Biothérapies et risques infectieux en neurologie

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XXIIe Journée Régionale de Pathologie Infectieuse

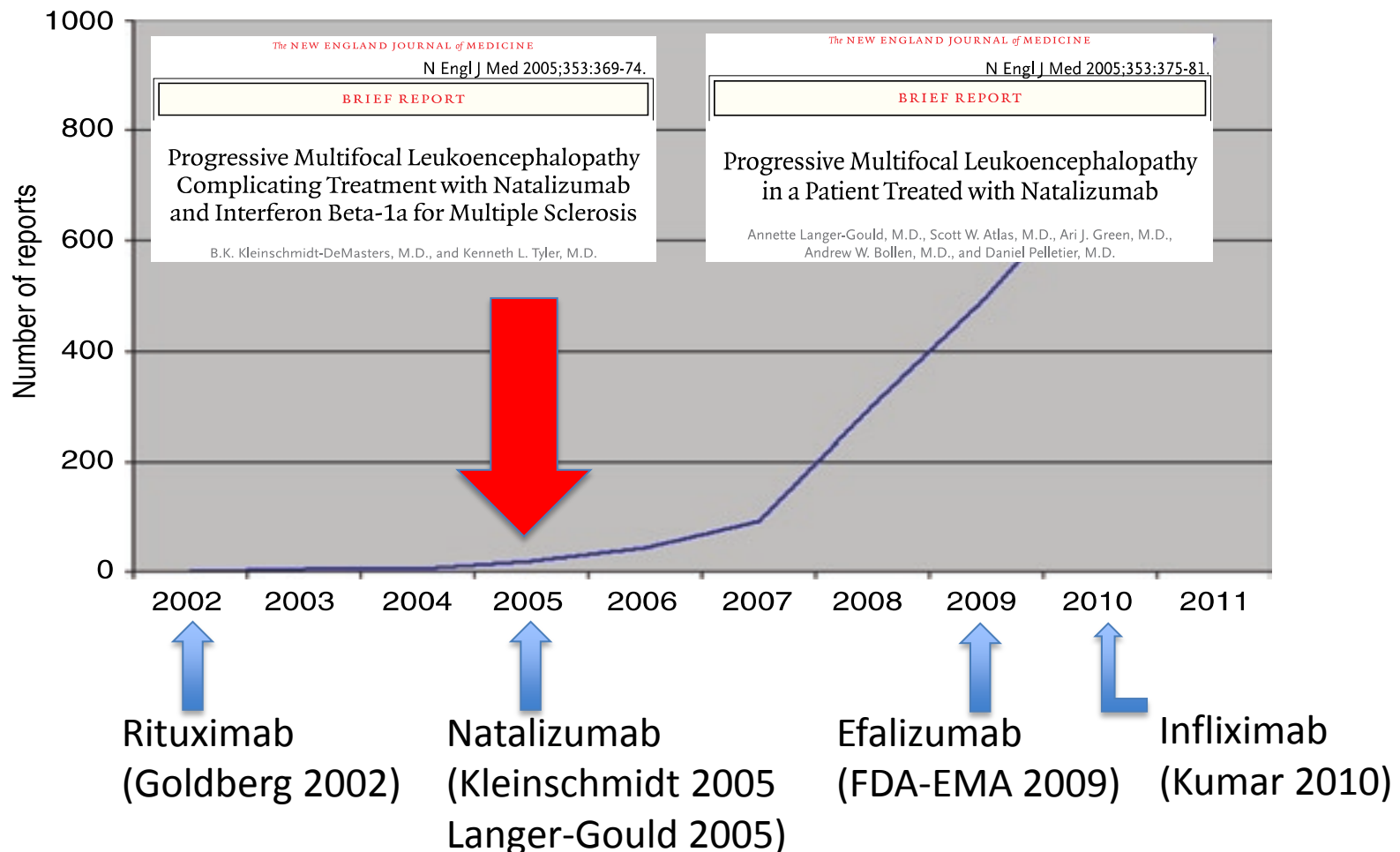Lille, 13 octobre 2015

Lieu 14
Date

Liens d'intérêts

