Update on DMTs in Multiple Sclerosis

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3/4/2017

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ROCKY MOUNTAIN
MS CENTER
— the answers begin here —

uchealth

Disclosures

•Honoraria	Prime CME
•Board Member	NMSS
•Research	Med Day; Novartis; Biogen; PCORI; NMSS
•Editorial	Editor, Neurology: Clinical Practice

Objectives

- Define the natural history of multiple sclerosis (MS) and need for early, effective therapy
- Provide updates on presently available MS disease modifying therapies
- Describe new disease modifying therapies for MS
- Describe potential remyelination strategies for MS
- Describe neuroprotective approaches in MS for MS

Inflammation and Neurodegeneration in MS

Relapsing ⟷ Progressive

Disease Mechanisms

Relapsing	Progressive
• Oxidative injury • Mitochondrial dysfunction • Inflammation • Microglia activation • Oxidative burst • Expression of NADPH oxidases • iNOS expression	• Oxidative injury • Mitochondrial dysfunction • Mitochondrial DNA deletions • Iron accumulation with aging (eg, oligodendrocytes, microglia, axons, neurons, astrocytes)

Pathological Changes

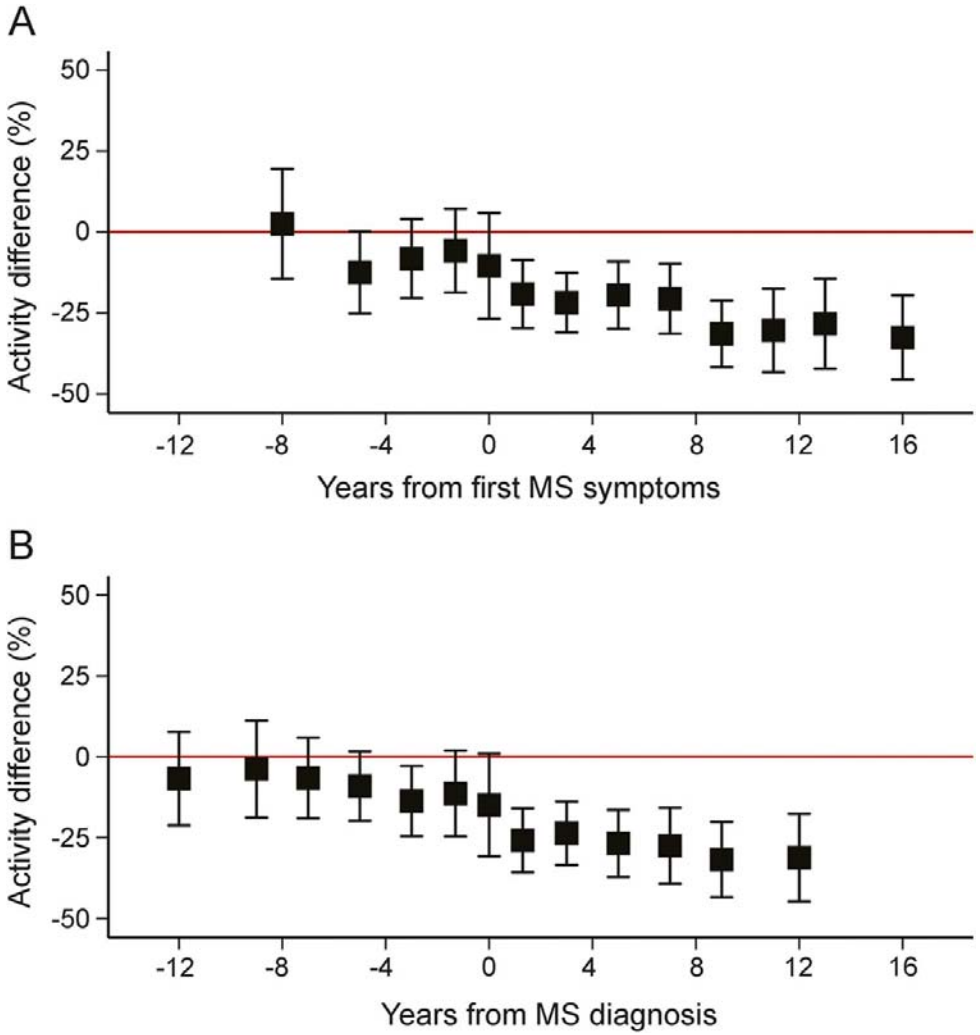
• New waves of lymphocytes entering the CNS • Breakdown of BBB • New active CNS lesions • Focal demyelination • Initial remyelination in active lesions • Brain Atrophy	• Meningeal inflammatory aggregates • Slow expansion of pre-existing lesions • Subpial cortical demyelination • Widespread degeneration of the white and grey matter • Brain atrophy

NADPH = nicotinamide adenine dinucleotide phosphate-oxidase; iNOS = inducible nitric oxide synthase; CNS = central nervous system; BBB = blood-brain barrier. Lassmann H, et al. *Nat Rev Neurol*. 2012;8(11):647-656; Ontaneda D, Fox RJ. *Curr Opin Neurol*. 2015;28(3):237-243.

Potential Approaches to Treat MS

- Immunotherapies
- Neuroprotective strategies
- Remyelination approaches
- Replace damaged cells

Figure 2 Relative physical activity by time of multiple sclerosis (MS) symptoms or diagnosis



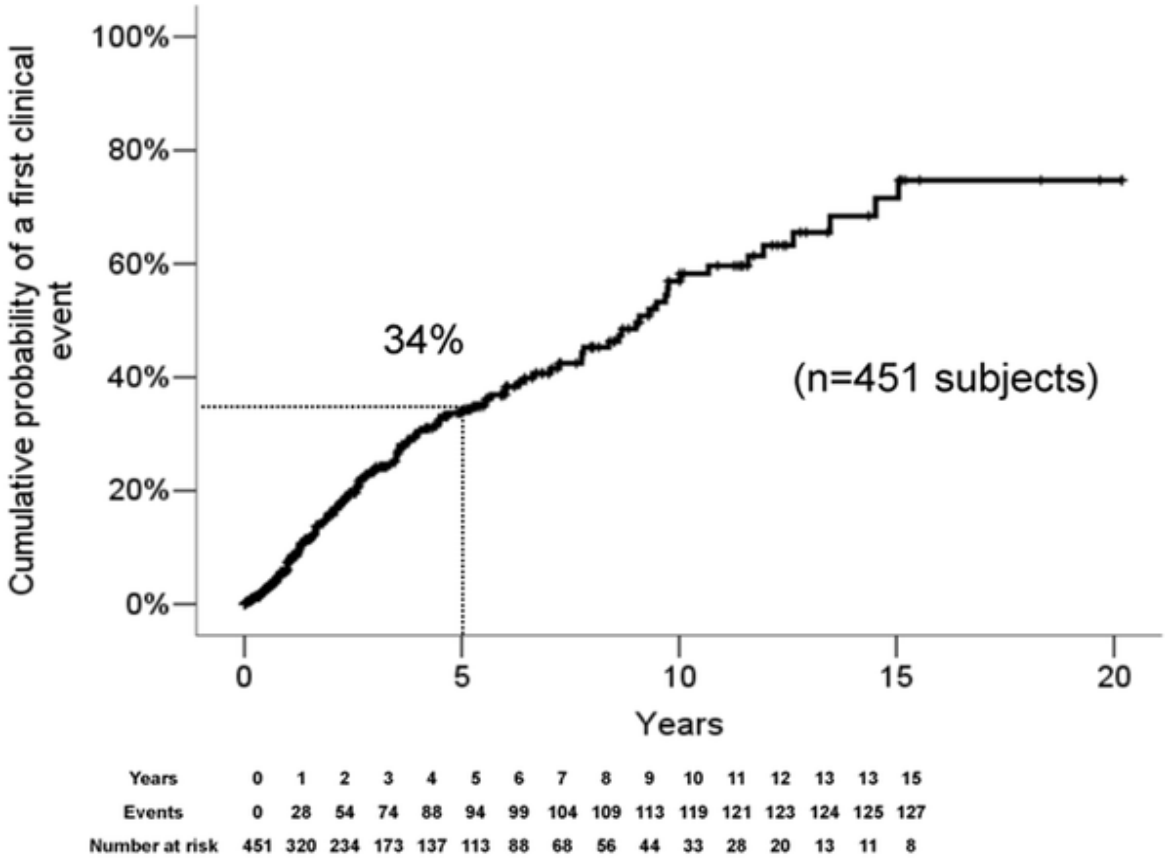
Kirsten S. Dorans et al. Neurology 2016;87:1770-1776

Radiologically Isolated Syndrome

Asymptomatic patients with classic MS findings on MRI.

Will they go on to develop MS?

- 1/3 will develop clinical MS over 2-5 yrs.
- 91% develop radiographic dissemination over 6-30 months

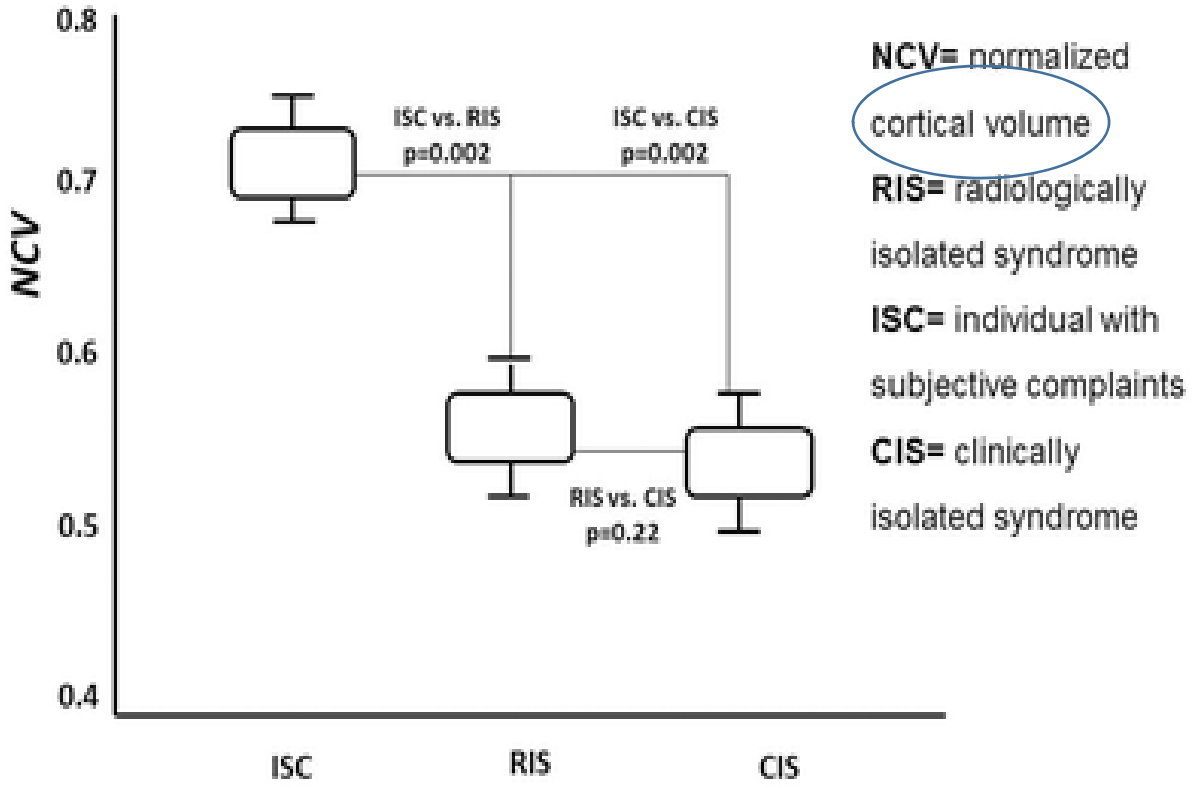


42% - MRI for Headache
194/300 (64.7%) with + OCBs

30% at 5 years in ONTT
51% in ONTT if 3+ brain MRI lesions

Lebrun et al, Arch Neurol 2009;
Okuda et al, PLoS ONE 2014

Brain Atrophy in Radiologically Isolated Syndromes



Journal of Neuroimaging
Volume 25, Issue 1, pages 68-71, 13 OCT 2014 DOI: 10.1111/jon.12182
http://onlinelibrary.wiley.com/doi/10.1111/jon.12182/full#jon12182-fig-0002

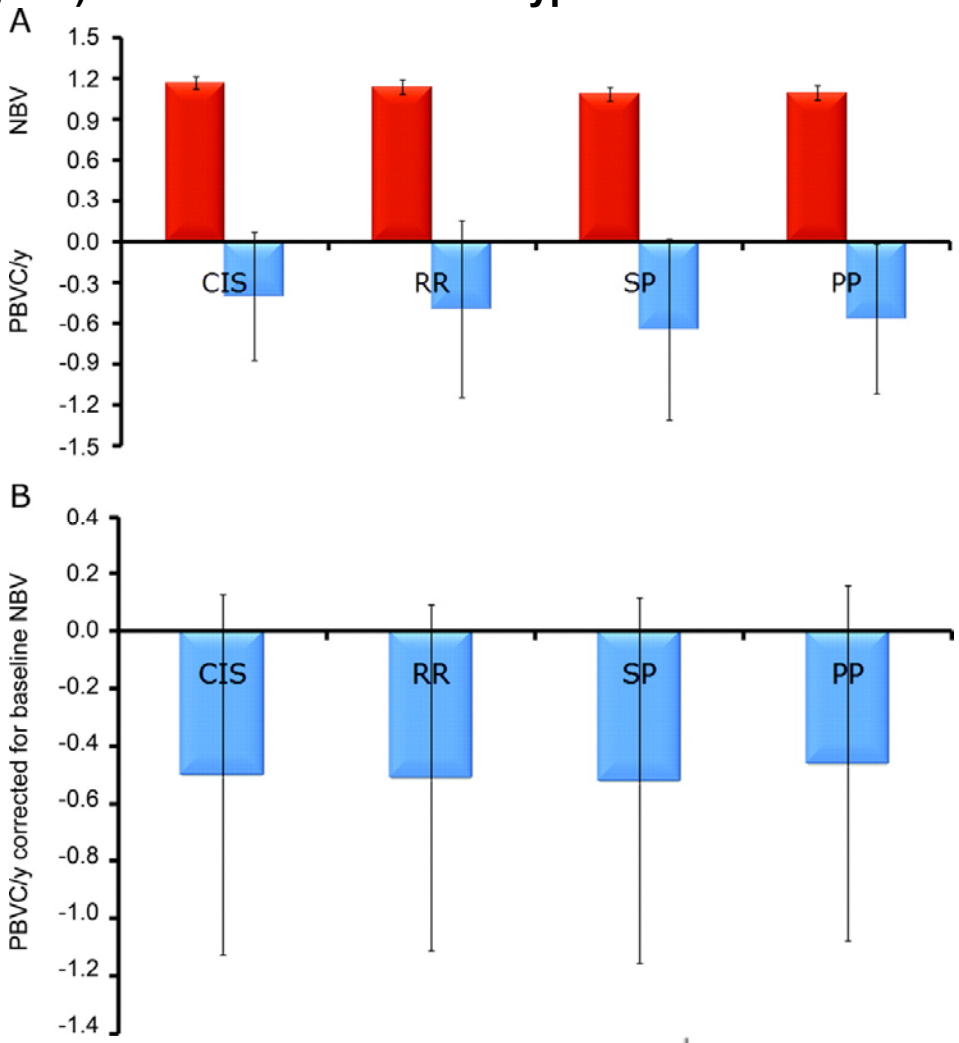
Figure 1 Brain atrophy measures in the different multiple sclerosis (MS) subtypes (A) Values of percent brain volume change (PBVC)/y (blue) and normalized brain volume (NBV) (expressed in liters, red) in the different MS subtypes.

