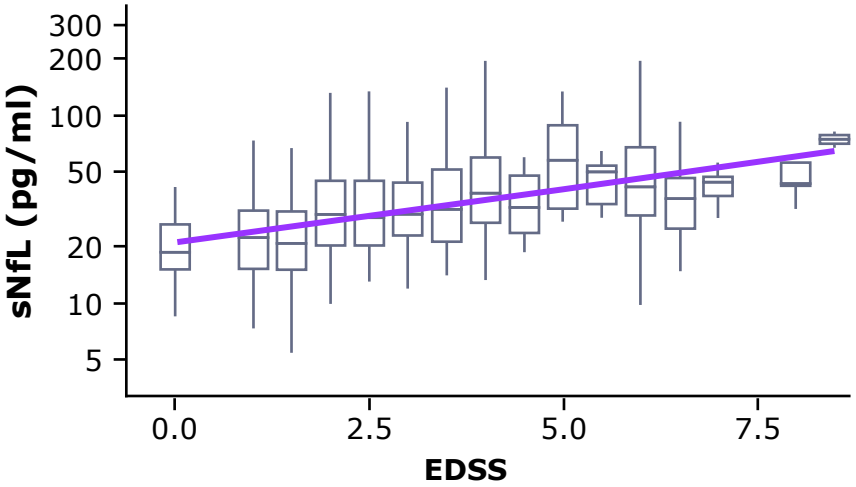
Ziemssen et al. *Journal of Neuroinflammation* 2019;16:272

Baseline sNfL Predicts Disability and Disease Activity

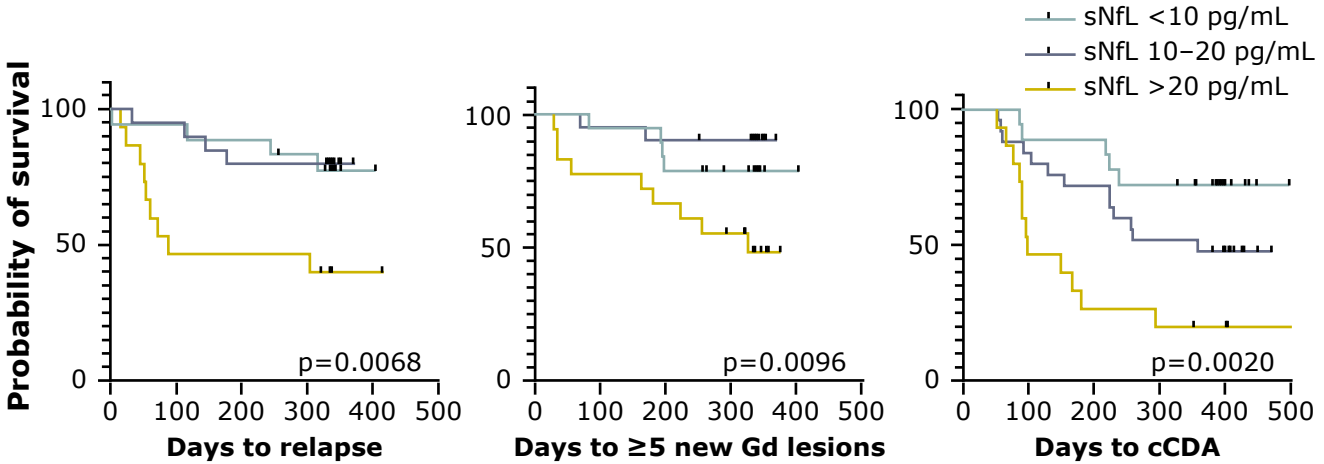
Neurofilament light chain protein (NfL)[1,3]

CSF biomarker
+ direct contact with CNS
+ relatively high abundance

Blood biomarker
+ safe, quick, and easy collection + available at different timepoints



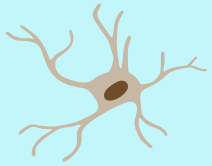
sNfL was associated with EDSS score[1]



sNfL were significantly associated with probability of relapse, MRI activity and time to cCDA[2]

1. Disanto G, et al. Ann Neurol. 2017;81(6):857-870; 2. Thebault S, et al. Mult Scler Relat Disord. 2022;59:103535; 3. Gaetani L, et al. J Neurol. 2019;266(9):2157-2163.

