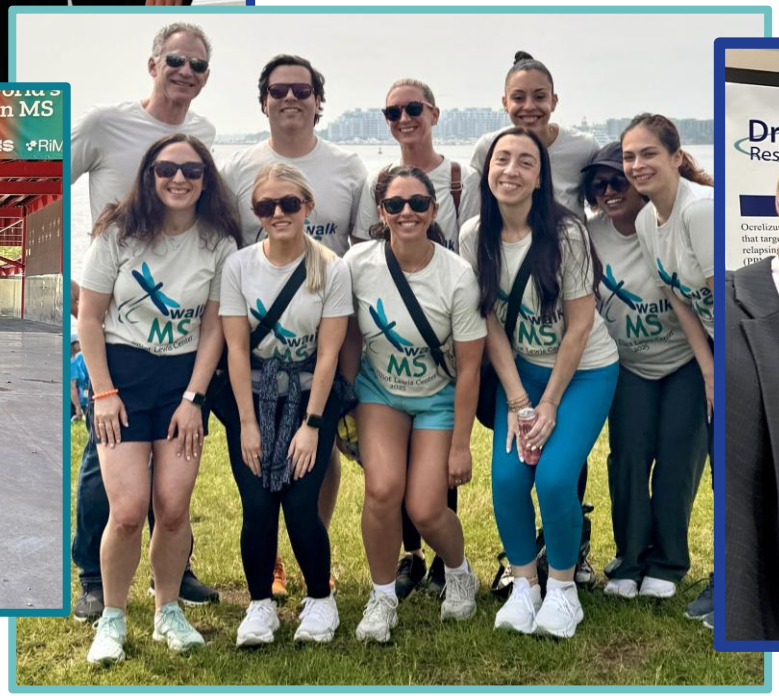
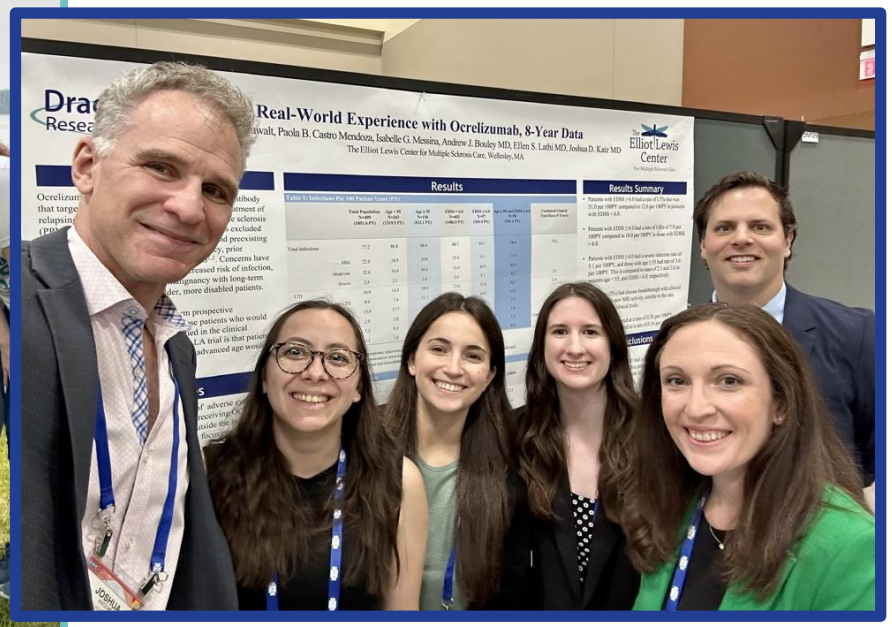
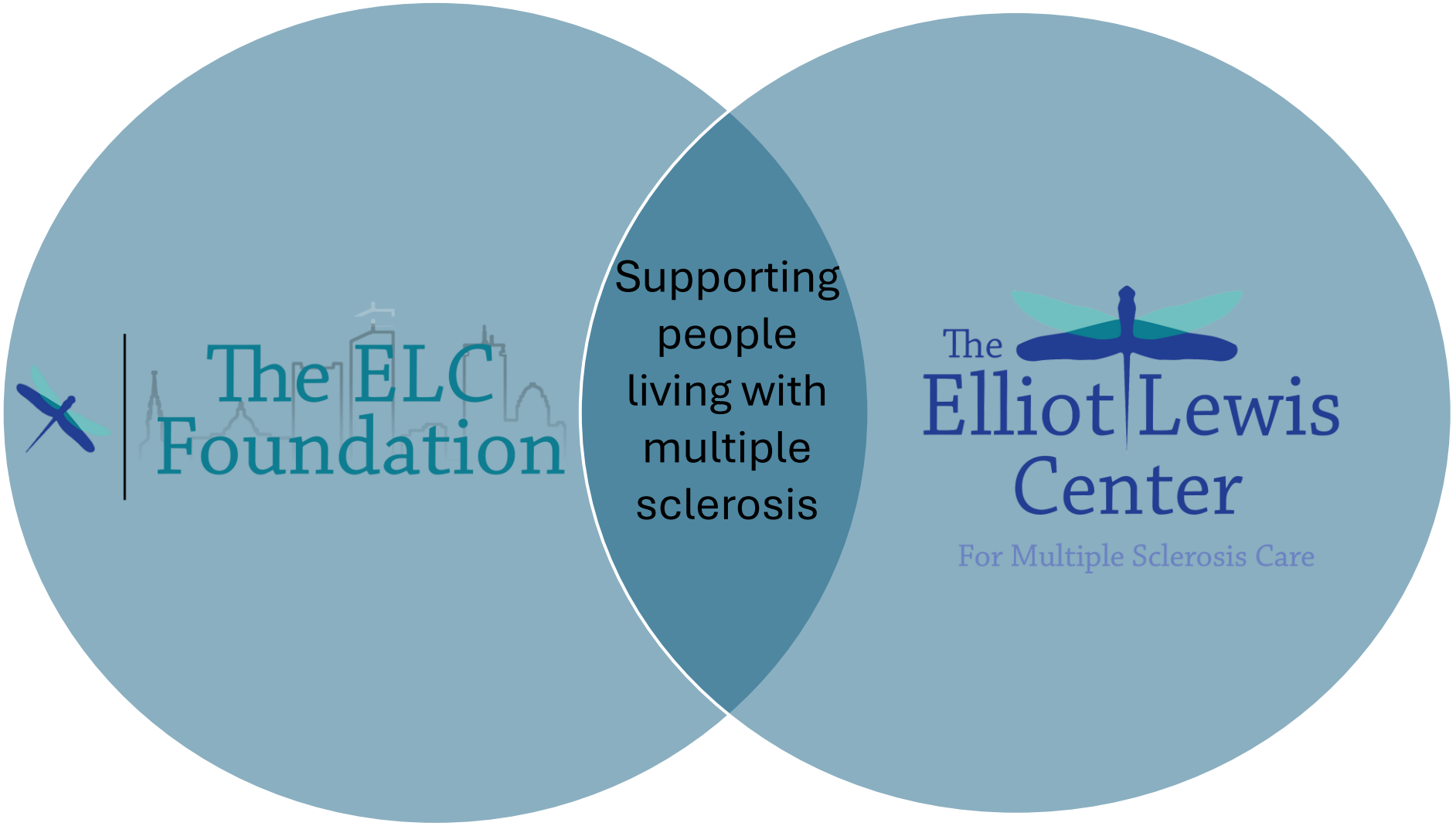
Welcome to Education Day 2025!

The Elliot Lewis Center





The ELC Foundation


The ELC Foundation
Supporting people living with multiple sclerosis
The Elliot Lewis Center
For Multiple Sclerosis Care

501(c)(3) non-profit corporation

founded in 2011 by Dr. Lathi

- Educational programs
  - ELC Education Day
  - Support Groups
  - MS Specialist Education

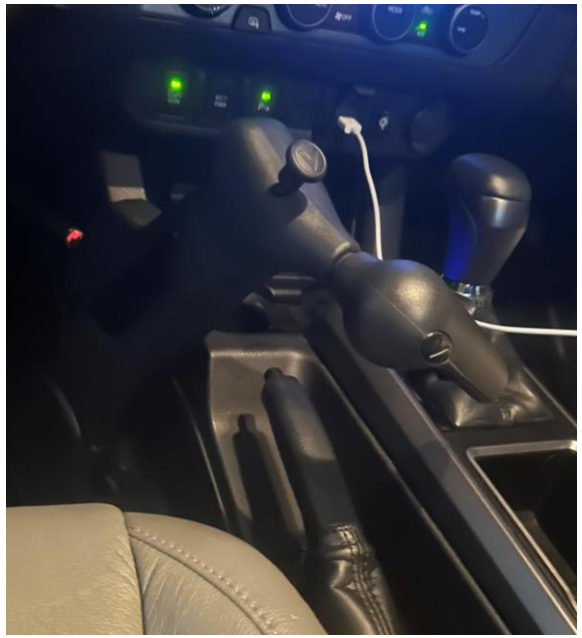
- Financial Assistance Program
  - Help fund needs for MS patients not covered by insurance


The ELC Foundation
Your Gift Supports Patients With MS
Join The ELC Foundation in our annual fundraising campaign to support patients with multiple sclerosis. People with MS often face financial obstacles that limit access to basic necessities. The ELC Foundation supports a financial assistance program and education for patients with MS.
Give a tax deductible contribution today.
Donate at www.ELCfoundation.org

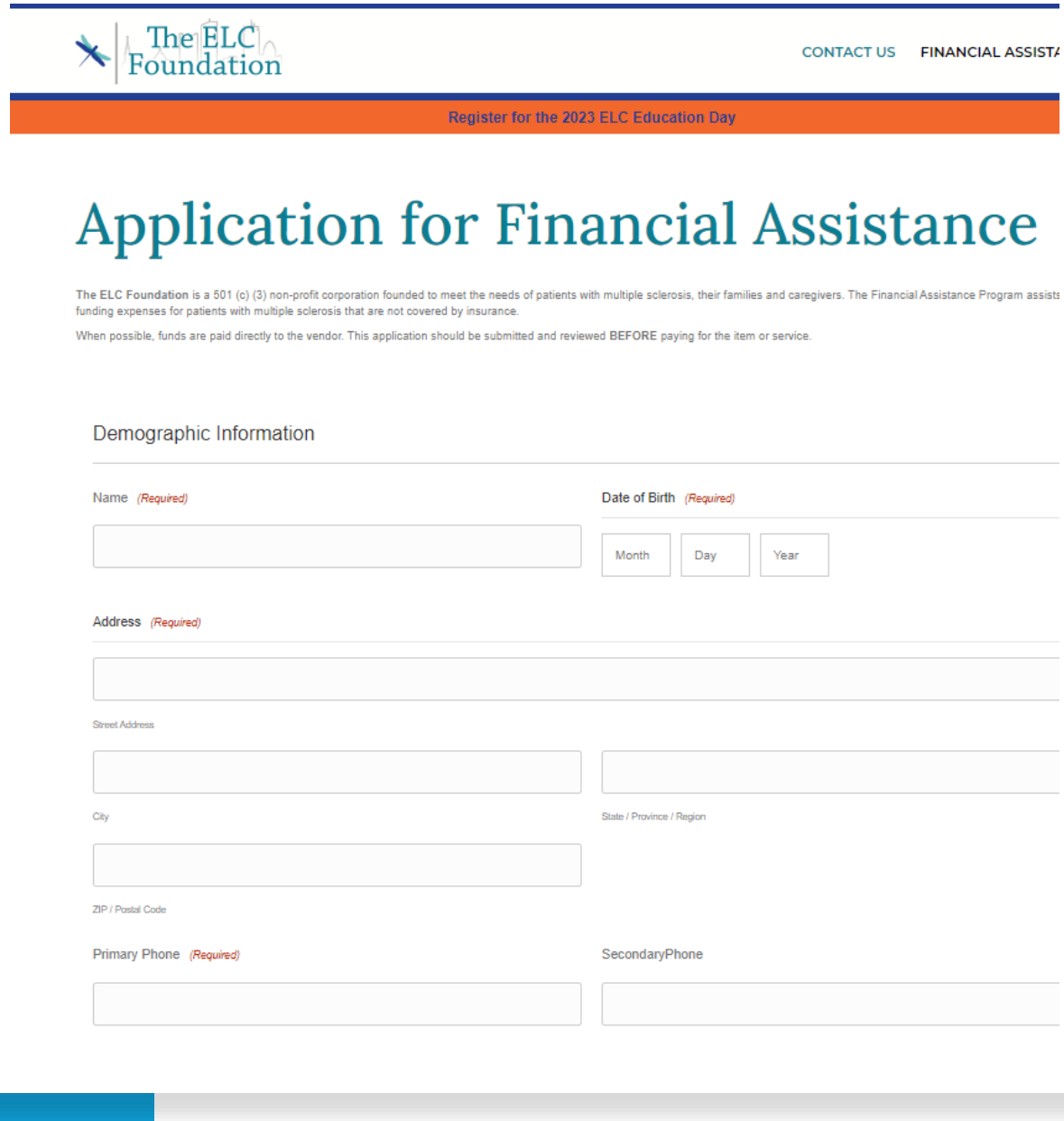
In 2025 the Financial Assistance Program supported…

- Home Physical & Occupational Therapy Evaluations
- Home adaptations including a stairlift, and bathroom modification
- Adaptive hand controls for driving
- Durable medical equipment including the Zoomer Chair, scooters and walkers
- Mobility aides including the Bioness and Cionic sleeve

Durable Medical Equipment

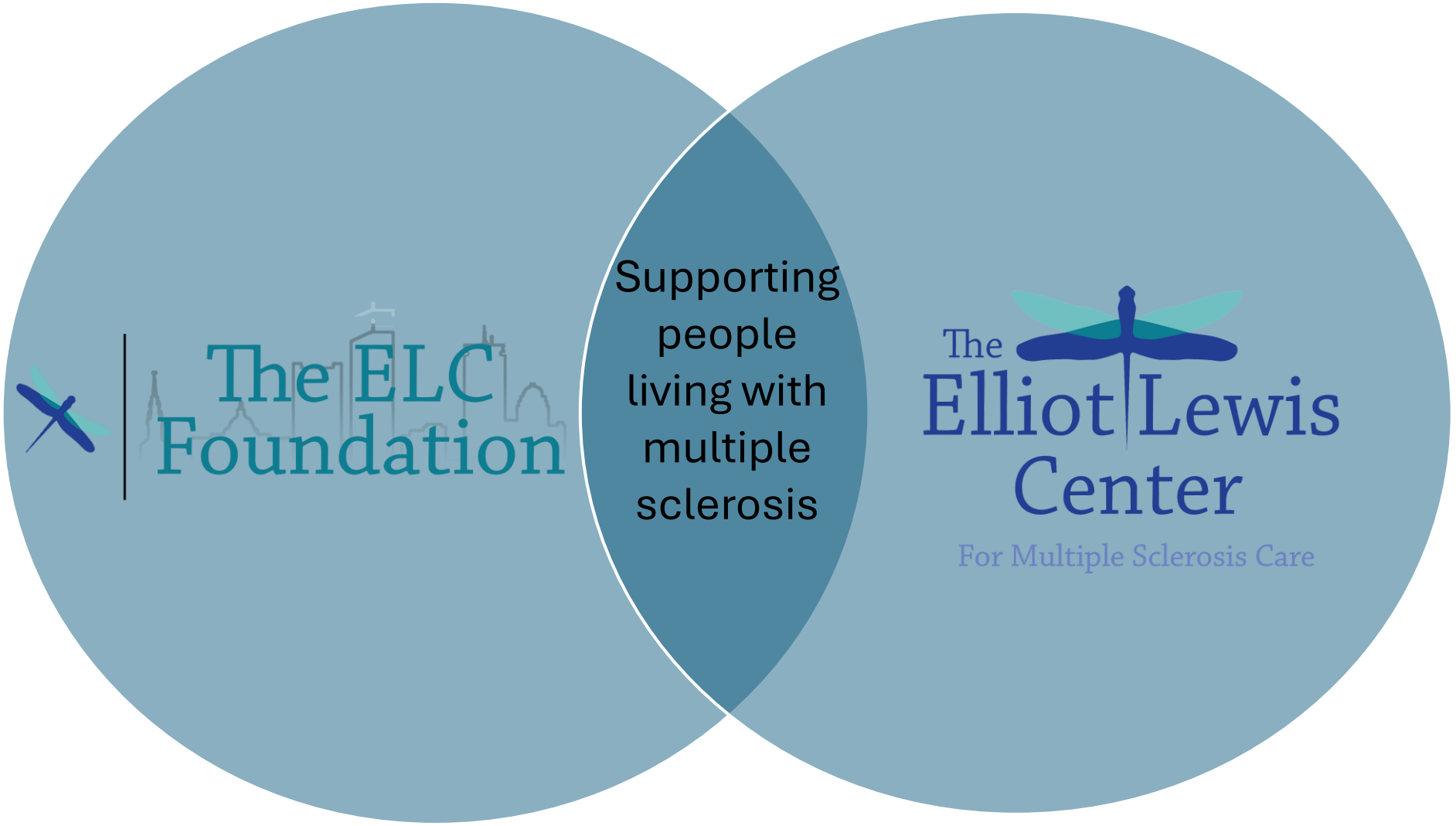


Adaptive driving programs &
Car modifications



Apply Online

www.ELCFoundation.org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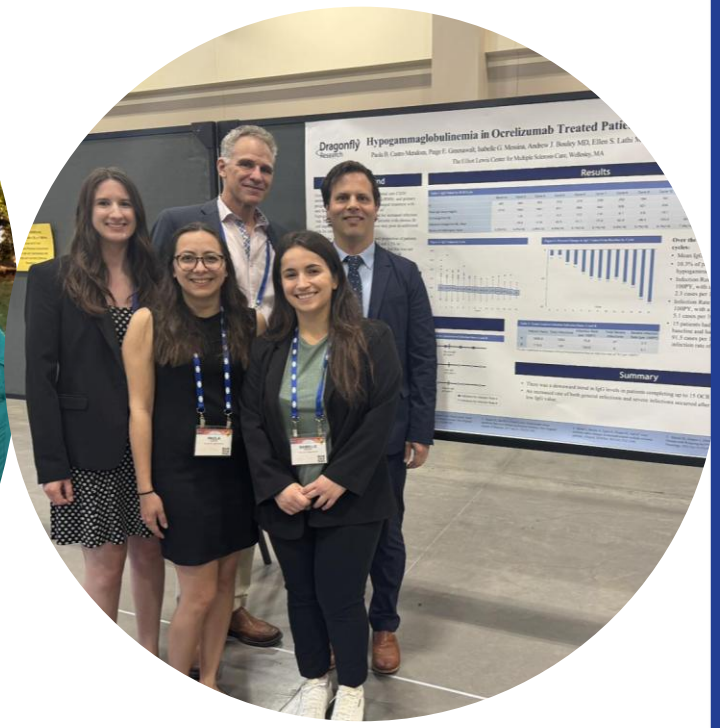


The Elliot Lewis Center

Open Enrollment is NOW

- Massachusetts Health Connector
  - November 1st though January 23rd

  www.MAhealthconnector.org
- Medicare
  - October 15th through December 7th

- Evaluate your plan
- Are your medications covered?
- What is your annual cost?
- Should you make a change?

Look Beyond the Monthly Premium
Consider the Annual Cost

- **Total annual cost** : premium + deductibles + co-pays + out-of-pocket maximums + network

Lower premium / higher deductible

- Less expensive monthly payment
- Tend to have higher out-of-pocket maximums and could have higher patient cost share once the deductible is met

$300/month + $6,000 ded = $9,600 year

Higher premium / lower deductible

- More expensive monthly payment
- Tend to have lower out-of-pocket maximums and patient cost share

$500/month + $1,000 ded = $7,000 year

A plan with a higher premium might result in **lower total cost** over the year.

Question	Original Medicare (Parts A+ B)	Medicare Advantage (Part C)
Can I see my doctor?	Any provider who accepts Medicare (99% of clinicians)	Limited to in-network providers; fewer choices
Are infusions covered?	Yes, under Part B; usually no pre-approvals	Often require pre-approvals, which could delay treatment
Out-of-pocket costs?	Premiums: Part A: $0 for most Part B: Standard Part B premium ($185 in 2025, 2026 TBD) Deductible: Fixed for Part A and Part B Annual cost limit: No limit, unless you have Medigap (which could bring Part B costs down to $0)	Premiums: Vary by plan. Part C premium is in addition to any required premiums for Part A and Part B Deductibles: Vary by plan Annual cost limit: Limit varies by plan. Medigap is NOT available under Medicare Advantage
Flexibility?	Can add Medigap and Part D	Locked into network and plan rules. Most plans include prescription drug coverage, but you can purchase a separate Part D plan if your plan does not.

Resources

The Elliot Lewis Center

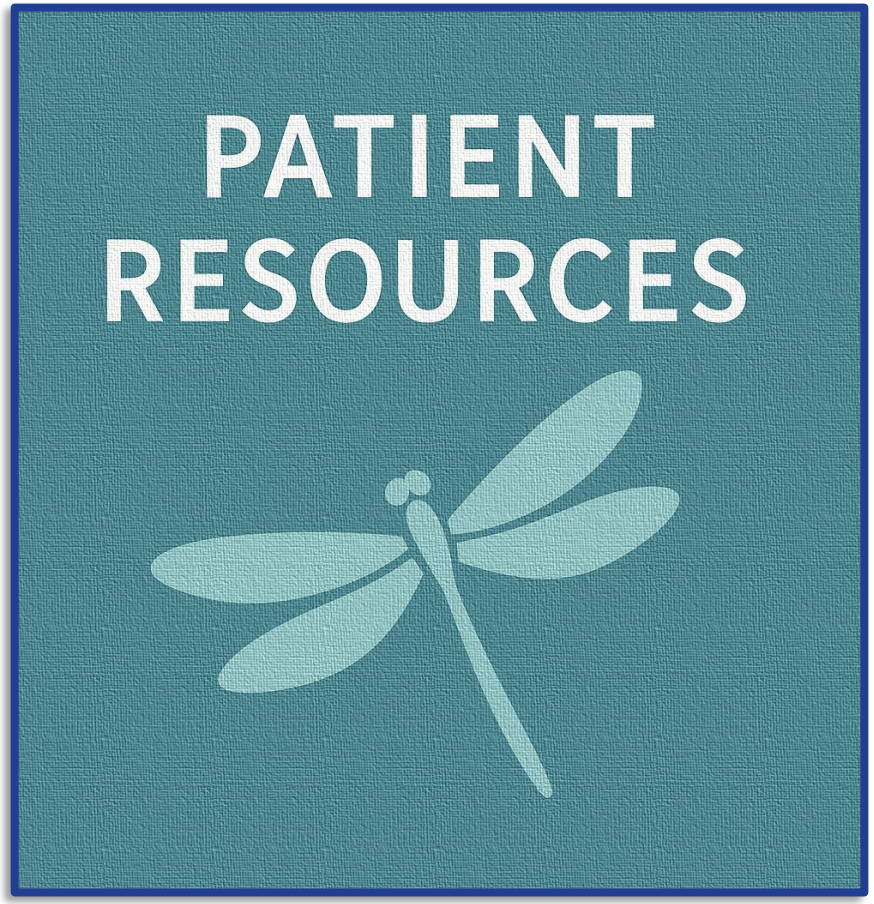
- https://elliotlewisms.com/patient-resources/

SHINE Counselors

- https://www.mass.gov/info-details/serving-the-health-insurance-needs-of-everyone-shine-program

2026 Open Enrollment Guide for Patients by Infusion Access Foundation

- https://www.infusionaccessfoundation.org/blog/2026-open-enrollment-guide-for-patients




ELC EDUCATION
DAY
2025
THE ELLIOT LEWIS CENTER

ELC Education Day

2025

11/1/2025

Andrew Bouley, MD

The Elliot Lewis Center
For Multiple Sclerosis Care

Objectives

1

Aging and MS

1. Stop Therapy?
2. De-escalate?
3. Extended Interval Dosing?

2

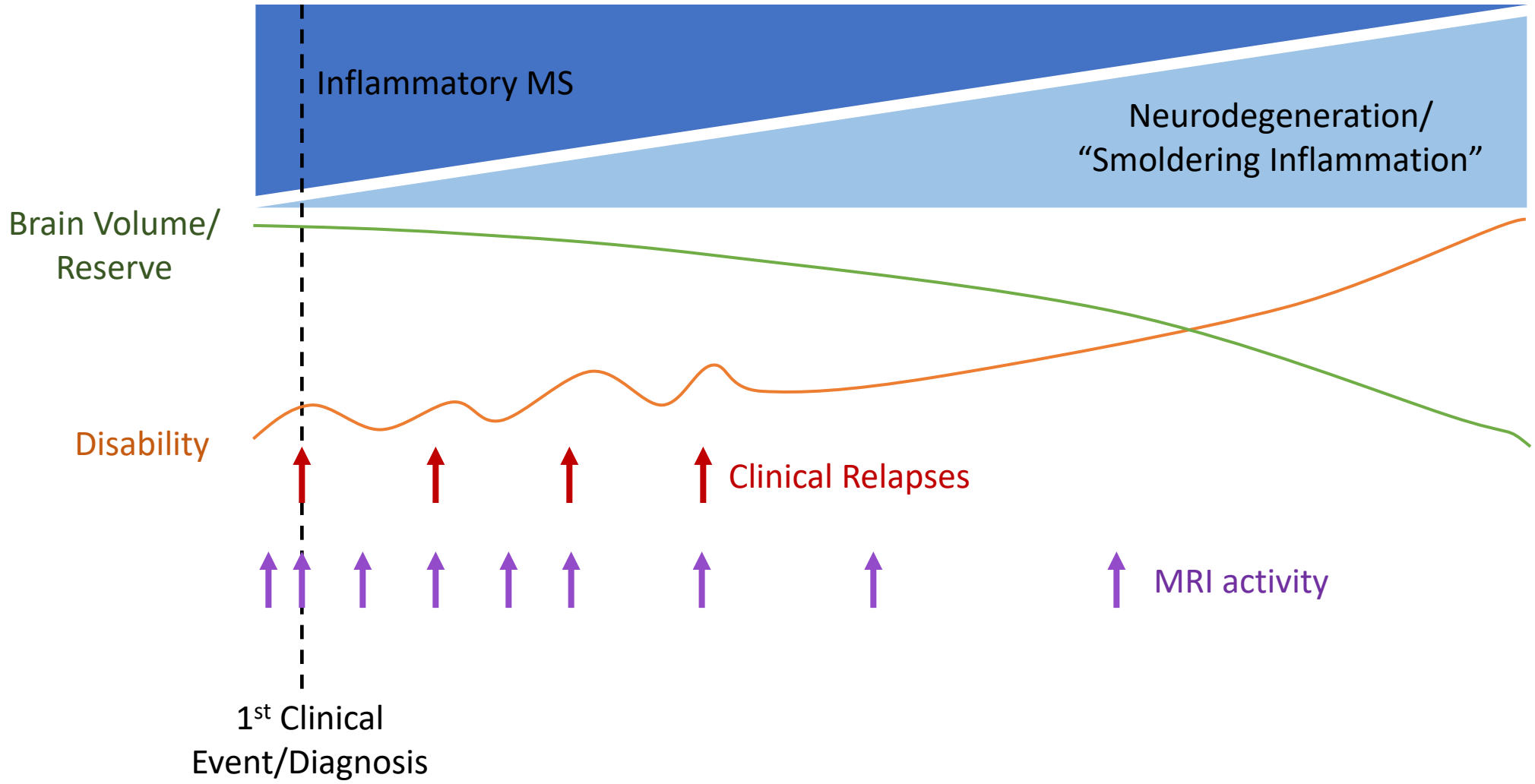
Vitamins

&

Supplements

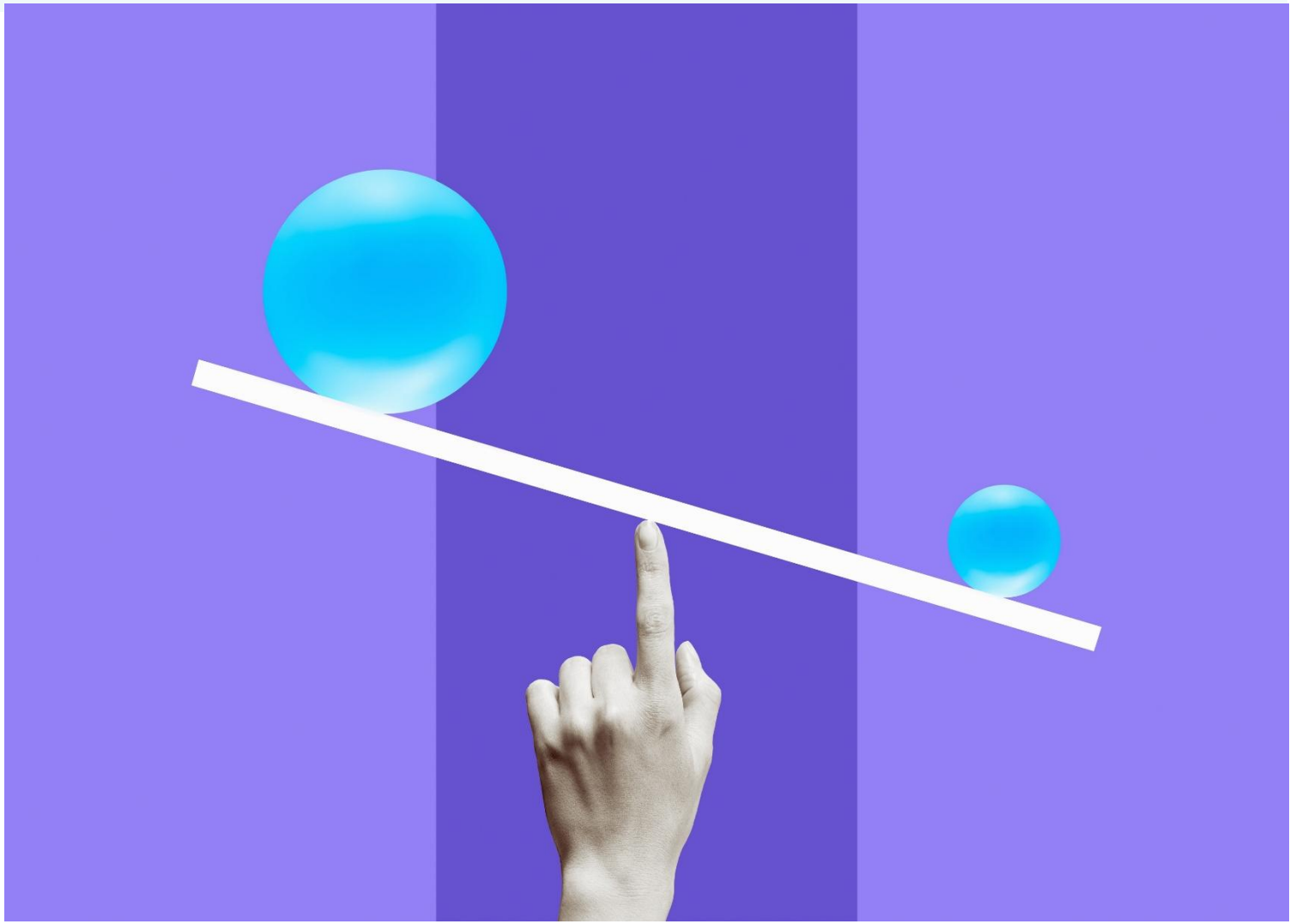
Aging and MS

New Inflammation Decreases with Age



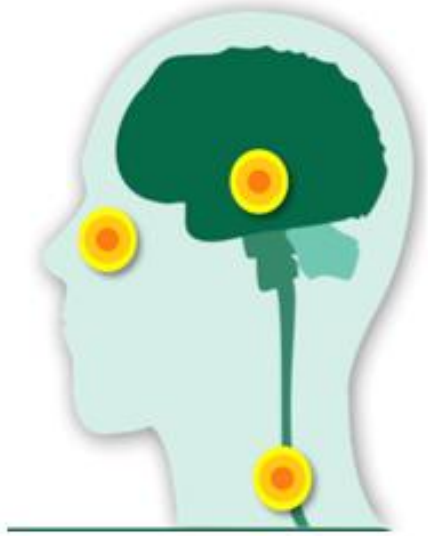
Aging and MS

- **MS inflammation** ↓
- **Immune system** ↓

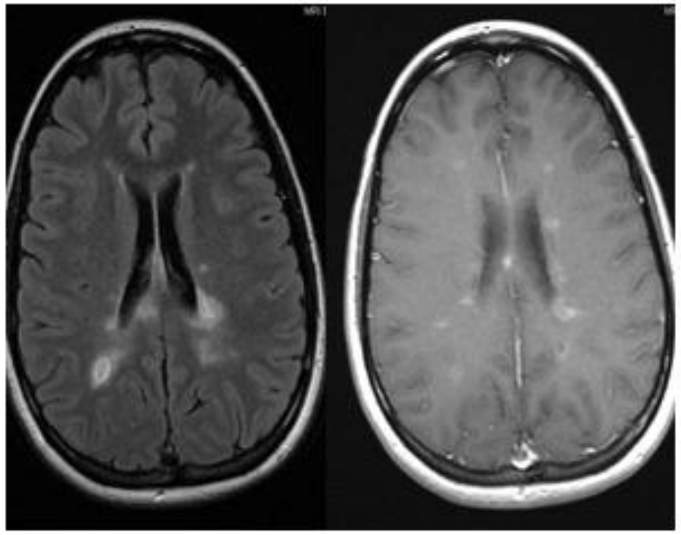


Current MS DMTs

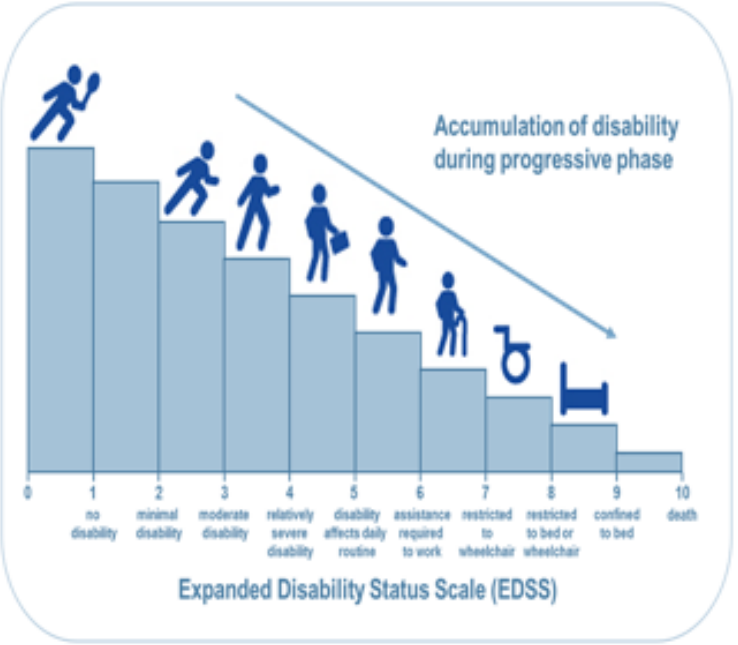
Relapses



New MRI lesions



Relapse associated disability RAW



Stop Treatment?

Prospective observational study (Birnbaum, 2017)

- 77 SPMS, stable for 2 to 20 years
- 11.7% risk of recurrence (usually within 1-2 yrs)

- "DMTs can be stopped safely in older patients (≥ 7 decades), with an almost 90% probability of remaining free of acute recurrence."

Table 1. Results in study groups A and B

Characteristic	Value	*P* value
Group A (patients advised to stop DMT) (n = 77)		
Female sex, No. (%)	66 (86)	
Age, median (range), y	61 (47–76)	
Time on DMT, median (range), y	11 (2–20)	
Time off DMT, median (range), y	4 (1–11)	
EDSS score, median	6	
Stable patients, No. (%)	68 (88.3)	
Worsened patients (clinical or MRI), No. (%)	9 (11.7)	
Age—stable, median, y	61	
Age—worsened, median, y	56	.0003
EDSS score—stable, median	6	
EDSS score—worsened, median	5.5	.24
Time on DMT—stable, median, y	10.25	
Time on DMT—worsened, median, y	11.5	.120

Birnbaum G. Stopping Disease-Modifying Therapy in Nonrelapsing Multiple Sclerosis: Experience from a Clinical Practice. Int J MS Care. 2017 Jan-Feb;19(1):11-14. doi: 10.7224/1537-2073.2015-032. PMID: 28243181; PMCID: PMC5315318.

