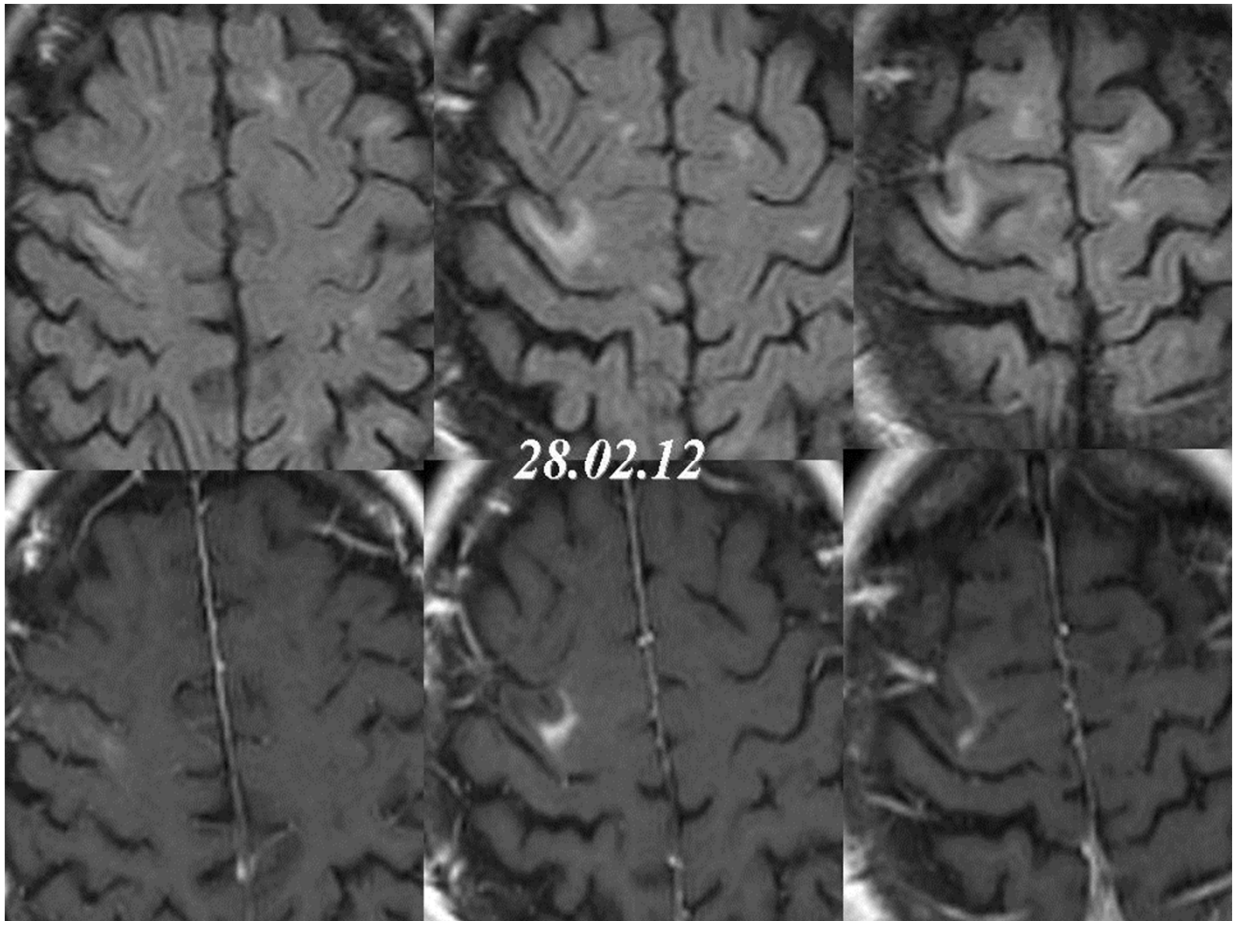
RM 28.02.12



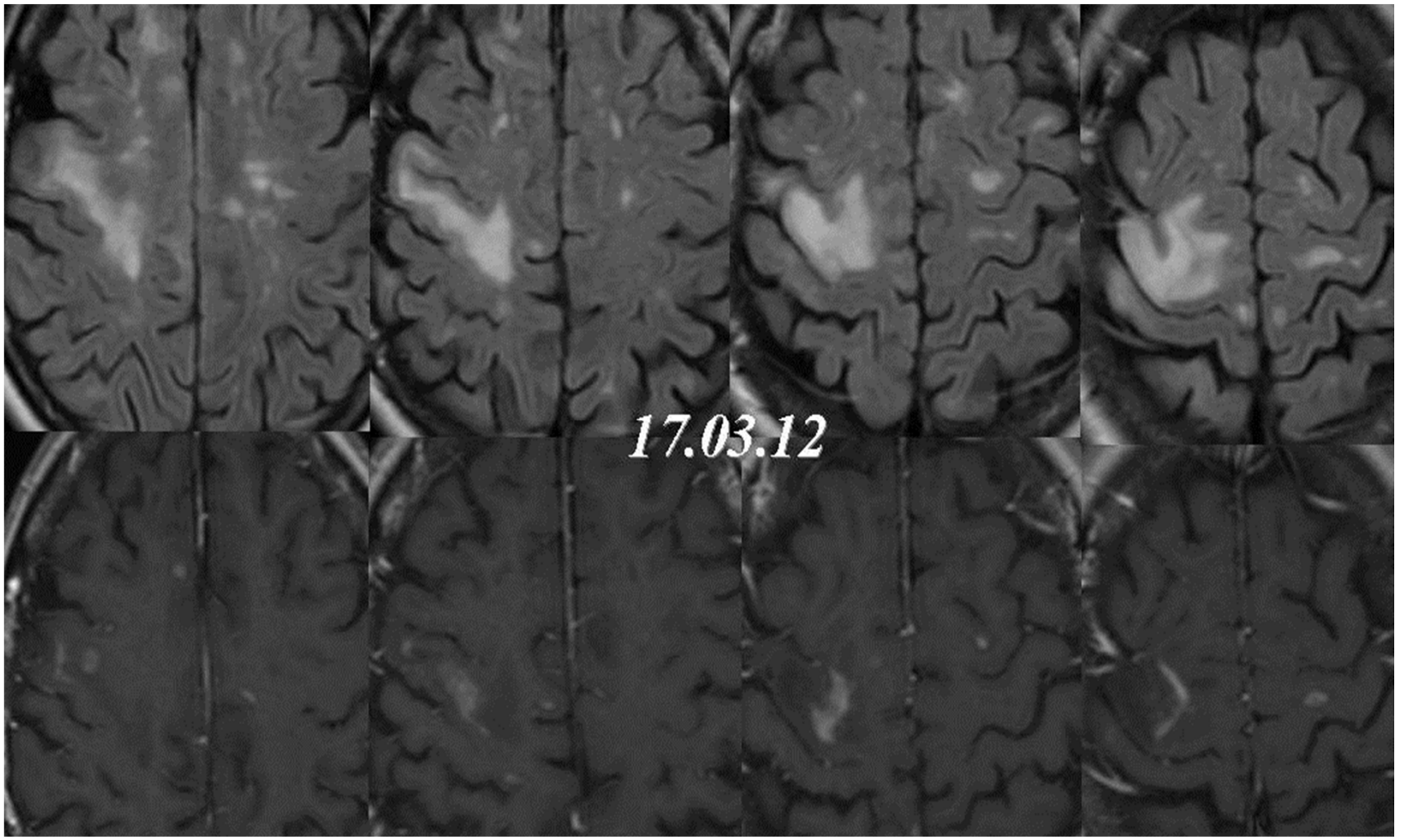
Trattamento steroideo e.v.

40 giorni dopo la precedente, nuova puntura lombare per ricerca di JCV-DNA liquorale:

Negativa presso 3 laboratori

Positiva presso laboratorio NIH (limite 20 copie/ml): ***bassa carica virale 37 copie/ml.***

RM 17.03.12



IRIS: Trattamento steroideo e.v. *alte dosi*

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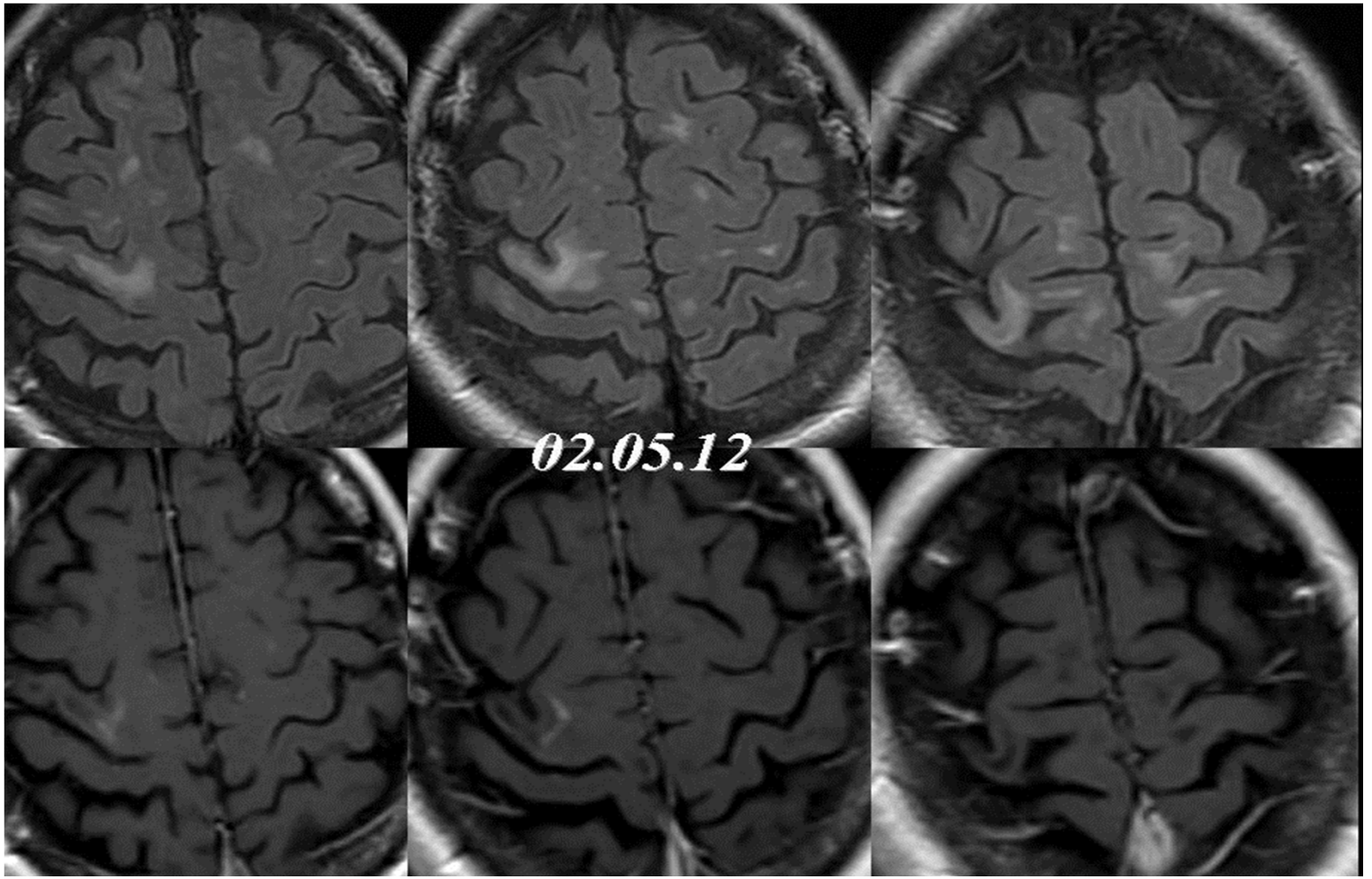
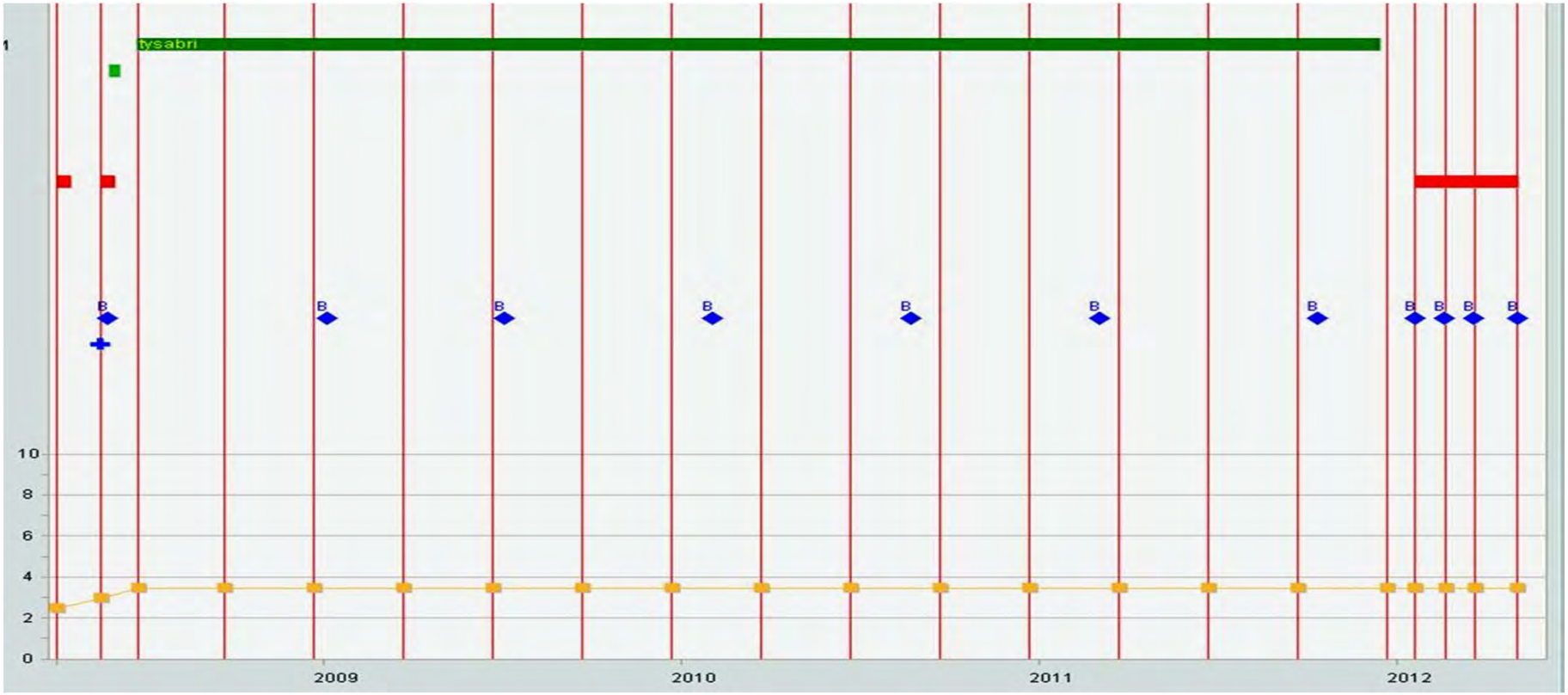
RM 02.05.12



Prosegue trattamento steroideo e.v. *pulse*

Situazione 05.12



Fondazione Istituto San Raffaele G. Giglio di Cefalu

CONCLUSIONI

1. ***L'esame obiettivo attuale è sempre invariato rispetto all'esordio dei sintomi***
   EDSS è tuttora 3.5 (5/2015)
2. ***Ha interrotto dopo 6 mesi meflochina + mirtazapina e steroide pulse***
3. ***La sintomatologia mioclonica/tremorigena:***
   No risposta a gabapentin e clonazapem
   Recentemente introdotto levetiracetam.