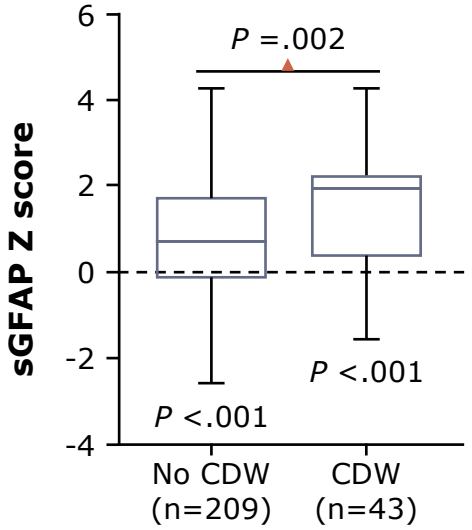
Serum GFAP better predicts disability and disease activity[1]



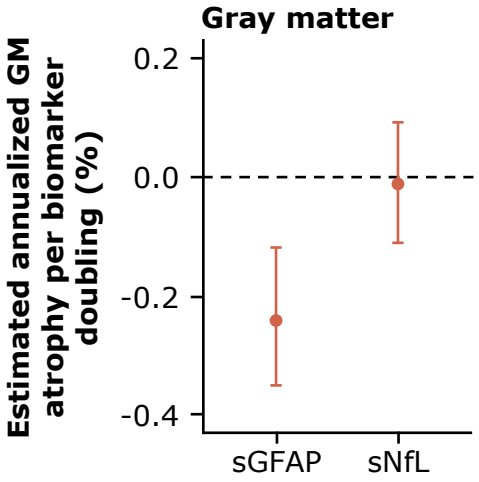
Glial fibrillary acidic protein (GFAP)[1-3]

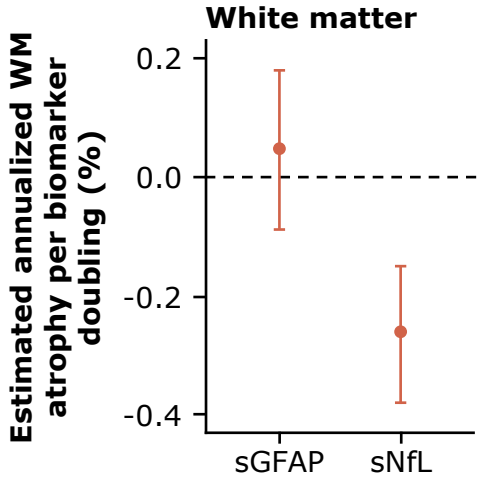
CSF biomarker
+ direct contact with CNS
+ relatively high abundance

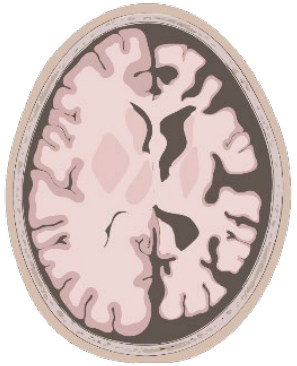
Blood biomarker
+ safe, quick, and easy collection + available at different timepoints



Associations of sGFAP with gray and white matter atrophy[1]





