Firenze 2 dicembre 2013

Nuove terapie orali per la SM

Maria Pia Amato

Dipartimento NEUROFARBA
Sezione Neuroscienze
SOD Neurologia I – AOU Careggi

Caratteristiche fondamentali della Sclerosi Multipla

- Malattia infiammatoria e degenerativa, a carattere demielinizzante del SNC
- Patogenesi autoimmune e eziologia non identificata
- Esordio tra i 20 ed i 40 anni, più frequente nel sesso femminile (D:U 2-3:1).
- Il 3-5 % dei casi esordisce prima dei 18 aa.
- Evoluzione cronica con accumulo di disabilità irreversibie nel tempo
- La più frequente causa di disabilità neurologica nei giovani adulti, dopo gli incidenti stradali

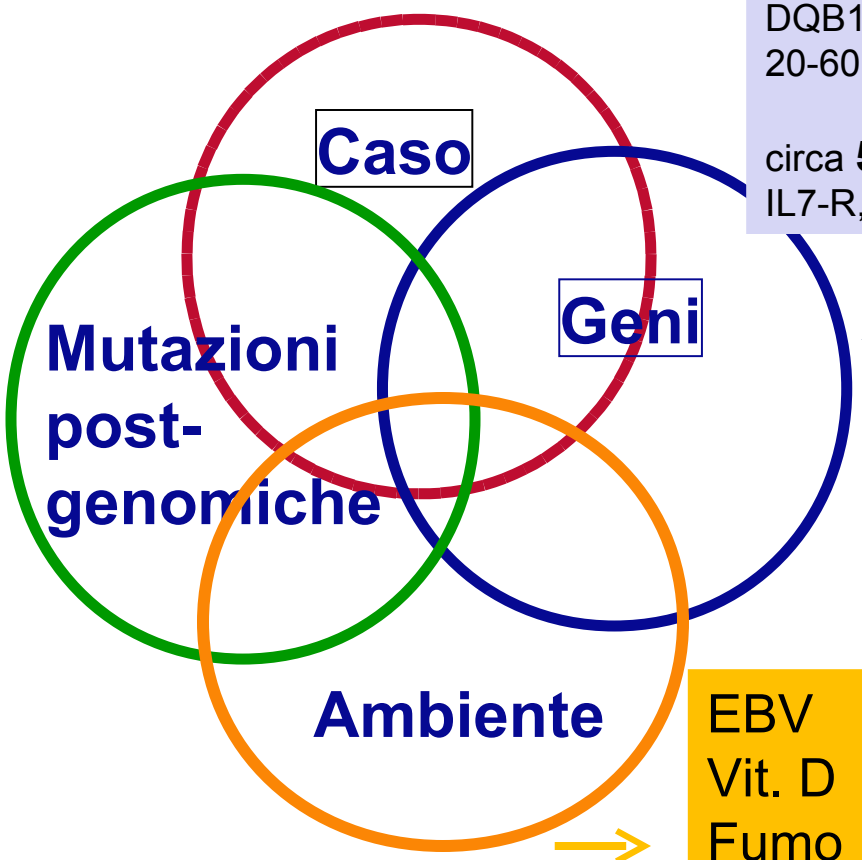
Fattori di genere nella SM

- Maggiore prevalenza nel sesso femminile
- Incremento progressivo del rapporto F:M nelle ultime sei decadi
- Decorso favorevole in gravidanza con riduzione del tasso di ricaduta, «rebound» dopo il parto

Eziopatogenesi Multifattoriale
Interazione geni-ambiente

HLA DR2 (HLA-DRB1*1501,HA-DQB1*0602)
20-60% della suscettibilità genetica

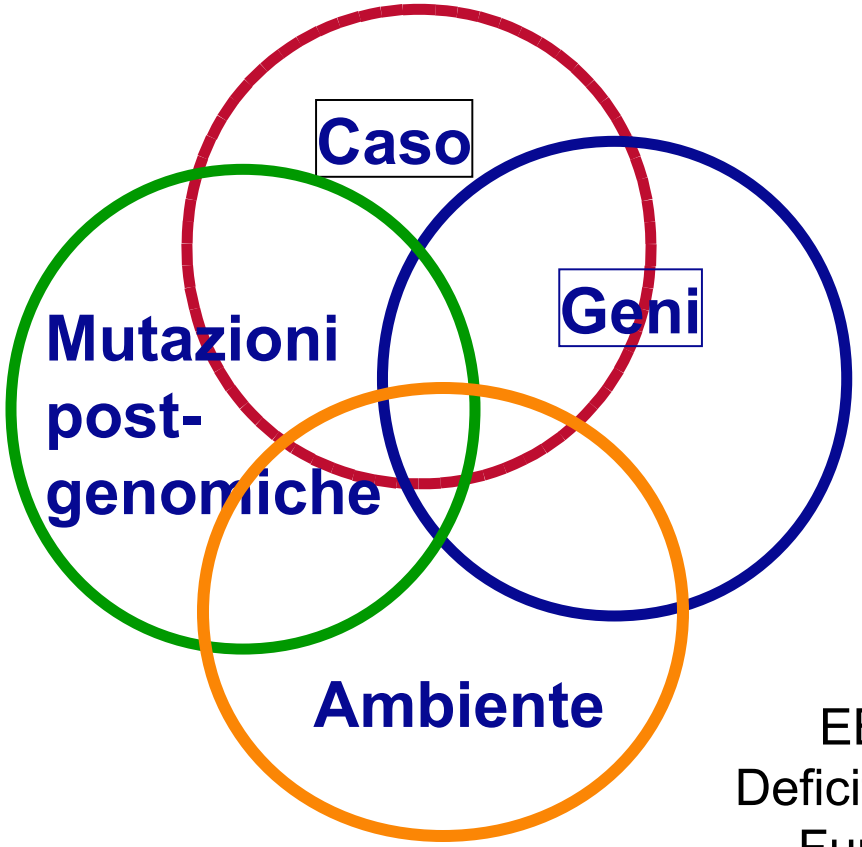
circa **50 non-HLA loci**, es. IL2-R, IL7-R, OR<1.3



EBV
Vit. D
Fumo
Sodio nella dieta

www.centers.it

Eziopatogenesi Multifattoriale
Interazione geni-ambiente

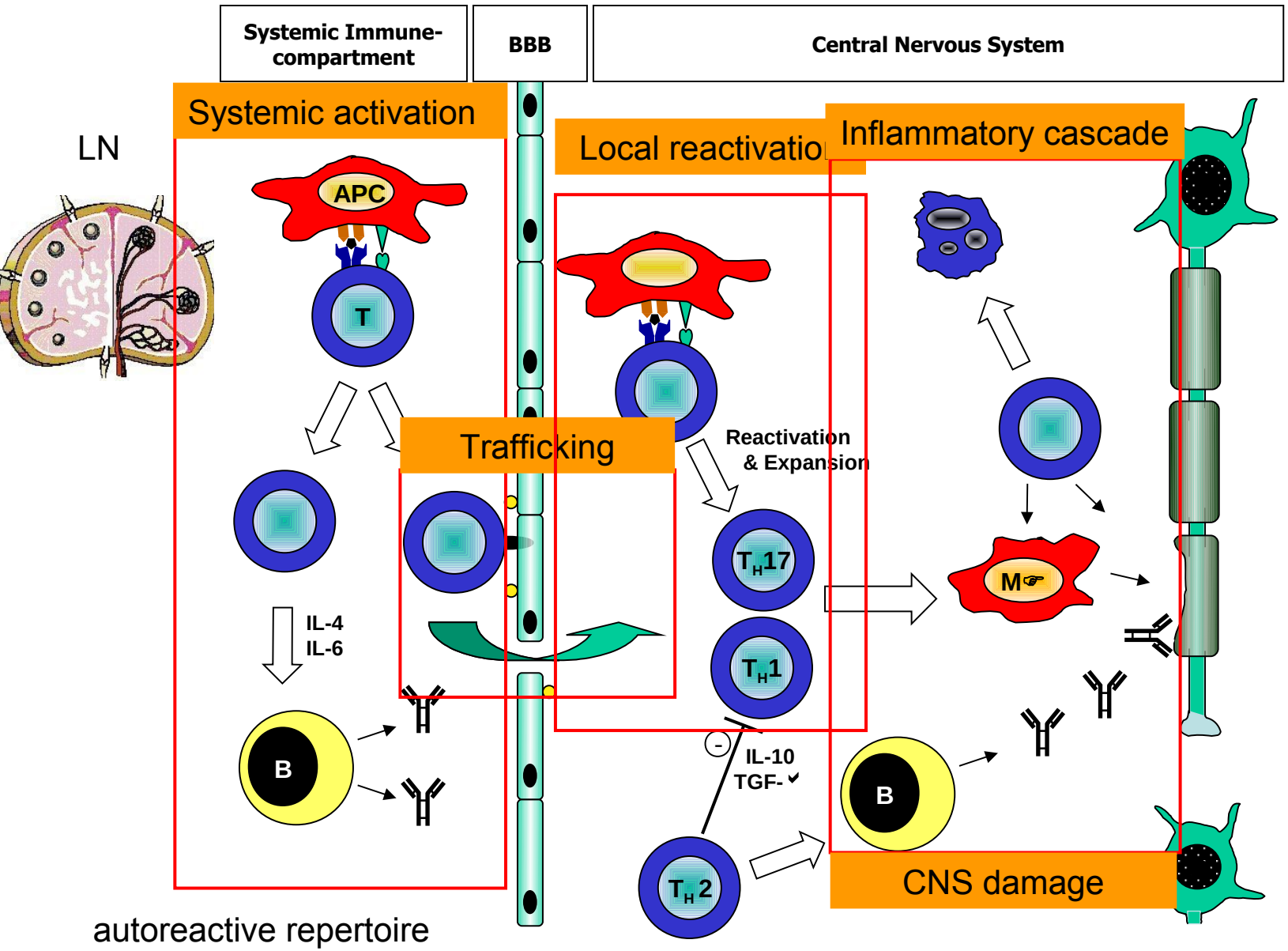


HLA DR 2
Circa 50 loci non-HLA

EBV
Deficit vit. D
Fumo
?

www.centers.it

MS immunopathogenesis



Ruolo eziologico di fattori genetici

- **Sesso:** incidenza 2-4 volte superiore nel sesso femminile
  Rapporto tendenzialmente paritetico nei casi con età di esordio < 10aa. o >45aa.

- **Etnia:**
- Più frequente nelle popolazioni caucasiche

- **HLA**: associazione con DR2 nei caucasici
  - **HLA-DRB1*1501,HA-DQB1*0602**: 20-60% della suscettibilità genetica
  - circa 50 loci non-HLA (OR <1.3)

- **Ricorrenza familiare** (15-20%)
  - maggior rischio di malattia nei familiari di primo grado del paziente
  - riduzione del rischio con l'allontanarsi del grado di parentela

Rischio di malattia in base al grado di parentela

(Sadovnick, 2001)

	Rischio ricorrenza (%)	Rischio Relativo vs. popolazine generale	% di condivisione genetica col probando
Popolazione generale	0.2	1	0
Parenti 1° (fratelli)	3-5	15-25	50
Gemelli Dizigoti	3-5	15-25	50
Gemelli Monozigoti	35	190	100
Parenti 1° di Adottivi *	0.2	1	0
Fratellastri *	1.3	6.5	25
Nati da SM coniugale	29.5	147.5	50
Fratelli di pz nati da genitori consanguinei	9	45	

*non differenza se cresciuti nella stessa famiglia o separati, effetto della trasmissione materna

Rischio di malattia aggiustato per età in base al grado di parentela *(Sadovnick, 2001)*

	Recurrence risk (%)	Relative Risk to general population	% Genetic sharing whit the proband
General population	0.2	1	0
First-degree relative (sib)	3-5	15-25	50
Dizygotic twin	3-5	15-25	50
Monozygotic twin	35	190	100
Adpted first-degree relative	0.2	1	0
Half-sib (*)	1.3	6.5	25
Offspring of conjugal MS	29.5	147.5	50
Sib. of probands born from consanguineous mating	9	45	

(*) no difference in risk in case of growth in the same or in different environment

Presence of a maternal parent of origin effect

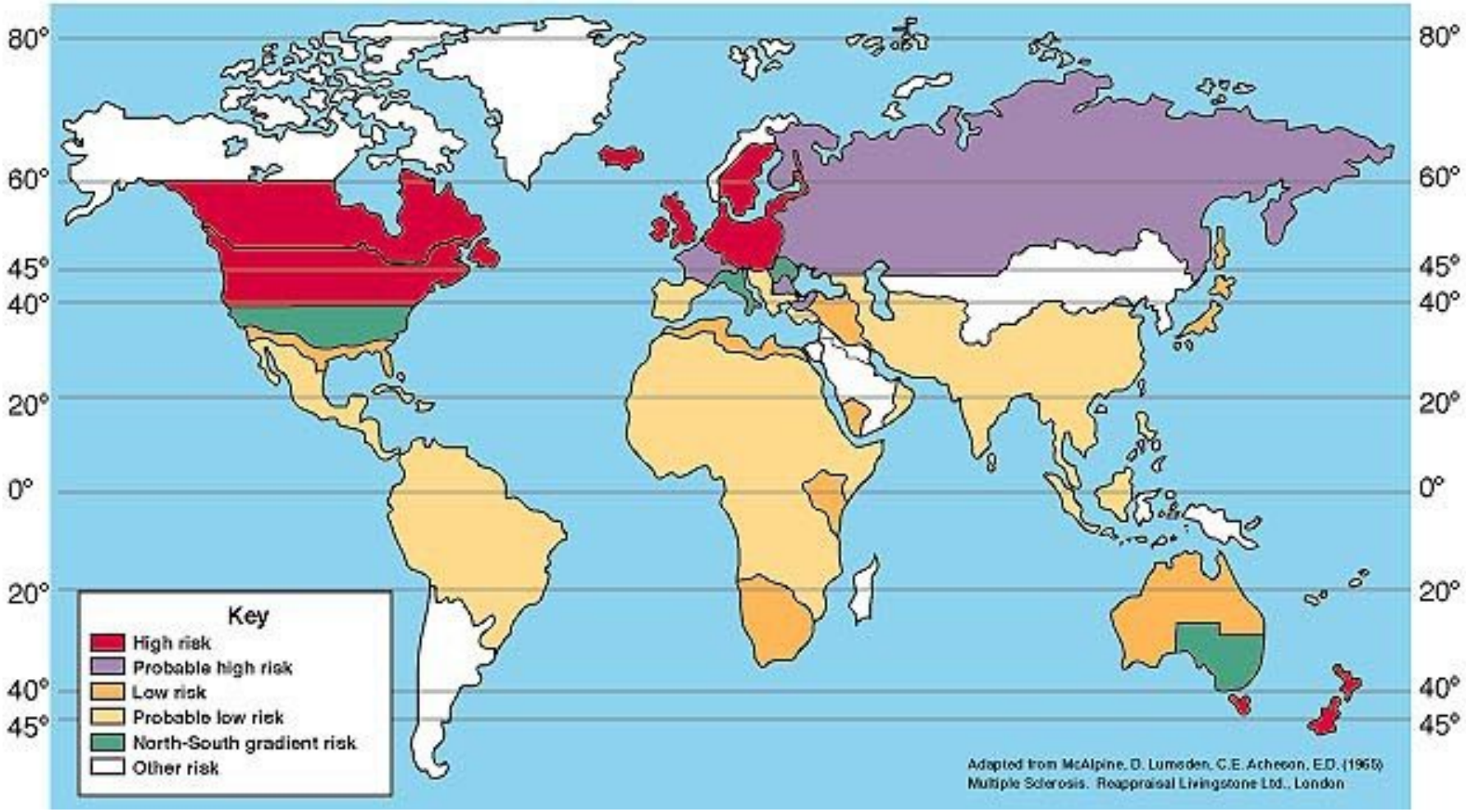
Studi sui gemelli

Studio	Gemellarità	Concordanza %
Bammer, 1960	MZ DZ	29 44
Bobovik, 1978	MZ DZ	33 0
French Group, 1992	MZ DZ	**11** **5**
Mumford, 1994	MZ DZ	40 6
Willer, 2003	MZ DZ	31 8
Hansen, 2005	MZ DZ	30 6
Ristori, 2005	MZ DZ	**14** **4**

Ruolo eziologico di fattori ambientali

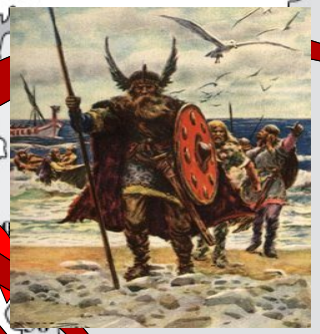
- Discordanza nei gemelli monozigoti
- Distribuzione geografica disomogenea: gradiente latitudinale di prevalenza
- "Clusters" (es. Isole Faroe)
- "Trend" temporali di incidenza
- Studi sui migranti (età critica di esposizione: prime due decadi di vita)

Prevalenza (N. casi x 100.000 abitanti) della SM nel mondo



“La SM è una malattia Nordica”- la “Saga dei Vichinghi”

(Davenport, 1921; Kurtzke, 1993; Poser, 1995)



America Settentrionale

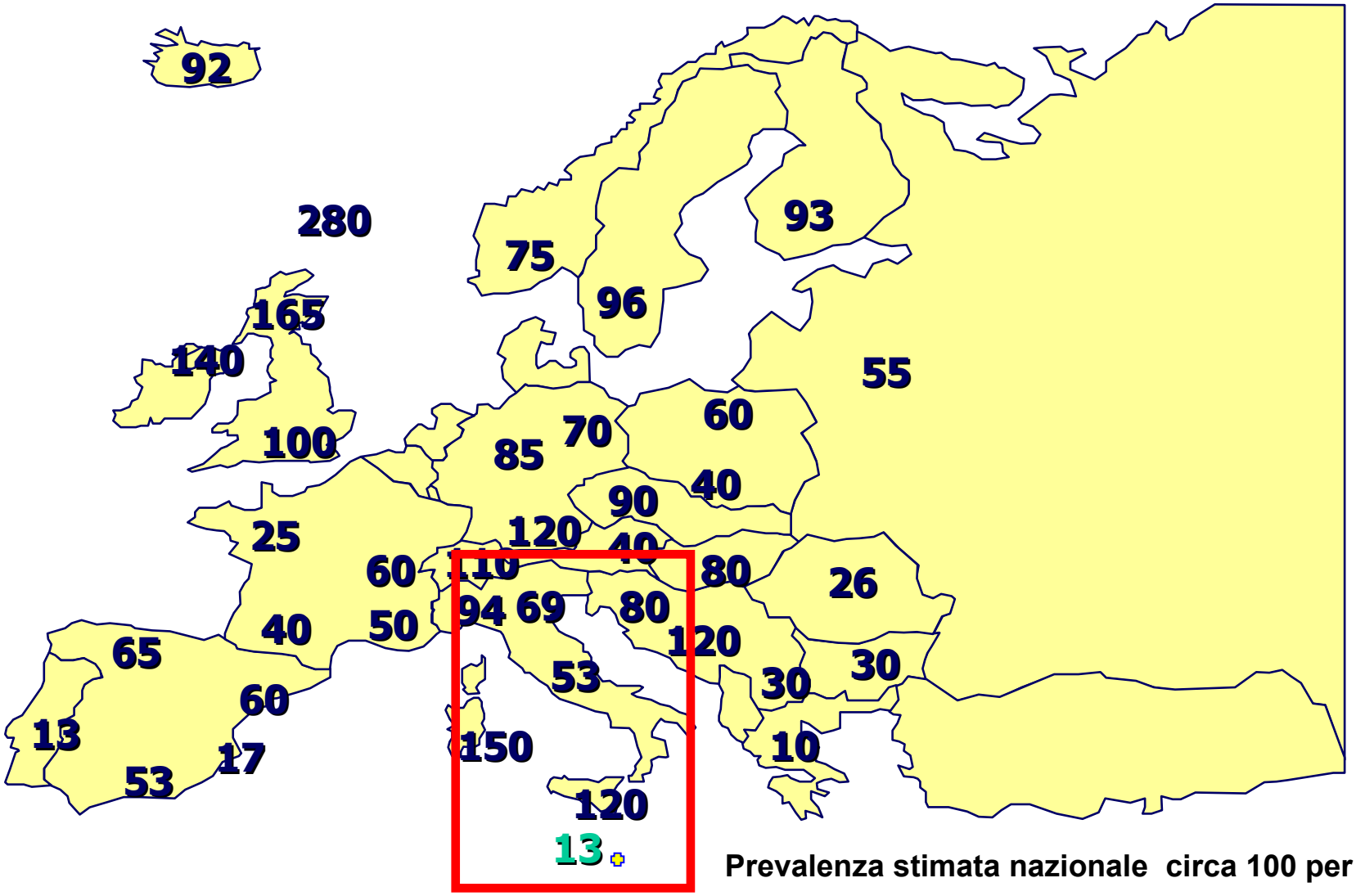
Australasia

Sud Europa

Sud Africa

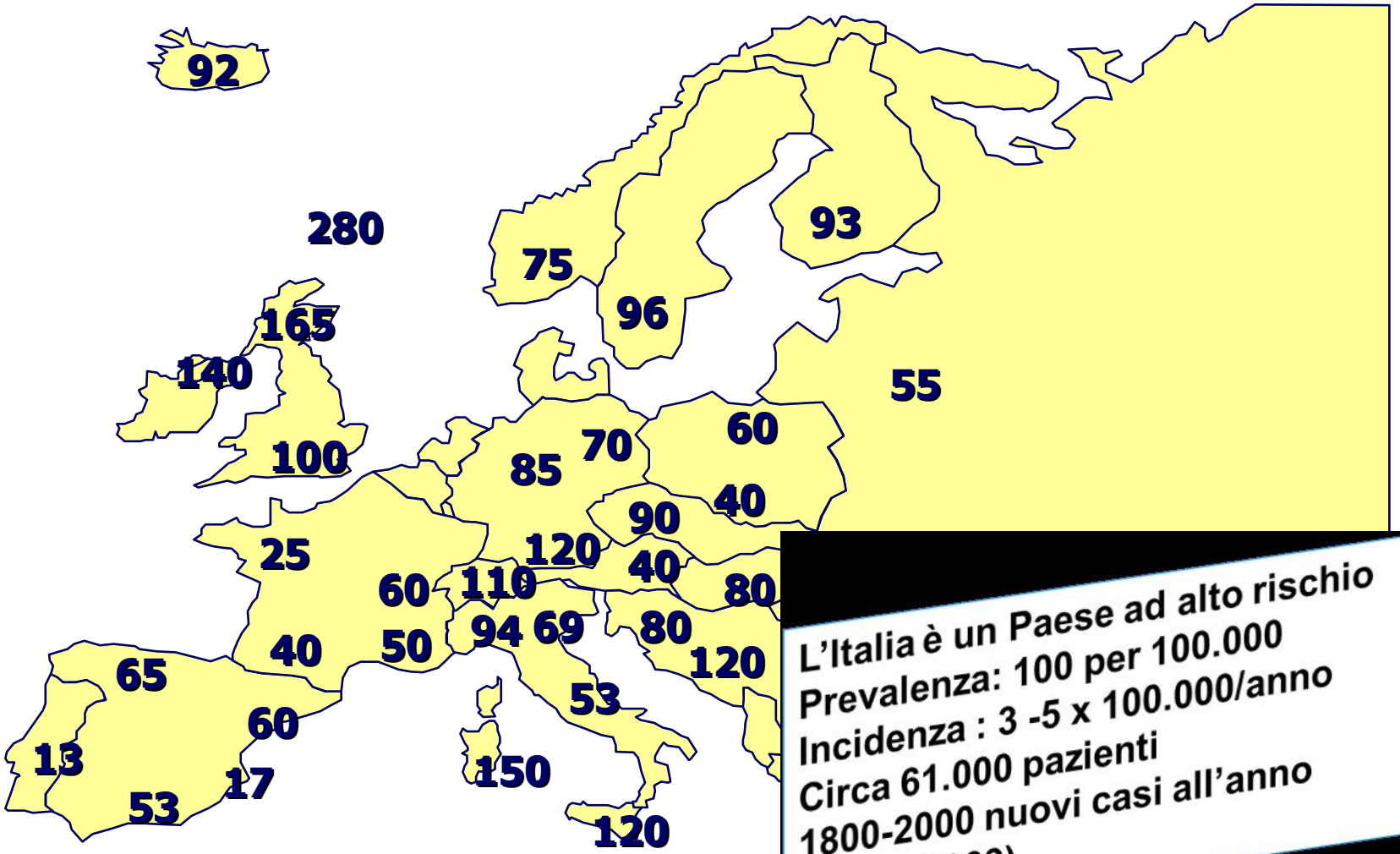
Figure 1 Multiple sclerosis prevalence rates in Europe (adjusted for the E an population; in brackets crude rates when adjustment was not possible).

Prevalenza x 100.000 della SM in Europa e in Italia



Prevalenza stimata nazionale circa 100 per 100.000

Prevalenza x 100.000 della SM in Europa e in Italia



L'Italia è un Paese ad alto rischio
Prevalenza: 100 per 100.000
Incidenza : 3 -5 x 100.000/anno
Circa 61.000 pazienti
1800-2000 nuovi casi all'anno
(AISM, 2009)

Migration studies

Study of MS risk among migrants from Europe to South Africa:

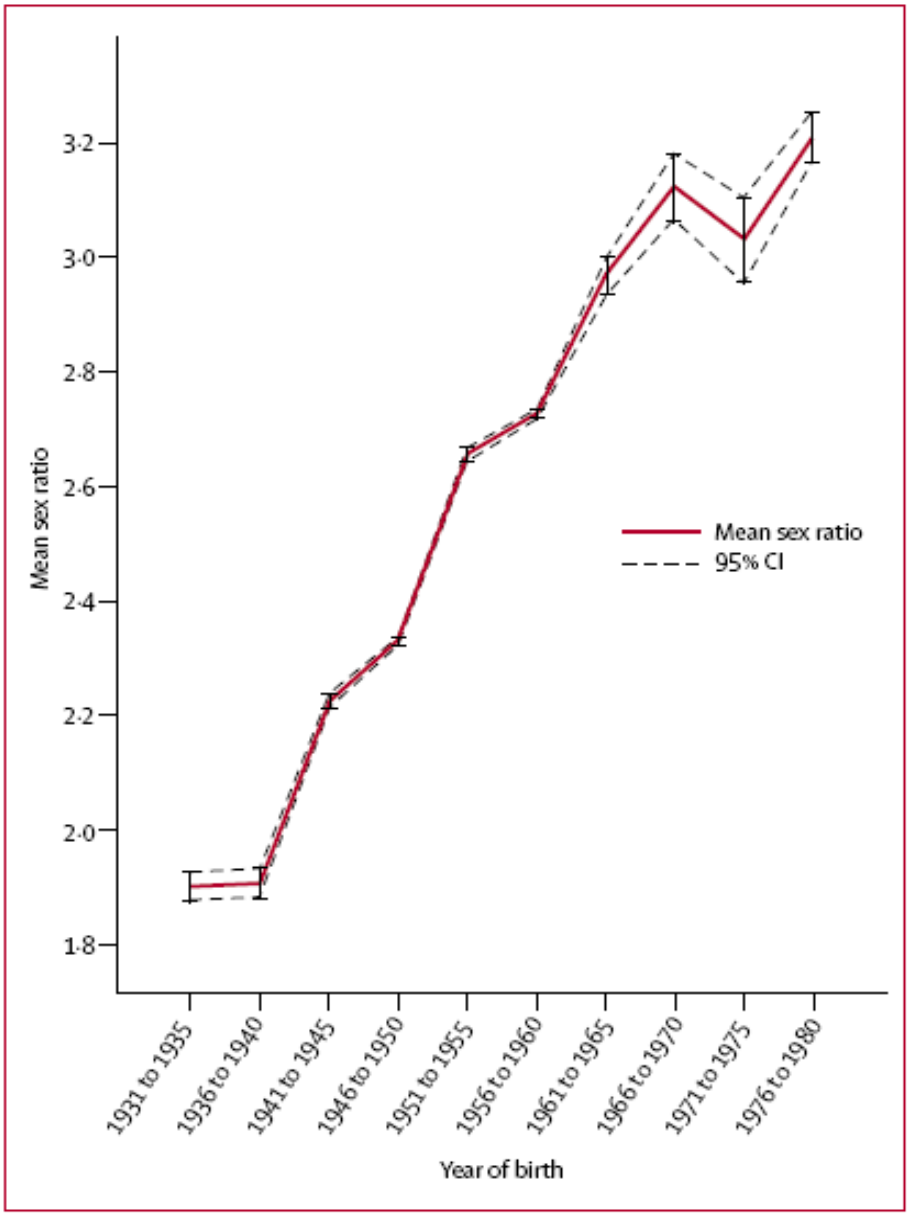
Individuals migrating after the age of 15 retain the higher risk of their country of origin

Individuals migrating before the age of 15 acquire the lower risk of their new residence

MS is initiated by unknown environmental exposures early in life and the clinical onset is preceded by a long latent period

Dean. Neuroepidemiology 1984

EIDEMIOLOGIA DELLA SM



Incremento del rapporto F:M per anno di nascita in pazienti con SM, dal 1936 al 1980

Ipotesi

- *Modificazioni ambientali*
- *Interazione geni-ambiente*
  - Fumo
  - Ingresso nel mondo del lavoro
  - Maggior numero di nullipare
  - Maggiore età alla nascita del primo figlio

Koch-Henriksen, Sorensen, Lancet Neurol 2010

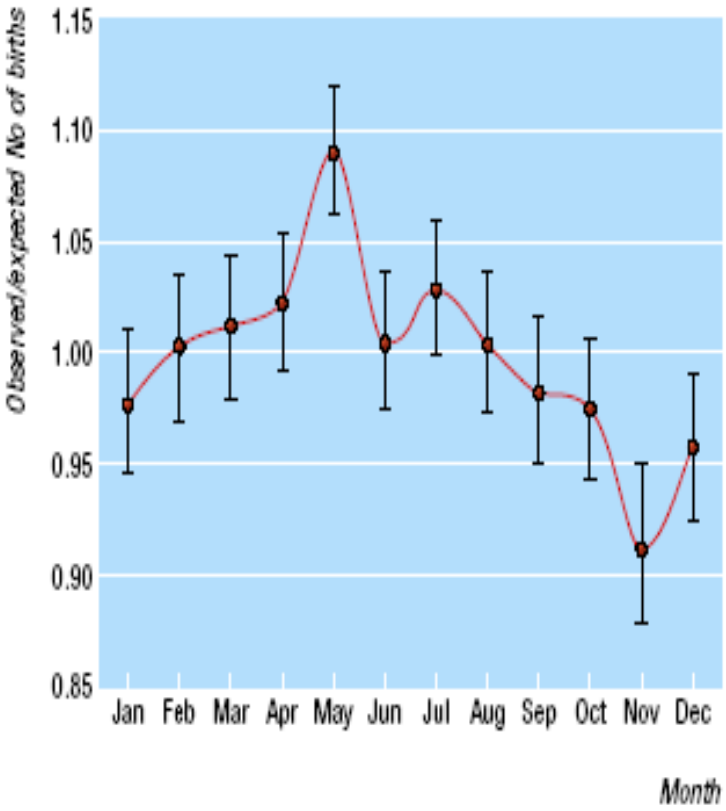


Fig 1 Pooled analysis of observed/expected births in people with multiple sclerosis in Canadian, British, Danish, and Swedish studies (n=42 045) with 95% confidence intervals

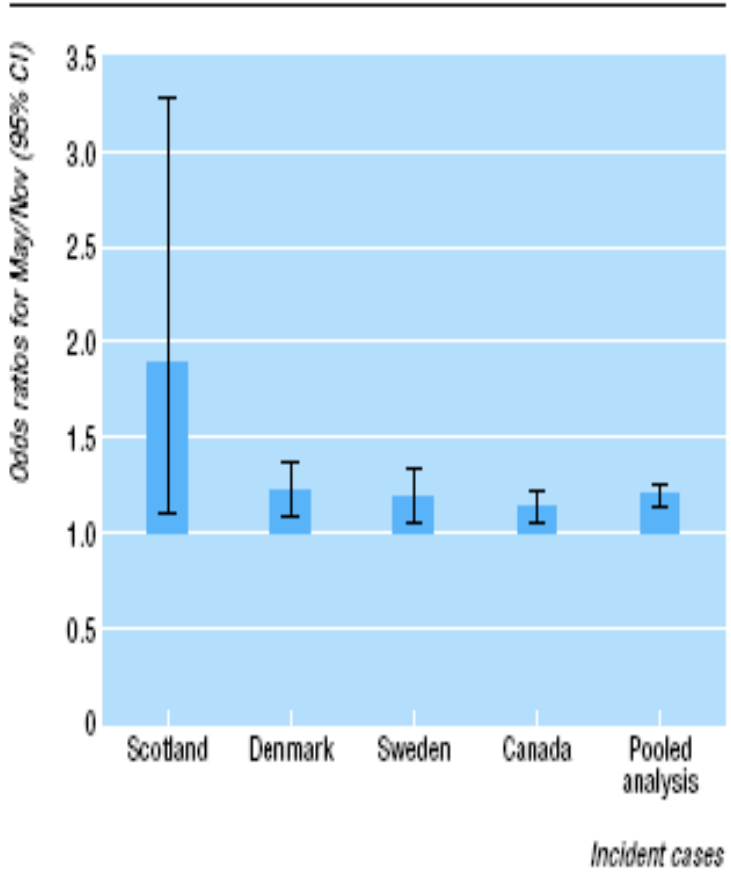


Fig 2 Odds ratios for people with multiple sclerosis being born in May/November among incident cases in northern hemisphere countries

Circa 18.000 pazienti in Canada e 11.000 in GB

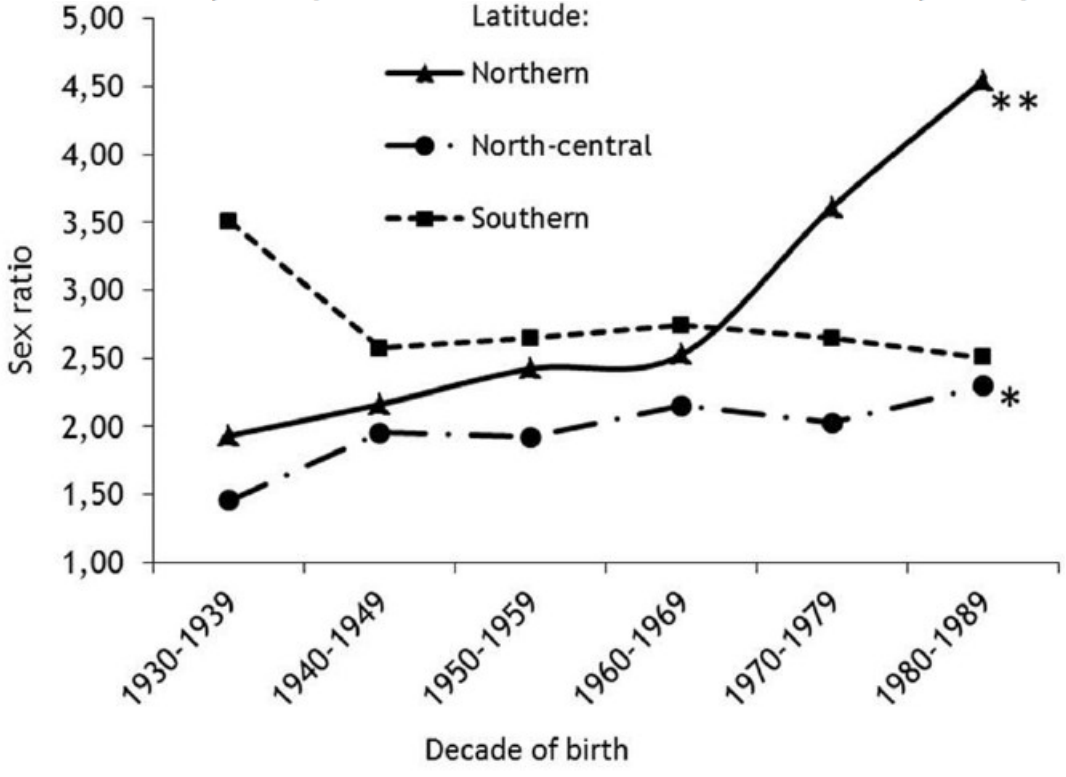
(Willer, BMJ 2005)

OPEN ACCESS Freely available online

PLOS | ONE 2012

Geographical Variations in Sex Ratio Trends over Time in Multiple Sclerosis

Maria Trojano[1]*, Guglielmo Lucchese[1], Giusi Graziano[2], Bruce V. Taylor[3], Steve Simpson, Jr.[3], Vito Lepore[2], Francois Grand'Maison[4], Pierre Duquette[5], Guillermo Izquierdo[6], Pierre Grammond[7], Maria Pia Amato[8], Roberto Bergamaschi[9], Giorgio Giuliani[10], Cavit Boz[11], Raymond Hupperts[12], Vincent Van Pesch[13], Jeannette Lechner-Scott[14], Edgardo Cristiano[15], Marcela Fiol[16], Celia Oreja-Guevara[17], Maria Laura Saladino[18], Freek Verheul[19], Mark Slee[20], Damiano Paolicelli[1], Carla Tortorella[1], Mariangela D'Onghia[1], Pietro Iaffaldano[1], Vita Direnzo[1], Helmut Butzkueven[21,22,23], on behalf of the MSBase Study Group, the New Zealand MS Prevalence Study Group¶



- Variazione del rappoto F/M aa 1930-1989 (15.996 casi)
- Variazione globale da 2.35 a 2.73
- Latitudine N 83°-45° da 1.93 a 4.55
- Latitudine N 45°-35° da 1.46 a 2.30
- Latitudine S 12°-55° stabile

Figure 1. Plot of gender ratio by six birth decades in MS patients stratified by Latitude. *p-value for trend *0.0425; **<0.0001.*

doi:10.1371/journal.pone.0048078.g001

Rapporto F/M in pazienti con SM
Paesi Nord-Europei e Sud-Europei

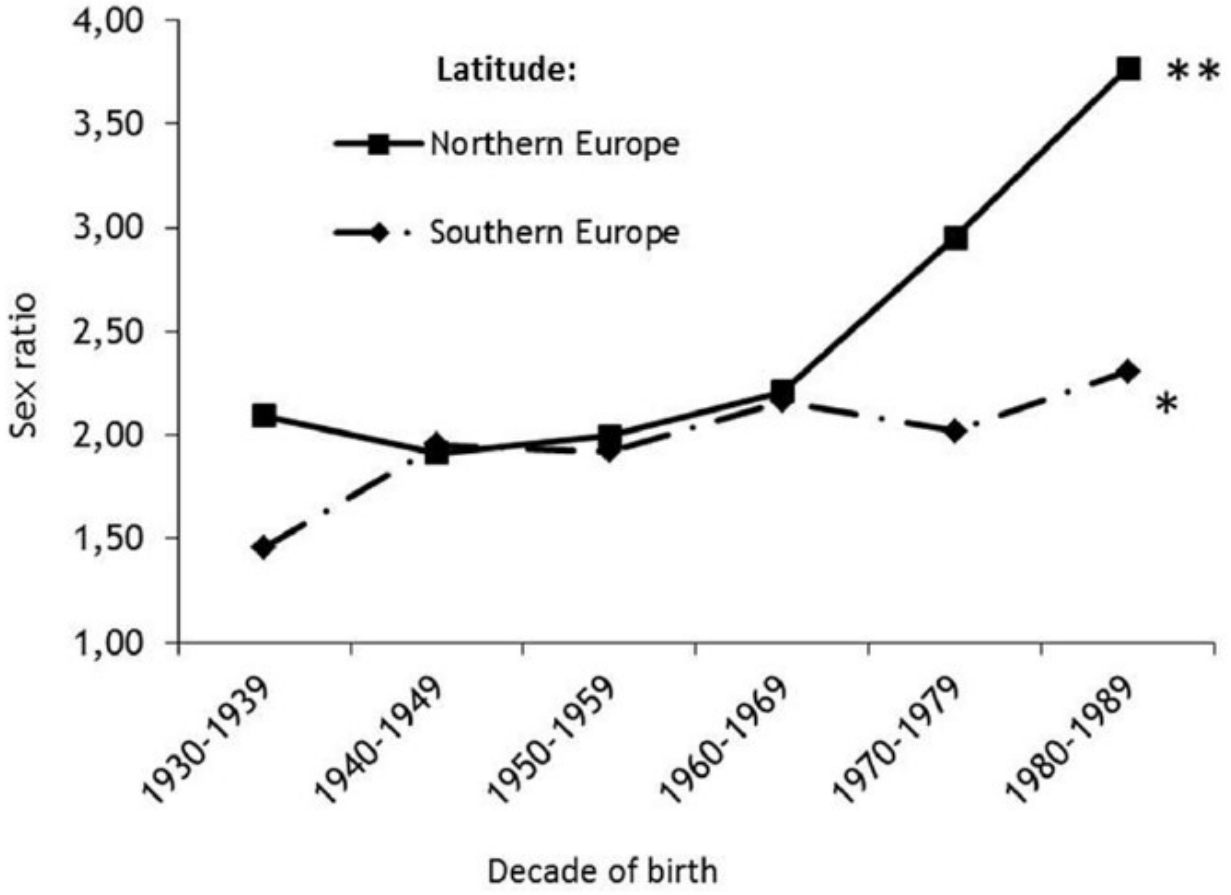


Figure 2. Plot of gender ratio by six birth decades in MS patients from Northern and Southern Europe. *p-value for trend *0.0426; **<0.0004.*
doi:10.1371/journal.pone.0048078.g002

Rapporto F/M nei pazienti con SM stratificati per decorso RR o PP

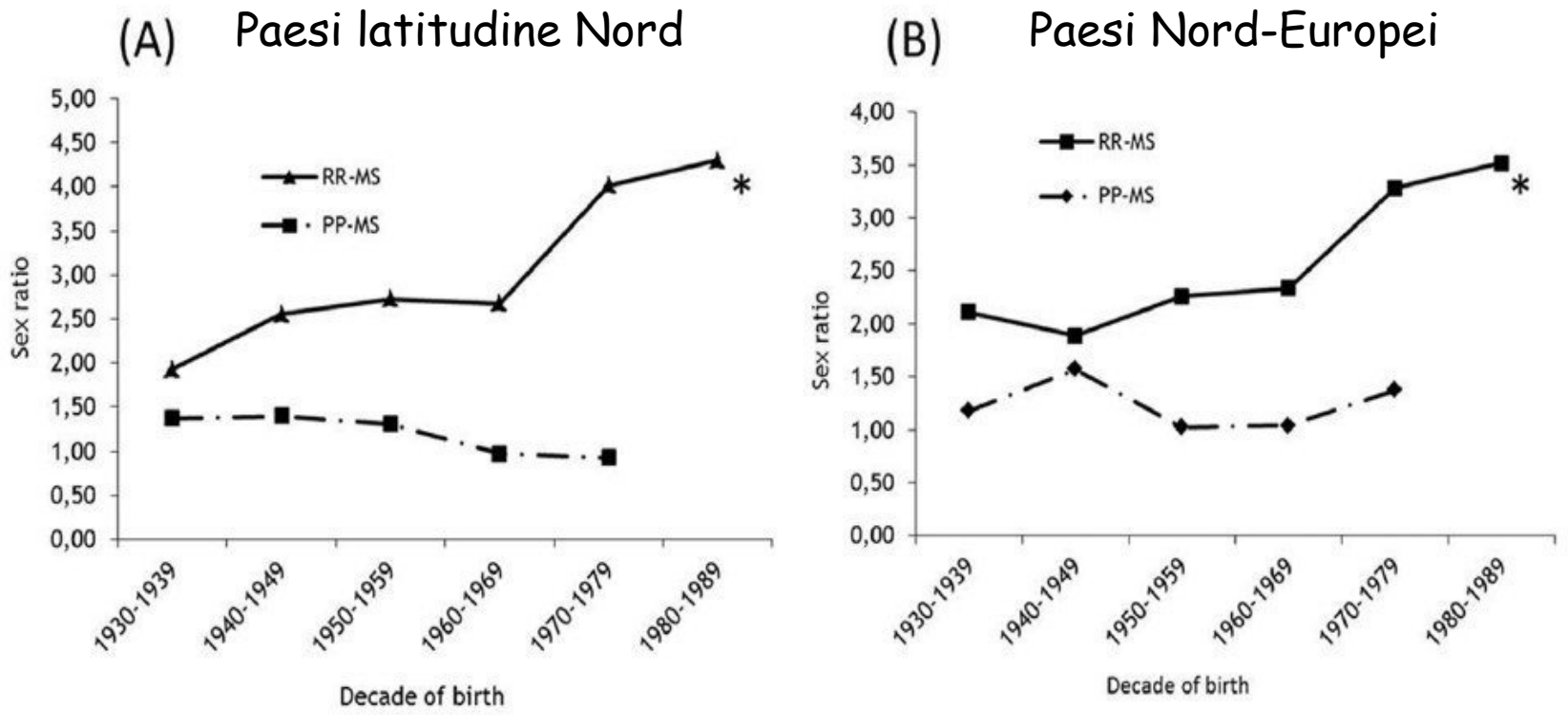
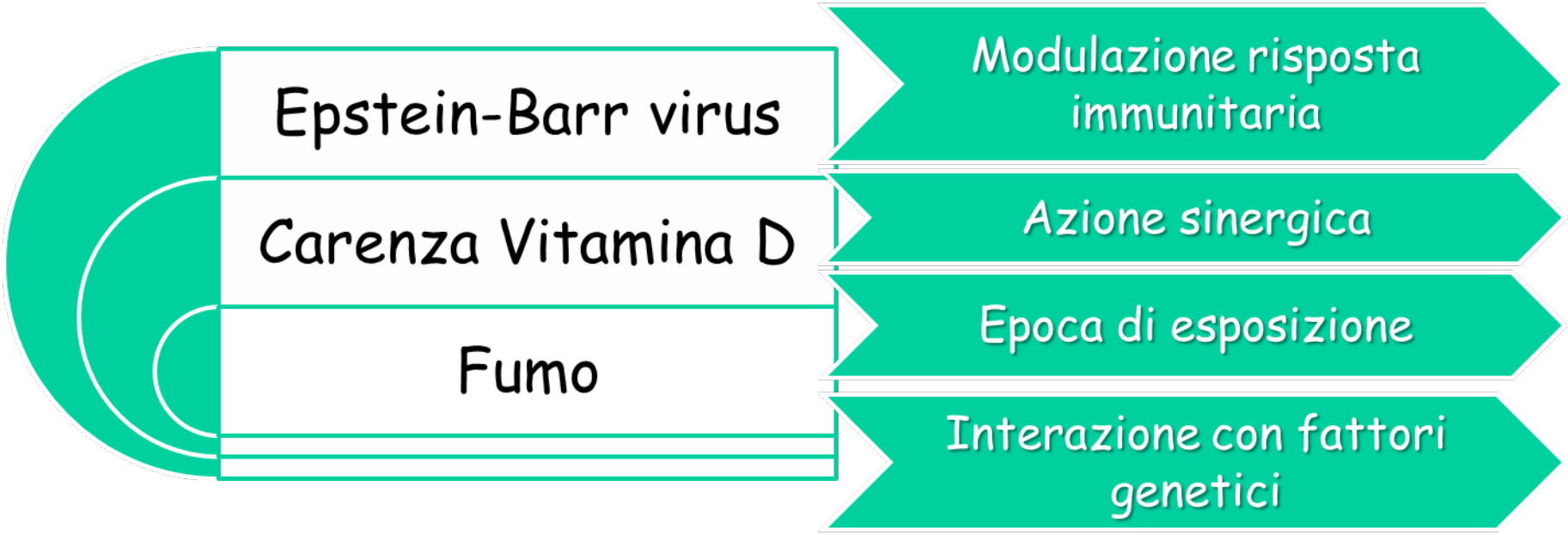


Figure 4. Plot of gender ratio by six birth decades in MS patients from Northern Latitude Area (A) and Northern Europe (B) stratified by Relapsing Remitting (RR) and Primary Progressive (PP) disease course. *p-value for trend* *<0.001.

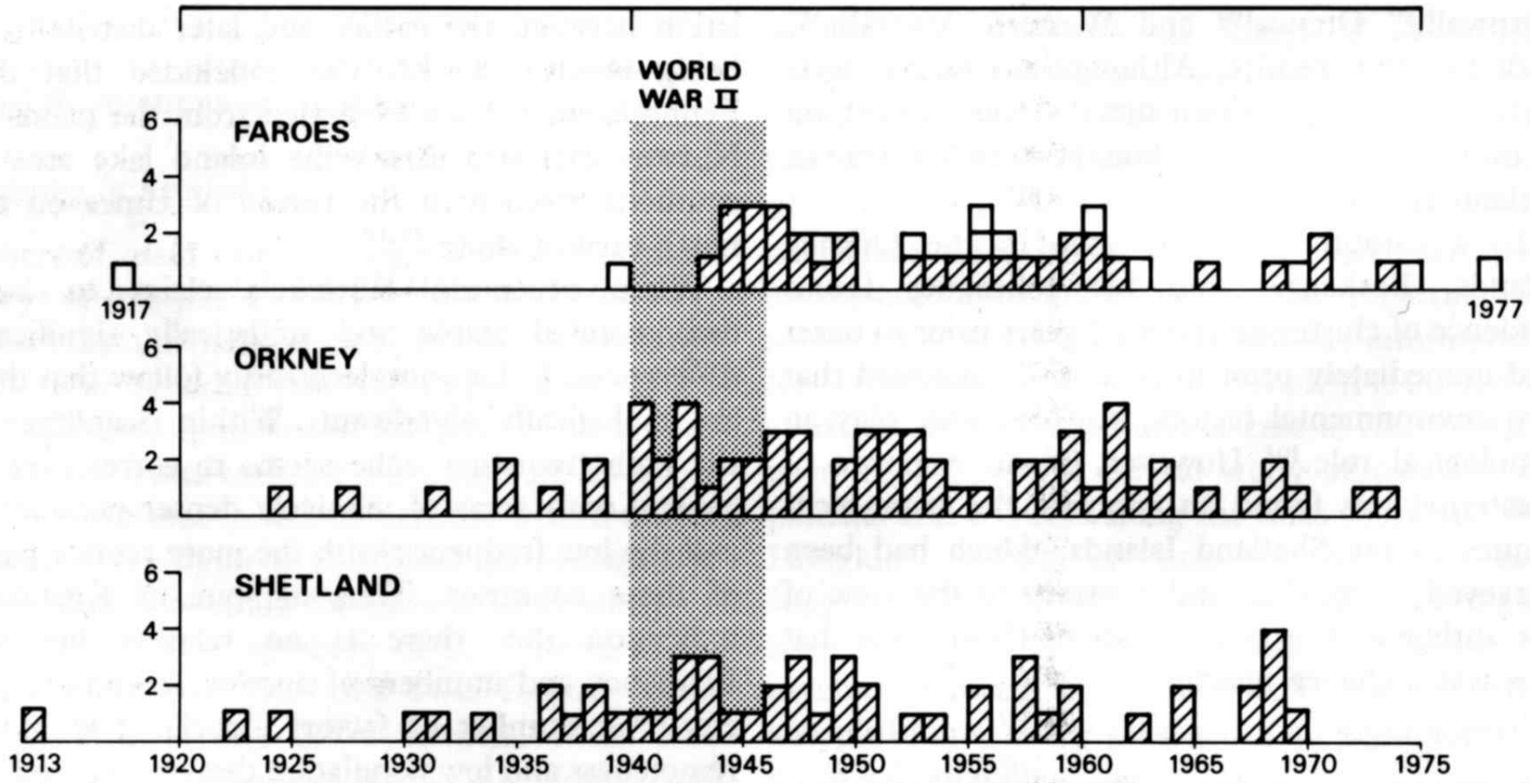
doi:10.1371/journal.pone.0048078.g004

Fattori ambientali



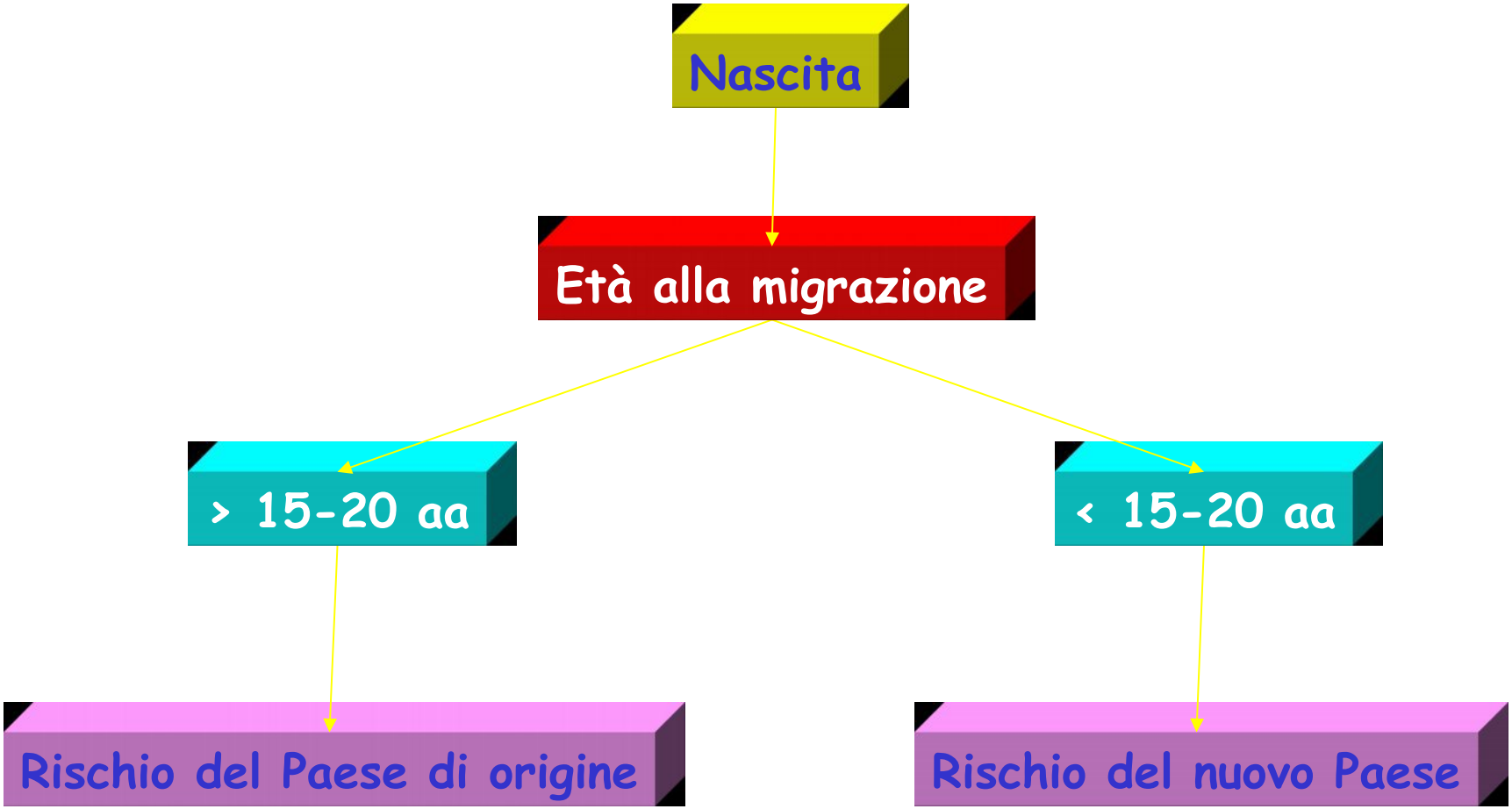
"Clusters"

Isole Faroes, Orkney e Shetland (Scozia)



Kurtzke and Hyllested, 1988

Età alla migrazione e rischio di SM



Studi sui migranti

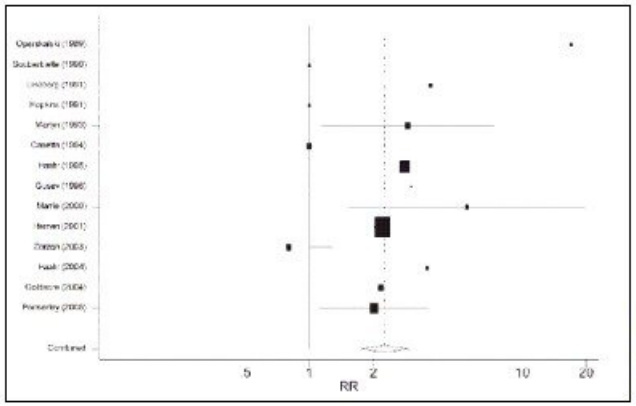
Corollari:

- **Età critica** di esposizione ai possibili fattori di rischio / causali correlati all'ambiente: prime 2 decadi di vita

- **Periodo di latenza** lungo tra esposizione e comparsa della malattia

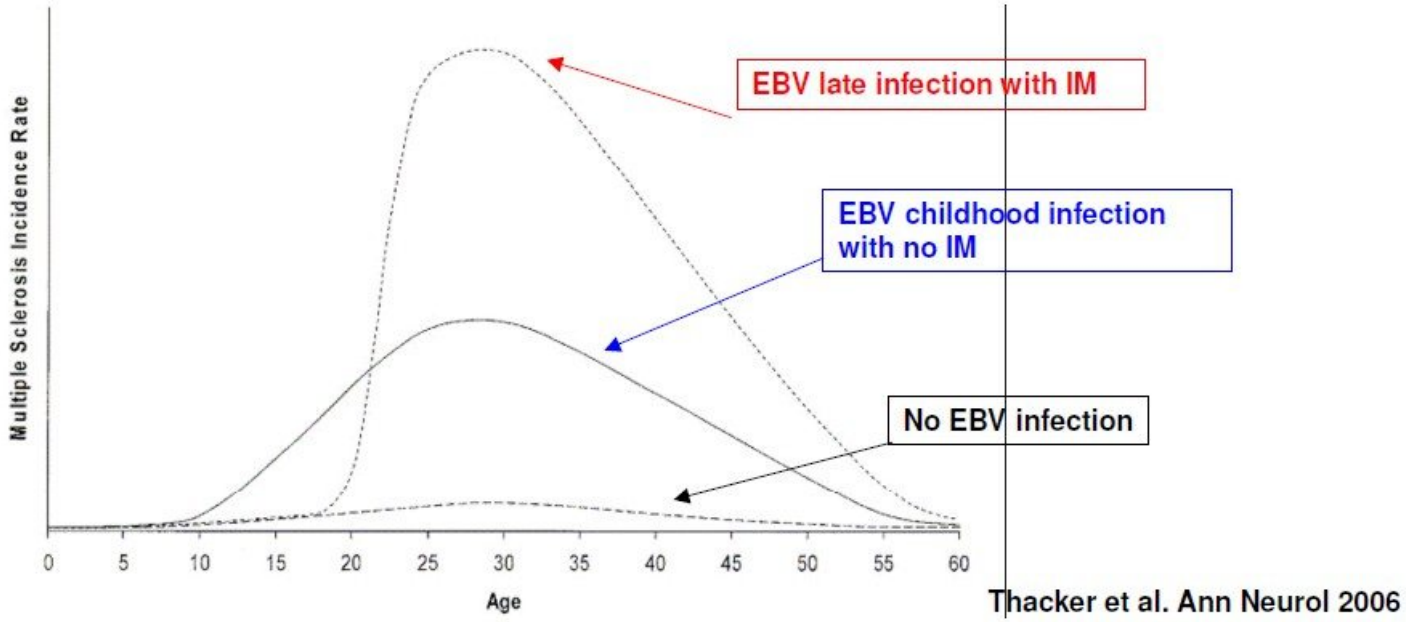
Lista di agenti infettivi che sono stati associati alla SM

- Rabies 1946
- Measles 1964
- Herpes simplex 1972
- Virus parainfluenza I 1972
- Chimpanzee cytomegalovirus 1979
- Coronavirus 1979
- Tick encephalitis 1982
- HTLV-1 1985
- Virus simian V 1987
- MS-associated human endogenous retrovirus (HERV) 1995
- Human herpes virus 6 (HHV6) 1995
- Epstain-Barr Virus
- Clamydia pneumoniae 1999



Infectious mononucleosis (EBV) and MS

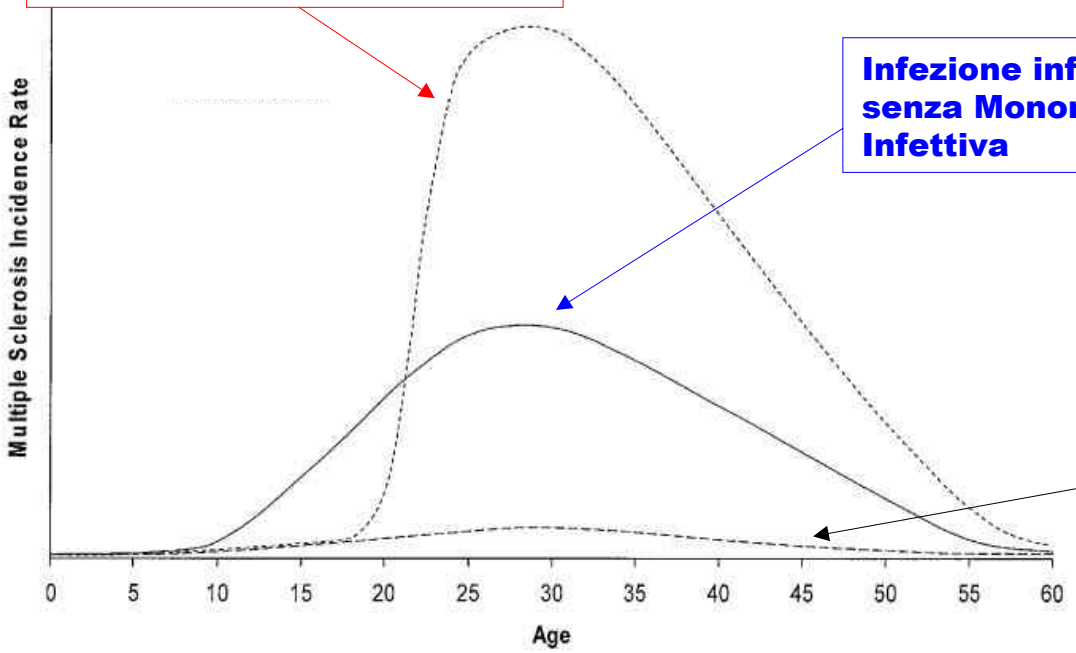
Meta-analysis of 14 studies on the association between IM and MS



Thacker et al. Ann Neurol 2006

- **Metanalisi di 14 studi caso-controllo e di coorte**
  (Thacker et al, Ann Neurol 2006)

- I titoli di ATC anti EBVNA1 sono fortemente correlati al rischio di SM
  (Munger 2011, Ascherio 2012)



Mononucleosi infettiva (EBV) e rischio per SM

- **Metanalisi di 14 studi caso-controllo e di coorte** (Thacker et al, Ann Neurol 2006)
- **I titoli di ATC anti EBVNA1** sono fortemente correlati al rischio di SM (Munger 2011, Ascherio 2012)

	Canada and northern USA	Southern USA	South America	Europe	Number of seropositive patients/number of patients with definitive serology* (%)	p value*
EBV (remote)	57 (81%)	13 (93%)	22 (85%)	16 (100%)	108/126 (86%)	0·18
CMV	32 (44%)	3 (20%)	17 (68%)	9 (56%)	61/124 (49%)	0·04
HSV	28 (39%)	3 (21%)	19 (73%)	10 (63%)	60/133 (45%)	0·003
Parvovirus B19	37 (64%)	8 (57%)	13 (54%)	5 (33%)	63/107 (59%)	0·18
VZV	64 (90%)	14 (93%)	19 (79%)	13 (87%)	110/126 (87%)	0·77

Data are number of seropositive patients (%), unless specified otherwise. Patients with insufficient samples or patients with indeterminate results excluded. *For comparison of seroprevalence for each virus across the four regions. Logistic regression was done, adjusting for age at sampling, with Canada/northern USA arbitrarily designated as the reference. Exploratory analysis, unadjusted for multiple comparisons.

Table 5: Viral seroprevalence by region of enrolment in the participants with MS

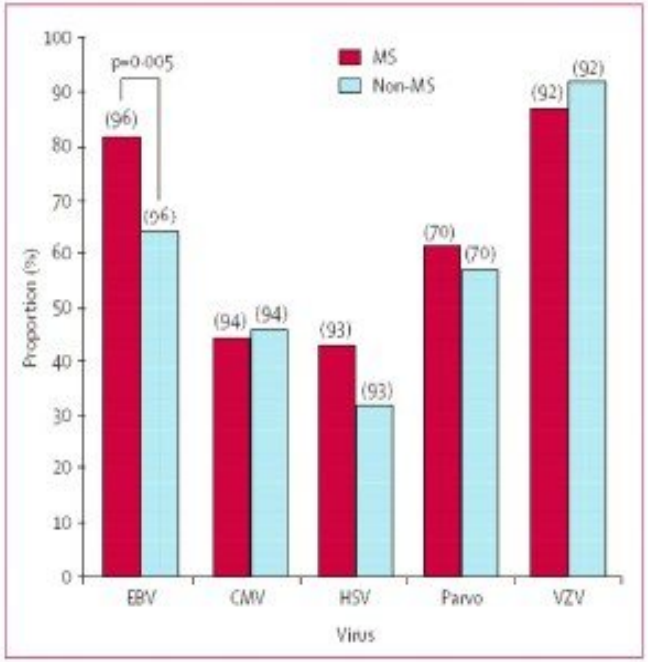


Figure 2: Seroprevalence of common childhood viruses in children with MS and in control participants

Observational studies: viral serology

Serological evidence of remote infection with EBV has been documented in over 85% of children with MS versus 40–60% in age-matched healthy children *(Alotaibi et al, 2004; Pohl et al, 2006; Banwell et al, 2007)*

Banwell et al. Lancet Neurology 2007

EBV e SM: dati liquorali

Identificazione nel liquor di IgG reattive alle proteine dell'EBV da parte di 3 gruppi indipendenti:

- ✓ Rand, J Neurol Sci 2000
- ✓ Bray Neurology 1992
- ✓ Cepok, J Clin Invest 2005

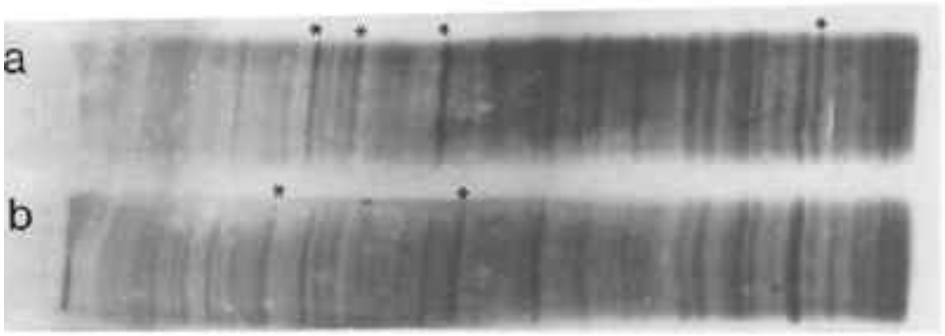


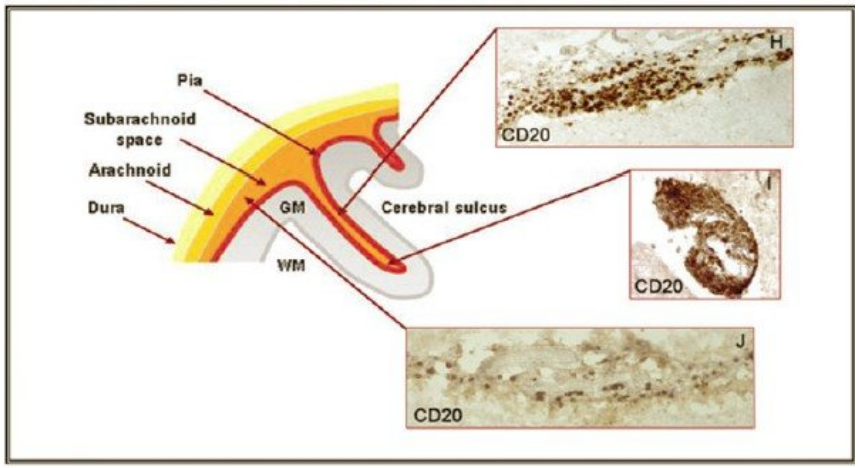
FIGURE 1. IEF gels of CSF obtained from one patient with MS. CSF were obtained in 1974 and 1982 (*a* and *b*, respectively). The procedure of IEF and immunofixation with antibody to human IgG H chains followed by silver staining is described in the text. Location of bands (*) that are more prominent in lane *a* or *b*.

EBV e follicoli ectopici di cellule B intrameningeali
(Serafini et al., JEM 2007)

Su tessuti di pazienti trovati markers di presenza e attivazione dell'EBV, a livello di follicoli di cellule B submeningeali, specie in pazienti in fase progressiva di malattia

<u>Ipotesi</u>: La persistenza e la periodica riattivazione del virus nel SNC potrebbe giocare un ruolo nella patogenesi della SM

Follicoli ectopici intrameningeali di cellule B esprimono markers dell'EBV



Su tessuti di pazienti trovati markers di presenza e attivazione dell'EBV, a livello di follicoli di cellule B submeningeali, specie in pazienti in fase progressiva di malattia

Ipotesi: La persistenza e la periodica riattivazione del virus nel SNC potrebbe giocare un ruolo nella patogenesi della SM

Serafini, 2007
Magliozzi, 2007

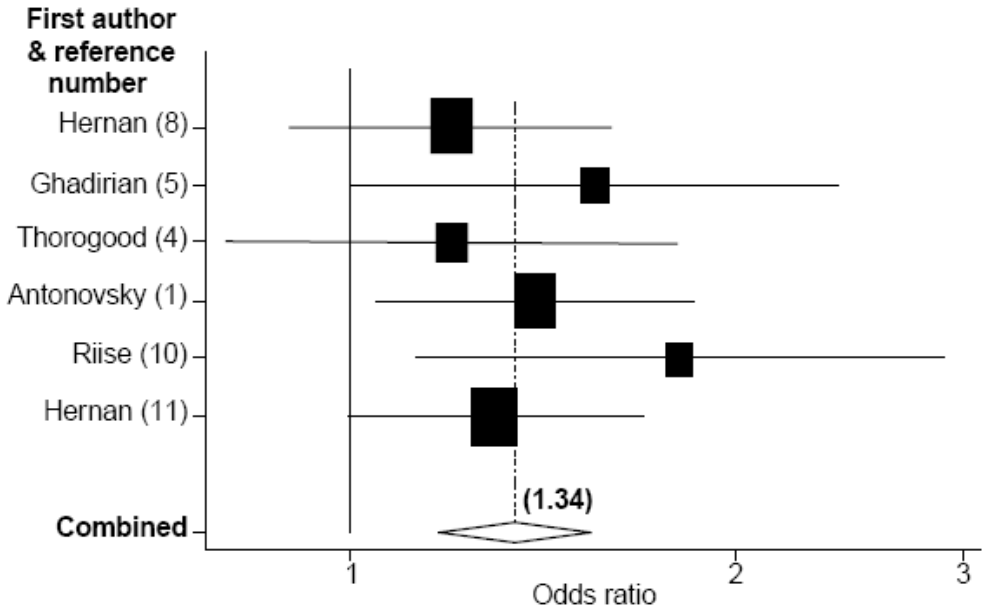
Dato controverso/non confermato
in studi successivi
(Lassman 2010, Owens and Bennet 2012, Tracy, 2012)

Infezioni virali e autoimmunità

- ✓ Meccanismo dello "spettatore innocente"
- ✓ Meccanismo di stimolazione superantigenica
- ✓ Mimetismo molecolare

EZIOLOGIA DELLA SCLEROSI MULTIPLA: FATTORI AMBIENTALI

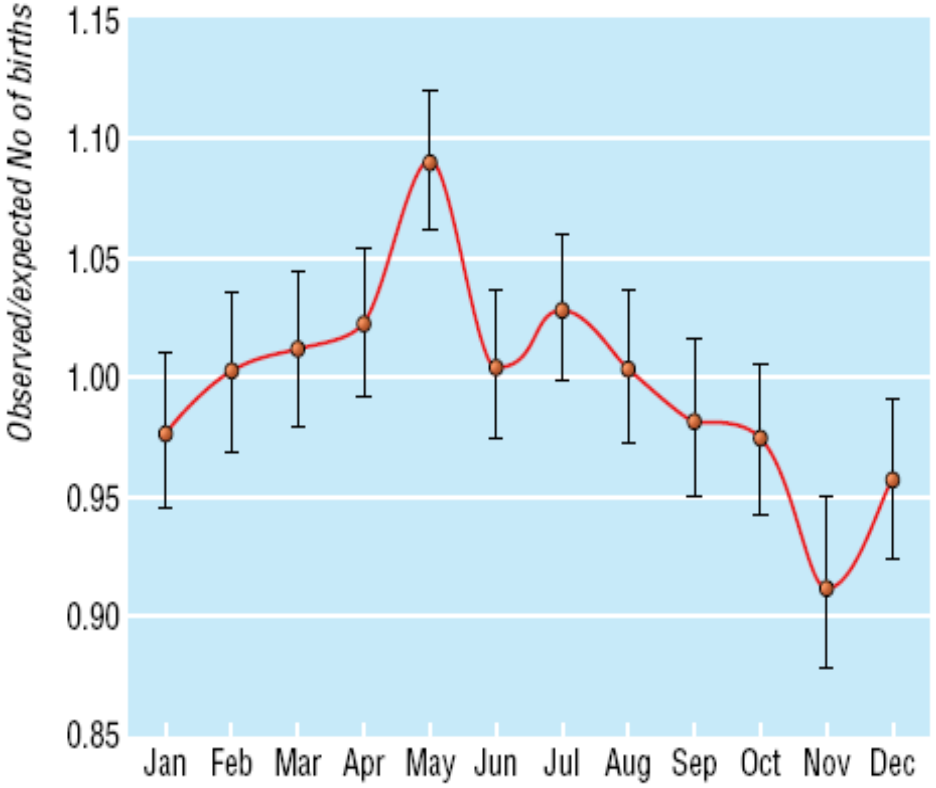
Ruolo del fumo



Possibile ruolo del fumo, anche passivo (Mikaeloff, 2007) come fattore di rischio e fattore modificante il decorso nella SM

(Review article: Fleming and Cook, Neurology 2006)

EZIOLOGIA DELLA SCLEROSI MULTIPLA: Mese di nascita



Mese di nascita e rischio per SM

<u>Ipotesi:</u>

- Carenza di Vit. D nel periodo prenatale?
- Infezioni nella vita intrauterina?

Circa 18.000 pazienti in Canada e 11.000 in GB
(Willer, BMJ 2005)

Metabolismo della vit. D

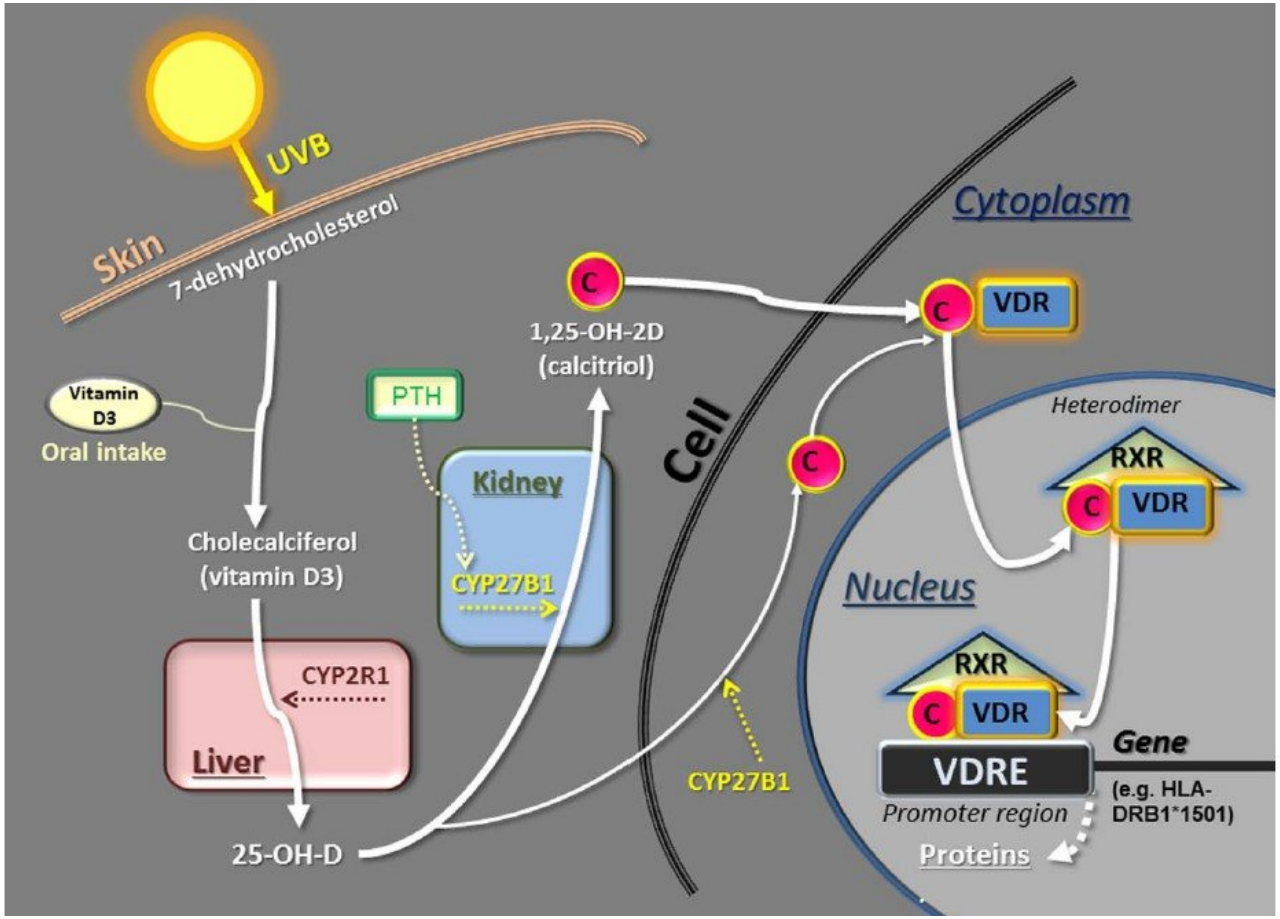
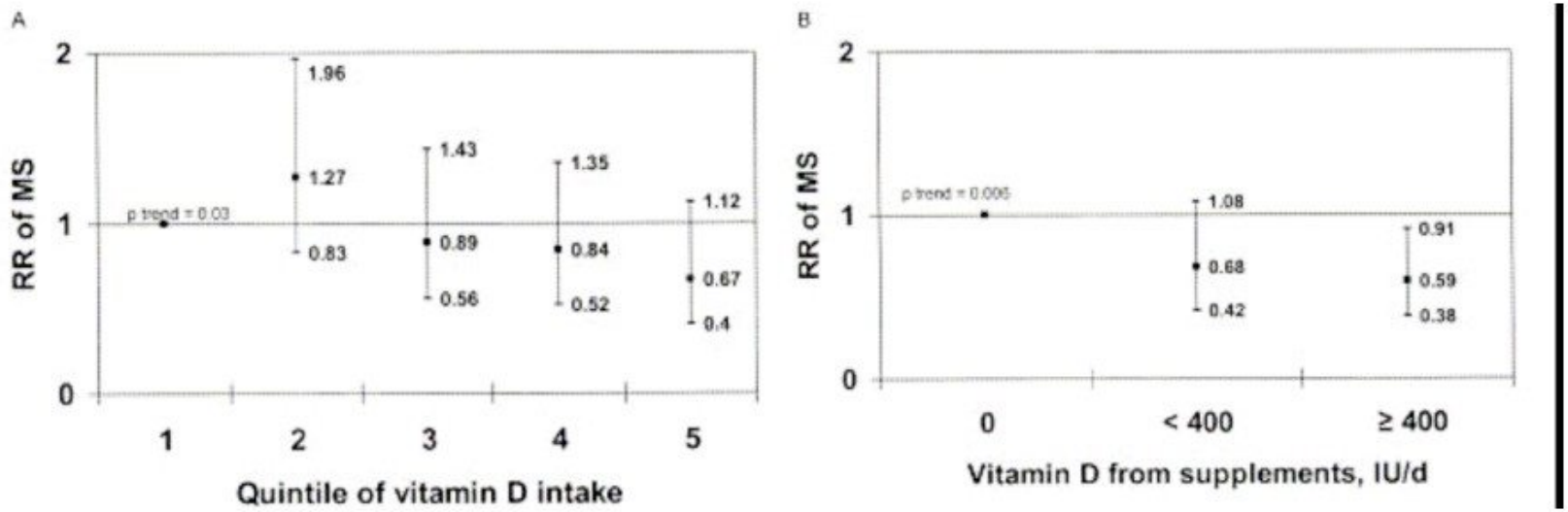


Figure 1. Schematic representation of vitamin D metabolism.
Note that, at the gene level, the heterodimer comprising calcitriol may stimulate or repress protein synthesis, depending on the cell. C, calcitriol; CYP2R1, vitamin D-25-hydroxylase; CYP27B1, 1α-hydroxylase; PTH, parathyroid hormone; RXR, retinoid X receptor; UVB, ultraviolet B radiation; VDR, vitamin D receptor; VDRE, vitamin D-responsive element.