DISCOMS

DISCOMS

- Multicenter, randomized, non-inferiority trial
- ≥55, any MS type, no relapses for 5 years/new MRI lesions for 3 years
- Patients assigned 1:1 to continue or discontinue

- **Primary endpoint**: % of patients with new relapse or new/enlarging MRI lesion over 2 years

Corboy, John RBourdette, Dennis et al. Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): a multicentre, randomised, single-blind, phase 4, non-inferiority trial. The Lancet Neurology, Volume 22, Issue 7, 568 - 577

DISCOMS: Results

- **259 patients** total, 128 (49%) continued, 131 (51%) discontinued
- Event rate: **12.2%** (n=16) in discontinue group vs **4.7%** (n=6) in the continue group
- The (absolute) difference in event rates was **7.5%**, though *predefined non-inferiority margin was 8%*
- Those that discontinue are 2.6 times more likely to have a new event (RR)

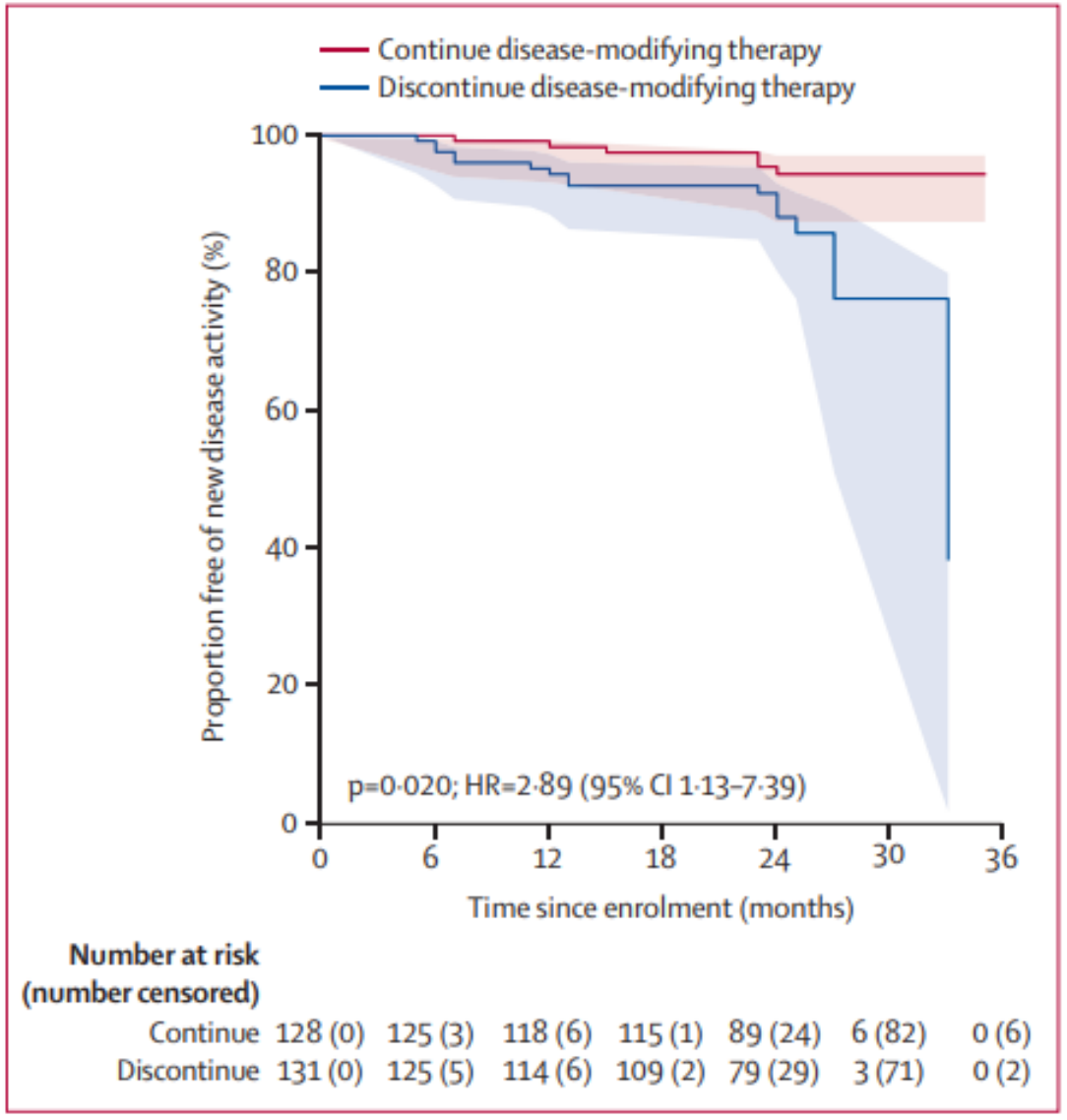


Figure 2: **Time to relapse or new brain MRI lesion**

Caveats:

	Continue	Discontinue
Disease modifying therapy at randomisation		
Interferon beta-1a	47 (37%)	46 (35%)
Interferon beta-1b	5 (4%)	12 (9%)
Glatiramer acetate	44 (34%)	35 (27%)
Teriflunomide	4 (3%)	4 (3%)
Dimethyl fumarate	15 (12%)	23 (18%)
Fingolimod	12 (9%)	6 (5%)
Natalizumab	1 (0·8%)	3 (2%)
Ocrelizumab	0 (0%)	2 (2%)

Safety?

- Goal of stopping therapy is to reduce risk…
- More patients with serious adverse events and URIs in the discontinue group!

	Continue disease-modifying therapy group (n=128)		Discontinue disease-modifying therapy group (n=131)	
	Number of events	Number of participants (%)	Number of events	Number of participants (%)
Overall				
Adverse events	347	109 (85%)	422	104 (79%)
Mild (grade 1)	155	77 (60%)	202	81 (62%)
Moderate (grade 2)	182	83 (65%)	208	83 (63%)
Severe (grade 3+)	10	8 (6%)	12	9 (7%)
Serious adverse events	30*	20 (16%)	40*	18 (14%)
Deaths†	1	1 (<1%)	2	2 (2%)
Common or treatment-related adverse events‡				
Upper respiratory infection	20	19 (15%)	37	30 (23%)
Urinary tract infection	27	17 (13%)	26	11 (8%)
Musculoskeletal pain	17	17 (13%)	14	14 (11%)
Fall	13	12 (9%)	14	13 (10%)
Osteoarthritis	10	10 (8%)	6	6 (5%)
Influenza	4	4 (3%)	10	10 (8%)
COVID-19	3	3 (2%)	7	7 (5%)
Multiple sclerosis relapse	1	1 (<1%)	3	3 (2%)
Leg oedema	1	1 (<1%)	0	0
Abdominal pain	1	1 (<1%)	0	0
Leptomeningeal enhancement	0	0	1	1 (<1%)
Elevated prostate specific antigen	1	1 (<1%)	0	0
Abnormal white blood cell count	0	0	1	1 (<1%)
Abnormal glucose concentration	0	0	1	1 (<1%)
Injection reaction	0	0	1	1 (<1%)

DISCOMS: Conclusions

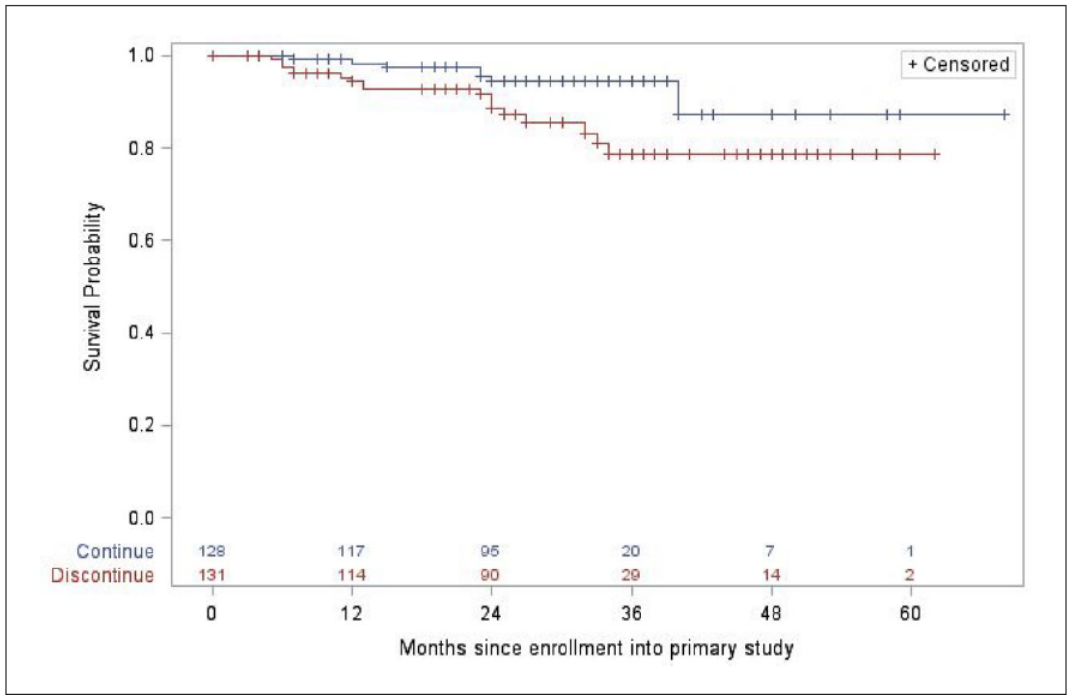
- “Discontinuation of DMT might be reasonable option in patients older than 55 years who have stable MS, but might be associated w/ a small increased risk of new MRI activity”

- Satisfaction: More patients “satisfied” in discontinue group (91% vs 78%)
  - Of the 16 participants in the discontinue group who had an event, 56% **DID NOT** resume therapy

- All 6 patients with active MRI (T1 Gd+) lesions had discontinued therapy, and all had been on interferon-β or glatiramer acetate

DISCOMS Extension

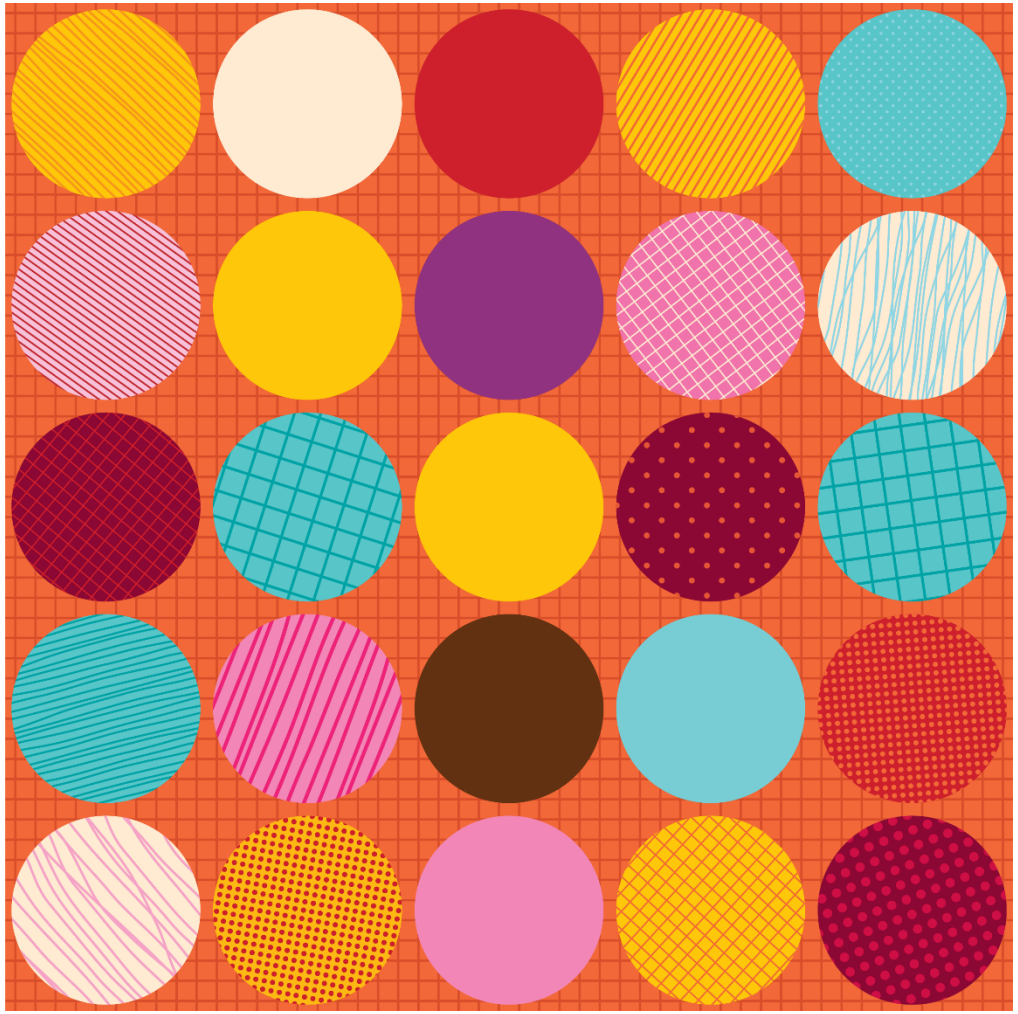
- Follow-up on original patients, 1 study visit and MRI at least 30 months after enrollment
- Only 74 patients included (30/89 continuers and 44/81 discontinuers)
- No new relapses, 3 new MRI lesions (1/30 continuer, 2/44 discontinuers)
- Primary endpoint: time to relapse or brain activity – **shorter for discontinuers**



DOT-MS

- Netherlands trial, randomized
- ≥ 18, no relapses or MRI activity in previous 5 years while on 1st line DMT
- Primary endpoint: Relapse and/or ≥3 new T2 lesions or ≥2 T1 Gd+

- **TERMINATED EARLY**!
- 8/45 (**17.8%**) participants in the discontinue group vs 0/44 in the continue group had an event



DOT-MS

Table 2. Number of Participants With an Inflammatory Event

Event	No./total No. (%)		Conditional power
	Continuation	Discontinuation	
Primary outcome event (relapse or significant MRI activity)	0/44 (0)	8/45 (17.8)	<.001
Relapse	0/44 (0)	2/45 (4.4)	NA
Significant MRI activity[a]	0/44 (0)	7/45 (15.6)	NA
Any MRI activity[b]	1/44 (2.3)	11/45 (24.4)	<.001

Table 1. Baseline Characteristics

Characteristic	Participants, No. (%)	
	Continuation (n = 44)	Discontinuation (n = 45)
Age, median (IQR), y	55.0 (50.0-59.0)	54.0 (47.0-58.0)
Sex		
Female	28 (63.6)	32 (71.1)
Male	16 (36.4)	13 (28.9)
Time since symptom onset, median (IQR), y	13.3 (9.9-22.2)	14.1 (9.4-19.6)
Time since last documented relapse, median (IQR), y	9.8 (6.8-13.3)	9.4 (7.1-12.3)
Multiple sclerosis subtype		
Relapsing-remitting	39 (88.6)	41 (91.1)
Secondary progressive	5 (11.4)	4 (8.9)
Total duration of disease-modifying therapy use, median (IQR), y	11.4 (7.7-17.9)	11.1 (7.8-13.8)
Disease-modifying therapy at randomization		
Interferon beta	18 (40.9)	17 (37.8)
Glatiramer acetate	11 (25.0)	12 (26.7)
Teriflunomide	8 (18.2)	4 (8.9)
Dimethyl fumarate	7 (15.9)	12 (26.7)
Expanded Disability Status Scale score, mean (SD)	3.1 (1.6)	3.1 (2.0)
Symbol Digit Modalities Test score, mean (SD)[a]	51.6 (11.4)	51.7 (13.3)
Timed 25-Foot Walk test score, mean (SD)[b]	5.4 (1.3)	5.2 (1.0)
Nine-Hole Peg Test, mean (SD)	23.2 (6.1)	23.5 (7.8)
Neurofilament light chain, mean (SD), pg/mL	12.0 (5.9)	11.0 (5.0)
Glial fibrillary acidic protein, mean (SD), pg/mL	87.3 (47.0)	83.8 (34.5)

Coerver EME, Fung WH, de Beukelaar J, et al. Discontinuation of First-Line Disease-Modifying Therapy in Patients With Stable Multiple Sclerosis: The DOT-MS Randomized Clinical Trial. JAMA Neurol. 2025;82(2):123–131. doi:10.1001/jamaneurol.2024.4164

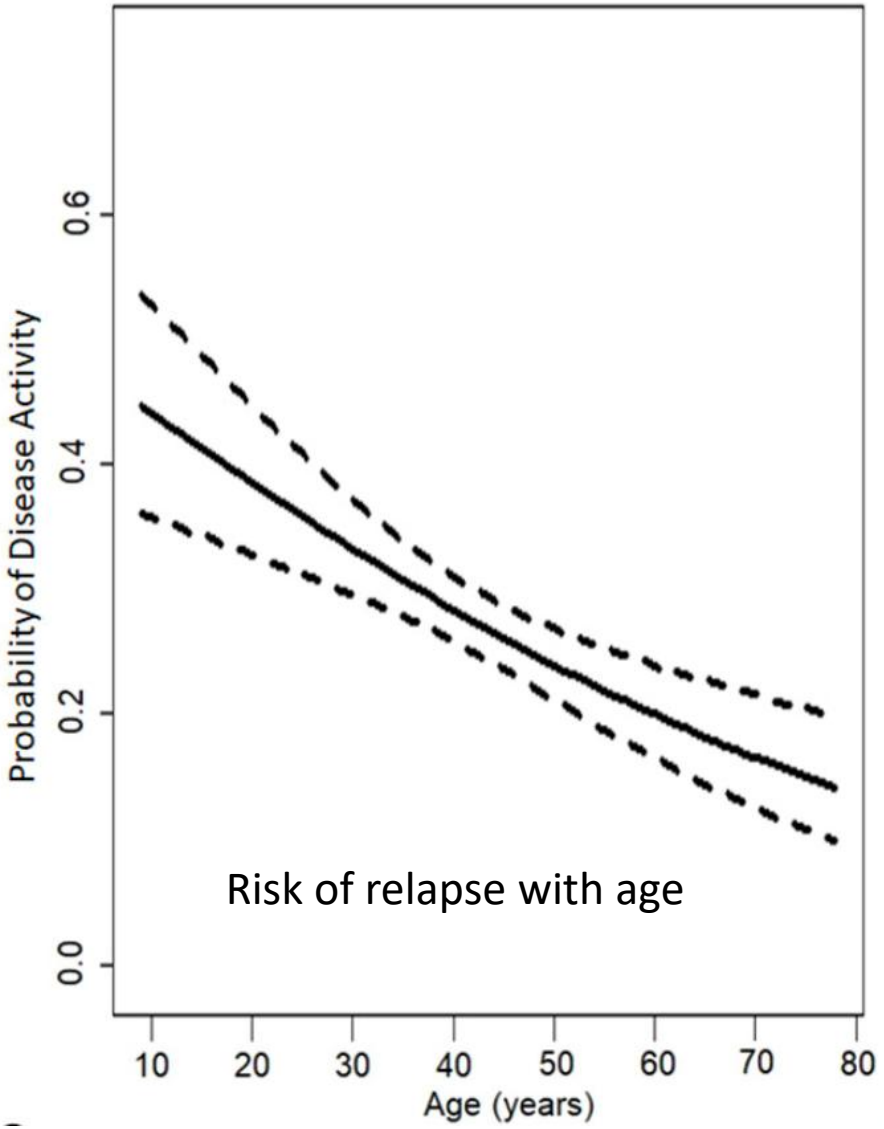
Considerations

- Maybe we should not stop DMT, or at least wait until a later age?
- Should we de-escalate therapy to reduce risks?

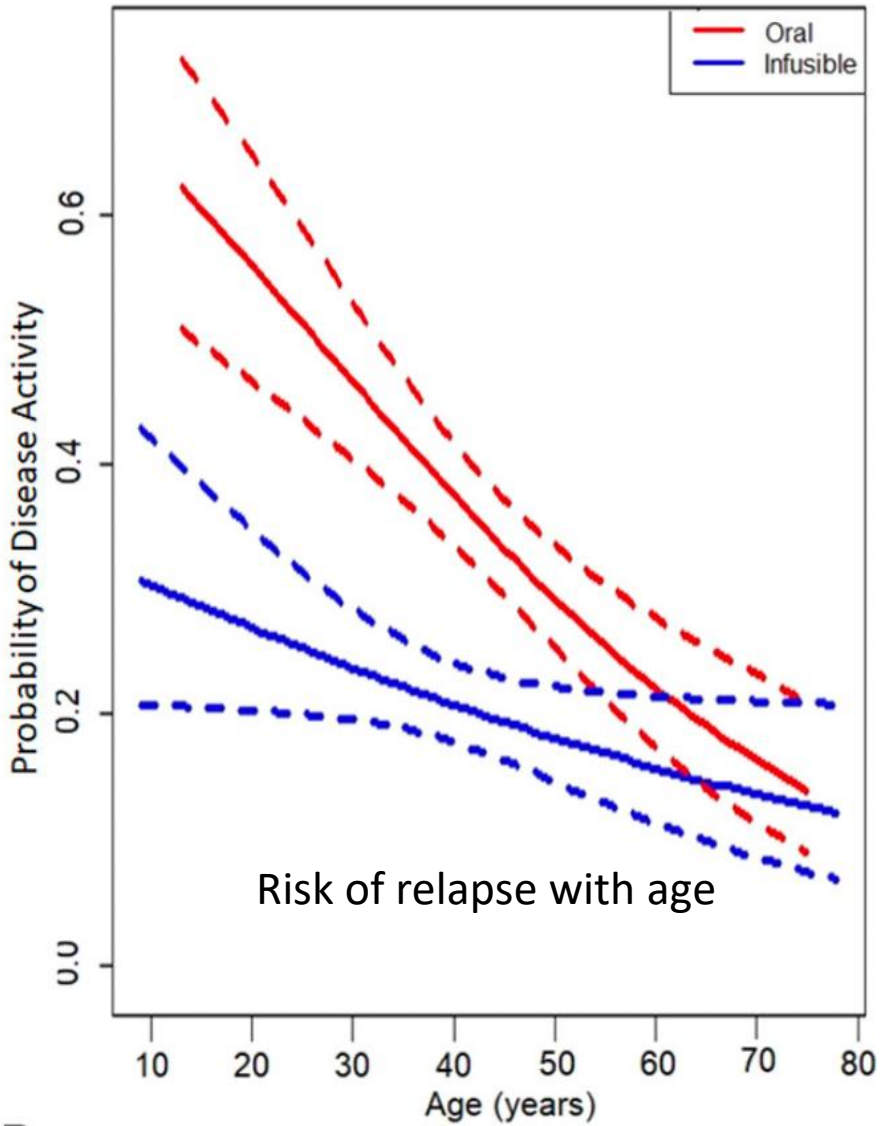
De-escalate Therapy?

De-escalation? Sure…

- Single center with 1264 patients evaluating risk of relapse/MRI activity over 2 years



Risk of relapse with age



Risk of relapse with age

Vollmer BL, Wolf AB, Sillau S, Corboy JR, Alvarez E. Evolution of Disease Modifying Therapy Benefits and Risks: An Argument for De-escalation as a Treatment Paradigm for Patients With Multiple Sclerosis. Front Neurol. 2022 Jan 25;12:799138. doi: 10.3389/fneur.2021.799138. PMID: 35145470; PMCID: PMC8821102.

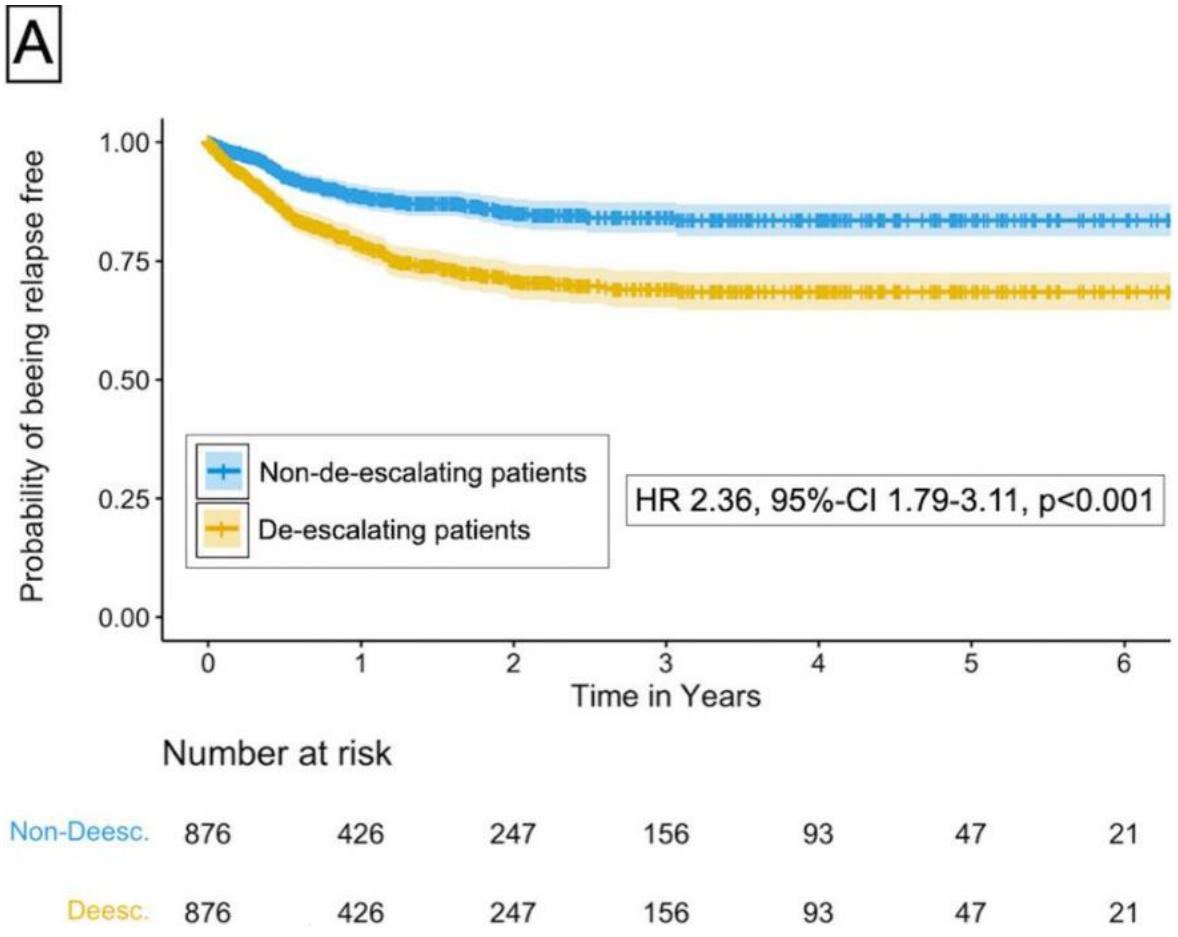
De-escalation? Maybe NOT…

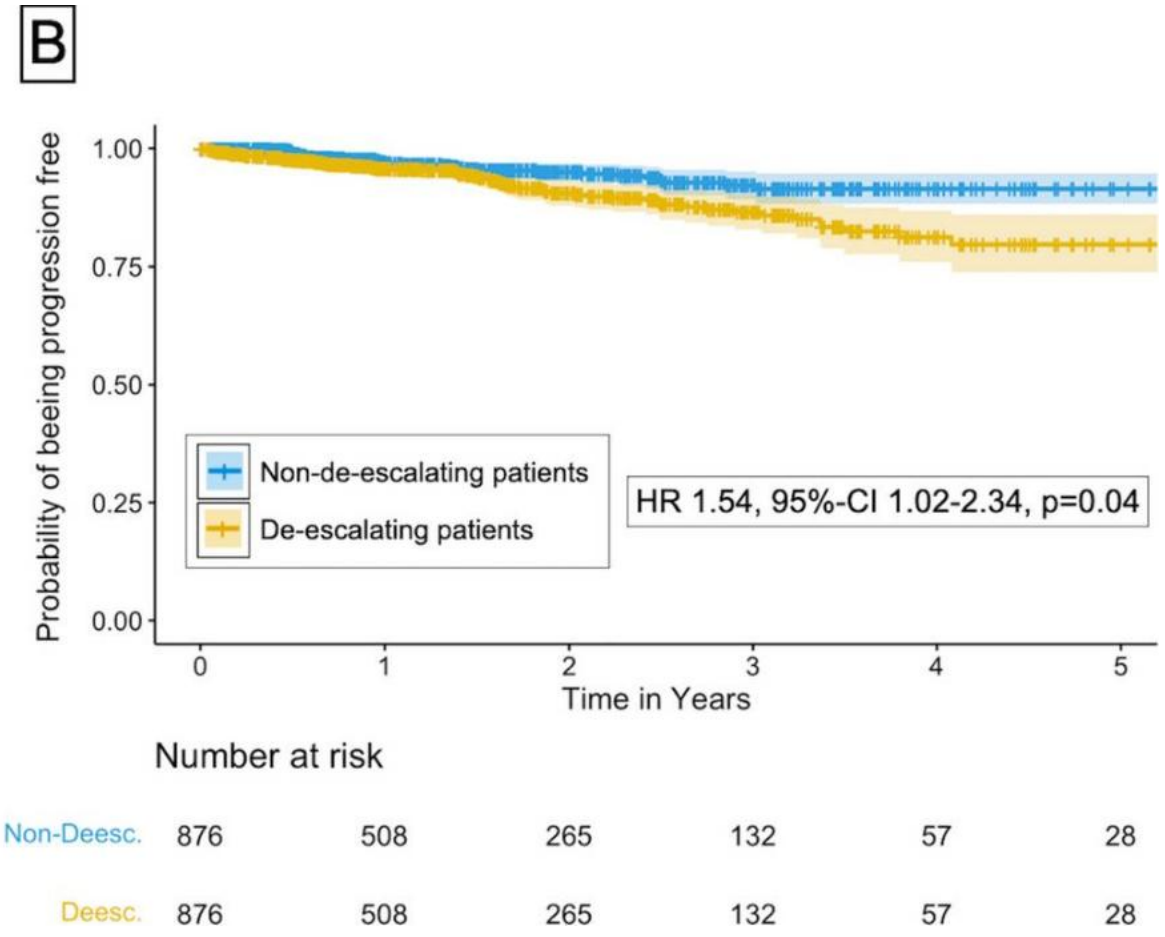
MSBase
Neuro-Immunology Registry

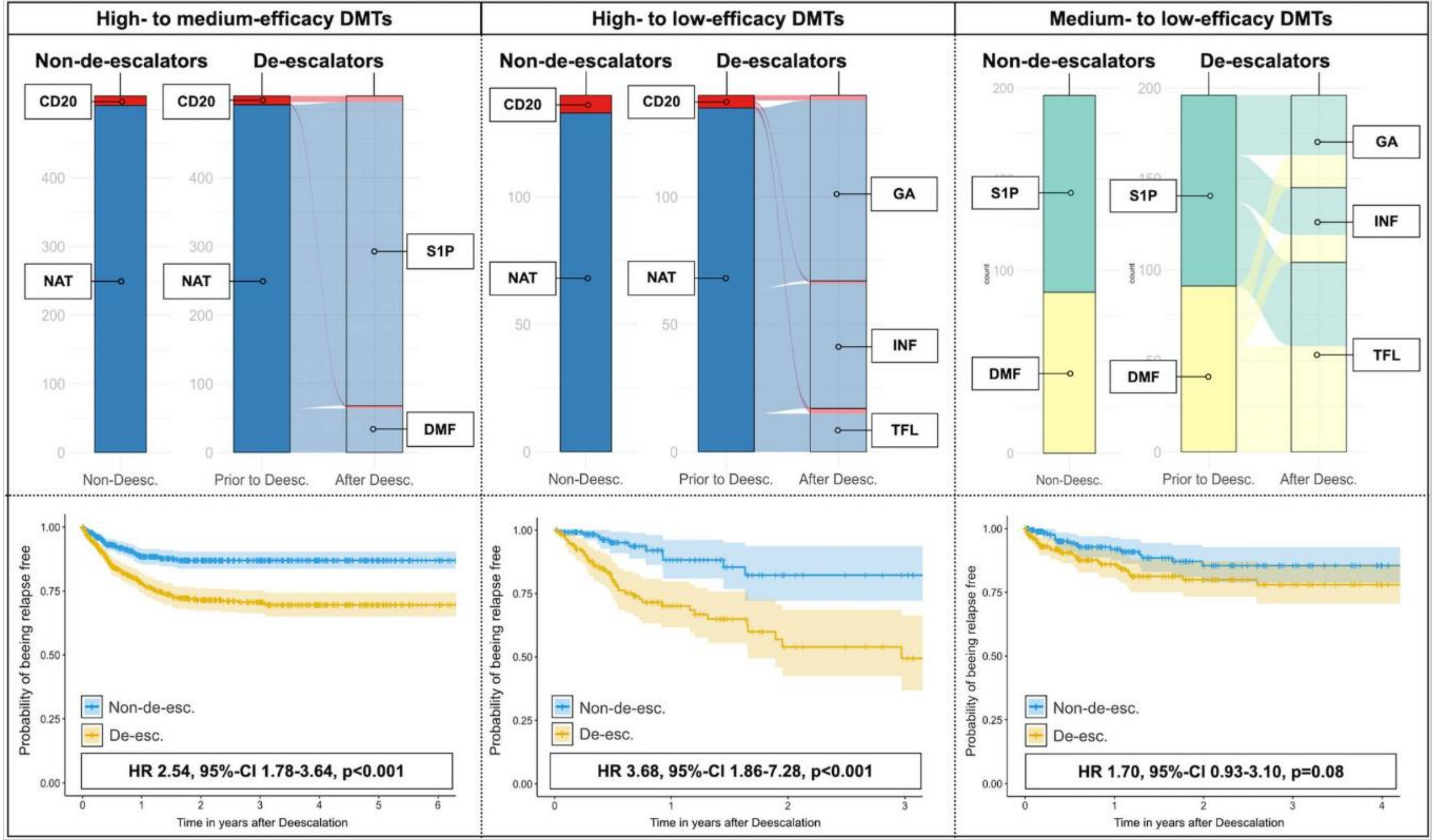
- Retrospective study from MSBase (international database)
- >87,000 patients were screened and matched
- 856 de-escalating patients were matched with 547 non-de-escalating patients, for a total of 876 de-escalating events

Müller J, Sharmin S, Lorscheider J, Horakova D, Kubala Havrdova E, Eichau S, Patti F, Grammond P, Buzzard K, Skibina O, Prat A, Girard M, Grand'Maison F, Alroughani R, Lechner-Scott J, Spitaleri D, Barnett M, Cartechini E, Sa MJ, Gerlach O, van der Walt A, Butzkueven H, Prevost J, Castillo-Triviño T, Yamout B, Khoury SJ, Yaldizli Ö, Derfuss T, Granziera C, Kuhle J, Kappos L, Roos I, Kalincik T; MSBase Study Group. Treatment De-escalation in Relapsing-Remitting Multiple Sclerosis: An Observational Study. CNS Drugs. 2025 Apr;39(4):403-416. doi: 10.1007/s40263-025-01164-w. Epub 2025 Feb 14. PMID: 39953338; PMCID: PMC11909097.

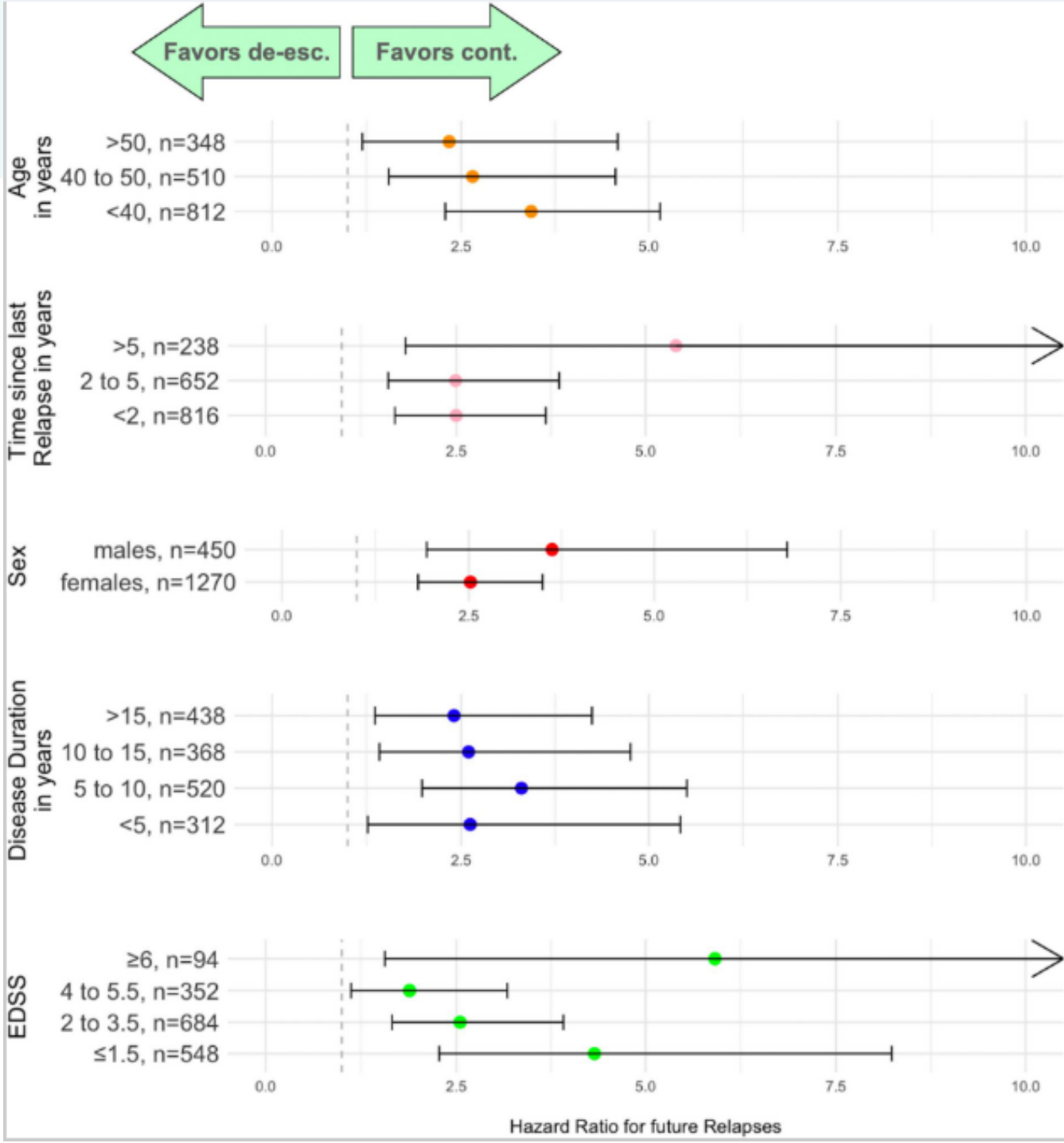
De-escalating increased risk of relapses and progression






High- to medium-efficacy DMTs
High- to low-efficacy DMTs
Medium- to low-efficacy DMTs
Non-de-escalators
De-escalators
CD20
NAT
S1P
DMF
GA
INF
TFL
count
Non-Deesc.
Prior to Deesc.
After Deesc.
Probability of beeing relapse free
Non-de-esc.
De-esc.
HR 2.54, 95%-CI 1.78-3.64, p<0.001
HR 3.68, 95%-CI 1.86-7.28, p<0.001
HR 1.70, 95%-CI 0.93-3.10, p=0.08
Time in years after Deescalation

Subgroup Analysis



Patients with more disability?