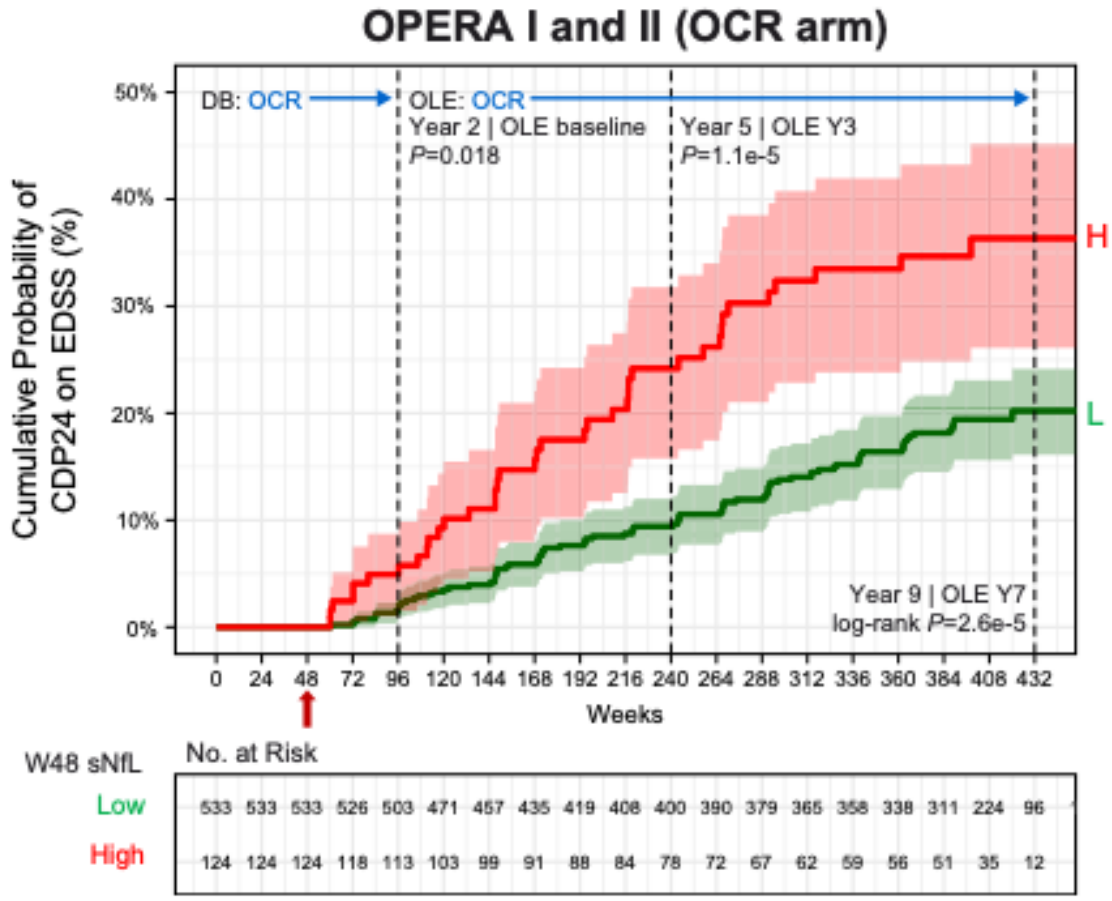


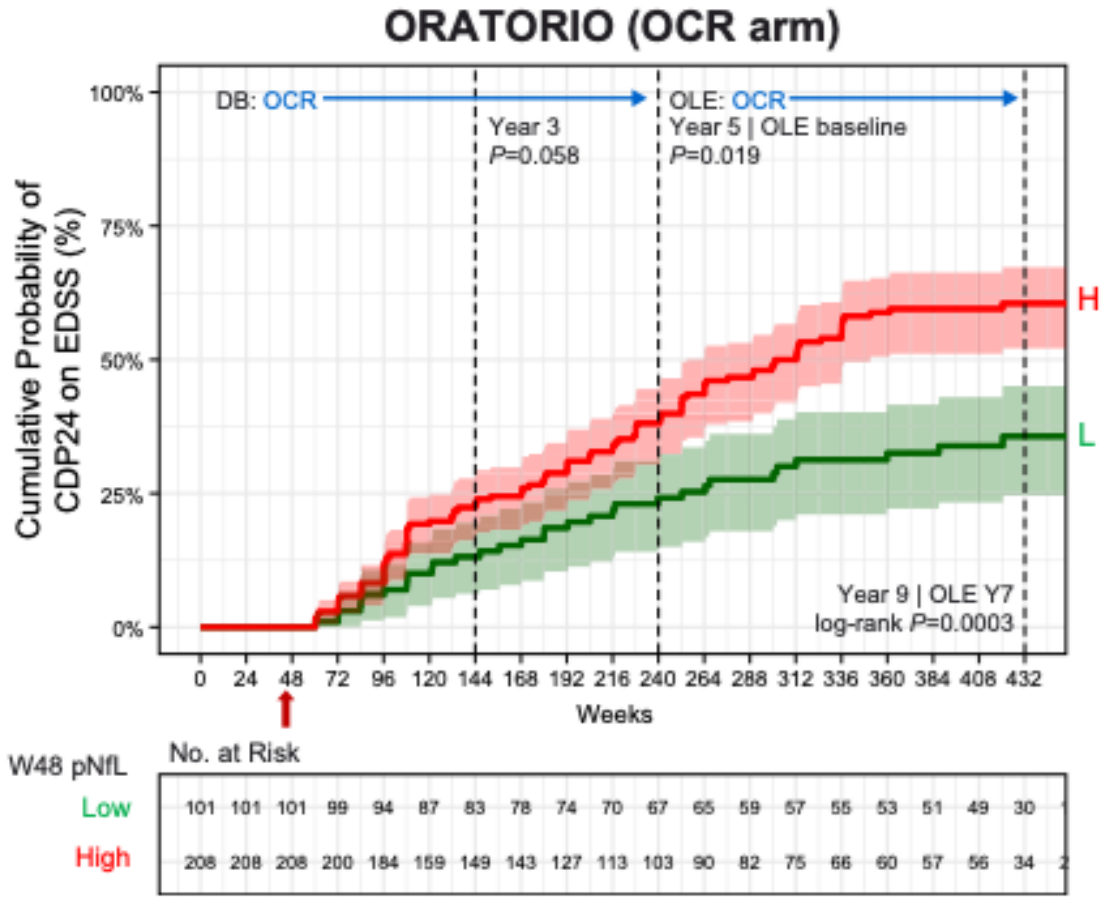
sGFAP were significantly associated with CDW[1]

