MS AN UPDATE TODAY

Δρ Μάριος Παντζαρής,

Ανώτερος Νευρολόγος,

Διευθυντής Γ' Νευρολογικής Κλινικής,

Αναπλ. Καθηγητής, Σχολή Μοριακής Ιατρικής,

Ινστιτούτο Νευρολογίας και Γενετικής Κύπρου

THE CYPRUS INSTITUTE OF NEUROLOGY & GENETICS

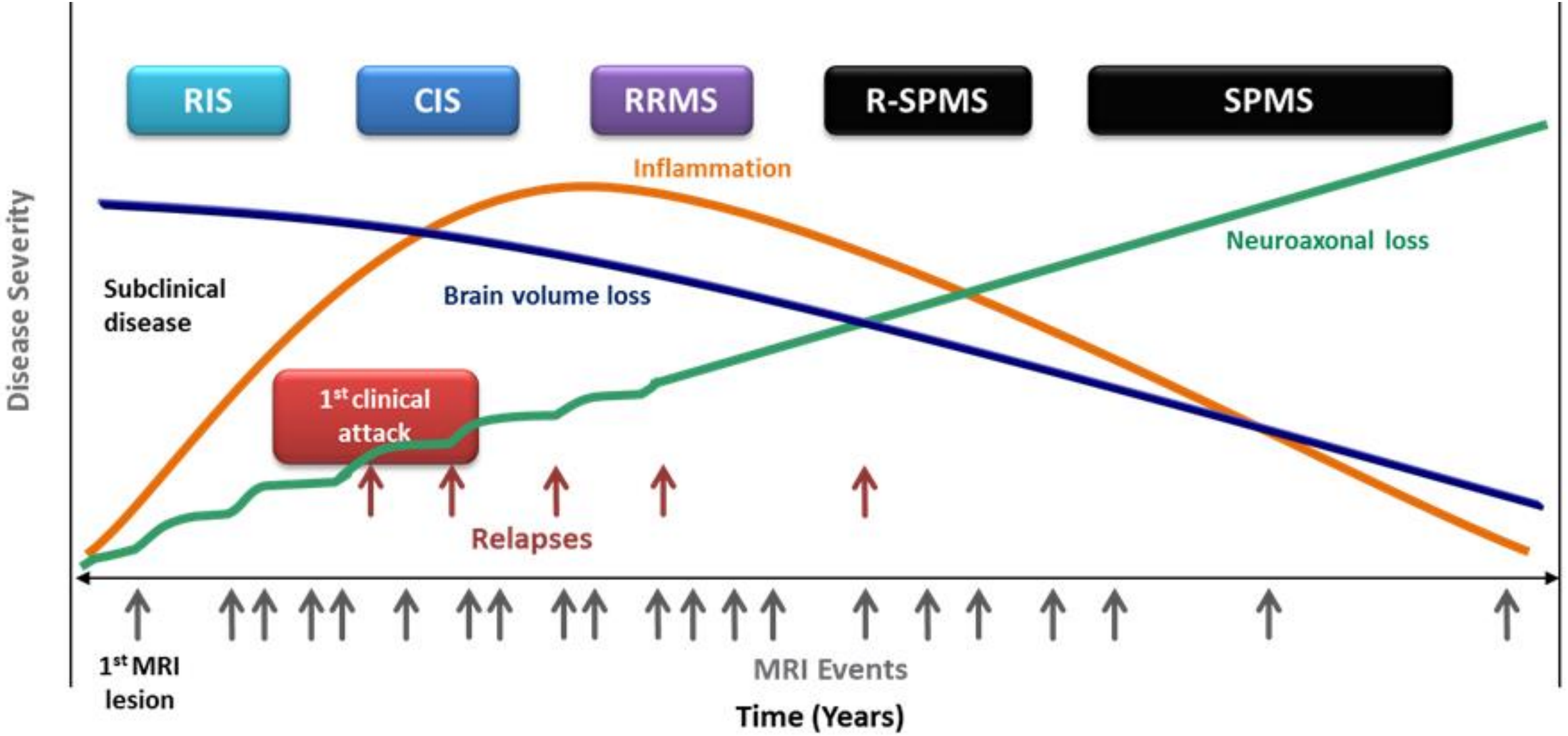
CYPRUS SCHOOL of molecular medicine

A SCHOOL OF THE CYPRUS INSTITUTE OF NEUROLOGY & GENETICS

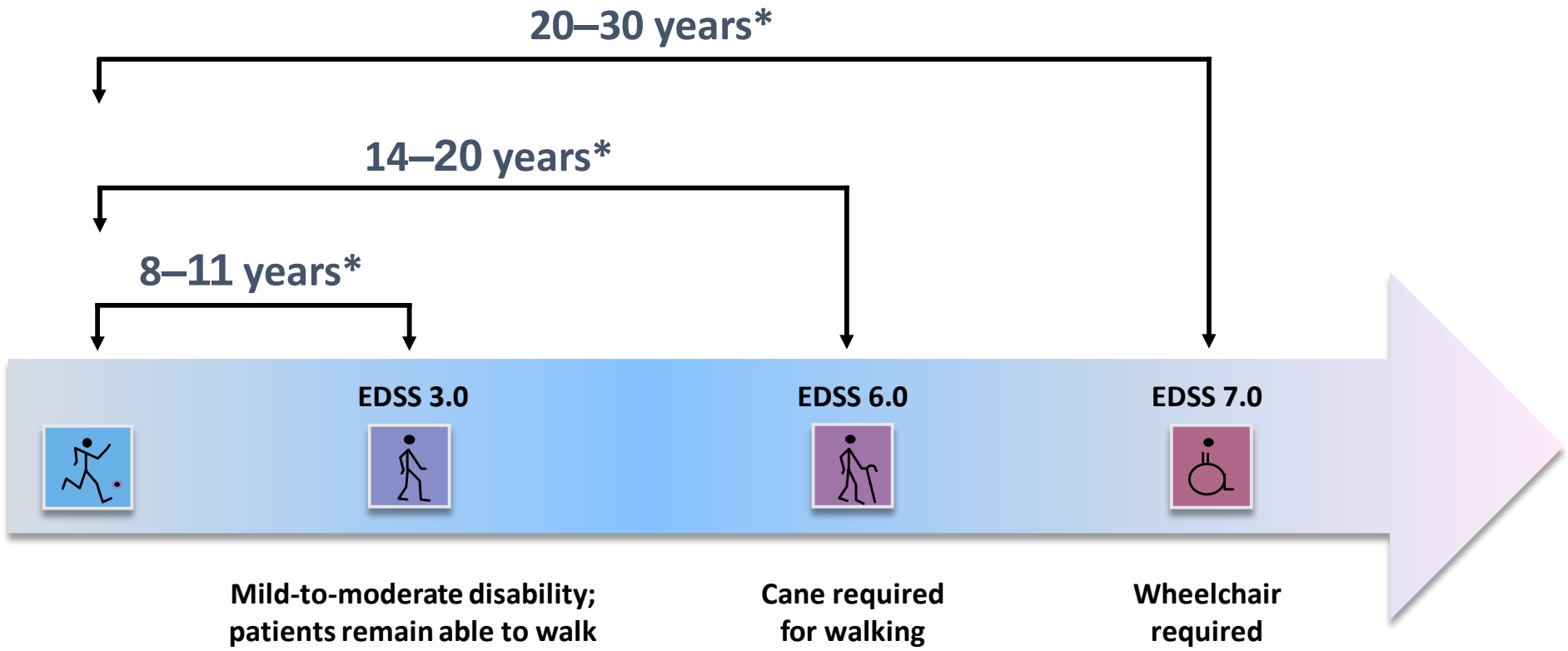
Cyprus Multiple Sclerosis Association

Λεμεσός 17 Νοεμβρίου 2019

MULTIPLE SCLEROSIS COURSE AND PATHOLOGY



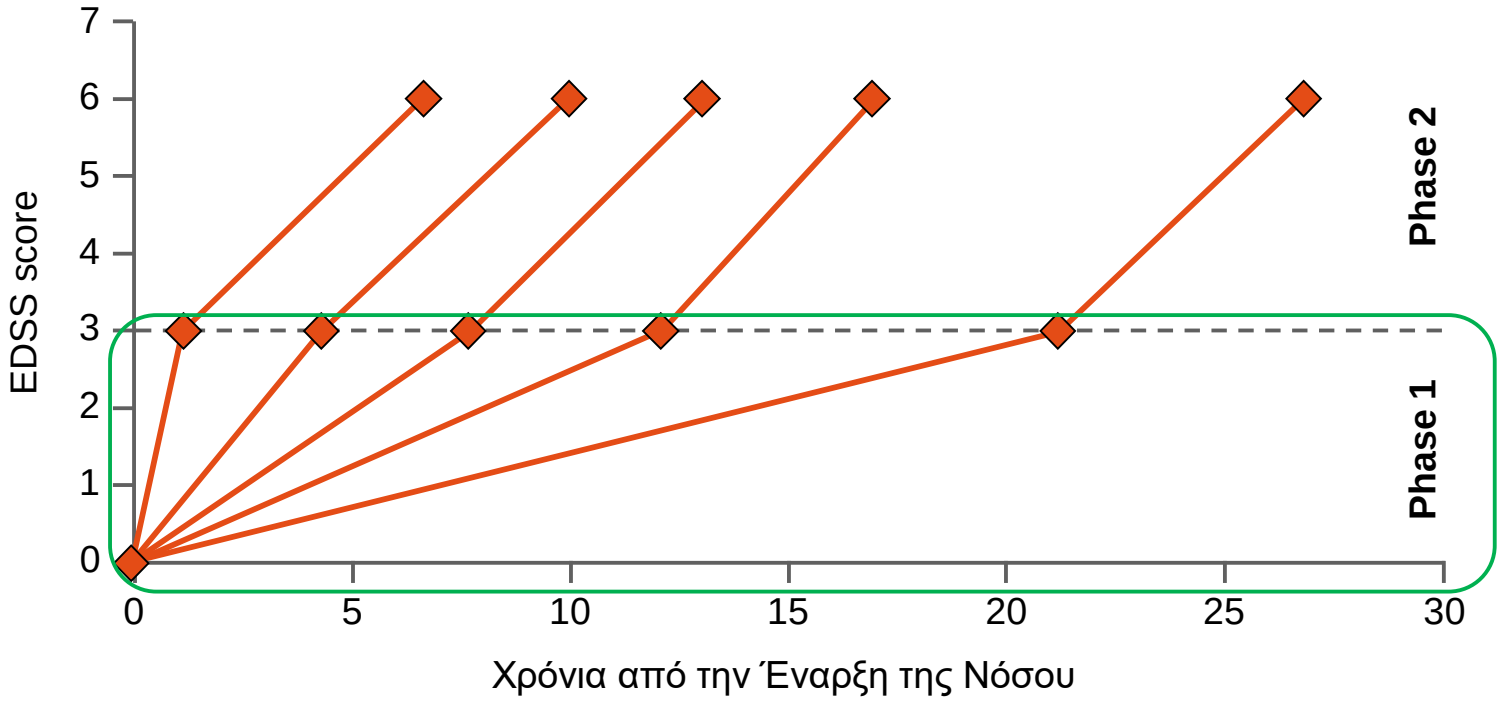
Φυσική Πορεία Νόσου- Natural Course: RRMS



*Median number of years from first relapse. EDSS=Expanded Disability Status Scale; RRMS=relapsing-remitting multiple sclerosis.
Compston A, et al, eds. *McAlpine's Multiple Sclerosis.* 4th ed. London, England: Churchill Livingstone; 2005; Confavreux C, et al. *N Engl J Med.* 2000;343(20):1430-1438; Ebers GC, et al. *J Neurol.* 2006;253(suppl 6):VI/3-VI/8; Weinshenker BG, et al. *Brain*. 1989;112(Pt 1):133-146.

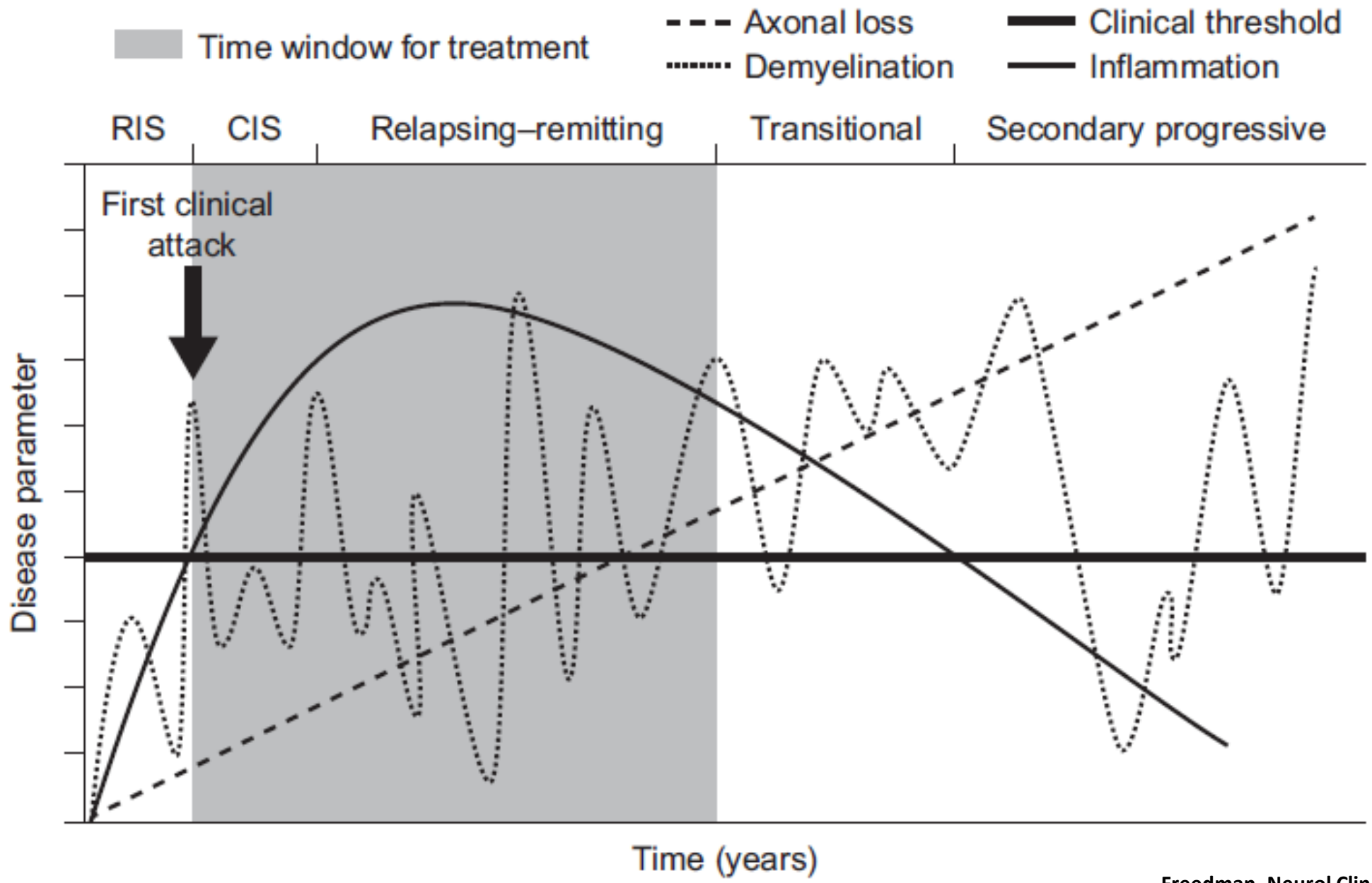
Υπόθεση Δύο σταδίων στην Πολλαπλή Σκλήρυνση
Two stages theory in Multiple Sclerosis

Διαφορετικά επίπεδα επιδείνωσης στην έναρξη ακολουθούνται από σταθερή επιδείνωση αργότερα



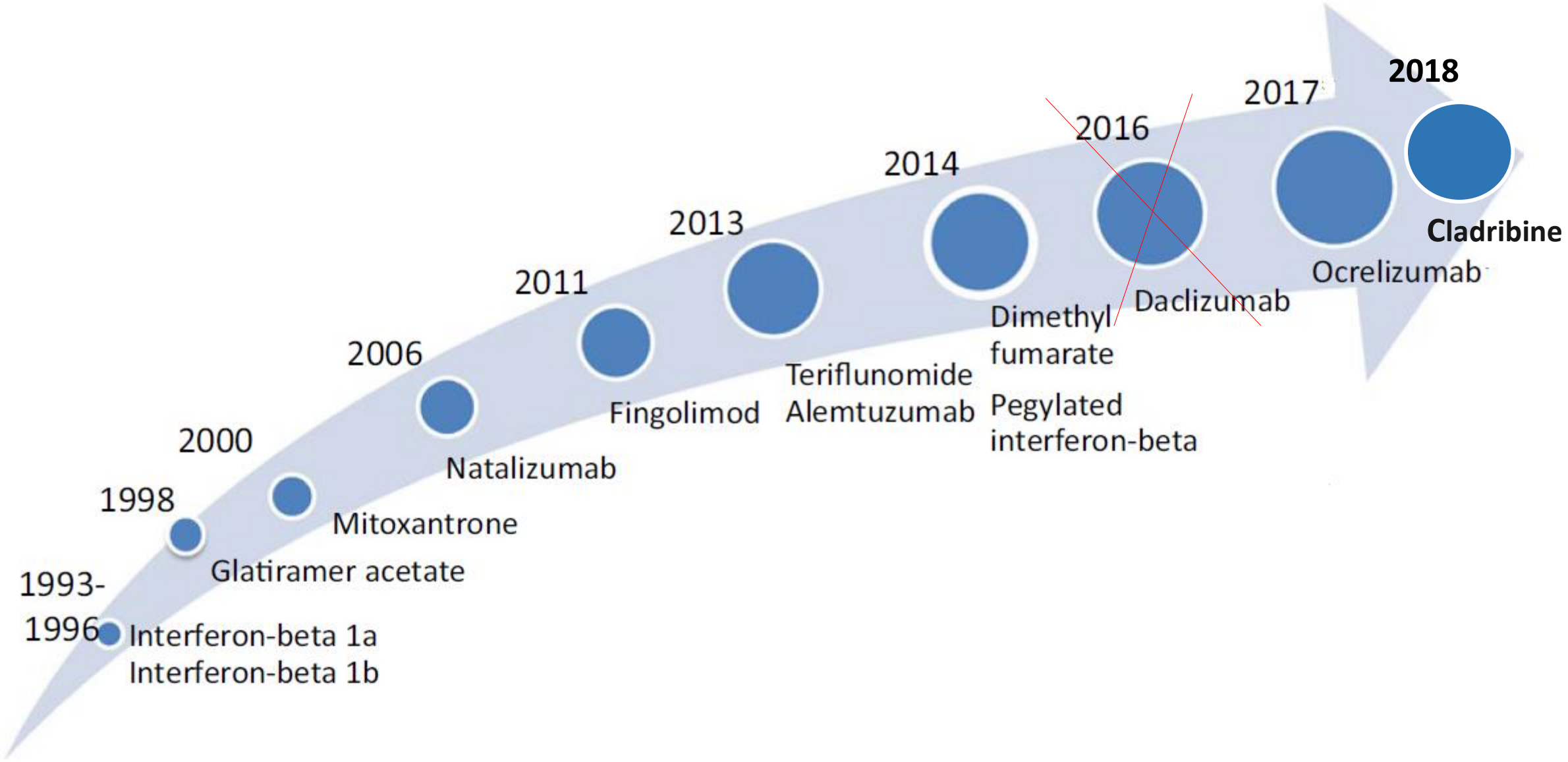
N=718 patients with MS who reached both EDSS 3 and EDSS 6. Phase 1: mean time from DSS 3 to DSS 6; Phase 2: mean time from multiple sclerosis clinical onset to DSS 3)
Leray E *et al. Brain* 2010

TIME WINDOW OF BEST TREATMENT EFFECTIVENESS

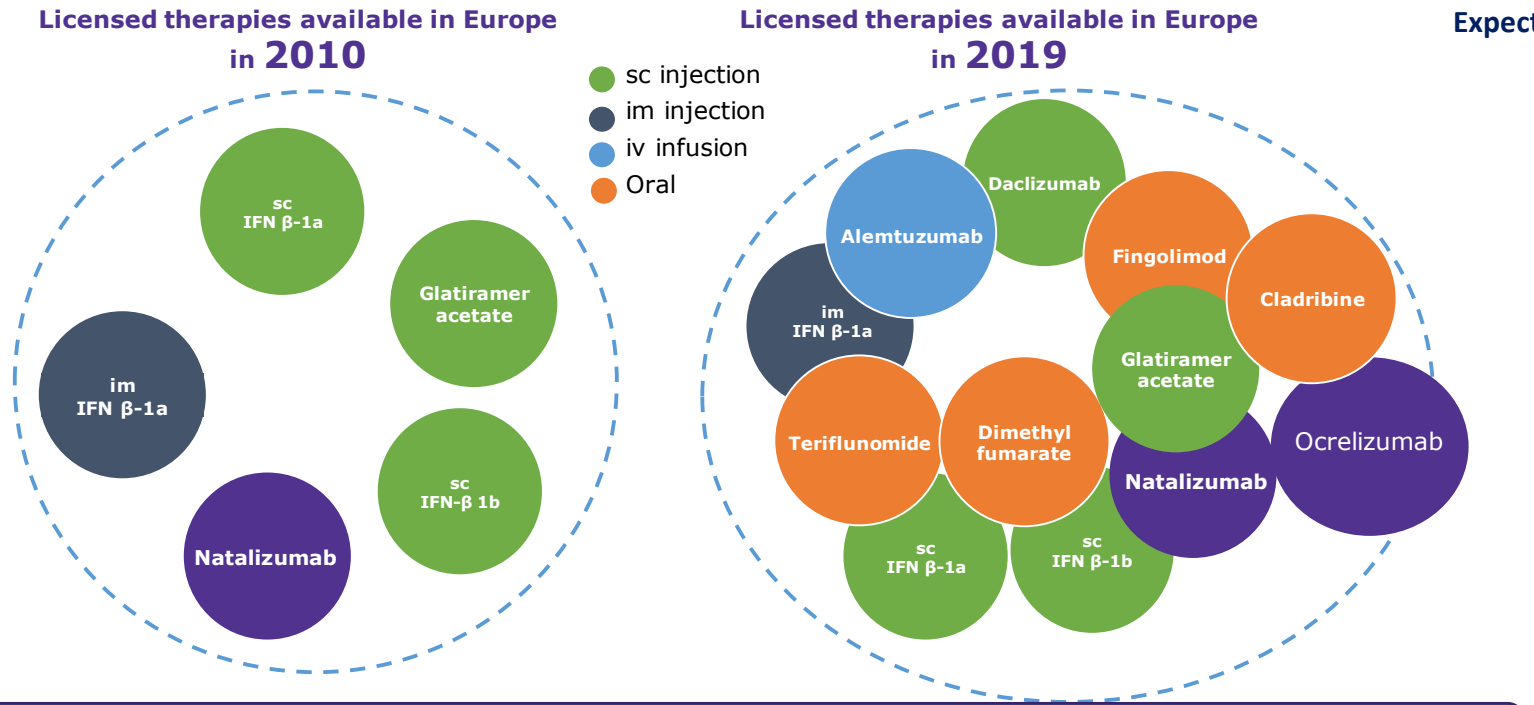


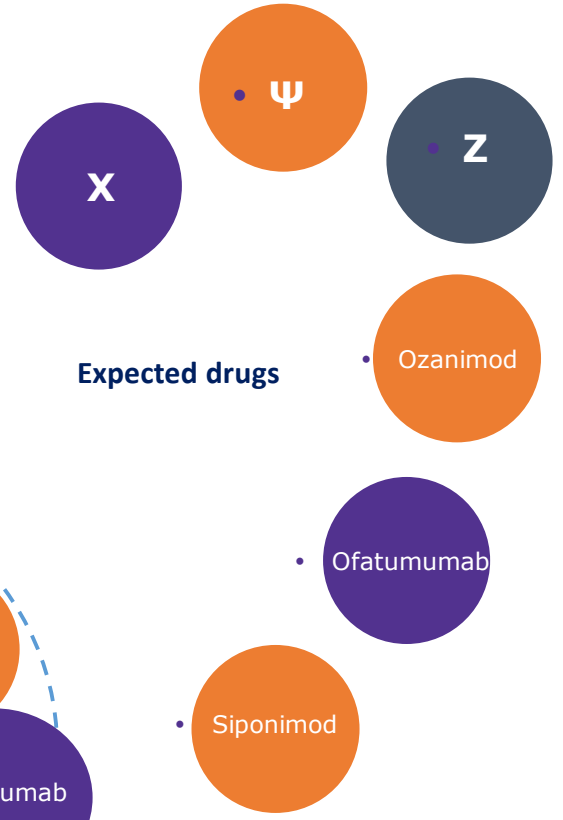
Freedman, Neurol Clin Pract 2011; 1: 66–68 [25].

OUR ARMAMENTARIUM IN MULTIPLE SCLEROSIS TREATMENT



The MS therapeutic landscape has changed dramatically in the last few years





Currently, in the EU there are 10 approved DMDs for MS

DMD, disease-modifying drug; IFN, interferon; im, intramuscular; iv, intravenous; sc, subcutaneous

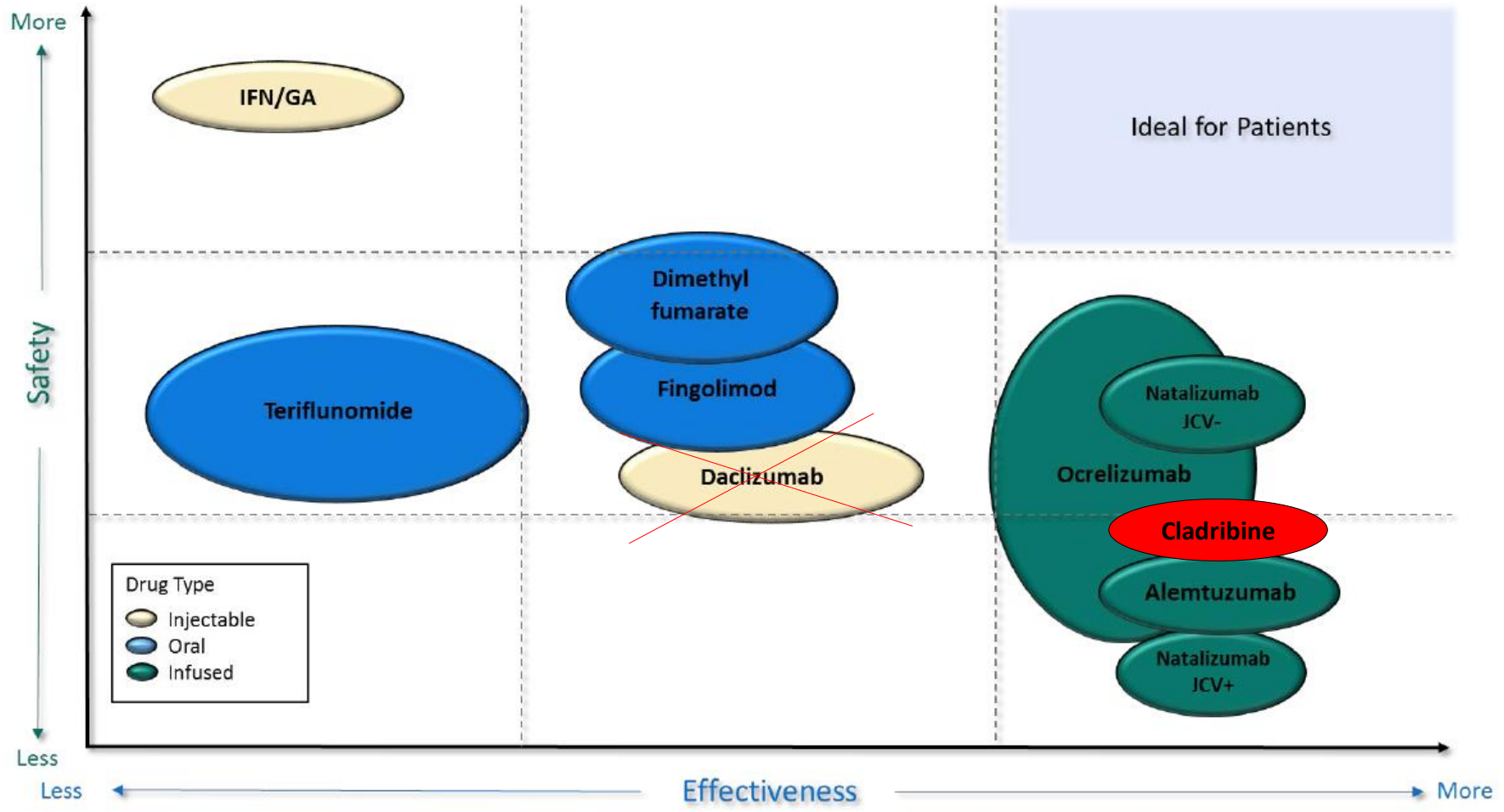
ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value

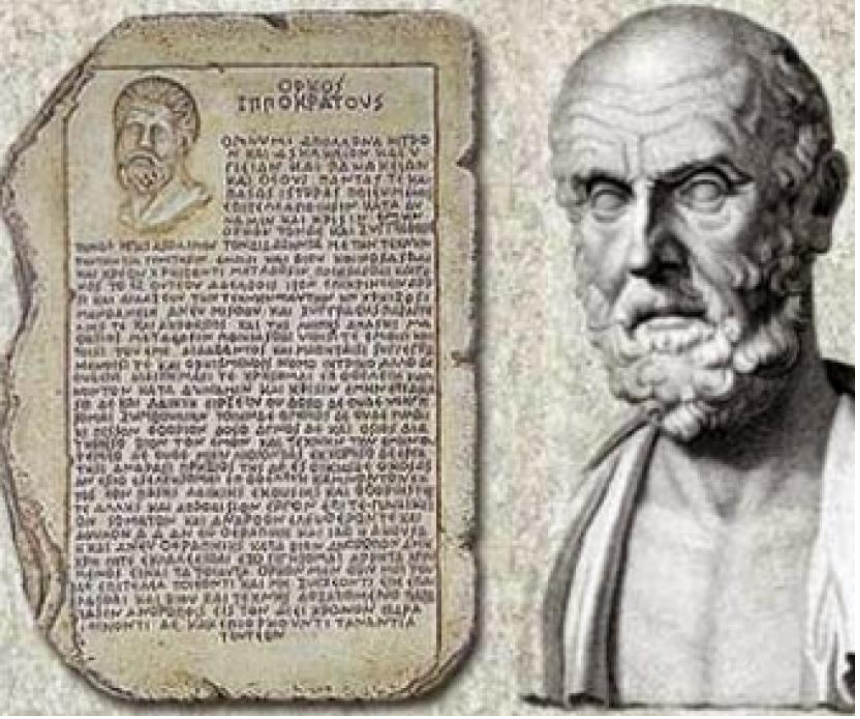
Evidence Report

January 26, 2017

Evidence Report



Wider and taller shapes indicate greater uncertainty. Not drawn to scale.



