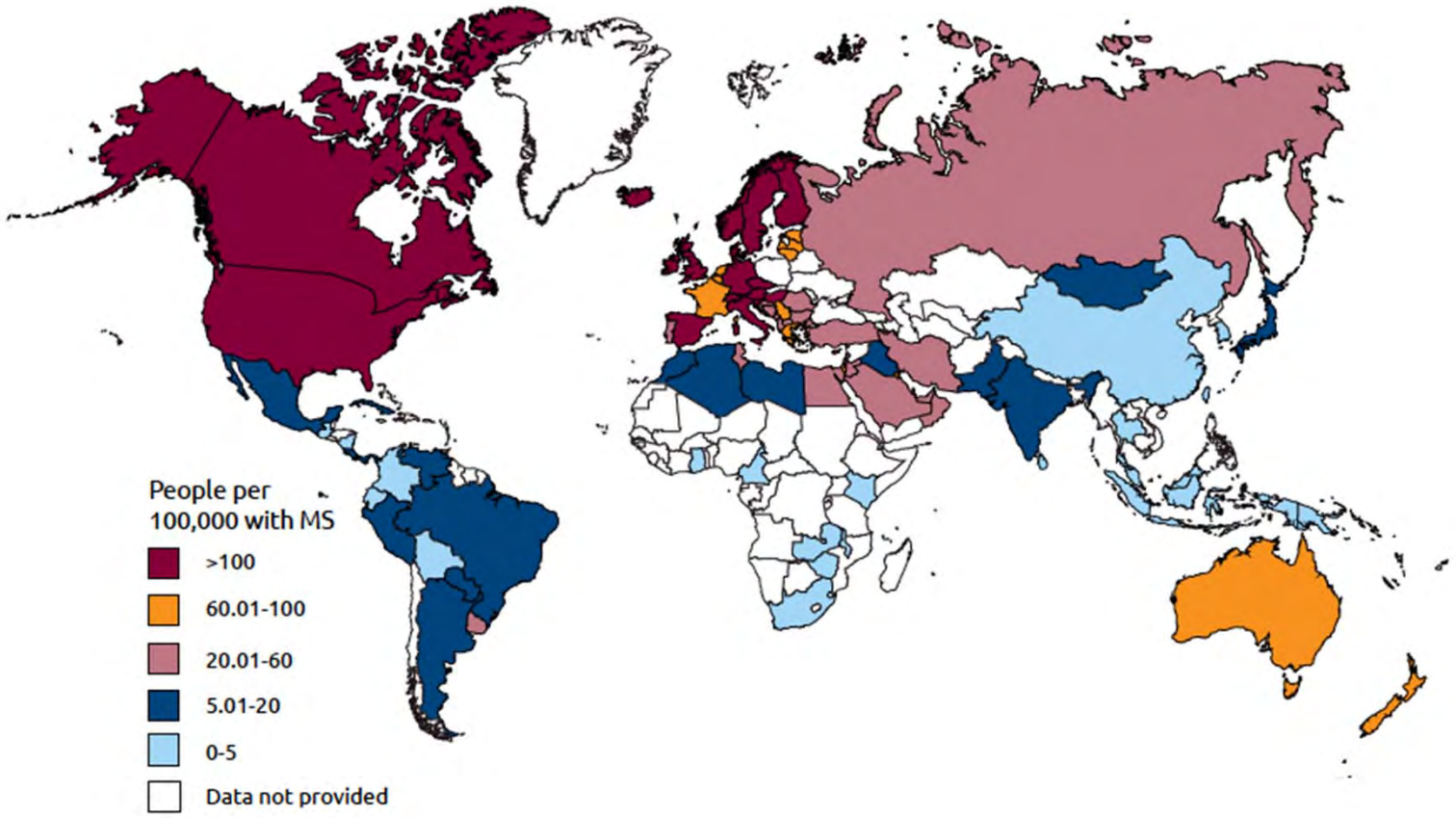
# *"Focus on sclerosi multipla: il Farmacista del SSN tra clinica, terapia e innovazione"*

Palermo, 7 maggio 2015

**Strategie terapeutiche: attualità ed innovazione**

**Luigi M.E. Grimaldi**

# GLOBAL PREVALENCE OF MULTIPLE SCLEROSIS BY COUNTRY (2013)




Data from the Atlas of MS 2013 www.atlasofms.org

# La Sclerosi Multipla a Caccamo

| Abitanti | Pazienti SM | Prevalenza |
|---|---|---|
| 8526 | 21-28 | 246-328/100.000 |

PLOS | ONE

RESEARCH ARTICLE

# Trace Elements in Scalp Hair Samples from Patients with Relapsing-Remitting Multiple Sclerosis

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PLOS ONE | DOI:10.1371/journal.pone.0122142 April 9, 2015

MS patients showed a significantly lower hair concentration of aluminum and rubidium (median values: Al = 3.76 μg/g vs. 4.49 μg/g and Rb = 0.007 μg/g vs. 0.01 μg/g;) and higher hair concentration of U (median values U: 0.014 μg/g vs. 0.007 μg/g) compared to healthy controls.

# Raccomandazioni terapeutiche

Generalità

# Patient Scenario

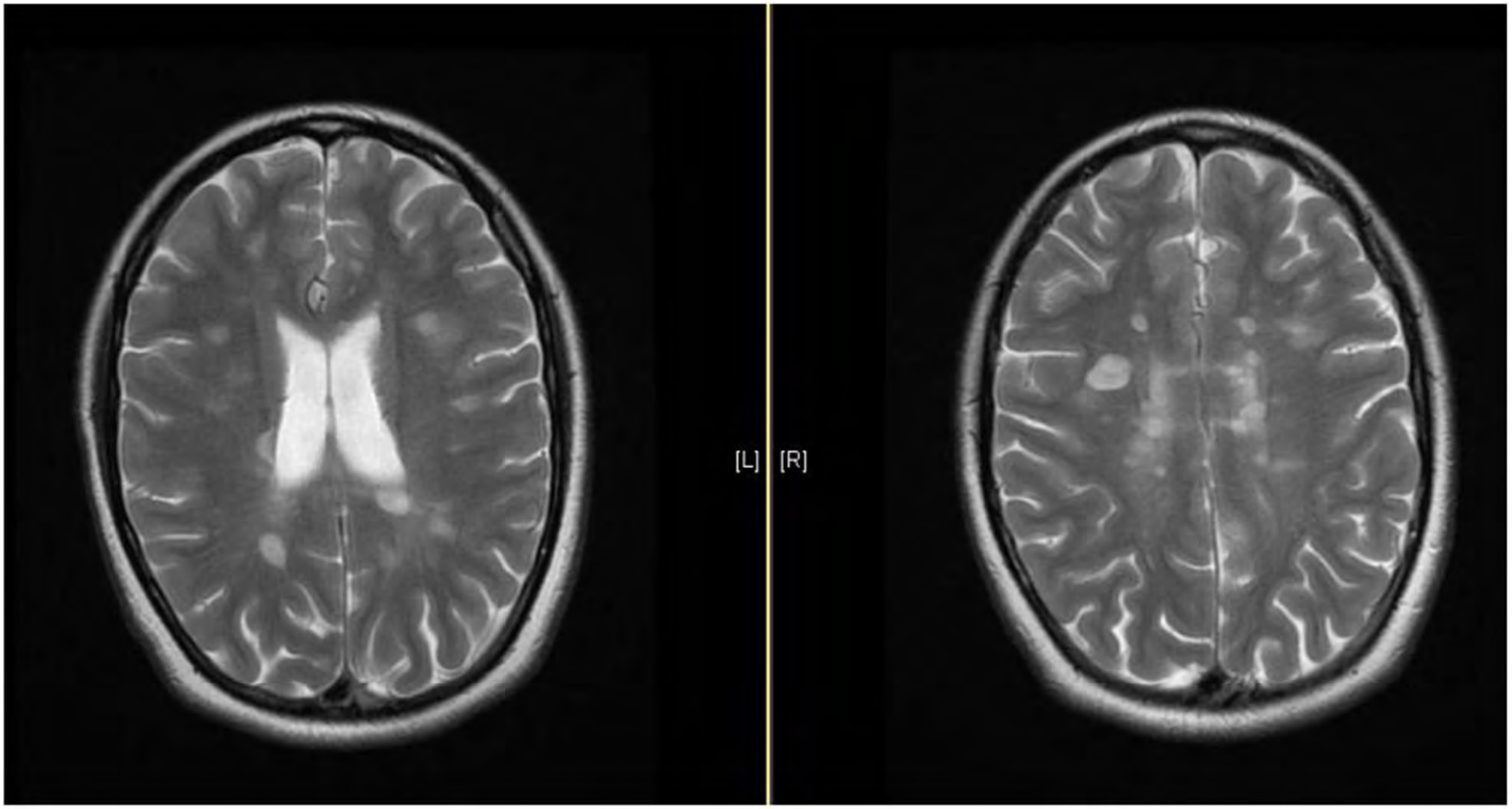
**19-year-old female law student and marathon runner**

**History**


***EDSS 1.0***

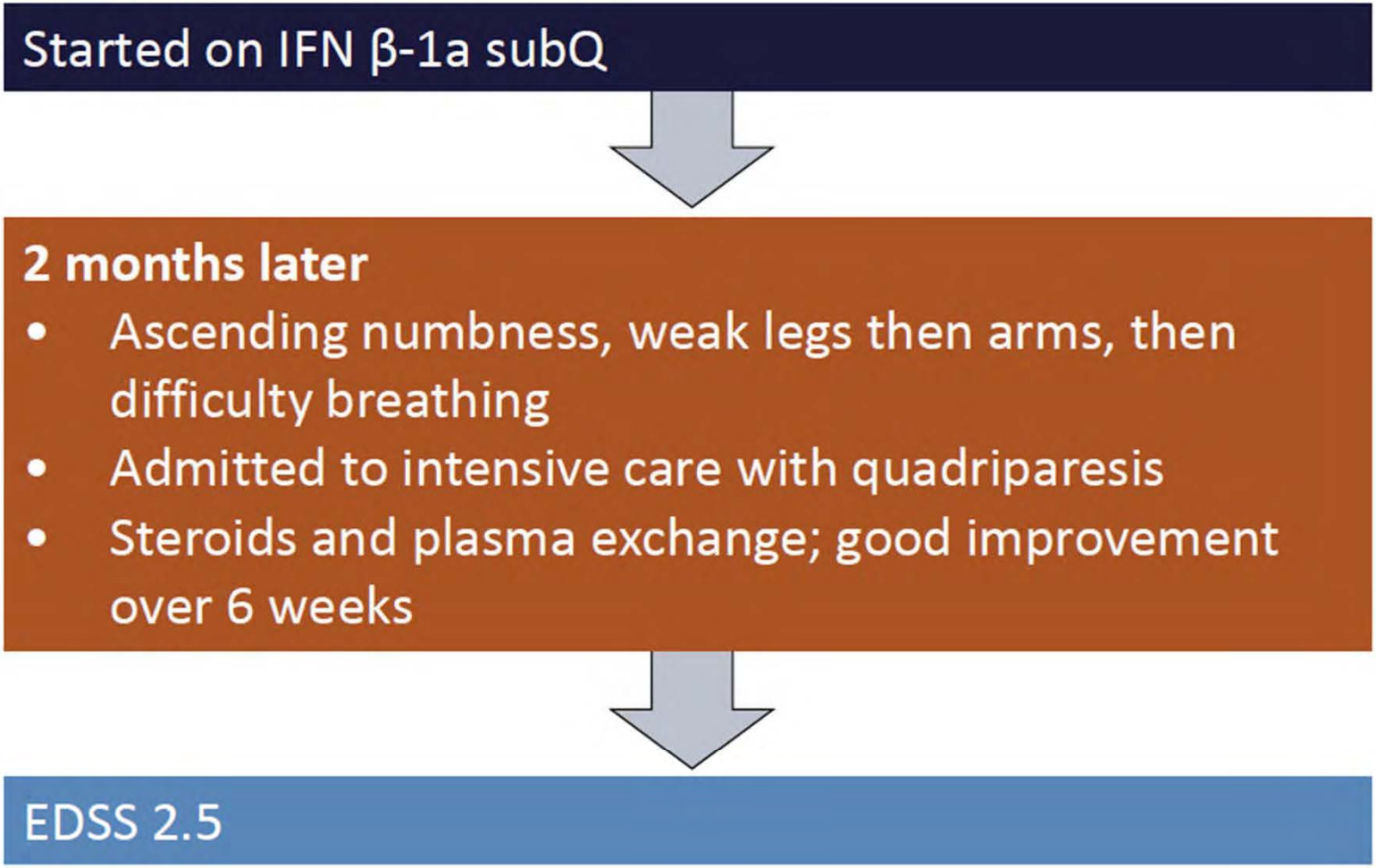
EDSS: Expanded Disability Status Scale.