Baseline sGFAP were associated with loss of gray matter volume and prognostic capacity for future PIRA[1]

1. Meier S, et al. JAMA Neurol. 2023;80(3):287-297; 2. Barro C, et al. Neurol Neuroimmunol Neuroinflamm. 2022;10(1):e200052; 3. Jiang X, et al. Mult Scler. 2023;29(9):1070-1079.

sNfL Predicts Non-Relapsing Progression: Following Anti-CD20 Therapy with Ocrelizumab





Bar-Or A. et al. *eBioMedicine* 2023;93:104662

Unmet Clinical Needs in Managing MS Progression

Diagnosing progressive forms of MS is not straightforward, as patients may not have clear symptoms

Limited tools are available to monitor neurological progression accurately

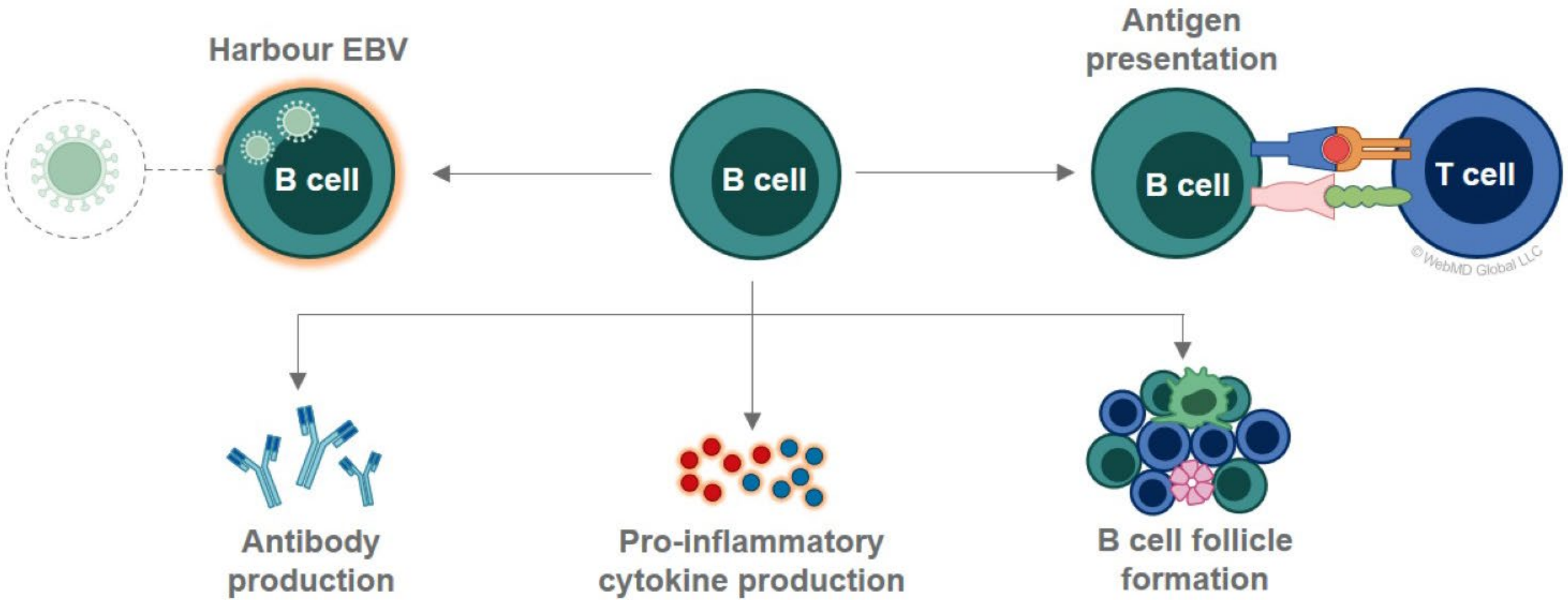
None of the treatments currently available dramatically alter the course of progression

Many patients with progressive MS have insufficient access to comprehensive multidisciplinary care

