MS och immunmodulerande terapi-när är det dags att avsluta behandlingen?

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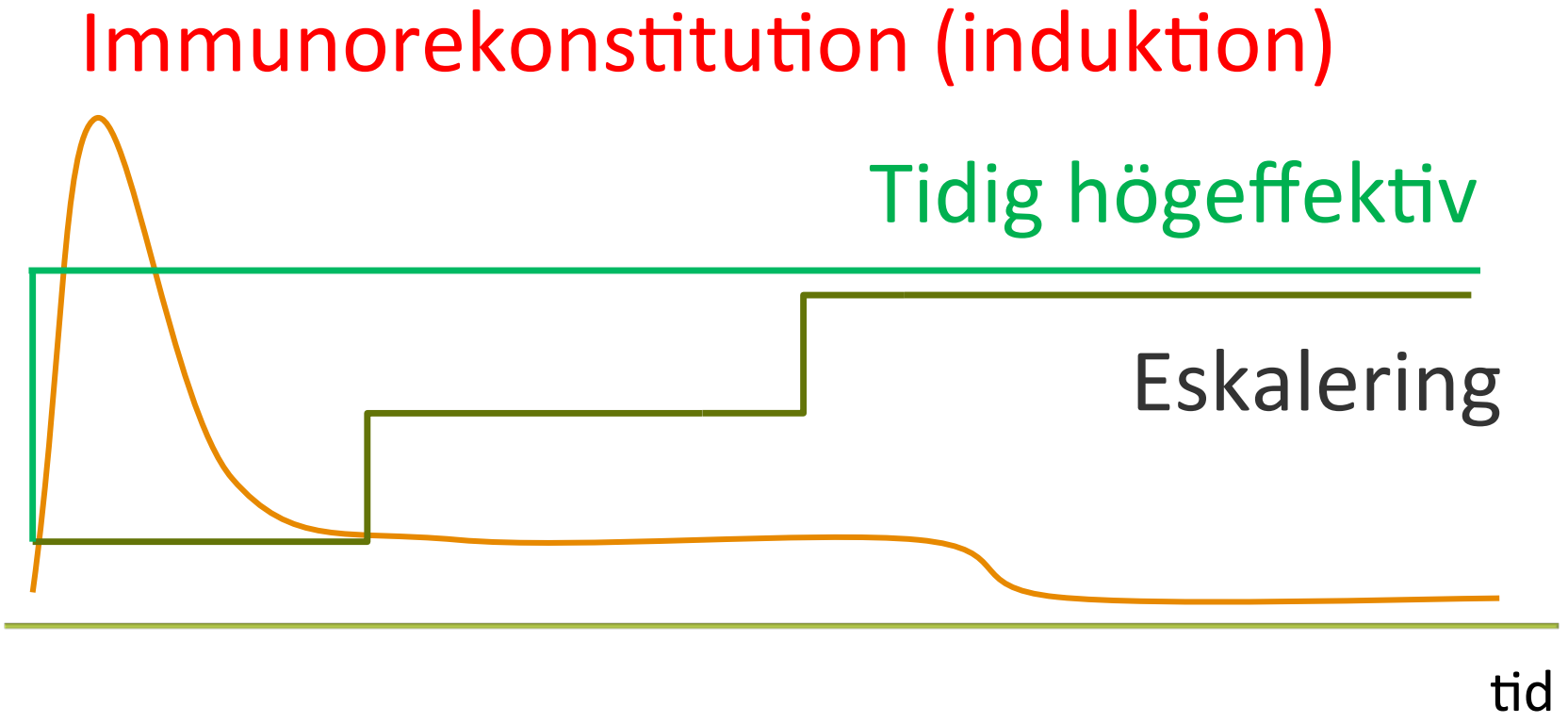
Disclosures

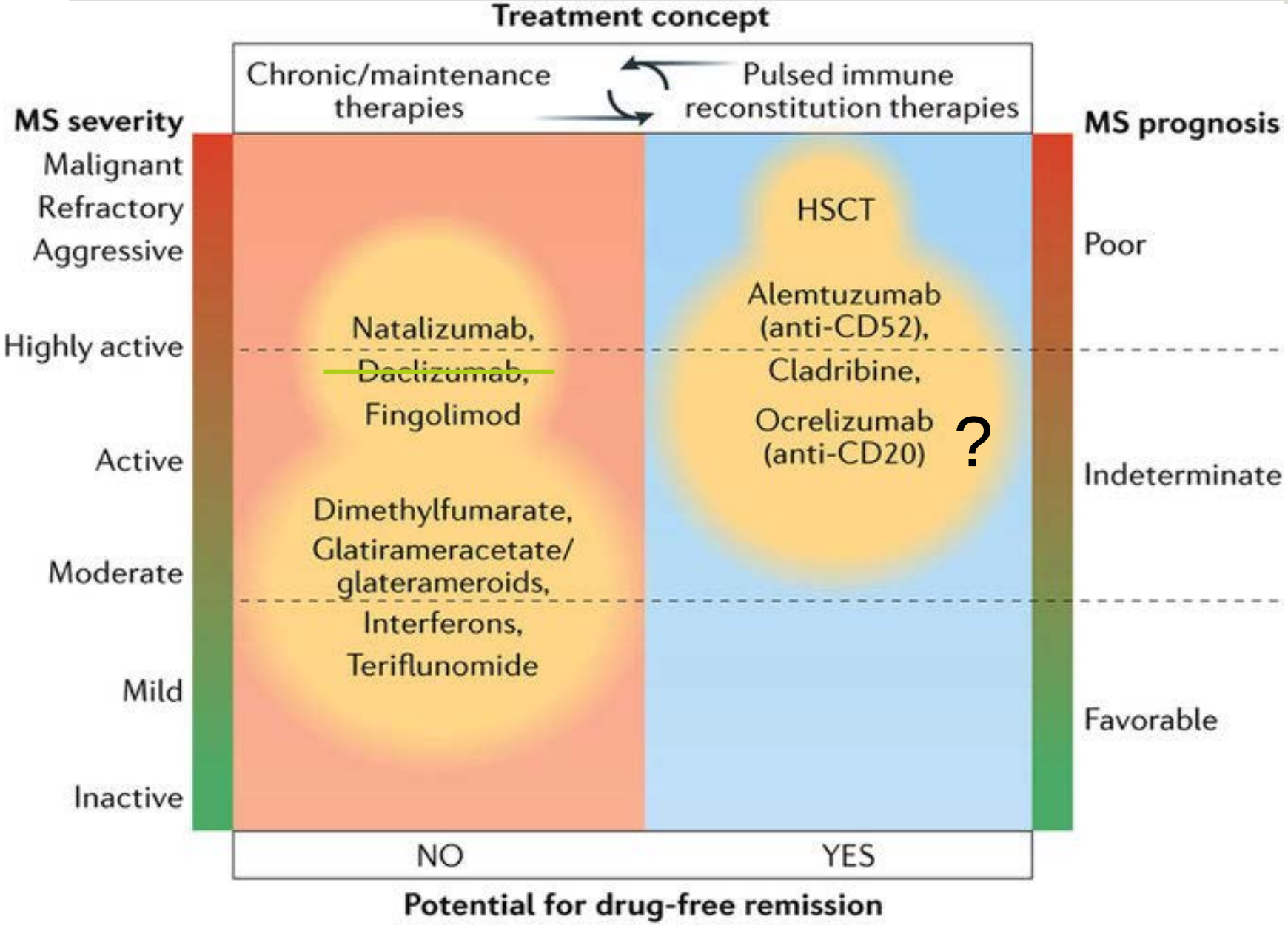
Jan Lycke has received travel support and/or lecture honoraria from Biogen, Novartis, Teva, Merck and Genzyme/SanofiAventis; has served on scientific advisory boards for Almirall, Teva, Biogen, Novartis, Merck and Genzyme/SanofiAventis; serves on the editorial board of the Acta Neurologica Scandinavica; has received unconditional research grants from Biogen, Novartis and Teva.

Presentation

- Behandlingsstrategier vid MS
- Avslutande av immunomodulerande terapi
  - Behandlingssvikt
  - Intolerans och risker
  - Graviditet och amning
  - Stabilt tillstånd/benignt förlopp?
    - Risker vid byte (Rebound?)
  - Progressivt förlopp
  - Ålder
- Sammanfattning