Fattori che possono influenzare la sopravvivenza nei pts con PML

Fattori che sembrano essere associati a > sopravvivenza

- Precocità della diagnosi
- Minor età alla diagnosi PML
- Minor EDSS pre-PML
- Monofocalità alla RMN

Fattori che non sembrano influenzare la sopravvivenza

- Sesso
- Precedente terapia immunosoppressiva
- Durata SM
- Tempo di esposizione a Natalizumab al momento della diagnosi di PML
- Carico DNA JCV in CSF alla diagnosi PML
- RMN GAD+ alla diagnosi

Vermersch P, et al. Neurology. 2011

Problemi: sospensione riattivazione, “rebound”

Natalizumab Dosage Suspension: Are We Helping or Hurting?

Timothy W. West, MD, and Bruce A. C. Cree, MD, PhD, MCR

ANNALS of Neurology 2010; 68: 395-399

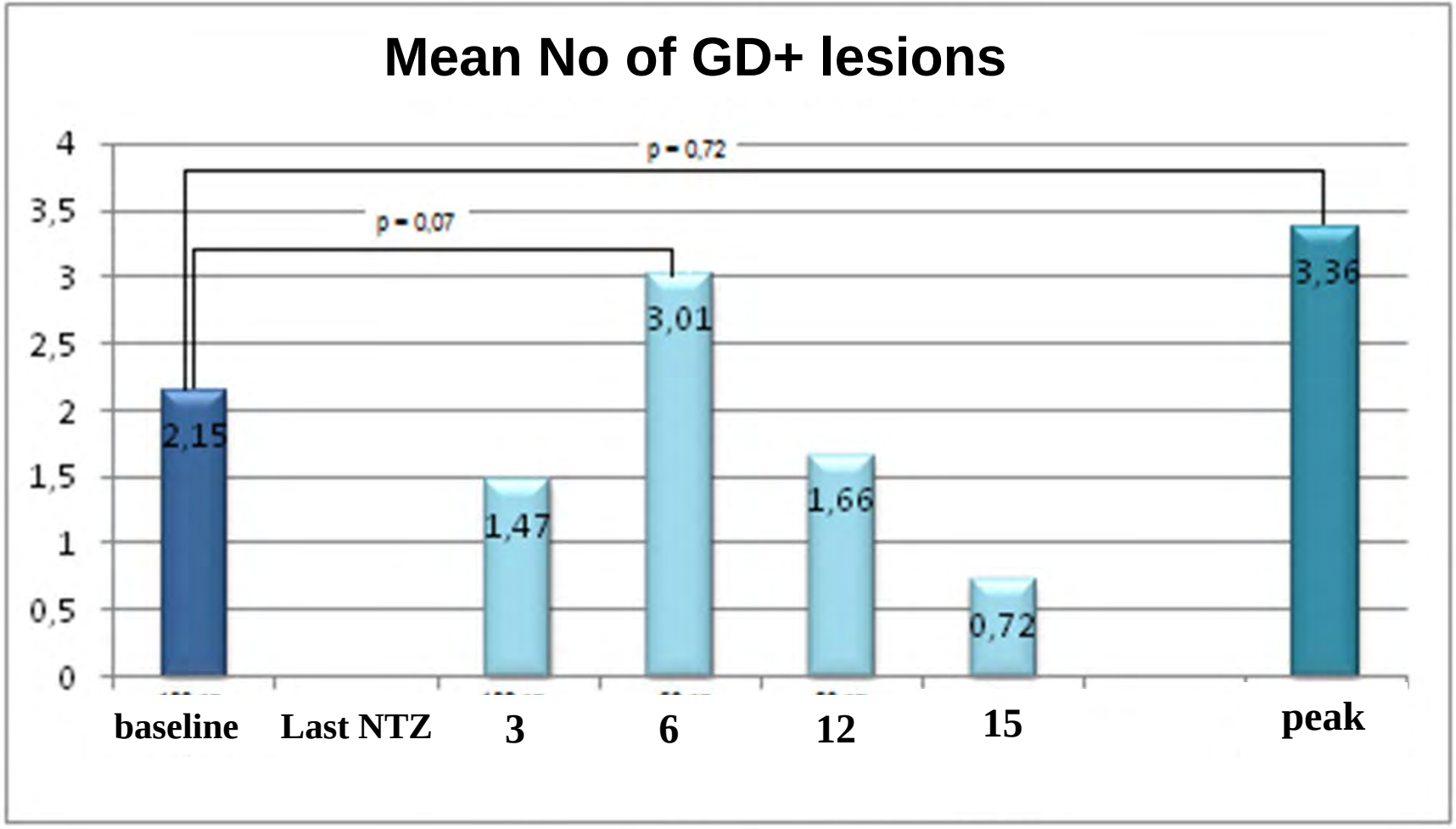
- Il **28% dei pazienti** che sospendono hanno una relapse.
- **Tre mesi** è il tempo mediano che intercorre tra sospensione e ripresa di malattia
- *Tra i 19 pazienti che hanno una ricaduta, 7 hanno **incremento dell’EDSS da 3 a 6.***

LETHAL MULTIPLE SCLEROSIS RELAPSE AFTER NATALIZUMAB WITHDRAWAL

Neurology® Rigau et al. 2012; 79: 2214-2216

- Grave relapse 3,5 mesi dopo la sospensione (37 somm.), resistente a metilprednisolone, PLEX, mitoxantrone
- Decesso per danno bulbare

Effetto rimbalzo all'interruzione del natalizumab



Dopo la sospensione: steroidi....

European Journal of Neurology 2011 doi:10.1111/j.1468-1331.2011.03577.x

SHORT COMMUNICATION

Pulse monthly steroids during an elective interruption of natalizumab: a post-marketing study

G. Borriello, L. Prosperini, C. Mancinelli, C. Giannì, F. Fubelli and C. Pozzilli

Multiple Sclerosis Centre, S. Andrea Hospital, Department of Neurology and Psychiatry, Sapienza University, Rome, Italy

Keywords:
magnetic resonance imaging, multiple sclerosis, natalizumab, observational study, progressive multifocal leukoencephalopathy, rebound, steroids

Received 10 May 2011
Accepted 21 July 2011

Background and purpose: Temporary discontinuation of natalizumab is sometimes considered as the observed risk of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis (MS). However, interruption of natalizumab may result in a re-start of disease activity.

Methods: In this prospective post-marketing study, 23 patients with MS treated with natalizumab elected a trial of treatment interruption (90–150 days) because of safety concerns on the risk of developing PML. To reduce the risk of disease activity return, patients received monthly intravenous (i.v.) steroid pulses before natalizumab re-start.

Results: Despite the steroid coverage, seven patients (30.4%) had an active scan during the natalizumab interruption period; of these, four also had a concomitant clinical exacerbation.

Conclusions: Our findings suggest that i.v. steroids are not currently recommendable as drug coverage during a scheduled treatment interruption period.

Dopo la sospensione: GA…Fingolimod…

J Neurol. 2011 Sep;258(9):1665-9. doi: 10.1007/s00415-011-5996-y. Epub 2011 Mar 23.

De-escalation from natalizumab in multiple sclerosis: recurrence of disease activity despite switching to glatiramer acetate.

Havla J, Gerdes LA, Meinl I, Krumbholz M, Faber H, Weber F, Pellkofer HL, Hohlfeld R, Kümpfel T.

Institute of Clinical Neuroimmunology, Medical Campus Grosshadern, Ludwig-Maximilians-University, Marchioninistr. 15, 81377 Munich, Germany.

Eur J Neurol. 2013 Jan;20(1):87-94. doi: 10.1111/j.1468-1331.2012.03794.x. Epub 2012 Jun 28.

Effect of glatiramer acetate on disease reactivation in MS patients discontinuing natalizumab.

Rossi S, Motta C, Studer V, De Chiara V, Barbieri F, Monteleone F, Fornasiero A, Coarelli G, Bernardi G, Cutter G, Stüve O, Salvetti M, Centonze D.

Clinica Neurologica, Dipartimento di Neuroscienze, Università Tor Vergata, Rome, Italy.

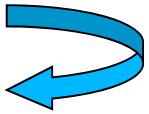
Acta Neurol Scand. 2013 Jan 22. doi: 10.1111/ane.12082. [Epub ahead of print]

Switching from natalizumab to fingolimod: an observational study.

Sempere AP, Martín-Medina P, Berenguer-Ruiz L, Pérez-Carmona N, Sanchez-Perez R, Polache-Vengud J, Feliu-Rey E.

Neurology Department, Hospital General Universitario de Alicante, Alicante, Spain.

- 63% relapse clinica
- 75% ripresa attività RMN



Teriflunomide !?

When switching from natalizumab to teriflunomide, timing is key

- teriflunomide, a potential multiple sclerosis therapy, strongly interferes with BK replication; less effective against JC virus, but the mutated variants in multiple sclerosis CNS have not been studied.
- 30 triple-positive, nat-treated MS patients, discontinued on teriflunomide: 23/30 still on TRF after 1 year (no relapse, no PML)

Effectiveness of Switching to Rituximab over Fingolimod or Dimethyl Fumarate after Natalizumab in Preventing Disease Activity in Multiple Sclerosis.

Enrique Alvarez MD/PhD[1], Brandi Vollmer[1], Jace Blacburn[1], John Corboy MD[1], Timothy Vollmer MD[1], Stefan H Sillau PhD[1], Kavita V Nair PhD[1], Julie Seibert MD[1]

[1]Rocky Mountain MS Center at Anschutz Medical Center (University of Colorado), Aurora, Colorado, USA

Background

- Natalizumab discontinuation has been associated with rebound/return of disease activity. Studies have highlighted the importance of minimizing washouts after natalizumab when switching to fingolimod. Little evidence exists on switching to DMF or rituximab.

Objective

- To compare the efficacy and discontinuation rates of treatments after switching from natalizumab to rituximab, fingolimod (FTY), or dimethyl fumarate (DMF) in the treatment of multiple sclerosis (MS).

Methods

- Patients with MS who initiated treatment prior to November, 2013 with rituximab, FTY, or DMF at the Rocky Mountain MS Center at Anschutz Medical Campus (University of Colorado Denver) were identified.
- A retrospective chart review from electronic medical records was conducted where clinician reported data was collected including demographic information, treatment start and stop dates, drug reactions, clinical relapses, MRI lesions, and laboratory data.
- Patients were further stratified to those who had been on natalizumab for at least 12 months prior to switching to rituximab, FTY, or DMF.
- A maximum of a 6 month transition period/wash out was allowed.
- Initiation of treatment with rituximab, FTY, or DMF had to occur prior to November 2013 in order for patients to have the ability to be on drug for at least one year
- The primary outcome was **discontinuation rates** measured at 12 months.
- Secondary outcomes include **MRI activity** with gadolinium enhancing lesions measured at 12 months.
- Unadjusted descriptive analysis was conducted between the two groups on the outcomes of interest

Results and Discussion

- Most patients had minimal transition times/wash outs to other treatments when switching from natalizumab (Median is 0-1 months).
- Few patients experienced relapses and <10% had enhancing lesions.
- Switching to rituximab from natalizumab with minimal transition time/wash out was not associated with rebound of disease activity.
- Using minimal transition times/switching times was well tolerated and appeared safe in all three groups.
- The study is limited by small numbers and only 1 year of follow up; plans are to continue to follow and add to these cohorts.
- Propensity matching is planned in order to evaluate how well balanced the groups are.

Results

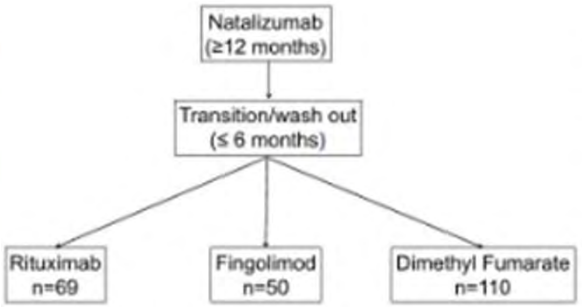


Table 1. Baseline demographics

	Rituximab N=69	Dimethyl fumarate N=50	Fingolimod N=110
Age (Mean, SD)	47.33 (10.09)	48.60 (11.32)	47.25 (11.36)
Gender			
Female	48 (69.57 %)	36 (72.00 %)	76 (69.09 %)
Male	21 (30.43 %)	14 (28.00 %)	34 (30.91 %)
Race			
White	55 (79.71 %)	44 (88.00%)	102 (92.73 %)
Black	8 (11.59 %)	2 (4.00 %)	1 (0.91 %)
Other	3 (4.35 %)	2 (4.00 %)	2 (1.82 %)
Unknown	3 (4.35 %)	2 (4.00 %)	5 (4.55 %)
Ethnicity			
Hispanic	4 (5.80 %)	1 (2.00%)	7 (6.36 %)
Non-hispanic	60 (86.96 %)	46 (92.00 %)	97 (88.18 %)
Unknown	5 (7.25 %)	3 (6.00 %)	6 (5.45)
Diagnosis			
RRMS	49 (71.01 %)	37 (74.00 %)	93 (84.55 %)
SPMS	17 (24.64 %)	11 (22.00 %)	15 (13.64 %)
PPMS	3 (4.35 %)	2 (4.00 %)	2 (1.82 %)
Disease Duration (Years, Mean, SD)	13.96 (8.62)	12.32 (8.15)	12.48 (7.40)

Table 2. Outcomes

	Rituximab N=69	Dimethyl Fumarate N=50	Fingolimod N=110
Discontinued prior to completing 12 months of new DMT	0 (0%)	12 (24.0%) p<0.001 vs rituximab	19 (17.3%) p<0.001 vs rituximab
Relapse	1 (1.5%)	2 (4.0%) n.s. vs rituximab	2 (1.8%) n.s. vs rituximab
Enhancing lesions present	0 (0%)	3 (6.0%) p=0.04 vs rituximab	10 (9.1%) p=0.01 vs rituximab
Mean number of enhancing lesions	0	4.7	4.0
Transition/wash out time in months	1	0	1

Conclusion

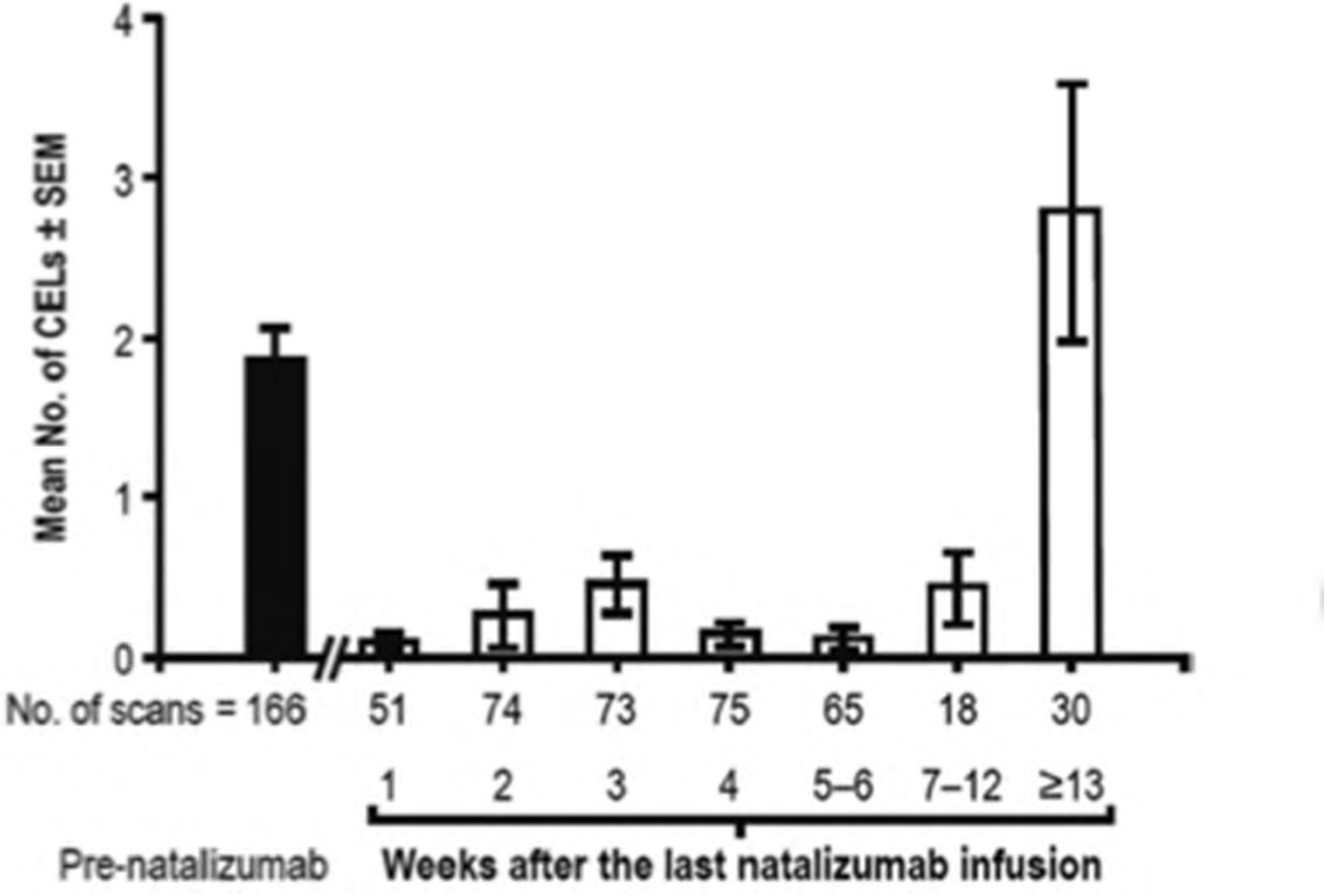
- Using minimal transition times from natalizumab to rituximab, fingolimod, or DMF was associated with little disease activity. Switching to rituximab was associated with fewer enhancing lesions and discontinuation of treatment than fingolimod or DMF in the first year of treatment.