Vitamin D and risk for MS

- average annual hours of sunshine and the average December daily solar radiation at place of birth strongly and inversely correlated with MS (r=- 0.73 and r=- 0.80, respectively) *(Acheson et al, 1960)*
- similar results in Australia and among immigrants to Israel *(Sutherland et al, 1962; van der Mei et al, 2001; Leibowitz et al, 1967)*
- inverse correlation in Switzerland between MS prevalence and altitude (marker of sunlight intensity) *(Kurtzke, 1967)*
- skin cancer mortality rate in MS about 50% less than expected (p = 0.03) *(Goldacre et al, 2004)*
- the average time spent in the sun during weekends and holidays in childhood assessed using a questionnaire, by an interview and by assessing the degree of actinic damage, was consistently associated with a lower risk for MS (RRs of MS among subjects who reported an average time in the sun of 2+ hours between the ages of 6 and 10 were 0.47 (95% CI, 0.26–0.84) *(van der Mei et al, 2003)*
- the use of vit D supplements during periods of low sunlight exposure reduces the risk for MS (Northern Norway) *(Kampman et al, 2007)*

Vitamin D and risk for MS



(A) Relative risk of MS according to vitamin D intake. p for trend = 0.03.
(B) Relative risk of MS according to use of vitamin D supplements. p for trend = 0.006.

Munger et al. Neurology 2004
Ascherio, Munger. Ann Neurol 2007

Possibile ruolo della vit.D come fattore di rischio e fattore modificante il decorso di malattia

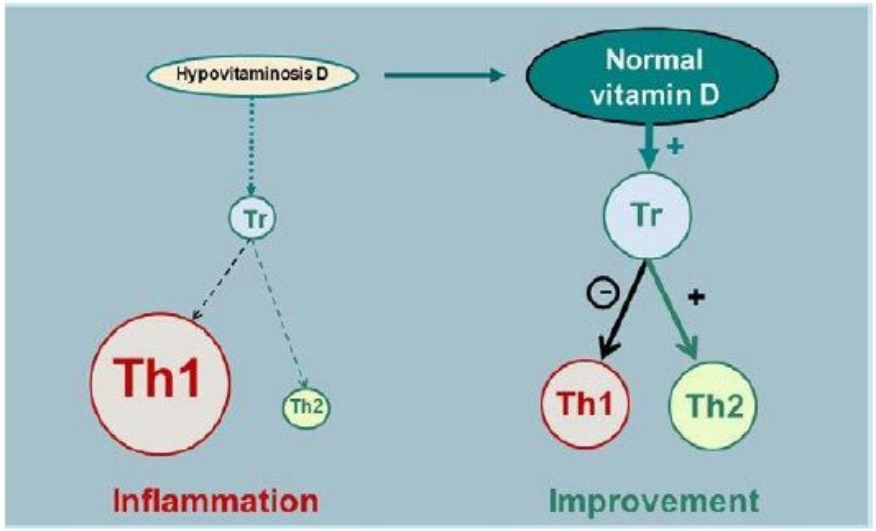


Figure 2. Schematic representation of one of the hypothetical immunomodulatory effects of vitamin D (through calcitriol).
Tr, regulatory T lymphocyte; Th1, lymphocyte T helper 1 ('aggressive'); Th2, lymphocyte T helper 2 ('protective').

- Dati EAE
- Stud osservazionali
- (Munger, 2004, Ascherio 2007)
- Meta-analisi di 5 trial randomizzati sull'associazione di alte dosi Vit D e relapse
- (OR 0.98, IC95% 0.45-2.16) (James, MSJ 2013)

Possibile ruolo della vit.D

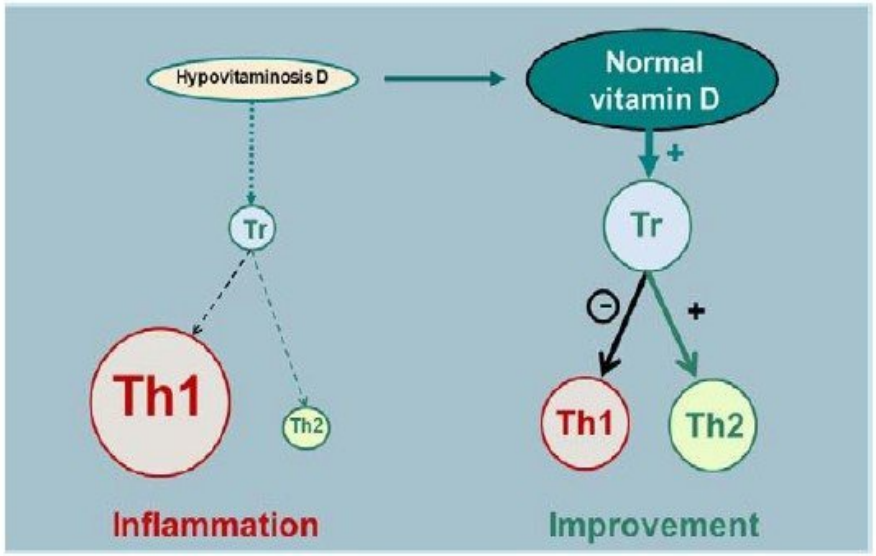


Figure 2. Schematic representation of one of the hypothetical immunomodulatory effects of vitamin D (through calcitriol).
Tr, regulatory T lymphocyte; Th1, lymphocyte T helper 1 ('aggressive'); Th2, lymphocyte T helper 2 ('protective').

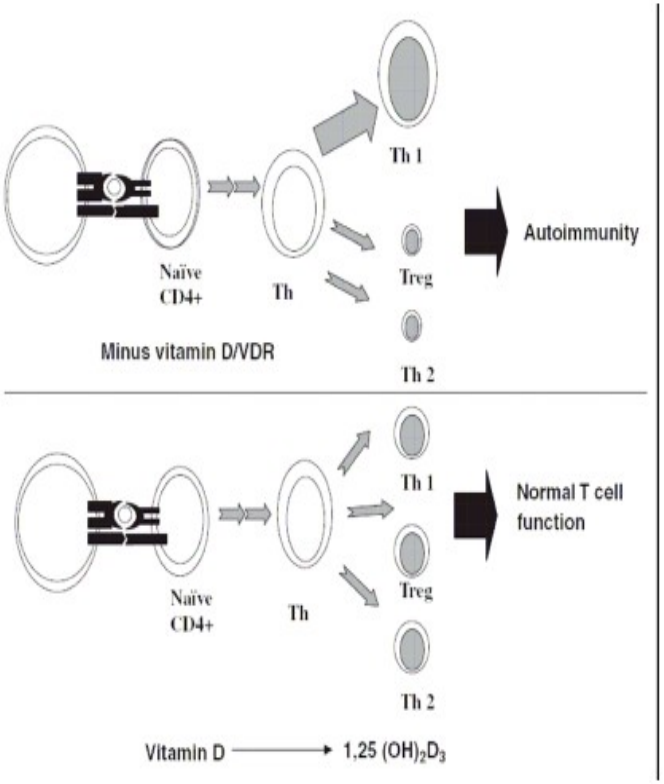
- Dati sperimentali nell' EAE: importanza dell'espressione del gene per VDR
- Studi epidemiologici di associazione tra SM e bassi livelli di 25-OH-D (<75nmol/l)
- Trial non randomizzati e randomizzati: meta-analisi di 5 trial randomizzati non significativa *(James, MSJ 2013)*
- Ampi trial randomizzati in corso in Europa e Nord-America

Review : Pierrot-Deseilligny and Souberbielle, ther Adv Neurol Disord, 2013

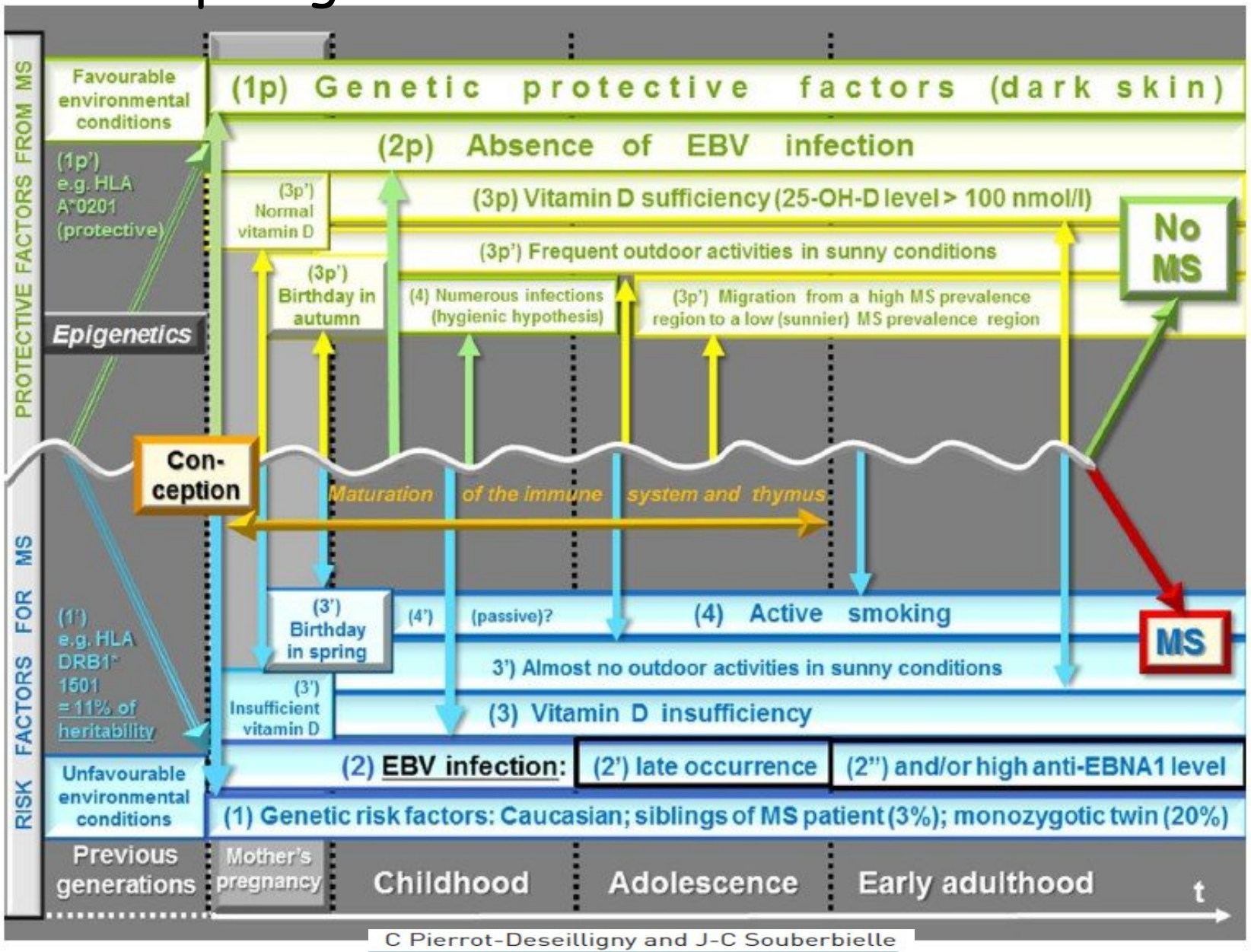
EZIOLOGIA DELLA SCLEROSI MULTIPLA: FATTORI AMBIENTALI ruolo della vitamina D

Immune system and vitamin D

Mounting evidence from experimental and epidemiological studies is now converging to implicate sunlight exposure and the resulting increase in vitamin D as an important contributor.



SM: patogenesi multifattoriale

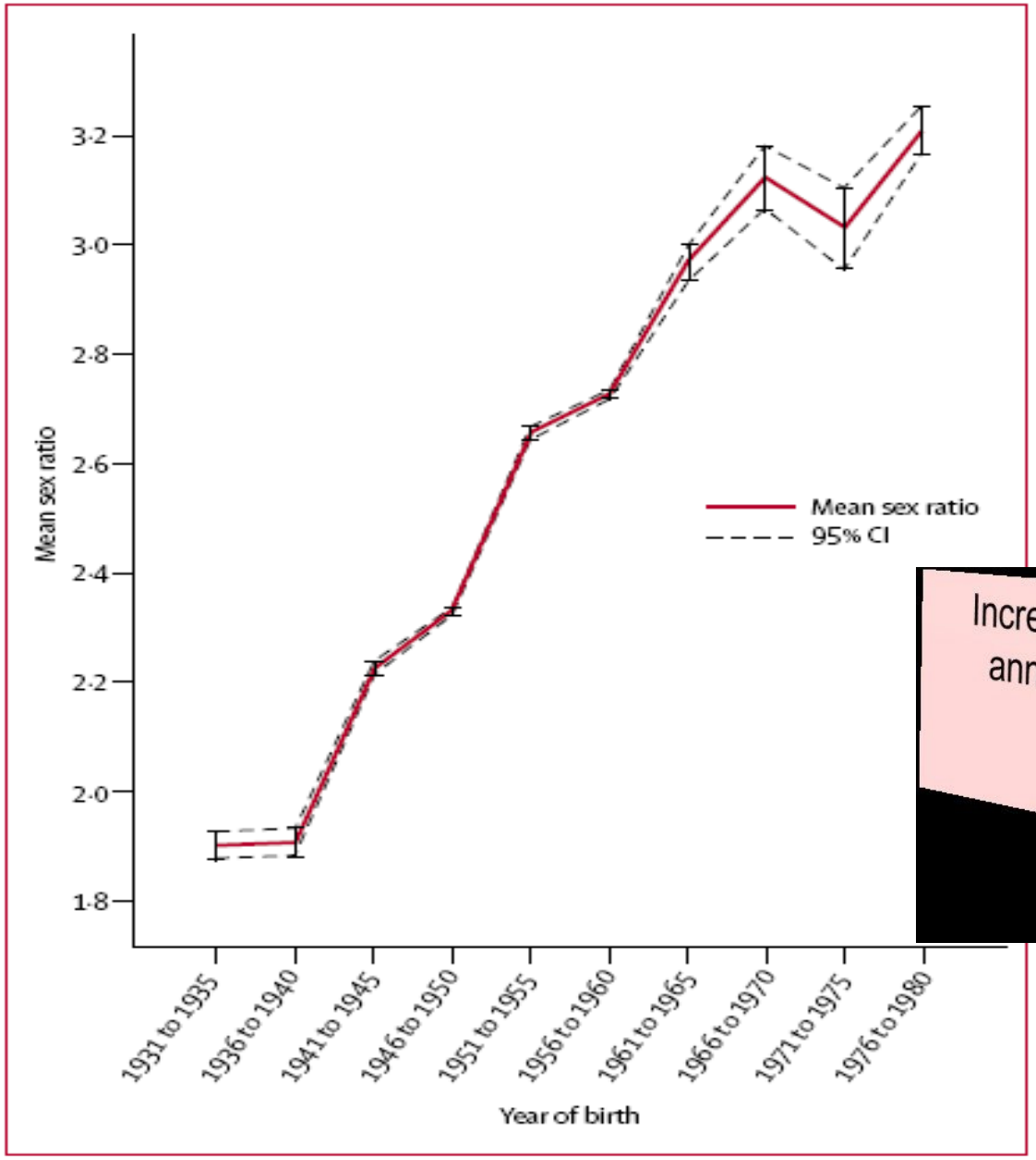


C Pierrot-Deseilligny and J-C Souberbielle

Ther Adv Neurol Disord

(2013) 6(2) 81–116

EPIDEMIOLOGIA DELLA SM



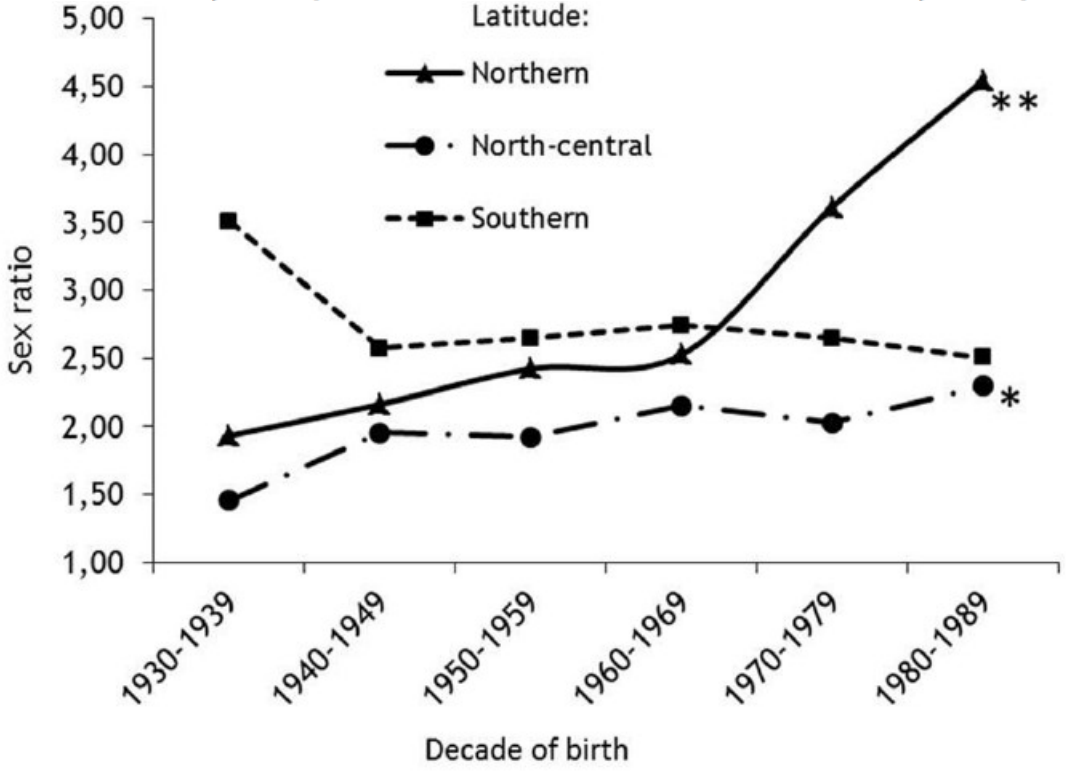
Incremento del rapporto F:M per anno di nascita in pazienti con SM, dal 1936 al 1980 (Orton, 2006)

OPEN ACCESS Freely available online

PLOS | ONE 2012

Geographical Variations in Sex Ratio Trends over Time in Multiple Sclerosis

Maria Trojano[1]*, Guglielmo Lucchese[1], Giusi Graziano[2], Bruce V. Taylor[3], Steve Simpson, Jr.[3], Vito Lepore[2], Francois Grand'Maison[4], Pierre Duquette[5], Guillermo Izquierdo[6], Pierre Grammond[7], Maria Pia Amato[8], Roberto Bergamaschi[9], Giorgio Giuliani[10], Cavit Boz[11], Raymond Hupperts[12], Vincent Van Pesch[13], Jeannette Lechner-Scott[14], Edgardo Cristiano[15], Marcela Fiol[16], Celia Oreja-Guevara[17], Maria Laura Saladino[18], Freek Verheul[19], Mark Slee[20], Damiano Paolicelli[1], Carla Tortorella[1], Mariangela D'Onghia[1], Pietro Iaffaldano[1], Vita Direnzo[1], Helmut Butzkueven[21,22,23], on behalf of the MSBase Study Group, the New Zealand MS Prevalence Study Group¶



- 15.996 casi
- Variazione del rapporto F/M aa 1930-1989
- Variazione globale da 2.35 a 2.73
- Latitudine N 83°-45° da 1.93 a 4.55
- Latitudine N 45°-35° da 1.46 a 2.30
- Latitudine S 12°-55° stabile

Figure 1. Plot of gender ratio by six birth decades in MS patients stratified by Latitude. *p-value for trend *0.0425; **<0.0001.*

doi:10.1371/journal.pone.0048078.g001

Rapporto F/M in pazienti con SM
Paesi Nord-Europei e Sud-Europei

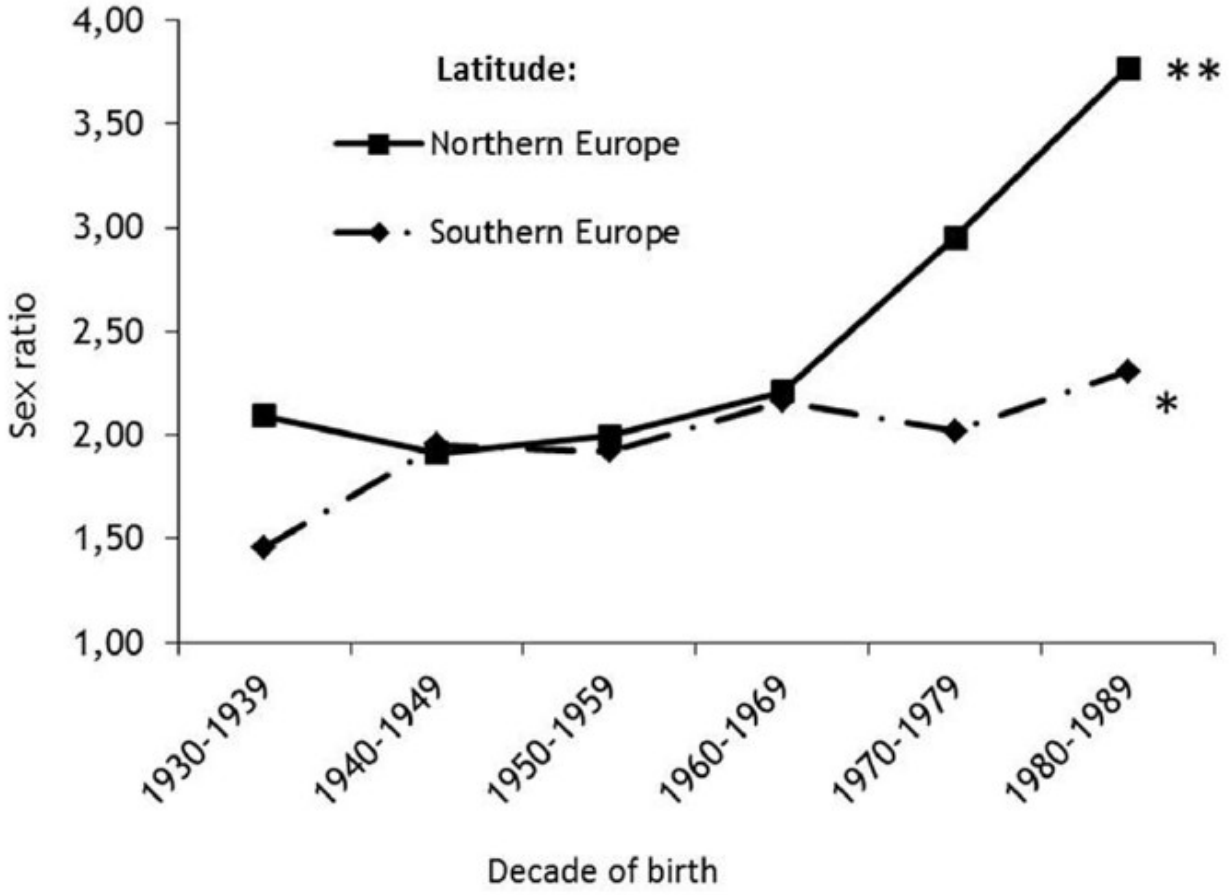


Figure 2. Plot of gender ratio by six birth decades in MS patients from Northern and Southern Europe. *p-value for trend *0.0426; **<0.0004.*
doi:10.1371/journal.pone.0048078.g002

Rapporto F/M nei pazienti con SM stratificati per decorso RR o PP

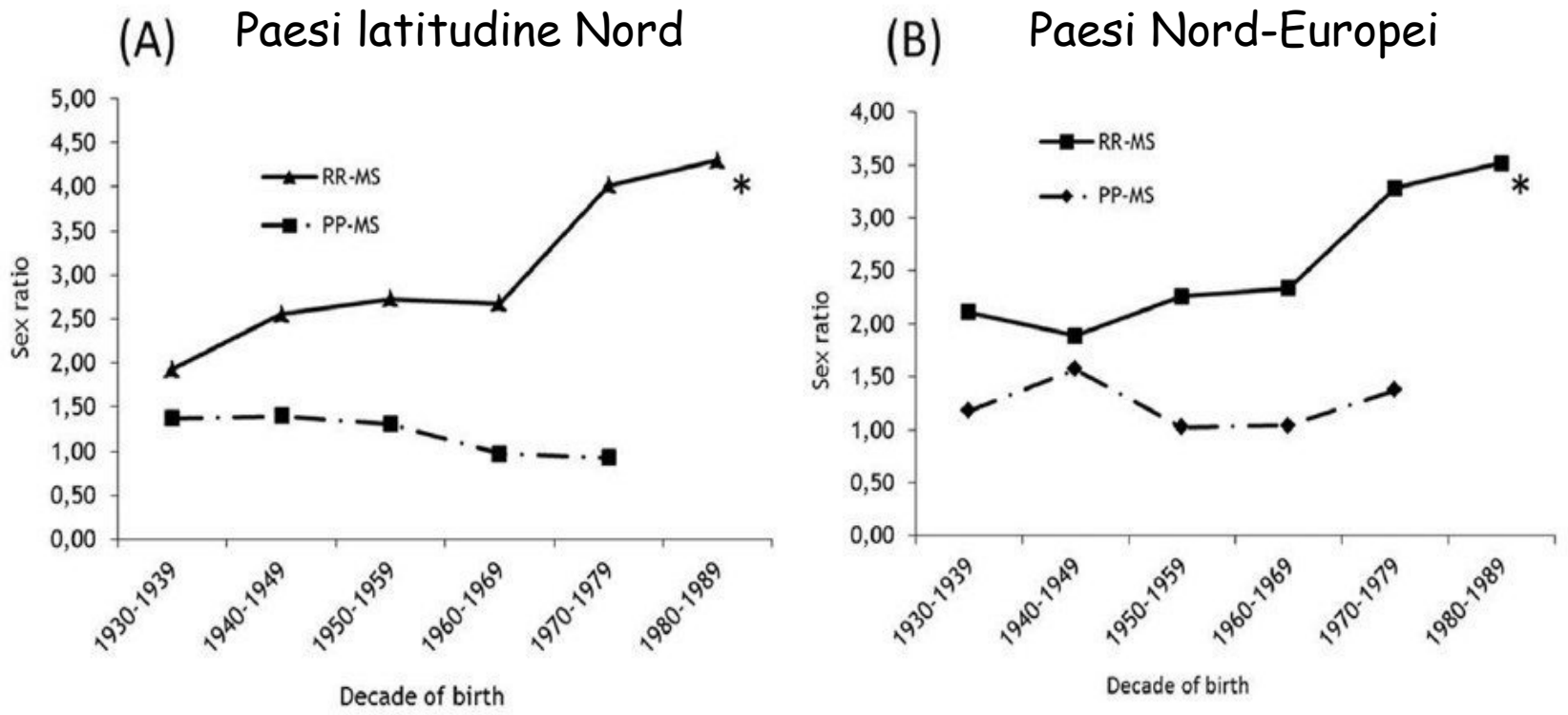


Figure 4. Plot of gender ratio by six birth decades in MS patients from Northern Latitude Area (A) and Northern Europe (B) stratified by Relapsing Remitting (RR) and Primary Progressive (PP) disease course. *p-value for trend* *<0.001.

doi:10.1371/journal.pone.0048078.g004

Ipotesi

- Interazione geni-ambiente
- Modificazioni stile di vita nel sesso femminile
  - *Fumo*
  - *Dieta*
  - *Obesità*
  - *Esposizione al sole*
  - *Deficit vit.D*
  - *Ingresso nel mondo del lavoro*
  - *Contraccettivi*
  - *Maggior numero di nullipare*
  - *Maggiore età alla nascita del primo figlio*

Koch-Henriksen and Sorensen, Lancet Neurol 2010

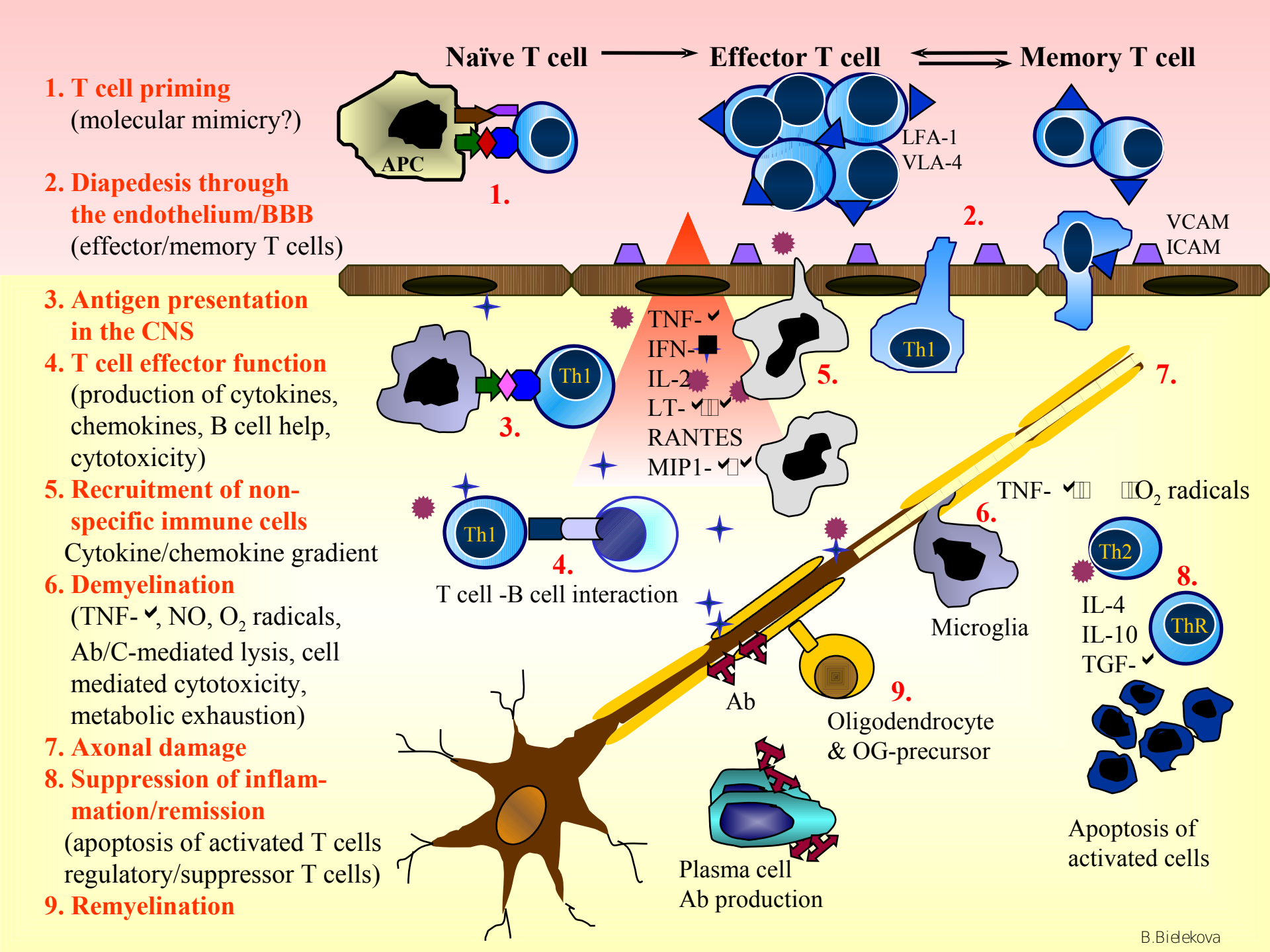
Agenda

- Ipotesi eziopatogenetiche
- Inquadramento clinico e prognostico

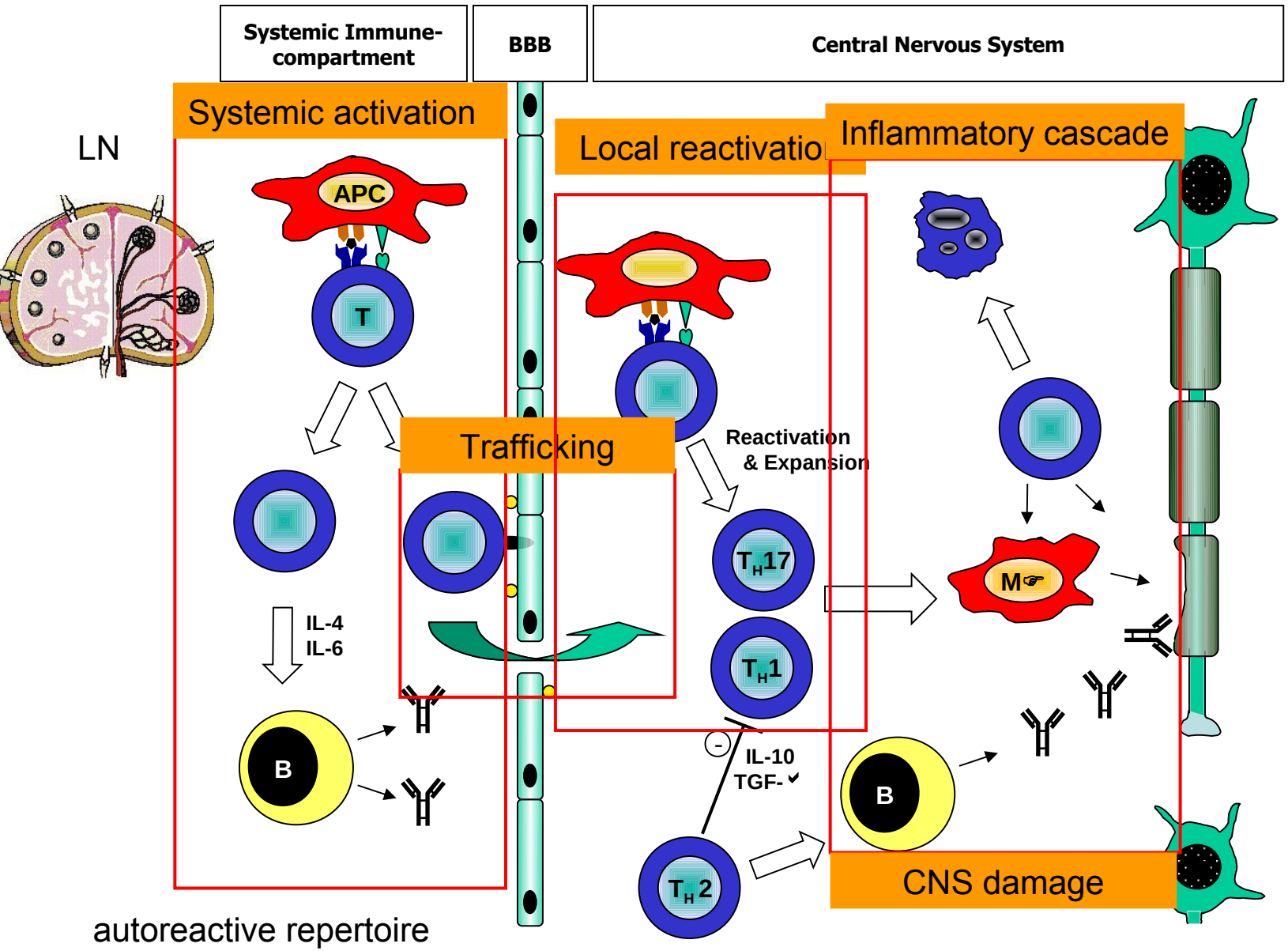
Figure 4. Modulation of multiple sclerosis risk from conception to the time of disease triggering.
Note that (a) risk factors for MS are multiple, genetic and environmental (lower part of the figure), (b) opposite conditions or other factors may be protective from MS occurrence (upper part of the figure), (c) interactions are numerous between all these risk and protective factors and (d) may occur throughout the first part of life, from conception until MS triggering. Note also that the period from conception to adolescence is crucial for the maturation of the immune system and thymus and could be particularly important for the interactions of the different protective and risk factors. In these successive events or situations, the likely risk factors are (see text): (1) unfavourable genetics, (1') including HLA-DRB1*1501; (2) EBV infection, which may be a crucial event for subsequent MS (years later), with particularly an increase in MS risk if (2') the primo-infection occurs late and (2") is followed by a high anti-EBNA1 level; (3) vitamin D insufficiency, also increasing MS risk, (3') including conditions likely related to this insufficiency or to insufficient exposure to sun; and (4) smoking, also contributing to this risk, even if (4') it is only passive in childhood (however, with only one study having been reported so far). Reverse or other conditions could be protective: (1p) favourable genetics, (1p') including HLA-A*0201; (2p) absence of EBV infection; (3p) vitamin D sufficiency, (3p') including conditions likely related to a normal vitamin D status or sufficient exposure to sun; and (4p) numerous infections during childhood (hygienic hypothesis), possibly protective from subsequent auto-immune diseases. EBV, Epstein–Barr virus; HLA, human leukocyte antigen system; MS, multiple sclerosis.

Evidenze (indirette) di patogenesi autoimmune

- Infiltrato linfo-monocitario nelle lesioni
- Presenza di bande oligoclonali (IgG) nel liquor
- Associazione con ATG HLA, ed altri geni coinvolti nella risposta immune
- Associazione con altre patologie disimmuni
- Efficacia delle terapie immunomodulanti e immunosopppressive
- Analogia con modelli sperimentali (EAS)


Naïve T cell
Effector T cell
Memory T cell
1. T cell priming
(molecular mimicry?)
2. Diapedesis through the endothelium/BBB
(effector/memory T cells)
3. Antigen presentation in the CNS
4. T cell effector function
(production of cytokines, chemokines, B cell help, cytotoxicity)
5. Recruitment of non-specific immune cells
Cytokine/chemokine gradient
6. Demyelination
(TNF-, NO, O2 radicals, Ab/C-mediated lysis, cell mediated cytotoxicity, metabolic exhaustion)
7. Axonal damage
8. Suppression of inflam-mation/remission
(apoptosis of activated T cells regulatory/suppressor T cells)
9. Remyelination
APC
1.
LFA-1
VLA-4
2.
VCAM
ICAM
Th1
3.
TNF-
IFN-
IL-2
LT-
RANTES
MIP1-
5.
7.
Th1
4.
T cell -B cell interaction
TNF-
O2 radicals
6.
Microglia
Th2
8.
IL-4
IL-10
TGF-
ThR
Ab
9.
Oligodendrocyte
& OG-precursor
Plasma cell
Ab production
Apoptosis of
activated cells
B.Bielekova

MS immunopathogenesis

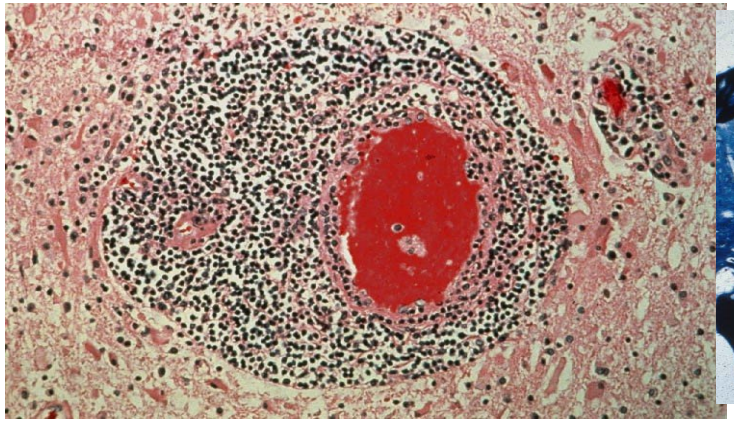


Anatomia patologica (Charcot, 1848)

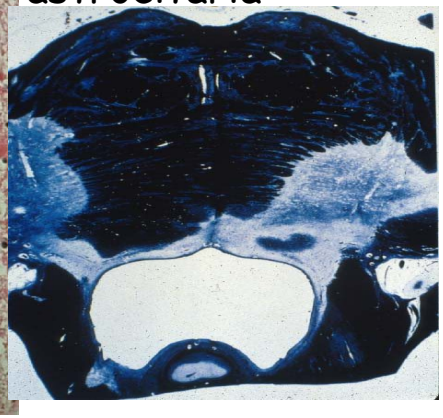
Lesione fondamentale:

- infiltrato infiammatorio nella SB del SNC
- demielinizzazione focale
- variabile danno assonale
- evoluzione verso la cicatrice gliale

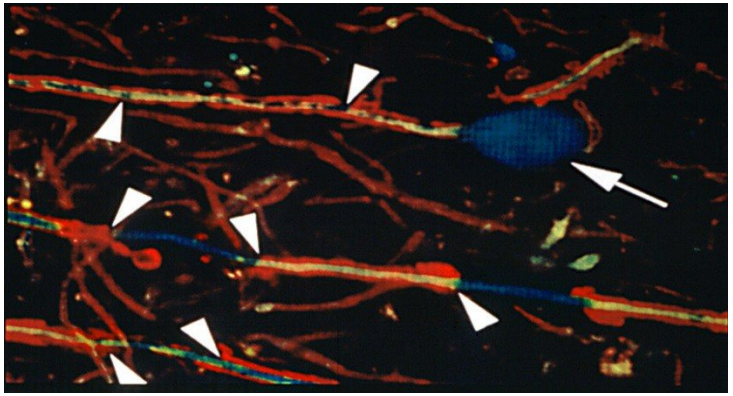
Infiltrato infiammatorio



Demielinizzazione/gliosi astrocitaria

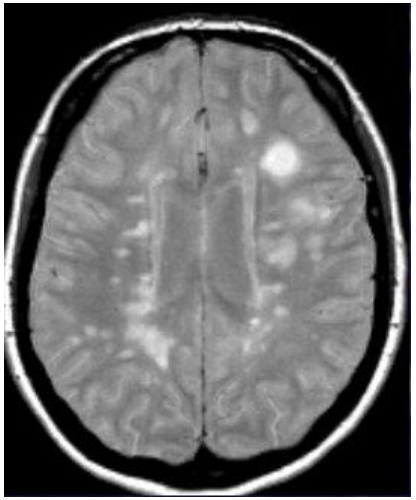


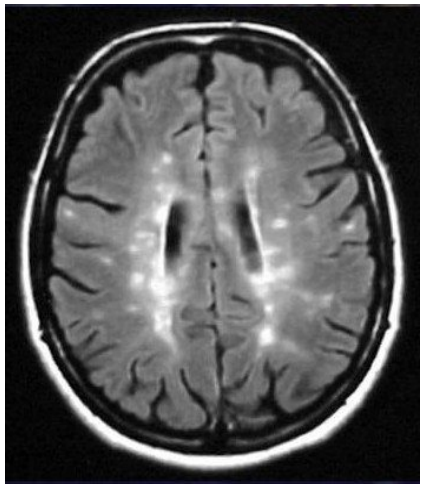
Danno assonale (transezione)



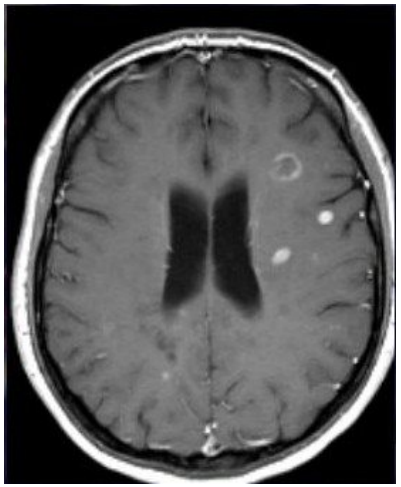
Sintomi- Localizzazione delle lesioni nella SB

Lesioni Periventricolari

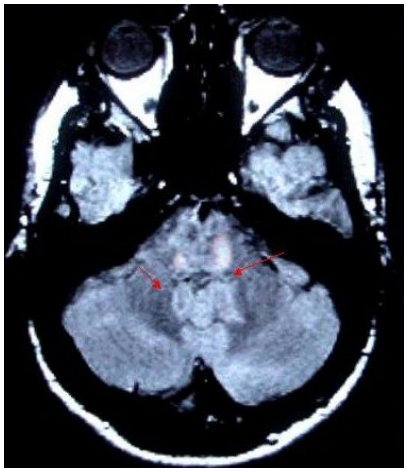




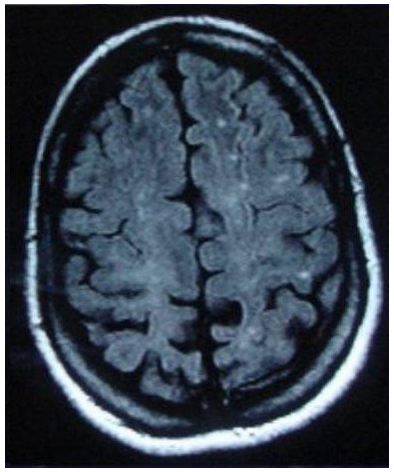
Lesione Gd-positiva



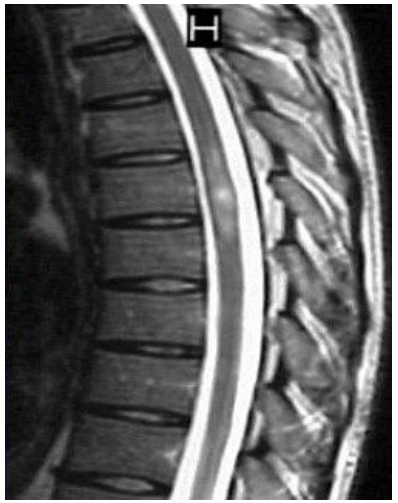
Lesioni Infratentoriali



Lesioni Juxtacorticali

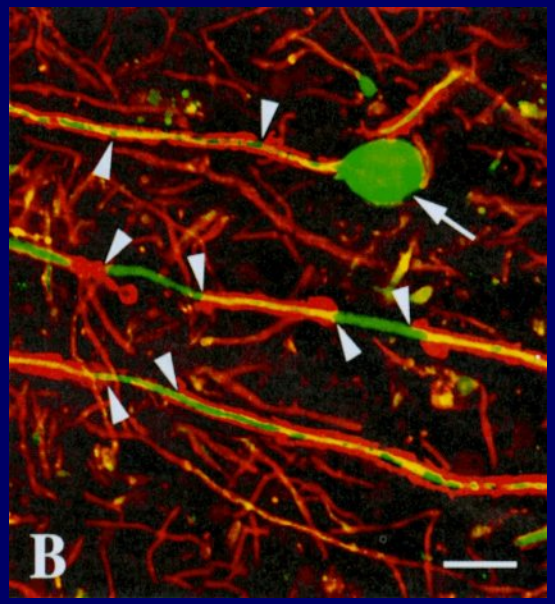


Lesione spinale



Danno assonale precoce

- La transezione assonale è irreversibile e molto abbondante nelle aree di infiammazine (Trapp et al. 1998)
- Il danno assonale acuto progredisce più rapidamente nelle prime fasi di malattia (Kuhlmann et al. 2002)



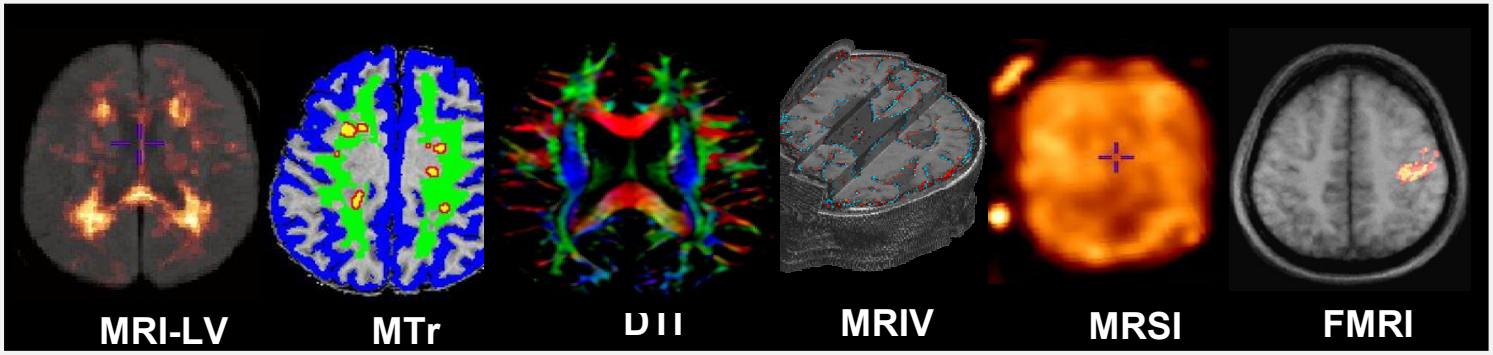
Trapp et al., NEJM 1998

Le conseguenze

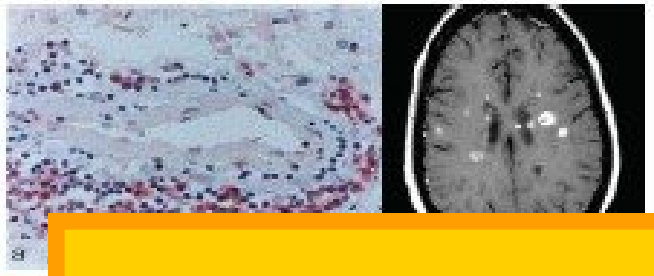
- La perdita assonale oltre la soglia di compensazione (ridondanza, plasticità) si associa a disabilità irreversibile e progressione clinica di malattia (Rieckmann et al. 2005)
- Importanza della **terapia precoce**, per **prevenire l'accumulo di danno assonale**

INOLTRE

- **Danno assonale** cronico in lesioni apparentemente inattive
- Coinvolgimento della **sostanza grigia**
- **Diffuso interessamento della sostanza bianca e grigia «apparentemente normali»**, al di fuori delle lesioni



Una malattia in 2 stadi

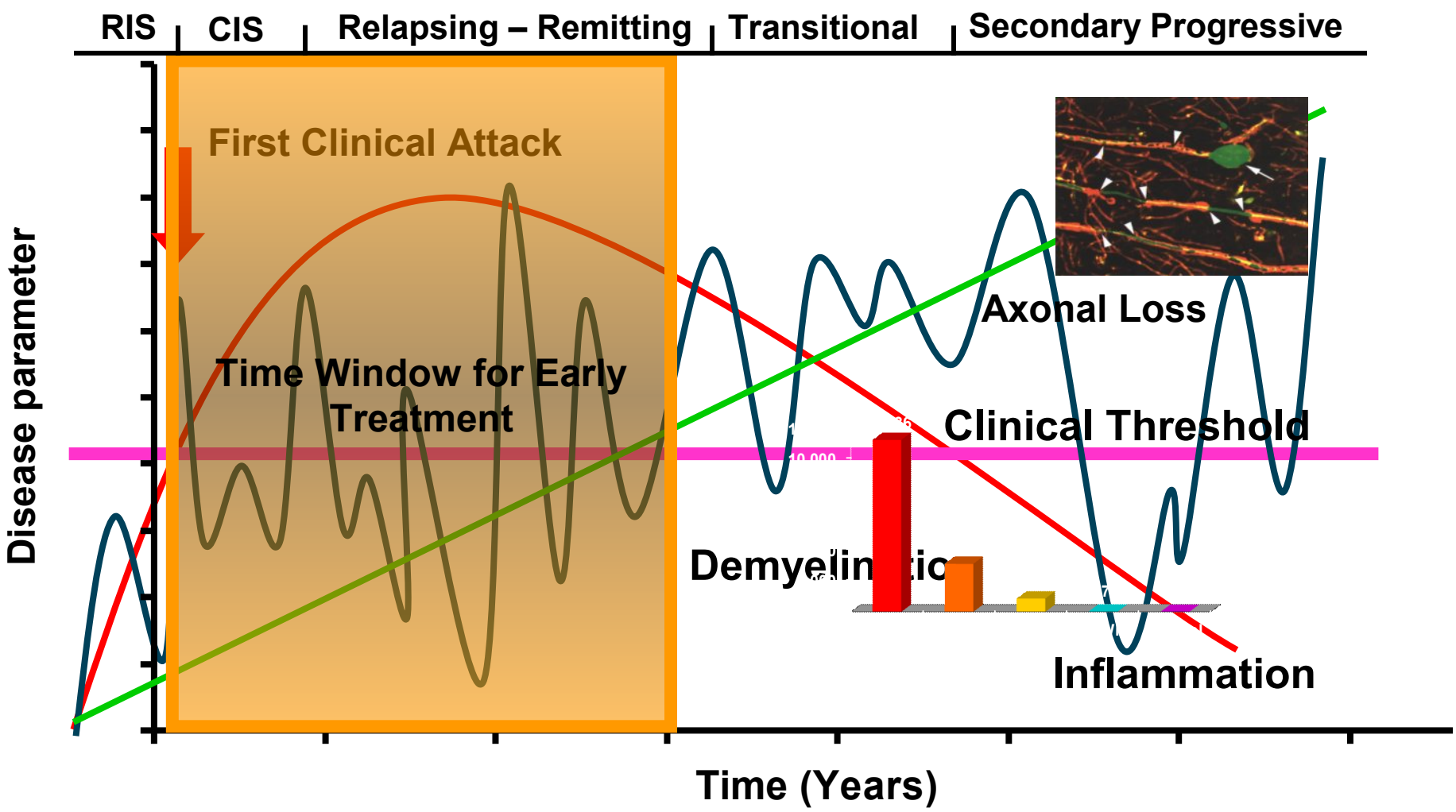


Finestra temporale per il trattamento precoce

MS: Pathological vs.

New Diagnostic Criteria Have Changed the Definition of CIS

ease



TIME IS BRAIN

Editorial

Multiple Sclerosis

'Time is brain' also in multiple sclerosis

Multiple Sclerosis
15(10) 1133–1134

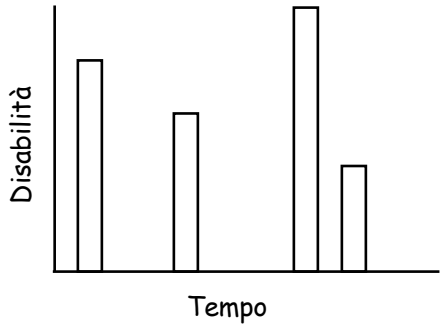
DOI: 10.1177/1352458509345920
msj.sagepub.com
SAGE

In MS, irreversible damage leading to disability is silently accumulating, even with the first event and continues to do so, even in the absence of symptoms. *Maybe we need a lesson from our stroke colleagues* to recognize that in MS 'time is also brain', only we measure it in terms of weeks or months instead of seconds or minutes. (Mark S. Freedman)

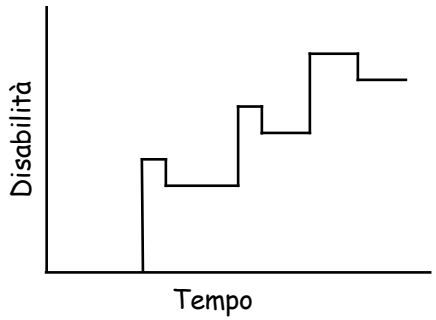
Decorso di malattia

Lublin e Reingold, 1996

Recidivante remittente
85% dei casi all'esordio

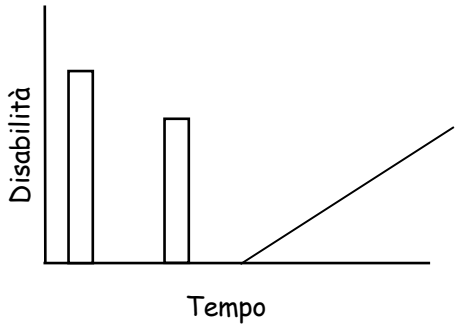


Senza esiti

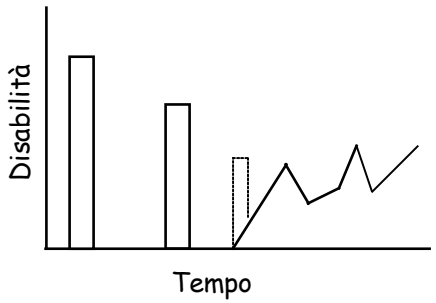


Con esiti

Secondaria Progressiva
(dopo 15-20 aa dall'esordio)

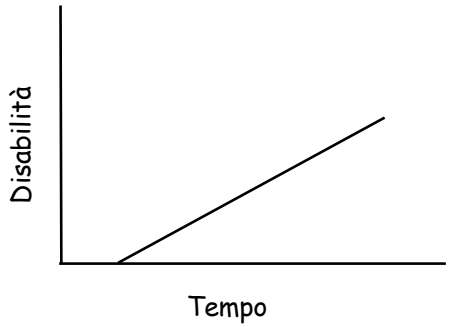


Senza ricadute

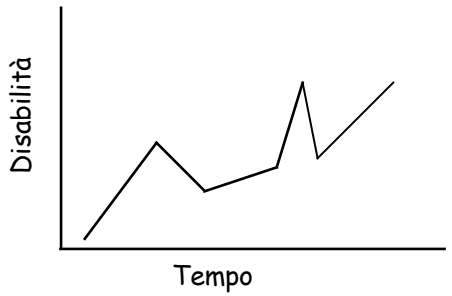


Con ricadute

Primaria Progressiva
10-15% dei casi all'esordio

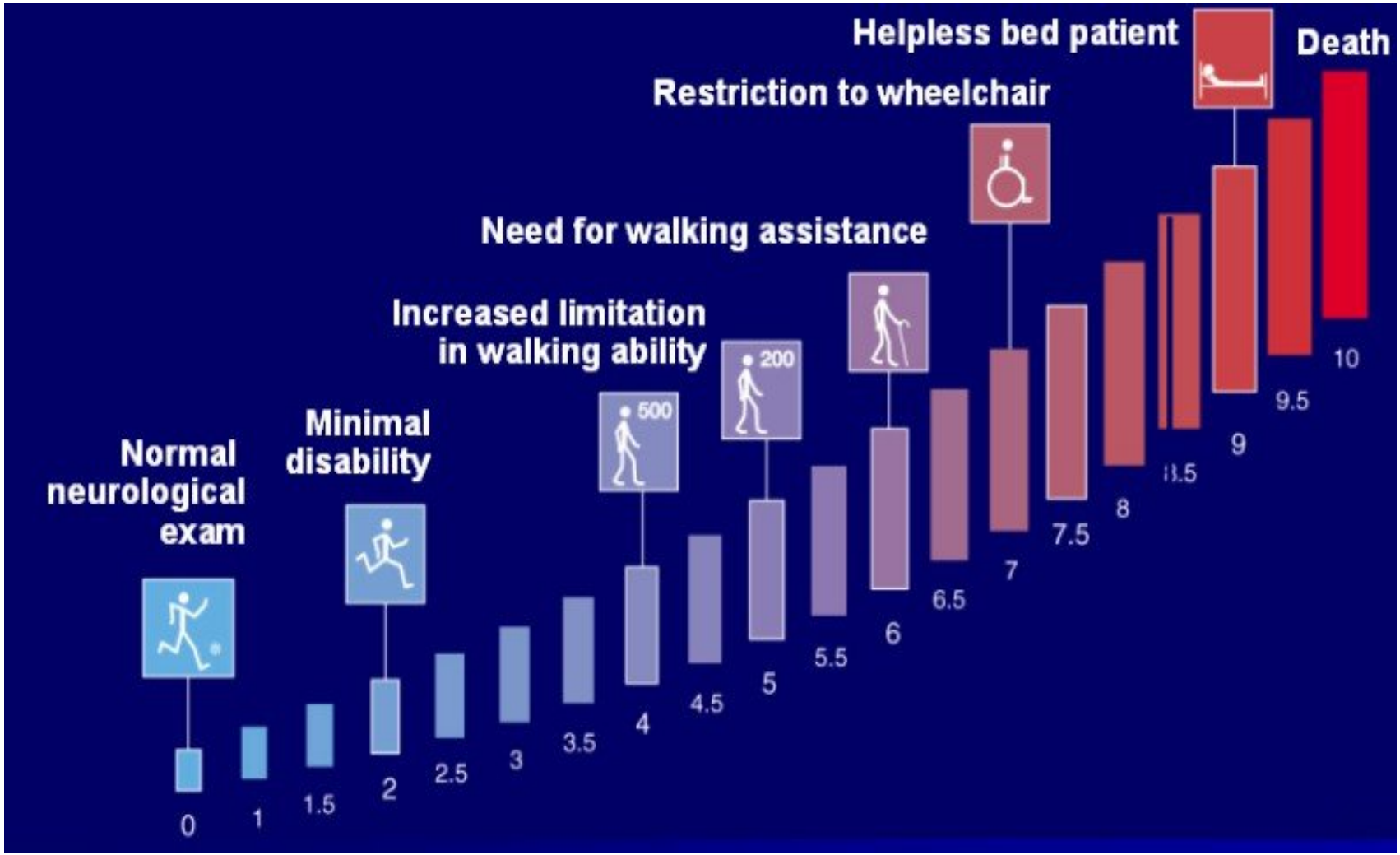


Senza ricadute



Con ricadute

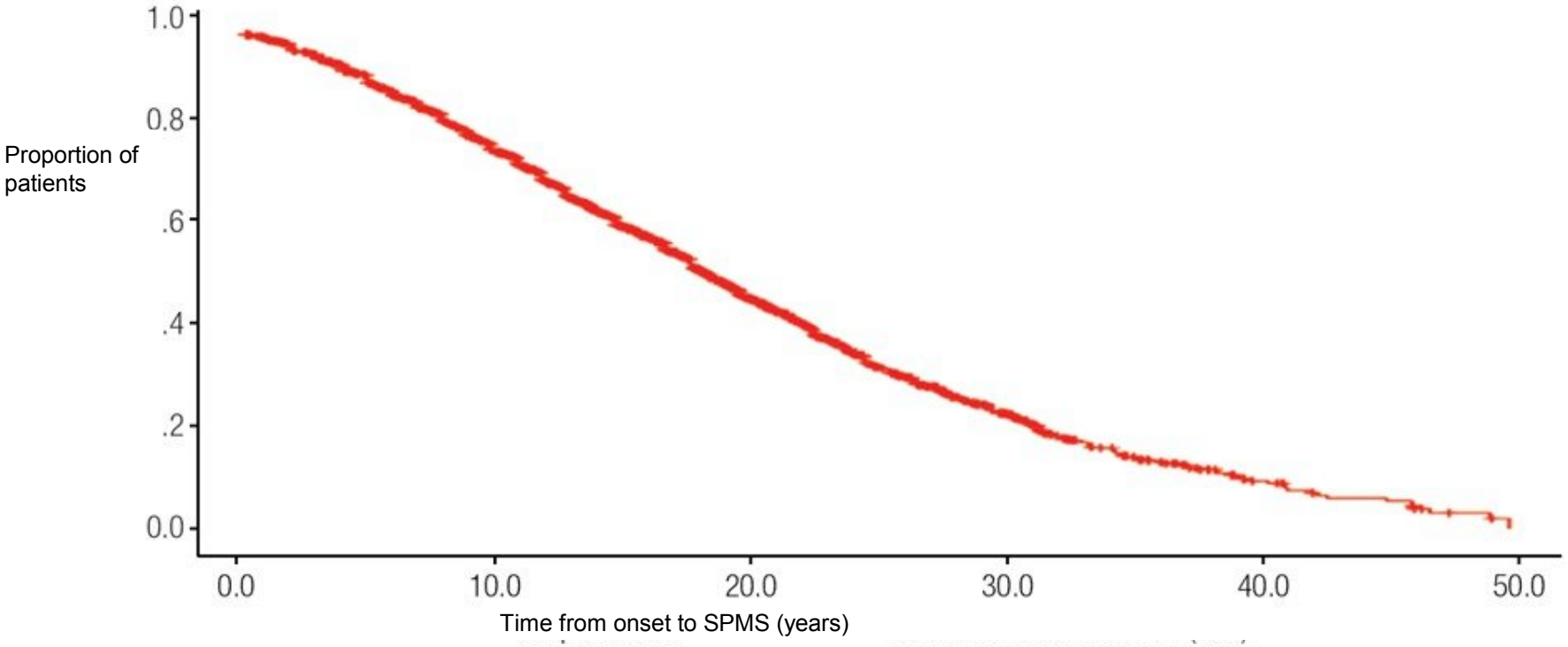
La misura della disabilità nella SM – Expanded Disability Status Scale-



(Kurtzke, 1983)

PROGRESSIONE DI MALATTIA NON TRATTATA :

50% dei pazienti con RRSM diventa SP in 15-20 aa. dall'esordio



85% RRMS

11-15 years from onset

• 50% SPMS

•50% need cane

26 years from onset

90% SPMS

30 years from onset

83% need cane

~ 34% restricted on bed

Tremlett et al. Multiple Sclerosis 2008; 14: 314-324

Farmaci DMD
hanno davvero cambiato la storia della SM?