Two Time Points

Median 14 Months Apart

All 963 Untreated

Conclusion ".. brain atrophy proceeds relentlessly throughout the course of MS"



N. De Stefano et al. Neurology 2010;74:1868-1876

AMERICAN ACADEMY OF NEUROLOGY

Table 1 *Baseline characteristics of patients*

	Interferon beta-1b, n = 292	Placebo, n = 176
Women	207 (70.9)	124 (70.5)
Age at first event, y	30 (24–37.5)	30 (25–36)
White	286 (97.9)	174 (98.9)
Steroid treatment of first event	209 (71.6)	123 (69.9)
Clinical presentation of first event		
Monofocal onset	153 (52.4)	93 (52.8)
Optic nerve	45 (29.4)	35 (37.6)
Brainstem/cerebellar	33 (21.6)	22 (23.7)
Spinal	52 (34.0)	25 (26.9)
Other (cerebral)	23 (15.0)	11 (11.8)
Multifocal onset	139 (47.6)	83 (47.2)
EDSS at baseline	1.5 (0–4.0)	1.5 (0–4.0)
CSF sample taken at first event	198 (67.8)	116 (65.9)
Of these: CSF typical for MS	171 (86.4)	96 (82.8)
MRI at screening		
T2 hyperintense lesions		
No. of T2 lesions	18.0 (7.0–38.5)	17.0 (7.5–36.5)
No. of patients with ≥9 T2 lesions	207 (70.9)	123 (69.9)
Volume of T2 lesions, mm^3	1951.5 (592–5029)	1858.5 (641–3479)
Gadolinium (Gd+) enhancing lesions		
No. of Gd+ lesions	0 (0–1.0)	0 (0–1.0)
Patients with ≥1 Gd+ lesion	127 (43.5)	70 (39.8)
Volume of Gd+ lesions, mm^3	0 (0–155)	0 (0–140)

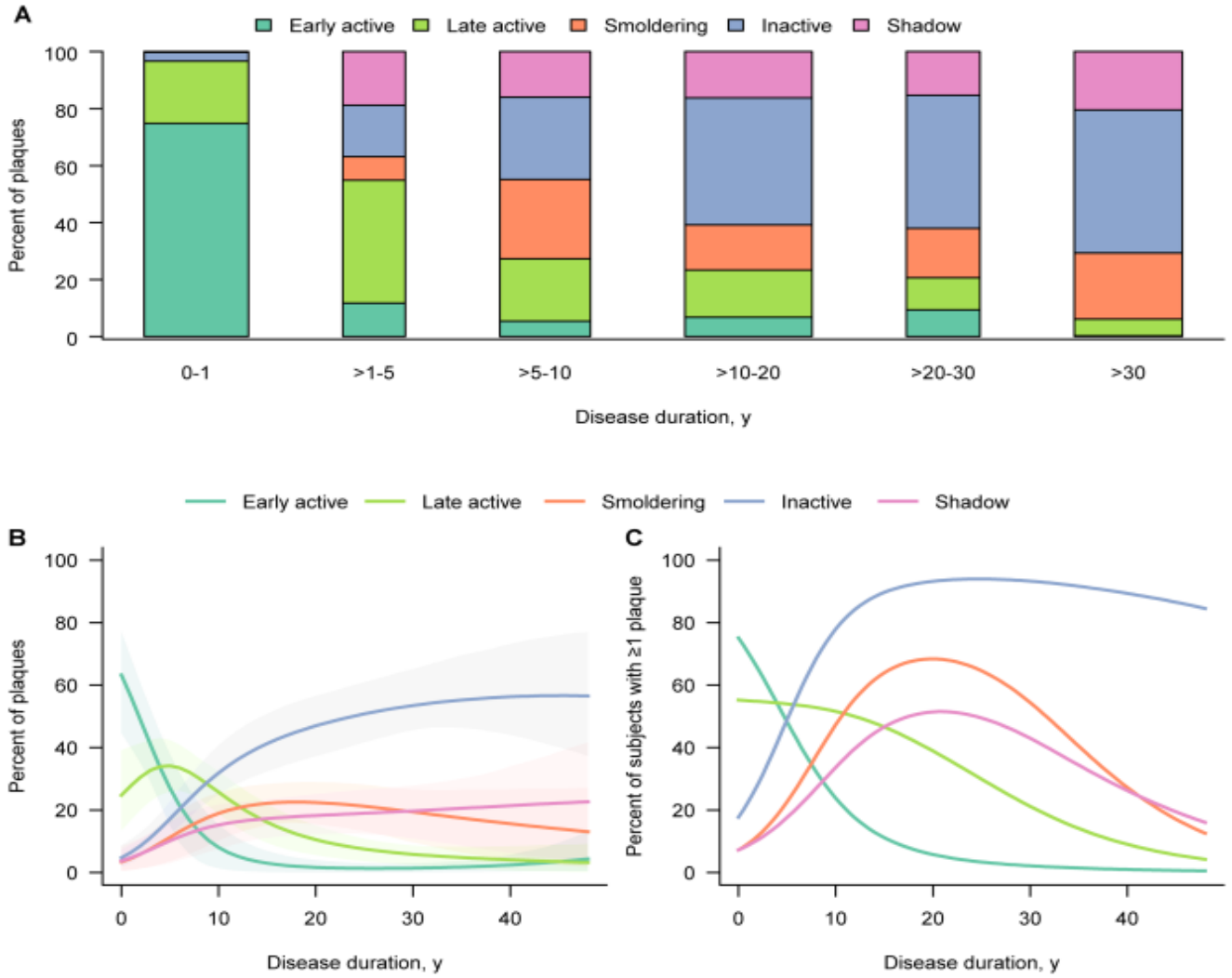
Values are n (%) or median (Q1–Q3) (1st to 3rd quartile).

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

Kappos L, Polman CH, Freedman MS, etal. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology*. 2006;67(7):1242-1249.

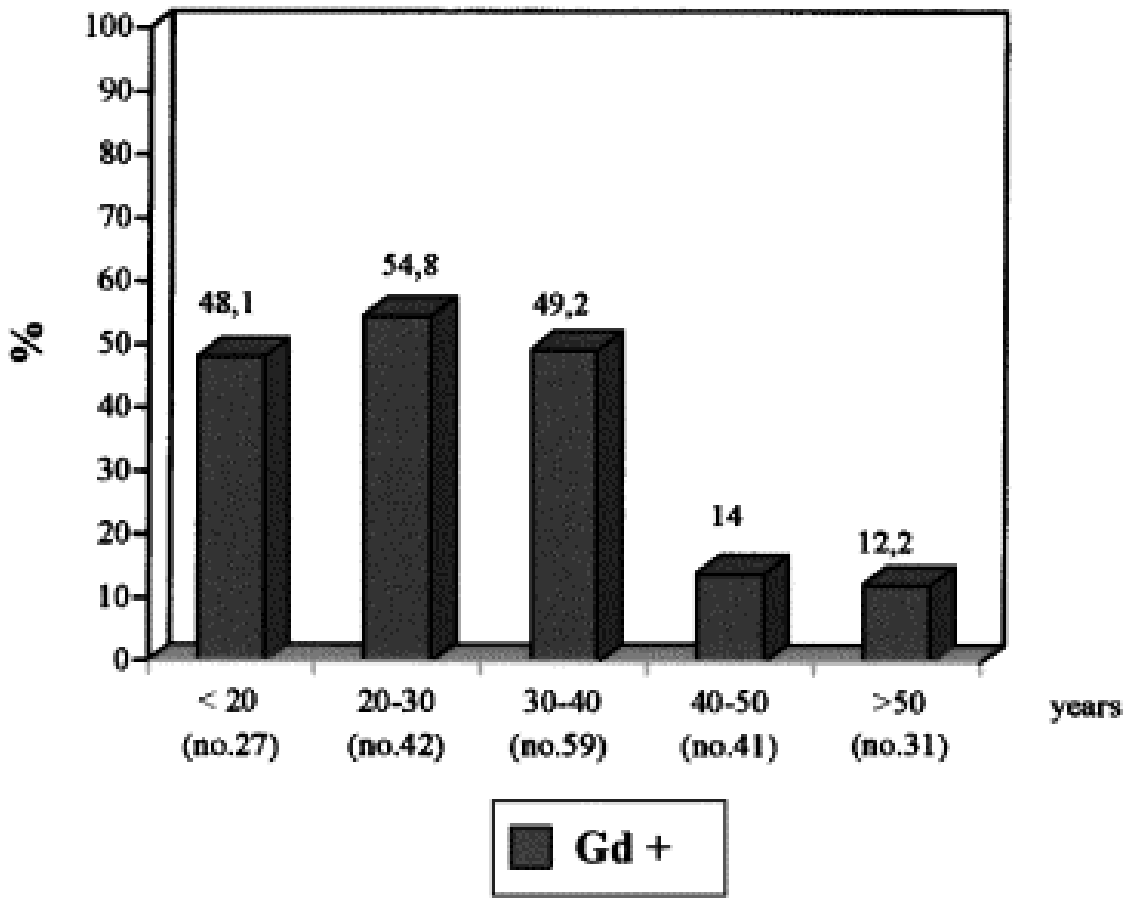
The BENEFIT Trial

Clinical and pathological insights into the dynamic nature of white matter multiple sclerosis plaques



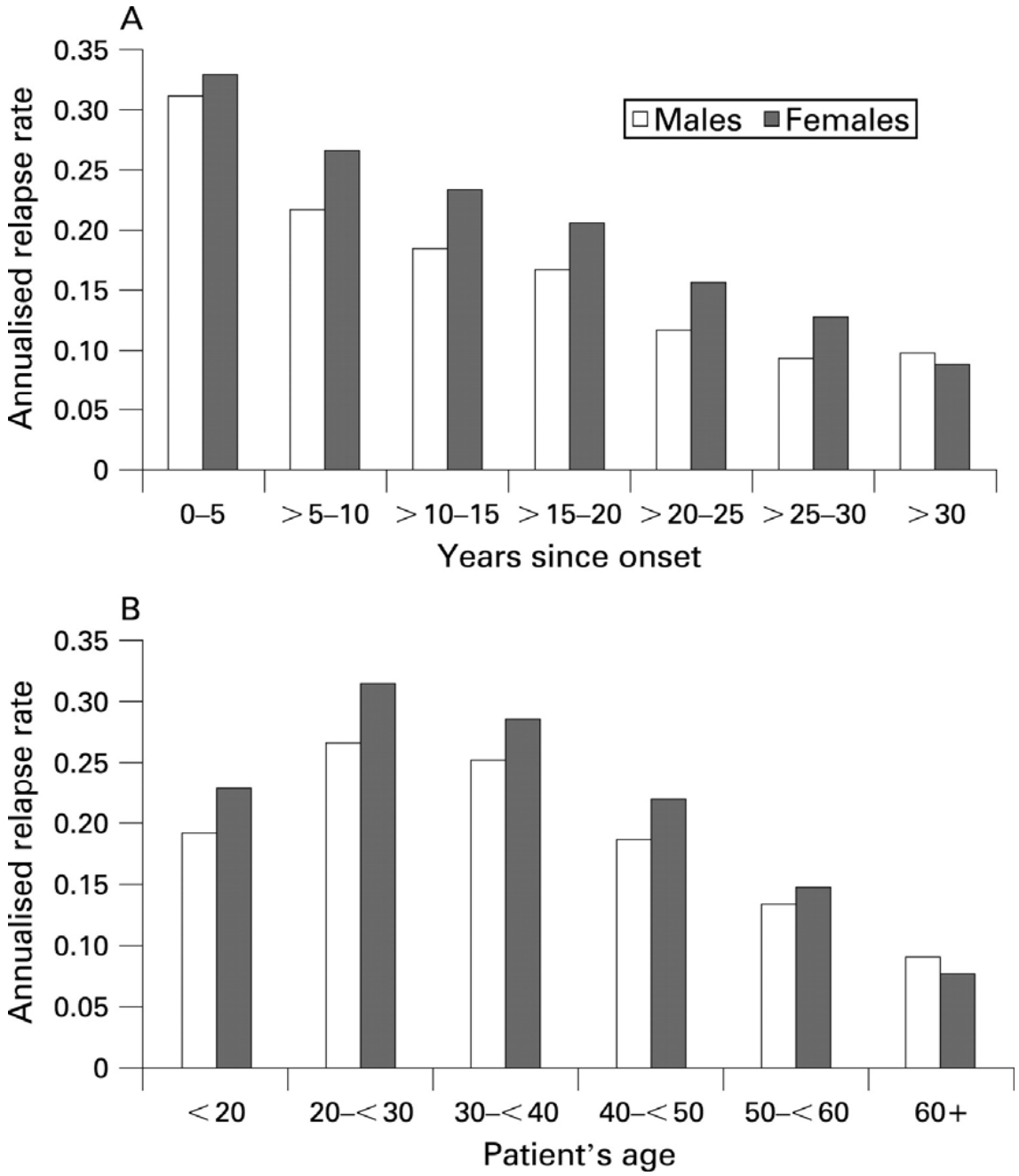
Annals of Neurology78(5): pages 710-721, 24 AUG 2015 DOI: 10.1002/ana.24497

Fig. 1. Frequency of enhancing scans in patients with different decades of age. Bars represent enhancing scans. Overall 35% with enhancing lesions. (Over 50 has error, is 9.6% (3/31)).



Carla Tortorella, et al, Age-related gadolinium-enhancement of MRI brain lesions in multiple sclerosis. Journal of the Neurological Sciences, Volume 239, Issue 1, 2005, 95–99. http://dx.doi.org/10.1016/j.jns.2005.08.006

Relapse Rate for Men and Women from Onset and by Current Age (A) from Onset (n=2477), (B) by Patient's Current Age (n=2477)



"From the population perspective, the impact of any therapeutic agent targeting the inflammatory processes in MS, and hence ability to modify recurrence of relapses, has the greatest potential during periods of high relapse activity."

Tremlett et al. *J Neurol Neurosurg Psych.* 2008;79:1368-1374. BCMS Database

From: Early Relapses, Onset of Progression, and Late Outcome in Multiple Sclerosis

JAMA Neurol. 2013;70(2):214-222. doi:10.1001/jamaneurol.2013.599. Scalfari, et al.

Table 1. Clinical and Demographic Features of Patients With Low and High Early Relapse Frequency[a]

Variable	Early Relapses, Frequency: 1-2 Attacks (n = 572)	Early Relapses, Frequency: ≥3 Attacks (n = 158)	*P* Value
Sex			
Men, No. (%)	180 (31.5)	48 (30.4)	.79[b]
Women, No. (%)	392 (68.5)	110 (69.6)	
Ratio F/M	2:1	2:3	
Type of disease at end of follow-up, No. (%)			
RR MS	166 (29.0)	55 (34.8)	.16[b]
SP MS	406 (71.0)	103 (65.2)	
Disease duration, mean (SD), y	26.2 (10.3)	19.3 (7.1)	<.001[c]
Age at disease onset, mean (SD), y	28.8 (9.2)	27.4 (8.2)	.11[c]
Duration of the RR phase,[d] mean (SD), y	11.7 (7.5)	6.9 (5.5)	<.001[c]
Age at onset of progression,[d] mean (SD), y	41.5 (9.9)	35.3 (9.5)	<.001[c]
Kaplan-Meier estimated time to DSS score levels, mean (median), y[e]			
DSS 3	13.5 (11)	8.3 (4)	<.001[f]
DSS 6	21.6 (19)	14.6 (10)	<.001[f]
DSS 8	32.4 (31)	20.4 (21)	<.001[f]

Abbreviations: DSS, Disability Status Scale; MS, multiple sclerosis; RR, relapsing remitting; SP, secondary progressive.

[a] Low frequency indicates 1 to 2 attacks in the first 2 years; high frequency, 3 or more attacks.

[b] Calculated using the χ^2 test.