More posters by University of Colorado Denver (UCD)

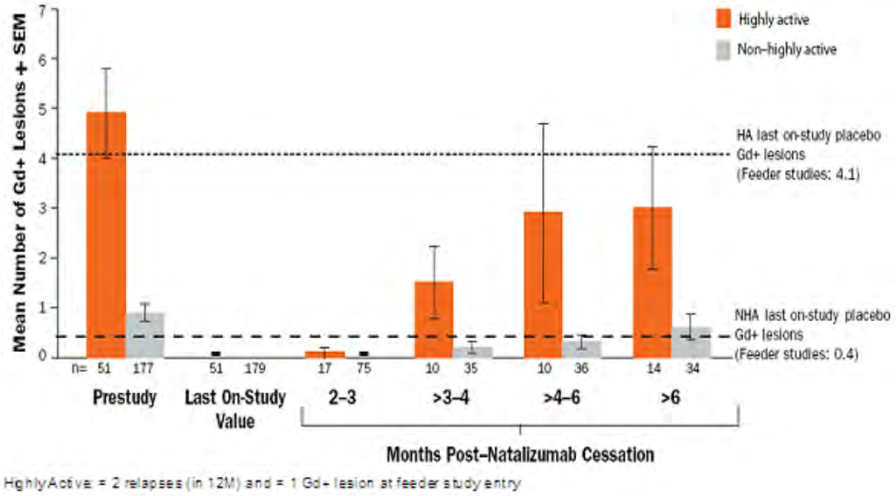
- Information comparing outcomes of dimethyl fumarate versus fingolimod at one year at UCD - poster # P3.244
- Information on the experience of rituximab at UCD - poster # P3.262
- For more information on this poster contact:

Brandi Vollmer at *brandi.vollmer@ucdenver.edu*
Enrique Alvarez MD/PHD at *enrique.alvarez@ucdenver.edu*

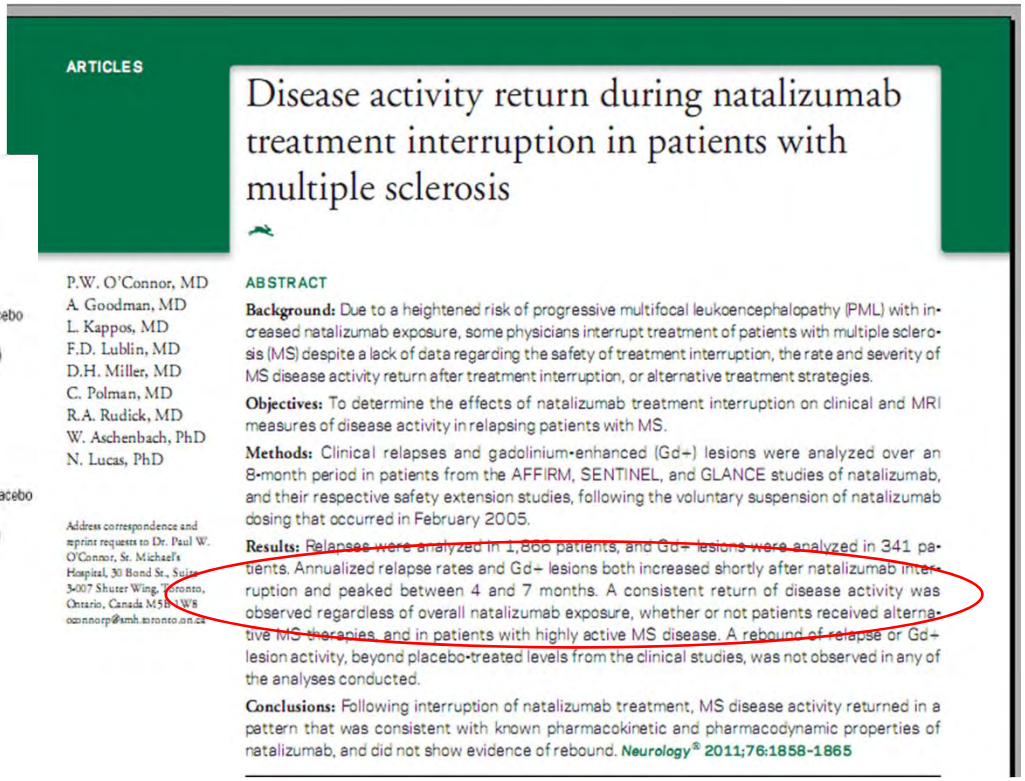
Numero medio di lesioni GD+ in esami di RM encefalica a varie settimane dall'ultima infusione di natalizumab



Grimaldi LME et al., 2012



HighlyActive = 2 relapses (in 12M) and = 1 Gd+ lesion at feeder study entry



ARTICLES

Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis

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ABSTRACT

Background: Due to a heightened risk of progressive multifocal leukoencephalopathy (PML) with increased natalizumab exposure, some physicians interrupt treatment of patients with multiple sclerosis (MS) despite a lack of data regarding the safety of treatment interruption, the rate and severity of MS disease activity return after treatment interruption, or alternative treatment strategies.

Objectives: To determine the effects of natalizumab treatment interruption on clinical and MRI measures of disease activity in relapsing patients with MS.

Methods: Clinical relapses and gadolinium-enhanced (Gd+) lesions were analyzed over an 8-month period in patients from the AFFIRM, SENTINEL, and GLANCE studies of natalizumab, and their respective safety extension studies, following the voluntary suspension of natalizumab dosing that occurred in February 2005.

Results: Relapses were analyzed in 1,866 patients, and Gd+ lesions were analyzed in 341 patients. Annualized relapse rates and Gd+ lesions both increased shortly after natalizumab interruption and peaked between 4 and 7 months. A consistent return of disease activity was observed regardless of overall natalizumab exposure, whether or not patients received alternative MS therapies, and in patients with highly active MS disease. A rebound of relapse or Gd+ lesion activity, beyond placebo-treated levels from the clinical studies, was not observed in any of the analyses conducted.

Conclusions: Following interruption of natalizumab treatment, MS disease activity returned in a pattern that was consistent with known pharmacokinetic and pharmacodynamic properties of natalizumab, and did not show evidence of rebound. *Neurology*® 2011;76:1858–1865

Fattori predisponenti riattivazione:

- Alta attività RM (GAD+)
- Alta ARR
- Minor durata malattia

009

Subcutaneous natalizumab 300 mg every 4 weeks is comparable to standard intravenous dosing in REFINE: a study exploring the safety, tolerability, and efficacy of multiple natalizumab treatment regimens in patients with relapsing multiple sclerosis

Trojano M,[1] Ramió-Torrentà L,[2] Grimaldi LME,[3] Lubetzki C,[4] Schippling S,[5] Evans K,[6] Gheuens S,[6] Muralidharan K,[6] Natarajan A,[6] Mikol D[6]

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67th Annual Meeting of the American Academy of Neurology
April 18-25, 2015
Washington, DC

INTRODUCTION

- In patients with relapsing-remitting multiple sclerosis (RRMS), the currently approved natalizumab regimen of 300 mg administered intravenously (IV) every 4 weeks (q4wk) has been shown to significantly reduce disease activity as reflected by brain magnetic resonance imaging (MRI), clinical relapse rate, and confirmed progression of disability relative to placebo over 2 years.[1]
- The efficacy of natalizumab IV q4wk appears to be maintained over the long term.[2,3]
- It is not known if alternative dosing regimens or routes of administration could maintain the beneficial effects achieved in patients initially treated with the approved dosing regimen while providing lower drug exposure and potentially enhanced patient convenience.

OBJECTIVE

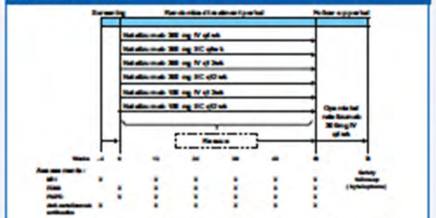
- To examine the efficacy, safety, and tolerability of natalizumab administered via various regimens in clinically stable natalizumab-treated RRMS patients.

METHODS

Study design

- REFINE was an exploratory, dose- and frequency-blinded, prospective, randomized, dose-ranging study in RRMS patients who had received natalizumab for at least 12 months and were relapse free in the last year.
- The planned duration of the study for enrolled patients was 72 weeks, which included 60 weeks of randomized treatment and 12 weeks of open-label natalizumab treatment (Figure 1).

Figure 1. Study design



EDSS=Expanded Disability Status Scale; MRI=magnetic resonance imaging; PD=pharmacodynamics; PK=pharmacokinetics; q12wk=every 12 weeks; SC=subcutaneous.

- Patients were blinded to natalizumab dose and frequency but not to route of administration, and they attended clinic visits every 4 weeks.
  - All patients received study treatment every 4 weeks. Patients randomized to the q12wk treatment arms received matching placebo at the intervening 4-week visits.
- Key inclusion and exclusion criteria are listed in Table 1.
- Safety across the 6 treatment arms was followed by a Data and Safety Monitoring Committee (DSMC), which could recommend closure of individual treatment arms in the event of safety concerns, including increased disease activity.

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria
Age 18 to 55 years, inclusive
Free of MS relapse, as determined by enrolling investigator, for 12 months prior to randomization
Received ≥11 doses of natalizumab in the 12 months prior to randomization with no missed doses in the 3 months prior to randomization
Experienced (i) ≥2 documented clinical relapses or (ii) 1 relapse and ≥1 Gd+ lesion on MRI unrelated to the relapse in the 12 months prior to the initiation of natalizumab
Key exclusion criteria
Positive for anti-natalizumab antibodies at screening
MRI positive for Gd+ lesions at study entry

Gd+=gadolinium-enhancing; MS=multiple sclerosis.

Endpoints and assessments

- The primary endpoint in REFINE was the cumulative number of combined unique active lesions, calculated as the sum of the number of new Gd+ and new or newly enlarging T2 hyperintense lesions (non–gadolinium-enhancing on T1-weighted scans).
- Additional endpoints included:
  - Annualized relapse rate at week 60;
  - The proportion of patients relapsing by week 60;
  - Pharmacokinetics, assessed by serum natalizumab concentrations using an enzyme-linked immunosorbent assay;
  - PD, as assessed by α4 integrin saturation; and
  - Immunogenicity (anti-natalizumab antibodies) and incidence of adverse events and serious adverse events.
- Clinical relapses, adverse events, and serious adverse events were recorded throughout the study.

Rescue and stopping criteria

- Patients could receive rescue treatment with high-dose corticosteroids or open-label natalizumab, at the discretion of the investigator, if they met any of the following rescue criteria:
  - One new Gd+ lesion >0.8 cm³ or ≥2 Gd+ lesions of any size;
  - One new or enlarging T2 lesion >0.8 cm³ or ≥2 new or enlarging T2 lesions of any size, compared with a previous scan performed as part of this study;
  - Clinical relapse;
  - Confirmed EDSS progression, defined as an increase in EDSS score of ≥1.5 points from a baseline score of 0.0, of ≥1.0 point from a baseline score of 1.0–5.5, or of ≥0.5 points from a baseline score of ≥6.0, confirmed at least 12 weeks after the initial increase.
- Patients who received only corticosteroids could continue in the randomized treatment period, whereas patients who were rescued with open-label natalizumab were advanced to the week 60 visit.

Statistical analyses

- Baseline characteristics were analyzed using summary statistics.
- The modified intent-to-treat population, defined as all randomized patients who received ≥1 dose of study treatment and had ≥1 efficacy assessment, was used for all analyses of efficacy; populations were defined separately for each analysis of PK, PD, and safety.
- Efficacy endpoints were summarized using summary statistics for continuous or count variables or frequency distributions for categorical variables. Because this study was exploratory, no formal comparisons were made.
- The unadjusted annualized relapse rate was calculated as the total number of relapses experienced in the group divided by the total study time in days during the randomized treatment period. The ratio was multiplied by 365.25.
- The proportion of patients meeting MRI rescue criteria or experiencing a relapse was estimated using the Kaplan-Meier method.

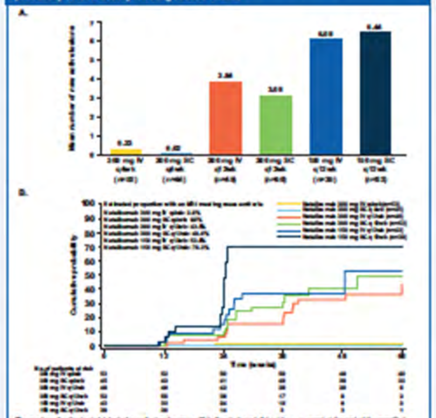
RESULTS

- REFINE enrolled a total of 290 patients. Baseline demographics and disease characteristics were comparable across the 6 treatment arms (Table 2).
  - No patients had Gd+ lesions at baseline, as the presence of Gd+ lesions was exclusionary.
- All patients had received ≥12 months of natalizumab treatment at baseline.
- During the randomized treatment period, the four q12wk treatment arms were closed early at the recommendation of the DSMC because of increased disease activity.
  - Less than 20% of patients in each of the q12wk treatment arms were exposed to all 15 planned doses, compared with ≥76% of patients in each of the q4wk treatment arms.
  - The 150 mg SC q12wk arm was closed first, at a time when 34% of patients in that arm met MRI rescue criteria compared with 0% in the 300 mg IV q4wk arm.

Efficacy

- At week 60, the total mean number of combined unique active lesions since baseline in the natalizumab 300 mg SC q4wk treatment arm (0.32) was comparable to that in the 300 mg IV q4wk arm (0.23) (Figure 2A).
- The estimated proportion of patients with an MRI meeting rescue criteria was ≤2.0% in the 300 mg IV and SC q4wk arms. The cumulative probability of MRI activity was higher in the q12wk arms, although patient numbers were small (Figure 2B).
- At week 60, the annualized relapse rate in the natalizumab 300 mg IV q4wk treatment arm (0.07) was comparable to that in the 300 mg SC q4wk arm (0.06).
  - Annualized relapse rates were greater in the q12wk treatment arms (0.20 for 300 mg IV q12wk, 0.30 for 300 mg SC q12wk, 0.47 for 150 mg IV q12wk, and 0.18 for 150 mg SC q12wk).
- The estimated proportion of patients with a relapse was 7.8% in the 300 mg IV q4wk arm and 9.1% in the 300 mg SC q4wk arm. The cumulative probability of relapse was higher the q12wk arms (range, 21.2%–60.8%), although patient numbers were small.