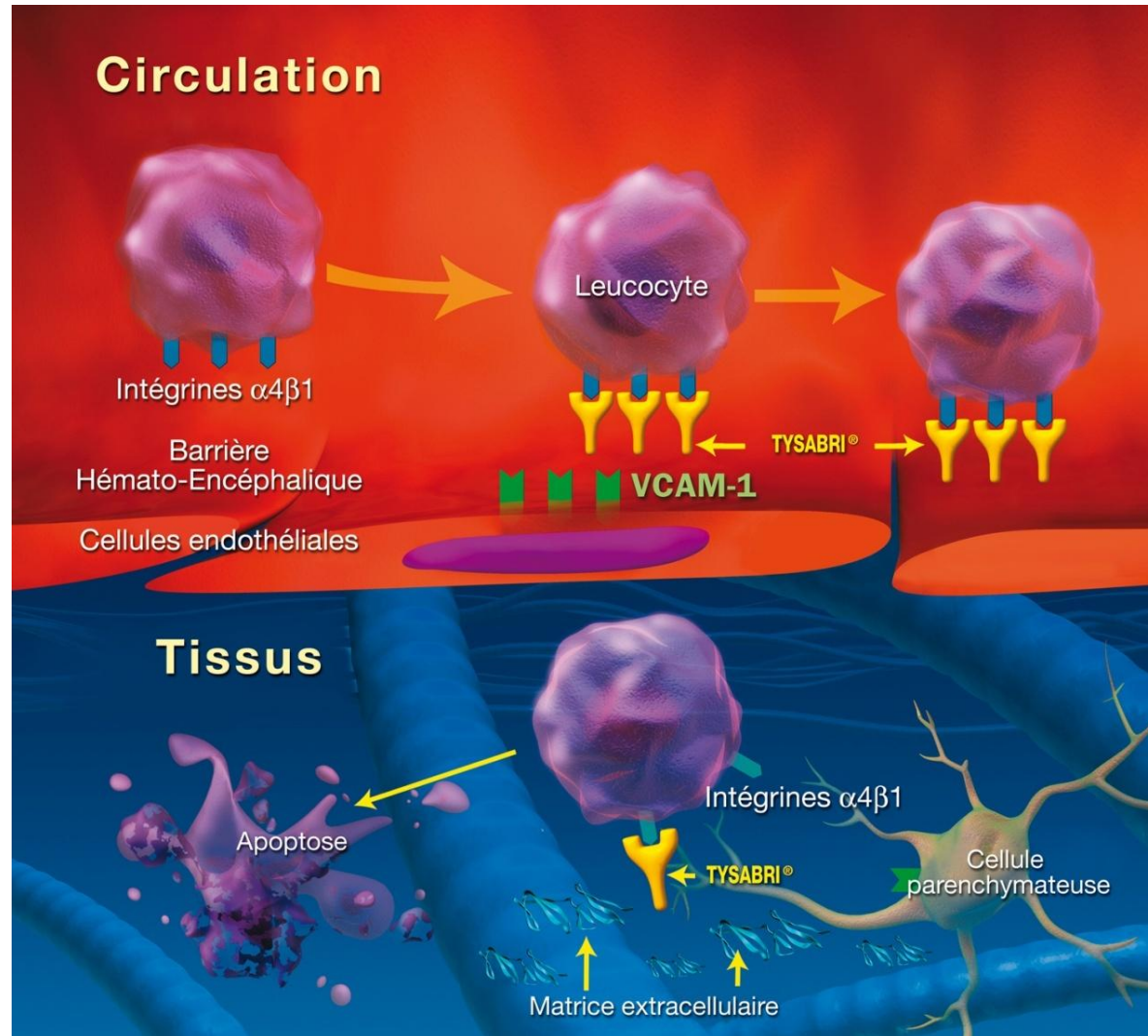**Honoraires, Congrés, et Soutiens à la recherche de:**

BIOGEN, TEVA, GENZYME-SANOFI, BAYER, MERCK-SERONO, NOVARTIS, ROCHE, ALMIRALL

PML epidemiology

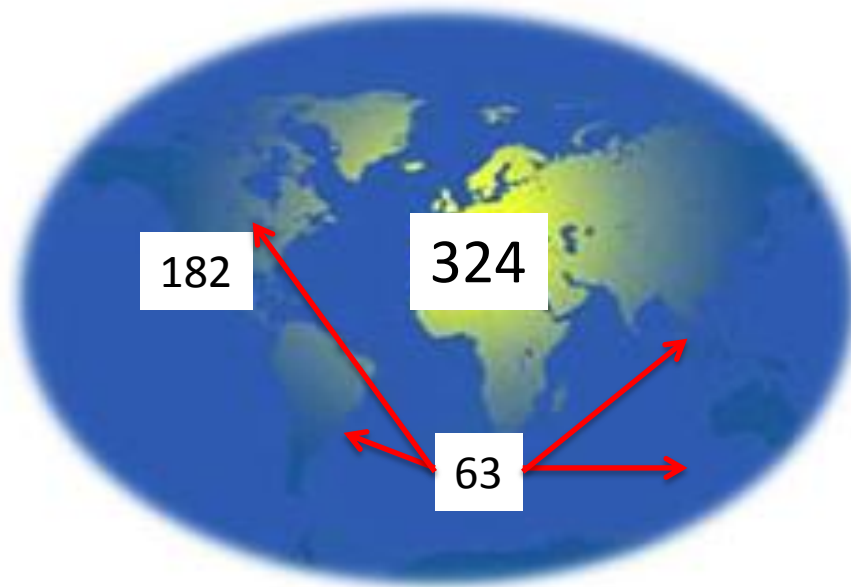Hallervorden 1930, Astrom 1958, Padgett et al. 1971 (JCV), AIDS (up to 5% develop PML)