# Patient Scenario: MRI



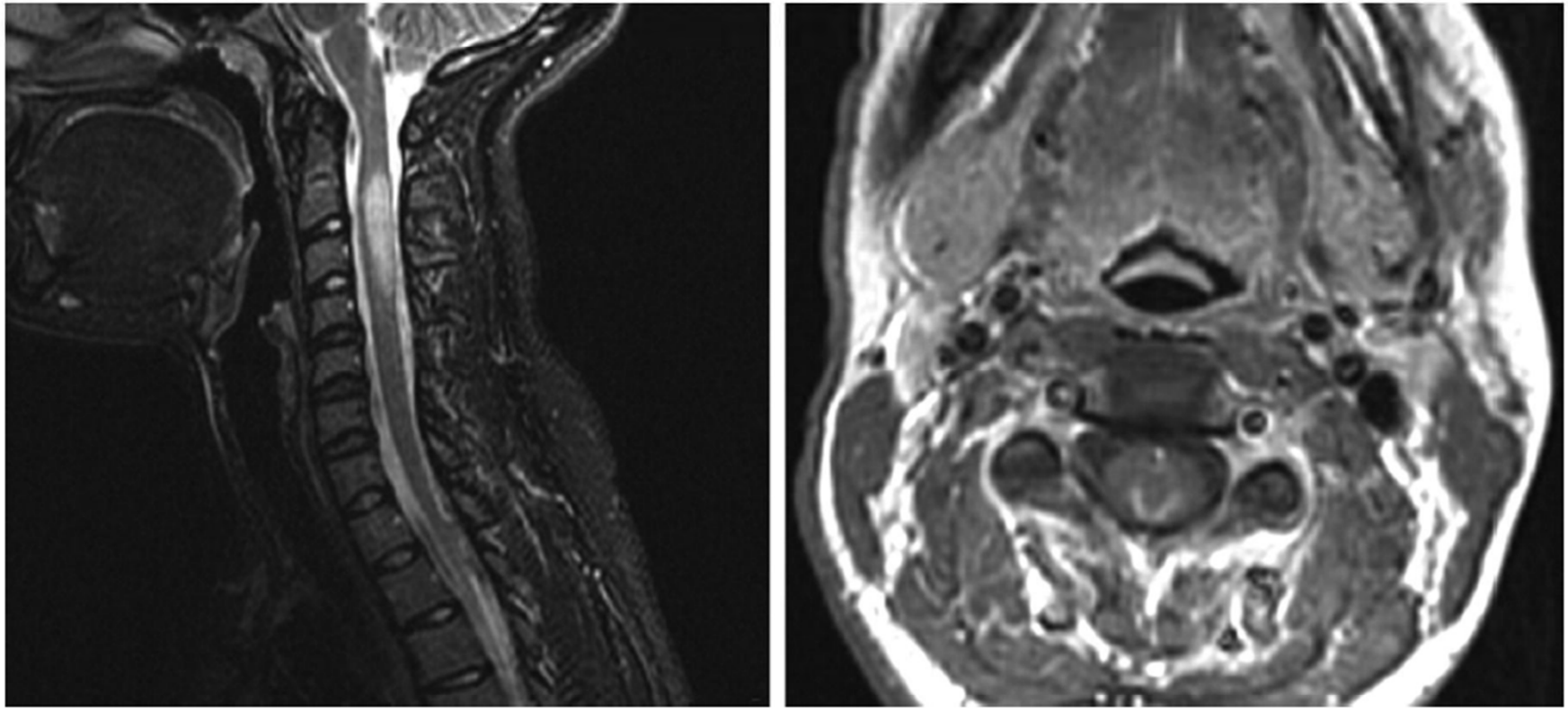

MRI: magnetic resonance imaging.

# Patient Scenario: Treatment




IFN: interferon; subQ: subcutaneous.

# Patient Scenario: MRI



# What Is "Highly Active Disease"?

**RES: "rapidly evolving severe multiple sclerosis"**

- ≥2 disabling relapses in previous year
- ≥1 gadolinium-enhancing MRI lesion or significant increase in MRI T2-lesion load

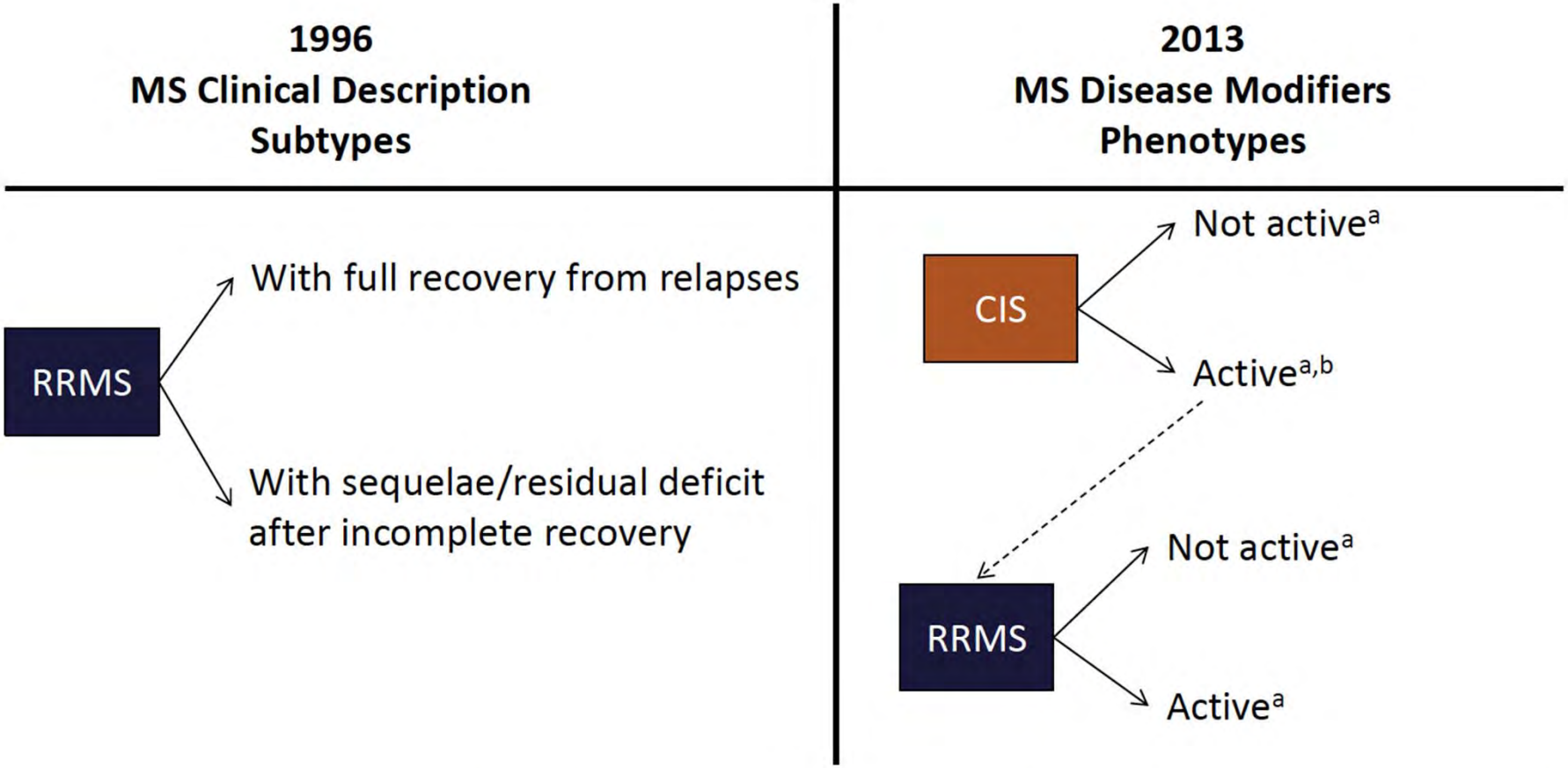
→ *Licensed indication for natalizumab in many regions*

**HAD: "high disease activity despite interferon β"**

- ≥1 relapse in the previous year on interferon β
- ≥1 gadolinium-enhancing MRI lesions or at least nine T2-hyperintense lesions on cranial MRI

→ *Licensed indication for fingolimod in many regions*

# 1996 vs 2013 MS Phenotype Descriptions for Relapsing Disease: Potential Implications on Initial Patient Management[1]

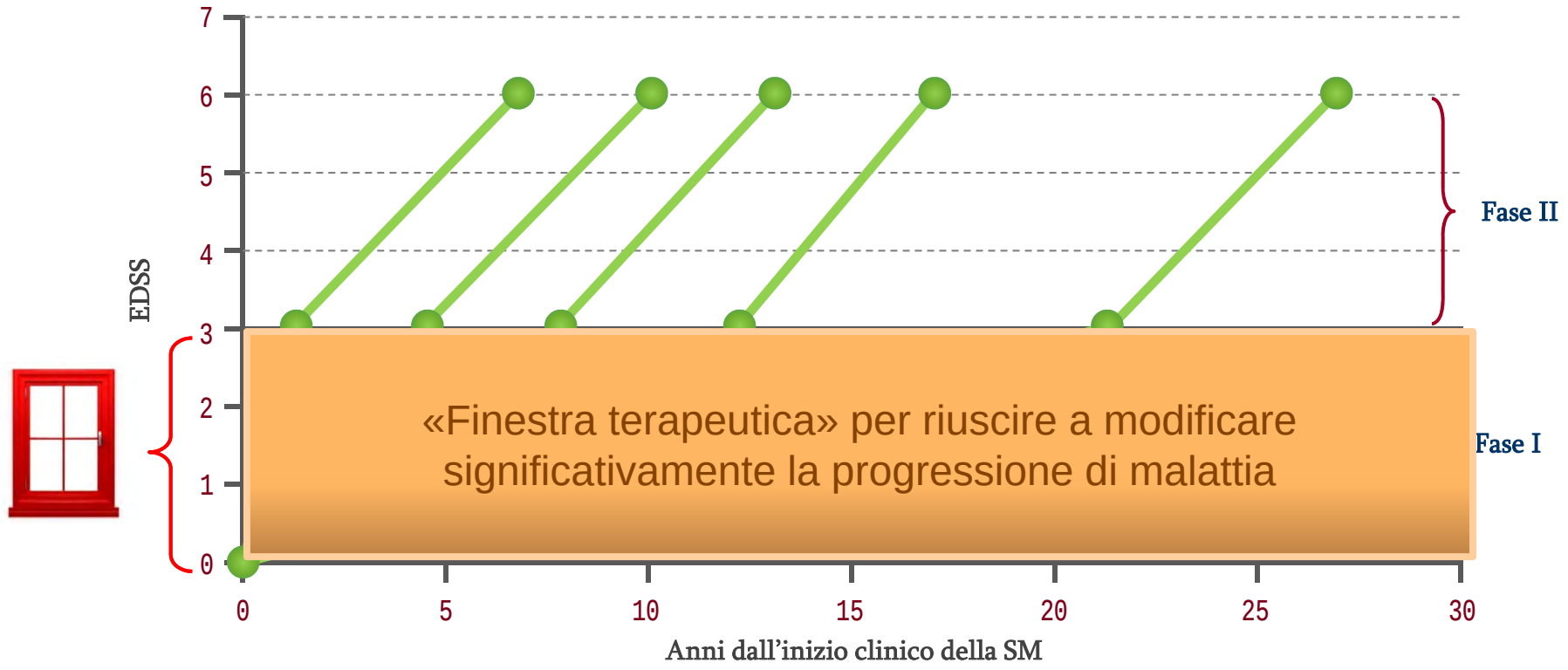



[a] Activity determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually); if assessments are not available, activity is "indeterminate."
[b] CIS; if subsequently clinically active and fulfilling current MS diagnostic criteria, becomes RRMS.

RRMS: relapsing-remitting MS.