Θεραπεύουμε τον άνθρωπο και όχι την αρρώστια.
Ιπποκράτης

CHOOSING THE BEST ESTIMATED TREATMENT PER INDIVIDUAL

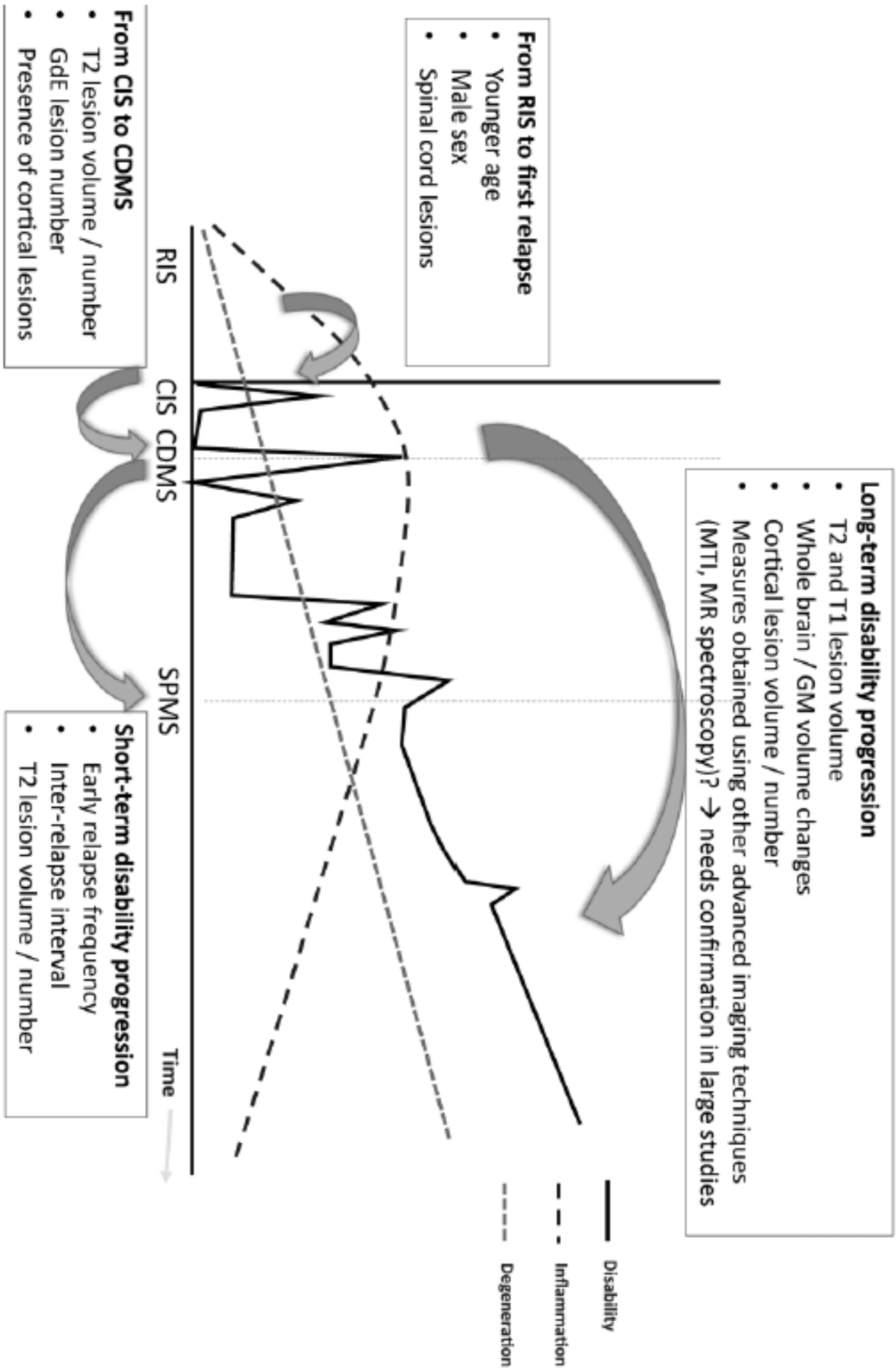
MULTIPLE SCLEROSIS JOURNAL | MSJ

Supplement

The clinical perspective: How to personalise treatment in MS and how may biomarkers including imaging contribute to this?

Multiple Sclerosis Journal
2016, Vol. 22(2S) 18–33
DOI: 10.1177/1352458516650739

Patrick Vermersch, Thomas Berger, Ralf Gold, Carsten Lukas, Alex Rovira, Bianca Meesen, Declan Chard, Manuel Comabella, Jacqueline Palace and Maria Trojano



MULTIPLE SCLEROSIS JOURNAL | MSJ

Supplement

The clinical perspective: How to personalise treatment in MS and how may biomarkers including imaging contribute to this?

Multiple Sclerosis Journal
2016, Vol. 22(2S) 18–33
DOI: 10.1177/1352458516650739

Patrick Vermersch, Thomas Berger, Ralf Gold, Carsten Lukas, Alex Rovira, Bianca Meesen, Declan Chard, Manuel Comabella, Jacqueline Palace and Maria Trojano

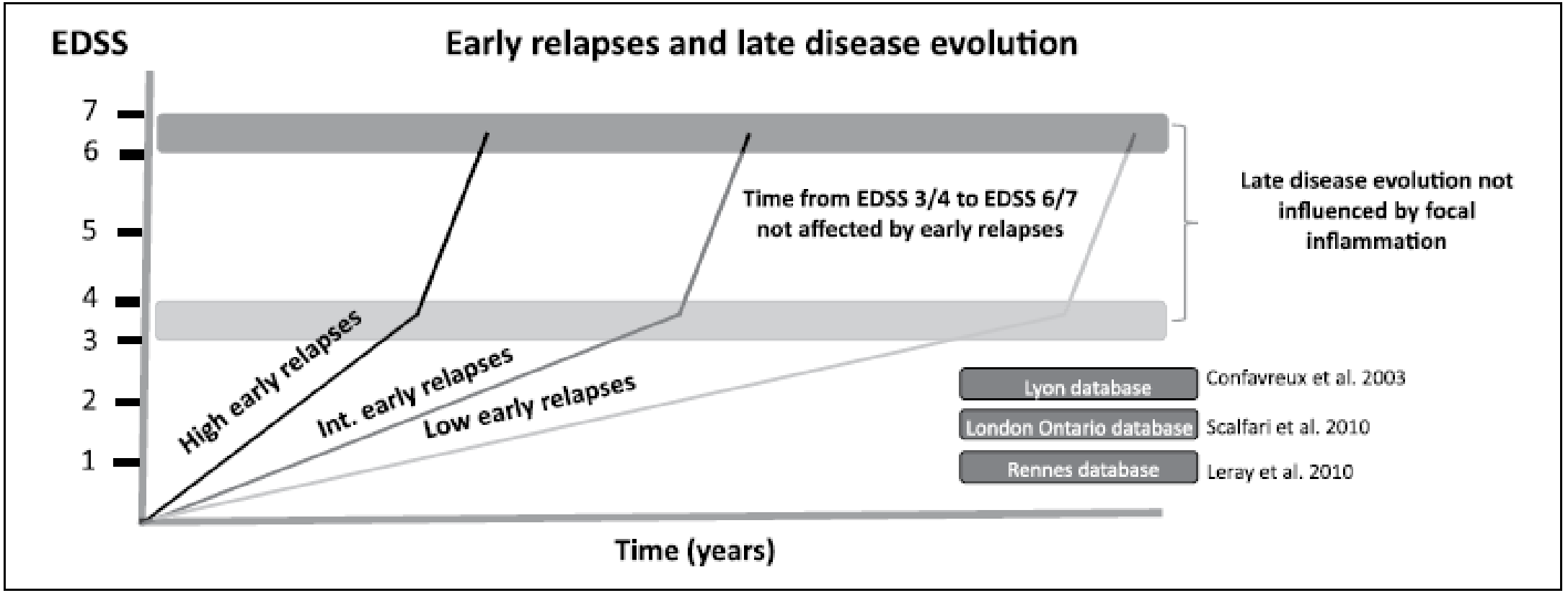


Figure 2. Early relapse rate predicts time to progressive MS, but not late disability progression.[10]

SUBOPTIMAL RESPONSE TO TREATMENT
TREATMENT OPTIMIZATION-
ESCALATING TREATMENT

Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations

*Mark S. Freedman, Daniel Selchen, Douglas L. Arnold, Alexandre Prat, Brenda Banwell, Michael Yeung, David Morgenthau, Yves Lapierre, on behalf of the Canadian Multiple Sclerosis Working Group**

Table 1: Recommendations for determining the level of concern when considering treatment modification based on relapses.*

Criteria	Level of concern		
	Low	**Medium**	**High**
Rate	1 relapse in the second year of treatment	1 relapse in the first year of treatment	>1 relapse in the first year of treatment
Severity	Mild • Steroids not required • Minimal effect on ADL • 1 functional domain affected • No or mild motor/ cerebellar involvement	Moderate • Steroids required • Moderate effect on ADL • >1 functional domain affected • Moderate motor/ cerebellar involvement	Severe • Steroids/ hospitalization required • Severe effect on ADL • >1 functional domain affected • Severe motor/ cerebellar involvement
Recovery (duration)	• Prompt recovery • No functional deficit	• Incomplete recovery at 3 months • Some functional impairment	• Incomplete recovery at 6 months • Functional impairment

* The level of concern determined by meeting at least one criterion. ADL=activities of daily living

Can J Neurol Sci. 2013; 40: 307-323

Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations

*Mark S. Freedman, Daniel Selchen, Douglas L. Arnold, Alexandre Prat, Brenda Banwell, Michael Yeung, David Morgenthau, Yves Lapierre, on behalf of the Canadian Multiple Sclerosis Working Group**

Table 2: Recommendations for determining the level of concern when considering treatment modification based on disability progression

Criteria	Level of concern		
EDSS score	**Low**	**Medium**	**High**
≤ 3.5	≤ 1 points	2 points at 6 months*	>2 points at 6 months* 2 points at 12 months*
4.0 to 5.0	< 1 point	1 point at 6 months*	>1 point at 6 months* 1 point at 12 months*
≥ 5.5		0.5 points at 6 months*	>0.5 points at 6 months
Clinically documented progression	No motor Minor sensory	Some motor, cerebellar or cognitive Multiple EDSS domains affected	Pronounced motor, cerebellar or cognitive Multiple EDSS domains affected
T25FW**	≤ 20% confirmed at 6 months	> 20% and < 100% increase confirmed at 6 months	≥ 100% increase confirmed at 6 months

*If EDSS progression alone is used to assess response to treatment, any change requires subsequent confirmation at 3-6 months.

**Timed 25-foot Walk tested at baseline with aid, if required

Can J Neurol Sci. 2013; 40: 307-323

Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations

*Mark S. Freedman, Daniel Selchen, Douglas L. Arnold, Alexandre Prat, Brenda Banwell, Michael Yeung, David Morgenthau, Yves Lapierre, on behalf of the Canadian Multiple Sclerosis Working Group**

Table 3: Recommendations for determining the level of concern when considering treatment modification based on annual MRI findings

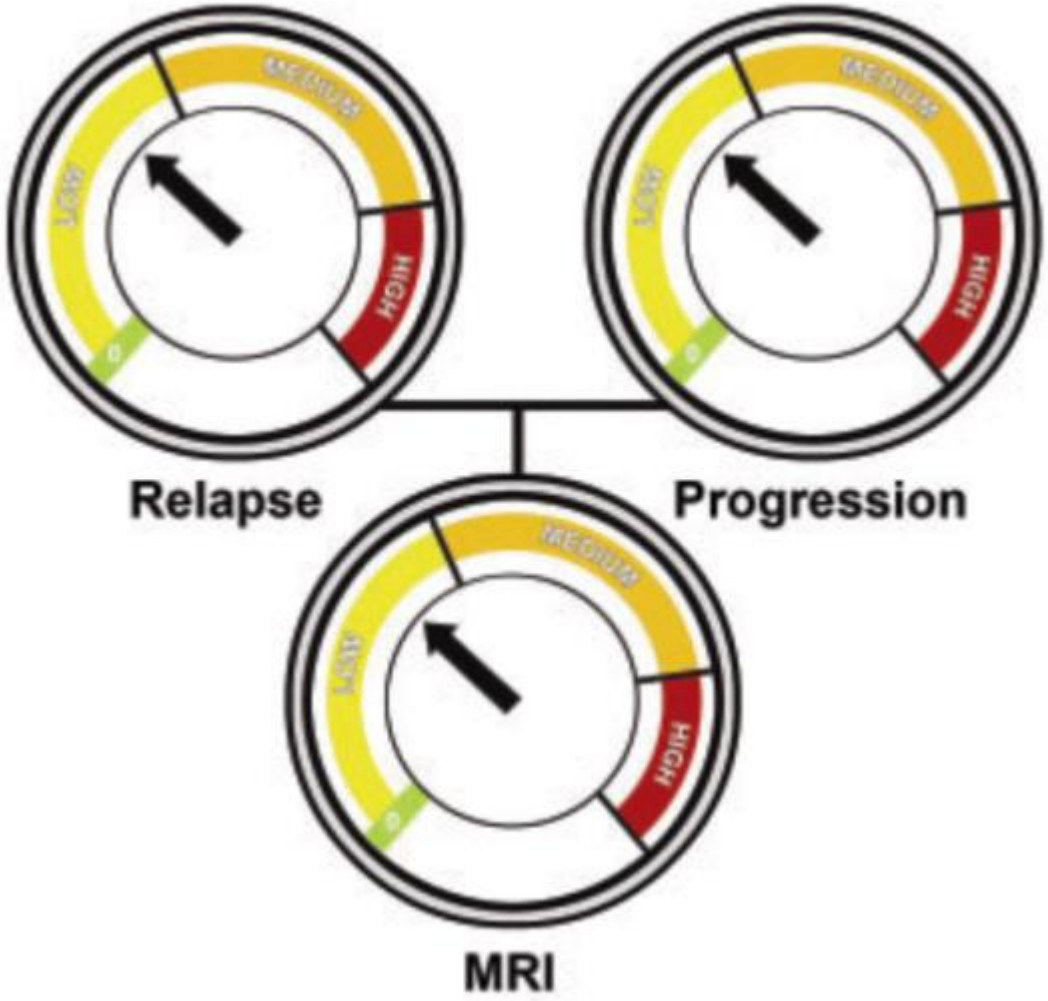
	Level of concern		
Activity on MRI*	**Low**	**Medium**	**High**
New Gd-enhancing lesions OR Accumulation of new T2 lesions per year	1 lesion	2 lesions	≥3 lesions

Note: Routine follow-up MRI with gadolinium (Gd) is recommended 6-12 months after initiating therapy for RRMS (or in CIS if therapy is not initiated). Note: New T2 lesions that are also enhancing on the same scan are only counted once as unique active lesions. *The presence of Gd-enhancing lesions is more reliable than new T2 lesion counts. New T2 lesion counts require high-quality comparable MRI scans and interpretation by highly qualified individuals[77].

Can J Neurol Sci. 2013; 40: 307-323

Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations

*Mark S. Freedman, Daniel Selchen, Douglas L. Arnold, Alexandre Prat, Brenda Banwell, Michael Yeung, David Morgenthau, Yves Lapierre, on behalf of the Canadian Multiple Sclerosis Working Group**



Each gauge represents a continuum from no concerns (**0 on the dial**) through **low**, **medium** or **high** levels of concern.

Consider three 'low' and whatever higher than this combination as a possible suboptimal treatment indicator that warrant a change in management

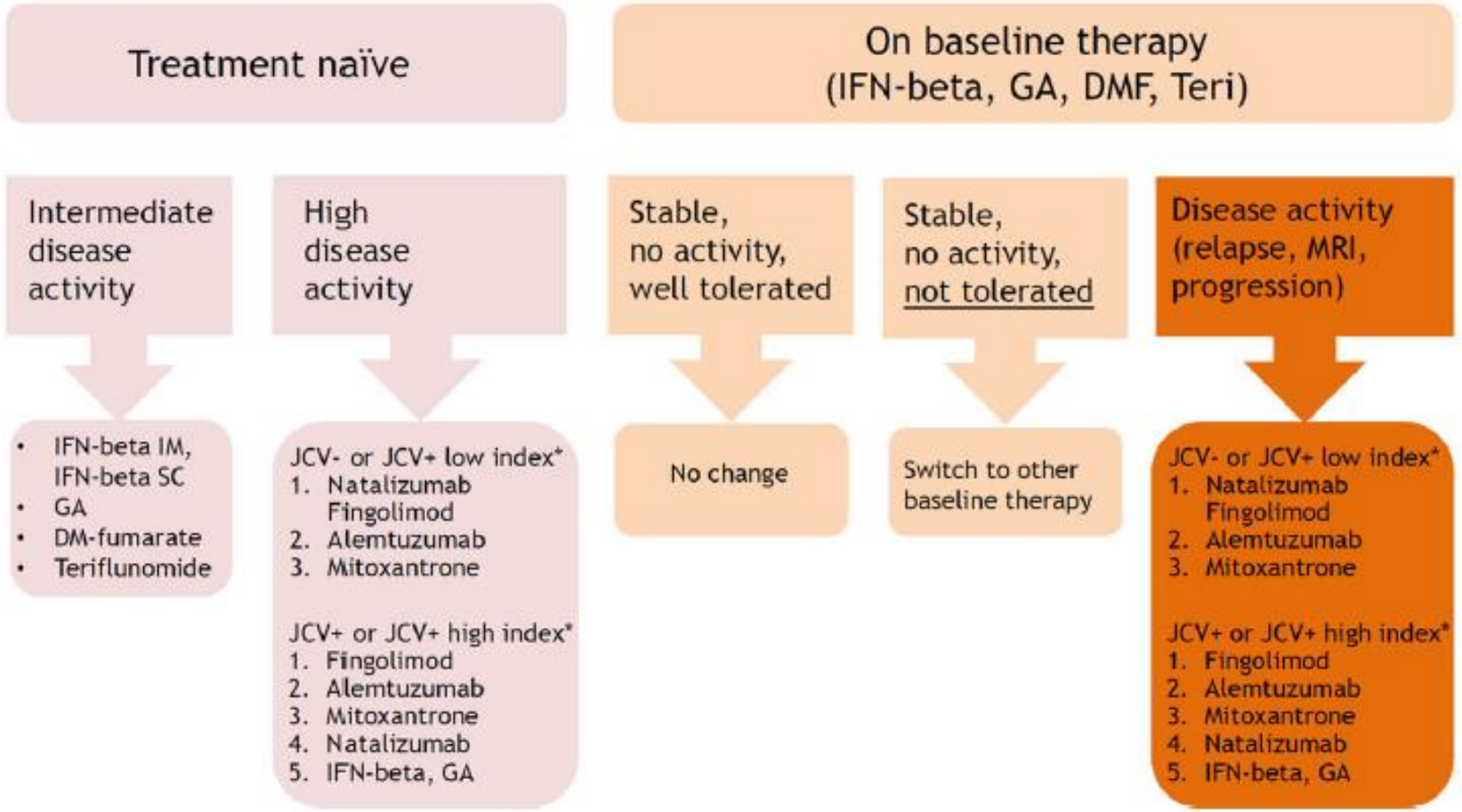
Can J Neurol Sci. 2013; 40: 307-323

Neurotherapeutics (2016) 13:47–57
DOI 10.1007/s13311-015-0412-4

REVIEW

Advances in and Algorithms for the Treatment of Relapsing-Remitting Multiple Sclerosis

Jens Ingwersen[1] · Orhan Aktas[1] · Hans-Peter Hartung[1]

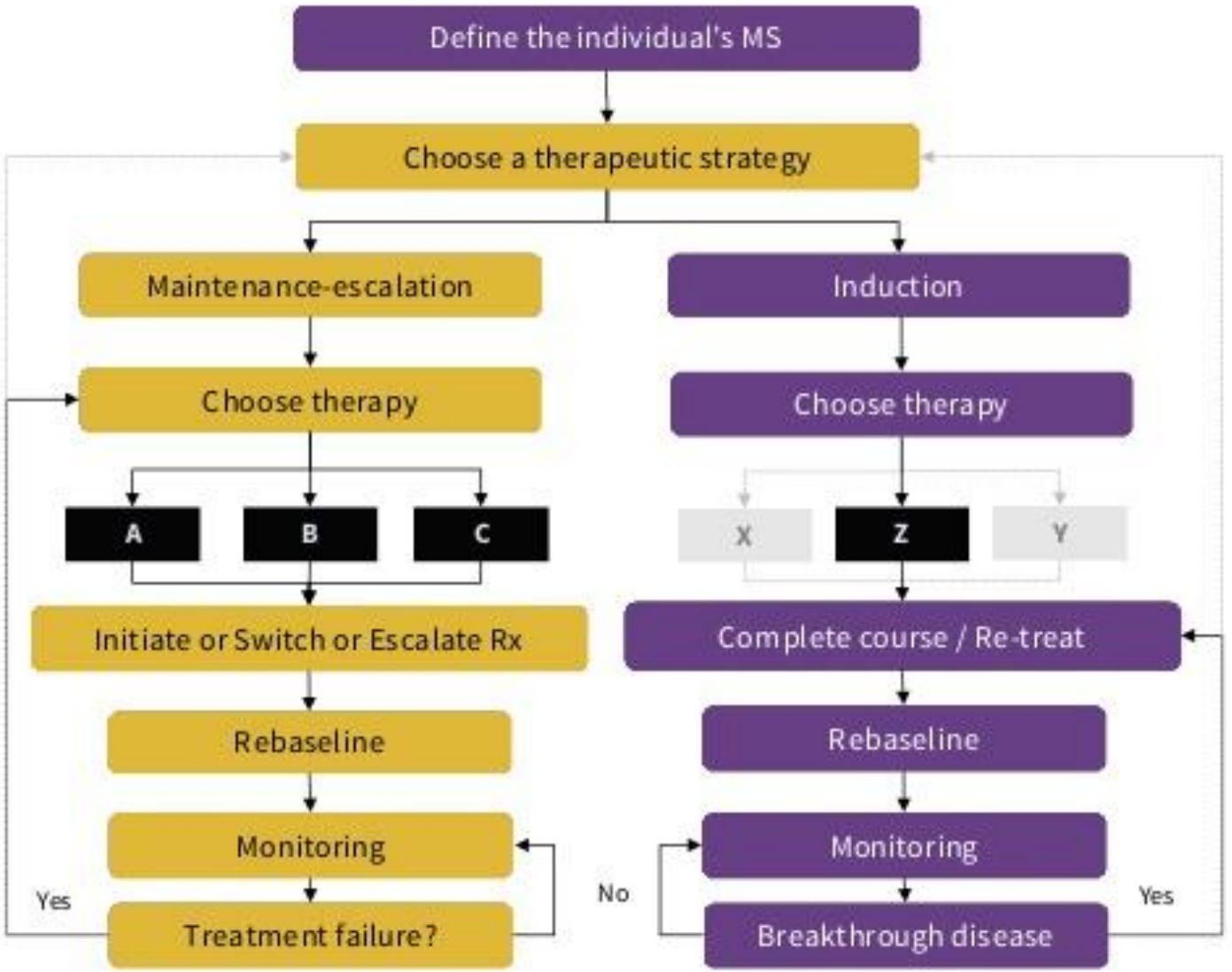


Induction Therapy

- **In Multiple Sclerosis??**

This treatment strategy involves the use of immuno-suppressant strategies for the minimum amount of time needed to gain adequate control over disease activity. **Once disease control has been achieved, treatment can be switched to maintenance therapy** with a better tolerated drug.

Evolving Paradigm: Individualised Treatment Based on Projected Disease Course



- MS prognosis based on clinical and MRI indices
- Life style and goals
- Shared goals for therapy

- MSer's preferences?
- Your choice?

- MSer's preferences?
- Your choice?

- Only one licensed induction therapy at present

Rebaselining:
- IFNβ, natalizumab, fingolimod, teriflunomide, Dimethyl-Fumarate=3-6 months
- Glatiramer acetate=9 months
- Alemtuzumab=24 months

Individual measures:
- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Drug or inhibitory markers, e.g. NABs?

Giovannoni et al. MSARD 2015 in press.