[c] Calculated using the Wilcoxon signed rank test.

[d] Includes SP patients only.

[e] DSS scores are explained in the "Subjects and Outcomes" subsection of the "Methods" section.

[f] Calculated using the log-rank test.

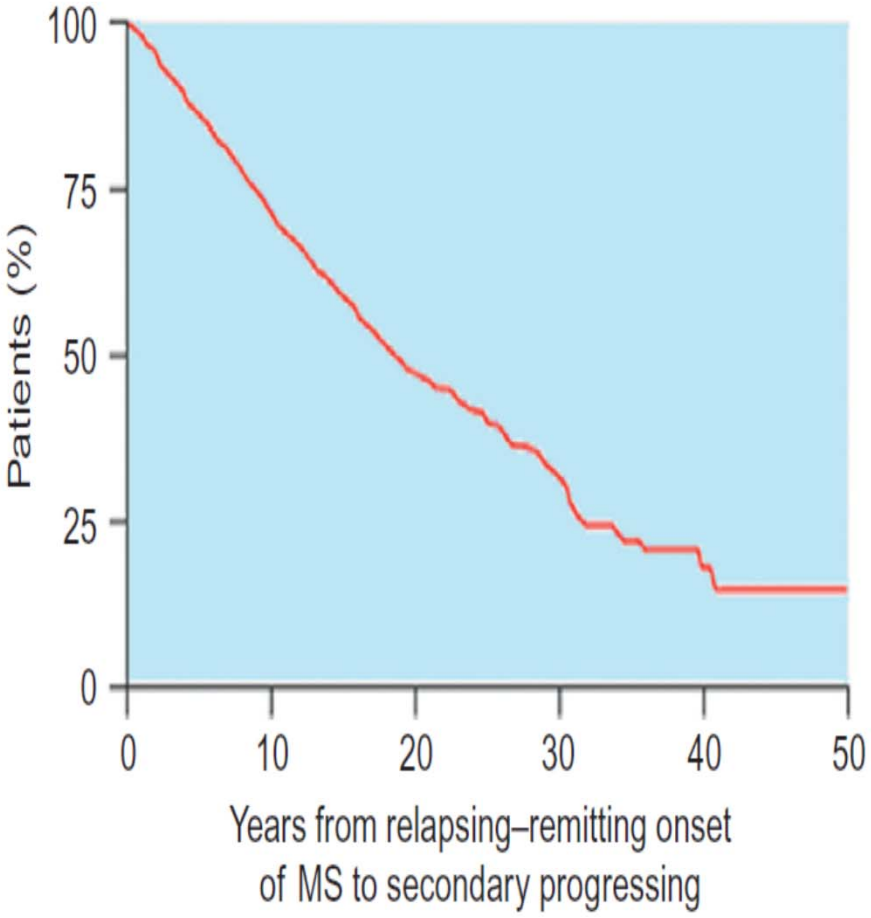


Fig. 15.6. Kaplan–Meier estimates for the time (years) from the onset of multiple sclerosis (MS) to the onset of the secondary progressive phase among 1562 patients with a relapsint-remitting initial course in the Lyon, France, MS cohort. (Reproduced from Vukusic and Confavreux, 2003.)

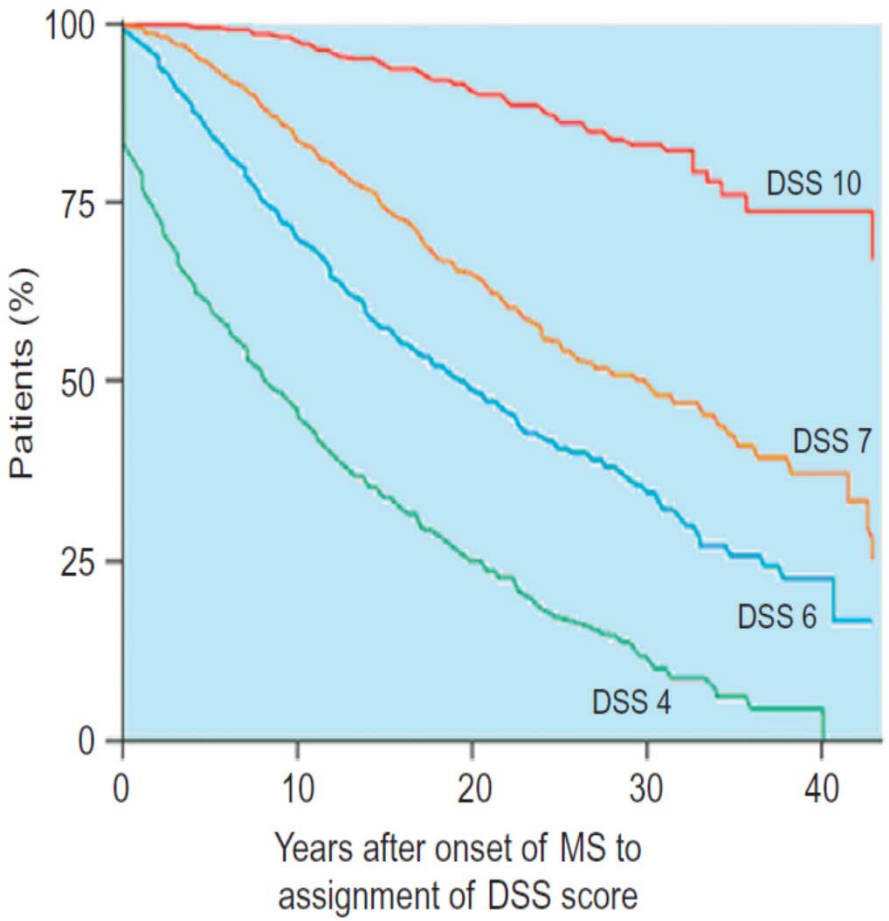


Fig. 15.7. Kaplan–Meier estimates for the time (years) from the onset of multiple sclerosis (MS) to the assignment of an irreversible score of 4, 6, 7, and 10 on the Kurtzke disability status scale (DSS), among 1844 patients in the Lyon, France, MS cohort. (Reproduced from Confavreux and Compston, 2006; adapted from Confavreux et al., 2000, 2003.)

HandbookOf Clinical Neurology. 2014;122:343-69. doi: 10.1016/B978-0-444-52001-2.000145.
Confavreux and Vukusic

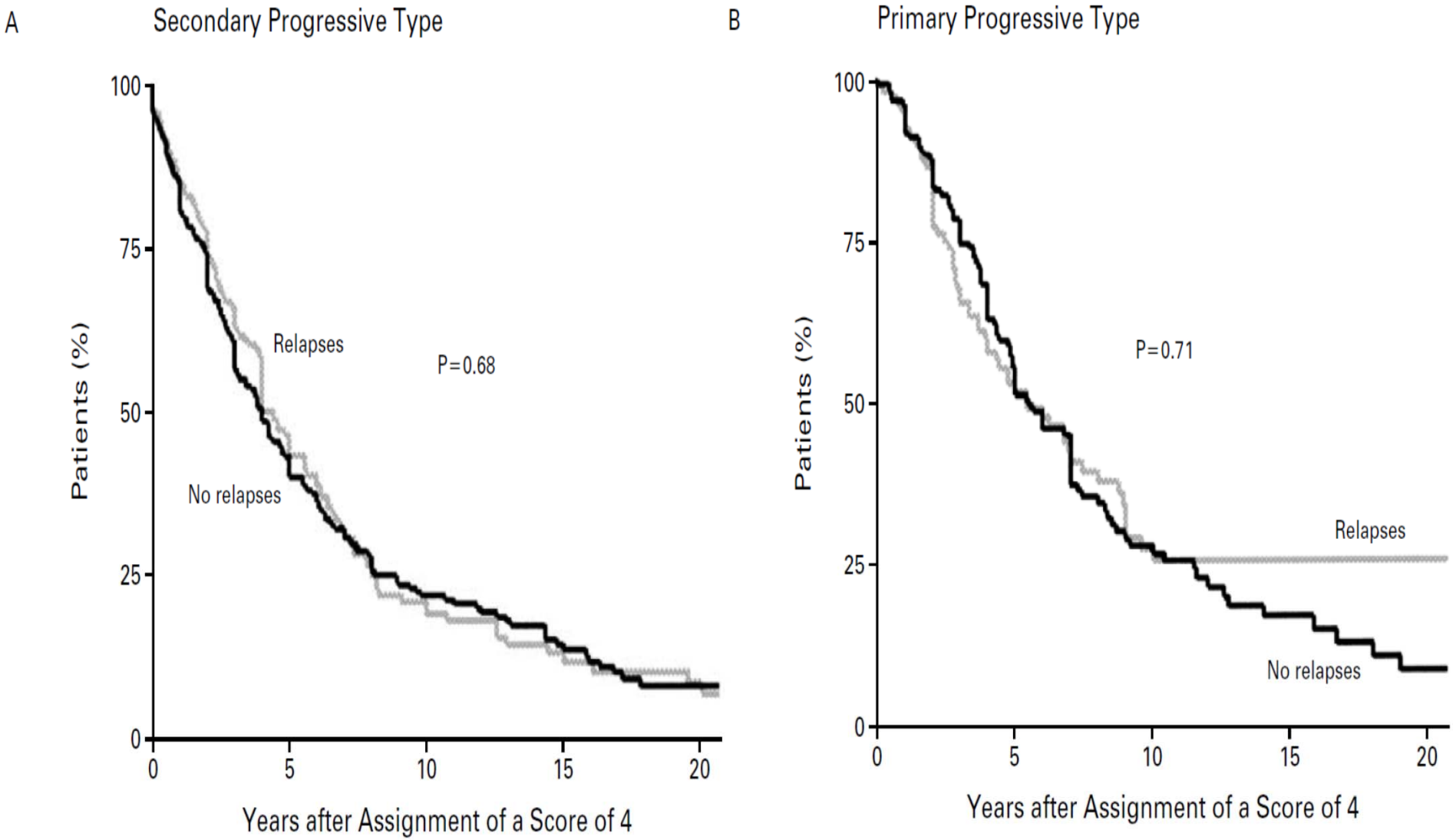


Figure 3. Kaplan–Meier Estimates of the Time from the Assignment of a Score of 4 on the Kurtzke Disability Status Scale to the Assignment of a Score of 6 among the 496 Patients with the Secondary Progressive Type of Multiple Sclerosis (Panel A) and the 282 Patients with the Primary Progressive Type of Multiple Sclerosis (Panel B), According to the Presence or Absence of Superimposed Relapses.

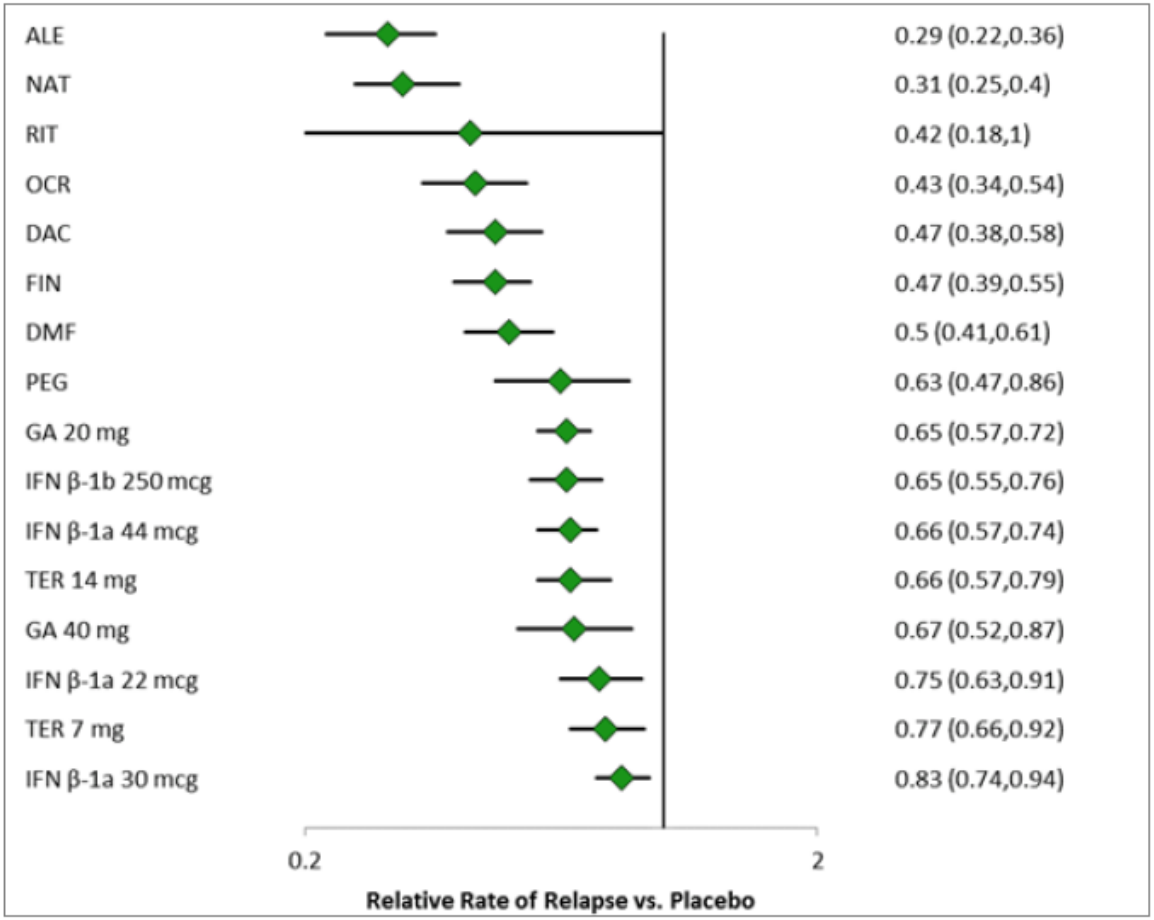
N Engl J Med. 2000 Nov 16;343(20):1430-8. Relapses and progression of disability in multiple sclerosis. Confavreux et al EDSS = 4: Fully ambulatory without aid, up and about

Modern Era of Approved MS Disease Modifying Therapy

- 1993 Interferon β-1b (Bestaseron)
- 1996 Interferon β-1a, 30 mcg IM weekly (Avonex)
- 1996 Glatiramer acetate 20 mg daily (Copaxone)
- 2000 Mitoxantrone (Novantrone)
- 2002 Interferon β-1a, 22 mcg/44 mcg SQ TIW (Rebif)
- 2004 Natalizumab (Tysabri)
- 2010 Fingolimod (Gilenya)
- 2012 Teriflunomide (Aubagio)
- 2013 Dimethyl fumarate (Tecfidera)
- 2014 GA (Copaxone), 40 mg TIW; Interferon β-1a, 125 mcg SQ Pegylated Q 2 weeks (Plegridy); Alemtuzumab (Lemtrada)
- 2015 Generic GA (Glatopa)
- 2016 Daclizumab (Zinbryta)
- 2017 Ocrelizumab (Ocrevus) by 3/28/17?