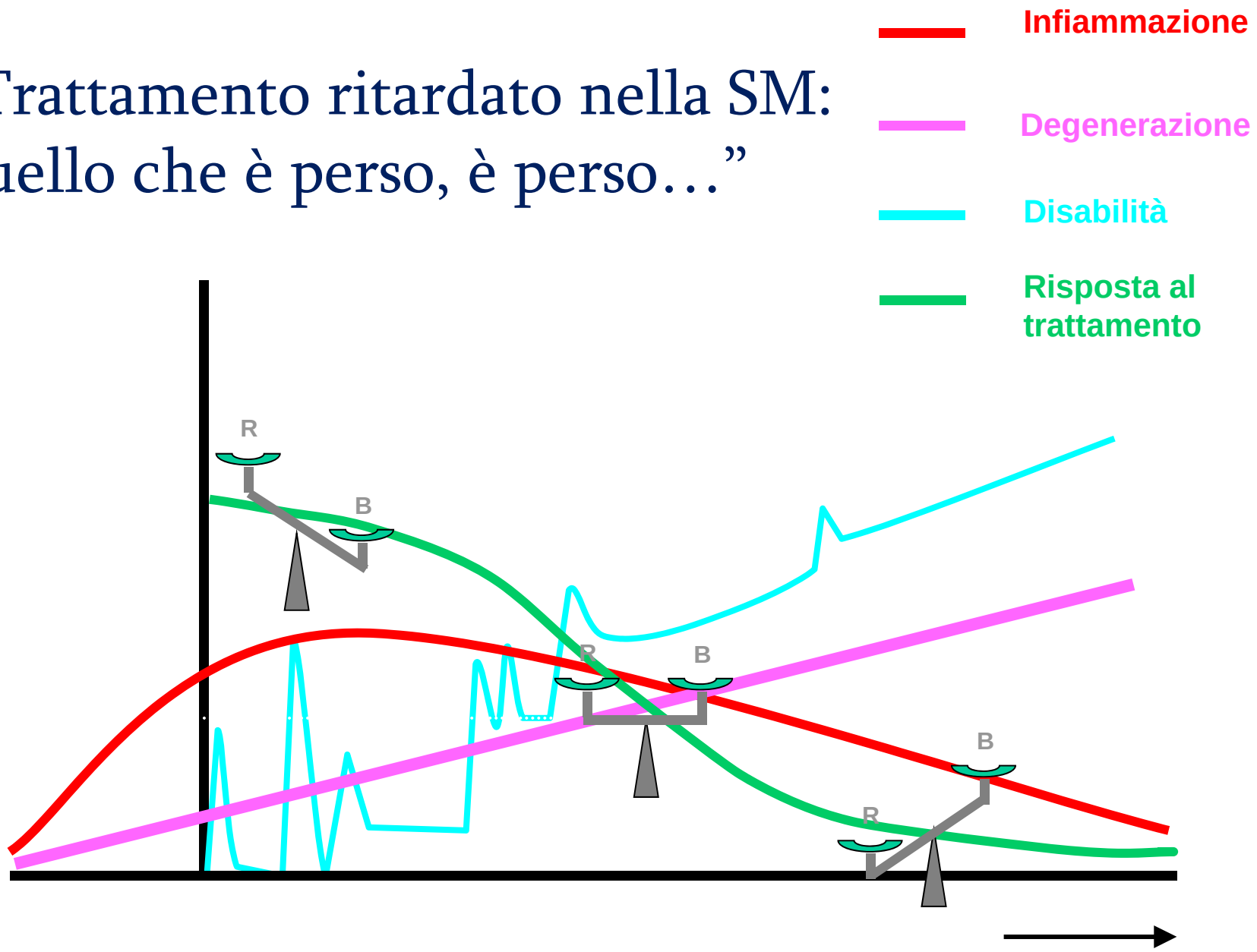
1. Lublin FD et al. *Neurology*. 2014;83:278-286.

# Perché è così importante trattare il più precocemente ed efficacemente possibile?




Leray E. et al. Brain. 2010 Jul;133(Pt 7):1900-13.

# “Trattamento ritardato nella SM: quello che è perso, è perso…”



# Caratteristiche della struttura clinica di appartenenza

**111 *respondent*** facenti capo a **99 centri**

- **71 centri degenza ordinaria***
- **27 centri day hospital***

| **h. Una volta che è stato concordato con il paziente il trattamento *disease modifying* più indicato e il paziente lo ha accettato, qual è il tempo medio prima che il paziente assuma la prima dose di farmaco?** | | | | |
|---|---|---|---|---|
| Interferone beta / glatiramer acetato | media | 10,5 | media | 11,7 |
| | mediana | 7,0 | mediana | 7,0 |
| Teriflunomide | media | 14,2 | media | 13,1 |
| | mediana | 10,0 | mediana | 10,0 |
| Dimetilfumarato | media | 18,7 | media | 13,1 |
| | mediana | 14,0 | mediana | 10,0 |
| Fingolimod | media | 22,5 | media | 24,9 |
| | mediana | 20,0 | mediana | 20,0 |
| Natalizumab | media | 19,6 | media | 21,4 |
| | mediana | 15,0 | mediana | 20,0 |
| Alemtuzumab | media | 33,8 | media | 27,0 |
| | mediana | 20,0 | mediana | 21,0 |

* Dato disponibile per 98 centri

# Treatment Selection and Experience in MS: A Survey of Neurologists[1]

- Survey employed to understand how neurologists (N = 102) make decisions regarding the prescription of DMTs for patients with MS

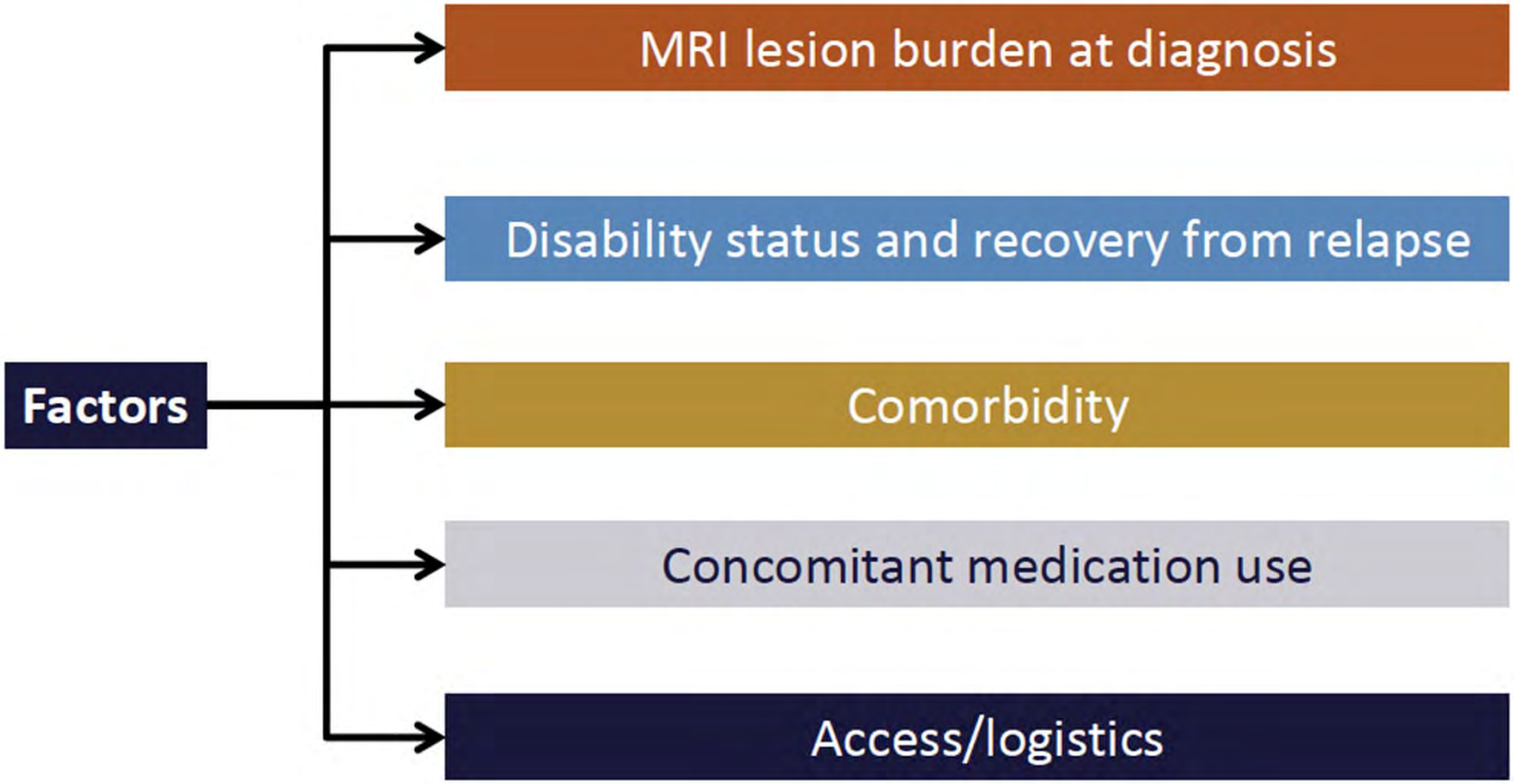
**Important Factors for DMT Selection**

| Rank (Order of Importance) | Factor |
|---|---|
| 1 | Efficacy |
| 2 | Safety |
| 3 | Tolerability |
| 4 | Patient Preference |
| 5 | Convenience (ie, dosing frequency and administration method) |

- Modality with the highest neurologist-reported percentage of patients who were "Very/Extremely Satisfied" with their treatment was oral therapy

1. Hanson KA et al. *Patient Prefer Adherence*. 2014;8:415-422.

# Additional Factors to Consider During Treatment Selection



# Selecting Disease-Modifying Therapy: DCE Results[1]

**Mode of administration** most important attribute guiding patients' preferences, with *'oral application'* being most desired

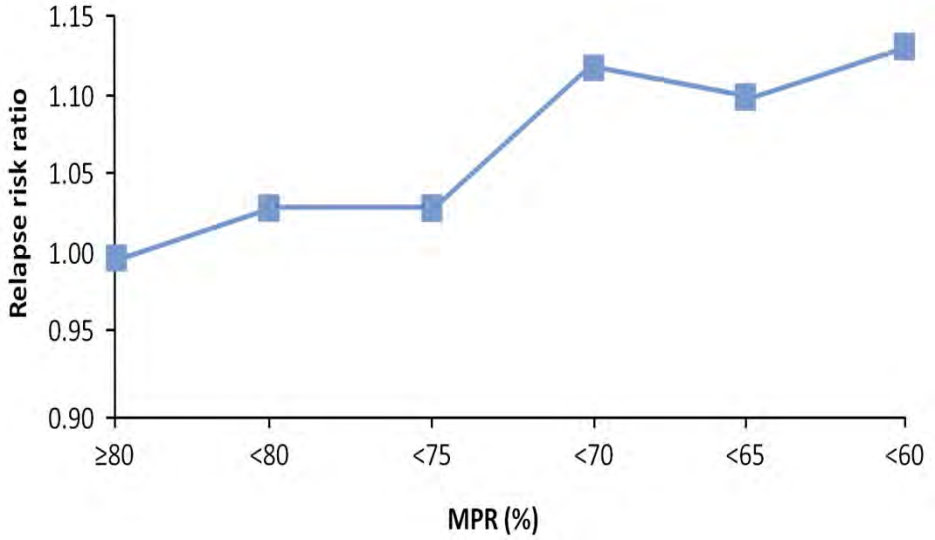
Second most relevant attribute was **frequency of administration**

Another DCE showed efficacy is of primary importance to patients with MS, but drug delivery characteristics can play important role in treatment decision making[2]

1. Bergmann A et al. AAN 2014. Abstract P3.137. 2. Shingler SL et al. *J Med Econ*. 2013;16:1036-1042.

# Poor treatment adherence is associated with greater risk of relapse in MS

- Patients with long gaps in treatment are at greater risk of relapse compared with more adherent patients[1]
- Lower adherence to MS therapy is associated with a higher risk of relapse[2]