Relevant Issues while Thinking of Induction Therapy

- MS is universally a severe disease and brain degeneration and atrophy present from the early stages and are gradually accelerated in all patients.
- There is a narrow window for effective intervention which is usually in the early phases of the disease where inflammatory processes predominate.
- We should be aware and take into consideration of the existing and well described **patients' characteristics** that would help us to successfully identify the **"patients at risk"** for severe future disability progression or transformation to Secondary Progressive MS in a rather short period of time (aggressive disease) either from the very beginning (naïve high risk patients) or very soon after initiating an MS treatment (definition non-responders/ high risk patients).
- Induction therapies have a long-term effect in the majority of the patients. We may need to think of using more conservative treatment plans following induction and succeeding the remission of the disease but yet information is lacking

Severe, Highly Active, or Aggressive Multiple Sclerosis

Mark S. Freedman, MSc, MD, FAAN, FRCPC;
Carolina A. Rush, MD, FRCPC

Review Article CONTINUUM

Continuum (Minneap Minn) 2016;22(3):761–784

TABLE 4-1 Factors Associated With a Poorer Prognosis in Multiple Sclerosis

- ▶ **Demographics**
  - Male
  - Older than 40 years at onset
  - African American, African Latin American
- ▶ **Relapse Characteristics**
  - Severity of relapse
    - Moderate/severe (≥1 point change on EDSS or ≥2 point change on any individual KFS, or ≥1 point change on any two KFS)
    - Steroid requirement
    - Hospital admission
  - Type of attack
    - Multifocal
    - Partial or incomplete recovery
    - Affecting motor, cerebellar, sphincteric, or cognitive functions
  - Frequency
    - Frequent relapses in the first 2–5 years
    - Short interattack interval
- ▶ **Disease Course**
  - Rapid accrual of disability (EDSS of 3.0 within 5 years with superimposed relapses)
  - Progressive from onset
- ▶ **MRI Features**
  - At onset
    - High T2 lesion burden
    - More than two gadolinium-enhancing lesions
    - Presence of T1-hypointense lesions (black holes)
    - Early discernable atrophy
    - Infratentorial versus supratentorial lesions
  - Follow-up MRI while on treatment
    - Presence of new T2 lesions
    - More than one gadolinium-enhancing lesion

EDSS = Expanded Disability Status Scale; KFS: Kurtzke Functional System; MRI = magnetic resonance imaging.

Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations

*Mark S. Freedman, Daniel Selchen, Douglas L. Arnold, Alexandre Prat, Brenda Banwell, Michael Yeung, David Morgenthau, Yves Lapierre, on behalf of the Canadian Multiple Sclerosis Working Group**

Relapses

High
>1 relapse in the first year of treatment
Severe • Steroids/ hospitalization required • Severe effect on ADL • >1 functional domain affected • Severe motor/ cerebellar involvement
• Incomplete recovery at 6 months • Functional impairment

EDSS Change

High
>2 points at 6 months* 2 points at 12 months*
>1 point at 6 months* 1 point at 12 months*
>0.5 points at 6 months
Pronounced motor, cerebellar or cognitive Multiple EDSS domains affected
≥ 100% increase confirmed at 6 months

MRI Lesions*

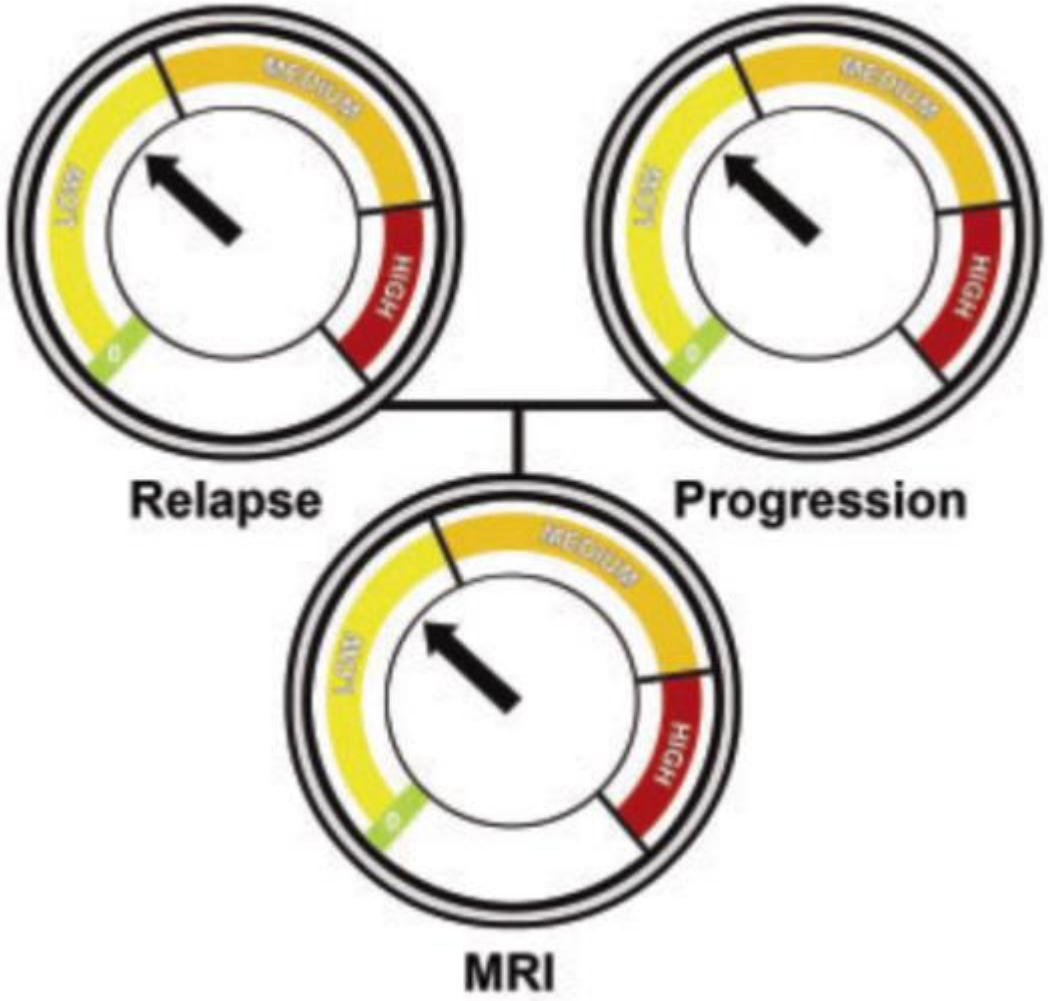
High
≥3 lesions

*The presence of Gd-enhancing lesions is more reliable than new T2 lesion counts.

Can J Neurol Sci. 2013; 40: 307-323

Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations

*Mark S. Freedman, Daniel Selchen, Douglas L. Arnold, Alexandre Prat, Brenda Banwell, Michael Yeung, David Morgenthau, Yves Lapierre, on behalf of the Canadian Multiple Sclerosis Working Group**



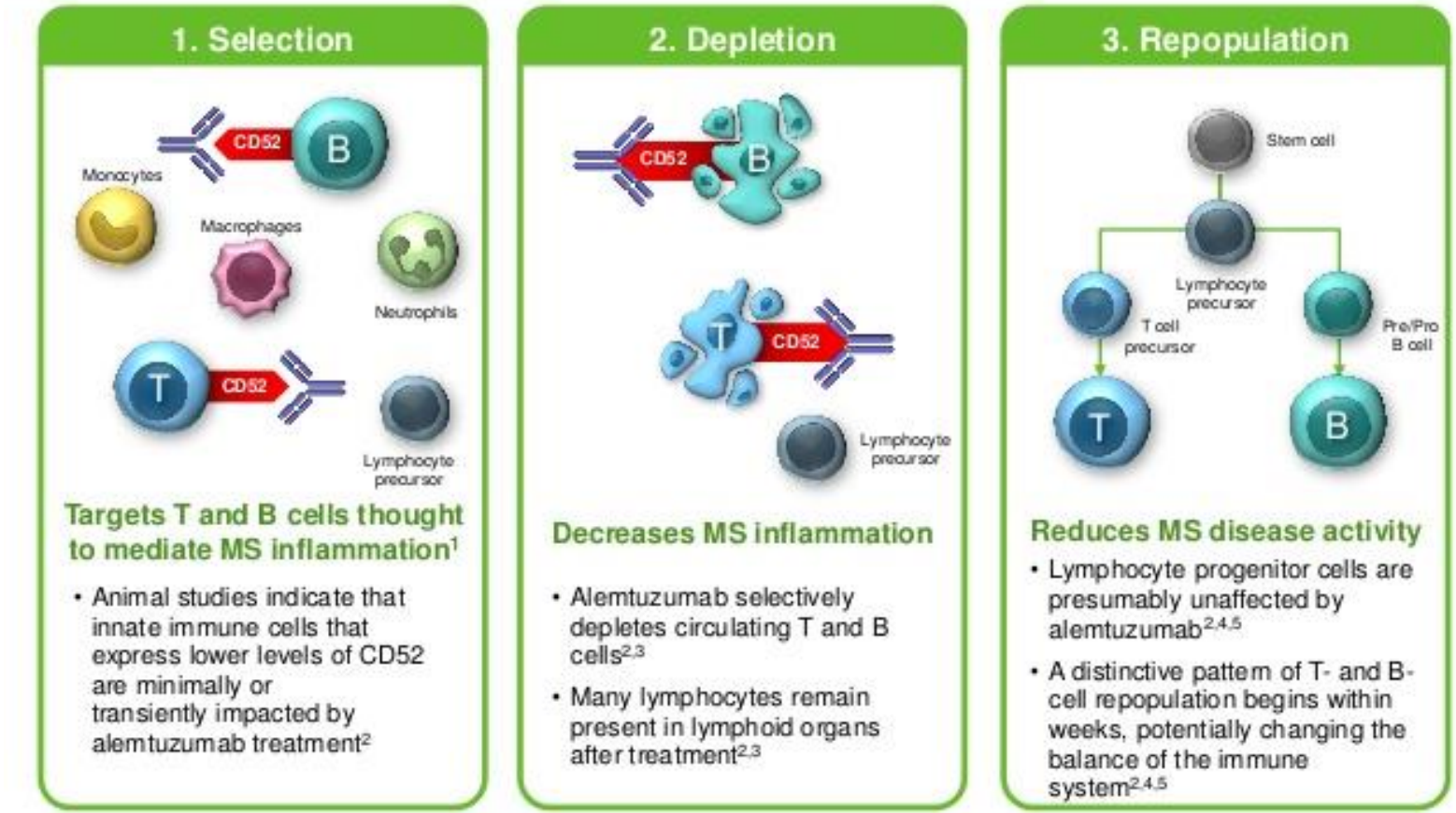
Each gauge represents a continuum from no concerns (**0 on the dial**) through **low**, **medium** or **high** levels of concern.

Consider two or more "highs" as a possible aggressive disease indicator that warrants an induction therapy

Can J Neurol Sci. 2013; 40: 307-323

ALEMTUZUMAB

Alemtuzumab: Mechanism of Action



1. Weber MS et al. *Results Probl Cell Differ* 2010;51:115-26; 2. Hu Y et al. *Immunology* 2009;128:260-70; 3.Turner MJ et al. *J Neuroimmunol* 2013;261:29-36; 4. Cox AL et al. *Eur J Immunol* 2005;35:3332-42; 5. Fox EJ. *Exp Rev Neurother* 2010;10:1789-97.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alemtuzumab vs. Interferon Beta-1a in Early Multiple Sclerosis

The CAMMS223 Trial Investigators* N Engl J Med 2008;359:1786-801.

METHODS

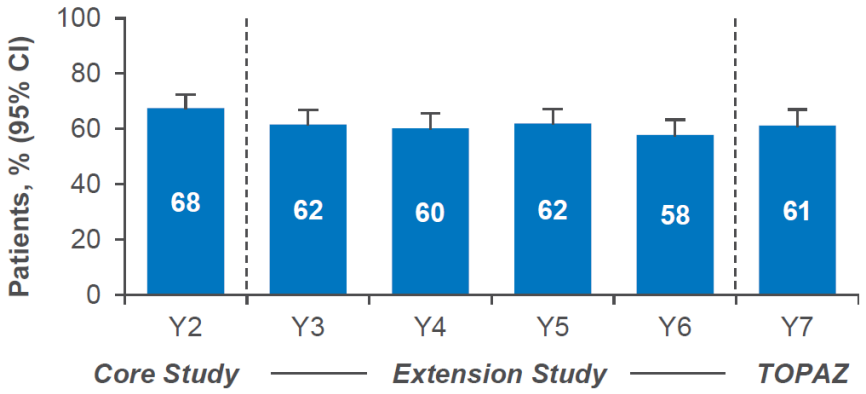
In this phase 2, randomized, blinded trial involving previously untreated, early, relapsing–remitting multiple sclerosis, we assigned 334 patients with scores of 3.0 or less on the Expanded Disability Status Scale and a disease duration of 3 years or less to receive either subcutaneous interferon beta-1a (at a dose of 44 μg) three times per week or annual intravenous cycles of alemtuzumab (at a dose of either 12 mg or 24 mg per day) for 36 months.

RESULTS

Alemtuzumab significantly reduced the rate of sustained accumulation of disability, as compared with interferon beta-1a (9.0% vs. 26.2%; hazard ratio, 0.29; 95% confidence interval [CI], 0.16 to 0.54; P<0.001) and the annualized rate of relapse (0.10 vs. 0.36; hazard ratio, 0.26; 95% CI, 0.16 to 0.41; P<0.001). The mean disability score on a 10-point scale improved by 0.39 point in the alemtuzumab group and worsened by 0.38 point in the interferon beta-1a group (P<0.001). In the alemtuzumab group, the lesion burden (as seen on T_2-weighted magnetic resonance imaging) was reduced, as compared with that in the interferon beta-1a group (P=0.005).

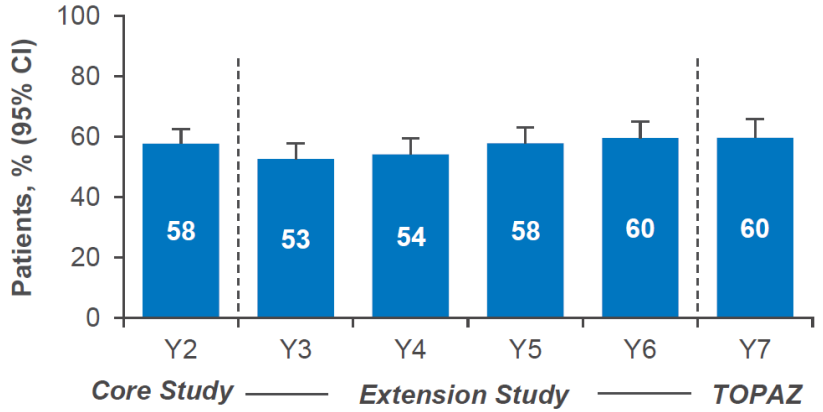
NEDA Clinical Data: 7-Year Follow-up of CARE-MS I & II Patients

NEDA Over 7 Years (CARE-MS I)[1]



	Y2	Y3	Y4	Y5	Y6	Y7
Free of clinical disease activity	85%	82%	84%	84%	85%	86%
Free of MRI disease activity	77%	72%	70%	69%	66%	68%

NEDA Over 7 Years (CARE-MS II)[2]



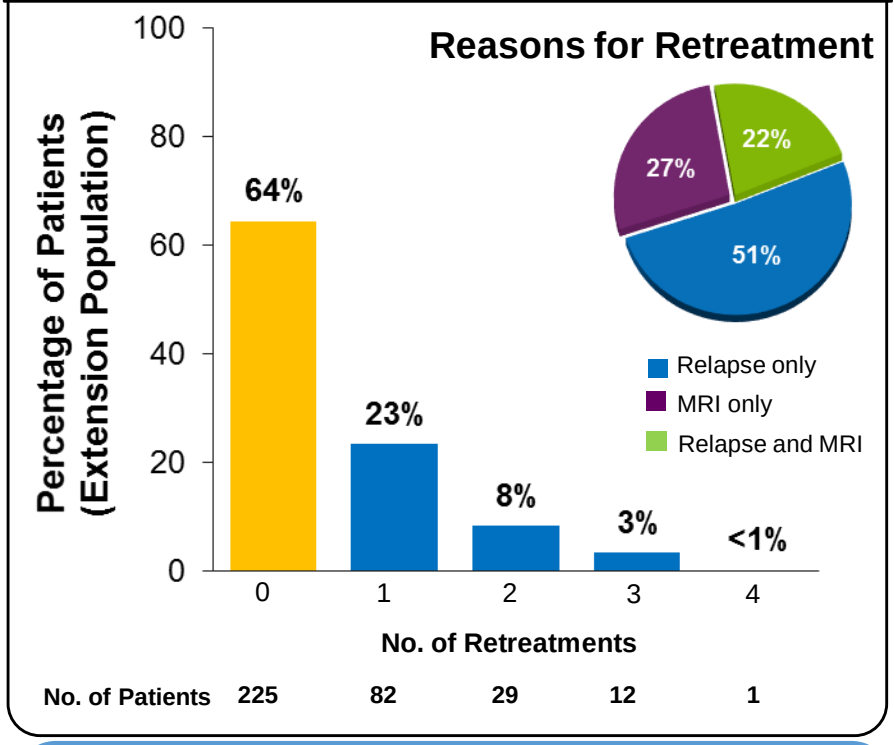
	Y2	Y3	Y4	Y5	Y6	Y7
Free of clinical disease activity	73%	76%	74%	79%	85%	85%
Free of MRI disease activity	76%	68%	70%	68%	69%	67%

- NEDA was achieved by the majority of patients in each year (Years 3–7)[1,2]

NEDA: absence of clinical disease activity (relapses and 6-month CDW) and MRI disease activity (new gadolinium-enhancing T1 and new/enlarging T2 hyperintense lesions)
NEDA: No evidence of disease activity. CDW: Confirmed disability worsening
1. Coles AJ, et al. ECTRIMS 2017, P1188 ; 2. Singer BA, et al. ECTRIMS 2017, P736

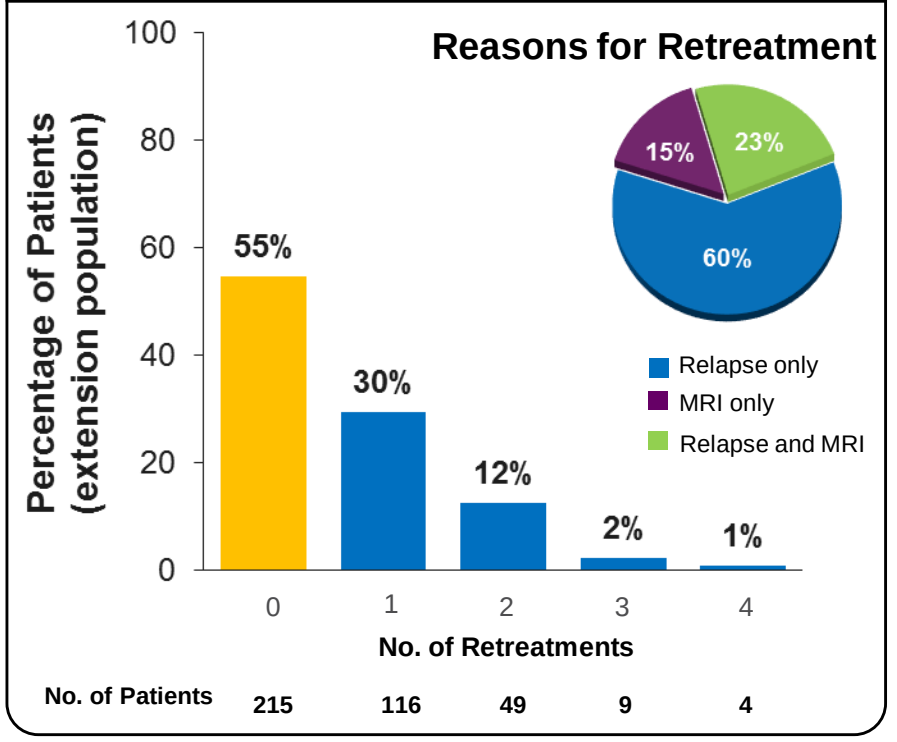
Majority of Patients Did Not Receive Alemtuzumab Retreatment or Another DMT Through Year 6

CARE-MS I[1]



- Through 6 years, 221 (63%) of the patients who entered the extension did not receive alemtuzumab retreatment or another DMT
- 225 (64%) did not receive alemtuzumab retreatment
- 340 (97%) did not receive another DMT

CARE-MS II[2]



- Through 6 years, 196 (50%) of the patients who entered the extension did not receive alemtuzumab retreatment or another DMT
- 215 (55%) did not receive alemtuzumab retreatment
- 353 (90%) patients did not receive another DMT

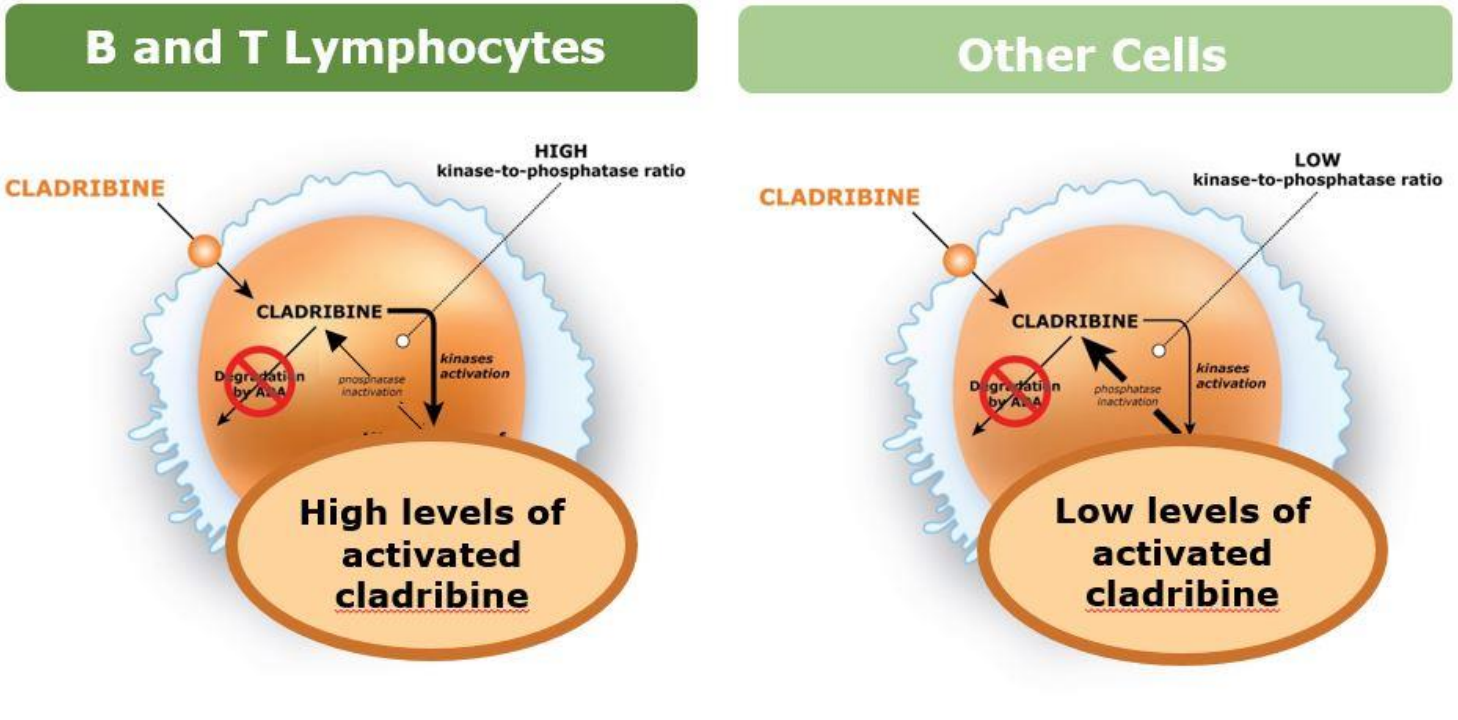
1. Wiendl H, Dive D, Dreyer M, et al. ECTRIMS 2016. P682. 2. LaGanke C, de Sèze J, Freedman MS, et al. ECTRIMS 2016. P681.

Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing

In addition to the restriction, EMA's safety committee (PRAC) has recommended an update of the product information for Lemtrada to inform patients and healthcare professionals about cases of:

- immune-mediated conditions, including autoimmune hepatitis (with damage to the liver) and haemophagocytic lymphohistiocytosis (overactivation of the immune system which may affect different parts of the body);
- problems with the heart and blood vessels occurring within 1–3 days of receiving the medicine, including bleeding in the lungs, heart attack, stroke, cervicocephalic arterial dissection (tears in the lining of the arteries in the head and neck);
- severe neutropenia (low levels of neutrophils, a type of white blood cell that fights infections).

CLADRIBINE

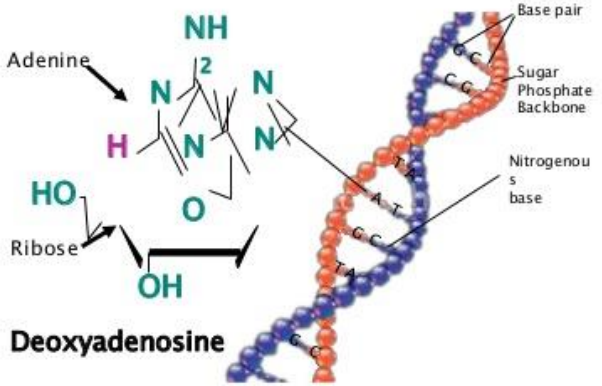


ADA, adenosine deaminase. Saven A, Piro LD. *Ann Intern Med* 1994;120:784–91.
Leist TP, Weissert R. *Clin Neuropharmacol* 2011;34:28–35.

Cladribine is an analog of deoxyadenosine

- Cladribine is an analog of deoxyadenosine, one of the building blocks of DNA, that differs from the naturally occurring nucleoside, deoxyadenosine by a **chlorine** substitution for hydrogen[1,2]
- Cladribine is resistant to deamination by the enzyme **adenosine deaminase** (**ADA**) by virtue of its structural design[1,2]

2-chlorodeoxyadenosine (cladribine)



Deoxyadenosine

1. Carson DA et al. Proc Natl Acad Sci USA 1980;77:6865–9. 2. Beutler E. Lancet 1992;340:952–6

Phosphorylation of cladribine to its active triphosphate form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), is particularly efficiently achieved in lymphocytes, due to their constitutively high deoxycytidine kinase (DCK) and relatively low 5'-nucleotidase (5'-NTase) -(phosphatase) levels.

MAVENCLAD® delivered consistent clinical and radiological efficacy across the overall study population[1–4]

Reduction in ARR[2]

58%

p<0.001
vs placebo

p<0.001
MAVENCLAD® [n=433]: 0.14 vs. placebo [n=437]: 0.33
Primary endpoint

47%

p=0.0016
vs placebo

Reduction in 6-month confirmed EDSS progression[3]

p=0.0016
MAVENCLAD® [n=433] vs placebo [n=437]
Time to 6-month EDSS progression:
HR 0.53 (0.36–0.79)
Post hoc analysis

Reduction in T1 Gd+ lesions[2]

86%

p<0.001
vs placebo

p<0.001
MAVENCLAD® [n=433]: 0.12 vs. placebo [n=437]: 0.91
Secondary endpoint

73%

p<0.001
vs placebo

Reduction in active T2 lesions[2]

p<0.001
MAVENCLAD® [n=433]: 0.38 vs placebo [n=437]: 1.43
Secondary endpoint

Data from 2-year CLARITY trial. ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SmPC, Summary of Product Characteristics; T2, active T2-weighted.