Figure 2. (A) Combined unique active MRI lesions at week 60 and (B) cumulative probability of MRI activity meeting rescue criteria



The number of patients at risk includes patients who were still in the study and did not have an event at the end of the specified time. The number of patients at risk at week 60 is the number who were censored that week.

Pharmacokinetics and pharmacodynamics

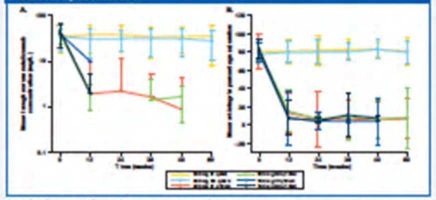
- Mean serum natalizumab concentration was determined in 273 patients.
  - Over time, trough serum concentrations of natalizumab remained similar to baseline concentrations in the two q4wk treatment arms, while trough concentrations decreased by week 12 and remained low or below the limit of quantitation throughout the study in the four q12wk treatment arms (Figure 3A).
- Mean trough α4-integrin saturation was assessed in 263 patients.
  - Patients in the two q4wk treatment arms maintained high trough α4-integrin saturations throughout the randomized treatment period, with mean values ranging from 76.8% to 83.1% (Figure 3B).
  - For patients in the four q12wk arms, mean trough α4-integrin saturations decreased (range, 16%–24.3%) by week 12 and remained in this range throughout the randomized treatment period.

Table 2. Baseline demographics and disease characteristics

Characteristic	Natalizumab 300 mg IV q4wk (n=64)	Natalizumab 300 mg SC q4wk (n=45)	Natalizumab 300 mg IV q12wk (n=52)	Natalizumab 300 mg SC q12wk (n=54)	Natalizumab 150 mg IV q12wk (n=47)	Natalizumab 150 mg SC q12wk (n=38)	Total (N=290)
Age							
Mean (SD)	38.4 (7.84)	36.3 (8.92)	38.7 (8.43)	38.7 (7.85)	38.7 (8.61)	36.0 (9.03)	37.9 (8.41)
Median (min, max)	38 (23, 55)	35 (19, 54)	39 (20, 54)	39 (20, 54)	39 (20, 55)	35 (21, 56)	38 (19, 56)
Sex, female, n (%)	39 (72)	29 (64)	37 (71)	41 (76)	34 (72)	24 (63)	204 (70)
Body weight, kg							
n	53	45	51	53	47	37	286
Mean (SD)	69.99 (16.579)	70.82 (14.609)	69.30 (12.629)	68.37 (13.747)	65.67 (12.666)	69.26 (19.110)	68.93 (14.894)
Median (min, max)	69.0 (48.0, 125.0)	68.3 (50.0, 115.0)	68.1 (48.0, 101.0)	66.0 (46.0, 110.5)	63.0 (45.0, 105.8)	66.0 (45.0, 142.0)	66.7 (45.0, 142.0)
EDSS score at baseline							
Mean (SD)	2.99 (1.326)	2.54 (1.369)	2.67 (1.357)	2.78 (1.595)	2.83 (1.561)	2.87 (1.536)	2.78 (1.453)
Median (min, max)	3.0 (0.0, 6.5)	2.5 (0.0, 6.0)	2.5 (0.0, 6.0)	2.5 (0.0, 6.5)	2.5 (0.0, 6.0)	2.5 (0.0, 6.0)	2.5 (0.0, 6.5)
Time since diagnosis of MS, y							
Mean (SD)	9.7 (5.20)	9.0 (6.06)	9.5 (5.51)	9.8 (6.08)	9.6 (6.63)	8.9 (4.66)	9.5 (5.71)
Median (min, max)	9 (3, 28)	8 (1, 24)	8 (1, 30)	7 (2, 28)	9 (2, 29)	8 (3, 22)	8 (1, 30)
Time since initiation of natalizumab, y							
Mean (SD)	3.2 (1.50)	2.7 (1.34)	3.1 (1.46)	2.9 (1.35)	2.9 (1.22)	2.8 (1.39)	3.0 (1.38)
Median (min, max)	3 (1, 6)	2 (1, 6)	3 (1, 6)	3 (1, 6)	3 (1, 5)	3 (1, 5)	3 (1, 6)
No. of natalizumab infusions prior to randomization							
Mean (SD)	36.2 (15.14)	31.0 (16.01)	37.0 (15.53)	34.7 (16.43)	35.8 (15.74)	34.4 (15.22)	34.9 (15.68)
Median (min, max)	33 (13, 66)	25 (11, 67)	36 (12, 64)	34 (11, 69)	33 (13, 68)	31.5 (13, 63)	33 (11, 69)

SD=standard deviation.

Figure 3. (A) Trough serum natalizumab concentration and (B) trough α4-integrin saturation by treatment arm



Safety, tolerability, and immunogenicity

- Adverse events were consistent with the known safety profile of natalizumab (data not shown).[4]
  - Rates of adverse events related to IV and SC administration, such as injection site reactions and reports of pain, were low (Table 3).
- Twenty-three patients (8%) had ≥1 serious adverse event during the randomized treatment period. Of these patients, 7 had serious adverse events that led to withdrawal from the study.
  - One fatal case of metastatic pulmonary adenocarcinoma (in the 300 mg SC q12wk arm) was reported. There was a positive family history; the death was considered not related to the study treatment.
  - There was 1 case of PML (in the 300 mg IV q4wk arm, with anti–JC virus antibody positive status, no prior immunosuppressant use, and total natalizumab exposure of 34 infusions).
- Anti-natalizumab antibodies were absent in the 300 mg IV and SC q4wk arms.
  - Persistent antibodies were detected in 1 patient in the 300 mg IV q12wk arm and 1 patient in the 150 mg IV q12wk arm.

Table 3. Incidence of adverse events of interest by preferred term

Event, n (%)	Natalizumab 300 mg IV q4wk (n=64)	Natalizumab 300 mg SC q4wk (n=45)	Natalizumab 300 mg IV q12wk (n=52)	Natalizumab 300 mg SC q12wk (n=54)	Natalizumab 150 mg IV q12wk (n=47)	Natalizumab 150 mg SC q12wk (n=38)	Total (N=290)
Drug hypersensitivity	1 (2)						1 (<1)
Hypersensitivity		1 (2)					1 (<1)
Erythema	2 (4)	1 (2)					3 (1)
Pruritus		1 (2)	1 (2)				2 (<1)
Dermatitis	1 (2)						1 (<1)
Dermatitis allergic		1 (2)					1 (<1)
Pruritus generalized				1 (2)			1 (<1)
Rash					1 (2)		1 (<1)
Rash generalized			1 (2)				1 (<1)
Rash maculopapular				1 (2)			1 (<1)
Urticaria		1 (2)					1 (<1)
Injection site pain		1 (2)		3 (6)		3 (8)	7 (2)
Administration site pain		1 (2)					1 (<1)
Injection site erythema				1 (2)			1 (<1)
Injection site hematoma				1 (2)			1 (<1)
Injection site reaction		1 (2)					1 (<1)

CONCLUSIONS

- Administration of natalizumab q12wk was associated with increased MRI and relapse activity, leading to early closures of the q12wk study arms.
- Natalizumab 300 mg SC q4wk was comparable to standard 300 mg IV q4wk dosing with respect to clinical and MRI efficacy, PK/PD, safety, and immunogenicity.

References

[illegible]

Disclosures

[illegible]

Acknowledgments

[illegible]

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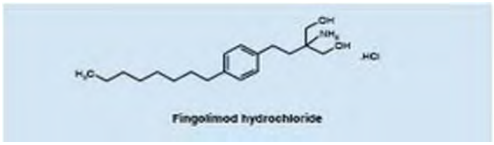
Fingolimod (FTY720)



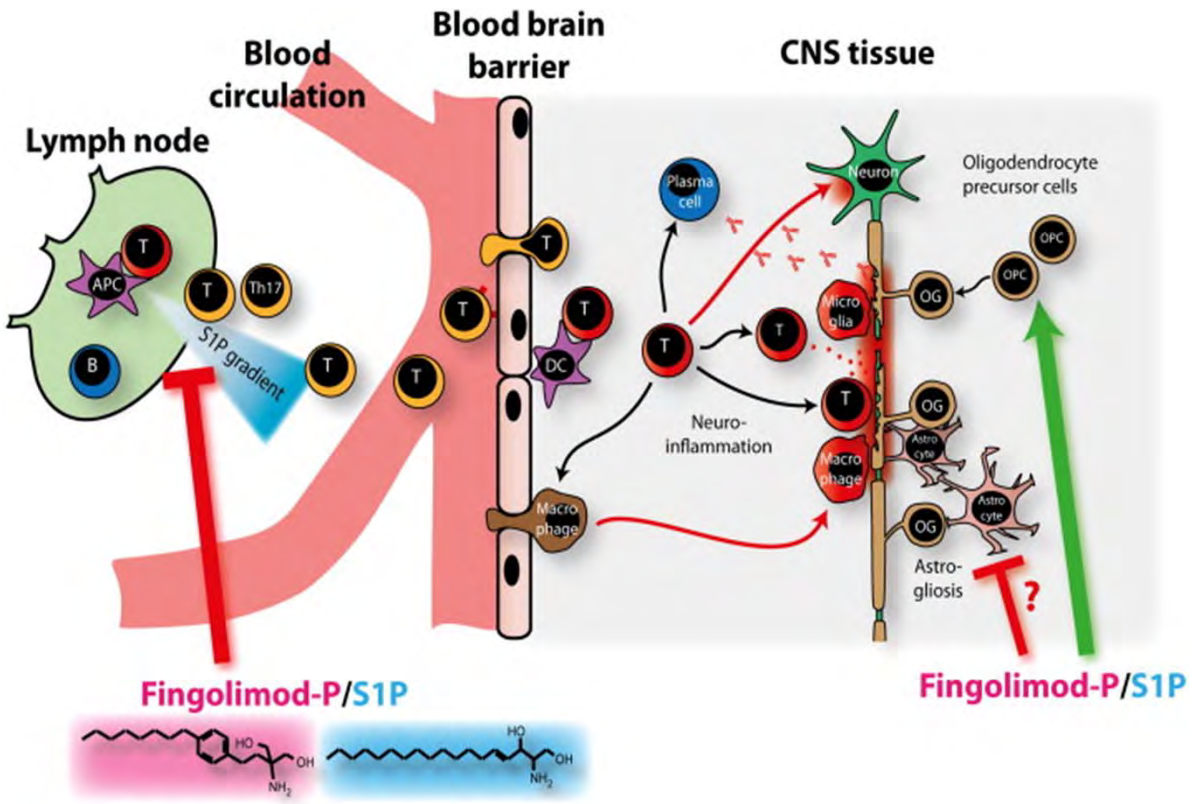
- **Analogo sintetico del *Myrocin*, metabolita dei funghi**

  Isaria sinclairii e _Myrothecium verruccaria_
- **Analogo strutturale e modulatore dei recettori sfingosina-1-fosfato (S1PR) che si lega con differente affinità a 4 dei 5 recettori conosciuti (S1P1, S1P3, S1P4, S1P5)**
- **22 settembre 2010 approvato FDA come terapia I linea SMRR**
- **17 marzo 2011 approvato EMA e 22 novembre 2011 AIFA (GU n.272)in SMRR ad alta attività di malattia nonostante il trattamento con INF beta (A), forma grave a rapida evoluzione (B)**
- **Dose orale singola quotidiana (0.5 mg)**
- **Emivita media di 6-9 gg**
- **Raggiunge lo steady state in 1-2 mesi**
- **È un profarmaco (necessita fosforilazione)**

Fingolimod: mda

Figolimod determina:

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



trattiene i linfociti circolanti (<2% linfociti totali) nei linfonodi riducendone la conta periferica e la loro circolazione nel SNC

Sequestro selettivo: non interferisce con l' immunosorveglianza

Studi registrativi: outcomes clinici

Outcome	FREEDOMS 2-year placebo control	TRANSFORMS 1-year IFNβ-1a, IM control
ARR (⬇)	54%***	52%***
Time to relapse, HR (⬆)	52%***	48%***
Proportion relapse-free (⬆)	49%***	18%***
Time to disability progression, 3 month, HR (⬆)	30%*	29%
Time to disability progression, 6 month, HR (⬆)	37%**	-
MSFC mean difference, z-score (⬆)	0.09*	0.07*

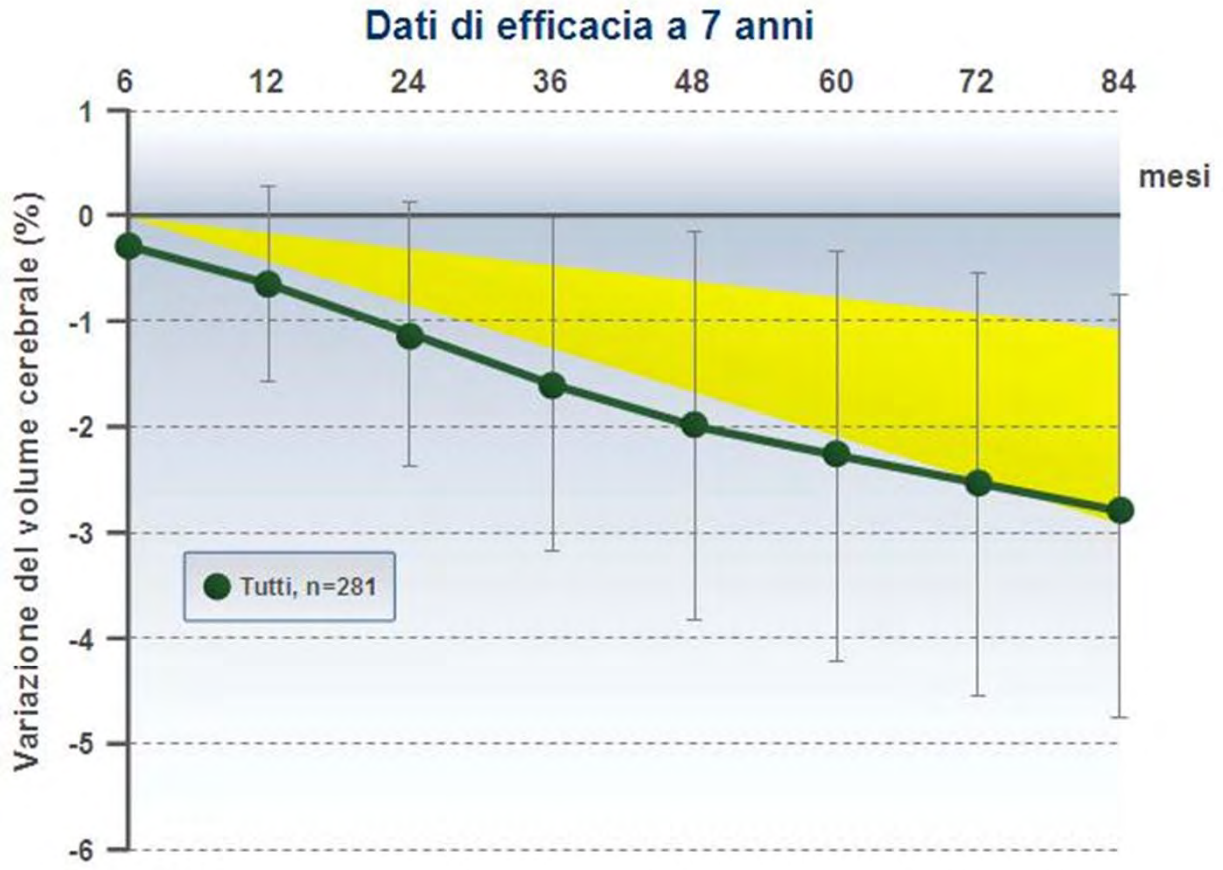
Data shown are for fingolimod 0.5 mg; *p≤0.05; **p≤0.01; ***p≤0.001
ARR, annualised relapse rate; HR, hazard ratio; IFN, interferon; IM, intramuscular; MSFC, Multiple Sclerosis functional composite