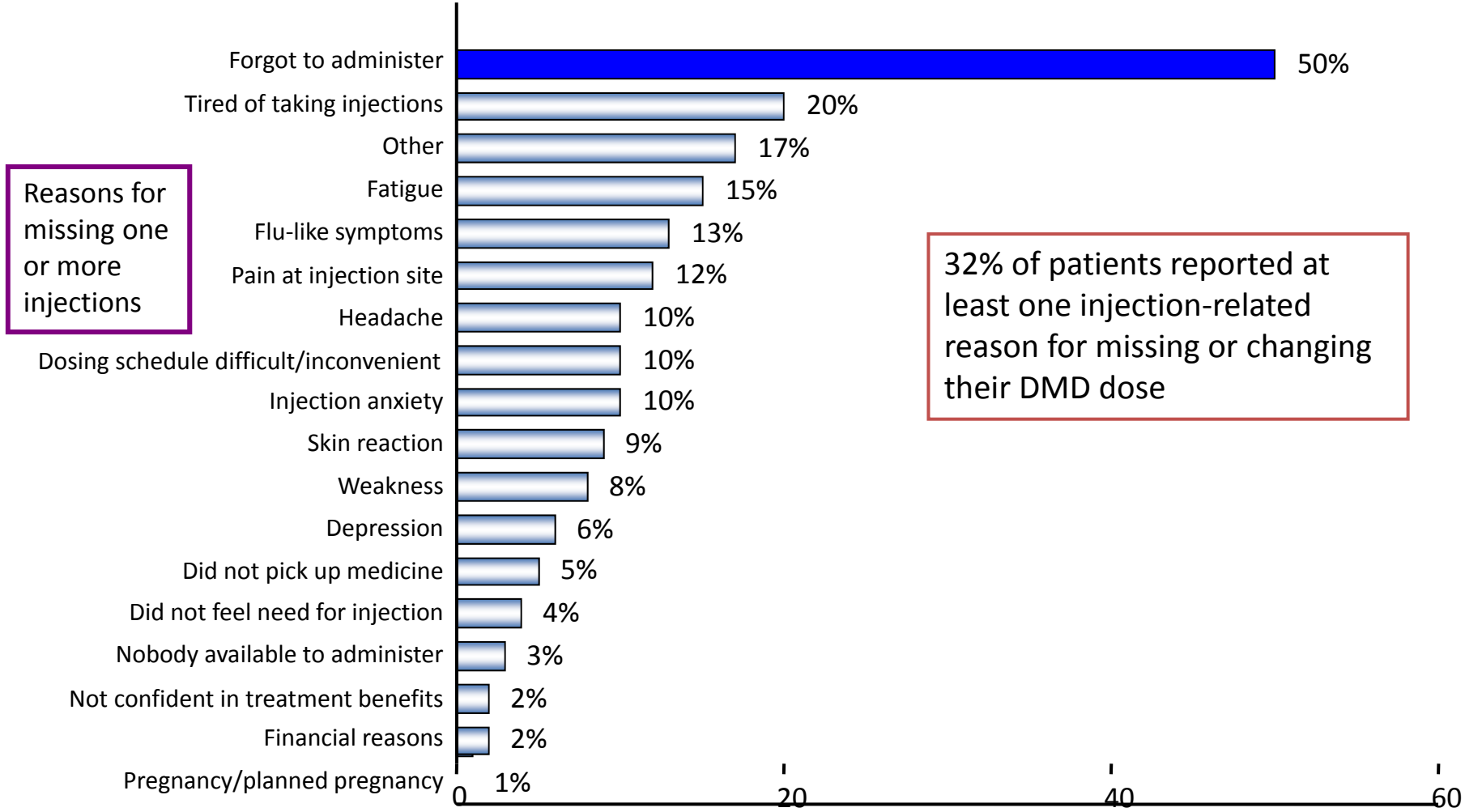



Good adherence is the key to optimizing outcomes

MPR, medication possession ratio

1. Al-Sabbagh A et al. J Neurol 2008;255(Suppl. 2):S79; 2. Steinberg SC et al. Clin Drug Invest 2010;30:89–100

# The GAP study Reasons for non-adherence to injectable therapies




DMD, disease-modifying drug; GAP, global adherence project

Devonshire V et al. Eur J Neurol 2010;18:69–77

# Adherence is not necessarily linked to treatment route

- Chronic diseases: long-term adherence similar with oral or injectable therapy[1]

| Study | | CLARITY[2] 96 weeks | FREEDOMS[3] 24 months | TRANSFORMS[4] 12 months | PRISMS[5] 24 months |
|---|---|---|---|---|---|
| **Drug** | | **Cladribine** | **Fingolimod** | **Fingolimod** | **sc IFN β-1a** |
| Posology | | qd for 5 consecutive days: 3.5 mg/kg, twice a year for 2 years; 5.25 mg/kg, 4 times in year 1, twice in year 2 (po) | 0.5 or 1.25 mg, qd (po) | 0.5 or 1.25 mg, qd (po) | 44 or 22 μg, tiw (sc) |
| Patients randomized, n | | 1326 | 1272 | 1292 | 560 |
| Patients completing study, n (%) | Total | 1184 (89) | 1033 (81) | 1153 (89) | 533 (95) |
| | Low dose | 398 (92) | 369 (87) | 398 (93) | 177 (94) |
| | High dose | 406 (89) | 333 (78) | 369 (88) | 179 (97) |
| | Placebo* | 380 (87) | 332 (80) | 386 (90)* | 177 (95) |
| Patients completing treatment, n (%) | Total | 1165 (88) | 945 (74) | 1123 (87) | 502 (90) |
| | Low dose | 91%† | 345 (81) | 385 (90) | 167 (88) |
| | High dose | 86%† | 298 (70) | 358 (85) | 165 (90) |
| | Placebo* | 86%† | 303 (73) | 380 (88)* | 170 (91) |

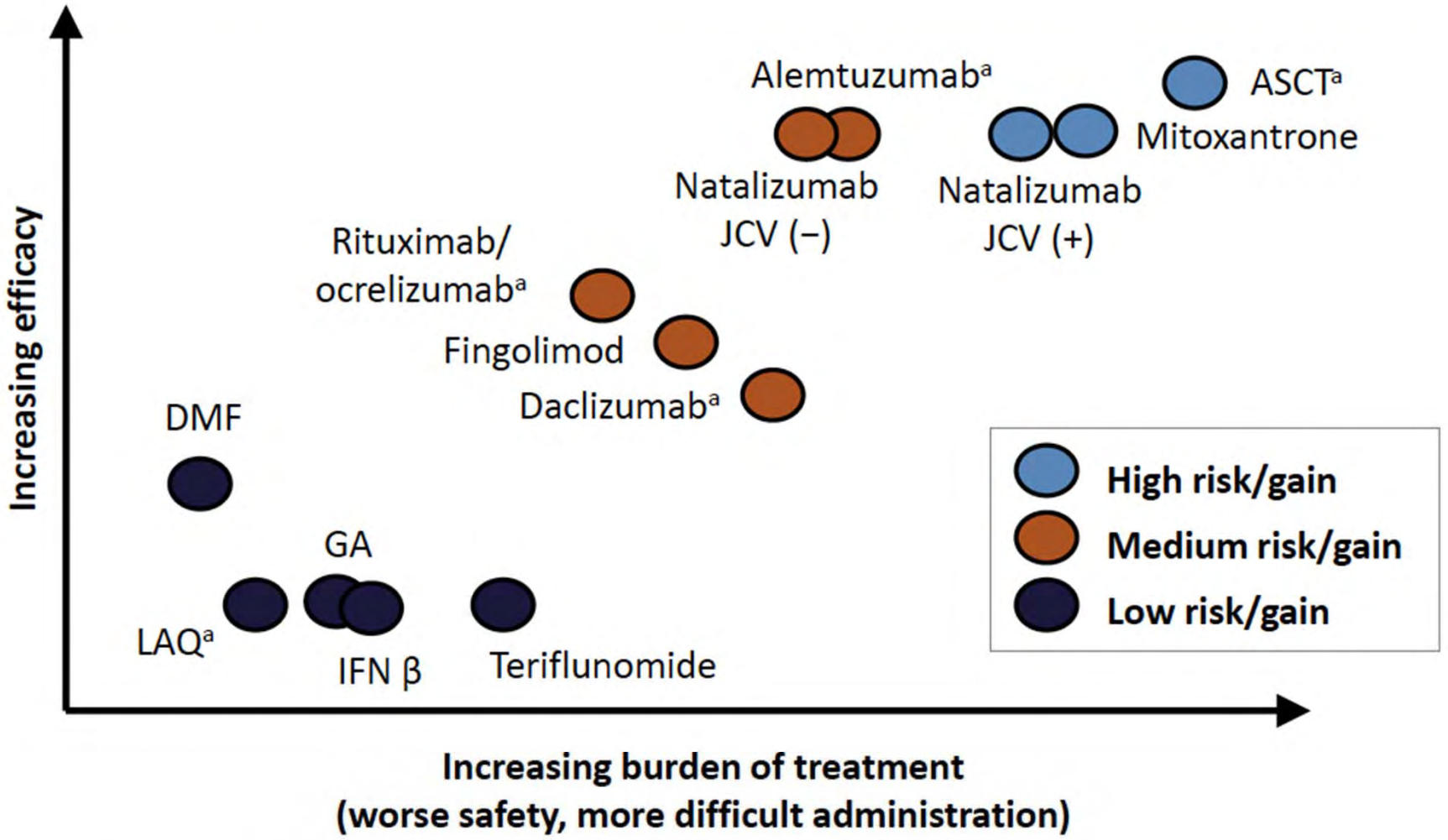
*IFN in the TRANSFORMS study; †n not provided in publication
AE, adverse event; im, intramuscular; po, orally; qd, once daily; sc, subcutaneous; tiw, three times weekly

1. WHO. Adherence to Long-term Therapies: Evidence for Action. 2003 (http://whqlibdoc.who.int/publications/2003/9241545992.pdf);
2. Giovannoni G et al. N Engl J Med 2010;362:416–26; 3. Kappos L et al. N Engl J Med 2006;355: 1124–40; 4. Cohen JA et al. N Engl J Med 2010;362:402–15;
5. PRISMS Study Group. Lancet 1998;352:1498–504

# Raccomandazioni terapeutiche

Specifiche per DMT

# Risk/Gain Comparison of Different Therapies[a] for MS[1]




[a] Not available or licensed in all regions.

ASCT: autologous stem cell transplantation; DMF: dimethyl fumarate; GA: glatiramer acetate; JCV: JC virus; LAQ: laquinimod; MS: multiple sclerosis.

1. Modified from Hauser SL et al. *Ann Neurol.* 2013;74:317-327.

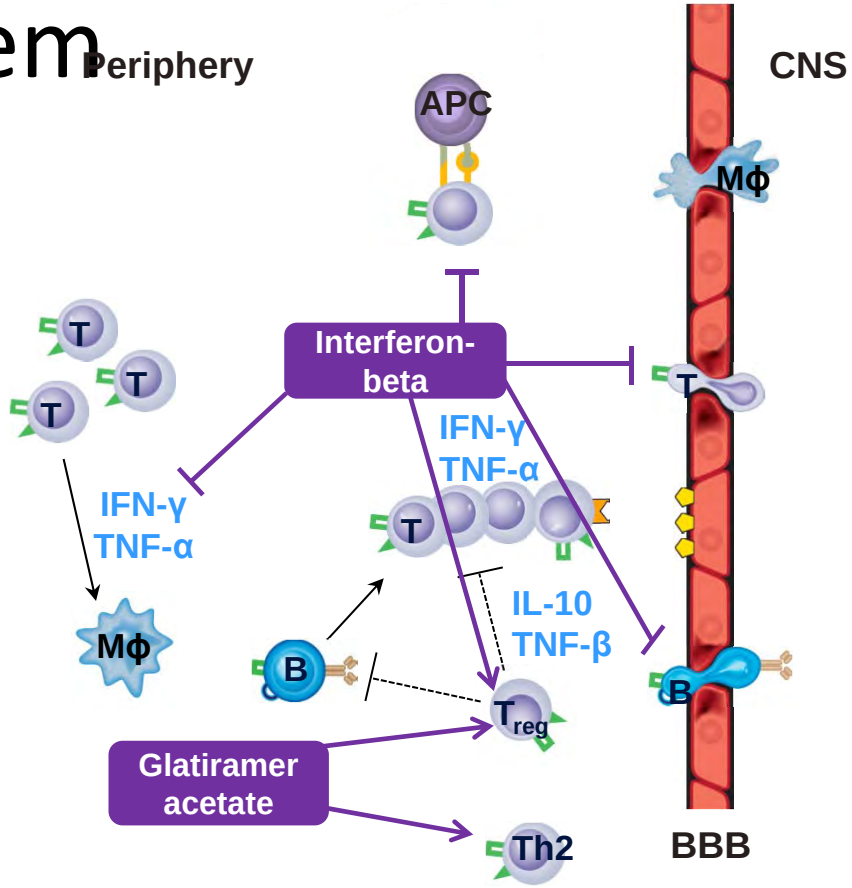
# Traditional Therapies for RRMS Have Generalized Effects on the Immune System

## Proposed effects of IFNB-1b[1]

- Enhancement of suppressor T-cell activity
- Reduction of pro-inflammatory cytokine production
- Down-regulation of antigen presentation
- Inhibition of lymphocyte trafficking to the CNS
- It is not known if these effects play an important role in the observed clinical activity of IFNB-1b in MS