1. Giovannoni G et al. Lancet Neurol 2011;10:329–37; 2. Giovannoni G et al. N Engl J Med 2010;362:416–26; 3. Cook S et al. AAN 2016 [P3.058]; 4. MAVENCLAD® EU SmPC, September 2017

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Safety and efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study

Multiple Sclerosis Journal
1–11
DOI: 10.1177/1352458517727603

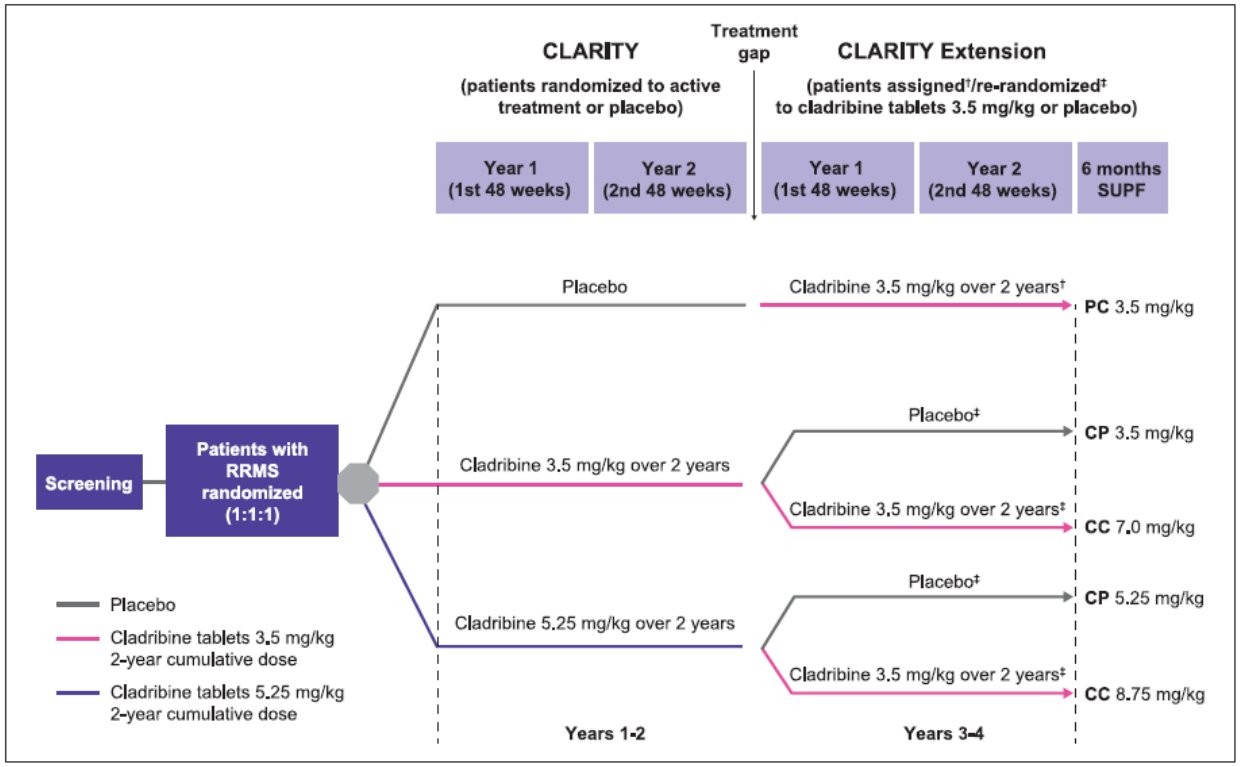


Table 4. Summary of clinical efficacy endpoints.

	CP 3.5 mg/kg ($n = 98$)	CP 5.25 mg/kg ($n = 92$)	CC 7 mg/kg ($n = 186$)	CC 8.75 mg/kg ($n = 186$)	PC 3.5 mg/kg ($n = 244$)
Annualized relapse rate (97.5% CI)	0.15 (0.09, 0.21)	0.13 (0.08, 0.19)	0.10 (0.06, 0.13)	0.12 (0.08, 0.16)	0.10 (0.07, 0.13)
Proportion of patients qualifying relapse-free, *n* (%)	68 (75.6)	61 (75.3)	134 (81.2)	132 (76.7)	180 (79.6)
Proportion of patients who remained free of confirmed 3-month EDSS progression, *n* (%)	71 (72.4)	72 (78.3)	144 (77.4)	142 (76.3)	185 (75.8)

INDUCTION THERAPIES

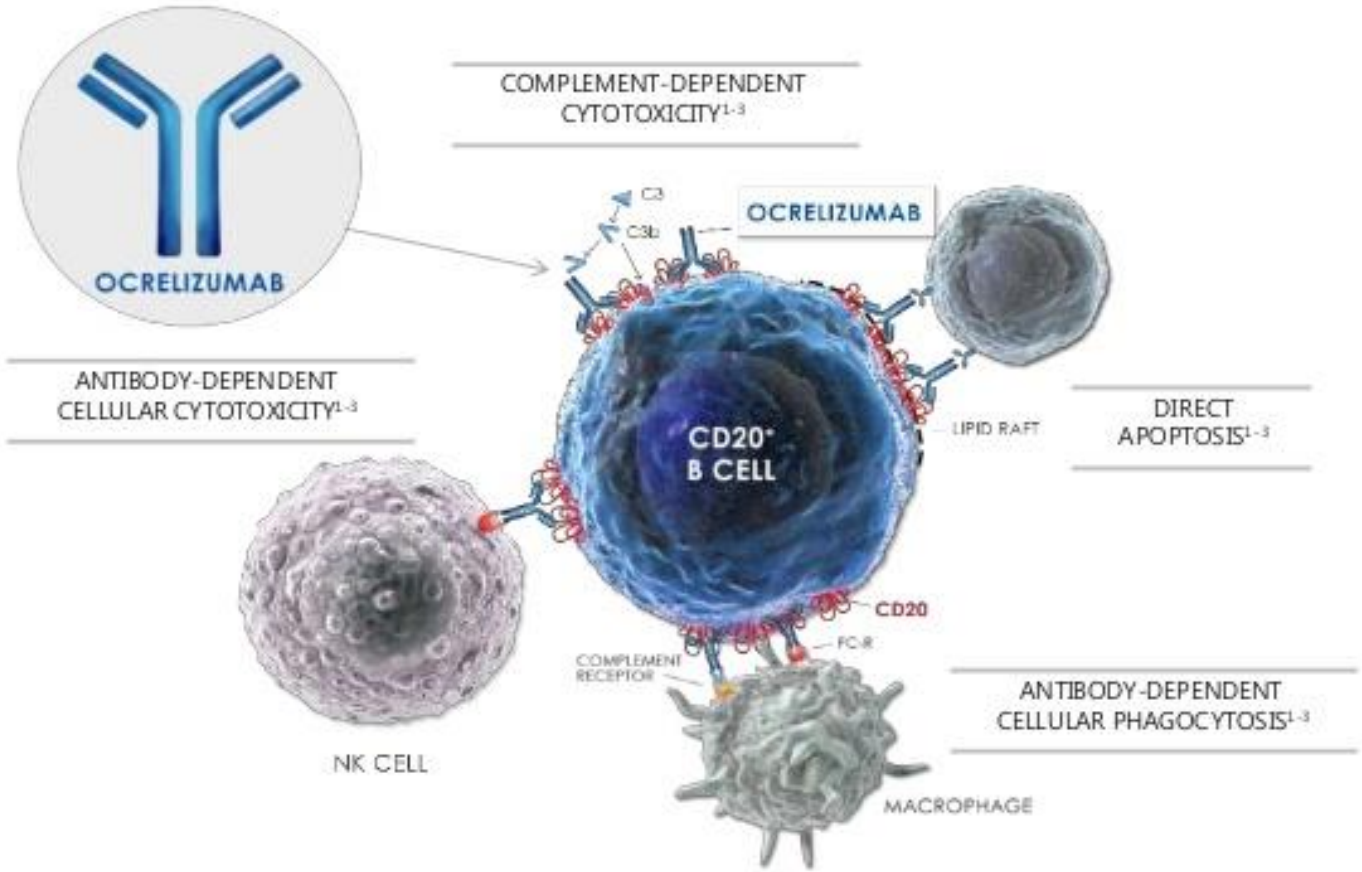
- **MAVENCLAD (Cladribine)**

The recommended cumulative dose of MAVENCLAD is 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight

Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.

OCRELIZUMAB

Ocrelizumab is a humanized mAb that depletes CD20+ B cells via multiple mechanisms



mAb, monoclonal antibody.

1. Jaglowski SM, *et al. Blood* 2010;116:3705–14; 2. Winiarska M, *et al. Front Biosci* 2011;16:277–306; 3. Klein C, *et al.* MAbs 2013;5:22–33.

OCRELIZUMAB

This indicates either a long-term depletion effect or, more likely, an induction effect with long term-efficacy following only a short series of treatments, given the similarity of the putative mechanisms of action with cladribine and alemtuzumab[1]

1. EBioMedicine 16 (2017) 41–50

Week 144 Results of a Phase II, Randomized, Multicenter Trial Assessing the Safety and Efficacy of Ocrelizumab in Patients with Relapsing–Remitting Multiple Sclerosis (RRMS) (S31.004)

Stephen Hauser, David Li, Peter Calabresi, Paul O'Connor, Amit Bar-Or, Frederik Barkhof, Annette Sauter, David Leppert, Donna Masterman, Jeroen Tinbergen and Ludwig Kappos

BACKGROUND: A Phase II RRMS trial showed that ocrelizumab (OCR) reduced Gd+ lesions by >89% and annualized relapse rate (ARR) by >73% vs placebo at Week 24. Week 144 data are presented here.
DESIGN/METHODS: At baseline, 220 RRMS patients were randomized 1:1:1:1 to intravenous OCR 600 mg (A); OCR 2000 mg (B); placebo (C); or open-label intramuscular IFN beta-1a 30 µg (D). At Weeks 24, 48, and 72 all patients received OCR: groups A, C, and D received 600 mg per cycle; group B received 1000 mg at Weeks 24 and 48, switching to 600 mg at Week 72. After 96 weeks, patients went into follow-up (FU).
RESULTS: Across groups, 86–91% of randomized patients entered FU after 96 weeks, including patients who had withdrawn from treatment. 67–78% of patients completed to Week 144. Safety: Rates of AEs, SAEs, and serious infections with both OCR doses were similar to placebo during the double-blind period and did not increase throughout the study. Two patients died in FU, 14 and 19 months after last OCR administration (both were B-cell repleted; events unrelated to OCR). No new serious infections were reported since last OCR administration.
Efficacy: Between Weeks 96 and 144, 1/69 patients in group B experienced new Gd+ T1 lesions (n=11 lesions) and 2/69 patients had new or newly enlarging T2 lesions (n=3; n=32 lesions). No group A patients had any newly active lesions. ARR for OCR 600 mg after ≥3 cycles was 0.035-0.189 between Weeks 96 and 144 (irrespective of B-cell status). Between Weeks 96 and 144, 6/160 patients had 12 weeks' confirmed sustained disease progression.

NEUROLOGY February 12, 2013; 80 (7 Supplement) March 20,2013

Bakhuraysah et al. Stem Cell Research & Therapy (2016) 7:12
DOI 10.1186/s13287-015-0272-1

Stem Cell Research & Therapy

REVIEW Open Access

Hematopoietic stem cell transplantation for multiple sclerosis: is it a clinical reality?

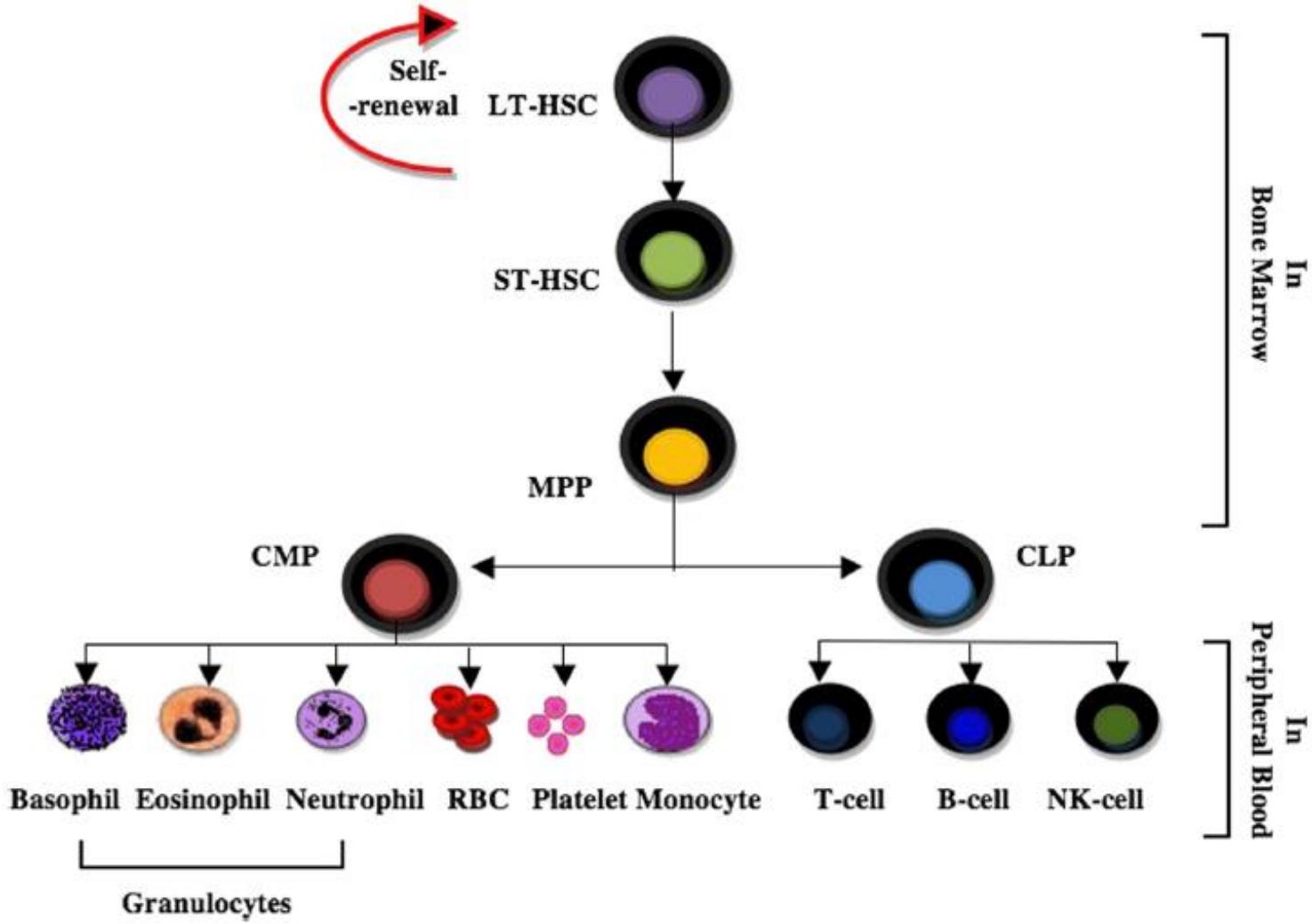
Maha M. Bakhuraysah, Christopher Siatskas and Steven Petratos*

Hematopoietic hierarchy model.

Hematopoietic stem cells (HSCs) are divided into long-term (LT)-HSC and short-term (ST)-HSC types. A LT-HSC with long-term self-renewal activity is converted into a ST-HSC and then HSCs give rise to a multipotent progenitor (MPP).

A MPP commits in bone marrow to become either common myeloid progenitor (CMP) or common lymphoid progenitor (CLP).

The CMP and CLP give rise to mature blood cells in peripheral blood, such as granulocytes, red blood cells (RBC), platelets, monocytes, T cells, B cells, and natural killer (NK) cells



Long-term results of stem cell transplantation for MS

A single-center experience

Neurology® 2011;76:1066-1070

A. Fassas, MD
V.K. Kimiskidis, MD
I. Sakellari, MD
K. Kapinas, MD
A. Anagnostopoulos, MD
V. Tsimourtou
K. Sotirakoglou, PhD
A. Kazis, MD

ABSTRACT

Objective: To report long-term results of a phase I/II study conducted in a single center in order to investigate the effect of hemopoietic stem cell transplantation (HSCT) in the treatment of multiple sclerosis (MS).

Methods: Clinical and MRI outcomes of 35 patients with aggressive MS treated with HSCT are reported after a median follow-up period of 11 (range 2–15) years.

Results: Disease progression-free survival (PFS) at 15 years is 44% for patients with active CNS disease and 10% for those without ($p = 0.01$), median time to progression was 11 (95%

Conclusion: HSCT is not a therapy for the general population of patients with MS but should be reserved for aggressive cases, still in the inflammatory phase of the disease, and for the malignant form, in which it can be life-saving. HSCT has an impressive and sustained effect in suppressing disease activity on MRI.

Autologous hematopoietic stem cell transplantation in multiple sclerosis

A phase II trial

Objective: To assess in multiple sclerosis (MS) the effect of intense immunosuppression followed by autologous hematopoietic stem cells transplantation (AHSCT) vs mitoxantrone (MTX) on disease activity measured by MRI.

Methods: We conducted a multicenter, phase II, randomized trial including patients with secondary progressive or relapsing-remitting MS, with a documented increase in the last year on the Expanded Disability Status Scale, in spite of conventional therapy, and presence of one or more gadolinium-enhancing (Gd1) areas. Patients were randomized to receive intense immunosuppression (mobilization with cyclophosphamide and filgrastim, conditioning with carmustine, cytosinearabinoside, etoposide, melphalan, and anti-thymocyte globulin) followed by AHSCT or MTX 20 mg every month for 6 months.

Results: AHSCT reduced by 79% the number of new T2 lesions as compared to MTX (rate ratio 0.21, p 5 0.00016). It also reduced Gd1 lesions as well as the annualized relapse rate. **No difference was found in the progression of disability.**

Neurology® 2015;84:981–988

Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial

Harold L Atkins, Marjorie Bowman, David Allan, Grizel Anstee, Douglas L Arnold, Amit Bar-Or, Isabelle Bence-Bruckler, Paul Birch, Christopher Bredeson, Jacqueline Chen, Dean Fergusson, Mike Halpenny, Linda Hamelin, Lothar Huebsch, Brian Hutton, Pierre Laneuville, Yves Lapierre, Hyunwoo Lee, Lisa Martin, Sheryl McDiarmid, Paul O'Connor, Timothy Ramsay, Mitchell Sabloff, Lisa Walker, Mark S Freedman

www.thelancet.com **Published online June 9, 2016** **http://dx.doi.org/10.1016/S0140-6736(16)30169-6**

Evidence from this study

This study is the first showing the complete long-term suppression of all inflammatory activity in a cohort of patients with active and progressing multiple sclerosis who have received a myelo-ablative HSCT regimen. The frequent, planned, comprehensive clinical and MRI follow-up lends strength to our conclusion. With a median follow-up of 6·7 years (range 3·9–12·7), 16 (70%) of 23 patients were free from further progression and many patients had improvements in disability (35% of patients had a sustained improvement in their Expanded Disability Status Scale score). The rate of brain atrophy decreased to that expected for healthy controls.

One of 24 patients died of transplantation-related complications

frontiers in Immunology

Regenerating Immunotolerance in Multiple Sclerosis with Autologous Hematopoietic Stem Cell Transplant

REVIEW
published: 12 March 2018
doi: 10.3389/fimmu.2018.00410

Jennifer C. Massey[1,2,3,4], Ian J. Sutton[2,4], David D. F. Ma[1,3,4] and John J. Moore[1,3,4]*

Empirical clinical observations support the notion that the immune reconstitution (IR) that occurs following AHSCT is associated with a sustained therapeutic benefit; however, neither the pathogenesis of MS nor the mechanism by which AHSCT results in a therapeutic benefit has been clearly delineated.

Although the antigenic target of the aberrant immune response in MS is not defined, accumulated data suggest that IR following AHSCT results in an immune tolerant state through deletion of pathogenic clones

Furthermore, some evidence exists that AHSCT may induce a rebooting of thymic function and regeneration of a diversified naïve T cell repertoire equipped to appropriately modulate the immune system in response to future antigenic challenge.

frontiers in Immunology

Regenerating Immunotolerance in Multiple Sclerosis with Autologous Hematopoietic Stem Cell Transplant

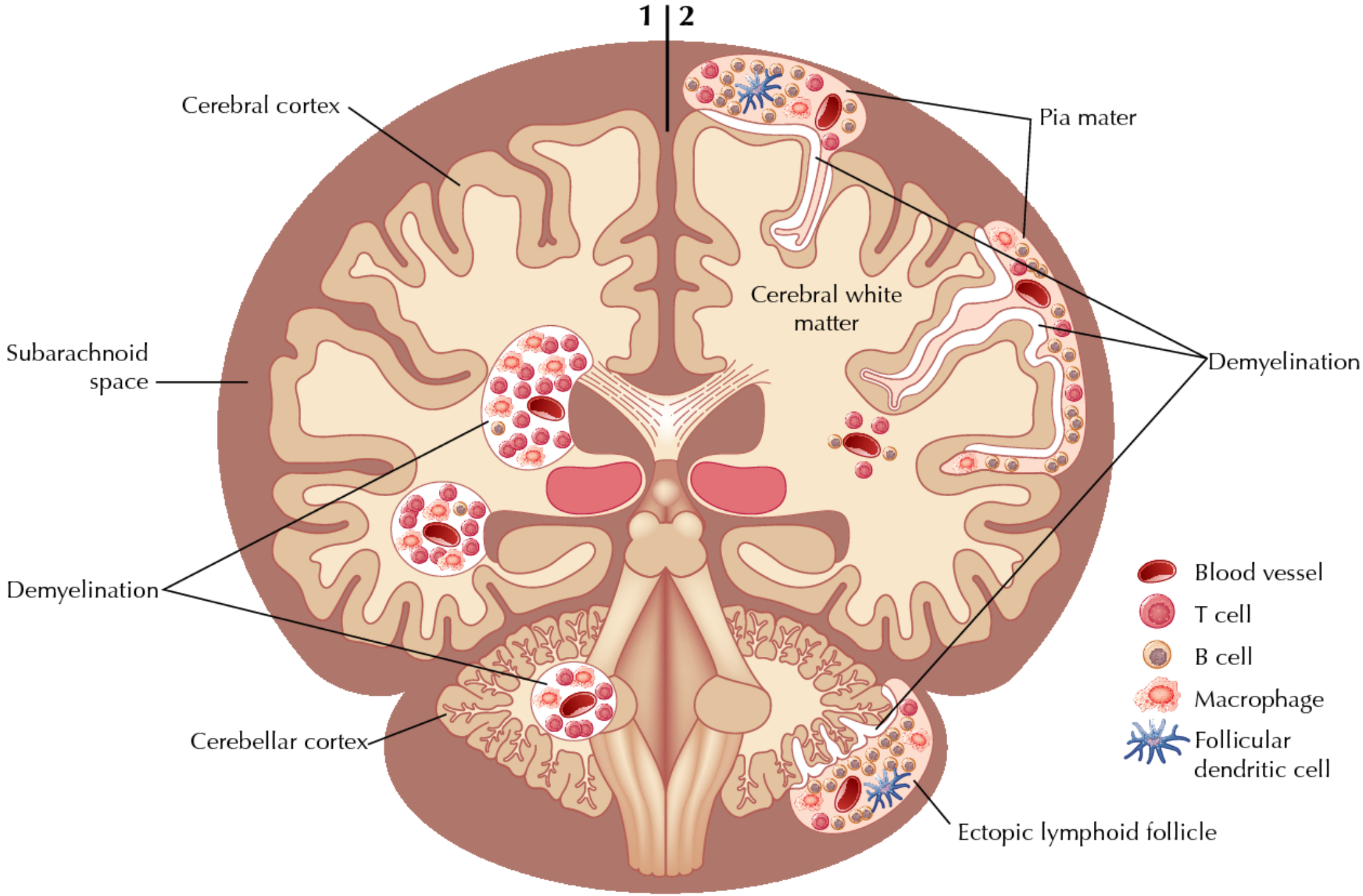
REVIEW
published: 12 March 2018
doi: 10.3389/fimmu.2018.00410

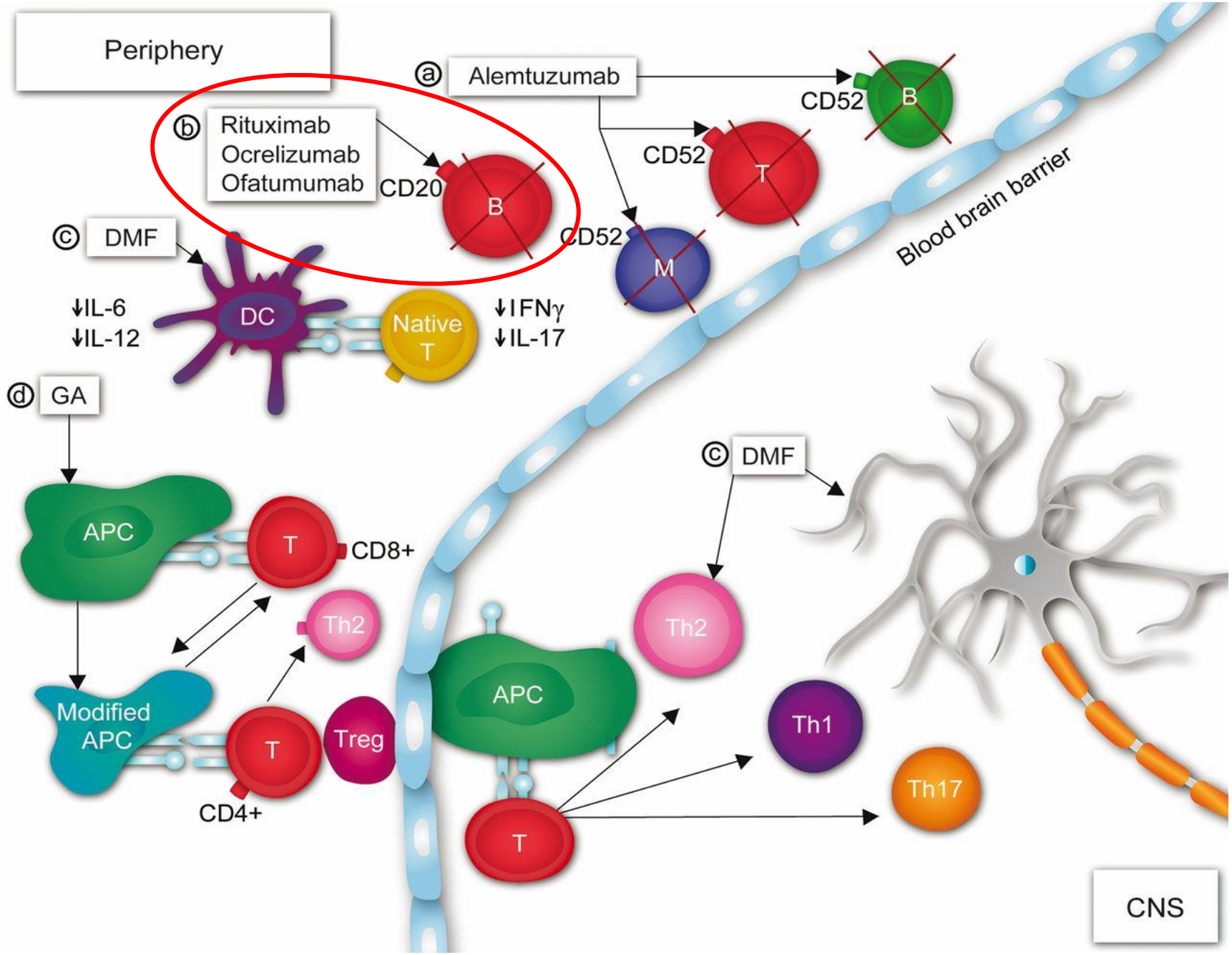
Jennifer C. Massey[1,2,3,4], Ian J. Sutton[2,4], David D. F. Ma[1,3,4] and John J. Moore[1,3,4]*

From 1995 to 2000, EBMT (European Bone Marrow Transplantation (EBMT) database) quoted a TRM (Treatment Related Mortality) rate of 7.3%, which fell to 1.3% in years 2001 to 2007. However, in a 2017 meta-analysis of clinical trials for AHSCT in MS, TRM was 0.3% in the 349 patients who were transplanted after 2005 and no TRM was observed in those who underwent low-intensity immunoablative conditioning.

A retrospective observational study from the EBMT autoimmune database found that a transplant center's experience, and not intensity of conditioning had the strongest correlate with TRM.