- Patients with more disability have an increased risk of infection
- MS may “burn out”
- ORATORIO – ocrelizumab had reduced progression in PPMS population
- Many patients with progressive MS were excluded from original trial

- **ORATORIO-HAND** randomized patients 1:1 OCR:placebo for ≥144 weeks. It includes patients excluded from the original trial:
  - EDSS 3.0-8.0 (as opposed to 3.0-6.5)
  - Age 18-65 (as opposed to 18-55)

Older, more disability, longer disease duration

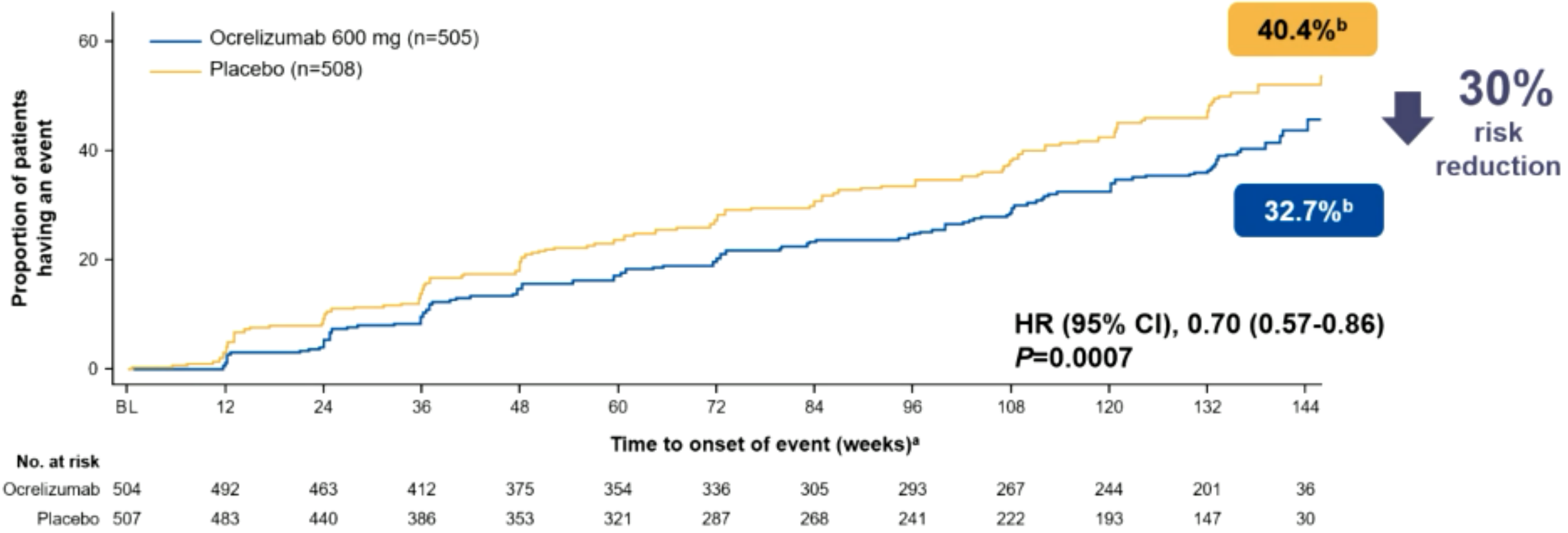
ECTRIMS 2025

Giovannoni et al. ECTRIMS 2025

	ORATORIO-HAND Ocrelizumab (n=505)	ORATORIO-HAND Placebo (n=508)	ORATORIO All patients (n=732)[1]
Age, median (range), years	48 (18-66)	47 (22-66)	46 (18-56)
≤55 years, n (%)	366 (72.5)	371 (73.0)	727 (99.3)
>55 years, n (%)[a]	139 (27.5)	137 (27.0)	5 (0.7%)
Female, %	57.4	54.7	49.3
EDSS score, median (range)	6.0 (3.0-8.0)	6.0 (2.5-8.0)	4.5 (2.5-7.0)
>6.5, n (%)	77 (15.2)	84 (16.5)	0
9HPT, median (range), sec	34.2 (25.1-216.9)	33.8 (24.5-221.8)	26.9 (11.1-300.0)
Presence of T1 Gd⁺ lesions, %	24.0	22.2	26.4
Duration since symptom onset, median (range), years	9.4 (0.7-27.6)	9.0 (0.7-37.4)	5.9 (0.9-32.9)
Prior DMT, %	8.3	6.1	11.6

Primary Endpoint in All Patients

Ocrelizumab Showed a 30% Risk Reduction on 12-Week Composite CDP on EDSS or 9HPT



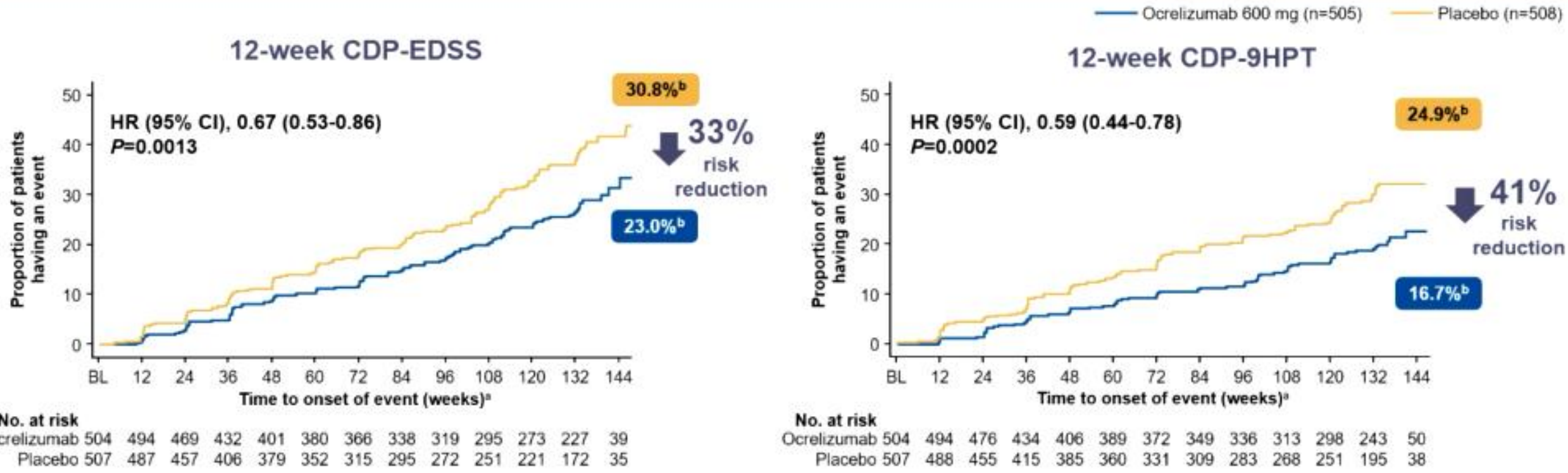
No. at risk													
Ocrelizumab	504	492	463	412	375	354	336	305	293	267	244	201	36
Placebo	507	483	440	386	353	321	287	268	241	222	193	147	30

ECTRIMS 2025

Giovannoni et al. ECTRIMS 2025

Secondary Endpoint in All Patients

Ocrelizumab Showed Significant Risk Reductions on Individual Components of Composite CDP

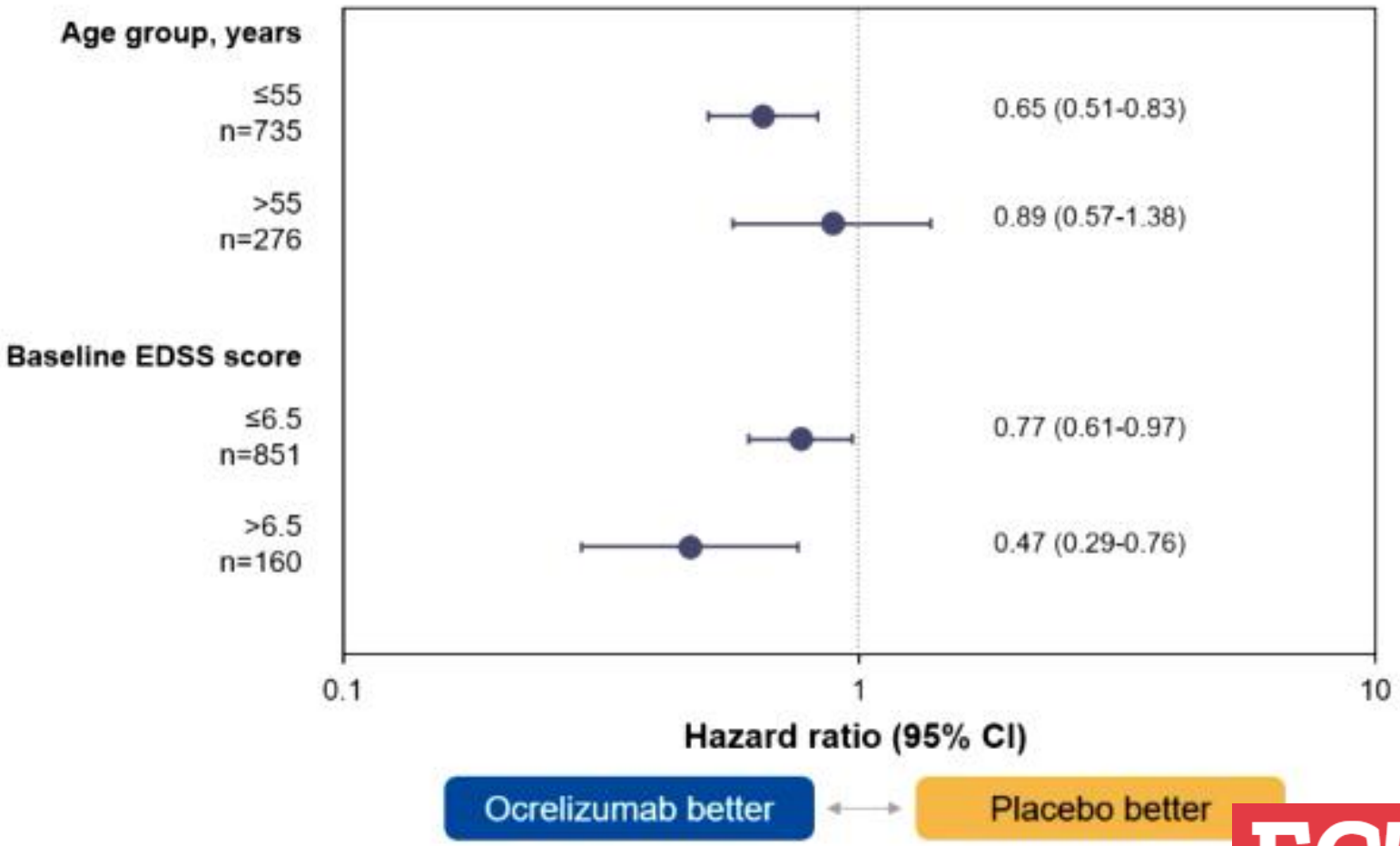


ECTRIMS 2025

Giovannoni et al. ECTRIMS 2025

Efficacy in Predefined Subgroups

A Reduction in the Risk of Disability Progression Was Also Seen in Older and More Disabled Patients



ECTRIMS 2025

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Safety in All Patients

The Overall Safety Profiles Were Similar Between the Two Arms

Patients with ≥1 event, n (%)		Ocrelizumab (n=506)	Placebo (n=506)
All adverse events		379 (74.9)	360 (71.1)
Adverse events leading to study treatment discontinuation		15 (3.0)	12 (2.4)
Serious adverse events		65 (12.8)	67 (13.2)
Infusion-related reactions[a]		105 (20.8)	22 (4.3)
Infections	including COVID-19	**245 (48.4)**	**226 (44.7)**
	excluding COVID-19	**190 (37.5)**	**187 (37.0)**
Serious infections	including COVID-19	**32 (6.3)**	**27 (5.3)**
	excluding COVID-19	**12 (2.4)**	**19 (3.8)**
Malignancies		5 (1.0)	3 (0.6)
Deaths		11 (2.2)	10 (2.0)

- Slightly more infections were observed in the ocrelizumab arm, but this difference was no longer evident when COVID-19 was excluded
- No opportunistic infections were observed

ECTRIMS 2025

Giovannoni et al. ECTRIMS 2025

Extended Interval Dosing (of B-Cell Therapy)

ExtenSion of the interval between anTI-CD20 doses in patients with Multiple sclerosis. a retrospective study on sAfeTy and Efficacy: the ESTIMATE20 study.

M. Santangelo[1], M. Laudisi [2], C. Ferri [2], S. Pilotto [3], E. Baldi [4] and M. Pugliatti.[2 3]

[1] Medical Faculty, University of Ferrara, Italy
[2] University Unit of Neurology. S. Anna University Hospital of Ferrara, Italy
[3] Dept. of Neuroscience and Rehabilitation, University of Ferrara, Italy
[4] Unit of Neurology, S. Anna University Hospital of Ferrara, Italy

SANT PAU Campus Salut Barcelona

Hospital de la Santa Creu i Sant Pau

Personalized dosing in MS: extended interval dosing of ocrelizumab, a real-world observational study

Lorena Martín-Aguilar[1], Nerea Blanco[1], Franco Appiani[2], Marta Caballero-Ávila[1], Nuria Vidal[1], Laura Martínez-Martínez[3], Luis Querol[1], Angela Vidal-Jordana[1,4].

1. Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.
2. Hospital Sanitas CIMA, Barcelona, Spain.
3. Inmunology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.
4. Centre d'Esclerosi Múltiple de Catalunya (Cemcat)

Extended versus standard interval dosing of anti-CD20 therapy in multiple sclerosis

UFHealth Multiple Sclerosis Program

Mahmoud Elkhooly[1], Rhea Jacob[2], Torge Rempe[2]

1) Dept of Neurology, Southern Illinois University; 2) Dept of Neurology, University of Florida

SIU MEDICINE

CLINICAL PREDICTORS OF B CELL REPOPULATION IN EXTENDED-DOSING INTERVALS OF RITUXIMAB IN MS

Silvia Susin-Calle*[1], Elvira Munteis [1], Cristina Esteban [1], Pablo Villoslada [1], Jose Enrique Martínez-Rodríguez [1]

[1] Neuroimmunology Unit, Neurology department, Hospital del Mar Research Institute, Barcelona

Extended vs. Standard Interval Dosing of Ocrelizumab in Multiple Sclerosis: A Meta-analysis with Meta-regression

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Alessandro Cruciani[1,2,4], Silvia Antonella Selvaggi[1,2], Carla Tortorella[3], Serena Ruggieri[3], Shalom Haggiag[3], Olga Ciccarelli[4], Claudio Gasperini[3], Luca Prosperini[3]

[1] Department of Medicine and Surgery, Unit of Neurology, Neurophysiology, Neurobiology, and Psychiatry, Università Campus Bio-Medico di Roma, Italy
[2] Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[3] Department of Neurosciences, San Camillo Forlanini Hospital, Rome, Italy
[4] Department of Neuroinflammation, Queen Square MS Centre, UCL Queen Square Institute of Neurology, University College London, UK

Why *should* we do EID?

- Some patients have prolonged immunosuppression with treatment
  - Decreased IgG
  - Increased infections, decreased vaccine responses
  - Concerns for malignancy

- Personalized treatment based on CD19+ cells?
  - Used in other disease states with rituximab

- Cost (per Google)
  - Ocrevus: $65,000-$78,000 per year
  - Briumvi: $59,000 per year
  - Kesimpta: $83,000-$88,000 per year

Why *shouldn't* we do EID?

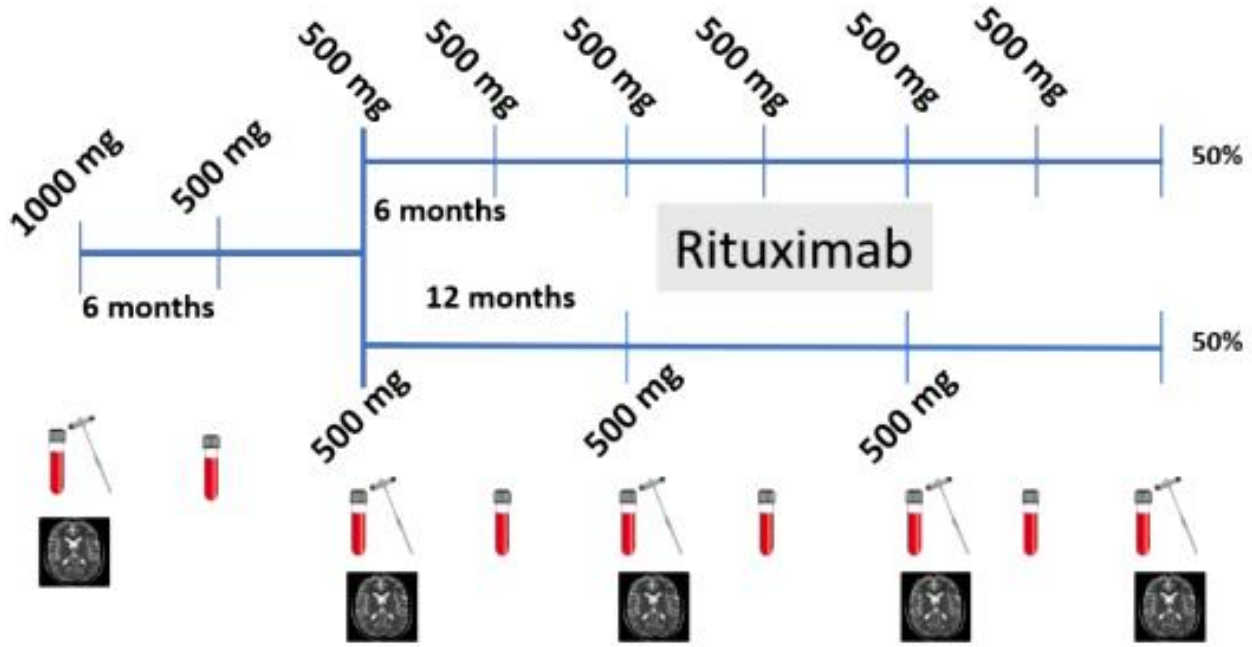
- What is the correct timing?
  - Every 12 months?
  - CD19+ B-cell or CD27+ memory B-cell counts?

- We don't know if EID dosing will significantly affect infection risk, the main goal of EID dosing

- "Wearing off" effect?

- Increase infusion reactions?

RIDOSE study outline



Assessments: EDSS and MRI 12-monthly, blinded relapse evaluations, biomarkers 6-monthly

Hypothesis: *Extended dose regimen (500 mg 12-monthly) is non-inferior to maintain NEDA-3 as 500 mg 6-monthly during year 2 – 4 in the trial*

RIDOSE Baseline Variables

- Mean age ~36 yo
- MS duration ~5y

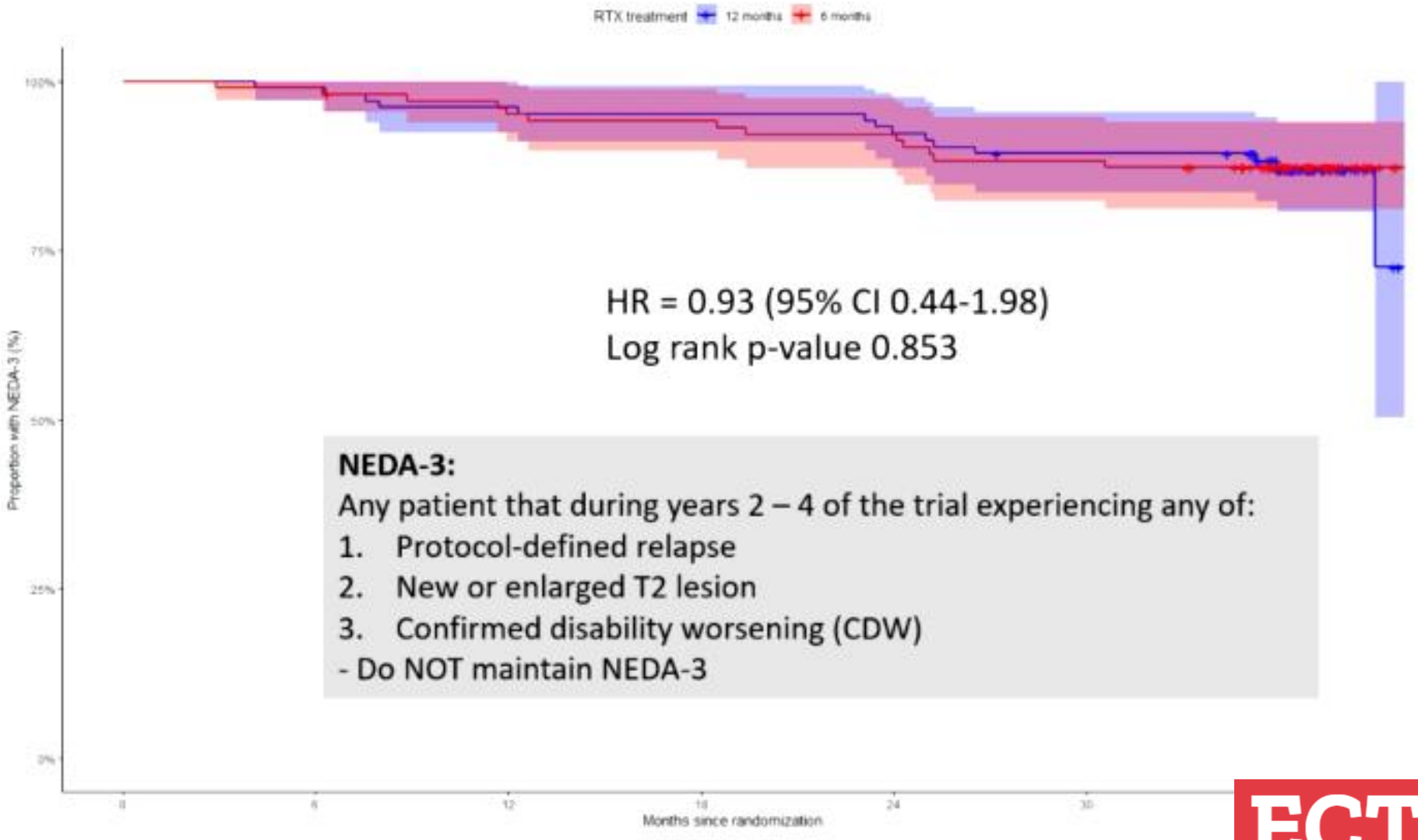
Patients:
- Relapsing-remitting MS or CIS
- Naive to RTX or previous up to 2 years of RTX treatment

ECTRIMS 2025

Svenningsson et al. ECTRIMS 2025

Svenningsson et al, RItuximab long-term DOSE trial in Multiple Sclerosis – RIDOSE-MS. A rater-blinded randomized phase 3 trial comparing standard with extended dosing intervals of rituximab in relapsing-remitting MS; ECTRIMS 2025

1° Endpoint NEDA-3 year 2 – 4



HR = 0.93 (95% CI 0.44-1.98)
Log rank p-value 0.853

Not NEDA:
12-month arm: 13.59%
6-month arm: 12.62%

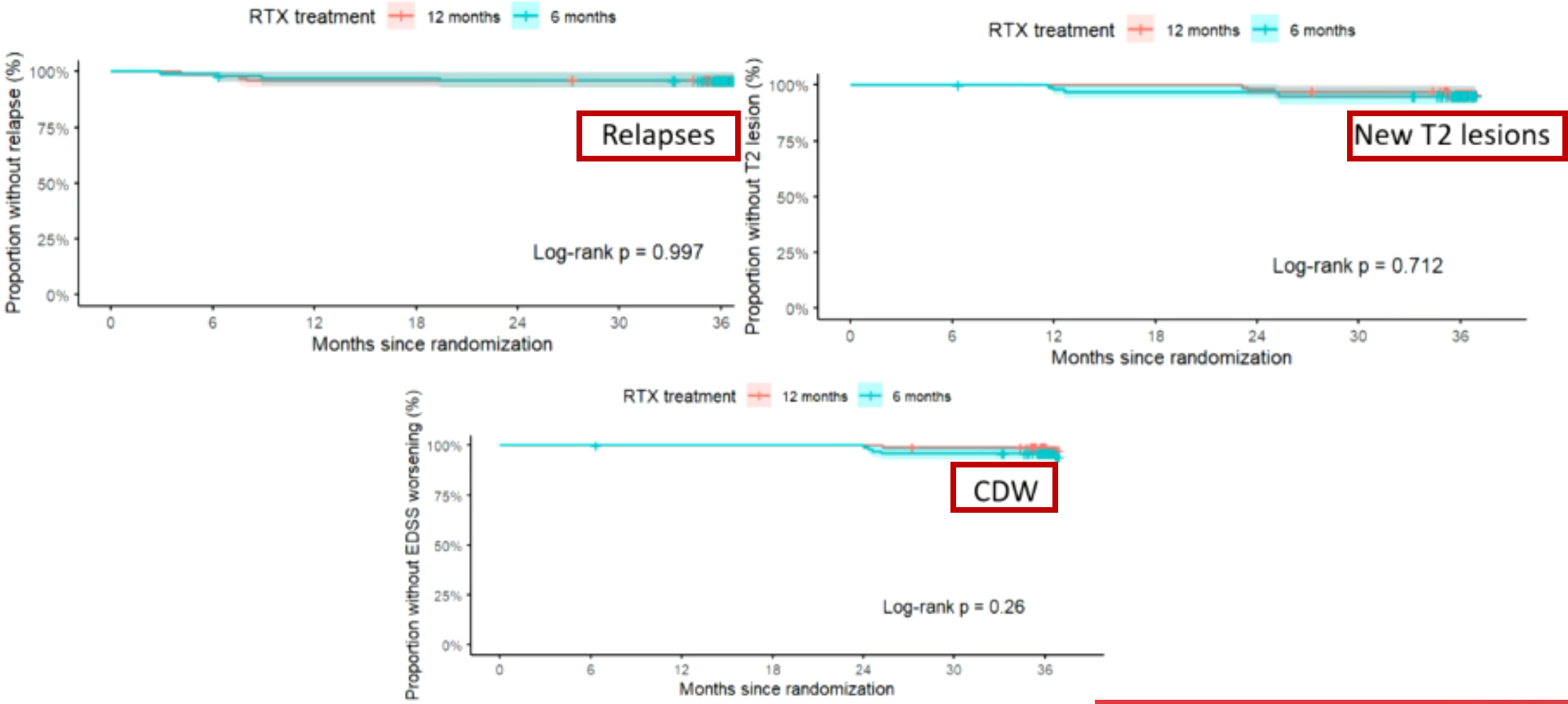
NEDA-3:
Any patient that during years 2 – 4 of the trial experiencing any of:
1. Protocol-defined relapse
2. New or enlarged T2 lesion
3. Confirmed disability worsening (CDW)

- Do NOT maintain NEDA-3

ECTRIMS 2025

Svenningsson et al. ECTRIMS 2025

2° Endpoints: NEDA components years 2 – 4



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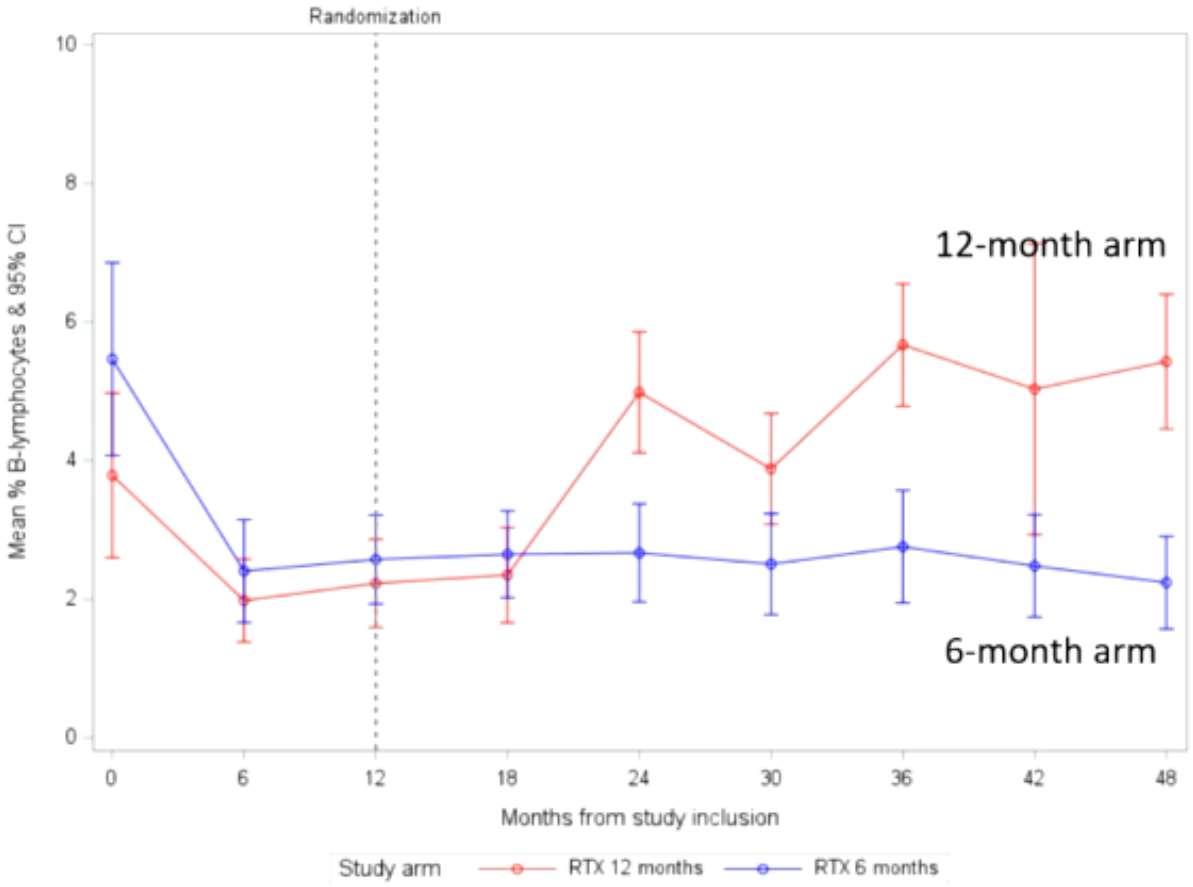
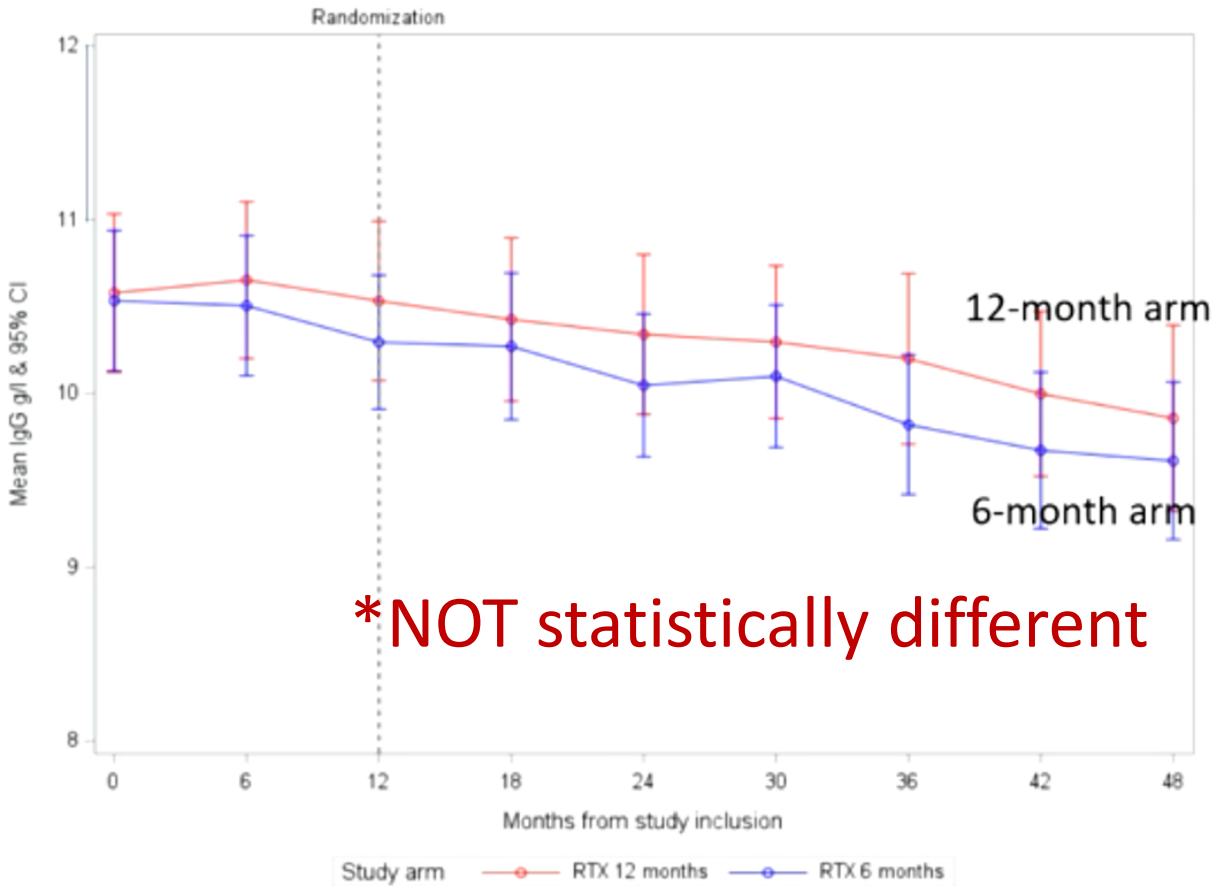
B-Cells



IgG



*NOT statistically different

ECTRIMS 2025

Svenningsson et al. ECTRIMS 2025

NO improvement in infection with EID

	6-month arm	12-month arm
Overall reported AE	379	380
Overall SAE	25	22
Overall infections	152	190
Severe infections	8	11
10 or more infections	1	4

ECTRIMS 2025

Svenningsson et al. ECTRIMS 2025

Review > Mult Scler Relat Disord. 2025 Aug 8:103:106668. doi: 10.1016/j.msard.2025.106668.
Online ahead of print.

Efficacy of alternative vs. standard dosing strategies of anti-CD20 monoclonal antibodies in multiple sclerosis: A systematic review and meta-analysis

Ida Mohammadi [1], Shahryar Rajai Firouzabadi [1], Sepehr Aghajanian [2], Aryan Aarabi [1], Fateme Mohammadifard [3], Samin Sadraei [1], Mohammadreza Alinejadfard [1], Masoud Etemadifar [4], Mehri Salari [5]

Recent meta-analysis review (16 studies included) suggests EID was not worse in:

- Relapse rate
- MRI activity
- Disability progression
- NEDA-3

B-Cell Therapy:

~~High dose,~~ standard dose,
delayed interval,or discontinue?

