Natalizumab (Tysabri) and PML- the current figures

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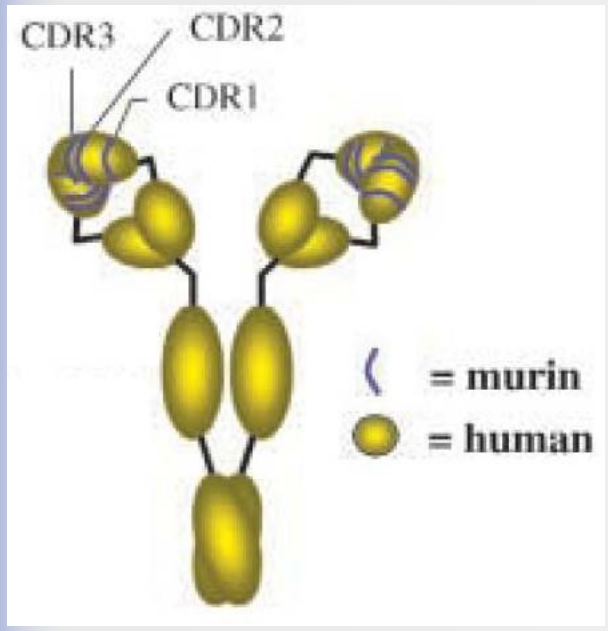
Humanised MAB Natalizumab



US Product Information
(www.tysabri.com)

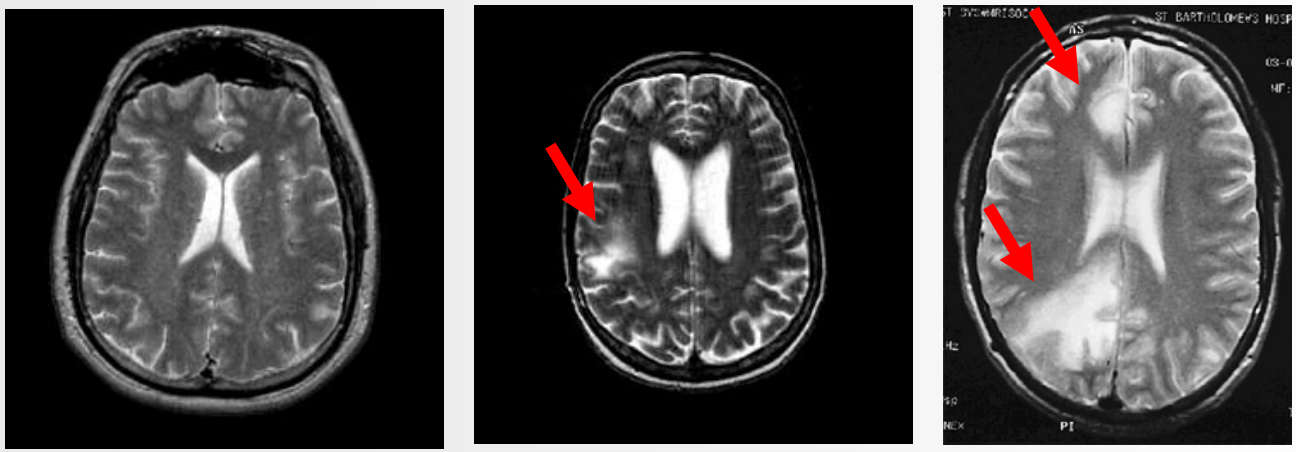
- **Specific binding to a4-integrin**
  a4b1- and a4b7-integrin
  (surface of all leukocytes with exceptions of neutrophile granulocytes)

=> Blocking interaction with receptor
(VCAM-1 und MAdCAM-1)

=> Blocking adhesion to endothelium and transmigration of leukocytes into the inflammatory tissue

- **Nov 2004: MA in the USA, MS**
- **Feb 2005: Suspension of use in the USA**
- **Feb 2006: Re-approval in the USA**
- **Jun 2006: Approval in EU**

Natalizumab (Tysabri) and PML



(MRI in an AIDS patient with PML)

Progressive Multifocal Leukoencephalopathy (PML)
Feb. 2005: 3 PML cases (2 MS+ 1CD) from CTs

- **Rare, progressive demyelinisation of the brain**
- **Caused by JC-Virus (Polyomavirus)**
- **Occurrence in patients with severe immunodeficiency:**
  - HIV+/AIDS (5% of AIDS pts.), organ transplantation etc
- **Single cases of PML also described in healthy subjects**

Natalizumab MS Indication

Tysabri indication US region

As monotherapy for the treatment of patients with **relapsing forms of MS** to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. **TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy**.