Studi registrativi: outcomes RMN

Outcome	FREEDOMS 2-year placebo control	TRANSFORMS 1-year IFNβ-1a, IM control
T2 lesion count (⬇)	74%***	35%**
Gd-enhancing lesion count (⬇)	82%***	55%***
Brain volume loss, atrophy (⬇)	38%***	40%***

Data shown are for fingolimod 0.5 mg; **p≤0.01; ***p≤0.001
ARR, annualised relapse rate; Gd, gadolinium; IFN, interferon; IM, intramuscular
fingolimod Summary of Product Characteristics, 4 April 2011

Fingolimod: dati perdita volume cerebrale a 7anni

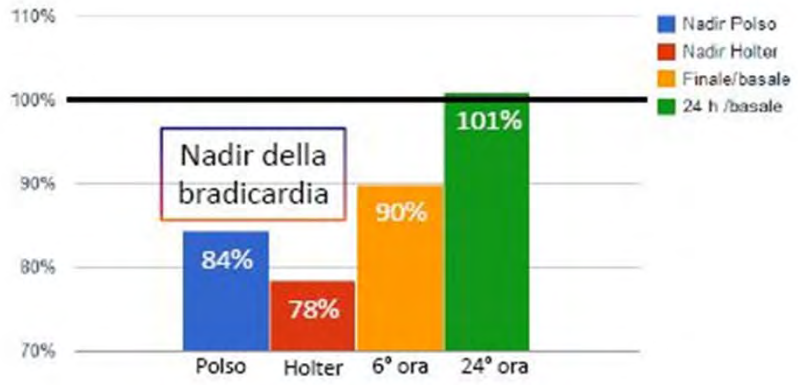


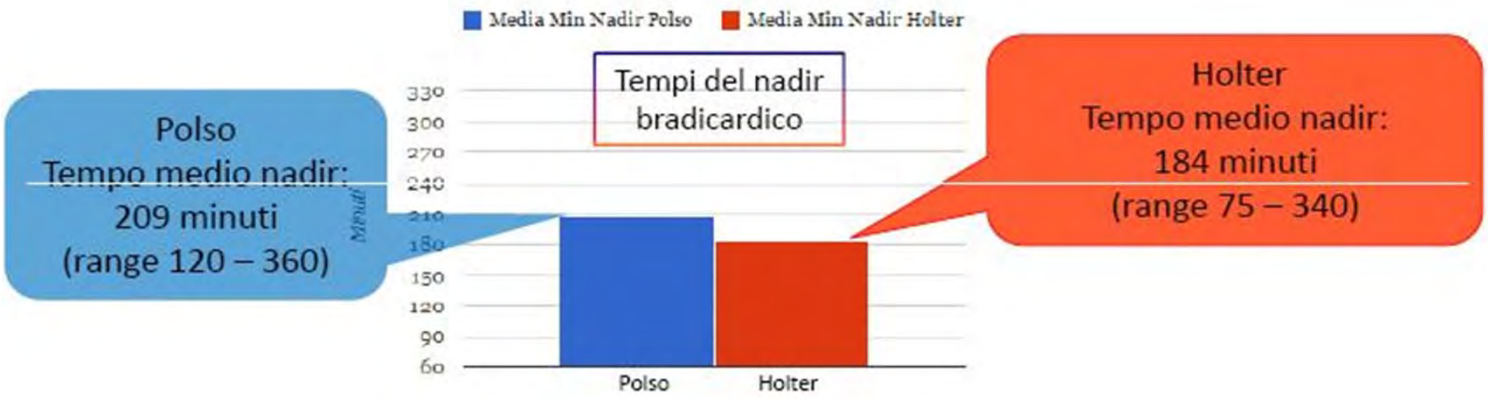
L'area gialla indica la stima del tasso di atrofia cerebrale in soggetti sani (0,1-0,4% all'anno)

J. Actel et al. Poster P01.129 AAN 2012

Fingolimod problemi: gestione prima dose

- Bradicardia: non vi è correlazione tra frequenza basale e nadir.
- Il rischio di BAV non è legato alla bradicardia.





- Attenti a terapie concomitanti e condizioni cliniche particolari

Fingolimod problemi: infezioni erpetiche

- 1.25 mg: due decessi (Zoster generalizzato ed encefalite erpetica)
- 1.25 mg tre SAE (due Zoster polisegmentale e Zoster genitale)

  - un caso di Zoster disseminato con completa risoluzione dopo trattamento con Aciclovir

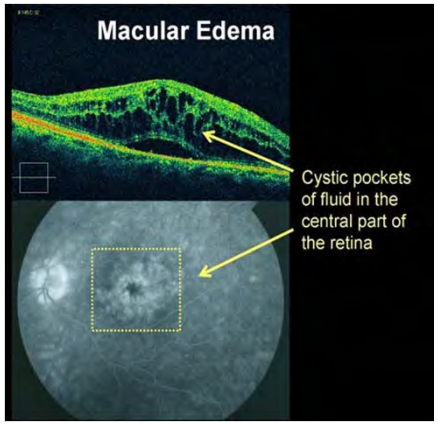
- **Recente caso in Italia di varicella zoster generalizzata con interessamento viscerale e decesso in pz Ab+ ⇨ necessità di valutare titolo anticorpale prima di inizio terapia?**

Gestione delle vaccinazioni:

- Sospendere il Fingolimod due mesi prima di effettuare un vaccino vivo atteuato
- Attendere un mese prima della ripresa della terapia con Fingolimod

Fingolimod problemi: edema maculare e gravidanza

- 0.4% negli studi clinici
- Aumentato rischio in pz con storia di uveite
  e con diabete mellito (OCT basale)
- Compare entro i primi 3-4 mesi
- Risoluzione spontanea dopo interruzione terapia
- Non dati su ricorrenza dopo ripresa trattamento



- Attraversa la placenta ed è teratogeno (classe C)
- La contraccezione va mantenuta per 2 mesi dopo la sospensione del farmaco
- È ampiamente secreto nel latte (studi animali)

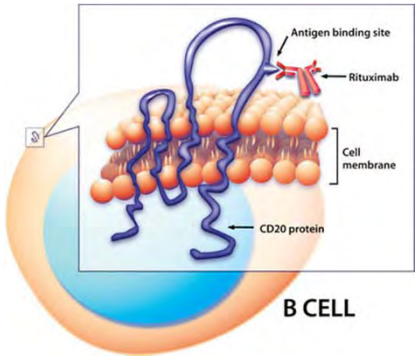
FINGOLIMOD: PML

In February 2015, a case of PML in a patient treated with fingolimod without prior history of natalizumab treatment was announced by Novartis.

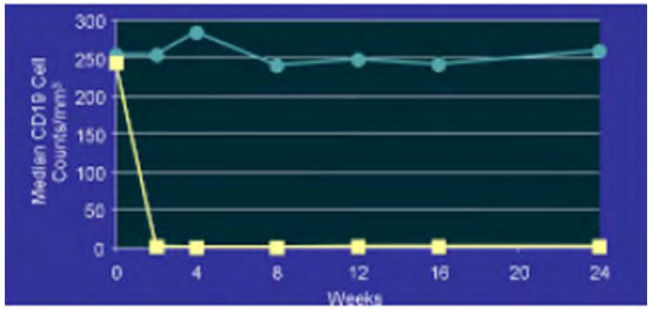
- The patient developed several new large lesions including cerebellar involvement that were thought to be atypical for MS.
- JCV in the spinal fluid was confirmed by PCR.
- Throughout the treatment period with fingolimod, absolute lymphocyte counts were in the range of 240 and 890 cells/µL, which is typical for treatment with this agent.
- The patient was not described as having manifested symptoms of PML and was reported to be "doing well."
- Vigilance for signs of PML(incl regular MRIs) must therefore also accompany treatment with this agent.

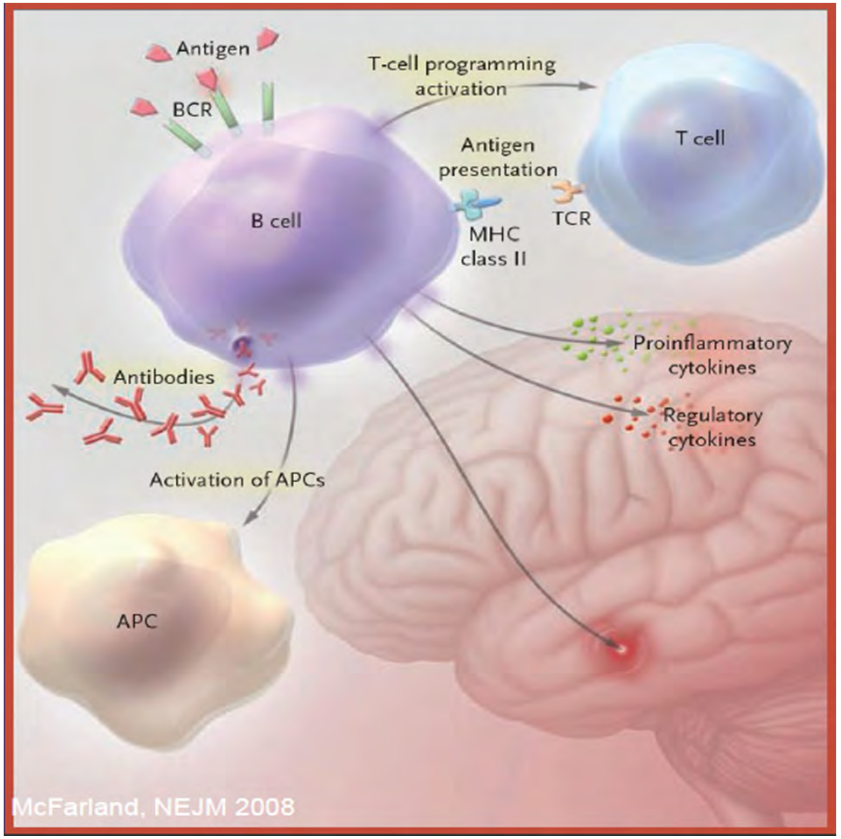
Paused

Rituximab



- Anticorpo monoclonale chimerico con target linfociti B CD20+
- Trattamento NHL in monoterapia o associazione e AR in associazione con Methotrexate
- Determina deplezione B-cells
- Non interessa la plasmacellule



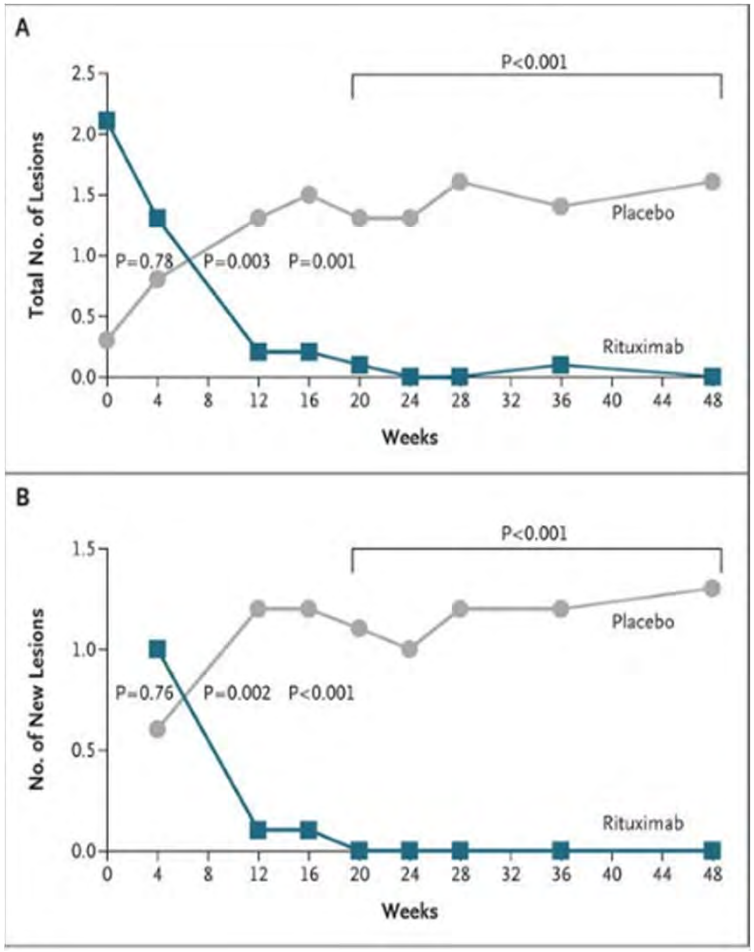


ORIGINAL ARTICLE

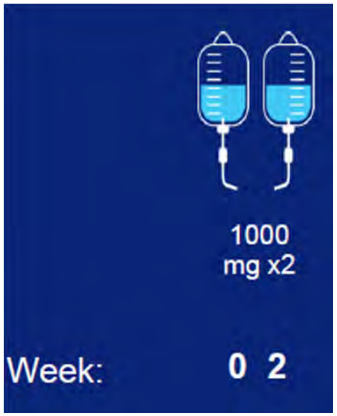
B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D., Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D., Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D., Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D., and Craig H. Smith, M.D. for the HERMES Trial Group

N Engl J Med 2008; 358:676-688 | February 14, 2008 | DOI: 10.1056/NEJMoa0706383



N° medio di lesioni GAD+ totali per settimana

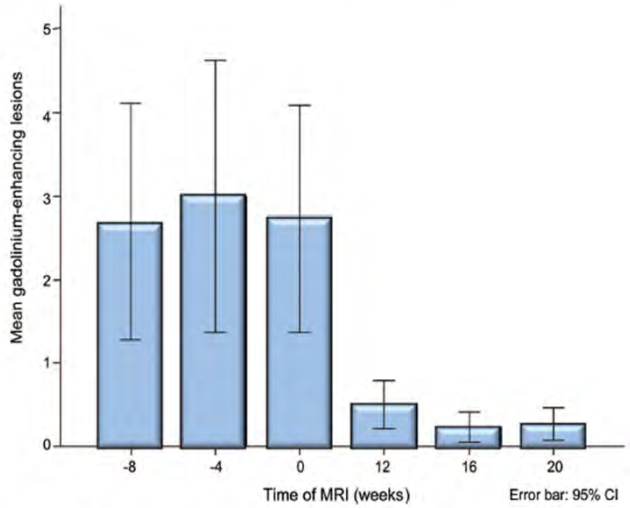


- Studio fase II RRSM

N° medio di nuove lesioni GAD+ per settimana

- Studio fase II/III PPMS: negativo. Hawker K et al, Ann Neurol, 2009.

Figure 3 Reduction in mean number of enhancing lesions after rituximab



CI = confidence interval.

Rituximab add-on therapy for breakthrough relapsing multiple sclerosis

A 52-week phase II trial

R.T. Naismith, MD
L. Piccio, MD, PhD
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ABSTRACT

Objective: B cells and the humoral immune system have been implicated in the pathogenesis of multiple sclerosis (MS). This study sought to evaluate the efficacy, safety, and tolerability of add-on therapy with rituximab, a monoclonal antibody that depletes circulating B cells, in subjects with relapsing MS with breakthrough disease defined by clinical and MRI activity (Class III evidence).