Vitamins & Supplements

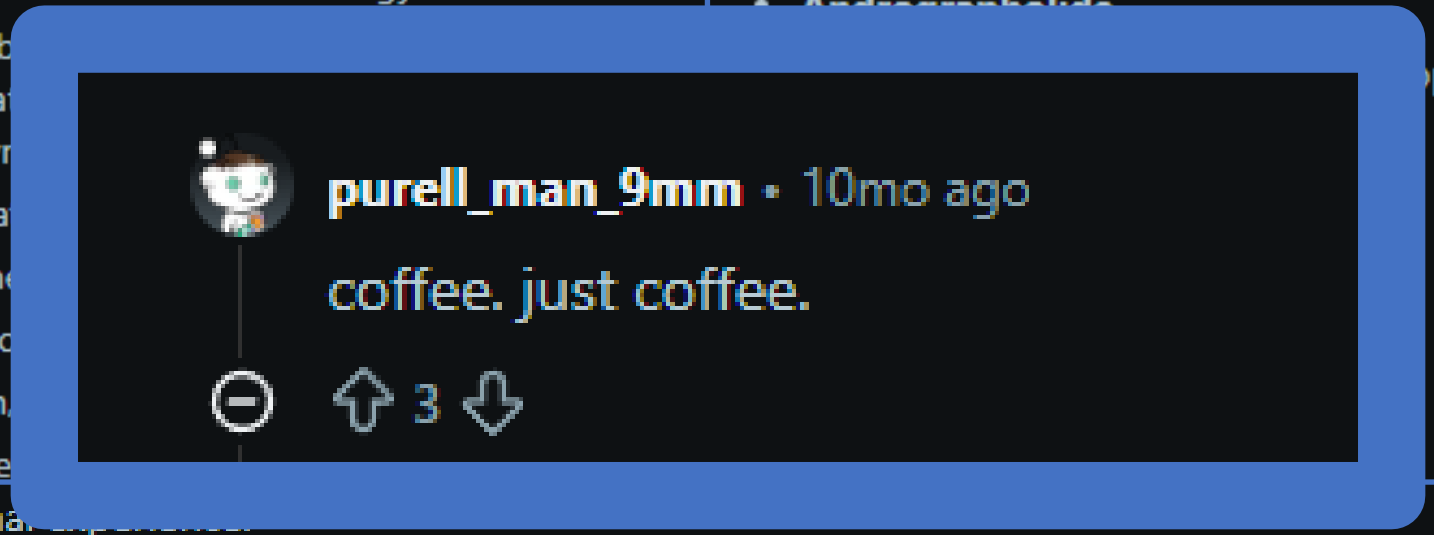
Reddit:

- **Vitamin D + K2**
- **Magnesium**
- **Fish Oil**
- **Flaxseed Oil**
- **Alpha-Lipoic Acid (ALA)**
- **Frankincense (Boswellia)**
- **Andrographolide**

The supplements I take and what they're for:

1. Vitamin B12 – Nerve health, reduces fatigue, cognitive support.
2. Astaxanthin – Powerful antioxidant, reduces inflammation, protects nerve
3. Vitamin D + K2 – Immune modulation, mood & energy.
4. Ashwagandha – Stress relief, b
   immune system and exacerba
   people reported worsened syr
5. NAC – Antioxidant, reduces fa
6. CoQ10 – Reduces fatigue & h
7. Magnesium Glycinate – Reduc
8. Candida Support – Gut health
9. Flaxseed Oil – brain and nerve

pper for better absorption)



From my persona

- Vitamin D 50,000 IU — Monthly
- B Complex — Daily
- Magnesium 250 mg — Daily for sleep hygiene
- Biotin — Every two days — For energy (You have to take a break for about two weeks to a month, as it caused acne on my face 😛)

Supplements are safe, right?

- **NOT FDA-Approved!!!**
- "**Natural" ≠ Safe**
- May interact with your Rx
- Supposed to adhere to Current Good Manufacturing Practices (CGMP)
  - Look for 3rd party testing (**USP**, NSF, Banned Substances Control Group, ConsumerLab)

Sketchy Supplements

Supplements pulled from the market for various hidden ingredients:

- Steroids
- Weight loss medications pulled from the market by FDA for safety
- Rx erectile dysfunction medications

Table. Pharmaceutical Adulterants Identified in Recalled Dietary Supplements Purchased at Least 8 Months After US Food and Drug Administration (FDA) Recalls

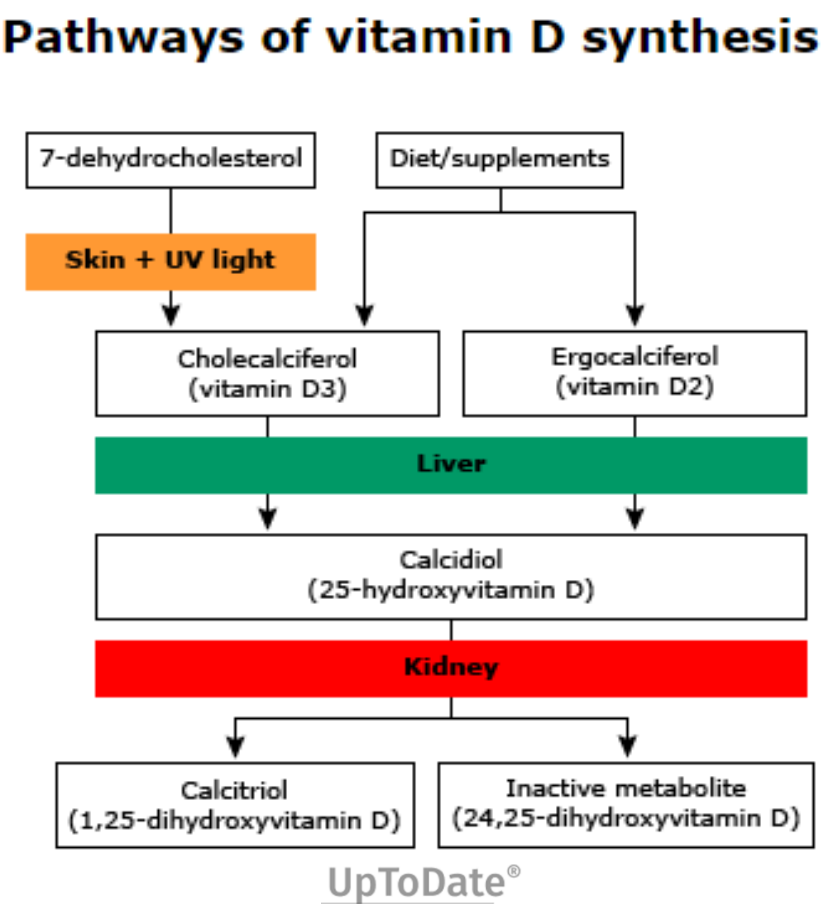
Recalled Supplement	Date of FDA Recall[a,b]	Date Purchased	Expiration Date on Purchased Supplement	Adulterant Found by FDA[a,c]	Adulterant Found After FDA Recall[c]
2a, 17a Methastadrol	November 3, 2009	August 2013	January 2014	Steroid or steroid-like compound or analog	Anabolic steroid
4-ad	September 16, 2010	July 2013	March 2015	Aromatase inhibitor	None identified
Açai-Man Mangosteen	February 3, 2012	July 2013	Not available	Tadalafil	None identified
Botanical Slimming 100% Natural Softgel	September 2, 2011	August 2013	Not available	Sibutramine	Sibutramine
E-pol: Inslinsified	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Two anabolic steroids
Everlax capsules	February 3 and 22, 2012	July 2013	Not available	Sibutramine	None identified
EverSlim	February 3, 2012	July 2013	January 2018	Sibutramine	Fluoxetine, sibutramine
Finaflex 550-XD	November 3, 2009	August 2013	June 2014	Steroid or steroid-like compound or analog	Two anabolic steroids
Forged Extreme Mass	November 3, 2009	August 2013	November 2011	Steroid or steroid-like compound or analog	Anabolic steroid
Joyful Slim	July 22, 2010	July 2013	December 2013	Desmethylsibutramine (an analog of sibutramine)	None identified
M-Drol	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Anabolic steroid
Magic Power Coffee	June 25, 2010	August 2013	February 2015	Hydroxythiohomosildenafil (an analog of sildenafil)	Sildenafil
Massdrol	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Anabolic steroid
Mince Belle	February 3, 2012	July 2013	Not available	Sibutramine	Fluoxetine, N-didesmethyl sibutramine (an analog of sibutramine)
Novedex XT	January 15 and October 7, 2010	July 2013	July 2013	Aromatase inhibitor and steroid or steroid-like compound or analog	Aromatase inhibitor and an anabolic steroid
On Cycle II Hardcore	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Two anabolic steroids
P-Plex	November 3, 2009, and January 15, 2010	August 2013	October 2012	Steroid or steroid-like compound or analog	Anabolic steroid impurities
Pandora: Sexual Enhancer for Women	December 23, 2010	July 2013	October 2013	Analog of sildenafil	None identified
RockHard Weekend	November 9, 2009, and December 22, 2010	July 2013	March 2014	Sulfoaildenafil (an analog of sildenafil)	None identified
Testra-flex	January 15, 2010	July 2013	May 2014	Steroid or steroid-like compound or analog	Anabolic steroid
Slim-30	July 16 and August 18, 2010	July 2013	December 2015	Desmethyl sibutramine (an analog of sibutramine)	None identified
Slim Forte Slimming Capsule	July 27, 2011	July 2013	April 2018	Sibutramine	Sibutramine, phenolphthalein
Slim Xtreme Herbal Slimming Capsule	May 11, 2011	July 2013	January 2015	Sibutramine	Sibutramine, phenolphthalein, benzyl sibutramine (an analog of sibutramine)
Stamina-RX	June 15, 2009	August 2013	September 2014	Benzamidenafil (an analog of sildenafil)	None identified
Trenadrol	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Anabolic steroid
X-TREN	November 3, 2009, and January 15, 2010	August 2013	September 2014	Steroid or steroid-like compound or analog	None identified
Zi Xiu Tang Bee Pollen Capsule	October 24, 2012	July 2013	July 2015	Sibutramine	Sibutramine, phenolphthalein

Cohen PA, Maller G, DeSouza R, Neal-Kababick J. Presence of Banned Drugs in Dietary Supplements Following FDA Recalls. JAMA. 2014;312(16):1691–1693. doi:10.1001/jama.2014.10308

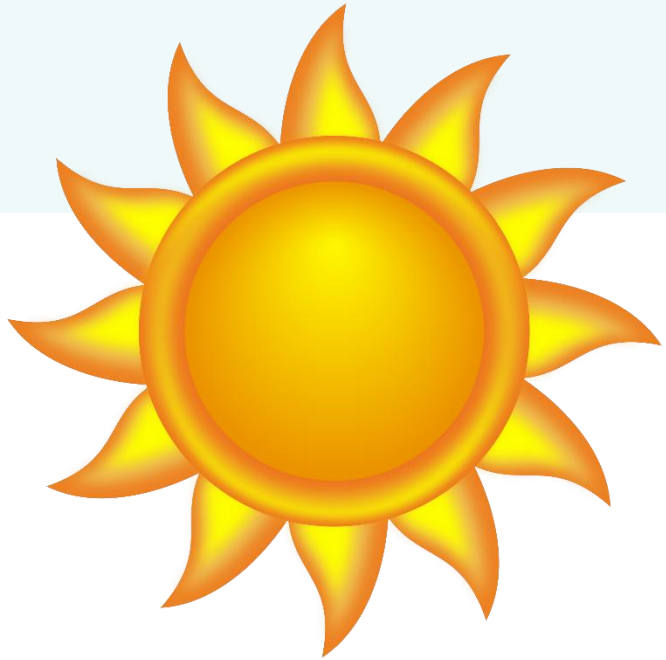
Vitamin D

- Vitamin D deficiency is a known risk factor for MS
- Vitamin D is involved in the immune system
  - Affects differentiation of B and T-cells
  - Can reduce trafficking at blood-brain barrier
  - Can reduce microglial and astrocytic activation

- Food sources:
  - Beef liver
  - Egg yolks
  - Fortified foods (milk, juices)
  - Oily fish (salmon, tuna)
  - Pork



How much is recommended?



- Recommended dose:
  - < 70: 600 IU (15mcg)
  - ≥ 70: 800 IU (20mcg)
- Reference range = 30-100 ng/mL

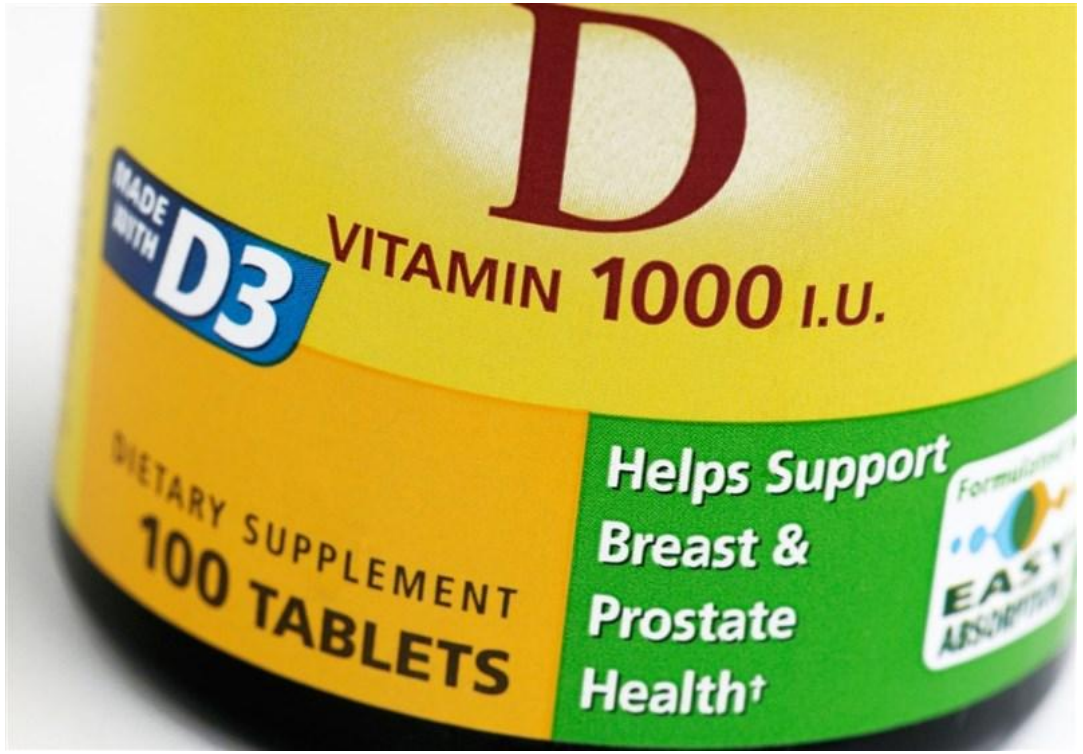
- VitD stores decline with age, especially in winter
- Malabsorption syndromes, steroids can lower VitD
- National Academy of Medicine: “Tolerable upper intake level” (UL) for Vit D if 4000 IU/day

- **BUT, many patients with MS are Vitamin D deficient and need more!!!**

Can you have too much Vitamin D?

- **Yes**, but I have never seen it!

- **Hypercalcemia**
  - Confusion
  - Excessive urination
  - Excessive thirst
  - Decreased appetite
  - Vomiting
  - Muscle weakness
  - Kidney stones
  - Irregular heart beat
  - Bone demineralization/bone pain



- "Risk" of Vit D toxicity with levels >100ng/ml in adults ingesting substantial amounts of calcium
- **Vitamin D "intoxication": >150 ng/mL**

What are the data for MS?

- Vitamin D as add-on therapy to IFN-β did NOT meet primary endpoints, but:
  - SOLAR trial found **fewer new/active lesions**
  - CHOLINE study found **reduced relapse rate, fewer T1 hypointensities, less disability progression**
- Pilot study of 30 patients w/ optic neuritis and VitD <75 nmol/L
  - 50,000 IU weekly **reduced relapse and MRI activity**
- PREVANZ Trial: Placebo controlled study with 204 patients with CIS testing did not show radiologic or clinical benefit at 48 weeks
  - ~50 patients in each group: placebo, 1000 IU/d, 5000 IU/d, and 10000 IU/d
- Meta-analyses without obvious effect on relapses/disability, but a trend towards reducing new lesions

D-Lay MS Trial

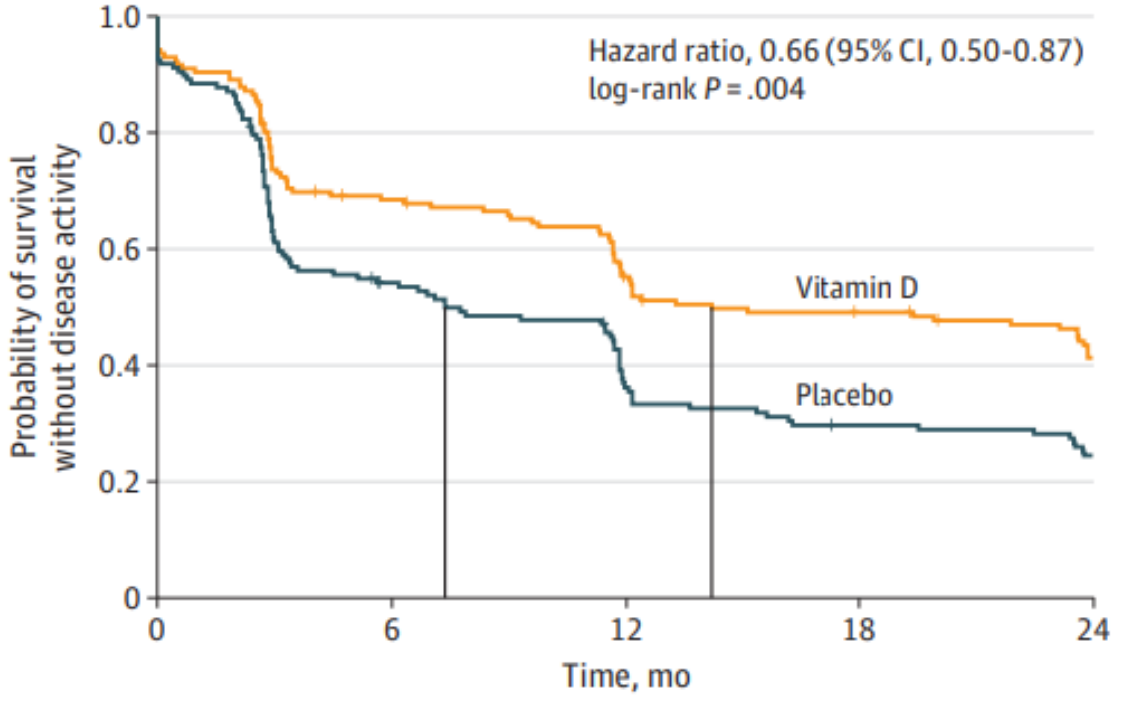
- 316 participants – CIS, ages 18-55, VitD <100 nmol/L, MRI with dissemination in space OR ≥ 2 lesions and presence of OCBs
- Randomized to 100,000 IU every other week for 24 months
- Primary outcome was relapse and/or MRI activity over 24 months of follow-up

- Disease activity seen in 60.3% of those with Vitamin D vs 74.1% in placebo group

JAMA | Original Investigation

High-Dose Vitamin D in Clinically Isolated Syndrome Typical of Multiple Sclerosis
The D-Lay MS Randomized Clinical Trial

Eric Thouvenot, MD, PhD; David Laplaud, MD, PhD; Christine Lebrun-Frenay, MD, PhD; Nathalie Derache, MD; Emmanuelle Le Page, MD; Elisabeth Maillart, MD; Caroline Froment-Tilikete, MD, PhD; Giovanni Castelnovo, MD; Olivier Casez, MD; Marc Coustans, MD; Anne-Marie Guennoc, MD; Olivier Heinzlef, MD; Laurent Magy, MD, PhD; Chantal Nifle, MD; Xavier Ayrignac, MD, PhD; Agnès Fromont, MD; Nicolas Gaillard, MD; Nathalie Caucheteux, MD; Ivania Patry, MD; Jérôme De Sèze, MD, PhD; Romain Deschamps, MD; Pierre Clavelou, MD, PhD; Damien Biotti, MD; Gilles Edan, MD, PhD; William Camu, MD, PhD; Hanane Agherbi, PhD; Dimitri Renard, MD; Christophe Demattei, PhD; Pascale Fabbro-Peray, MD, PhD; Thibault Mura, MD, PhD; Manon Rival, MD; for the D-Lay MS Investigators



No. at risk					
Vitamin D	156	104	82	71	58
Placebo	147	76	50	40	33

Polyunsaturated Fatty Acids (PUFAs)

- **Omega-3 Fatty Acids** - Found in fatty fish (salmon, mackerel, herring, sardines), fish oil products, flaxseed, walnuts
  - Some studies suggest they are anti-inflammatory and may have neurologic health benefits
  - α-linolenic acid (ALA) intake may reduce MS risk (from Nurses' Health Study)
  - Conflicting data:
    - Trial of 300 patients showed a trend toward benefit in disease progression, whereas other studies shown no improvement in clinical and MRI parameters
    - PUFA and ALA may reduce conversion from CIS to CDMS and reduce relapses (BENEFIT trial, 468 patients)
- **Omega-6 Fatty Acids** (linoleic acid) – Found in sunflower/safflower seed oil
  - Higher serum levels associated w/ lower risk of developing MS (maybe more so than Omega-3)
  - Conflicting studies, some suggest slower progression of disability

- *May interact with anticoagulants, diabetes/blood pressure supplements*
- *May need to supplement with Vitamin E (to protect PUFAs)*

Alpha Lipoic Acid (600mg BID)

- Important for mitochondrial function/making energy, acts as an antioxidant, may help prevent T-cells from entering CNS, beneficial in EAE mouse model
- Data:
  - Phase 2 study in SPMS (n=27) found less brain atrophy in patients with MS
  - Phase 2 study (RMS/SPMS, n=54) ***NO*** improvement in cognition
  - Meta-analysis showed possible reduction in EDSS
  - May be useful w/ neuropathy (at least diabetic neuropathy)
- *Side effects: GI symptoms, rash, headache, low blood sugar, interaction with other meds*

CoQ10 (500mg/d)

- Antioxidant, present in mitochondria, important in creating energy
- Studies (with small samples sizes):
  - Reduction in inflammatory markers in pwMS (TNFα, IL-6)
  - Improvement in depression, fatigue, even disability and pain
  - Some conflicting results, particularly with lower dose (200mg/d)

Biotin (Vitamin B7)

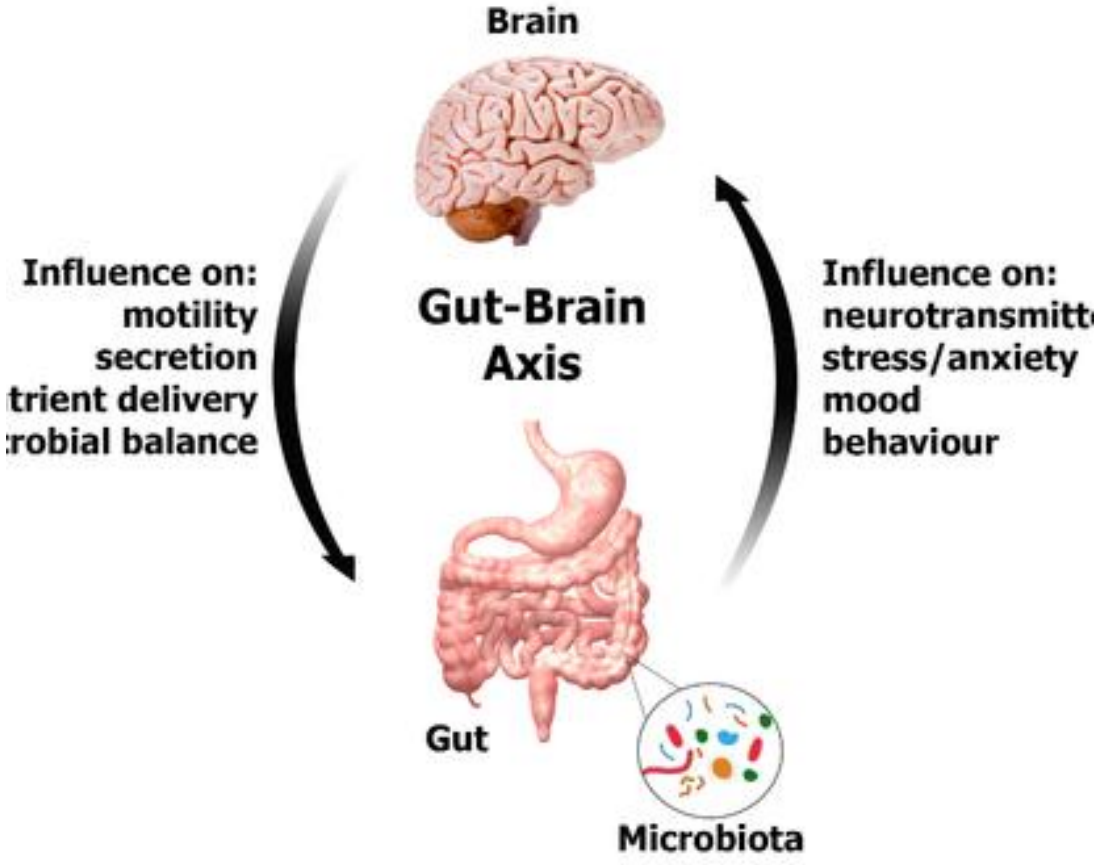
- Cofactor involved in fatty acid synthesis and energy production
- Hypothesized to promote axonal remyelination
- Initial studies promising:
  - Pilot study w/ 23 patients: some improvement in visual acuity, VEPs, improvement in exam
  - 154 patient study treated w/ 100mg 3x/d vs placebo
    - 12.6% of patients had improvement in EDSS, other treated patients had less progression

- Phase 3, double-blind, placebo-controlled study (MD1003) with 642 PPMS and SPMS patients
  - Did ***NOT*** meet its 1°endpoint of CDI
  - Walking measures, MRI measures, and NfL levels also not improved

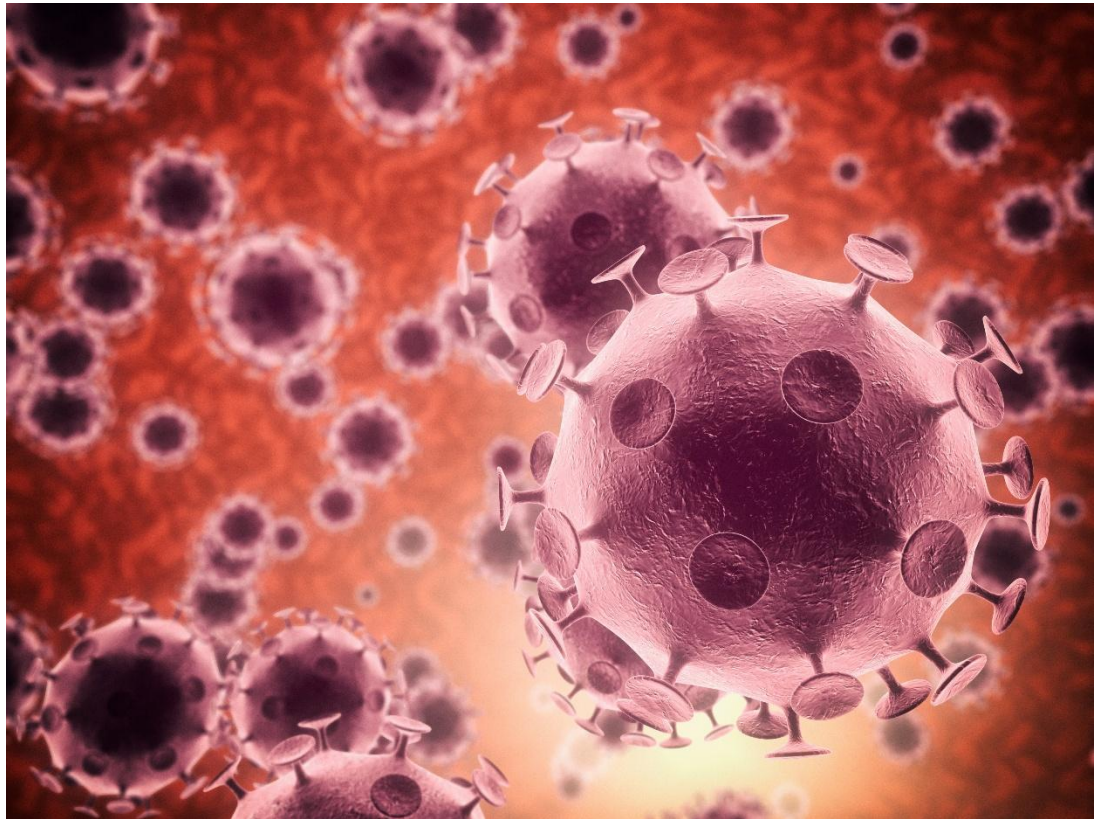
- **AND** high dose biotin can interfere with labs (troponin, TSH)

Probiotics

- Gut microbiome, immune system, and CNS connected
- Those with MS have altered gut microbiome
- Probiotics may help with mood, inflammatory markers



“Immune Boosters”



- Could potentially **exacerbate** MS

- Alfalfa
- Arnica
- **Ashwagandha** – suggested for MS fatigue and may have anti-inflammatory and antioxidant properties
- Astragalus
- Cats claw
- **Echinacea**
- Elderberry
- **Garlic**
- **Ginseng** (Asian and Siberian)
- Licorice
- Saw palmetto

Other Supplements

*May interact w/ blood thinners

- Acetyl L-carnitine (1000mg 2x/d) – amino acid, needed to turn fat into energy
  - May help with fatigue – conflicting data.
- Turmeric – anti-inflammatory/neuroprotective?
- Creatine – cognition/memory/neuroprotection?
  - Creatine metabolism dysfunctional in MS
- N-Acetylcysteine (NAC) – an antioxidant, Phase 2 trial underway (NACPMS)
  - Shown to increase glucose metabolism in brain → may improve cognition and attention, may improve anxiety symptoms
- Ginkgo biloba –May improve cognitive function in healthy people and those with dementia
  - May alleviate fatigue in MS
- Body protection compound 157 (BPC-157) – gastric peptide of amino acids, also being purported to be anti-inflammatory/neuroprotective

Other Supplements that I may recommend:

- **Magnesium** – can help with muscle cramping, constipation, sleep
  - Migraines: Magnesium oxide 400-600mg
  - Constipation: milk of magnesia/oxide/citrate/sulfate
  - Muscle cramps: Magnesium malate/citrate/glycinate/oxide/chloride
    - *Evidence is limited*
  - "Calming effect": Glycinate

- **Cranberry (& Vit C)**– may help prevent UTIs

Supplement Summary

- Vitamin D has the most data
- Others ***MAY*** reduce disease severity or help with symptoms, but data are limited
- Supplements are ***NOT*** harmless
  - St. John's Wort


Thank
You

MOVEMENT BREAK!

INTRODUCTIONS

JEAN FEDER-EWELL PT, MSPT, MSCS:

PT WITH MS SPECIALTY CERTIFICATION.
19 YEARS EXPERIENCE PRACTICING IN AN OUT PATIENT NEUROLOGICAL SETTING
6.5 YEARS AS AN MS SPECIALIST.

KERRYLEE MOORE, OTR/L :

OT WITH MORE THAN 2 YEARS OUTPATIENT EXPERIENCE TREATING PEOPLE LIVING WITH MS
THREE YEARS EXPERIENCE TREATING INPATIENT NEURO AT SPAULDING.

BENEFITS OF MOVEMENT:

- Decrease stiffness
- Helps manage fatigue
- Increase range of motion
- Manage pain
- Improve mood
- Improve sleep

TODAY'S MOVEMENT PROGRAM

- Everything can be done sitting down
- Everyone should try to take part within their ability
- Head to toe program
- Easy to do at home

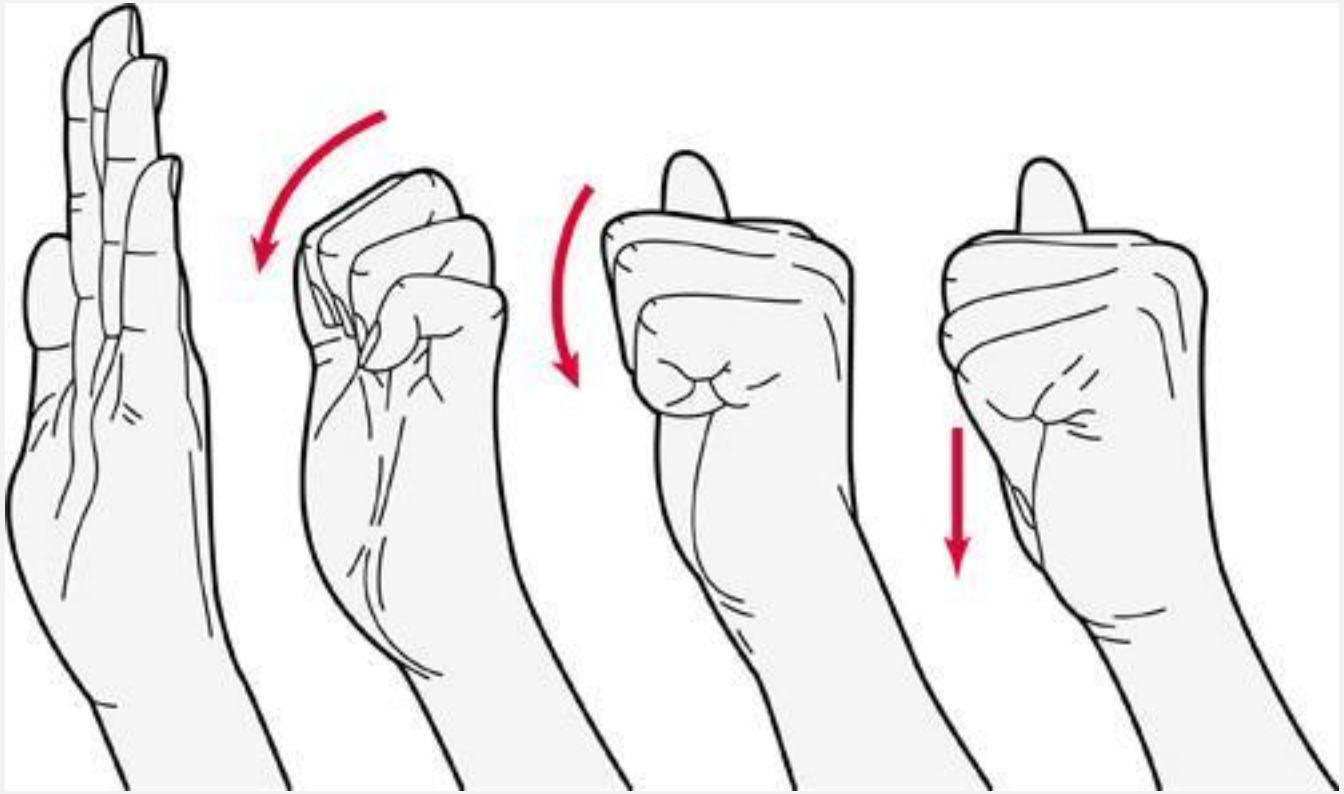
FIST OPEN/CLOSE

-Straighten fingers

All the way

-Bend fingers all the way

Repeat slowly

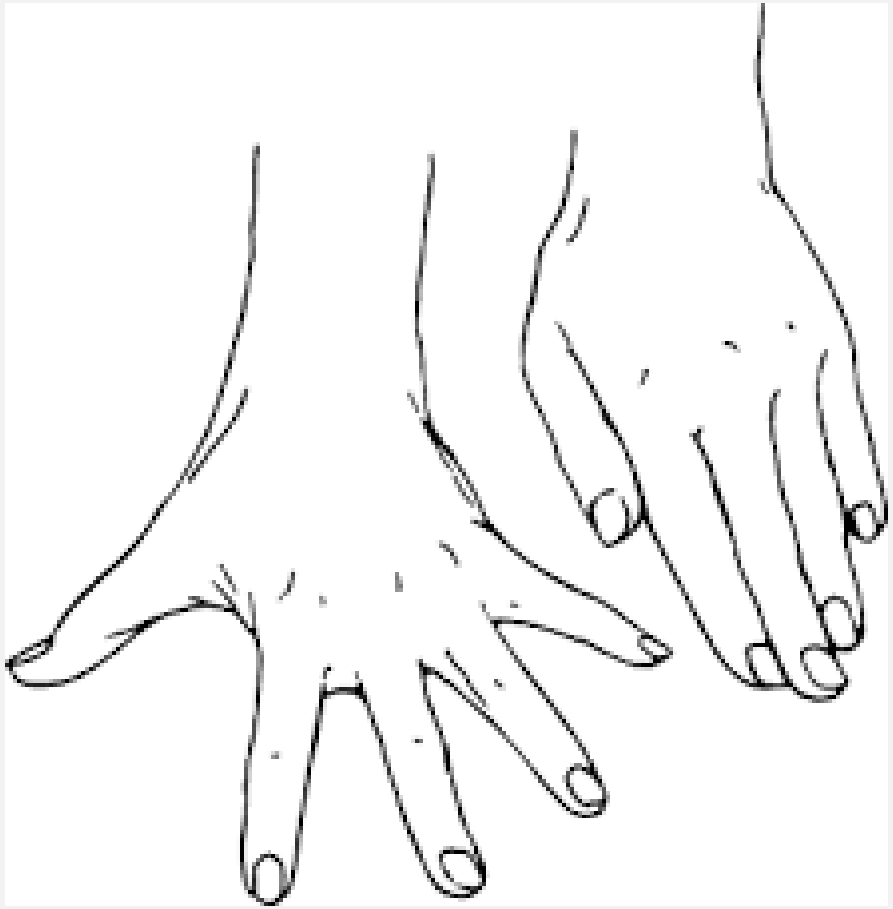


FINGER ABDUCTION/ADDUCTION

Slide fingers apart (open)