Tysabri indication EEA region

TYSABRI is indicated as single disease modifying therapy in **highly active relapsing remitting multiple sclerosis** for the following patient groups: Patients with **high disease activity despite treatment with a beta-interferon or patients with rapidly evolving severe relapsing remitting multiple sclerosis**

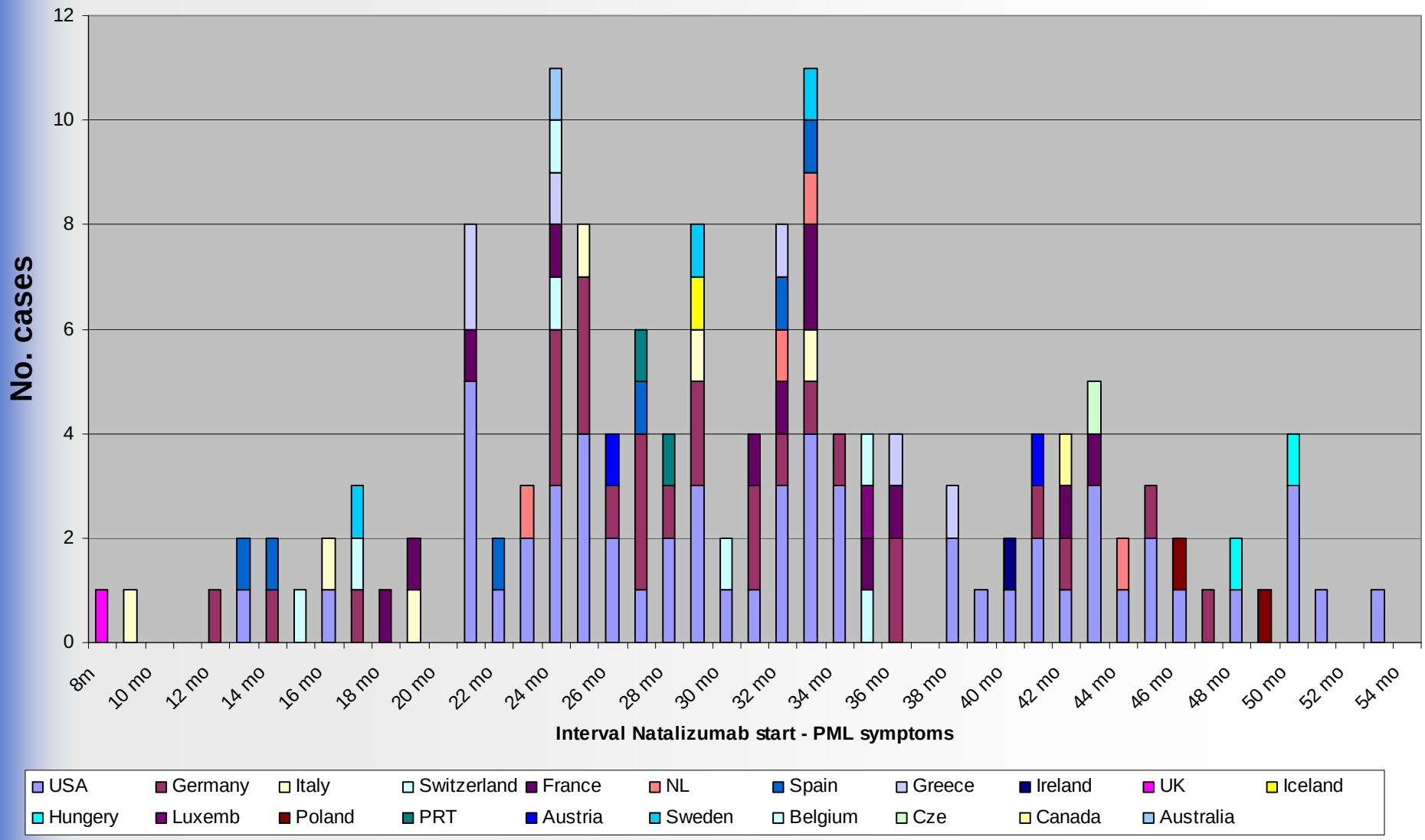
Overview PML cases after Natalizumab

• No. PML cases:	144*
• USA/ EEA	57/ 80
• MS/ CD	143/ 1
• Male/ female	1: 2.3
• Mean Age	44.7 yrs (15 – 71 yrs)
• USA/ EEA	48.1 yrs/ 42.1 yrs
• Fatal outcome	51.36 yrs
• Treatment duration to onset	
• Mean	30.8 months**
• USA/ EEA	32.7 mo/ 29.8 mo
• Median	30.5 mo

* confirmed PML cases until July 2011

** for pts. treated prior to suspension in USA only the 2nd course was considered

Tysabri Time to Onset of PML (n= 144 pts)