Methods: Thirty subjects with a relapse within the past 18 months despite use of an injectable disease-modifying agent, and with at least 1 gadolinium-enhancing (GdE) lesion on any of 3 pretreatment MRIs, received rituximab administered at 375 mg/m^2 weekly × 4 doses. Three monthly posttreatment brain MRI scans were obtained beginning 12 weeks after the first infusion. Multiple Sclerosis Functional Composite (MSFC) and Expanded Disability Status Scale (EDSS) were obtained at baseline and throughout the posttreatment follow-up.

Results: GdE lesions were reduced after treatment with rituximab, with 74% of posttreatment MRI scans being free of GdE activity compared with 26% free of GdE activity at baseline ($p < 0.0001$). Median GdE lesions were reduced from 1.0 to 0, and mean number was reduced from 2.81 per month to 0.33 after treatment (88% reduction). MSFC improved as well ($p = 0.02$). EDSS remained stable.

Conclusion: Rituximab add-on therapy was effective based upon blinded radiologic endpoints in this phase II study. In combination with standard injectable therapies, rituximab was well-tolerated with no serious adverse events. B-cell-modulating therapy remains a potential option for treatment of patients with relapsing MS with an inadequate response to standard injectable therapies.

Classification of evidence: This study provides Class III evidence that add-on rituximab reduces gadolinium-enhancing brain lesions in multiple sclerosis. *Neurology*® 2010;74:1860-1867

Casi di PML con Rituximab (all'Aprile 2010)

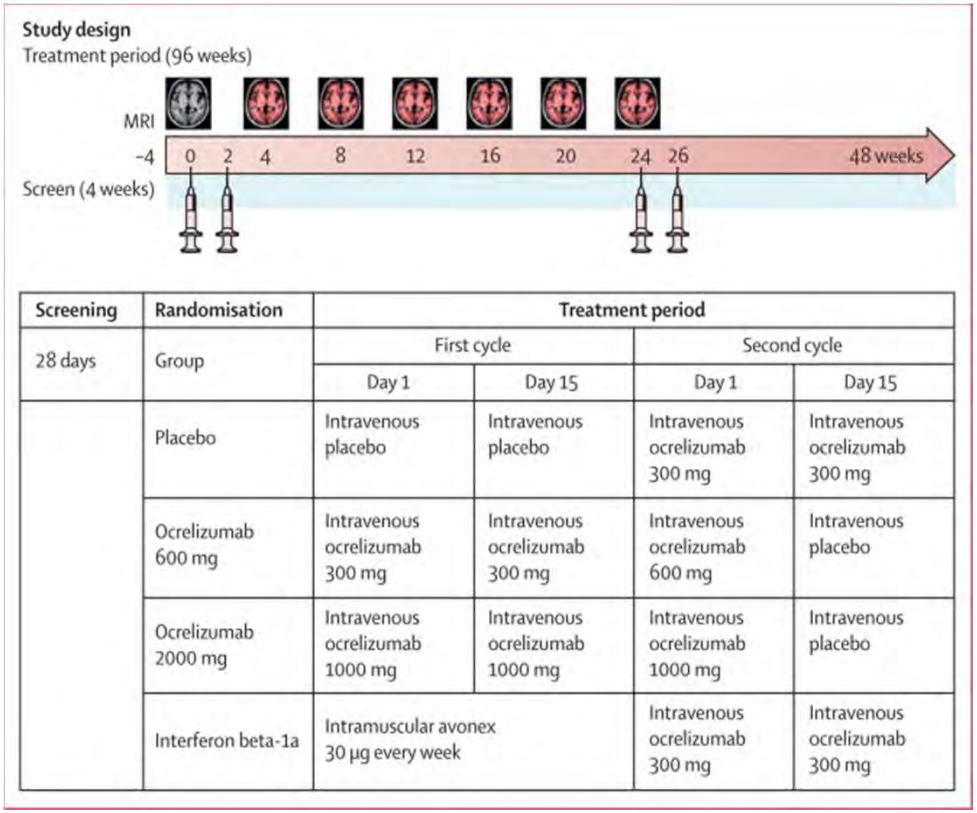
118,000 patients have been treated for RA with Rituximab

Disease	Number of confirmed PML cases
MS	0
RA	7
SLE + other autoimmune diseases	5 + 5
Oncology + hematology	135 + 2
unknown indications	2

Ocrelizumab

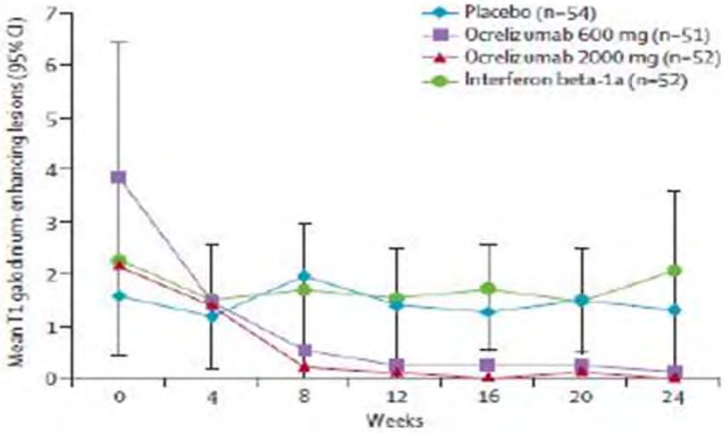
- Anticorpo ricombinante umanizzato antiCD20 Bcell
- Minor immunogenicità rispetto a Rituximab

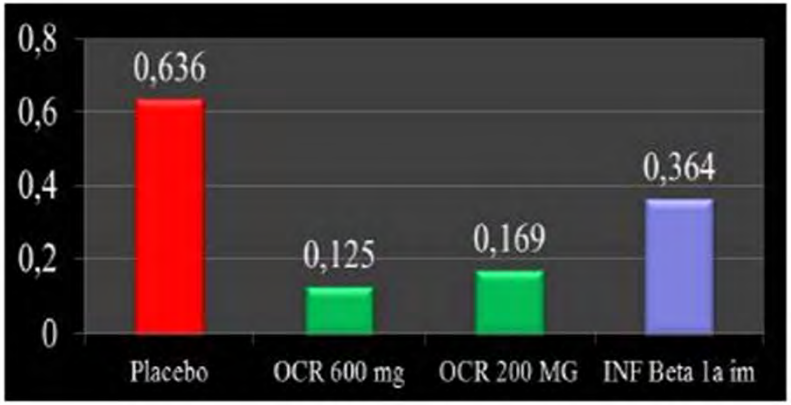
Studio di fase II multicentrico randomizzato



Screening	Randomisation	Treatment period			
28 days	Group	First cycle		Second cycle	
		Day 1	Day 15	Day 1	Day 15
	Placebo	Intravenous placebo	Intravenous placebo	Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 300 mg
	Ocrelizumab 600 mg	Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 600 mg	Intravenous placebo
	Ocrelizumab 2000 mg	Intravenous ocrelizumab 1000 mg	Intravenous ocrelizumab 1000 mg	Intravenous ocrelizumab 1000 mg	Intravenous placebo
	Interferon beta-1a	Intramuscular avonex 30 µg every week		Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 300 mg

Ocrelizumab





Risultati significativi sia per la riduzione delle lesioni GAD + che per l'ARR

Mean Gad+ (24w): ↓ versus placebo: 89% (600 mg), 92% (2000 mg).
Relapse Rate vs placebo (24w): ↓ 80% (600 mg), ↓ 73% (2000 mg)

Kappos L. ECTRIMS 2011, Kappos et al. Lancet 2011

ALEMTUZUMAB:
MECHANISM OF ACTION

- Humanized monoclonal antibody used for B-cell chronic lymphocytic leukemia
- Targets CD52, a glycoprotein expressed by B and T lymphocytes and other immune system components
- Widespread and sustained depletion of CD52 positive cells, followed first by slow repopulation of B cells and eventually of T cells.
- Possible "sparing" of T cells with a regulatory phenotype, thus inducing a durable "resetting" of the immune system

Paused

- DOSING STRATEGY:

  IV Infusion for 5 days at *year 1*

  IV infusion for 3 days at *year 2*

Hu Y, et al. Investigation of the mechanism of action of alemtuzumab in a human CD52 transgenic mouse model. Immunology. 128(2), 260-70 (2009).
Cox AL, et al. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. Eur J Immunol. 35, 3332–42 (2005).

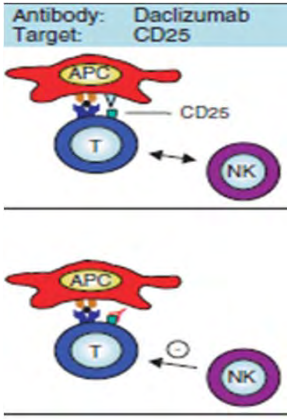
ALEMTUZUMAB VS INTERFERON-B1A: CARE-MS PHASE III STUDIES

	CARE – MS1		CARE – MS2	
	IFN-B1a	Alemtuzumab (12mg)	IFN-B1a	Alemtuzumab (12mg)
Ann. relapse rate	0.39	0.18	0.52	0.26
Risk reduction		54.9% (*P*<0.0001)		49.4% (*P*<0.0001)
Sustained disability (% pts)	11	8	21.1	12.7
Risk reduction		30% (*P*=0.22)		42% (*P*=0.0084)
Δ EDSS from baseline	- 0.14	- 0.14	0.24	- 0.17
Net EDSS change				0.41 (*P*<0.0001)

Paused

Cohen JA et al. *Lancet.* 2012;380:1819-1828.
Coles AJ et al. *Lancet.* 2012;380: 1829-1839.

Daclizumab



- Anticorpo monoclonale umanizzato diretto contro il recettore linfocitario per l'IL-2 (anti CD-25)
- Inibisce l' attivazione dei linfociti T mediata dall'IL-2
- Indicato nella profilassi del rigetto del trapianto di rene allogenico
- Studi fase II/III: CHOICE, SELECT, DECIDE

ascesso muscolo psoas (decesso)

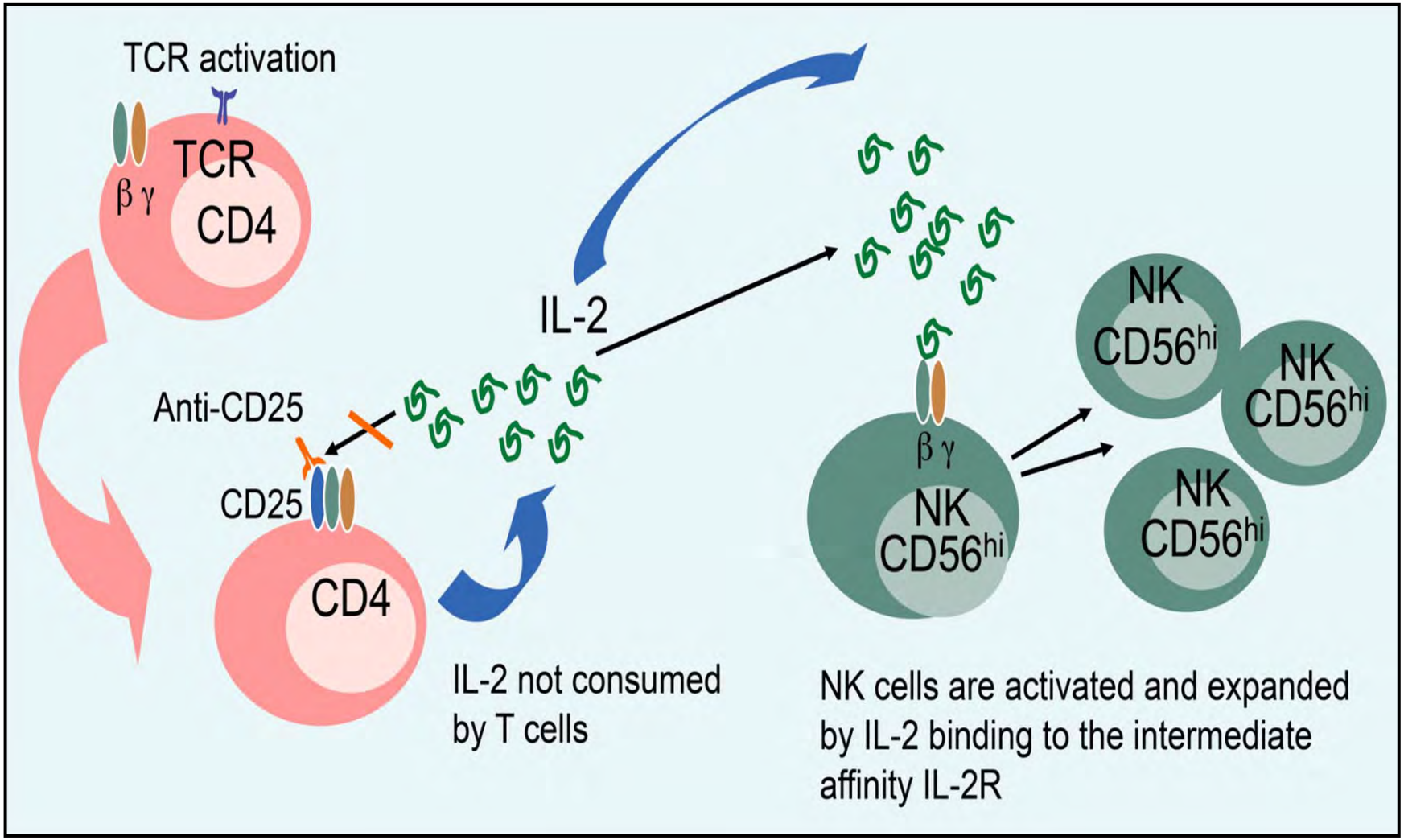
Lancet. 2013 Apr 3. pii: S0140-6736(12)62190-4. doi: 10.1016/S0140-6736(12)62190-4. [Epub ahead of print]

Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial.

Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, Stefoski D, Robinson R, Riester K, Rana J, Elkins J, O'Neill G; for the SELECT study investigators.

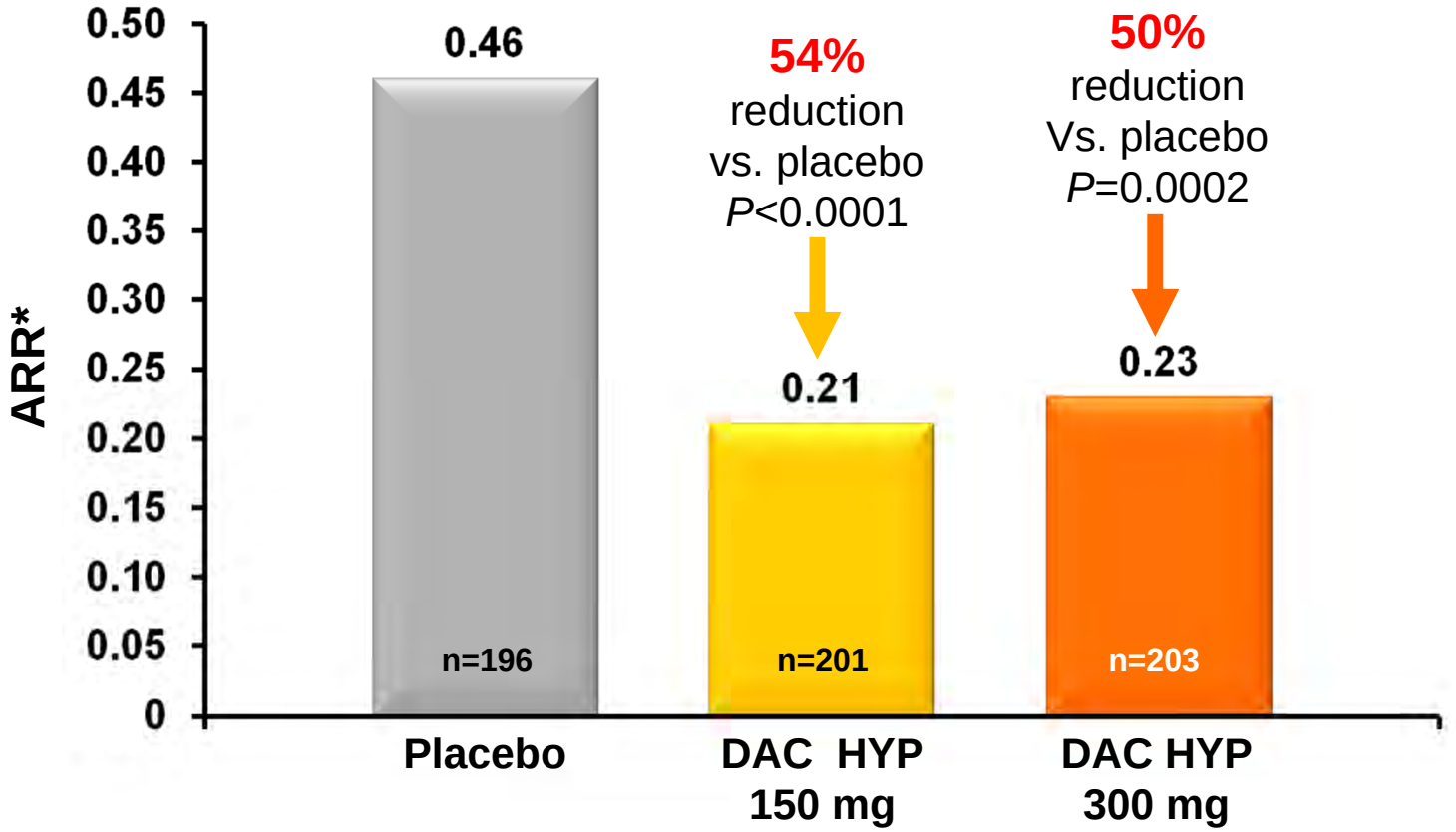
St Josef-Hospital, Ruhr-University Bochum, Bochum, Germany. Electronic address: ralf.gold@ruhr-uni-bochum.de.