Slide fingers together (close)

Repeat slowly

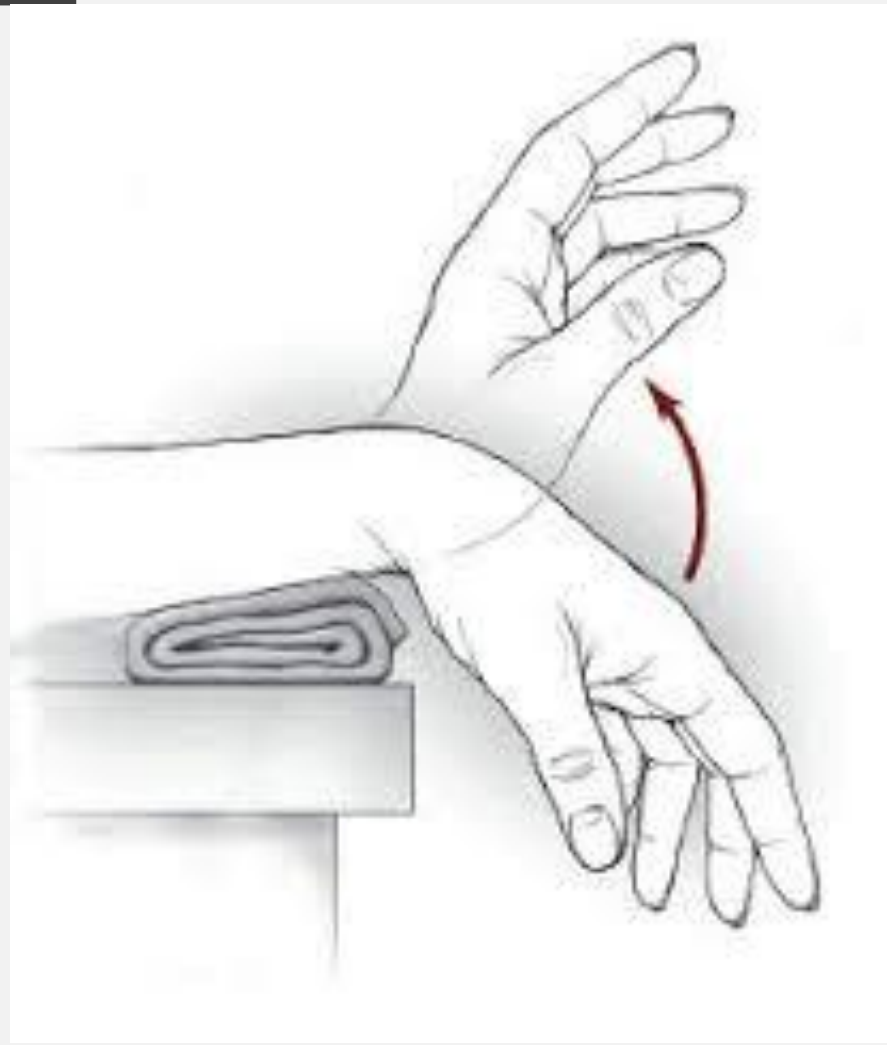


WRIST FLEXION/EXTENSION

Rest wrist on table or lap

Move wrist up slowly

Move wrist down slowly

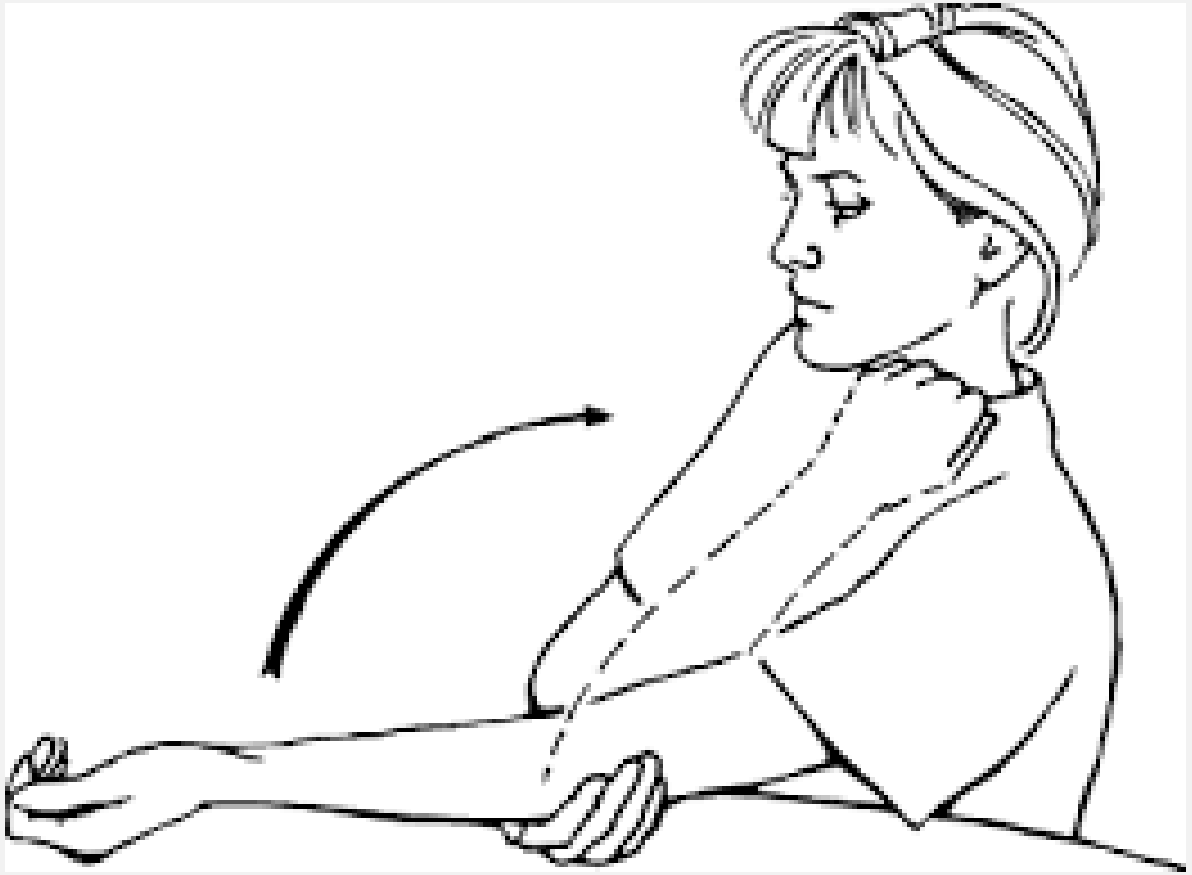


ELBOW FLEXION/EXTENSION

Rest Forearm down

Bend elbow all the way,
slowly

Straighten elbow all the way,
slowly

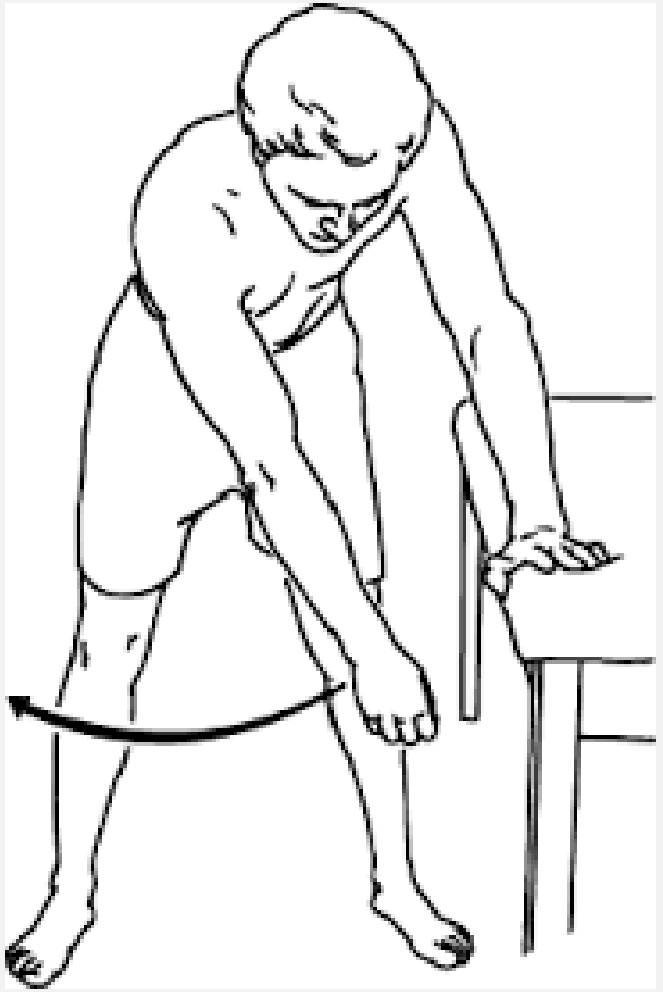


PENDULUMS

Can do sitting or standing

Lean forward and let arm dangle (dead weight)

Gently swing, side to side/front to back/ circles



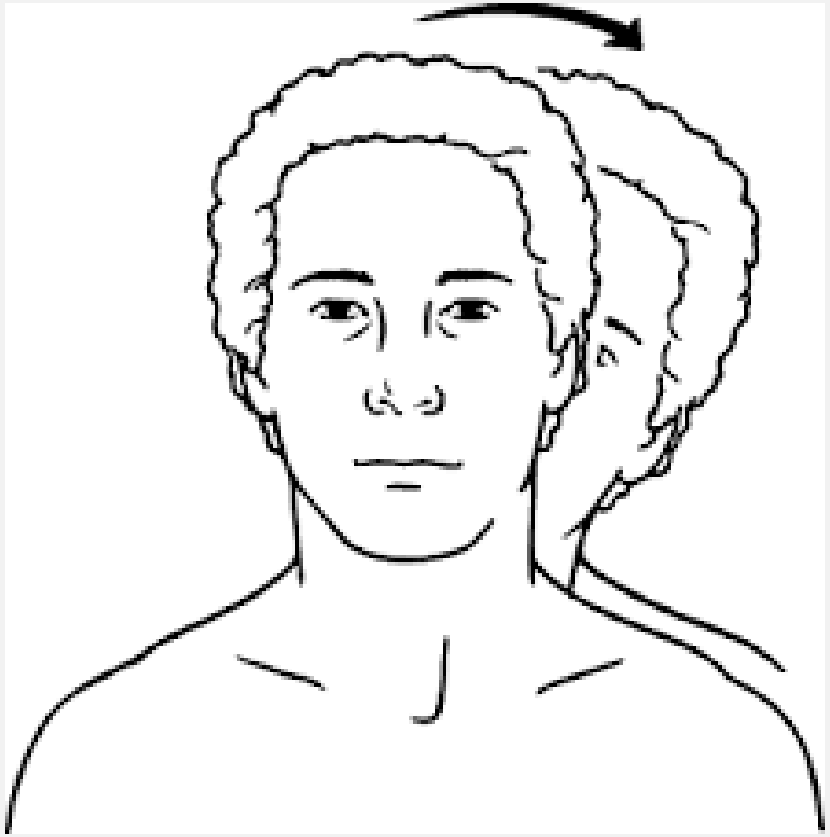
CERVICAL SIDE BEND

Sit up tall

Keep shoulders down

Slowly move head side to side (ear to shoulder)

There should be **NO** pain or dizziness

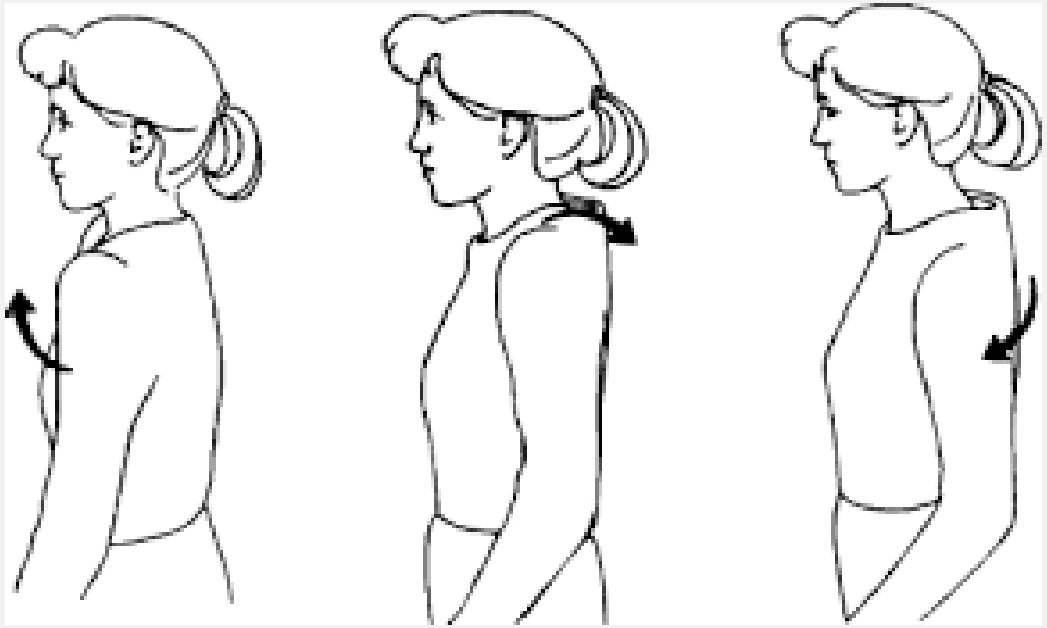


BACKWARDS SHOULDER ROLLS

Sit up tall

Pull belly button in

Gently roll shoulders backwards



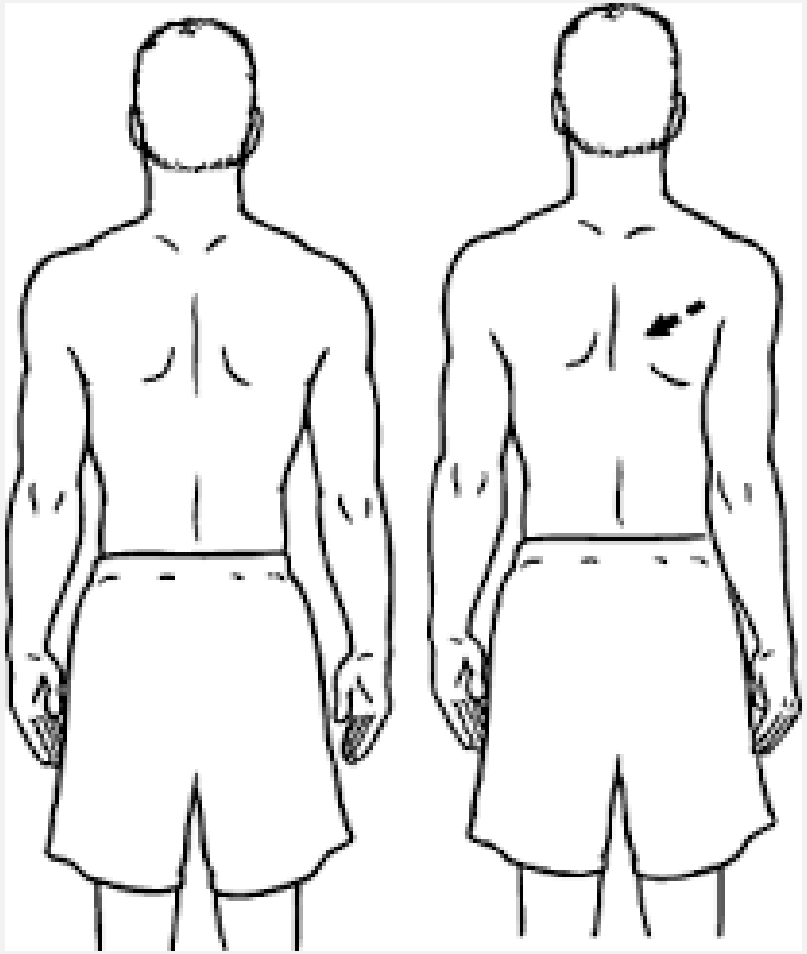
SCAPULAR RETRACTION

Sit or stand up tall

Pull belly button to spine

Pinch shoulder blades together by squeezing shoulders down and back

Slowly



UPPER TRUNK ROTATION

Sit tall in your chair

Pull belly button to spine

(do not hold breath)

Slowly rotate body with hips staying still in chair.

Repeat alternating sides

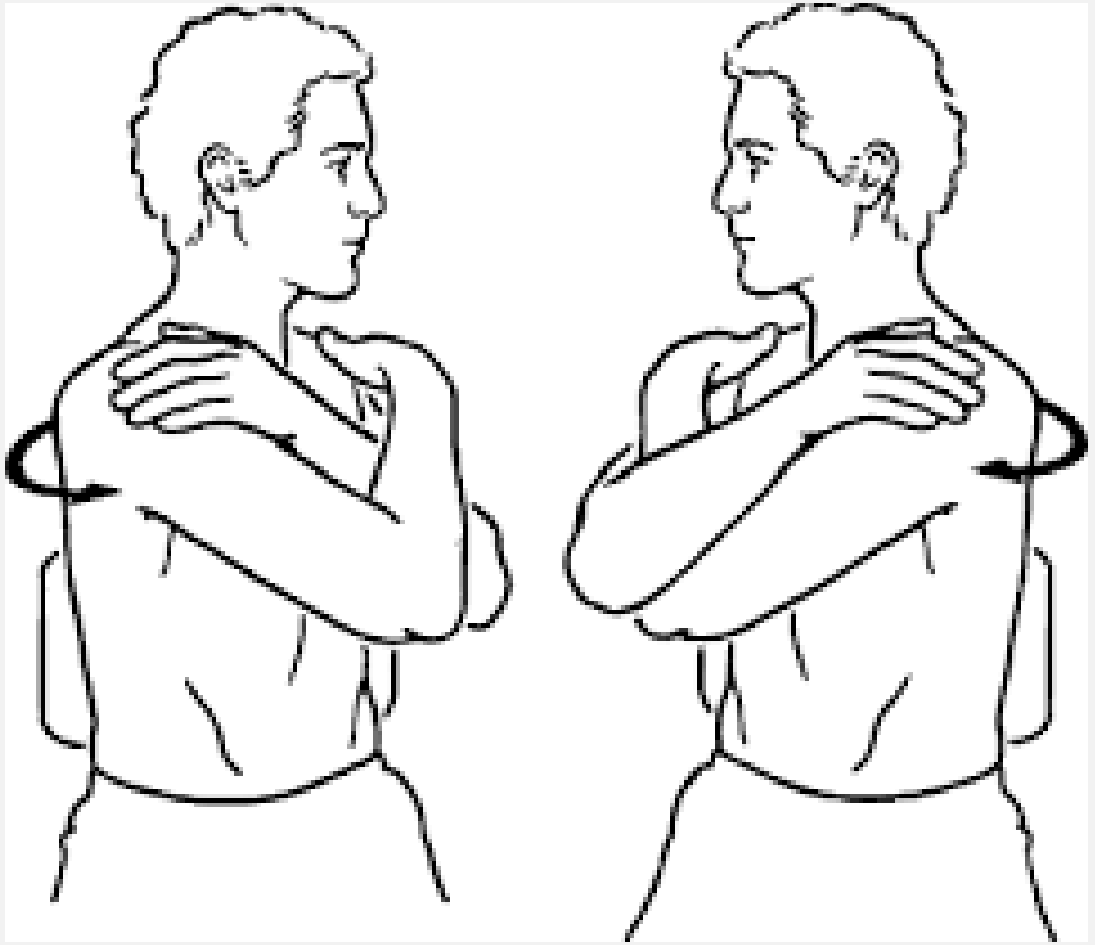
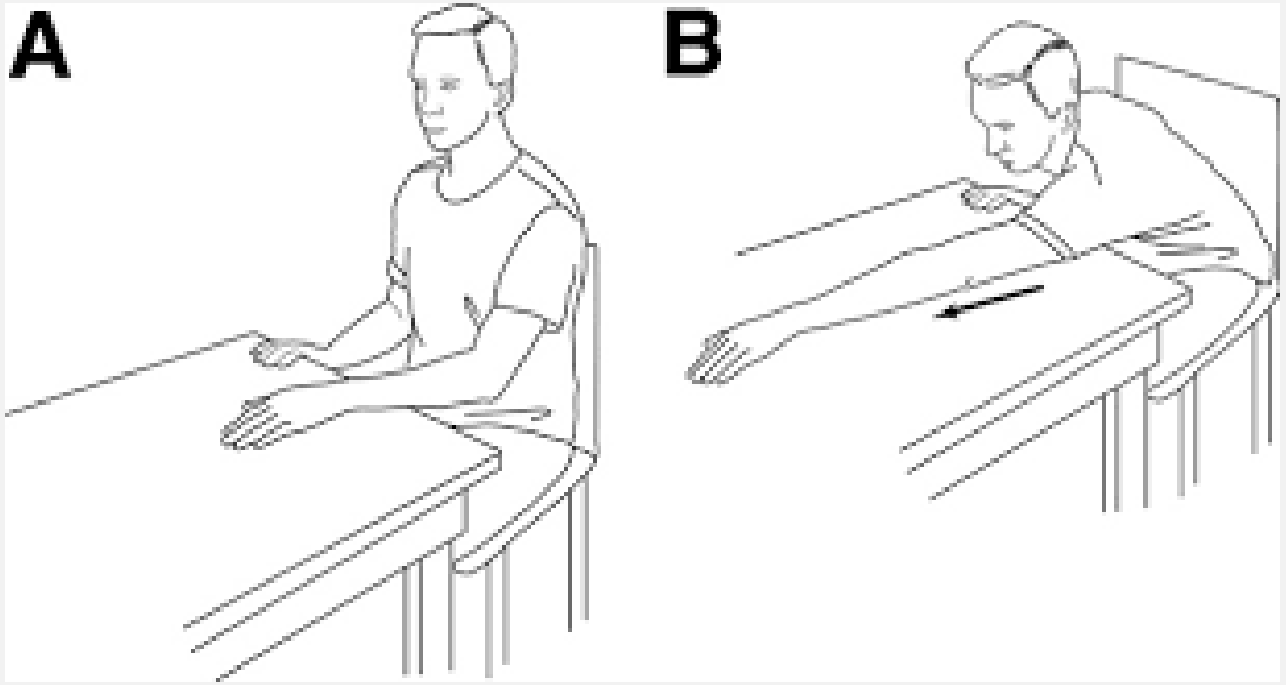


TABLE SLIDES

Sit facing the table

Put both hands resting on the table

Slide both arms forward



MARCHING

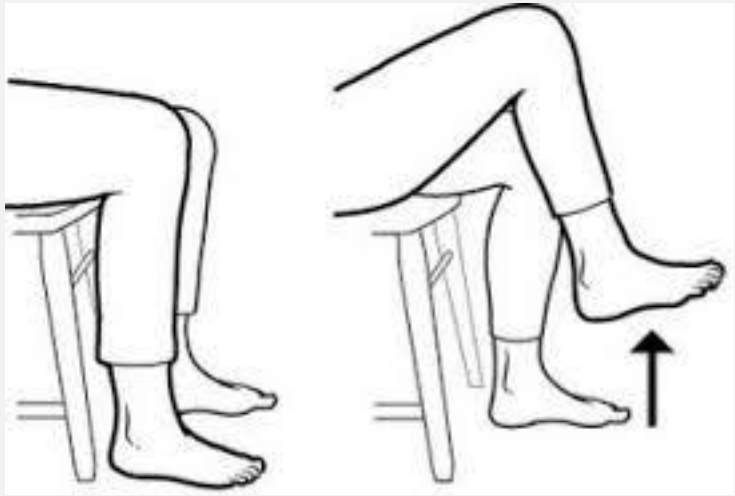
Can be done sitting or standing:

Sit or stand tall

Slowly bring on knee up

Do not let back bend down

Do not lift hip with back

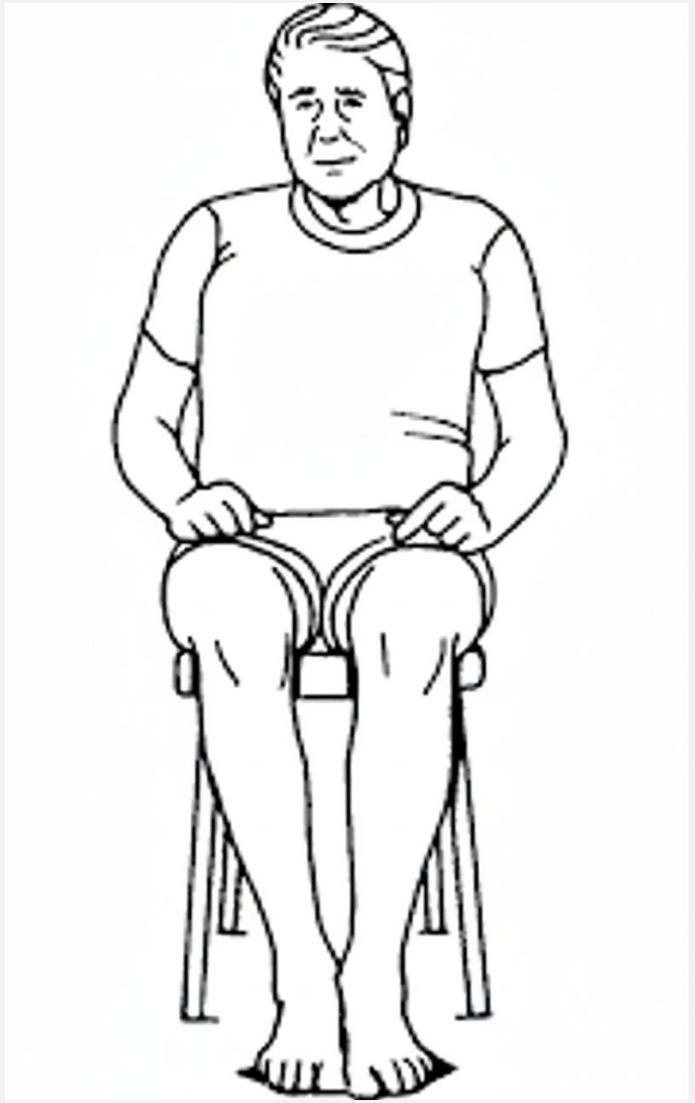


SEATED HIP ABDUCTION (BUTTERFLIES)

Sitting tall in your chair

Keep feet together and bring knees apart.

Slowly open and close your legs



LONG ARC QUAD (SEATED LEG KICKS)

Sitting back and tall in your chair

Kick leg straight out Slowly

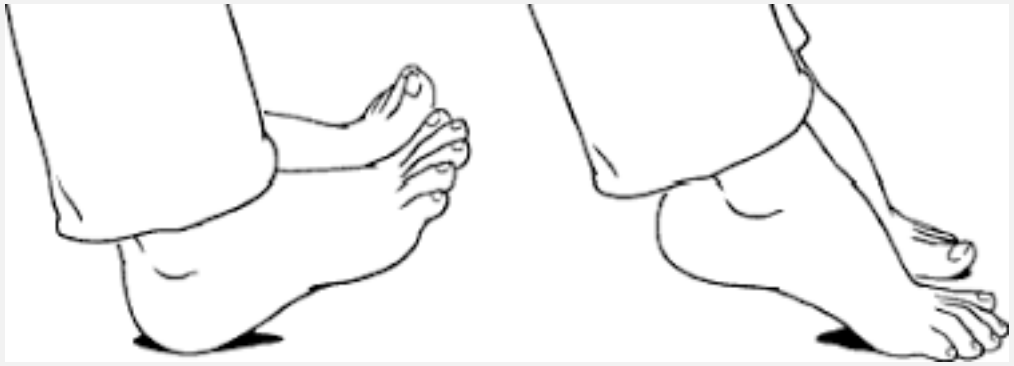
Alternate legs

ANKLE DORSIFLEXION/PLANTARFLEXION (SEATED TOE RAISES/HEEL RAISES)

Lift toes slowly

Then lift heels slowly

Alternate directions



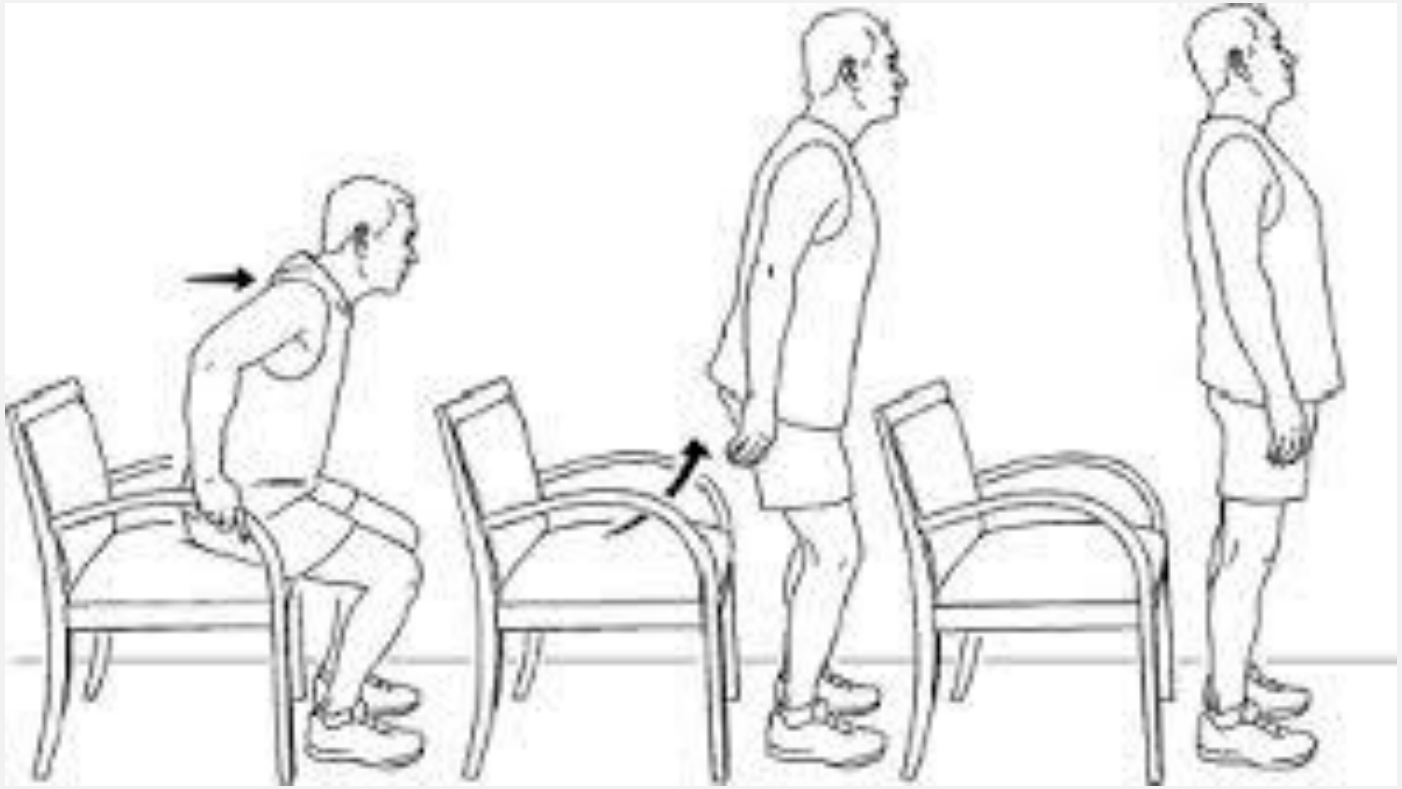
SIT TO STAND

Scoot to the front of chair

Lean forward (nose over toes)

Push forward to stand

Use hands if needed




AND NOW
BACK TO OUR
REGULARLY
SCHEDULED
PROGRAMMING


THANK


New Treatments for MS
BTK inhibitors
Frexalimab
CAR T
Vidufludimus Calcium
Foralumab

FIRST FDA APPROVED DMT 1993

expedited publication

Interferon beta-1b is effective in relapsing-remitting multiple sclerosis.

I. Clinical results of a multicenter, rand
double-blind, placebo-controlled tr

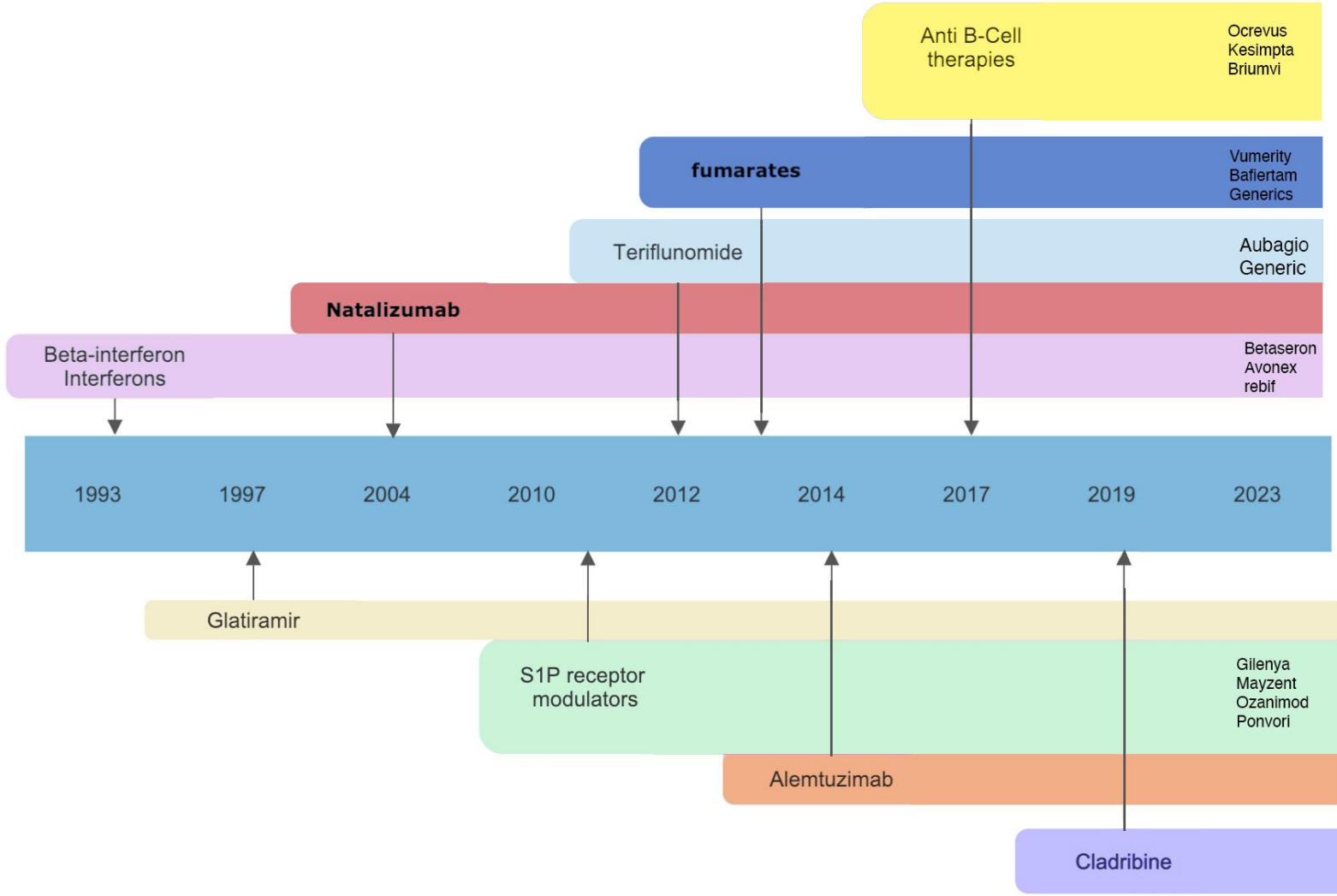
14 Mb

The IFNB Multiple Sclerosis Study Group*

Article abstract—We report a multicenter, randomized, double-blind, placebo-controlled trial of interferon beta-1b (IFNB) in 372 ambulatory patients with relapsing-remitting multiple sclerosis (MS). Entry criteria included an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 and at least two exacerbations in the previous 2 years. One-third of the patients received placebo, one-third 1.6 million international units (MIU) of IFNB, and one-third 8 MIU of IFNB, self-administered by subcutaneous injections every other day. The primary end points were differences in exacerbation rates and proportion of patients remaining exacerbation-free. The annual exacerbation rate for patients receiving placebo was 1.27; for 1.6 MIU IFNB, 1.17; and for 8 MIU IFNB, 0.84 after 2 years. Exacerbation rates were significantly lower in both treatment groups compared with the placebo group (8 MIU versus placebo, $p = 0.0001$; 1.6 MIU versus placebo, $p = 0.0101$; and 8 MIU versus 1.6 MIU, $p = 0.0086$), suggesting a dosage effect. The reduction in exacerbation severity in the 8 MIU group was attributable to a twofold reduction in the frequency of moderate and severe attacks. More patients in the 8 MIU group ($n = 36$) were exacerbation-free at 2 years compared with the placebo group ($n = 18$; $p = 0.007$). EDSS scores changed little from baseline in both the placebo and treatment arms. Accordingly, a significant change in disability could not be discerned in this trial. Finally, in serial MRIs, MS activity was significantly less in the high-dose IFNB group. IFNB treatment was well tolerated: the significant reductions in exacerbation rates, severity of exacerbations, and accumulation of MRI abnormalities occurred in the absence of serious side effects. IFNB is the only treatment that has substantially altered the natural history of MS in a properly controlled clinical trial.