Tre olika behandlingsstrategier

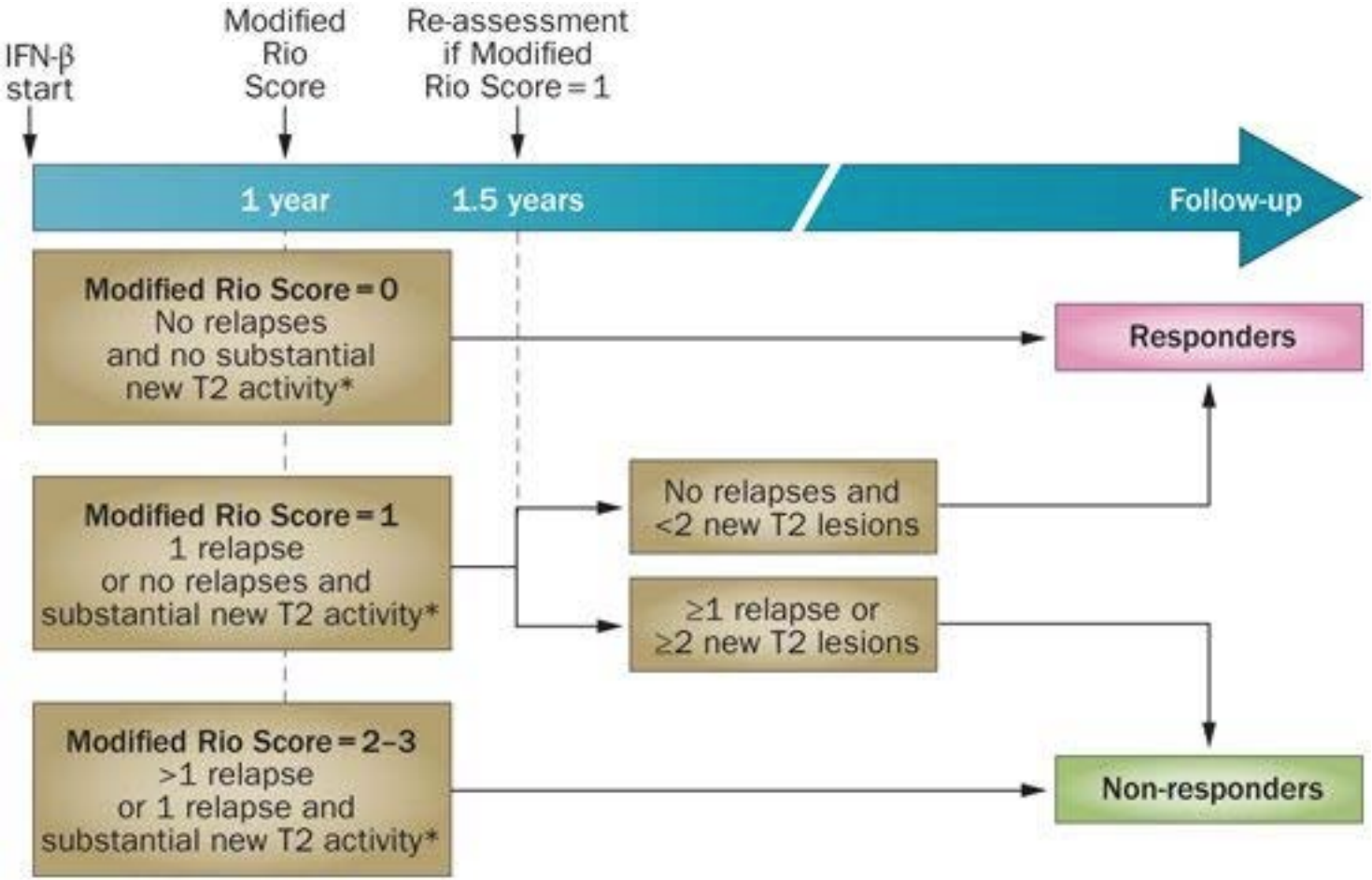




Wiendl et al 2017

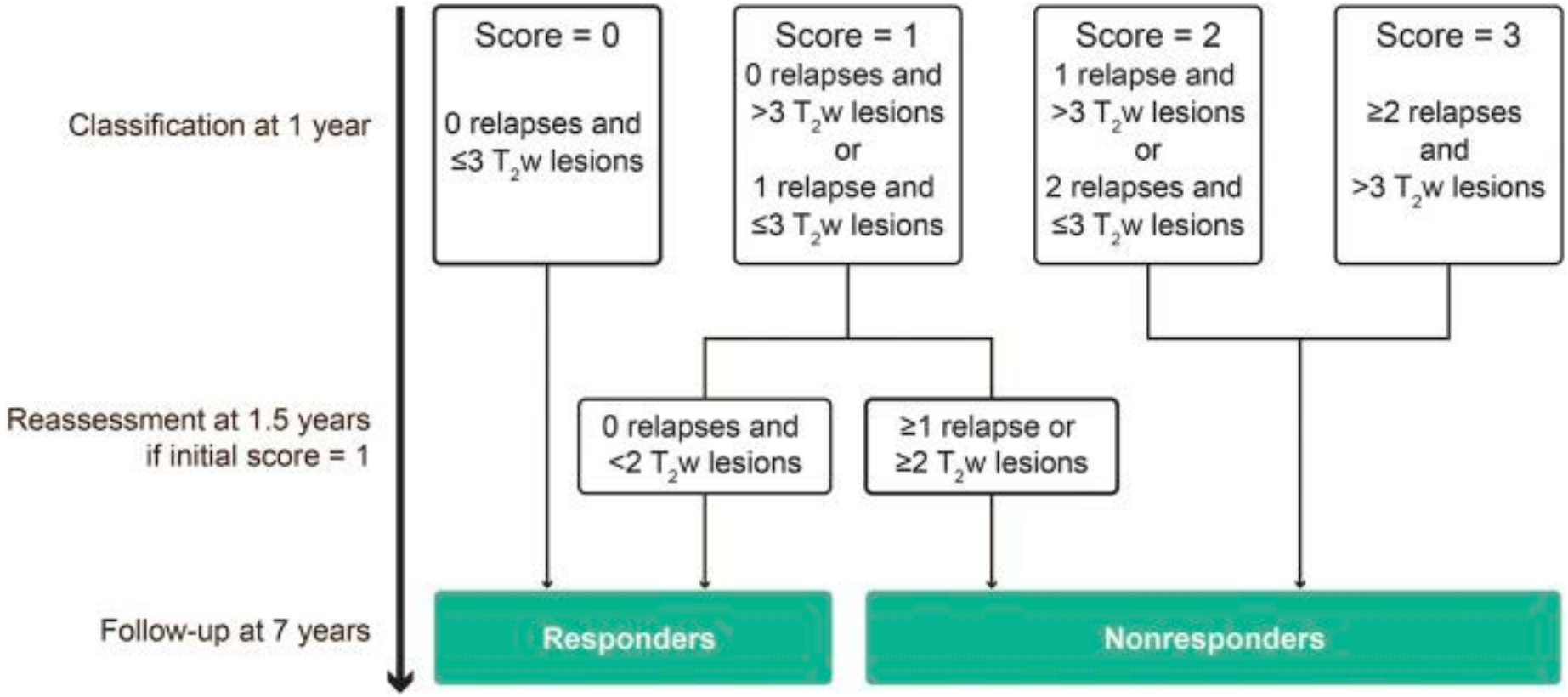
Nature Reviews | Neurology

Behandlingssvikt-Rio score



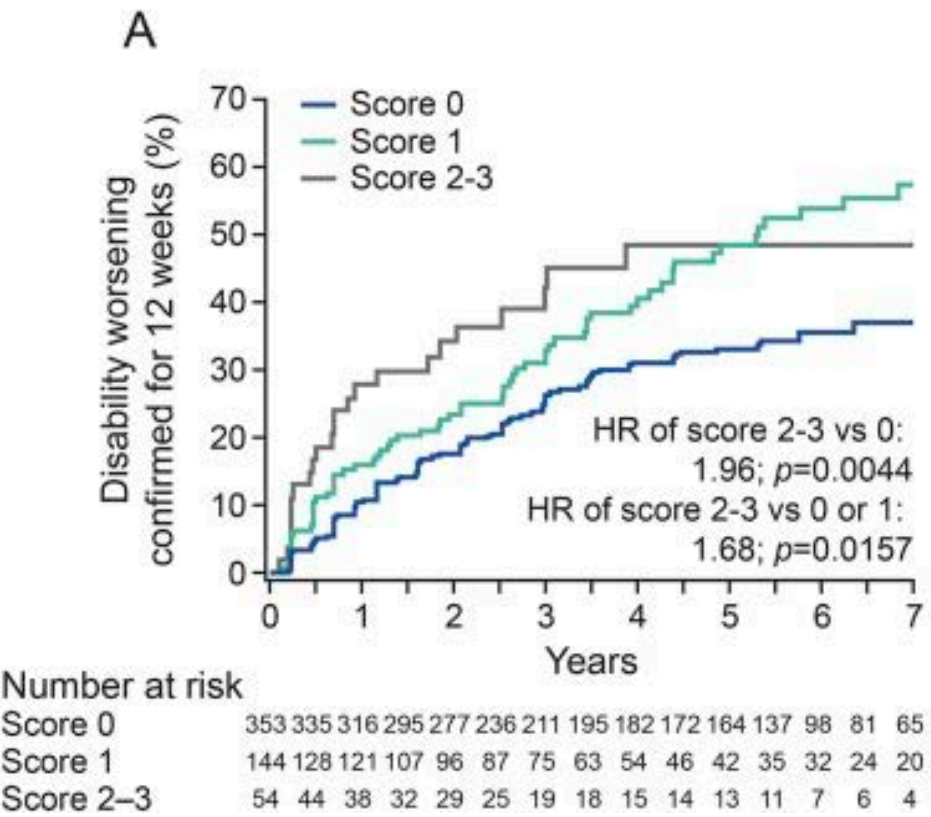
Sormani & De Stefano, Nature Rev 2013

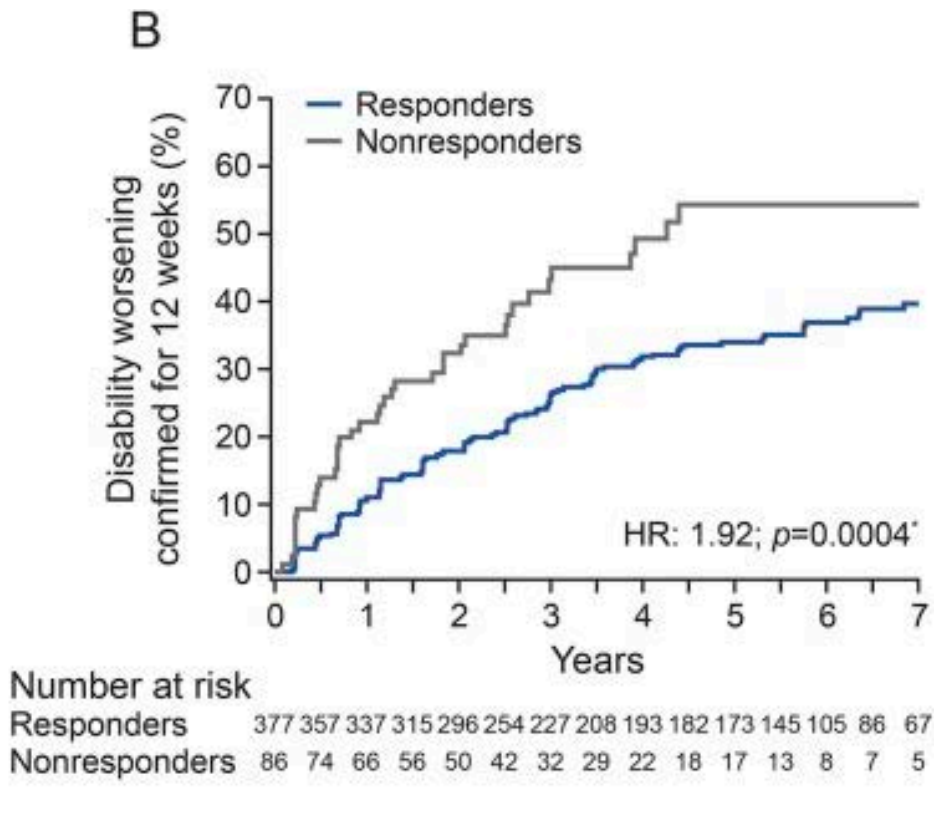
Post hoc analys av TEMSO studien med modifierad Rio score



Sormani 2017, Neurol Neuroimmunol and Neuroinflammation

Prediktivt värde av score i TEMSO studien



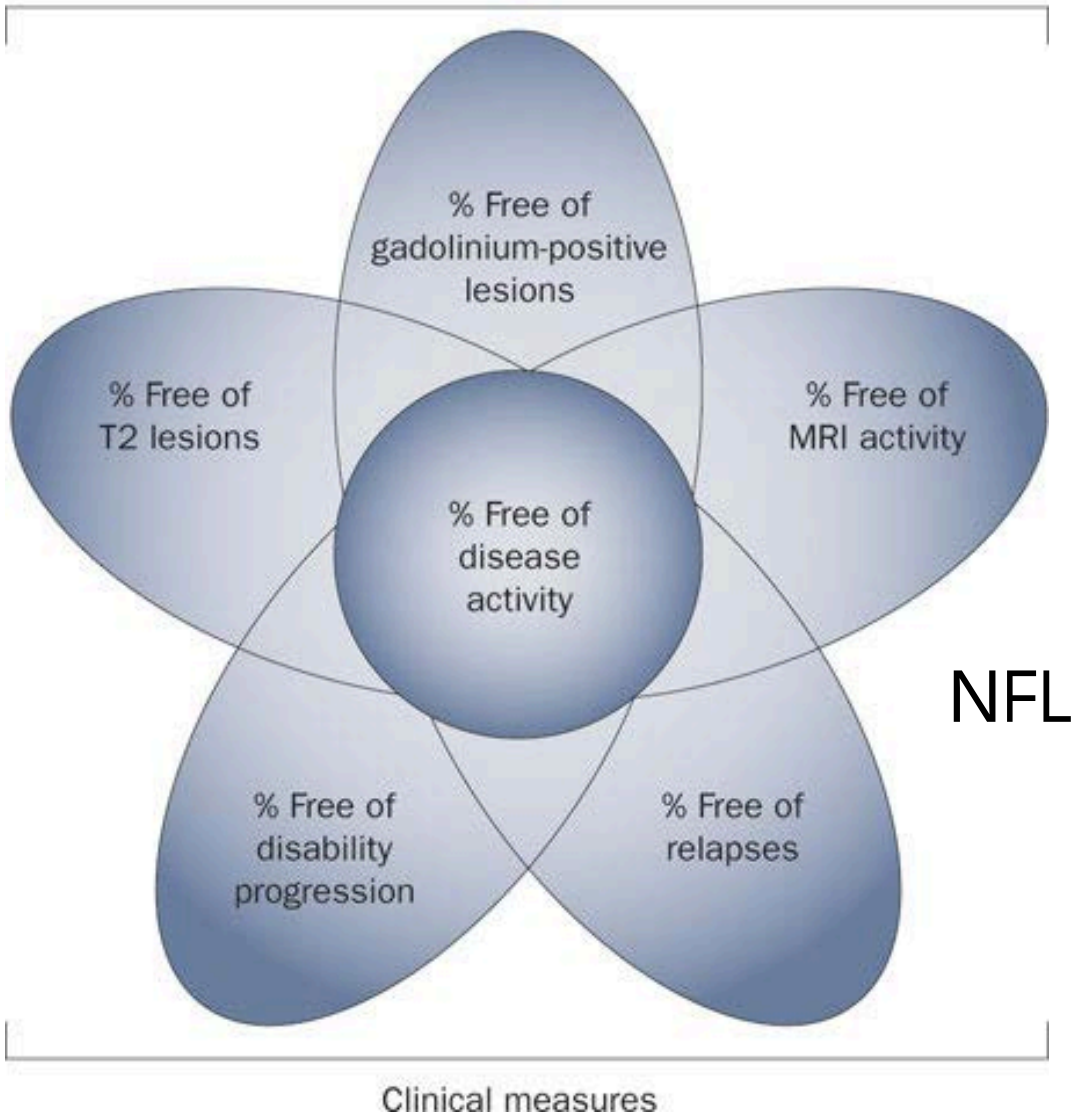


Sormani 2017, Neurol Neuroimmunol and Neuroinflammation

Behandlingssvikt vid RRMS?

- Utvärdera patienten innan behandlingsstart:
  - skov, EDSS, MRI, NFL….
- Utvärdering efter minst 6 månaders behandling
  - olika behandlingsmekanismer styr tid till effekt
- Kriterie på svikt:
  - Skov och/eller
  - Kontrastladdande lesioner 6 månaders MRI och/eller
  - 2 eller flera tillväxande eller nya T2 och/eller
  - förhöjt NFL?

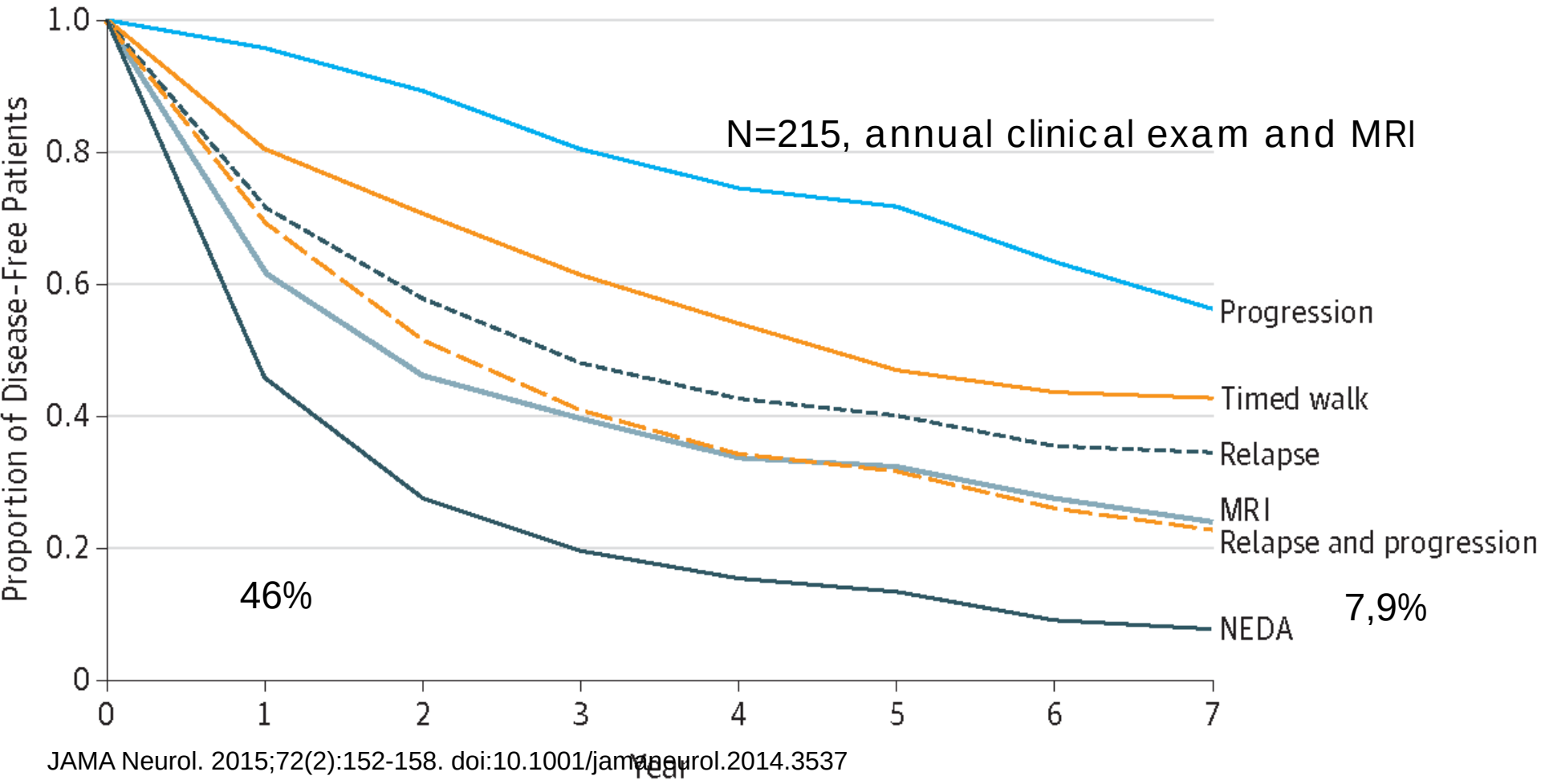
No evidence of disease activity (NEDA)



NFL?

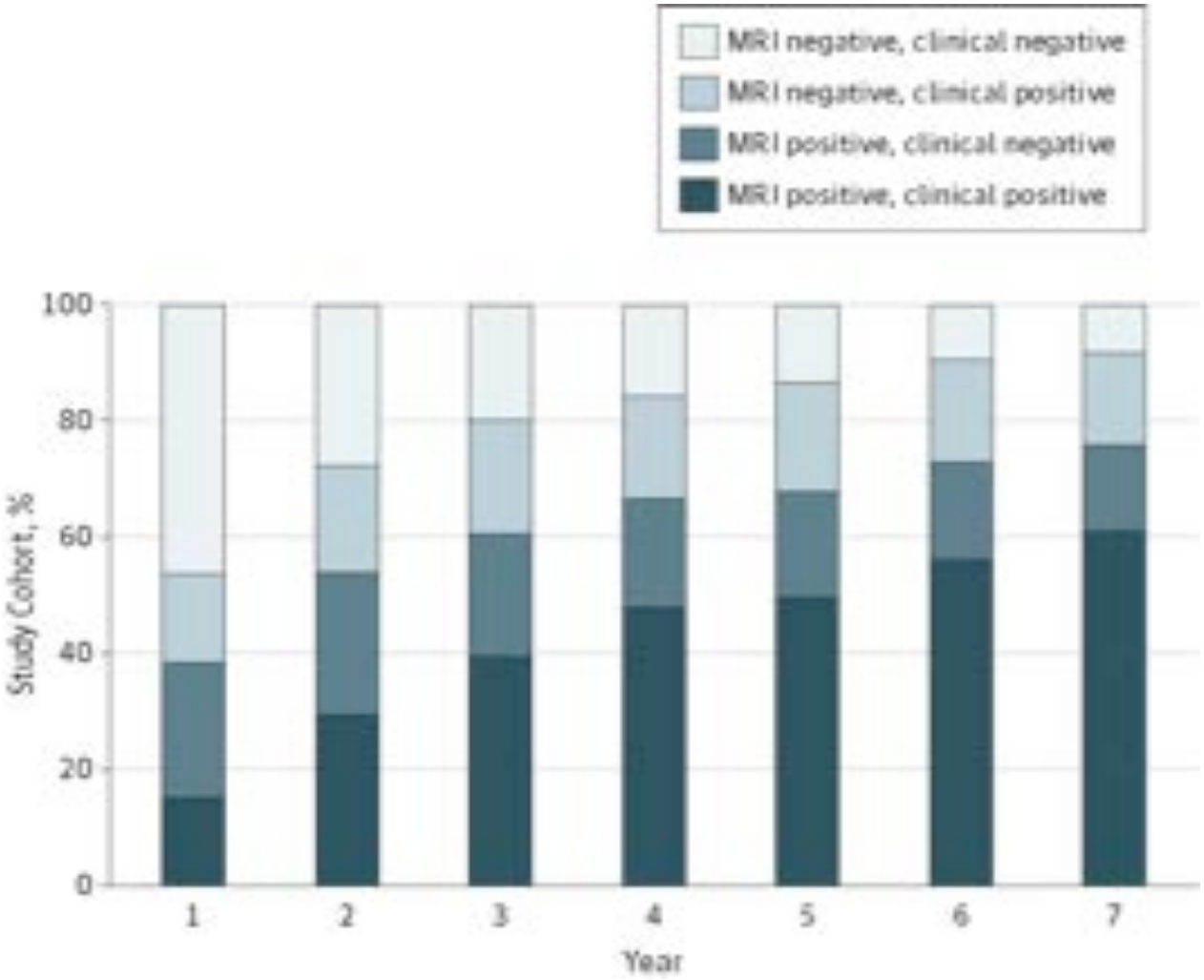
Evaluation of No Evidence of Disease Activity in a 7-Year Longitudinal Multiple Sclerosis Cohort

NEDA at 2 years had predictive value of 78,3% at 7 y follow-up



JAMA Neurol. 2015;72(2):152-158. doi:10.1001/jamaneurol.2014.3537

Proportion of Patients With and Without Magnetic Resonance Imaging (MRI) or Clinical Disease Activity During 7 Years



Disproportion between clinical and MRI

- 42.9% at year 2
- 30.6% at year 7.