Hypothesized Immunomodulatory Effects of Daclizumab Treatment



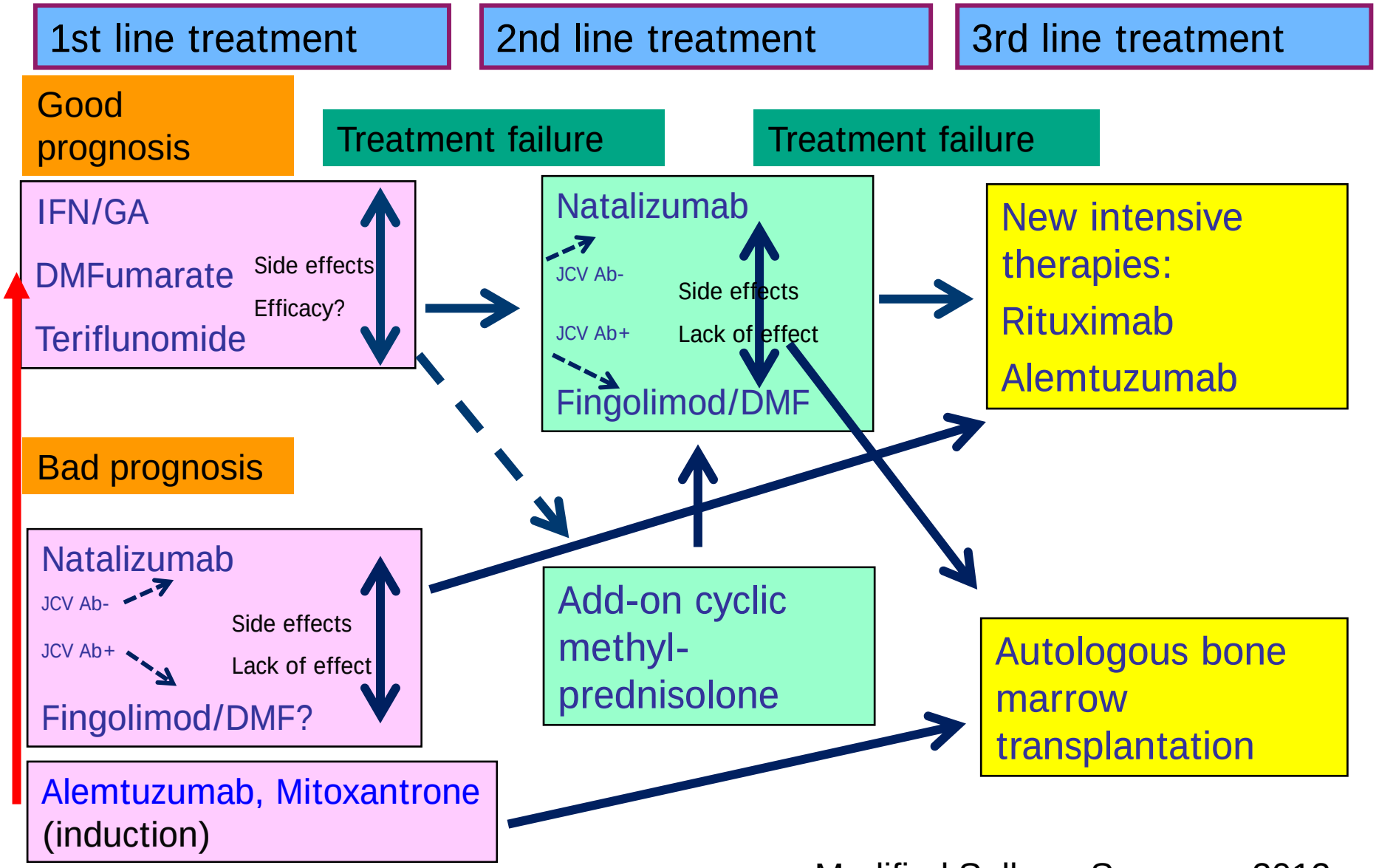
Bielekova B, et al. *Proc Natl Acad Sci USA* 2006;103: 5941–5946. Martin J, et al. *J Immunol* 2010;185:1311–1320.

Phase 2 SELECT:
Reduction in Annualized Relapse Rate



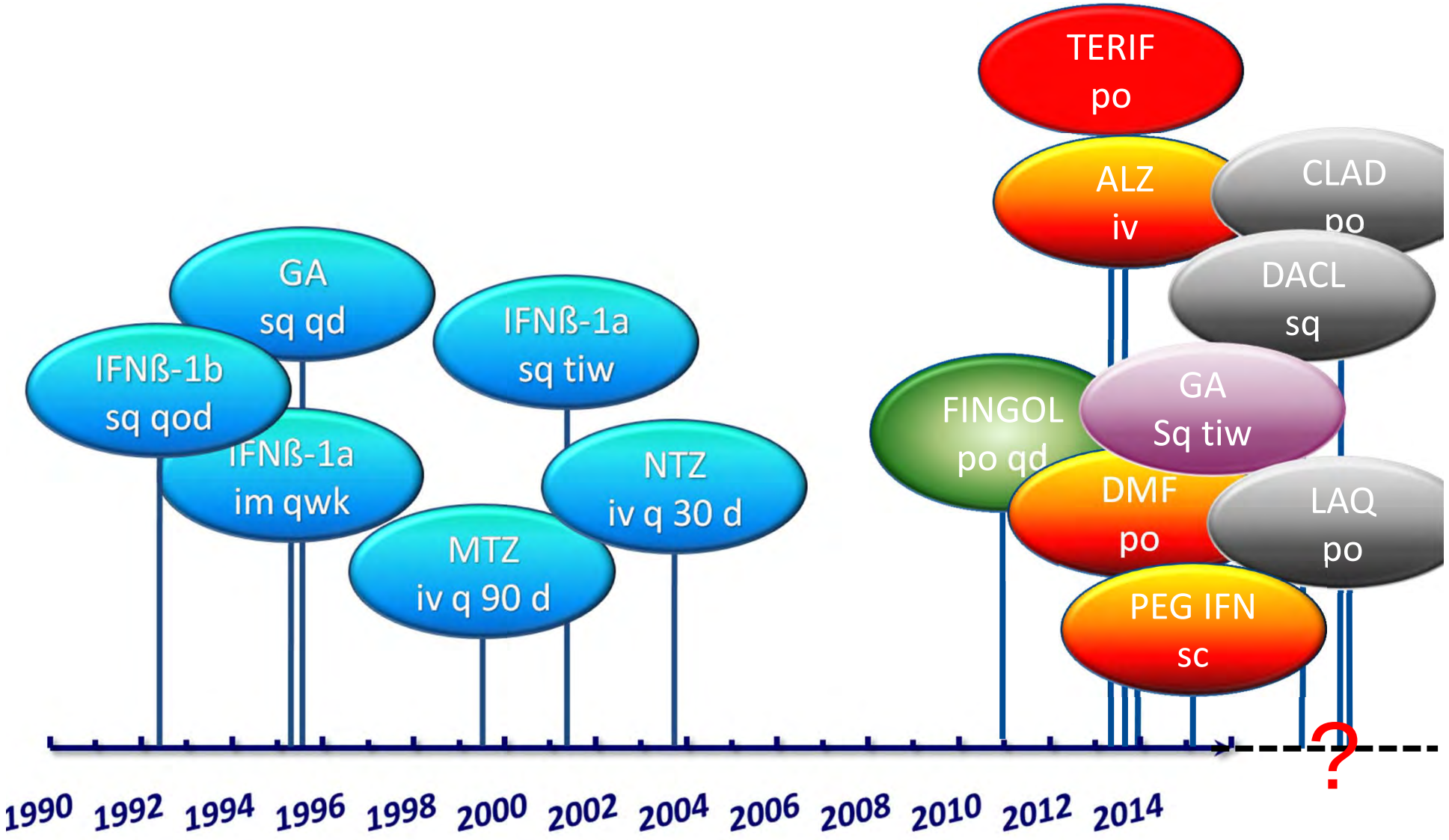
*Estimated from a negative binomial regression model adjusted for number of relapses in 1-year period prior to study entry, baseline EDSS score (≤2.5 vs >2.5), and age (≤35 vs >35 years). Gold R et al. Lancet 2013.

Algoritm for Treatment of Relapsing MS (2015)



Modified Solberg Sorensen 2012

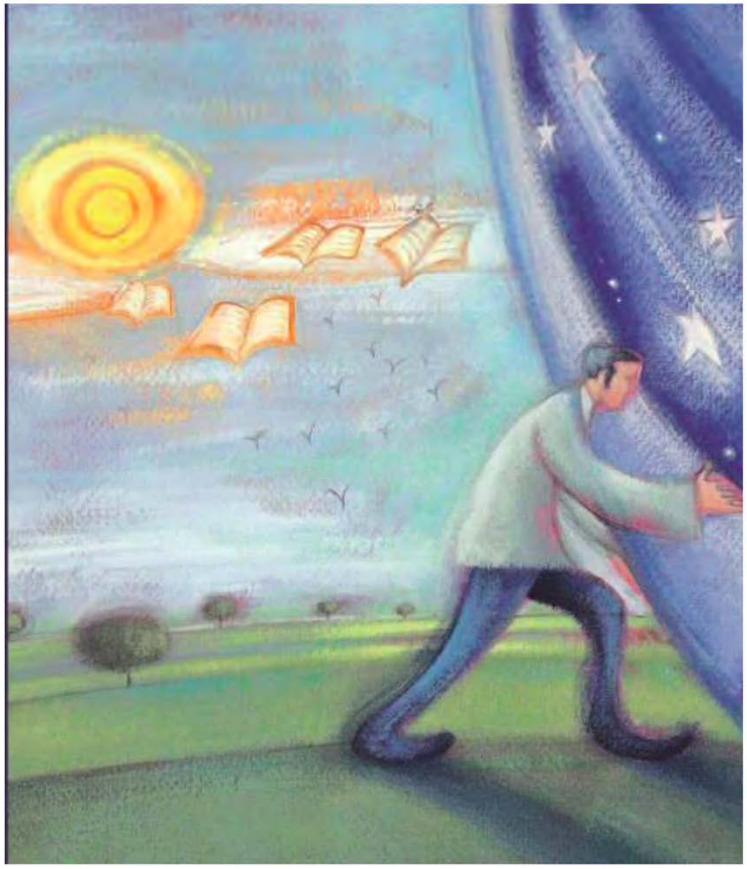
Present and “near future” Disease Modifying Drugs



REPUBBLICA ITALIANA
REGIONE SICILIANA

ASSESSORATO DELLA SANITÀ

PERCORSO DIAGNOSTICO TERAPEUTICO ASSISTENZIALE INTEGRATO PER LA SCLEROSI MULTIPLA



CRITICITA'

1. **Definizione percorsi e distribuzione compiti**
2. **Tetto di spesa (regionale?)**
3. **Sostenibilità economica attività Centri SM**
4. **Inserimento farmaci in PTORS (automatico?)**
5. **Prescrizione (es. uso sequenziale dei DMT)**
6. **Dispensazione (territoriale?)**
7. **Registri (di malattia, di terapia, etc.)**
8. **Accesso alle diagnostiche (RMN centralizzata?)**
9. **Rete riabilitativa specifica**
10. **Terapie sintomatiche**

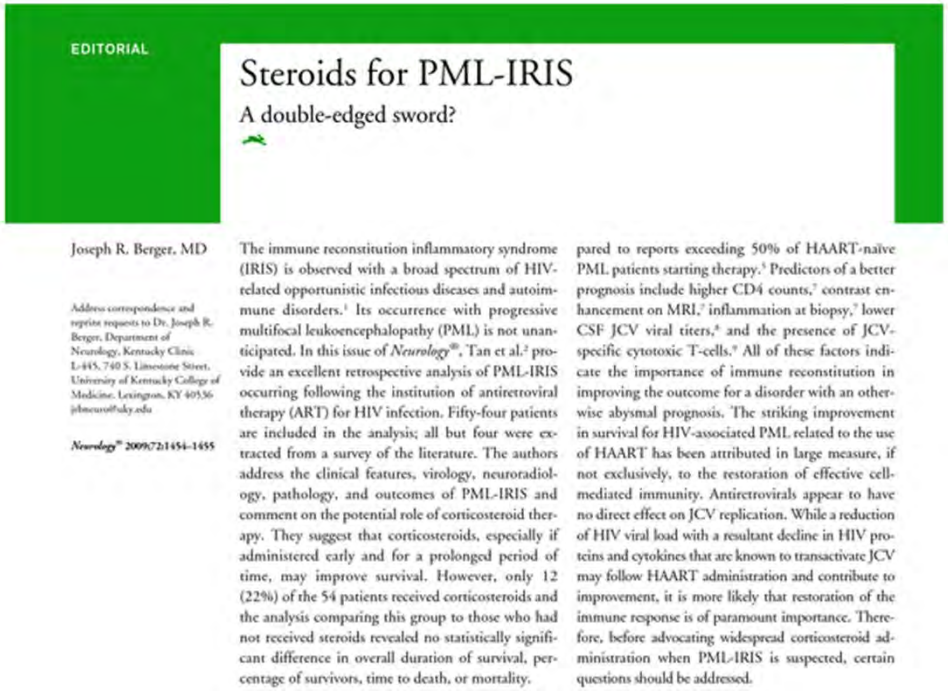
Criticità Terapeutiche PML post-NTZ

- Diagnosi
  - Precocità
  - Sede lesione virale
  - Numero copie virali
- Sospendere NTZ?
- IRIS: diagnosi; è “buona” o “cattiva”?
- Plasmaferesi: sempre?
- Steroidi solo se edema e impregnazione?
- Quale anti-virale?
- Terapia anti-epilettica? quando inserirla?
- Come trattare la brutta SM sottostante?

Parere personale: è buona!

- All'interno dell' IRIS si tenta di eliminare il JCV
- I 2 pazienti deceduti non avevano Gd-enhancement
- Una "modulazione" / timing dell'IRIS è auspicabile per bilanciare pros & cons

Trattamento steroideo della PML-IRIS



EDITORIAL

Steroids for PML-IRIS

A double-edged sword?