MS DMT Comparative Effectiveness For ARR

Figure 3. Forest Plot of DMTs vs. Placebo for Annualized Relapse Rate

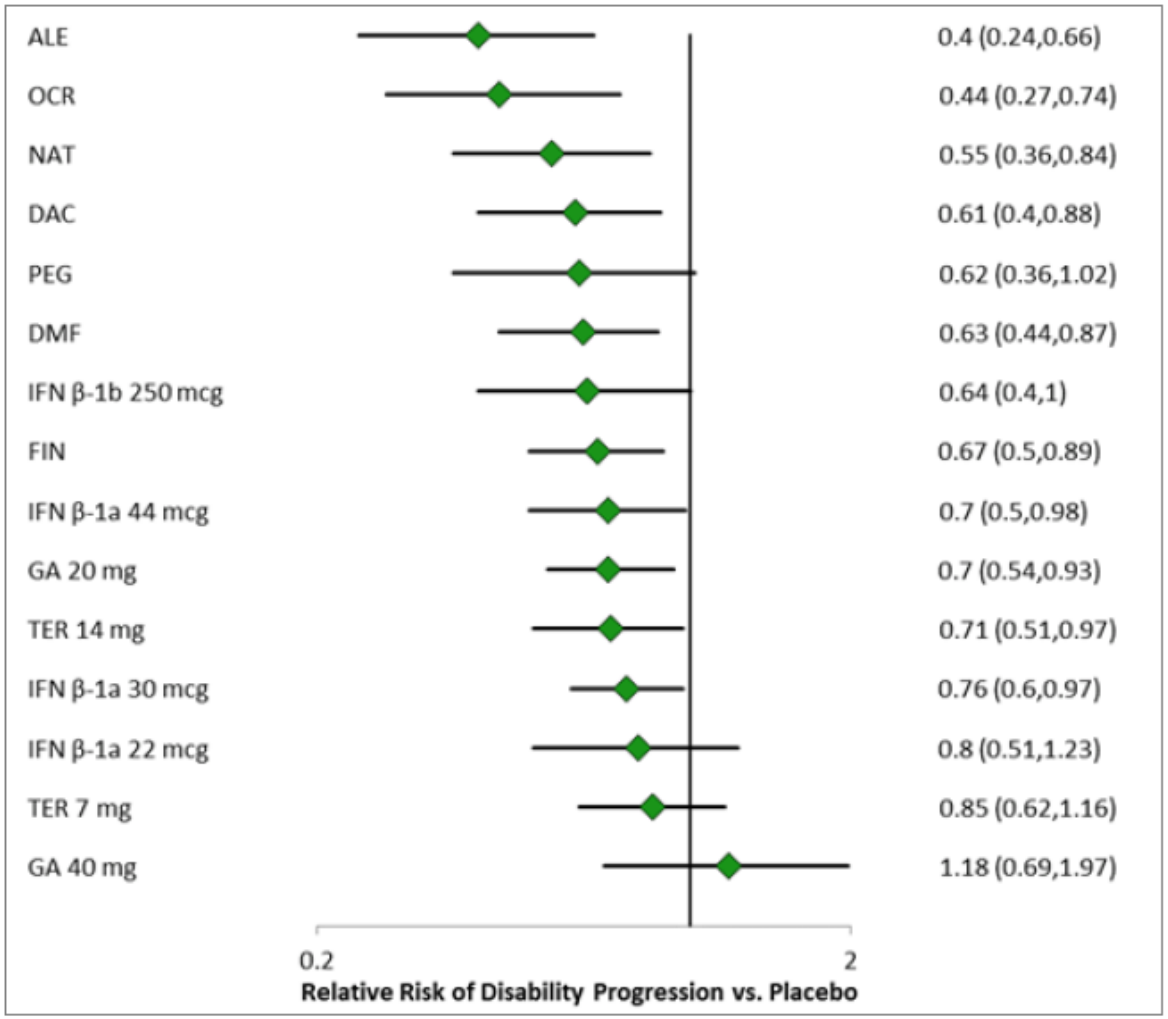


Legend: The diamonds represent the point estimate from the NMA for the relative risk of relapse rate for each drug compared to placebo and the horizontal bars represent the 95% credible intervals. Any numbers less than 1 indicate a reduction in the relapse rate compared to placebo.

Draft Evidence Report: DMTs for RRMS and PPMS

Ability to Prevent SAD for MS DMTs

Figure 4. Forest Plot of DMTs vs. Placebo for Disability Progression



Legend: The diamonds represent the point estimate from the NMA for the relative risk of disability progression for each drug compared to placebo and the horizontal bars represent the 95% credible intervals. Any numbers less than 1 indicate a reduction in disability progression compared to placebo.

Draft Evidence Report: DMTs for RRMS and PPMS

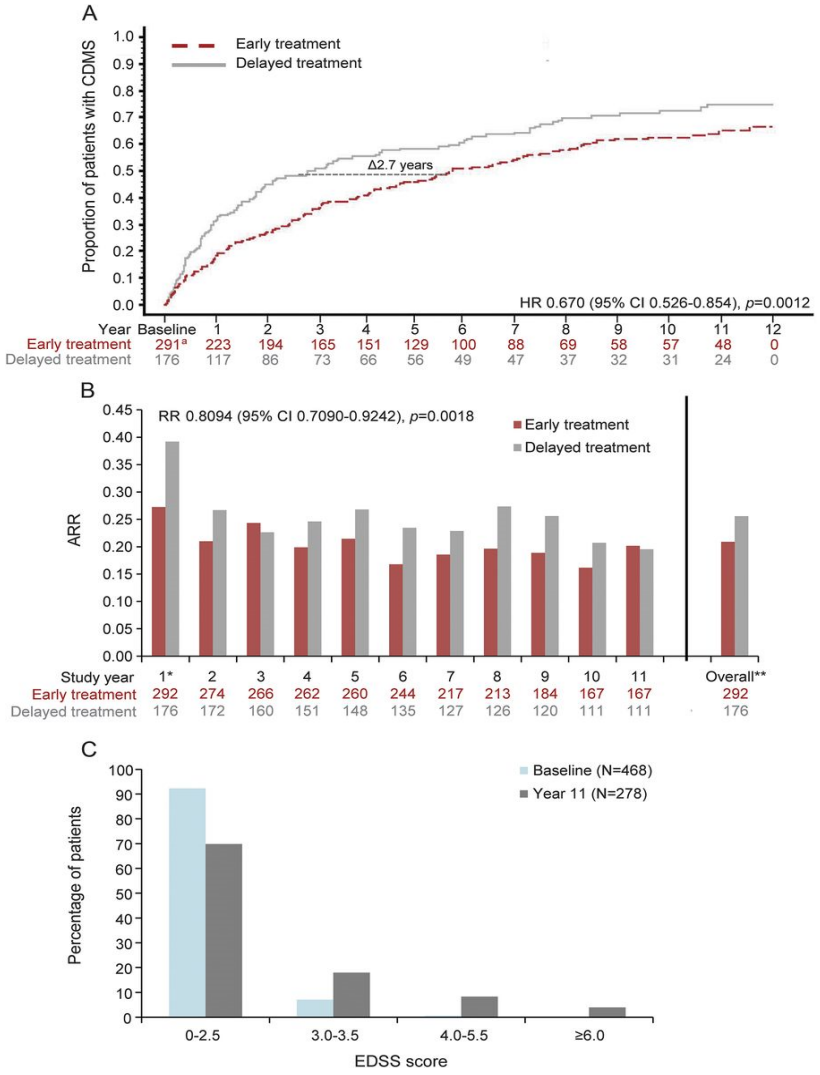
Figure 2 Kaplan-Meier estimates of probability of CDMS (A), ARR (B), and EDSS scores (C) in the BENEFIT 11 population

At 11 years,
ie mean age 41

30% with EDSS ≥ 3

And

32.7% unemployed or underemployed due to MS

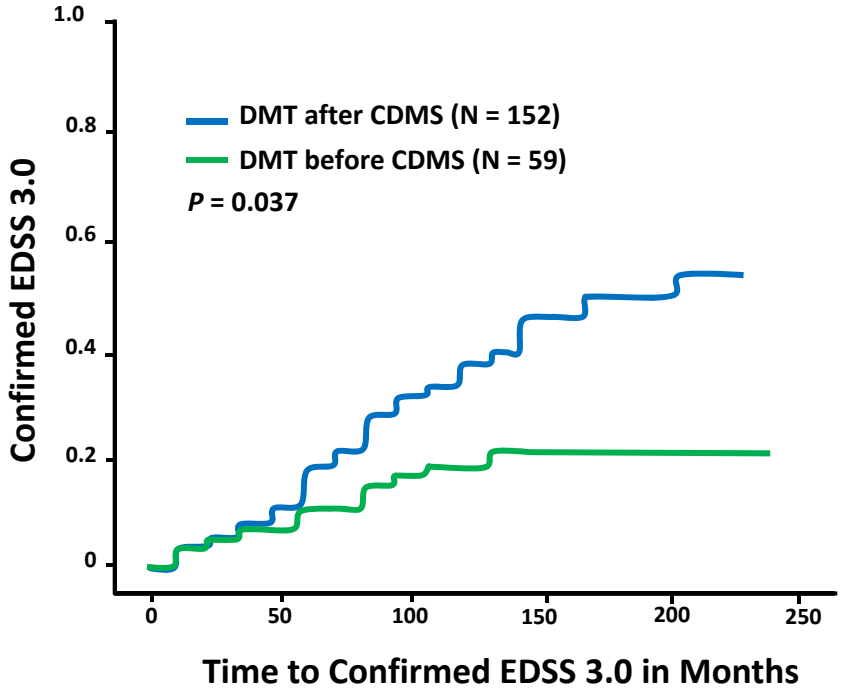


Ludwig Kappos et al. [The 11-year long-term follow-up study from the randomized BENEFIT CIS trial.](#)
Neurology 2016;87:978-987

MS Prognosis and Benefit of Early Treatment Initiation

- Long-term prognostic factors:
  - MRI (high impact)
  - Oligoclonal bands (medium impact)
  - Demographics (low impact)
  - Spinal cord lesions and high NfL are poor prognostic factors
- Suppressing relapses in early MS delays disease progression
- DMTs are more effective if used earlier

Time to EDSS 3 in CIS Patients Treated Before or After CDMS Onset (Barcelona Cohort)

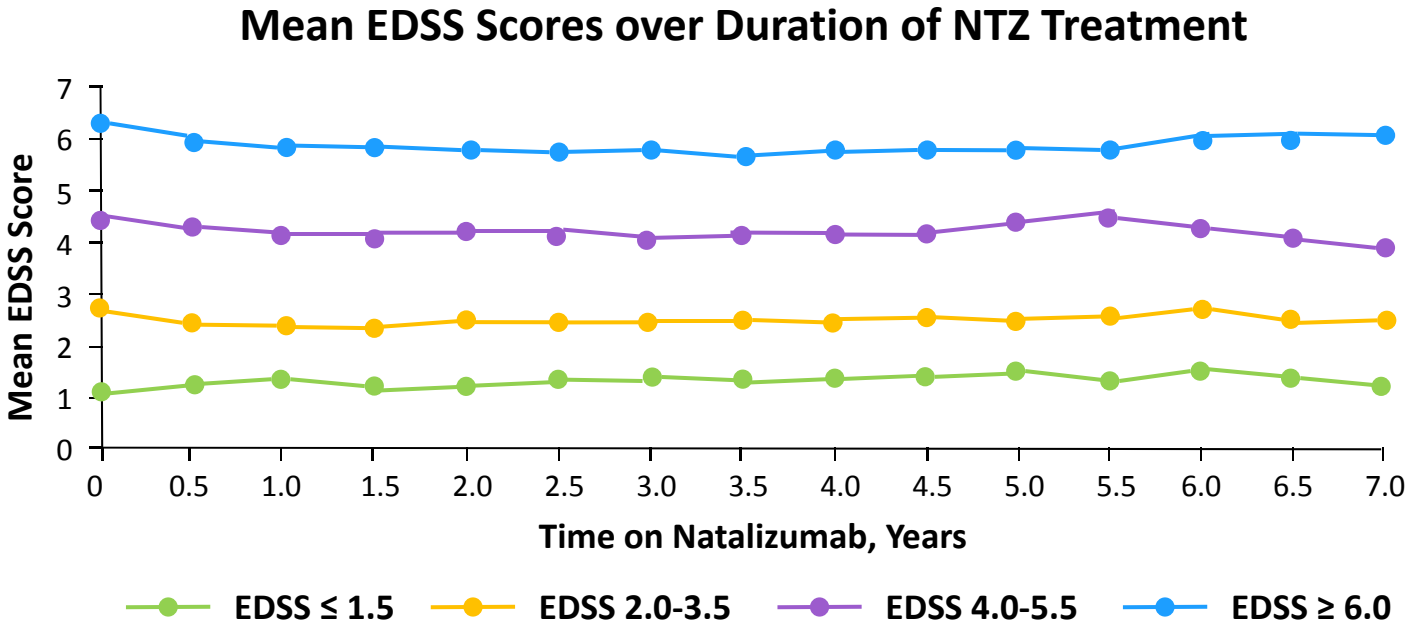


MRI = magnetic resonance imaging; NfL = neurofilament light chain; EDSS = Expanded Disability Status Scale; CDMS = clinically definite multiple sclerosis.

Montalban X, et al. ECTRIMS 2016; London, England. Abstract 97; Tintore M, et al. *Brain*. 2015;138(Pt 7):1863-1874; Tintore M, et al. ECTRIMS 2016; London, England. Abstract 185.

Long-Term Real-World Efficacy of Natalizumab: TOP 7-Year Results

- Multinational Observational Study of NTZ-Treated RRMS Patients in Clinical Practice Settings



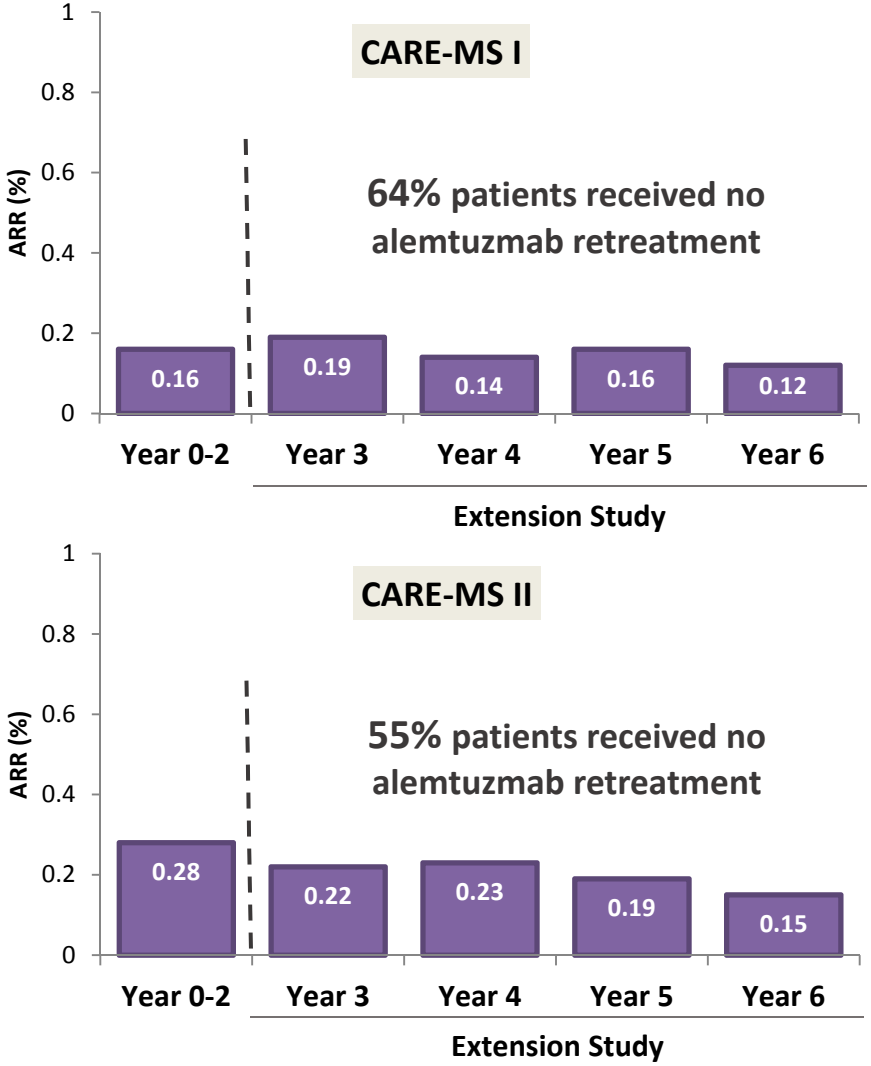
- **Mean EDSS scores remained stable over 7-years of NTZ treatment**
- **↓ ARR regardless of baseline disability (85% - 92%, $p < 0.0001$)**
- **Low rate EDSS worsening regardless of baseline disability (23% - 37%)**

NTZ = natalizumab.