The biological mechanisms of MS progression are still not fully understood

Better diagnostic, prognostic, and predictive imaging markers are needed

CAR T-Cell Therapy in MS: Role of B Cells



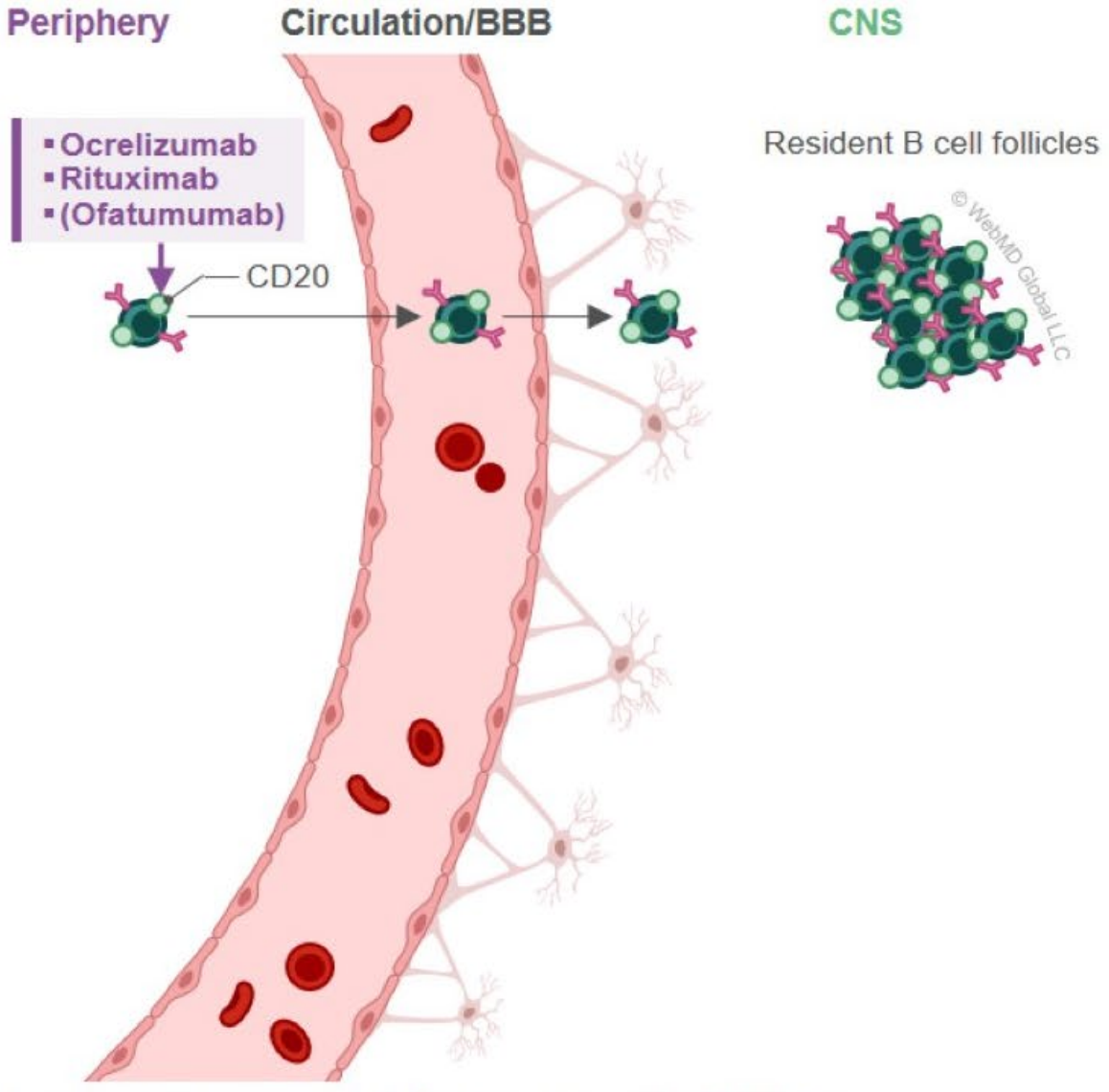
EBV, Epstein Barr virus.
Silva BA, et al. Mult Scler Relat Disord. 2021;50:102845.

CAR T-Cell Therapy in MS: CNS Penetration

CD20 targeting Mabs are large IgG1 isotype antibodies[1]

Large size limits penetration of the BBB[2]

Resident B cells are associated with PMS and cortical demyelination[2]



1. Marshall MJE, et al. Front Immunol. 2017;8:1245; 2. Tsitokana ME, et al. Int J Mol Sci. 2023;24:2632.

Figure adapted from: Bierhansl L, et al. Nat Rev Drug Discov. 2022;21:578-600.