PROGRESSIVE MS


1
2
Cerebral cortex
Pia mater
Cerebral white matter
Subarachnoid space
Demyelination
Demyelination
Cerebellar cortex
Ectopic lymphoid follicle
Blood vessel
T cell
B cell
Macrophage
Follicular dendritic cell

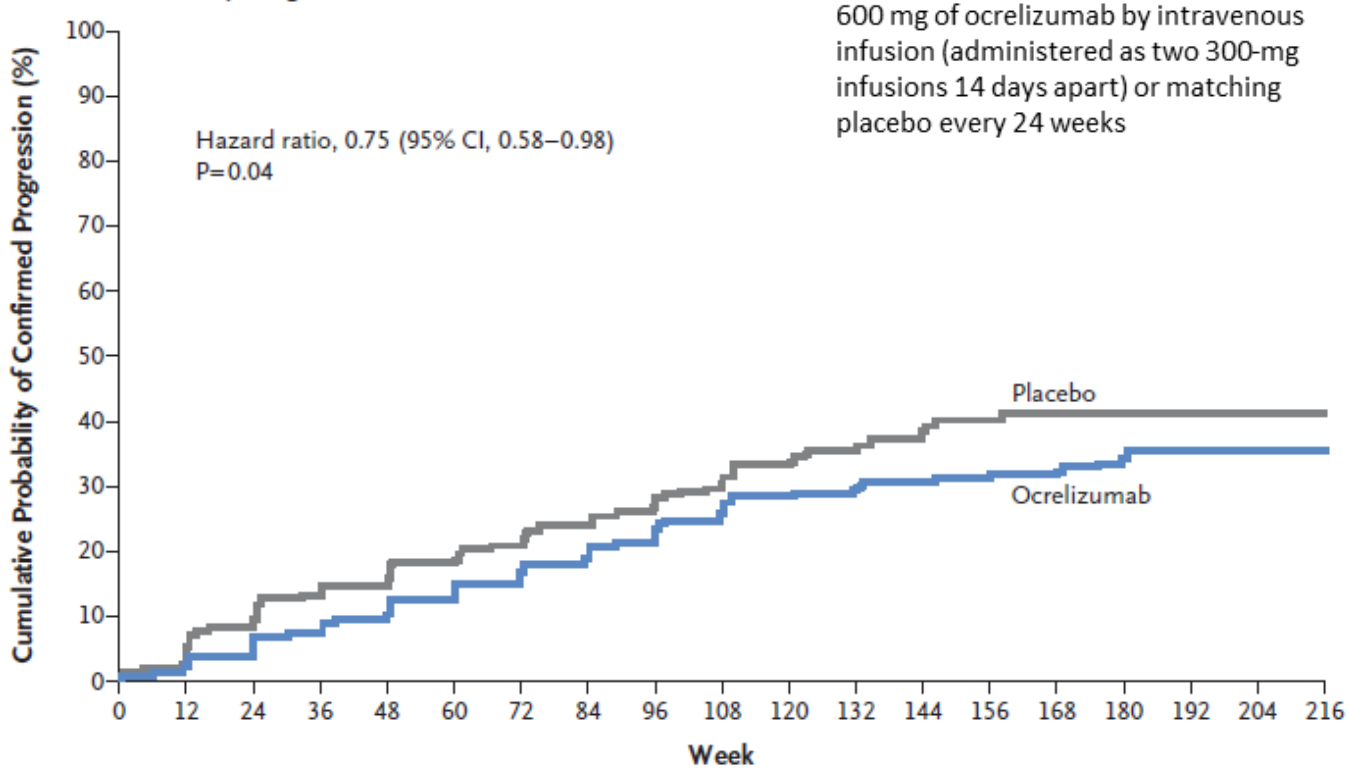

Periphery
ⓐ Alemtuzumab
CD52
B
CD52
T
ⓑ Rituximab
Ocrelizumab
Ofatumumab
CD20
B
CD52
M
Blood brain barrier
ⓒ DMF
↓IL-6
↓IL-12
DC
Native T
↓IFNγ
↓IL-17
ⓓ GA
ⓒ DMF
APC
T
CD8+
Th2
Th2
Modified APC
T
Treg
CD4+
APC
Th1
Th17
T
CNS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 19, 2017 VOL. 376 NO. 3

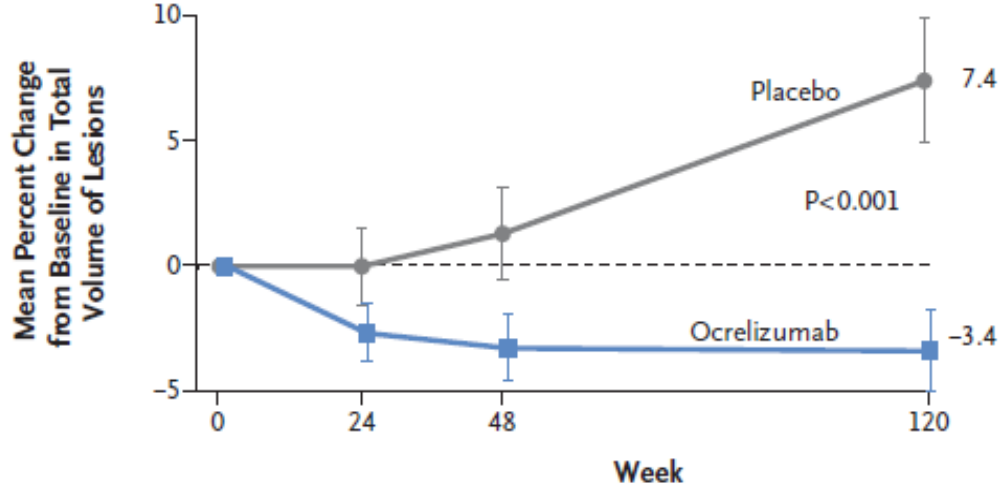
Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

24-Wk Confirmed Disability Progression



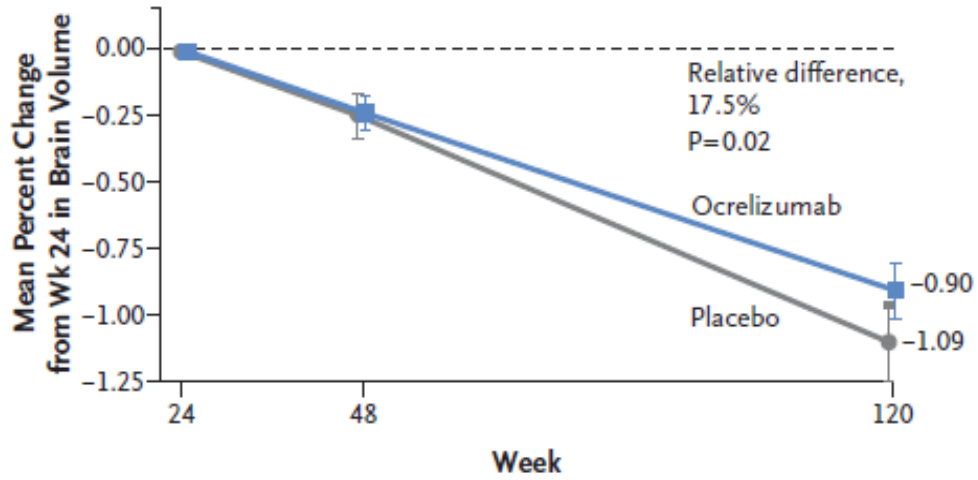
No. at Risk																			
Placebo	244	234	214	202	193	183	176	166	157	148	139	125	89	70	50	33	22	7	2
Ocrelizumab	487	465	454	437	421	397	384	367	349	330	313	290	217	177	144	87	50	21	7

A Total Volume of Brain Lesions on T_2-Weighted MRI



No. at Risk				
Placebo	234	233	220	183
Ocrelizumab	464	459	454	400

B Brain Volume



No. at Risk			
Placebo	203	200	150
Ocrelizumab	407	403	325

See comment in PubMed Commons belowAnn Neurol. 2009 Oct;66(4):460-71. doi: 10.1002/ana.21867.

Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial.

Hawker K[1], O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, Hauser S, Waubant E, Vollmer T, Panitch H, Zhang J, Chin P, Smith CH; OLYMPUS trial group.

METHODS:

Using 2:1 randomization, 439 PPMS patients received two 1,000 mg intravenous rituximab or placebo infusions every 24 weeks, through 96 weeks (4 courses). The primary endpoint was time to confirmed disease progression (CDP), a prespecified increase in Expanded Disability Status Scale sustained for 12 weeks. Secondary endpoints were change from baseline to week 96 in T2 lesion volume and total brain volume on magnetic resonance imaging scans.

RESULTS:

From baseline to week 96, rituximab patients had less ($p < 0.001$) increase in T2 lesion volume; brain volume change was similar ($p = 0.62$) to placebo. **Subgroup analysis showed time to CDP was delayed in rituximab-treated patients aged <51 years (hazard ratio [HR] = 0.52; p = 0.010), those with gadolinium-enhancing lesions (HR = 0.41; p = 0.007), and those aged <51 years with gadolinium-enhancing lesions (HR = 0.33; p = 0.009) compared with placebo.** Adverse events were comparable between groups; 16.1% of rituximab and 13.6% of placebo patients reported serious events. Serious infections occurred in 4.5% of rituximab and <1.0% of placebo patients. Infusion-related events, predominantly mild to moderate, were more common with rituximab during the first course, and decreased to rates comparable to placebo on successive courses.

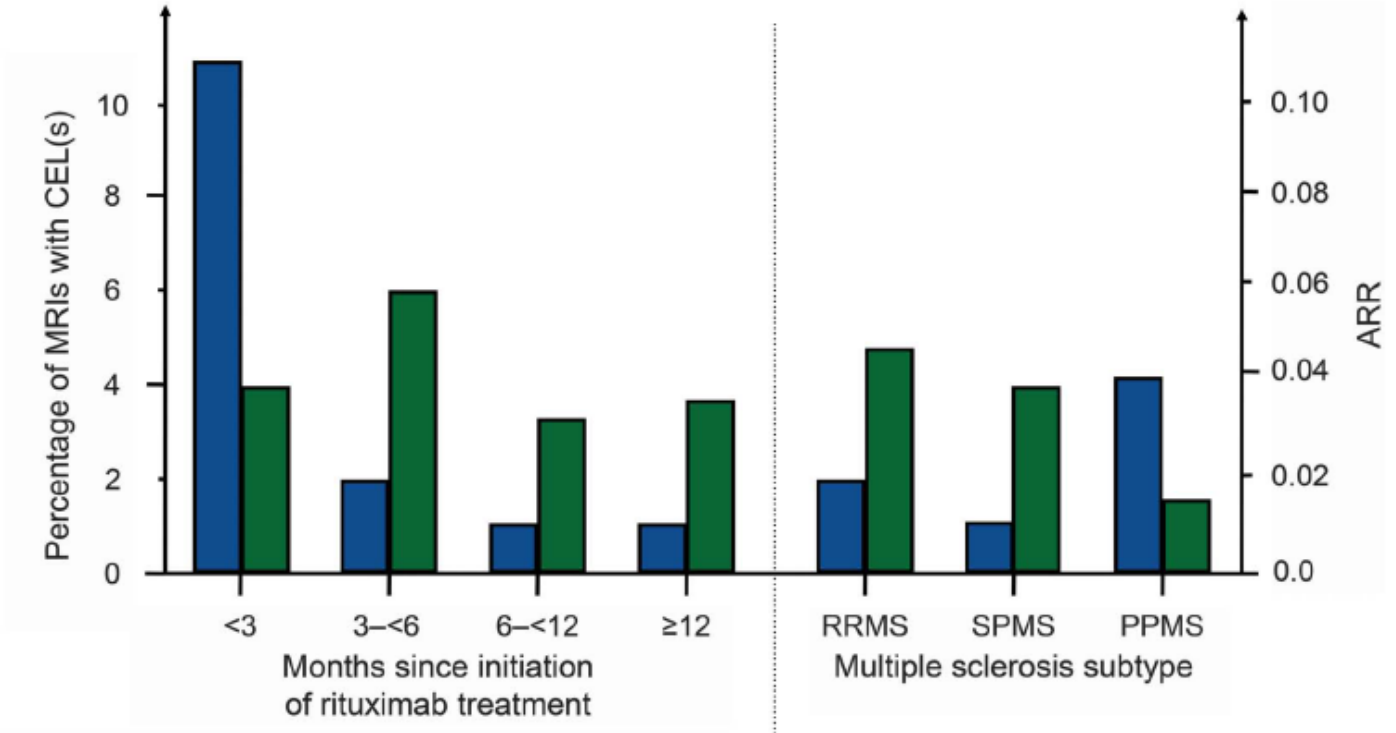
Published Ahead of Print on October 19, 2016 as 10.1212/WNL.0000000000003331

Rituximab in multiple sclerosis

A retrospective observational study on safety and efficacy

Atrophy rate.

The mean annual change in BPF on rituximab treatment was 20.19% (0.95).



No. of patients with MS at risk	822	796	738	602	557	198	67
No. of MRIs	125	176	334	755	1013	271	106
No. of MRIs with CELs (no. of CELs)	14 (37)	3 (3)	4 (8)	10 (27)	23 (56)	3 (14)	4 (5)
Percentage of MRIs with CEL(s)	11	2	1	1	2	1	4
Person-time (years) on rituximab	202.8	192.7	338.7	755.7	981.2	372.3	136.4
No. of relapses	8	11	12	28	43	14	2
ARR	0.039	0.057	0.035	0.037	0.044	0.038	0.015

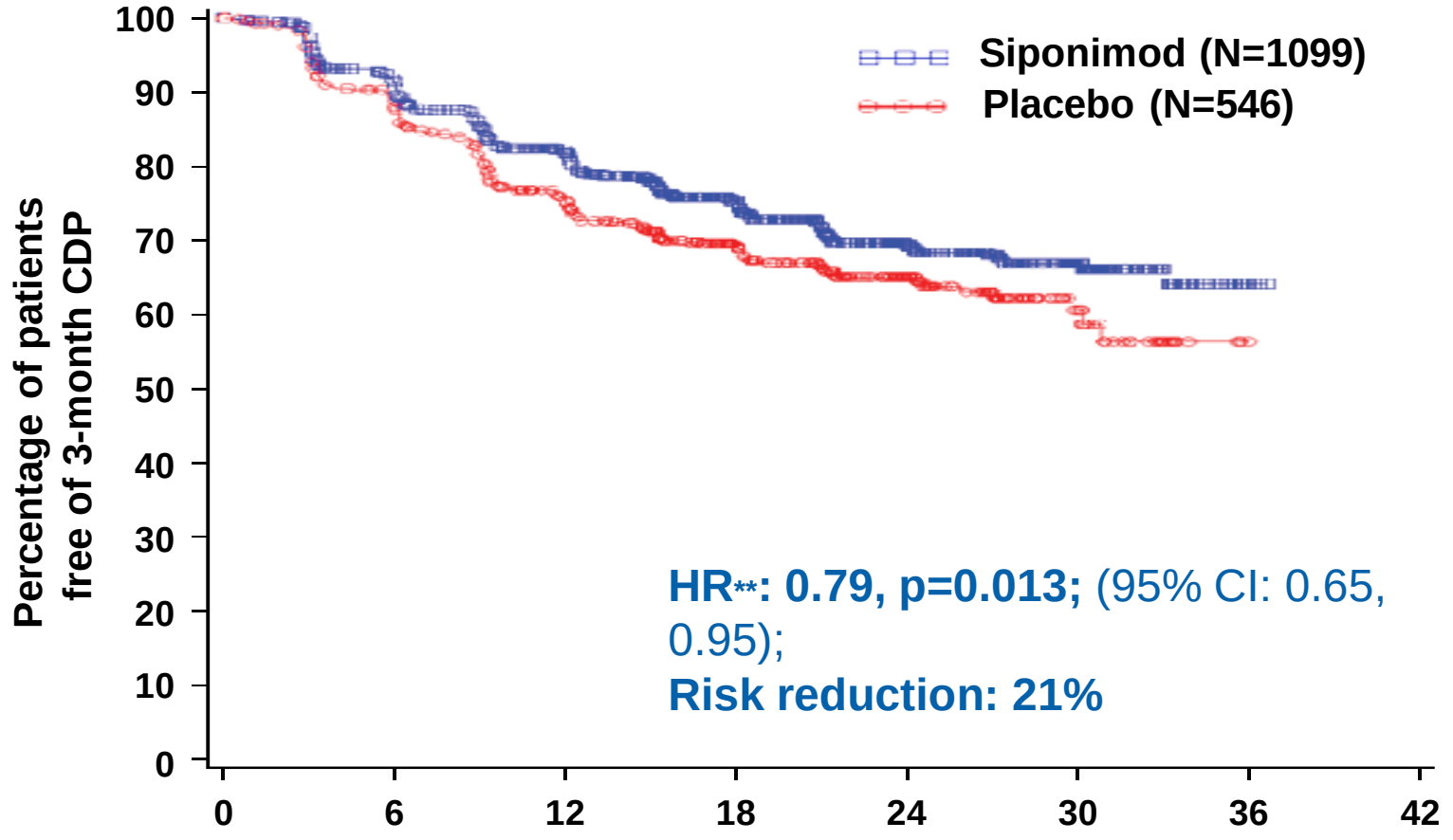
Efficacy and safety of siponimod in secondary progressive multiple sclerosis - Results of the placebo controlled, double-blind, Phase III EXPAND study

Ludwig Kappos[1], Amit Bar-Or[2], Bruce Cree[3], Robert Fox[4], Gavin Giovannoni[5], Ralf Gold[6], Patrick Vermersch[7], Sophie Arnould[8], Tatiana Sidorenko[8], Christian Wolf[9], Erik Wallström[8], Frank Dahlke[8]

Oral Presentation 250; ECTRIMS 2016

[1]Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital, Basel, Switzerland; [2]Neuroimmunology Unit, Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada; [3]Multiple Sclerosis Centre, University of California San Francisco, San Francisco, CA, USA; [4]Mellen Centre for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, Ohio, USA; [5]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [6]Department of Neurology, St. Josef-Hospital/Ruhr-University Bochum, Bochum, Germany; [7]Department of Neurology, University of Lille, France; [8]Novartis Pharma AG, Basel, Switzerland; [9]Lycalis sprl, Brussels, Belgium

Primary endpoint: Time to 3-m Confirmed Disability Progression (CDP) vs placebo*



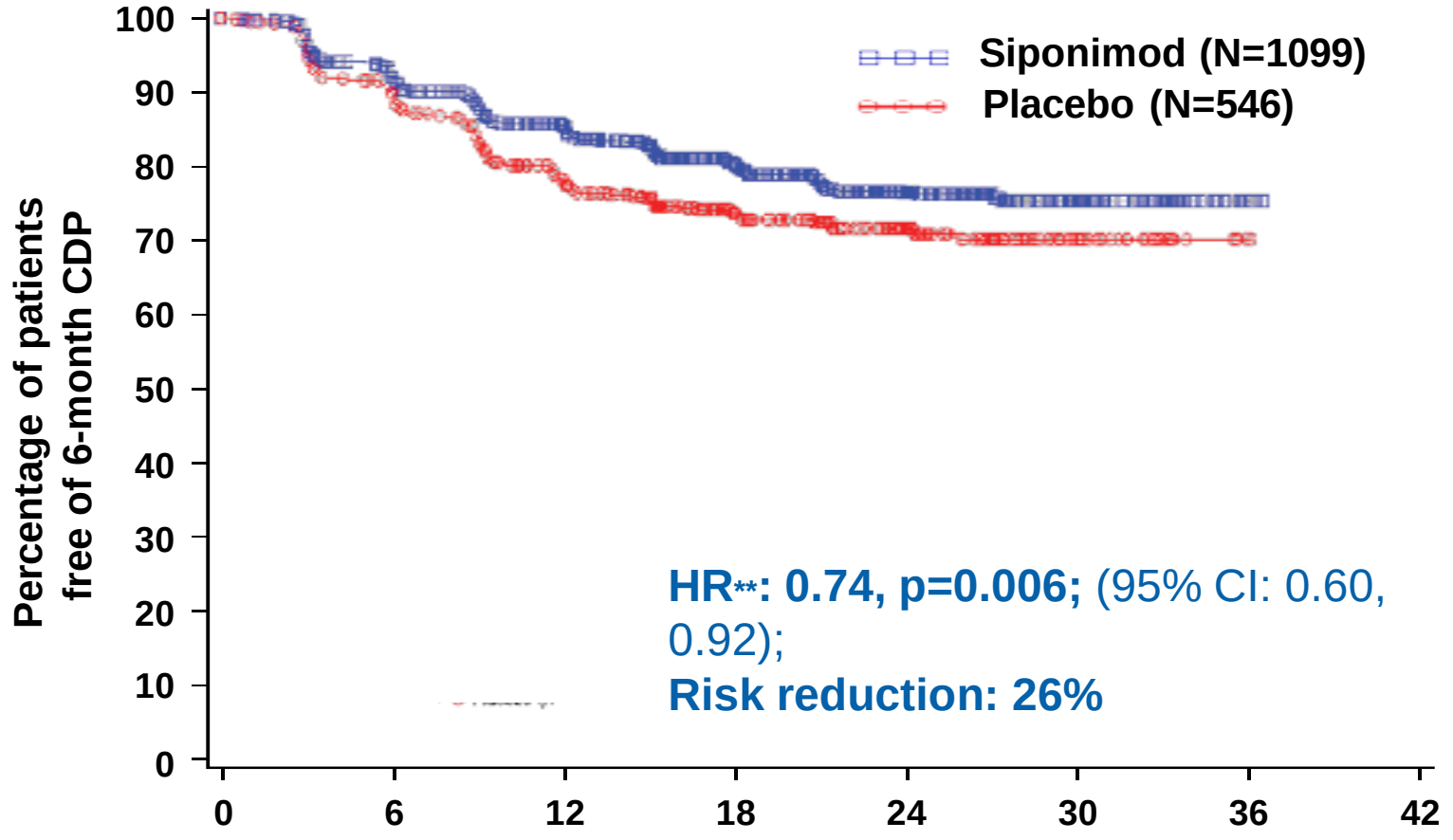
Number of patients at risk

Siponimod	1099	947	781	499	289	101	4	0
Placebo	546	463	352	223	124	35	0	0

*Full Analysis Set **Cox regression analysis

3-m: 3-month; CDP: confirmed disability progression; HR: hazard ratio

Secondary endpoint: Time to 6-m CDP vs placebo*



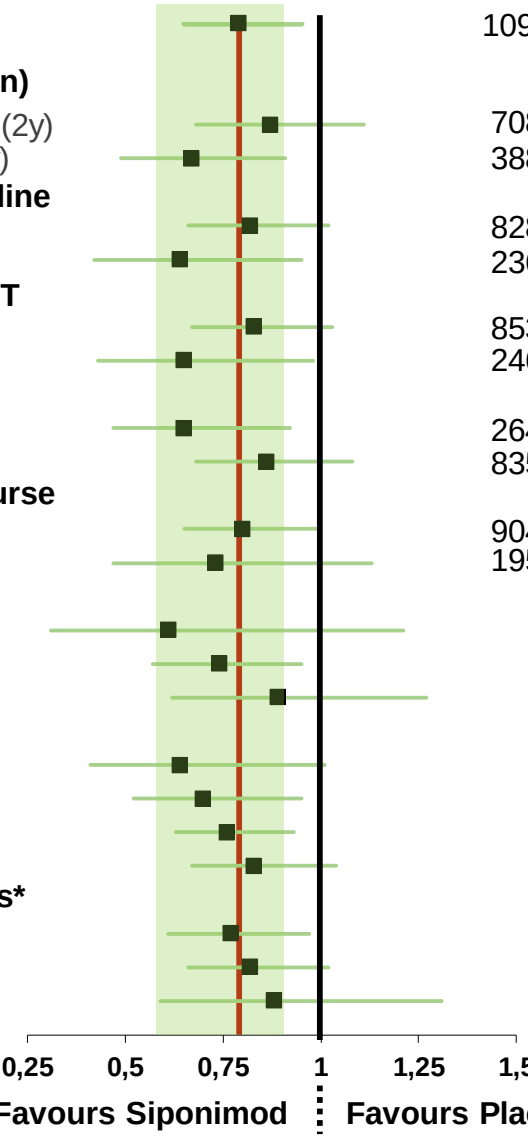
Number of patients at risk

Siponimod	1099	960	811	525	306	106	5	0
Placebo	546	473	361	230	128	37	1	0

*Full Analysis Set **Cox regression analysis

6-m: 6-month; CDP: confirmed disability progression; HR: hazard ratio

Primary endpoint 3-month CDP by predefined subgroups



	Number of patients			Number of patients with CDP	
	Siponimod	Placebo	HR (95% CI)	Siponimod	Placebo
Overall	1099	546	**0.79** (0.65, 0.95)	288	173
SPMS group (Baseline definition)					
SPMS with no prior relapses (2y)	708	343	**0.87** (0.68, 1.11)	190	101
SPMS with prior relapses (2y)	388	202	**0.67** (0.49, 0.91)	98	72
Number of Gd+ lesions at baseline					
0	828	415	**0.82** (0.66, 1.02)	219	128
≥1	236	114	**0.64** (0.42, 0.95)	61	40
Previously treated with any DMT					
Yes	853	427	**0.83** (0.67, 1.03)	231	134
No	246	119	**0.65** (0.43, 0.98)	57	39
Rapidly evolving MS					
Yes	264	146	**0.65** (0.47, 0.92)	82	60
No	835	400	**0.86** (0.68, 1.08)	206	113
Moderate or severe disease course					
Yes	904	459	**0.8** (0.65, 0.99)	232	141
No	195	87	**0.73** (0.47, 1.13)	56	32
Baseline age*					
20 years			**0.61** (0.31, 1.21)		
40 years			**0.74** (0.57, 0.95)		
60 years			**0.89** (0.62, 1.27)		
Baseline EDSS*					
3.0			**0.64** (0.41, 1.01)		
4.0			**0.7** (0.52, 0.95)		
5.0			**0.76** (0.63, 0.93)		
6.0			**0.83** (0.67, 1.04)		
MS duration since 1st symptoms*					
10 years			**0.77** (0.61, 0.97)		
20 years			**0.82** (0.66, 1.02)		
30 years			**0.88** (0.59, 1.31)		

*Model estimate

'Provocative' Results With Stem Cells in Progressive MS

Sue Hughes

September 26, 2019

STOCKHOLM — A new trial of autologous mesenchymal stem cells in progressive multiple sclerosis (MS) has shown encouraging results, with significant benefits vs placebo in several measures of disability.

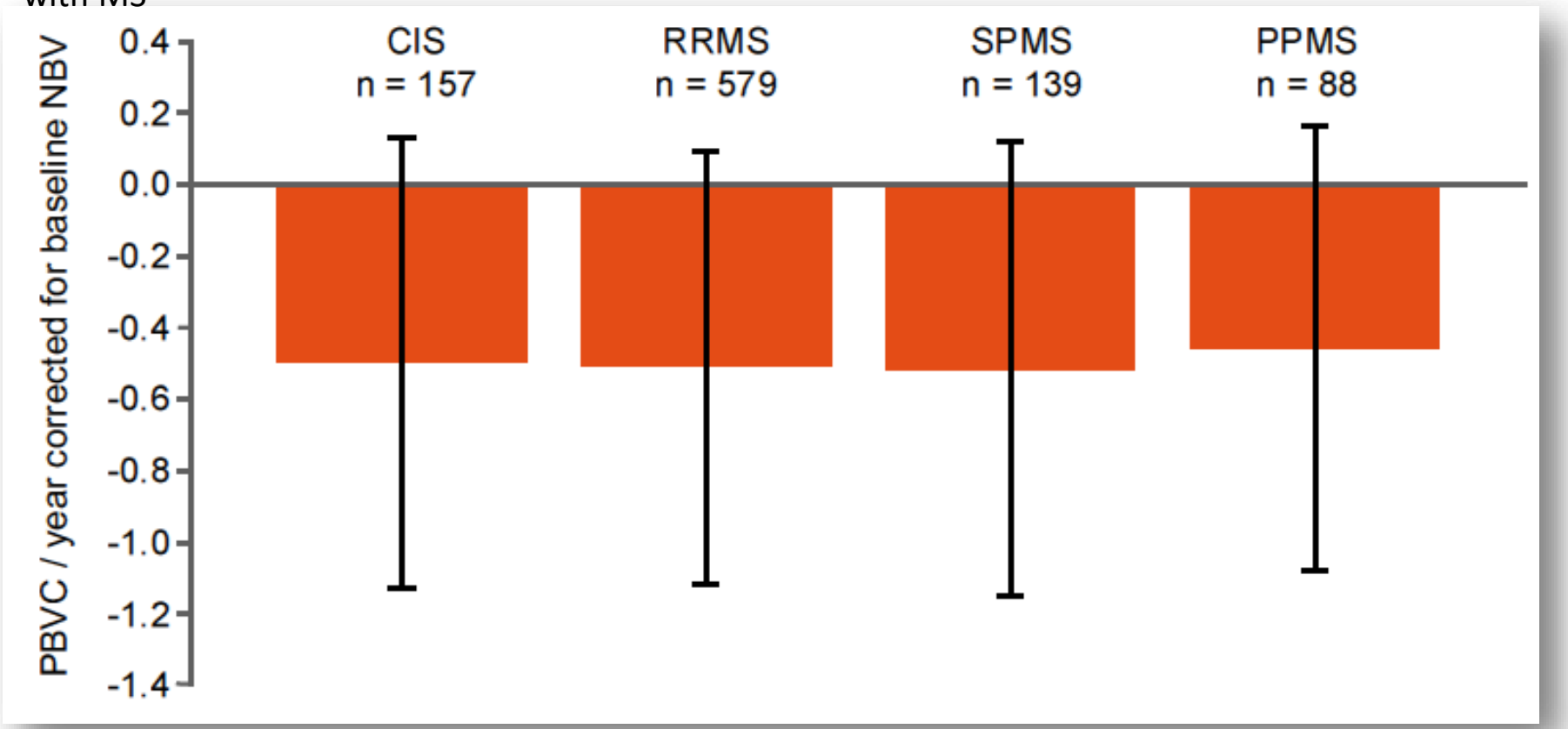
The double-blind placebo-controlled phase 2 study — described as "very pioneering" and "provocative" by outside commentators — was presented at the recent 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2019.