ORIGINAL ARTICLES

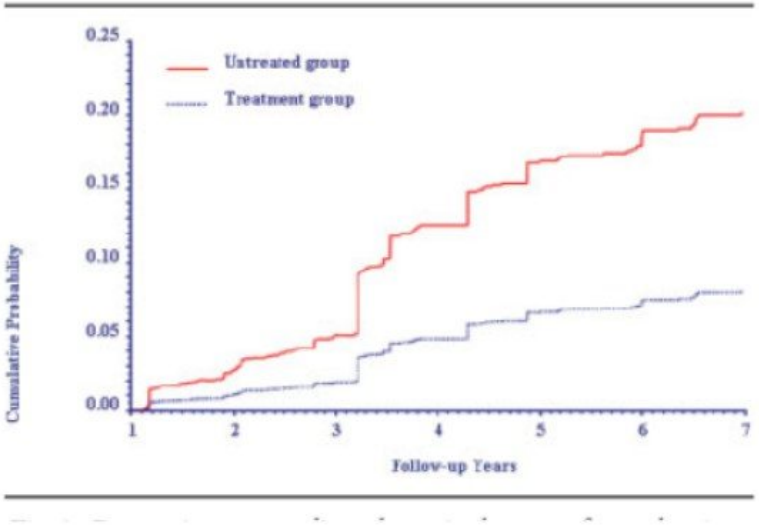
New Natural History of Interferon-β–Treated Relapsing Multiple Sclerosis

Maria Trojano, MD,[1] Fabio Pellegrini, MscStat,[2] Aurora Fuiani, MD,[1] Damiano Paolicelli, MD,[1] Valentina Zipoli, MD,[3] Giovanni B. Zimatore, MD,[1] Elisabetta Di Monte, MD,[1] Emilio Portaccio, MD,[3] Vito Lepore, MD,[1] Paolo Livrea, MD,[1] and Maria Pia Amato, MD[3]

Ann Neurol 2007

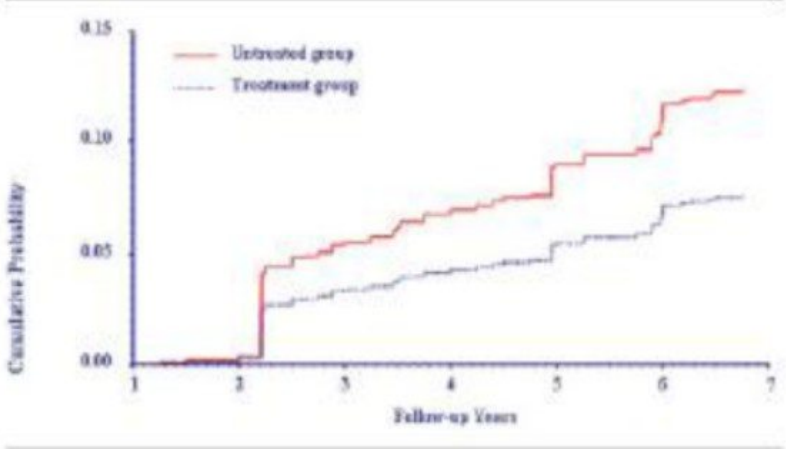
1504 pz RR, 7aa di FU: 1103 con β-IFN e 401 non trattati

IFNβ ritarda il tempo e l'età di conversione a SP e a EDSS 4 e 6



End point: secondary progression

Time to EDSS 4 and 6



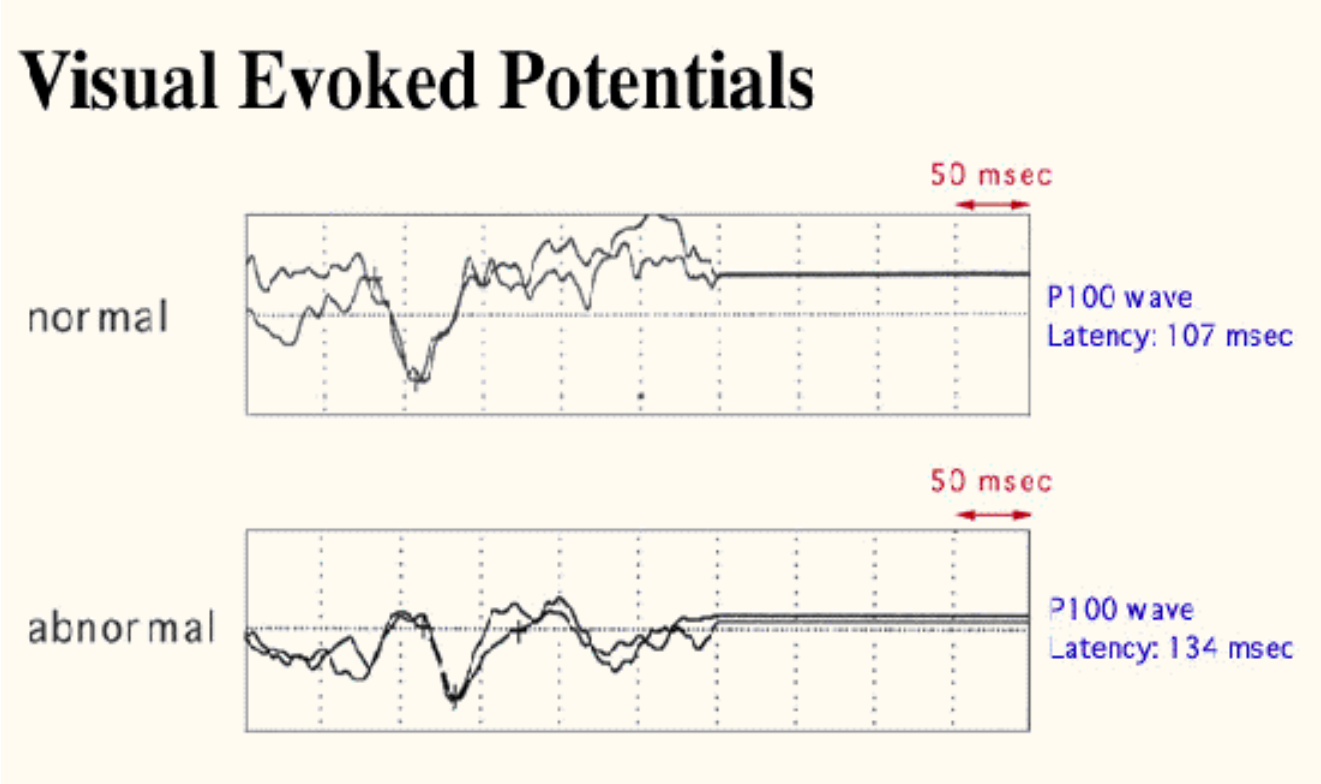
Meccanismi di recupero

- Risoluzione dell'infiammazione
- Ridistribuzione dei canali del Na^+
- Rimielinizzazione a opera di precursori *OG*
- Rimodellamento assonale
- Plasticità funzionale/Ridondanza del SNC

Meccanismi di progressione

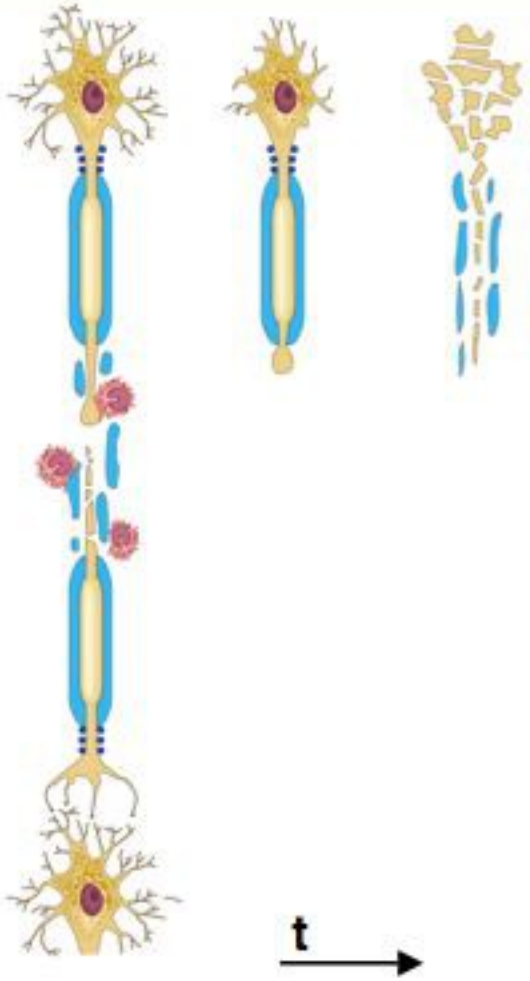
- Fallimento della rimielinizzazione
- Esaurimento dei precursori *OG*
- Superamento capacità di recupero/plasticità
- Accumolo di danno assonale irreversibile

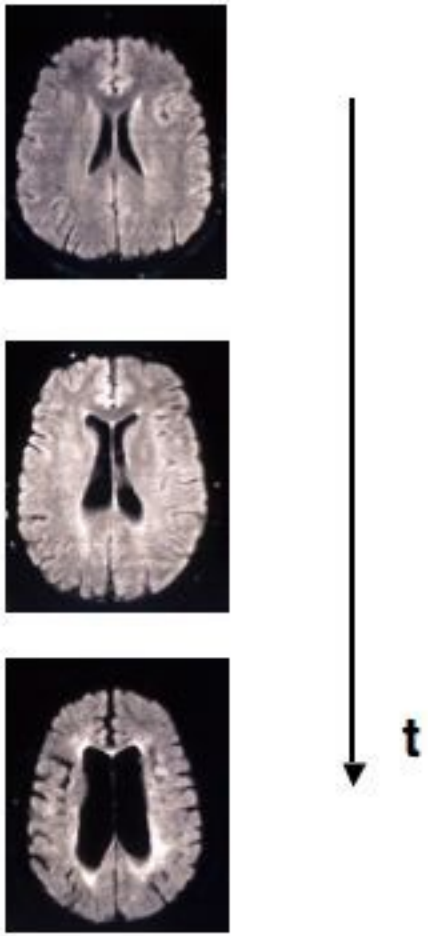
Potenziali Evocati Visivi (PEV)



Alterazione caratteristica:
aumento di latenza con morfologia conservata

Axon pathology



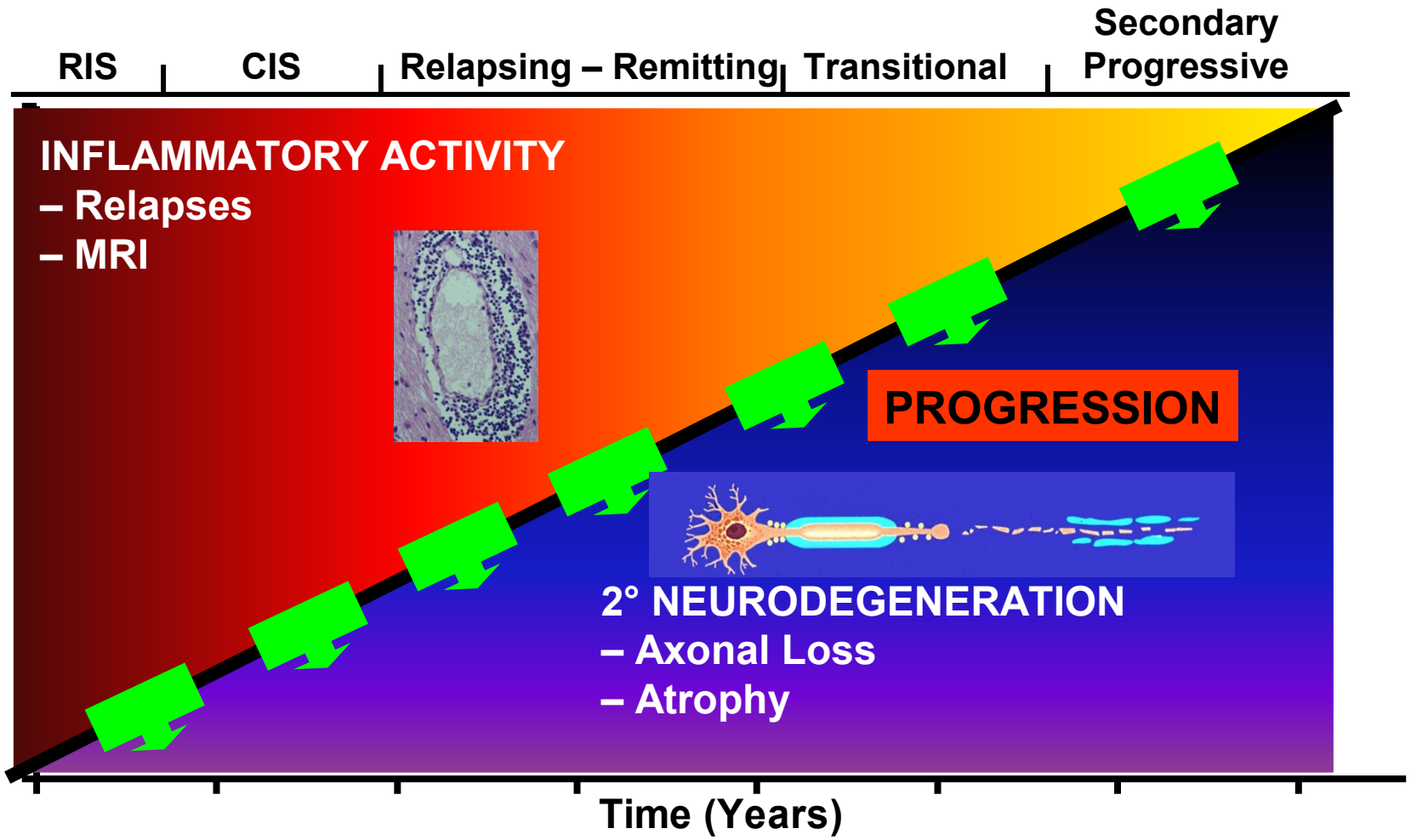


Progressi nella gestione clinica del paziente con SM

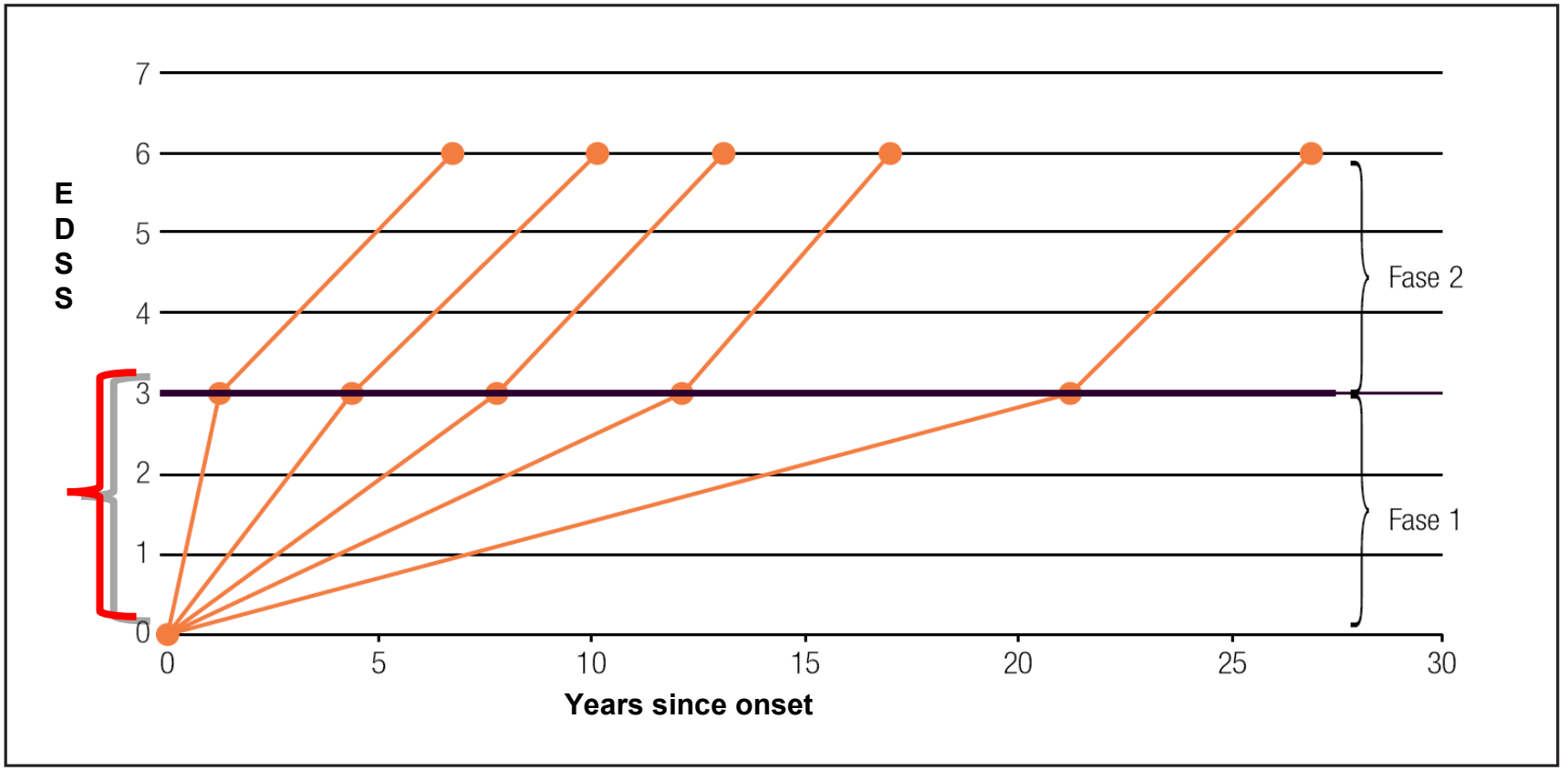
Diagnosi più precoce	→	Trattamento preventivo precoce
Migliori conoscenze patogenesi	→	Nuovi targets (Mabs, nuovi orali)
Utilizzo di biomarkers	→	Identificazione non-responders (RM, ATC anti IFN, anti Mabs)
Infiammazione e degenerazione	→	Limiti delle terapie attuali
Importanza dei sintomi per la QdV	→	Terapia sintomatica

<u>Gestione moderna del paziente</u>
Presa in carico globale
Approccio multidisciplinare
Complessità clinico-assistenziale

SM: UNA MALATTIA IN DUE STADI



Terapeutic window : different evolution of disability progression according EDSS



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

Aim of therapy in MS

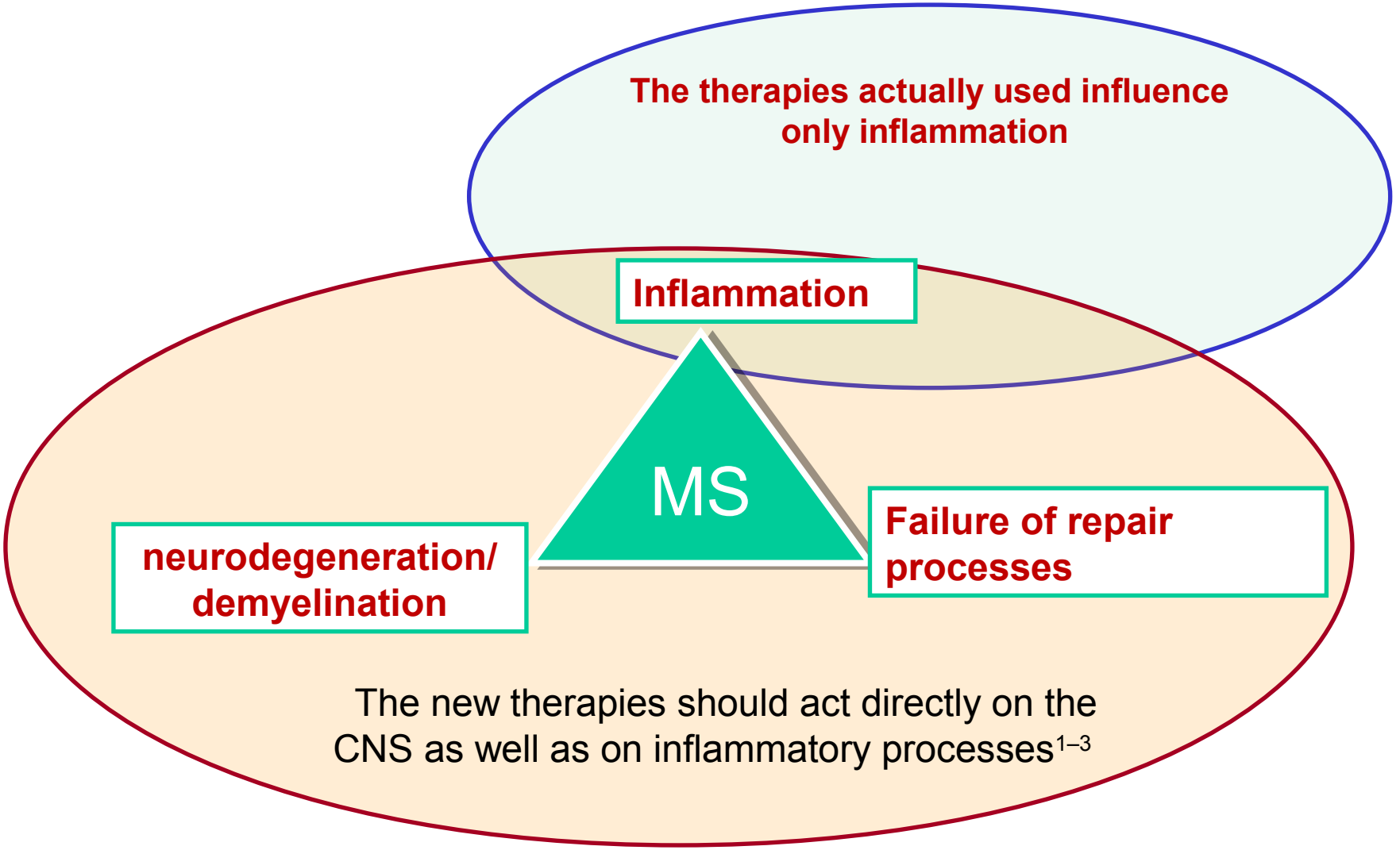
To Suppress disease activity
(Disease Free)

To suppress clinical activity (relapses) and subclinical activity (MRI) with reduction of permanent disability progression

To Increase Adherence/Compliance:
- More efficacy
- Easy to use/good tolerability

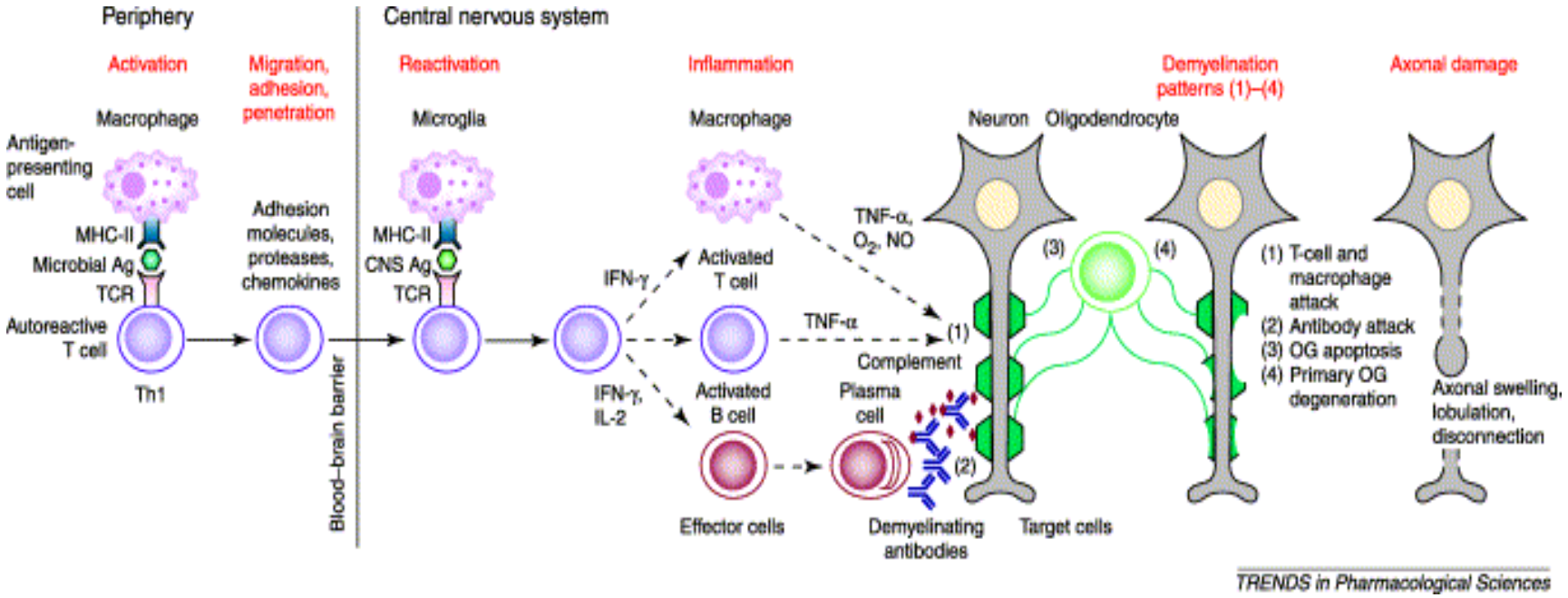
Gasperini et al; Expert Opin Emerg Drugs (2011), 16(4):697

The therapies in MS should be influence both the inflammation and neurodegeneration



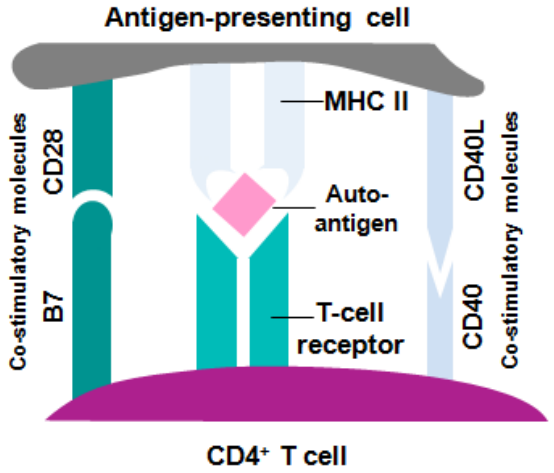
1. Hemmer B and Hartung H-P. Ann Neurol 2007; 2. Confavreux C.et al Clin Neurol Neurosurg 2006;
3. Barkhof F et al. Nat Rev Neurol 2009

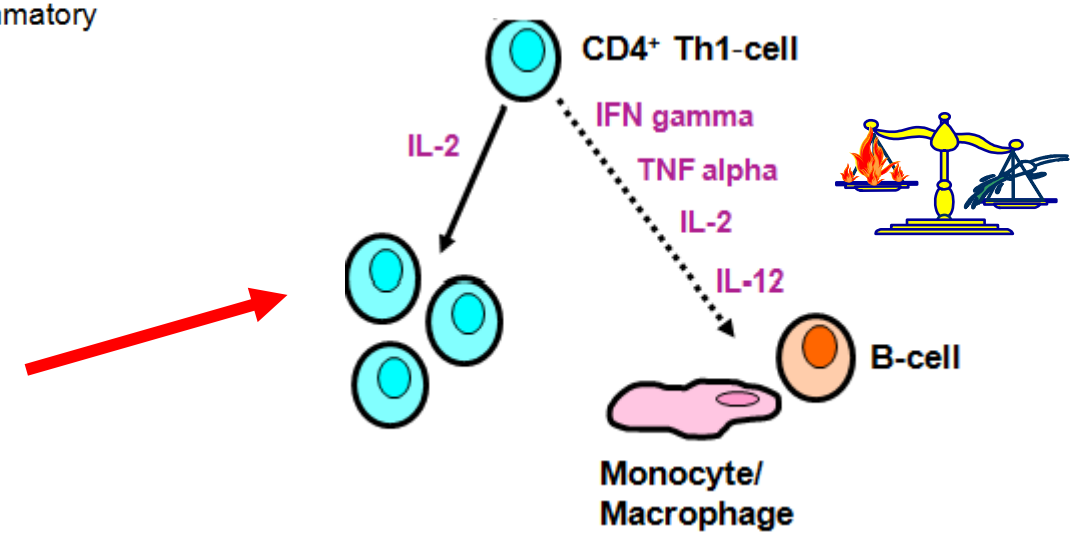
THE IMMUNOPATHOGENESIS OF MULTIPLE SCLEROSIS: from immunosoppresion to neuroprotection



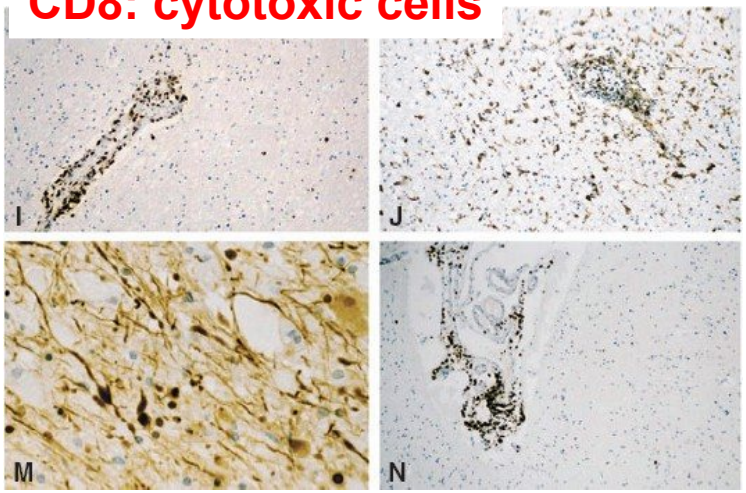
T Lymphocytes: key roles in MS

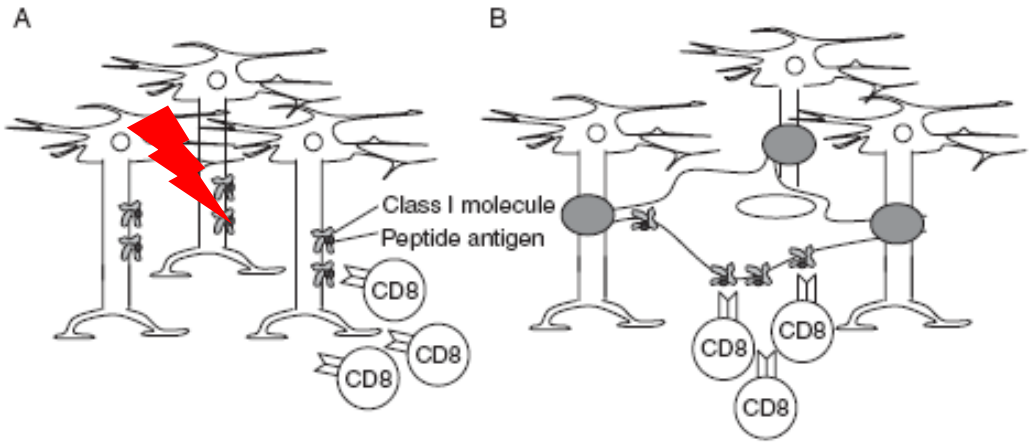
Events at the immune synapse initiate a proinflammatory immune response



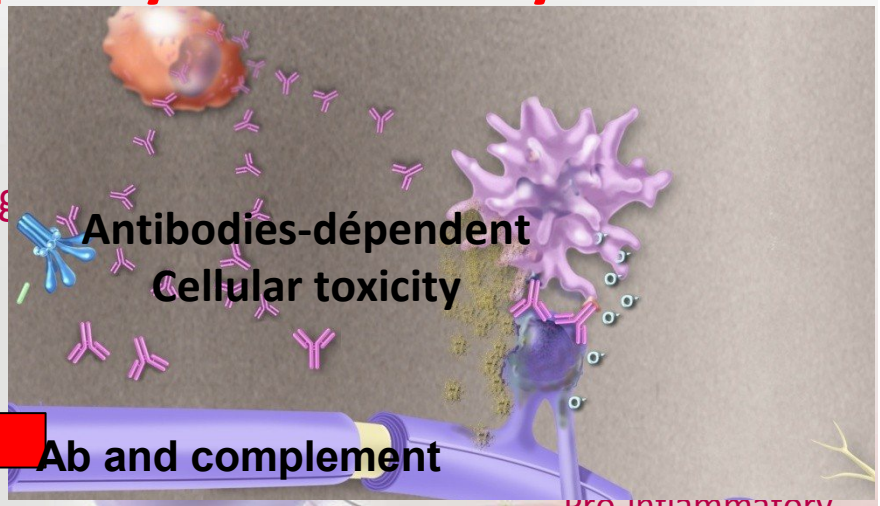


CD8: cytotoxic cells





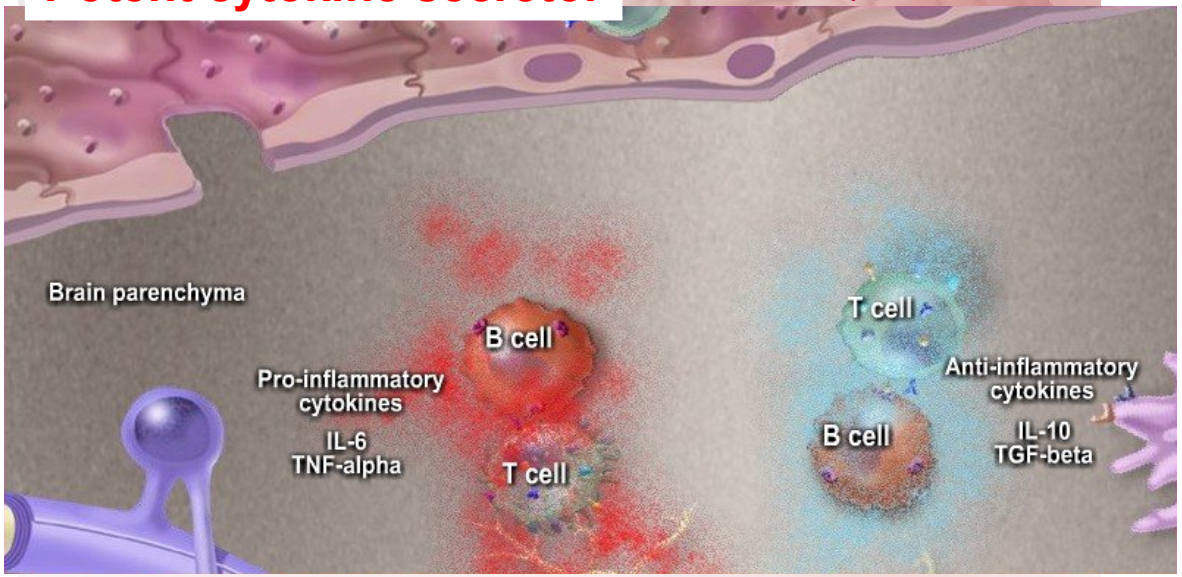
B lymphocytes: not only antibodies



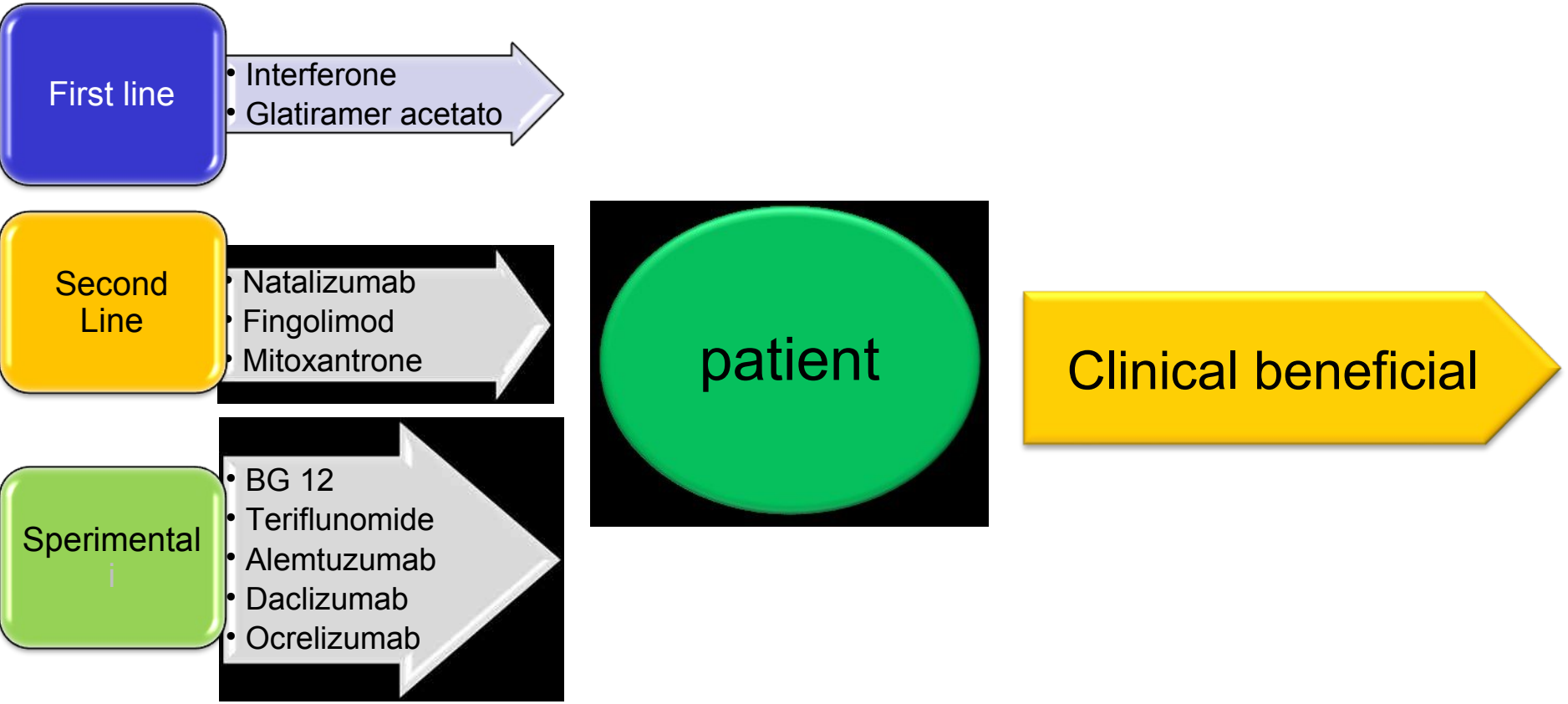
Cellular toxicity

Potent cytokine secretor

Regulatory cytokines



Current vs future therapies

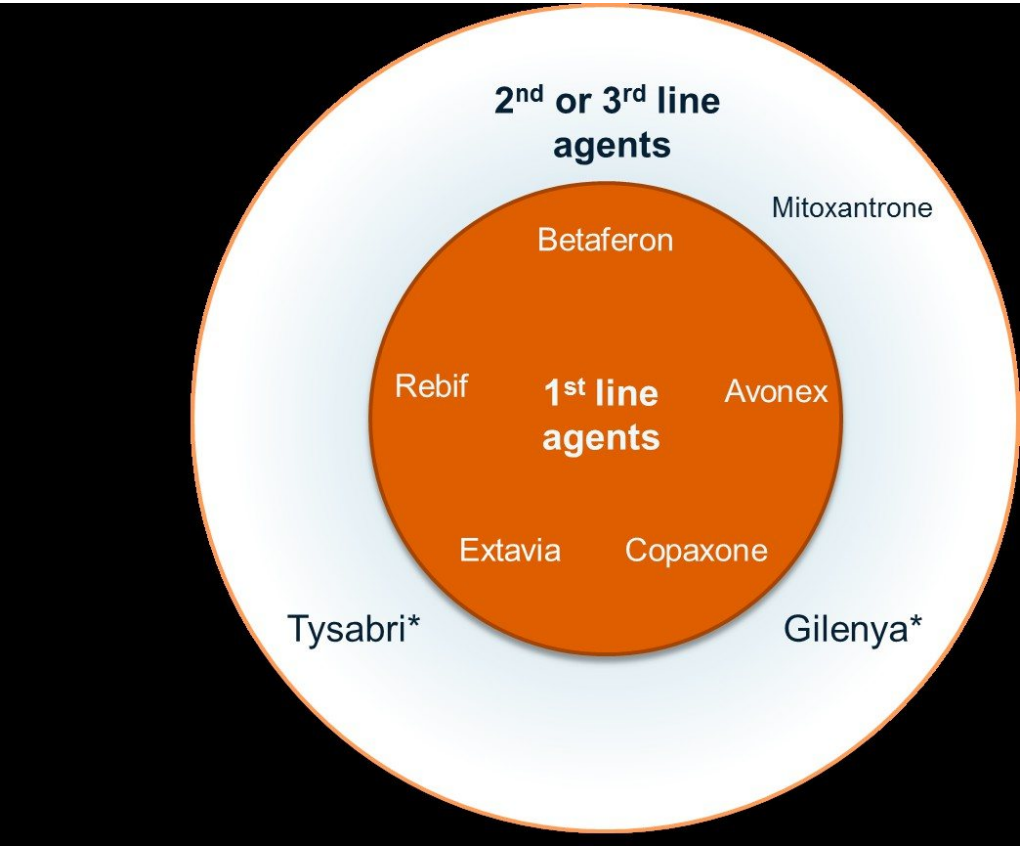


MS therapeutic landscape 2012 (Europe)

	Indications (EU)			1st approval	Experience in clinical practice
	CIS	RRMS	SPMS		5 Years 10 Years 15 Years
Betaferon	✓	✓	✓	1993[1]	
Avonex	✓	✓	-	1996	
Rebif	✓	✓	(✓)[2]	1998	
Copaxone	✓	✓	-	1996[3]	
Tysabri	-	(✓)[4]	-	2006[5]	
Mitoxantrone	-	-	(✓)[6]	2002	
Gilenya		(✓)[7]		Nov 2010[8]	

[1]USA, in Europe 1996
[2]relapsing SPMS
[3]Israel, USA 1997, in Europe 2001
[4]2nd line therapy for INFB failures or 1st line for patients with rapidly progressing RRMS
[5]2005 approved in US but withdrawn shortly after due to 3 cases of PML. Re-introduced in 2006
[6]Rapidly progressing MS, non-response to other treatments
[7]In Europe approved 2nd line therapy for INFB failures or 1st line for patients with rapidly progressing RRMS, in Australia, Canada, Switzerland and US approved 1st line with Risk Evaluation Mitigation Strategy
[8]USA,1st line in Australia, Canada, Switzerland, Saudi Arabia and US, 2nd line therapy in Europe

We broadly classify available treatments in 1st and 2nd line agents



- **First-line agents**
  - Well established benefit/risk profiles over the short and long-term
  - Are ideally used earlier in the course of the disease
- **Second-line agents**
  - Benefit/risk profiles not fully established
  - Generally a stronger impact on the immune system than first-line agents, e.g. immunosuppressive properties
  - Safety concerns

When making treatment decisions, we should keep in mind: MS often progresses over several decades[1] and thus MS management requires a long-term approach

Characteristics of the first-line agents IFNB and glatiramer acetate (GA)

- Broad datasets available from many controlled studies as well as various clinical settings, support their use in MS – from CIS to approximately 20 years of treatment

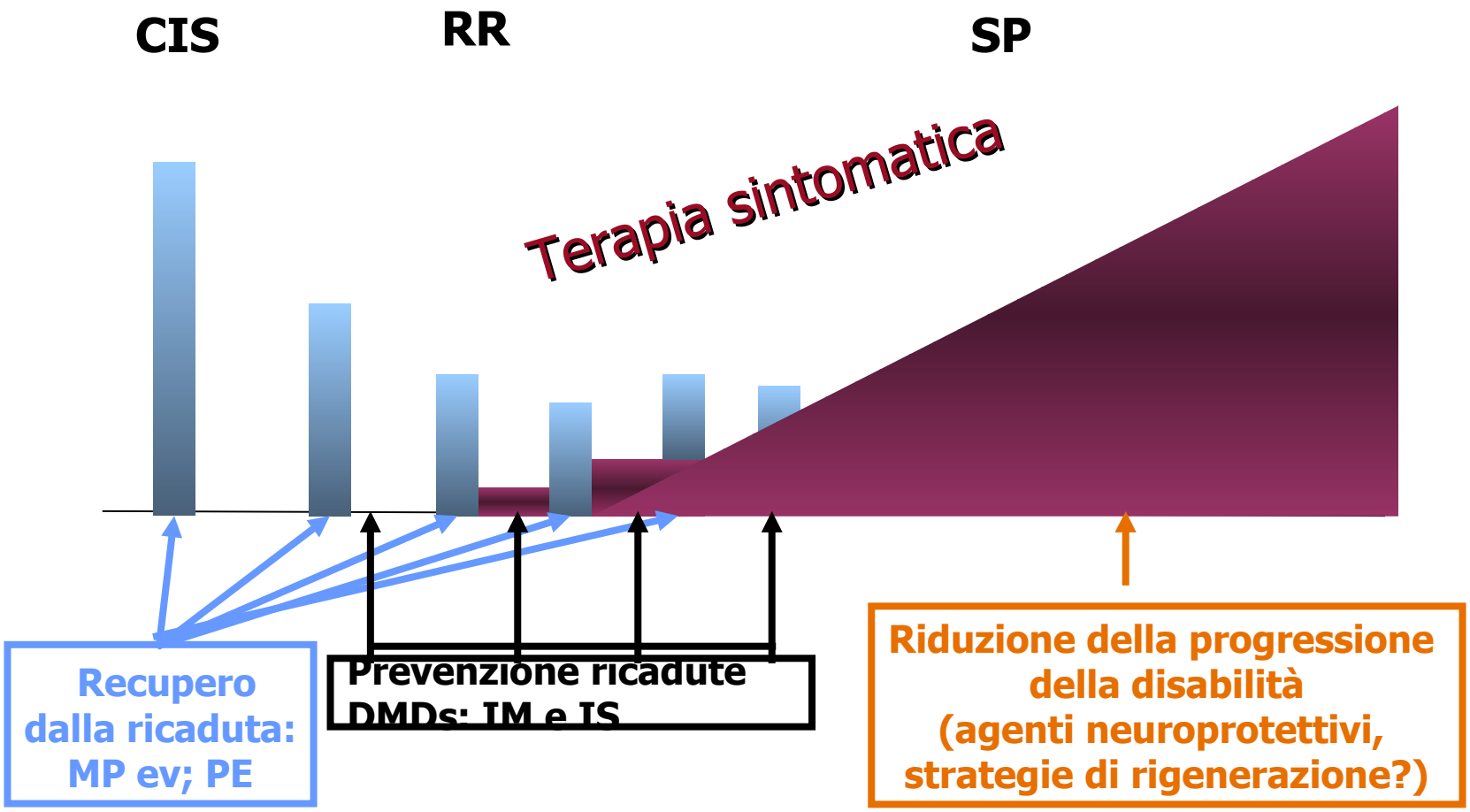
  They reduce:

  - The frequency and severity of relapses
  - The development of new brain lesions (MRI)
  - The development of disability progression

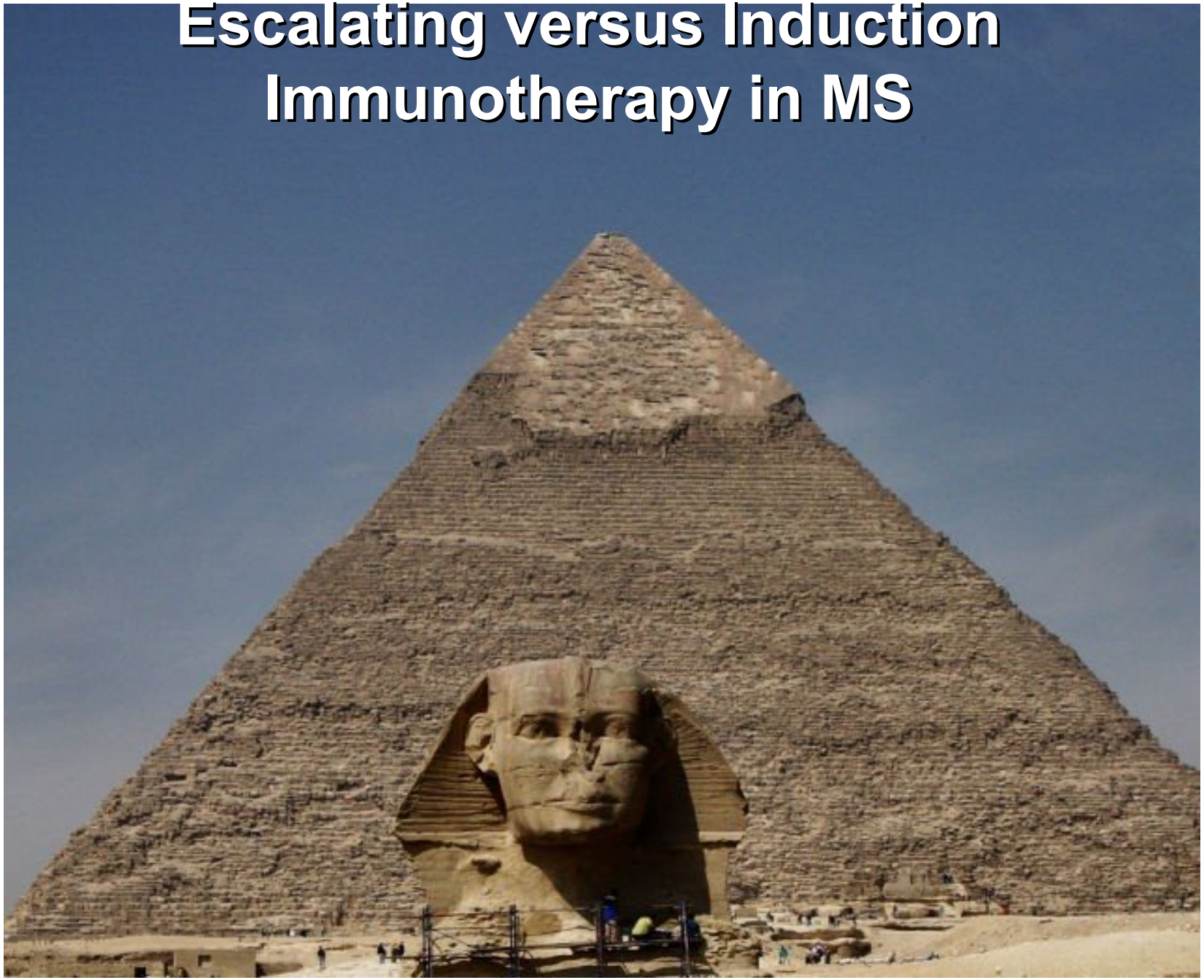
  Treatment needs to start early and therapy needs to be maintained over the long run

  Safety profiles are well established

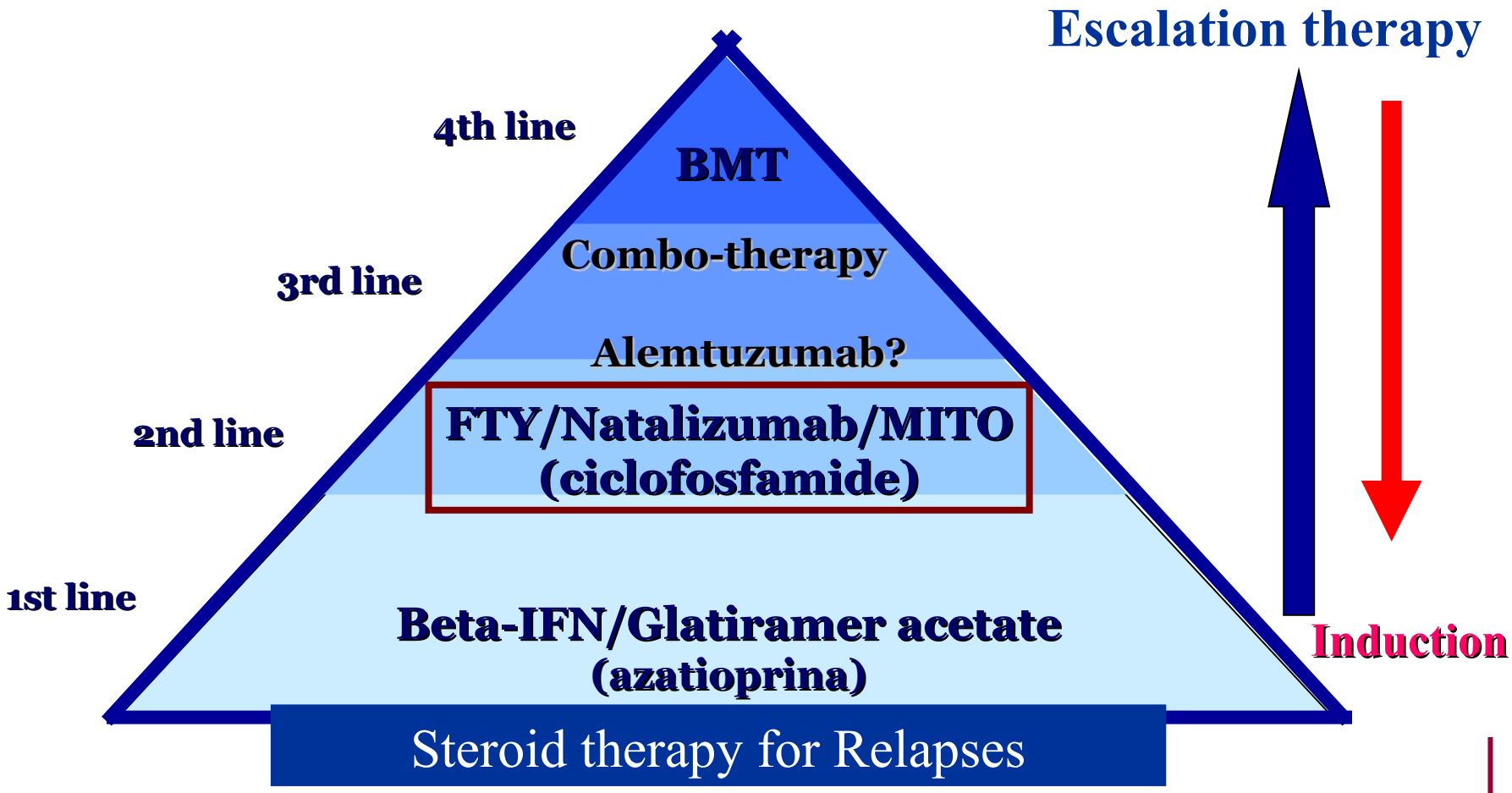
Terapia in relazione al decorso



Escalating versus Induction Immunotherapy in MS

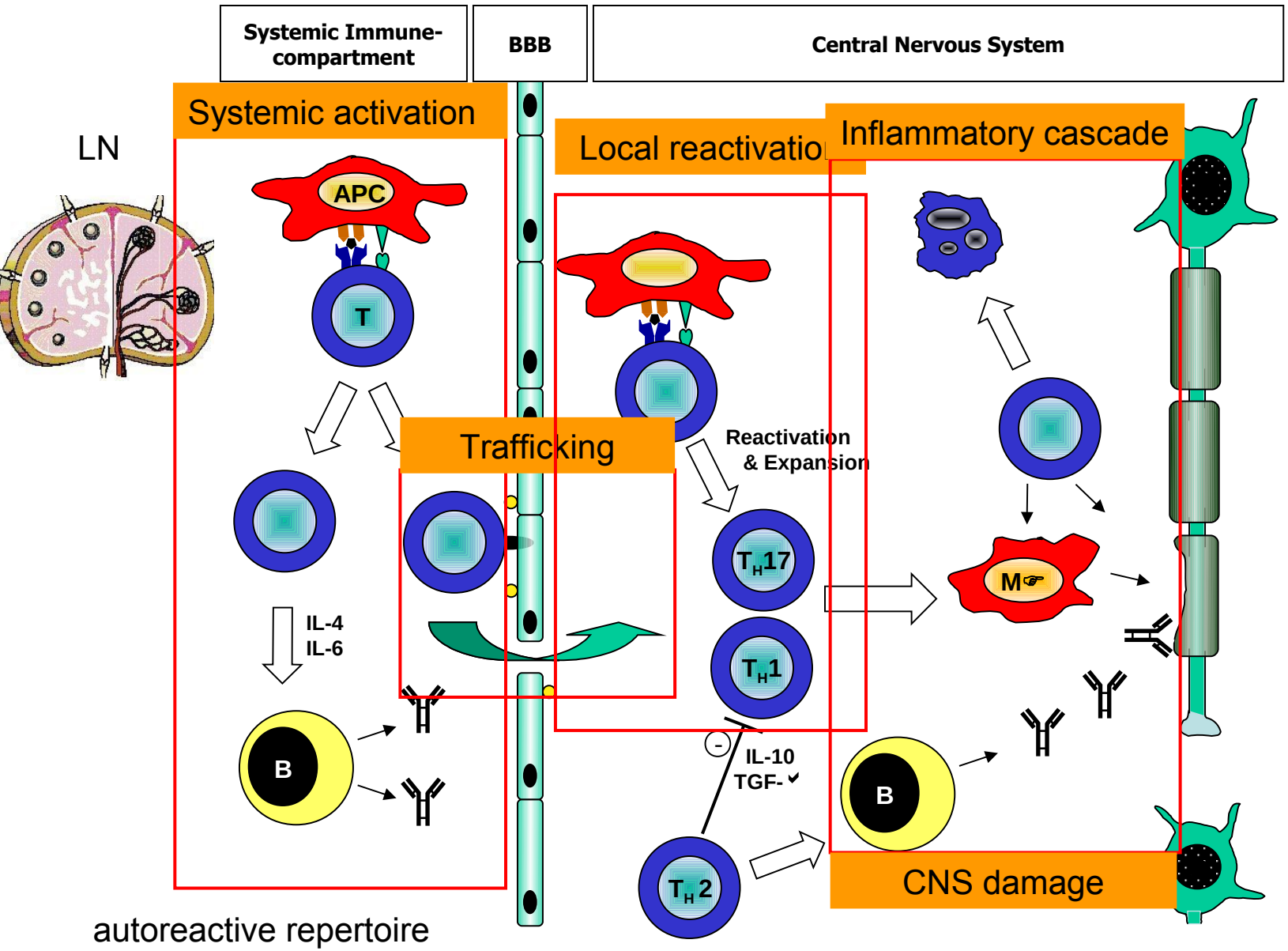


Recommendations for MS treatments



Modificato da Multiple Sclerosis Therapy Consensus Group

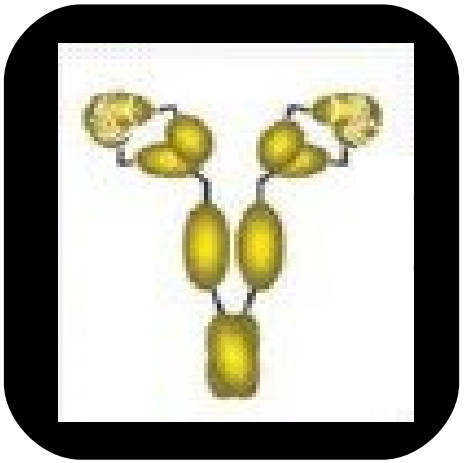
MS immunopathogenesis



Nuove prospettive terapeutiche

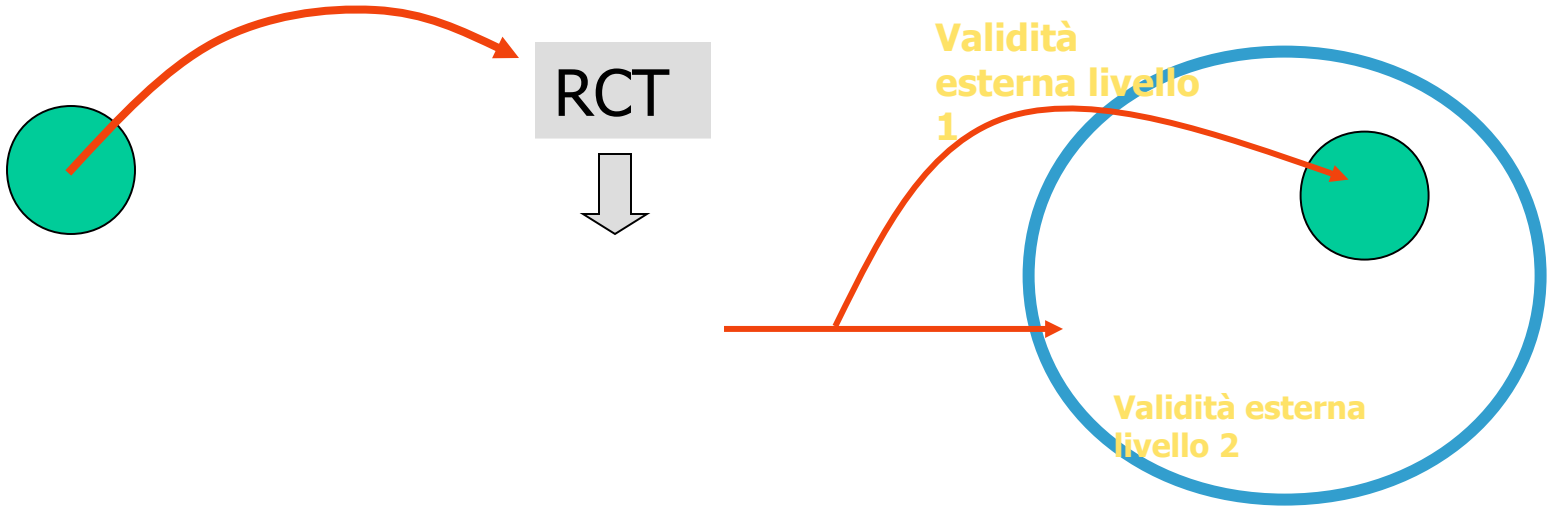
TERAPIE ORALI

ANTICORPI MONOCLONALI

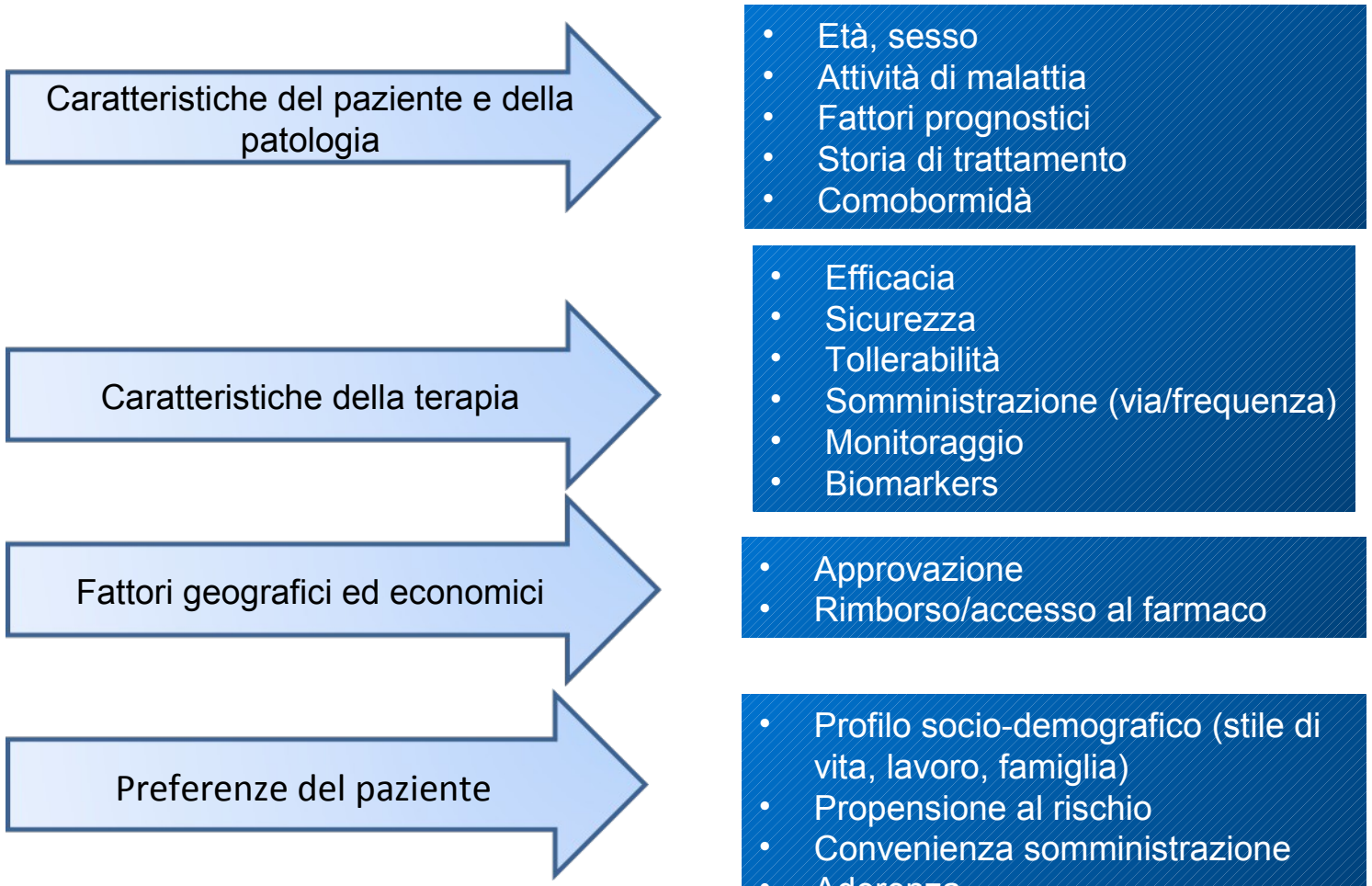


Trial clinico Randomizzato Controllato di Fase 3

limiti



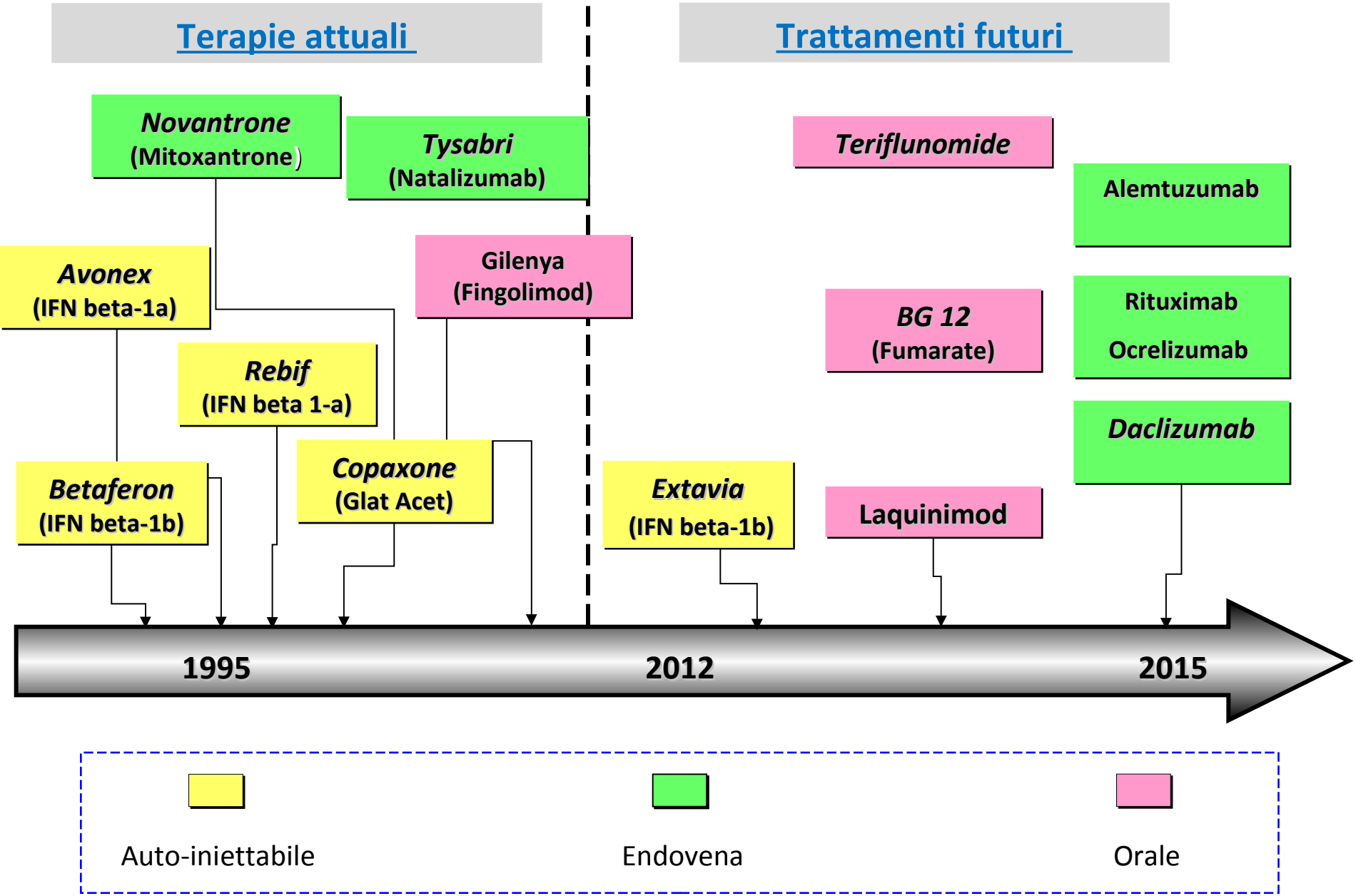
«Complessità terapeutica» il farmaco giusto al paziente giusto nel momento giusto



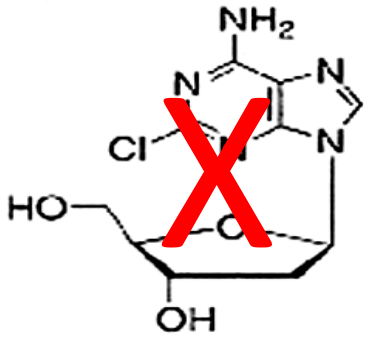
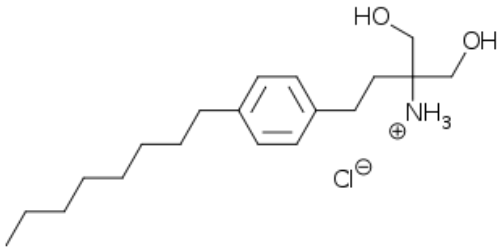
Bisogni Insoddisfatti

- Nuovi meccanismi di azione: attività «neuroprotettiva»
- Efficacia nelle forme progressive
- Bilancio ottimale efficacia/sicurezza nel lungo termine
- Massima tollerabilità e accettabilità
- Strategie «individualizzate»
- Terapia dei sintomi
- Quali novità?

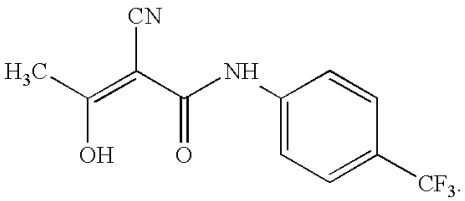
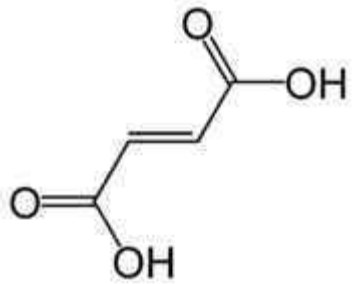
Multiple Sclerosis: pipeline



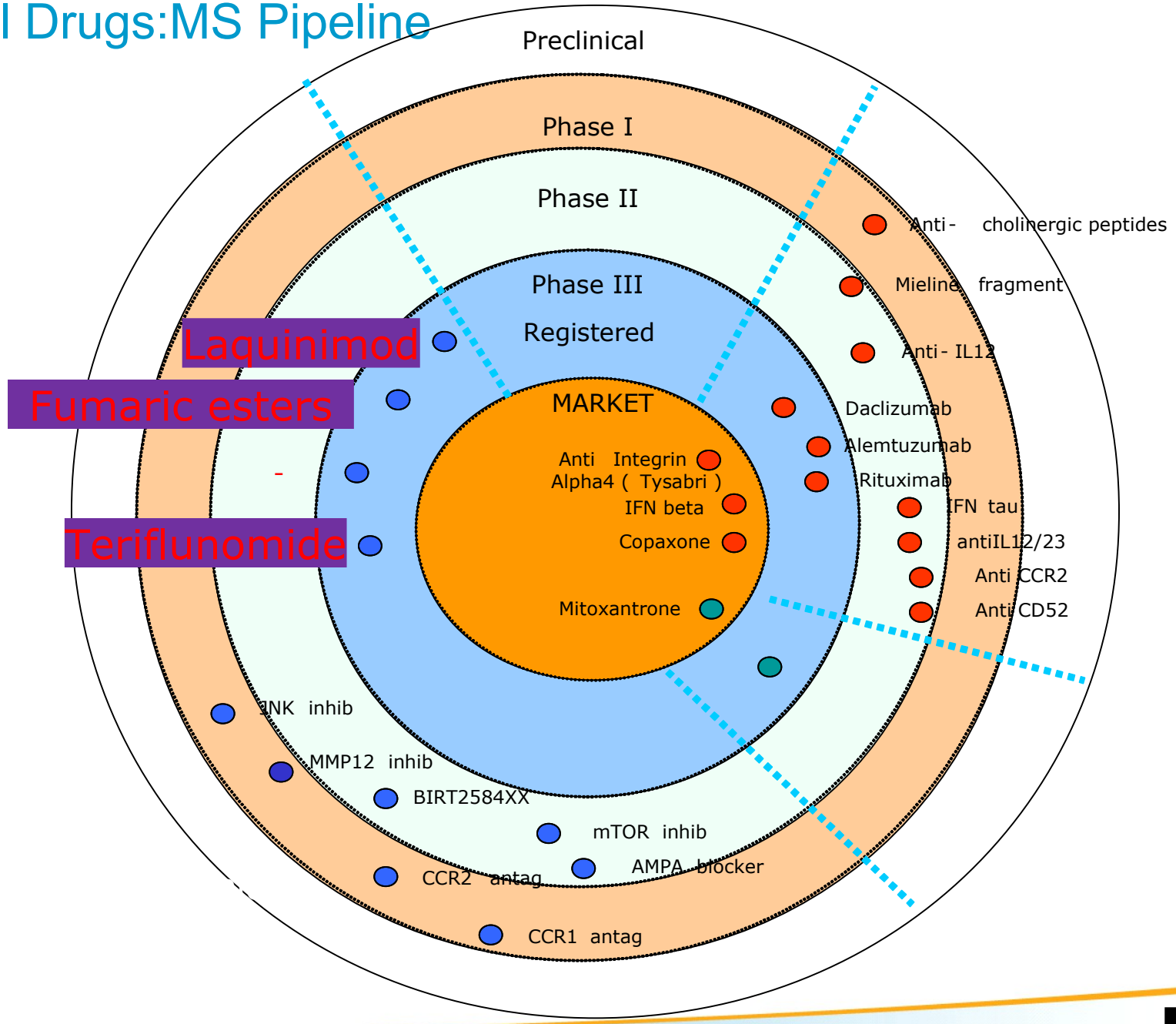
Terapie Orali/1

CLADRIBINA  	***Analogo delle purine*** Influenza la sintesi del DNA e il metabolismo cellulare soprattutto a livello dei linfociti T	Mielosoppressione (dose-dipendente) Infezioni opport.	**Fase III** CLARITY (ext) ONWARD ORACLE
FINGOLIMOD  	***Agonista del recettore delle sfingosine*** Blocca il traffico dei linfociti T che rimangono intrappolati nei linfonodi	Bradicardia Ipertensione arteriosa Ostruzione vie aeree Encefalite HSV-1 Infezione da VZV Neoplasie cutanee	**Fase III** FREEDOMS TRANSFORMS INFORMS

Terapie Orali/2

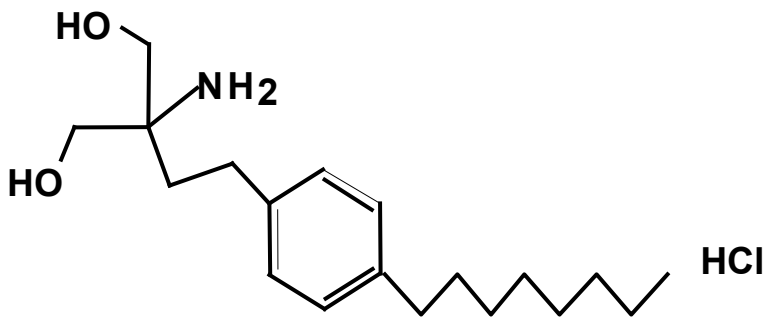
TERIFLUNOMIDE 	**Inibitore della sintesi delle pirimidine** Metabolita attivo della Leflunomide Effetto antiproliferativo	Nasofaringiti, artralgie Alopecia Nausea, diarrea, ↑ ALT	**Fase III** TEMSO ***Add-on*** IFN beta, GA
BG-12 	**Composto intermedio del ciclo di Krebs** Induce shift TH-1•TH-2 Effetto neuroprotettivo	Flushing, Disturbi gastroenterici Dolori muscolari Cefalea	**Fase III** CONFIRM DEFINE
LAQUINOMIDE 	**Derivato della Linomide** Probabilmente induce shift TH-1•TH-2	Potenziale epatotossicità Dispepsia Edemi declivi	**Fase III** BRAVO ALLEGRO

Oral Drugs:MS Pipeline



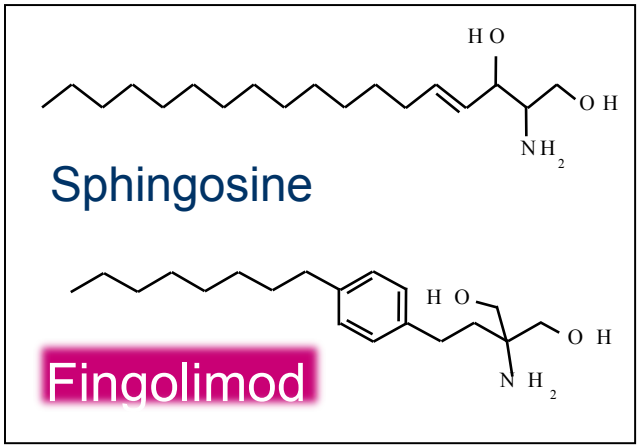
Fingolimod
Gilenya ®

Analogo sintetico di una sostanza naturale ("miriocina") estratta da un fungo (*Isaria sinclairii*)

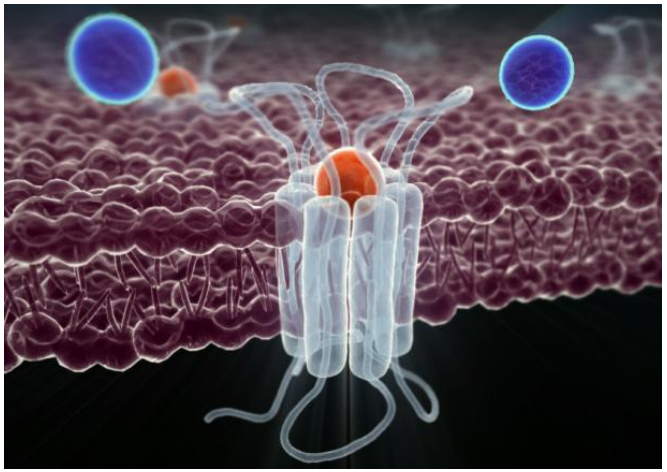


Fujita et al. *J Antibiot* 1994;47:208–15

Fingolimod è un analogo strutturale della sfingosina

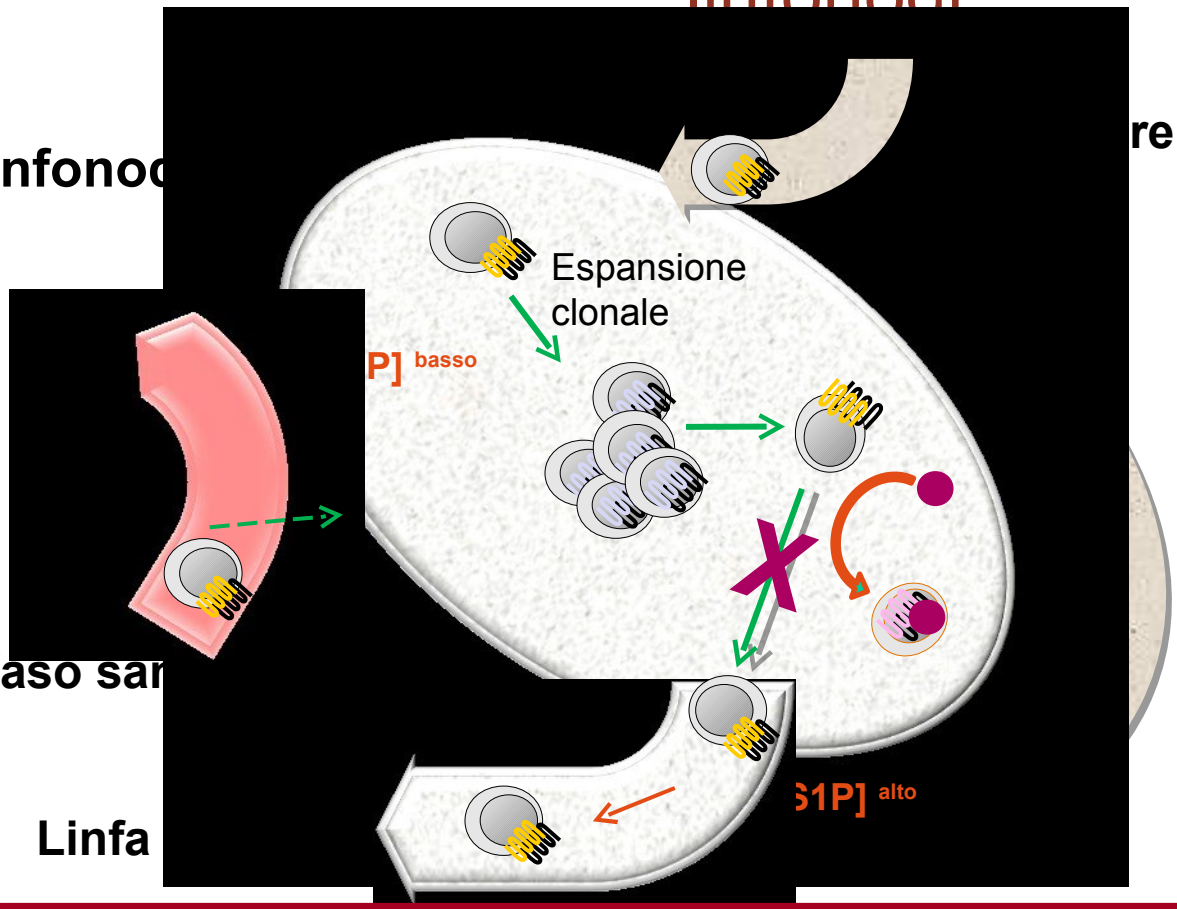


La sua struttura chimica è molto simile a quella della **sfingosina**, uno sfingolipide naturale delle cellule di mammifero che viene fosforilato all'interno della cellula e che agisce



- tramite specifici recettori accoppiati alla proteina G (**recettori S1P**).

Fingolimod inibisce la fuoriuscita dei linfociti dai linfonodi



Fingolimod

Recettore $S1P_1$

Linfocita

Fingolimod determina:

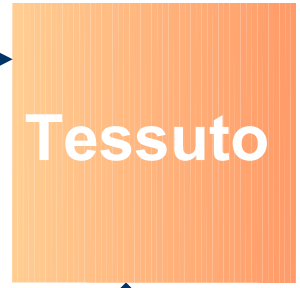
- Internalizzazione del recettore $S1P_1$
- Inibizione della fuoriuscita dei linfociti

Fingolimod trattiene i linfociti circolanti nei linfonodi riducendone la conta periferica e la loro circolazione nei siti di infiammazione nel SNC

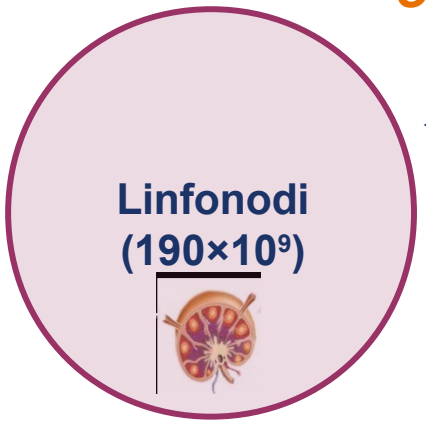
All'interno dei linfonodi comunque I linfociti rimangono attivi e capaci di partecipare alla risposta immunitaria

… trattenendo solo i linfociti che transitano regolarmente dagli organi linfatici…..

CCR7-



CCR7+



In circolo:

- **Linfociti T naïve**
  Tn (**CCR7+** CD45RA+)
- **Linfociti T centrali della memoria (compresi T_H17)**
  TCM (**CCR7+** CD45RA-)
- **Linfociti B**

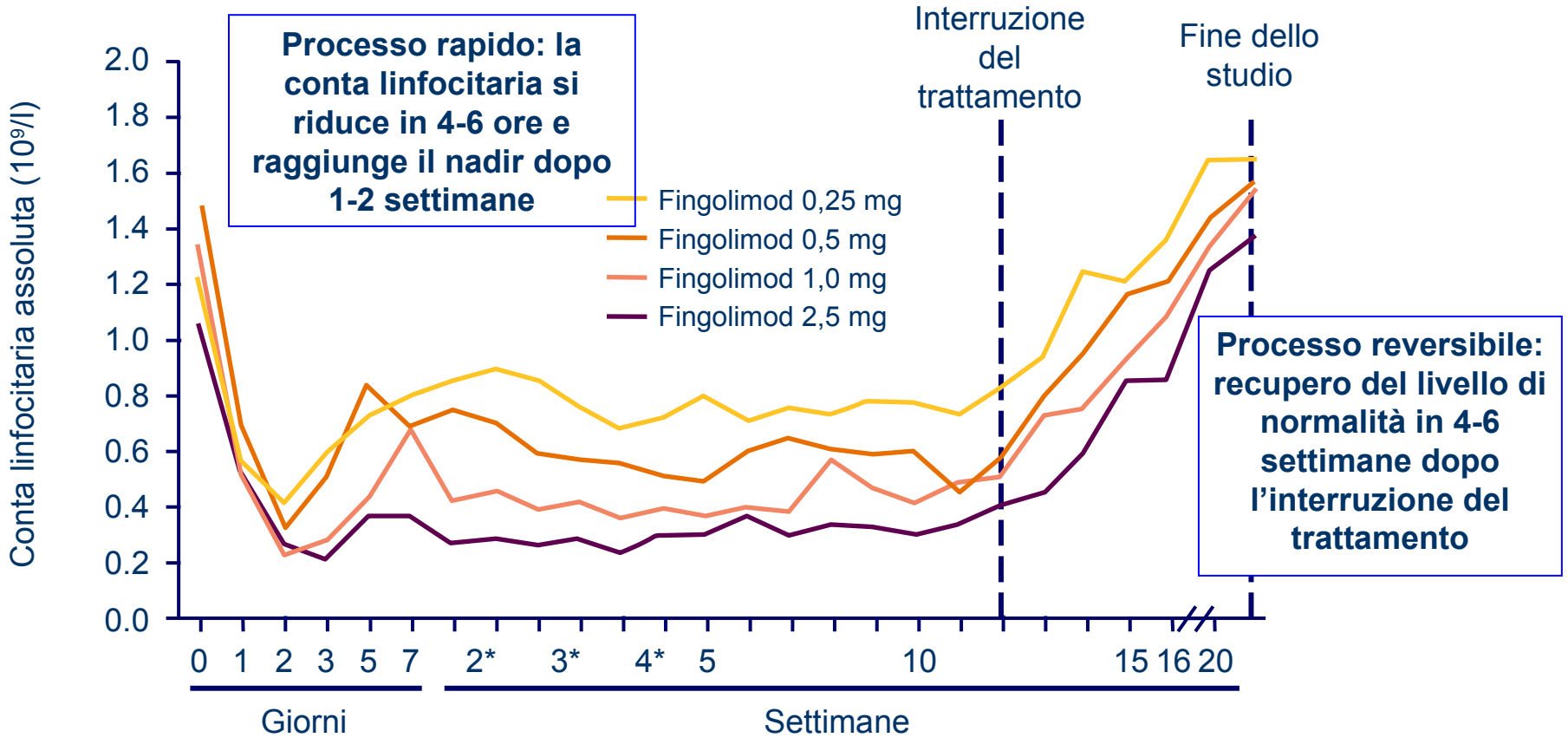
Tipi di linfociti trattenuti da fingolimod

Maggiormente residenti nel sangue/tessuti:

- **Linfociti T effettori della memoria**
  TEM (**CCR7-** CD45RA-)
  TEMRA (**CCR7-** CD45RA+)

Tipi di linfociti risparmiati da fingolimod

… l’effetto sui linfociti è reversibile



*Due esami nei mesi 2, 3 e 4

R Schmoulder et al. Pharmacodynamic effects of oral fingolimod (FTY720). *Poster presentato all’ECTRIMS 2006*

I recettori S1P sono espressi sia sui linfociti sia sulle cellule nervose

- Esistono 5 sottotipi di recettori S1P e sono coinvolti nella regolazione di diversi processi biologici;
- Fingolimod interagisce con 4 dei 5 sottotipi di recettori S1P (non lega S1P2).