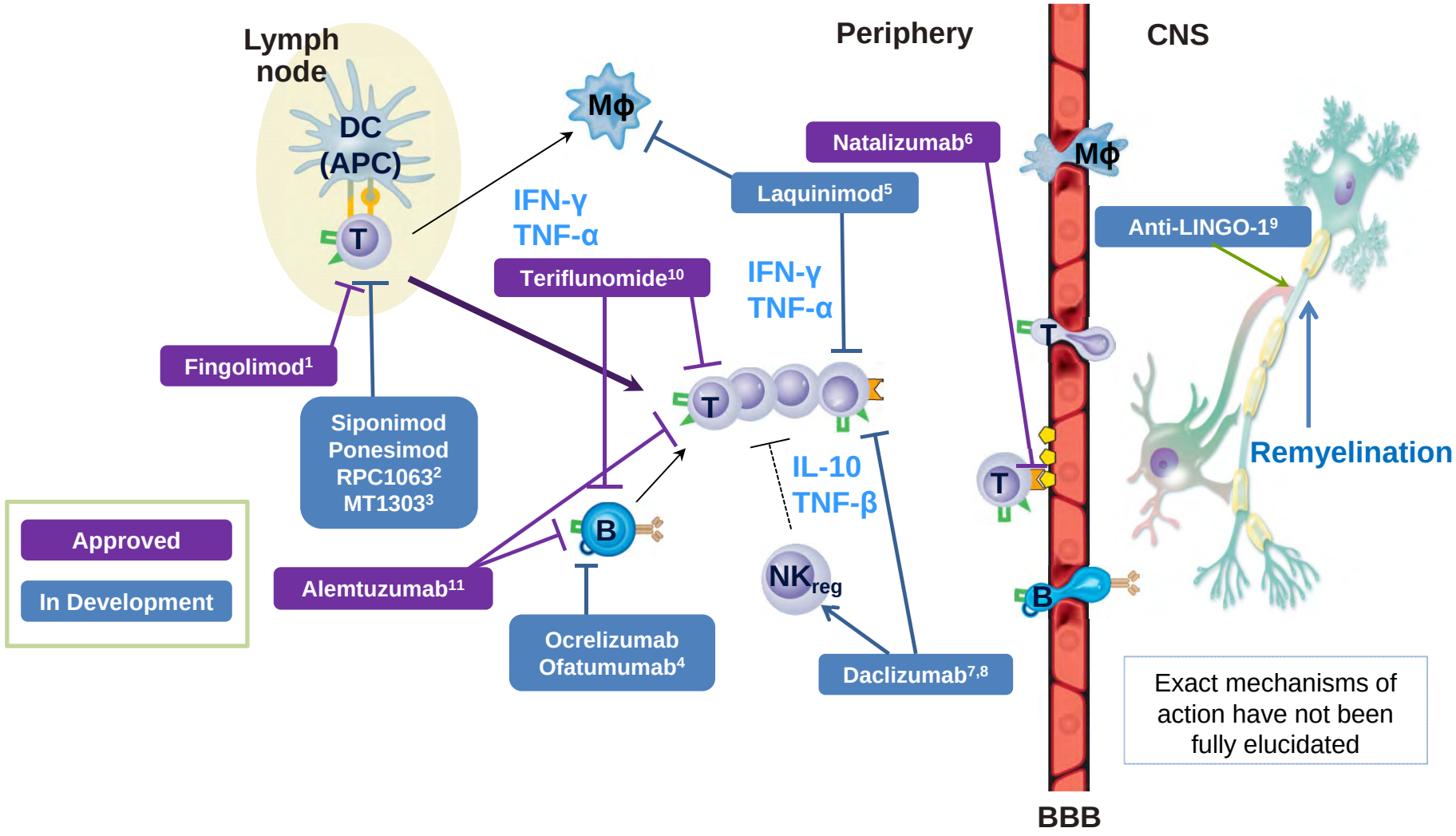
## Proposed effects of glatiramer acetate[2]

- Modulation of immune processes believed to be responsible for MS pathogenesis
- Potential activation of suppressor T cells in the periphery (based on animal and in vitro systems)
- The mechanisms by which GA exerts its effects in patients with MS are not fully understood




Exact mechanisms of action have not been fully elucidated

# Newer Agents (Approved and in Development) Have Specific Targets



# Efficacy of Injectable DMTs in CIS

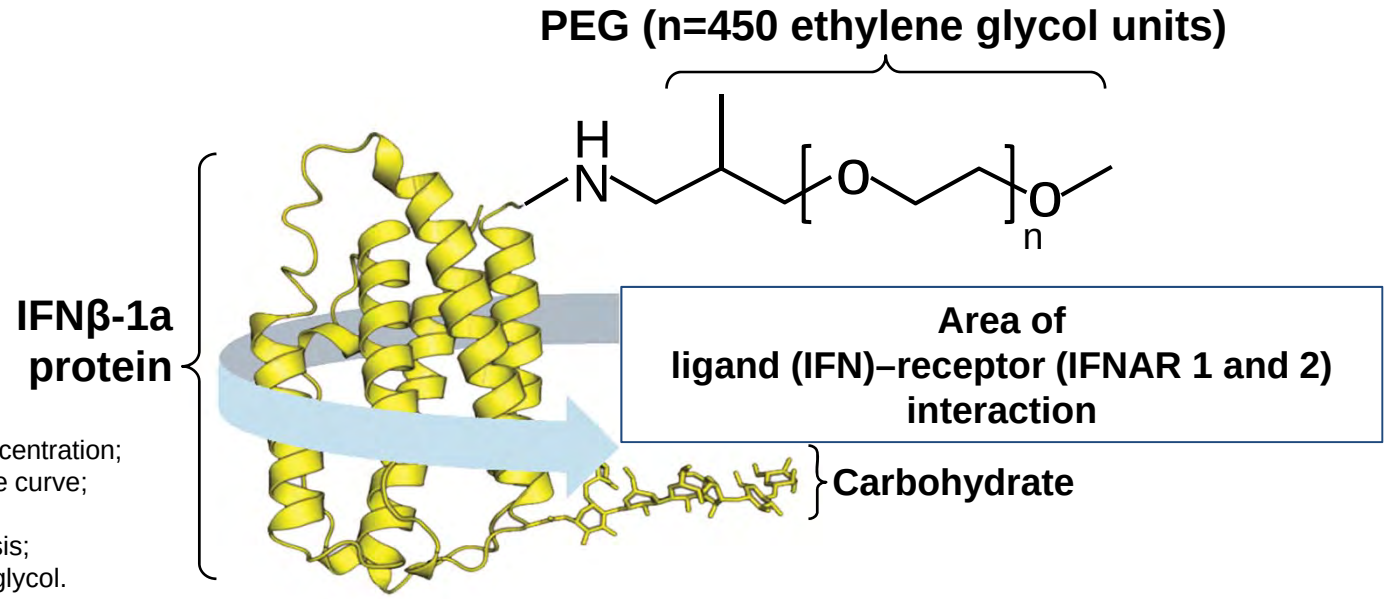
| Study | Treatment Arms | Clinical Outcome |
|---|---|---|
| **CHAMPS**[1] (N = 383) | IFN β-1a 30 mcg IM 1x/wk vs PBO | • IFN β-1a IM reduced risk for CDMS compared with PBO; rate ratio = 0.56: *P* = .002 |
| **BENEFIT**[2] (N = 468) | IFN β-1b 250 mcg subQ every other day vs PBO | • IFN β-1b reduced risk for CDMS by 50% compared with PBO (*P* < .0001) |
| **PRECISE**[3] (N = 481) | GA 20 mg/day subQ vs PBO | • GA reduced risk for CDMS by 45% compared with PBO (*P* = .0005) |
| **REFLEX**[4] (N = 517) | IFN β-1a 44 mcg 3x/wk subQ or IFN β-1a 44 mcg 1x/wk subQ vs PBO | • IFN β-1a 3x/wk reduced risk for CDMS by 52% compared with PBO (*P* = .0004)<br>• IFN β-1a 1x/wk reduced risk for CDMS by 47% compared with PBO (*P* = .0023) |

IFN: interferon; IM: intramuscular; GA: glatiramer acetate; PBO: placebo; subQ: subcutaneous.

1. Jacobs LD et al. *N Engl J Med*. 2000;343:898-904. 2. Kappos L et al. *Neurology*. 2006;67:1242-1249. 3. Comi G et al. *Lancet*. 2009;374:1503-1511. 4. Comi G et al. *Lancet Neurol*. 2012;11:33-41.

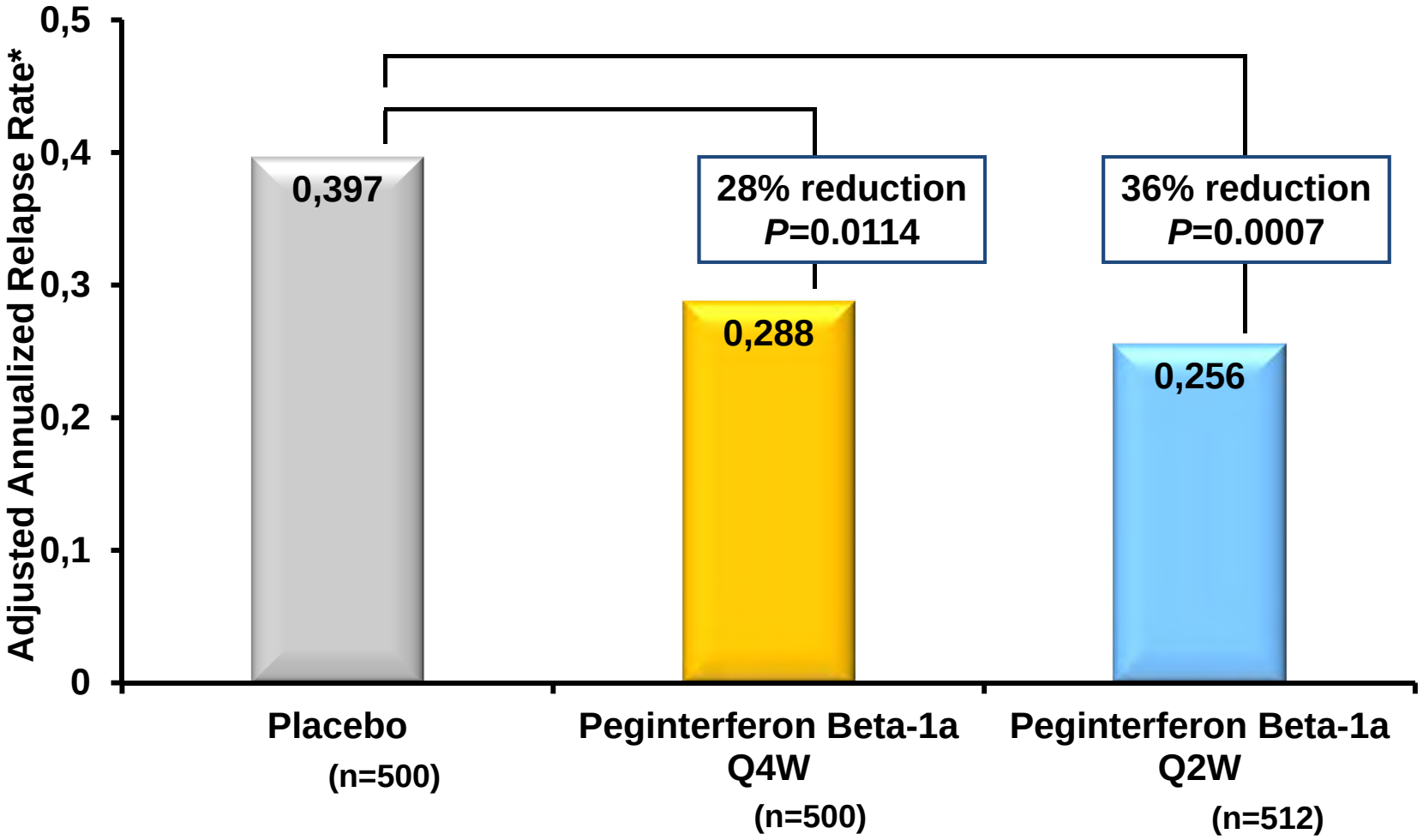
# PEGYLATED INTERFERON BETA-1A

- Pegylated form of interferon beta-1a (IFNβ-1a)
  - Longer half life and greater exposure ($C_{max}$ and AUC) than unmodified IFNβ-1a
  - Reduced frequency of administration while maintaining efficacy and safety of beta interferon in relapsing MS




$C_{max}$=maximum concentration;
AUC=area under the curve;
IFN=interferon
MS=multiple sclerosis;
PEG=polyethylene glycol.