CAR T-Cell Therapy in MS: CNS Penetration

CD20 targeting Mabs are large IgG1 isotype antibodies[1]

Large size limits penetration of the BBB[2]

Resident B cells are associated with PMS and cortical demyelination[2]

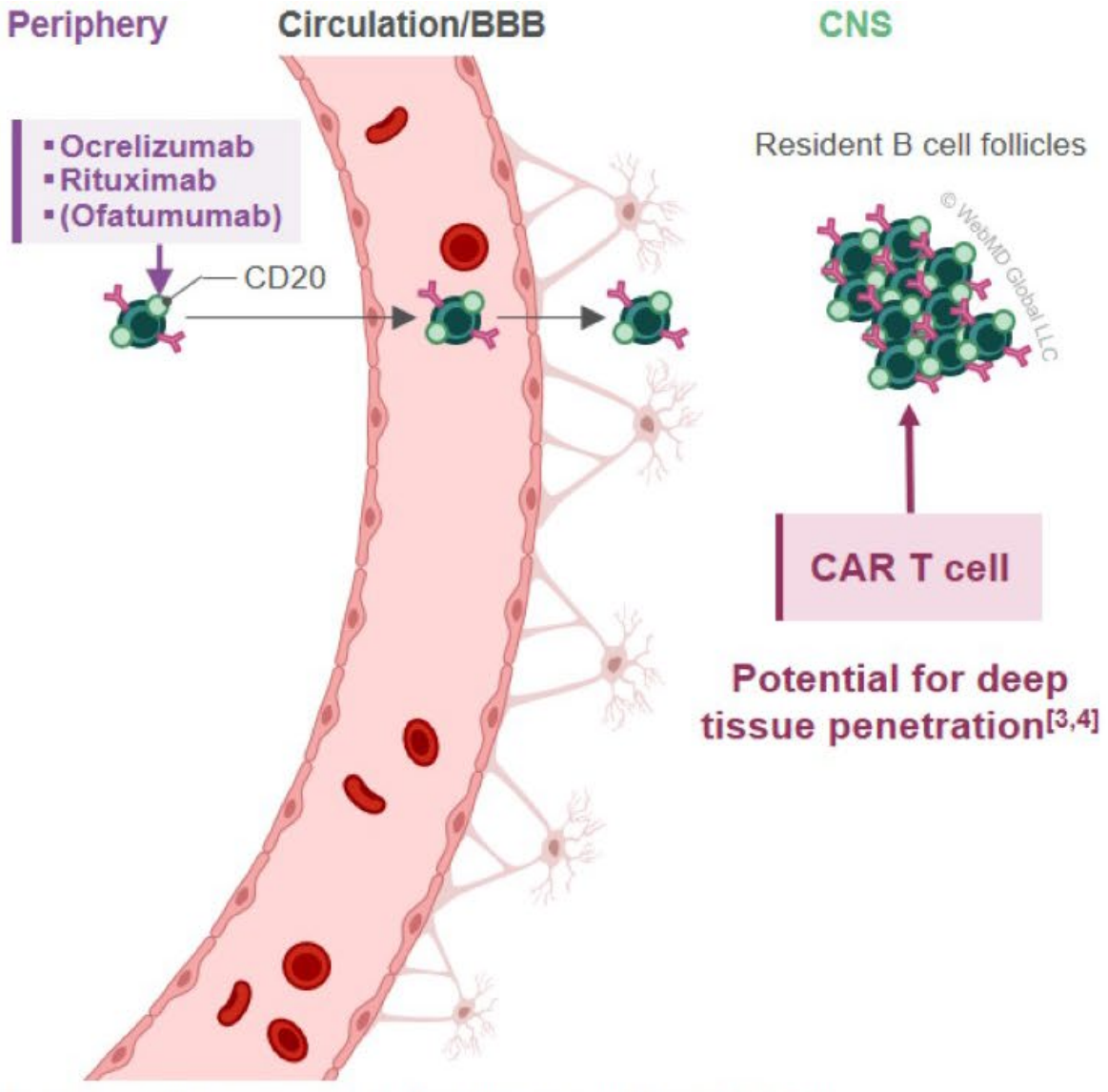


Figure adapted from: Bierhansl L, et al. Nat Rev Drug Discov. 2022;21:578-600.

1. Petereit HF, et al. Mult Scler, 2009;15:189-192; 2. Tsitokana ME, et al. Int J Mol Sci. 2023;24:2632;
3. Magliozzi R, et al. Brain. 2007;130(Pt 4):1089-1104; 4. Del Baldo G, et al., Front Immunol. 2023;14:1142597.

Conclusions

- Multiple Sclerosis is a condition that can be diagnosed with accuracy
- Numerous treatments are successful at targeting focal inflammation and reducing relapses and MRI activity but fall short on disease progression
- None of the current medications have been successful at targeting compartmentalized inflammation except possibly the BTKi
- There is a strong unmet need for CNS-penetrating therapies capable of addressing compartmentalized inflammation and stopping progression
- There are no successful therapies for remyelination or repair