Natalizumab: mechanism of action

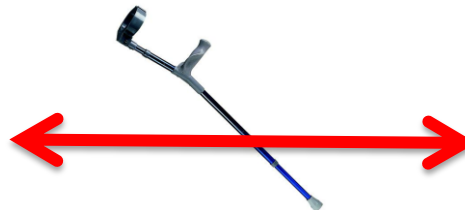# Natalizumab-associated PML epidemiology
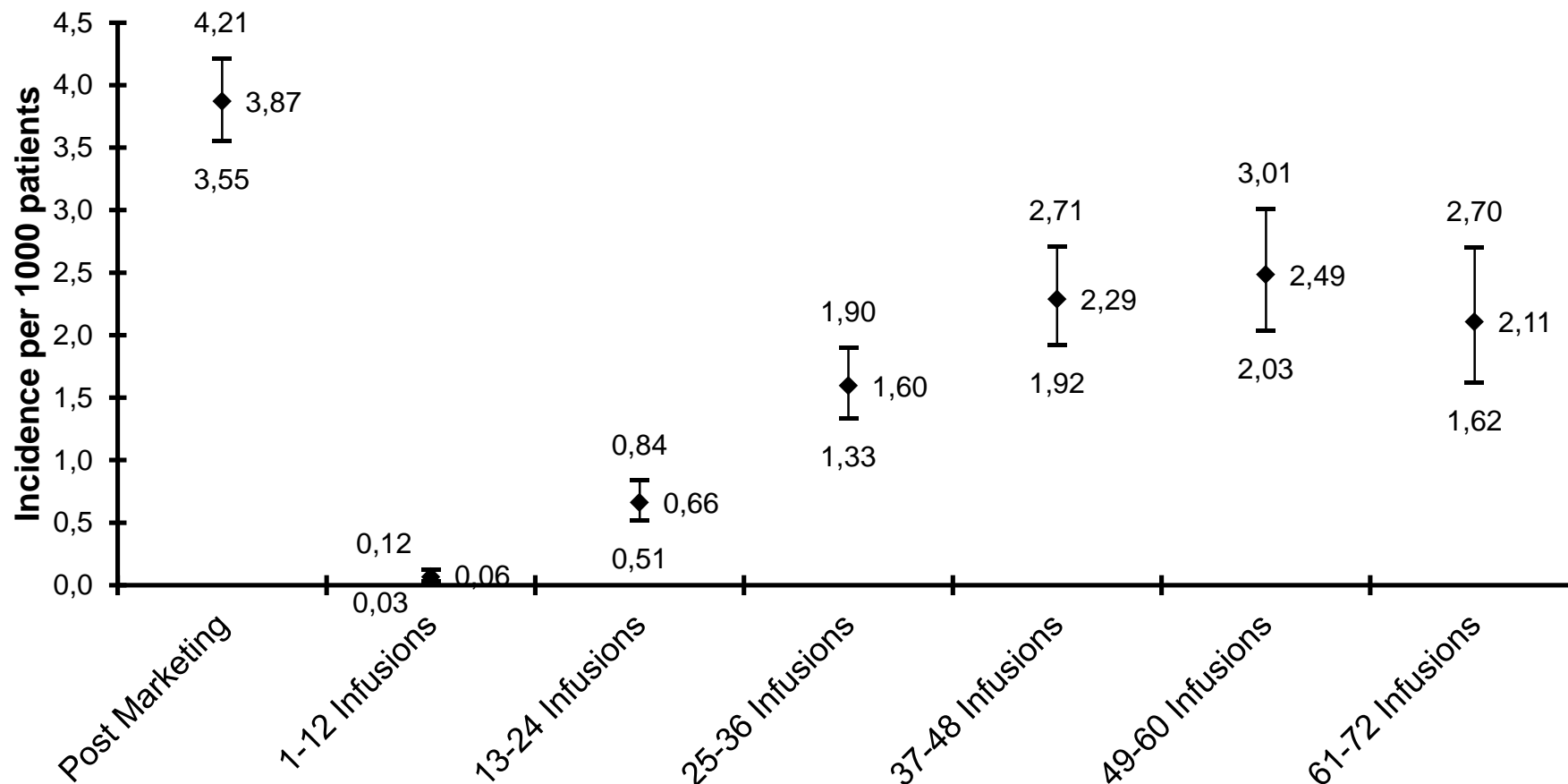
- 580 reported cases through September 5, 2015

patients 22%

Within 2-3 months
Median time to death: 2.2 months
Range: 0.1 to 15.2 months
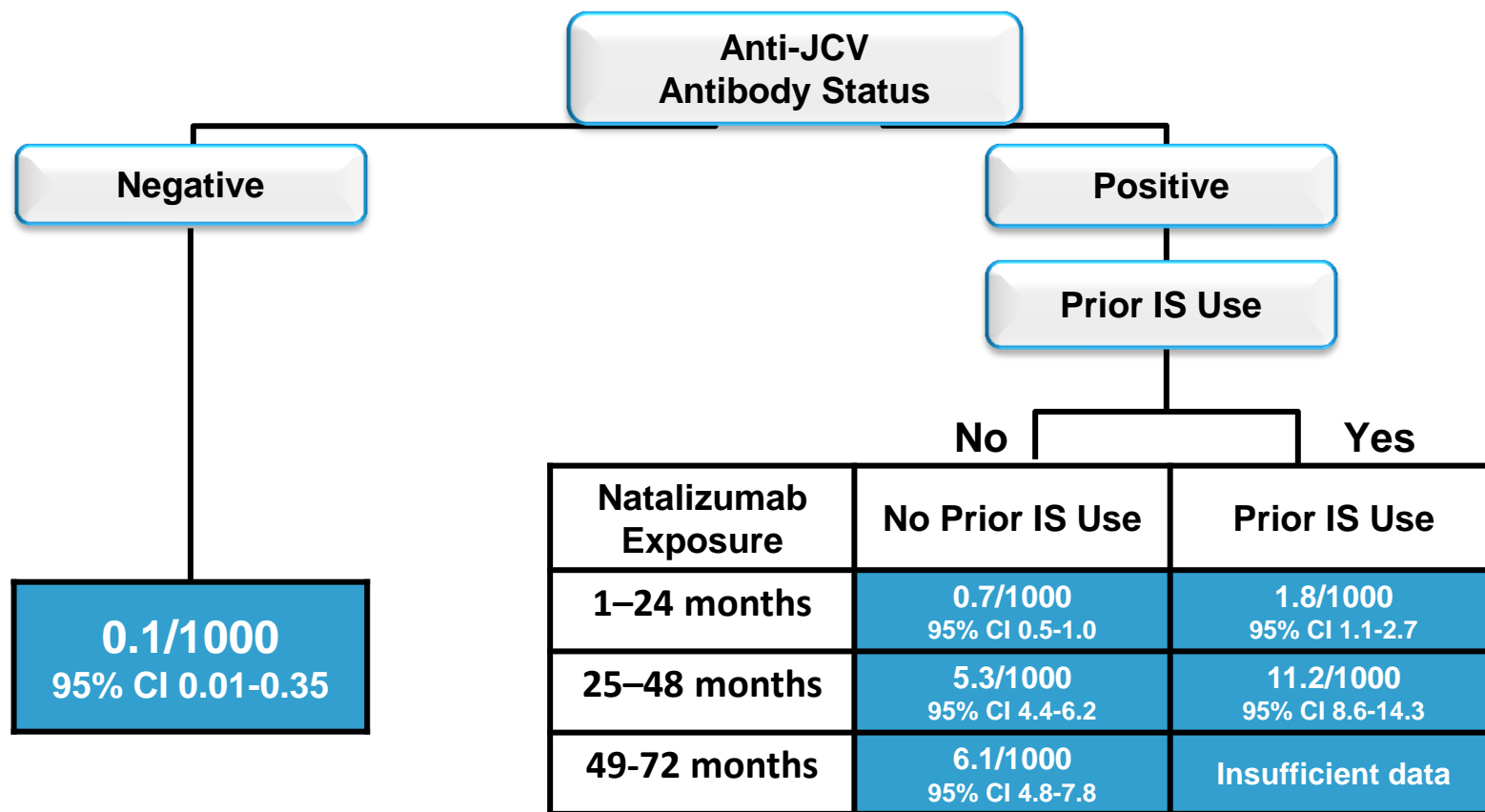
182