MRI but not clinical

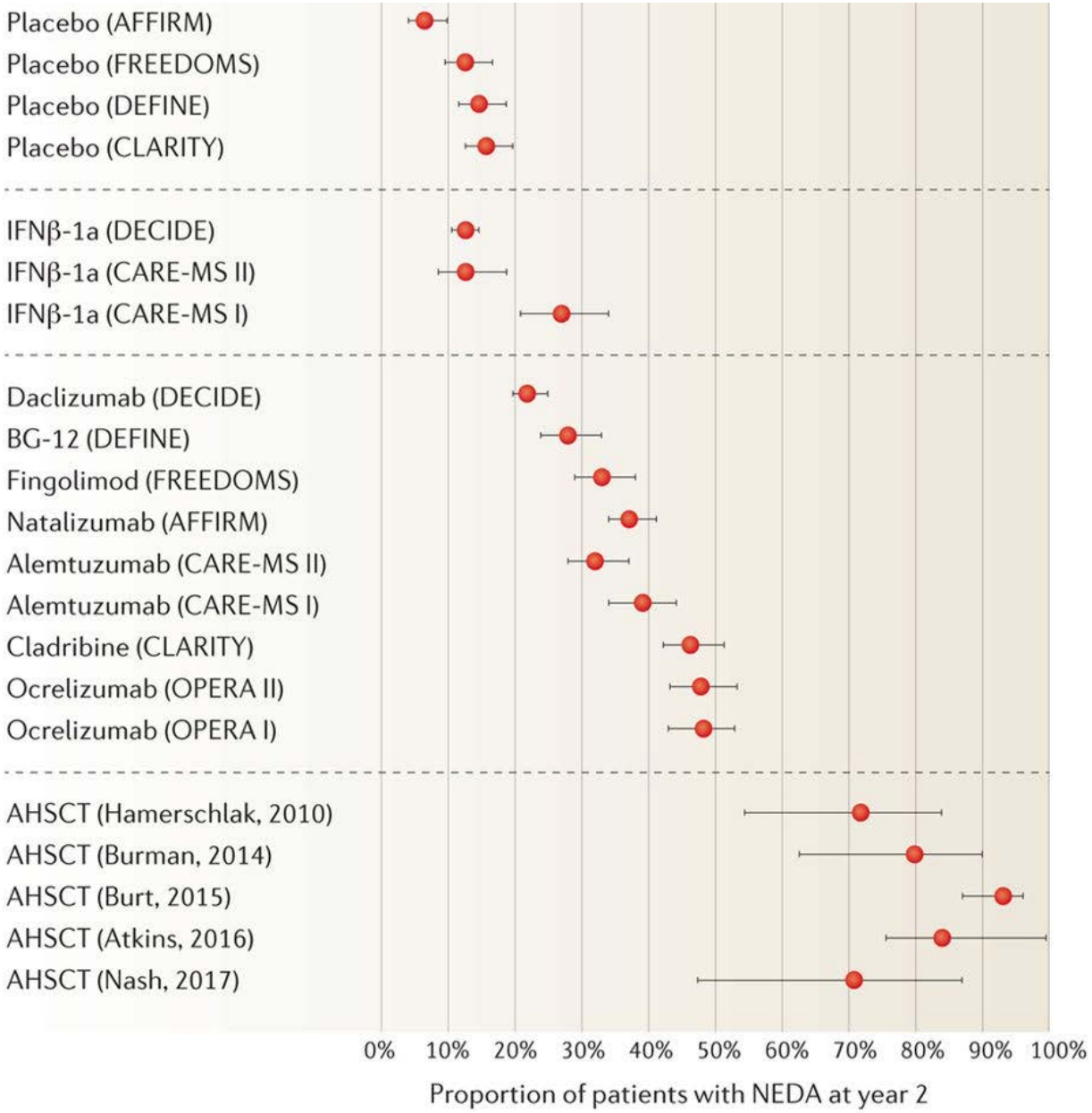
- 15.0% in year 1
- 15.8% in year 7

Clinical but not MRI

- 23.5% at year 1
- 14.8% at year 7.

JAMA Neurol. 2015;72(2):152-158. doi:10.1001/jamaneurol.2014.3537

NEDA vid olika MS behandlingar

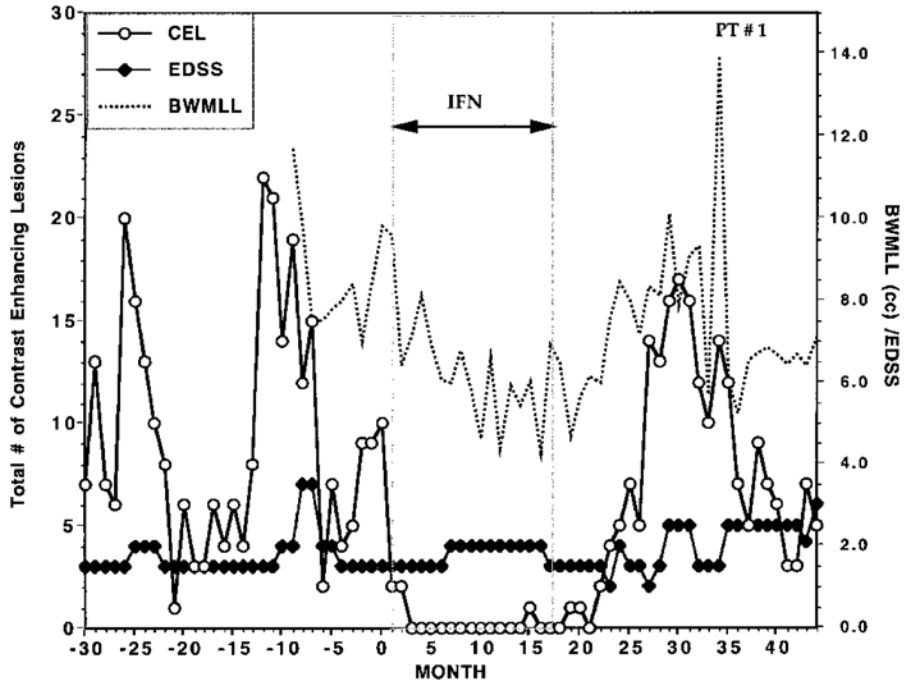


Nature Reviews | Neurology

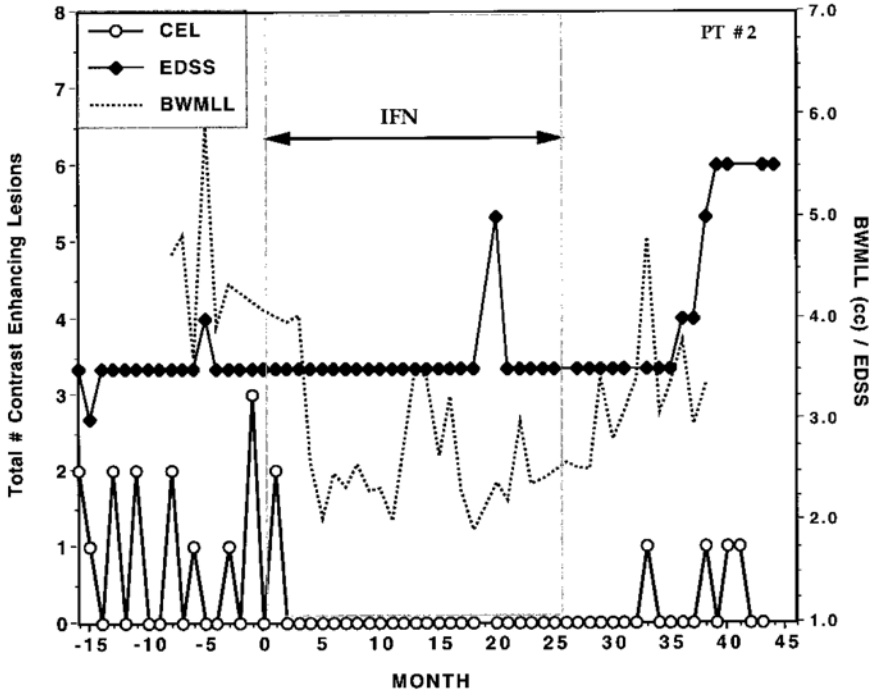
Erfarenheter av att avsluta immunomodulerande behandling av RRMS

- INF beta
- Natalizumab
- Rebound
  - Natalizumab
  - Fingolimod
  - DMF

INF beta behandling och sjukdomsaktivitet



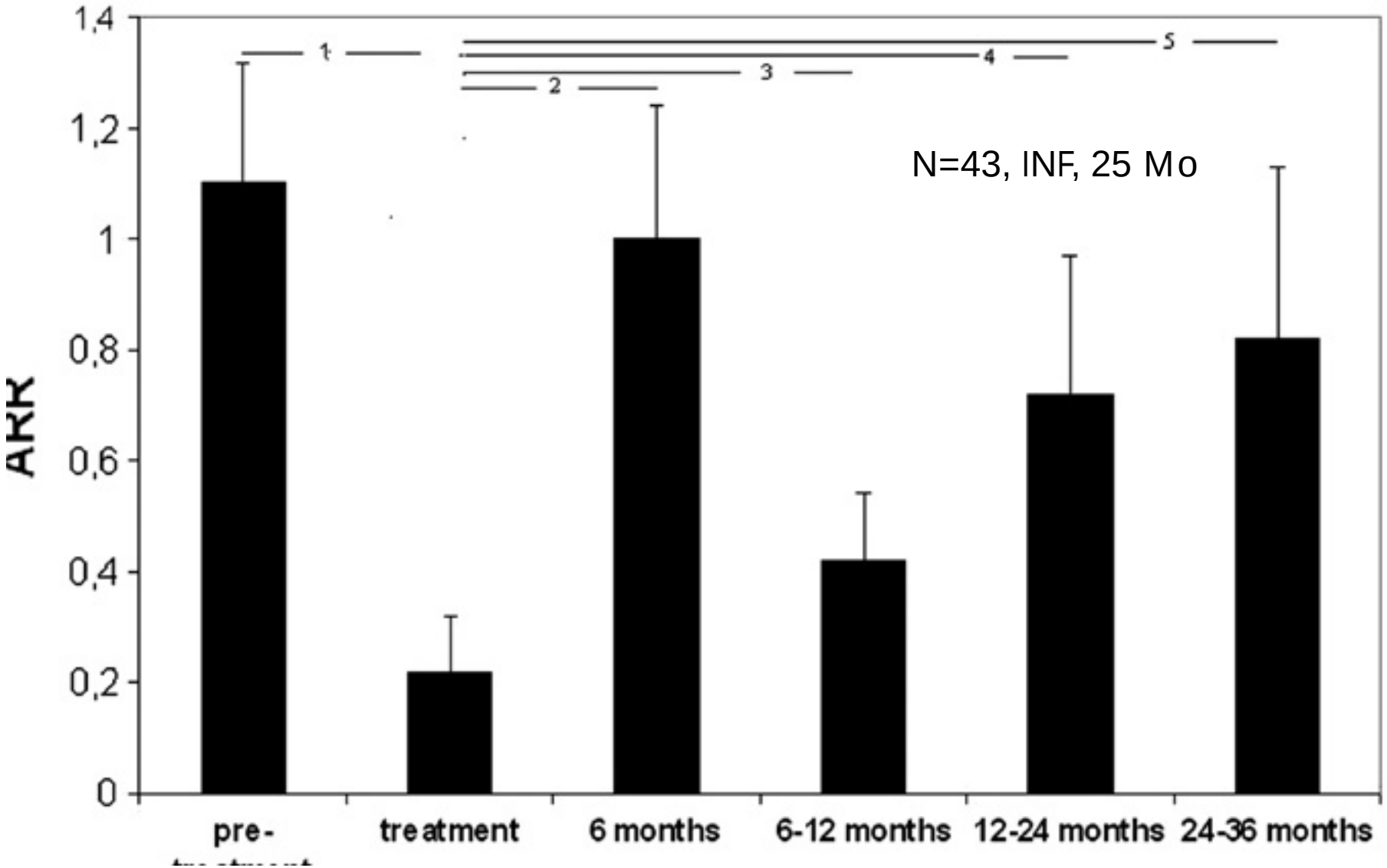
Patient 1



Patient 2

Multple Sclerosis (2000) 6, 86-90

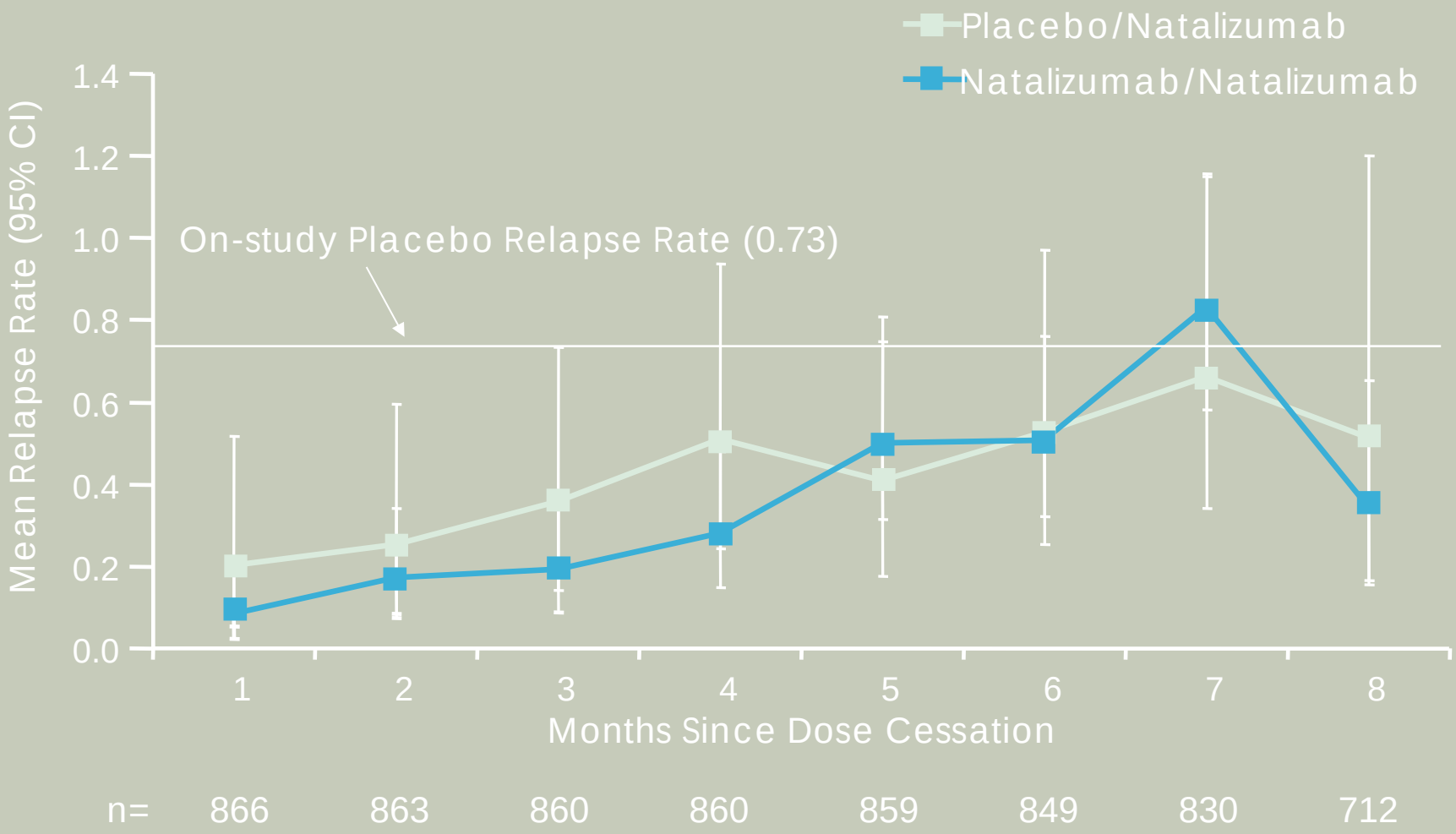
INF beta termination: 65% relapse within 34 months, 8 within 30 days