Kappos L, et al. ECTRIMS 2016; London, England. Poster P1228.

Alemtuzumab Has Durable Efficacy Over 6 Years
CARE-MS I and II Extension Studies

- **High retention rates through Year 6:**
  - 93% (CARE-MS I)
  - 88% (CARE-MS II)
- **Most patients had stable/improved EDSS:**
  - 81% (CARE-MS I)
  - 77% (CARE-MS II)
- **Distinct pattern of T-cell and B-cell repopulation may contribute to durable efficacy**



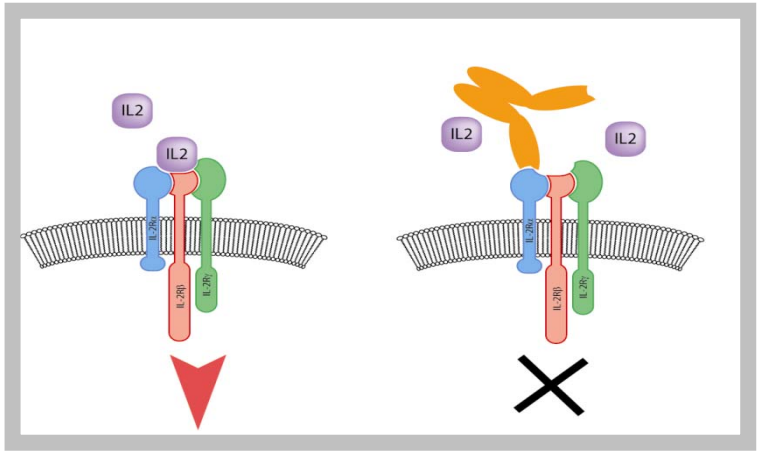
Coles A, et al. ECTRIMS 2016; London, England. Abstract 213; Fox EJ, et al. ECTRIMS 2016; London, England. Abstract P1150.

Why Early, Highly Effective Therapy is Best Choice For Most

1. At clinical onset, MS patients already have significant signs of disease activity
2. Risk of new inflammatory disease activity is greatest early, and is directly associated with risk of disability, ie early disease activity matters greatly
3. Vast majority of patients progress to EDSS score of 3 or above, significant impairment due to MS, ie MS is a bad disease. Even mortality is increased 2+ fold vs controls.
4. None of the MS DMTs completely suppress new inflammatory disease activity, but there are clear and significant differences in efficacy between MS DMTs
5. Treatment effects of presently-available DMTs are greatest in younger patients, regardless of phenotype

Daclizumab

- Humanized Mouse anti-Human CD25 (aka Tac)
  - 90% Human – 10% Mouse (CDR)
- Activity
  - Blocks IL-2 binding to the high affinity IL-2 Receptor
- Lots of skin reactions, LFT issues, lymph node issues
- Response related to CD56br cells?



Clinical End Points According to Treatment Group

DECIDE Trial

Dac-HYP vs Interferon

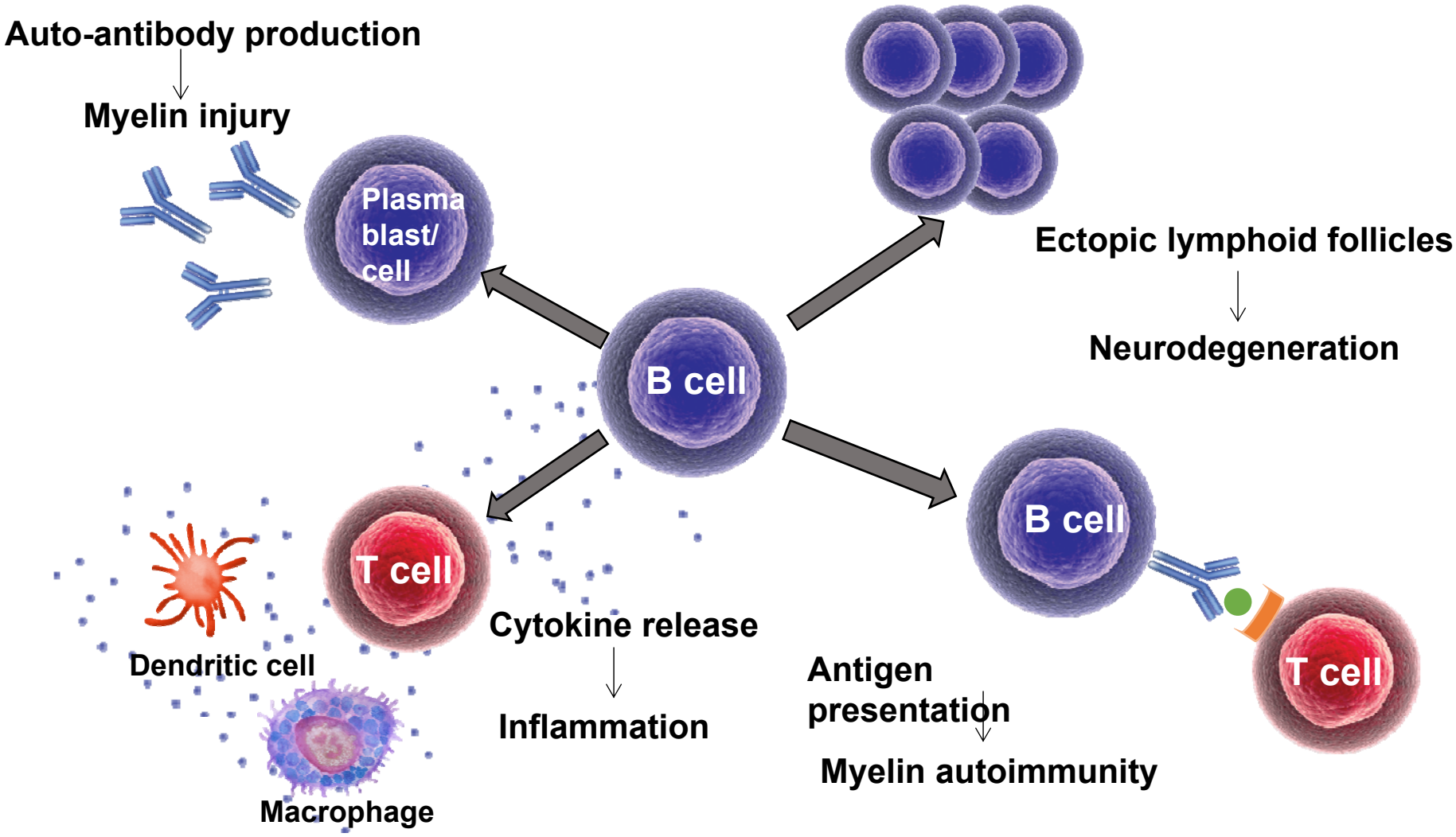
Table 2. Clinical End Points According to Treatment Group.*

End Point	Interferon Beta-1a (N=922)	Daclizumab HYP (N=919)	P Value
Primary end point			
Adjusted annualized relapse rate			
Rate (95% CI)	0.39 (0.35–0.44)	0.22 (0.19–0.24)	<0.001
Percent reduction vs. interferon beta-1a (95% CI)	45 (36–53)		
Secondary end points†			
New or newly enlarged hyperintense lesions on T_2-weighted images over period of 96 wk‡			
Adjusted mean no. (95% CI)	9.4 (8.5–10.5)	4.3 (3.9–4.8)	<0.001
Percent reduction vs. interferon beta-1a (95% CI)	54 (47–61)		
Disability progression confirmed at 12 wk at wk 144			
Estimated percent of patients§	20	16	0.16
Hazard ratio, daclizumab HYP vs. interferon beta-1a (95% CI)	0.84 (0.66–1.07)		
Proportion of patients free from relapse at wk 144			
Estimated percent of patients§	51	67	—
Hazard ratio for relapse, daclizumab HYP vs. interferon beta-1a (95% CI)	0.59 (0.50–0.69)		
Clinically meaningful worsening on the MSIS-29 physical subscale score at wk 96¶			
Estimated percent of patients with worsening	23	19	—
Percent reduction in the odds of worsening vs. interferon beta-1a (95% CI)	24 (5–40)		

* The number of patients is the intention-to-treat population for each treatment group, excluding patients with missing data for baseline covariates unless otherwise noted. CI denotes confidence interval.
† Secondary end points were rank-ordered (in the order listed here) and were tested with the use of a sequential closed-testing procedure. If a comparison did not indicate significance (at the 0.05 significance level), all lower-ranked end points were not considered to be statistically significant within the closed-testing procedure. Thus, the end points for the percentage of patients who were relapse free at week 144 and for clinical worsening on the basis of MSIS-29 physical subscale score were not tested because the P value for the secondary end point of disability progression confirmed at 12 weeks was 0.16.
‡ The analysis was performed in the subgroup of the intention-to-treat population who had a postbaseline scan, which included 841 patients in the interferon beta-1a group and 864 in the daclizumab HYP group.
§ The percentage of patients was estimated by means of the Kaplan–Meier product-limit method.
¶ Clinically meaningful worsening was defined as an increase of at least 7.5 points from baseline in the MSIS-29 physical subscale score. Data for 10 patients in the interferon beta-1a group and for 13 in the daclizumab HYP group were excluded owing to missing baseline covariates.

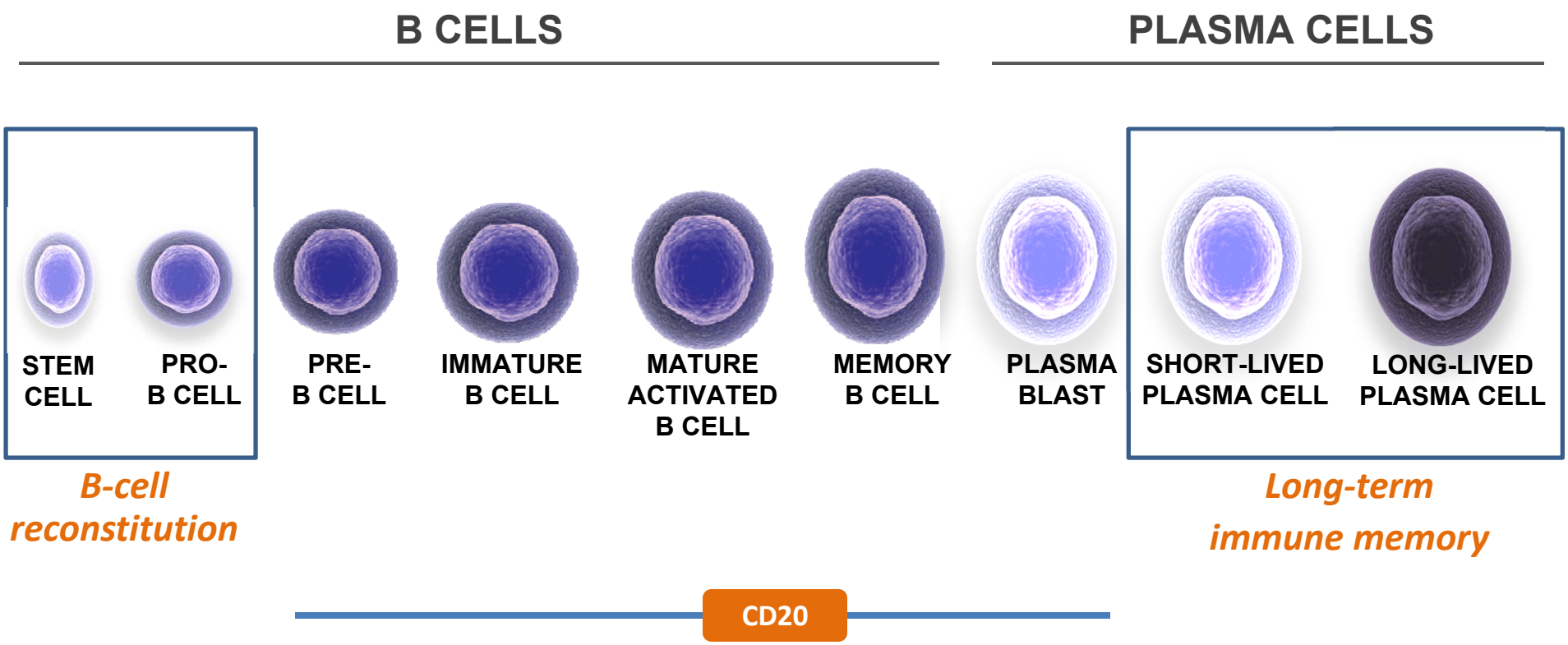
Kappos L et al. N Engl J Med 2015;373:1418-1428.

Diverse Functional Roles of B Cells in MS



Claes N, et al. *Front Immunol*. www.dx.doi.org/10.3389/fimmu.2015.00642. Accessed 10/3/16.

Selective Depletion of CD20+ B Cells:
Preserving B-cell Reconstitution and Immune Memory



Depleted by rituximab, ocrelizumab (Phase 3), ofatumumab (Phase 2), ublituximab (Phase 2)

Krumbholz M, et al. *Nat Rev Neruol.* 2012;8(11):613-623; von Budingen HC, et al. *Eur Neurol*. 2015;73(3-4):238-246.