PLANS FOR AUTOIMMUNE DISEASE

Development path in MS

Multiple sclerosis development strategy

Establish Phase 1 Clinical Proof of Concept in MS

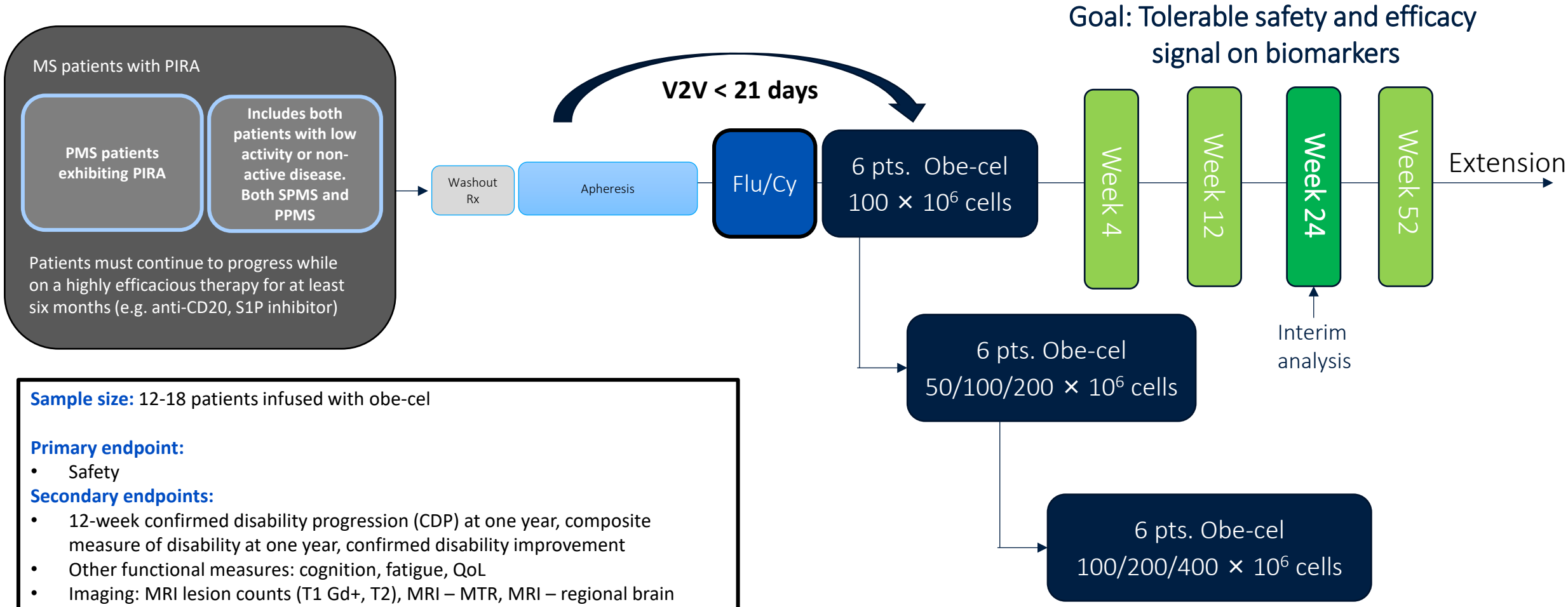
- 3 x 6 dose escalation design - a higher dose may be required for CNS effect
- Biomarker readouts to provide nearer term evidence of biological effect at 6 months +
- Definitive clinical outcomes based on clinical disability progression at 12 months +

Initiate Phase 2/3 study in progressive MS patients exhibiting PIRA

- Anticipate a randomised phase 2/3 study design as path to approval
- Phase 1 clinical PoC is derisking for initiation of development in other neurology indications

Anticipate dosing first patient in Phase 1 trial by year end 2025

Modified single arm, Phase 1 study in MS



Sample size: 12-18 patients infused with obe-cel

Primary endpoint:
- Safety

Secondary endpoints:
- 12-week confirmed disability progression (CDP) at one year, composite measure of disability at one year, confirmed disability improvement
- Other functional measures: cognition, fatigue, QoL
- Imaging: MRI lesion counts (T1 Gd+, T2), MRI – MTR, MRI – regional brain volumes, MRI – cervical spinal cord volume, SEL, PRL)
- Biomarkers (blood and CSF): OCBs, IgG index, NfL, GFAP, Kappa chains, PK

Interim analysis at 6 months:
- Biomarkers including OCBs, IgG index, NfL, MRI lesions, MTR, Kappa chains, PK

What does good look like?

Early evidence of Biological Effect and Impact on CNS Inflammation

- Changes in confirmed disability progression and relapse rates are expected in the follow up year and beyond

- In the shorter term both fluid and imaging biomarkers may support evidence of biological effect and impact on CNS inflammation, with trends across biomarkers providing increased confidence in clinical outcomes.