324

63

most are alive (78%)

Global Natalizumab PML Risk Estimates by Treatment Epoch

The observed clinical trial PML incidence in patients who received a mean of 17.9 monthly doses of natalizumab was 1.00 per 1000 natalizumab - treated patients (95% CI 0.20-2.80) (Yousry TA, et al. N Engl J Med. 2006;354:924-933). The post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.

Incidence estimates by treatment epoch are calculated based on natalizumab exposure through February 28, 2015 and 541 (538 MS, 3 CD) confirmed PML cases as of March 3, 2015 (165 US, 326 EEA, 50 ROW). The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to natalizumab (e.g., for 25 to 36 infusions all PML cases diagnosed during this period is divided by the total number of patients ever exposed to at least 25 infusions and therefore having risk of developing PML during this time). Biogen Idec, data on file.

Risk Stratification Tool: The Presence of Anti-JCV Antibodies, Prior Immunosuppressant Use, Treatment Duration*

Anti-JCV Antibody Status

Negative

Positive

Prior IS Use

No — Yes

0.1/1000
95% CI 0.01-0.35

Natalizumab Exposure	No Prior IS Use	Prior IS Use
1–24 months	0.7/1000 95% CI 0.5-1.0	1.8/1000 95% CI 1.1-2.7
25–48 months	5.3/1000 95% CI 4.4-6.2	11.2/1000 95% CI 8.6-14.3
49-72 months	6.1/1000 95% CI 4.8-7.8	Insufficient data

Data beyond 6 years of treatment are limited. There are insufficient data to adequately determine PML risk in anti-JCV antibody positive patients with prior IS use and >48 months of natalizumab exposure.

*Based on natalizumab exposure and 343 confirmed PML cases as of March 5, 2013. Prior IS data in overall natalizumab-treated patients based on proportion of patients with IS use prior to natalizumab therapy in TYGRIS as of May 2011; and prior IS data in PML patients as of March 5, 2013. The analysis assumes that 55% of natalizumab-treated MS patients were anti-JCV antibody positive and that all PML patients test positive for anti-JCV antibodies prior to the onset and diagnosis of PML. The estimate of PML incidence in anti-JCV antibody negative patients is based on the assumption that all patients received at least 1 dose of natalizumab . Assuming that all patients received at least 18 doses of natalizumab, the estimate of PML incidence in anti-JCV antibody negative patients was generally consistent (0.16/1000; 95% CI 0.02–0.56).

Risk of PML: index value

Index result	PML risk estimates by index threshold in anti-JCV antibody positive patients with no prior IS use		
	PML risk estimates (no prior immunosuppression use)		
	1-24 Months	25-48 Months	49-72 Months
<=0.9	1 in 10,000	1 in 3,333	1 in 2,500
<=1.1	1 in 10,000	1 in 1,429	1 in 1,429
<=1.3	1 in 10,000	1 in 1,000	1 in 833
<=1.5	1 in 10,000	1 in 833	1 in 769
>1.5	1 in 1,000	1 in 123	1 in 118

PML risk estimates for anti-JCV antibody index thresholds were calculated based on the current PML risk stratification algorithm (from September 2012) and predicted probabilities shown in Table 1 for the population at or below that particular index (0.9–1.5) and for the population above an index of 1.5. For index thresholds below 0.9, patient numbers were insufficient to allow for calculation of risk

Plavina et al., 2014

Negative at baseline (n=81)