Ocrelizumab Superior to IFNβ-1a in Reducing ARR (OPERA I and II Phase 3 Results)

Key Inclusion Criteria:

- RMS diagnosis
- 18–55 years
- ≥ 2 clinical relapses within last 2 years
  or
  1 relapse in last year
- EDSS of 0.0–5.5

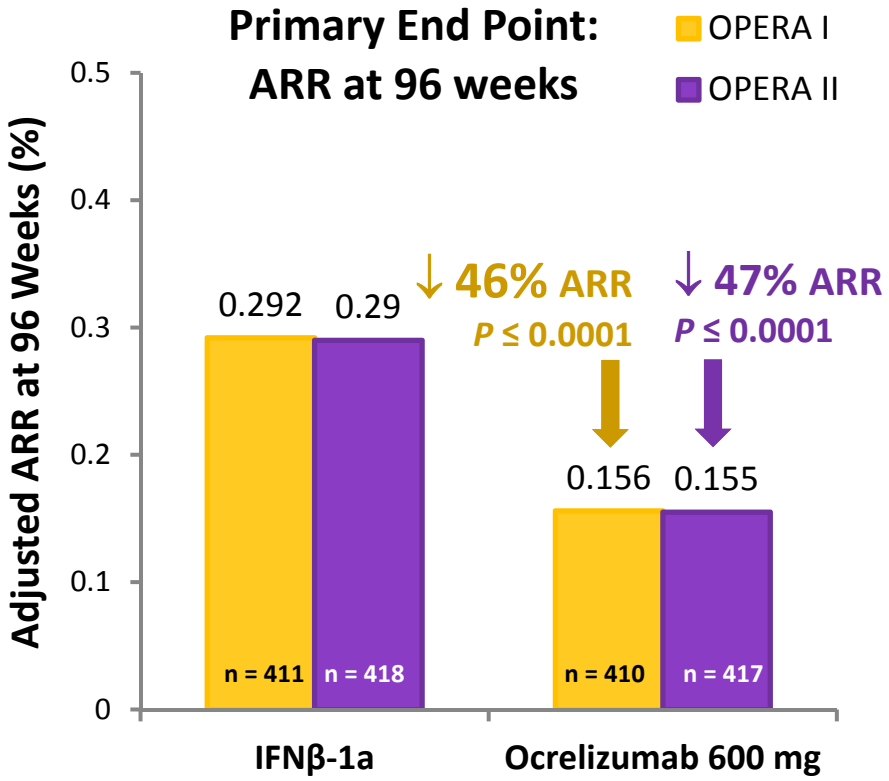
Ocrelizumab
Dose 1: 300 mg IV x 2 (Days 1, 15)
Doses 2–4: 600 mg IV x 1 (q24weeks)

vs

IFNß-1a
Dosed 44 µg sc 3 x per week

1:1

72-week treatment period
+
24-week post-treatment screening period (OLE)

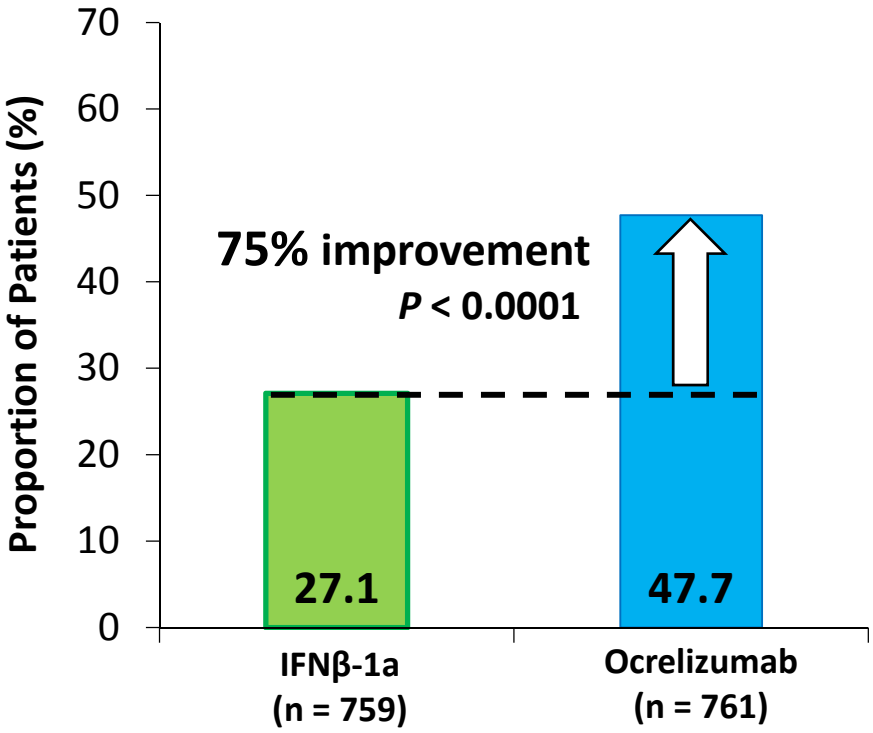


- **48 weeks after last infusion: safety follow-up period**
- **After initial 72-week treatment: optional treatment continuation (OLE)**

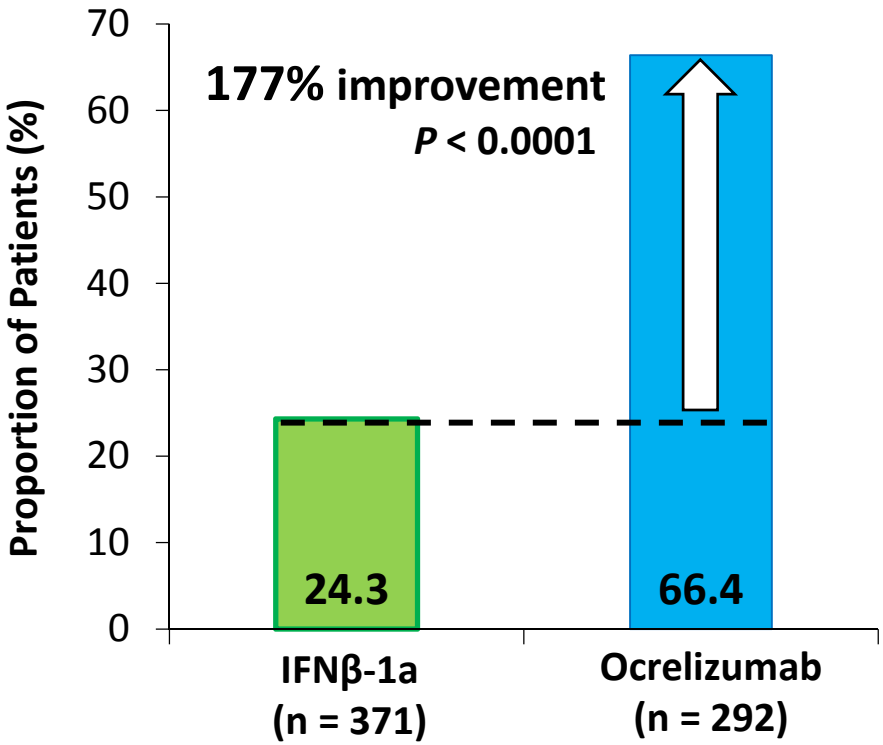
RMS = relapsing multiple sclerosis; OLE = open-label extension. **Ocrelizumab** versus Interferon Beta-1a in Relapsing Multiple Sclerosis. **Hauser** SL, et al N Engl J Med. 2017 Jan 19;376(3):221-234. doi: 10.1056/NEJMoa1601277. PMID: 28002679

Ocrelizumab Increases Proportion of Patients with NEDA Post-Hoc Analysis of Pooled OPERA I and II Data

NEDA at Week 96



NEDA During Weeks 24–96 in Patients with Early Disease Activity (Weeks 0–24)



- **OCR significantly ↑ NEDA during the 96-week double-blind treatment period**
- **Majority of patients with early disease activity (Weeks 0–24) achieved NEDA with OCR**

NEDA definition: no protocol-defined relapses; no 12-week CDP; no new/enlarging T2 lesions and T1 GD+ lesions.
OCR = ocrelizumab.
Giovannoni F, et al. ECTRIMS 2016; London, England. Abstract P1593.

Safety of Ocrelizumab in OPERA I/II & ORATORIO:
Infusion-Related Reactions and Infections

	OPERA I and OPERA II		ORATORIO	
n (%)	IFNβ-1a 44 µg (n = 826)	OCR 600 mg (n = 825)	PBO (n = 239)	OCR 600 mg (n = 486)
Total IRRs	80 (9.7)	283 (34.3)	61 (25.5)	194 (39.9)
Mild-to-moderate IRRs	79 (9.6)	262 (31.7)	57 (23.8)	188 (38.7)
Severe IRRs	1 (0.1)	20 (2.4)	4 (1.7)	6 (1.4)
Total number of patients with ≥ 1 AE	433 (52.4)	482 (58.4)	162 (67.8)	339 (69.8)
URTI	87 (10.5)	125 (15.2)	14 (5.9)	53 (10.9)
Nasopharyngitis	84 (10.2)	122 (14.8)	65 (27.2)	110 (22.6)
UTI	100 (12.1)	96 (11.6)	54 (22.6)	96 (19.8)
Influenza	-	-	21 (8.8)	56 (11.5)
Herpes infections	28 (3.4)	49 (5.9)	7 (2.9)	21 (4.3)
Serious infections and infestations	24 (2.9)	11 (1.3)	14 (5.9)	30 (6.2)
Deaths related to infections*	0	0	0	2 (0.4)

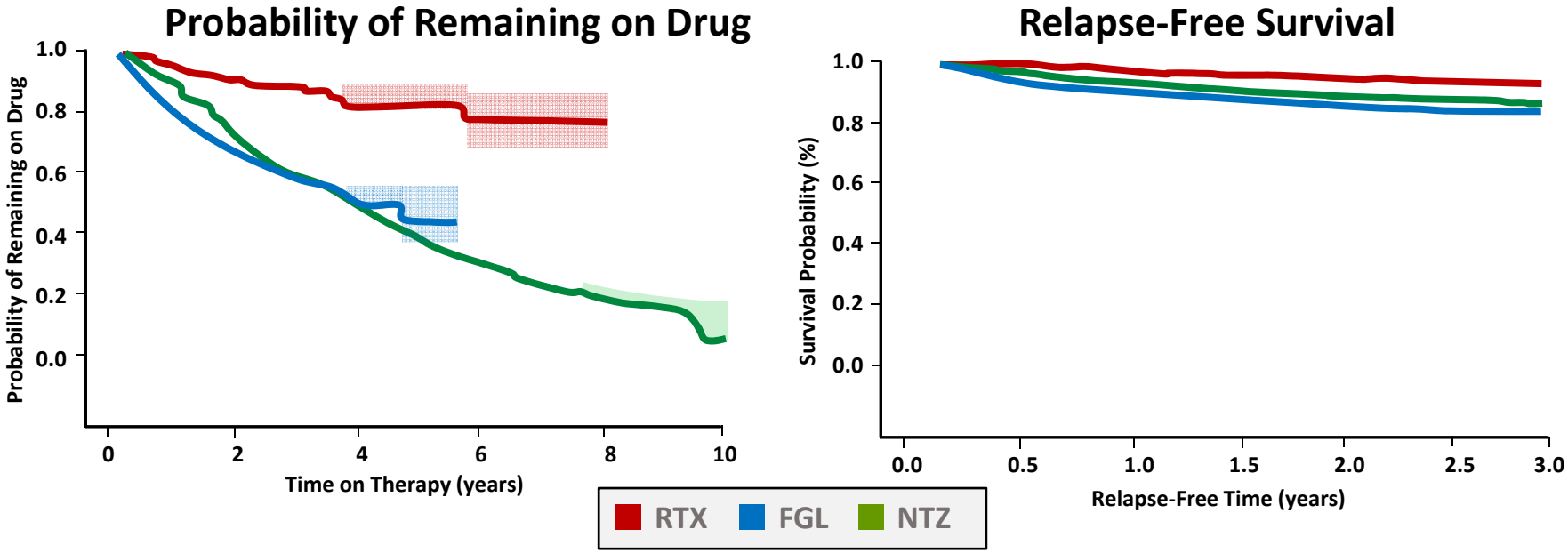
- **IRRs occurred most frequently after the first infusion; decreased in incidence/severity with further infusions**
- **Most IRRs were preventable with premedications and manageable with infusion adjustments and symptomatic treatment**
- **Rate of withdrawal from treatment due to IRRs or AEs remained low**

***Aspiration pneumonia and pneumonia.**
IRRs = infusion-related reactions; URTI = upper respiratory tract infection; UTI = urinary tract infection.
De Seze J, et al. ECTRIMS 2016; London, England. Poster P720; Hartung HP, et al. ECTRIMS 2016; London, England. Poster P1248.

Rituximab in MS: Findings from the Swedish MS Registry

AIM: Compare Outcomes for MS* Patients Starting RTX, FGL, or NTZ

Baseline Characteristics	FGL (n = 1,374)	RTX (n = 1,837)	NTZ (n = 2,369)
Age (years)	38.5	40.6	34.4
Diagnosis time (years)	7.5	7.3	4.6
Baseline EDSS	2.0	2.0	2.5
First-line therapy (%)	13.2%	22.4%	28.1%

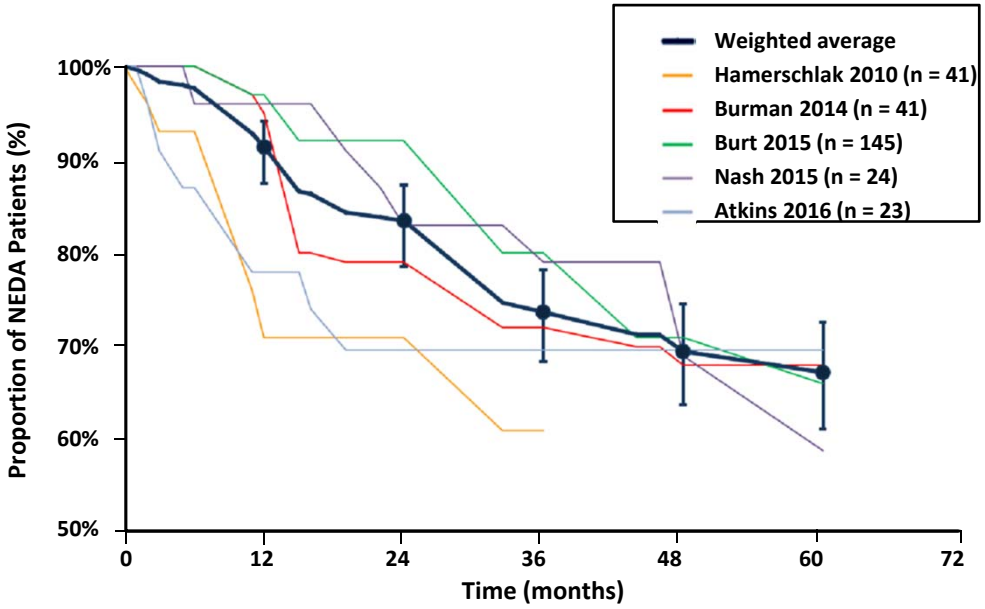


*RRMS at start of therapy; SPMS only if converted during or after treatment period.
RTX = rituximab.
Alping P, et al. ECTRIMS 2016; London, England. Abstract 165.

Autologous HSC Transplantation in MS: Meta-Analysis

- 15 studies (n = 764), 1995–2016
- Transplant-related mortality:
  - 2.1% (1.3–3.4%)
- Progression rate at 2 years:
  - 17.1% (9.7–24.5%)
- Proportion of NEDA patients:
  - After 2 years: 83% (78–87%)
  - After 5 years: 67% (61–73%)

Pooled estimation of NEDA over time since transplant



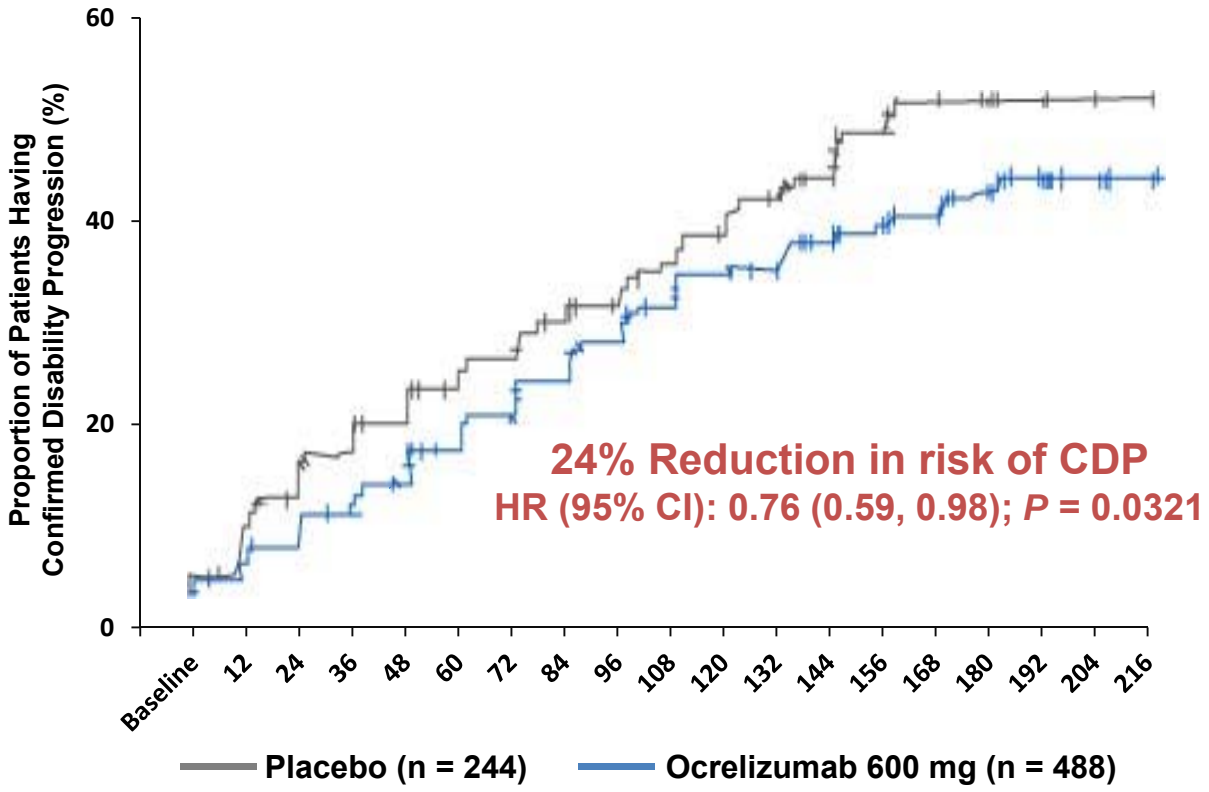
Suggests autologous HSC transplant may be an effective approach for treatment of aggressive forms of MS

HSC = hematopoetic stem cell.