Siger 2011, J Neurol Sci

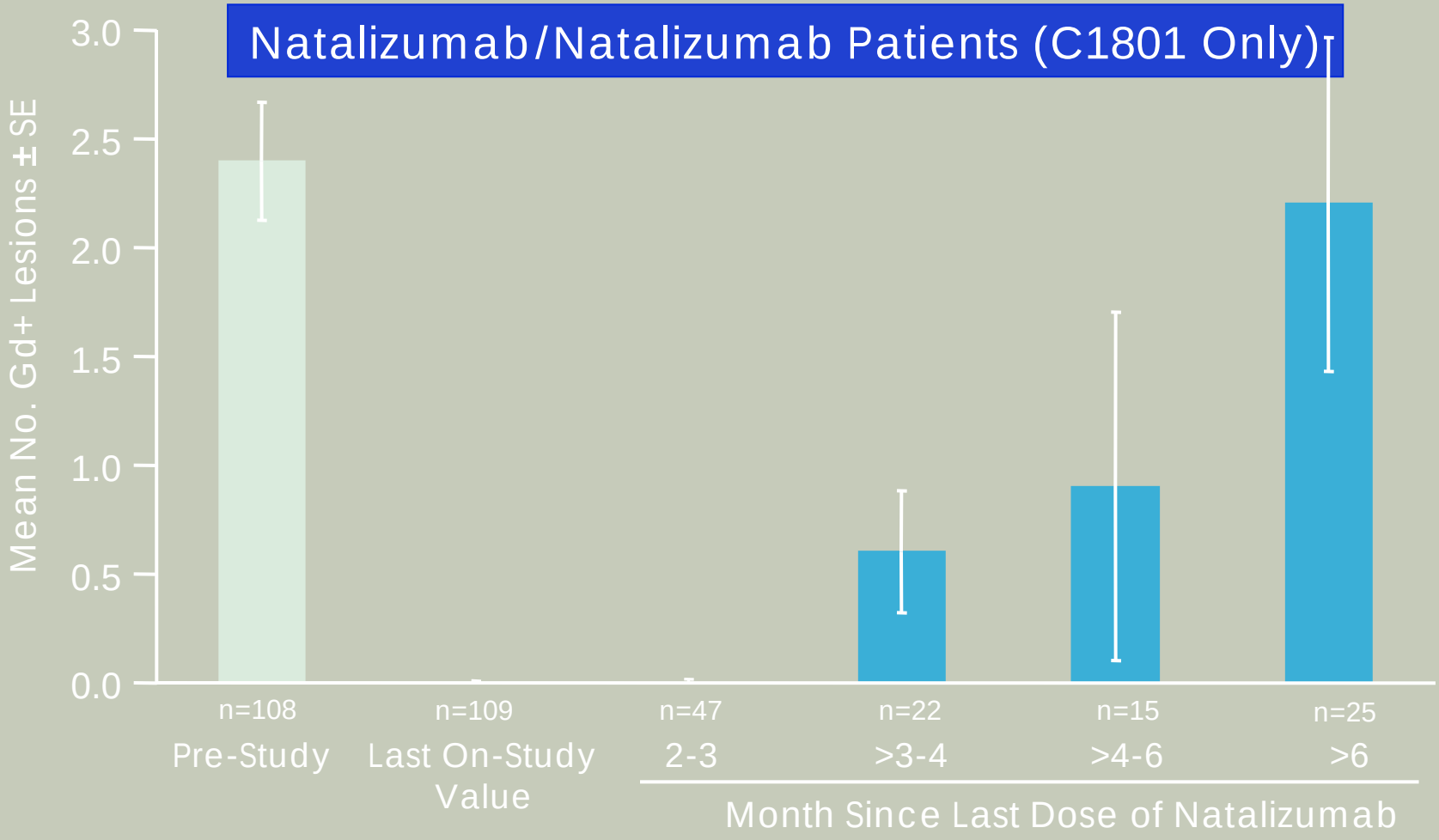
Post-Treatment Relapse Rate

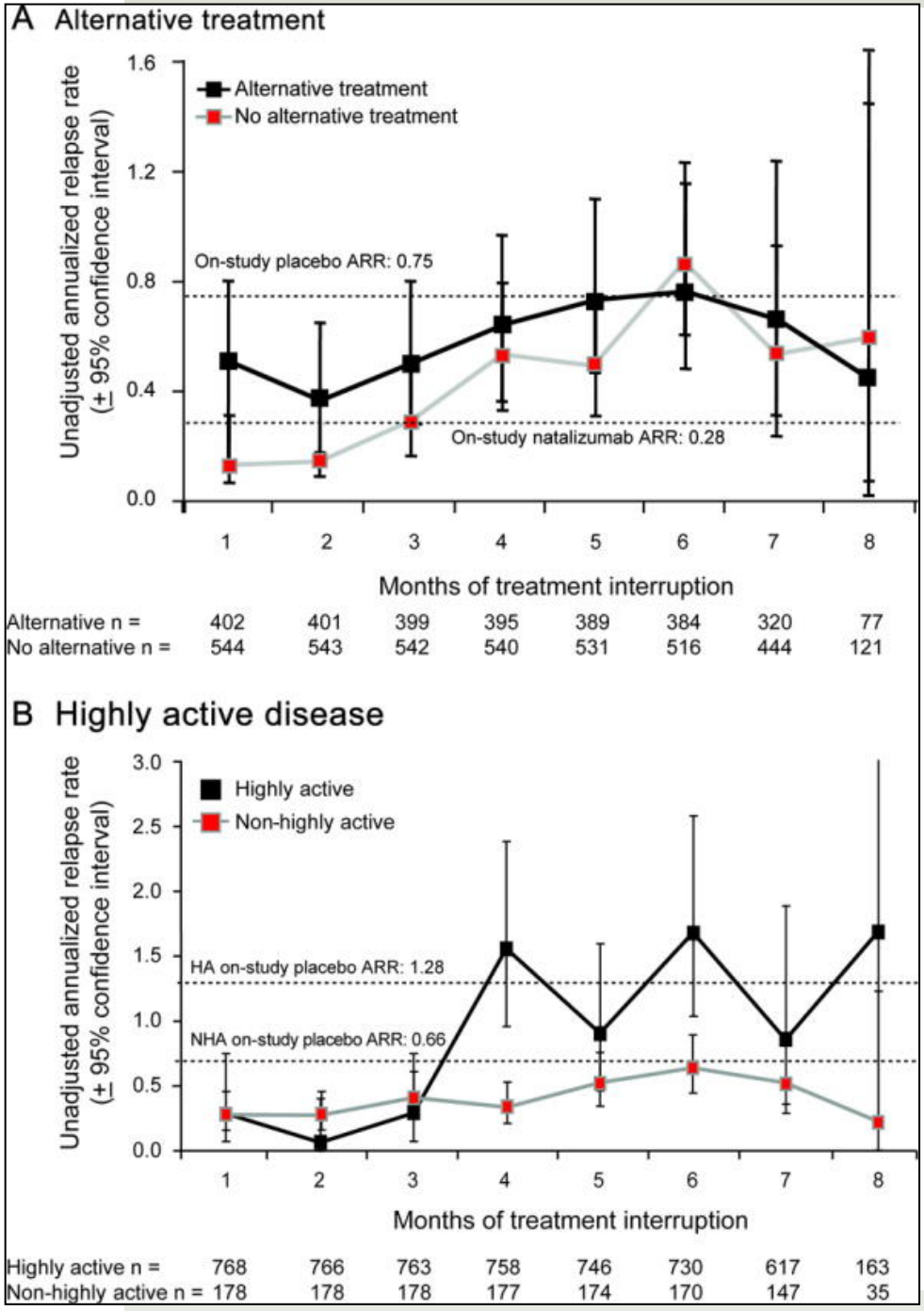
C1801 Patients



Gd+ Lesions By Time Since Final Dose

Patients with MRI Scan at Least 2 Months After Last Dose

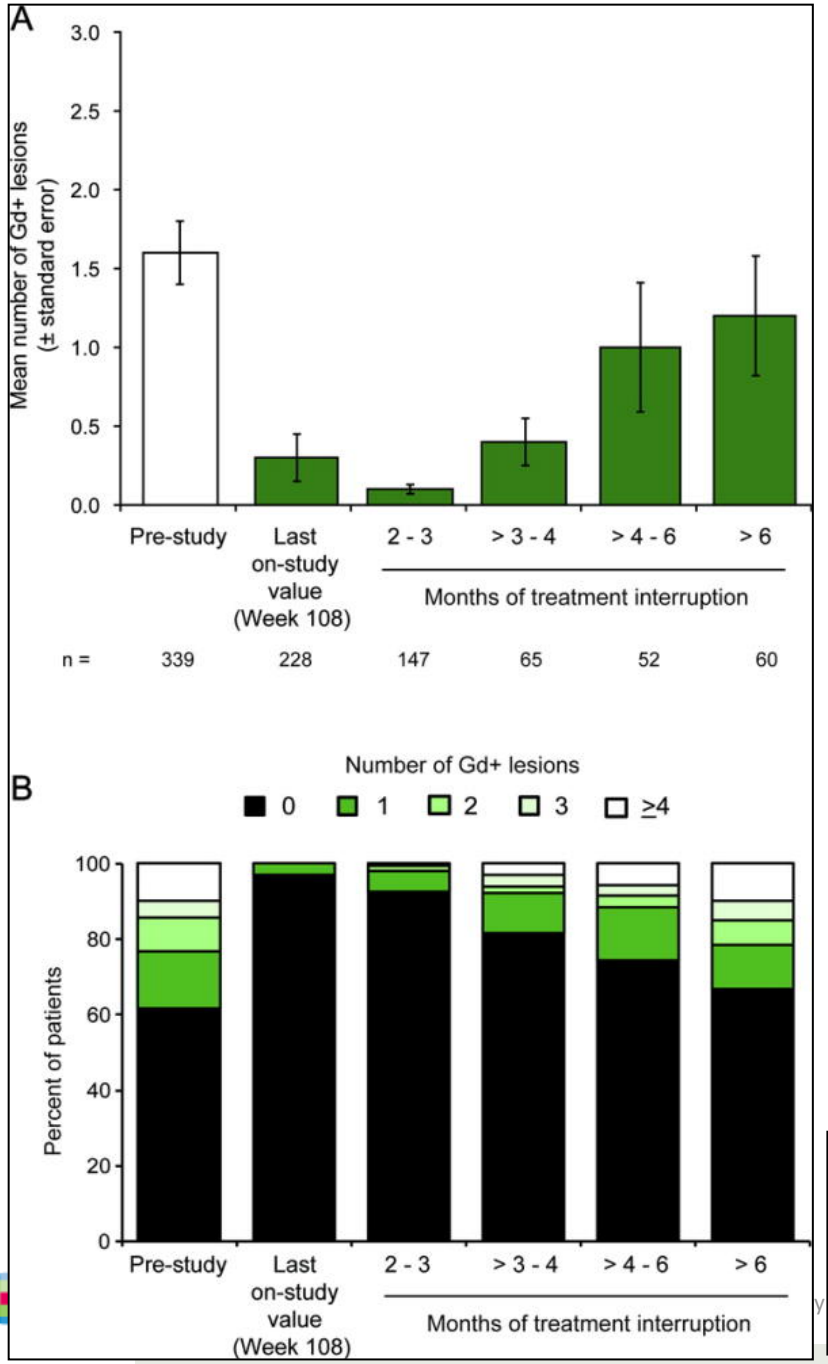




TYSABRI BEHANDLING AVSLUTAS

Efterföljande alternativ behandling hade inte tillräcklig effekt

Tidigare högaktiva återfick hög sjukdomsaktivitet



…MRI aktiviteten återkommer också

Gd+ lesion count (A), and percent of patients with 0 to >=4 Gd+ lesions (B) during treatment interruption in patients who received at least one natalizumab infusion. A total of 341 patients were evaluated.

Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis (e-Pub ahead of print).
OConnor, PW; Goodman, A; Kappos, L; Lublin, FD; Miller, DH; Polman, C; Rudick, RA; Aschenbach, W; Lucas, N