8.6%

Vermersch et al., 2015
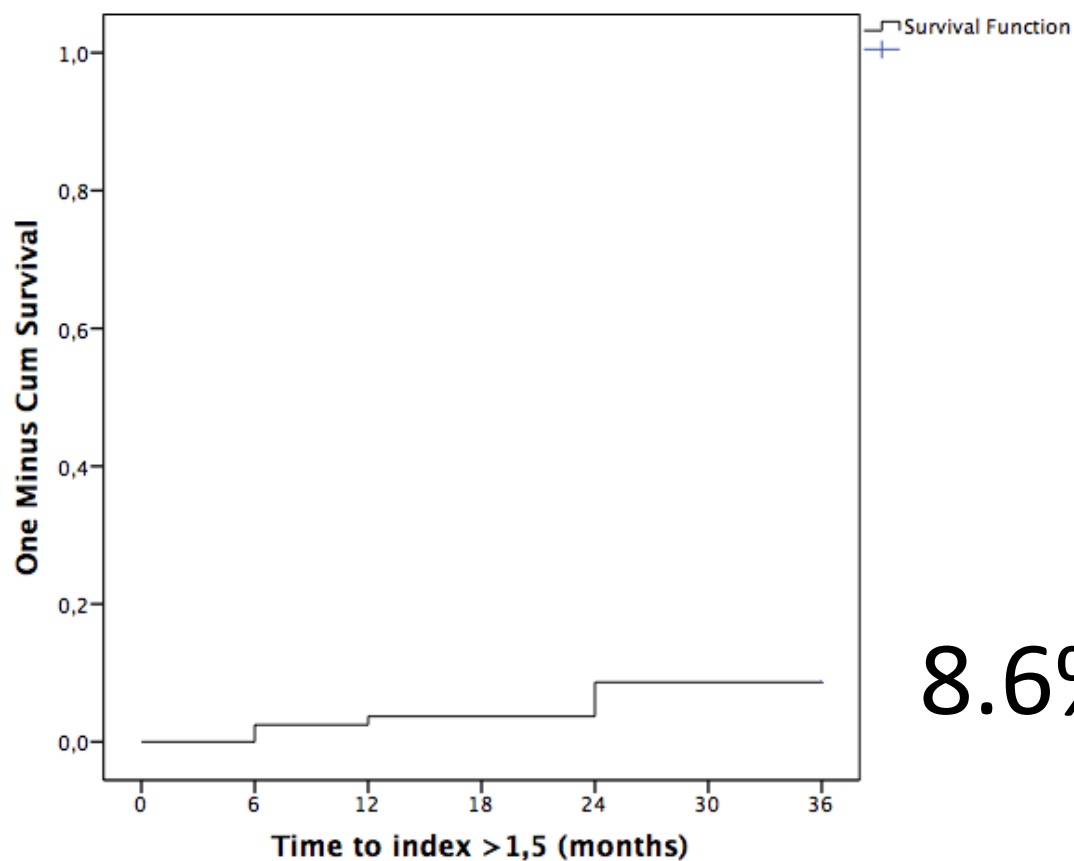
Factors that May Affect Survival in Patients with PML related to Tysabri

Factors that appear to be associated with improved survival

- **Younger age at PML diagnosis**
- **Lower pre-PML EDSS**
- **Shorter time from first symptoms of PML to diagnosis**
- **Localized PML extension on MRI at diagnosis**

Factors that do not appear to affect survival

- **Gender**
- **Prior immunosuppressant therapy**
- **MS duration**
- **TYSABRI exposure at PML diagnosis**
- **JCV DNA load in CSF at PML diagnosis**
- **Gd enhancement on MRI at diagnosis**

Biogen Idec, data on file

At this time, there are insufficient data to predict survival outcomes in patients treated with TYSABRI who develop PML. Longer-term data are required in order to more accurately predict such outcomes.

THE EARLIER, THE SMALLER, THE BETTER FOR NATALIZUMAB-ASSOCIATED PML: IN MRI VIGILANCE VERITAS

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Shibeshih Belachew, MD, PhD*