Recettore *(la grandezza del carattere indica la rilevanza dell'azione di fingolimod)*	**Affinità di legame di Fingolimod-P** (nM)	**Distribuzione** (mRNA)	**Funzioni chiave mediate**
$S1P_1$	0.3	**Linfociti** **Cellule nervose** ECs, SMCs Miociti atriali	• **Fuoriuscita dei linfociti dai linfonodi** • **Migrazione/funzione astrociti** • **Modulazione di processi** • Tono vasomotorio, barriere endoteliali • Battito cardiaco
$S1P_2$	>10,000	ECs, SMCs	• Tono vasomotorio, barriere endoteliali
$S1P_3$	3.0	**Cellule nervose** ECs, SMCs Miociti atriali	• **Migrazione/funzione astrociti** • Tono vasomotorio, barriere endoteliali • Battito cardiaco
$S1P_4$	0.3	Linfociti (molto bassa)	Sconosciute
$S1P_5$	0.3	**Oligodendrociti**	• **Modulazione di processi**

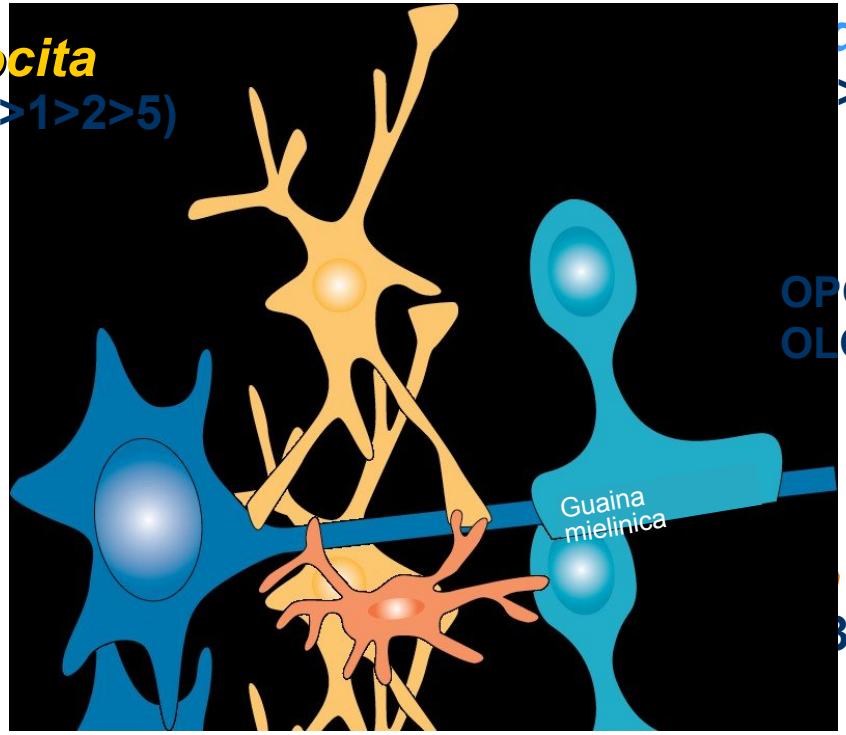
Brinkmann, *Pharm & Ther* 2007

Fingolimod ha azione diretta sui recettori S1P nel sistema nervoso centrale

- Fingolimod, grazie alla sua natura lipofila, attraversa la barriera emato-encefalica e raggiunge il sistema nervoso centrale
- Le cellule nervose (neuroni, astrociti, oligodendrociti, microglia) esprimono recettori S1P
- Studi preclinici suggeriscono un potenziale “neuroprotettivo”

Astrocita
(S1P3>1>2>5)

drocita
>3)



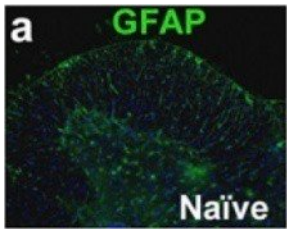
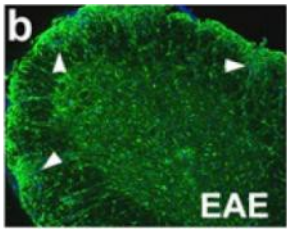
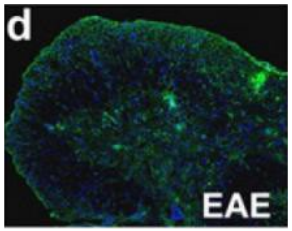
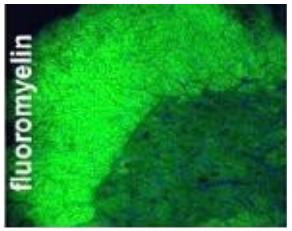
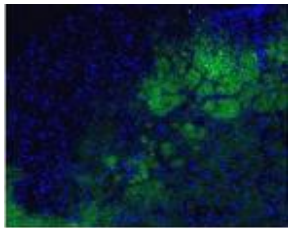
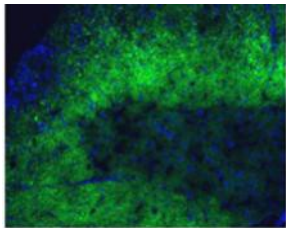
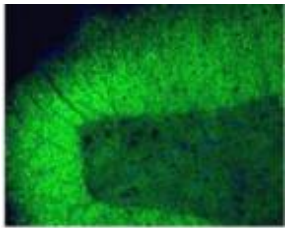
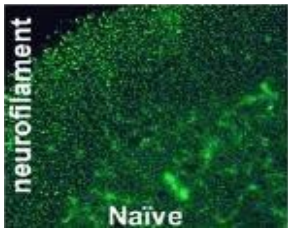
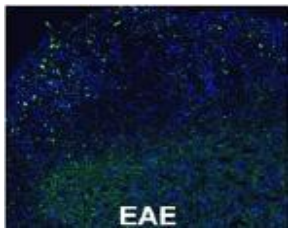
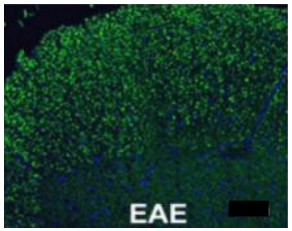
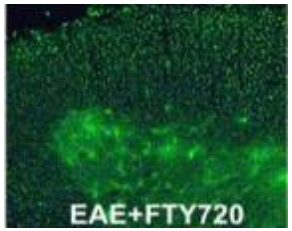
OPC: S1P1>S1P5>S1P3
OLG: S1P5>S1P1>S1P3

Neurone
(S1P1=3>2=5)

=5)

E’ in corso uno studio con fingolimod sulle forme PP

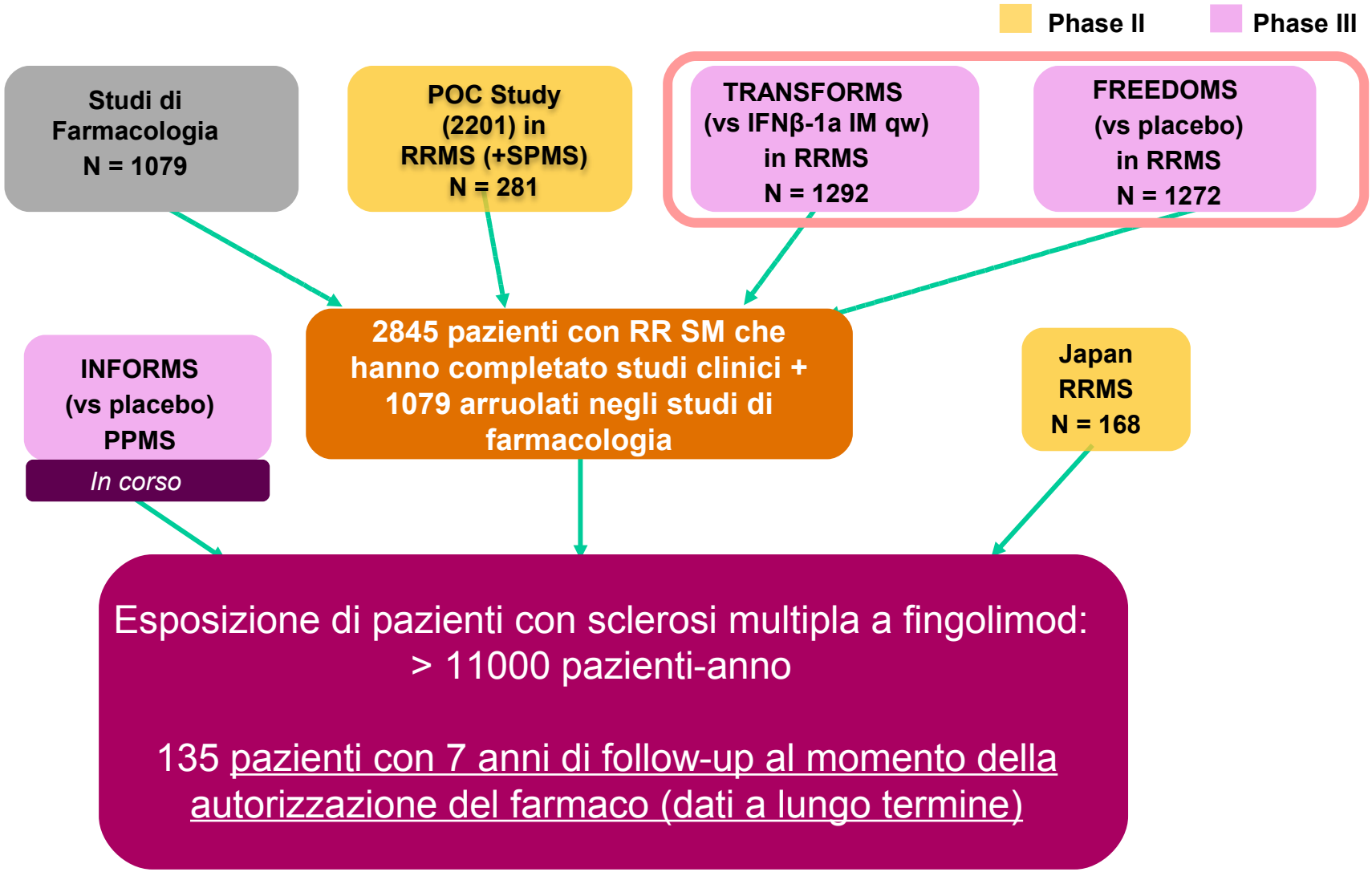
Fingolimod nel modello dell' EAE preserva l'integrità del tessuto cerebrale

Immunolabelling	Naïve-WT	EAE-WT	EAE-$S1P_1$- / -	EAE-WT + fingolimod
	$S1P_1$ present	$S1P_1$ present	$S1P_1$ absent on CNS cells	$S1P_1$ present
Anti-GFAP **Astrogliosis**				
Fluoromyelin **Myelination**				
Anti-neurofilament **Axonal staining**				

In these animals the disease severity was reduced

Histological data is from analysis of a slice of ventral lumbar spinal cord.
Reproduced with permission. Choi JW, et al. Proc Natl Acad Sci U S A 2011;108(2):751-6

Programma di sviluppo di fingolimod



POC, proof-of-concept

FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis)

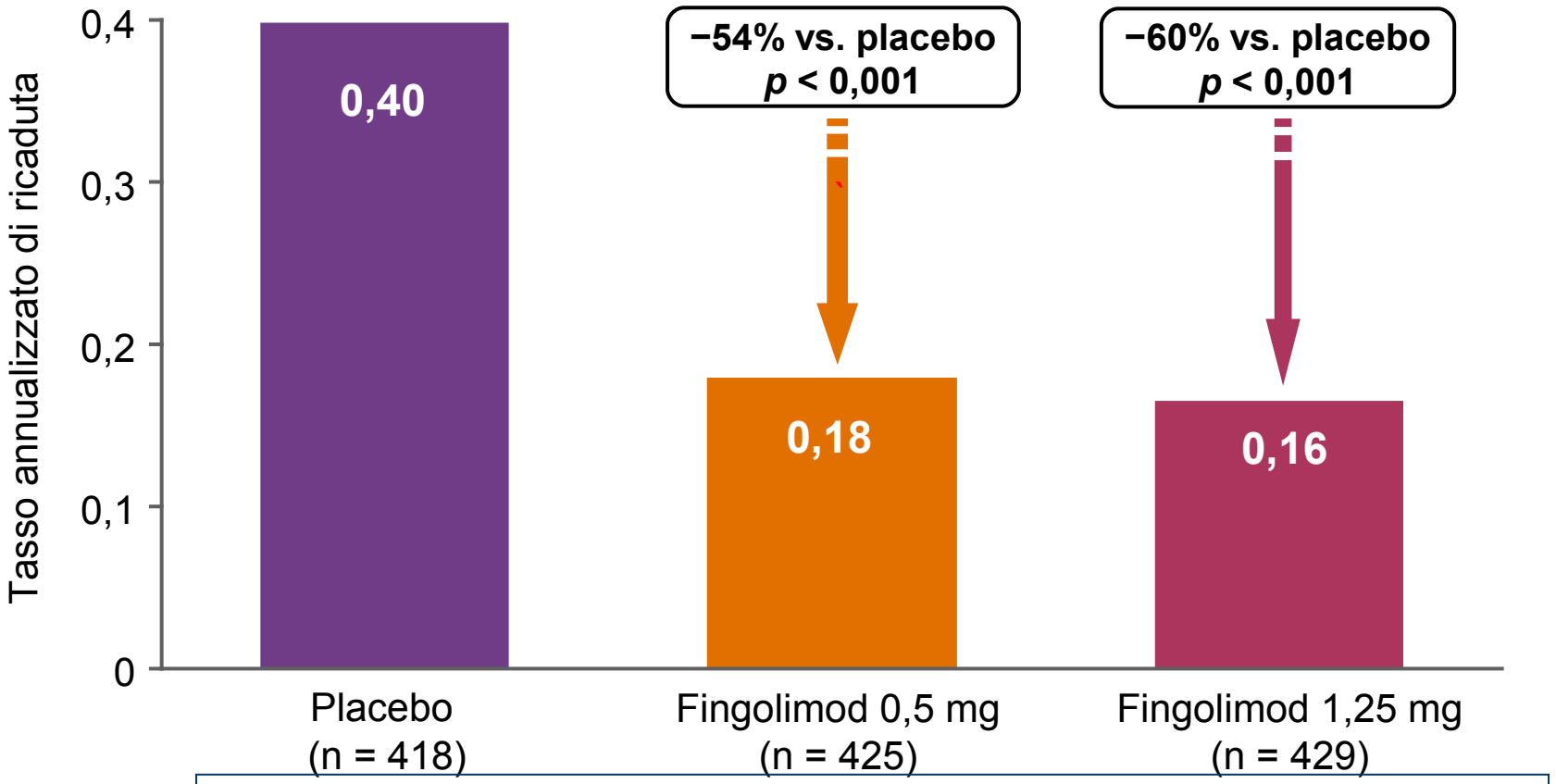
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 4, 2010 VOL. 362 NO. 5

A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

Ludwig Kappos, M.D., Ernst-Wilhelm Radue, M.D., Paul O'Connor, M.D., Chris Polman, M.D., Reinhard Hohlfeld, M.D., Peter Calabresi, M.D., Krzysztof Selmaj, M.D., Catherine Agoropoulou, Ph.D., Malgorzata Leyk, Ph.D., Lixin Zhang-Auberson, M.D., Ph.D., and Pascale Burtin, M.D., Ph.D., for the FREEDOMS Study Group*

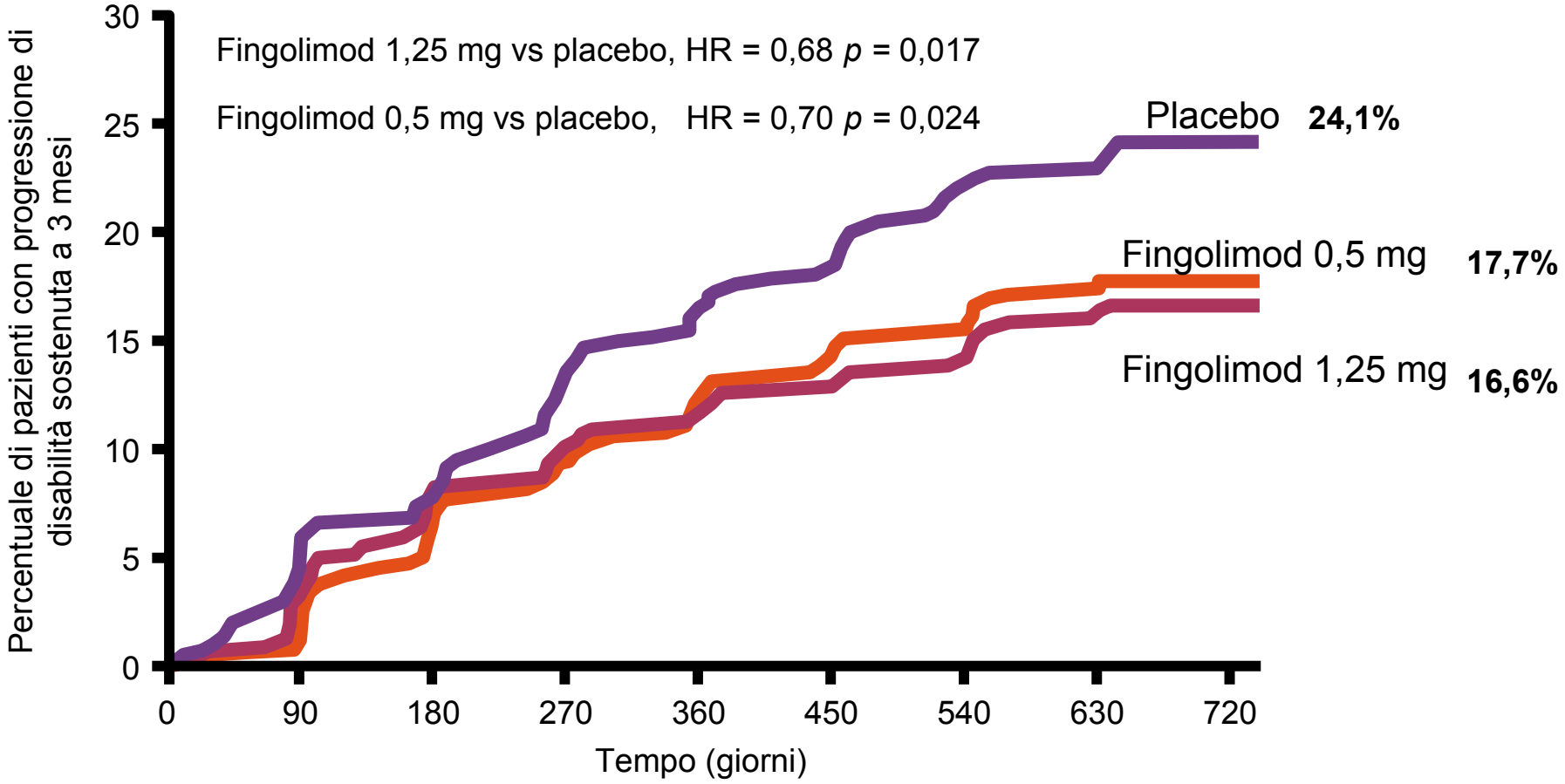
FREEDOMS : tasso annualizzato di ricaduta



ARR ridotto sia nei pazienti naïve sia nei pazienti precedentemente trattati (*p < 0,01* per tutti i confronti)

Negative binomial regression model adjusted for treatment group, country, number of relapses in previous two years and baseline Expanded Disability Status Scale as covariates

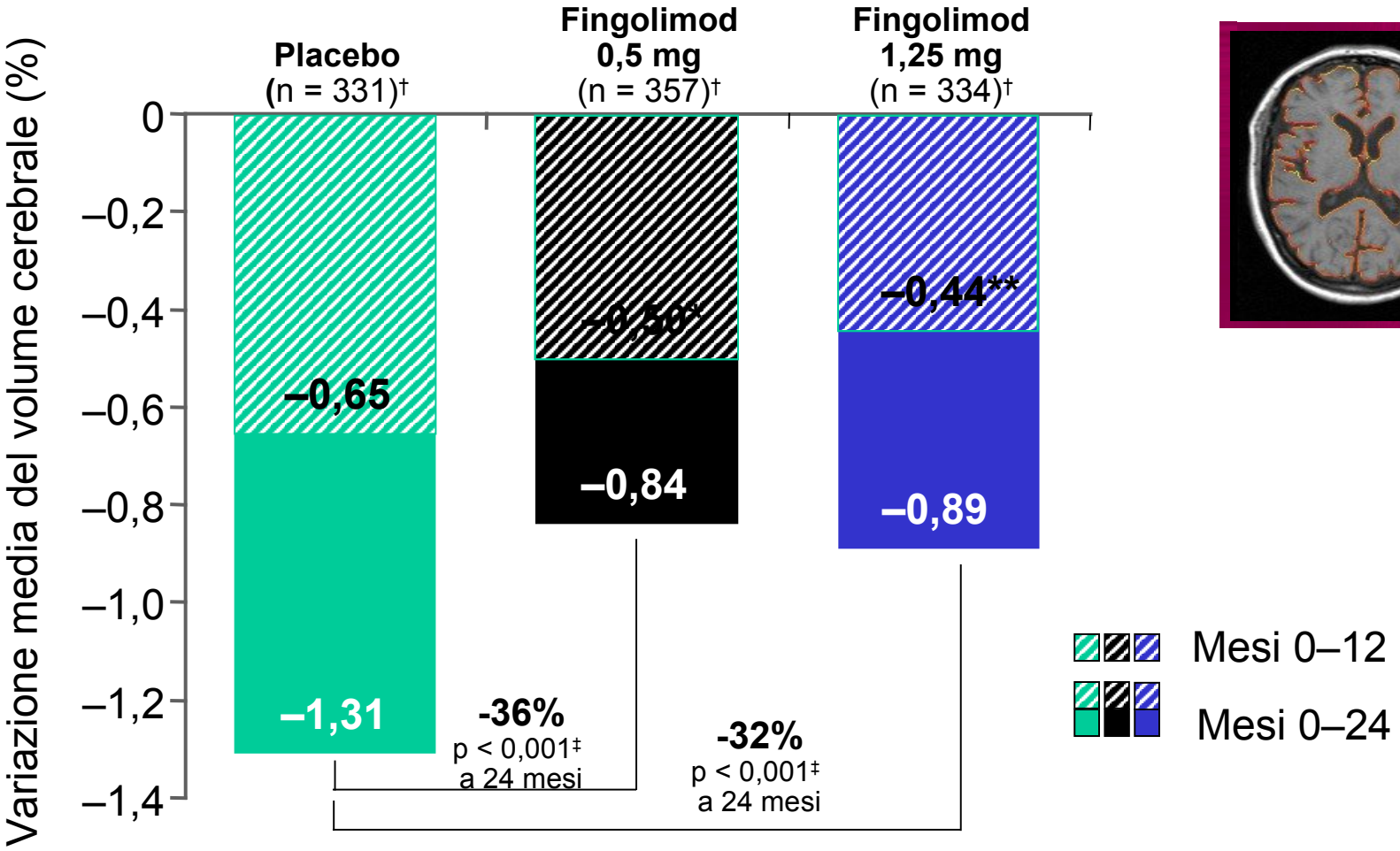
FREEDOMS Progressione della disabilità sulla EDSS confermata a 3 mesi



Riduzione della progressione della disabilità di circa il 30% vs placebo

Kappos *et al*. *NEJM* 2010;362(5):387–401

FREEDOMS:volume cerebrale



TRANSFORMS TRial Assessing injectable interferoN vS FTY720 Oral in RRMS)

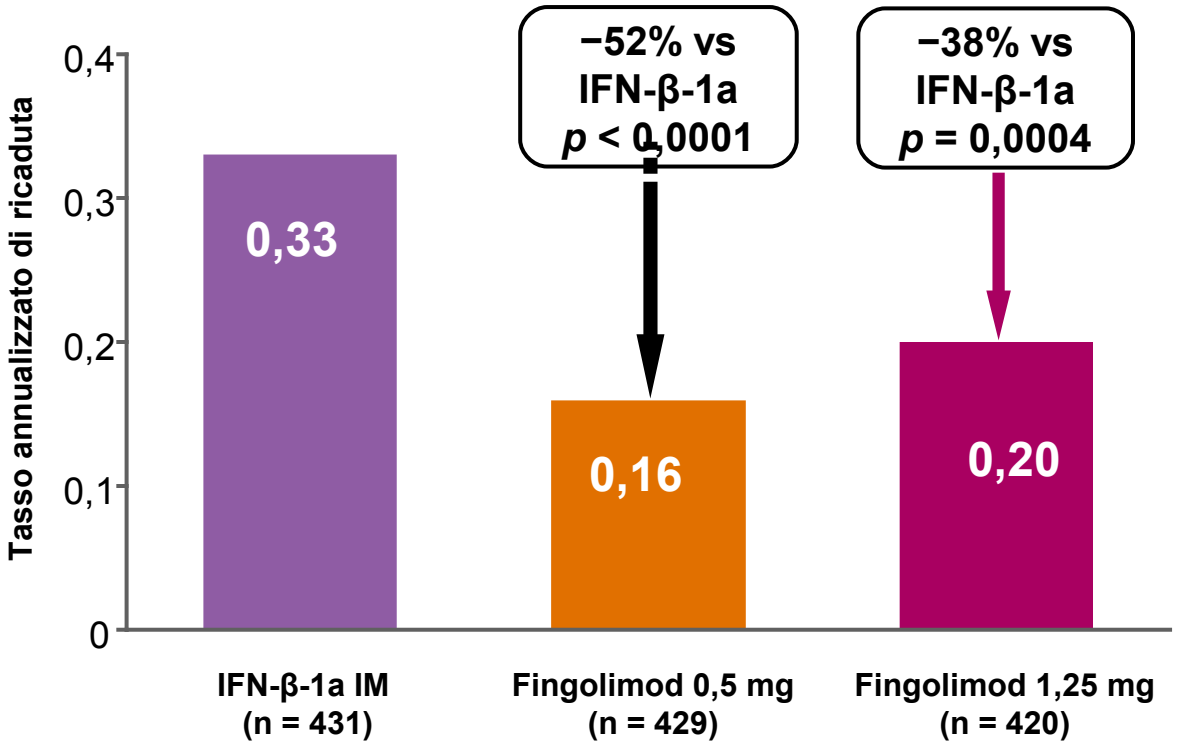
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis

Jeffrey A. Cohen, M.D., Frederik Barkhof, M.D., Giancarlo Comi, M.D., Hans-Peter Hartung, M.D., Bhupendra O. Khatri, M.D., Xavier Montalban, M.D., Jean Pelletier, M.D., Ruggero Capra, M.D., Paolo Gallo, M.D., Guillermo Izquierdo, M.D., Klaus Tiel-Wilck, M.D., Ana de Vera, M.D., James Jin, Ph.D., Tracy Stites, Ph.D., Stacy Wu, M.D., Shreeram Aradhye, M.D., and Ludwig Kappos, M.D., for the TRANSFORMS Study Group*

TRANSFORMS: tasso annualizzato di ricaduta



Riduzione del tasso annualizzato di ricaduta superiore al 50% al dosaggio di 0.5 mg rispetto a IFN-β-1a

Popolazione ITT. Modello di regressione binomiale negativa aggiustato per le covariate: gruppo di trattamento, nazione, numero di recidive nei 2 anni precedenti al basale e punteggio EDSS al basale; recidive confermate; *p* = 0,159 per fingolimod 0,5 vs. 1,25 mg

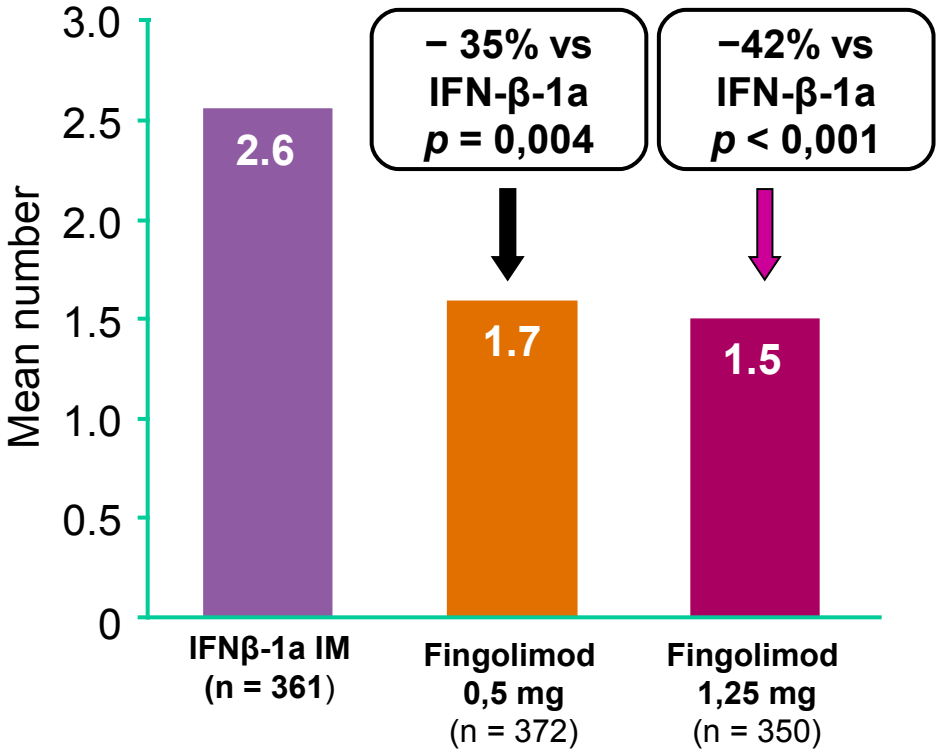
Cohen *et al*. *NEJM* 2010;362(5);402–15

TRANSFORMS : disabilità

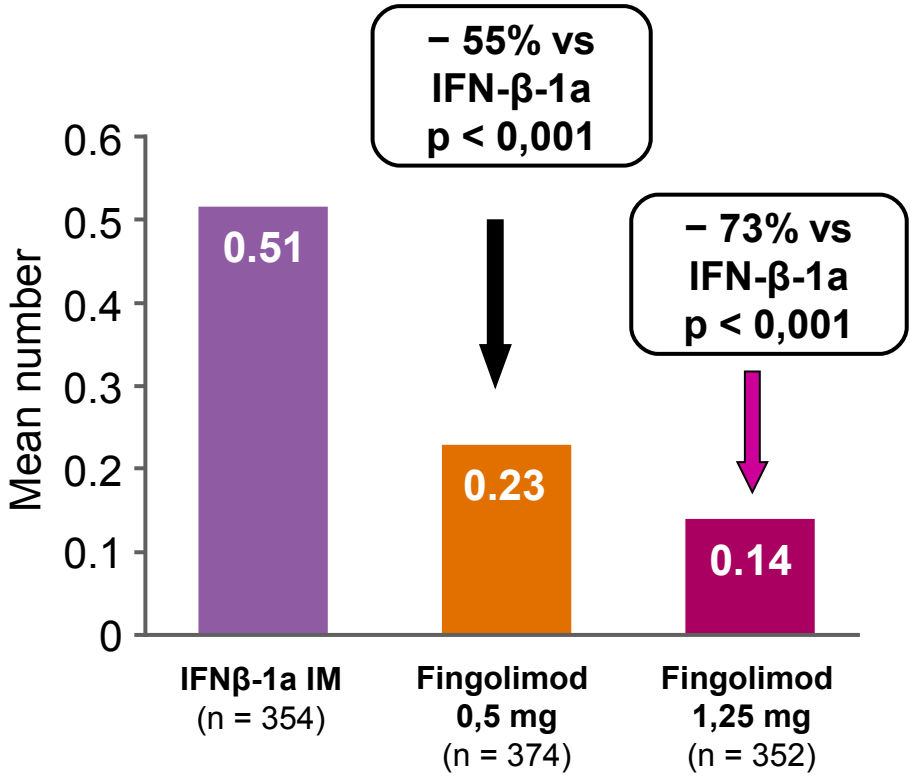
	IFNβ-1a IM	Fingolimod orale	
		0,5 mg	1,25 mg
	(n = 431)	(n = 429)	(n = 420)
Pazienti senza progressione di disabilità confermata a 3 mesi, % (IC 95%)‡	92,1 (89,4, 94,7)	94,1 (91,8, 96,3) *p = 0,25*	93,3 (90,9, 95,8) *p = 0,50*
Variazione a 12 mesi rispetto al basale			
EDSS* score, media ± DS	+0,01 ± 0,78	–0,08 ± 0,79 *p = 0,06*	–0,11 ± 0,90 *p = 0,02*

TRANSFORMS : attività alla risonanza magnetica

Numero di lesioni in T2 nuove/aumentate di volume a 12 mesi



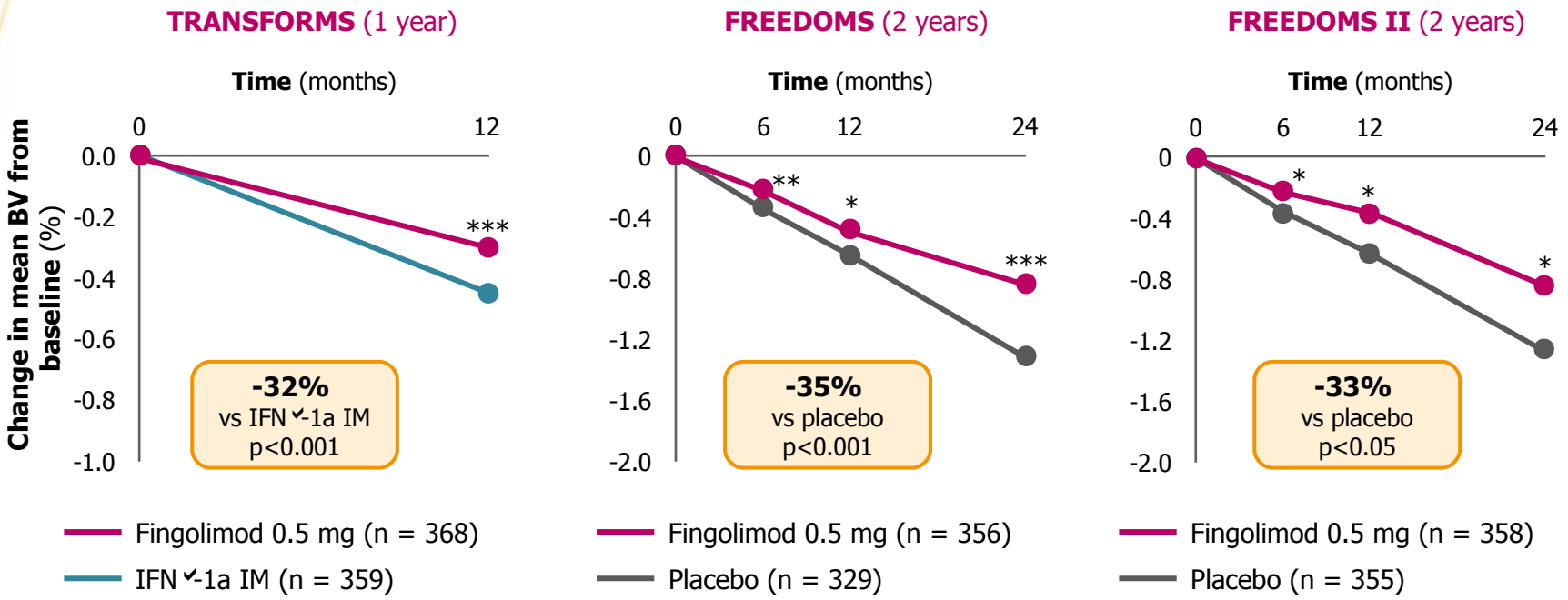
Numero di lesioni Gd+ a 12 mesi



Entrambi i dosaggi di fingolimod riducono l'attività di malattia alla RM in confronto a IFN-β-1a

Analysis included patients with available magnetic resonance imaging (MRI) scans
Gd+, gadolinium-enhancing; IFNβ-1a IM, interferon β-1a intramuscularly
Cohen *et al*. *NEJM* 2010;362(5);402–15

Fingolimod has an early and sustained effect on the rate of brain atrophy compared with placebo and IFN ✓-1a IM



- Caution is required when comparing studies due to differences in baseline characteristics and endpoint definitions

ITT population with evaluable MRI images. Note: n numbers for FREEDOMS data reflect the number of patients with available data at 24 months. *p<0.05; **p<0.01; ***p<0.001 vs comparator; p-values are for comparisons over Months 0–6, Months 0–12, Months 0–24. BV, brain volume; ITT, intent-to-treat. Gilenya™ Prescribing Information

Kappos L, et al. N Engl J Med 2010; 362: 387-401, and Cohen JA, et al. N Engl J Med 2010; 362: 402-415.
Radue EW et al. Poster P724 presented at ECTRIMS 2012. Reproduced with permission.

Indicazione approvata da EMA

Fingolimod –solo la dose 0.5 mg -- è indicato come **monoterapia** *disease-modifying* nella **SMRR** ad elevata attività nei seguenti gruppi di pazienti adulti:

Pazienti con un'elevata attività di malattia nonostante la terapia con interferone-beta. (non rispondenti a terapie di prima linea)

oppure

Pazienti con sclerosi multipla recidivante-remittente grave ad evoluzione rapida,

Fingolimod: sicurezza e tollerabilità

Il profilo di tollerabilità di fingolimod dipende dalla sua farmacodinamica

Fingolimod ha affinità per 4 sottotipi dei recettori S1P (S1P1, S1P3, S1P4, S1P5)

Resistenza delle vie aeree

Muscolatura bronchiale liscia

S1P3 (S1P1, S1P2?)

Angiogenesi

Vasodilatazione

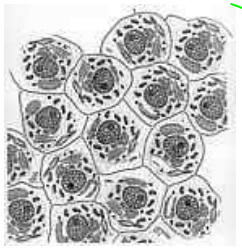
S1P1

S1P3 / S1P1?

Aumento della barriera endoteliale

S1P1

Endotelio Vascolare



S1P3

Diminuzione della barriera endoteliale

S1P

S1P3 (S1P1, S1P2?)

Muscolatura vascolare liscia

Tono vascolare

S1P3 (S1P1 nell'uomo?)

Miociti atriali

Riduzione della frequenza cardiaca

Conduzione atrio-ventricolare

Il profilo di tollerabiltà di fingolimod (studi FREEDOMS E TRANSFORMS)

- **Eventi avversi più importanti in pazienti trattati con fingolimod:**
  - **Edema maculare: incidenza 0,2% con fingolimod 0,5 mg/die, (10 dei 13 casi nei primi 4 mesi di esposizione, regressione/remissione all'interruzione del trattamento)**
  - **Incremento del livello ematico di transaminasi: incremento reversibile e asintomatico di ALT >3×ULN nell'8% dei pazienti trattati con fingolimod 0,5 mg. Nessun caso di danno epatico permanente.**
  - **Lieve incremento della pressione arteriosa: 1,1 mm Hg per fingolimod 0,5 mg/die a 2 anni**
  - **Bradicardia: riduzione transitoria della frequenza cardiaca alla prima somministrazione di farmaco; nadir alla 4ª-5ª ora con diminuzione di 7-8 bpm con fingolimod 0,5 mg/die Bradicardia sintomatica <0,5% (3 casi) con fingolimod 0,5 mg/die.**

    Blocco AV di I grado nel 4,8% dei pazienti trattati con fingolimod 0,5 mg/die; blocco AV II grado nello 0,2% dei pazienti trattati con fingolimod 0,5 mg/die.

necessità di somministrare la prima dose in ospedale con monitoraggio PA, frequenza cardiaca ed ECG per almeno 6 ore

Il profilo di tollerabiltà di fingolimod (studi FREEDOMS E TRANSFORMS)

- **Neoplasie cutanee :??** Controllo dermatologico con mappatura dei nei “a rischio” prima del trattamento, successivi controlli
- **Infezioni**
- **2 casi di infezioni herpetiche fatali nei CTs:** 1 caso di priminfezione da VZ disseminata (epatite fulminante) e 1 di encefalite herpetica, *entrambi nel gruppo ad alte dosi*
  - Solo la bassa dose (0.5 mg)è stata commercializzata
  - Necessità di eseguire sierologia per VZ e, se negativa, vaccinazione per VZ un mese prima di iniziare la terapia

Nel post-marketing

-

- 1 caso fatale di VZ disseminato in un soggetto sieropositivo per VZ (possibile ruolo della terapia steroidea concomitante)

- Un caso di PML in un soggetto trattato con fingolimod che era stato precedentemente trattato con natalizumab

- Un caso di PML in un soggetto trattato con fingolimod per 6 mesi, precedentemente trattato con IFNB e Aza per un mese circa, in cui la diagnosi di SM è dubbia

- Due casi fatali di sindrome da attivazione macrofagica

Gravidanza

- FDA: categoria C
- In studi sull'animale il farmaco è risultato teratogeno (azione sull'angiogenesi).
- E' consigliato eseguire test gravidico prima dell'inizio della terapia
- **E' consigliato un metodo contraccettivo durante la terapia**
- **In caso di gravidanza programmata è consigliato wash out per almeno 2 mesi**
  - **Rebound alla sospensione?**
- E' stato istituito un registro delle gravidanze

Raccomandazioni per l'utilizzo di fingolimod nella pratica clinica

Bradiaritmia	Osservazione della prima somministrazione di farmaco per tutti i pazienti (prime 6 ore). In caso di bradiaritmia, i pazienti devono essere mantenuti in osservazione fino a scomparsa dei sintomi. Richiesta una valutazione cardiologica prima dell'inizio del trattamento in pazienti a rischio; Non utilizzo del farmaco in pts in trattamento con anti-aritmici di classe I o III; Re-start con monitoraggio delle 6 ore se interruzione prolungata (>14 giorni).
Infezioni (Emocromo)	**Se la conta linfocitaria < 0,2x 109/L interrompere il trattamento fino a ripresa della conta normale**. Posticipare l'inizio del trattamento in caso di severa infezione virale in corso. Considerare la sospensione del trattamento in caso di gravi infezioni (da definire caso per caso). <u>Sierologia VZV</u> Controllo Ab antivaricella prima dell'inizio del trattamento in caso di pazienti naive o se il paziente non è stato vaccinato. Consigliata la vaccinazione e l'inizio del trattamento dopo 1 mese.
Edema maculare	(Per pazienti con diabete o anamnesi di uveite, valutazione oftalmologica allo screening e durante il trattamento) Valutazione oftalmologica (non si menziona OCT) a 3-4 mesi dall'inizio del trattamento. Interruzione de trattamento in caso conferma di edema maculare.
Funzionalità epatica	Monitoraggio più frequente se enzimi epatici > 5 ULN (transaminasi e bilirubina) e interruzione del trattamento in caso di rialzo permanente. Posticipare l'inizio del trattamento in caso di epatite virale attiva in corso.
Gravidanza	Test di gravidanza negativo prima dell'inizio del trattamento. Utilizzo di un metodo contraccettivo adeguato in donne fertili durante il trattamento e per 2 mesi dopo l'interruzione. Interruzione del trattamento in caso di gravidanza. Registro delle gravidanze.

Conclusioni

- Il dosaggio 0,5 mg/die ha evidenziato la stessa efficacia del dosaggio 1,25 mg/die con un miglior profilo di sicurezza/tollerabilità.
- Il dossier registrativo, per il solo dosaggio 0,5 mg/die, è stato sottomesso a FDA ed EMA nel dicembre 2009.

FDA: approvazione del 21 settembre 2010

1 INDICATIONS AND USAGE

GILENYA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

EMA: approvazione della Commissione Europea del 17 marzo 2011.

Fingolimod: conclusioni

Fingolimod

↓

Riduzione significativa del tasso annualizzato di ricadute vs IFN β-1a pari al 52%

↓

Riduzione significativa della progressione della disabilità (30% dopo 3 mesi; 37% dopo 6 mesi)

↓

Fingolimod ha dimostrato di agire sulla componente infiammatoria della SM, ma potrebbe anche di avere effetti diretti sul sistema nervoso centrale[1, 2] **(in corso trial su SMPP)**

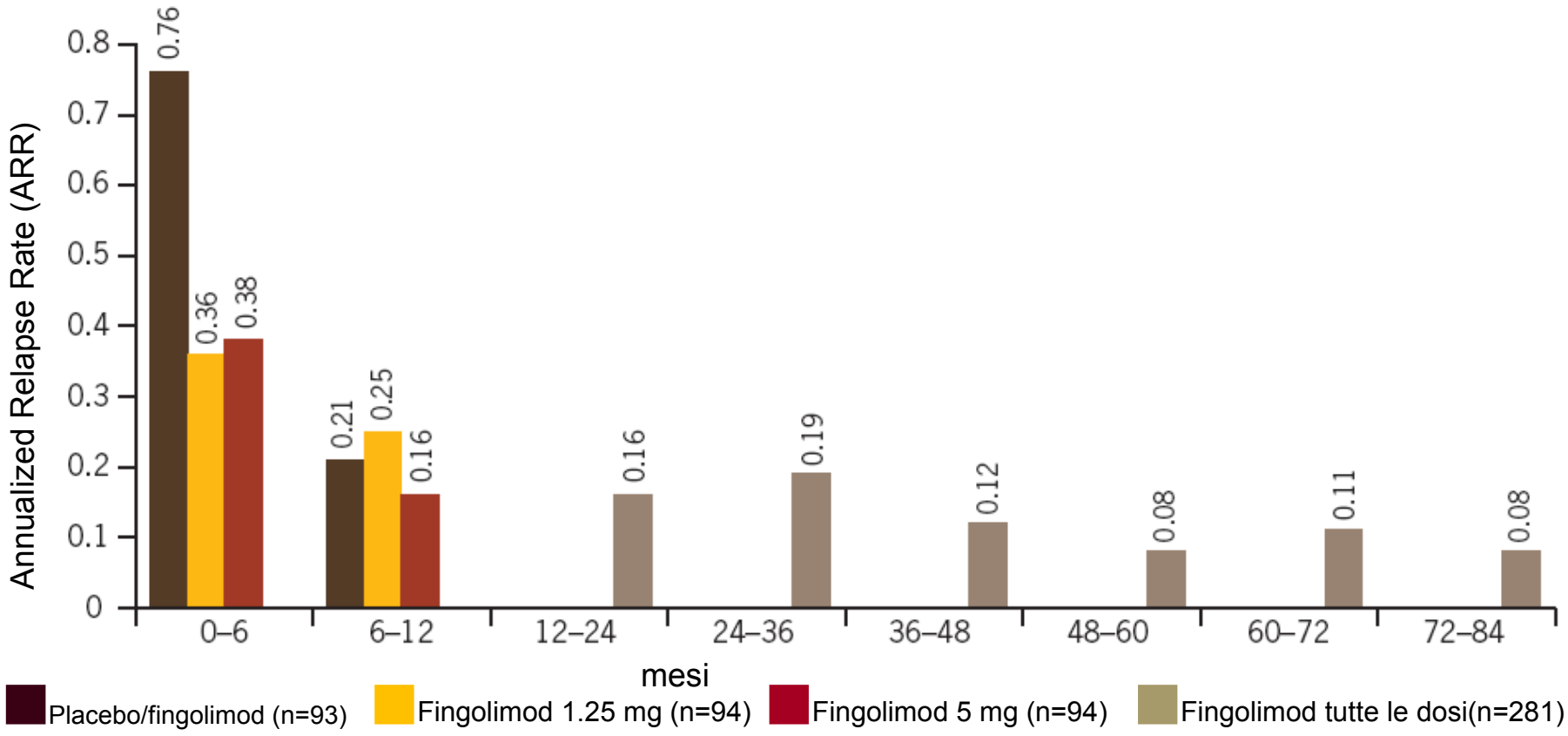
↓

È il **primo farmaco orale** per la sclerosi multipla, con un nuovo meccanismo d'azione.

1. Mehling M *et al.* Neurology 2008;71(16):1261–7; 2. Dev KK *et al.* Pharmacol Ther 2008;117(1):77–93

Fingolimod : ARR

Extension Phase II Follow-up 7 years

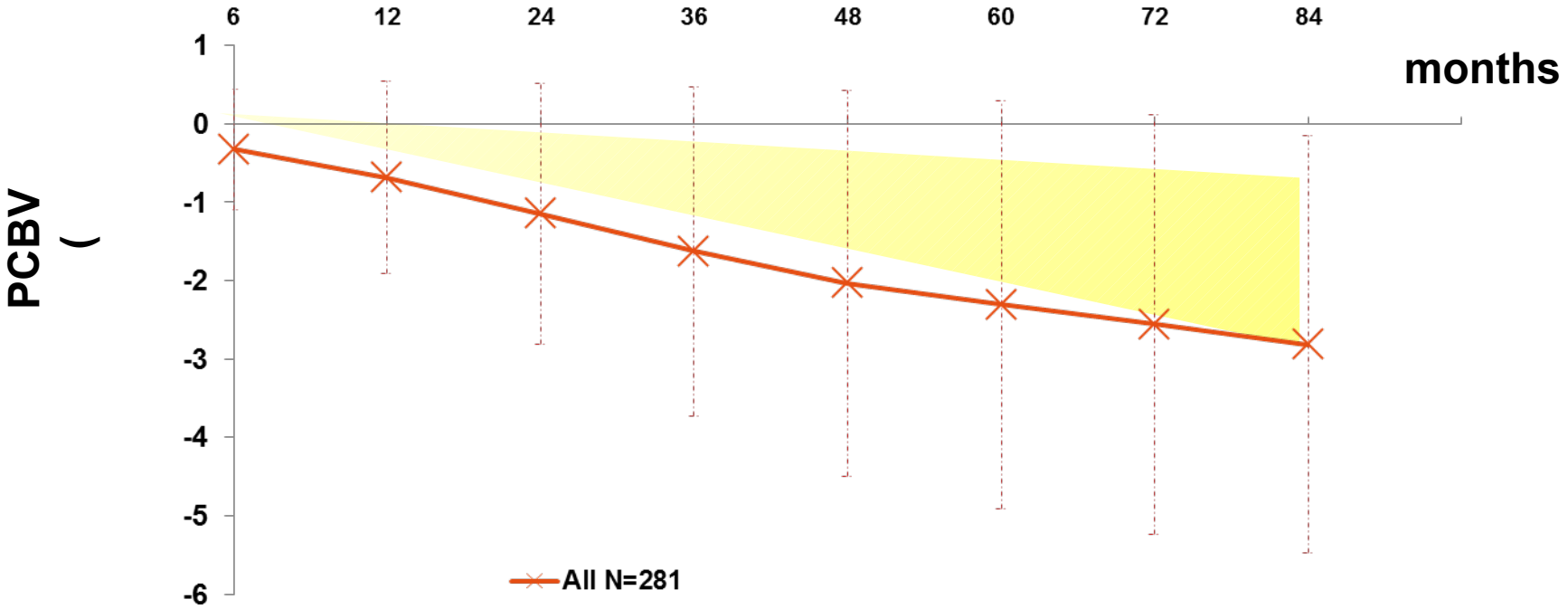


Antel J et al, Poster P01.129 AAN 2012

Fingolimod

Significant reduction on brain atrophy development over time

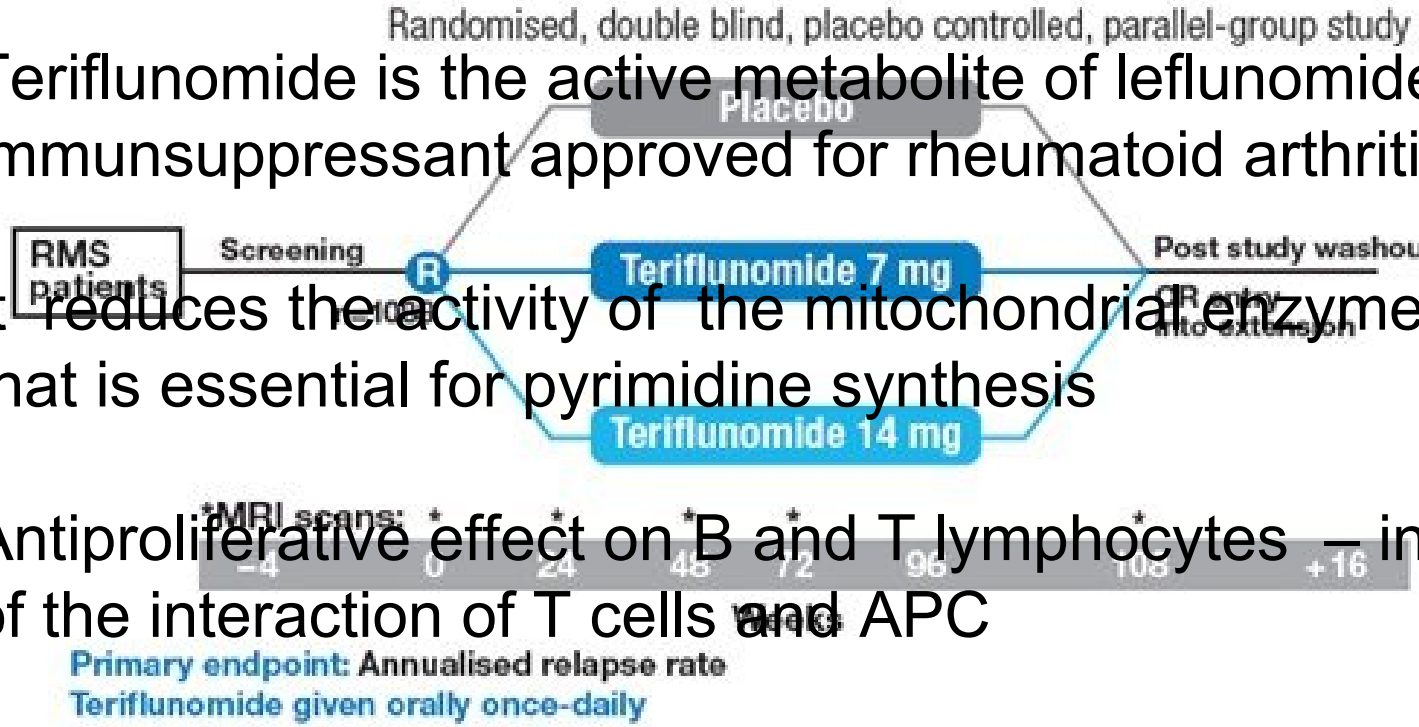
Follow-up 7 years



Brain atrophy in healthy controls
(0,1-0,4 % all'anno)

J. Antel et al, Poster P01.129 AAN 2012

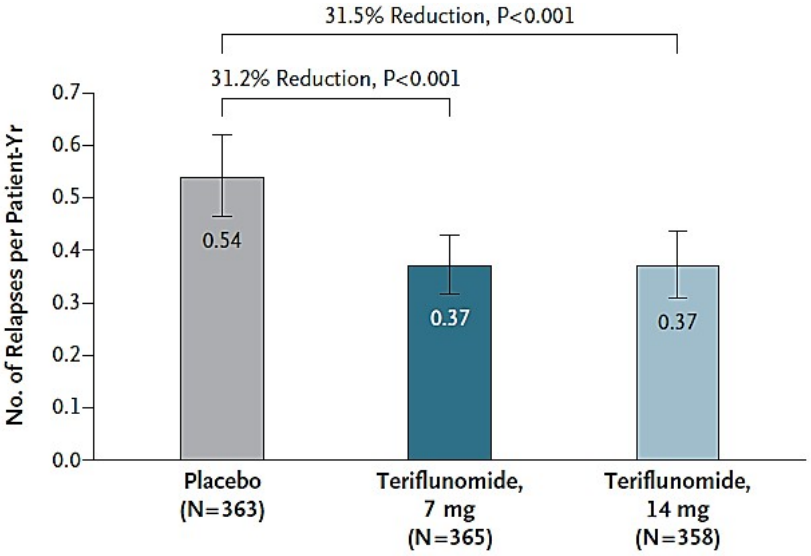
Teriflunomide

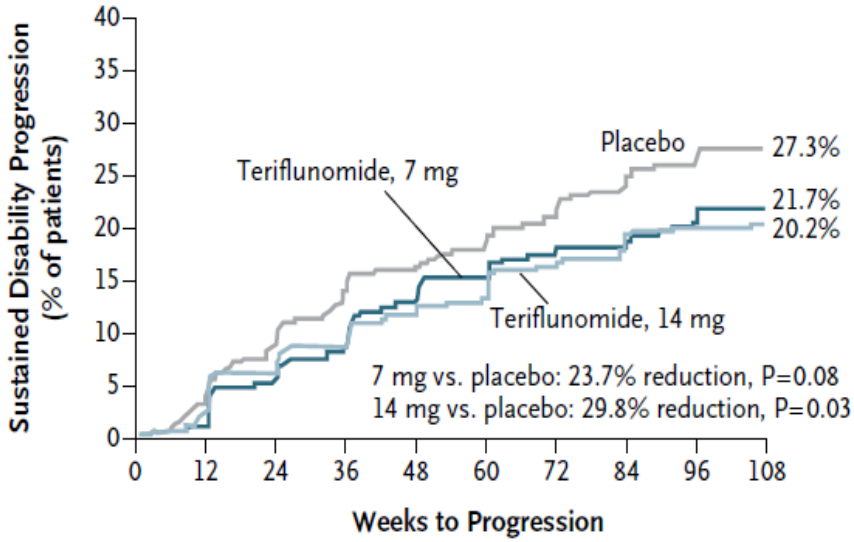


- Teriflunomide is the active metabolite of leflunomide, an immunsuppressant approved for rheumatoid arthritis
- It reduces the activity of the mitochondrial enzyme DODH that is essential for pyrimidine synthesis
- Antiproliferative effect on B and T lymphocytes – inhibition of the interaction of T cells and APC
- potential teratogenic effect - liver dysfunction- neutropenia

TEMSO Fase III

- **Total lesion volume**: ↓ del 67% con 14 mg versus placebo (p=0.0003)
- **Annualized Relapse Ratio (ARR)**: ↓ 31% - 7 e 14 mg versus placebo
- **Disability progression**: ↓ del 29,8% con 14 mg (p=0.03)





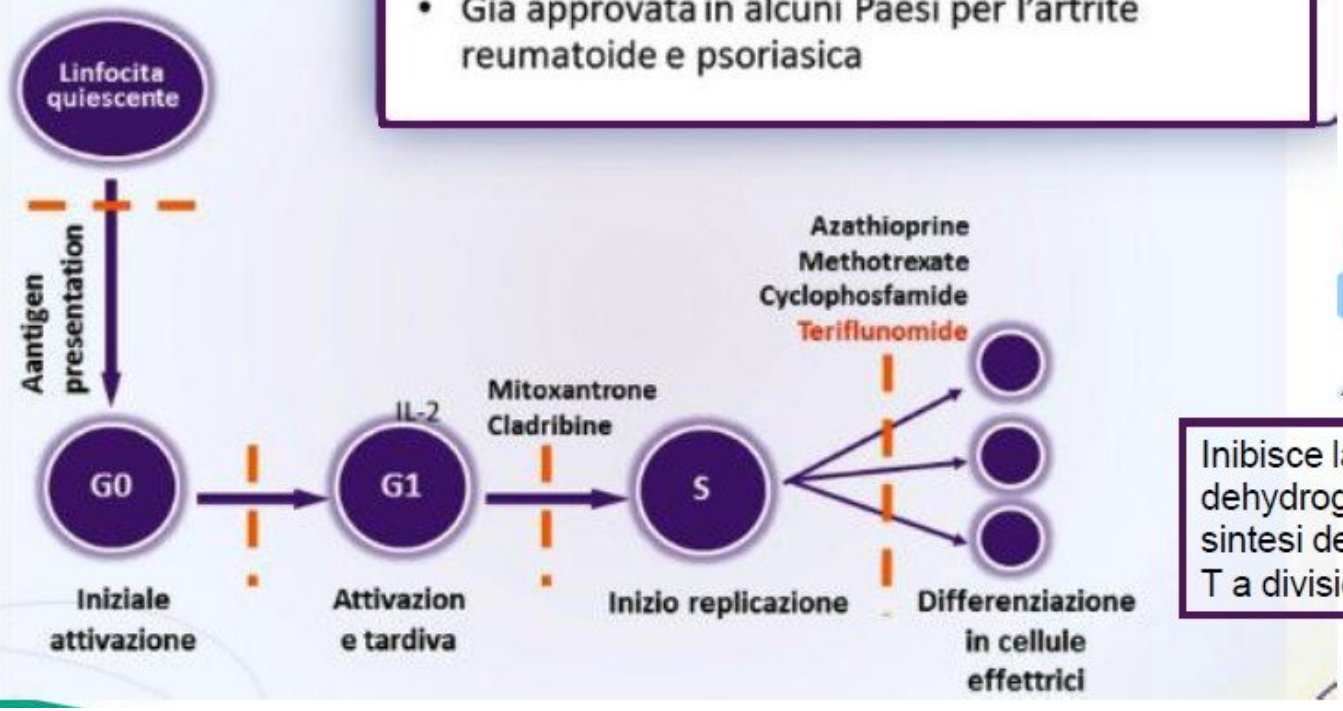
AE: neutropenia -↑ALT – gastrointestinal disorders - alopecia

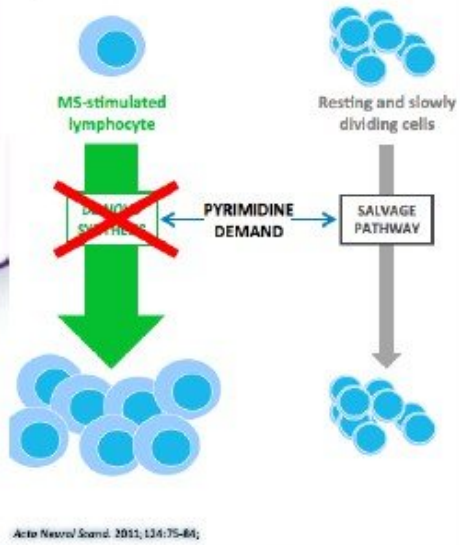
O'Connor P. et al. ECTRIMS 2010, Wolinsky J. ECTRIMS 2010, O'Connor P. et al. NEJM 2011

Teriflunomide

Teriflunomide

- Blocca la replicazione cellulare dei linfociti attivati
- Apparentemente non ha effetti sulle cellule progenitrici, per cui non ha un effetto citotossico diffuso sul sistema immunitario
- Già approvata in alcuni Paesi per l'artrite reumatoide e psoriasica

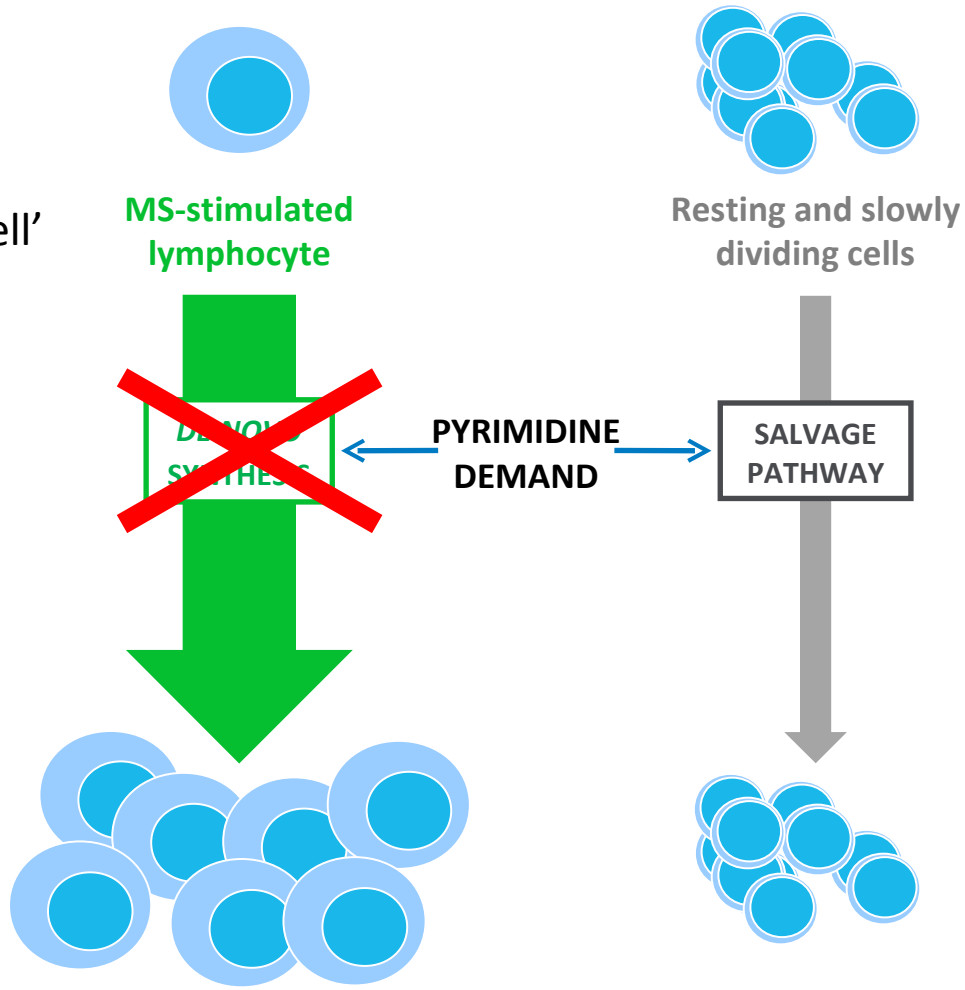




Inibisce la dihydro-orotate dehydrogenasi, enzima per la sintesi delle pirimidine dei Linf. B e T a divisione rapida.

Teriflunomide

- Teriflunomide è il principale metabolita attivo della leflunomide
- Leflunomide è indicata per la terapia dell' artrite reumatoide negli adulti
- Teriflunomide inibisce selettivamente e reversibilmente la diidro-orotato deidrogenasi, un enzima mitocondriale chiave nella sintesi de novo delle pirimidine richiesta dai linfociti B e T attivati
  - Attraverso questo effetto citostatico, teriflunomide può limitare la risposta immune nella SM[2,3]



1. Claussen M and Korn T. *Clin Immunol.* 2012;142:49-56; 2. Gold R and Wolinsky JS. *Acta Neurol Scand.* 2011;124:75-84;
3. Warnke C et al. *Neuropsychiatr Dis Treat.* 2009;5:333-340

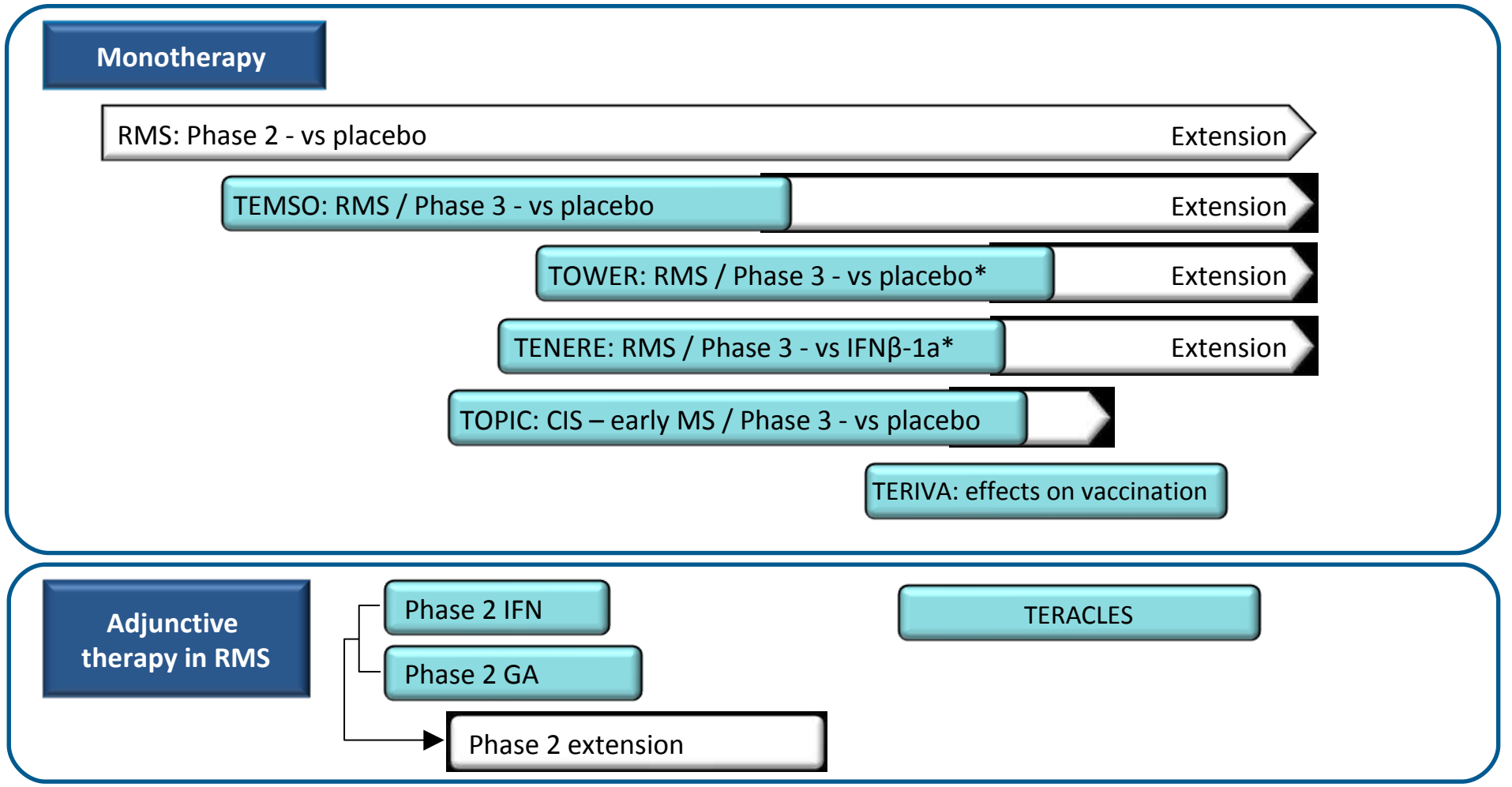
TERIFLUNOMIDE (Aubagio®)

- Teriflunomide è approvata per il trattamento della SM recidivante-remittente in USA, Australia e Argentina
- Due dosi: 7 and 14 mg, una volta al dì
- Recentemente approvata da EMA: solo la dose 14 mg , una volta al dì

- Due trial di fase III, TEMSO and TOWER
  - TEMSO (TEriflunomide Multiple Sclerosis Oral) (NCT00134563)[1]
  - TOWER (Teriflunomide Oral in people With relapsing multiplE scleRosis) (NCT00751881)[2]

1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Kappos L et al. *Mult Scler J.* 2012;18:9–53

Teriflunomide Extensive Clinical Program



*Extensions ongoing for TOWER and TENERE. CIS, clinically isolated syndrome; GA, glatiramer acetate; IFN, interferon

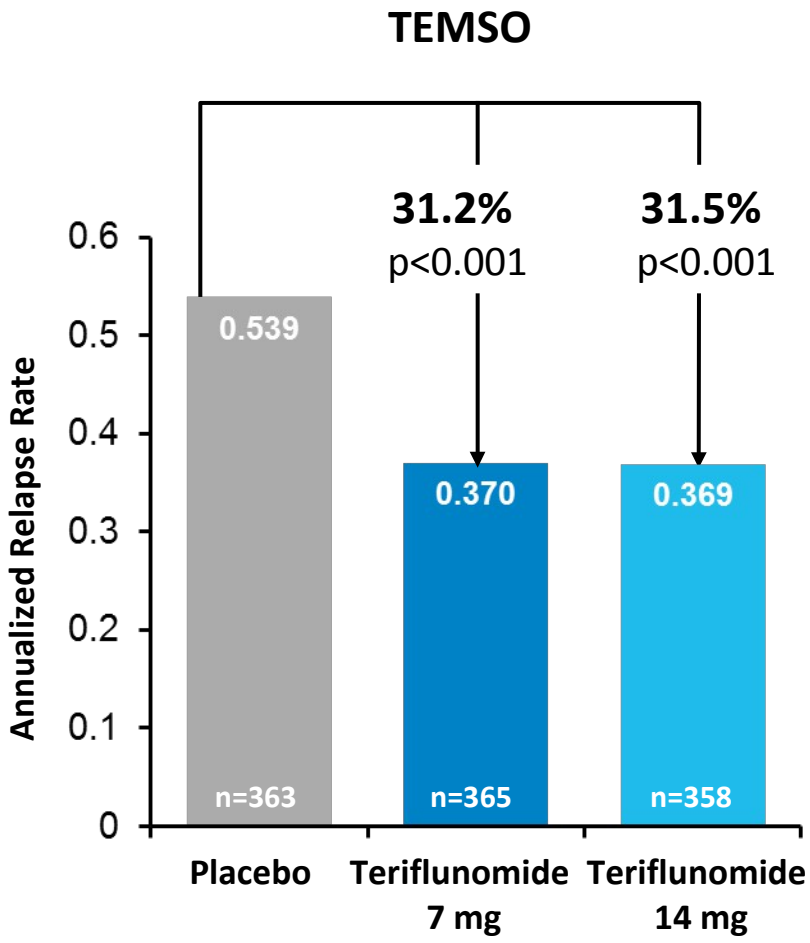
TEMSO and TOWER: Study Overviews

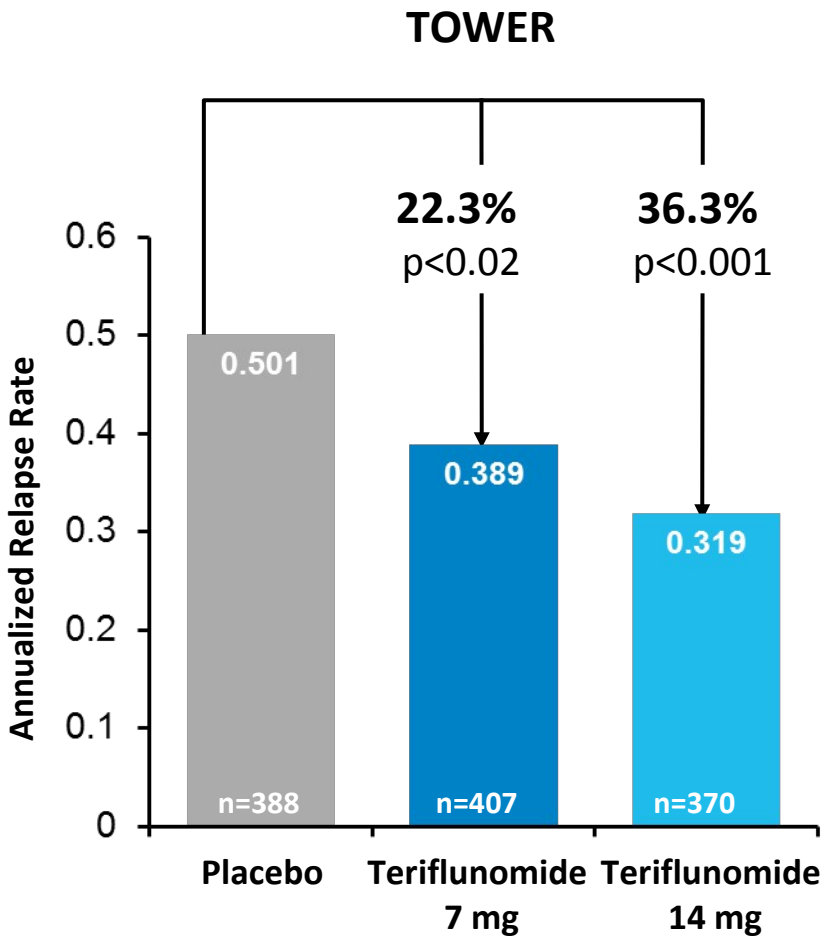
	TEMSO	TOWER
Study design	Multicenter, multinational, randomized (1:1:1), double-blind, parallel-arm, placebo-controlled phase 3	
Patients	1088	1169
Study duration	Fixed study treatment duration, 108 weeks	Variable study treatment duration, 48–152 weeks (mean 78 weeks) Study ended when last patient randomized completed 48 weeks of treatment
Patient population	Patients with relapsing MS (McDonald criteria)[1,2] Age 18–55 years EDSS score ≤5.5 at screening ≥2 relapses within 2 years or 1 relapse within 1 year prior to randomization	
Treatment arms	Placebo Teriflunomide 7 mg Teriflunomide 14 mg	
Primary outcome	Annualized relapse rate (ARR)	
Key secondary outcome	Disability progression (confirmed over 12 weeks)	
Secondary outcomes	MRI measures of disease Subject-reported fatigue[a] Safety and tolerability	Subject-reported fatigue[a] Subject-reported quality of life[b] Safety and tolerability

[a]Fatigue Impact Scale; [b]Short Form-36 Health Survey. EDSS, Expanded Disease Status Scale

1. McDonald WI et al. *Ann Neurol.* 2001;50:121-127 (TEMSO); 2. Polman C et al. *Ann Neurol.* 2005;58:840-846 (TOWER)

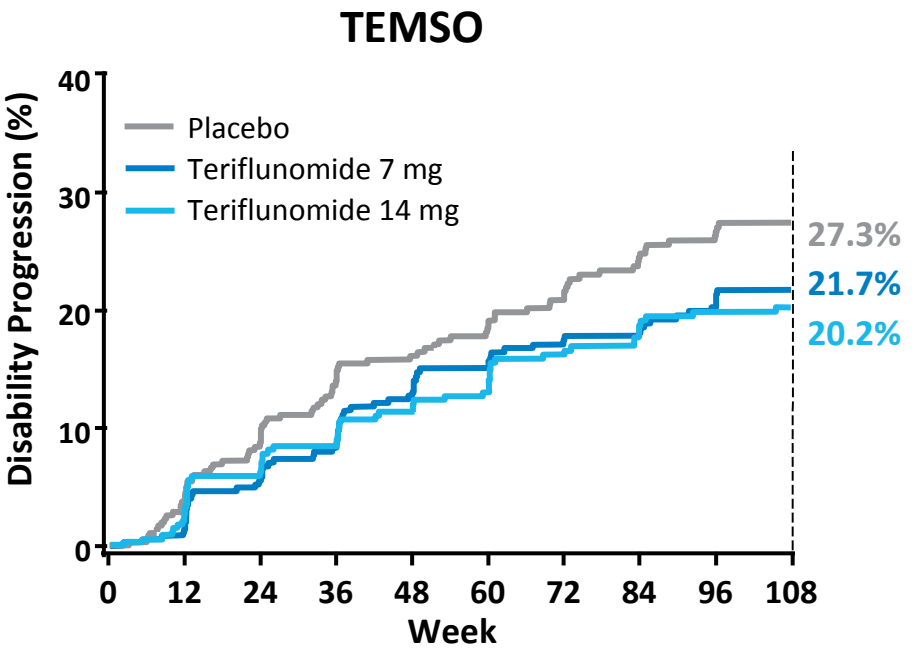
TEMSO and TOWER: Annualized Relapse Rates