Joseph R. Berger, MD

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Neurology® 2009;72:1454–1455

The immune reconstitution inflammatory syndrome (IRIS) is observed with a broad spectrum of HIV-related opportunistic infectious diseases and autoimmune disorders.[1] Its occurrence with progressive multifocal leukoencephalopathy (PML) is not unanticipated. In this issue of *Neurology*®, Tan et al.[2] provide an excellent retrospective analysis of PML-IRIS occurring following the institution of antiretroviral therapy (ART) for HIV infection. Fifty-four patients are included in the analysis; all but four were extracted from a survey of the literature. The authors address the clinical features, virology, neuroradiology, pathology, and outcomes of PML-IRIS and comment on the potential role of corticosteroid therapy. They suggest that corticosteroids, especially if administered early and for a prolonged period of time, may improve survival. However, only 12 (22%) of the 54 patients received corticosteroids and the analysis comparing this group to those who had not received steroids revealed no statistically significant difference in overall duration of survival, percentage of survivors, time to death, or mortality.

pared to reports exceeding 50% of HAART-naïve PML patients starting therapy.[3] Predictors of a better prognosis include higher CD4 counts,[3] contrast enhancement on MRI,[3] inflammation at biopsy,[3] lower CSF JCV viral titers,[4] and the presence of JCV-specific cytotoxic T-cells.[5] All of these factors indicate the importance of immune reconstitution in improving the outcome for a disorder with an otherwise abysmal prognosis. The striking improvement in survival for HIV-associated PML related to the use of HAART has been attributed in large measure, if not exclusively, to the restoration of effective cell-mediated immunity. Antiretrovirals appear to have no direct effect on JCV replication. While a reduction of HIV viral load with a resultant decline in HIV proteins and cytokines that are known to transactivate JCV may follow HAART administration and contribute to improvement, it is more likely that restoration of the immune response is of paramount importance. Therefore, before advocating widespread corticosteroid administration when PML-IRIS is suspected, certain questions should be addressed.

- nell'IRIS da HIV prednisone, 1-2 mg/kg per 1-2 settimane, seguito da progressiva riduzione terapeutica

Terapie farmacologiche per PML

- Antivirali
  - Citarabina (-)
  - Zidovudina (-)
  - Cidofovir (-)
- Meflochina (?)
- Immunomodulanti (IFNs, IL-2, Maraviroc, Teriflu) (?)
- 5HT-R blockers (mirtazapina, citalopram) (?)
- CTL eterologhe (in trapiantato da donatore) (+)

anti-CCR5 Maraviroc inhibits PML

Maraviroc and JC Virus–Associated Immune Reconstitution Inflammatory Syndrome

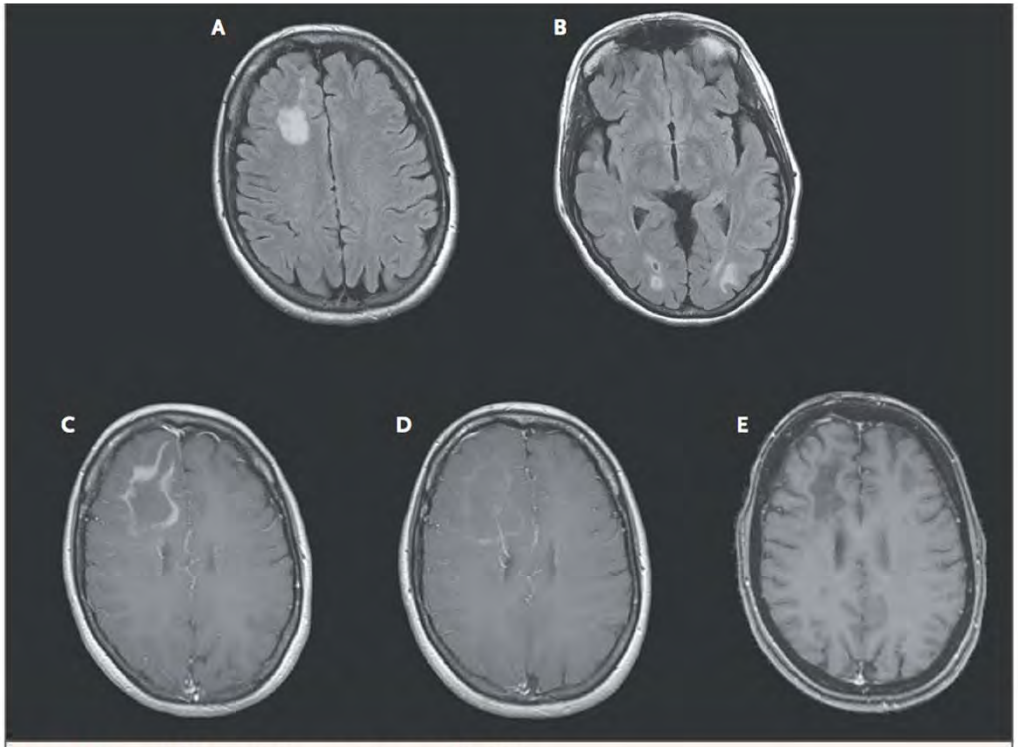


Figure 1. Sequential Magnetic Resonance Images of the Brain.

When the patient presented for treatment, axial fluid-attenuated inversion recovery images showed multilobar progressive multifocal leukoencephalopathy (Panels A and B). A T_1-weighted image after gadolinium infusion showed frank immune reconstitution inflammatory syndrome (IRIS) after the patient discontinued maraviroc (Panel C). After the patient began to receive maraviroc again, a T_1-weighted image after gadolinium infusion showed regression of IRIS (Panel D). A T_1-weighted image after gadolinium infusion obtained 2 months after gradual discontinuation of maraviroc showed stable lesions with no enhancement (Panel E).

N ENGL J MED 370;5 NEJM.ORG JANUARY 30, 2014

A new “classic” mAB approach to PML

Contents lists available at ScienceDirect

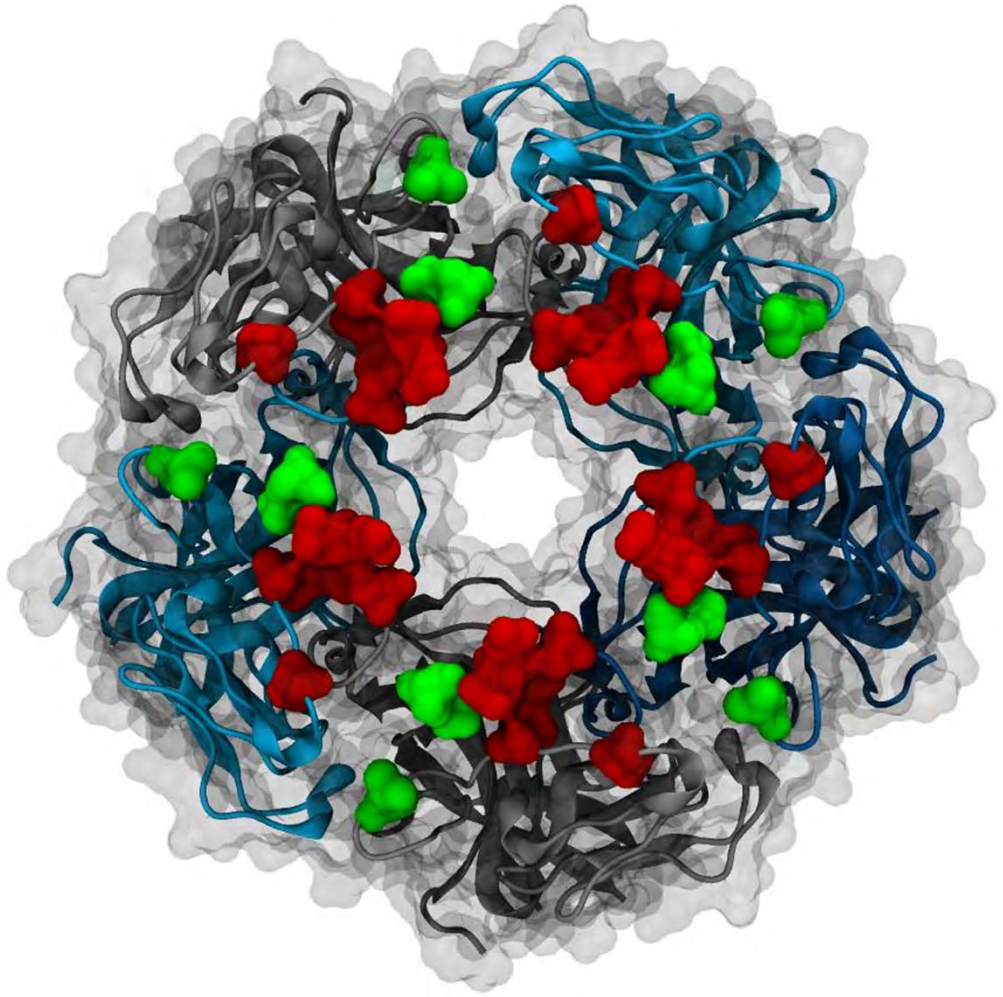
Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Cloning of the first human anti-JCPyV/VP1 neutralizing monoclonal antibody: Epitope definition and implications in risk stratification of patients under natalizumab therapy

Roberta Antonia Diotti [a,1], Nicasio Mancini [a,*,1], Nicola Clementi [a], Giuseppe Sautto [a], Guisella Janett Moreno [a], Elena Criscuolo [a], Francesca Cappelletti [a], Petr Man [b,c], Eric Forest [d], Louise Remy [d], Simone Giannecchini [e], Massimo Clementi [a], Roberto Burioni [a,*]

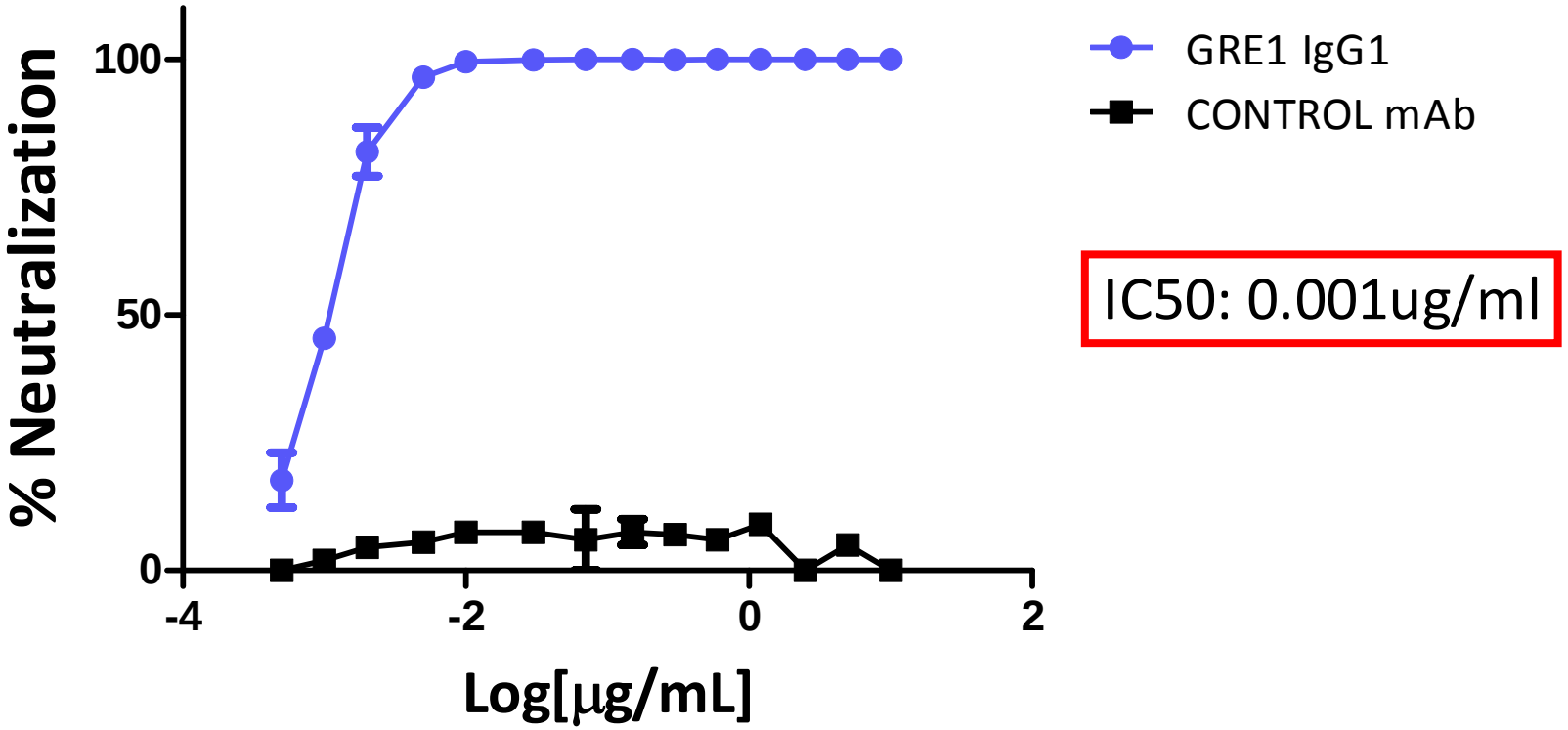
JCV/VP1 neutralizing epitopes



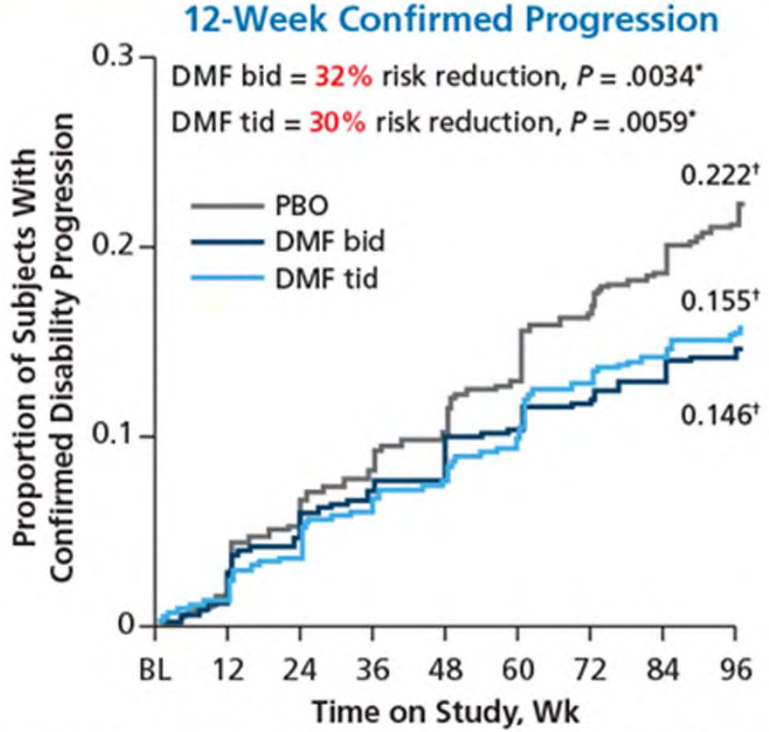
Green = JCV/VP1 residues involved in cellular receptor binding

Red = JCV/VP1 residues involved in GRE1 binding

Anti-JCV GRE1 IgG1 HuMAb neutralizing activity



DEFINE and CONFIRM Integrated Analysis: Time to 12-Week Confirmed Disability Progression[a]



- Similar risk reduction versus placebo seen for 24-week confirmed disability progression

* *P* value based on a stratified Cox proportional hazards model. † Kaplan-Meier estimate of the proportion of subjects with confirmed progression within 2 years.

[a] Pooled ITT population. Confirmed progression of disability is defined as at least a 1.0-point increase on the EDSS from a baseline EDSS score ≥1.0 confirmed at 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS score of 0.0 confirmed at 12 weeks.