Neurology. 76(22):1858-1865, May 31, 2011.
DOI: 10.1212/WNL.0b013e31821e7c8a

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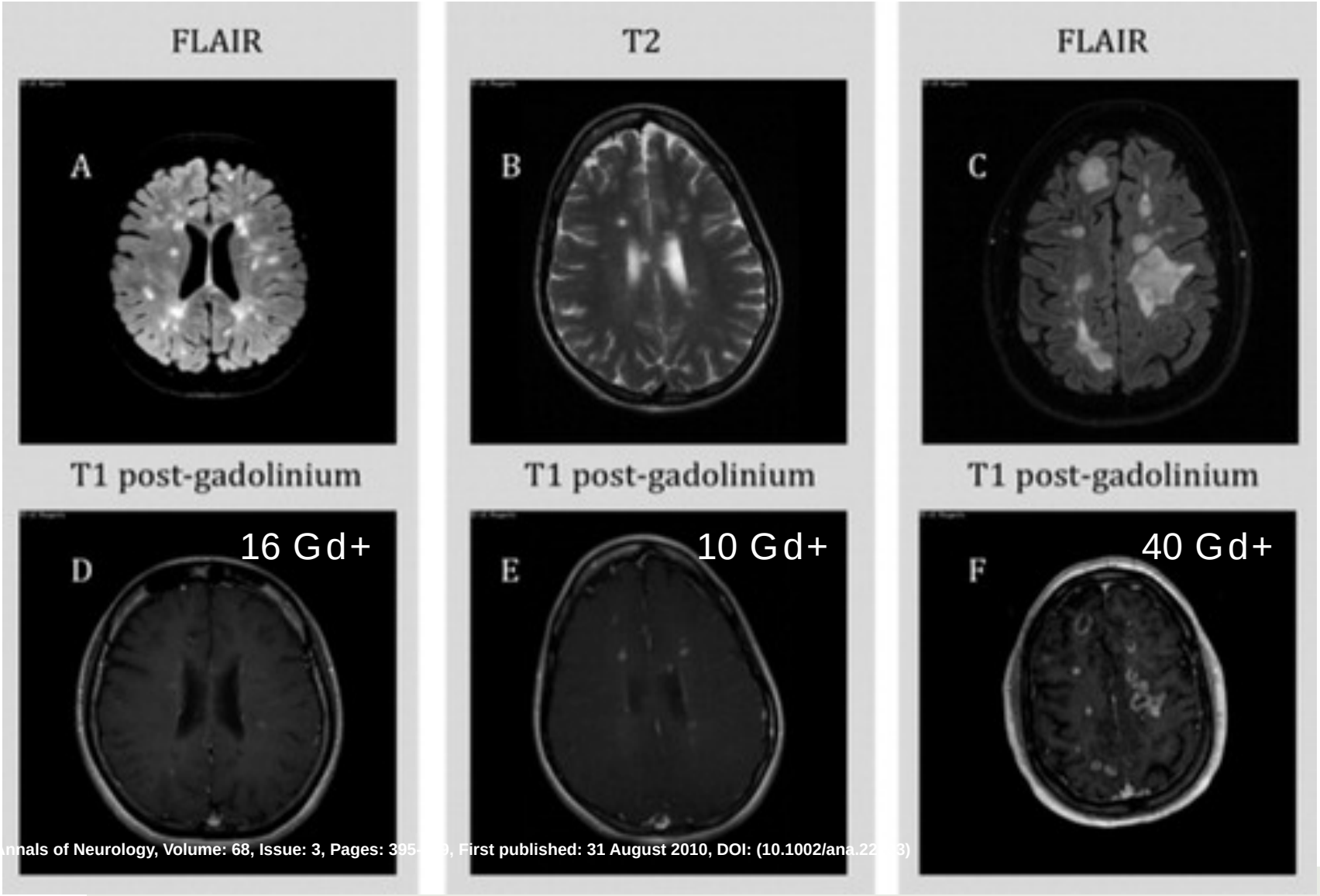
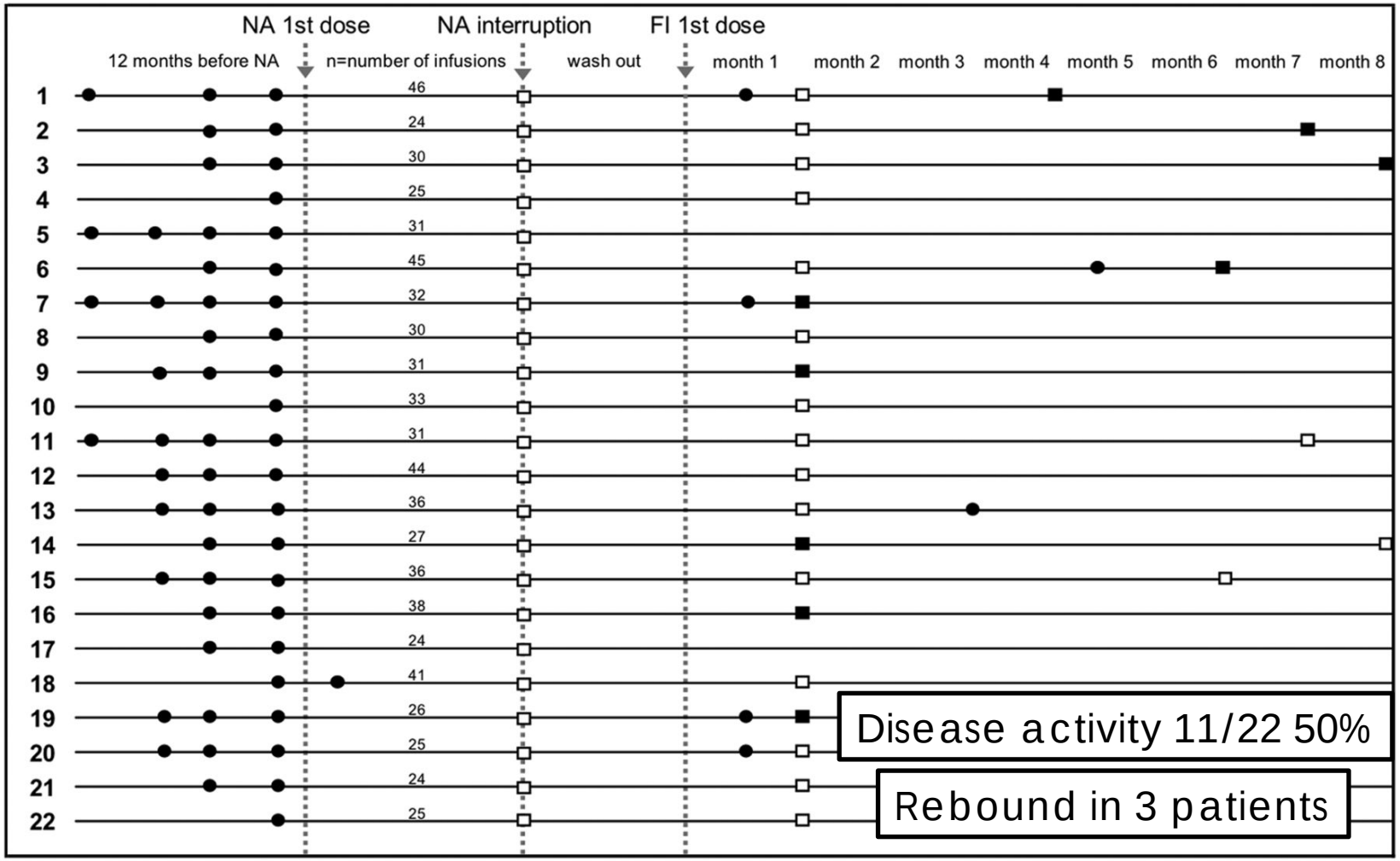
MRI activity after natalizumab dosage suspension



nals of Neurology, Volume: 68, Issue: 3, Pages: 395-[illegible], First published: 31 August 2010, DOI: (10.1002/ana.22[illegible]3)

22 RRMS who were JC-virus ab pos

Figure 1. Clinical and magnetic resonance imaging (MRI) findings in 22 relapsing–remitting multiple sclerosis (RRMS) patients who shifted from natalizumab to fingolimod.



Rinaldi F et al. Mult Scler 2012;18:1640-1643

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MULTIPLE SCLEROSIS JOURNAL
Formerly Multiple Sclerosis

Rebound risk assessment

Prosperini, Ther Adv Neurol Disord
2019, Vol. 12: 1–17
Meta analysis of 6 articles, n=1183

- High risk of re-acivation/rebound
  - Younger age
  - High disease activity, relapses and Gd + lesions prior to NTZ
  - Few NTZ infusions
  - Switch to DMT with inferior efficacy
  - Wash out period extends 2 months

Rebound Syndrome in Patients With Multiple Sclerosis After Cessation of Fingolimod Treatment

Table 1. Five Cases of Fingolimod Rebound

Case No.	Reason for Discontinuation	Time to Rebound, wk	ARR Prior to Fingolimod	ARR During Fingolimod	Lymphocyte Count Subsets During Rebound, /μL	Gadolinium^{+} Lesions (New T2 Lesions), No.		
						Prior	During	After
1	Breast cancer; brainstem relapse	6	NA	0.25	960[a]	NA	1 (>10)	10 (10)
2	Attempt pregnancy	4	1.0	0.55	1320	0 (5)	0 (1)	9 (9)
3	Attempt pregnancy	4	0.60	0.33	1070	0 (0)	1 (7)	2 (25)
4	Adverse effects	12	0.45	0	990	2 (NA)	0 (0)	>10 (>10)
5	Self-discontinuation	12	0.8	0	70[b]	0 (2)	0 (NA)	>30 (>30)

Abbreviations: ARR, annualized relapse rate; NA, not applicable.

SI conversion factor: To convert lymphocyte count to × 10^9/L, multiply by 0.001.

[a] CD4, 346; CD8, 288; CD19, <10.

[b] CD4, 3; CD8, 7; CD19, 4.

JAMA Neurol. 2016;73(7):790-794. doi:10.1001/jamaneurol.2016.0826

Rebound Syndrome in Patients With Multiple Sclerosis After Cessation of Fingolimod Treatment

Table 2. Published Reports of Severe Disease Reactivation After Ceasing Fingolimod

Source	Cases	Response to Steroids	Lymphocyte Counts During Rebound	Time Until Rebound After Ceasing Fingolimod, wk	New MRI Lesions (Enhancing Lesions), No.
De Masi et al,[5] 2015	F, 32 y	No	Normal	4	NA[a]
Berger et al,[6] 2015	M, 29 y; F, 15 y; F, 41 y; F, 22 y	Partial; Partial No[b]; No[c]	Below normal	4-16	Range: 20-120 (11-45)
La Mantia et al,[7] 2014	F, 36 y	Yes	Normal	8	20 (20)
Sempere et al,[8] 2013	F, 31 y	Partial	NA	11	14 (14)
Beran et al,[9] 2013	F, 31 y	Yes	NA	5	NA[d]
Piscolla et al,[10] 2013	F, 19 y	None given; PLEX with good recovery	Normal	12.5	>35 (>25)
Hakiki et al,[11] 2012[e]	F, 33 y	Yes	Normal	12	>25 (>25)
Havla et al,[4] 2012	M, 45 y	Partial	Normal	12	>20 (>20)

Abbreviations: F, female; M, male; MRI, magnetic resonance imaging; NA, not applicable; PLEX, plasma exchange.

[a] Exact number not given in this article but described as "increased lesion load."

[b] No response to steroids; given PLEX with good recovery.

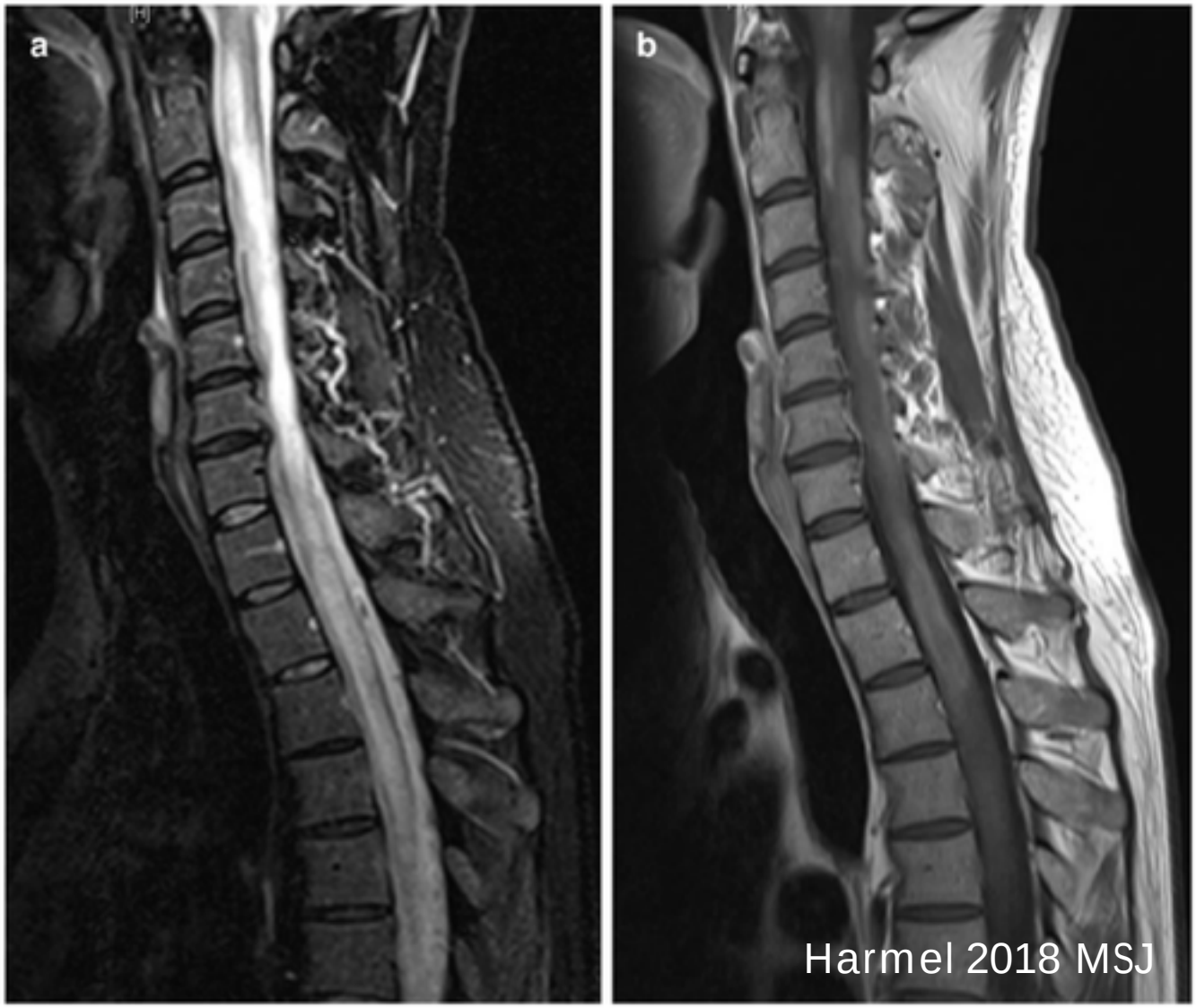
[c] No response to steroids; given PLEX with minimal response.

[d] Exact number not given in this article but described as "numerous."

[e] The 5 other cases reported in this article did not fit our predetermined criteria for rebound syndrome as defined in the Methods section.

JAMA Neurol. 2016;73(7):790-794. doi:10.1001/jamaneurol.2016.0826

Rebound 2 months after cessation of DMF

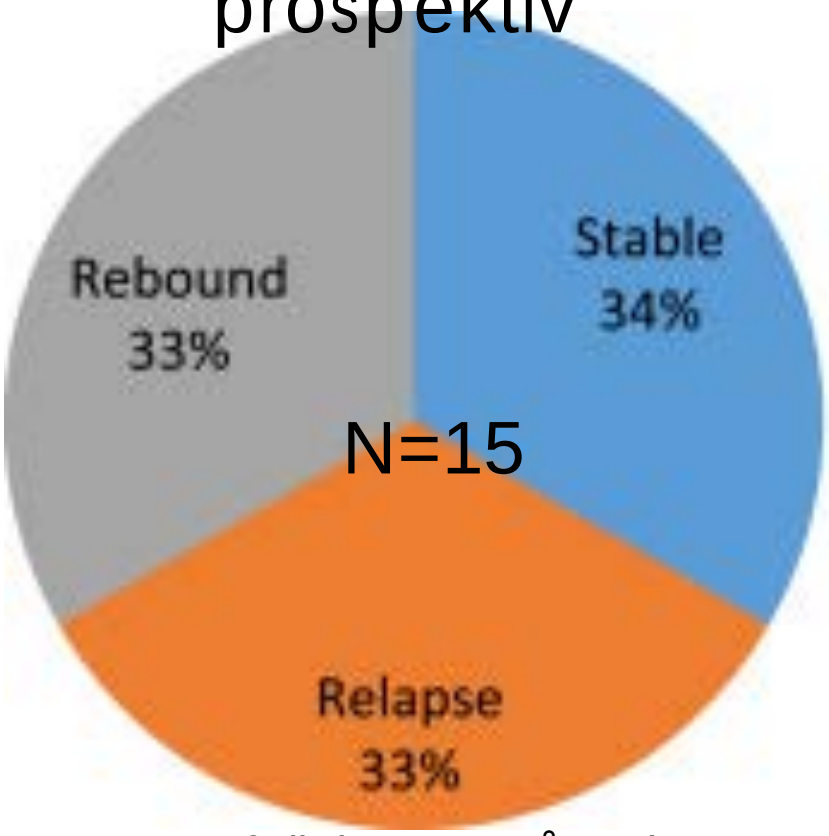


Avsluta behandling vid "stabil MS"