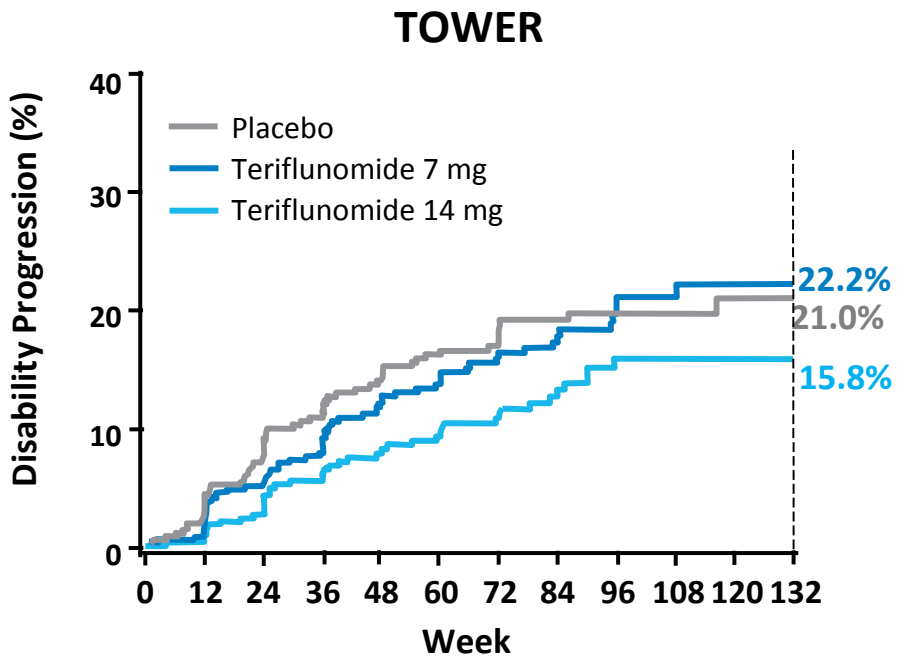




1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Kappos L et al. *Mult Scler J.* 2012;18:9-53. Modified intent-to-treat populations

TEMSO and TOWER: Disability Progression



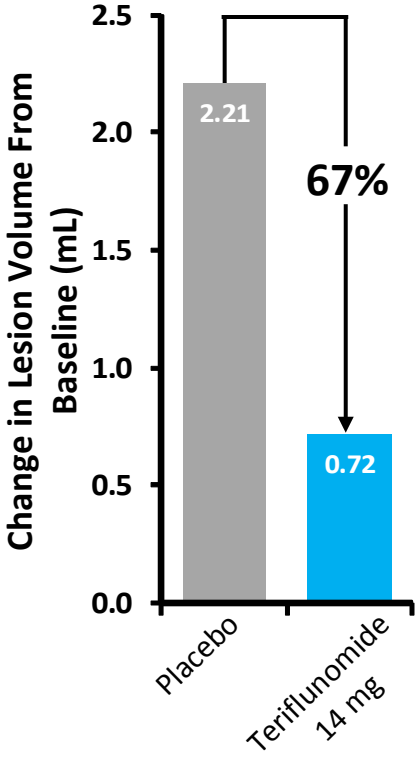


	TEMSO	TOWER
7 mg vs placebo	HR 0.763 p=0.0835	HR 0.955 p=0.7620
14 mg vs placebo	HR 0.702 p=0.0279	HR 0.685 p=0.0442

1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Kappos L et al. *Mult Scler J.* 2012;18:9-53. Modified intent-to-treat populations
HR, hazard ratio. Disability progression is defined as an increase from baseline of ≥1.0 point on the EDSS, confirmed for at least 12 weeks

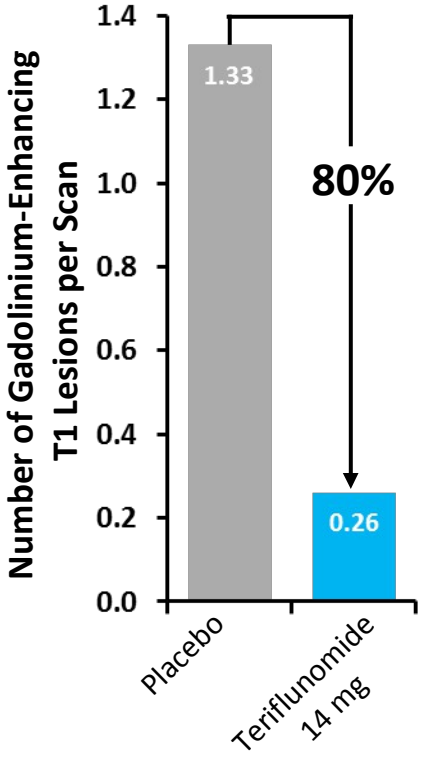
TEMSO:
MRI Outcomes

Burden of Disease[a]



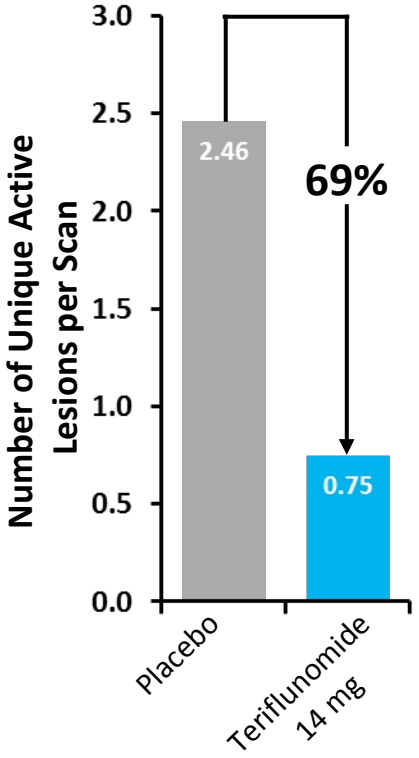
Relative Reduction 67% (p<0.001)[c]

Gd-Enhancing Lesions



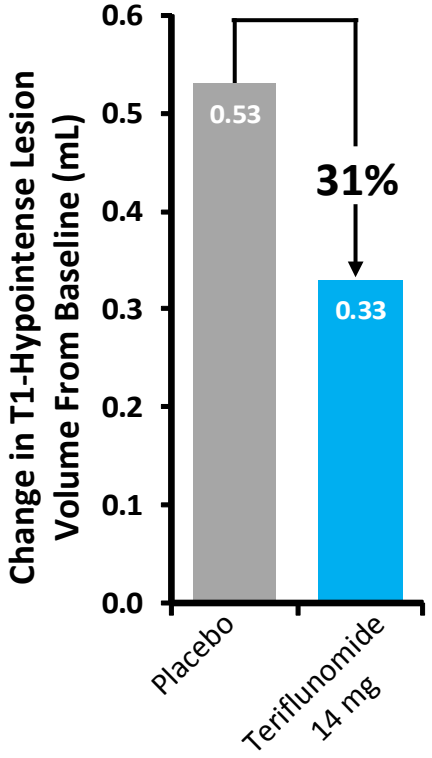
Relative Risk Reduction 80% (p<0.001)

Unique Active Lesions[b]



Relative Risk Reduction 69% (p<0.001)

T1-Hypointense Lesion Volume



Relative Reduction 31% (p=0.02)[c]

[a]Total volume of all abnormal brain tissue, calculated as the sum of the total volume of T2 lesion component and T1-hypointense lesion component; [b]Enhanced lesions plus unenhanced new and substantially enlarged T2-hyperintense lesions; [c]Percent relative reduction (percent change for treatment relative to placebo of the change from baseline [based on transformed data] at Week 108). Modified intent-to-treat populations

1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Wolinsky J et al. *Mult Scler J.* 2013 [Epub ahead of print]

TEMSO and TOWER:
Overview of Treatment-Emergent Adverse Events

TEAEs, n (%)	TEMSO			TOWER		
	Placebo (n=360)	Teriflunomide 7 mg (n=368)	Teriflunomide 14 mg (n=358)	Placebo (n=385)	Teriflunomide 7 mg (n=409)	Teriflunomide 14 mg (n=371)
All	315 (87.5)	328 (89.1)	325 (90.8)	320 (83.1)	344 (84.1)	320 (86.3)
Serious	46 (12.8)	52 (14.1)	57 (15.9)	47 (12.2)	52 (12.7)	44 (11.9)
Treatment discontinuation	29 (8.1)	36 (9.8)	39 (10.9)	24 (6.2)	53 (13.0)	58 (15.6)
Death	0	0	0	1 (0.3)[a]	1 (0.2)[b]	2 (0.5)[c]

[a]Respiratory infection following paraplegia; [b]Motor vehicle accident; [c]One suicide, one death due to Gram-negative septicemia There was no evidence that teriflunomide was a causative factor in any of the deaths in TOWER Safety populations. TEAE, treatment-emergent adverse event. 1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Kappos L et al. *Mult Scler J.* 2012;18:9–53

TEMSO and TOWER: TEAEs Occurring More Frequently With Teriflunomide Treatment

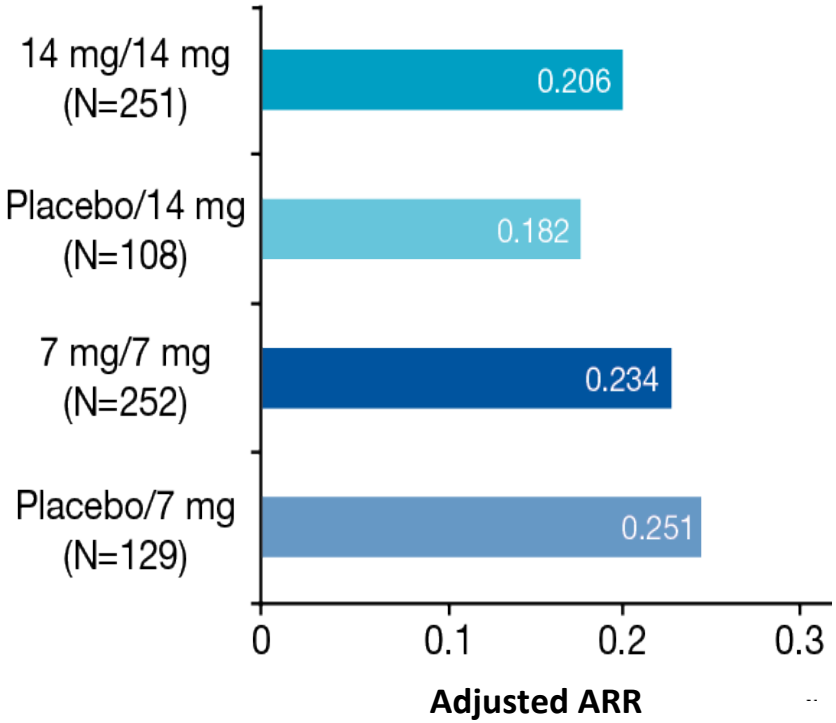
Incidence ≥10% in either teriflunomide treatment group and >2% in comparison with placebo, in TEMSO or TOWER

	TEMSO			TOWER		
Patients, %	Placebo (n=360)	Teriflunomide 7 mg (n=368)	Teriflunomide 14 mg (n=358)	Placebo (n=385)	Teriflunomide 7 mg (n=409)	Teriflunomide 14 mg (n=371)
ALT increase	7	12	14	8	11	14
Hair thinning[a]	3	10	13	4	10	13
Diarrhea	9	15	18	7	12	11
Headache	18	22	19	11	15	12
Influenza	10	9	12	6	5	6
Nausea	7	9	14	9	8	10

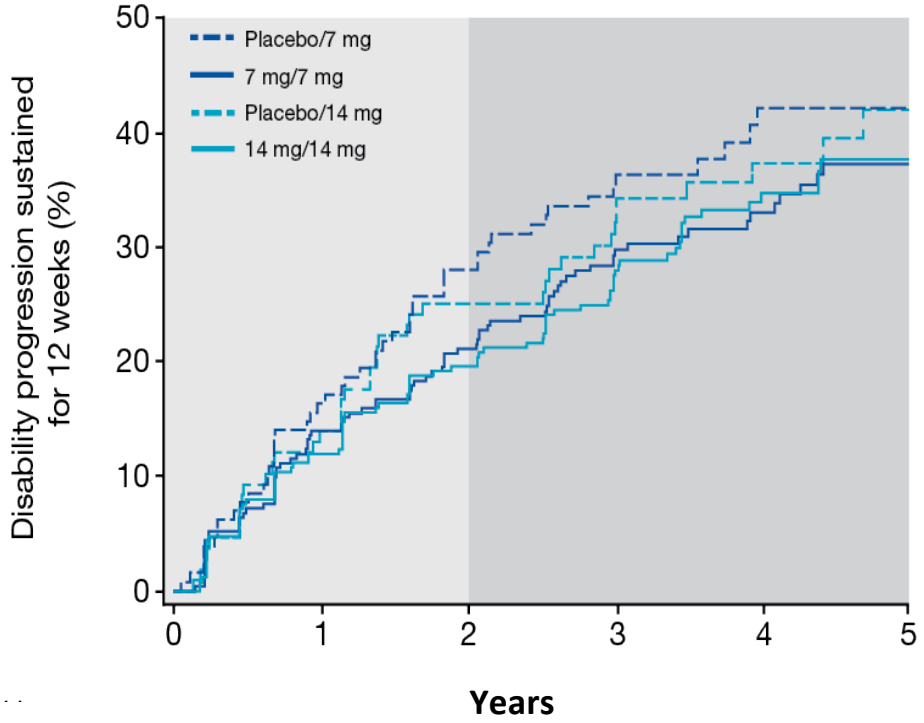
[a]Medical Dictionary for Regulatory Activities preferred term 'alopecia', described by investigators as 'hair thinning'
Safety populations. Events ordered by decreasing frequency in either teriflunomide group. ALT, alanine aminotransferase
1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Kappos L et al. *Mult Scler J.* 2012; 18:9-53

TEMSO Extension:
ARR and Sustained Disability Progression

Adjusted ARR*



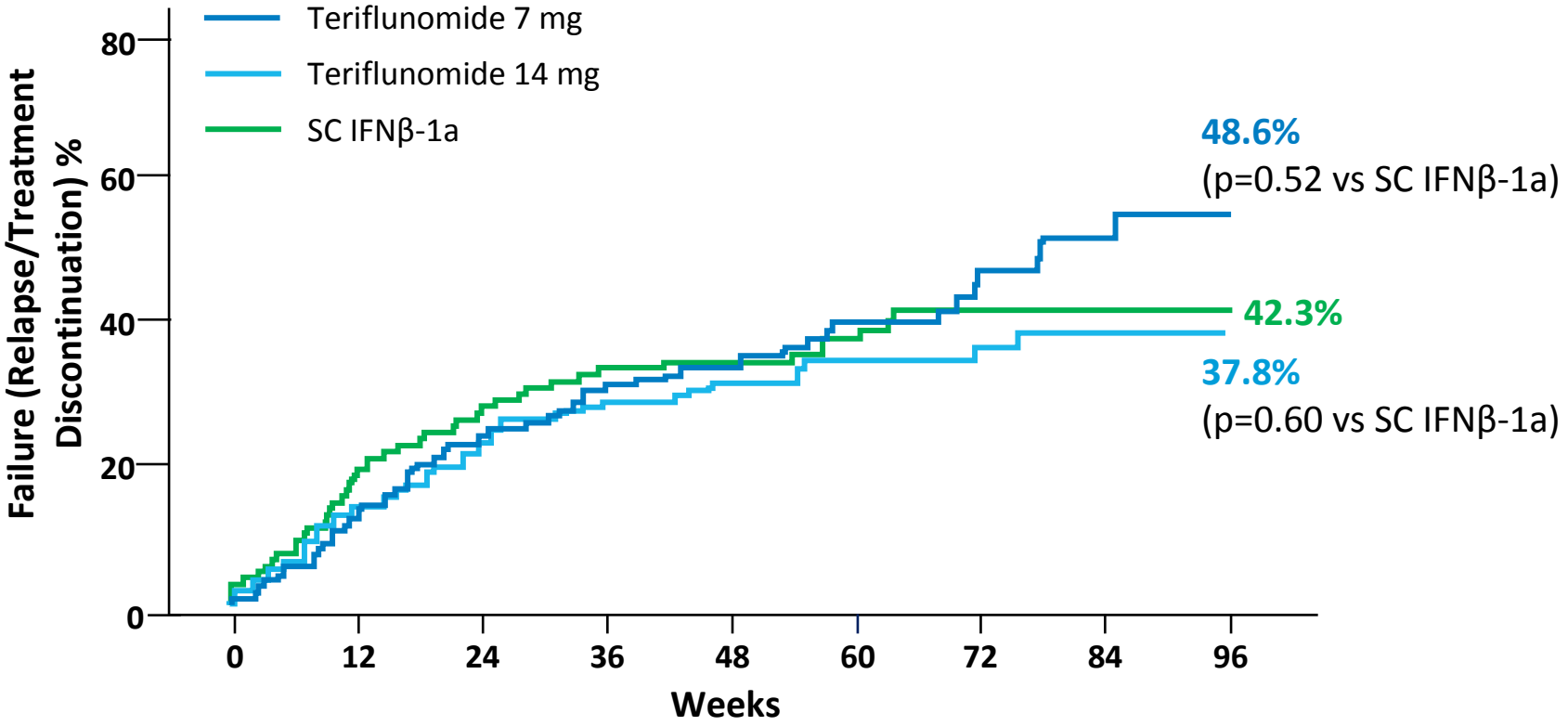
Disability Progression*



- The adjusted ARR was low in all treatment groups 5 years after randomization
- Disability progression was lower in patients initially randomized to teriflunomide

No placebo comparison in open-label extension. 1. Comi et al. *Mult Scler J.* 2011;17(Suppl 17):S182.P439

TENERE:
Teriflunomide vs IFNβ-1a s.c.: Time to Failure



- **No statistical superiority was observed between teriflunomide (7 mg or 14 mg) and SC IFNβ-1a on time to failure, the primary composite endpoint**
- Additional analyses showed **greater treatment satisfaction and fewer discontinuations** with teriflunomide than IFNβ-1a therapy

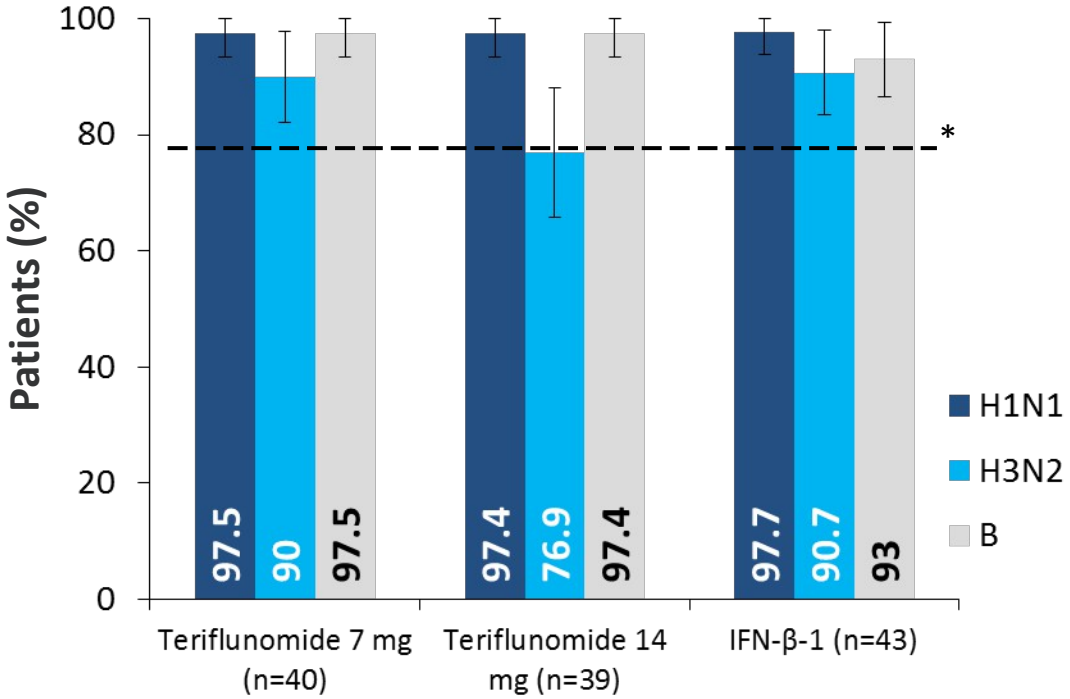
Median duration of exposure (all treatment groups): 63.64 weeks; actual maximum duration: ~115 weeks. SC, subcutaneous

1. Vermersch P et al. Fourth Cooperative Meeting of CMSC and ACTRIMS, 30 May–2 June 2012, San Diego, CA, USA

TERIVA:
Immune Response to Seasonal Influenza Vaccination

- Patients treated with teriflunomide generally mounted an effective immune response to seasonal influenza vaccination
- All treatment groups achieved antibody titers ≥40 in 70% of patients, in accordance with the European criteria for efficacy of influenza vaccination in adults aged 18 to 60 years[1]

Proportion of Patients With Influenza Antibody Titers ≥40 at 28 Days Post Vaccination



*European criteria for 18 to 60 year olds requires achievement of antibody titers ≥40 by 70% of patients, indicated by the dashed line

1. European Medicines Agency for the Evaluation of Medicinal Products guidelines. 2. Bar-Or A et al. *Mult Scler J.* 2012;18:(S4)279-508(P925)

Teriflunomide: Summary

Efficacy

- In TEMSO and TOWER, both doses of teriflunomide significantly reduced ARR compared with placebo
- Teriflunomide 14 mg had a significant effect on the risk of 12-week disability progression compared with placebo in both studies; this was not observed with the 7 mg dose
- MRI-assessed disease activity was significantly decreased with both teriflunomide doses
- In the TEMSO extension study, after 5 years, disability progression was lower in patients initially randomized to teriflunomide
- The TENERE study showed greater patient satisfaction with teriflunomide than IFNβ-1a therapy

Safety

- Teriflunomide has a well-characterized safety profile
- Patients treated with teriflunomide mounted an effective immune response to seasonal influenza vaccination

Teriflunomide has a favorable benefit:risk ratio as a treatment for RMS

TEMSO and TOWER:
Baseline Demographics and Disease Characteristics

		TEMSO	TOWER
Demographics	**Age, years** Mean (SD) Median (range)	 37.9 (8.8) 38.0 (18-55)	 37.9 (9.3) 38.0 (18-56)
	Female, n (%)	785 (72.2)	831 (71.1)
	Race, n (%) Caucasian/White Asian Other	 1058 (97.5) 15 (1.4) 12 (1.1)	 960 (82.1) 169 (14.5) 40 (3.4)
Disease and Treatment History	**Time since first symptom of MS, years** Mean (SD) Median (range)	 8.7 (6.9) 6.8 (0.3-35.7)	 8.0 (6.7) 6.3 (0.1-36.9)
	Number of relapses within past 2 years Mean (SD) Median (range)	 2.2 (1.1) 2.0 (1-12)	 2.1 (1.2) 2.0 (1-9)
	MS subtype, n (%) Relapsing–remitting Secondary progressive Progressive relapsing	 995 (91.5) 51 (4.7) 42 (3.9)	 1138 (97.5) 9 (0.8) 20 (1.7)
	Baseline EDSS score Mean (SD) Median (range)	 2.68 (1.3) 2.50 (0–6.0)	 2.70 (1.4) 2.50 (0–6.5)
	Previous DMT received in past 2 years, n (%)	294 (27.0)	384 (32.8)

1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Kappos L et al. *Mult Scler J.* 2012;18:9–53
Randomized populations. DMT, disease-modifying therapy; SD, standard deviation

TEMSO and TOWER: Infections

Patients with infection, n (%)	TEMSO			TOWER		
	Placebo (n=360)	Teriflunomide 7 mg (n=368)	Teriflunomide 14 mg (n=358)	Placebo (n=385)	Teriflunomide 7 mg (n=409)	Teriflunomide 14 mg (n=371)
All patients	209 (58.1)	220 (59.8)	222 (62.0)	197(51.2)	198 (48.4)	165 (44.5)
Serious infections	8 (2.2)	6 (1.6)	9 (2.5)	11 (2.9)	14 (3.4)	11 (3.0)
Leading to discontinuation	4 (1.1)	1 (0.3)	3 (0.8)	1 (0.3)	4 (1.0)	5 (1.3)
uspected opportunistic infections	0	0	0	1 (0.3)	1 (0.2)	3 (0.8)
eaths[a]	0	0	0	1 (0.3)	0	1 (0.3)

- A similar incidence of infections, serious infections, and infections leading to treatment discontinuation occurred across all treatment groups

[a]TOWER placebo: respiratory infection; teriflunomide 14 mg: bacterial sepsis (*Klebsiella*)

1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Genzyme data on file

TEMSO and TOWER: Hepatic Events

Patients with hepatic AEs, n (%)	TEMSO			TOWER		
	Placebo (n=360)	Teriflunomide 7 mg (n=368)	Teriflunomide 14 mg (n=358)	Placebo (n=385)	Teriflunomide 7 mg (n=409)	Teriflunomide 14 mg (n=371)
Any AE	**43 (11.9)**	**71 (19.3)**	**69 (19.3)**	**58 (15.1)**	**75 (18.3)**	**81 (21.8)**
Serious AEs	**9 (2.5)**	**7 (1.9)**	**9 (2.5)**	**11 (2.9)**	**8 (2.0)**	**6 (1.6)**
AEs leading to discontinuation	**15 (4.2)**	**16 (4.3)**	**13 (3.6)**	**12 (43.1)**	**15 (3.7)**	**18 (4.9)**
LT 3x ULN 5x ULN 10x ULN 20x ULN	 24 (6.7) 9 (2.5) 5 (1.4) 2 (0.6)	 23 (6.3) 9 (2.5) 3 (0.8) 1 (0.3)	 24 (6.7) 8 (2.2) 4 (1.1) 2 (0.6)	 22 (5.7) 14 (3.6) 5 (1.3) 2 (0.5)	 31 (7.6) 10 (2.5) 2 (0.5) 0	 29(7.8) 11 (3.0) 2 (0.5) 0
LT ≥3x ULN + bilirubin ≥2x ULN[a]	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.5)	1 (0.2)	0

[a]Criteria for Hy's Law; Alternative explanations for elevation were hepatitis C, gallbladder problems, and CMV infection (TEMSO); concomitant cortisone-pulse therapy and hepatitis C (placebo) Gilbert's syndrome and alcoholic liver enzyme (teriflunomide 7 mg) (TOWER)
ULN, upper limit of normal. 1. O'Connor P et al. *N Engl J Med.* 2011;365:1293-1303; 2. Genzyme data on file

Teriflunomide Clinical Trial Database: Retrospective Analysis of Pregnancy Outcomes

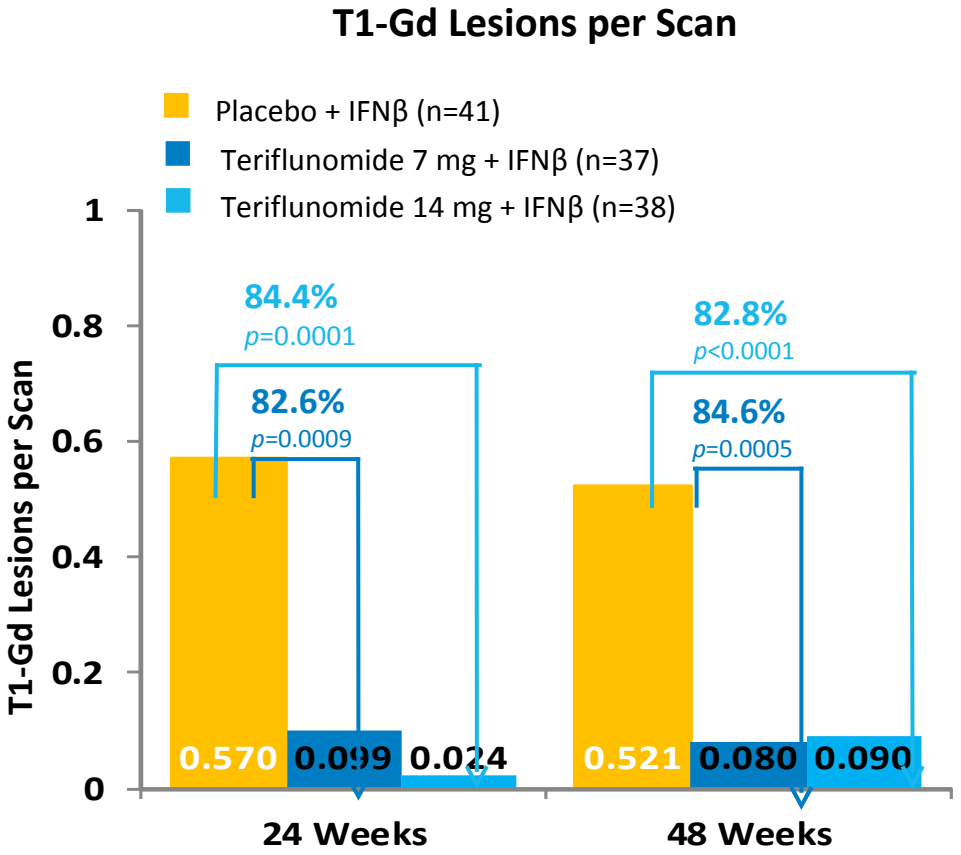
	Pregnancy outcome Data cut-off: August 21, 2012				
Treatment	**Live birth**	**Induced abortion**	**Spontaneous abortion**	**Ongoing pregnancy**	**Total**
Teriflunomide	12	20	10	2	**44**
Blinded therapy	2	13	4	3	**22**
Interferon-β	2	0	0	0	**2**
Placebo	1	0	1	0	**2**

- All newborns were healthy and did not present with any structural or functional problems at the data cut-off
- The rate of spontaneous abortion was within the range reported for the non-MS population[1]
- Newborns exposed to study treatment
  - Mean birth weight 3318 g (range 2780–4150 g)
  - Mean gestational age 38 weeks (range 36–42 weeks)
  - No malformations

1. García-Enguídanosa A et al. *Eur J Obstet Gynecol Reprod Biol*.2002;102:111-119; 2. Jung Henson L et al. *Neurology.* 2013:S30.005.

IFN-β Adjunct: Clinical Efficacy Outcomes

- Significant effect on reducing the risk of T1-Gd lesions per scan compared with IFNβ alone
  - 14 mg dose also significantly reduced the volume of T1 Gd-enhancing lesions per scan; not observed with 7 mg dose
- Dose-dependent effect on ARR was observed, but did not reach statistical significance compared with IFNβ alone[1]



1. Freedman MS et al. *Neurology.* 2012;78:1877-885

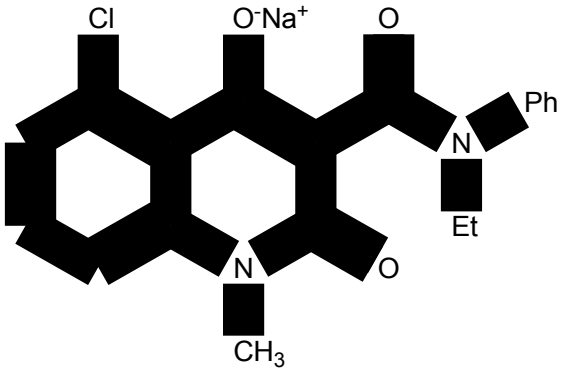
Sicurezza

- Con teriflunomide in generale buona tollerabilità e sicurezza
  - Aumento delle transaminasi
  - Disturbi GI
  - Assottigliamento dei capelli
  - Neuropatia periferica

- Teratogenicità nell'animale –categoria FDA X
- Indicata la contraccezione nella donna e nell'uomo
- In caso di programma di gravidanza eliminazione tramite colestiramina o carbone attivo

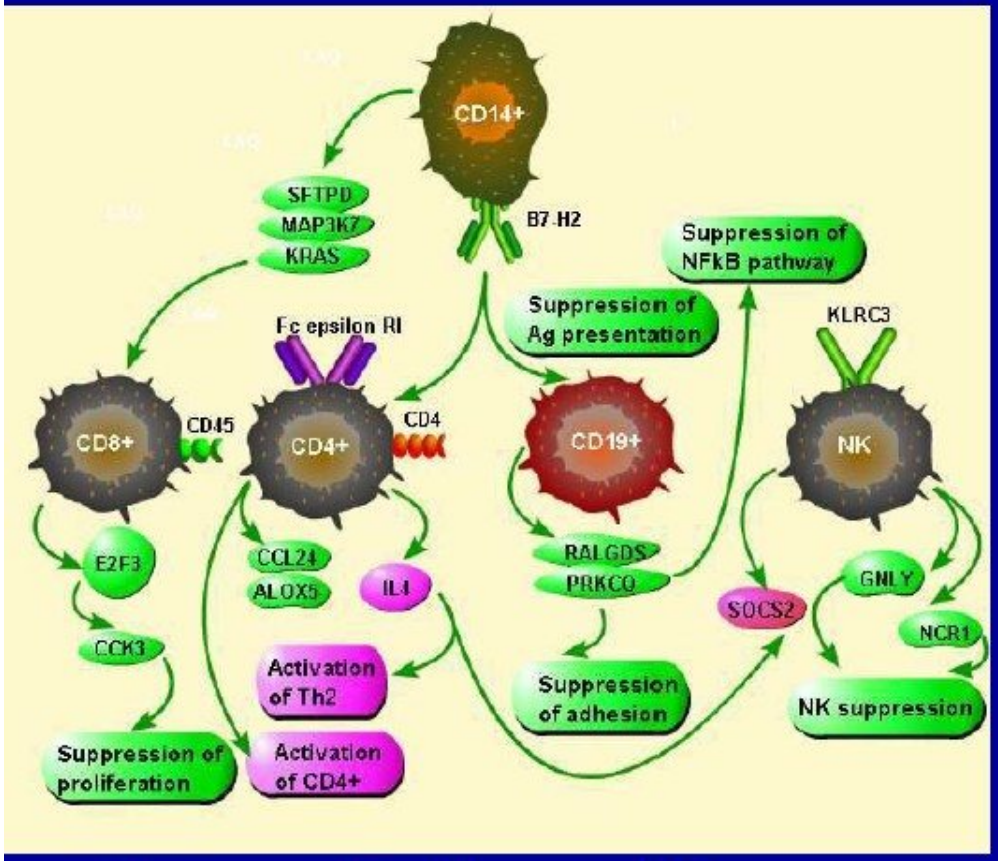
Laquinimod

Prodotto sintetico analogo della linomide

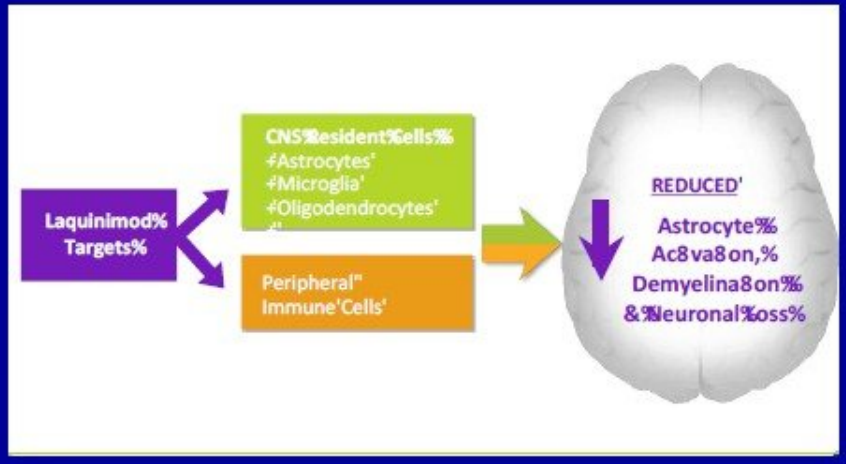


- Indicazione – Relapsing Remitting MS
- Via di somministrazione orale 0.6 mg una volta al dì
- Due stidu fase III: **ALLEGRO** (versus PLACEBO)
  - **BRAVO** (Braccio placebo e braccio IFNB 1A (Avonex)

LAQUINIMOD:
immunomodulazione a livello molecolare



Strutturalmente simile alla Linomide, ma farmacologicamente e chimicamente diverso, riduce l'entità dell'EAE senza determinare una immunosoppressione estesa



Overexpression/downregulation

Mechanism of action

- The broad profile of efficacy in animal models of inflammatory diseases suggests that laquinimod affects a pivotal pathway of inflammation
- **Laquinimod acts as an immunomodulator**:
  - Modulation of Th1/Th2 disease-specific proinflammatory autoimmune responses
  - Reduced leukocyte infiltration
  - Down regulation of inflammatory and of MHC class II genes
- Laquinimod does not affect the ability of animals to mount cellular and humoral immune responses

MS-LAQ-301 (*ALLEGRO*) (0.6'mg,'placebo)' → ***ALLEGRO* Extension** ''''''(0.6'mg)'

24 –Month Study, 1106 Patients,
Comi G, et al. N Engl J Med. 2012;366(11):1000-9.

Ongoing — 1106 pts

MS-LAQ-302 (*BRAVO*) (0.6'mg,'placebo,'IM'IFN-β-1a)" → ***BRAVO* Extension** ''''''''''''(0.6'mg)'

24-Months Study, 1331 Patients,
Presented during the 2011 ECTRIMS Conference

Ongoing — 1331 pts

The NEW ENGLAND JOURNAL of MEDICINE

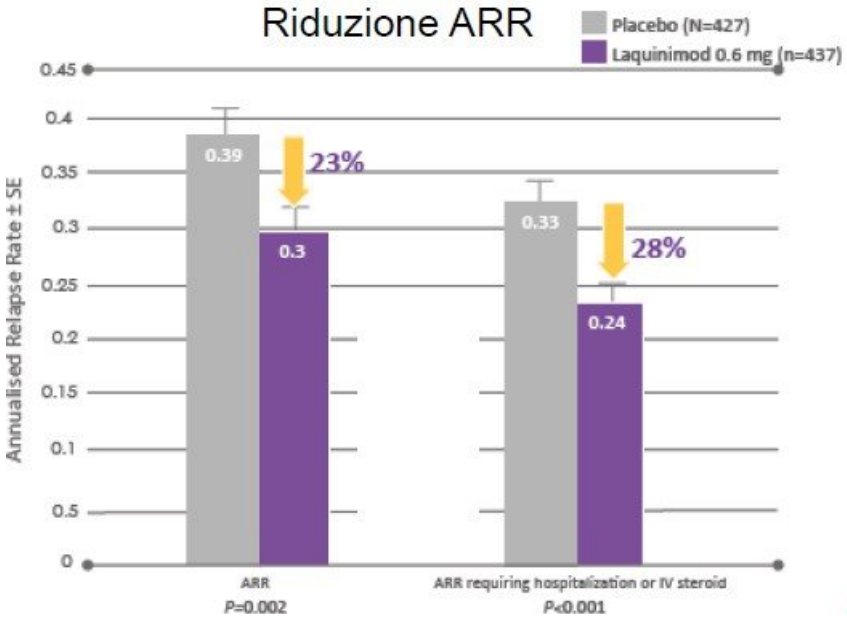
ORIGINAL ARTICLE

Placebo-Controlled Trial of Oral Laquinimod for Multiple Sclerosis

Giancarlo Comi, M.D., Douglas Jeffery, M.D., Ludwig Kappos, M.D., Xavier Montalban, M.D., Alexey Boyko, M.D., Maria A. Rocca, M.D., and Massimo Filippi, M.D., for the ALLEGRO Study Group*

N Engl J Med 2012;366:1000-9.

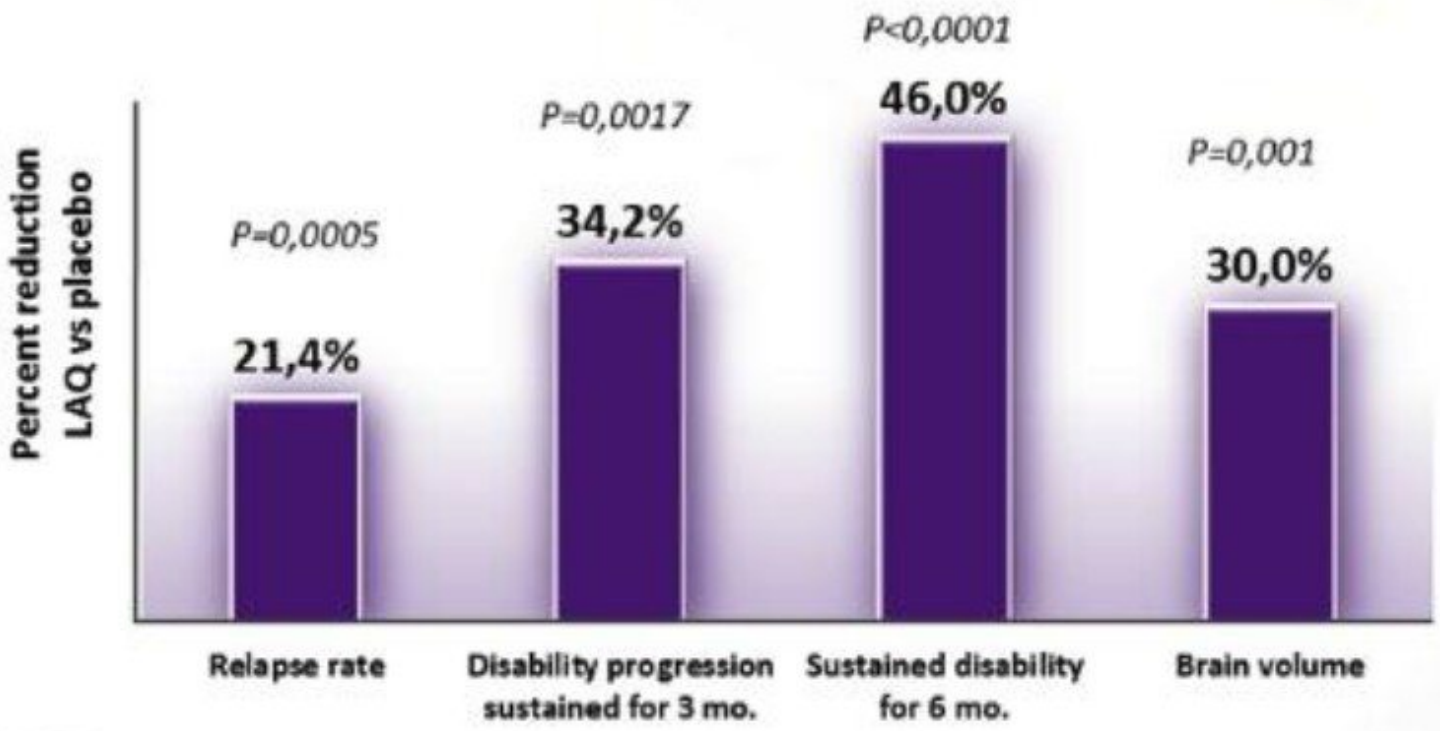
ALLEGRO



36%
del rischio di progressione a 3 mesi

A confirmed progression of EDSS is defined as at least 1-point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or at least 0.5-point increase if baseline EDSS was 5.5 or higher, confirmed 3 months later. Progression could not be confirmed during an MS relapse.

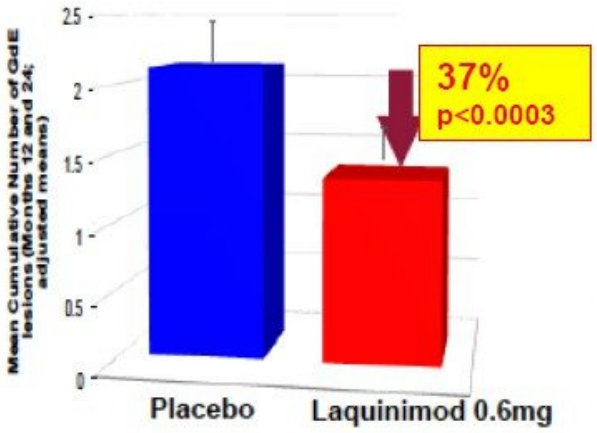
Analisi cumulativa dei Trial BRAVO e ALLEGRO



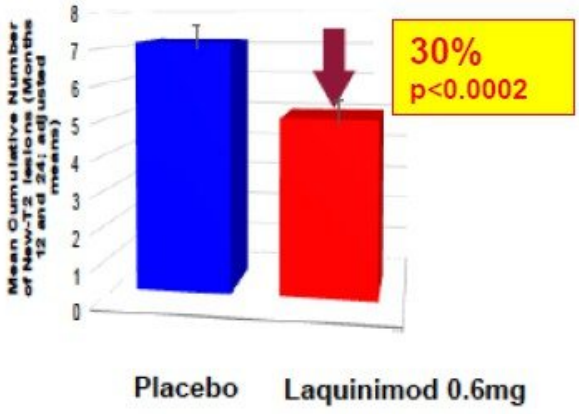
doi: 10.1212/WNL.78.1_MeetingAbstracts.S01.007Neurology April 24, 2012; 78(Meeting Abstracts 1): S01.007

MRI

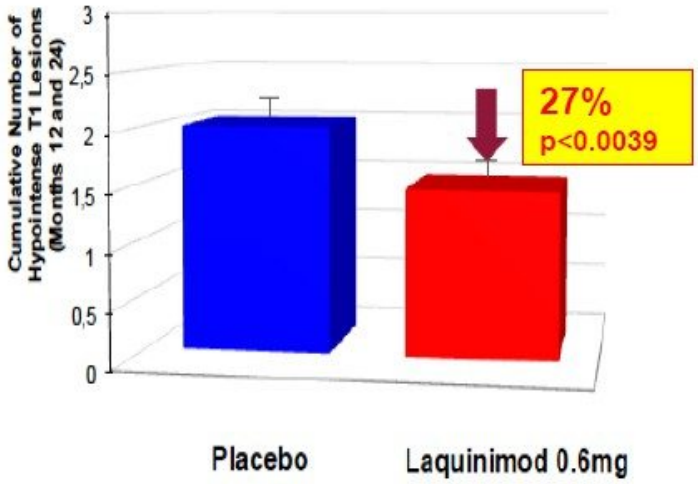
Gd+ lesions



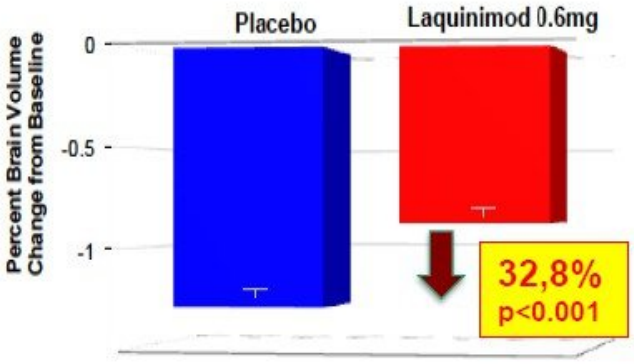
New T2 lesions



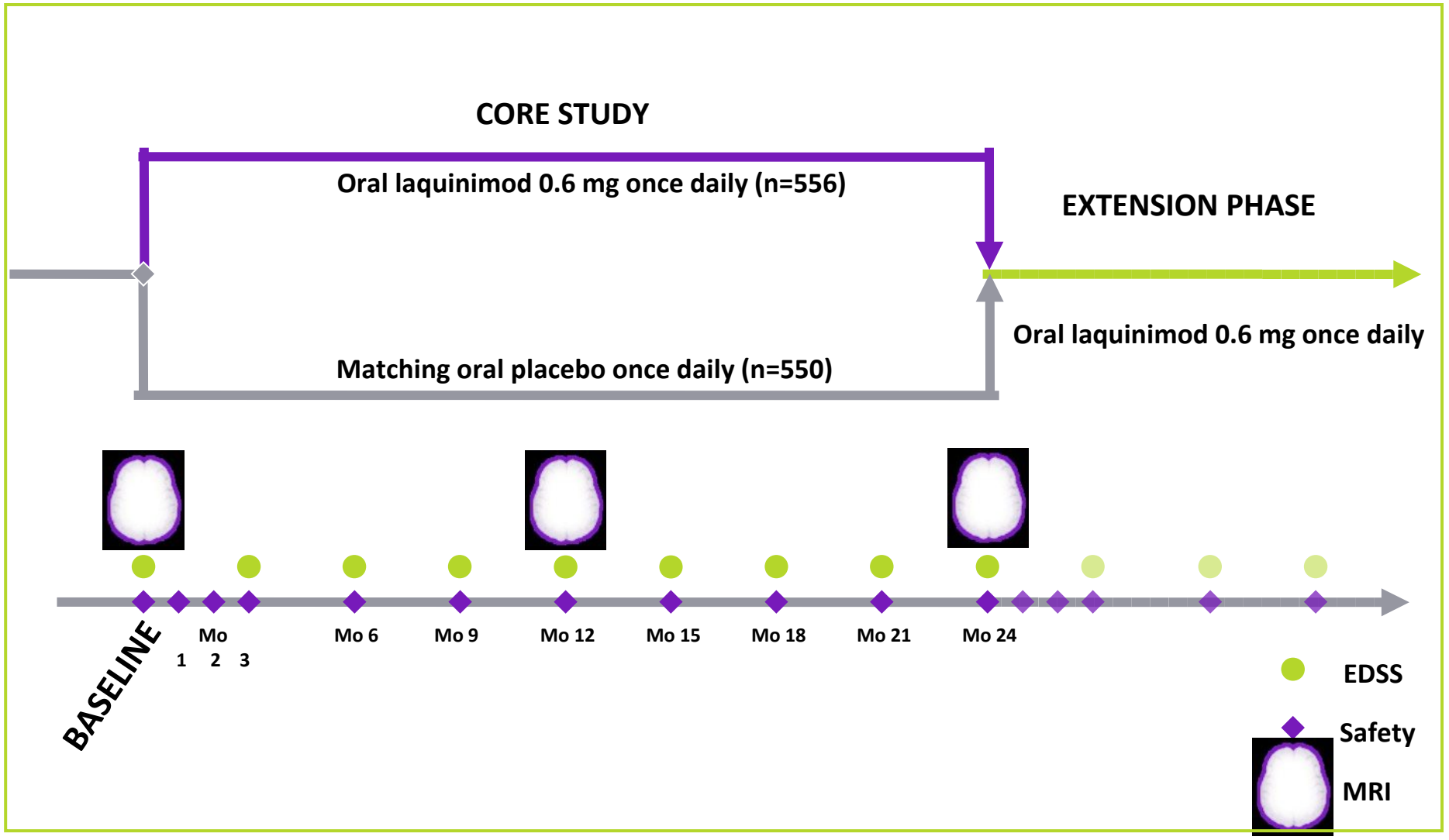
New hypointense-T1 lesions



Percentage change of brain atrophy

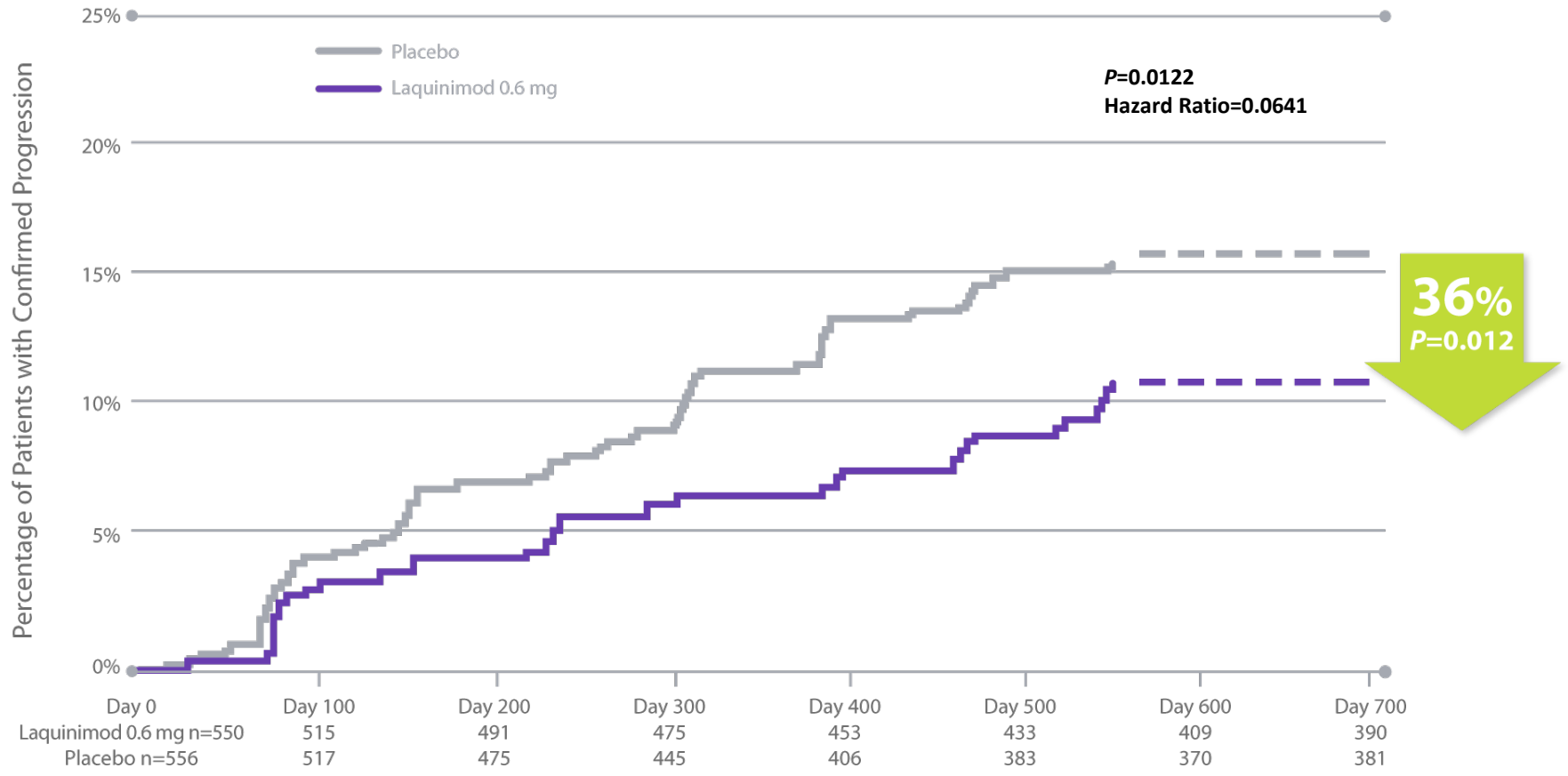


ALLEGRO STUDY DESIGN



Reference: Comi G et al. Presented at: 63rd Annual Meeting of the American Academy of Neurology; April 9-16, 2011; Honolulu, HI. *Neurology.* 2011;76(14).

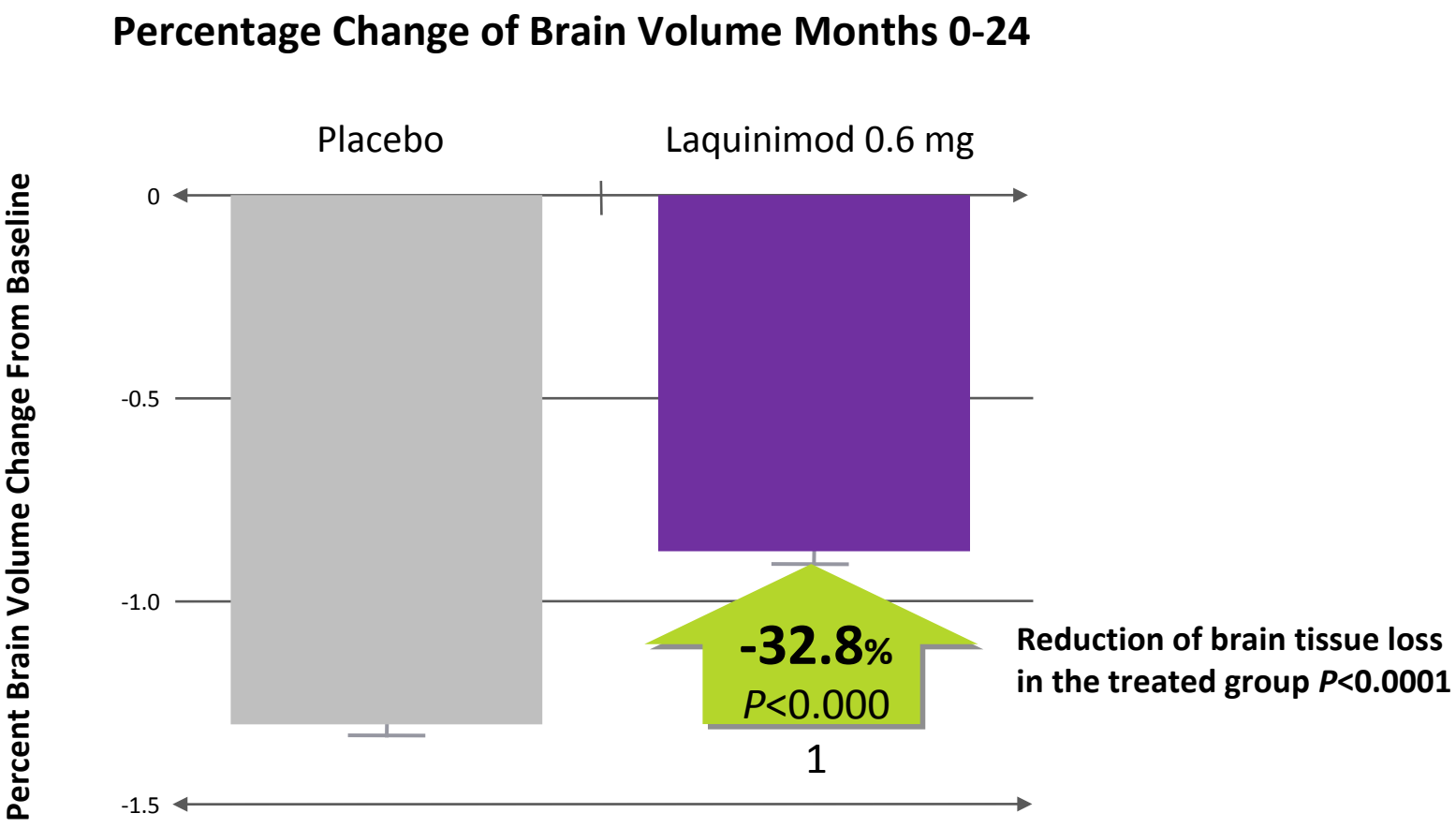
LAQUINIMOD PROVIDES EARLY AND MARKED REDUCTION IN DISABILITY PROGRESSION



A confirmed progression of EDSS is defined as at least 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or at least 0.5 point increase if baseline EDSS was 5.5 or higher, confirmed 3 months later. Progression could not be confirmed during an MS relapse.

Reference: 1. Comi G et al. Presented at: 63rd Annual Meeting of the American Academy of Neurology; April 9-16, 2011; Honolulu, HI. *Neurology.* 2011;76(14).

LAQUINIMOD SIGNIFICANTLY REDUCES BRAIN TISSUE LOSS



Reference: 1. Comi G et al. Presented at: 63rd Annual Meeting of the American Academy of Neurology; April 9-16, 2011; Honolulu, HI. *Neurology.* 2011;76(14).

SICUREZZA E TOLLERABILITA' DI LAQUINIMOD NEI TRIAL

Aumento degli enzimi epatici, TRANSITORIO

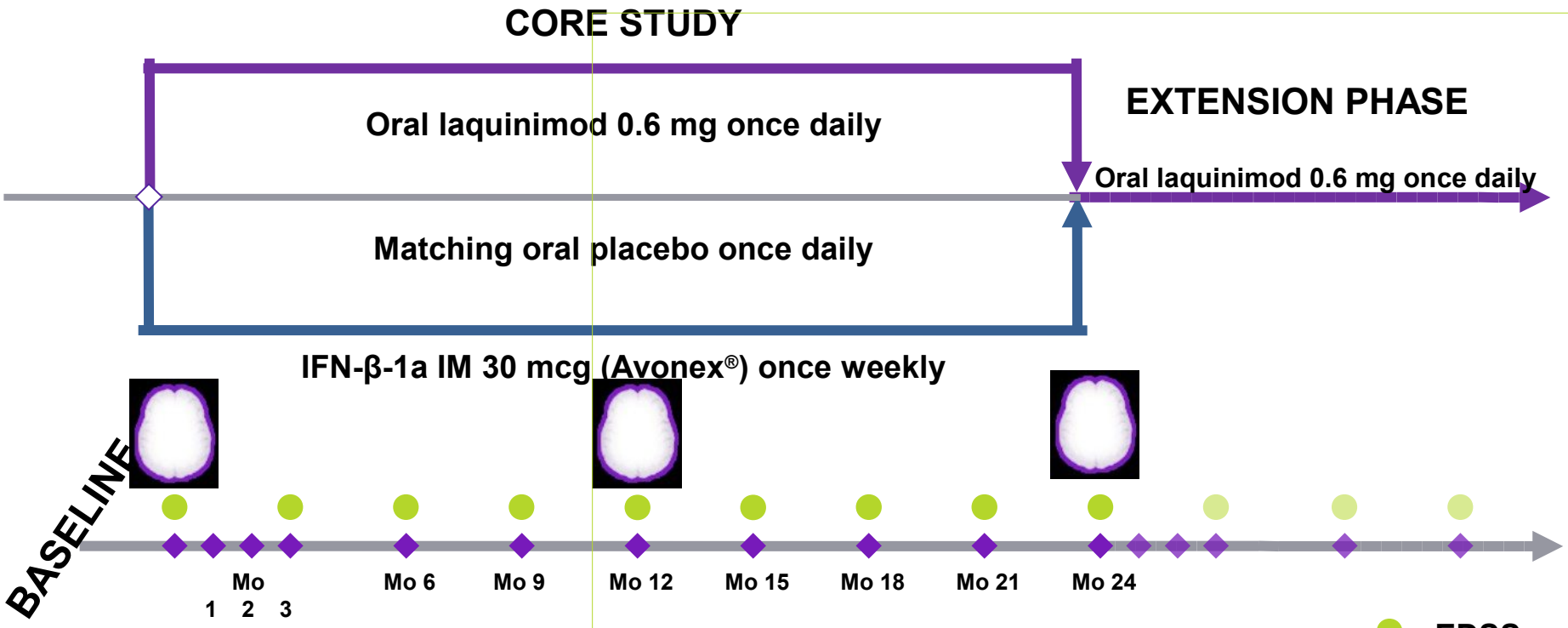
Dolore addominale
Dolore lombare

Tosse

Buona tollerabilità e sicurezza, non segnali di immunosoppressione (infezioni oortunistiche, tumori)

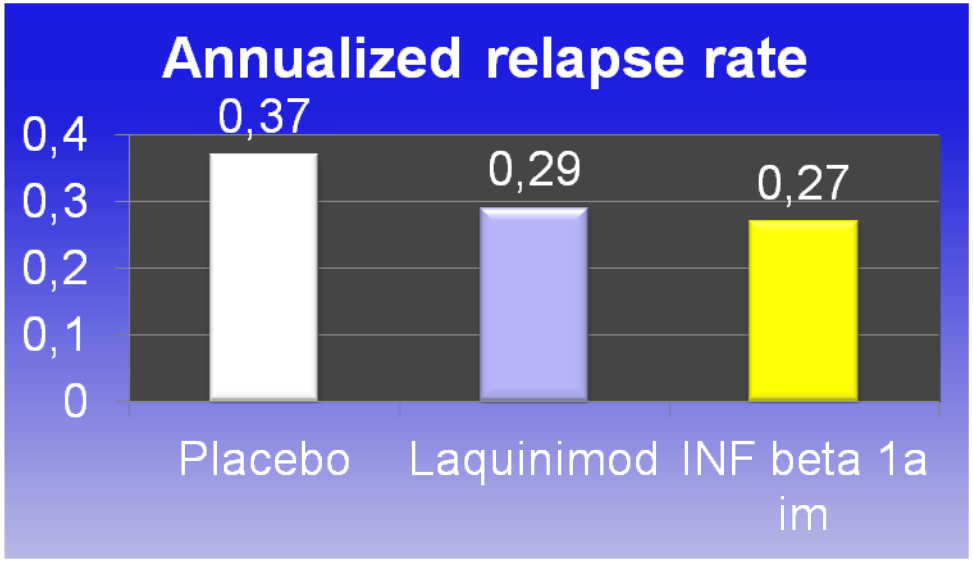
Reference: 1. Comi G et al. Presented at: 63rd Annual Meeting of the American Academy of Neurology; April 9-16, 2011; Honolulu, HI. Neurology. 2011;76(14).

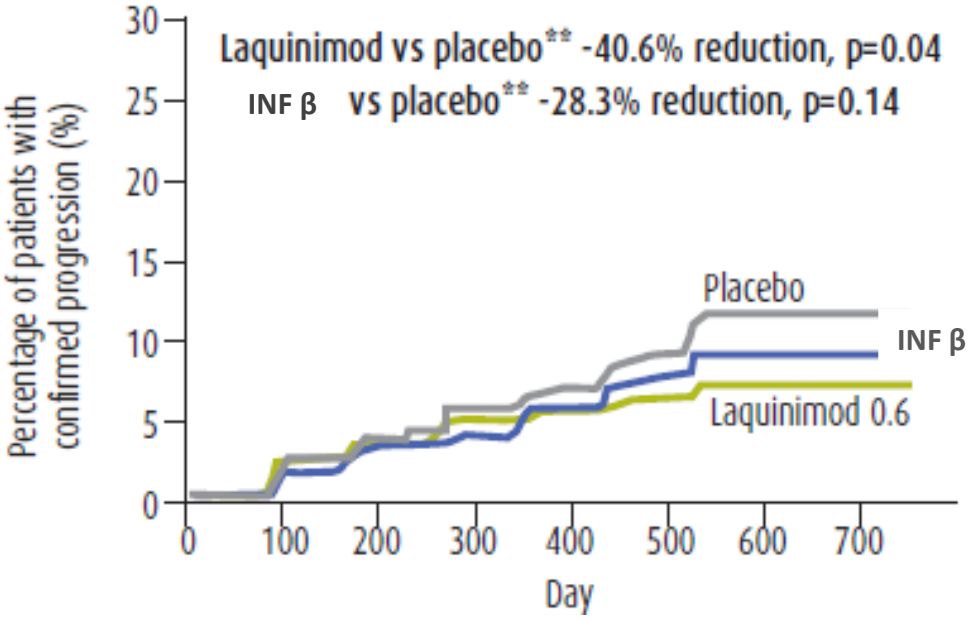
BRAVO Study Design



Purpose: To assess the efficacy, safety, and tolerability of laquinimod over placebo in a double-blind design and of a reference arm of Interferon β-1a IM 30 mcg (Avonex®) in a rater-blinded design

Modest reduction in annualized relapse rate 21% (mean ±SE: 0.30±0.02 vs. 0.39±0.03, P = 0.003)





Reduction in the risk of confirmed disability progression 40.6% vs placebo (p=0.04)

Brain Atrophy*

Progression of brain atrophy was reduced by laquinimod compared to placebo 27.5% ($p < 0.0001$)

No difference between IFN-beta-1a IM and Placebo was observed on brain atrophy

*Adjusted for baseline Normalized Brain Volume at baseline, T2 lesion volume and GdE-T1 status

Vollmer T, et al. Presented at: 5th Joint Triennial Congress of the European and Americas Committee for Treatment and Research in Multiple Sclerosis. October 19-22, 2011. Amsterdam, NL. Abstract 148. Multiple Sclerosis. 2011;17:S507.

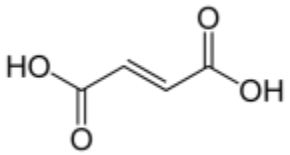
Safety & Tolerability

Safety and tolerability profile compared to placebo similar to that shown in ALLEGRO; no new safety signals

No signal of immunosuppression

Vollmer T, et al. Presented at: 5th Joint Triennial Congress of the European and Americas Committee for Treatment and Research in Multiple Sclerosis. October 19-22, 2011. Amsterdam, NL. Abstract 148. Multiple Sclerosis. 2011;17:S507.

BG-12 (Tecfidera®)



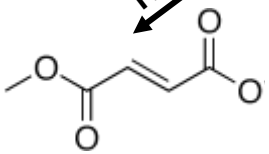
Fumarate

BG-12 (dimethyl fumarate [DMF])

↔

DMF

Rapid metabolism



Monomethyl fumarate (MMF)

- Il fumarato è una molecola essenziale per la respirazione ossidativa cellulare (ciclo dell'acido citrico)
- BG-12 è un derivato di seconda generazione del fumarato. Contiene DMF in capsule
- Forma farmaceutica che migliora la tollerabilità gastro intestinale.
- DMF dopo l'assorbimento è rapidamente convertito in MMF

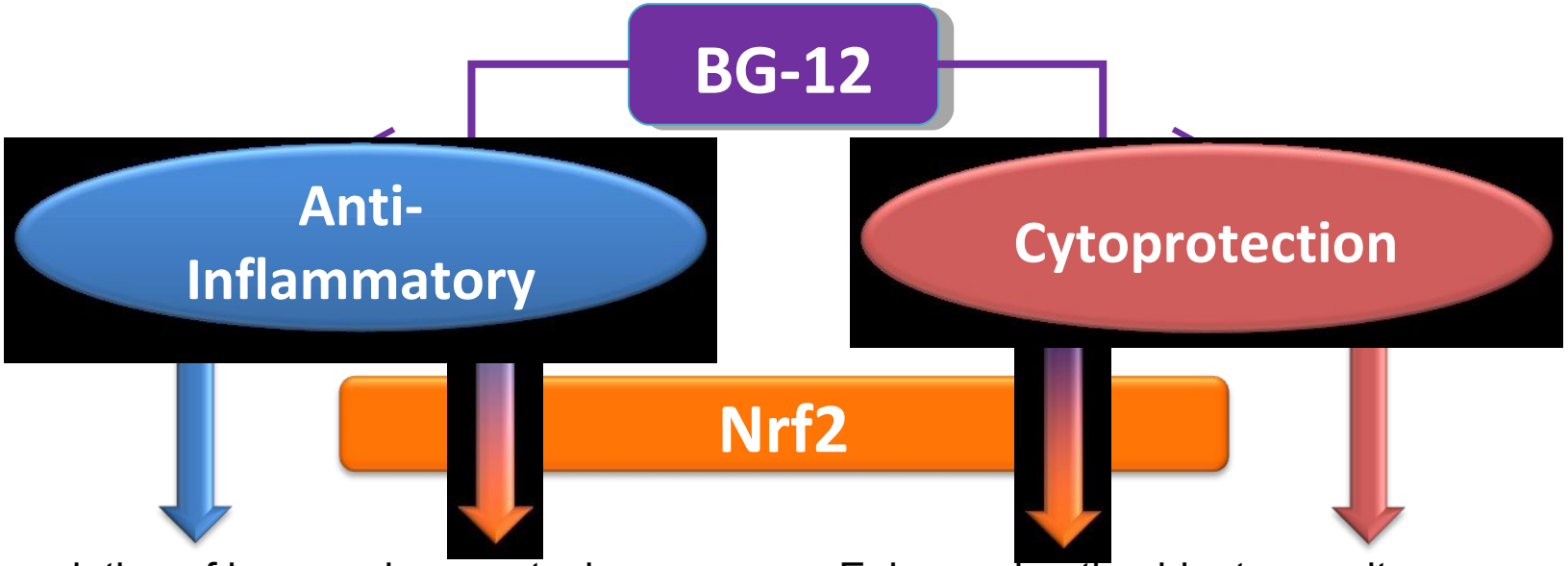
Moharregh-Khiabani D et al. *Curr Neuropharmacol.* 2009;7:60-64.

FUMADERM® e BG-12

- FUMADERM® è stato approvato per il trattamento della psoriasi volgare severa in Germania dal **1994**; indicazione poi estesa anche alla psoriasi moderata

Componenti di FUMADERM® (enteric coated tablet)		**Componenti di BG-12** (enteric coated encapsulated micro-tablets within a gelatin capsule)	
Dimethyl fumarate	120 mg	Dimethyl fumarate	120 mg
Ethylhydrogen fumarate Ca-Salt	87 mg	Ethylhydrogen fumarate Ca-Salt	---
Ethylhydrogen fumarate Mg-Salt	5 mg	Ethylhydrogen fumarate Mg-Salt	---
Ethylhydrogen fumarate Zn-Salt	3 mg	Ethylhydrogen fumarate Zn-Salt	---

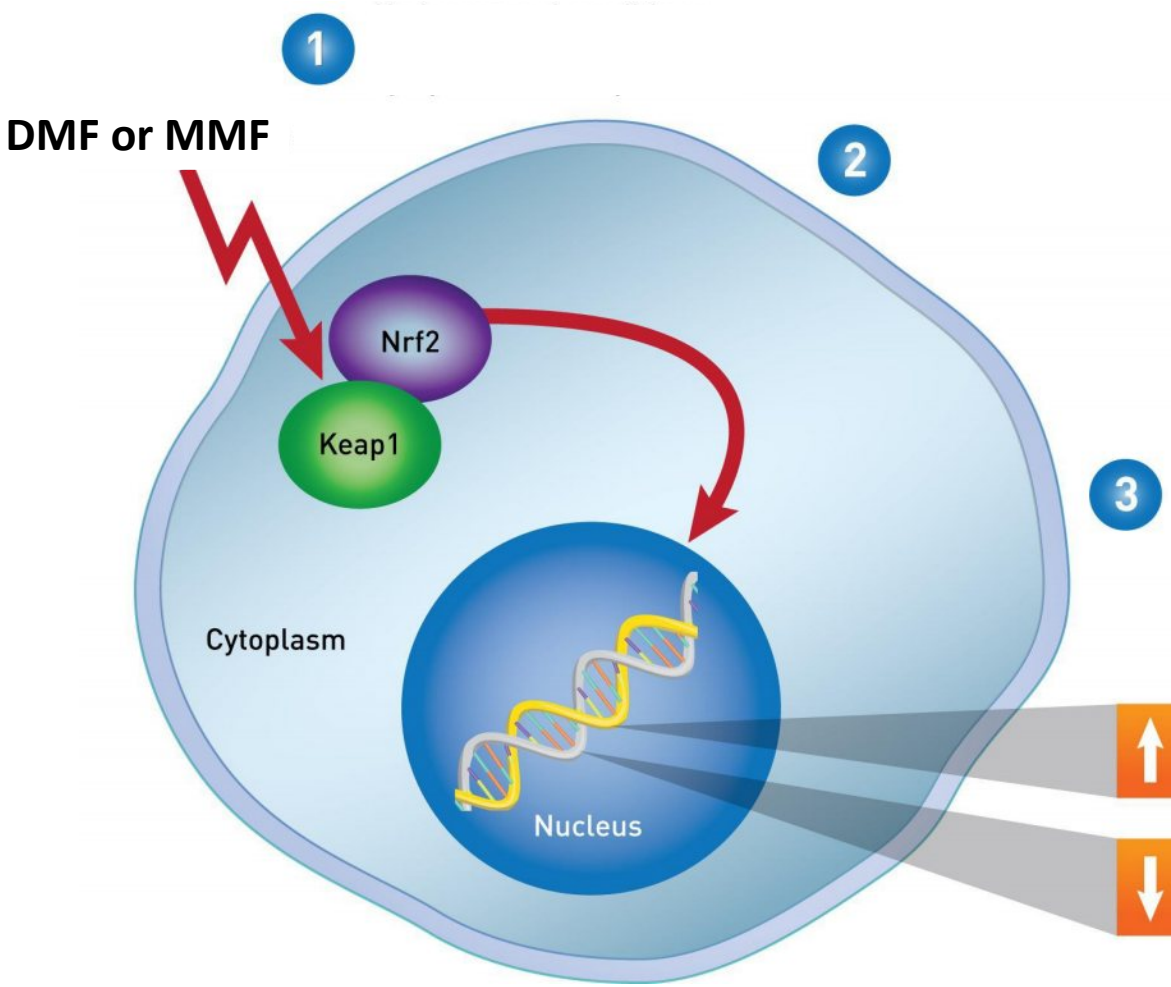
Potential Mechanisms of BG-12 Action



- Regulation of immune homeostasis
- Attenuation of pro-inflammatory cytokine production
- Regulation of NF-κB activation
- Reduced activation of macrophages, microglia, astrocytes
- Reduced CNS infiltration of immune cells
- Shift Th1/Th2/Th17 balance towards anti-inflammatory phenotype
- Improved integrity of BBB

- Enhanced anti-oxidant capacity
- Protection against toxic oxidative stress
- Regulation of OS stress-induced intracellular Ca++ accumulation
- Enhanced mitochondrial function
- Potential protection against multiple forms of neurodegenerative stimuli
  - Oxidative stress
  - Demyelination
  - Excitotoxicity

BG-12-Dependent Activation of the Nrf2 Pathway



Phase 2 Antioxidant Response

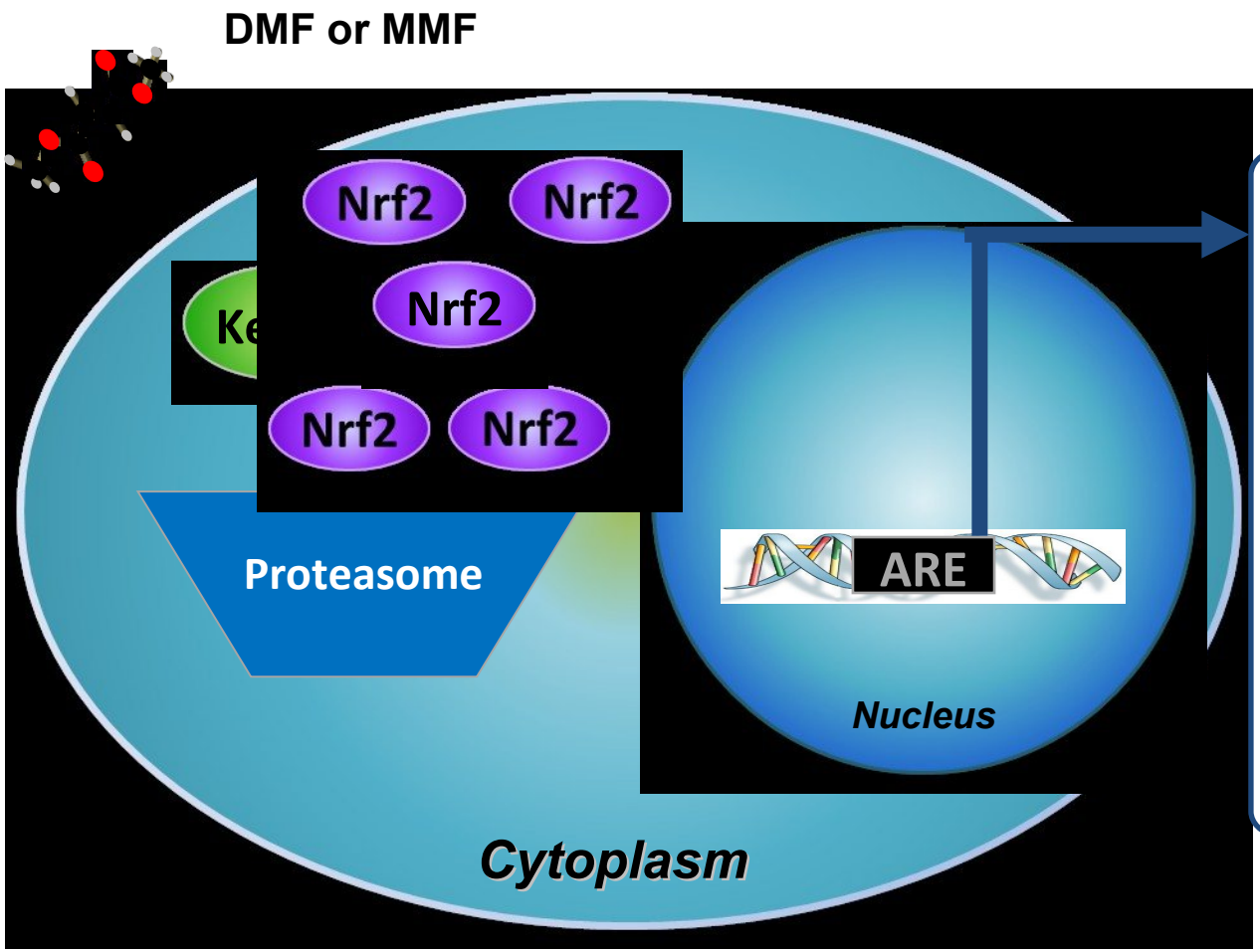
Target Gene Function

- **Direct antioxidants**
- **Free radical metabolism**
- **Normalization of energy metabolism**
- **Inhibition of inflammation**
- **Repair/degradation of damaged proteins and DNA**

Nrf2=nuclear factor (erythroid-derived 2)-like 2; Keap1=kelch-like ECH-associated protein.

van Horssen J et al. *Biochim Biophys Acta.* 2011;1812:141-150; Nguyen T et al. *J Biol Chem.* 2009;284:13291-13295.