Sormani MP, et al. ECTRIMS 2016; London, England. Abstract P751.

Efficacy of Ocrelizumab in PPMS
Phase 3 ORATORIO Results

Primary End Point:
Significant Reduction in 12-week CDP



Key Secondary End Points:

24-week CDP
25% reduction in risk of CDP
(*P* = 0.0365)

Progression rate of walking time
29% reduction vs placebo
(*P* = 0.0404)

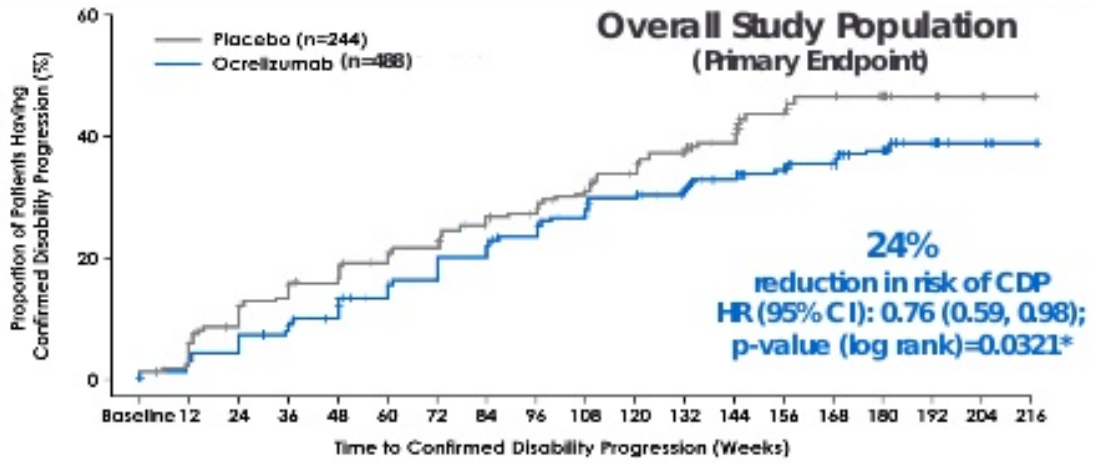
Rate of BVL
17.5% reduction vs placebo
(*P* = 0.0206)

T2 lesion volume
7.4% increase on placebo
-3.4% decrease on ocrelizumab
(*P* < 0.001)

Mean Age 45

Montalban X, et al. ECTRIMS 2015; Barcelona, Spain. Abstract 228.

Effect of Gad+ Lesions



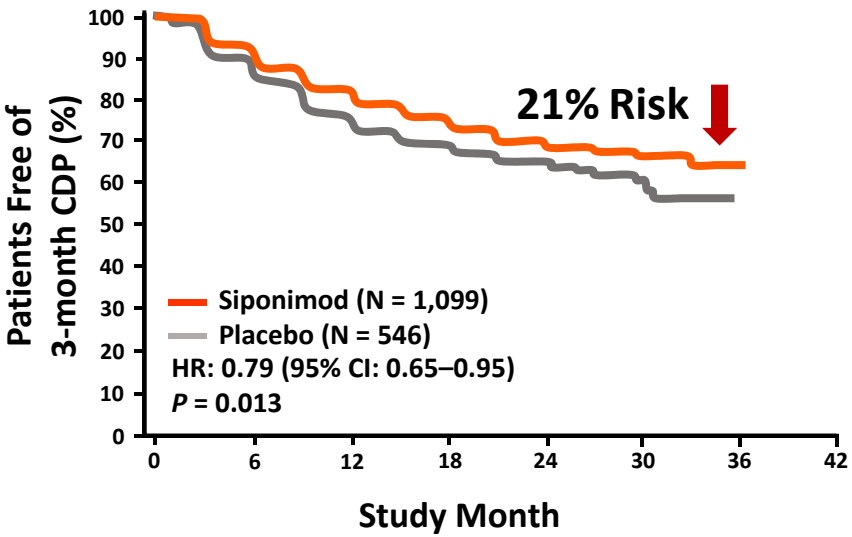
	Total	Placebo (N=244)		Ocrelizumab (N=488)		Hazard Ratio	95% CI
	n	n	Events	n	Events		
Overall population	731	244	96	487	160	0.76	(0.59, 0.98)
T1 Gd+ lesions	198	60	27	133	43	0.65	(0.40, 1.06)
No T1 Gd+ lesions	533	183	68	350	115	0.84	(0.62, 1.13)

*Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression. CDP, confirmed disability progression; Gd+, gadolinium-enhancing; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent to treat.

from J. Wolinski ACTRIMS 2016 Oratorio 1b Platform

Efficacy and Safety of Siponimod in SPMS:
Results from EXPAND Phase 3 Trial

Primary End Point:
Time to 3-month CDP vs PBO



Secondary End Points:

- **6-month CDP: 26% risk ↓ (*P* = 0.006)**
- **Consistent effects on ARR, T2 lesion volume, and change in brain volume**
- **No significant effect on T25FW**

GI = gastrointestinal.

Kappos L, et al. ECTRIMS 2016; London, England. Abstract 250.

Number of Patients with AEs Occurring in ≥ 5%

	Siponimod N = 1,099		Placebo N = 546	
AEs by System Organ Class	**N**	**%**	**N**	**%**
Infections and infestations	539	49	268	49
Nervous system disorders	416	38	175	32
Musculoskeletal and connective tissue disorders	289	26	149	27
GI disorders	269	25	110	20
General disorders and administration site conditions	268	24	110	20
Investigations	263	24	80	15
Injury, poisoning, and procedural complications	238	22	114	21
Skin and subcutaneous tissue disorders	188	17	93	17
Psychiatric disorders	169	15	83	15
Vascular disorders	160	15	60	11
Cardiac disorders	131	12	55	10
Respiratory, thoracic, and mediastinal disorders	117	11	71	13
Neoplasms benign, malignant, and unspecified	113	10	45	8
Eye disorders	111	10	54	10
Metabolism and nutrition disorders	85	8	28	5
Renal and urinary disorders	84	8	37	7
Ear and labyrinth disorders	55	5	38	7

Higher — Lower

Frequency

Mean Age 49

“There remains, however, an urgent need for treatments that protect against demyelination and axonal loss, or promote remyelination/regeneration.”

J Neurol. 2004 Sep;251 Suppl 5:v57-v64.
Alternatives to current disease-modifying treatment in MS: what do we need and what can we expect in the future?
Kappos L, Kuhle J, Gass A, Achtnichts L, Radue EW.

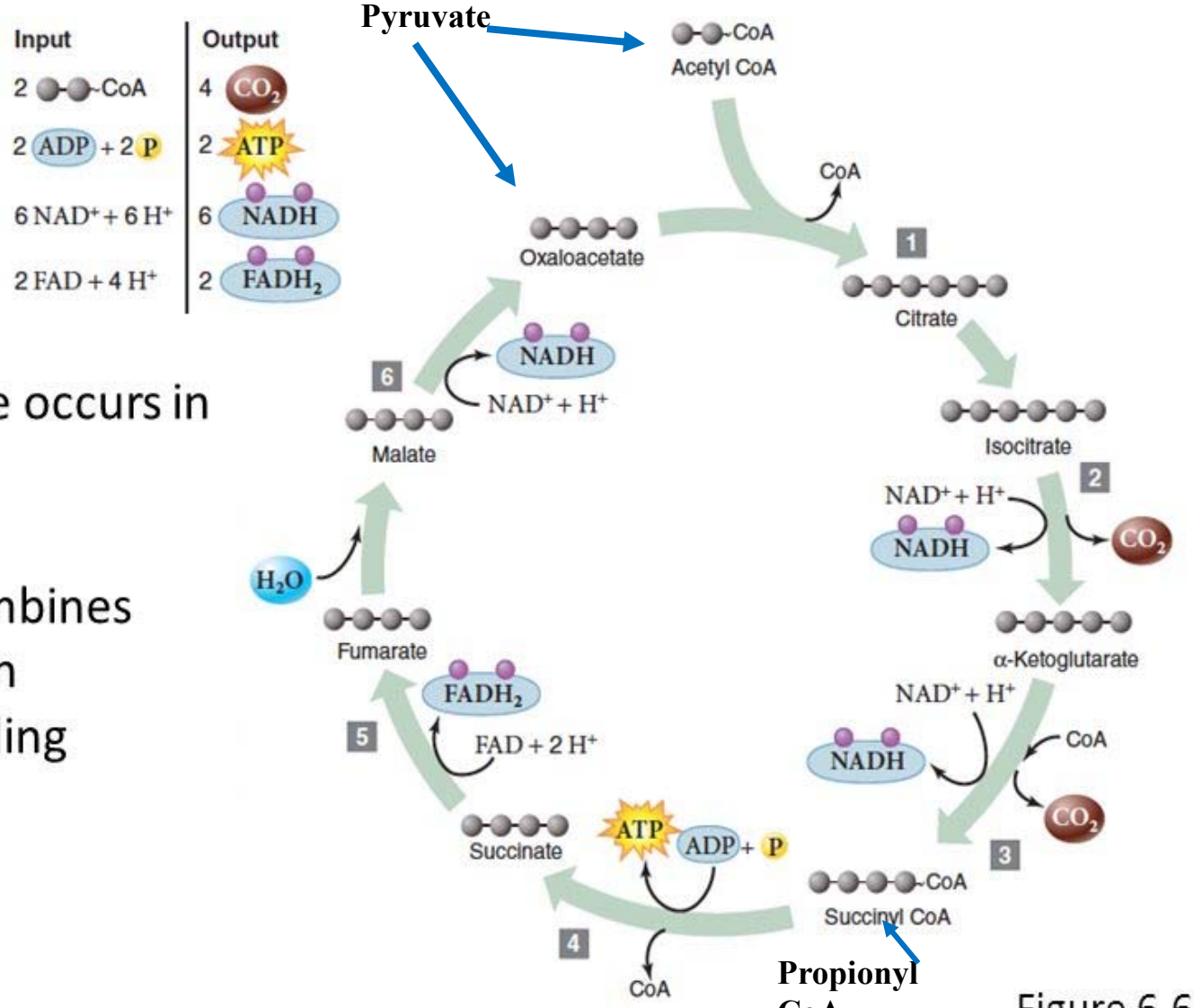
Potential Remyelination

- Most molecules focused on removing inhibitors of remyelination
- Studied in acute and chronic models
  - Optic neuropathy with OCT and VEP may be very good choice
- Anti-LINGO, Clemastine, rHiGm22 and others
- Results somewhat disappointing to date
  - Modest effects in tests, limited or no effects seen clinically
  - ? Naïve to believe you can remyelinate axons in a chronic model
    - Modest ongoing remyelination in older patients with chronic disease
    - Dropout of axons limits substrate upon which to remyelinate

Aerobic Respiration Yields Many ATP

The Krebs cycle occurs in several steps.

Acetyl CoA combines with a 4-carbon molecule, yielding citrate.



Section 6.5

Figure 6.6

A Increased number, size, activity, and speed of movement of mitochondria reported as the "axonal mitochondrial response to demyelination

B During the preprogressive stage of multiple sclerosis, inflammatory products injure mitochondria in several cell types, including neurons within the lesions, resulting in mitochondrial cytochrome c oxidase-1 dysfunction and subsequent energy deficiency. Additionally, oxidative injury of DNA leads to the formation of mtDNA deletions in both the white matter (1) and grey matter. Over time, and with age, abnormal mitochondria are amplified in neuronal cell bodies.

C The resulting biochemical deficiency of the mitochondrial respiratory chain complexes or enzymes in neuronal cell bodies acts as a reservoir of abnormal mitochondria, which then undergo aberrant displacement to the demyelinated axon and cause energy failure and increased reactive oxygen species production in the axon.