>5 års behandling. Ingen klinisk eller MRI aktivitet

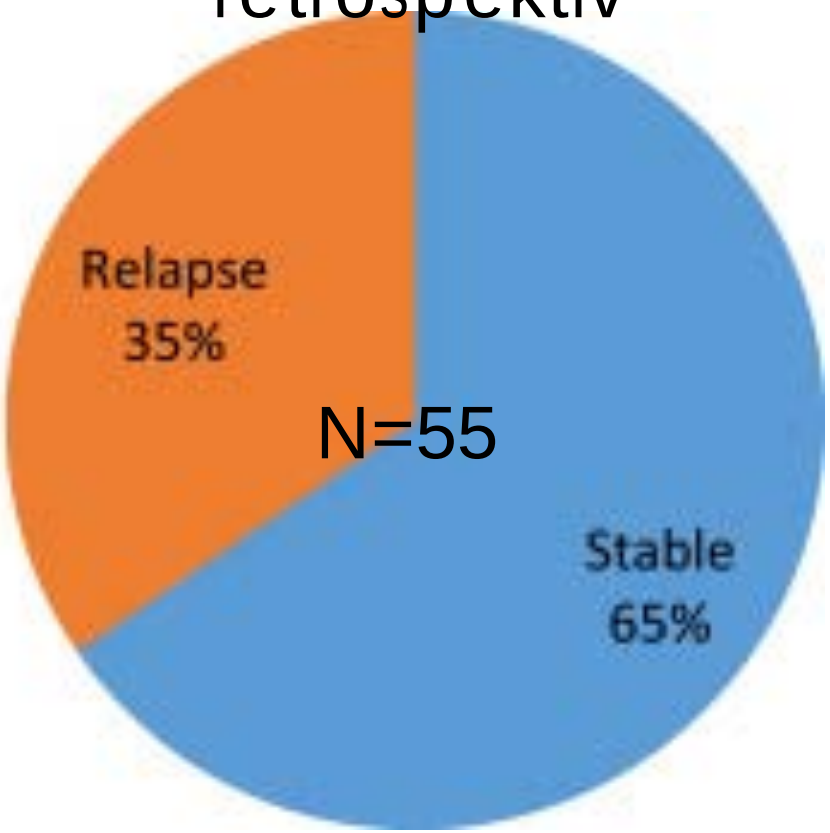
Fagius 2017, MSRD

Natalizumab prospektiv



Uppföljning 19 månader

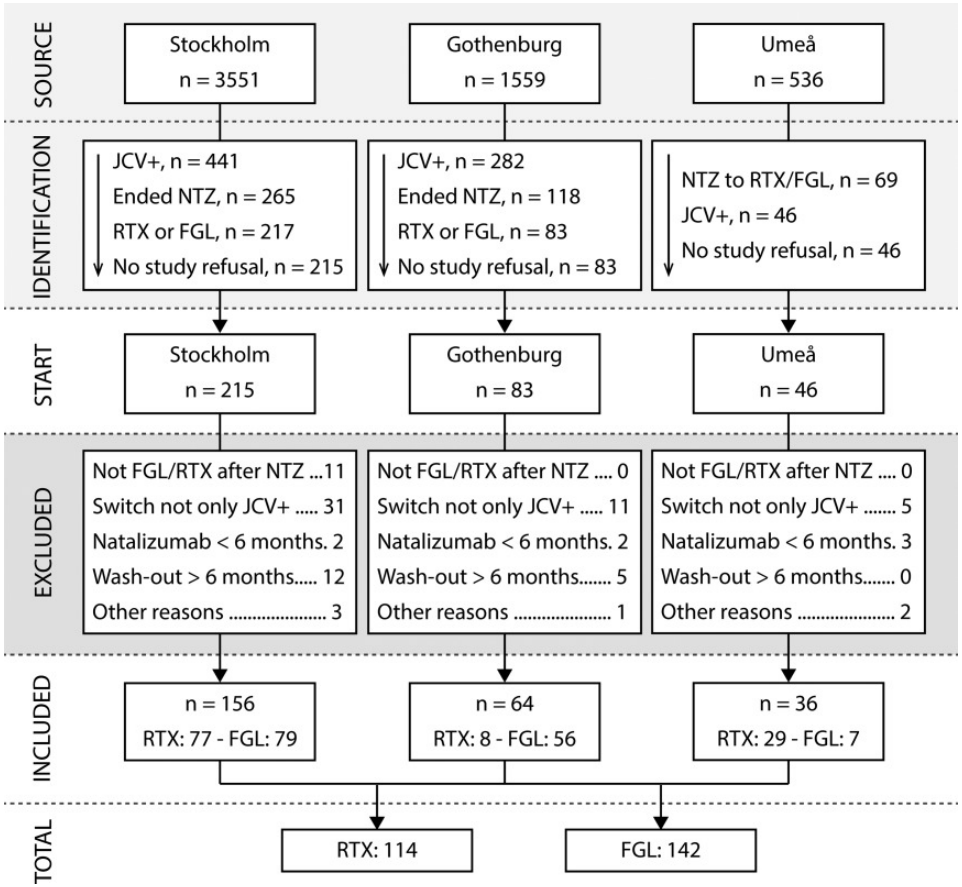
First line DMT retrospektiv

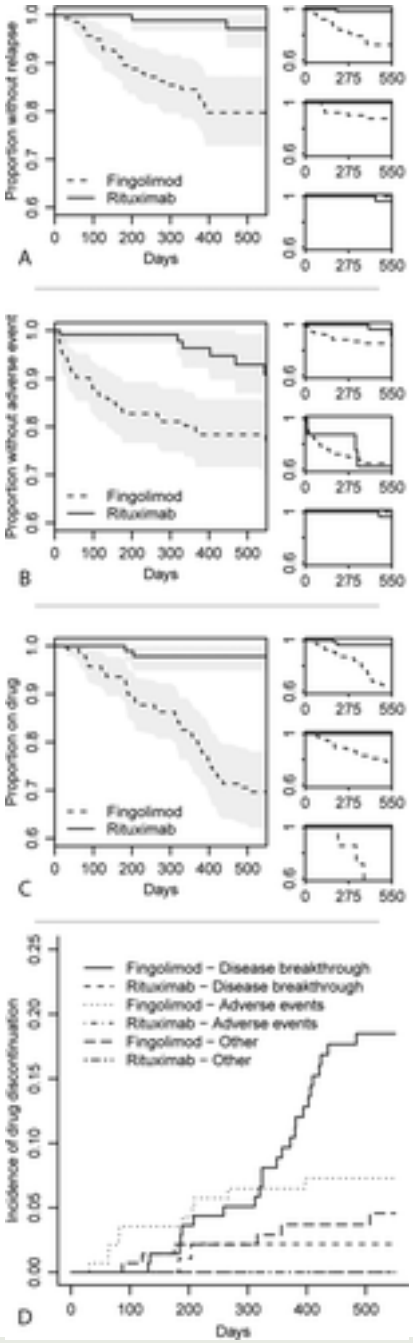


Uppföljning 56 månader

Rituximab versus fingolimod after natalizumab in multiple sclerosis patients

Alping, Ann Neurol 2016

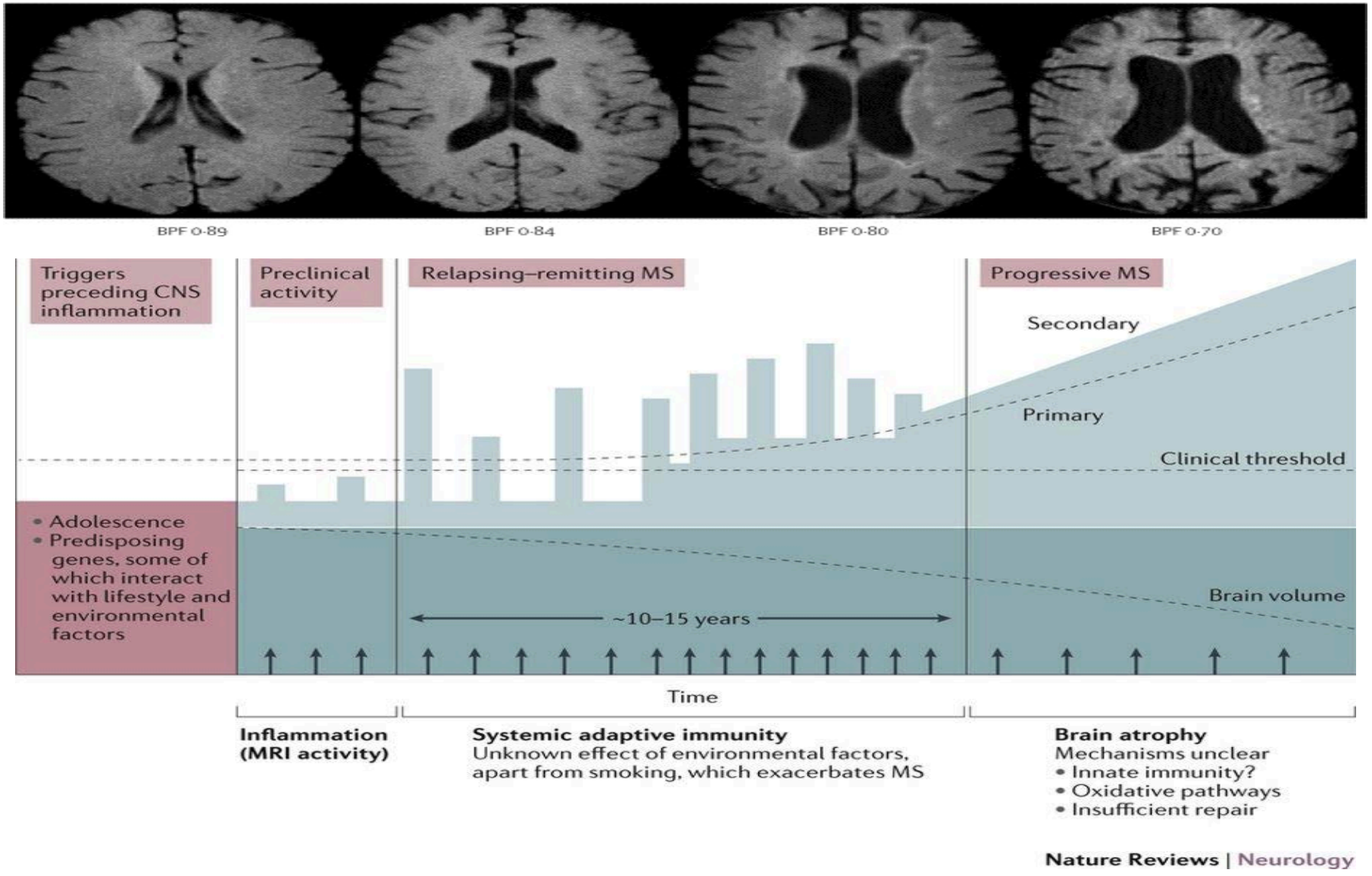




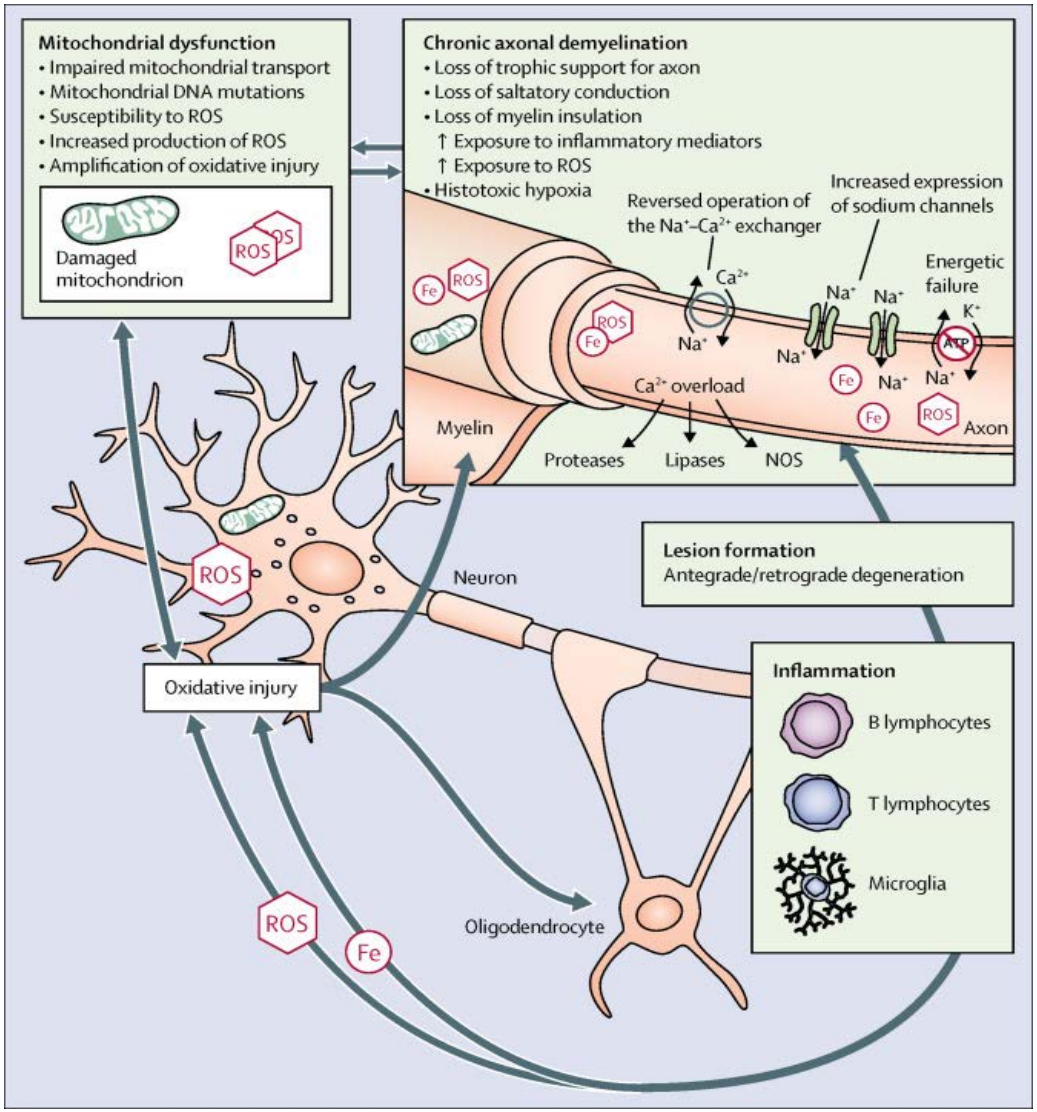
Avsluta behandling vid RRMS?
Prediktion och utfall (Mult Scler. 2017 Aug;23(9):1241-1248.)