Both intravenous and intrathecal administration of the stem cells showed beneficial clinical effects compared with placebo in terms of Expanded Disability Status Scale (EDSS) changes and several other functional outcomes, but the intrathecal route appeared superior to intravenous administration, reported Dimitrios Karussis, Hadassah University Hospital, Jerusalem, Israel.

Η ΠΣ ως νευροεκφυλιστική νόσος
Νεότερα δεδομένα

Accelerated brain volume loss occurs across all stages of the disease

n= 963 People with MS



De Stefano N and MAGNIMS Group. Neurology 2010

Brain atrophy: an *in-vivo* measure of disease activity in multiple sclerosis

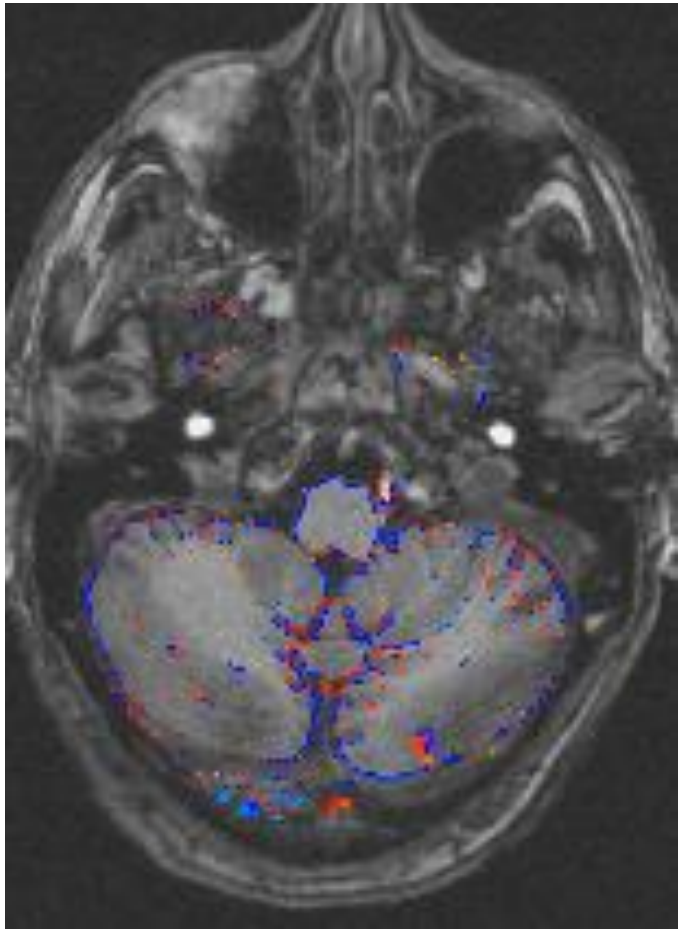
Swiss Med Wkly. 2013;143:w13887

Ernst Wilhelm Radue[a], Kerstin Bendfeldt[a], Nicole Mueller-Lenke[a], Stefano Magon[c], Till Sprenger[a,b,c]

Since there is only a **limited correlation between the clinical features of MS and findings on conventional magnetic resonance imaging (MRI),** for the evaluation of such therapies new outcome measures are warranted. **Grey matter atrophy occurs in the earliest stages of MS, progresses faster than in healthy individuals, and shows significant correlations with MRI lesion load, cognitive function and measures of physical disability;** indeed, brain atrophy is the best predictor of subsequent disability and can be readily measured using MRI. Furthermore, it is becoming clear that **currently available therapies differ in their effects on brain atrophy, and this may have important implications for the management of MS.**

SIENA / SIENAX

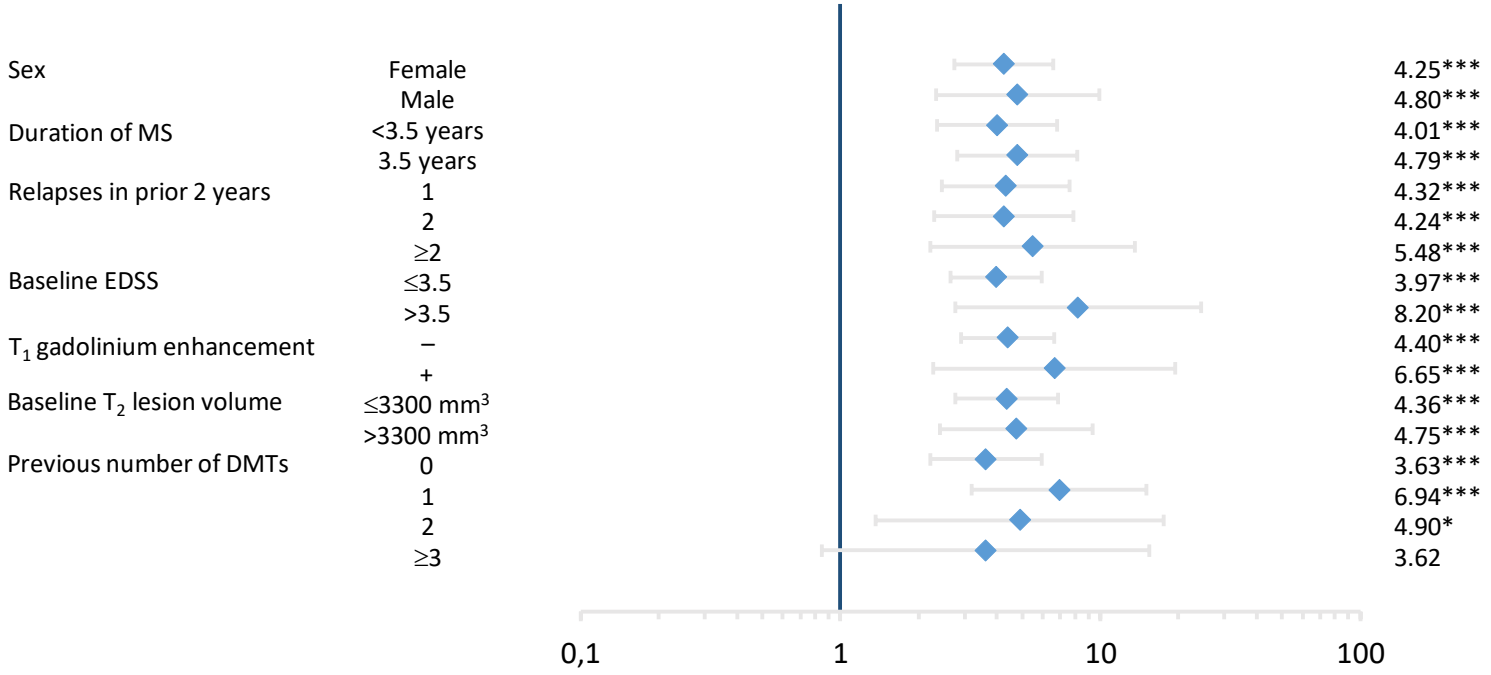
- SIENA estimates percentage brain volume change (PBVC) between two input images.
- SIENAX estimates total brain tissue volume from a single image, normalized to skull size.



Smith SM, Zhang Y, Jenkinson M, *et al*. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 2002; 17:479–489.
Smith SM, Jenkinson M, Woolrich MW, *et al*. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; 23(Suppl 1):208–219.

Fingolimod consistently achieved NEDA-4 over 2 years vs placebo: pooled data from FREEDOMS and FREEDOMS II

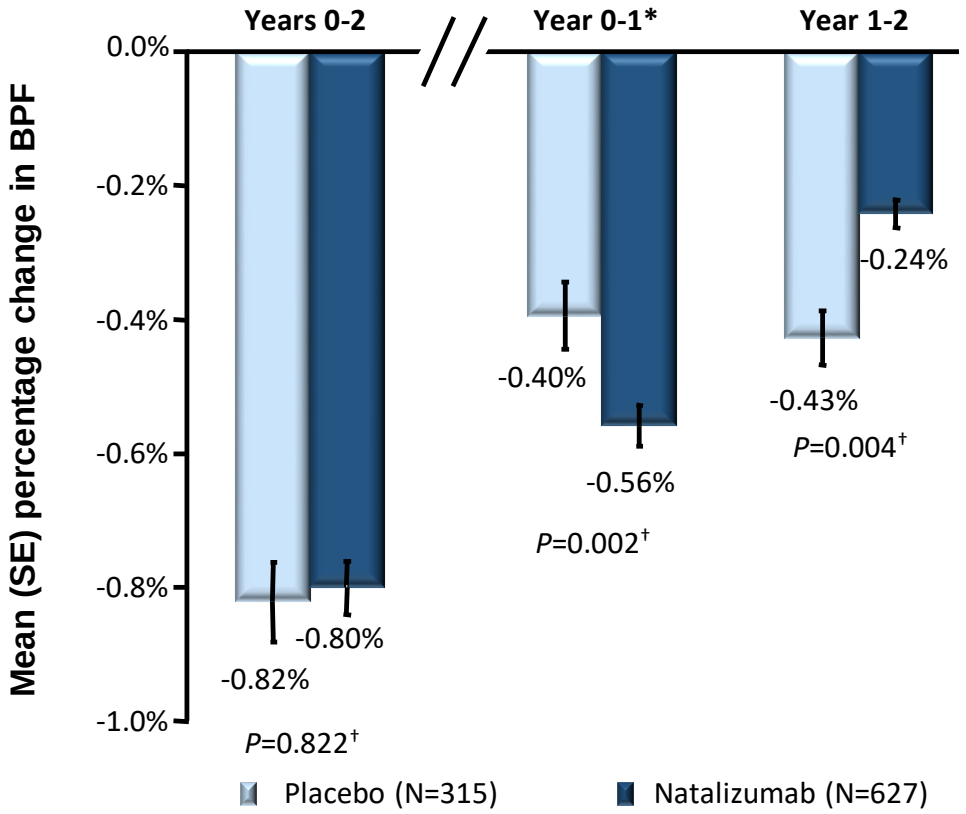
Odds ratio of achieving NEDA-4† for fingolimod vs placebo



Patients receiving fingolimod 4-5x more likely to achieve NEDA-4 vs placebo

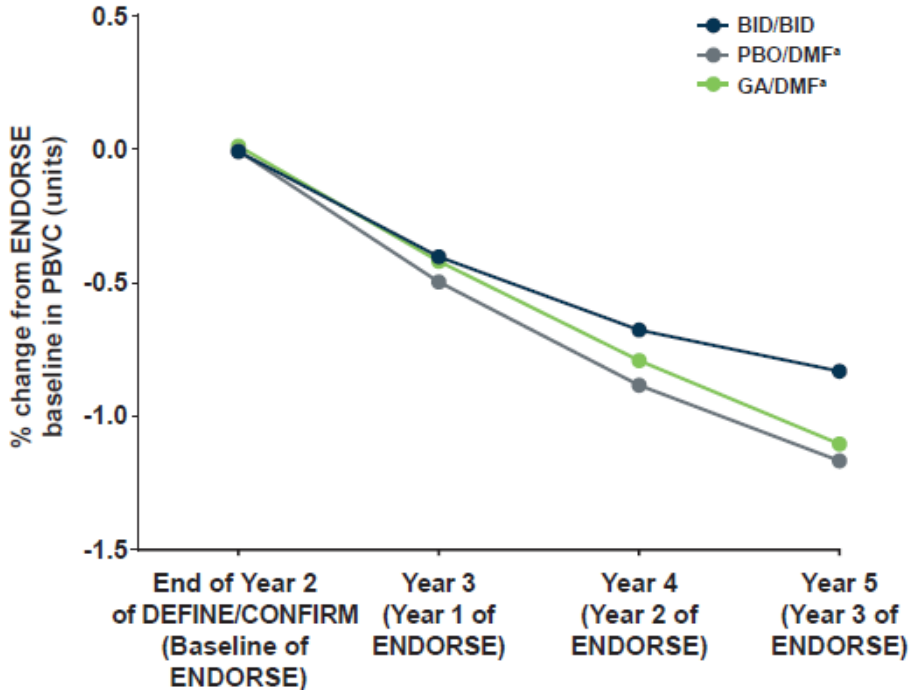
Post-hoc analysis of pooled data from FREEDOMS and FREEDOMS II (n=1556: fingolimod 0.5 mg, n=783; placebo, n=773)
*p<0.05; ***p<0.001. †NEDA-4 defined as no MRI lesion activity, no confirmed relapses, no 6-month confirmed disability progression and <0.4% mean annual brain volume loss. Freedman MS *et al.* Poster P626 presented at ***ECTRIMS* 2015.** Reproduced with kind permission from MS Freedman

Natalizumab and brain volume change (AFFIRM Study)



†Difference between treatments; ‡Change from baseline; Miller DH et al. *Neurology* 2007;68:1390-1401.

Dimethyl Fumarate
ENDORSE: Αποτελέσματα 5ετίας
Επίδραση στην εγκεφαλική ατροφία

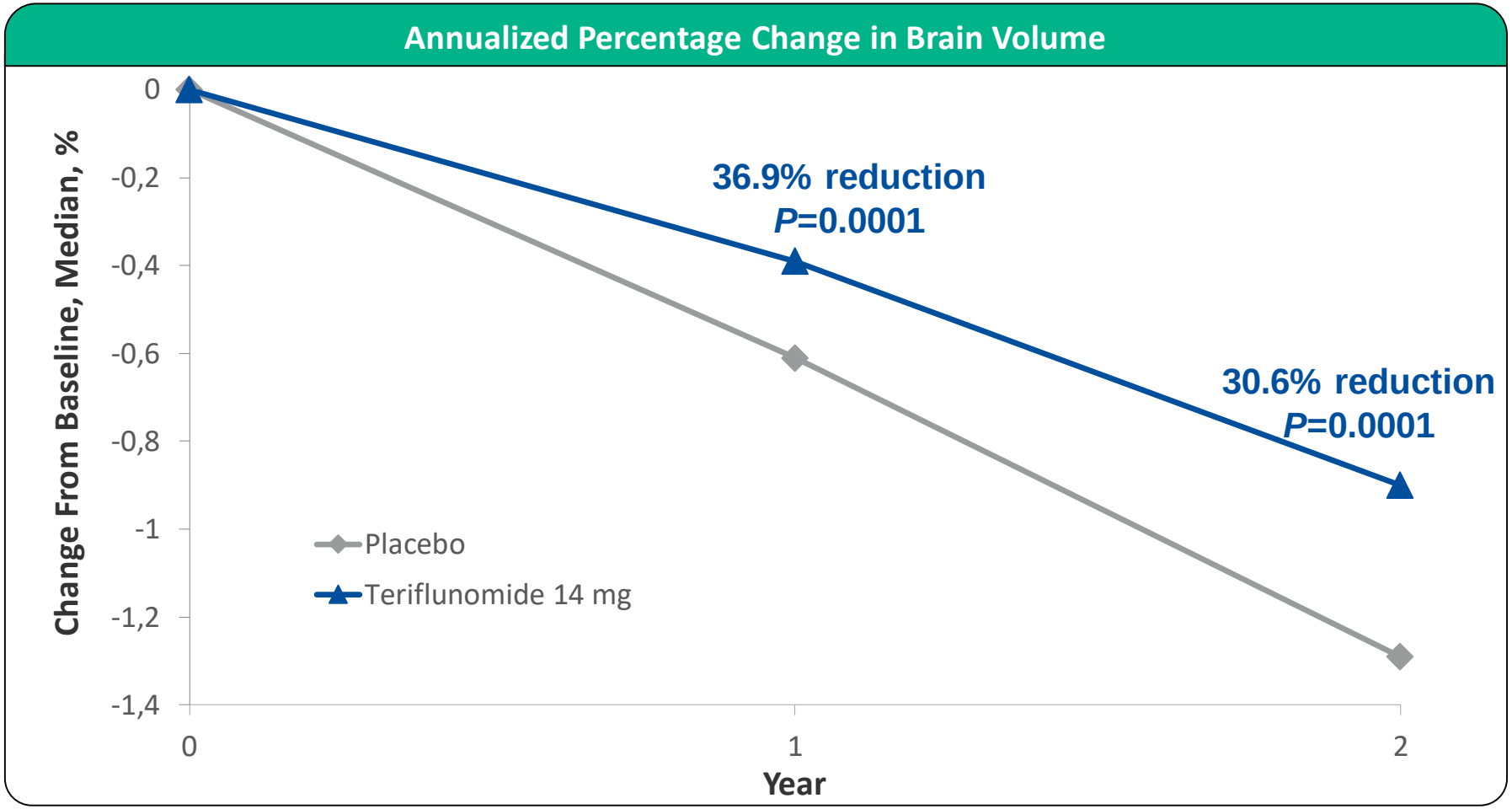


In the BID/BID group, the rate of brain volume loss was slowed compared with placebo (**P=0.0304**) and significantly slowed across all time points compared with PBO/BID and GA/BID.

Η ευνοϊκή επίδραση του DMF στην εγκεφαλική ατροφία συνεχίζεται σε διάστημα 5 ετών, ενώ πιθανώς ισχυρότερη επίδραση εμφανίζεται στους ασθενείς που έλαβαν DMF από το 1ο έτος της μελέτης

Kappos L et al . Presented at ANN; April 18-25, 2015 Washington DC. P7.243

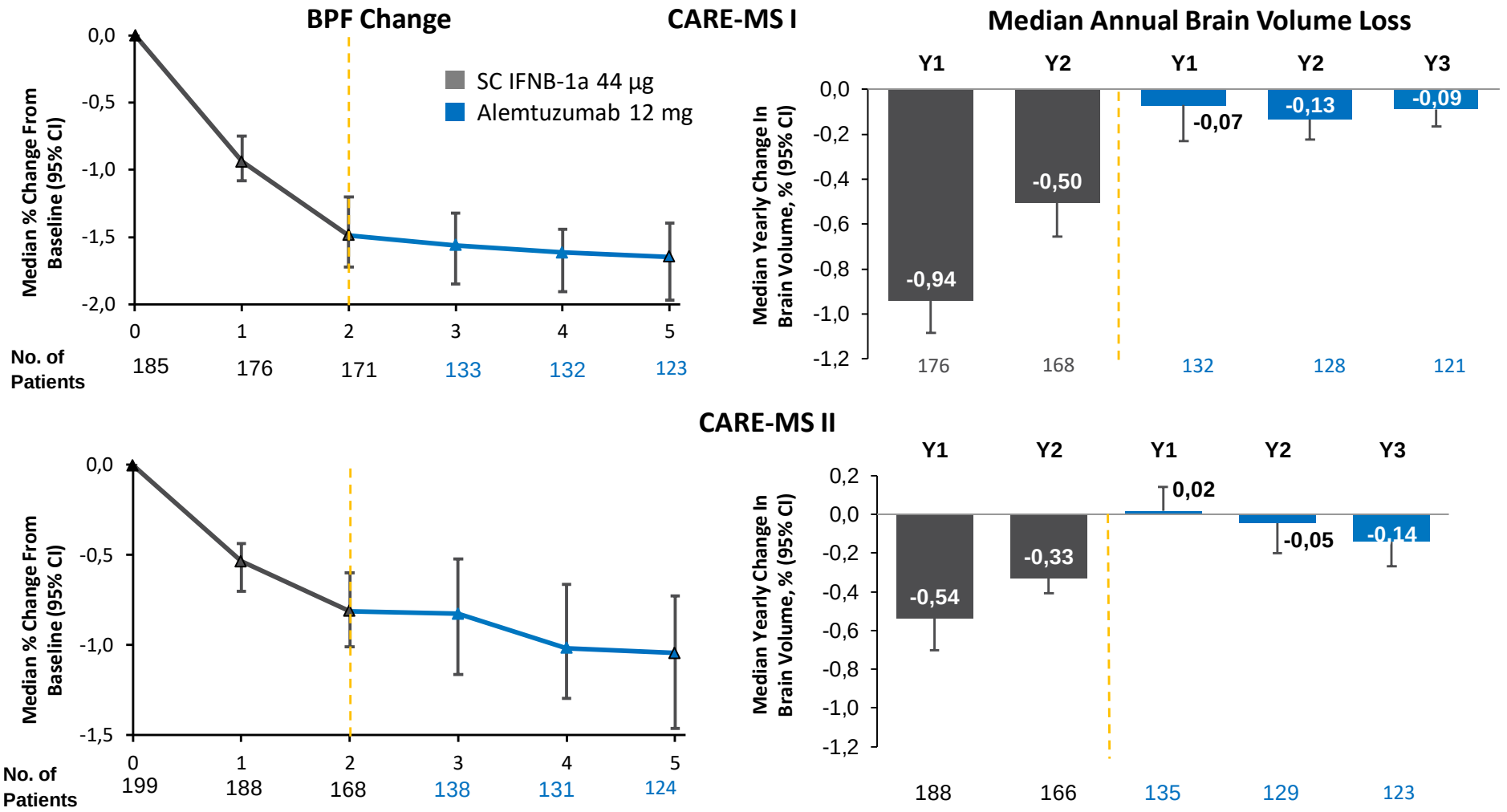
TEMSO Η τεριφλουνομίδη μειώνει σημαντικά την εγκεφαλική ατροφία



- Teriflunomide 7 mg vs placebo at Year 1: 34.4% reduction, *P*=0.0011; Year 2: 27.6% reduction, *P*=0.0019

A SIENA analysis of the TEMSO MRI dataset Late breaking news ECTRIMS 2015

Slowing Brain Volume Loss After Switching from SC IFNB-1a to Alemtuzumab



Barkhof F et al. AAN 2016, P6.183.

Beyond NEDA (no evident disease activity)

NEDA

END-ORGAN DAMAGE

Relapses

Unreported relapses

Clinical disease progression

Subclinical relapses: focal MRI activity

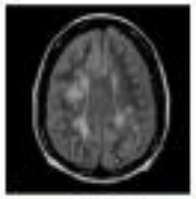
Focal gray and white matter lesions not detected by MRI