# Phase 3 ADVANCE: Primary Endpoint Annualized Relapse Rate

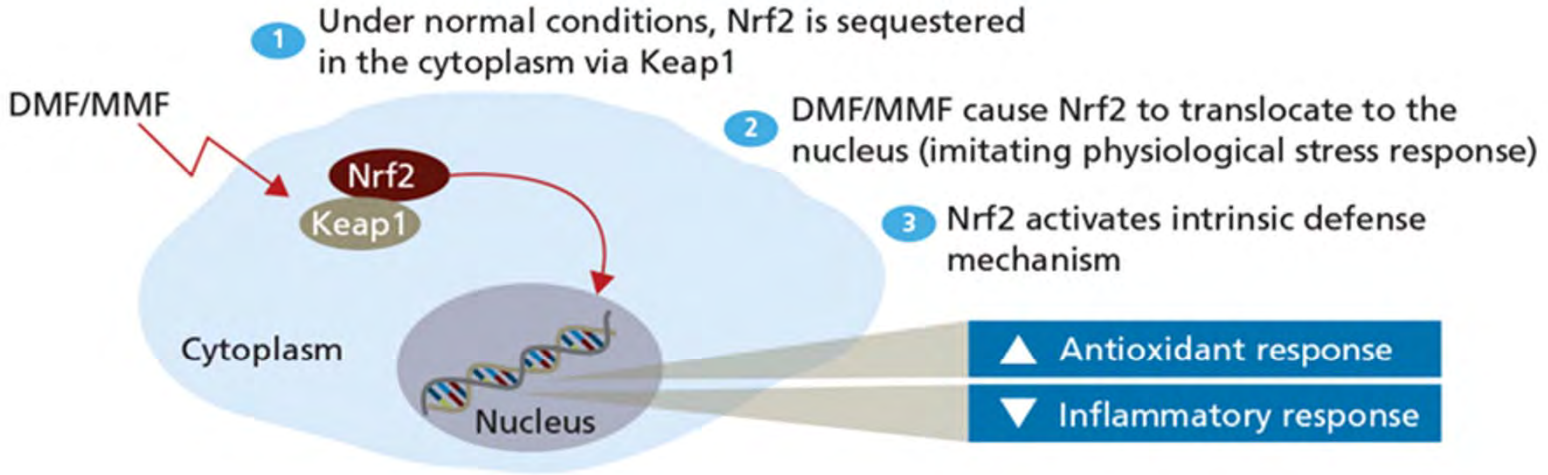



*Based on negative binomial regression; adjusted for baseline EDSS score (<4, ≥4), baseline relapse rate, age (<40 years, ≥40 years).
Calabresi PA et al. ECTRIMS 2013.

# Dimethyl Fumarate (DMF): Mechanism of Action

- **Dimethyl fumarate[1]**
  - Is an ester of fumaric acid, a naturally occurring molecule essential for oxidative respiration (Krebs cycle)
  - Formulated as enteric-coated microtablet (120 mg, 240 mg)
  - Rapidly converted presystemically to monomethyl fumarate (MMF)

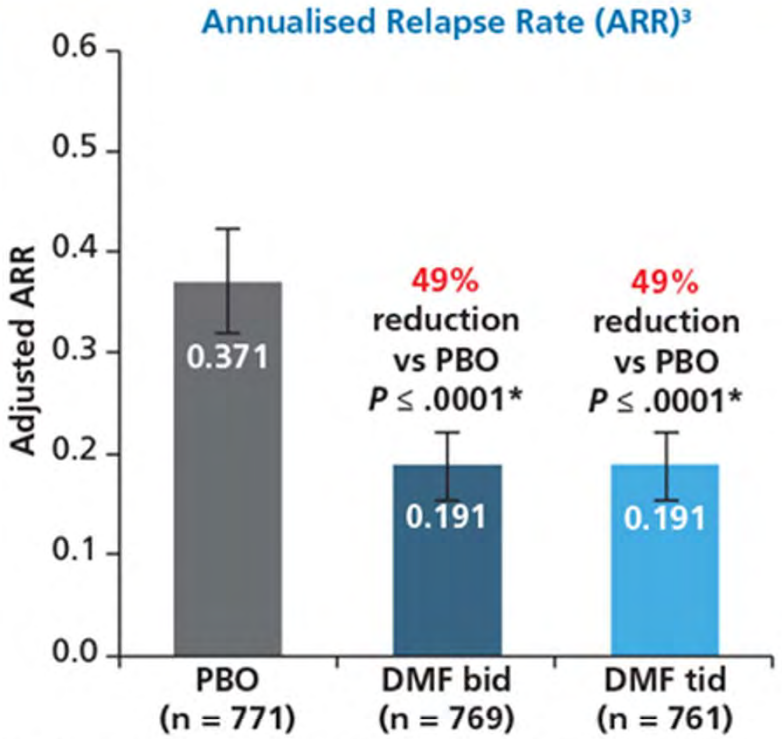
## Upregulating the Nrf2 Pathway to Induce Antioxidant Response and Decrease Inflammatory Response[a,2]




[a] The exact mechanism by which dimethyl fumarate exerts its therapeutic effect in MS is not fully understood.

# DEFINE and CONFIRM Integrated Analysis[a]: Relapse Outcomes With Dimethyl Fumarate

| 2-Year Multicentre, Double-Blind, PBO-Controlled, Dose-Comparison Studies | |
|---|---|
| **DEFINE[1]** | **CONFIRM[2,b]** |
| N = 1,237<br>MRI cohort, N = 540 | N = 1,430<br>MRI cohort, N = 681 |
| **Arms** | |
| DMF 240 mg bid<br>DMF 240 mg tid<br>PBO | DMF 240 mg bid<br>DMF 240 mg tid<br>PBO<br>GA (reference) |

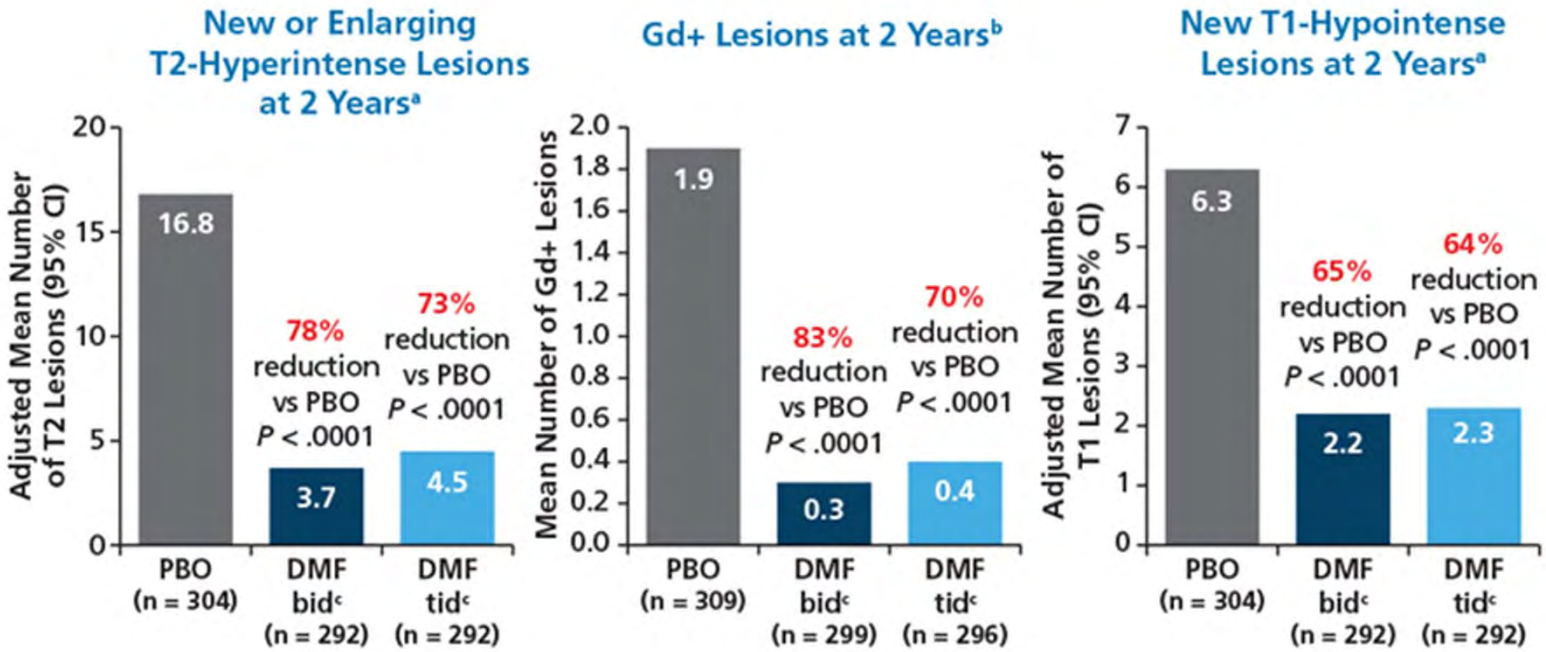



* *P* value based on Poisson regression (due to underdispersion using negative binomial distribution) adjusted for baseline EDSS score (≤2.0 vs >2.0), study, region, number of relapses in the 1 year prior to study entry, and baseline age (<40 vs ≥40 years).

[a] Integrated ITT population; only relapses confirmed by the INEC are included in the analysis.

[b] Double-blind only for DMF and placebo; rater-blinded for all arms; INEC fully blinded to all arms.

# DEFINE and CONFIRM Integrated Analysis: MRI Outcomes With Dimethyl Fumarate at 2 Years[1]




[a] Negative binomial regression adjusted for study, region, and baseline volume of T2-hyperintense lesions or T1-hypointense lesions. [b] Ordinal logistic regression adjusted for study, region, and baseline number of Gd+ lesions. [c] DMF, delayed-release DMF.

# Dimethyl Fumarate Safety Profile Based on Clinical Studies[1,a]

| Patients, % | PBO (n = 836) | DMF bid (n = 769) | DMF tid (n = 823) |
|---|---|---|---|
| MS relapse | 43 | 29 | 26 |
| Flushing[b] | 5 | 34 | 29 |
| Nasopharyngitis | 20 | 22 | 22 |
| Headache | 16 | 17 | 17 |
| Diarrhoea[b] | 10 | 14 | 17 |
| UTI[b] | 11 | 14 | 12 |
| URTI | 11 | 13 | 12 |
| Nausea[b] | 9 | 12 | 14 |
| Fatigue | 11 | 12 | 13 |
| Back pain | 11 | 12 | 10 |
| Upper abdominal pain[b] | 6 | 10 | 11 |
| Proteinurea[b] | 7 | 9 | 10 |

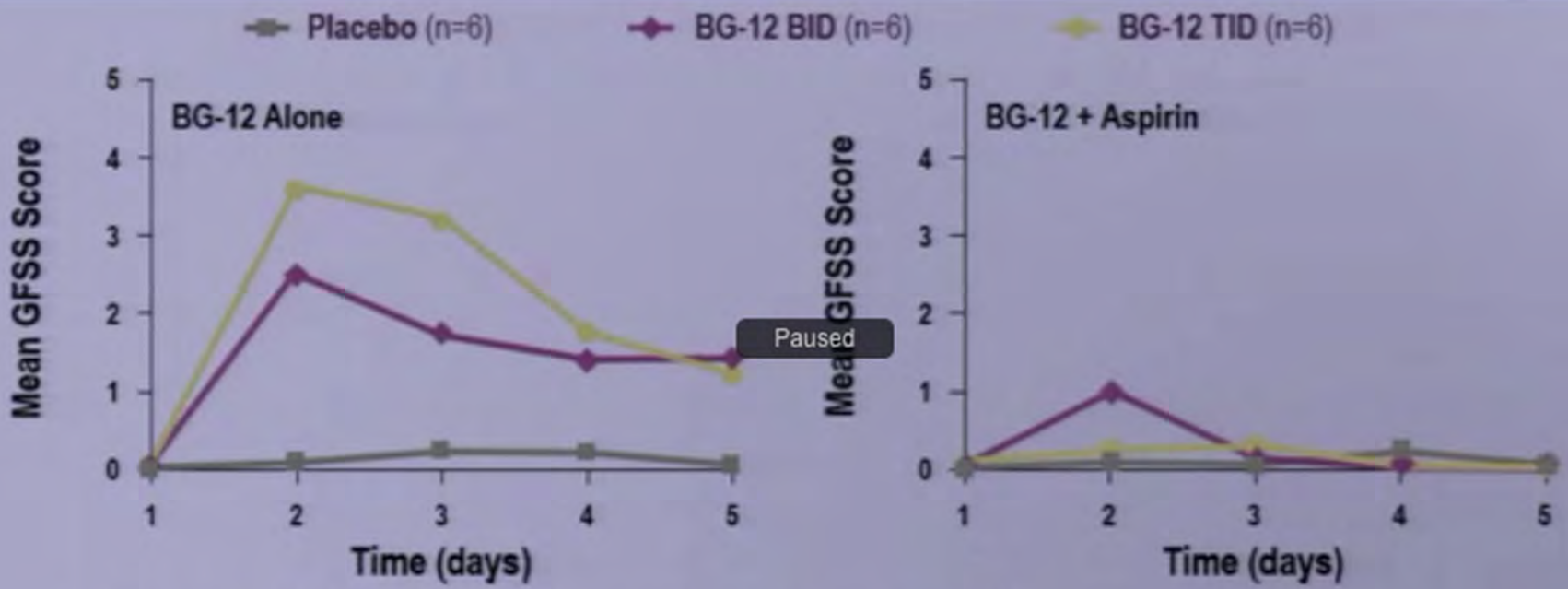
**The most common AEs leading to study drug discontinuation were:**

- Flushing[2] (3%)
- Gastrointestinal events[2] (4%)
  - Diarrhoea
  - Nausea
  - Vomiting
  - Upper abdominal pain
  - Abdominal pain

[a] One phase 2 study and two phase 3 studies (DEFINE and CONFIRM). [b] Indicates ≥3% higher incidence in either DMF group vs PBO.