BG-12 attiva il pathway dell'Nrf2 un meccanismo di difesa naturale contro lo stess ossidativo



Phase 2 Antioxidant Response

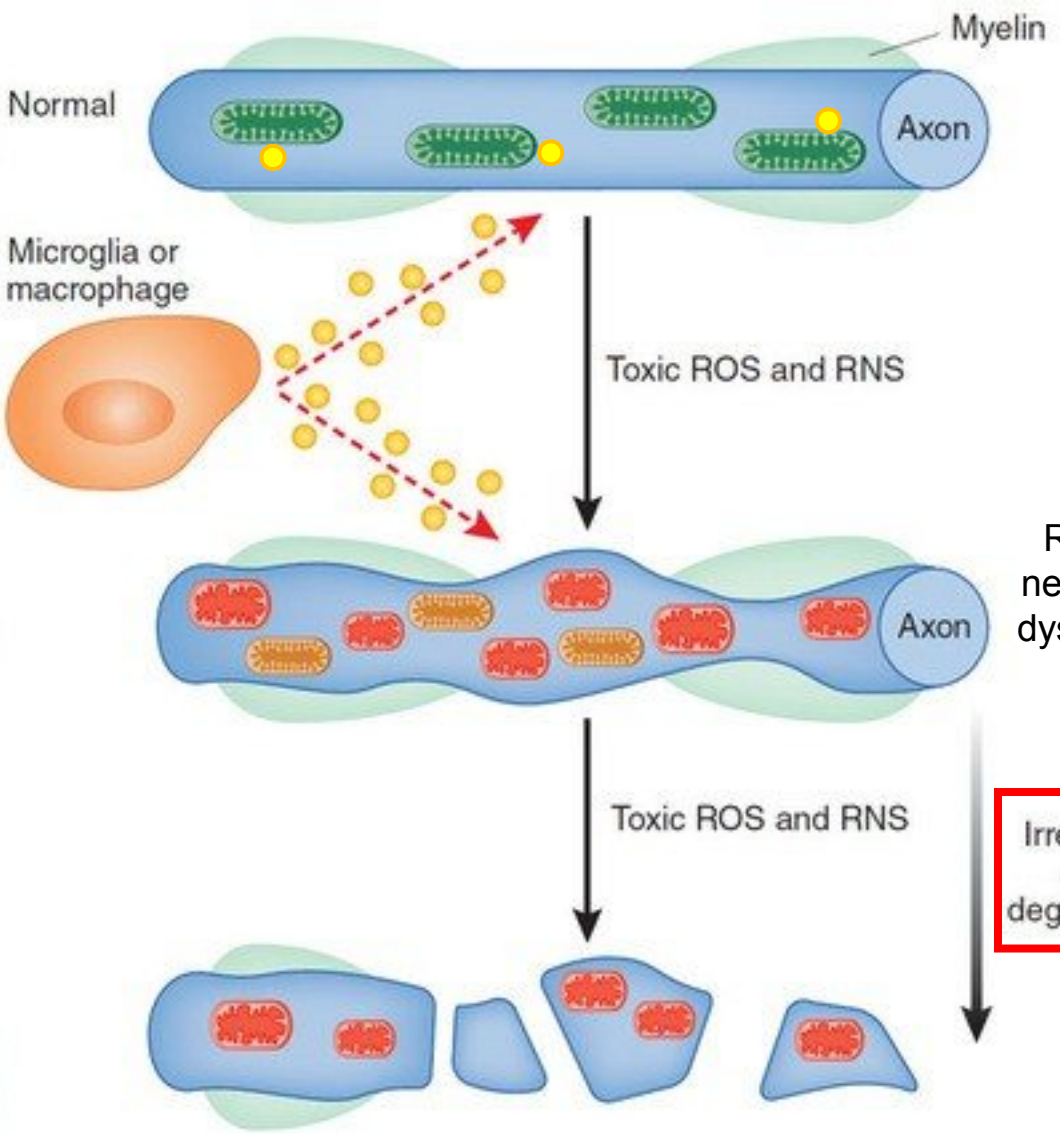
Target Gene Function

- **Direct antioxidants**
- **Free radical metabolism**
- **Normalization of energy metabolism**
- **Inhibition of inflammation**
- **Repair/degradation of damaged proteins and DNA**

Nrf2=nuclear factor (erythroid-derived 2)-like 2; MOA=mechanism of action; DMF=dimethyl fumarate; MMF=monomethyl fumarate; Keap1=kelch-like ECH-associated protein 1; ARE=antioxidant response element.
van Horssen J et al. *Biochem Biophys Acta.* 2011;1812:141-150; Linker RA et al. *Brain.* 2011;134:678-692.

Oxidative Stress: Relevance in MS

Activated macrophages and microglia produce excess reactive oxygen and nitrogen species (ROS, RNS)

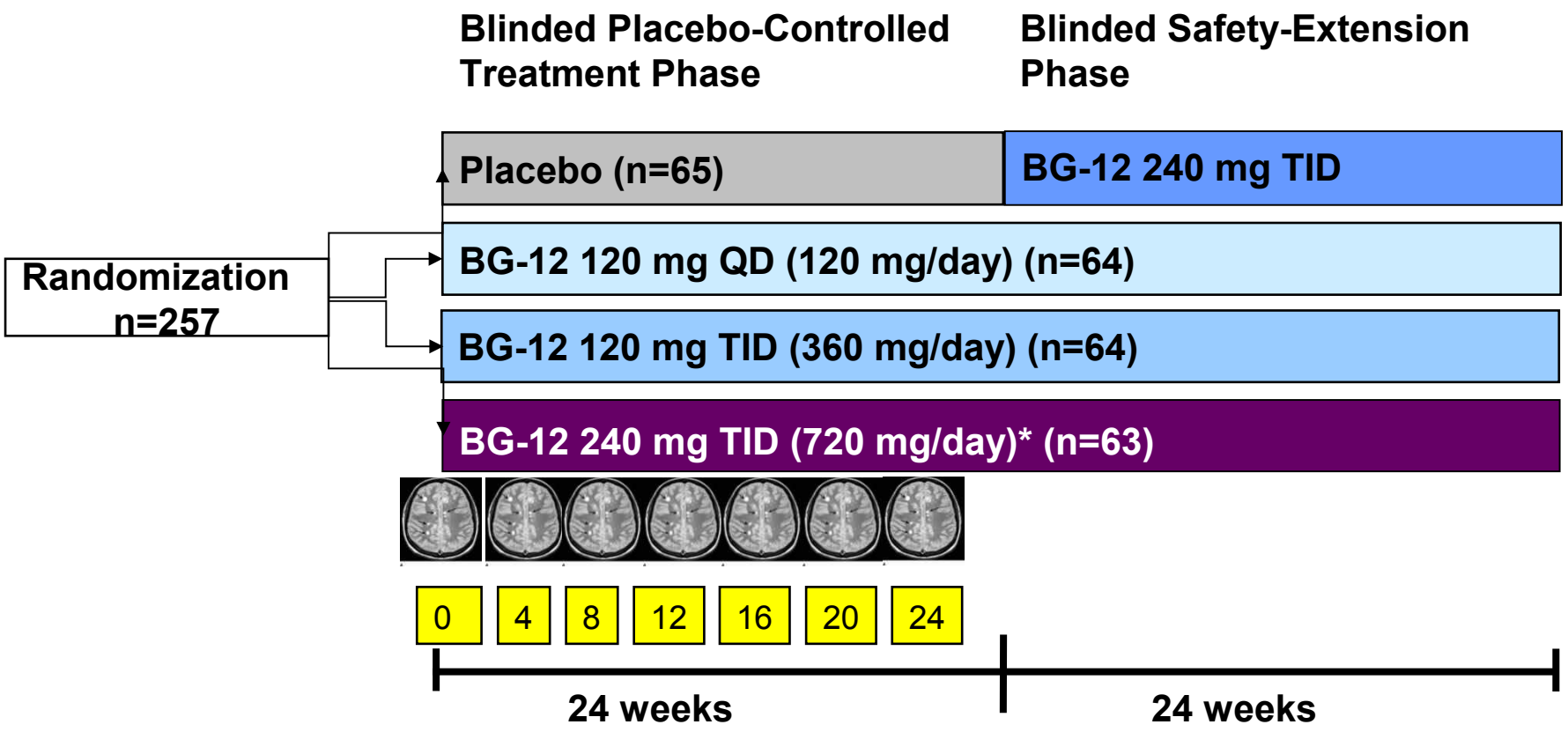


Endogenous ROS detoxified by homeostatic mechanisms

ROS & RNS permeate into neurons, cause mitochondrial dysfunction, DNA, protein and lipid damage, causing significant cellular stress

Adapted from Craner and Fugger (2011) Nat Med 17:423-426

Phase 2 Study Design



Primary endpoint:

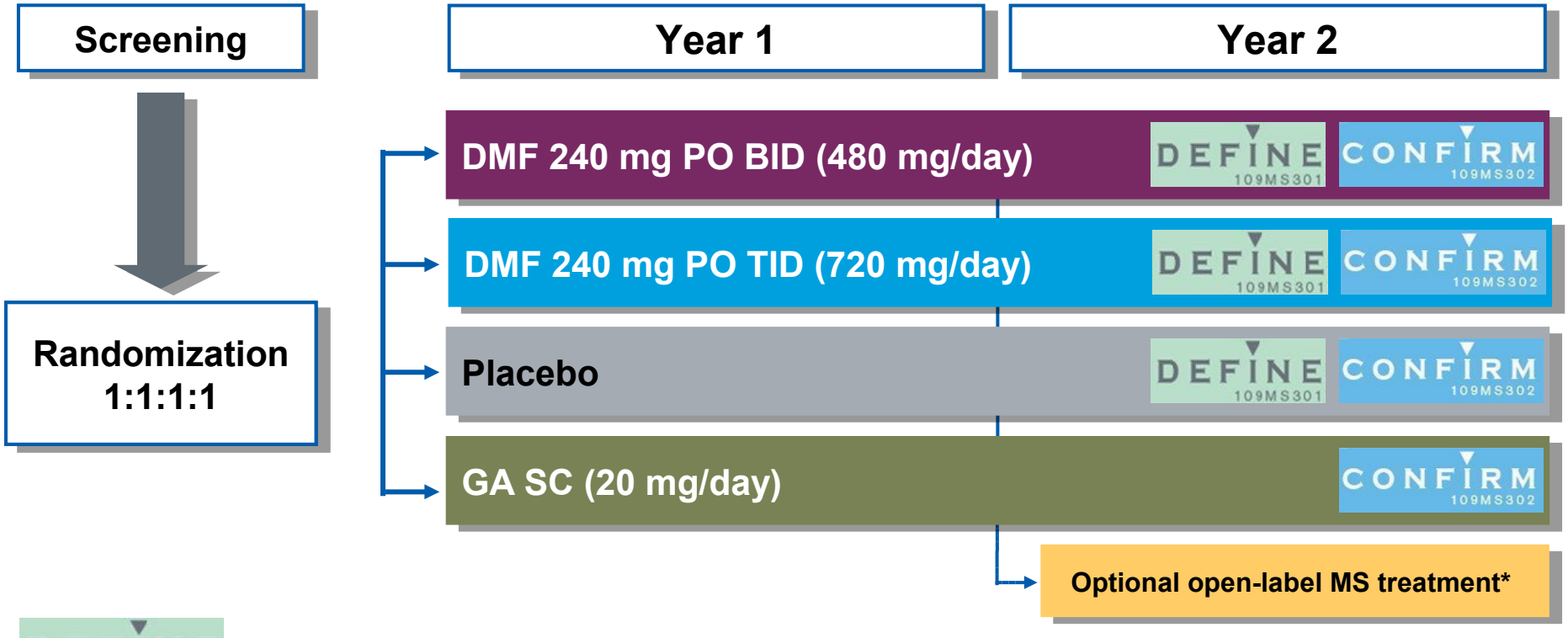
Total number of new Gd+ lesions on MRI scans performed at Weeks 12-24

Kappos L et al. *Lancet* 2008;372(9648):1463-1472

Phase 3 Studies in RRMS

- Clinical trial program includes >2500 patients from ~35 countries
- Two multicenter, parallel-group, randomized, placebo-controlled, dose-comparison, phase 3 clinical studies and an extension study on-going
  - **DEFINE** (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis)
  - **CONFIRM** (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis)
  - **ENDORSE** (Extension Study of Dimethyl Fumarate to Evaluate Long-term Safety and Efficacy)

DMF Phase 3 Study Schematic: DEFINE and CONFIRM



DEFINE 109MS301 — **Multicenter, double-blind, dose-comparison study (N=1237; MRI N=540)**

CONFIRM 109MS302 — **Multicenter, double-blind, reference comparator, dose-comparison study (N=1430; MRI N=681)†**

*Any patient with significant protocol-defined disability progression may switch to open-label MS treatment at any time; DEFINE: any patient with 1 INEC-confirmed relapse on or after Week 24 may switch to open-label MS treatment after 48 weeks on study; †double-blind only for DMF and placebo; rater-blinded for all arms; INEC fully blinded to all arms.

DEFINE=Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS; CONFIRM=Comparator and an Oral Fumarate in Relapsing-Remitting MS; PO=by mouth; TID=3 times daily; BID=twice daily; GA=glatiramer acetate; SC=subcutaneous; INEC=independent neurology evaluation committee.

Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

DMF Phase 3: Differences in Key Study Design Elements

DEFINE Endpoints

Primary

- Proportion of patients relapsing at 2 years

Secondary

- Number of new or newly enlarging T2-hyperintense lesions over 2 years
- Number of Gd+ lesions at 2 years
- Annualized relapse rate
- Rate of disability progression at 2 years

Criteria for alternative MS medication (rescue therapy) use

- Confirmed disability progression at any time OR the subject has completed 48 weeks of blinded treatment and experiences at least 1 confirmed relapse any time after 24 weeks

Exclusion criteria

CONFIRM Endpoints

Primary

- Annualized relapse rate

Secondary

- Number of new or newly enlarging T2-hyperintense lesions over 2 years
- Number of new T1-hypointense lesions at 2 years
- Proportion of patients relapsing at 2 years
- Rate of disability progression at 2 years

Criteria for alternative MS medication (rescue therapy) use

- Confirmed disability progression at any time OR the subject has completed 48 weeks of blinded treatment and experiences 2 confirmed relapses

Exclusion criteria

- Any prior treatment with GA

Secondary endpoints in order of statistical power, tested in rank order using a closed testing procedure to control for overall type I error (false positive rate); tertiary endpoints included reduction in number of new T1-hypointense lesions at 2 years (DEFINE) and number of Gd+ lesions at 2 years (CONFIRM); Gd+=gadolinium-enhancing. Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

DMF Phase 3: Key Study Design Elements

DEFINE Endpoints

Primary

- Proportion of patients relapsing at 2 years

Secondary

- Number of new or newly enlarging T2-hyperintense lesions over 2 years
- Number of Gd+ lesions at 2 years
- Annualized relapse rate
- Rate of disability progression at 2 years

CONFIRM Endpoints

Primary

- Annualized relapse rate

Secondary

- Number of new or newly enlarging T2-hyperintense lesions over 2 years
- Number of new T1-hypointense lesions at 2 years
- Proportion of patients relapsing at 2 years
- Rate of disability progression at 2 years

Secondary endpoints in order of statistical power, tested in rank order using a closed testing procedure to control for overall type I error (false positive rate); tertiary endpoints included reduction in number of new T1-hypointense lesions at 2 years (DEFINE) and number of Gd+ lesions at 2 years (CONFIRM); Gd+=gadolinium-enhancing. Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

DMF Phase 3 Study Comparison

Characteristic	DEFINE			CONFIRM			
	Placebo	DMF BID	DMF TID	Placebo	DMF BID	DMF TID	GA
# of subjects per treatment group	408	410	416	363	359	345	350
Primary endpoint	Proportion of subjects relapsed at 2 years			Annualized relapse rate at 2 years			
Criteria for alternative MS medication (rescue therapy) use	Confirmed disability progression at any time OR the subject has completed 48 weeks of blinded treatment and experiences at least 1 confirmed relapse any time after 24 weeks			Confirmed disability progression at any time OR the subject has completed 48 weeks of blinded treatment and experiences 2 confirmed relapses			
Inclusion/exclusion criteria				Any prior treatment with GA (exclusion criteria)			

BID=twice daily; TID=3 times daily; GA=glatiramer acetate; MS=multiple sclerosis.

Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

DEFINE: Summary of Baseline Patient Demographics and Disease Characteristics – ITT

Characteristic	Placebo (n=408)	DMF 240 mg BID (n=410)	DMF 240 mg TID (n=416)
Age, years, mean (SD)	38.5 (9.1)	38.1 (9.1)	38.8 (8.8)
Female, %	75	72	74
Years since first MS symptoms			
mean (SD)	8.5 (6.8)	8.5 (6.8)	7.8 (6.3)
median (min, max)	7.0 (0, 32)	7.0 (0, 42)	6.0 (0, 32)
Prior approved treatments for RRMS, %*	42	40	40
Relapses in prior year, mean (SD)	1.3 (0.7)	1.3 (0.7)	1.3 (0.6)
EDSS score, mean (SD)	2.48 (1.24)	2.40 (1.29)	2.36 (1.19)

*Patients may have received more than one prior medication for multiple sclerosis.
DEFINE=Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS; ITT=intention-to-treat; BID=twice daily; TID=3 times daily; SD=standard deviation; MS=multiple sclerosis; RRMS=relapsing-remitting MS; EDSS=Expanded Disability Status Scale.
Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Biogen Idec, data on file.

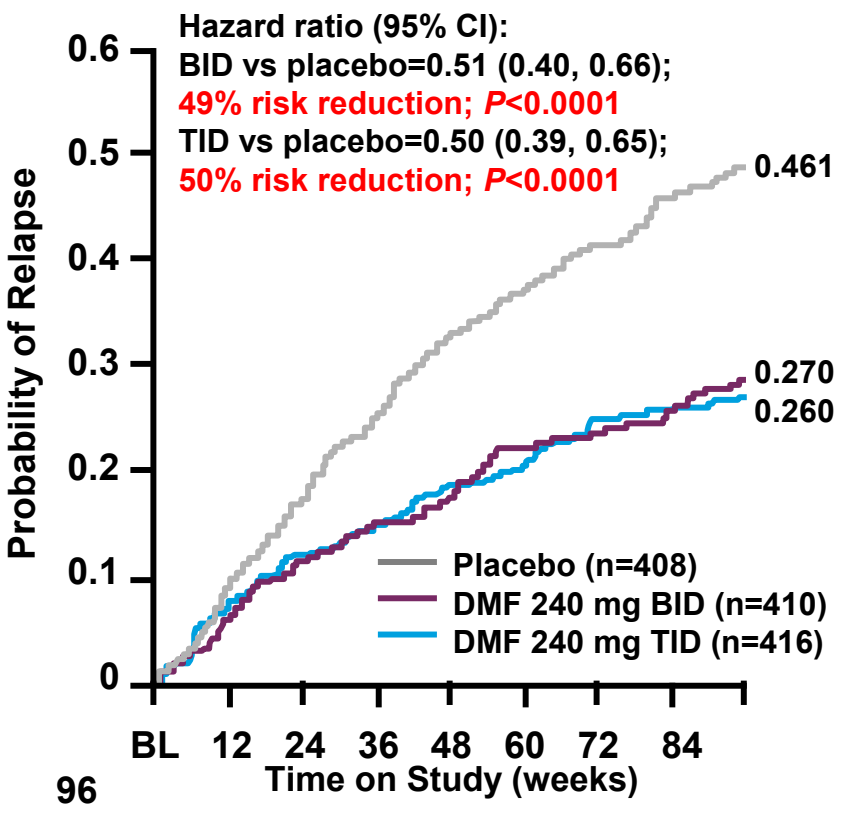
CONFIRM: Summary of Baseline Patient Demographics and Disease Characteristics – ITT

Characteristic	Placebo (n=363)	BG-1 240 mg BID (n=359)	BG-1 240 mg TID (n=345)	G (n=350)
Age, years, mean (SD)	36.9 (9.24)	37.8 (9.35)	37.8 (9.39)	36.7 (9.06)
Female, %	69	68	72	71
Years since first MS symptoms,				
mean (SD)	7.6 (5.98)	8.2 (6.89)	7.8 (6.70)	7.1 (5.92)
median (min, max)	6.0 (0, 33)	7.0 (0, 35)	6.0 (0, 33)	6.0 (0, 29)
Prior approved treatments for RRMS, %*	31	28	29	29
Relapses in prior year, mean (SD)	1.4 (0.80)	1.3 (0.63)	1.4 (0.72)	1.4 (0.64)
EDSS score, mean (SD)	2.59 (1.17)	2.56 (1.20)	2.52 (1.19)	2.57 (1.22)

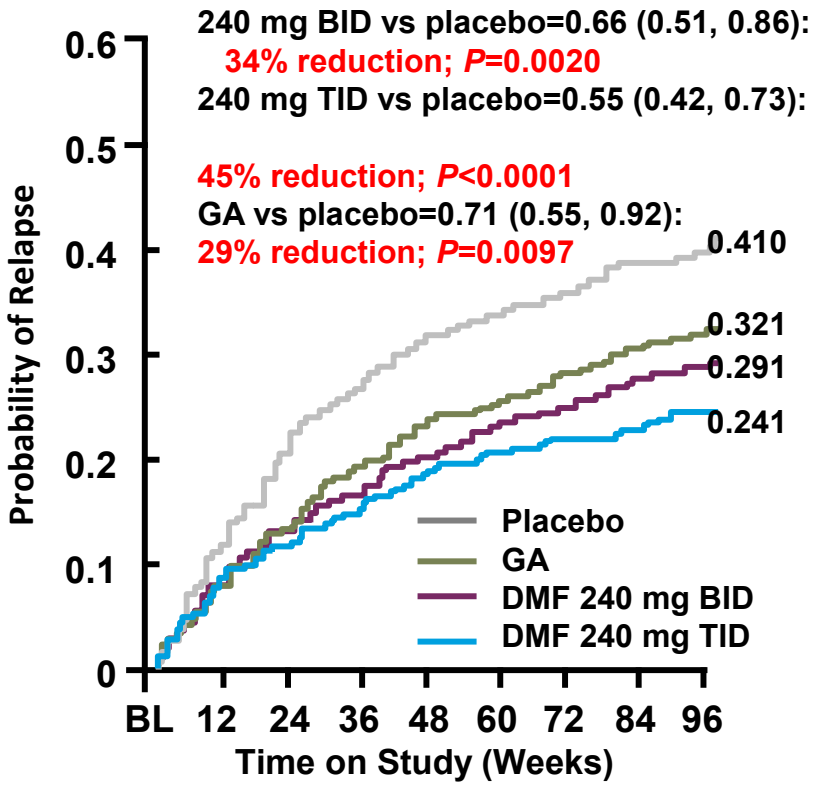
*Patients may have received more than one prior DMT. Prior use of GA was an exclusion criteria.
CONFIRM=Comparator and an Oral Fumarate in Relapsing-Remitting MS; ITT=intention-to-treat; BID=twice daily; TID=3 times daily; GA=glatiramer acetate; SD=standard deviation; MS=multiple sclerosis; RRMS=relapsing-remitting MS; EDSS=Expanded Disability Status Scale; DMT=disease-modifying therapy.
Fox R et al. Presented at AAN; April 21–28, 2012; New Orleans, LA. S01.003; Biogen Idec, data on file.

DEFINE and CONFIRM: Probability of Relapse

DEFINE

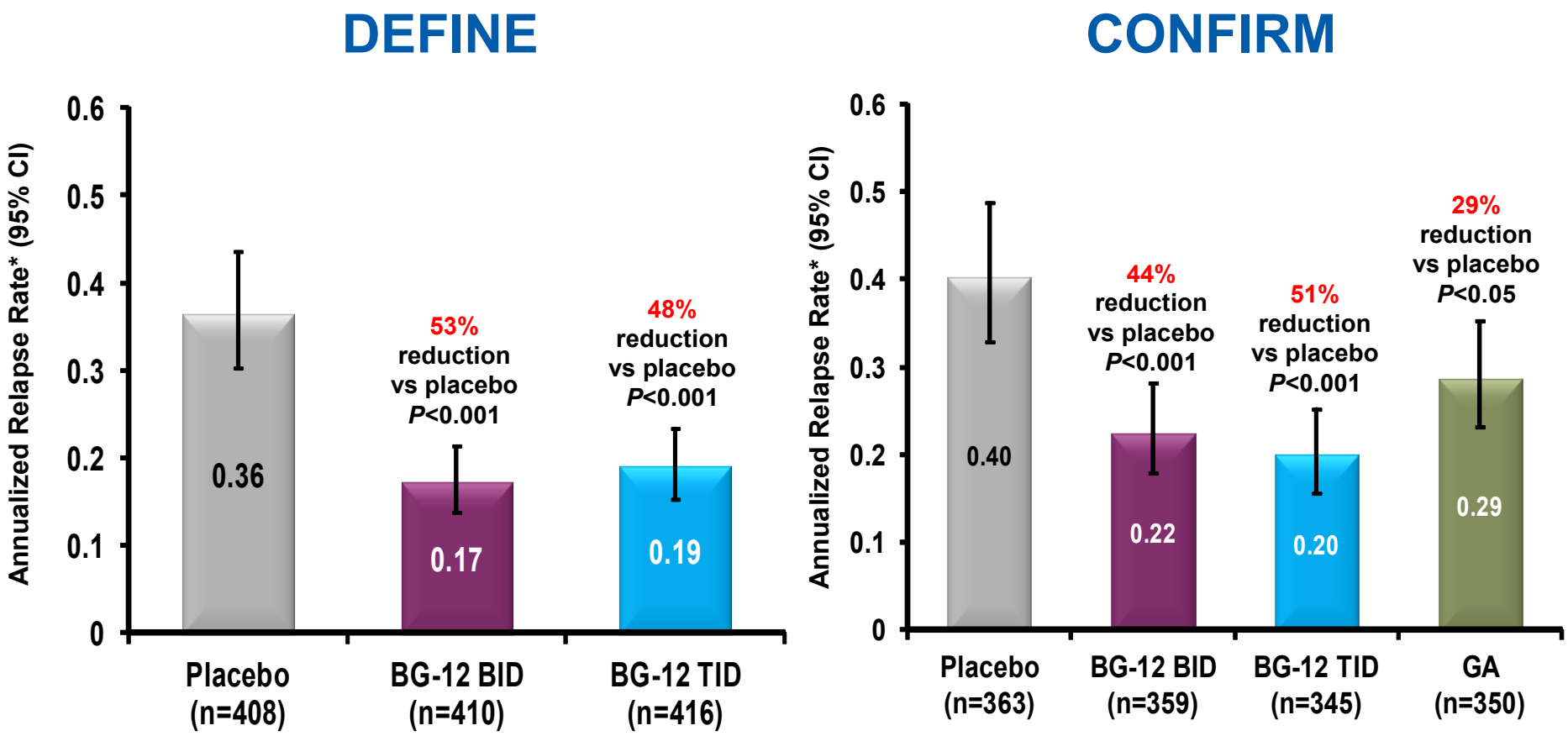


CONFIRM



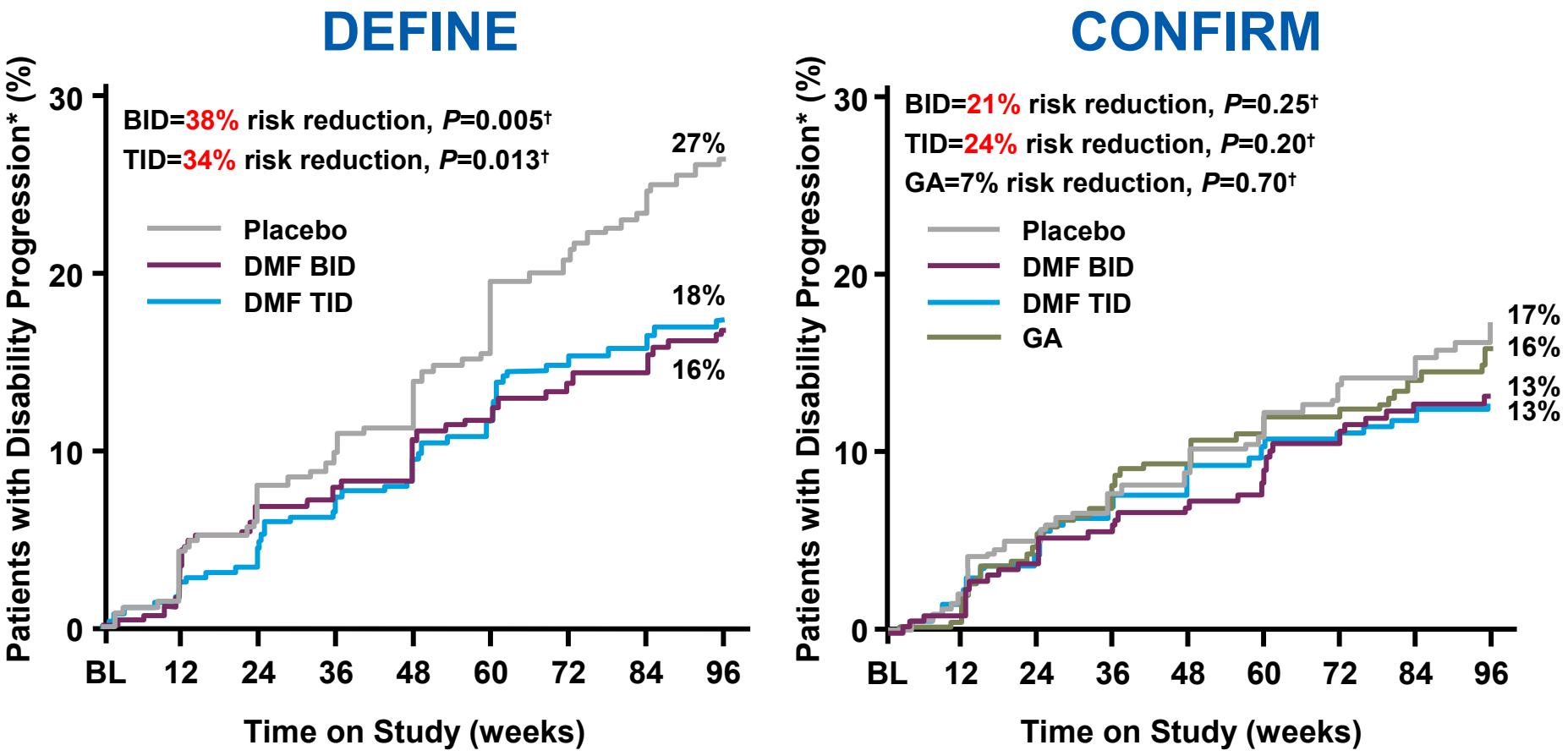
INEC=Independent Neurology Evaluation Committee; CI=confidence interval; BID=twice daily; TID=three times daily; BL=baseline.

Annualized Relapse Rate at 2 Years



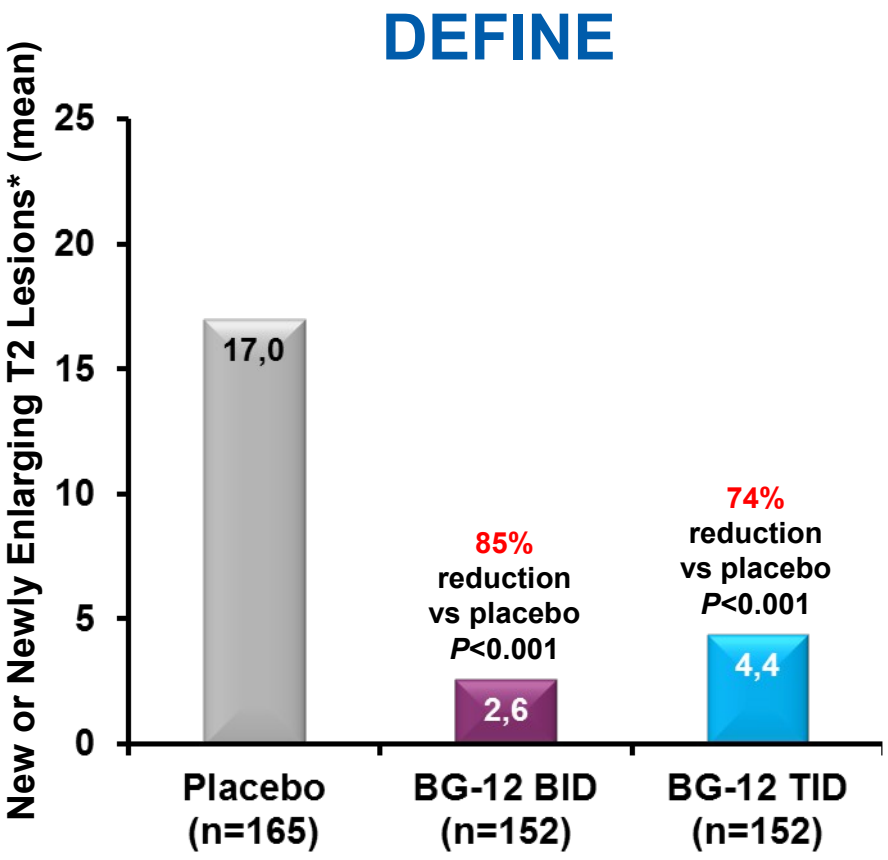
*Annualized relapse rate calculated with negative binomial regression, with prespecified adjustment for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40 years), region, and number of relapses in the 1 year prior to study entry; data after switch to alternative MS therapy were excluded; CI=confidence interval; EDSS=Expanded Disability Status Scale. Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

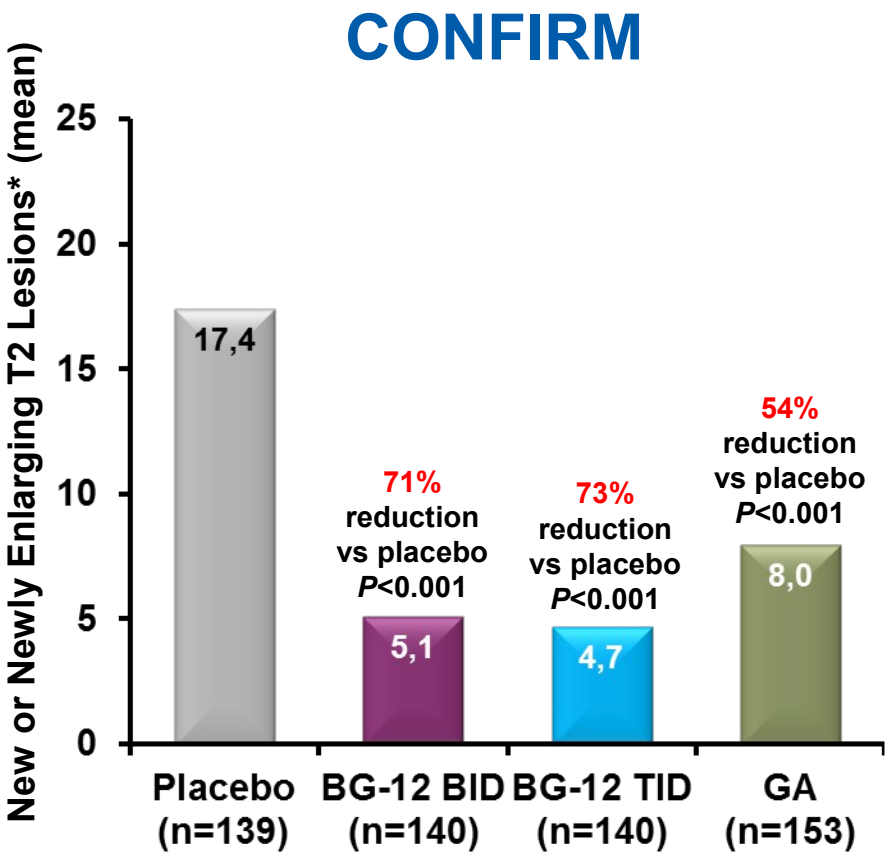
12-Week Confirmed Disability Progression



*Estimated proportion of patients with progression and time to progression up to 96 weeks based on the Kaplan-Meier product limit method; †based on Cox proportion hazards model, adjusted for baseline EDSS score (≤2.0 vs >2.0), region, and baseline age (<40 vs ≥40 years).
BID=twice daily; TID=3 times daily; BL=baseline; GA=glatiramer acetate; EDSS=Expanded Disability Status Scale.
Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

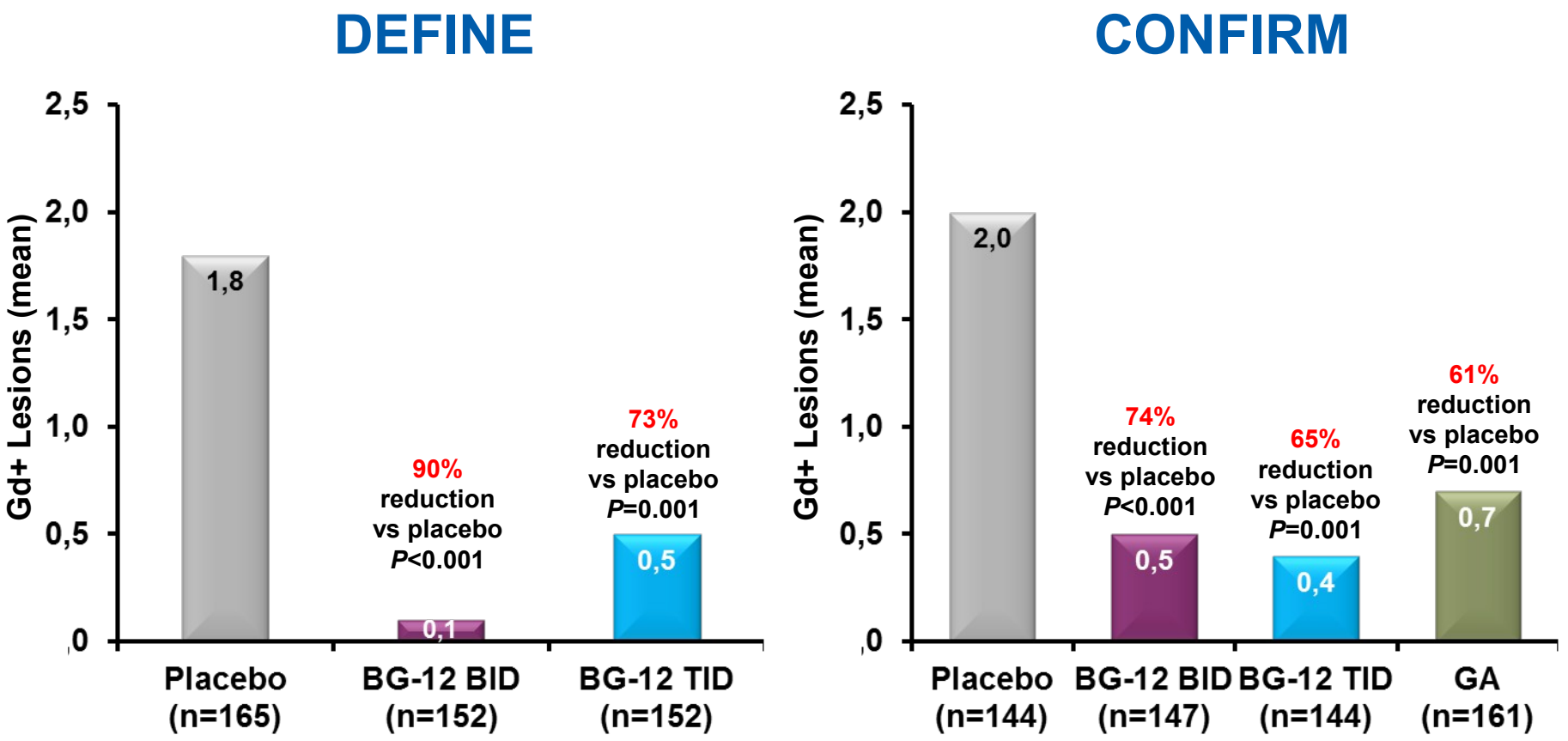
MRI Results: Mean Number of New or Newly Enlarging T2-Hyperintense Lesions at 2 Years*





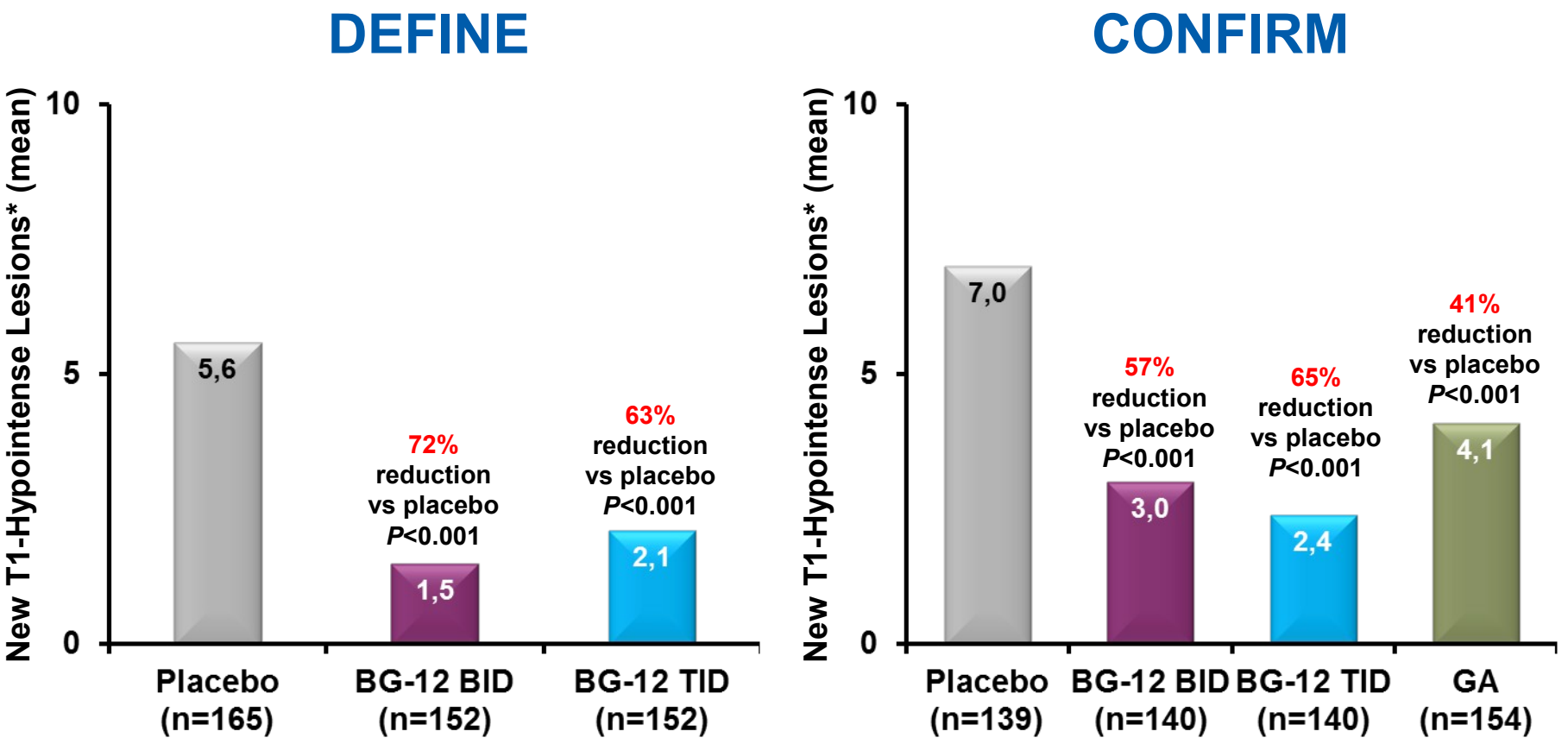
*Negative binomial regression analysis, adjusted for region and baseline T2 lesion volume.
MRI=magnetic resonance imaging; BID=twice daily; TID=3 times daily; GA=glatiramer acetate.
Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

MRI Results: Mean Number of Gd+ Lesions at 2 Years*



*Ordinal logistic regression analysis, adjusted for region and baseline number of Gd+ lesions.
MRI=magnetic resonance imaging; Gd+=gadolinium-enhancing; BID=twice daily; TID=3 times daily; GA=glatiramer acetate.
Gold R et al. *N Engl J Med*. 2012;367:1098-1107; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

MRI Results: Mean Number of New T1-Hypointense Lesions at 2 Years*



*Negative binomial regression analysis, adjusted for region and baseline T1 lesion volume.
MRI=magnetic resonance imaging; BID=twice daily; TID=3 times daily; GA=glatiramer acetate.
Arnold DL et al. Presented at ECTRIMS, October 19–22, 2011. Amsterdam, The Netherlands. P831; Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

ORIGINAL ARTICLE

Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis

Ralf Gold, M.D., Ludwig Kappos, M.D., Douglas L. Arnold, M.D., Amit Bar-Or, M.D., Gavin Giovannoni, M.D., Krzysztof Selmaj, M.D., Carlo Tornatore, M.D., Marianne T. Sweetser, M.D., Ph.D., Minhua Yang, M.S., Sarah I. Sheikh, M.D., and Katherine T. Dawson, M.D., for the DEFINE Study Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 20, 2012 VOL. 367 NO. 12

Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis

Robert J. Fox, M.D., David H. Miller, M.D., J. Theodore Phillips, M.D., Ph.D., Michael Hutchinson, F.R.C.P., Eva Havrdova, M.D., Mariko Kita, M.D., Minhua Yang, M.S., Kartik Raghupathi, M.S., Mark Novas, M.D., Marianne T. Sweetser, M.D., Ph.D., Vissia Viglietta, M.D., Ph.D., and Katherine T. Dawson, M.D., for the CONFIRM Study Investigators*

Endpoints dello studio

Endpoint primario

- Numero totale di nuove lesioni Gd+ alla RM a 12, 16, 20 e 24 settimane

Endpoints secondari alla RM

- Numero cumulativo di nuove lesioni Gd+ dalla quarta alla ventiquattresima settimana
- Numero di lesioni nuove/ingranditeT2-iperintense a 24 settimane

Obiettivi aggiuntivi

- Numero di nuove lesioni T1-ipointense a 24 settimane
- Sicurezza e tollerabilità
- Recidive, disabilità

Kappos L et al. *Lancet.* 2008;372:1463-1472.

RISULTATI

Effetto sulle lesioni Gd+

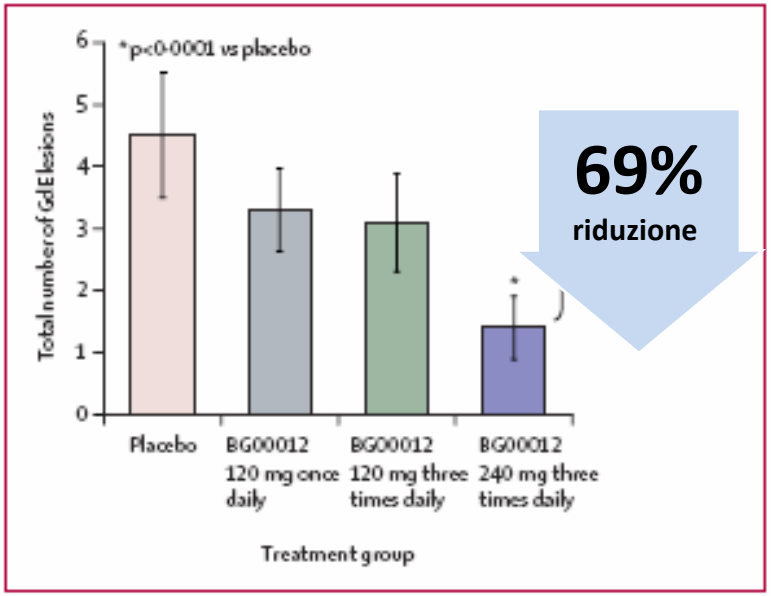


Figure 3: Mean total number of GdE lesions from scans at weeks 12, 16, 20, and 24 combined
Vertical bars= SE.

BG-12 240 mg TID

48% riduzione

- **Numero medio di lesioni T2 nuove o più estese (P < 0.01)**

53% riduzione

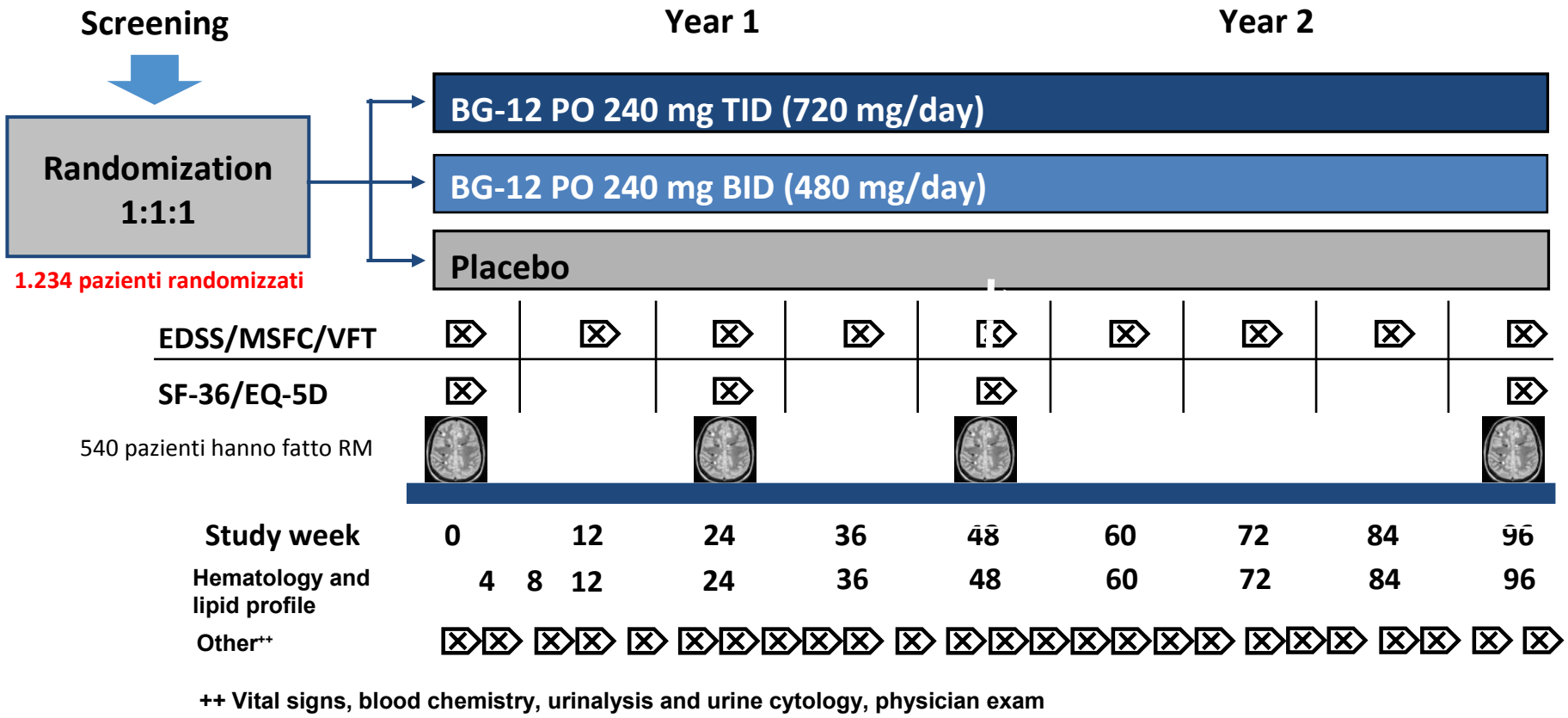
- **Numero medio di nuove lesioni T1 a 24 settimane (*P* = 0.014)**

32% riduzione

- **Tasso annualizzato di ricadute a 24 settimane (*P* = NS)**

Kappos L et al. *Lancet.* 2008;372:1463-1472.

DEFINE: schema dello studio



++ Vital signs, blood chemistry, urinalysis and urine cytology, physician exam

Criteri di inclusione

- SM RR secondo i criteri di McDonald (1–4)[1]
- 18 - 55 anni
- EDSS fra 0.0 and 5.0
- ≥ 1 ricaduta nell'anno precedente e lesioni tipiche alla RM o ≥ 1 lesioni Gd + alla RM encefalo effettuata entro 6 settimane prima della randomizzazione
- Consenso informato scritto

1. McDonald WI et al. *Ann Neurol.* 2001;50:120-127.

Endpoints

Endpoint primario

Percentuale di pazienti con ricadute

(confermata dall' INEC: Independent Neurology Evaluation Committee)

Endpoint secondari

- Tasso annualizzato di ricadute confermate dall'INEC
- Progressione di disabilità misurata con EDSS
- Numero di nuove o più estese lesioni iperintense in T2
- Numero di lesioni gadolinio positive

Endpoint terziari

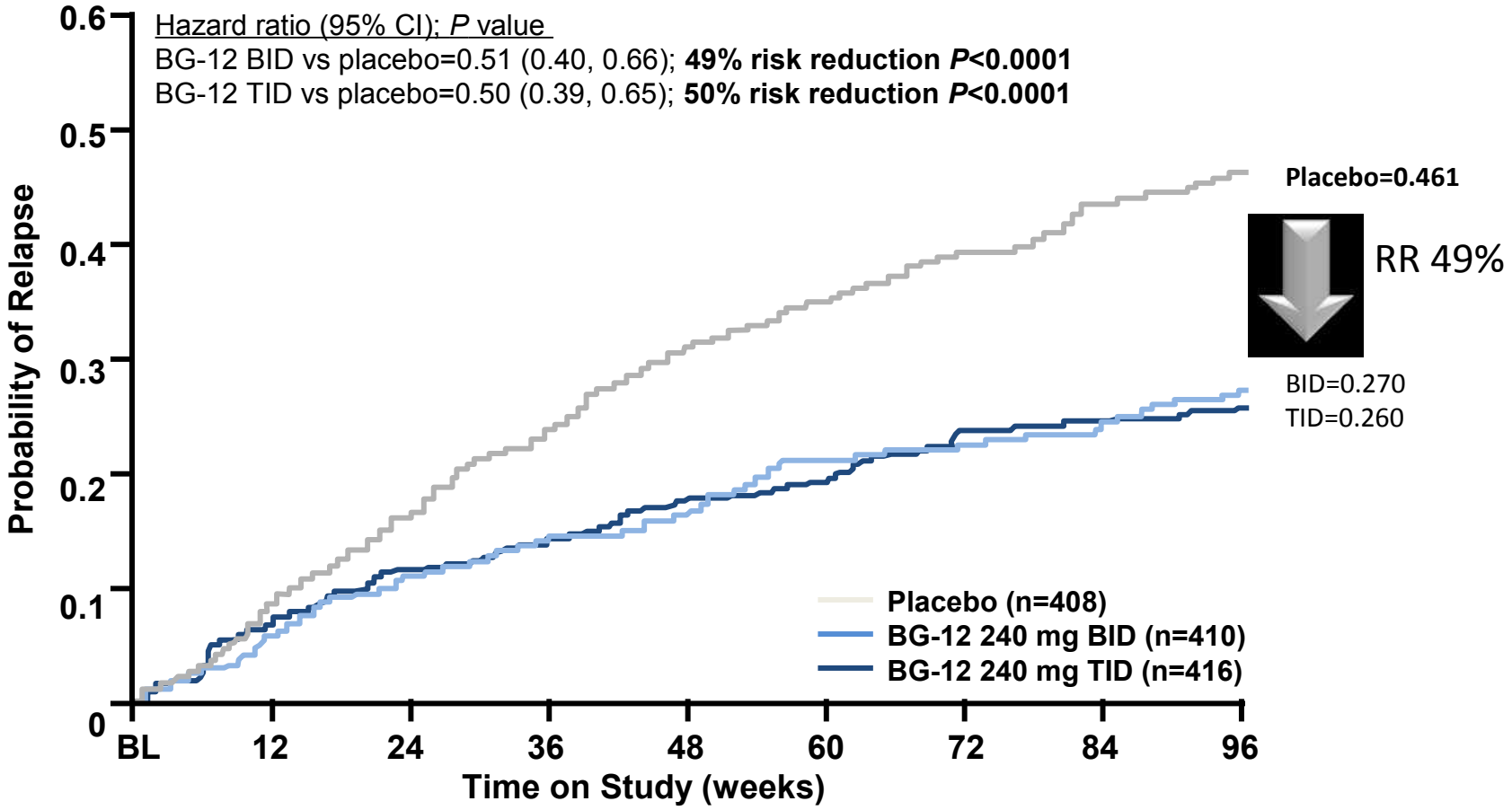
MSFC, Brain Atrophy, QOL, Relapses che richiedevano ciclo steroideo o ospedalizzazione

Tertiary Endpoints

- Disability
  - MSFC *z* score, PASAT, Sloan low-contrast visual acuity
- MRI
  - Brain atrophy (SIENA), magnetization transfer ratio (lesions and whole brain), T1 lesion counts and volumes, Gd+ and T2 lesion volume, conversion of Gd+ lesions into T1 lesions
- Patient-reported outcomes
  - SF-36, EQ-5D
- Relapses requiring IV steroids or hospitalization

MSFC=Multiple Sclerosis Functional Composite; PASAT=Paced Auditory Serial Addition Test; MRI=magnetic resonance imaging; SIENA=Structural Image Evaluation using Normalization of Atrophy; Gd+=gadolinium-enhancing; SF-36=Short Form (36) Health Survey; EQ-5D=EuroQol-5D Health Survey; IV=intravenous.

Endpoint primario
Proporzione di pazienti con ricadute (confermate da INEC)

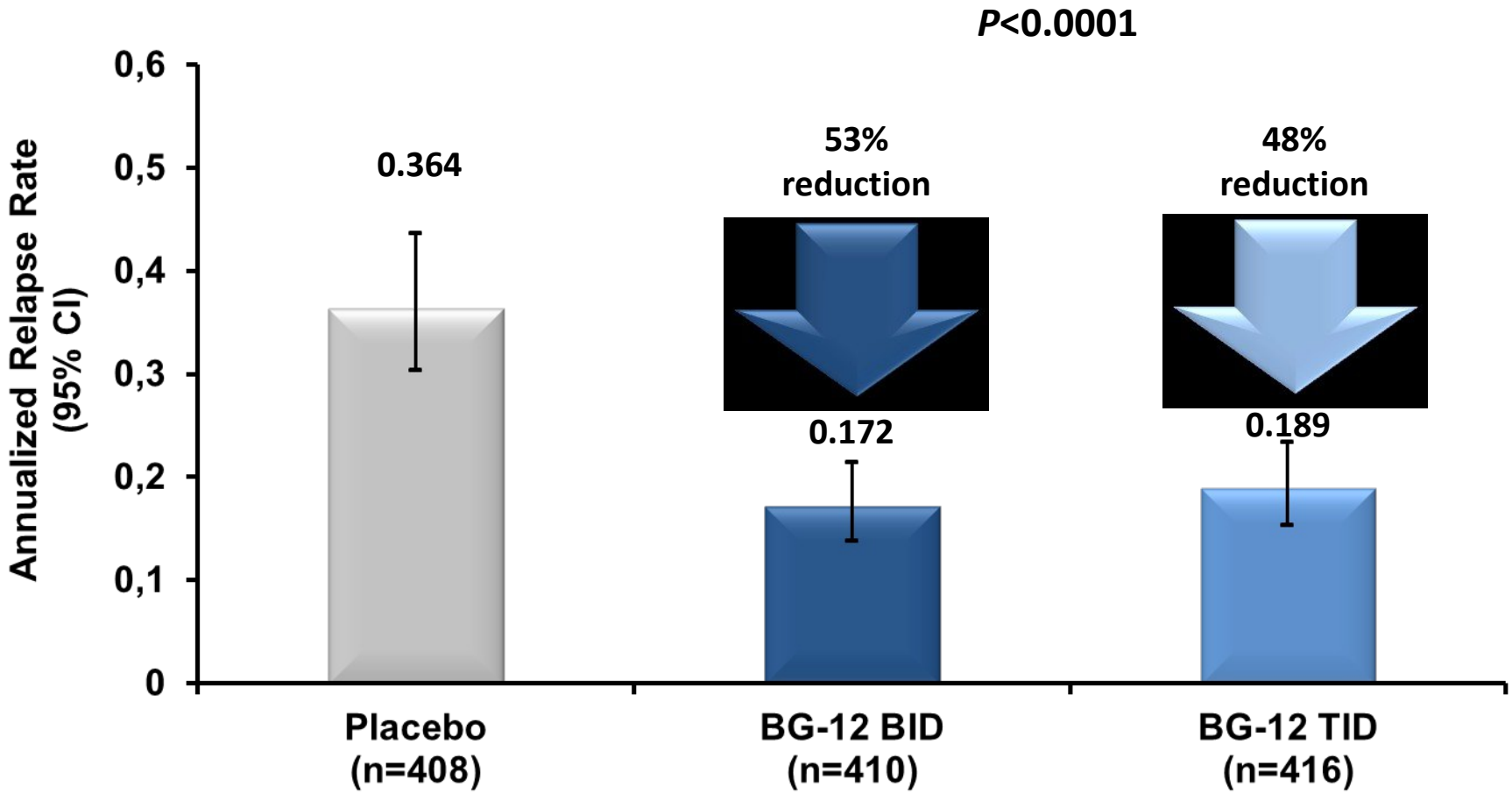


Number of Patients at Risk

Placebo	406	358	321	282	243	224	205	190	115
240 mg BID	410	353	324	303	288	287	255	243	154
240 mg TID	418	348	322	301	288	270	251	244	166

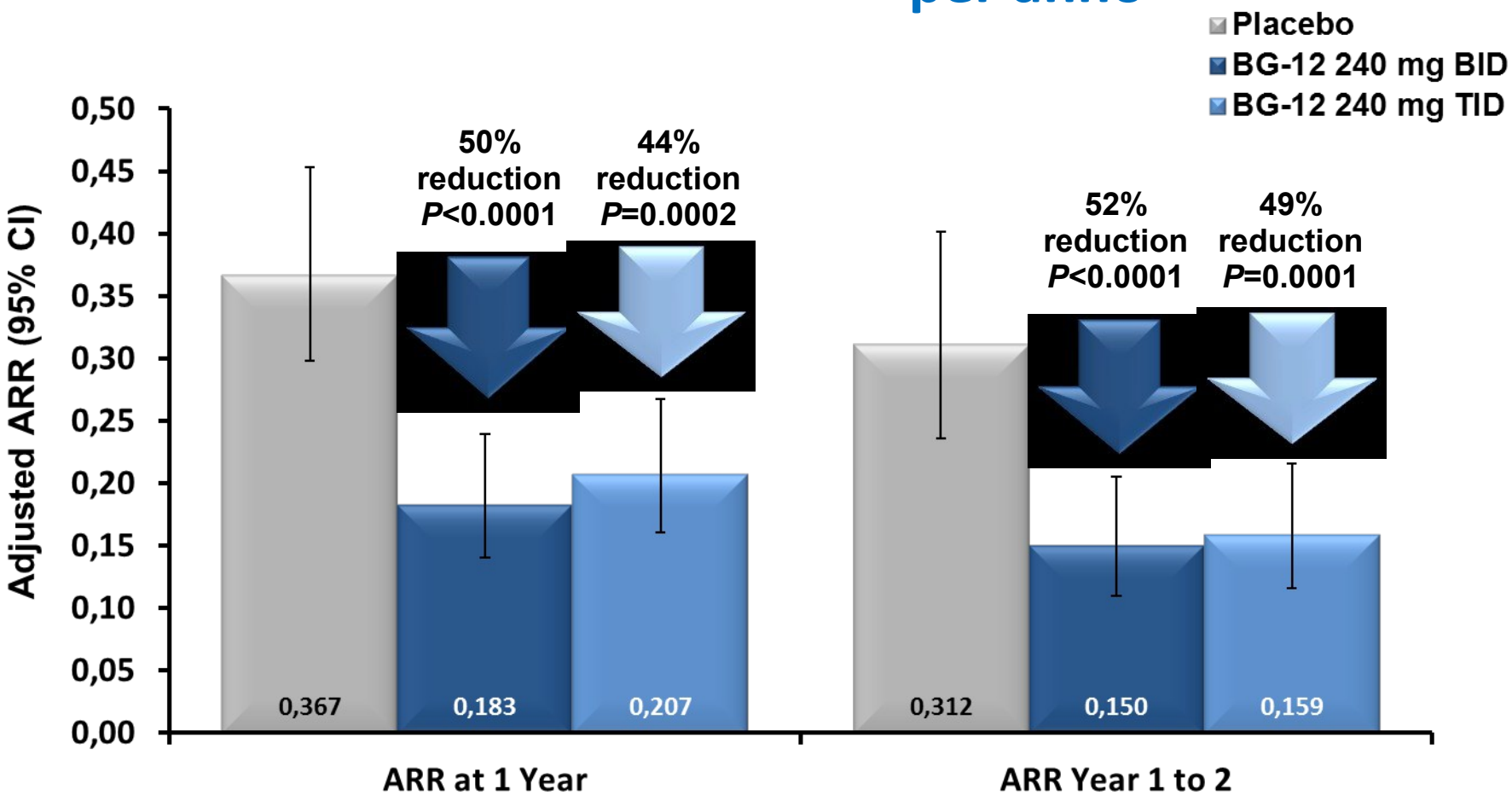
INEC=Independent Neurology Evaluation Committee; CI=confidence interval; BID=twice daily; TID=three times daily; BL=baseline.

Tasso annualizzato di ricadute (endpoint secondario)



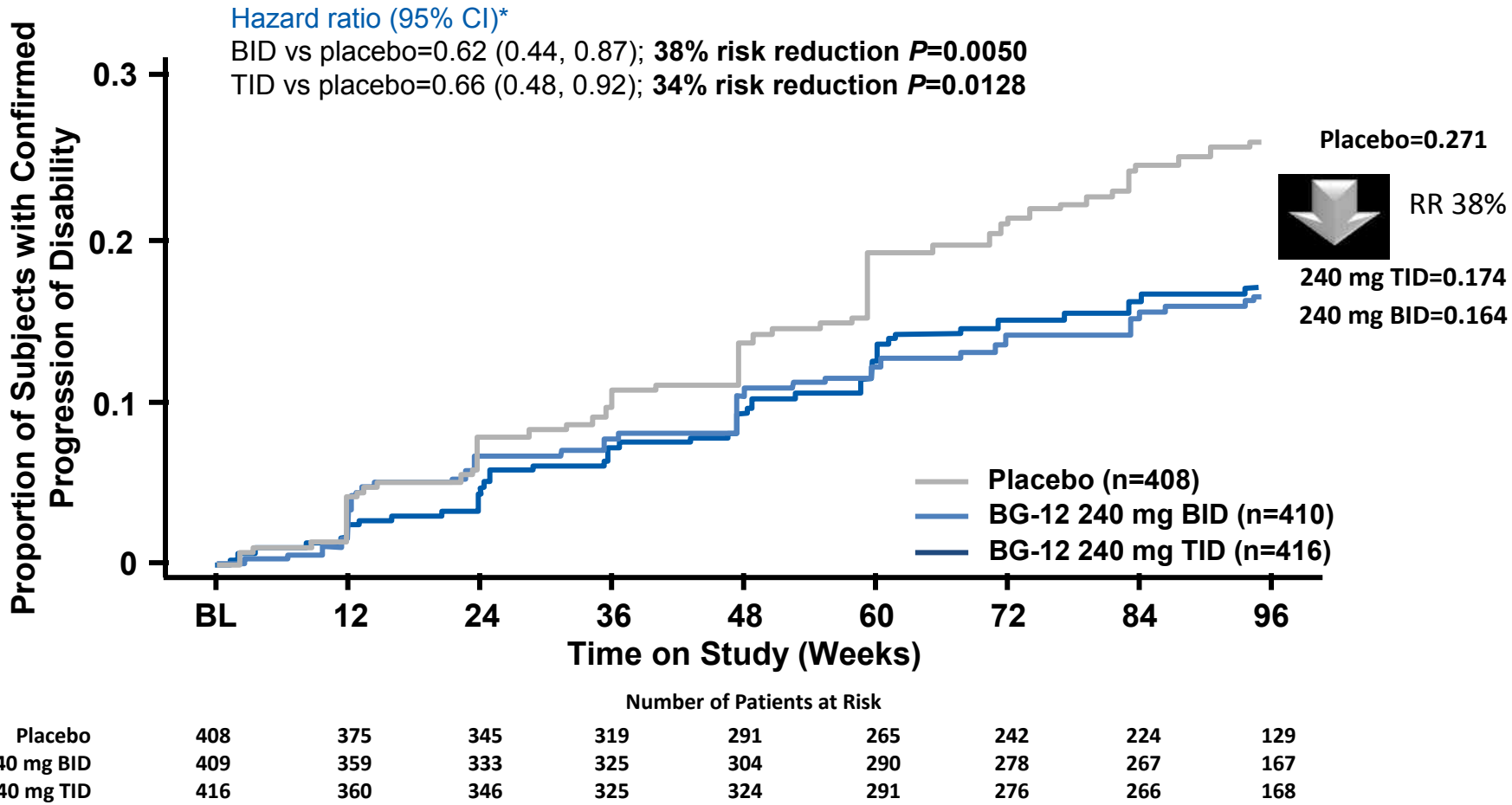
CI=confidence interval; BID=twice daily; TID=three times daily.

Tasso annualizzato di ricadute per anno*



*ARR is calculated as the total number of relapses occurred during the study for all subjects, divided by the total number of subject-years followed in the study. *P* values relative to placebo.
BID=twice daily; TID=three times daily; ARR=annualized relapse rate; CI=confidence interval.

Progressione di disabilità (mantenuta per 12 settimane) end-point secondario

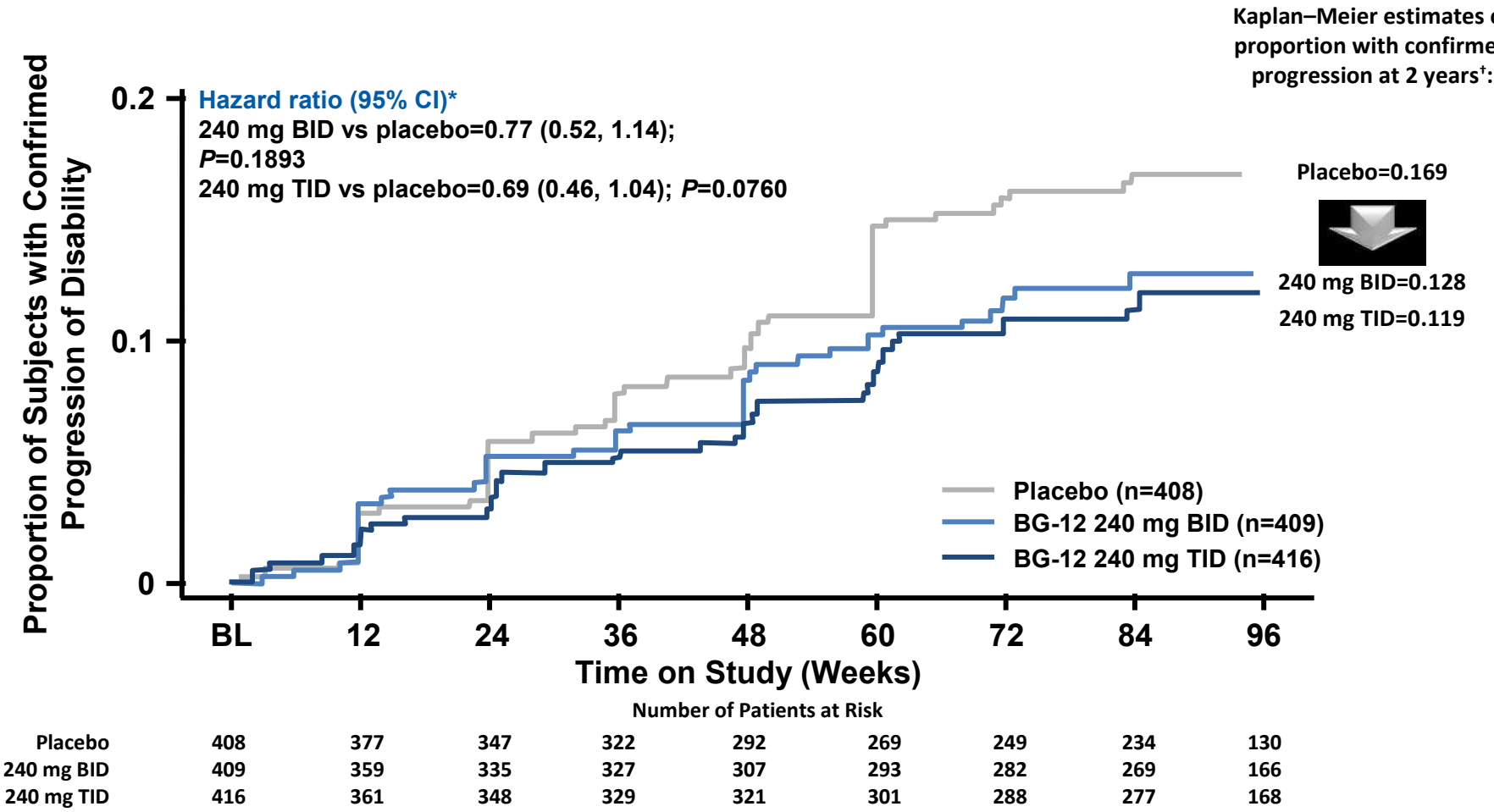


Number of Patients at Risk

Placebo	408	375	345	319	291	265	242	224	129
240 mg BID	409	359	333	325	304	290	278	267	167
240 mg TID	416	360	346	325	324	291	276	266	168

Note: confirmed progression of disability is defined as 1.0-point increase on the EDSS from a baseline EDSS score ≥1.0 sustained for 12 weeks. Subjects are censored if they withdrew from study or switched to alternative MS medication without a progression. **P* value and hazard ratio (active/placebo) based on a Cox proportional hazards model, adjusted for age (<40 vs ≥40 years), baseline EDSS score, and region; †Kaplan–Meier estimate of the proportion of subjects' confirmed progression within 2 years. EDSS=Expanded Disability Status Scale; ITT=intent-to-treat; CI=confidence interval; TID=three times daily; BID=twice daily; BL=baseline. SOURCE: 109MS301/CSR/E-PROG-12WK.SAS

Progressione di disabilità (mantenuta per 24 settimane) end-point secondario ITT Population



Number of Patients at Risk

Placebo	408	377	347	322	292	269	249	234	130
240 mg BID	409	359	335	327	307	293	282	269	166
240 mg TID	416	361	348	329	321	301	288	277	168

Note: confirmed progression of disability is defined as 1.0-point increase on the EDSS from a baseline EDSS score ≥1.0 sustained for 24 weeks. Subjects are censored if they withdrew from study or switched to alternative MS medication without a progression. **P* value and hazard ratio (active/placebo) based on a Cox proportional hazards model, adjusted for age (<40 vs ≥40 years), baseline EDSS score, and region; †Kaplan–Meier estimate of the proportion of subjects' confirmed progression within 2 years. EDSS=Expanded Disability Status Scale; ITT=intent-to-treat; CI=confidence interval; BID=twice daily; TID=three times daily; BL=baseline. SOURCE: 109MS301/CSR/E-PROG-12WK.SAS

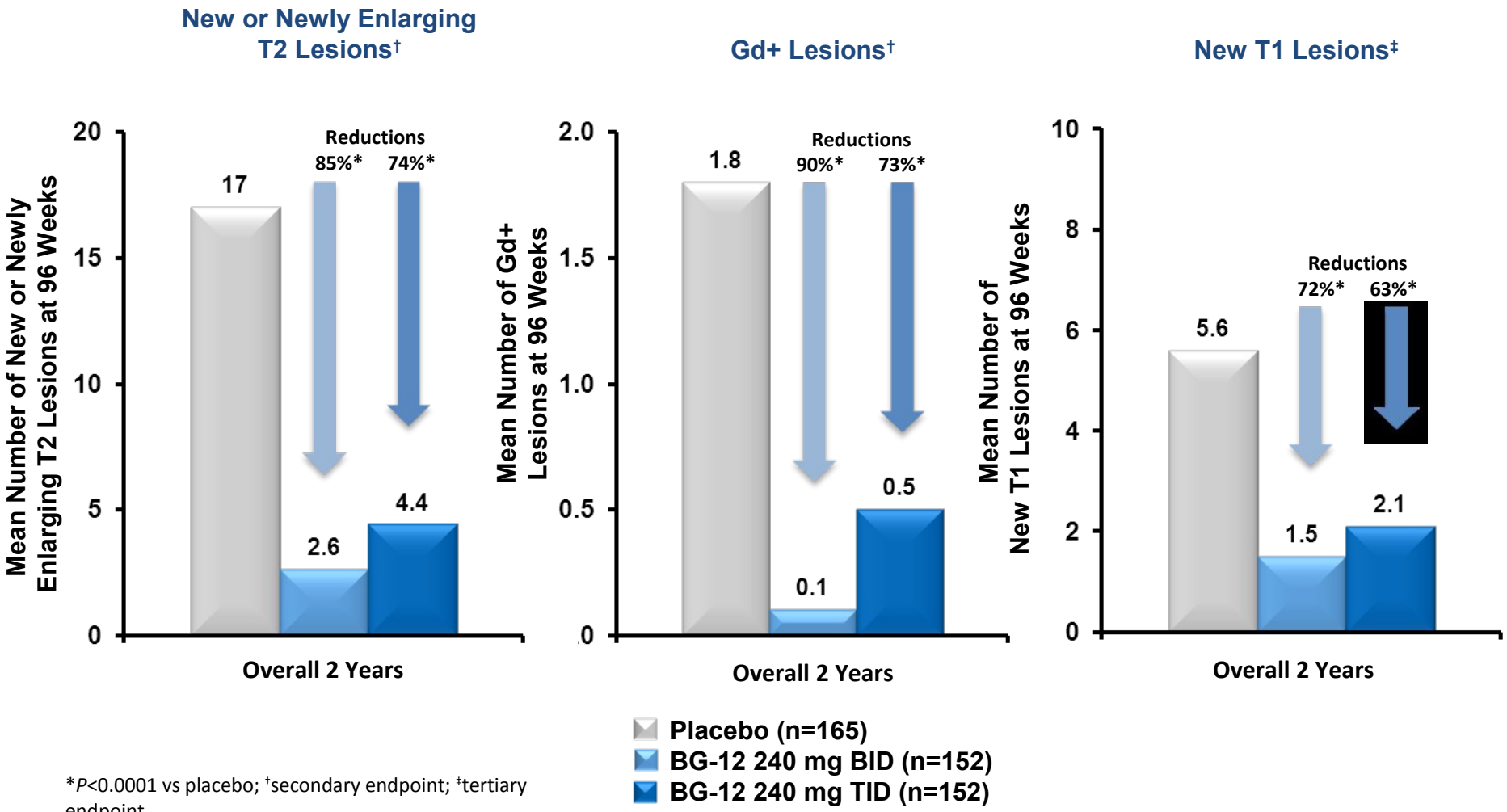
DEFINE:
RIASSUNTO DELL'EFFICACIA CLINICA

BG-12 BID vs placebo:

- Riduce la proporzione di ricadute del 49% (*P*<0.0001)
- Riduce il tasso annualizzato di ricadute (ARR) del 53% (*P*<0.0001)
- Riduce il rischio di progressione di disabilità (mantenuta a 12 settimane) del 38% (*P*=0.0050)

BID=due volte al giorno.