Olivier Outteryck, MD

Gustave Moonen, MD, PhD

Christian Sindic, MD, PhD

Mathieu Vokaer, MD

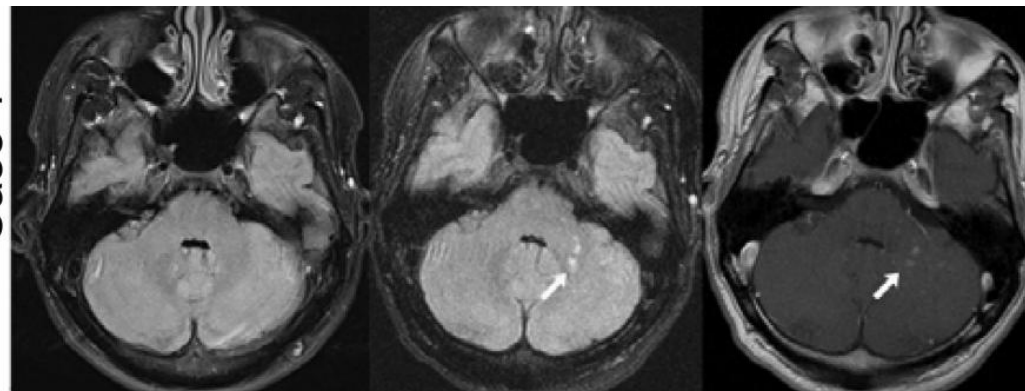Patrick Vermersch, MD, PhD
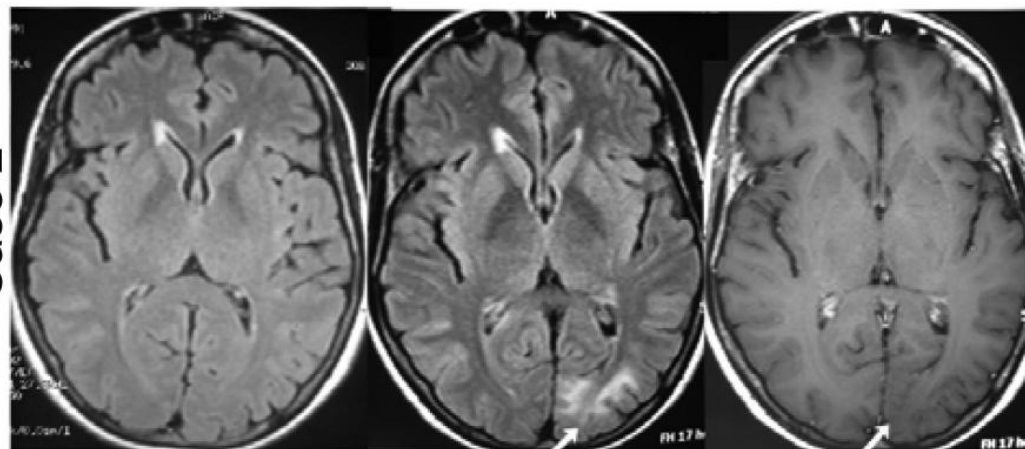
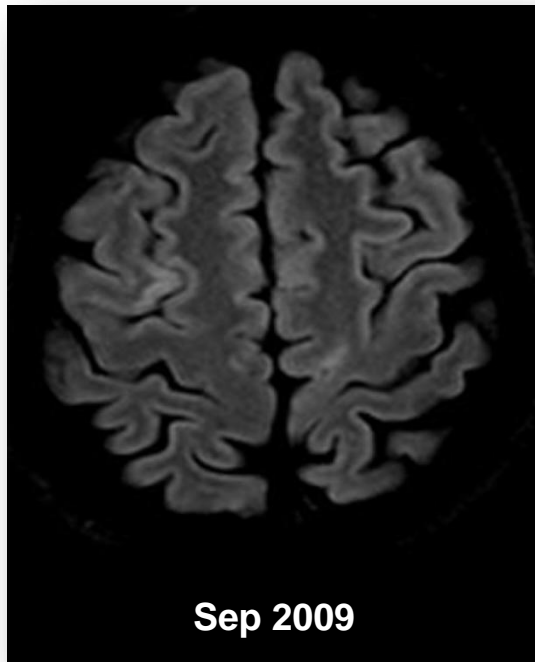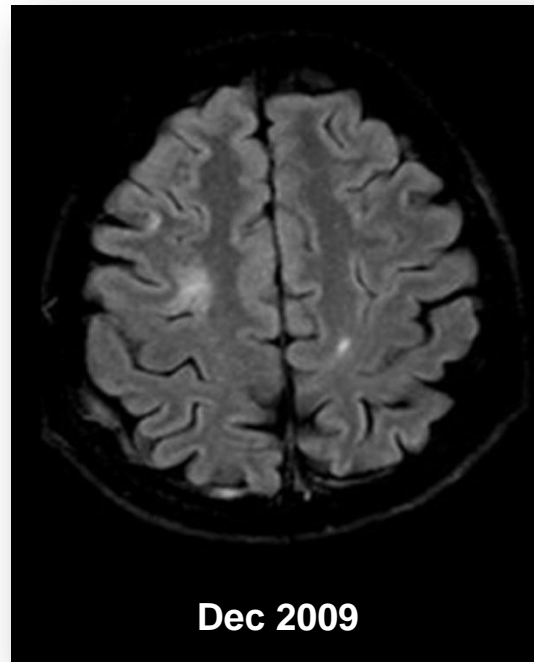Clinical and MRI vigilance

⬇

Possible positive outcome

21 pre-symptomatic cases
14 normal outcomes !