- Retrospektiv studie 221 RRMS, >12 månader DMT, >2 års uppföljning efter avslutad behandling
- Prediktorer: lägre risk för skov
  - >45 år
  - Inga skov under minst 4 år under pågående DMT
- Prediktorer: högre risk för progression
  - >45 år
  - Längre sjukdomsduration

To stop or not to stop disease modifying therapies in secondary progressive multiple sclerosis, that is the question

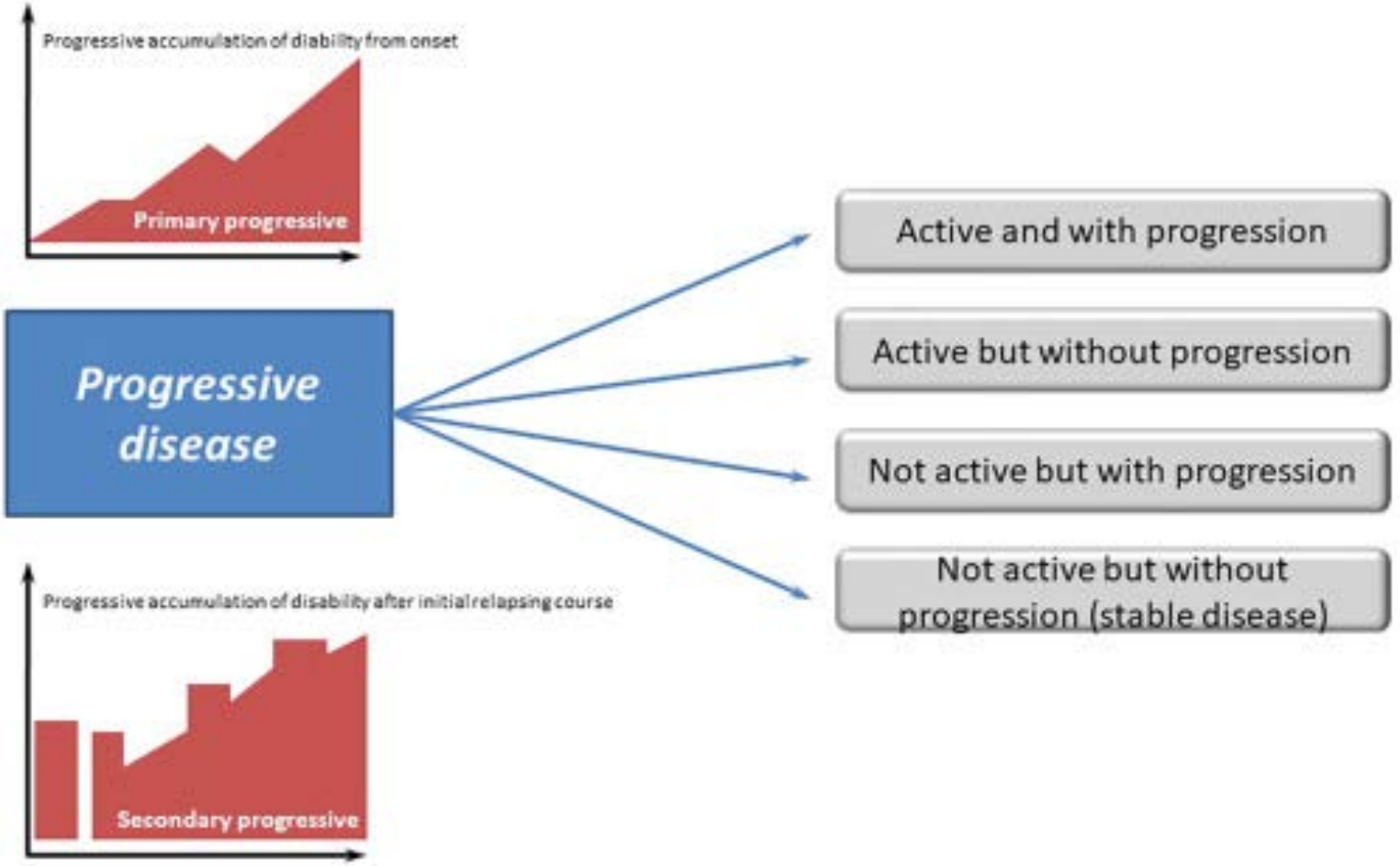


Pathogenesis of progression in multiple sclerosis



Ontaneda, Lancet 2017

Progressive phenotypes of multiple sclerosis



Clinical trials in PPMS Tur & Montalban 2017

Table 2. Main trials in PPMS.

Drug tested (vs placebo)	Trial	Condition (no. of patients randomised)	Duration	Primary endpoint	Results on the primary endpoint	Reference
GA SC 15 mg/12 hours	Phase 2	Chronic progressive MS ($n=106$); out of these, 31 had PPMS ($n=23$) or 'transitional progressive MS' ($n=8$)	24 months	Time to confirmed progression on the EDSS[a]	Negative[b]	Bornstein et al.[12]
GA SC 20 mg/day	Phase 3 (PROMiSe study)	PPMS ($n=943$)	Early termination for futility (initially planned: 36 months)	Time to 3-month CDP on the EDSS[a]	Negative	Wolinsky et al.[21]
IFNb-1a IM 30 µg or 60 µg weekly	Phase 2	PPMS ($n=50$)	24 months	Time to 3-month CDP on the EDSS[a]	Negative	Leary et al.[22]
IFNb-1b SC 8 MIU eod	Phase 2	PPMS and 'transitional progressive MS' ($n=73$)	24 months	Time to 3-month CDP on the EDSS[a]	Negative	Montalban et al.[23]
Rituximab IV 1000 mg/24 weeks	Phase 2/3 (OLYMPUS study)	PPMS ($n=439$)	96 weeks	Time to 3-month CDP on the EDSS[a]	Negative[c]	Hawker et al.[24]
Fingolimod PO 0.5 mg/day	Phase 3 (INFORMS study)[d]	PPMS ($n=970$)	36 months	Composite endpoint: time to 3-month CDP on either EDSS, or TWT, or NHPT	Negative	Lublin et al.[8]
Ocrelizumab IV 600 mg (300 mg ×2) /24 weeks	Phase 3 (ORATORIO study)[e]	PPMS ($n=732$)	120 weeks	Percentage of patients with 3-month CDP on the EDSS[a,f]	*Positive*	Montalban et al.[1]

PPMS: primary progressive multiple sclerosis; SC: subcutaneous; MS: multiple sclerosis; eod: every other day; CDP: confirmed disability progression; IFNb-1a/1b: interferon beta 1a/1b; IM: intramuscular injection; IV: intravenous; PO: per oral; EDSS: Expanded Disability Status Scale; TWT: timed walk test; NHPT: nine-hole peg test; GA: glatiramer acetate.

[a]The definition of EDSS progression depends on the baseline EDSS score.

[b]In the subset of 31 patients with either PPMS or transitional progressive MS, some hint of efficacy was observed; this motivated the phase 3 trial.

[c]In the subgroup of 72 patients with age <51 years and presence of gadolinium-enhancing lesions in the magnetic resonance imaging (MRI), rituximab significantly delayed progression of disability (vs placebo).

[d]The rationale for the INFORMS trial was provided by in vitro and in vivo studies that suggested that fingolimod could inhibit neurodegeneration. No phase 2 trial was performed with fingolimod in PPMS.

[e]The rationale for the ORATORIO trial was provided by the results of the subgroup analysis of the OLYMPUS trial (in younger patients with inflammatory activity). No phase 2 trial was performed with ocrelizumab in PPMS.

[f]Although the primary endpoint was the percentage of patients with CDP, this percentage was obtained through a time-to-event analysis.

Clinical trials in SPMS Tur & Montalban 2017

Table 1. Main trials in SPMS.

Drug tested (vs placebo)	Trial	Condition (no. of patients randomised)	Duration	Primary endpoint(s)	Results on the primary endpoint	Reference
IFN beta-1b SC 8 million IU eod	Phase 3 (EUSPMS study)[a]	SPMS ($n=718$)	Early termination due to obvious superiority of IFN (initially planned: 39 months)	Time to 3-month CDP on the EDSS[b]	*Positive*	European Study Group on IFN beta-1b in SPMS, phase 3[9]
IFN beta-1a SC 22 µg or 44 µg thrice weekly	Phase 3 (SPECTRIMS study)[a]	SPMS ($n=618$)	36 months	Time to 3-month CDP on the EDSS[b]	Negative	Li et al.[13] (SPECTRIMS Study Group)
IFNb-1b SC 250 µg or 160 µg/m^2 of body surface area eod	Phase 3 (NASPMS study)[a]	SPMS ($n=939$)	Early termination for futility (initially planned: 36 months)	Time to 6-month CDP on the EDSS[b]	Negative	Panitch et al.[14] (North American Study Group on IFN beta-1b in SPMS)
IFN beta-1a IM 60 µg/week	Phase 3 (IMPACT study)[a]	SPMS ($n=436$)	24 months	Change in the MSFC from baseline to 24 months	*Positive*	Cohen et al.,[15] Neurology 2002
IFN beta-1a SC 22 µg/week	Phase 3 (the Nordic SPMS study)[a]	SPMS ($n=371$)	36 months	Time to 6-month CDP on the EDSS[b]	Negative	Andersen et al.[16]
Mitoxantrone IV 12 mg/m^2 or 5 mg/m^2 of body surface area/3 months	Phase 3 (MIMS study)	SPMS or PRMS course ($n=188$)	24 months	Multivariate analysis of five clinical measures: EDSS changes (baseline-final); AI changes (baseline-final); No. of treated relapses; Time to first treated relapse; Change in standardised neurological status.	*Positive*	Hartung et al.[17]
IVIG 1 g/kg/month	Phase 3 (ESIMS study)[c]	SPMS ($n=318$)	24 months	Time to 3-month CDP on the EDSS[b]	Negative	Hommes et al.[7]
MBP8298 IV 500 mg/6 months	Phase 2	SPMS ($n=32$)	24 months	Change in the EDSS from baseline to 24 months	Negative[d]	Warren et al.[11]
MBP8298 IV 500 mg/6 months	Phase 3 (MAESTRO study)[e]	SPMS ($n=612$)	24 months	Time to 6-month CDP on the EDSS[b]	Negative	Freedman et al.[10]
Lamotrigine PO 400 mg/day	Phase 2	SPMS ($n=120$)	24 months	Rate of change of partial (central) cerebral volume over 24 months	Negative	Kapoor et al.,[18] Lancet Neurol 2010
Dronabinol PO (max. dose: 28 mg/day, titrated against bodyweight)	Phase unspecified (CUPID study)	SPMS ($n=302$), PPMS ($n=191$)	36 months	Time to 6-month CDP on the EDSS;[b] Change in the MSIS-29-PHYS from baseline to 36 months.	Negative	Zajicek et al.[19]
Simvastatin PO 80 mg/day	Phase 2	SPMS ($n=140$)	24 months	Annualised rate of whole-brain atrophy	*Positive*	Chataway et al.[4]
Natalizumab IV 300 mg/4 weeks	Phase 3 (ASCEND study)	SPMS ($n=887$)	24 months	Composite outcome: 6-month CDP on EDSS[b], or TWT (≥20%), or NHPT (≥20%)	Negative	Steiner et al.[20]
Biotin PO 100 mg/8 hours	Phase 2	Progressive MS: SPMS ($n=99$) or PPMS ($n=55$)	12 months	Proportion of patients with improvement of MS-related disability[f] at month 9, confirmed at month 12	*Positive*	Tourbah et al.[3]
Siponimod PO 2 mg/day	Phase 3 (EXPAND study)	SPMS ($n=1105$)	37 months	Time to 3-month CDP on the EDSS[b]	*Positive*	Kappos et al.[2]

SPMS: secondary progressive multiple sclerosis; IFNb-1a/1b: interferon beta 1a/1b; SC: subcutaneous; eod: every other day; CDP: confirmed disability progression; IM: intramuscular injection; MSFC: multiple sclerosis functional composite; IV: intravenous; PRMS: progressive–relapsing multiple sclerosis; EDSS: Expanded Disability Status Scale; AI: ambulation index; IVIG: Intravenous Immunoglobulin; PO: per oral; PPMS: primary progressive multiple sclerosis; MSIS-29-PHYS: physical impact subscale of the 29-item multiple sclerosis impact scale; TWT: timed walk test; MS: multiple sclerosis; NHPT: nine-hole peg test.

[a]The rationale for the phase 3 trials with IFNb in SPMS was provided by the results of trials carried out in RRMS.

[b]The definition of EDSS progression depends on the baseline EDSS score.

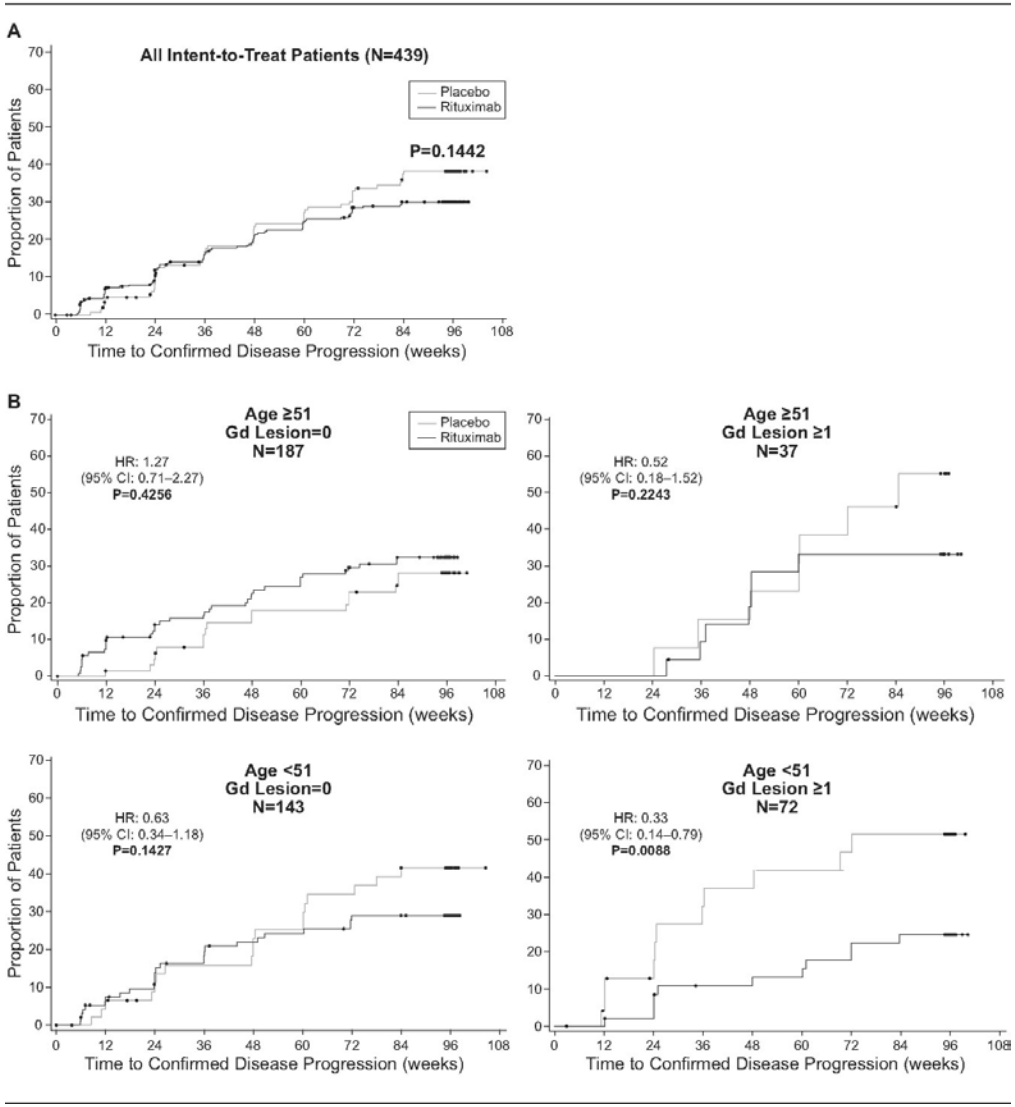
[c]The rationale for the ESIMS trial was provided by the results of uncontrolled studies and placebo-controlled trials in RRMS.

[d]Although the results for the main analysis were negative, in the subgroup of 20 patients with HLA haplotypes DR2 and/or DR4, MBP8298 treatment had a significant effect on the primary endpoint.

[e]The rationale for the MAESTRO study was provided by the results of the subgroup analysis with HLA haplotypes DR2 and/or DR4.

[f]Improvement was defined as follows: decrease of ≥0.5 point or ≥1 point in EDSS (if baseline score was 6–7 or 4.5–5.5, respectively) or a ≥20% decrease in timed walk test (TWT) time, compared with the best EDSS or TWT value recorded at either the screening or the randomisation visit.