- Reduction in oligoclonal bands (inline with other biomarkers) is the strongest early evidence of impact on disease progression biology → other than HSCT and CAR T therapy, no other treatment has had impact on OCBs

Initiated studies in autoimmune diseases as stepstone into new disease area

SL1 (CARLYSLE) study and subsequent pivotal SL2 study in refractory lupus nephritis:

- Patients treated in SL1 are representative for SL2 patient population, paving a clear path to a timely approval in patients with highest unmet medical need
- Opens the opportunity to future expansions into:
  - Earlier lines of lupus nephritis comparing against SOC
  - Other adjacent indication of similar pathology in the kidney, i.e. membranous glomerulo-nephritis
  - Non-nephritis SLE indications

MS1 is a dose escalation study designed to assess the safety and the potential of obe-cel in MS based on imaging, biomarkers and early clinical responses:

- Posterchild disease to differentiate from mABs and bispecific driven approaches as obe-cel crosses the blood brain barrier
- Insights will inform the path forward for MS in Progression Independent of Relapse Activity (PIRA)
- Serve as a springboard into other neurological indications, e.g. NMOSD or CNS lupus

PIPELINE IN A PRODUCT

Early stage pipeline

Translational programs with UCL

Early-stage pipeline supports long-term growth potential

Product	Indication	Target	Preclinical	Phase 1	Status
AUTO8	Multiple Myeloma	CD19 & BCMA			**Enrolling in MM; Phase 1 in amyloidosis initiated**
AUTO1/22*	Pediatric ALL	CD19 & CD22			**Initiating new cohort in Q2 2025**
AUTO6NG*§	Neuroblastoma	GD2			**Patient dosing ongoing; preliminary data expected in 2026**
AUTO4/5	TRBC1/2+ Peripheral TCL	TRBC1/2			**Moving back into translational research**
AUTO9*	Acute Myeloid Leukemia	CD33,123,CLL1			**Preclinical work ongoing**

UCL collaboration provides cost-efficient approach to generate early data for future growth opportunities, following the obe-cel pathway to approval

*UCL Collaboration

§ BioNTech holds option to co-fund and co-commercialise

AUTO8: BCMA & CD19 dual targeting CAR T for plasma cell diseases

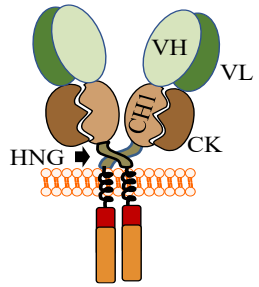
BCMA CAR

Novel FabCAR format designed to be very sensitive to low BCMA expression

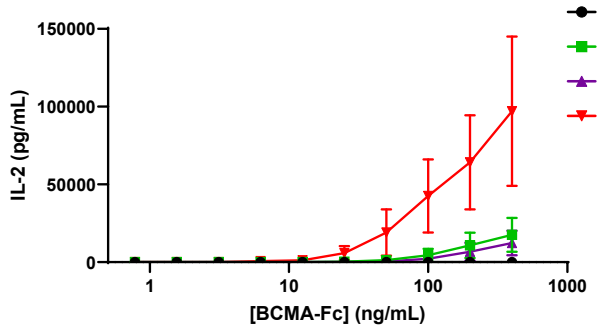
CD19 CAR

Coupled to CD19 CAR from obe-cel to drive persistence and durability of response

FabCAR format



Enhanced function compared to other BCMA CARs



Proof of Concept shown in r/r Multiple Myeloma

- Phase 1 MCARTY dose escalation study in RRMM
- Data presented at ASH in 2023 and 2024
- No notable tox at 50 and 150 million dose levels
- Response rate in line with other BCMA CAR
- Improved persistence in dual CAR cohort
- Initiated enrolment at 450 million dose level

Initiating a Phase 1 study in Light Chain (AL) Amyloidosis

- AL amyloidosis causes multi-organ failure from plasma cells secreting unstable proteins that deposit in organs
- High unmet medical need with very few treatment options in the second line r/r setting
- AUTO8 is designed to remove the disease-causing plasma cells and allow organ recovery
- Clinical study open for enrolment

Collaboration with UCL

Lee et al., ASH 2023, 2024

Upcoming milestones and financials

Oncology | Autoimmune

Anticipated Milestone or Catalyst	Anticipated Timing
Notification from UK regarding approval in adult r/r ALL	Q2 2025
Notification from EU regarding approval in adult r/r ALL	H2 2025
Initial data from PY01 trial in pediatric ALL	H2 2025
SLE Phase 1 trial presentation at medical conference	Q4 2025
First patient dosed in SL2 Phase 2 trial in lupus nephritis	YE 2025
First patient dosed in progressive MS Phase 1 trial	YE 2025

$588M
as of YE 2024

The Company is well capitalized to drive the launch and commercialization of obe-cel in r/r B ALL and obtain data in the lupus nephritis potential pivotal trial.

Autolus

Questions?

Autolus