Brain atrophy

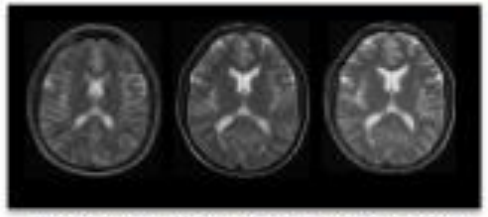
Spinal fluid neurofilament levels

Biomarkers

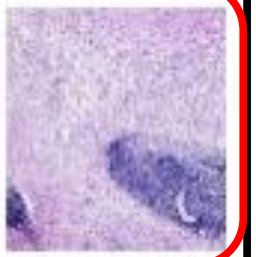
Clinical activity



Focal MRI activity

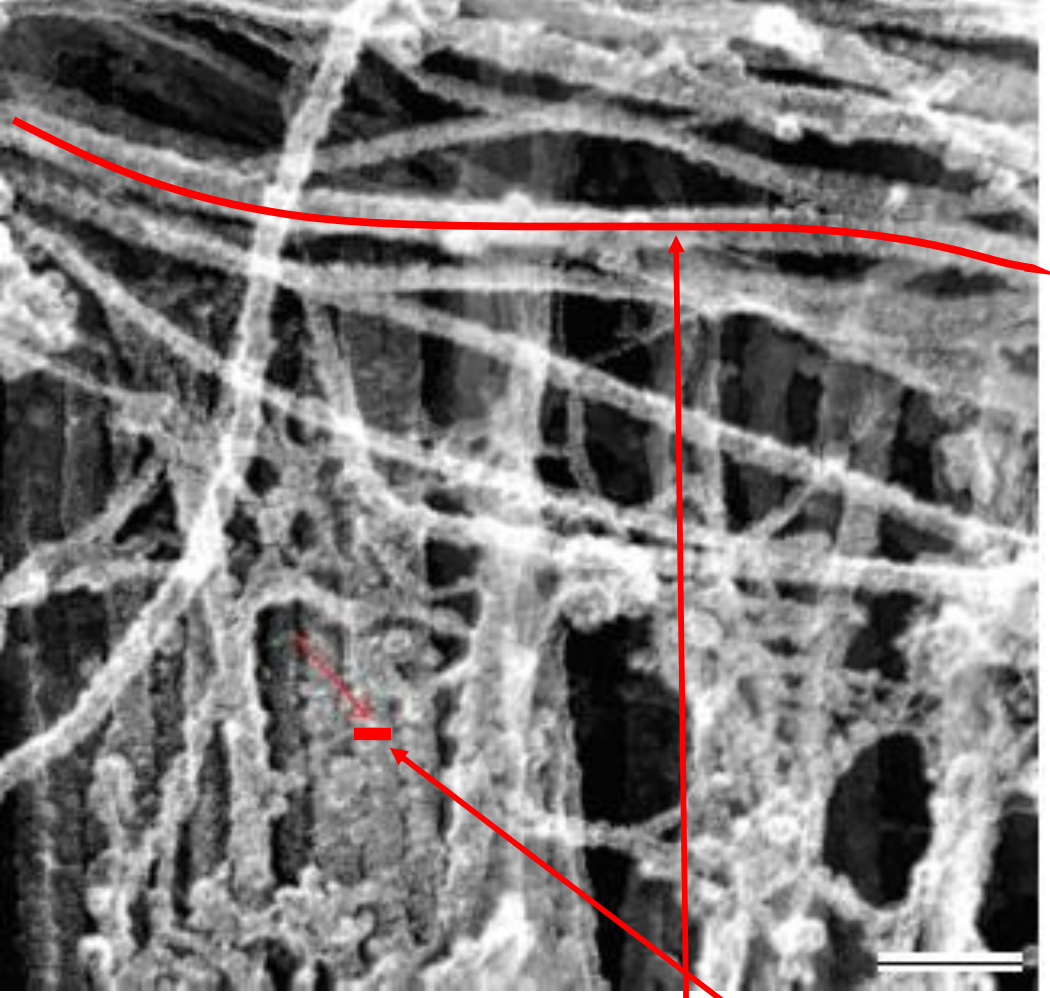


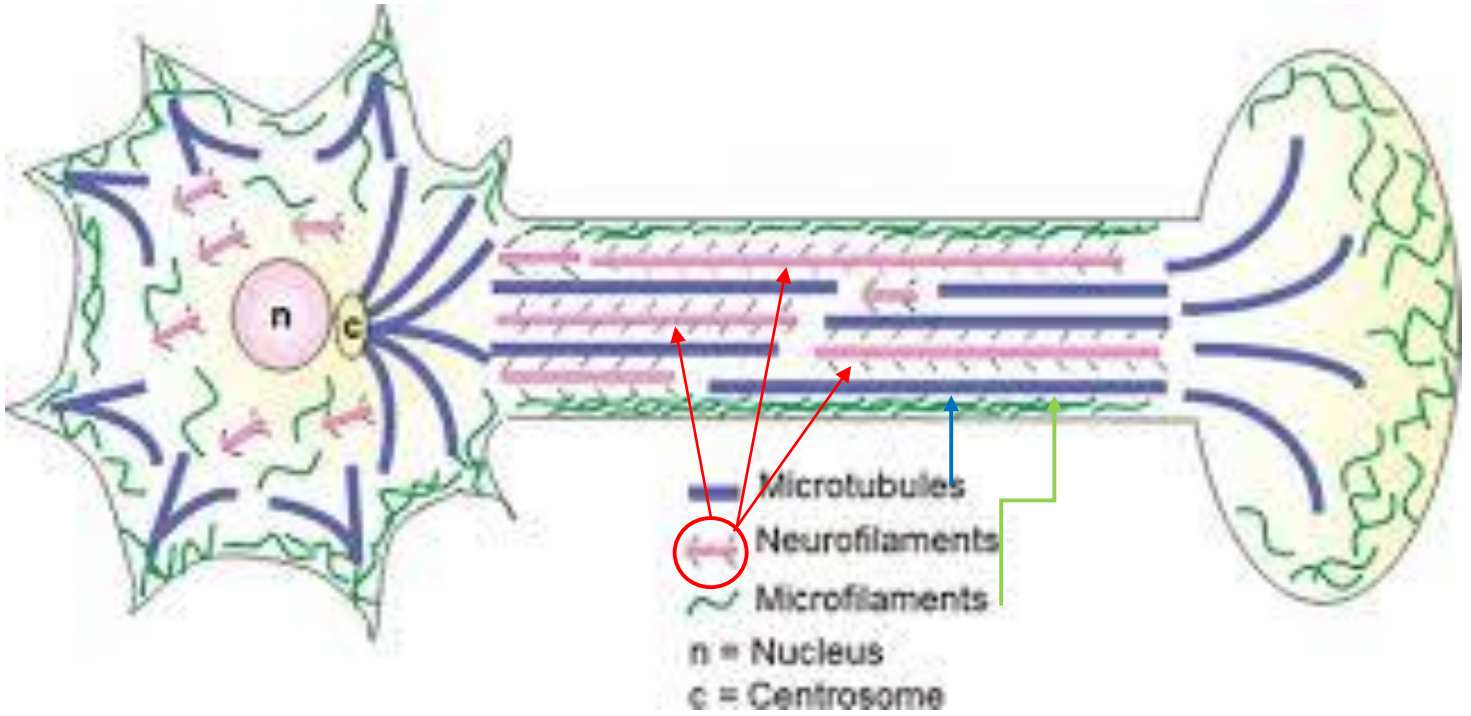
Hidden focal and diffuse MRI activity



Microscopic or biochemical pathology

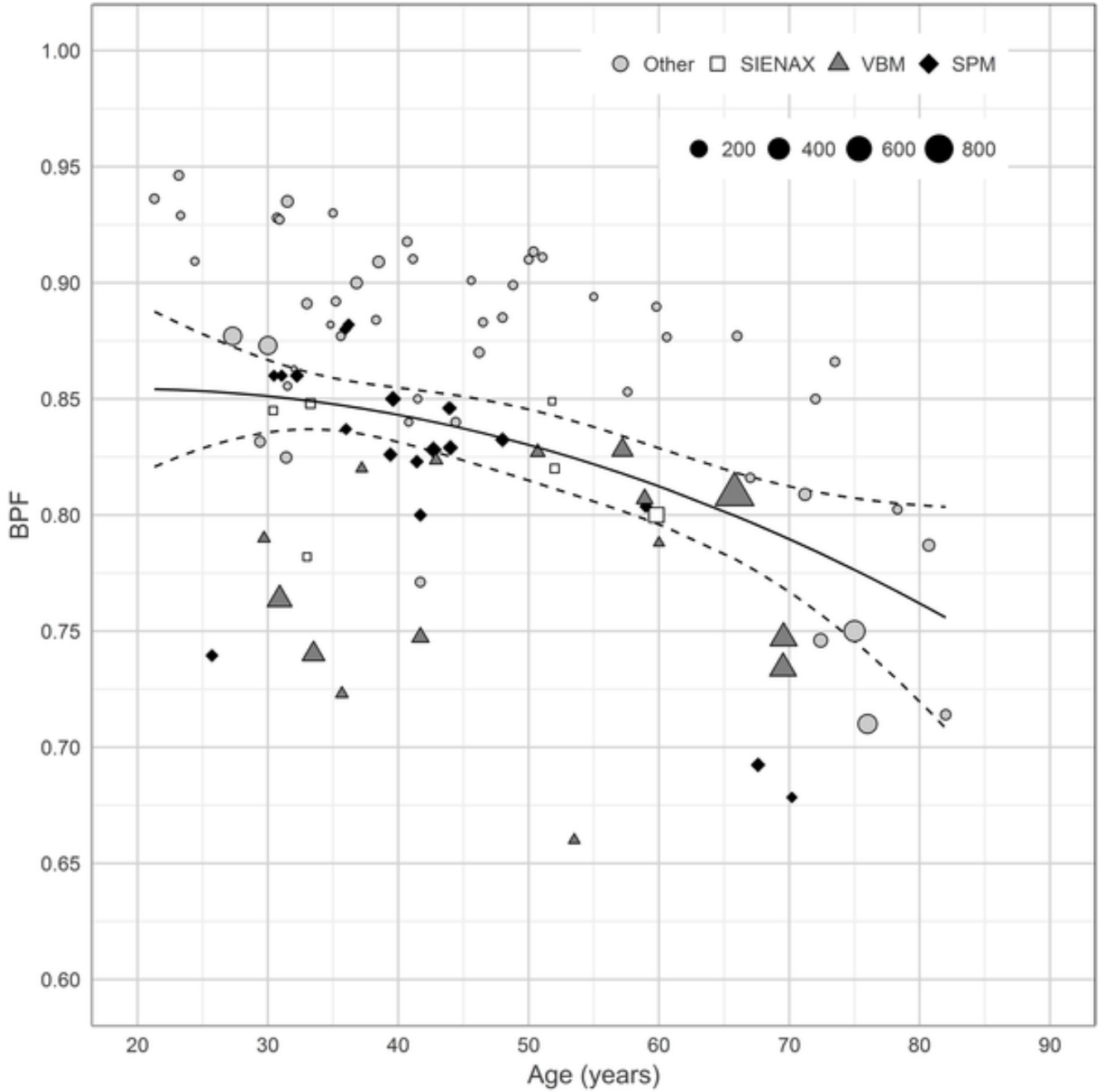
Neurofilaments (NF)





- Neurofilaments (NF) are intermediate filaments found in the cytoplasm of neurons. They are protein polymers measuring approximately 10 nm in diameter and many micrometers in length. **Together with microtubules and microfilaments, they form the neuronal cytoskeleton.**

http://dx.doi.org/10.5772/66926



Vågberg M, Granåsen G, Svenningsson A (2017) Brain Parenchymal Fraction in Healthy Adults—A Systematic Review of the Literature. PLOS ONE 12(1): e0170018. https://doi.org/10.1371/journal.pone.0170018
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0170018

Serum Neurofilament Light: A Biomarker of Neuronal Damage in Multiple Sclerosis

Giulio Disanto, MD, PhD,[1] Christian Barro, MD,[2] Pascal Benkert, PhD,[3] Yvonne Naegelin, MD,[2] Sabine Schädelin, MSc,[3] Antonella Giardiello, MD,[1] Chiara Zecca, MD,[1] Kaj Blennow, PhD,[4] Henrik Zetterberg, PhD,[4,5] David Leppert, MD,[2] Ludwig Kappos, MD,[2] Claudio Gobbi, MD,[1] Jens Kuhle, MD, PhD,[2] and the Swiss Multiple Sclerosis Cohort Study Group

A new ultrasensitive single-molecule array (Simoa) serum NfL (sNfL) assay in multiple sclerosis (MS).

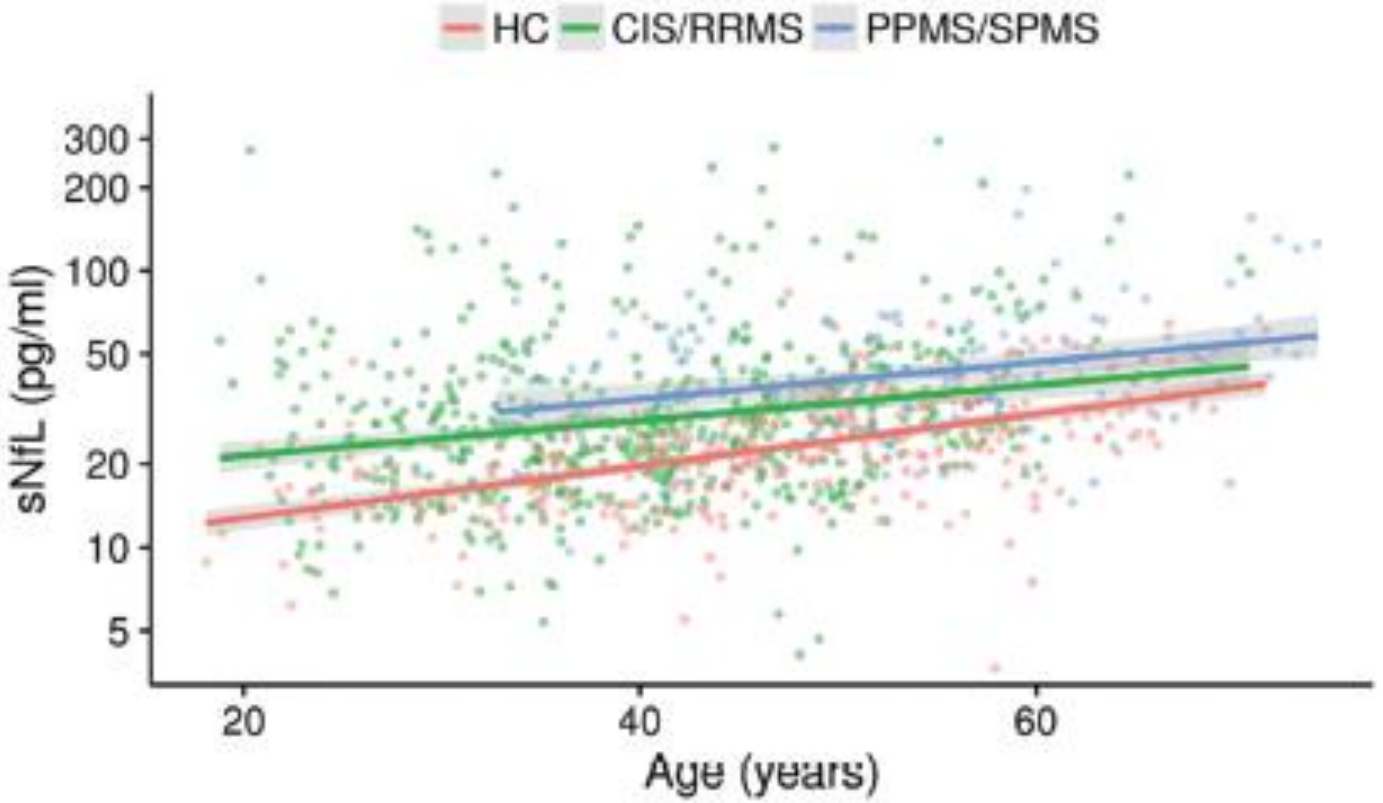
ANN NEUROL 2017;81:857–870

TABLE 1. Estimated sNfL Percentiles Including Bootstrap Confidence Intervals across Different Ages Calculated Based on sNfL from Healthy Control Samples

	sNfL Percentiles, pg/ml				
Age, yr	80th	90th	95th	97.5th	99th
30	20.9 (19.3–22.4)	24.3 (22.3–26.3)	27.9 (25.1–30.4)	31.6 (27.6–35.7)	37.2 (30.9–44.4)
35	23.3 (21.9–24.9)	27.1 (25.3–29.2)	31.1 (28.6–34.0)	35.2 (31.7–39.6)	41.5 (35.8–49.4)
40	26.0 (24.7–27.5)	30.3 (28.6–32.3)	34.7 (31.9–37.8)	39.3 (35.4–44.0)	46.3 (40.1–54.9)
45	29.1 (27.7–30.7)	33.9 (32.2–35.9)	38.9 (36.1–41.9)	44.1 (39.8–49.2)	51.9 (44.8–61.5)
50	32.7 (31.1–34.8)	38.1 (35.9–40.3)	43.6 (40.7–47.0)	49.5 (44.7–55.4)	58.3 (50.3–69.4)
55	36.5 (34.2–39.2)	42.5 (39.7–45.4)	48.7 (45.4–52.5)	55.2 (50.4–61.6)	65.0 (56.2–77.3)
60	40.5 (37.7–44.0)	47.2 (43.6–51.0)	54.0 (49.6–58.8)	61.3 (55.4–68.1)	72.1 (62.3–85.1)
65	44.6 (41.0–49.1)	52.0 (47.3–57.1)	59.5 (53.4–65.8)	67.5 (60.0–75.9)	79.5 (68.2–93.4)
70	48.8 (44.2–54.3)	56.9 (51.1–63.4)	65.1 (57.2–73.2)	73.9 (64.3–84.0)	87.0 (73.8–102.7)

sNfL = serum neurofilament light chain.

Serum Neurofilament Light: A Biomarker of Neuronal Damage in Multiple Sclerosis



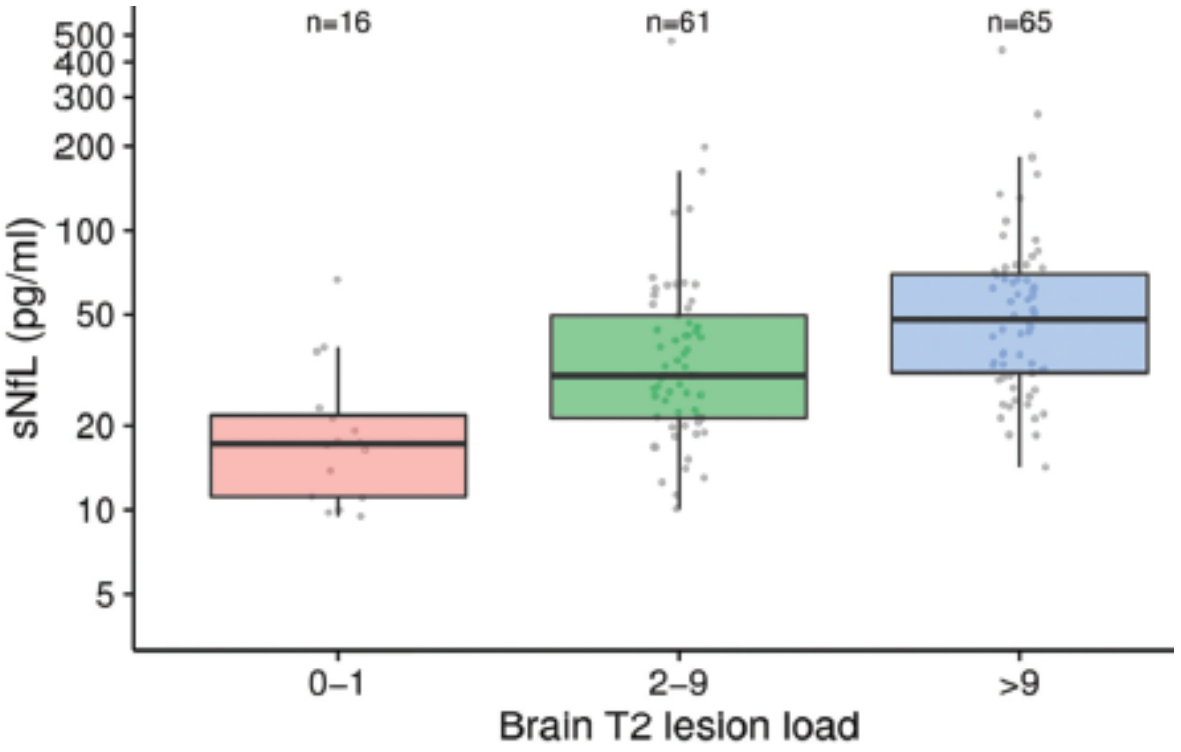
Association between age and serum neurofilament light chain (sNfL) levels in healthy controls (HC), clinically isolated syndrome (CIS)/relapsing–remitting multiple sclerosis (RRMS) patients, and primary progressive multiple sclerosis (PPMS)/ secondary progressive multiple sclerosis (SPMS)

Ann. Neurol. 2017;81:857–870

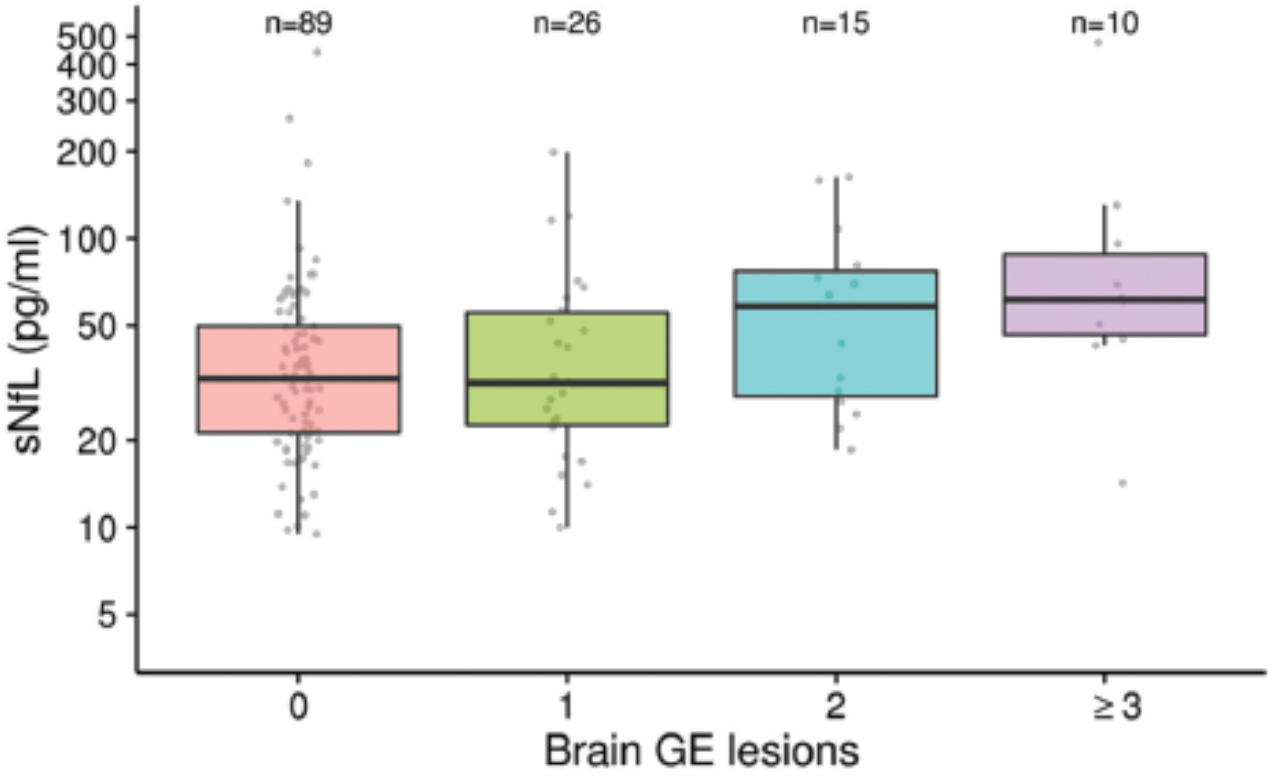
Serum Neurofilament Light: A Biomarker of Neuronal Damage in Multiple Sclerosis

Giulio Disanto, MD, PhD,[1] Christian Barro, MD,[2] Pascal Benkert, PhD,[3] Yvonne Naegelin, MD,[2] Sabine Schädelin, MSc,[3] Antonella Giardiello, MD,[1] Chiara Zecca, MD,[1] Kaj Blennow, PhD,[4] Henrik Zetterberg, PhD,[4,5] David Leppert, MD,[2] Ludwig Kappos, MD,[2] Claudio Gobbi, MD,[1] Jens Kuhle, MD, PhD,[2] and the Swiss Multiple Sclerosis Cohort Study Group

ANN NEUROL 2017;81:857–870

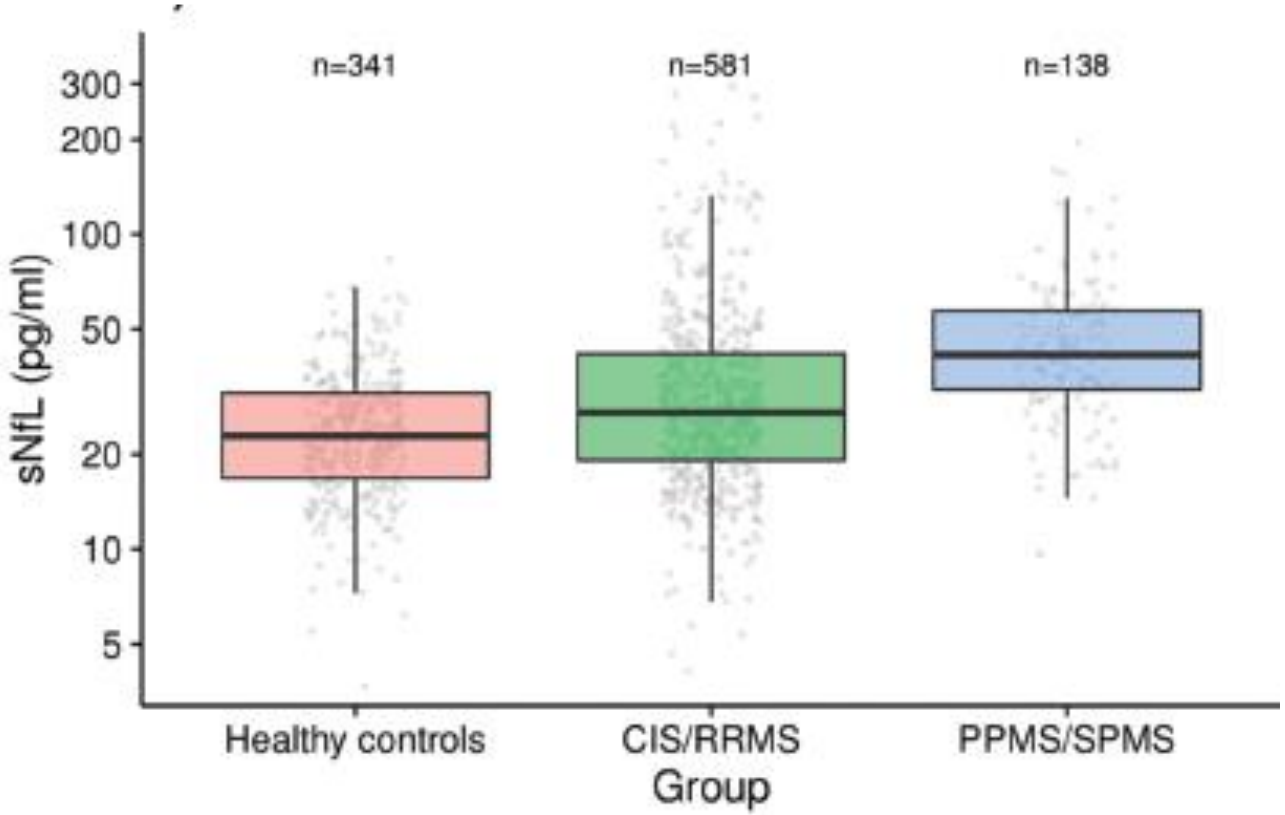


Association between brain T2 lesion load and sNfL levels (2–9 vs 0–1: b=1.849, p= 0.001; >9 vs 0–1: b= 2.524, p < 0.001).



Association between number of brain gadolinium-enhancing (GE) lesions and sNfL levels (1 vs 0: b =1.077, p= 0.630; 2 vs 0: b=1.551, p= 0.024; ≥3 vs 0: b=2.138, p=0.001)

Serum Neurofilament Light: A Biomarker of Neuronal Damage in Multiple Sclerosis



sNfL in HC versus CIS/RRMS and SPMS/PPMS

Ann. Neurol. 2017;81:857–870

REVIEW

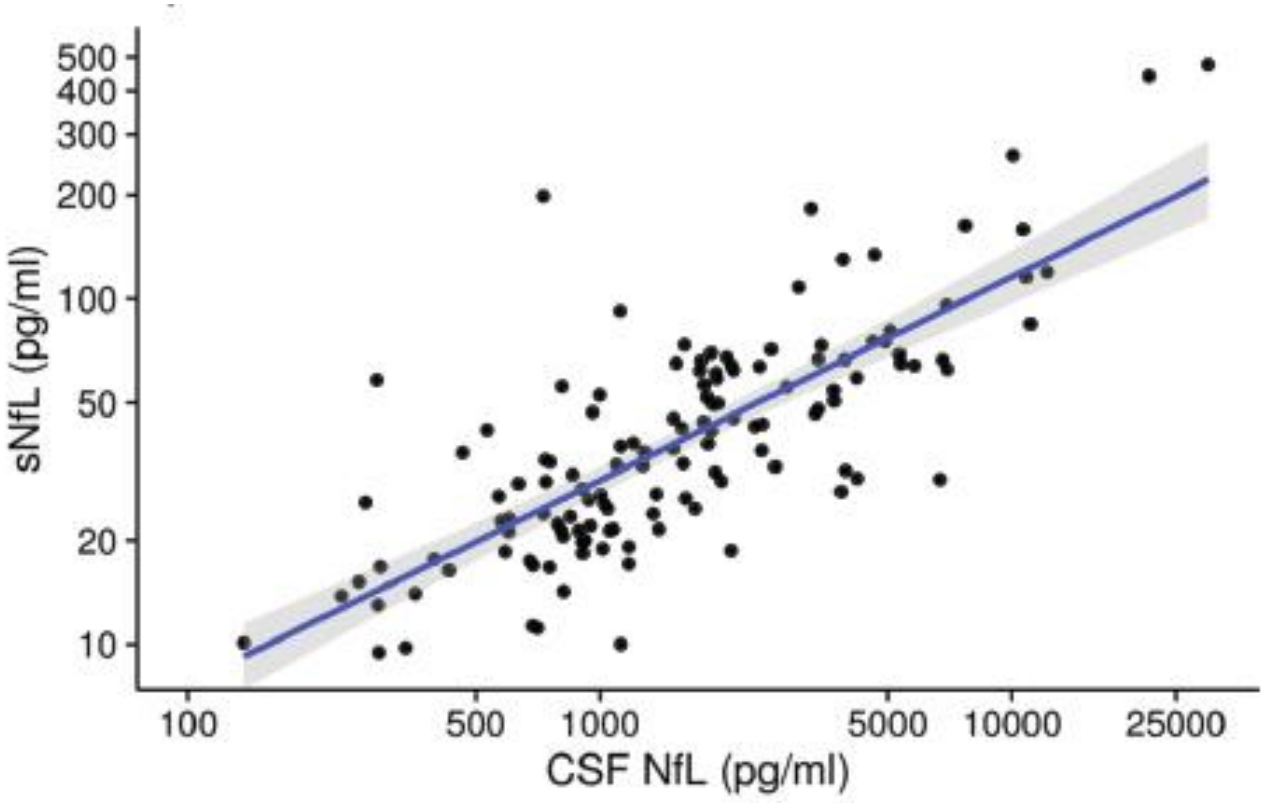
The cerebrospinal fluid in multiple sclerosis: far beyond the bands

DOI: 10.1590/S1679-45082017RW3706

einstein. 2017;15(1):100-4

- Neurofilaments are released in significant quantity following axonal damage or neuronal degeneration. In these situations, NfL is released into the interstitial fluid and into CSF.
- In MS, the CSF NfL concentrations increase after relapses, reaching their peak at 2 weeks after the beginning of symptoms, remaining elevated for at least 15 weeks after an exacerbation.

Association Between CSF and Serum NfL Levels



- A 10% increase in CSF NfL corresponds to an increase of approximately 5.9% in sNfL (n=142; ß=0.589, $p < 0.001$).

CSF, cerebrospinal fluid; Nfl, neurofilament light chain; sNfL, serum neurofilament light chain;
Gray band: 95% confidence interval.