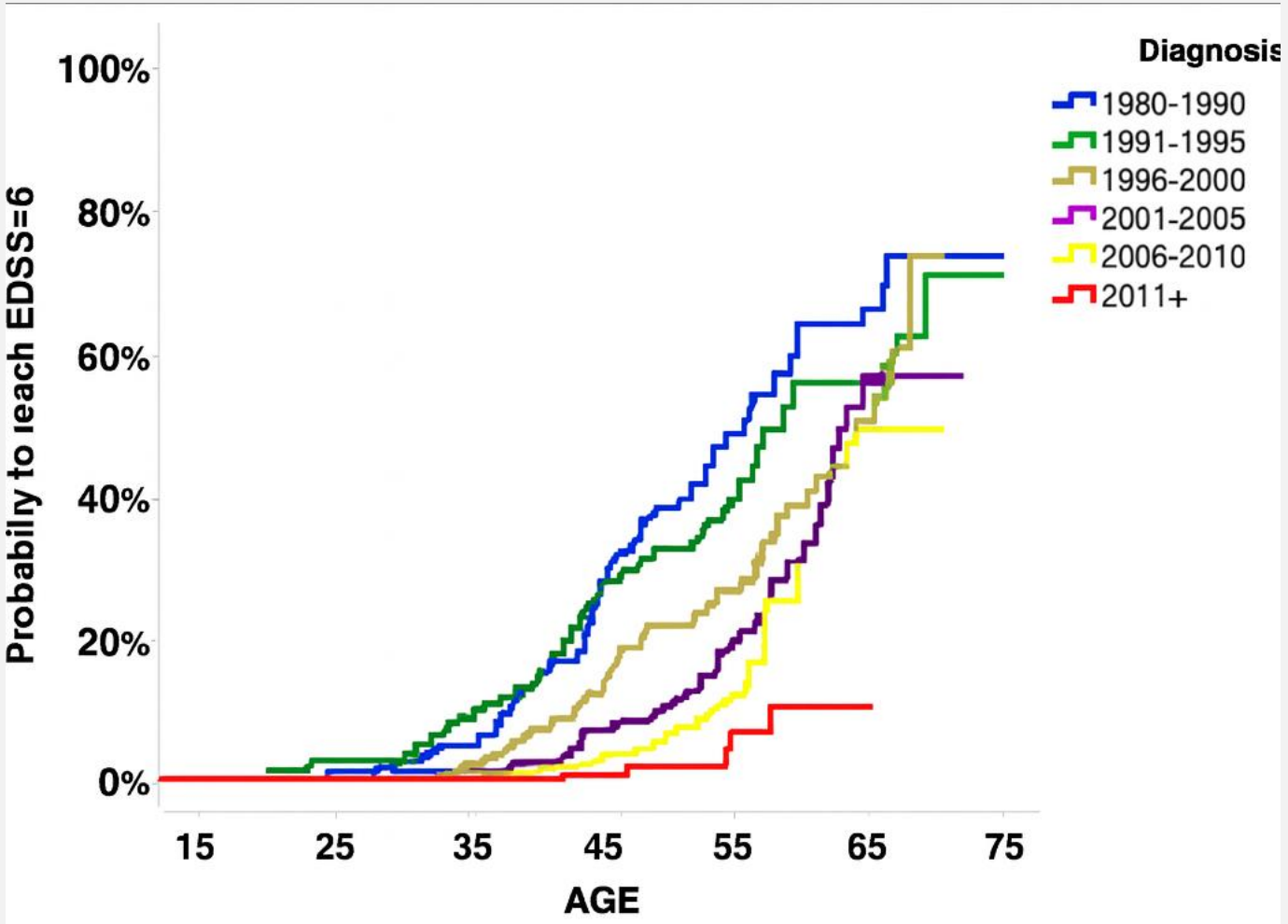
NEUROLOGY 1993;43:655-661

DEVELOPMENT OF MS DMTS



CURRENT AVAILABLE DMTS

Medication	Dosing	Efficacy	Advantage / *Disadvantage*	Common Side Effects	Rare Side Effects	Monitoring
Legacy Injectables Interferons Glatiramer	Daily to 2x per month	Low-Moderate	**Well established long-term safety** • *Requires self-injections • Medication may require refrigeration / Travel with syringes can be challenging*	**interferons:** Flu-like symptoms • Skin reactions • Depression **glatiramer:** Anaphylactoid reactions	Rare serious liver problems	Liver function test every 6 months for interferons
teriflunomide Aubagio / Generic	1 pill daily	Low-Moderate	**Very well tolerated • Gentle on immune system** • *May stay in body 2 years • requires washout procedure when switching meds*	Temporary hair thinning • Loose stools	Rash • Hypertension • Neuropathy	liver function tests ***every month*** x 6 months, then ever 6 months
fumarates Tecfidera Vumerity Bafiertam generics	1 pill twice daily	Moderate	**Minimal risk of infections • no interaction with any other medication** • *Twice daily dosing and best if taken with food*	Upset stomach & flushing	Persistent low lymphocyte count • (PML ***extremely*** **rare** in people with a persistently low lymphocyte count)	WBC, LFTs every 6 months,
S1Ps Gilenya Mayzent Zeposia Ponvory fingolimod	1 pill daily	Moderate	**Once a day • generally no noticeable side effects** • *Require cardiac screening • May interfere with vaccines • Gilenya has 6-hour first dose observation • Mayzent requires liver genotype testing • Risk of rebound if stopped • Most require titration*	Mild increased risk of respiratory infections and shingles • Can worsen migraines	PML • Cryptococcal (fungal) meningitis • Hypertension • Retinal edema	WBC, LFTs every 6 months, OCT retinal scan at baseline (and after 3-4 months with Gilenya and Mayzent)
Mavenclad cladribine	Dosed by weight: 8-10 days a year x 2 years	Moderate-High	**Well tolerated • Extended time off medicine between and after dosing** • Warning about malignancy risk • May effect vaccines	Mild fatigue after dosing • Transient low lymphocyte count	Prolonged low white cell count (lymphopenia)	WBC 1 month after your 2 monthly cycles and before 2nd dose
Tysabri natalizumab	IV 1-2 hours every 4 weeks (4-8 wks if JCV +	High	**Extremely well tolerated • Frequent contact with your doctor** • *Risk of rebound when stopping*	Occasional pre-dose fatigue	Herpes infections • *PML if JCV Positive*	JCV index every 3 months
Anti B-cell Therapies Ocrevus* Briumvi	IV: every 6 Months	High	**Well tolerated, infrequent treatments • Trial showing effect on primary progressive MS*** • *Given with low dose of steroids and antihisamine*	**Mild increased risk of common infections** • Can reduce effectiveness of vaccinations	Tiny risk of PML • Low antibody levels over time • Label has warning about possible risk of breast cancer*	CBC, B-cell count, Immunoglobulin levels every 6 months
Kesimpta	Sub Q Injection 1x month	High	**Administered at home**			
Lemtrada alemtuzimab	8-hour IV 5 days in a row, next year 3 days in a row	High	**Potential for disease control in ~50% for 7+ years after only 2 treatments** • *Monthly blood and urine tests REQUIRED for 4 years after last dose • Treatment with acyclovir for 2 -10 months*	Thyroid disorders 40% Fatigue and malaise for 7 days or more after infusion.	Delayed serious autoimmune disorders	Monthly CBC, thyroid, kidney function, urinalysis for at least 4 years after last dose



number at risk

1980-1990	95	87	59	41	31
1991-1995	113	101	67	24	5
1996-2000	237	217	130	52	7
2001-2005	277	244	133	52	10
2006-2010	324	239	120	42	4
2011+	241	157	97	22	0

SO WHY DO WE NEED NEW DMTS?

We need treatments for progressive MS

For relapsing MS

- Not everyone responds to our current treatments
- Side effects can limit options
  - JCV positive or allergic to Tysabri
  - Immunosuppression, hypogammaglobulinemia, frequent infections, colitis with anti-B cell

Treatments that repair damage and restore function

WHY DON'T OUR CURRENT TREATMENTS WORK WELL FOR PROGRESSIVE MS?

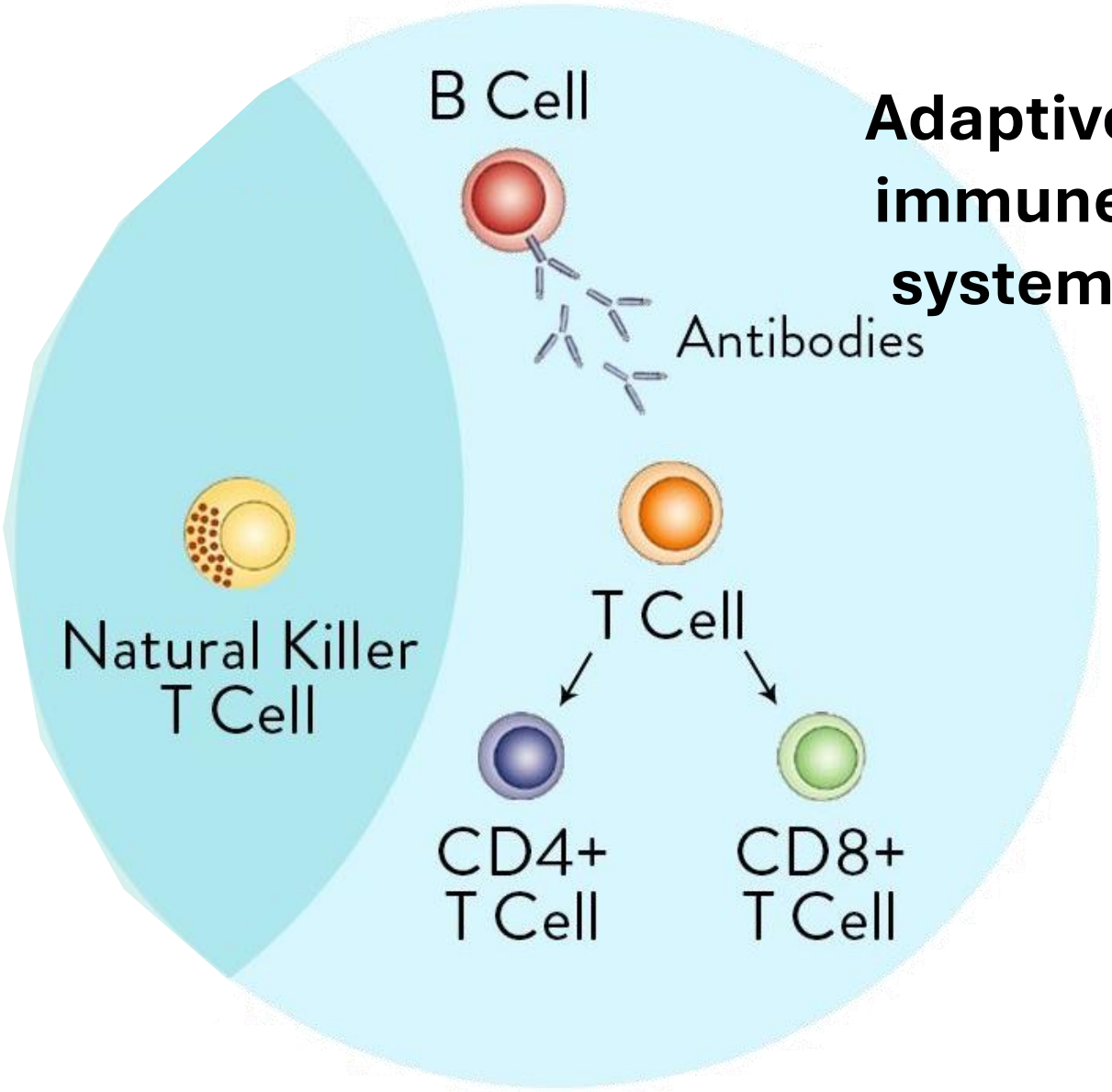
3 MAIN REASONS

Chronic inflammation drives disability progression

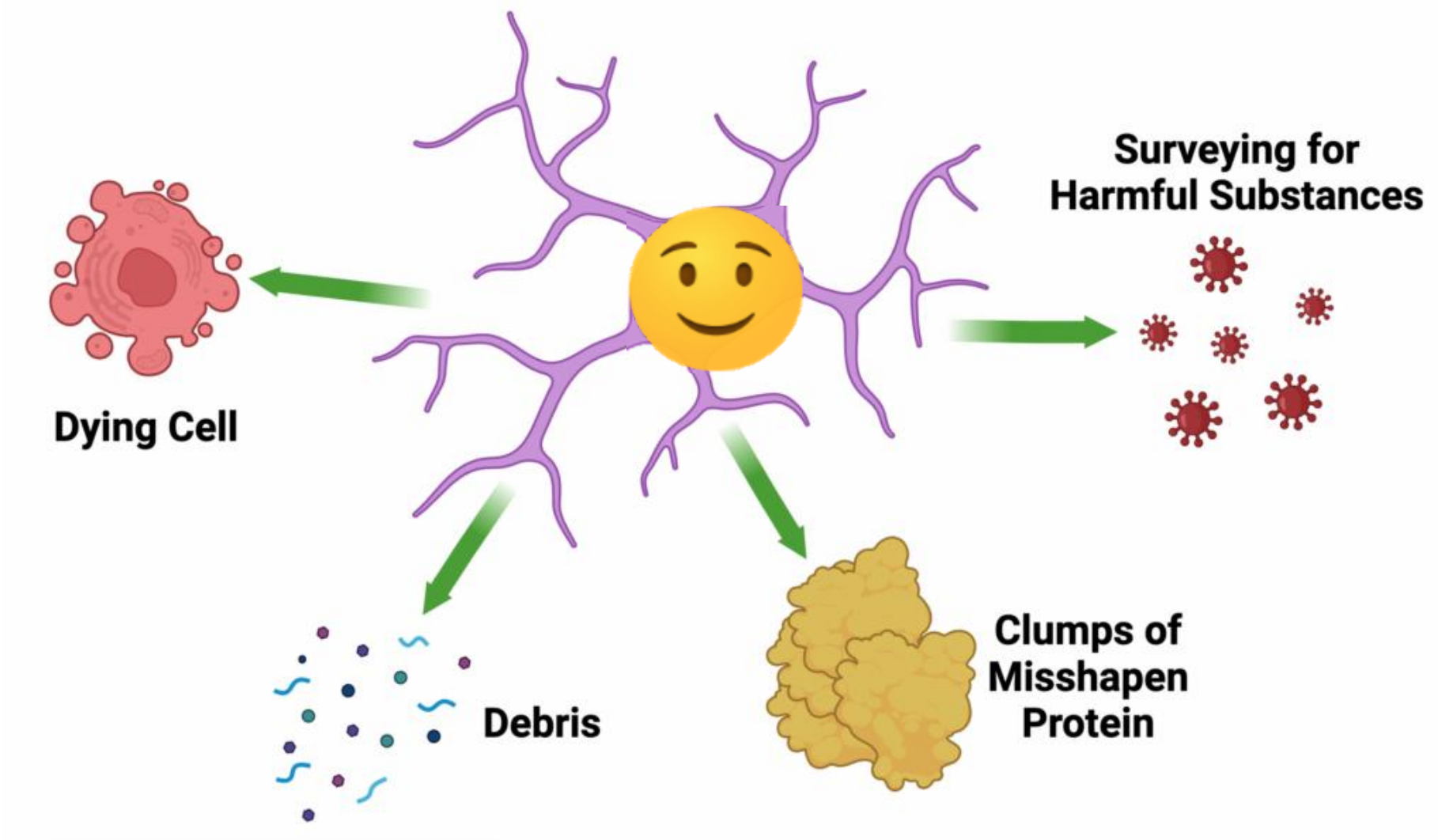
Innate immune system

Adaptive immune system

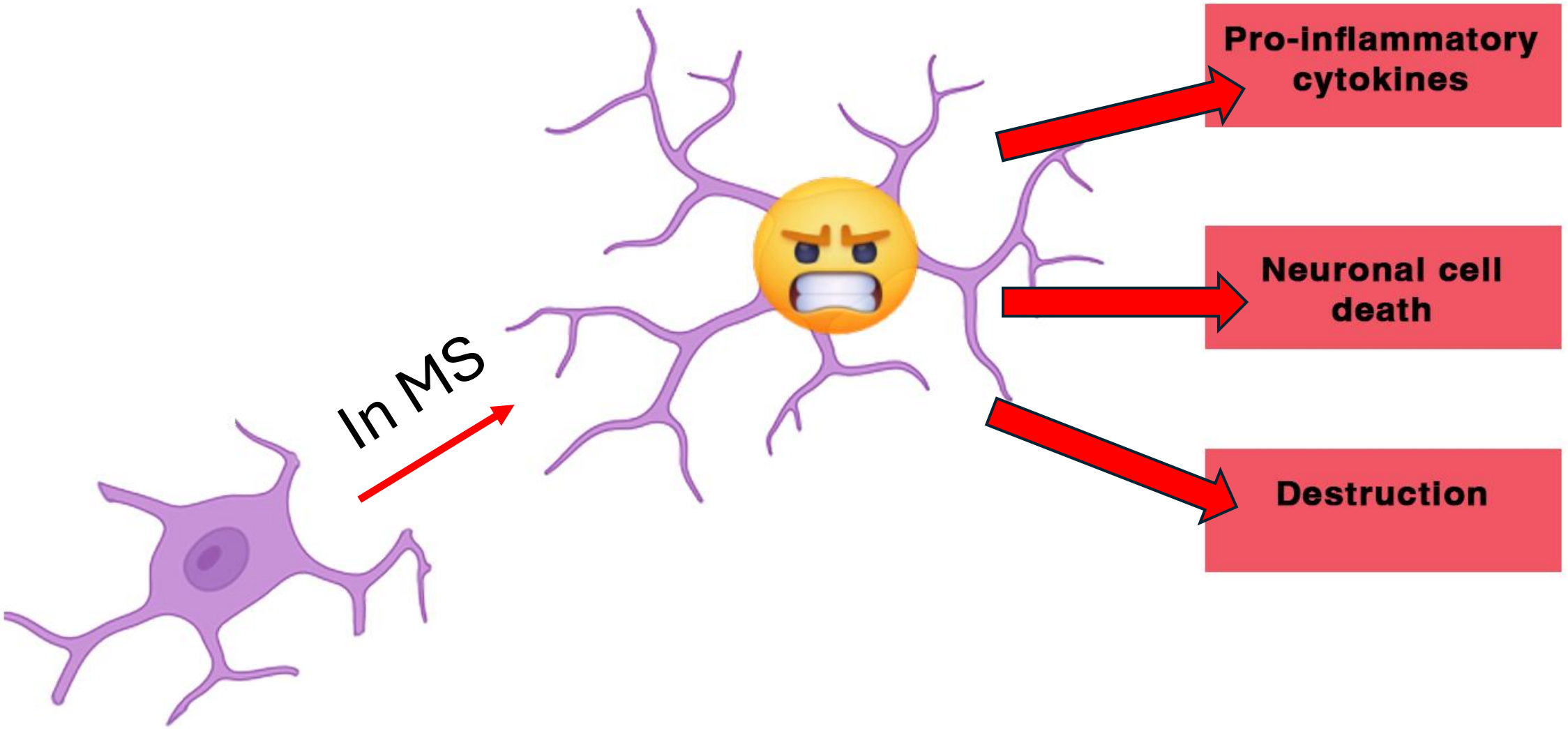
Current DMTs almost exclusively affect the adaptive immune system



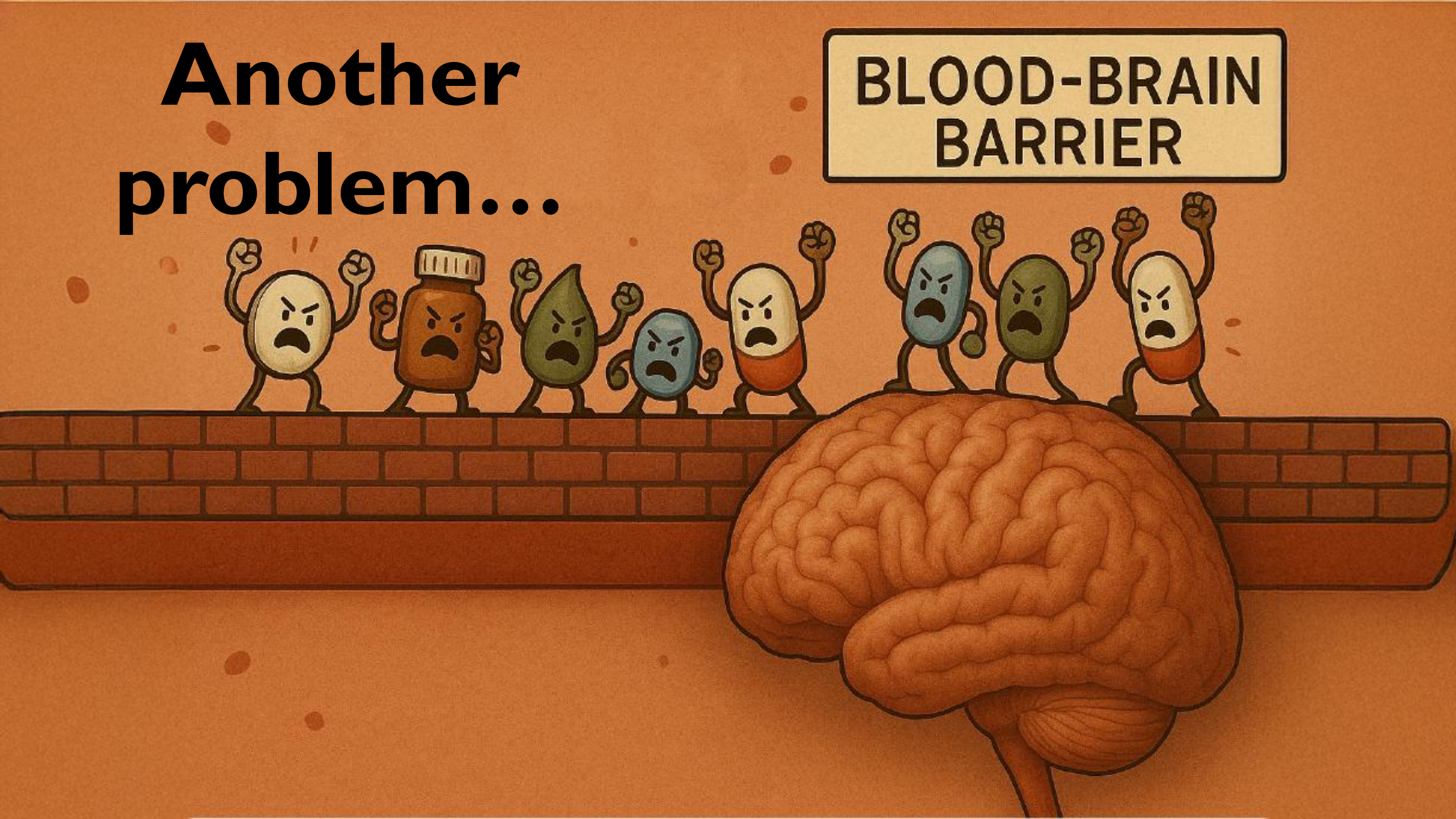
Microglia: Innate immune cells of the CNS
Maintenance workers



Current DMTs don’t impact microglia



Another problem…

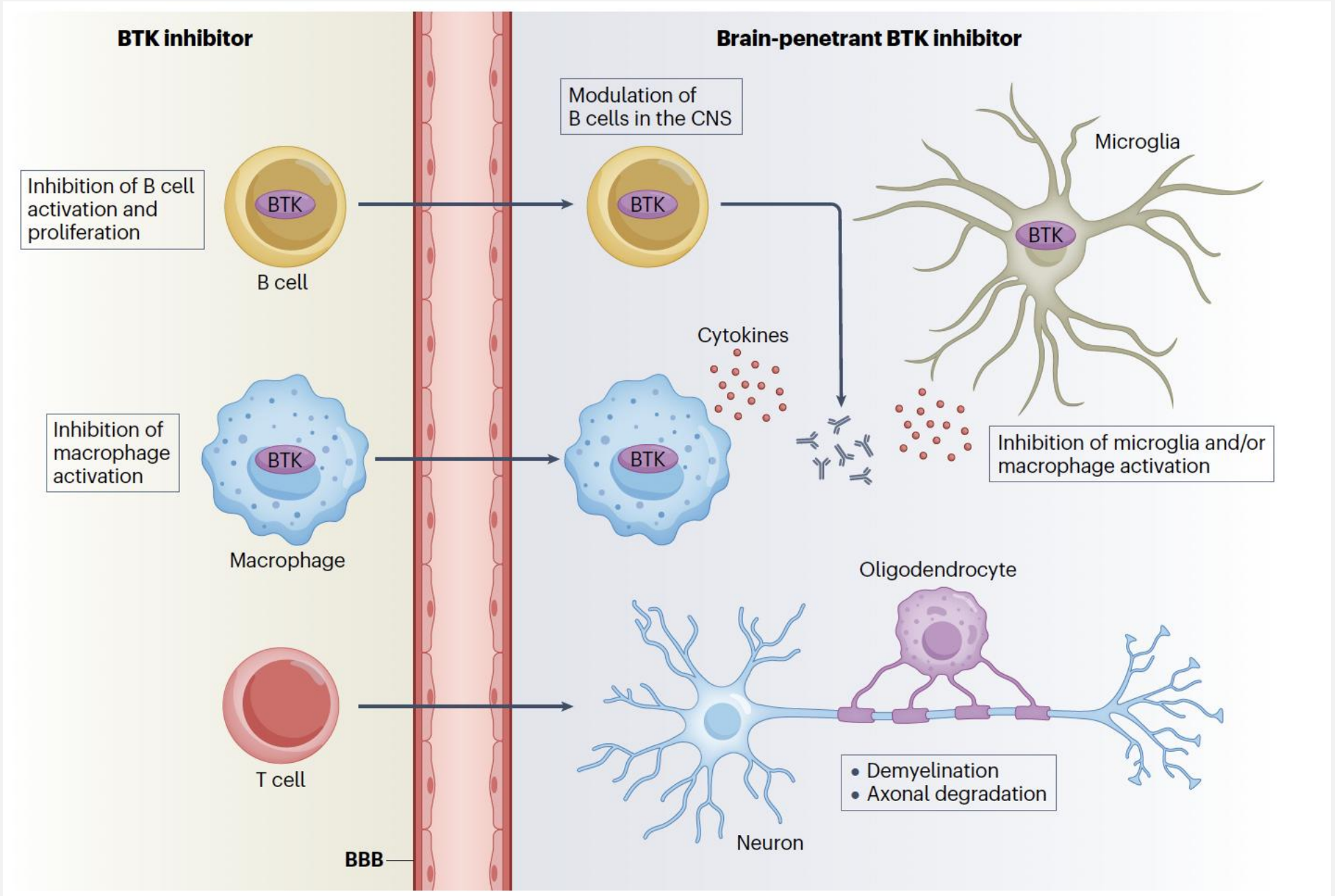


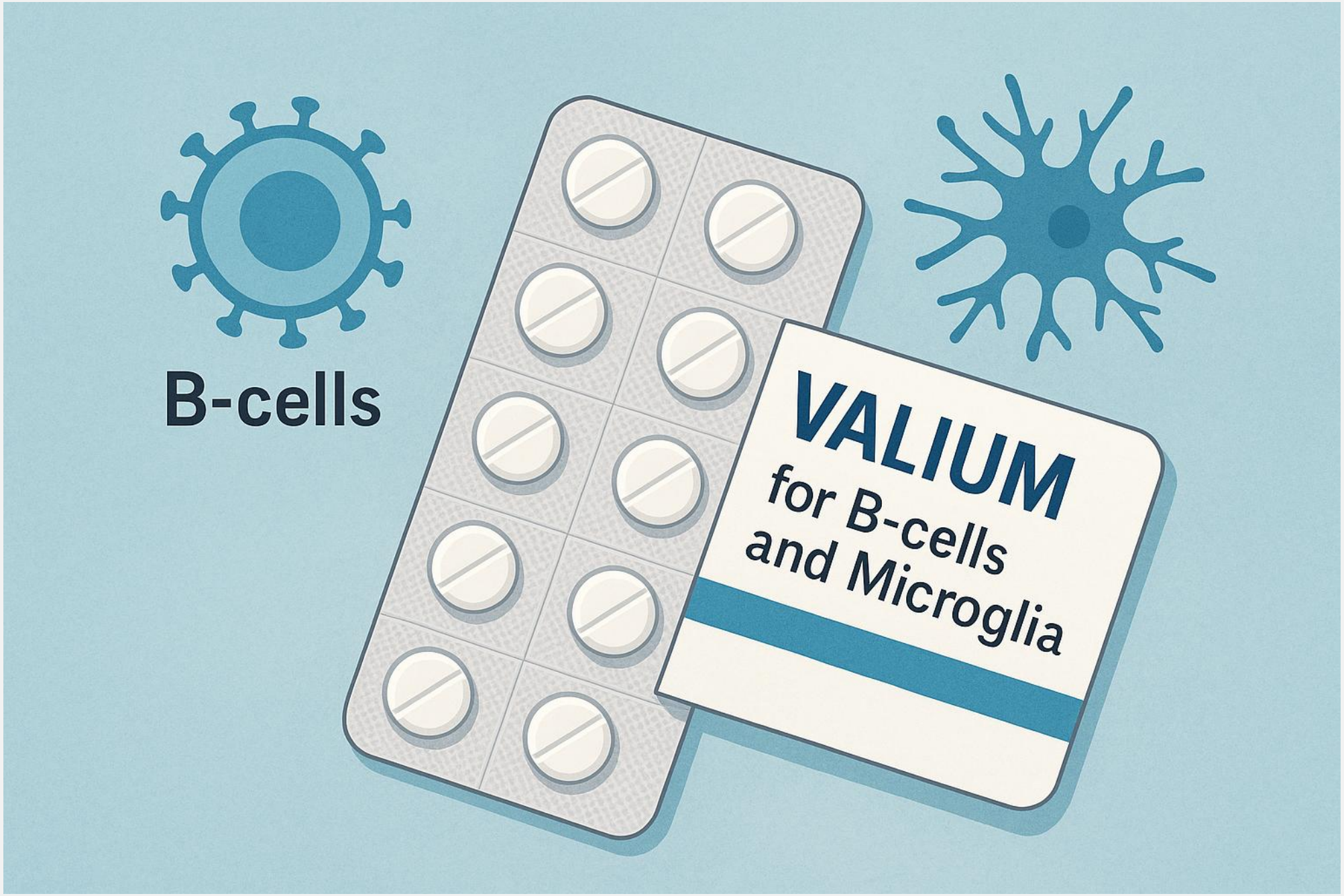
NEW TREATMENTS

- BTKs
- Frexalimab
- CAR T
- Foralumab
- Vidofludimus Calcium
- Pipe 307

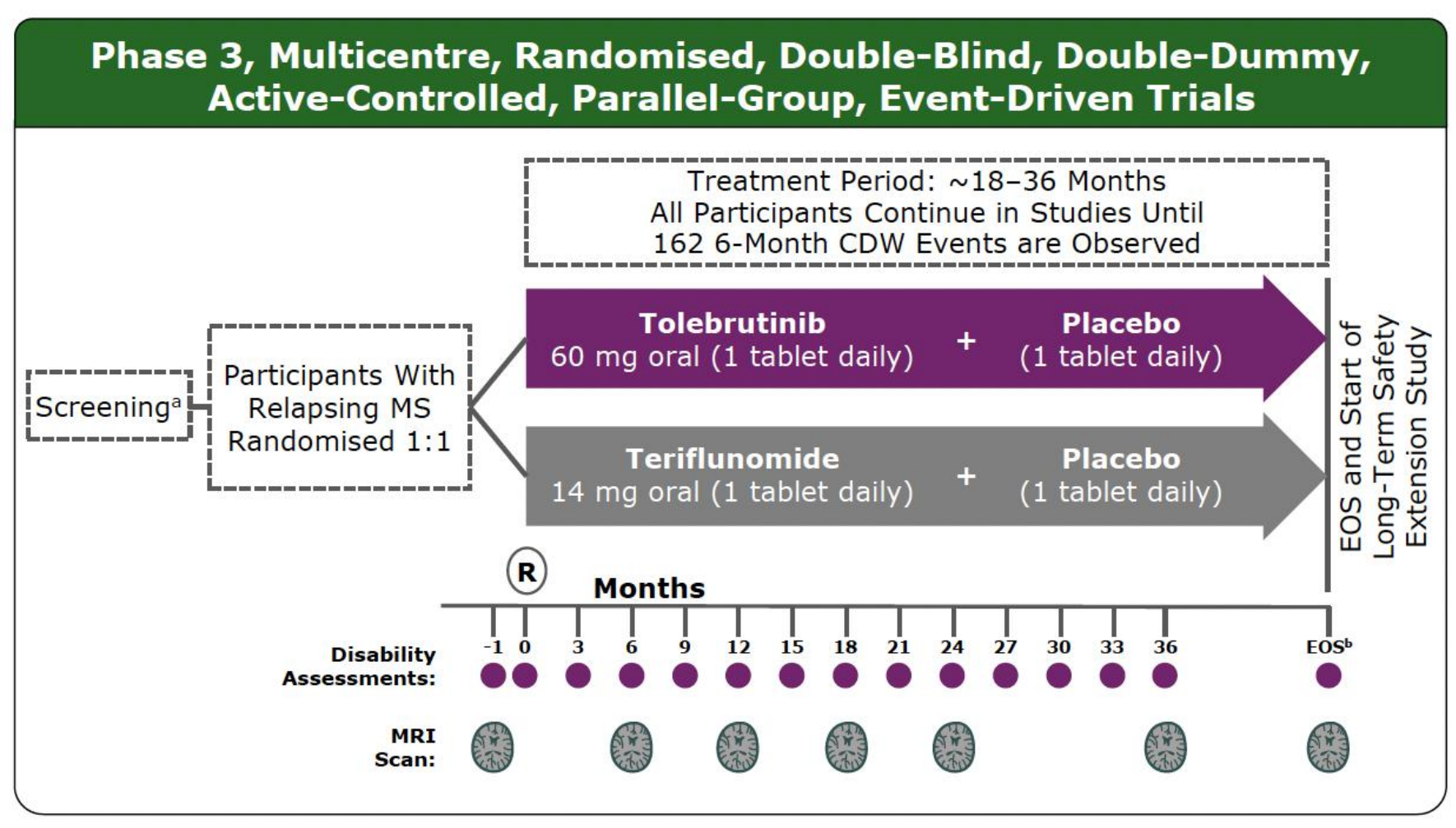
BTK INHIBITORS

- Bruton Tyrosine Kinase is an enzyme mainly expressed in hematopoietic cells
- Important for B-cell and microglia function
- BTK inhibition is not cytotoxic
- BTK inhibition is rapidly reversible


BTK inhibitor
Brain-penetrant BTK inhibitor
Modulation of B cells in the CNS
Microglia
Inhibition of B cell activation and proliferation
BTK
B cell
Cytokines
Inhibition of macrophage activation
Macrophage
Inhibition of microglia and/or macrophage activation
Oligodendrocyte
T cell
• Demyelination
• Axonal degradation
Neuron
BBB