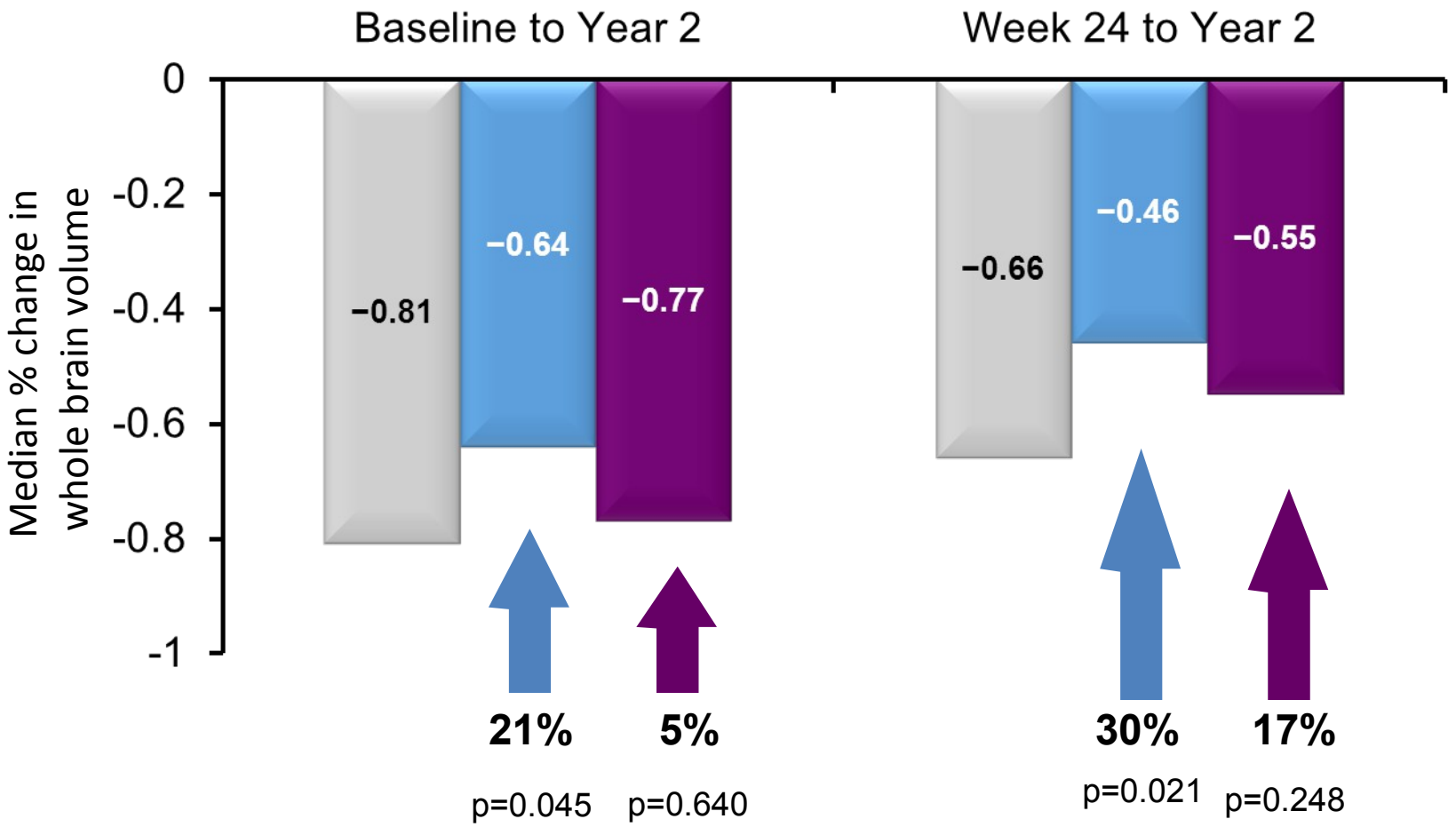
MRI Results



*P<0.0001 vs placebo; †secondary endpoint; ‡tertiary endpoint.

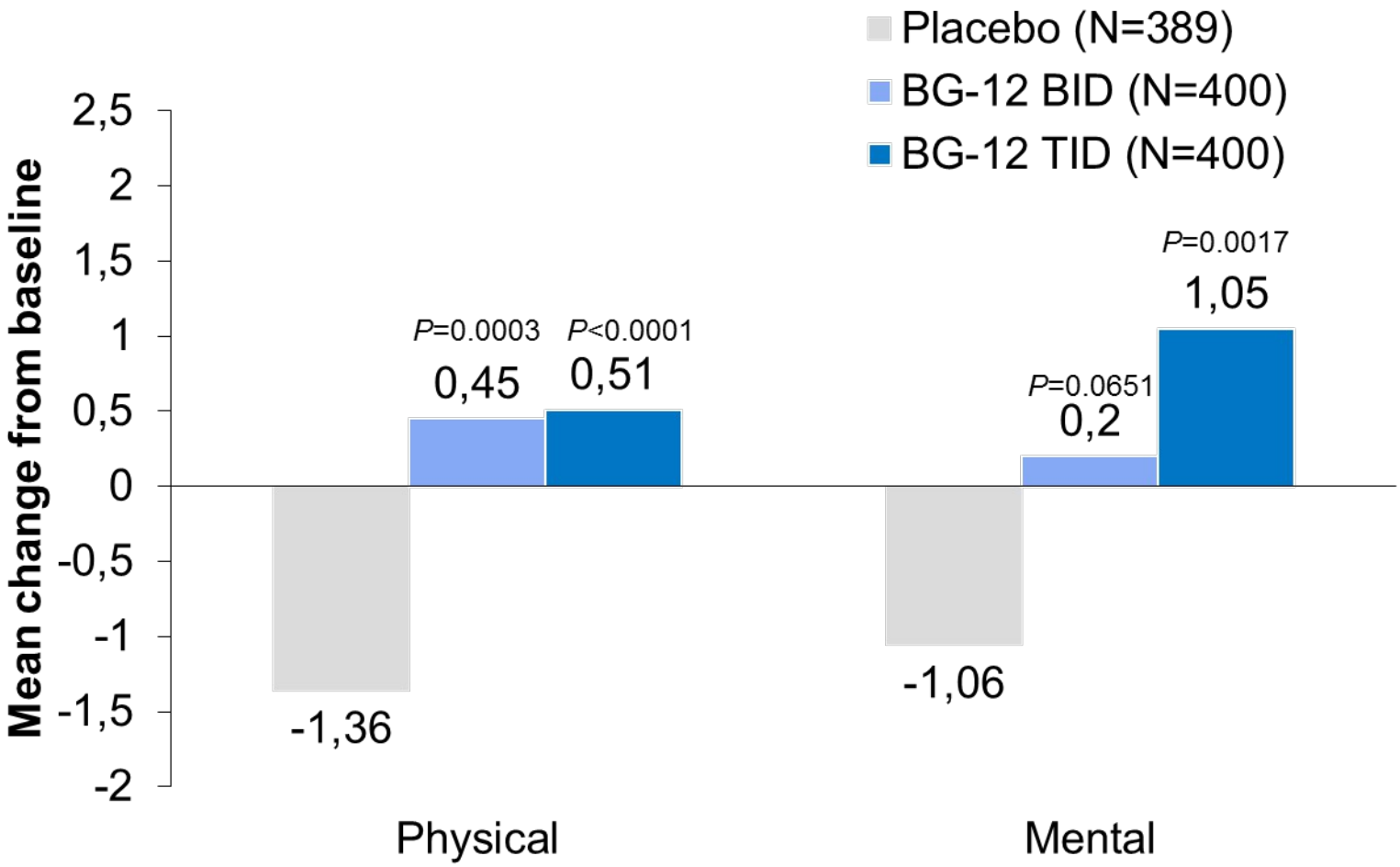
Gold R, et al. Presented at ECTRIMS, 2011, Amsterdam, The Netherlands. S34. Oral presentation; Arnold DL et al. Presented at ECTRIMS, 2011, Amsterdam, The Netherlands. P831; Arnold DL et al. Presented at AAN, 2012, New Orleans, LA, USA. S11.003.

Brain atrophy (% Change in Whole Brain Volume)

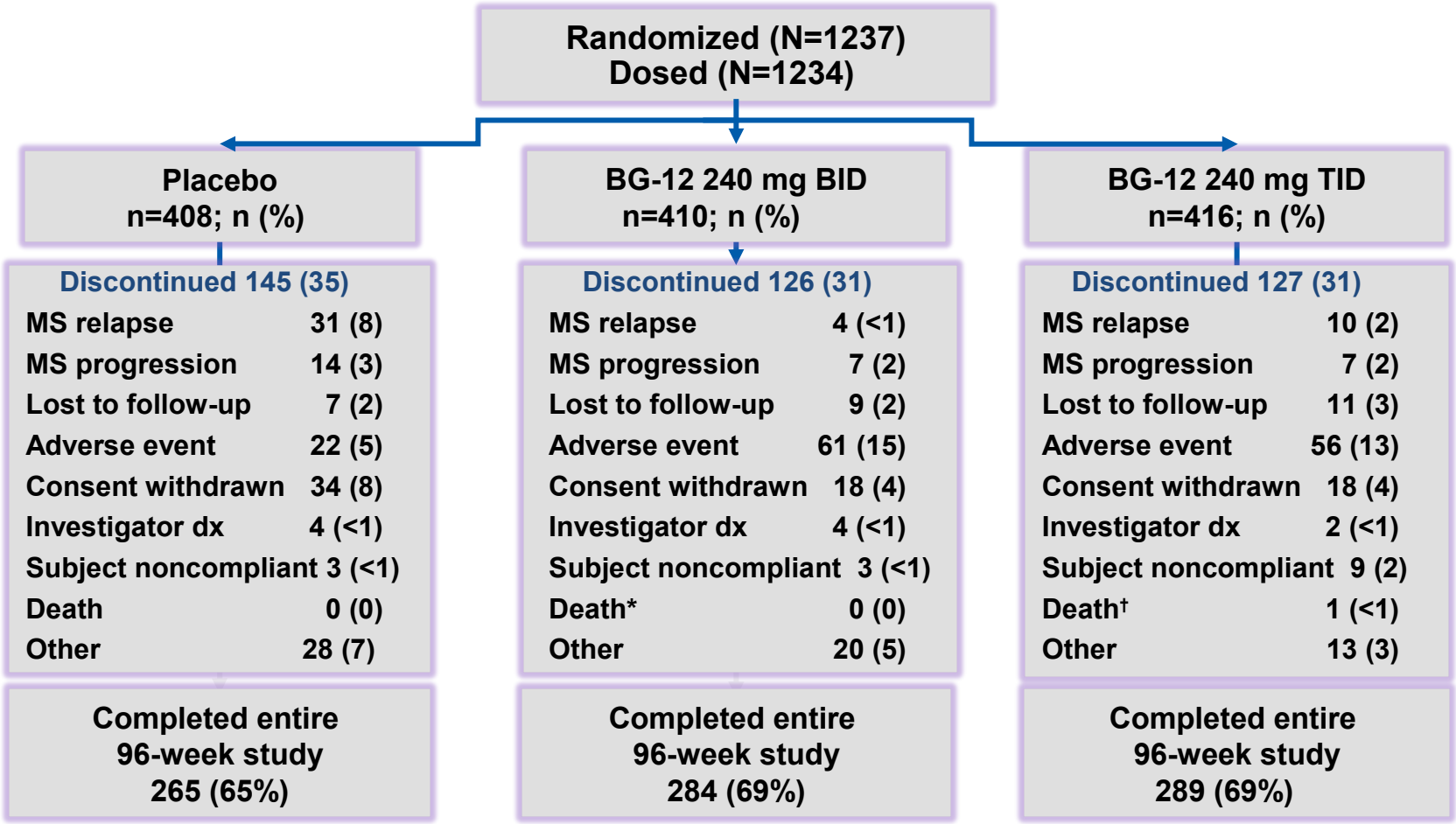


based on ANCOVA on ranked data, adjusted for region and normalized brain volume at baseline/Week 24.

Qualità di vita (SF-36): variazioni medie a 2 anni



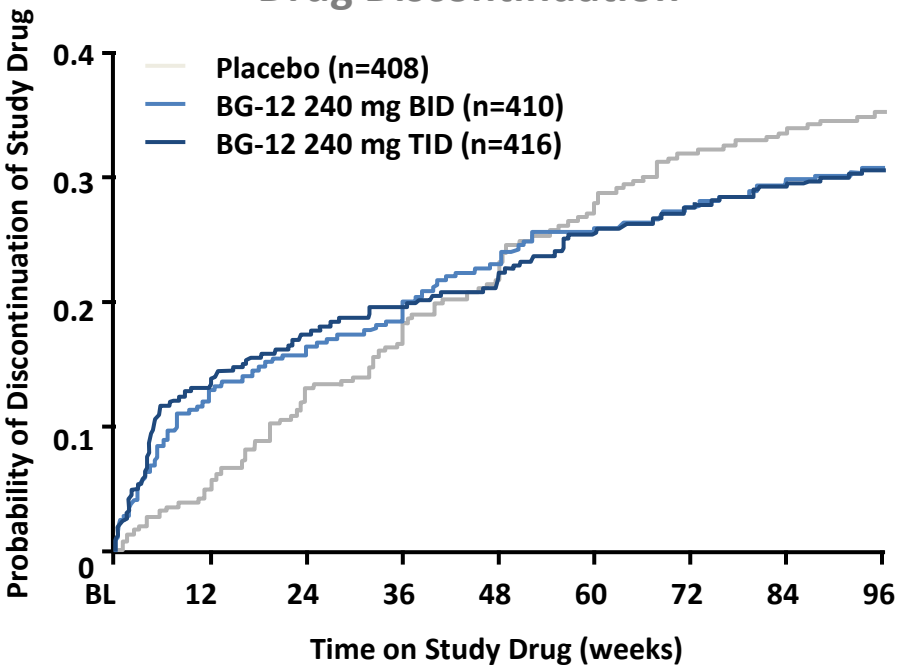
Treatment Discontinuation



*A patient died approximately 3 weeks after withdrawing from the study due to a cycling accident; †death was due to a motor vehicle accident. BID=twice daily; TID=three times daily; MS=multiple sclerosis; dx=discontinued.

DEFINE: Time to Discontinuation and Withdrawal: ITT Population

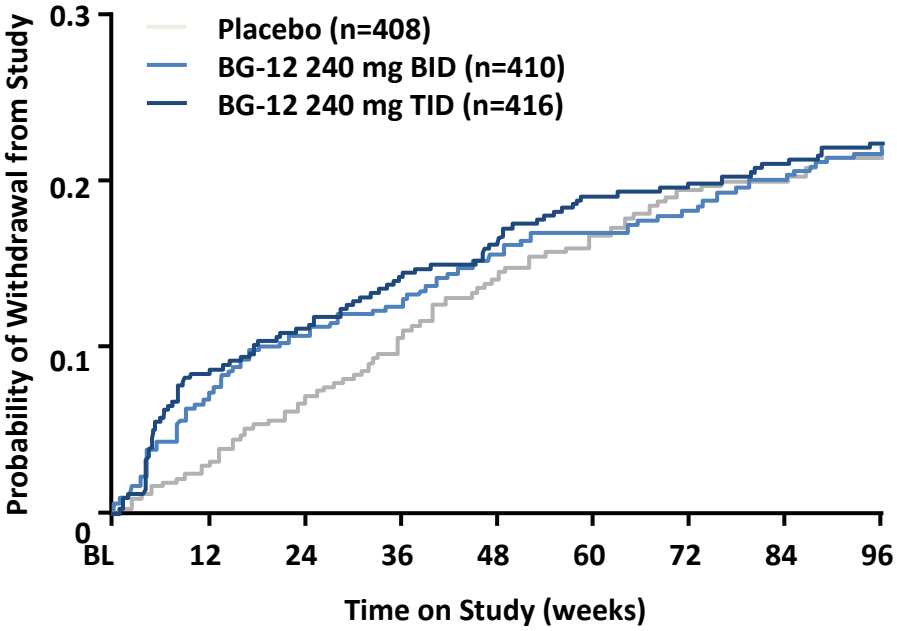
Drug Discontinuation



Number of Patients at Risk

Placebo								
408	387	354	336	313	293	276	272	134
240 mg BID								
410	357	344	331	313	304	297	269	135
240 mg TID								
416	359	344	335	324	310	302	294	150

Study Withdrawal

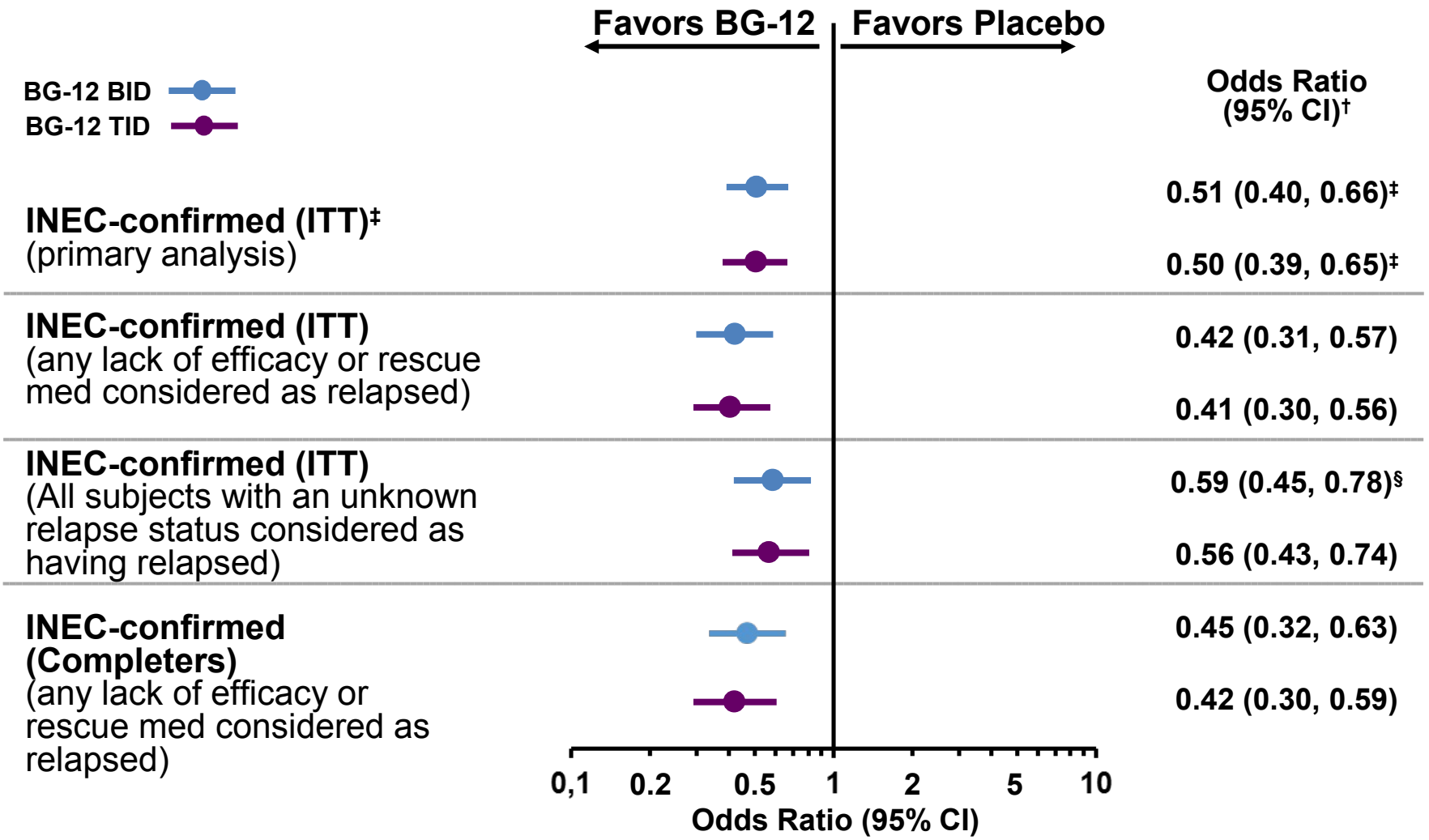


Number of Patients at Risk

Placebo								
408	395	379	365	350	340	329	327	242
240 mg BID								
410	382	366	359	346	341	336	328	237
240 mg TID								
416	380	370	356	348	337	334	329	247

ITT=intent-to-treat; BID=twice daily; TID=three times daily; BL=baseline.

Proportion of Patients Relapsed at 2-Years* (Sensitivity Analyses)



*Logistic regression models; †$P<0.0001$ for all categories unless otherwise stated;
‡hazard ratio for the primary analysis; §$P=0.0002$.

Safety: dati riassuntivi

BG-12 è stato ben tollerato e non sono state osservate significative differenze con il placebo nell'incidenza globale di AEs, SAEs e AEs che abbiano portano ad interruzione del trattamento.

AEs più comuni:

- **flushing (38-32%)**
- **disturbi GI** (diarrea: 15-19%; nausea 13%; vomito 16%; dolore addominale 11-9%)
- verificatisi precocemente durante il trattamento (**soprattutto nel 1° mese**)
- intensità da **lieve a moderata**
- raramente hanno portato ad interruzione del trattamento o drop-out

- Le infezioni erano ugualmente distribuite tra I gruppi
- **Non** si sono verificate **infezioni opportunistiche** nei pz in trattamento con BG-12
- **No**n si sono verificati **tumori maligni** nei paz in trattamento con BG-12

DEFINE: Common AEs in ≥5% of Subjects in Placebo or BG-12 Groups

Event, n (%)	Placebo (n=408)	BG-12 240 mg BID (n=410)	BG-12 240 mg TID (n=416)
Patients with any event	387 (95)	395 (96)	396 (95)
Flushing*	20 (5)	**154 (38)**	**132 (32)**
MS relapse	189 (46)	111 (27)	114 (27)
Nasopharyngitis	101 (25)	108 (26)	109 (26)
Headache	80 (20)	81 (20)	80 (19)
Diarrhea*	55 (13)	62 (15)	**78 (19)**
Fatigue	54 (13)	57 (14)	63 (15)
Upper respiratory infection	53 (13)	63 (15)	51 (12)
Urinary tract infection	53 (13)	55 (13)	54 (13)
Nausea*	38 (9)	**53 (13)**	**54 (13)**
Back pain	57 (14)	59 (14)	46 (11)
Upper abdominal pain*	28 (7)	**40 (10)**	**52 (13)**
Proteinuria*	34 (8)	38 (9)	**50 (12)**
Abdominal pain*	22 (5)	**46 (11)**	**37 (9)**
Arthralgia	39 (10)	46 (11)	37 (9)

*Indicates ≥3 percentage points higher in either BG-12 group vs placebo.
AE=adverse event; BID=twice daily; TID=three times daily; MS=multiple sclerosis.
Selmaj K et al. Presented at ECTRIMS, 2011, Amsterdam, The Netherlands. P994.

DEFINE: Common AEs in ≥5% of Subjects in Placebo or BG-12 Groups

Event, n (%)	Placebo (n=408)	BG-12 240 mg BID (n=410)	BG-12 240 mg TID (n=416)
Influenza	39 (10)	34 (8)	48 (12)
Pruritus*	19 (5)	**42 (10)**	**34 (8)**
Paresthesia	38 (9)	35 (9)	38 (9)
Vomiting*	24 (6)	40 (10)	**30 (7)**
Pain in extremity	29 (7)	37 (9)	29 (7)
Depression	33 (8)	29 (7)	33 (8)
Rash*	13 (3)	**34 (8)**	**27 (6)**
Hot flush*	8 (2)	**31 (8)**	**29 (7)**
ALT increased*	13 (3)	**29 (7)**	**27 (6)**
Erythema*	5 (1)	**20 (5)**	**33 (8)**
Hematuria	19 (5)	26 (6)	26 (6)
Sinusitis*	20 (5)	17 (4)	**34 (8)**
Gastroenteritis	21 (5)	28 (7)	21 (5)
Bronchitis	18 (4)	21 (5)	26 (6)

*Indicates ≥3 percentage points higher in either BG-12 group vs placebo.
AE=adverse event; BID=twice daily; TID=three times daily; ALT=alanine aminotransferase.
Selmaj K et al. Presented at ECTRIMS, 2011, Amsterdam, The Netherlands. P994.

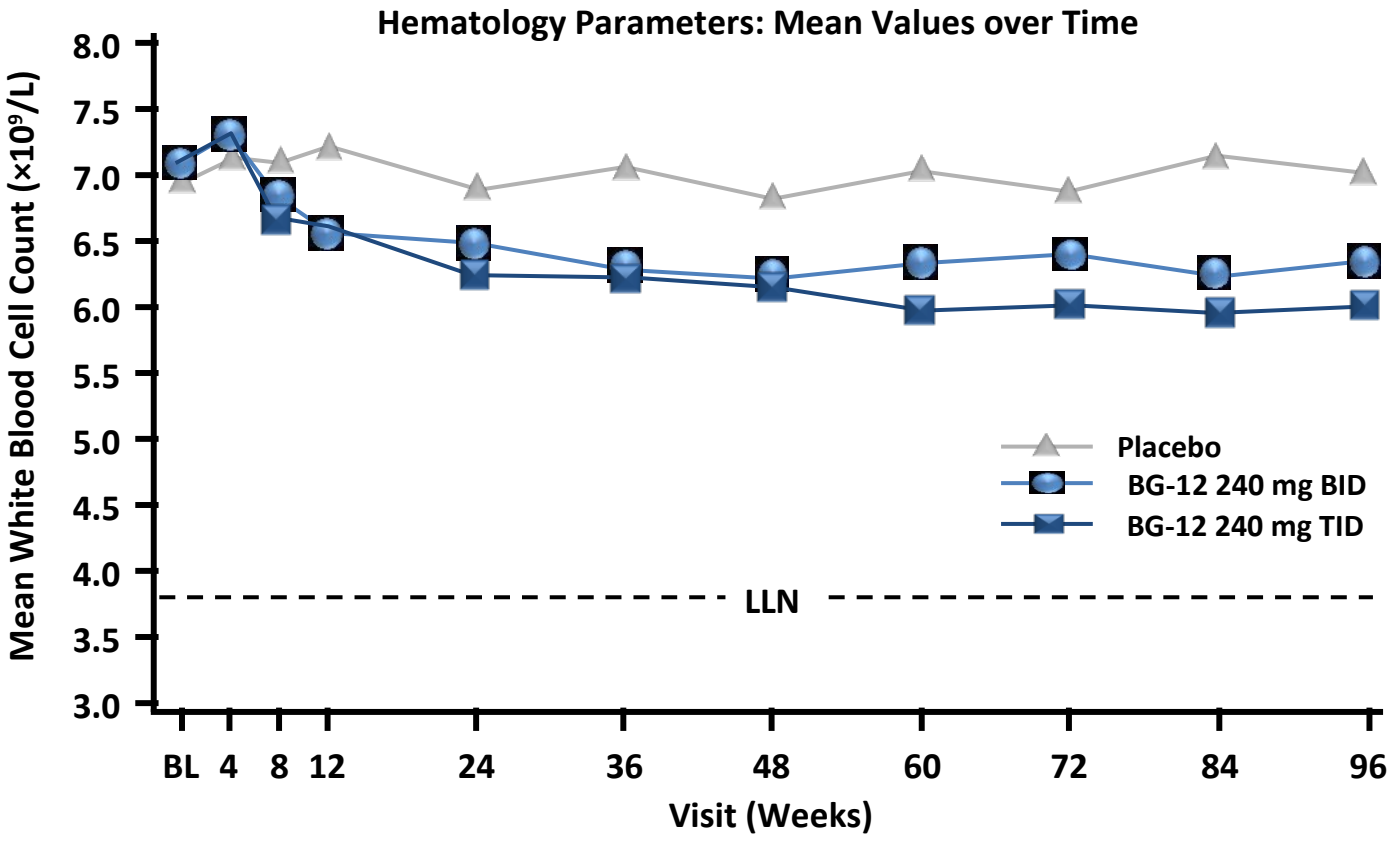
Serious AEs

- Incidence of 21%, 18%, and 16% in the placebo, BG-12 BID, and BG-12 TID treatment groups, respectively
  - MS relapse was the most common, with greater incidence in the placebo arm
  - Gastroenteritis, gastritis, ovarian cyst, headache, and pneumonia were the only other serious AEs in 2 or more patients in a BG-12 group

AE=adverse event; BID=twice daily; TID=three times daily; MS=multiple sclerosis

Gold R, et al. Presented at ECTRIMS, 2011, Amsterdam, The Netherlands. S34;
Selmaj K et al. Presented at ECTRIMS, 2011, Amsterdam, The Netherlands. P994.

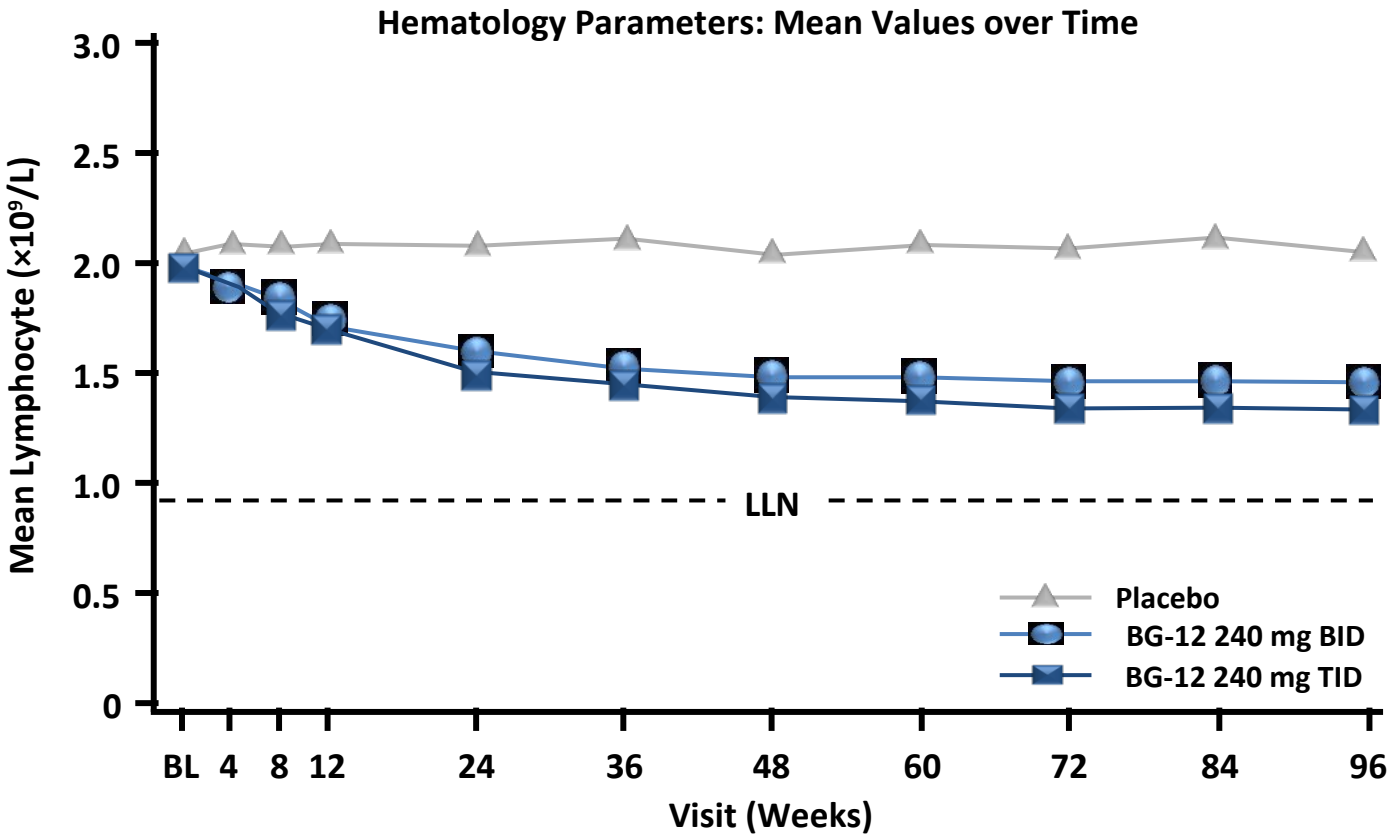
Livelli dei globuli bianchi



Placebo: n=407 (baseline) to 245 (week 96).
BG-12 240 mg BID: n=410 (baseline) to 271 (week 96).
BG-12 240 mg TID: n=416 (baseline) to 268 (week 96).

te: LLN is lower limit in standard unit. If there are multiple values of LLN for a given parameter, highest LLN is shown.
=twice daily; TID=three times daily; LLN=lower limit of normal; BL=baseline.

Livelli dei linfociti



Placebo: n=407 (baseline) to 245 (week 96).
BG-12 240 mg BID: n=410 (baseline) to 271 (week 96).
BG-12 240 mg TID: n=416 (baseline) to 268 (week 96).

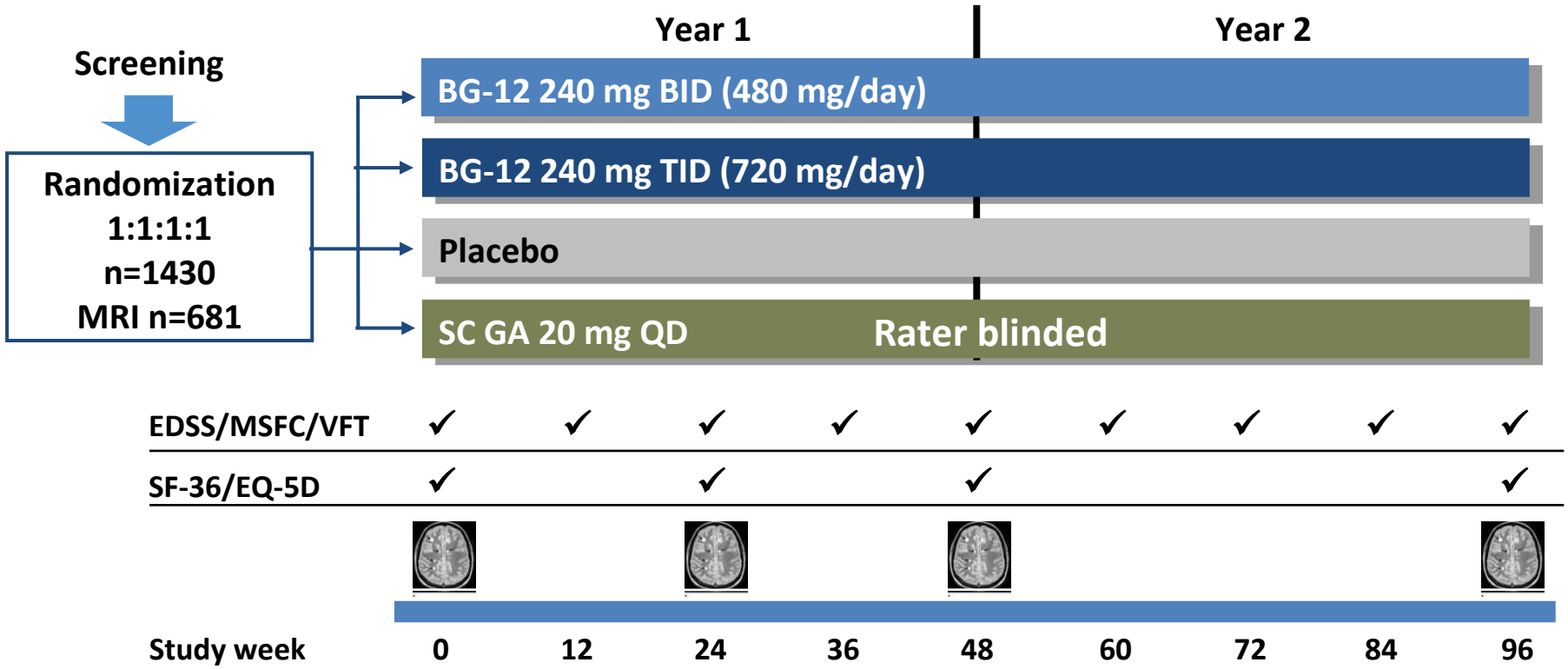
e: LLN is lower limit in standard unit. If there are multiple values of LLN for a given parameter, highest LLN is shown.
=twice daily; TID=three times daily; LLN=lower limit of normal; BL=baseline.

BG-12 (Tecfidera®)

- Approvato negli USA per la terapia della SM RR:
  - Cps.240 mg 2 volte al dì

- EMA: dopo parere positivo della CHMP , la molecola è stata recentemente riconosciuta come "nuovo principio attivo", garantendo maggiore protezione contro le copie generiche e spianando la strada per l'approvazione Europea

CONFIRM: Study Design



Laboratory and safety assessments performed monthly

Note: Patients with confirmed disability progression may have switched to IM IFNβ-1a or alternative MS treatment at any time; patients with confirmed relapse after 24 weeks may have switched to IM IFN ✓-1a or alternative MS treatment after 48 weeks on study. MRI=magnetic resonance imaging; BID=twice daily; TID=three times daily; SC=subcutaneous; GA=glatiramer acetate; QD=once daily; EDSS=Expanded Disability Status Scale; MSFC=Multiple Sclerosis Functional Composite; VFT=Visual Function Test; SF-36=Short-Form 36 Health Survey; EQ-5D=EuroQol-5D Health Survey; IM=intramuscular; IFNβ=interferon beta; MS=multiple sclerosis; QoL=quality of life.

DEFINE vs CONFIRM: BG-12 Phase 3 Study Comparison

Characteristic	DEFINE			CONFIRM		
	Placebo (n=408)	BG-12 240 mg BID (n=410)	BG-12 240 mg TID (n=416)	Placebo (n=363)	BG-12 240 mg BID (n=359)	BG-12 240 mg TID (n=345)
Primary endpoint	Proportion of subjects relapsed at 2 years			ARR at 2 years		
Alternative MS medication use criteria	Disease progression at any time *or* the subject has completed 48 weeks of blinded treatment and experienced at least 1 confirmed relapse any time after 24 weeks			Disease progression at any time *or* the subject has completed 48 weeks of blinded treatment and experienced 2 confirmed relapses		
Inclusion/ exclusion criteria				Any prior treatment with GA (exclusion criteria)		
Reference comparator				Patients treated with GA (n=350) were included as a comparator arm		

BID=twice daily; TID=three times daily; ARR=annualized relapse rate; MS=multiple sclerosis; GA=glatiramer acetate.

CONFIRM: Key Inclusion/Exclusion Criteria

- Inclusion criteria
  - Aged 18 to 55 years
  - RRMS[1]
  - Baseline EDSS score between 0.0 and 5.0
  - 1 relapse in prior 12 months, *or* Gd+ lesion(s) in prior 6 weeks
- Exclusion criteria
  - Prior treatment with GA
  - Progressive forms of MS
  - A relapse or corticosteroids within 50 days prior to randomization
  - Insufficient washout period from prior immunomodulatory therapies

RRMS=relapsing-remitting MS; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; GA=glatiramer acetate; MS=multiple sclerosis.

1. Polman C et al. *Ann Neurol.* 2005;58:840-846; Fox R, et al. Presented at AAN 2012, New Orleans, LA, USA. S01.003.

CONFIRM: Key Trial Endpoints

- Primary endpoint
  - ARR
- Secondary endpoints
  - Number of new or newly enlarging T2-hyperintense lesions*
  - Number of new T1-hypointense lesions*
  - Proportion of patients who relapsed at 2 years
  - 12-week sustained disability progression, as measured by EDSS
- Tertiary endpoints
  - Gd+ lesions
  - Quality-of-life measures
  - Comparison of benefit/risk for BG-12 vs placebo

*Imaging conducted at selected sites with MRI testing capability further validated by the MRI reading center.
ARR=annualized relapse rate; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; MRI=magnetic resonance imaging
Fox R, et al. Presented at AAN 2012, New Orleans, LA, USA. S01.003.

Baseline Patient Demographics (ITT)

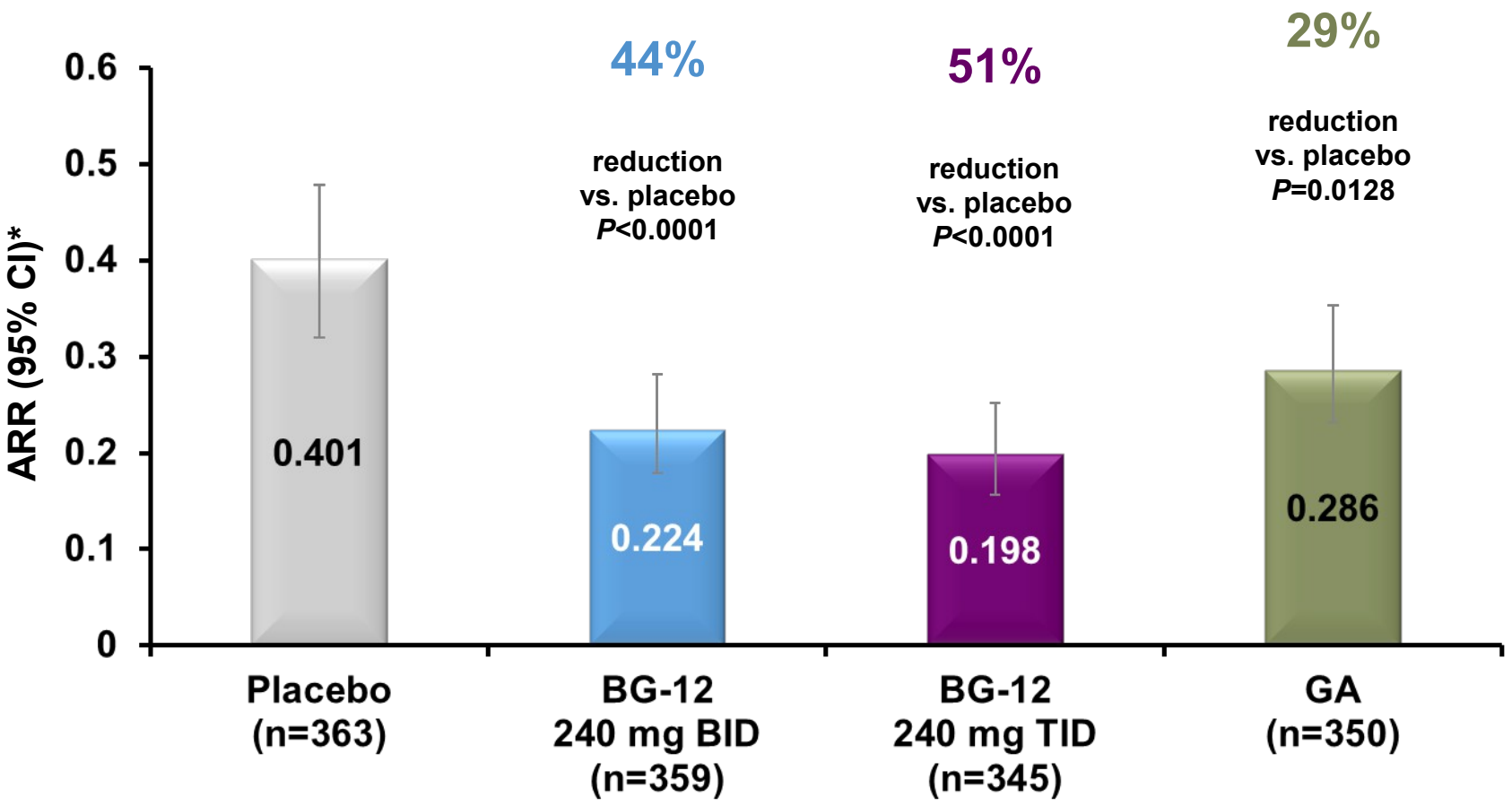
Characteristic	Placebo (n=363)	BG-12 240 mg BID (n=359)	BG-12 240 mg TID (n=345)	GA (n=350)
Age, years				
Mean (SD)	36.9 (9.24)	37.8 (9.35)	37.8 (9.39)	36.7 (9.06)
Range	18–56	18–55	18–55	18–55
Female, n (%)	251 (69)	245 (68)	250 (72)	247 (71)
Weight , kg, mean (SD)	72.64 (16.897)	71.90 (17.892)	72.48 (17.800)	71.38 (19.137)
Race, n (%)				
White	305 (84)	304 (85)	292 (85)	290 (83)
Asian*	28 (8)	28 (8)	26 (8)	25 (7)
Black/African American	9 (2)	2 (<1)	5 (1)	11 (3)
Unknown	11 (3)	11 (3)	10 (3)	11 (3)
Other	10 (3)	14 (4)	12 (3)	13 (4)

*Includes Indian patients who self-reported race as Asian.
ITT=intent-to-treat; BID=twice daily; TID=three times daily; GA=glatiramer acetate; SD=standard deviation.
Fox R, et al. Presented at AAN 2012, New Orleans, LA, USA. S01.003.

Baseline Disease Characteristics (ITT)

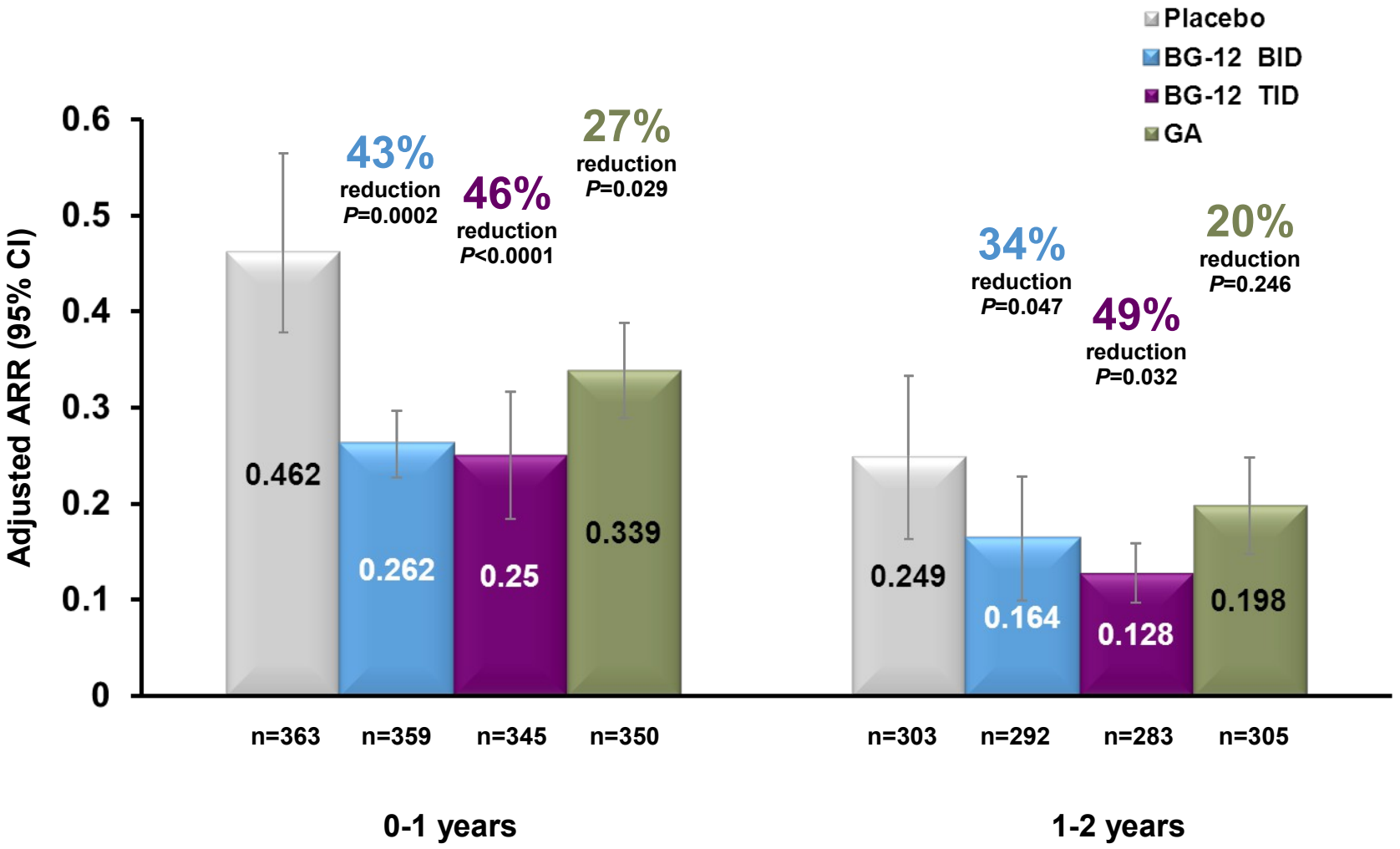
Characteristic	Placebo (n=363)	BG-12 BID (n=359)	BG-12 TID (n=345)	GA (n=350)
Time since first MS symptoms Years (SD)	7.6 (5.98)	8.2 (6.89)	7.8 (6.70)	7.1 (5.92)
Median disease duration in years (since diagnosis)	4.0	3.0	3.0	3.0
Median EDSS score	2.5	2.5	2.5	2.5
Any prior treatment for MS, %	40	41	40	40
Prior approved MS DMT (%)	31	28	29	29
IFNβ-1a	80 (22)	66 (18)	70 (20)	76 (22)
IFNβ-1b	43 (12)	42 (12)	39 (11)	33 (9)
Natalizumab	6 (2)	2 (<1)	6 (2)	2 (<1)
GA	1 (<1)	1 (<1)	3 (<1)	1 (<1)

Annualized Relapse Rate (Primary Endpoint)

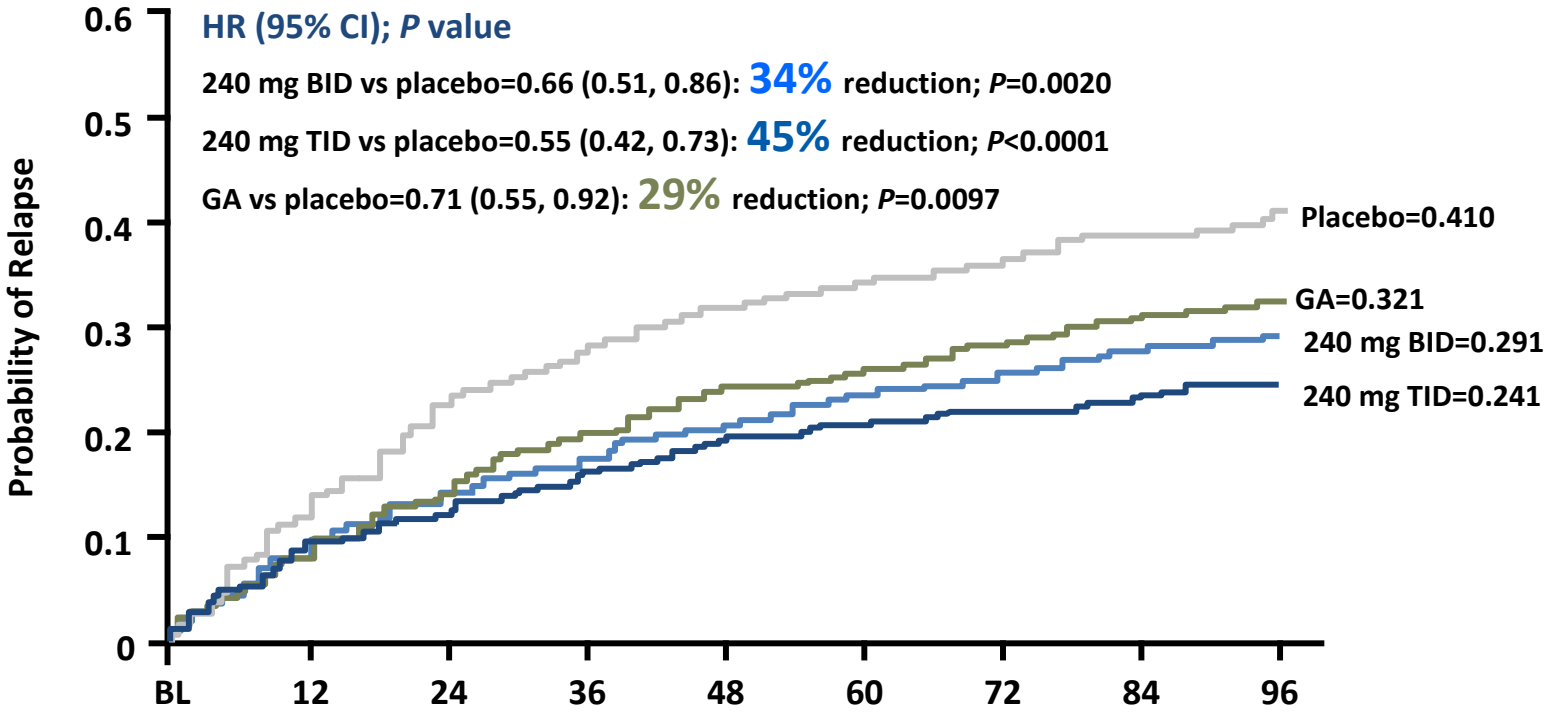


*ARR calculated with negative binomial regression, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40 years), region, and number of relapses in the year prior to study entry.

Annualized Relapse Rate by Year



Time to First Relapse (Proportion of Patients Relapsed, INEC Confirmed)



Patients at Risk, n

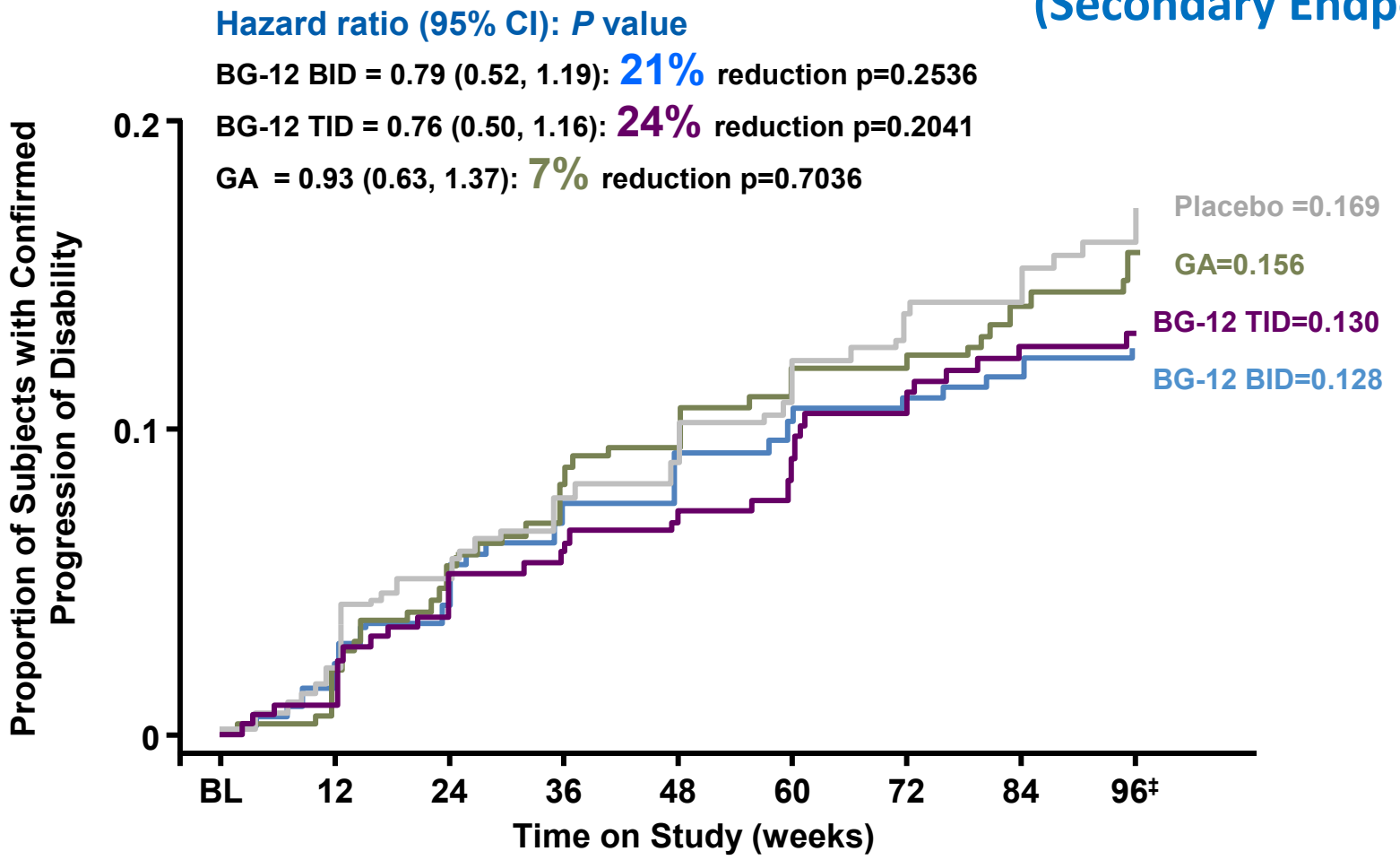
Placebo	363	311	265	243	220	201	188	177	122
240 mg BID	359	304	274	256	241	228	219	210	127
240 mg TID	345	292	269	249	235	229	220	210	143
GA	350	308	281	257	237	229	218	206	156

INEC=Independent Neurology Evaluation Committee; HR=hazard ratio; ; CI=confidence interval; BID=twice daily; TID=three times daily; GA=glatiramer acetate; BL=baseline.

Fox R, et al. Presented at AAN 2012, New Orleans, LA, USA. S001.003.

Time to 12-Week Confirmed Disability Progression

(Secondary Endpoint)



Patients at Risk									
240 mg BID	363	339	317	297	273	254	235	228	205*
240 mg TID	359	323	302	283	270	263	257	249	220*
GA	345	309	287	277	269	262	249	238	222*
	350	326	307	291	279	269	262	249	231*

*Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit).

Time to 24-Week Confirmed Disability Progression

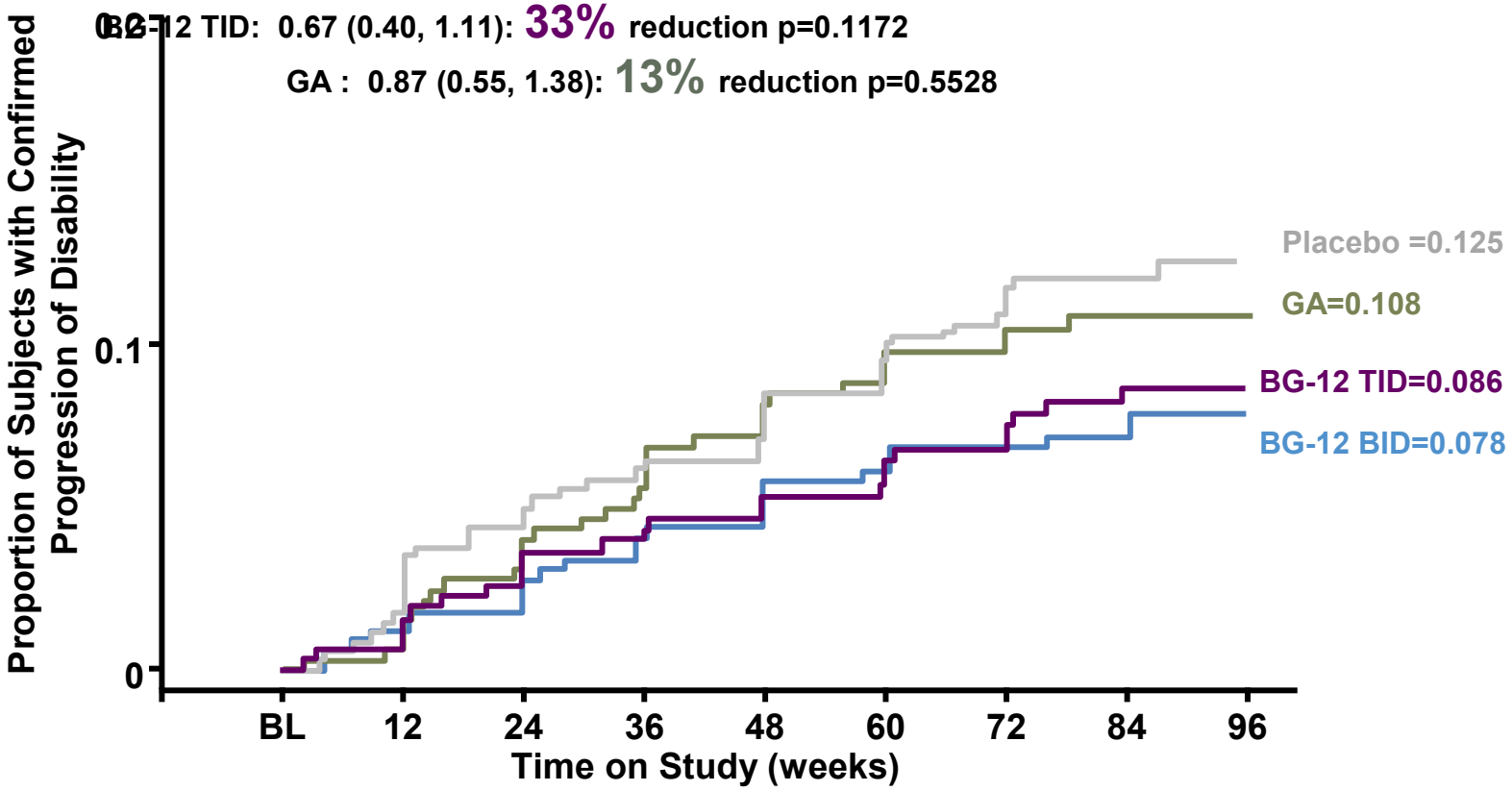
(Sensitivity Analysis)

Hazard ratio (95% CI): *P* value

BG-12 BID: 0.62 (0.37, 1.03): 38% reduction p =0.0630

BG-12 TID: 0.67 (0.40, 1.11): 33% reduction p=0.1172

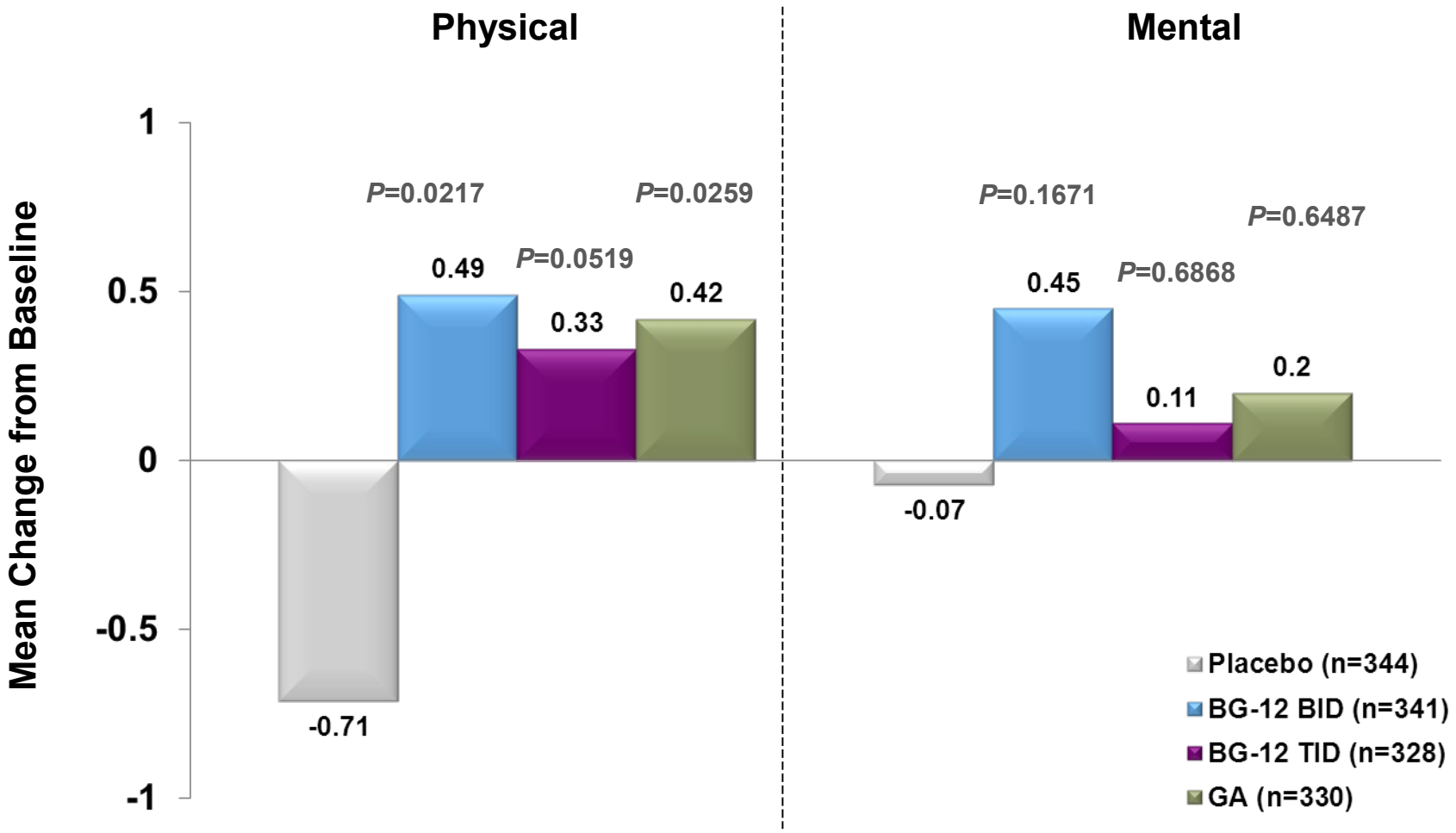
GA : 0.87 (0.55, 1.38): 13% reduction p=0.5528



Patients at Risk									
BG-12BID	359	325	308	291	277	272	266	258	220*
BG-12TID	345	309	290	280	273	268	255	242	222*
GA	350	328	312	297	284	274	265	252	231*

*Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit).

SF-36 Physical and Mental Components:
(Mean Change from Baseline)



*Higher score is more favorable

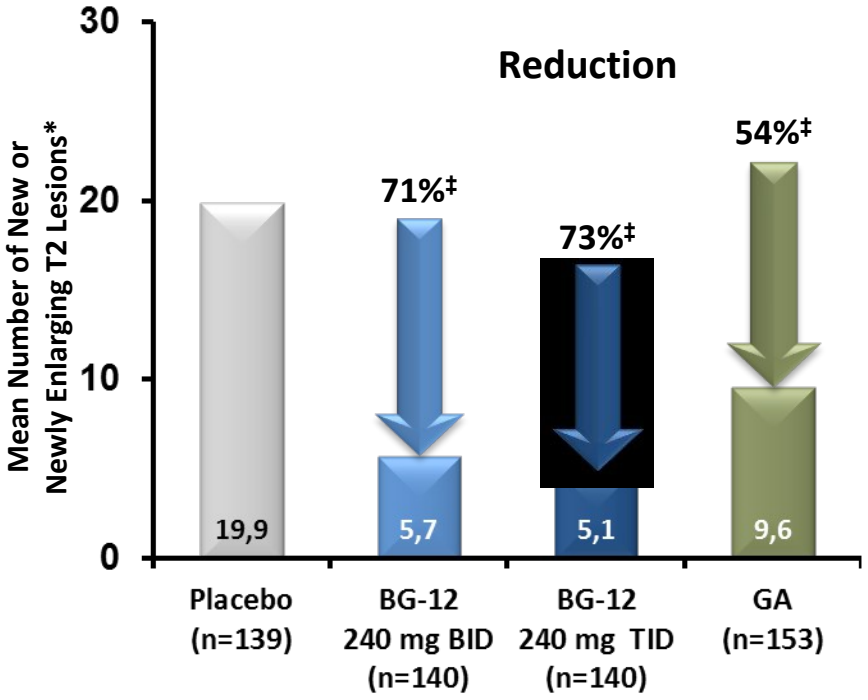
Summary of Key Efficacy Endpoints

- Both doses of BG-12 significantly improved clinical disease activity over time by reducing
  - ARR by 44% BID and 51%TID
  - Proportion of patients relapsed by 34% BID and 45% TID
  - Risk of 12-week sustained disability progression by 21% BID and 24% TID
- Consistent, positive treatment effects were seen in a broad patient population
- Treatment effects were seen early and maintained over the course of the study
- GA vs placebo at 2 years reduced
  - ARR by 29%
  - Proportion of patients relapsed by 29%
  - Accumulation of disability progression by 7%

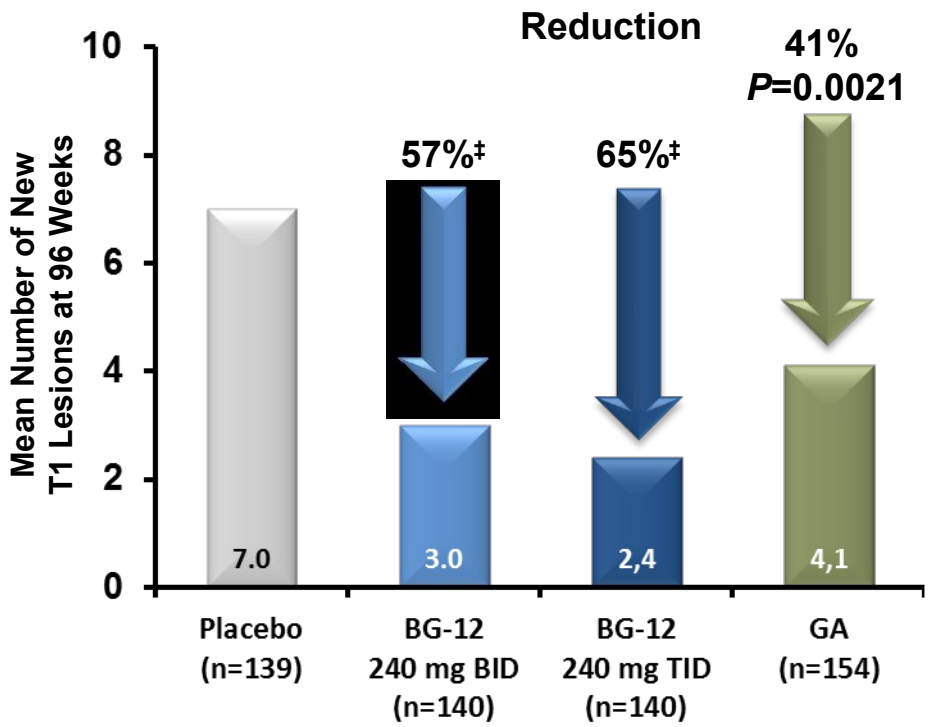
ARR=annualized relapse rate; BID=twice daily; TID=three times daily; GA=glatiramer acetate.

CONFIRM: MRI Results (Secondary Endpoints)

New or Newly Enlarging T2-Hyperintense Lesions at 2 Years*

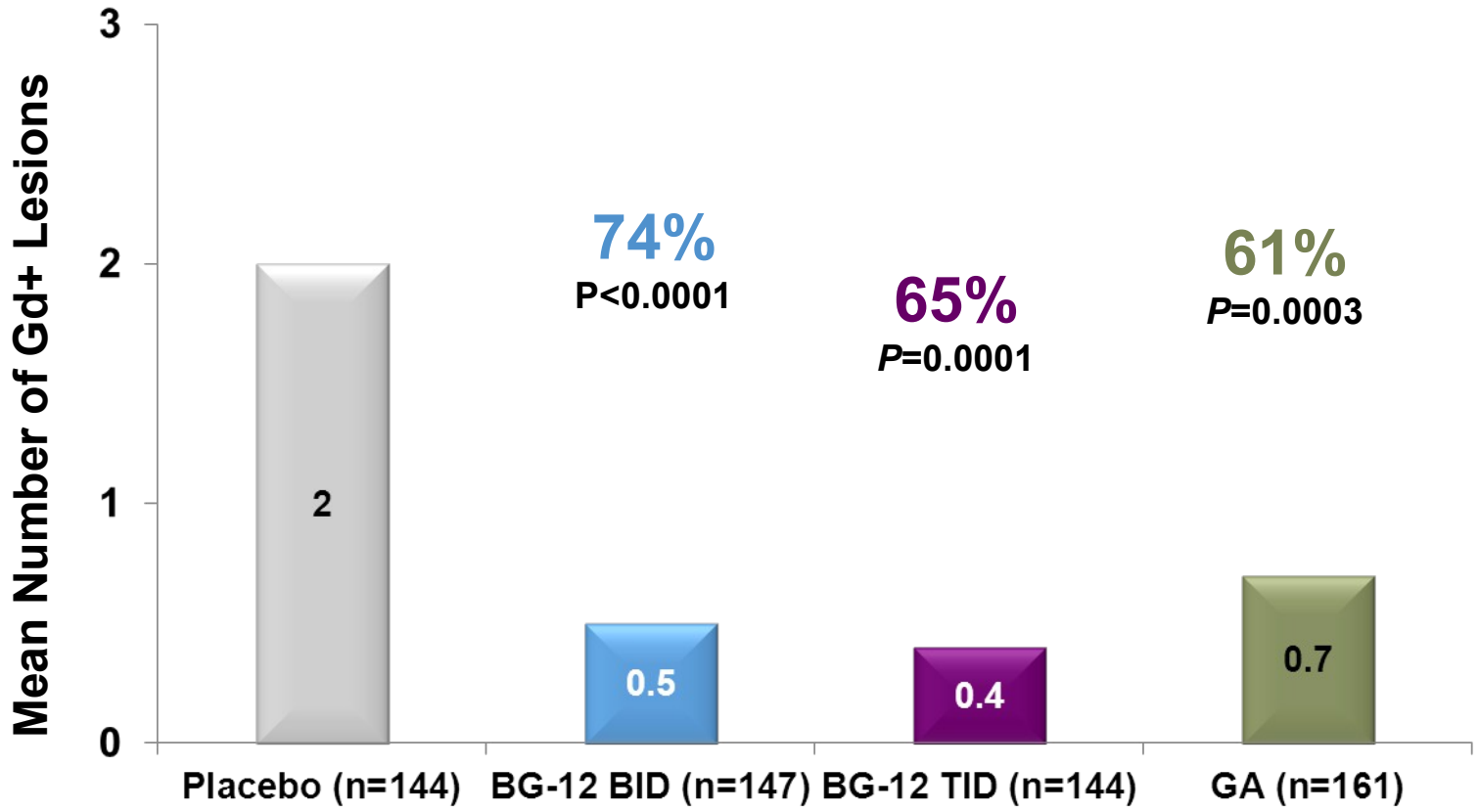


T1-Hypointense Lesions at 2 Years†



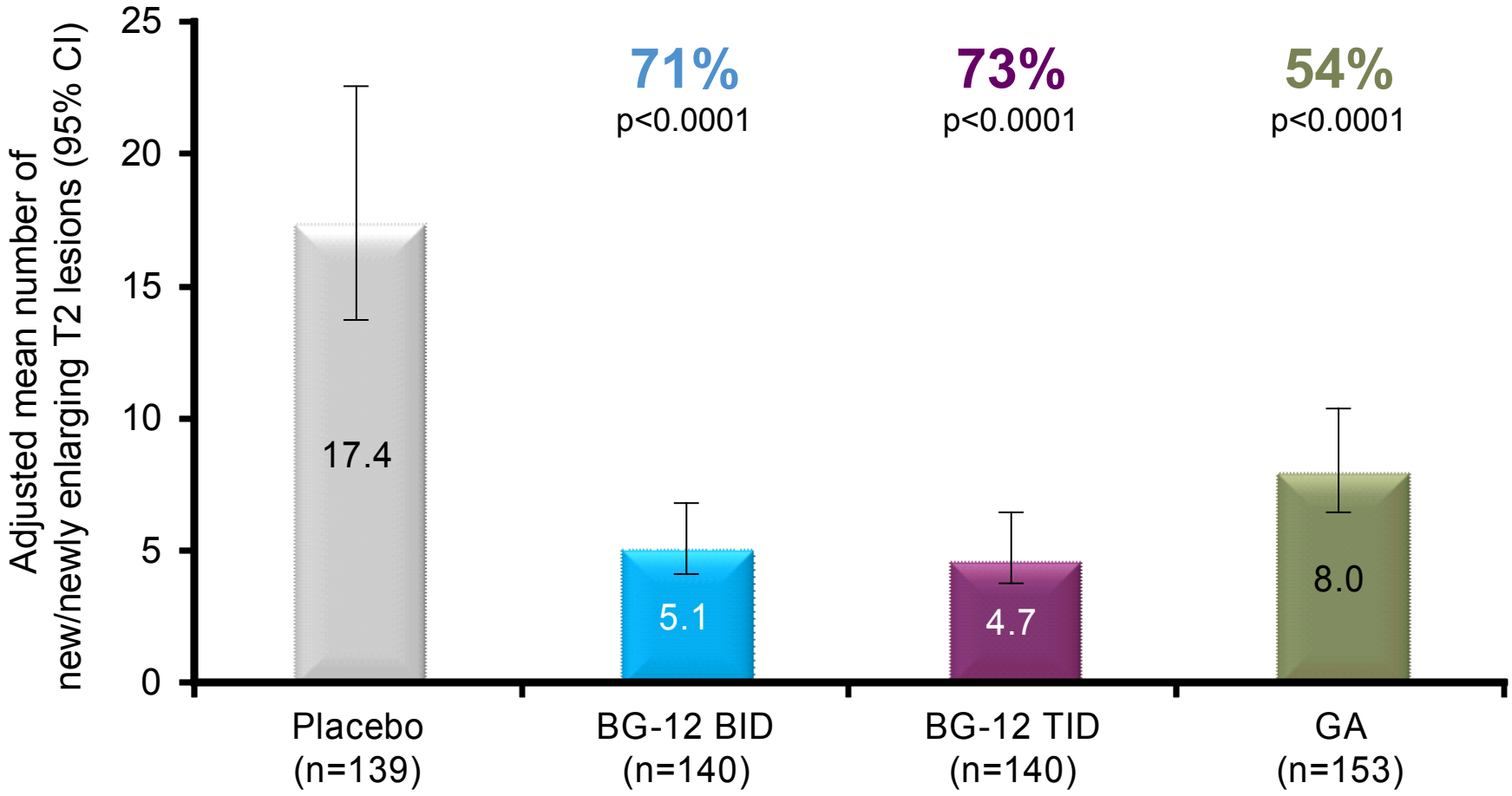
*Negative binomial regression analysis, adjusted for region and baseline T2 lesion volume; †Negative binomial regression analysis, adjusted for region and baseline T1 lesion volume; ‡*P*<0.0001 vs placebo;
MRI=magnetic resonance imaging; BID=twice daily; TID=three times daily; GA=glatiramer acetate.; Miller D, et al. Presented at AAN, 2012, New Orleans, LA, USA. S11.001.