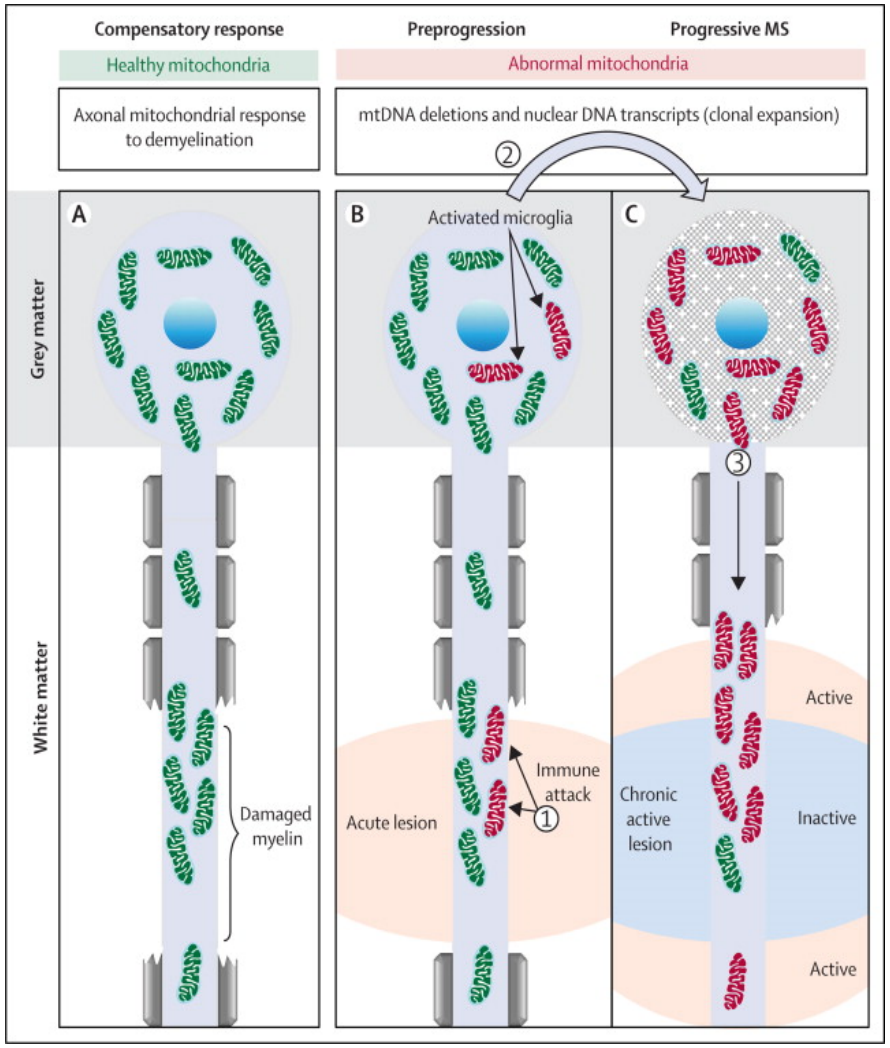


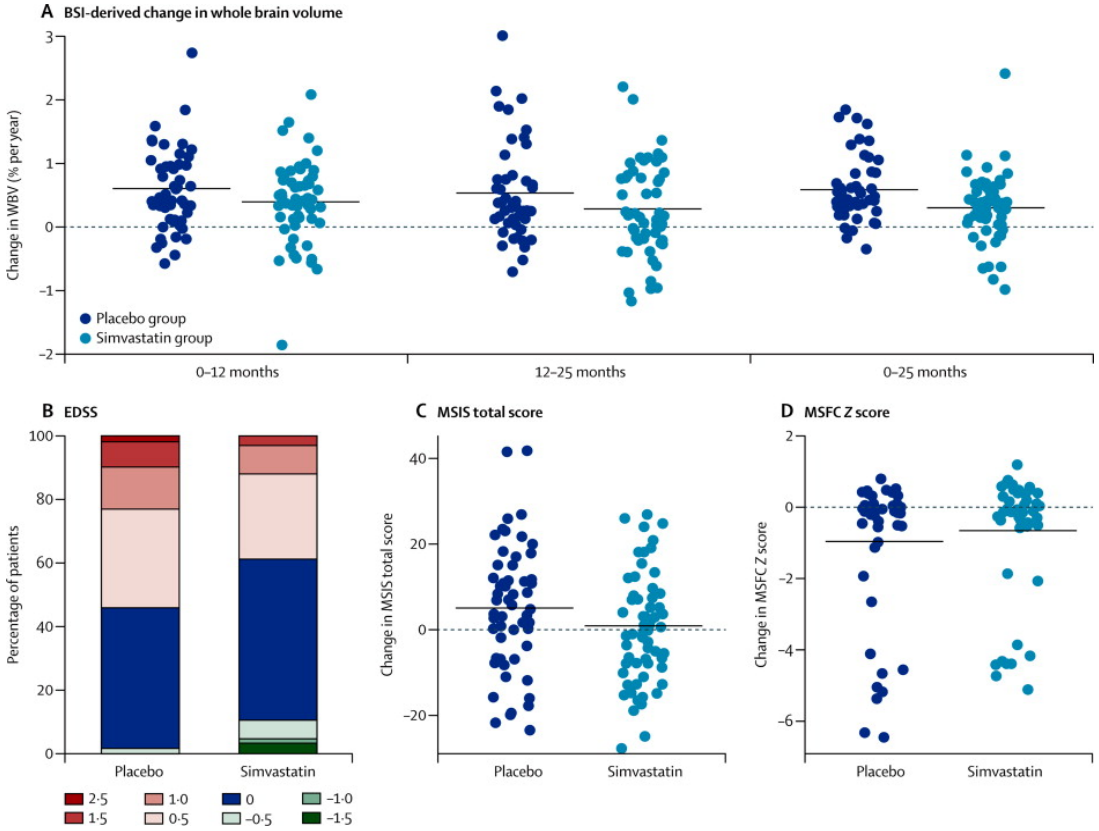
Figure 3

Pathological mechanisms in progressive multiple sclerosis

Lancet NeurologyVolume 14, Issue 2, 2015, 183–193
Don H Mahad, Bruce D Trapp, Hans Lassmann

http://dx.doi.org/10.1016/S1474-4422(14)70256-X

Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial



Change in Whole Brain Volume

Simvastatin: 0.288% change per year

Placebo: 0.584% Change per year

Figure 2. Primary MRI outcome and secondary clinical outcomesThe mean and individual patient values are shown for change in whole-brain volume (A); percentage of patients with a given change in EDSS (B); change 0 to 24 months MSIS-29 (C); and change 0 to 24 mo...

Jeremy Chataway, et al, Lancet Volume 383, Issue 9936, 2014, 2213–2221

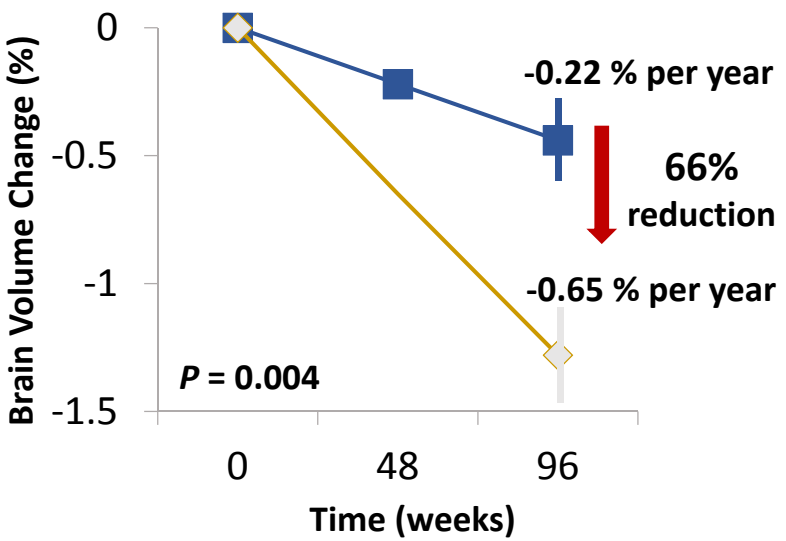
http://dx.doi.org/10.1016/S0140-6736(13)62242-4

Mean Age 48

Neuroprotective Effects of Lipoic Acid in SPMS:
Results of a Placebo-Controlled Pilot Trial

- LA is an inexpensive, oral antioxidant
- Mechanisms of action in progressive MS:
  - Maintenance of BBB
  - Inhibits microglial activation
  - Supports mitochondrial function
- 2-year RCT of lipoic acid 1,200 mg daily vs placebo

Percent Change Brain Volume (primary end point)



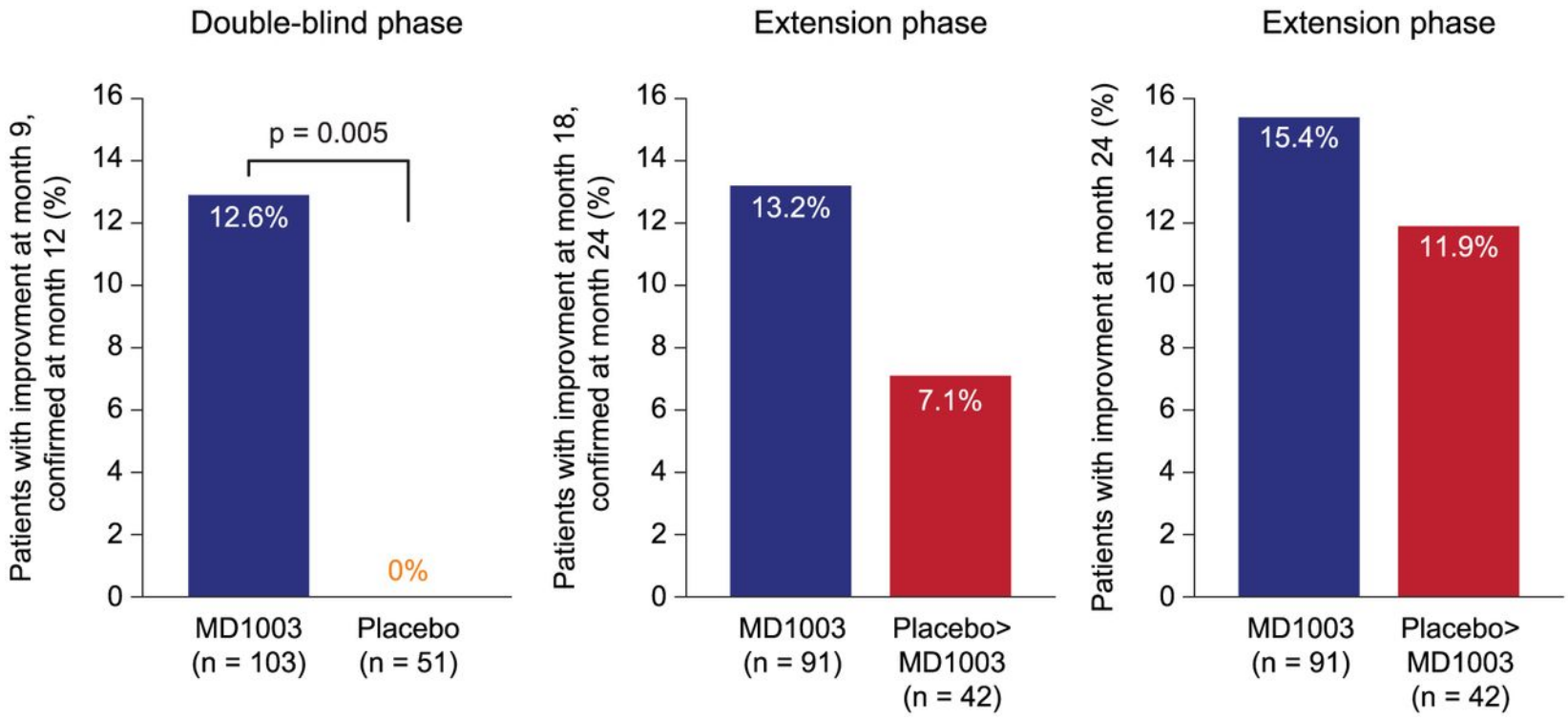
Demographics

	Lipoic acid (n = 27)	Placebo (n = 24)
Age (years)	57.9	59.7
MS duration (years)	30.9	29.1
EDSS median	5.5	6

- No other outcome was significant
- AEs:
  - GI upset (17% LA vs 3% PBO)
  - Falls (15% LS vs 38% PBO)
- Larger trial needed to confirm effects

Spain RI, et al. ECTRIMS 2016; London, England. Abstract 222.

Figure 2. Proportion of patients with reversal of MS-related disability.



Ayman Tourbah et al. Mult Scler 2016;1352458516667568

MULTIPLE SCLEROSIS JOURNAL
Formerly Multiple Sclerosis

Table 2. Baseline characteristics of the 13 patients who achieved the primary endpoint of the study.

Table 2. Baseline characteristics of the 13 patients who achieved the primary endpoint of the study.

Age (years)	Sex (F/M)	Centre	PPMS or SPMS	MS duration (years)	Baseline EDSS	Improvement		DMT
						EDSS	TW25	
68	M	1	PPMS	3.0	6.5	+	–	
50	M	1	SPMS	14.0	6.5	–	+	
52	M	2	PPMS	6.0	6.5	+	–	MPM
63	F	3	SPMS	12.0	4.5	+	–	INF
55	M	6	SPMS	18.0	7	–	+	
43	M	6	SPMS	10.0	5.5	+	+	CP
52	F	9	SPMS	16.0	6.5	+	–	MPM
59	M	11	SPMS	12.0	7	+	–	MPM
62	M	11	PPMS	37.0	4.5	+	–	MTX
43	M	14	PPMS	5.0	4.5	+	–	
64	M	14	SPMS	31.0	6.5	+	+	
46	F	15	SPMS	15.0	4.5	+	–	INF
46	M	16	SPMS	25.0	5.5	–	+	
Mean 54.0	23.1% F	–	69.2% SPMS	Mean 15.7	Mean 5.81	76.9%	38.5%	53.8%

CP: cyclophosphamide; DMT: disease-modifying therapy; F: female; EDSS: Expanded Disability Status Scale; INF: interferon; M: male; MPM: mycophenolate mofetil; MS: multiple sclerosis; MTX: methotrexate; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; TW25: timed 25-foot walk.

Ayman Tourbah et al. Mult Scler 2016;1352458516667568

MULTIPLE SCLEROSIS JOURNAL
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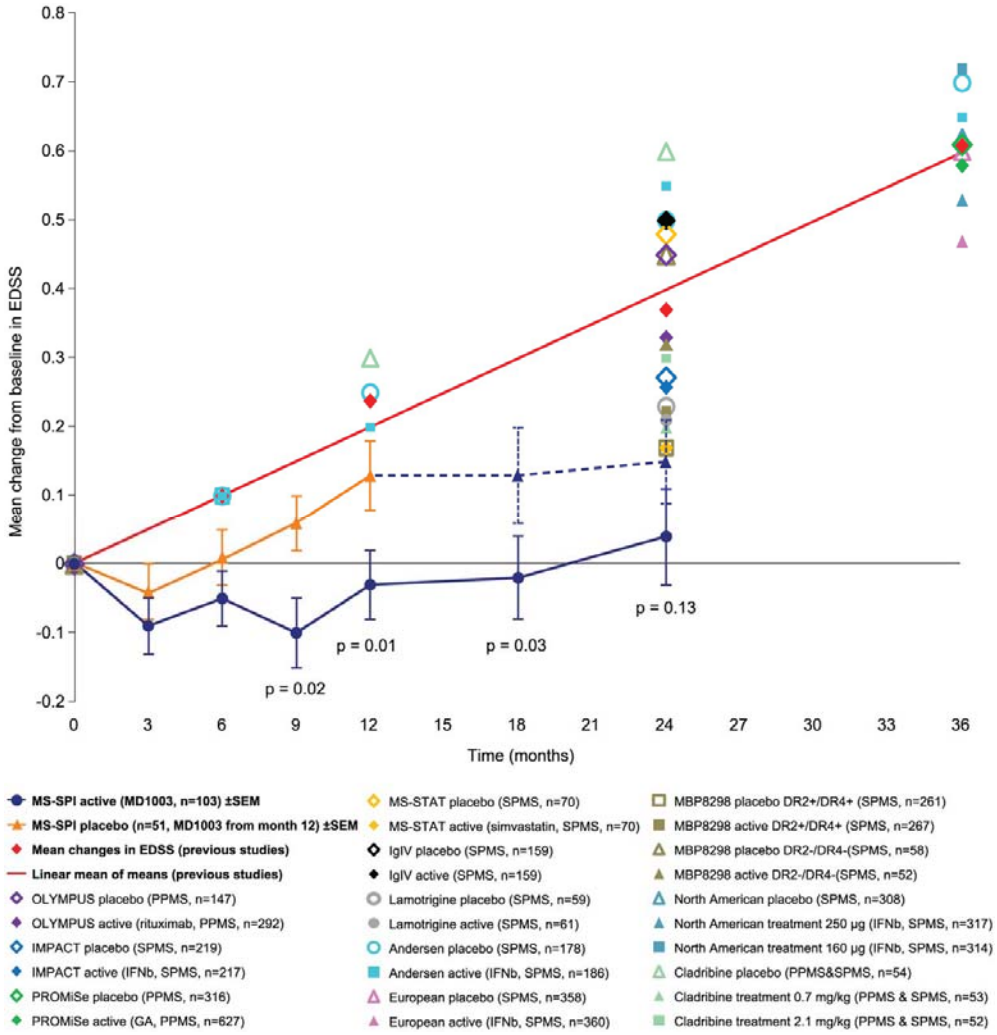
Figure 3. Mean change from baseline in EDSS during the 12-month double-blind placebo-controlled phase and 12-month extension phase.



Ayman Tourbah et al. Mult Scler 2016;1352458516667568

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MS Treatment Throughout Lifetime

Age 0-20	25	30	35	40	45	50	55	60	65	70	75	80+

Pre-Clinical

RIS **CIS** **RRMS** **Late RRMS**

Early Progression **Late Progression**

Good Behaviors*	X	X	X	X	X	X	X
Rx Symptoms/Palliate	No	X	X	X	X	X	X
Neuroprotection**	Maybe	X	X	X	X	X	X
DMT***	?	X	X	X	?	?	?
Re-Boot Immune Syst	No	If Severe	If Severe	No	No	No	No
Remyelination****	Maybe	Probably	Probably	Maybe	Maybe	?	?
Neural Stem Cells	?	?	?	?	?	?	?

* Including maintaining ideal body weight, exercise, no smoking, Vitamin D, minimizing co-morbidities

** Assumes data suggests appropriate approach(es), Biotin, Alpha Lipoic Acid

*** May expand approaches to address meningeal/cortical inflammatory and microglial activity

**** Assumes data suggests appropriate approach(es), and that amount of axonal dropout by later in life makes remyelinating strategies untenable

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Thank You!!