Preclinical PML detection by MRI

Asymptomatic

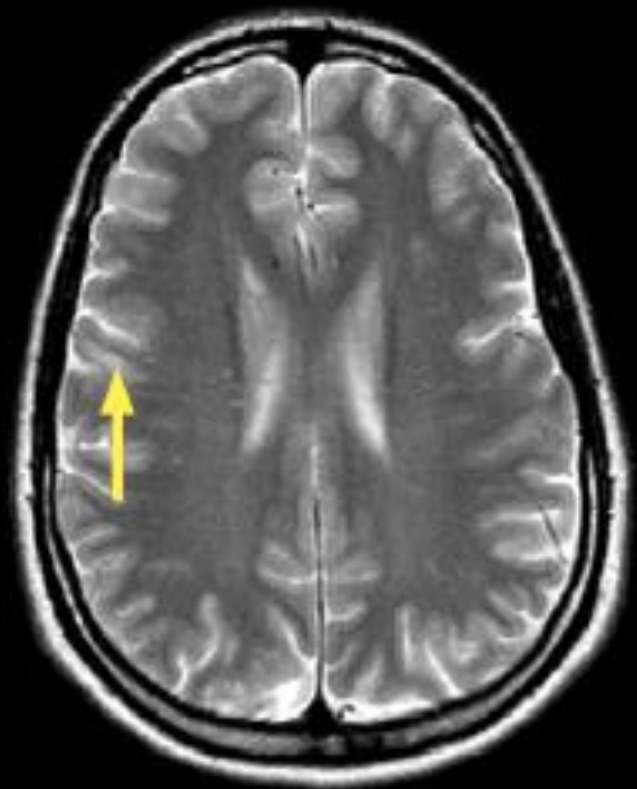**Asymptomatic**

Visual symptoms in Jan 10

Sep 2009

Dec 2009

Feb 2010
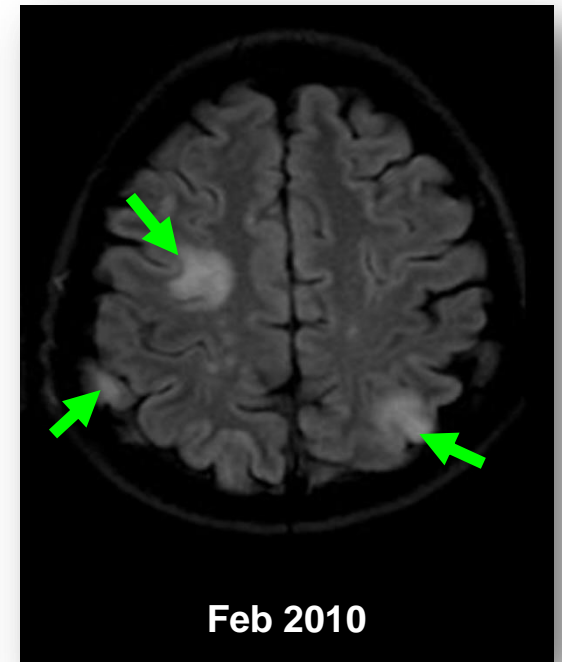
Unilobar → Widespread

Dong-Si et al, AAN, 2013; P04271

FLAIR is MRI sequence of choice

Preclinical PML Detection by MRI