Gd+ Lesions at 2 Years
(Tertiary Endpoint)



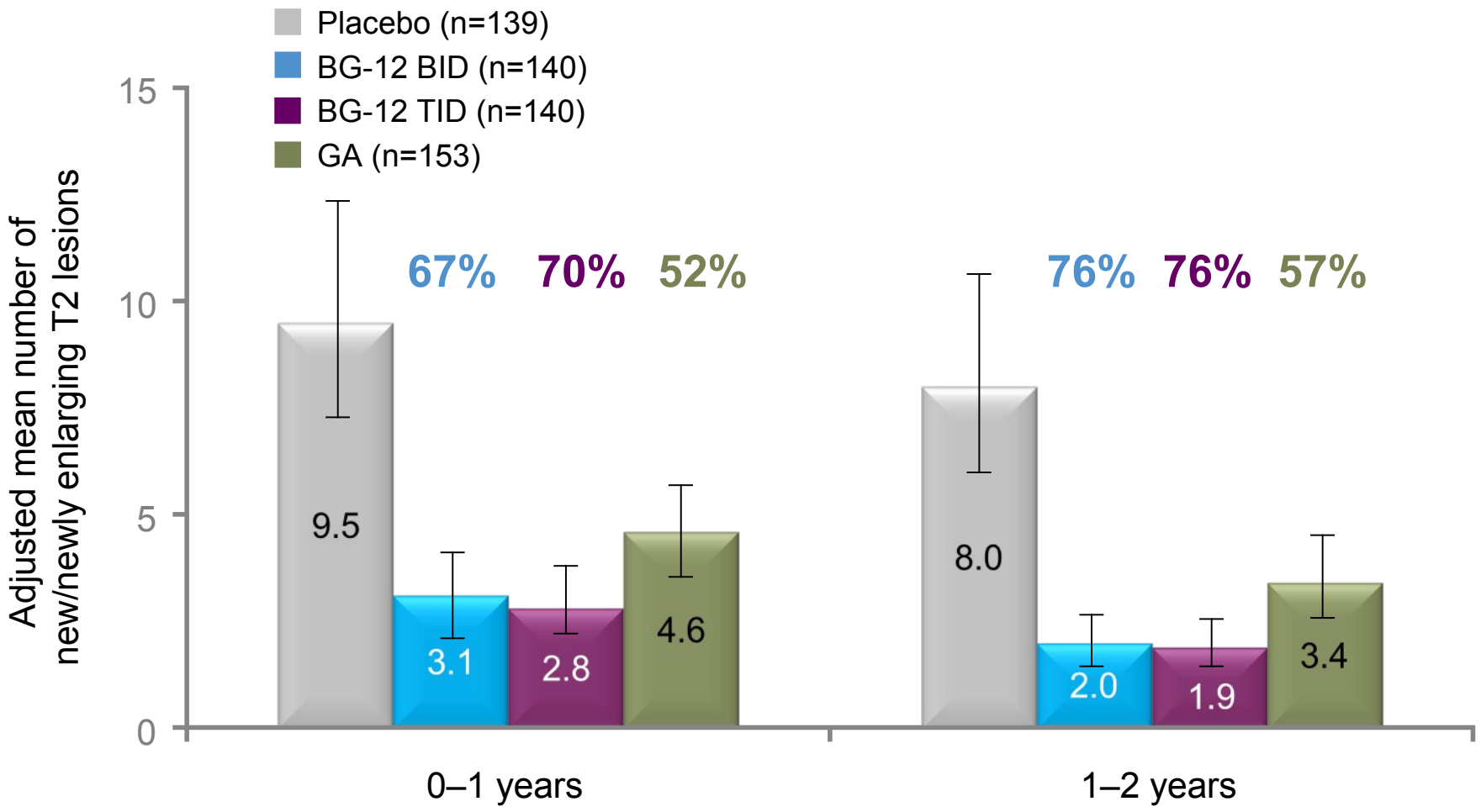
p-values are for comparisons vs placebo, based on ordinal logistic regression analysis, adjusted for region and baseline number of Gd+ lesions. Percentages are the reduction in odds of having greater Gd+ lesion activity, compared to placebo.

New or Newly Enlarging T2 Hyperintense Lesions Over 2 Years



p-values are for comparisons vs placebo, based on negative binomial regression analysis, adjusted for region and baseline T2 lesion volume.

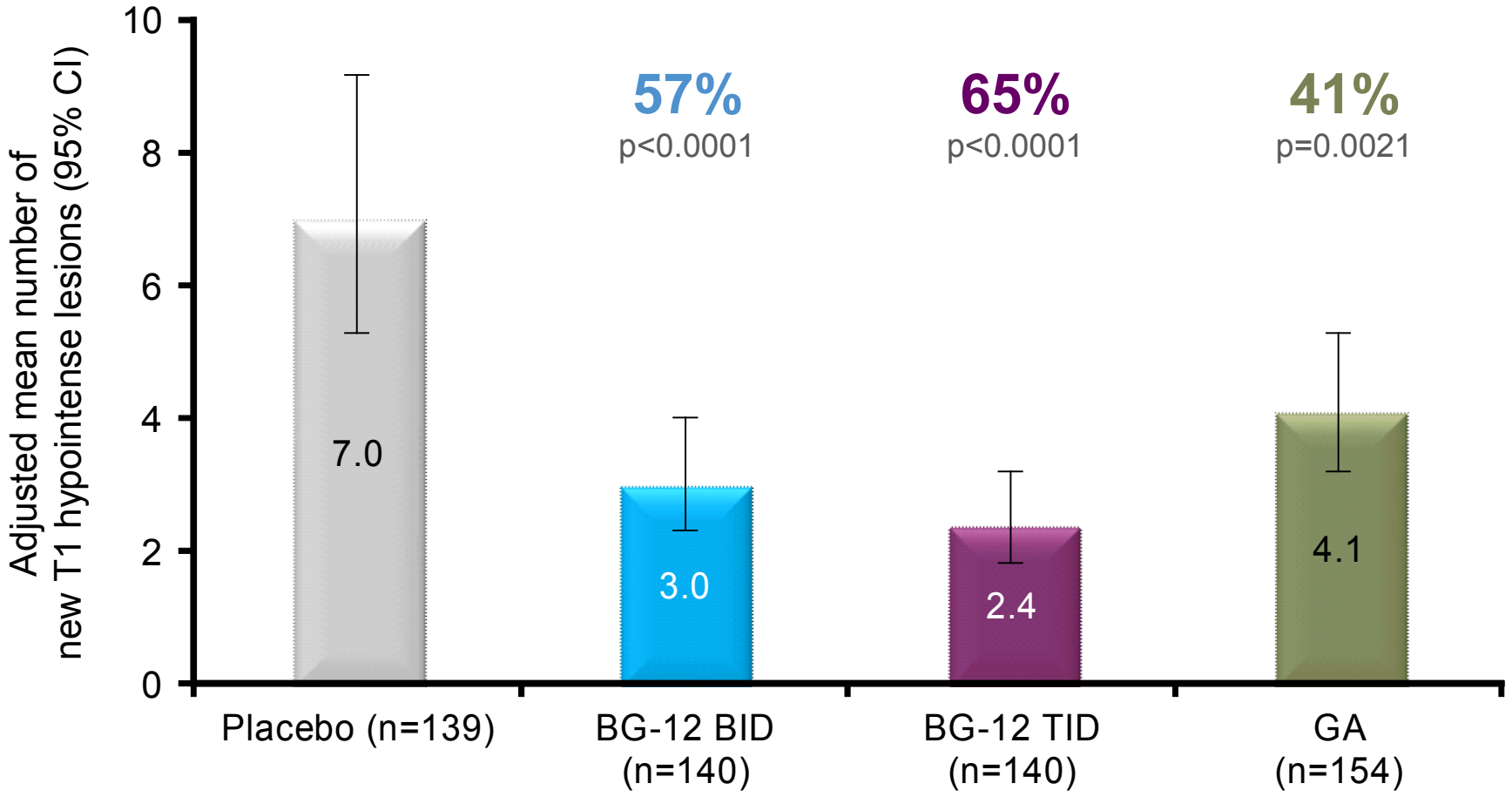
New or Newly Enlarging T2 Hyperintense Lesions By Year



All p values were <0.0001

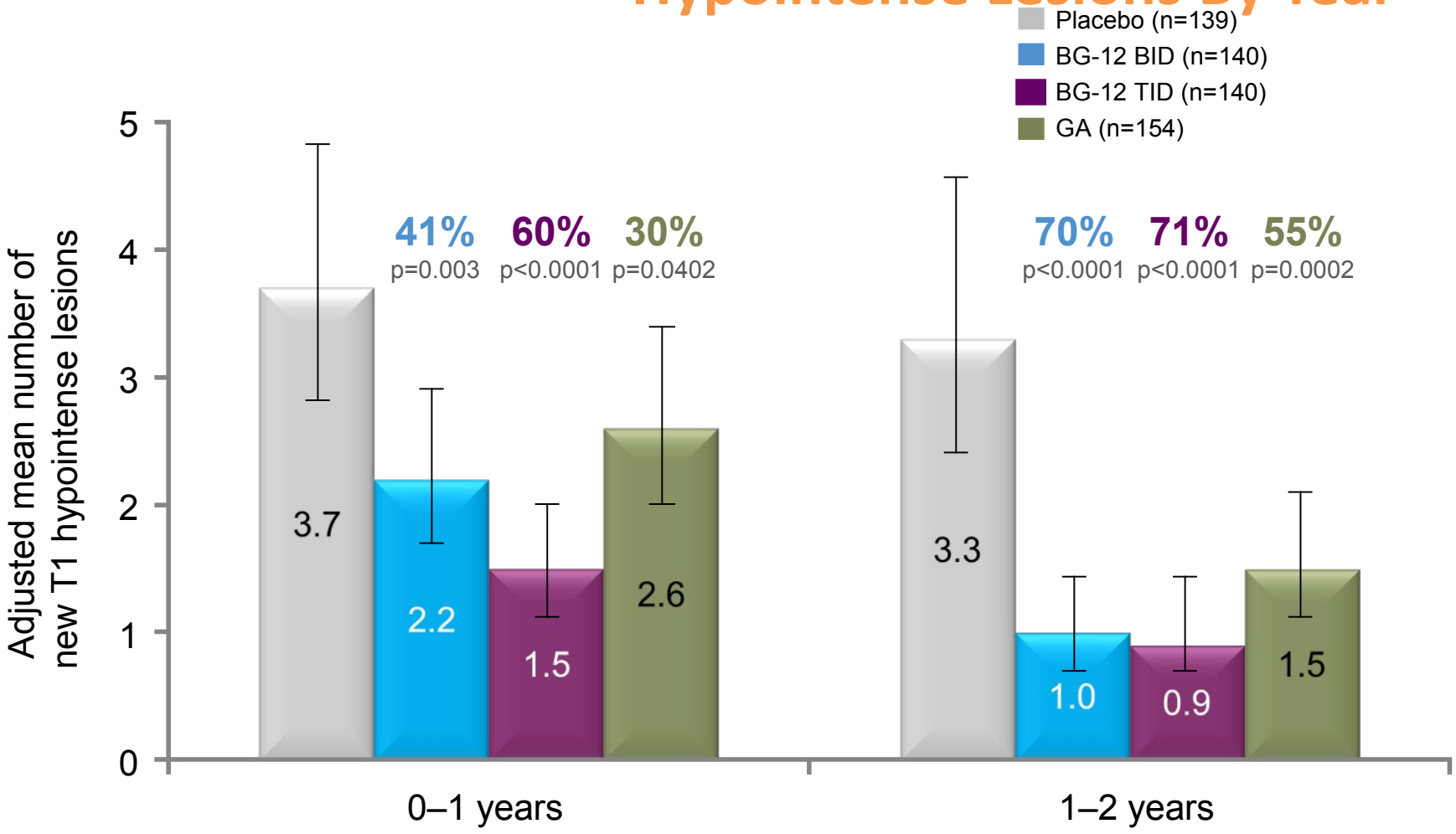
p-values are for comparisons vs placebo, based on negative binomial regression analysis, adjusted for region and baseline T2 lesion volume.

New (Non-enhancing) T1 Hypointense Lesions Over 2 Years



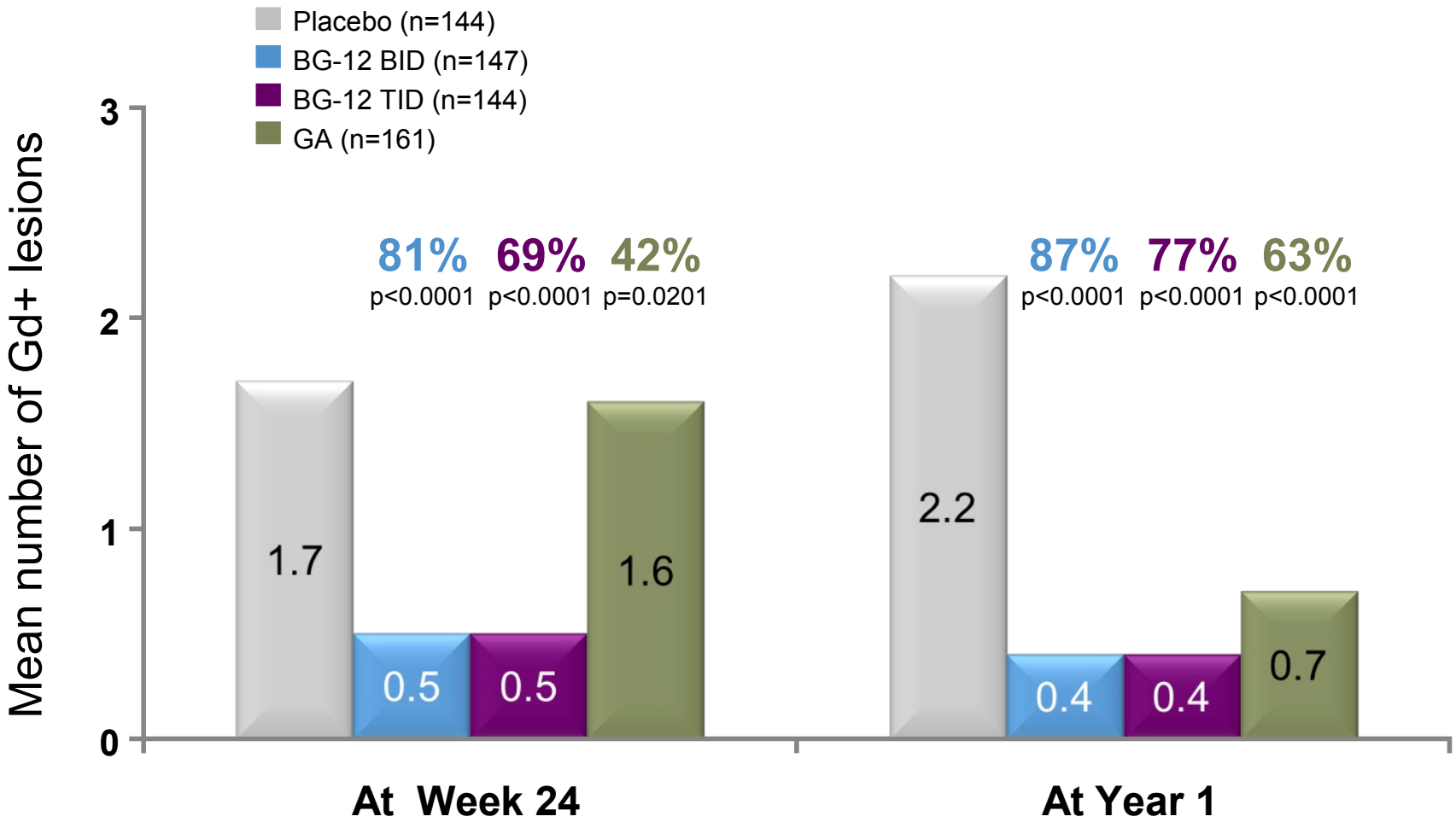
p-values are for comparisons vs placebo, based on negative binomial regression analysis, adjusted for region and baseline T1 lesion volume.

New (Non-enhancing) T1 Hypointense Lesions By Year



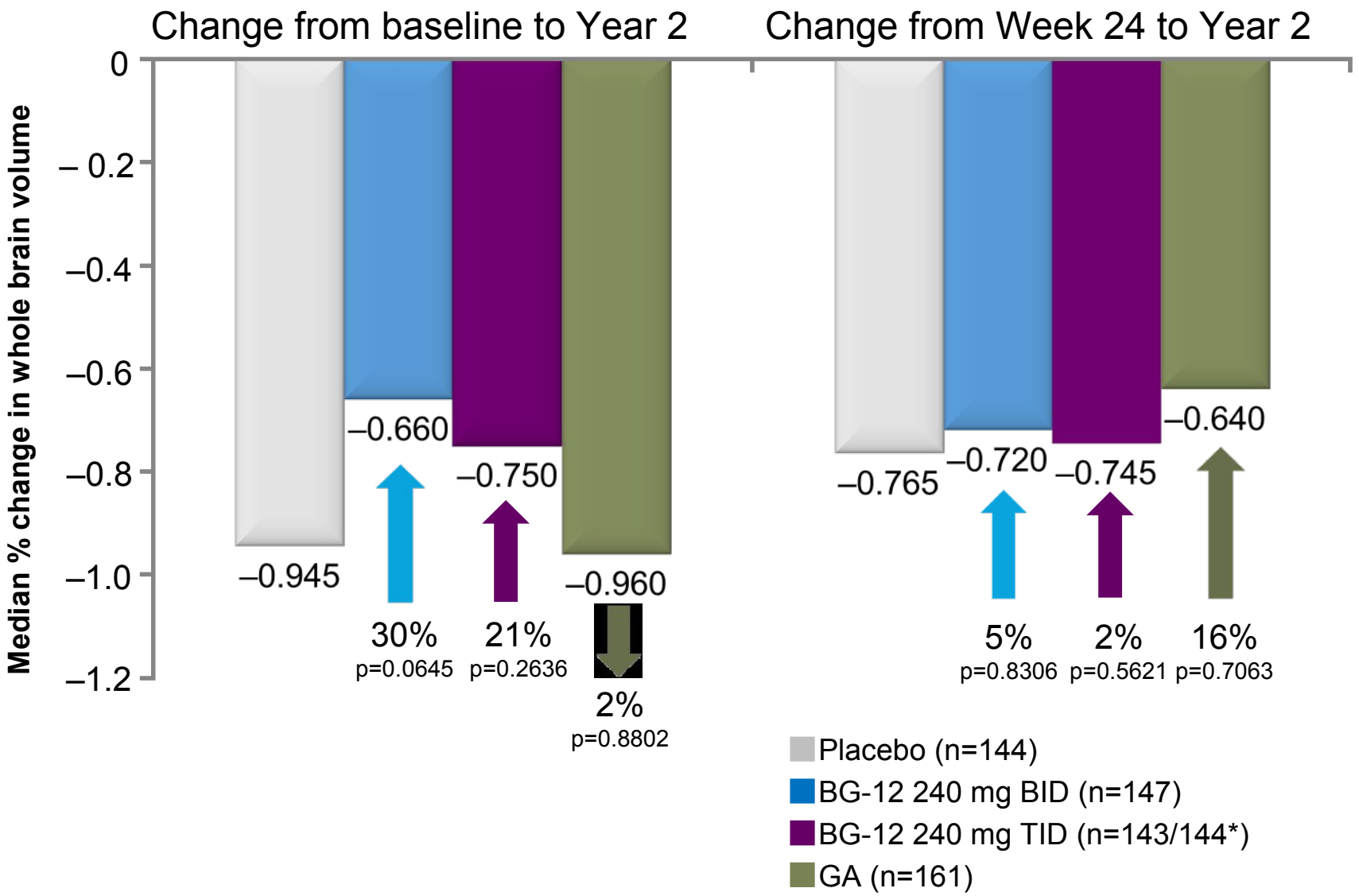
p-values are for comparisons vs placebo, based on negative binomial regression analysis, adjusted for region and baseline T1 lesion volume.

Gd+ Lesions At 24 Weeks and 1 Year



p-values are for comparisons vs placebo, based on ordinal logistic regression analysis, adjusted for region and baseline number of Gd+ lesions.
Percentages are the reduction in odds of having greater Gd+ lesion activity, compared to placebo.

Brain Atrophy (% Change in Whole Brain Volume)



CONFIRM: in breve

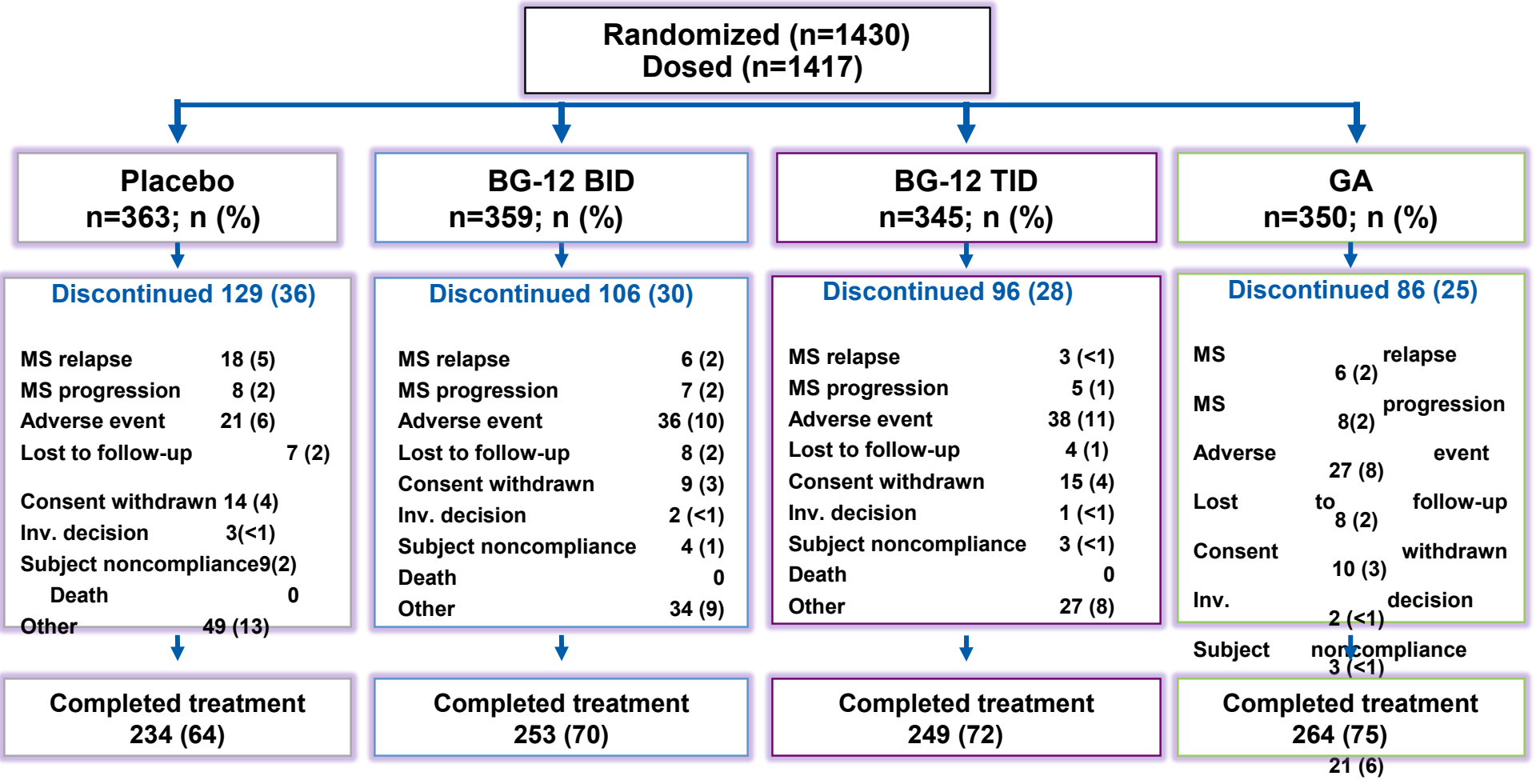
- BG-12 conferma una significativa attività nel ridurre le ricadute cliniche (circa 50%) e l'attività infiammatoria alla RM (nuove lesioni T2: 71%-73%)
- La prevenzione delle nuove lesioni ipointense in T1 (57%-65%) e il trend di riduzione dell'atrofia cerebrale (30%-21%) sono in linea col potenziale effetto neuroprotettivo
- Il profilo di sicurezza è in linea con i dati del DEFINE
- Non sono confermati I dati sulla EDSS
    - La proporzione di pazienti nel gruppo PL che progrediscono sulla EDSS è inferiore nel CONFIRM (17%) rispetto al DEFINE (27%)

Summary of MRI Results

Both doses of BG-12 reduced:

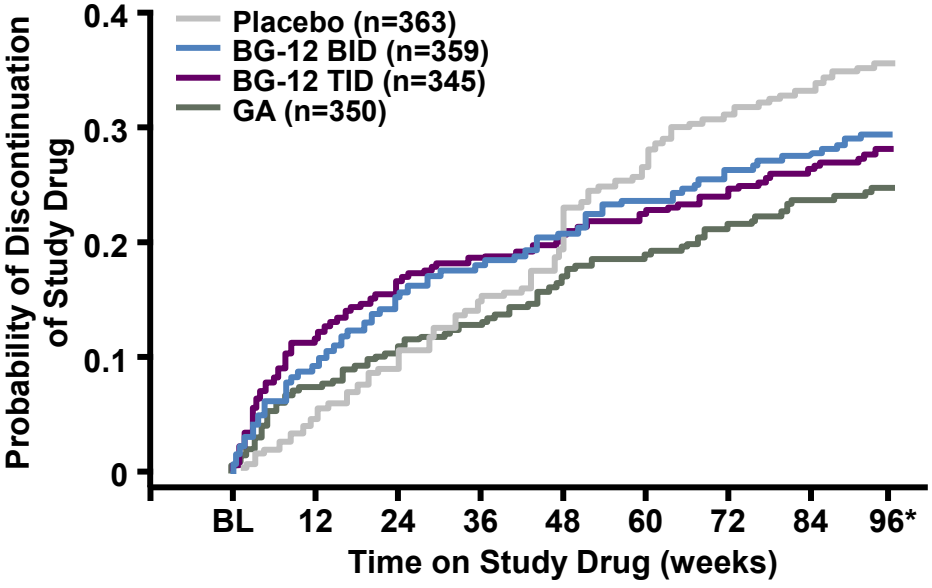
- New or newly enlarging T2 lesions by 71% (BID) and 73% (TID) at 2 years
- New T1 hypointense lesions by 57% (BID) and 65% (TID)
- Gd+ lesions by 74% (BID) and 65% (TID) at 2 years
- Brain atrophy by 30% (BID) and 21% (TID) at 2 years (NS)
- GA also reduced the number of new or newly enlarging T2, and the number of T1 hypointense and Gd+ lesions

Treatment Discontinuation



Time to Discontinuation and Withdrawal (ITT)

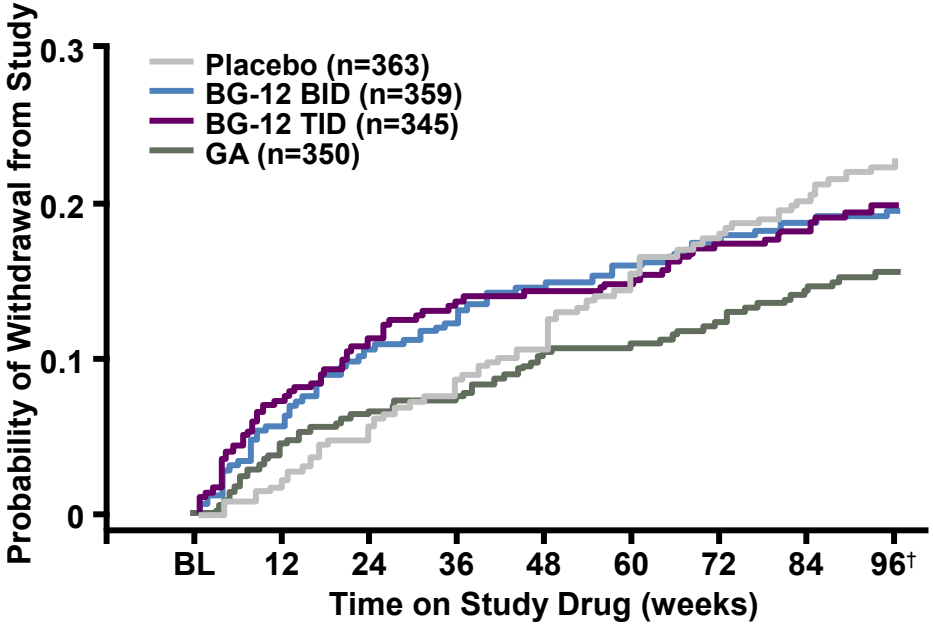
Drug Discontinuation



Number of Patients at Risk

Placebo	363	347	327	311	290	266	251	243	113
BG-12 BID	359	326	305	294	285	275	267	261	111
BG-12 TID	345	305	291	281	275	269	262	254	124
GA	350	324	313	305	292	285	277	268	130

Study Withdrawal



Number of Patients at Risk

Placebo	363	357	343	333	321	308	299	290	204
BG-12 BID	359	339	322	313	307	302	295	292	200
BG-12 TID	345	320	306	298	296	294	285	282	199
GA	350	337	328	325	314	312	307	299	231

Note: Missing/partial dates of last dose were imputed. *Numbers at risk 5 days prior to week 96 (earlier window of week 96 visit) are 217, 226, 230, and 247 for placebo, BG-12 240 mg BID, TID, and GA group, respectively. †Numbers at risk 5 days prior to week 96 (earlier window of week 96 visit) are 272, 271, 265, and 285 for placebo, BG-12 240 mg BID, TID, and GA group, respectively.

Safety Summary

- Overall the incidence of AEs, SAEs, discontinuations due to AEs, was similar across the 4 treatment groups
- The most common events with BG-12 were flushing and GI events.
  - Incidence was highest during the first month of the study, decreased during the second month, and was low (<1% for individual events) for the remainder of the study
- There was WBC and lymphocyte counts decrease with BG-12 but values remained within normal limits. There were no serious infections reported in patients with lymphocyte counts $<0.50 \times 10^9/L$.
- No increased risk of serious infections or malignancies was observed with BG-12

CONFIRM: Common AEs in ≥5% of Subjects in Any Group

Event, n (%)	Placebo (n=363)	BG-12 240 mg BID (n=359)	BG-12 240 mg TID (n=344)	GA (n=351)
Patients with any event	333 (92)	338 (94)	316 (92)	304 (87)
MS relapse	155 (43)	110 (31)	85 (25)	119 (34)
Flushing*	13 (4)	110 (31)	83 (24)	6 (2)
Nasopharyngitis	58 (16)	62 (17)	63 (18)	51 (15)
Headache	49 (13)	52 (14)	46 (13)	46 (13)
Diarrhea*	28 (8)	45 (13)	50 (15)	14 (4)
Urinary tract infection	42 (12)	52 (14)	41 (12)	46 (13)
Nausea*	29 (8)	40 (11)	51 (15)	15 (4)
Upper respiratory tract infection*	34 (9)	36 (10)	47 (14)	27 (8)
Back pain	33 (9)	35 (10)	36 (10)	32 (9)
Fatigue	33 (9)	37 (10)	33 (10)	30 (9)
Abdominal pain, upper*	17 (5)	36 (10)	33 (10)	4 (1)
Proteinuria	25 (7)	29 (8)	35 (10)	30 (9)
Abdominal pain	15 (4)	27 (8)	26 (8)	4 (1)
Rash	13 (4)	24 (7)	28 (8)	8 (2)

*Shading indicates any group ≥3 percentage points higher than the placebo group.
AE=adverse event; BID=twice daily; TID=three times daily; GA=glatiramer acetate; MS=multiple sclerosis.
Phillips JT, et al. Presented at AAN, 2012, New Orleans, LA, USA. S41.005.

CONFIRM: Common AEs in ≥5% of Subjects in Any Group (cont.)

Event, n (%)	Placebo (n=363)	BG-12 240 mg BID (n=359)	BG-12 240 mg TID (n=344)	GA (n=351)
Vomiting*	13 (4)	25 (7)	23 (7)	8 (2)
Arthralgia	26 (7)	20 (6)	27 (8)	17 (5)
Pain in extremity	29 (8)	21 (6)	26 (8)	21 (6)
Influenza	22 (6)	20 (6)	25 (7)	15 (4)
Pruritus*	11 (3)	20 (6)	24 (7)	7 (2)
Paraesthesia	31 (9)	21 (6)	21 (6)	15 (4)
Depression	35 (10)	24 (7)	15 (4)	30 (9)
ALT increased	25 (7)	16 (4)	22 (6)	20 (6)
Erythema*	5 (1)	16 (4)	21 (6)	6 (2)
Hot flush*	8 (2)	18 (5)	19 (6)	4 (1)
Albumin urine present	15 (4)	22 (6)	14 (4)	18 (5)
Bronchitis	14 (4)	14 (4)	22 (6)	16 (5)
Pyrexia	19 (5)	11 (3)	25 (7)	17 (5)
Sinusitis	11 (3)	18 (5)	18 (5)	11 (3)

*Shading indicates any group ≥3 percentage points higher than the placebo group.
AE=adverse event; BID=twice daily; TID=three times daily; GA=glatiramer acetate; ALT=alanine aminotransferase
Phillips JT, et al. Presented at AAN, 2012, New Orleans, LA, USA. S41.005.

CONFIRM: Common AEs in ≥5% of Subjects in Any Group (cont.)

Event, n (%)	Placebo (n=363)	BG-12 240 mg BID (n=359)	BG-12 240 mg TID (n=344)	GA (n=351)
Cough	17 (5)	16 (4)	18 (5)	9 (3)
Muscle spasms	14 (4)	13 (4)	21 (6)	8 (2)
Microalbuminuria	13 (4)	14 (4)	19 (6)	15 (4)
Oropharyngeal pain	14 (4)	12 (3)	21 (6)	15 (4)
Hypoaesthesia	21 (6)	11 (3)	19 (6)	16 (5)
Dyspepsia	8 (2)	12 (3)	16 (5)	6 (2)
Insomnia	18 (5)	15 (4)	10 (3)	13 (4)
Protein urine present	10 (3)	18 (5)	7 (2)	15 (4)
Vertigo	22 (6)	9 (3)	13 (4)	15 (4)
Injection-site erythema*	0	0	0	31 (9)
Injection-site pain*	0	0	0	29 (8)

*Shading indicates any group ≥3 percentage points higher than the placebo group.
AE=adverse event; BID=twice daily; TID=three times daily; GA=glatiramer acetate.
Phillips JT, et al. Presented at AAN, 2012, New Orleans, LA, USA. S41.005.

Serious AEs
≥2 Subjects in Any Treatment Group

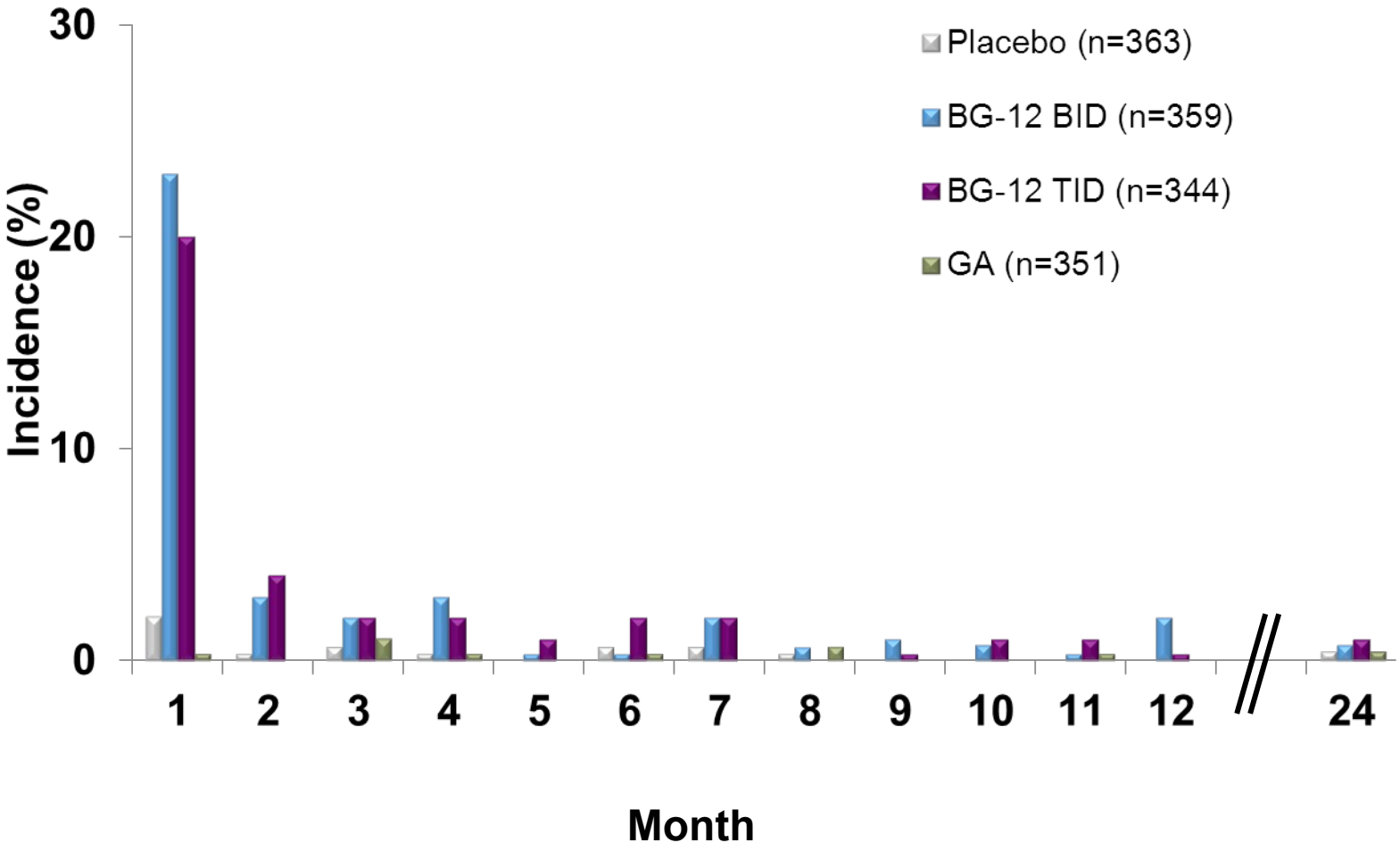
	Placebo (n=363)	BG-12 BID (n=359)	BG-12 TID (n=344)	GA (n=351)
Number (%) with SAE	79 (22)	61 (17)	54 (16)	60 (17)
MS relapse	51 (14)	39 (11)	30 (9)	36 (10)
Gastroenteritis	0	2 (<1)	2 (<1)	0
Cellulitis	0	2 (<1)	1 (<1)	0
Urinary tract infection	0	1 (<1)	1 (<1)	0
Pneumonia	1 (<1)	0	0	2 (<1)
Abdominal pain	0 (0)	2 (<1)	0	0
Vomiting	1 (<1)	1 (<1)	1 (<1)	0
Back pain	0	2 (<1)	0 (0)	0
Muscle strain	0	0 (0)	2 (<1)	0
Anaphylactic reaction	0	0	0	2 (<1)
Depression	0	0	1 (<1)	2 (<1)
Convulsion	2 (<1)	0	0	0
Abortion spontaneous	2 (<1)	0	0	0

Flushing

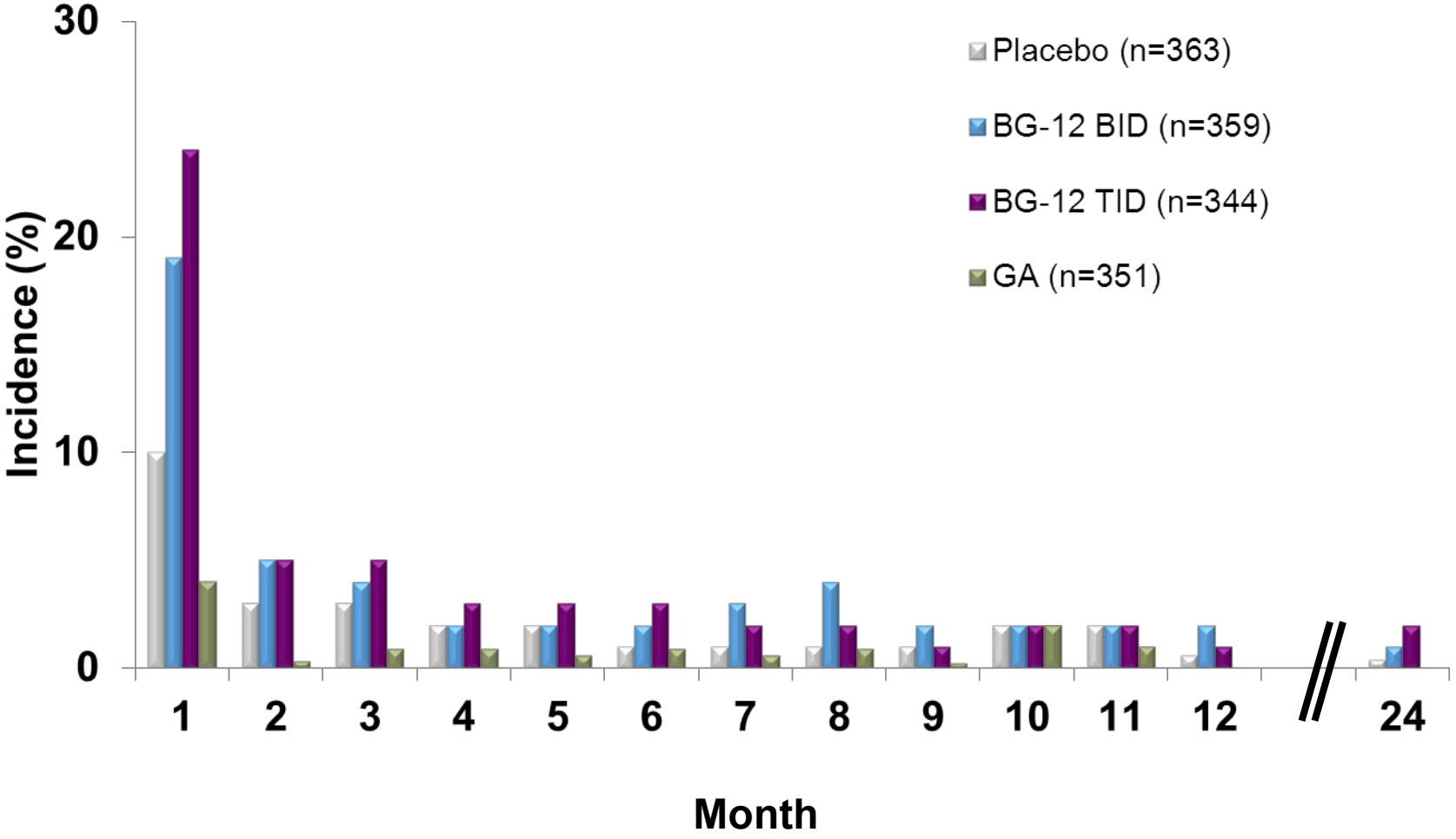
AE, n (%)	Placebo (n=363)	BG-12 BID (n=359)	BG-12 TID (n=344)	GA (n=351)
Flushing or hot flush	**21 (6)**	**124 (35)**	**95 (28)**	**9 (3)**
Flushing	**13 (4)**	**110 (31)**	**83 (24)**	**6 (2)**
Hot flush	**8 (2)**	**18 (5)**	**19 (6)**	**4 (1)**

- The majority of subjects had events that were mild to moderate in severity
- Highest incidence occurred during the first month of treatment
- None of the flushing events were serious

Incidence of Flushing and Hot Flush by Month

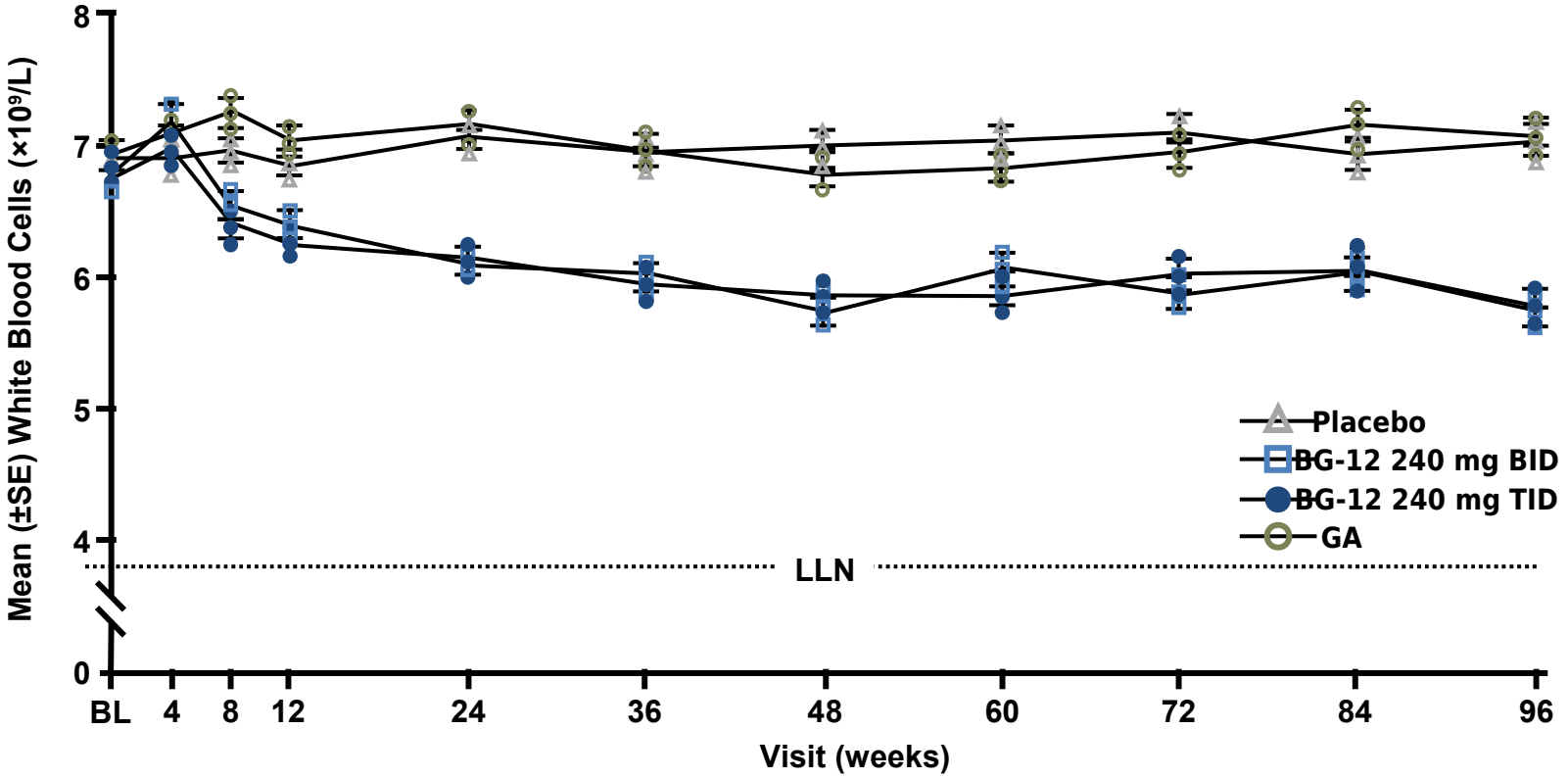


Gastrointestinal Events by Study Month



Gastrointestinal tolerability events were defined using specific Standardized MedDRA Queries

CONFIRM: WBC Counts

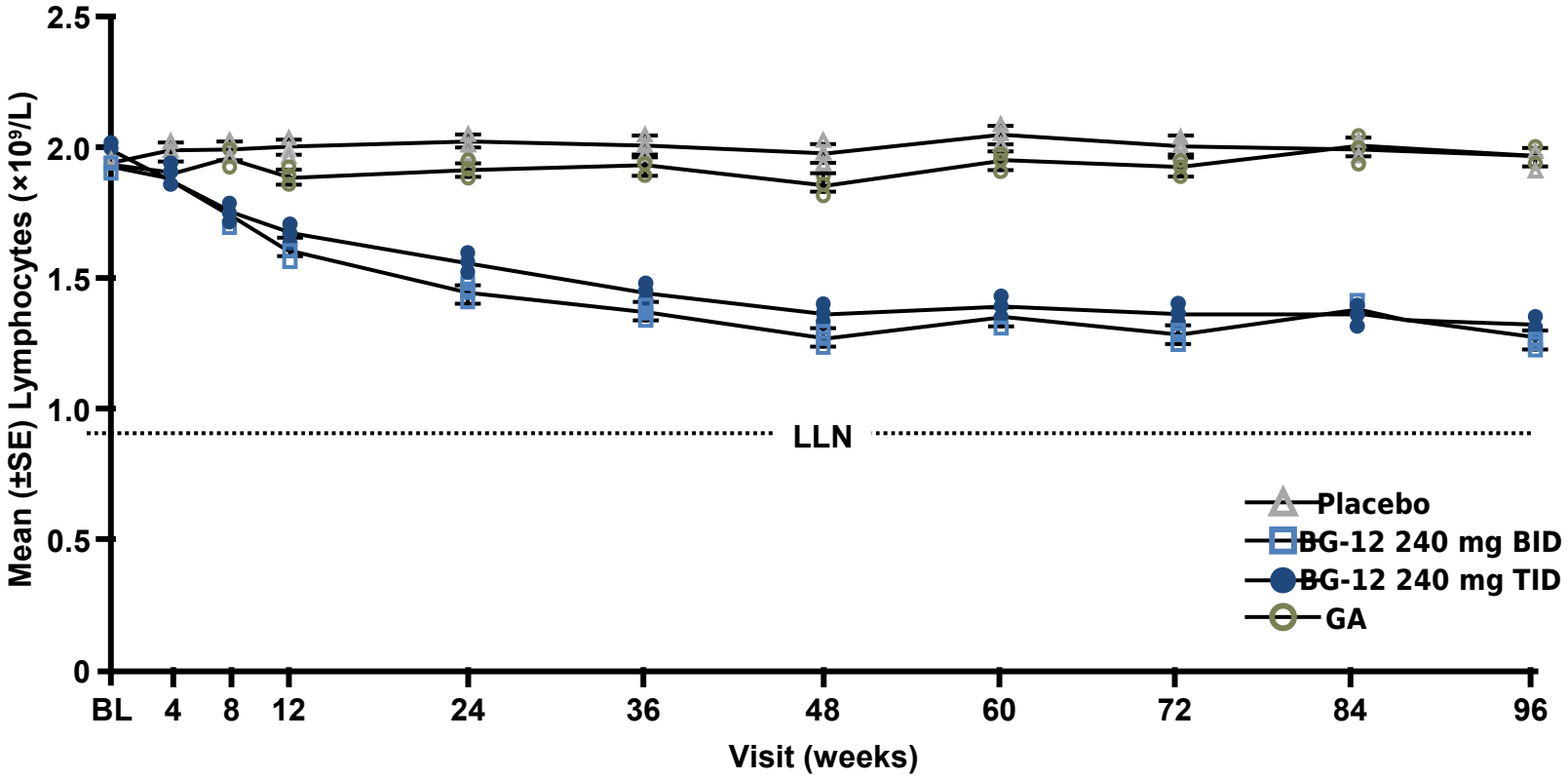


[redacted]

LLN is lower limit of normal in standard units. If there are multiple values of LLN for a given parameter, highest LLN is shown.
WBC=white blood cell; SE=standard error; BID=twice daily; TID=three times daily; GA=glatiramer acetate; BL=baseline.

Phillips JT, et al. Presented at AAN, 2012, New Orleans, LA, USA. S41.005.

CONFIRM: Lymphocytes



Placebo: n=363 (baseline) to 234 (week 96)
BG-12 240 mg BID: n=357 (baseline) to 256 (week 96)
BG-12 240 mg TID: n=342 (baseline) to 237 (week 96)
GA: n=350 (baseline) to 252 (week 96)

LLN is lower limit of normal in standard units. If there are multiple values of LLN for a given parameter, highest LLN is shown.
SE=standard error; BID=twice daily; TID=three times daily; GA=glatiramer acetate; BL=baseline.

Phillips JT, et al. Presented at AAN, 2012, New Orleans, LA, USA. S41.005.

CONFIRM: Infections

- The overall incidence of infection was similar in the placebo and GA treatment groups and slightly higher in both BG-12 groups
  - 50% in the placebo and GA groups
  - 56% in the BG-12 BID and BG-12 TID groups
- The slight differences between the BG-12 and placebo groups were due to differences in the incidences of nasopharyngitis, upper respiratory tract infection, sinusitis, and gastroenteritis.
- The incidence of serious infections was 1.4% in the placebo, 1.1% in the GA, and 1.9% and 2.0%, respectively, in the BG-12 BID and TID groups
- No cases of opportunistic infection in any group were reported

CONFIRM: Infections Reported as SAEs

Event, n (%)	Placebo (n=363)	BG-12 240 mg BID (n=359)	BG-12 240 mg TID (n=344)	GA (n=351)
Patients with any event	5 (1)	7 (2)	7 (2)	4 (1)
Gastroenteritis	0	2 (<1)	2 (<1)	0
Cellulitis	0	2 (<1)	1 (<1)	0
Urinary tract infection	0	1 (<1)	1 (<1)	0
Douglas abscess	0	0	1 (<1)	0
Gastroenteritis, viral	0	0	1 (<1)	0
H1N1 influenza	0	1 (<1)	0	0
Pelvic inflammatory disease	0	0	1 (<1)	0
Pyelonephritis, acute	0	0	1 (<1)	0
Viral infection	0	1 (<1)	0	1 (<1)
Appendicitis	0	0	0	1 (<1)
Pneumonia	1 (<1)	0	0	2 (<1)
Pyothorax	0	0	0	1 (<1)

Borrelia infection, bacterial endocarditis, influenza, sepsis, and tracheitis were each reported by 1 patient, all of whom were in the placebo group.
SAE=serious adverse event; BID=twice daily; TID=three times daily; GA=glatiramer acetate.

CONFIRM: Summary of AEs for BG-12

- Overall the incidence of AEs, serious AEs and discontinuations due to AEs was similar across the four treatment groups
- The most common events with BG-12 were flushing and GI events
  - Incidence was highest during the first month of the study, decreased during the second month, and was low (<2% for individual events) for the remainder of the study
- No increased risk of serious infections or malignancies was observed with BG-12
- There was a decrease in mean WBC and lymphocyte counts with BG-12, but values remained within normal limits. There were no serious infections reported in patients with lymphocyte counts $<0.5\times10^9$/L
- No increased risk of hepatic or renal injury was observed with BG-12 versus placebo

AE=adverse event; BID=twice daily; TID=three times daily; SAE=serious adverse event.

Phillips JT, et al. Presented at AAN, 2012, New Orleans, LA, USA. S41.005.

BG12 e bisogni terapeutici insoddisfatti «Take Home»

- Buon bilancio efficacia/sicurezza
- Convenienza della via di somministrazione
- Buona tollerabilità e accettabilità
- Potenziale attività «neuroprotettiva»
- Efficacia nelle forme progressive ?
- Individualizzazione del trattamento ?

	Fingolimod (FREEDOMS)[14]	Cladribine (CLARITY)[13]	Teriflunomide (TEMSO)[19]	Laquinimod (ALLEGRO)[20]	Laquinimod (BRAVO)[21]	Dimethyl fumarate (DEFINE)[22]
Reduction in annual relapse rate	54%	58%	31%	23%	Not significant (p=0·075); after statistical adjustment, 21% reduction, p=0·026	53%
Absolute reduction in annual relapse rate	0·22	0·19	Not yet reported	0·091	Not yet reported	Not yet reported
Confirmed reduction in EDSS progression	30%	33%	30%	36%	34%	38%
Reduction in number of new or enlarging T2 lesions on MRI	75%	73%	67%	30%	Not yet reported	85%
Reduction in number of gadolinium-enhancing lesions	82%	86%	Not yet reported*	37%	Not yet reported	90%
Disease-free patients in active versus placebo groups	33% versus 13%	44% versus 16%	Not yet reported	Not yet reported	Not yet reported	Not yet reported

Results of phase 3 trials have been reported for cladribine (Movectro, Merck Serono, Geneva, Switzerland) and fingolimod (Gilenya, Novartis, Basel, Switzerland). Phase 3 trials of teriflunomide (Sanofi-Aventis, Paris, France), laquinimod (Teva, Petah Tiqva, Israel), and dimethyl fumarate (Biogen Idec, Weston, MA, USA) have been completed. The data in this table should be interpreted with caution because most have not been peer reviewed yet[19-22] and some of the differences might be related to different patient characteristics or differences in trial methods rather than to differences in treatment effect. Efficacy results for fingolimod 0·5 mg/day, cladribine 3·5 mg/kg, teriflunomide 14 mg/day, laquinimod 0·6 mg/day, and dimethyl fumarate 240 mg twice a day are presented. EDSS=expanded disability status scale. *An additional one patient in four was free of gadolinium-enhancing T1 lesions compared with the placebo group.

Table 1: **Completed placebo-controlled phase 3 trials of oral treatments for patients with multiple sclerosis**

Grazie!

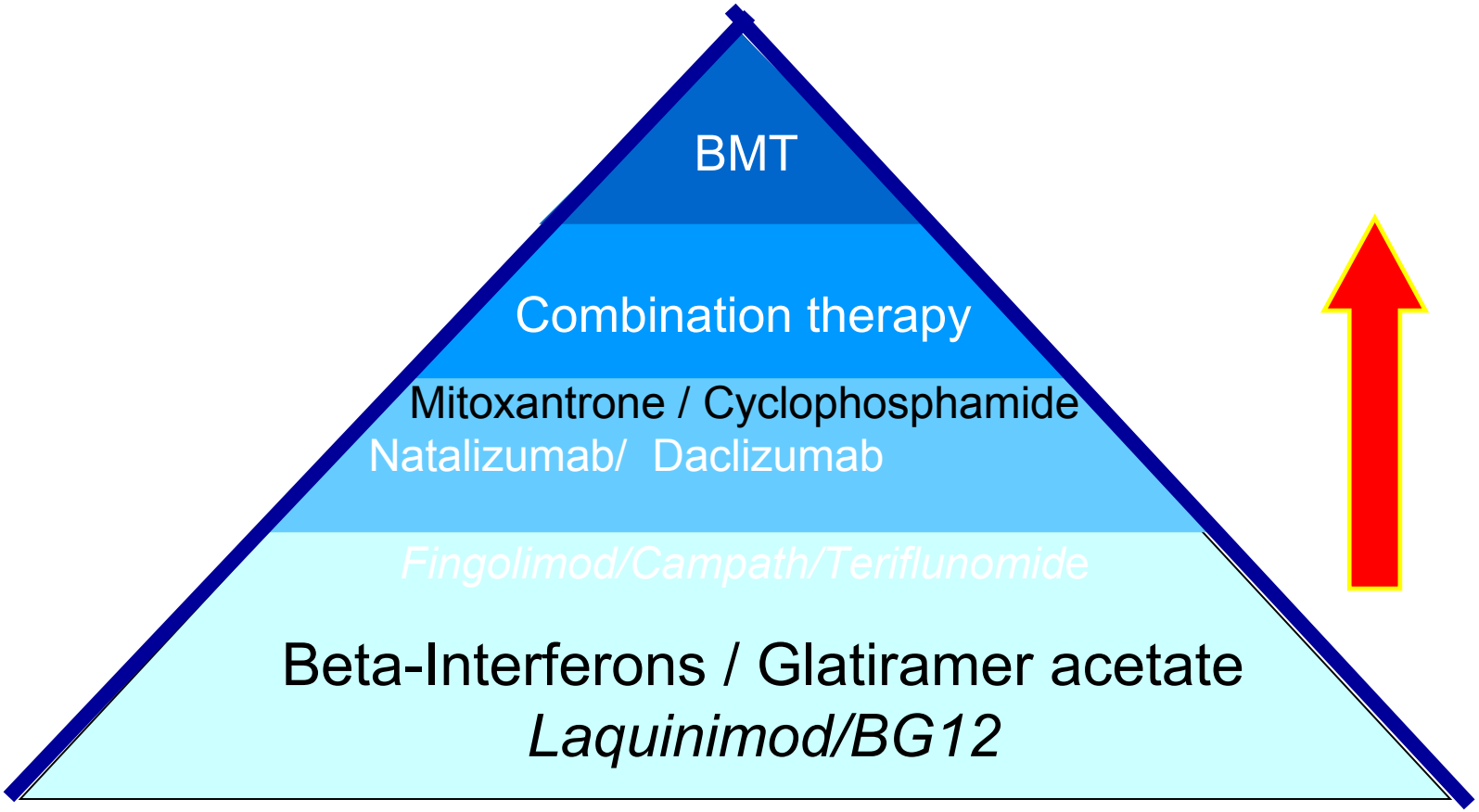
«…There remains a considerable unmet need

for safe treatment options that are more effective than current first-line agents and are appropriate for a large spectrum of patients with MS. Further exploration of the mechanism of action of BG-12 may help to guide future clinical studies.»

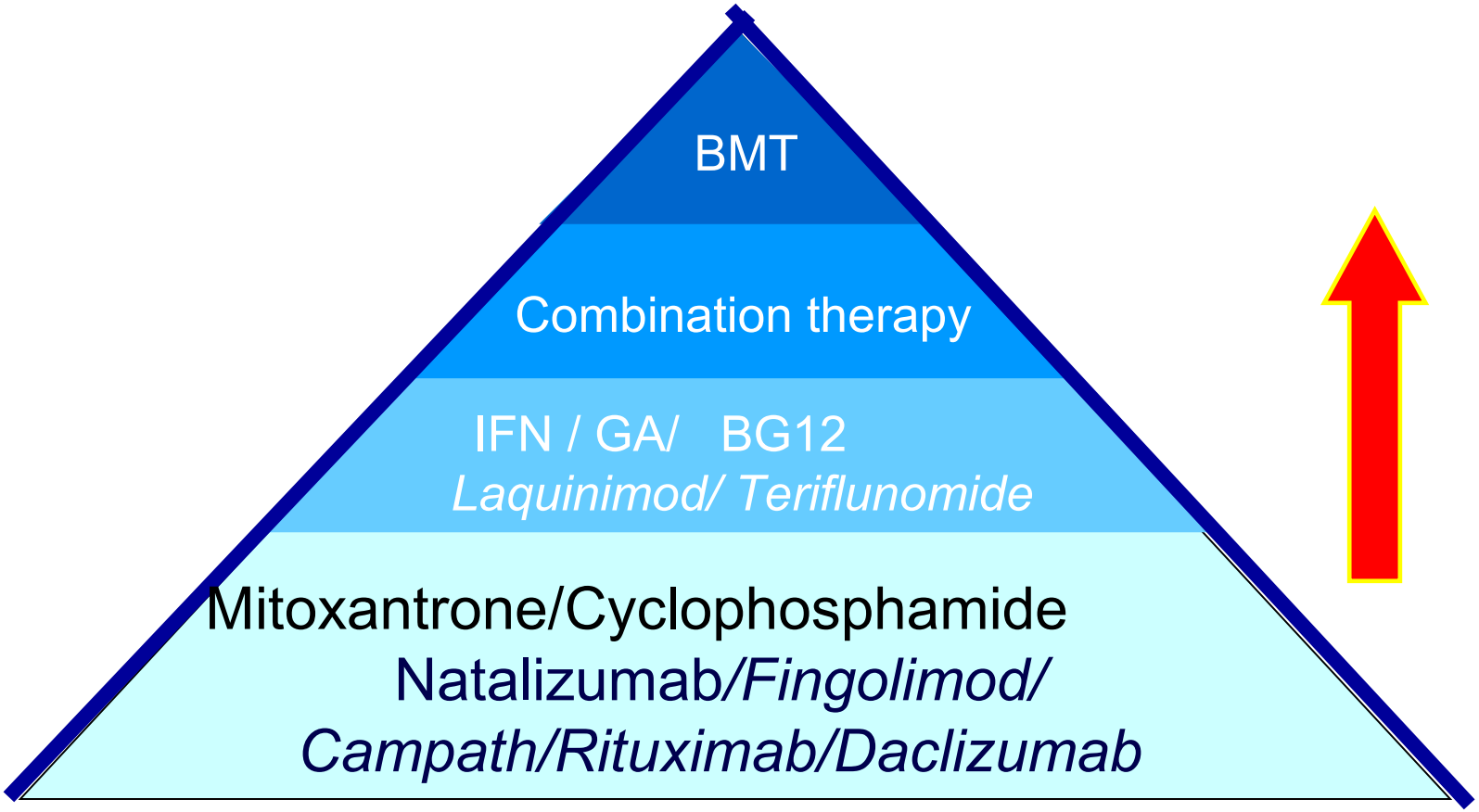
Gold, NEJM 2012

Risk/benefit

CONSENSUS GROUPS IN US AND EUROPE



Induction therapy

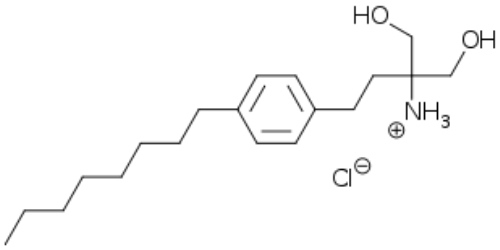
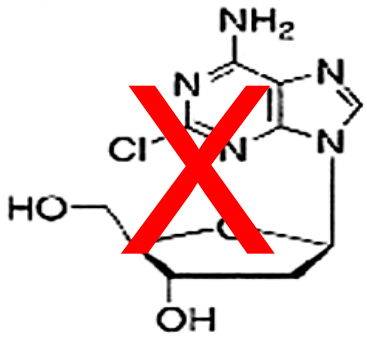


Thank you for you attention!

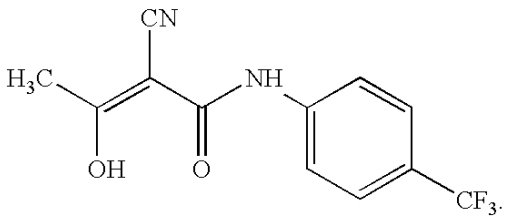
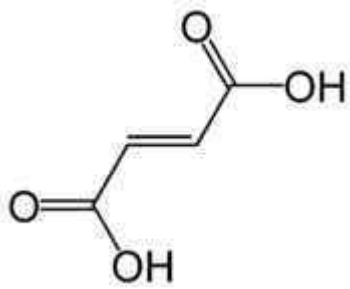
Teriflunomide Phase 3 (TEMSO): AEs ≥10% in Any Group — MedDRA Preferred Term

AEs, n (%)[a]	Placebo (n=360)	Teriflunomide 7 mg (n=368)	Teriflunomide 14 mg (n=358)
Any class	315 (87.5)	328 (89.1)	325 (90.8)
Nasopharyngitis	98 (27.2)	94 (25.5)	93 (26.0)
Headache	64 (17.8)	81 (22.0)	67 (18.7)
Diarrhea **Discontinuations**	32 (8.9) 0	**54 (14.7)** **1 (0.3)**	**64 (17.9)** **1 (0.3)**
Fatigue	51 (14.2)	47 (12.8)	52 (14.5)
ALT increased	24 (6.7)	**44 (12.0)**	**51 (14.2)**
Nausea **Discontinuations**	26 (7.2) 0	**33 (9.0)** **1 (0.3)**	**49 (13.7)** **0**
Hair-thinning[b]	12 (3.3)	**38 (10.3)**	**47 (13.1)**
Influenza	36 (10.0)	34 (9.2)	43 (12.0)
Back pain	47 (13.1)	39 (10.6)	41 (11.5)
Urinary tract infection	35 (9.7)	27 (7.3)	37 (10.3)
Pain in extremity	**47 (13.1)**	26 (7.1)	33 (9.2)

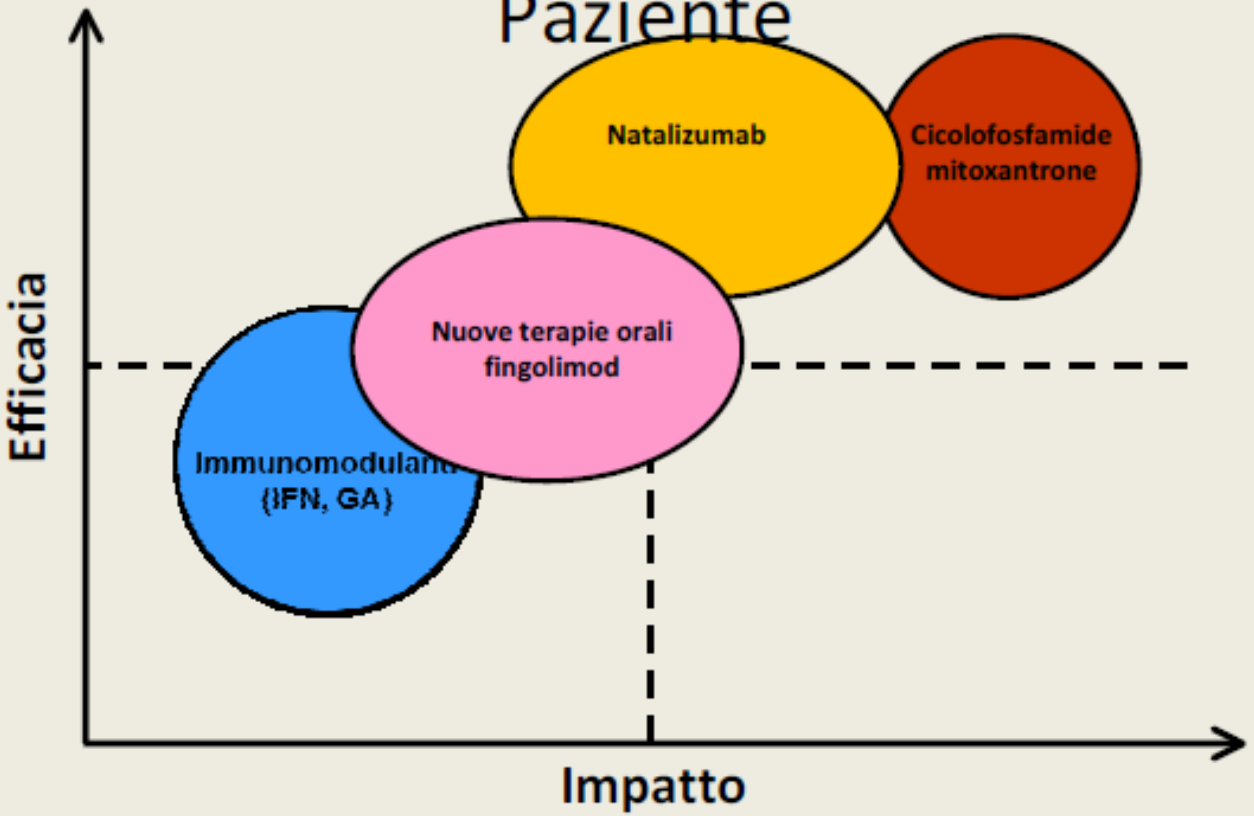
Terapie orali /1

FINGOLIMOD  **(Gilenya®)**	***Agonista del recettore delle sfingosine*** Blocca il traffico dei linfociti T che rimangono intrappolati nei linfonodi	Bradicardia Ipertensione arteriosa Ostruzione vie aeree Encefalite HSV-1 Infezione da VZV Neoplasie cutanee	**Fase III** FREEDOMS TRANSFORMS INFORMS
CLADRIBINA  	***Analogo delle purine*** Influenza la sintesi del DNA e il metabolismo cellulare soprattutto a livello dei linfociti T	Mielosoppressione (dose-dipendente) Infezioni opport.unistiche	**Fase III** CLARITY (ext) ONWARD ORACLE

Terapie orali /2

TERIFLUNOMIDE  	**Inibitore della sintesi delle pirimidine** Metabolita attivo della Leflunomide Effetto antiproliferativo	Nasofaringiti, artralgie Alopecia Nausea, diarrea, ↑ ALT	**Fase III** TEMSO ***Add-on*** IFN beta, GA
FUMARATO  	**Composto intermedio del ciclo di Krebs** Induce shift TH-1•TH-2 Effetto neuroprotettivo	Rash cutanei, prurito Disturbi gastroenterici Dolori muscolari Cefalea	**Fase III** CONFIRM DEFINE
LAQUINOMIDE 	**Derivato della Linomide** Prob. induce shift TH-1•TH-2	Potenz. epatotossico Dispepsia Edemi declivi	**Fase III** BRAVO ALLEGRO

Terapie della Sclerosi Multipla: Rapporto tra Efficacia ed Impatto sul Paziente



Impatto della terapia: *convenience*, monitoraggio, tollerabilità, sicurezza

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
19(1) 24–25

DOI: 10.1177/1352458512469700
msj.sagepub.com
SAGE

In the coming year we should abandon interferons and glatiramer acetate as first-line therapy for MS: Yes

Robert J Fox

Based upon the results from Phase III trials, these new oral therapies appear to be at least as effective (teriflunomide) or more effective (fingolimod, dimethyl fumarate) than the platform injectables. Tolerability is excellent, and the oral route of administration is understandably preferred by patients over injection. Safety issues in the 2-year trials have been rare, and open-label Phase IV observation studies to date have not identified new long-term safety problems. Global safety vigilance will continue for years to come. Importantly, both teriflunomide and dimethyl fumarate are closely related to approved therapies with over 15 years of strong safety experience in humans.

In the coming year we should abandon interferons and glatiramer acetate as first line therapy for MS: No

Ian Hillert

IFNb and GA have been shown to be inferior to the second-generation MS treatments mainly or only in reducing RR, a parameter questioned for its long-term relevance. Patient and neurologist preferences will determine whether the traditional injectables will remain useful. My guess is that a handful of efficacious, safe and tolerable first-line alternatives will be required to outcompete IFNb and GA. From an evidence

CONS

- Efficacia limitata
- ATC anti IFNB
- Più utili nelle forme poco aggressive
- Tollerabilità
- Aderenza: 30-40% non aderente entro i primi 2-3 aa dall'inizio

PROS

- Efficacia confermata: SMRR e CIS
- Maggiore efficacia del trattamento precoce
- Sicurezza nel lungo termine (21 aa.)
- Dati sulla sicurezza in gravidanza
- Dati sulla sicurezza nelle forme infantili
- In studio diversi devices e forme pegilate

Scelta terapeutica

- Selezione accurata del paziente
- Scelta individualizzata
- Bilancio rischio/beneficio
- Scelta condivisa

Grazie!