# DIMETHYLFUMARATE, FLUSHING, AND ASPIRIN

## Mean Flushing Severity Scores over Time




- Aspirin (inhibitor of prostaglandins) decreased incidence and severity of flushing; no effect on gastrointestinal symptoms
- Subject reported flushing scores were mild across treatment period and decreased over time, suggesting development of tolerance
- No effect of aspirin on pharmacokinetics of BG-12

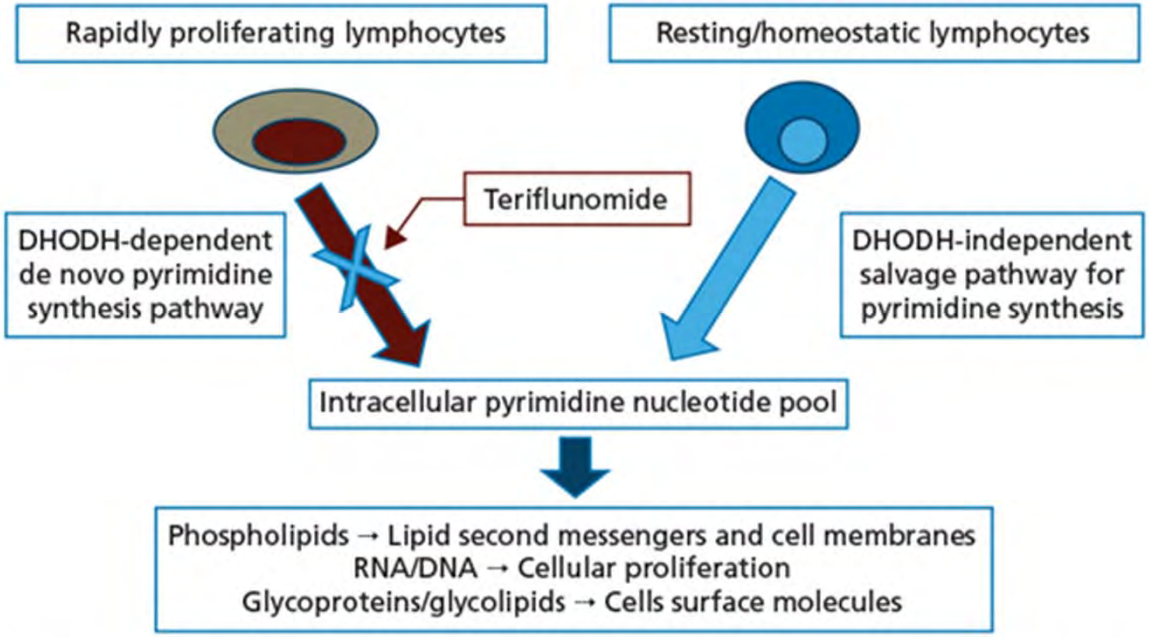
GFSS = Global Flushing Severity Scale.

Sheikh SI, et al. Presented at: 64th Annual Meeting of the AAN; April 21-28, 2012; New Orleans, Louisiana. Abstract P04.136.

# Teriflunomide: Mechanism of Action

- **Teriflunomide**
  - Active metabolite of leflunomide, a therapy approved for RA[1]
  - Immunomodulatory agent with anti-inflammatory properties[2]
  - Formulated as film-coated tablets (14 mg)[2]


## Working in the Peripheral Circulation to Reduce Rapid Lymphocyte Proliferation[2,3,a]

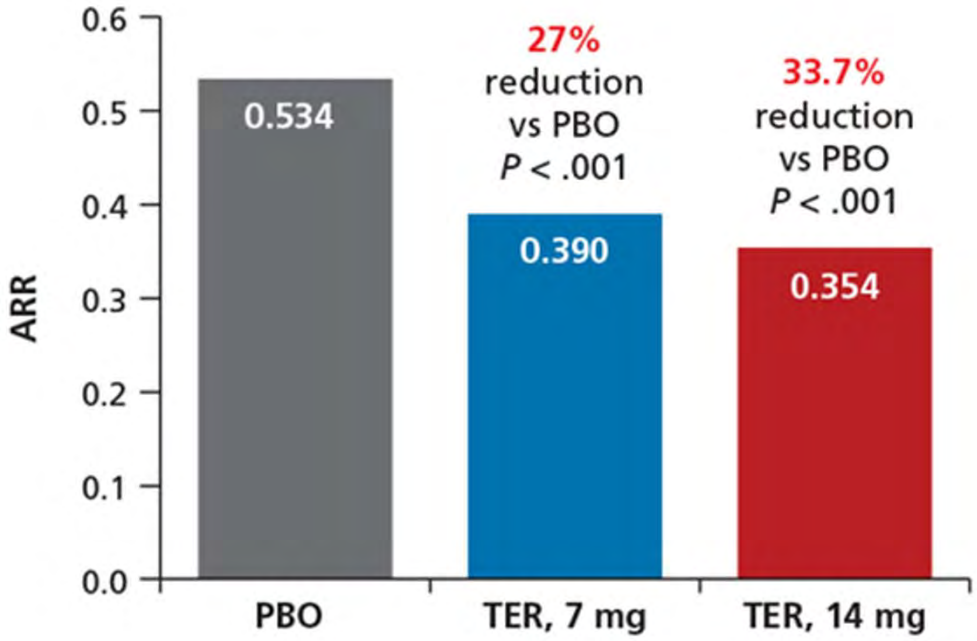



[a] The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood.

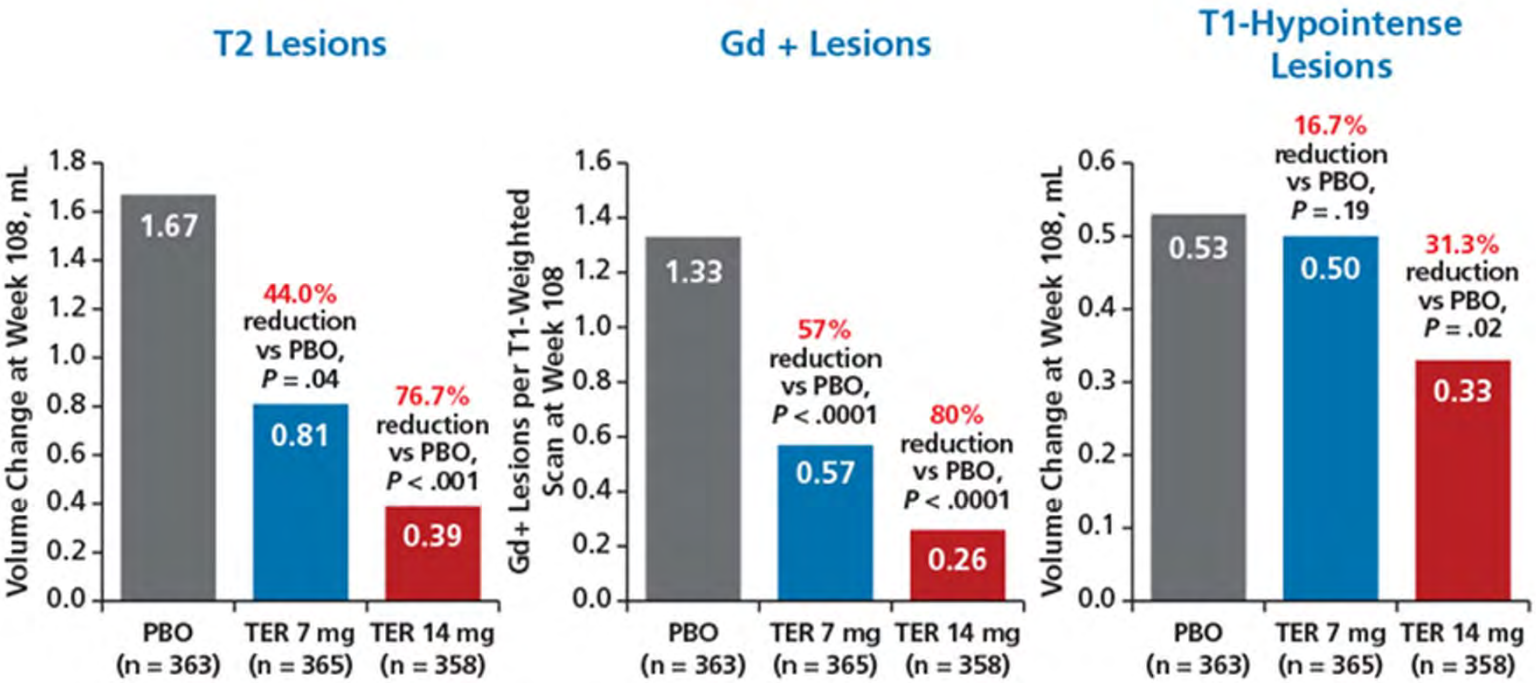
# Pooled Analysis of TEMSO and TOWER: Relapse Outcomes With Teriflunomide

| Randomised, Double-Blind, PBO-Controlled, Parallel-Group Studies | |
|---|---|
| **TEMSO[1]** | **TOWER[2]** |
| N = 1,088 | N = 1,169 |
| 108 wk | Variable duration ≥48 wk |
| **Arms** | |
| TER 7 mg<br>TER 14 mg<br>PBO | TER 7 mg<br>TER 14 mg<br>PBO |

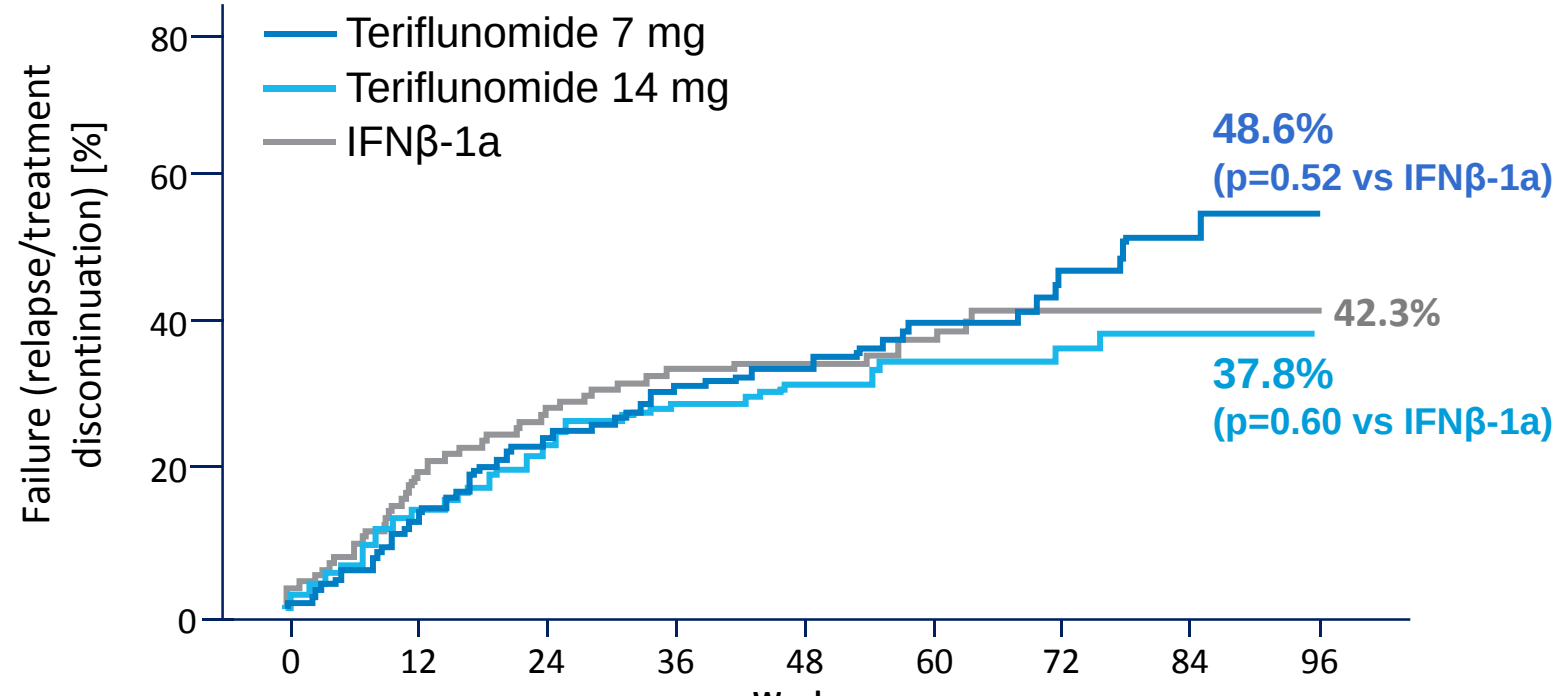
**Annualised Relapse Rate in the Pooled TEMSO and TOWER Studies[3] (mITT population)**