Olympus studien: rituximab vid PPMS



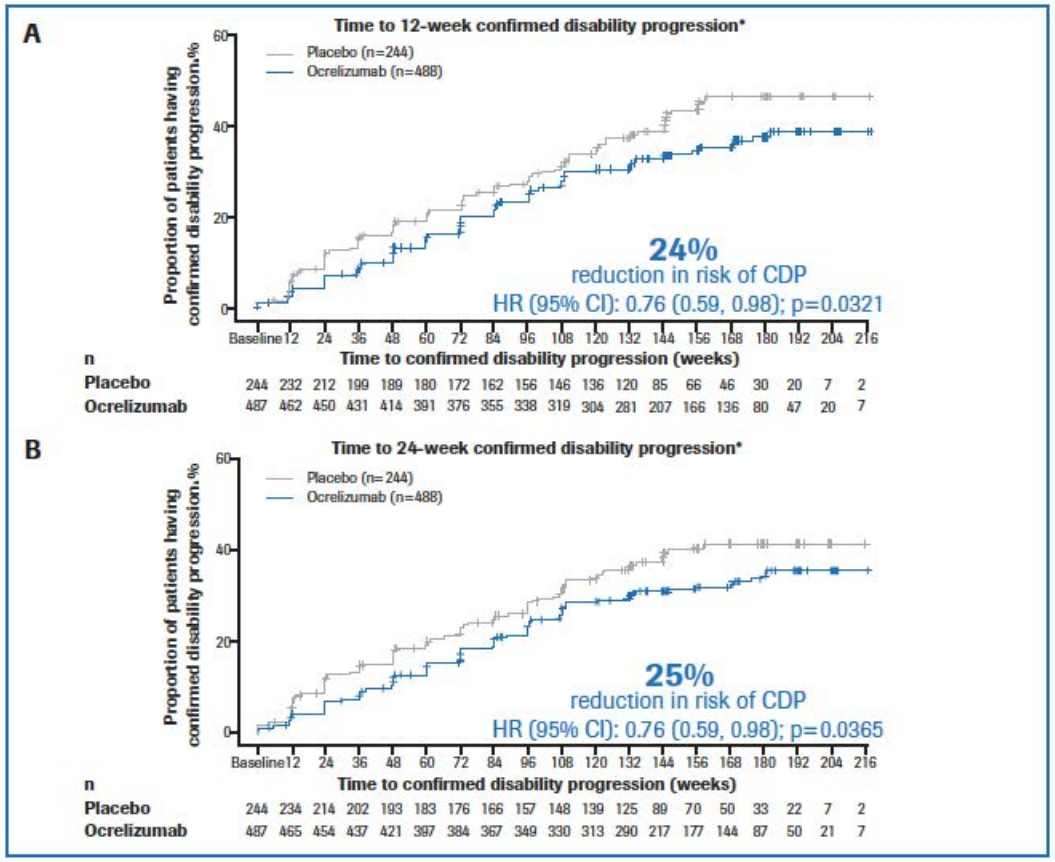
439 PPMS patients received two 1,000 mg intravenous rituximab or placebo infusions every 24 weeks, through 96 weeks (4 courses).

Ann Neurol 2009;66:460–471

ORATORIE studien

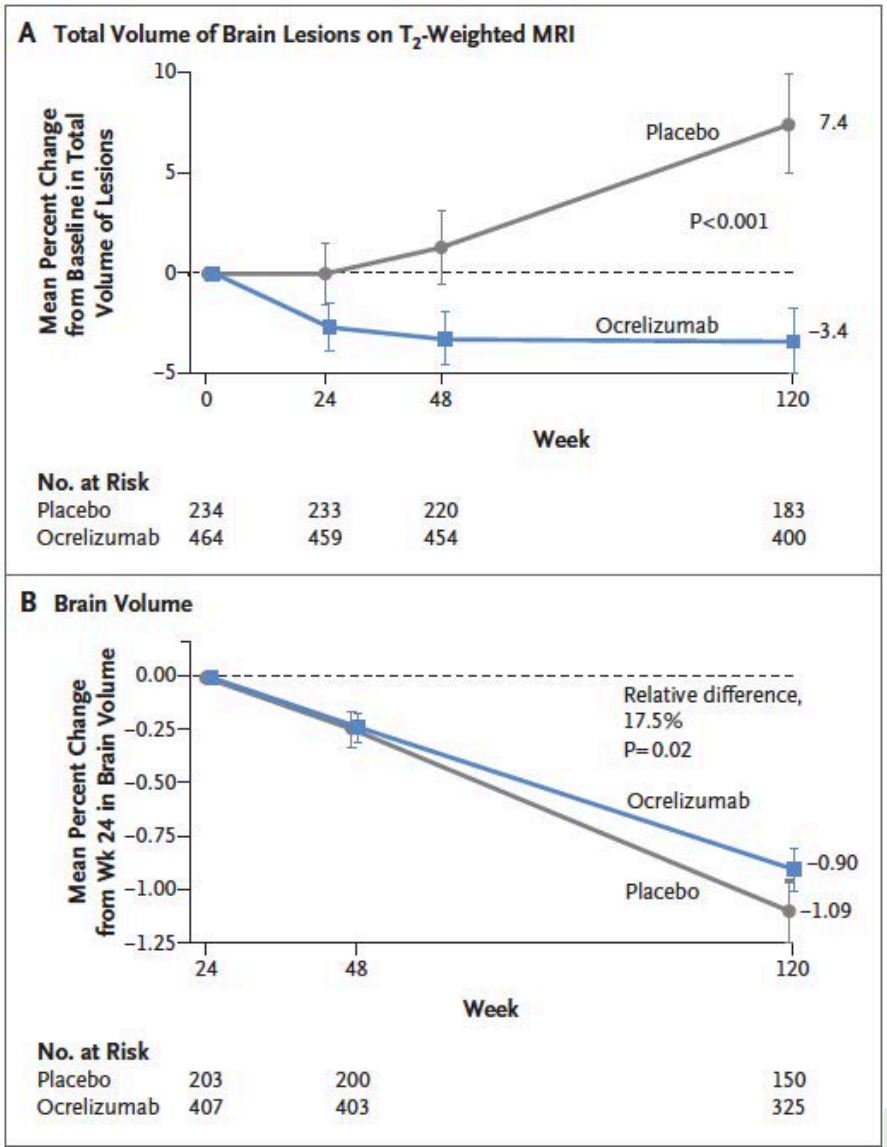
Ocrelizumab vs placebo vid PPMS

Figure 2: Time to onset of disability progression confirmed after ≥12 weeks (A) and ≥24 weeks (B)

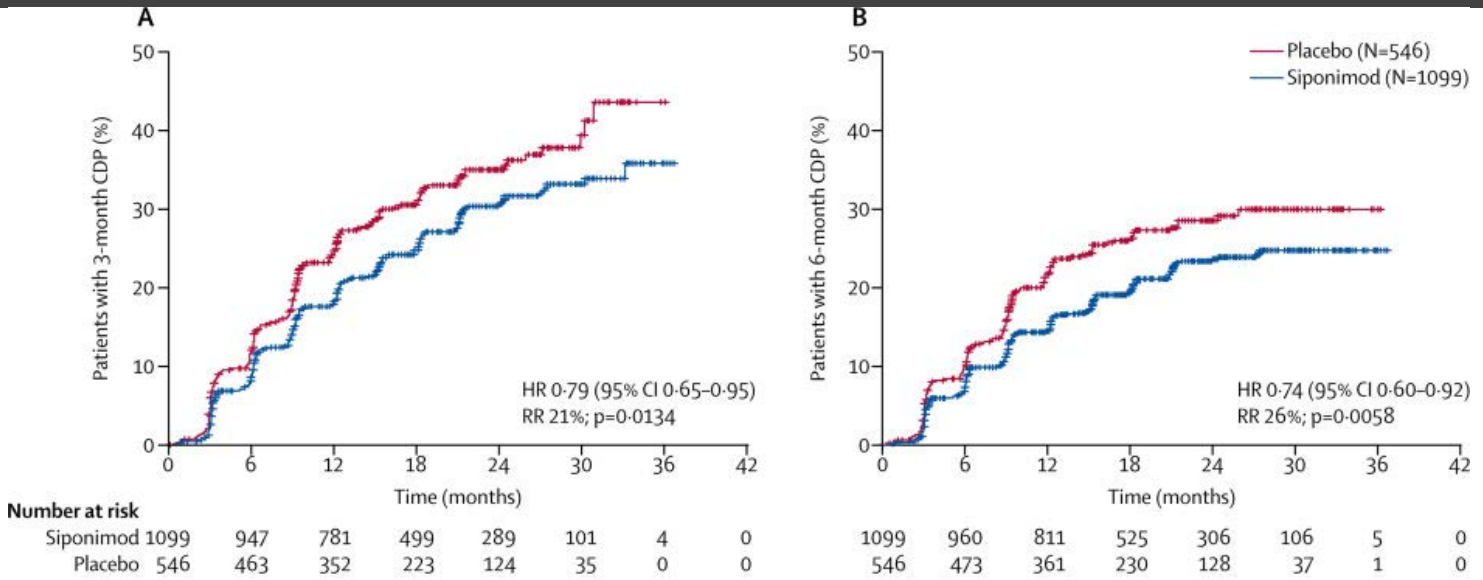


Reduktionen var 35% bland de som hade Gd+ lesioner vid baseline och 16% för de som inte hade det

ORATORIE studien: ocrelizumab påverkade degenerationen vid PPMS

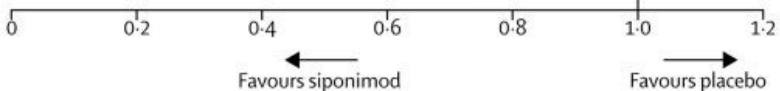


Siponimod minskade progressionen I SPMS
Lancet 2018; 391: 1263–73

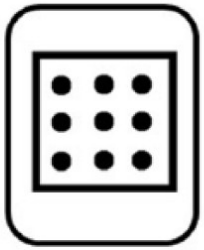


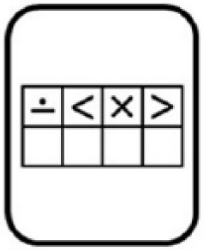
C

	Siponipod (n/N)	Placebo (n/N)	HR (95% CI)
3-month CPD, overall	**288/1099**	**173/546**	**0·79 (0·65–0·95)**
Superimposed relapses in the 2 years before enrolment			
Yes	98/388	72/202	0·67 (0·49–0·91)
no	190/708	101/343	0·87 (0·68–1·11)
Rapid progression			
Yes	82/264	60/145	0·65 (0·46–0·91)
No	206/835	113/400	0·86 (0·69–1·09)
Baseline MSSS ≥4			
Yes	232/904	141/459	0·80 (0·65–0·99)
No	56/195	32/87	0·73 (0·47–1·13)
6-month CPD, overall	**218/1099**	**139/546**	**0·74 (0·60–0·92)**



Utvärdering av progressiv MS behöver andra utvärderingsmetoder?



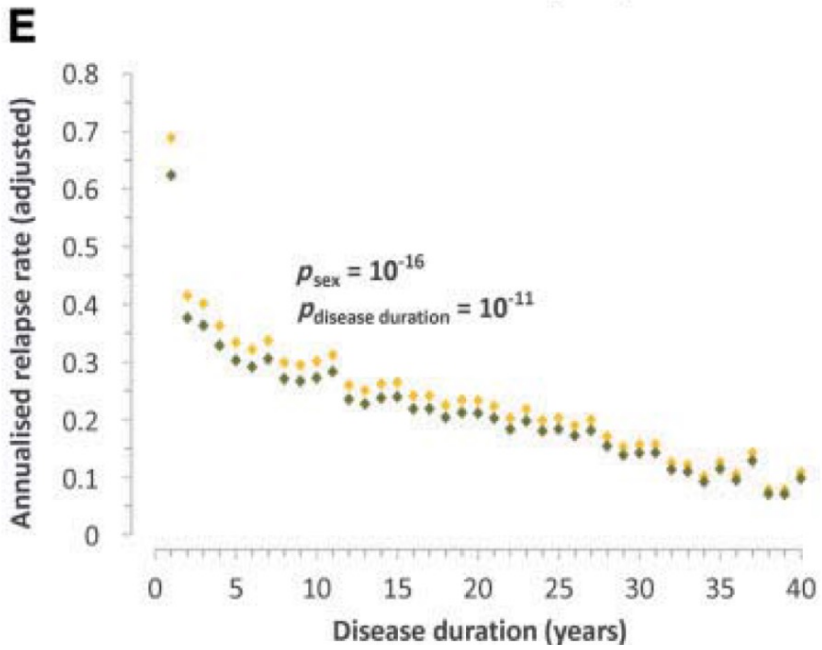


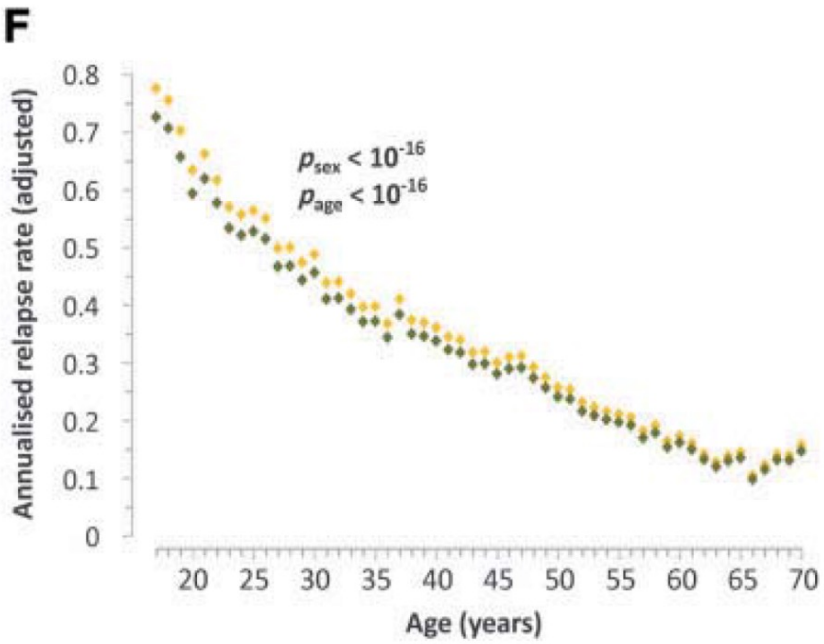
Timed 25 Foot Walk	9 Hole Peg Test	Symbol Digit Modalities Test	Low Contrast Letter Acuity
seconds	seconds	number correct	number correct
Raw Score Units			
20% [a]	15-20% [b]	4 points/10% [c]	7 letters [d]
Thresholds for Meaningful Change			

DMD behandling hos äldre MS

- Immunsystemet åldras
  - Inata immunsystemet intakt
  - Adaptiva immunsystemet åldras kontinuerligt under vuxet liv
- Inflammationsaktiviteten avtar med ålder
  - Färre skov
  - Få nya lesioner
- Komorbiditet
- DMD inte utprovade på personer >55-60 år
- Biverkningskänslig
- Noggrann risk-nytta värdering

Hur förhåller sig sjukdomsduration resp ålder till skovfrekvens?





Kalincik, Brain 2013

Late Onset MS (LOMS)
Very Late Onset MS (VLOMS)

- LOS defined as onset of MS after the age of 50 years, comprises 2.7–12% of MS patients. VLOMS <1%
- Almost 50% had PPMS
  - Subclinical RRMS?
- Ratio of women to men (1.4 : 1)
- Tend to have a motor deficit as the presenting symptom (63–90%)
- Senare debut, kortare duration till SPMS

Förslag I
När immunmodulerande terapi kan avslutas?

- Starta inte terapi vid obehandlad RIS/CIS/RRMS med flera års avsaknad av NEDA
- Starta inte terapi vid SPMS och PPMS med avsaknad av inflammatorisk aktivitet
- Behandling med immuno-rekonstitutions/induktions terapi (AHSCT, alemtuzumab, kladribin) följs upp på sedvanligt sätt.
- RRMS konvertering till SPMS?
  - Äldre (>55-60 år)?
  - NEDA (EDSS stabilt)?
  - Långsamt progressivt förlopp utan inflammatorisk aktivitet?
  - Flera års uppföljning?
  - Risk-nytta värdering?

Förslag II
När immunmodulerande terapi kan avslutas?

- RRMS äldre (55-60 år?) med "första linjens terapi" med flera års NEDA. Uppföljning med 6 månaders intervall första 2 åren.
- RRMS äldre (55-60 år?) med "andra linjens terapi" med flera års NEDA. Kan vara riskfyllt!
  - Öka infusionsintervallen (natalizumab, anti-CD 20 mak)
  - Övergång till "långverkande" DMD (1-2 infusioner anti-CD 20 mak alternativt kladribin)
- SPMS/PPMS yngre (<55-60 år) med fortsatt progression under behandling med avsaknad av inflammatorisk aktivitet. Uppföljning med 6 månaders intervall första 2 åren
- SPMS/PPMS äldre (>55-60 år)?
  - NEDA?
  - Långsamt progressivt förlopp utan inflammatorisk aktivitet?
  - Risk-nytta värdering?
- SPMS/PPMS med manifest svårare funktionsförlust (>7,0-8,0)
  - Långsamt progressivt förlopp utan inflammatorisk aktivitet?
  - Risk-nytta värdering?


Tack!