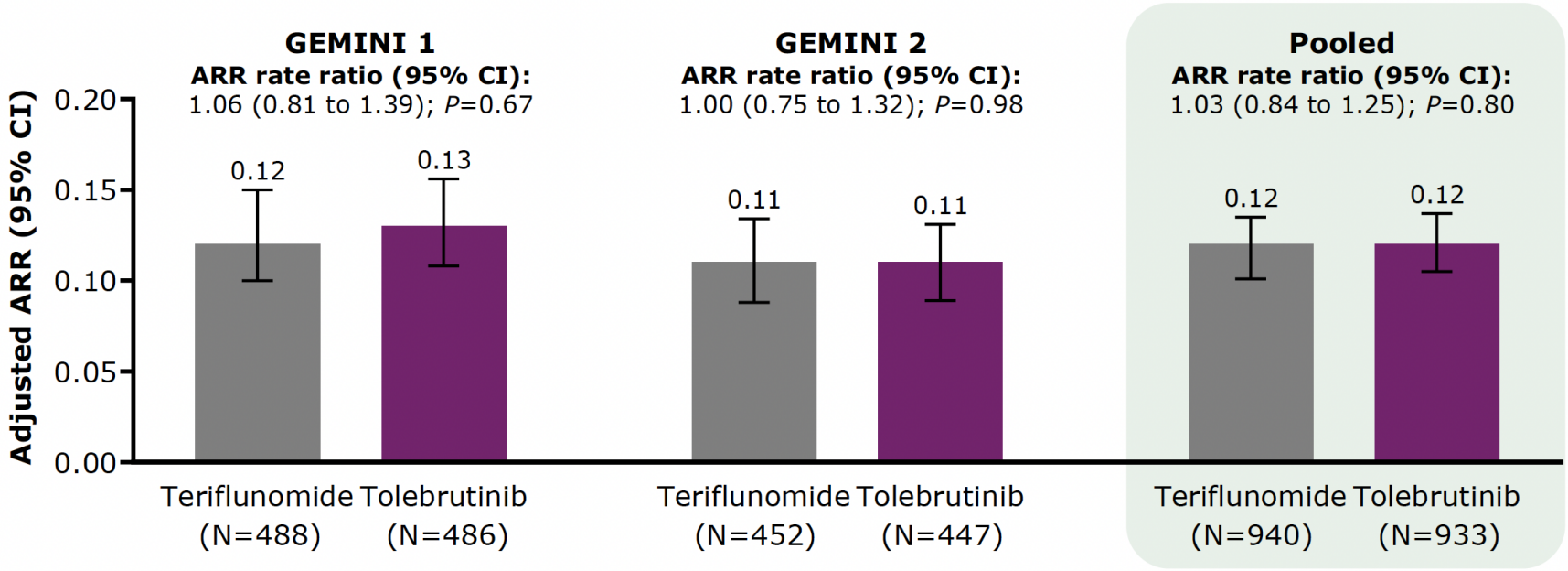

B-cells
VALIUM
for B-cells
and Microglia

TOLEBRUTINIB: GEMINI 1&2 IN RRMS



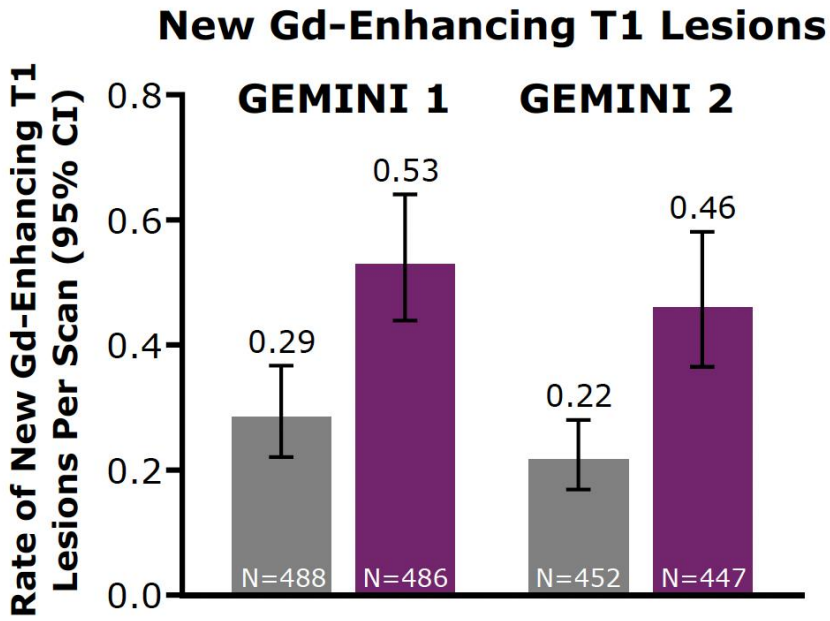
TOLEBRUTINIB: GEMINI 1&2 IN RRMS

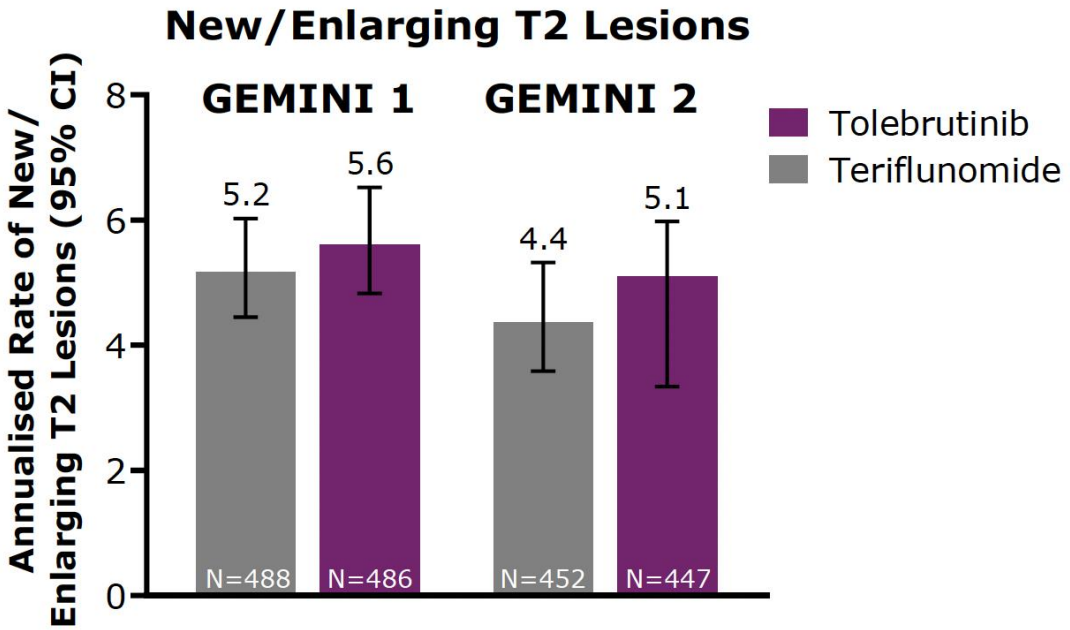
Primary Endpoint: Annualised Relapse Rate



TOLEBRUTINIB: GEMINI 1&2 IN RRMS

Secondary Endpoint: Brain Lesions on MRI

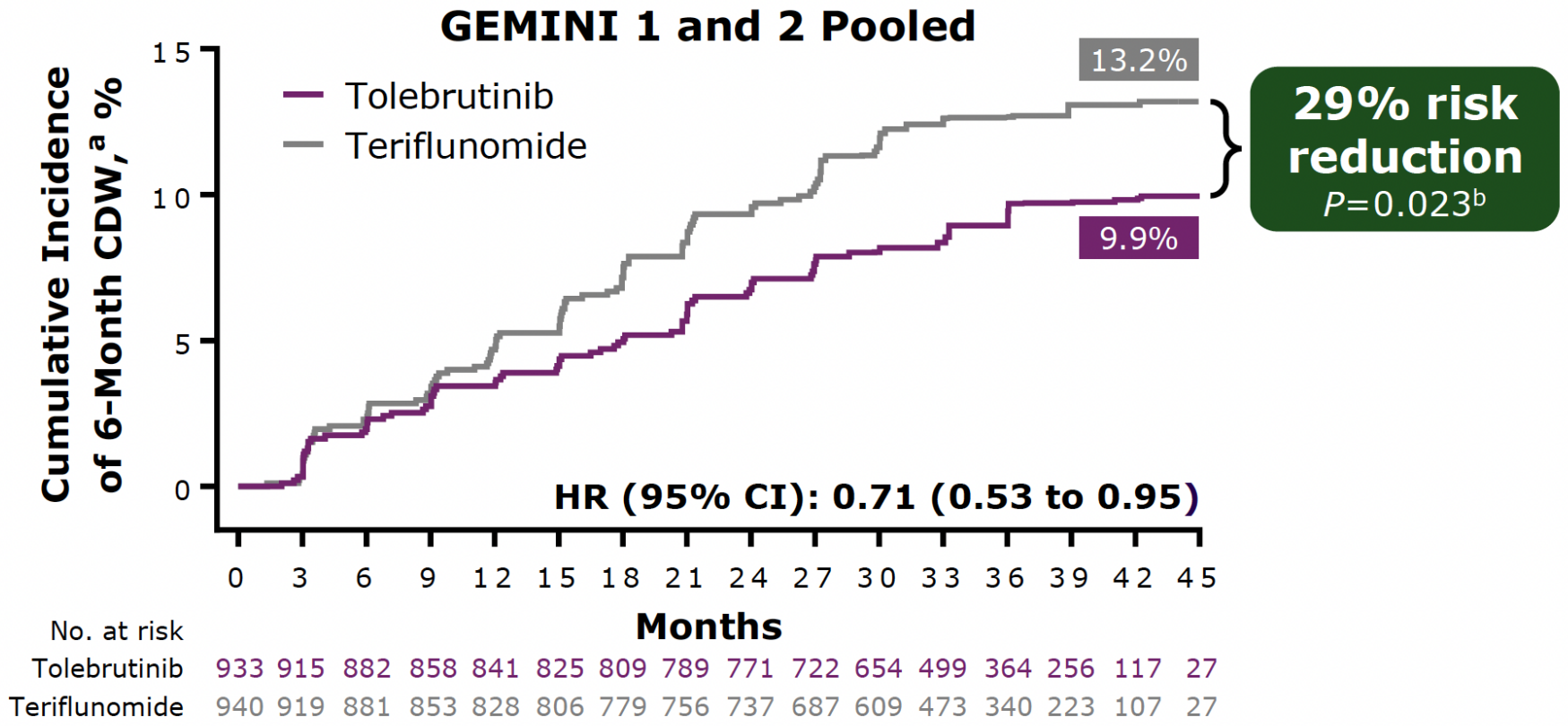




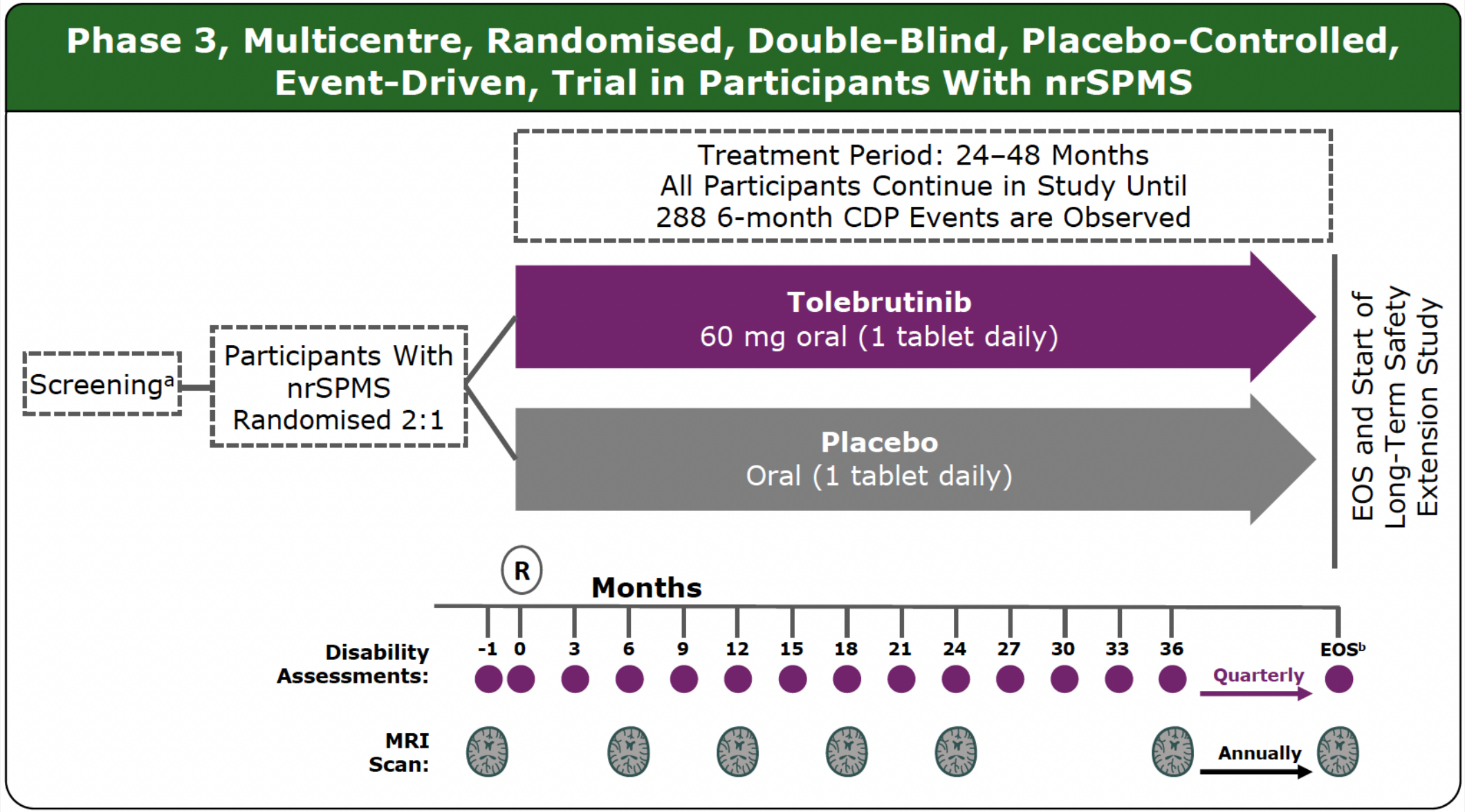
	GEMINI 1	GEMINI 2
Adjusted rate ratio (95% CI):	1.86 (1.36–2.55) *P*=0.0001[a]	2.12 (1.50–2.99) *P*<0.0001[a]
	1.08 (0.88–1.34) *P*=0.46[a]	1.17 (0.91–1.50) *P*=0.24[a]

TOLEBRUTINIB: GEMINI 1&2 IN RRMS

Key Secondary Endpoint: Time to 6-Month CDW

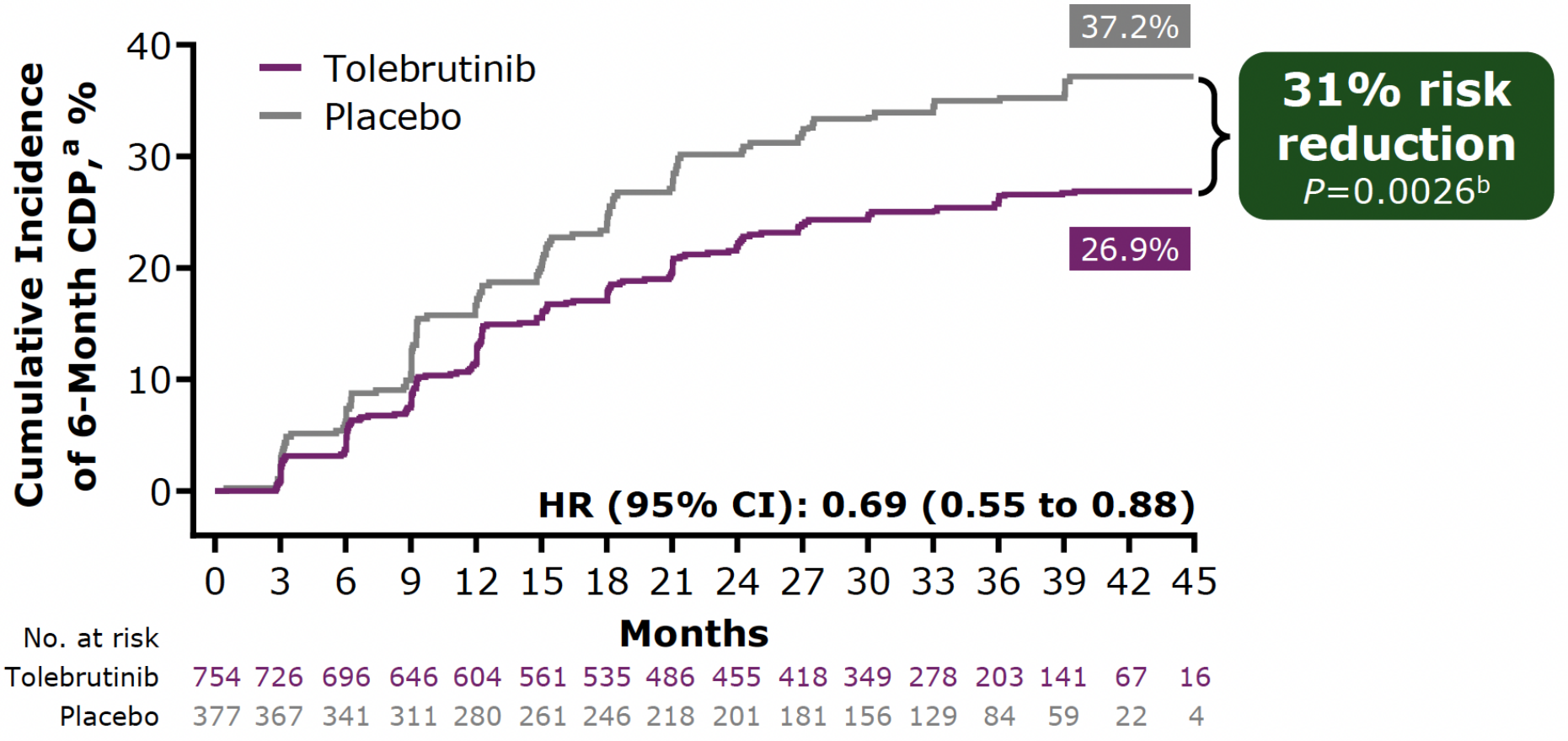


TOLEBRUTINIB: HERCULES 1&2 IN SPMS



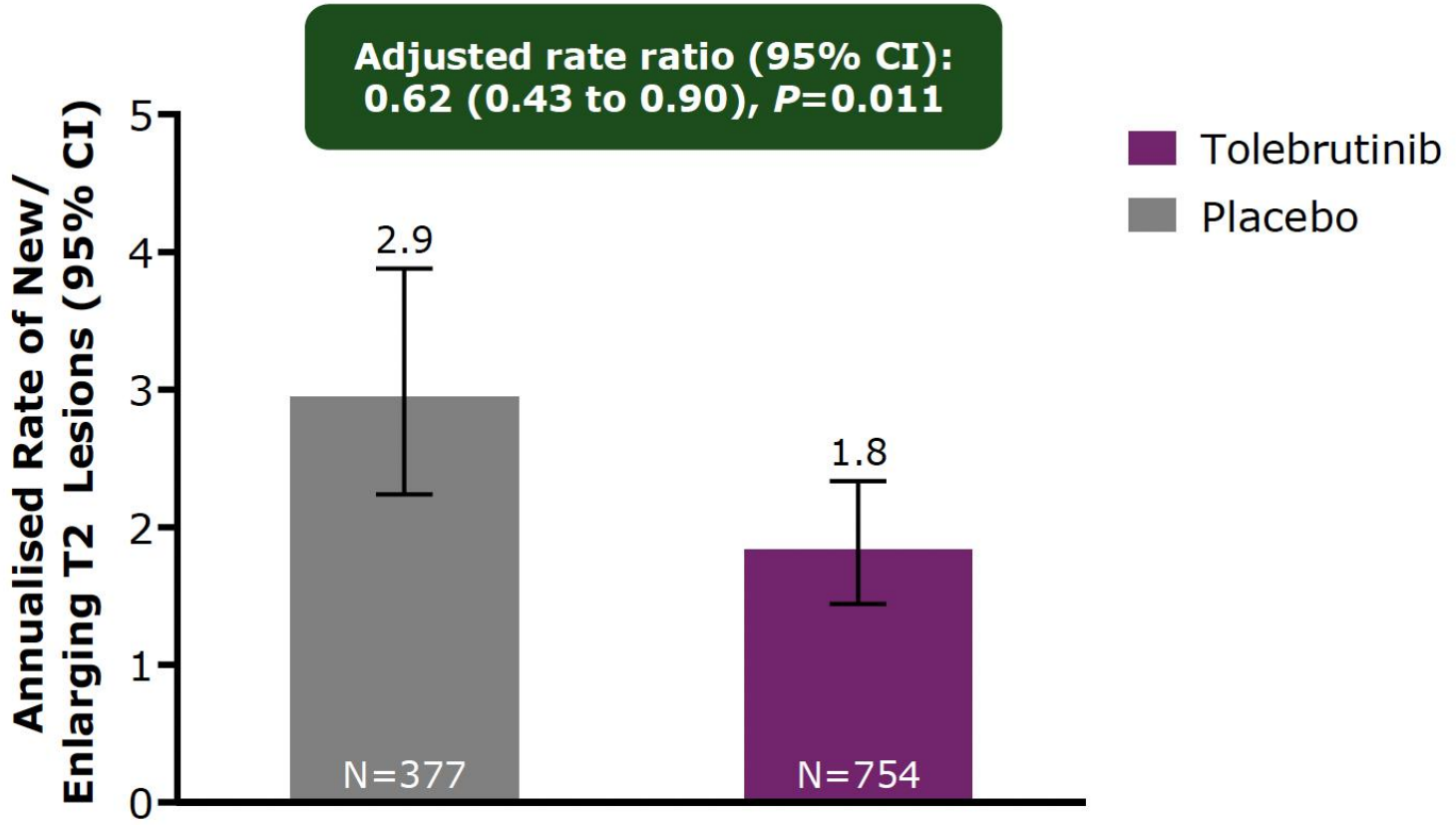
TOLEBRUTINIB: HERCULES 1&2 IN SPMS

Primary Endpoint: Time to 6-Month CDP



TOLEBRUTINIB: HERCULES 1&2 IN SPMS

Secondary Endpoint: New/Enlarging T2 Lesions



MORE DETAILS NEEDED!

Tolebrutinib Phase 3 HERCULES Trial in nrSPMS

Baseline Characteristics

Characteristic	Placebo (N=377)	Tolebrutinib (N=754)
Age, years	48.9 (8.0)	48.9 (8.0)
Female, n (%)	242 (64.2)	454 (60.2)
EDSS score[a] Mean (SD) Median (IQR)	 5.59 (0.94) 6.0 (5.0–6.3)	 5.49 (0.99) 6.0 (4.8–6.3)
Time since relapsing remitting MS symptom onset, years	17.6 (8.4)	17.1 (8.3)
Time since most recent relapse, years	7.6 (5.5)	7.4 (5.3)
Participants with ≥1 Gd-enhancing T1 lesions, n (%)	49 (13.1)	93 (12.5)
Number of T2 lesions, median (IQR)	49 (33–75)	50 (35–73)
T2 lesion volume, cm^3, median (IQR)	14.9 (7.5–28.3)	15.3 (7.2–25.8)
Participants with ≥1 prior DMTs, n (%)	288 (76.4)	549 (72.8)

MORE DETAILS GIVEN!

Sex

Male *Benefitted*

Female ??

EDSS

≤4.5 ??

≥4.5 *Benefitted*

Presence of Gad Lesions

Benefitted

Disease duration

≤5 years ??

5 to ≤ 10 *Benefitted*

≥10 *Benefitted*

Age

≤40 ??

>40 *Benefitted*

<50 *Benefitted*

≥50 *Benefitted*

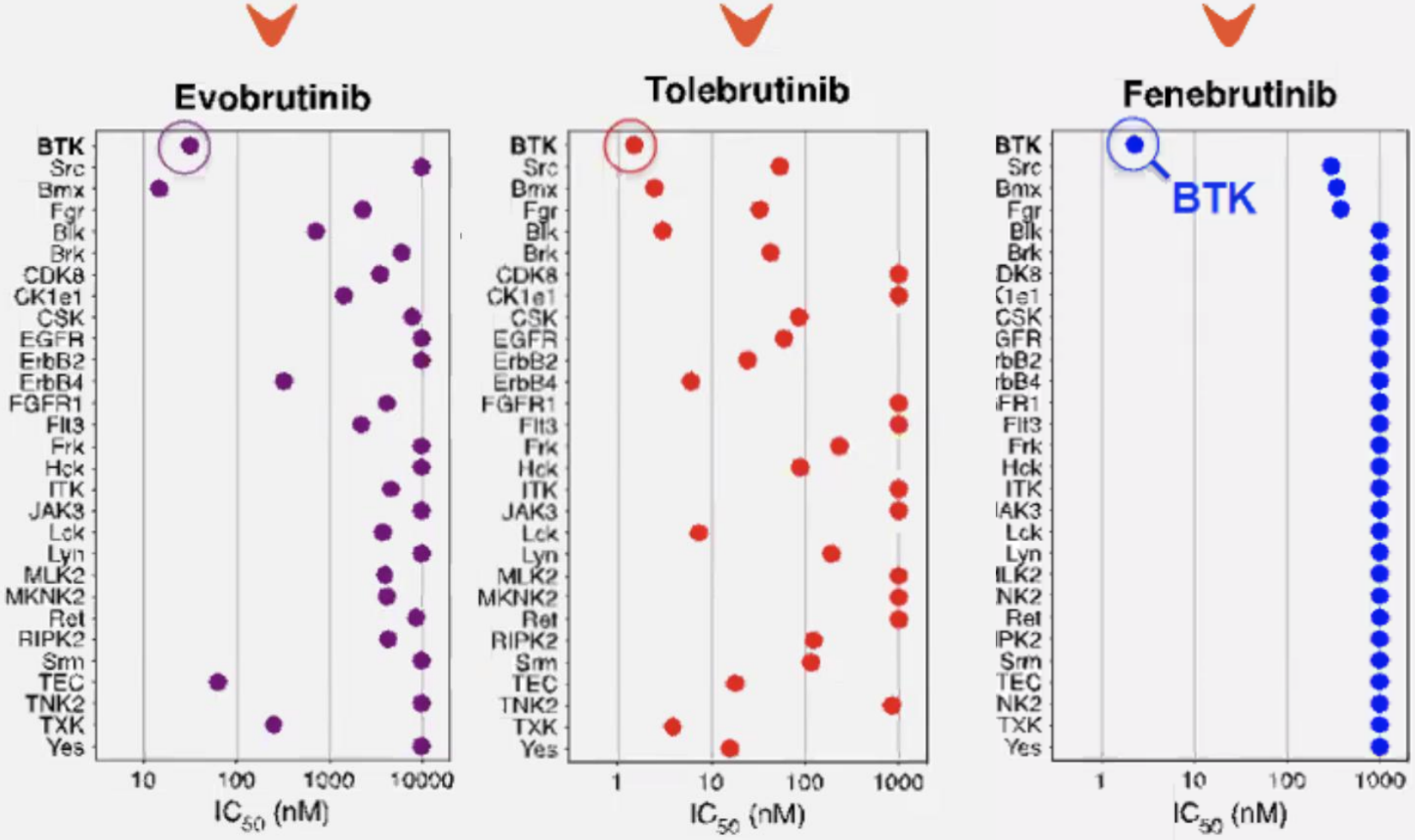
TOLEBRUTINIB MAY BE COMING SOON…

Potential Release Dates for BTK Inhibitors

MORE (BETTER?) BTKS COMING!

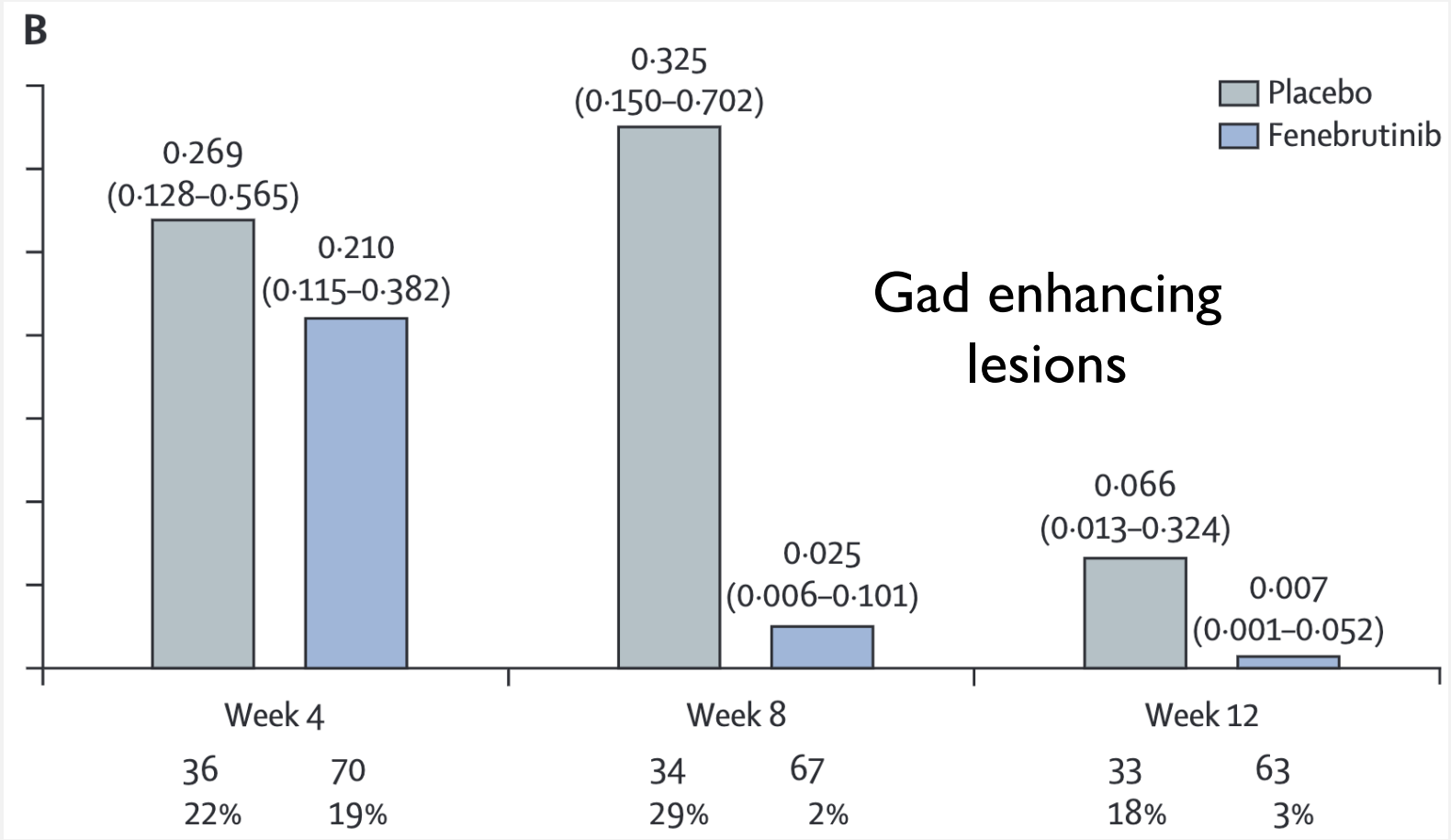
- ~~Evobrutinib~~
- Tolebrutinib
- Fenebrutinib
- Remibrutinib
- Orelabrutinib

- Better CNS penetration
- More selective
- Efficacy against relapses and MRI



COULD ONE DRUG WORK FOR ALL TYPES OF MS?

- FENopta: phase 2 for RMS
- Primary outcome MRI
- 69% reduction in G+ lesions compared to placebo
- ARR 0 in fenebrutinib vs 0.18 placebo
- CSF concentrations in active range to affect microglia



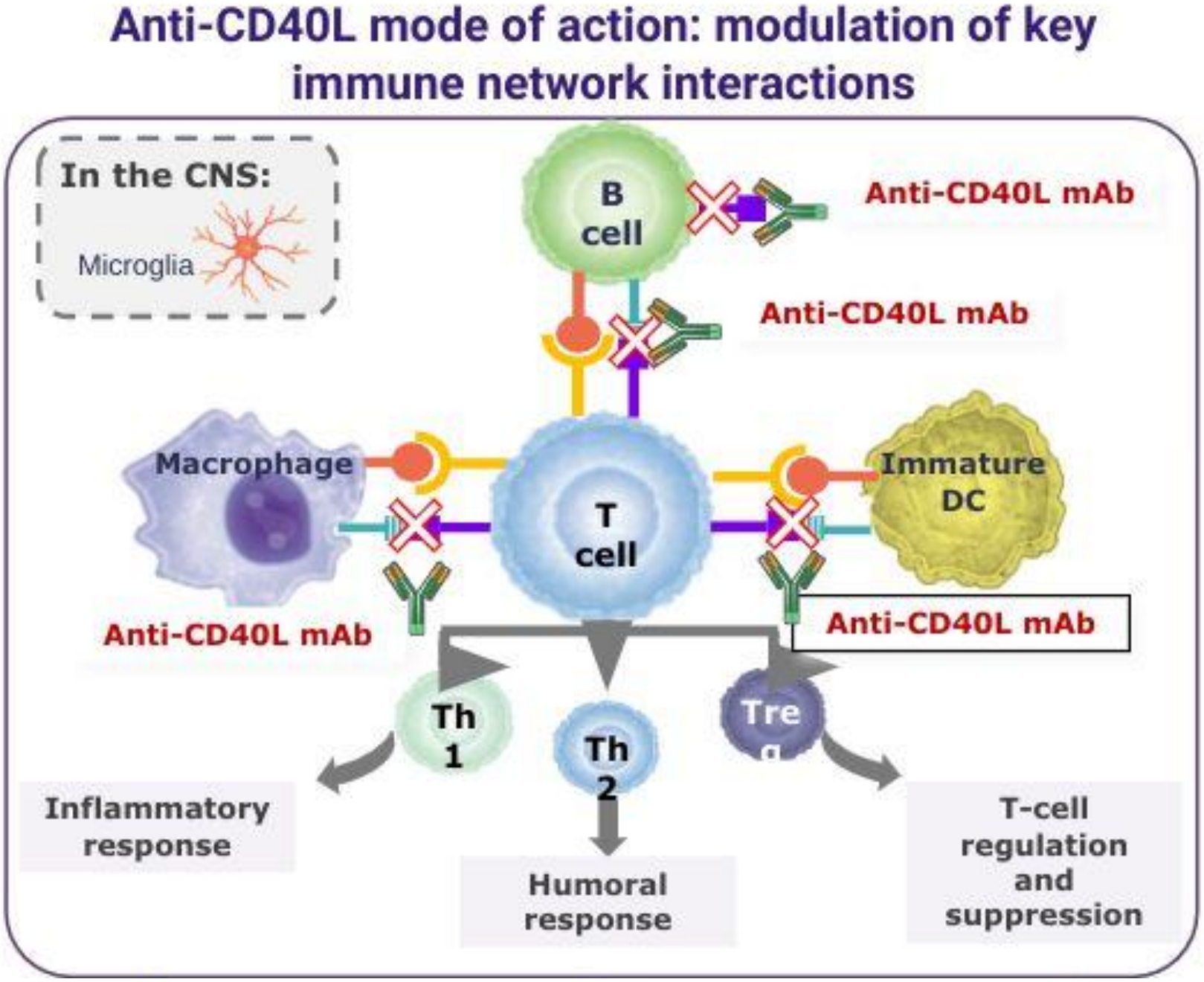
PENDING BTK TRIALS FOR PROGRESSIVE MS

- **FENTREPID**
  - phase III ocrelizumab vs fenobrutinib in PPMS
- **PERSEUS**
  - Phase III tolebrutinib vs placebo in PPMS
- *** REMODEL**
  - Remibrutinib in * RMS

FREXALIMAB

- Monoclonal antibody: Anti-CD40 Ligand on T-cells
- Affects interactions between T-cells, B-cells, AND microglia
- Not cell depleting
- IV every 4 weeks

BLUNTS
T-CELL
INTERACTIONS

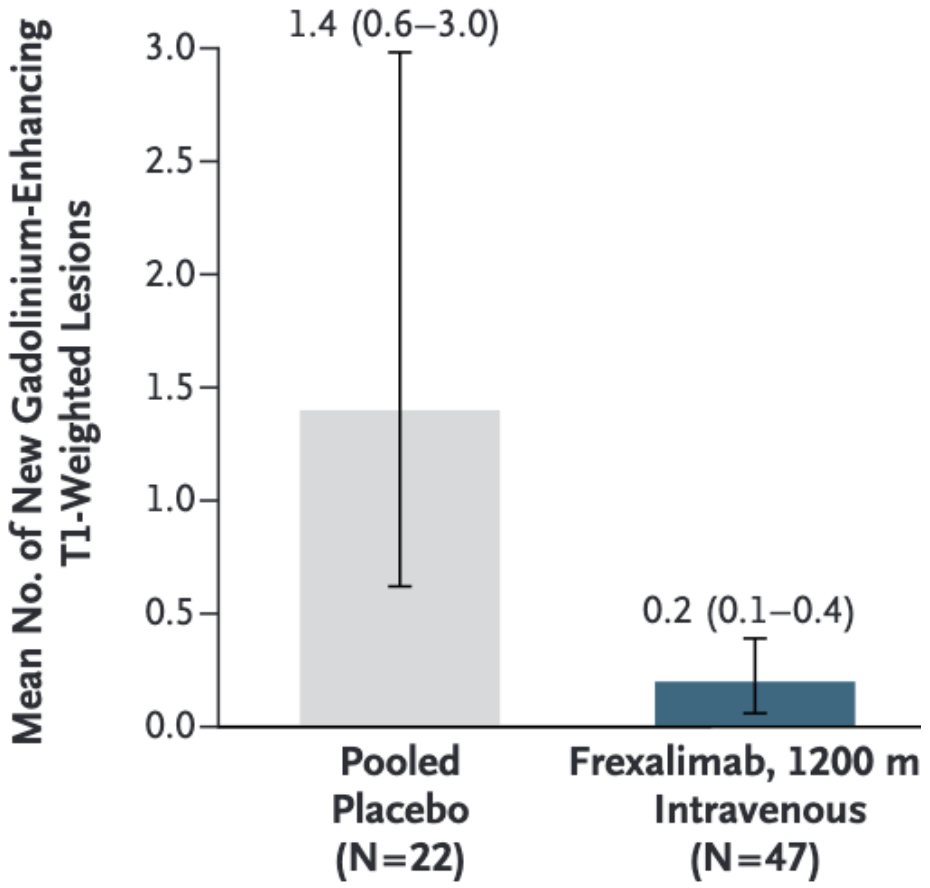


BLUNTS T-CELL INTERACTIONS

BLUNTS T-CELL INTERACTIONS

Frexalimab: Phase II RMS

- 129 patients, 1200mg IV every 4 weeks for 24 weeks
- Good safety profile: slight increased risk of infections
- No differences in disability (short study)
- Reduction in NfL levels
- Big reduction in new MRI lesions