# TEMSO: MRI Outcomes



# TENERE: Time to Failure




| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Teri 7 mg | 109 | 95 | 81 | 74 | 69 | 43 | 24 | 13 | 6 |
| Teri 14 mg | 111 | 95 | 84 | 77 | 71 | 44 | 30 | 21 | 9 |
| IFNβ-1a | 104 | 84 | 74 | 67 | 65 | 46 | 30 | 15 | 6 |

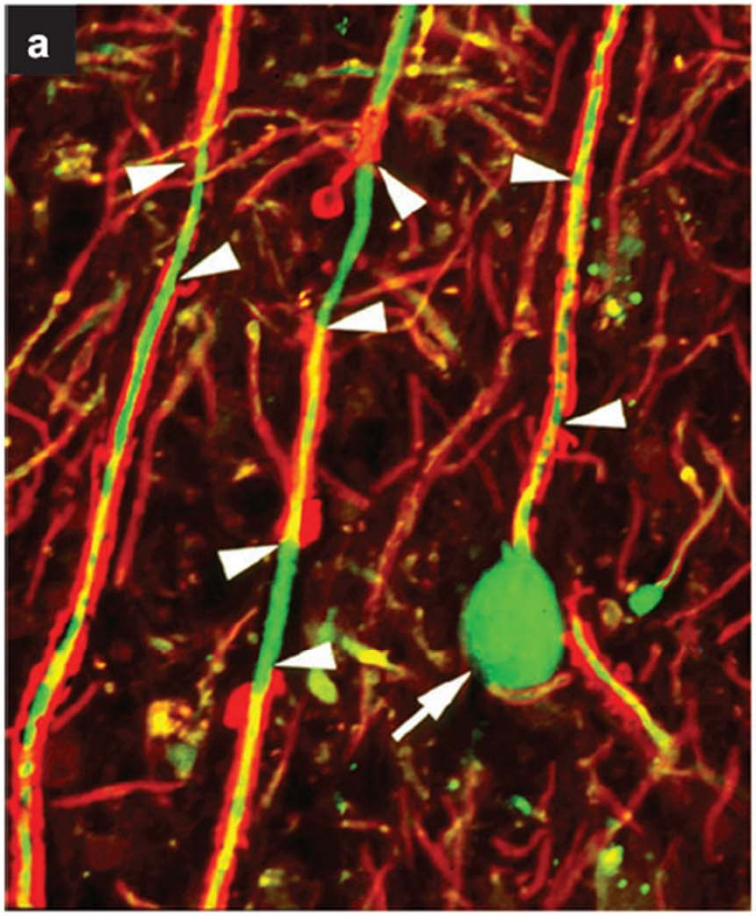
- No statistical superiority was observed between teriflunomide (7 mg or 14 mg) and IFNβ-1a on time to failure

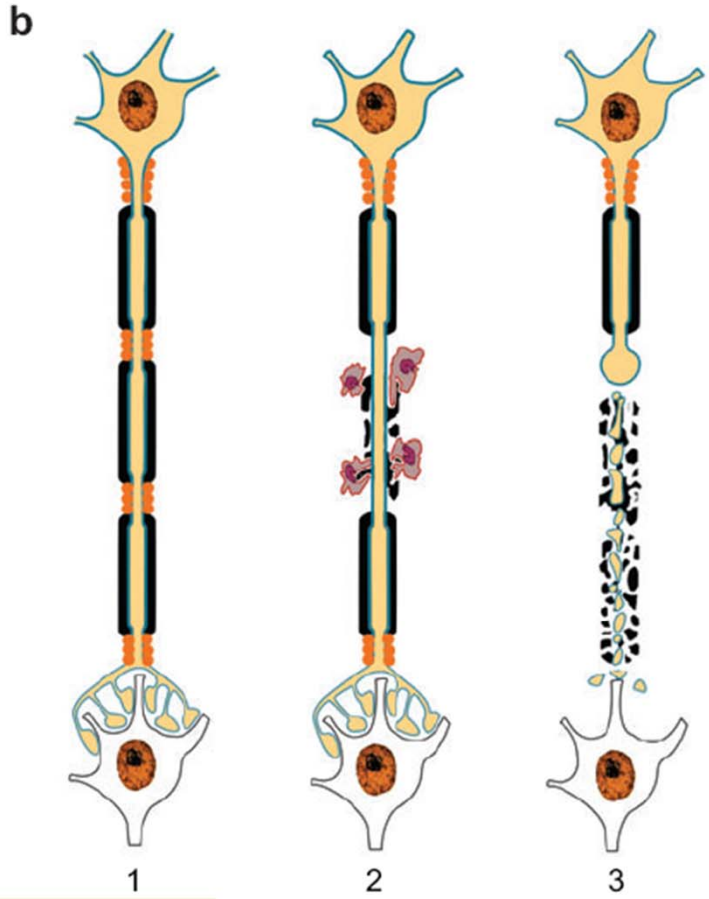
# TEMSO and TOWER: Common Adverse Events (≥10% in 14-mg Teriflunomide Group)

| Most Common AEs, % | TEMSO[1] | | TOWER[2] | |
|---|---|---|---|---|
| | PBO (n = 360) | TER 14 mg (n = 368) | PBO (n = 385) | TER 14 mg (n = 371) |
| Nasopharyngitis | 27.2 | 26.0 | 17.7 | 11.9 |
| Headache | 17.8 | 18.7 | 10.9 | 12.4 |
| Diarrhoea[a] | 8.9 | 17.9 | 7.3 | 11.1 |
| Fatigue | 14.2 | 14.5 | 10.6 | 10.2 |
| Elevated ALT[a] | 6.7 | 14.2 | 8.3 | 14.0 |
| Nausea[a] | 7.2 | 13.7 | 8.8 | 10.2 |
| Hair thinning or decreased hair density[a] | 3.3 | 13.1 | 4.4 | 13.5 |
| Influenza | 10.0 | 12.0 | – | – |
| Back pain | 13.1 | 11.5 | – | – |
| UTI | 9.7 | 10.3 | – | – |

[a] Indicates ≥3% higher incidence in teriflunomide group in either study vs PBO.

# ANTI-LINGO-1
# Demyelination & Axonal Injury In MS Lesions

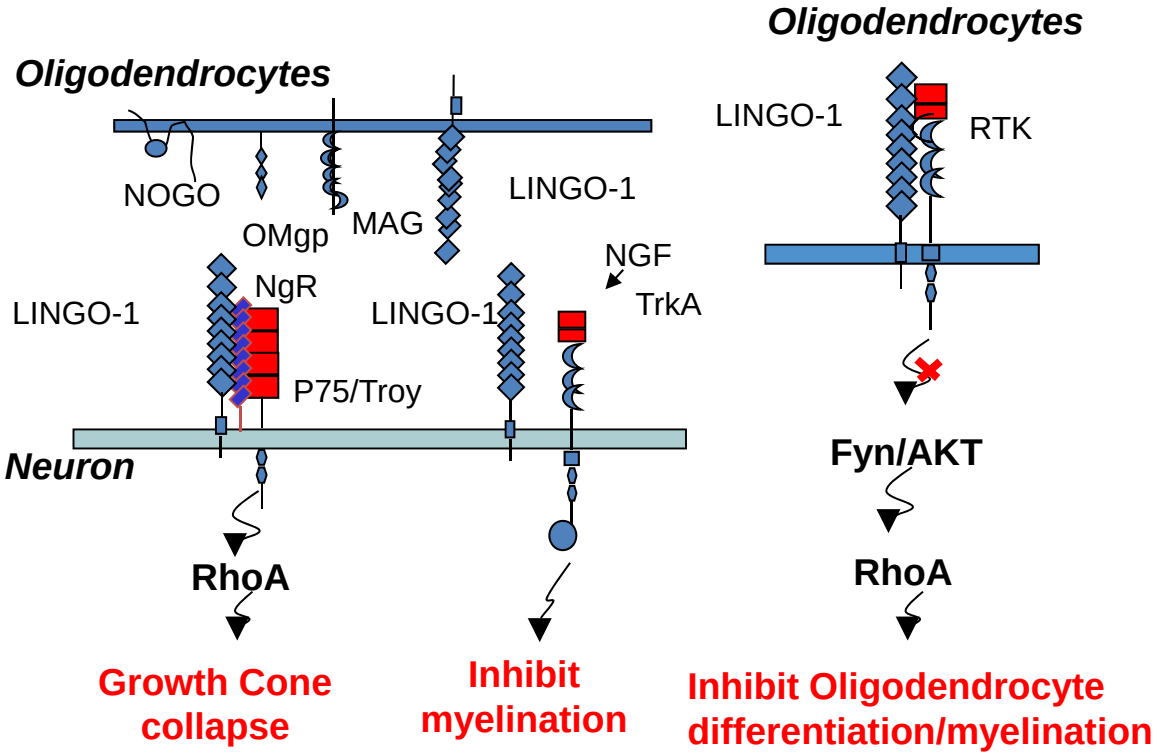


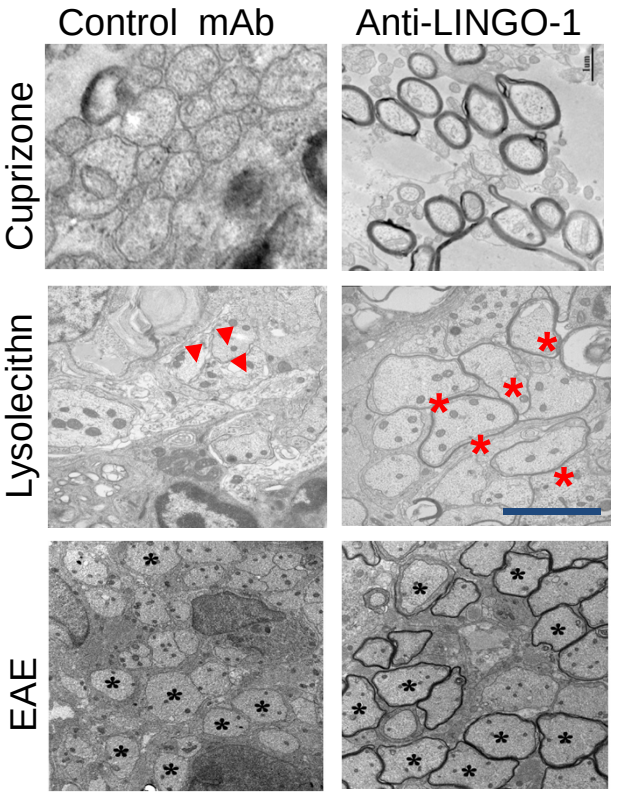

Annu. Rev. Neurosci. 2008. 31:247–69

# Anti-LINGO-1 Therapeutic Hypothesis

## LINGO-1 Inhibits Axon regeneration and remyelination[1,2]




## Anti-LINGO-1 promotes remyelination[1,3]




[1]Mi S, et al. *Ann Neurol*. 2009 Mar;65(3):304-15. ; [2]Ji B, et al, McCoy JM, Pepinsky RB, Mi S, Relton JK. *Mol Cell Neurosci*. 2006 Nov;33(3):311-20. ;[3]Mi S, et al. *Nat Med*. 2007 Oct;13(10):1228-33.

# BIIB033 Phase 2 Clinical Development Plan

RENEW
A Phase II Study Investigating ACUTE OPTIC NEURITIS

## PHASE 2 IN ACUTE OPTIC NEURITIS

- Proof of Concept study.
- Study population: subjects with a first episode of AON.
- The visual system is an excellent model to provide proof of concept with regards to
  - CNS remyelination (VEP/mfVEP)
  - Neuroaxonal protection (OCT)
  - Potential clinical benefit, i.e. visual acuity, low contrast letter acuity, visual quality of life.

SYNERGY
A Phase II Study Investigating anti-LINGO when used concurrently with Avonex® in subjects with relapsing forms of MS

## PHASE 2 IN RELAPSING FORMS OF MULTIPLE SCLEROSIS

- Proof of Concept and Dose Range Finding study.
- Study population: subjects with active, relapsing MS (RRMS and SPMS).
- Efficacy measures include physical and cognitive improvement, slowing of disease progression, and MRI recovery endpoints (MTR, DTI, black holes).