Ann. Neurol. 2017;81:857–870

JAMA Neurology | Original Investigation

Association Between Serum Neurofilament Light Chain Levels and Long-term Disease Course Among Patients With Multiple Sclerosis Followed up for 12 Years

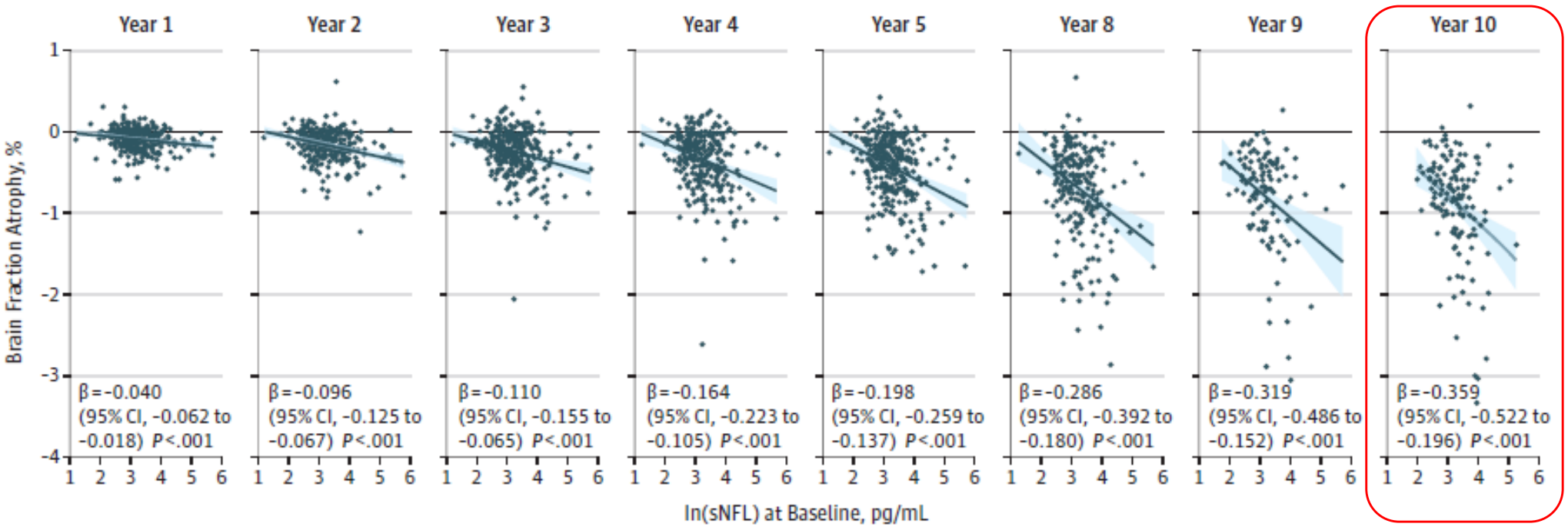
Ester Cantó, PhD; Christian Barro, MD; Chao Zhao, MSc; Stacy J. Caillier, BSc; Zuzanna Michalak, PhD; Riley Bove, MD; Davorka Tomic, DVM, PhD; Adam Santaniello, BSc; Dieter A. Häring, PhD; Jill Hollenbach, PhD; Roland G. Henry, PhD; Bruce A. C. Cree, MD, PhD, MAS; Ludwig Kappos, MD; David Leppert, MD; Stephen L. Hauser, MD; Pascal Benkert, PhD; Jorge R. Oksenberg, PhD; Jens Kuhle, MD, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2019.2137
Published online August 12, 2019.

Conclusions

Our findings from a large observational cohort followed up for 12 years at a single center suggest that (1) sNFL levels are associated with brain atrophy, (2) changes in sNFL levels are associated with disability worsening, and (3) sNFL levels may be influenced by treatment. For an individual patient, the biomarker prognostic power of sNFL level for clinical and magnetic resonance imaging outcomes was limited.

Figure 2. Association of Serum Neurofilament Light Chain (sNFL) Level at Baseline With Percentage of Brain Fraction Change Over Time

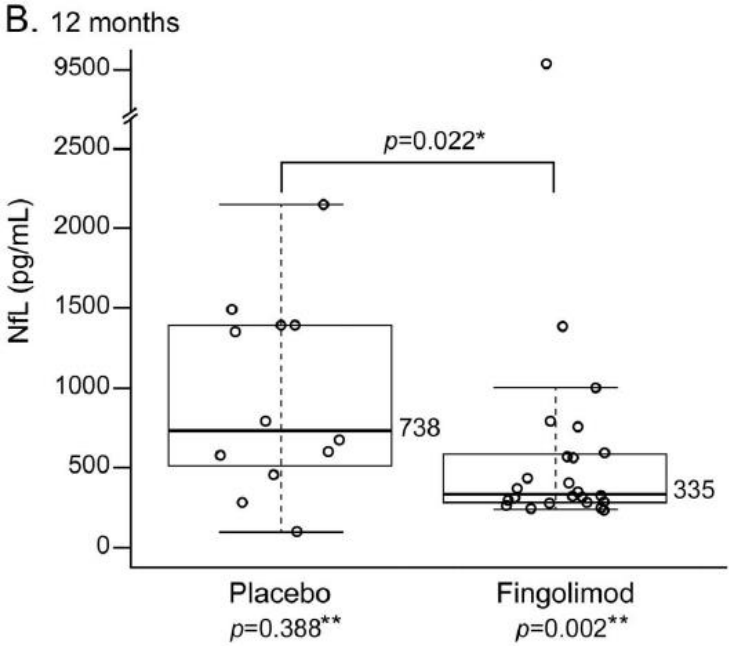


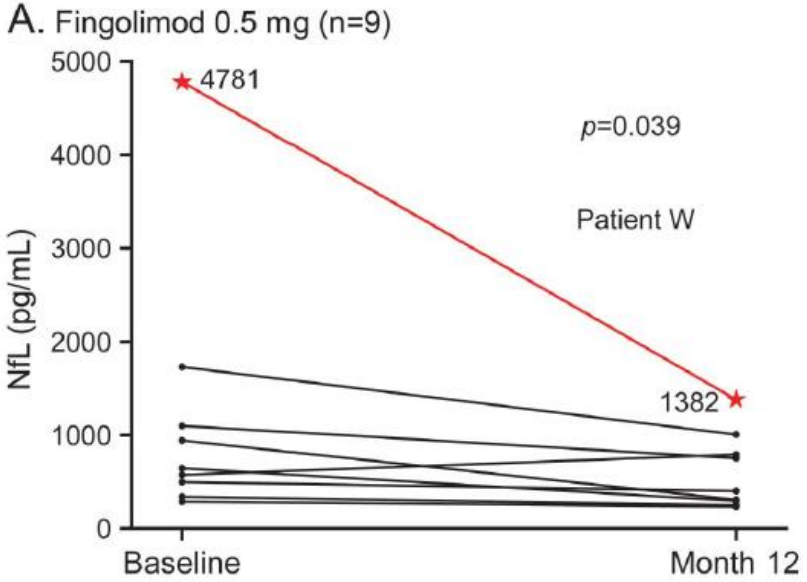
In a multivariable model including age, disease duration, and sex, baseline sNFL levels were significantly associated with the percentage of brain fraction change across time.

Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis

OPEN

Neurology® 2015;84:1639–1643





Phase 3 Fingolimod (FTY720) Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study

Reductions in NfL levels at month 12 correlated with an improvement in relapse and MRI outcomes.

Axonal Damage in Relapsing Multiple Sclerosis is Markedly Reduced by Natalizumab

Martin Gunnarsson, MD, PhD,[1] Clas Malmeström, MD, PhD,[2] Markus Axelsson, MD,[2] Peter Sundström, MD, PhD,[3] Charlotte Dahle, MD, PhD,[4,5] Magnus Vrethem, MD, PhD,[4] Tomas Olsson, MD, PhD,[6] Fredrik Piehl, MD, PhD,[6] Niklas Norgren, PhD,[7] Lars Rosengren, MD, PhD,[2] Anders Svenningsson, MD, PhD,[3] and Jan Lycke, MD, PhD[2]

ANN NEUROL 2011;69:83–89

The median pretreatment EDSS score was 4.0 (2.5–5.5, 25th–75th percentile) as compared to 3.5 (2.0–5.0, 25th–75th percentile) post-treatment ($p < 0.001$).

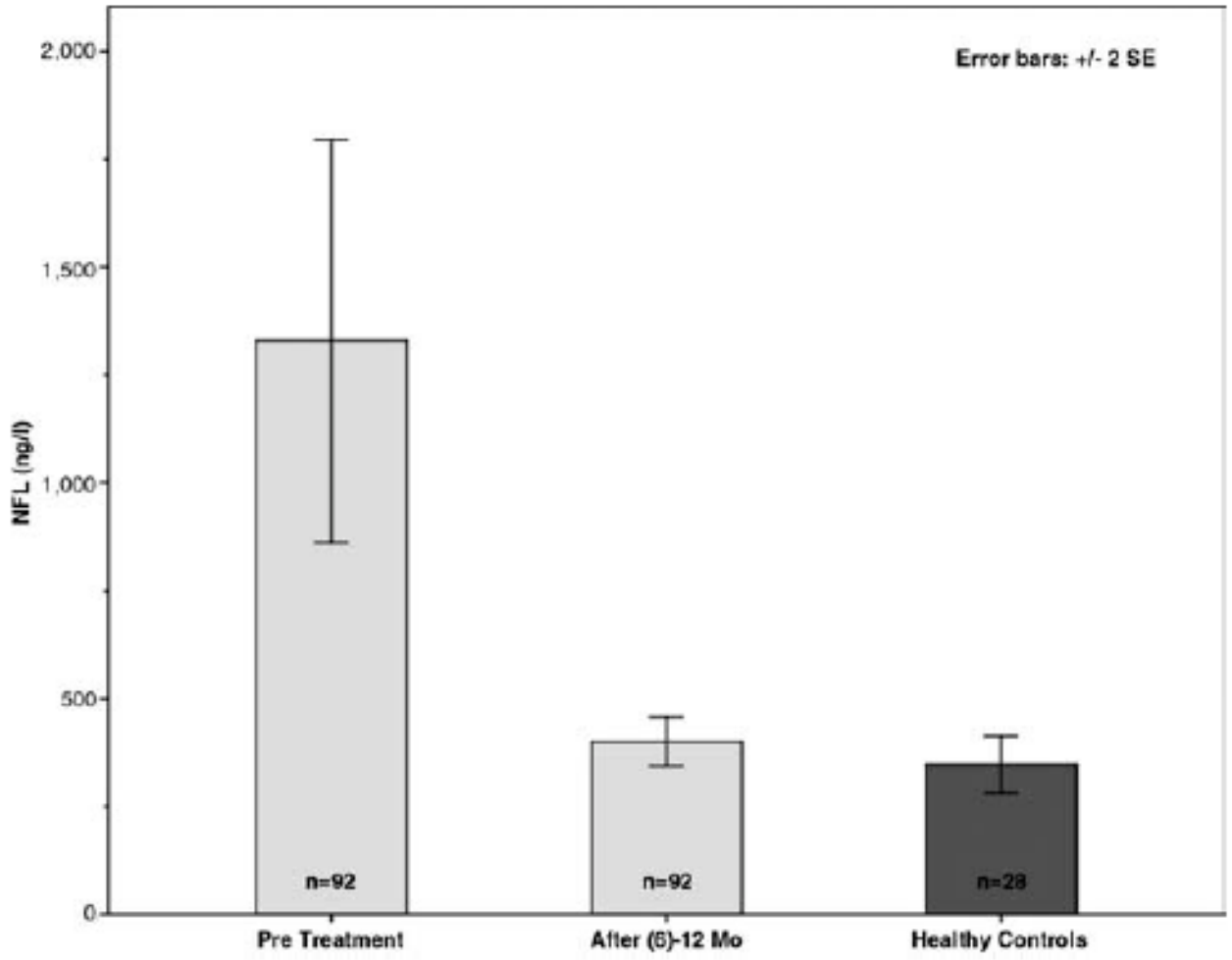


FIGURE 1: Neurofilament light in cerebrospinal fluid (CSF)

Neurology®
April 09, 2019; 92 (15 Supplement) **MAY 7, 2019**

Effect of Alemtuzumab on Serum Neurofilament Light Chain Levels: Comparison to SC IFNB-1a and Assessment Over 7 Years (CARE-MS I) (P3.2-045)

Jens Kuhle, Nadia Daizadeh, Christian Barro, Zuzanna Michalak, David Leppert, Jean Godin, Srinivas Shankara, Tarek A. Samad, Alan Jacobs, Luke Chung, Nora Roesch, Carina Kaiser, Ludwig Kappos, Evis Havari

Abstract

Objective: To assess the effect of alemtuzumab on serum neurofilament light (sNfL) levels in RRMS patients versus SC IFNB-1a over 2 years, and of alemtuzumab over 7 years.

Results:

Median sNfL levels were similar in alemtuzumab-treated (n=354) and SC IFNB-1a-treated (n=159) patients at baseline (31.7 pg/mL vs 31.3 pg/mL).

Median sNfL levels were significantly lower with alemtuzumab at 6 months post-treatment versus SC IFNB-1a (17.2 pg/mL vs 21.4 pg/mL; *P*<0.0001), with significant differences persisting at Month 24 (13.2 pg/mL vs 18.7 pg/mL; *P*<0.0001). At Month 24, more alemtuzumab-treated patients had reduction in sNfL levels (81% vs 72%), more had a reduction of ≥50% (69% vs 57%), and fewer patients had a sNfL level above the age-adjusted 80th percentile of non-MS healthy controls (12% vs 30%; *P*=0.0003).

sNfL levels remained stable and low in alemtuzumab-treated patients at Month 84 (median, 12.7 pg/mL), despite 57% receiving no additional treatment after the initial 2 courses.

Neurology®
April 09, 2019; 92 (15 Supplement) **MAY 10, 2019**

Ocrelizumab treatment reduced levels of neurofilament light chain and numbers of B cells in the cerebrospinal fluid of patients with relapsing multiple sclerosis in the OBOE study (S56.008)

Anne Cross, Jeffrey Bennett, Hans Christian von Büdingen, Robert Carruthers, Keith Edwards, Robert Fallis, Damian Fiore, Jeffrey Gelfand, Paul Giacomini, Benjamin Greenberg, David Hafler, Christopher Harp, Beverly Assman, Ann Herman, Carolina Ionete, Ulrike Kaunzner, Christopher Lock, Xiaoye Ma, Bruno Musch, Gabriel Pardo, Fredrik Piehl, Martin Weber, Tjalf Ziemssen, Amit Bar-Or

Abstract

Objective: To provide interim analysis (IA) results from the relapsing multiple sclerosis (RMS) cohort of OBOE (Ocrelizumab Biomarker Outcome Evaluation; NCT02688985), a cerebrospinal fluid (CSF) and blood biomarker study.

Results:

Pretreatment CSF and serum NfL levels correlated strongly (r=0.78; p<0.001). Both serum and CSF NfL levels correlated with numbers of T1 gadolinium-enhancing lesions and new/enlarging T2 lesions on brain MRI.

OCR significantly reduced serum NfL (−13.1%, −18.6% and −30.8%), CSF NfL (−24.5%, −40.0% and −54.7%) and CSF B cells (−85.5%, −84.8% and −94.0%) at Weeks 12, 24 and 52, respectively.

CSF T cells were reduced by ≈60% across the same time points, but reductions were significant only at Week 12.

Reference-arm samples showed no significant changes in CSF/serum NfL or CSF lymphocyte numbers over 12 weeks.

Neurology®
April 09, 2019; 92 (15 Supplement) **MAY 6, 2019**

Natalizumab Reduces Serum Concentrations of Neurofilament Light Chain in Secondary Progressive Multiple Sclerosis Patients From the Phase 3 ASCEND Study (S12.008)

Raju Kapoor, Finn Sellebjerg, Hans-Peter Hartung, Douglas Arnold, Mark S. Freedman, Douglas Jeffery, Aaron Miller, Keith R. Edwards, Carol M. Singh, Ih Chang, Zhang Ren, Dipen Sangurdekar, Bing Zhu, Devangi Mehta, Pei-Ran Ho, Nolan Campbell, Michael Edwards, Elizabeth Fisher, Bernd C. Kieseier, Richard A. Rudick, Tatiana Plavina

Abstract

Objective: To evaluate the associations of serum neurofilament light chain (sNfL) concentrations and disease activity, disability progression and response to natalizumab treatment in participants with secondary progressive multiple sclerosis (SPMS).

Results:

Baseline sNfL concentrations were associated ($p<0.0001$) with number of Gd+ lesions, T2 lesion volume, Timed 25-Foot Walk time (T25FW), 9-Hole Peg Test time (9HPT) at baseline, and brain atrophy over 96 weeks.

At week 96, sNfL concentrations were significantly higher in participants with progression [defined using EDSS ($p<0.01$), T25FW ($p<0.05$), or 9HPT ($p<0.01$)], compared to those without progression during the study.

sNfL concentrations at weeks 48 and 96 were significantly lower in natalizumab versus placebo participants (ratio 0.84/95% CI [0.79, 0.89], $p<0.001$ and ratio 0.80/95% CI [0.7, 0.85], $p<0.001$, respectively); statistically significant sNfL differences were observed in participants with and without Gd+ lesions at baseline, relapses in 2 years before study enrollment and inflammatory activity (Gd+ lesions, new T2 lesions or relapse) during the study.

Neurology®
April 10, 2018; 90 (15 Supplement) **APRIL 22, 2018**

Siponimod Reduces Neurofilament Light Chain Blood Levels in Secondary Progressive Multiple Sclerosis Patients (S8.006)

Jens Kuhle, Harald Kropshofer, Christian Barro, Rolf Meinert, Dieter A. Häring, David Leppert, Davorka Tomic, Frank Dahlke, Ludwig Kappos

Abstract

Objective: To explore whether siponimod (2.0 mg once-daily), compared with placebo, reduces neurofilament light chain (NfL) levels in blood of patients with secondary progressive multiple sclerosis (SPMS).

Results:

In the population treated for >21 months (N=525), NfL (GeoMean, pg/ml) levels at baseline were 28.8 in the placebo group and 30.7 in the siponimod group.

Over 21 months, blood NfL levels were increased by 9.2% in the placebo group and reduced by 5.7% with siponimod (p=0.0004).

In the rSPMS subgroup (n=212), blood NfL levels were increased by 7.1% in the placebo group and reduced by 10.5% with siponimod (p=0.0028).

the nrSPMS subgroup (n=312), NfL levels were elevated by 10.7% in the placebo group and decreased by 2.5% with siponimod (p=0.0328).

Νεότερα Φάρμακα και Επαναμυελίνωση-Remyelination

Ofatumumab Impresses in MS; Competition for Ocrelizumab Soon?

Sue Hughes

September 16, 2019

STOCKHOLM — A new B cell–depleting anti-CD20 monoclonal antibody has shown impressive results in two phase 3 studies in relapse-remitting multiple sclerosis (RRMS).

Ofatumumab (Novartis) yielded a reduction in relapse rates of more than 50%, a reduction in disability progression of more than 30%, and a reduction in gadolinium-enhancing T1 lesions of more than 90% in comparison with teriflunomide (*Aubagio*, Sanofi Genzyme) in the ASCLEPIOS I and II trials. Tolerability was also good; adverse events were similar in the ofatumumab and teriflunomide groups, and there were no unexpected safety signals.

The findings were presented at last week's 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2019.

Promising Phase 3 Results With New Oral MS Drug Ponesimod

Sue Hughes

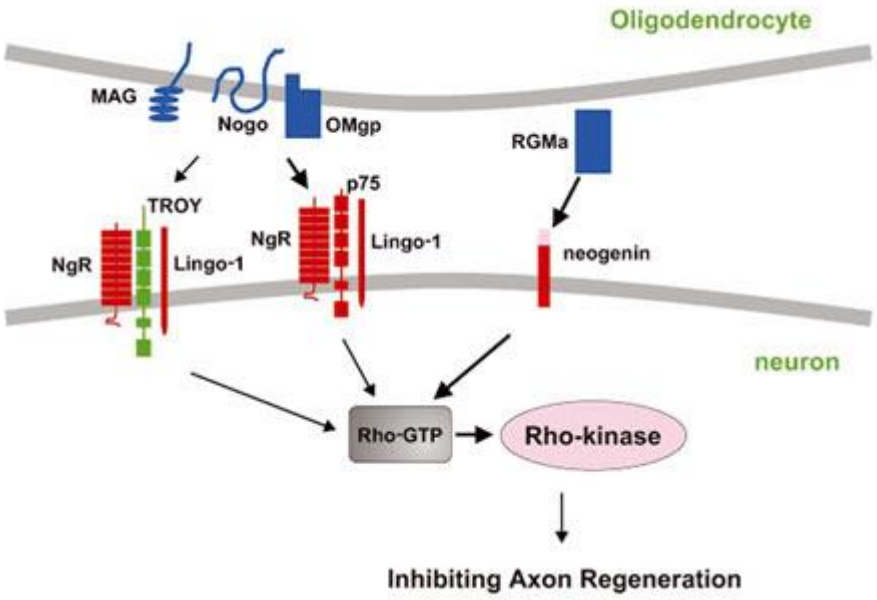
October 03, 2019

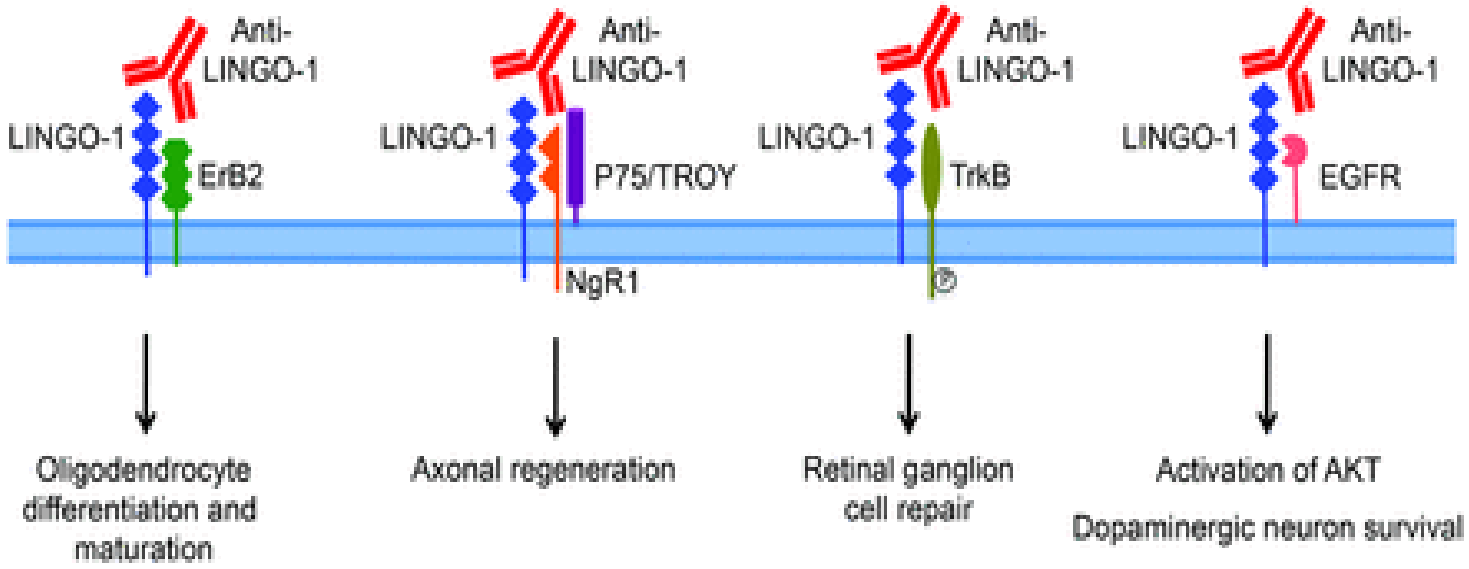
A new oral drug for relapsing remitting multiple sclerosis — ponesimod (Actelion Pharmaceuticals) — has shown promising results in a phase 3 trial vs the active comparator, teriflunomide (*Aubagio,* Genzyme/Sanofi).

Ponesimod showed significant reductions in relapse rate, new active lesions, and fatigue-related symptoms vs teriflunomide in the OPTIMUM trial, presented at the recent 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2019.

"Ponesimod showed a reassuring and benign safety profile and should be a valuable addition to the armamentarium for relapsing remitting MS," lead investigator Ludwig Kappos, MD, University Hospital Basel, Switzerland, concluded.

Ponesimod is in the same class of drugs as fingolimod, sphingosine-1-phosphate (S1P) receptor modulators, but whereas fingolimod targets several different S1P receptors, ponesimod is selective for the S1P1 receptor, the key S1P receptor involved in lymphocyte trafficking, Kappos explained.


Oligodendrocyte
MAG
Nogo
OMgp
RGMa
TROY
p75
NgR
Lingo-1
NgR
Lingo-1
neogenin
neuron
Rho-GTP
Rho-kinase
Inhibiting Axon Regeneration


Anti-
LINGO-1
LINGO-1
ErB2
Oligodendrocyte differentiation and maturation
Anti-
LINGO-1
LINGO-1
P75/TROY
NgR1
Axonal regeneration
Anti-
LINGO-1
LINGO-1
TrkB
P
Retinal ganglion cell repair
Anti-
LINGO-1
LINGO-1
EGFR
Activation of AKT
Dopaminergic neuron survival

Anti-LINGO-1

SCIENTIFIC REPORTS

OPEN

LINGO-1 antibody ameliorates myelin impairment and spatial memory deficits in experimental autoimmune encephalomyelitis mice

Received: 07 April 2015
Accepted: 20 August 2015
Published: 18 September 2015

Jun-Jun Sun[1,*], Qing-Guo Ren[1,*], Lin Xu[2,3] & Zhi-Jun Zhang[1]

We assessed cognitive function at early and late stages of EAE, determined brain expression of myelin basic protein (MBP) and investigated whether the LINGO-1 antibody could restore deficits in learning and memory and ameliorate any loss of MBP.
We found that deficits in learning and memory occurred in late EAE and identified decreased expression of MBP in the parahippocampal cortex (PHC) and fimbria-fornix. Moreover, the **LINGO-1 antibody significantly improved learning and memory in EAE** and partially restored MBP in PHC. Furthermore**, the LINGO-1 antibody activated the AKT/mTOR signaling pathway regulating myelin growth**. Our research demonstrates that **LINGO-1 antagonism may be an effective approach to the treatment of the cognitive impairment of multiple sclerosis** patients.

Biogen Idec Reports Positive Top-Line Results from Phase 2 Anti-LINGO-1 Trial in People with Acute Optic Neuritis

SHARE

Biogen Idec Reports Positive Top-Line Results from Phase 2 Anti-LINGO-1 Trial in People with Acute Optic Neuritis

- Data Offer Evidence of Proof of Biology in Acute Optic Neuritis -

- Phase 2 Multiple Sclerosis Trial Ongoing, Data Expected in 2016 Will Further Define Clinical Potential -

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Biogen Idec has announced top-line results from the Phase 2 acute optic neuritis (AON) RENEW trial in which treatment with anti-LINGO-1 showed evidence of biological repair of the visual system. Anti-LINGO-1 demonstrated an improvement in the study's primary endpoint, recovery of optic nerve latency (time for a signal to travel from the retina to the visual cortex), as measured by full field visual evoked potential (FF-VEP), relative to placebo. The study showed no effect on secondary endpoints, including change in thickness of the retinal layers (optic nerve neurons and axons) and visual function, as measured by spectral domain optical coherence tomography (SD-OCT) and low contrast letter acuity, respectively.

SYNERGY: Anti-LINGO Agent Misses Primary Endpoint in MS

LONDON — The phase 2b SYNERGY trial missed its primary endpoint of significantly improved disability and neurophysical function after treatment with the novel remyelinating agent opicinumab (Biogen) in patients with relapsing multiple sclerosis (MS).

Opicinumab, previously known as BIIB033, is a monoclonal antibody that blocks LINGO-1, a negative regulator of myelination. SYNERGY was a proof-of-concept trial for the drug, with more than 418 adults with MS.

Of the participants randomly assigned to 3 or 100 mg/kg of intravenous (IV) opicinumab, along with intramuscular interferon β-1a, 47% and 40%, respectively, had confirmed improvement on combined disability/ neurophysical/ cognitive function scores over 72 weeks vs 49% of those who received matching placebo.

The groups receiving the two middle doses of 10 or 30 mg/kg of concurrent opicinumab did have a greater proportion of improvement responders (63% and 65%, respectively) vs the placebo group, but the overall trend test for a "linear dose response" wasn't statistically significant.

Σας ευχαριστώ πολύ για την προσοχή σας