FREXALIMAB PENDING PHASE III STUDIES

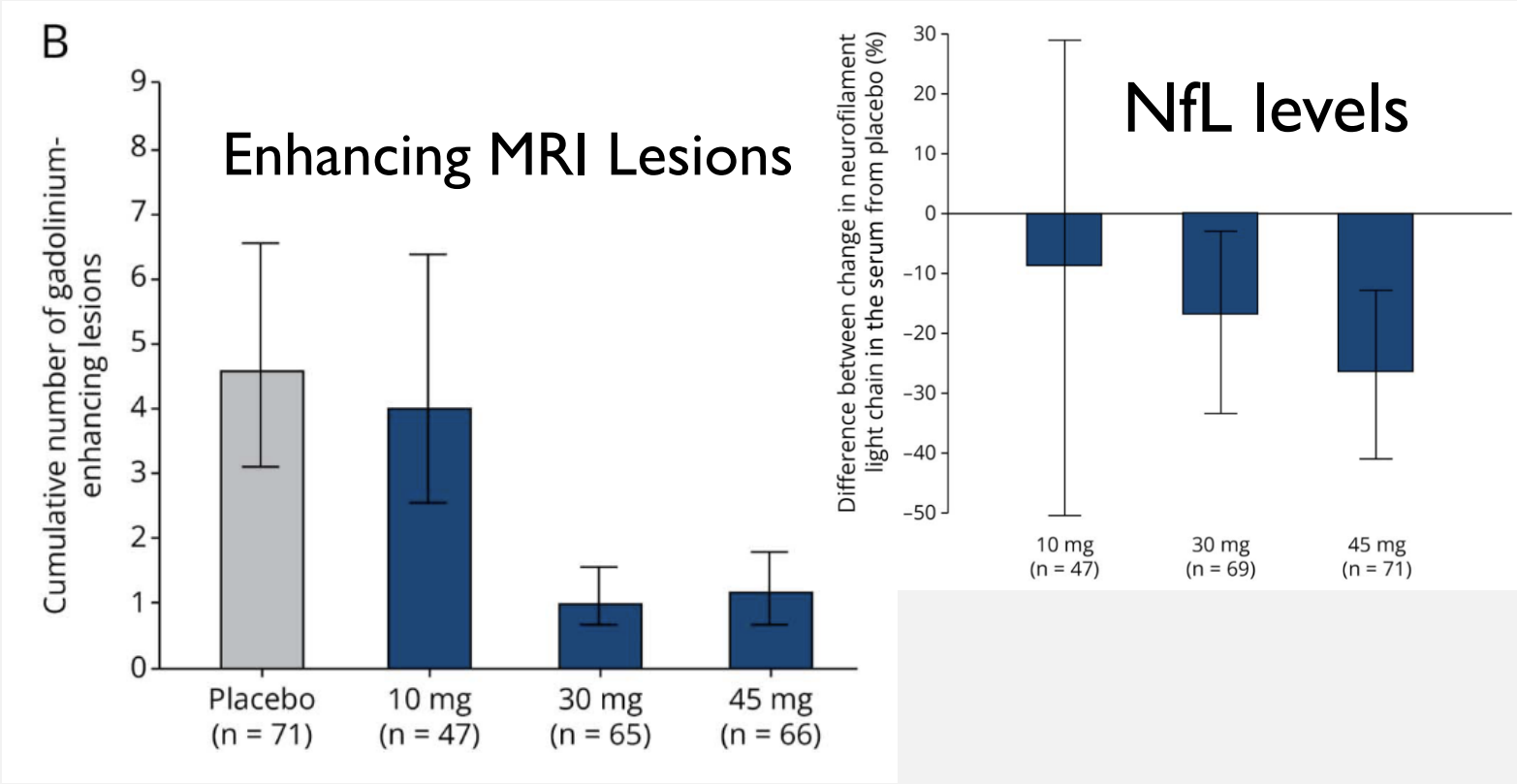
- FREXALT (RMS)
- FREVIVA (SPMS)

VIDOFLUDIMUS CALCIUM

- Blocks DHODH: like teriflunomide (Aubagio)
- More selective
- Activates NURR-1 (nuclear receptor-related 1): possibly neuroprotective

VIDOFLUDIMUS CALCIUM
RELAPSING MS

- Phase II x 24 weeks
- 268 patients, 3 doses and placebo
- Impact on relapses, MRI and NfL
- But not disability progression
- Phase 3 trials ongoing



	Vidofludimus 30mg	**Placebo**
Disability Progression*	1.6%	3.7%

VIDOFLUDIMUS CALCIUM

PROGRESSIVE MS PHASE II TRIAL

- 2:1 vs placebo
- 467 patients with PPMS or n/a-SPMS
- 24 weeks

- 20% reduction in 24 week disability progression (16.2% vs 20.3%)
- 30% reduction in PPMS subgroup*
- 15 % in patients with non-active SPMS

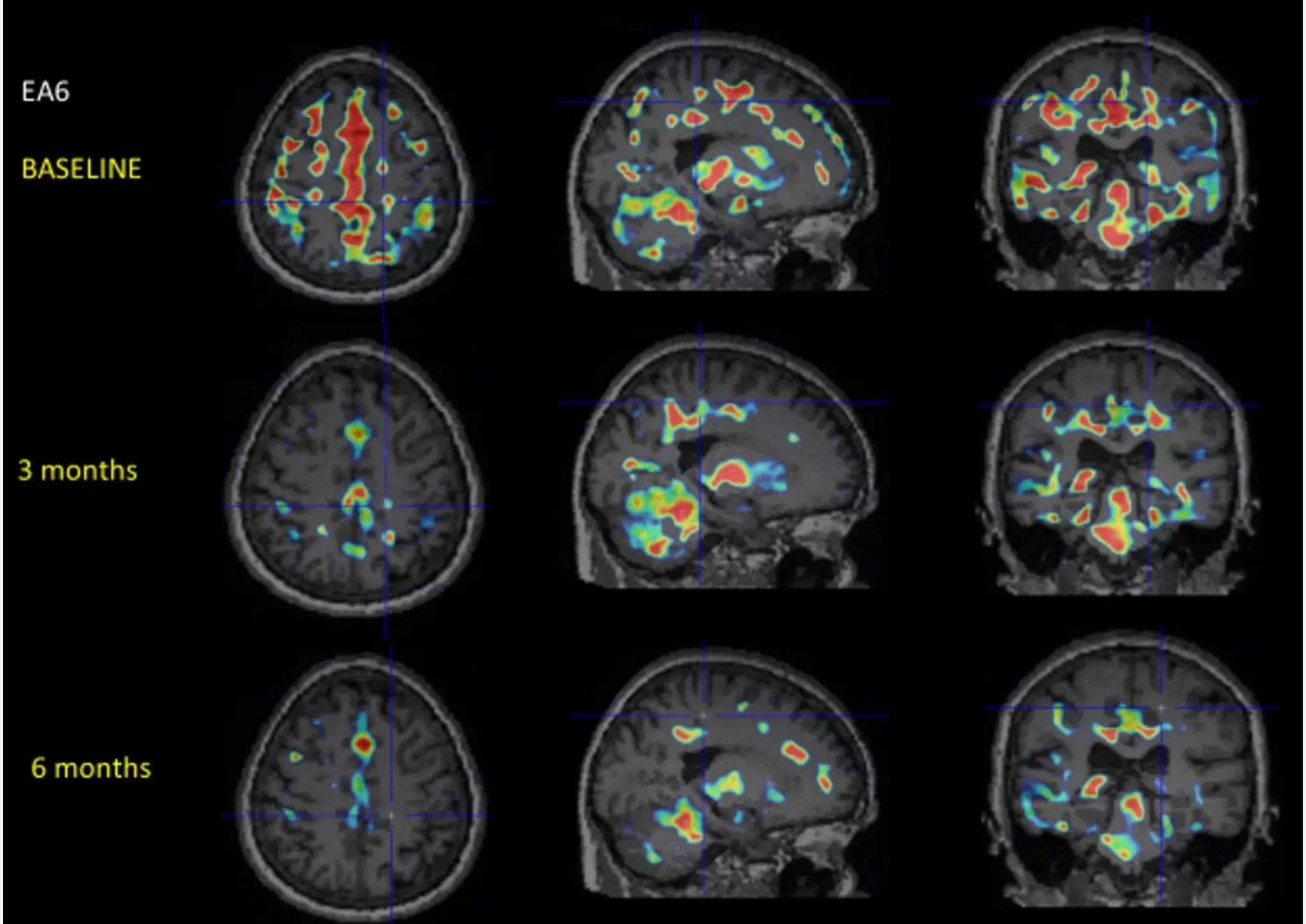

T-CELL
FORALUMAB

INTRA-NASAL FORALUMAB
ANTI CD-3 MONOCLONAL

- Blocking CD-3 blunts activation of T-cells
- Phase I trial of 3 doses vs placebo, daily x5 five days.
- Significant anti-inflammatory effect
  - Reduced inflammatory T-cell subsets
  - Increased CD8-naïve T-cells
  - boosted anti-inflammatory IL-10
  - Suppressed inflammatory molecule interferon gamma

FDG
PET

Activated microglia

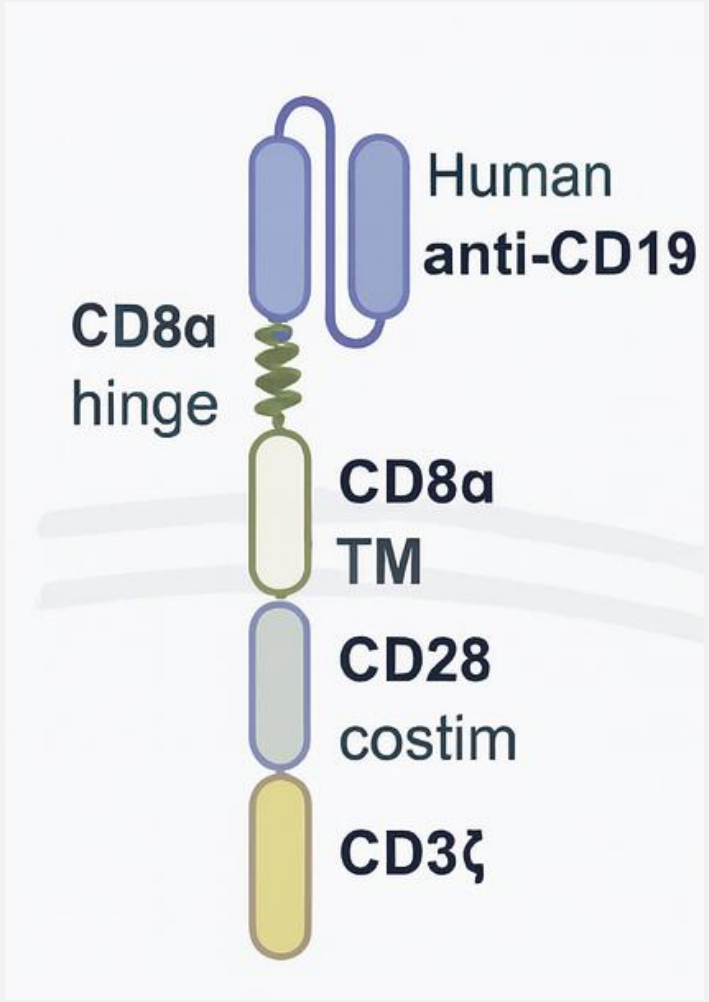


EXCITING BUT

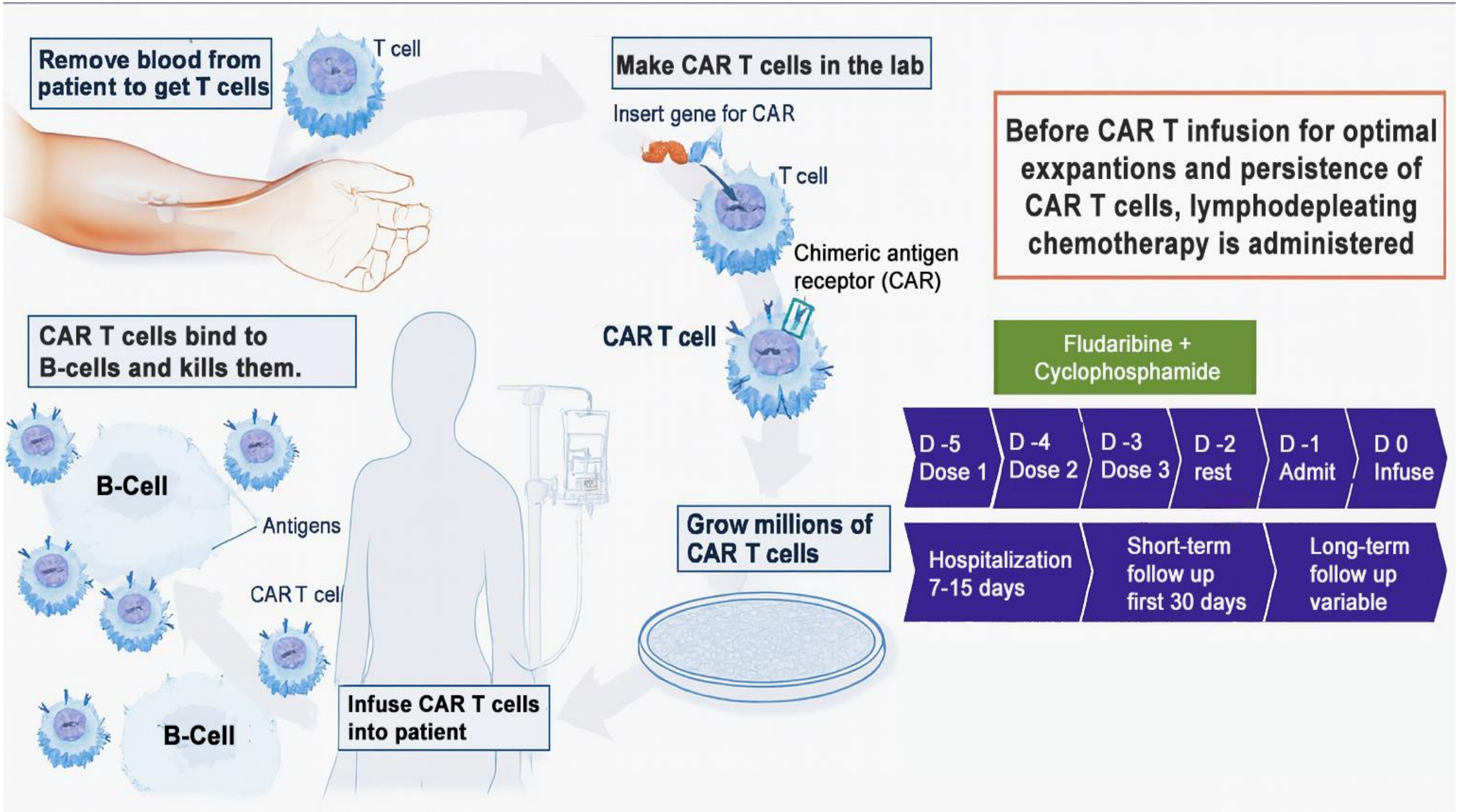
- Only 10 patients
- Not placebo controlled
- Full phase 2 pending

CAR T

- CAR T cells: **C**himeric **A**ntigen **R**eceptor
- Autologous T-lymphocytes genetically engineered to target a specific antigen
- The process is complicated and can only be done at specific hospitals



CAR T treatment process



CAR T

ADVANTAGES

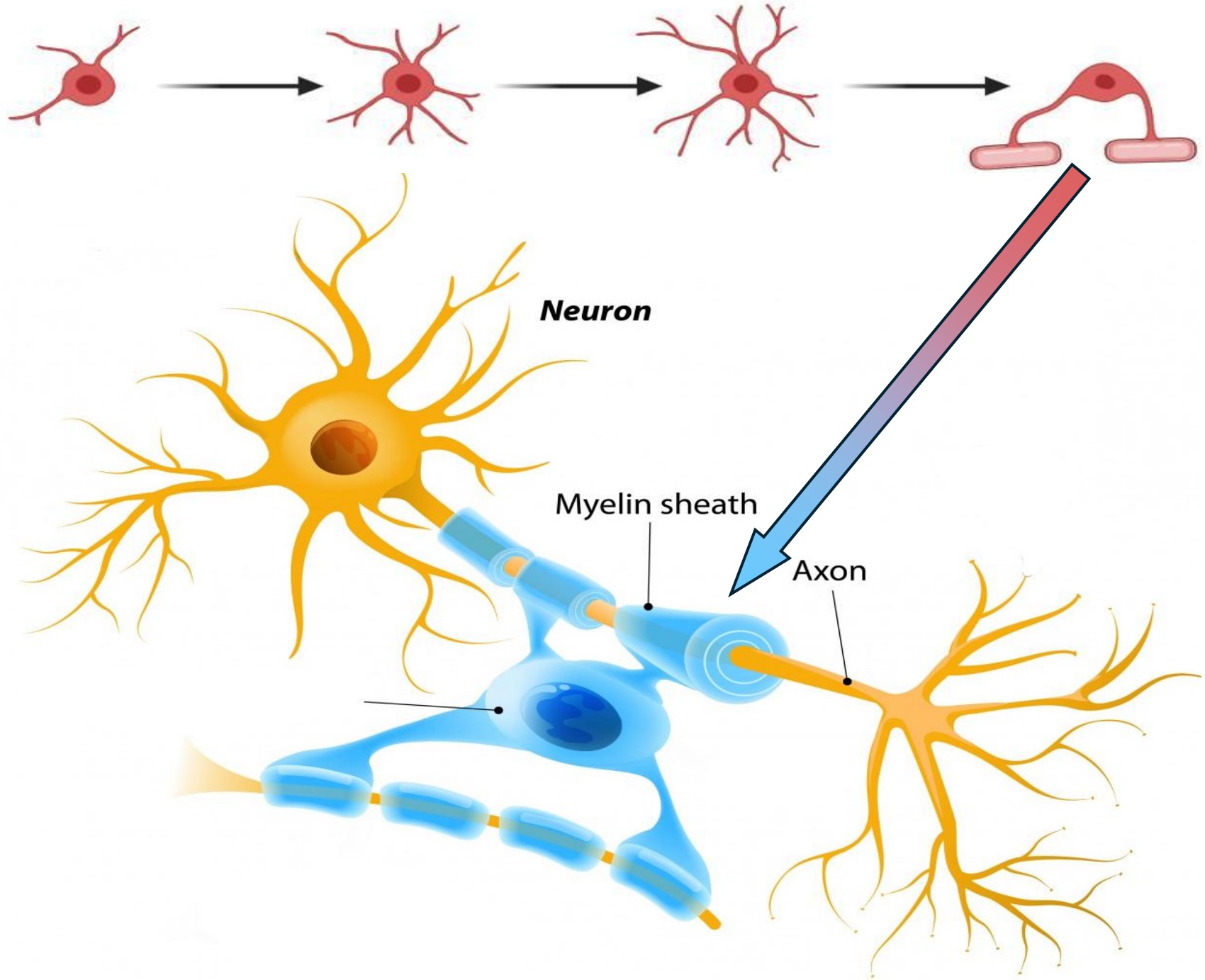
- Long-term anti B-cell treatment with single administration
- CNS penetration
- Favorable safety profile

DISADVANTAGES

- Requires specialized treatment centers
- Chemotherapy
- Potential for neurologic toxicity (ICANS)

REMYELINATION

Oligodendrocyte Precursor Cell (OPC)



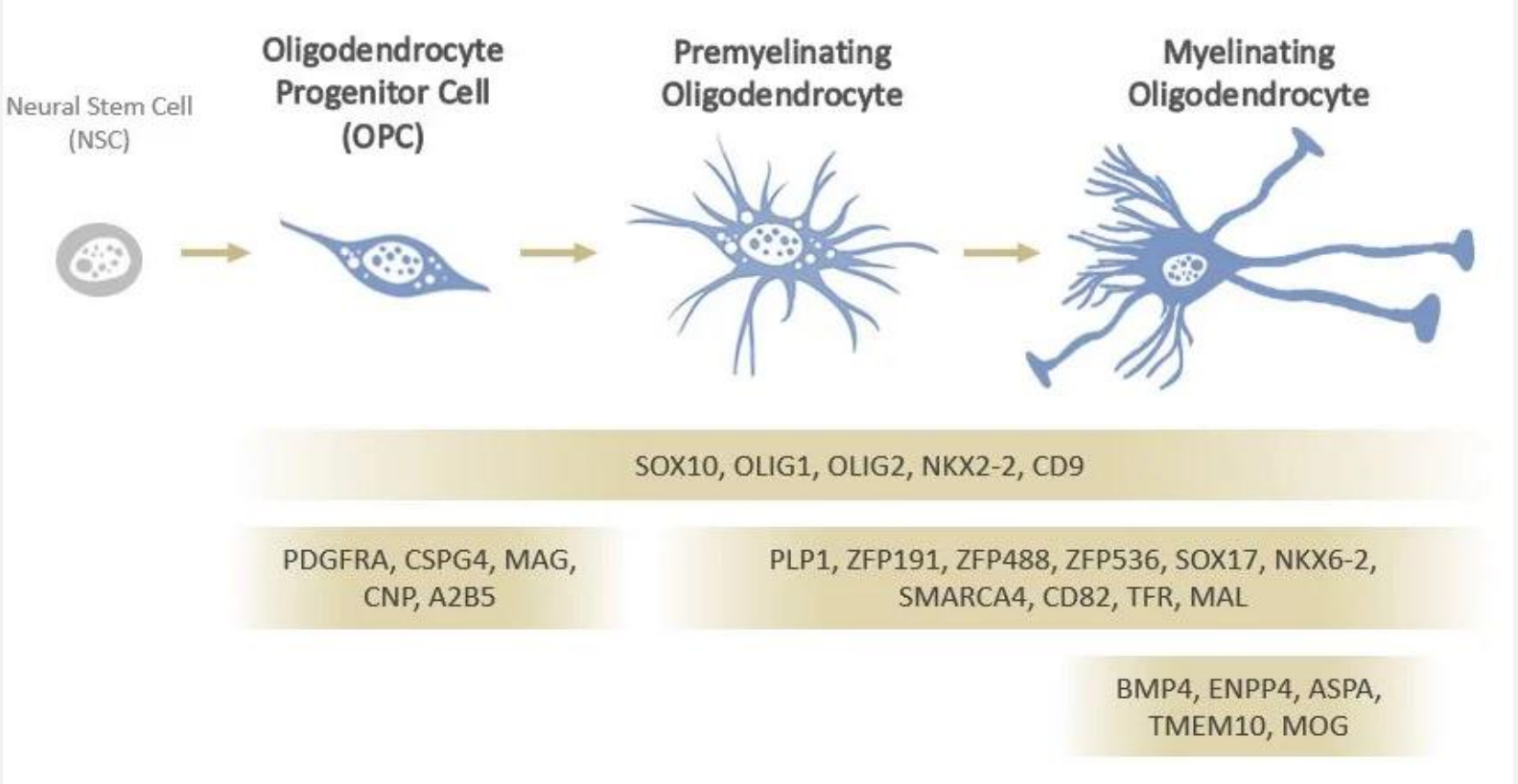
Oligodendrocyte

REMYELINATION IN THEORY

- Activate OPCs (Oligodendrocyte Precursor Cells)
- Remyelinated demyelinated axons
- Function is restored

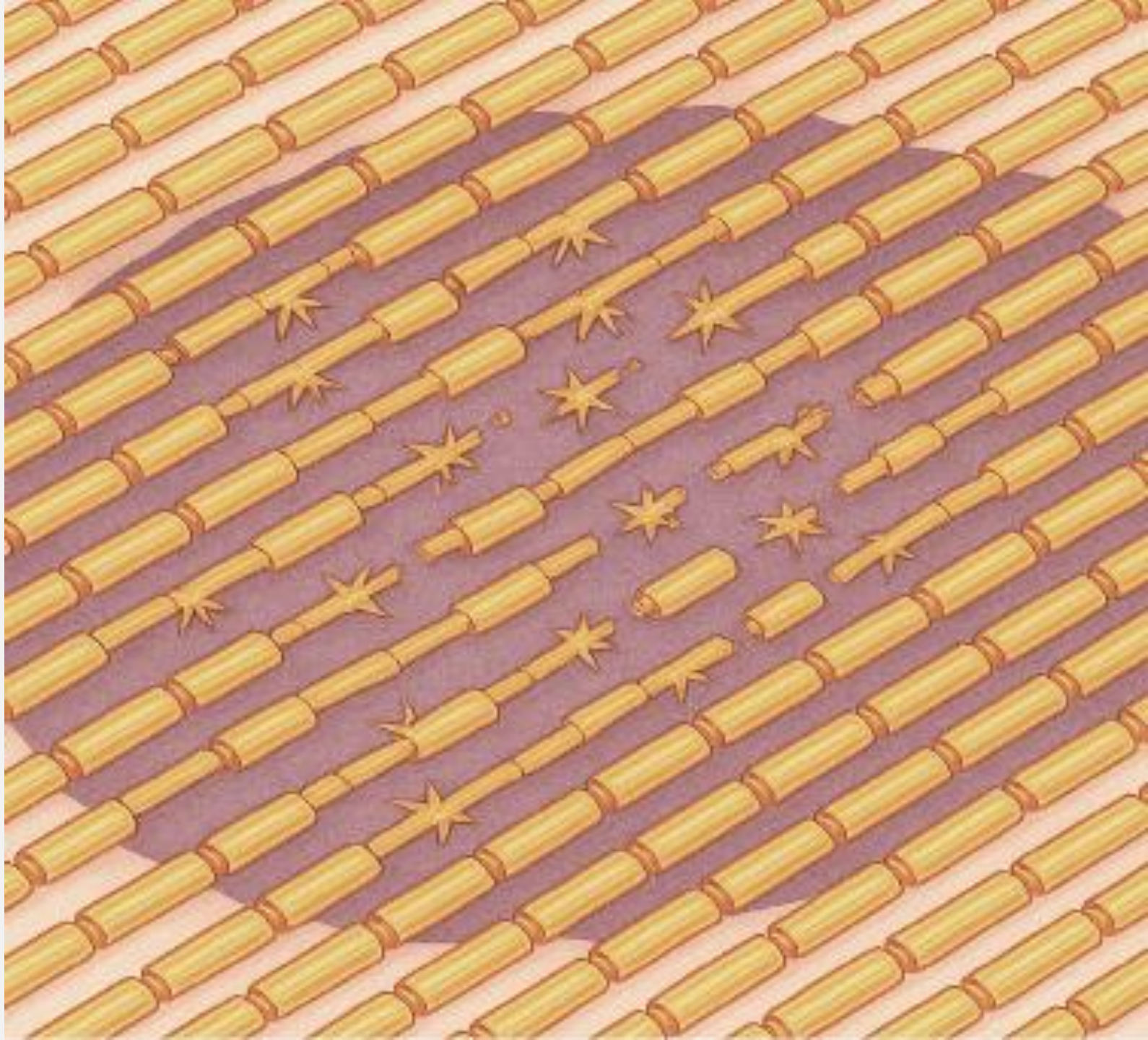
REMYELINATION IN REALITY

- Activating OPCs requires precisely sequenced steps
- Environment must be *just right* to get them to remyelinate
- There have to be axons to remyelinate



REMYELINATION IN REALITY

In chronic MS lesions there is up 40-70% axon loss



Remyelination may be hindered by chronic inflammation

CLEMASTINE REBUILD TRIAL 2017:

50 Patients who had optic neuritis

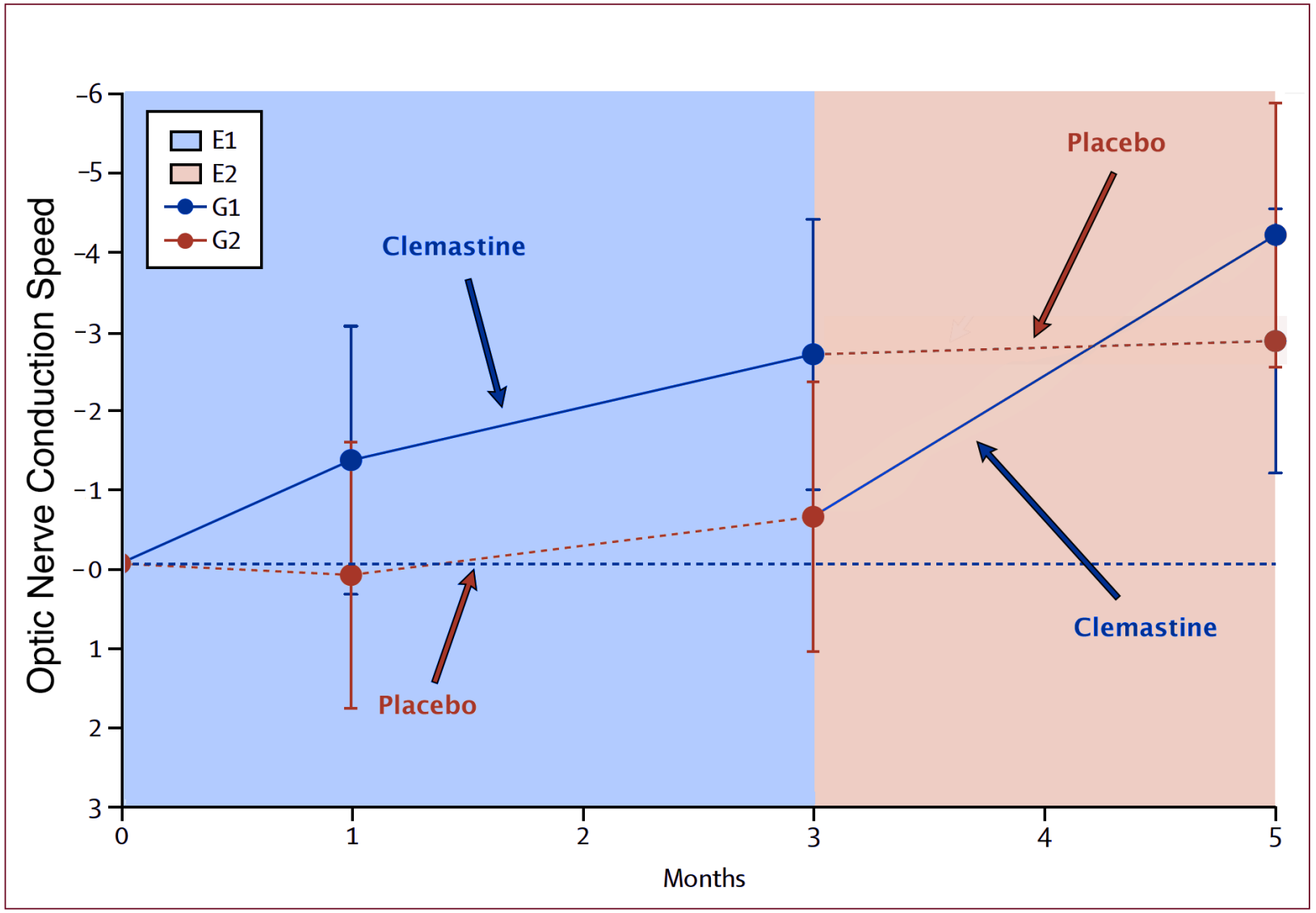
25 Patients

- Clemastine for 90 days 5.36m 2x day (OTC dose 1.34mg 2x day)
- Switched to placebo for 60 days

25 patients

- Placebo for 90 days
- Switched to Clemastine for 60 days

RESULTS

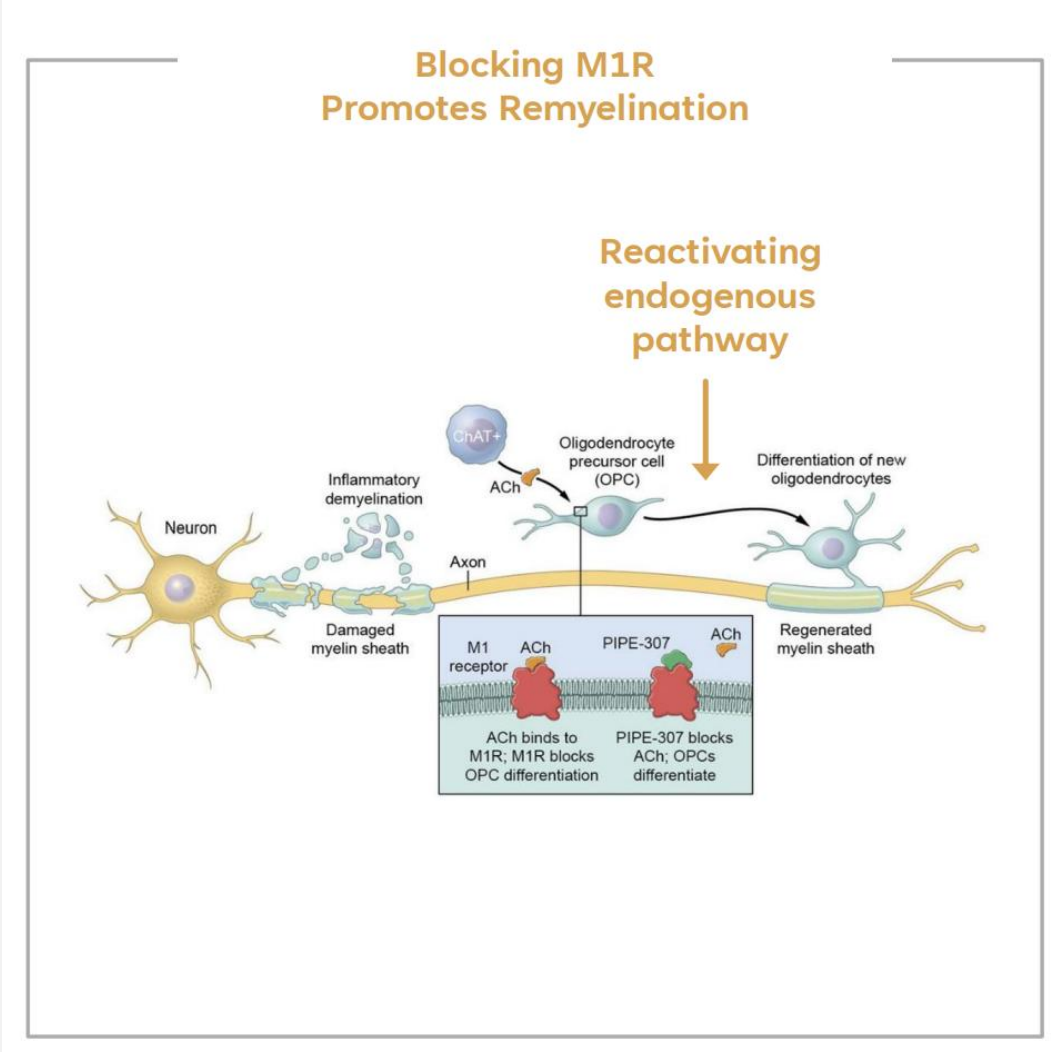

E1
E2
G1
G2
Clemastine
Placebo
Placebo
Clemastine
Optic Nerve Conduction Speed
−6
−5
−4
−3
−2
−1
−0
1
2
3
0
1
2
3
4
5
Months

CLEMASTINE + METFORMIN

- Rationale: In mouse studies metformin restored function of OPCs in old mice
- Trial: 70 patients with prior optic neuritis
- Randomized to placebo or metformin 1gm + clemastine 5.36mg BID x 6 months
- Measured VEPs
- Metformin and Clemastine was associated with small but significant reduction in VEP
- However, less than in the ReBuild trial (clemastine alone
- No clinical improvement

CONTINEUM THERAPUTICS PIPE-307, AN M1 ANTAGONIST FOR RRMS

- In mice PIPE-307 selectively blocks M1R (muscarinic receptor)
- Blocking M1 receptors stimulates OPCs
- Highly selective (less sedation)
- Penetrates CNS
- Phase 1: appears safe without cognitive side effects
- VISTA trial: 30 week phase II study. Outcomes of vision, cognition, upper and lower extremity function



NVG 291

- Chondroitin sulfate proteoglycan (CSPG) inhibits neuronal, axonal sprouting
- SQ injection: peptide that interacts with CSPG
- No studies in MS yet

NVG-291 IN MICE