Preclinical PML Detection by MRI

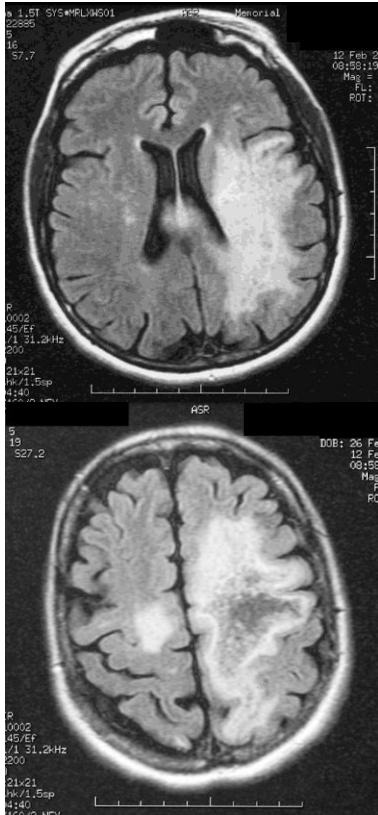Courtesy of VUMC University Medical Centre.
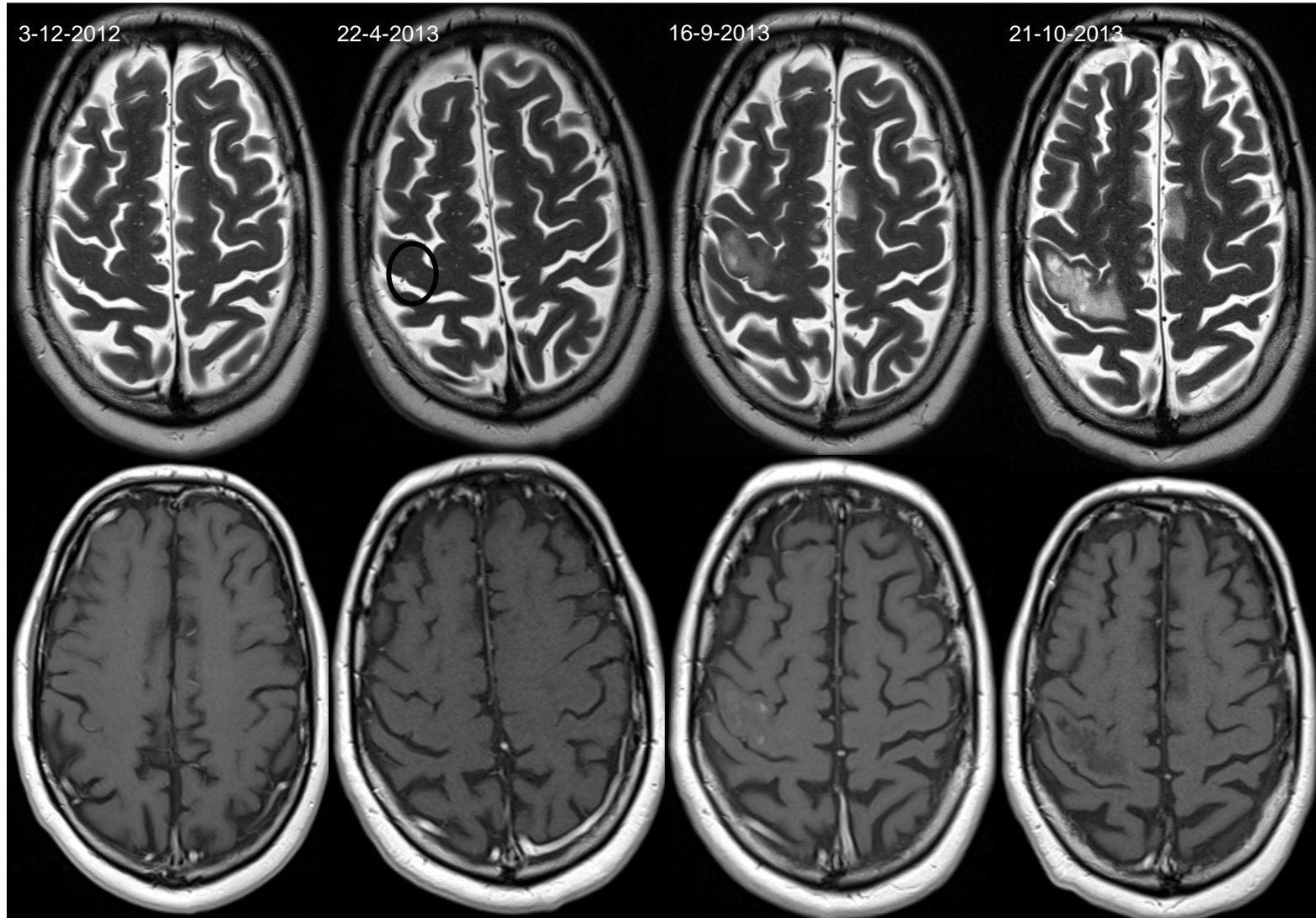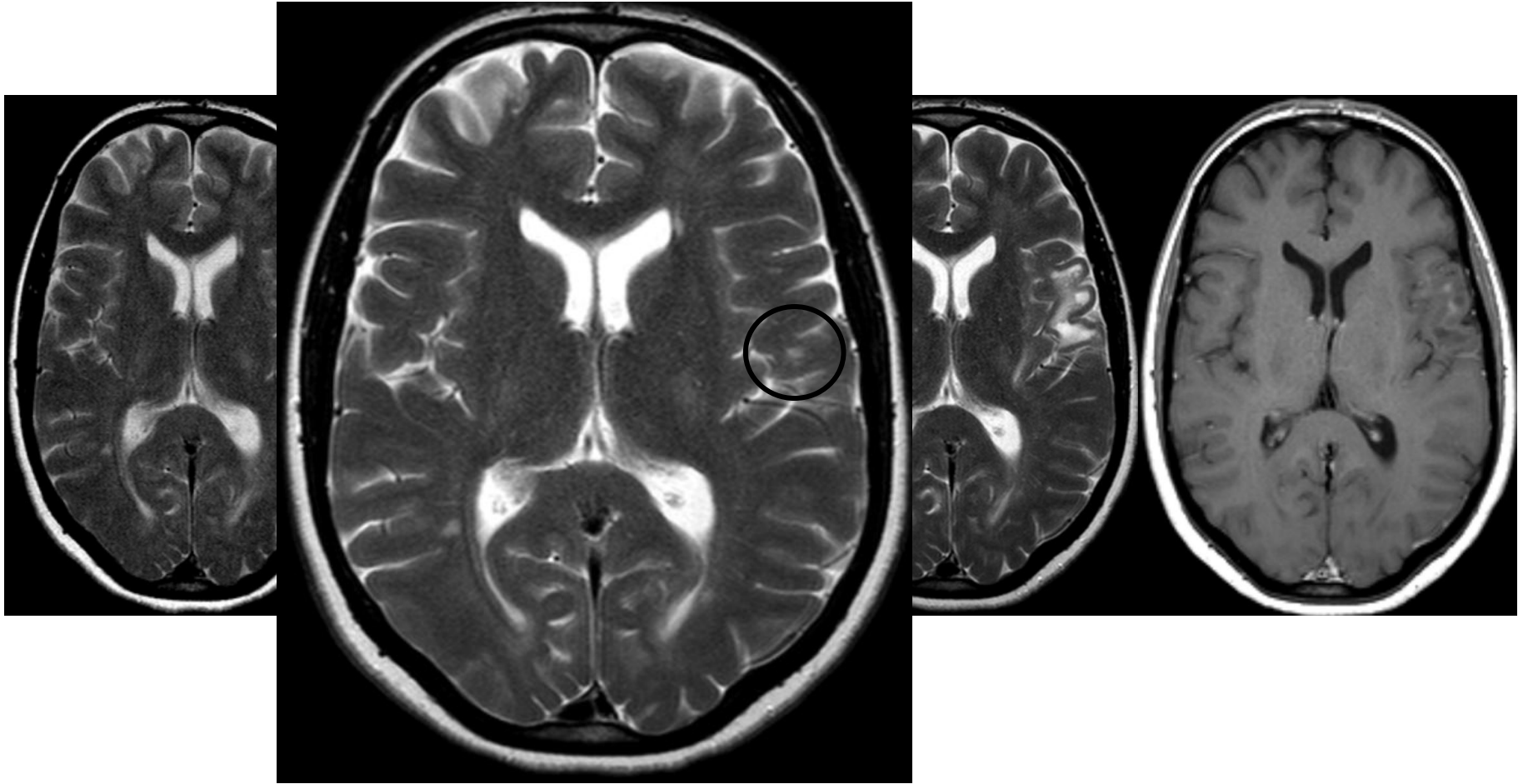
Janus face of natalizumab
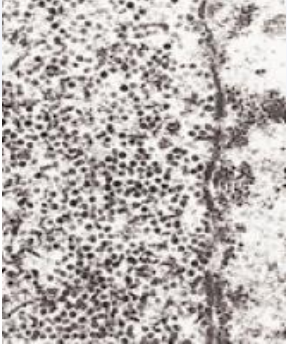
PML ⟷ Efficacy

Relapse rate
-68%
Disability progression
-42-54%