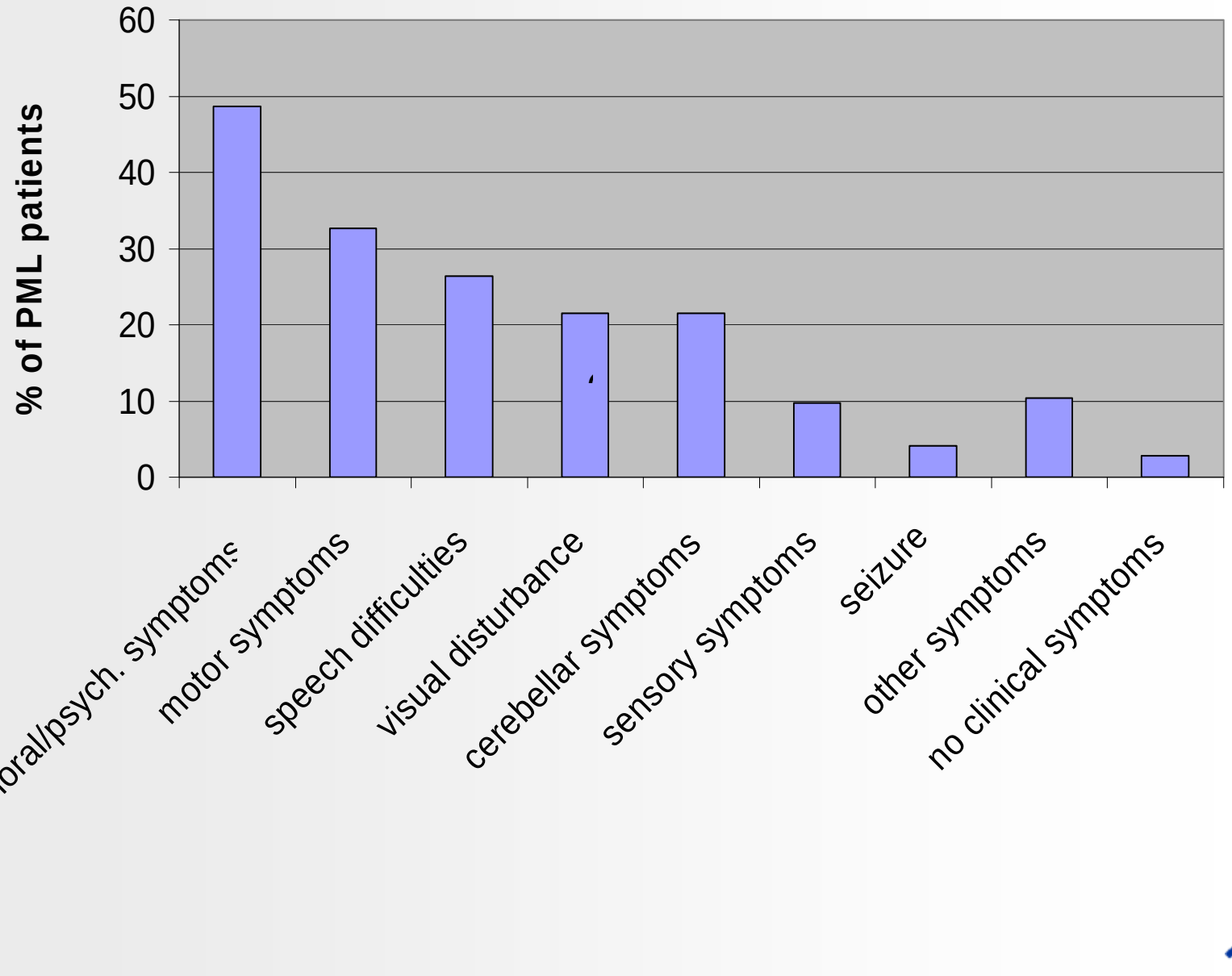


Tysabri PML Incidence Estimate Based on Patients Exposed, PML cases reported as of 01-Jun-2011

Infusions	EEA/ROW 95 % CI	USA 95% CI
1+	2.073 (1.652, 2.569)	1.045 (0.776, 1.377)
6+	2.407 (1.918, 2.083)	1.372 (1.018, 1.808)
12+	2.798 (2.225, 3.802)	1.734 (1.287, 2.285)
18+	3.029 (2.379, 3.802)	2.064 (1.522, 2.735)
24+	3.343 (2.586, 4.251)	2.326 (1.684, 3.132)
30+	2.620 (1.872, 3.566)	2.157 (1.466, 3.061)
36+	1.931 (1.211, 2.923)	1.519 (0.868, 2.465)
42+	1.710 (0.854, 3.058)	2.038 (1.115, 3.417)
48+	0.939 (0.193, 2.742)	1.261 (0.410, 2.940)

25 % of all pts.

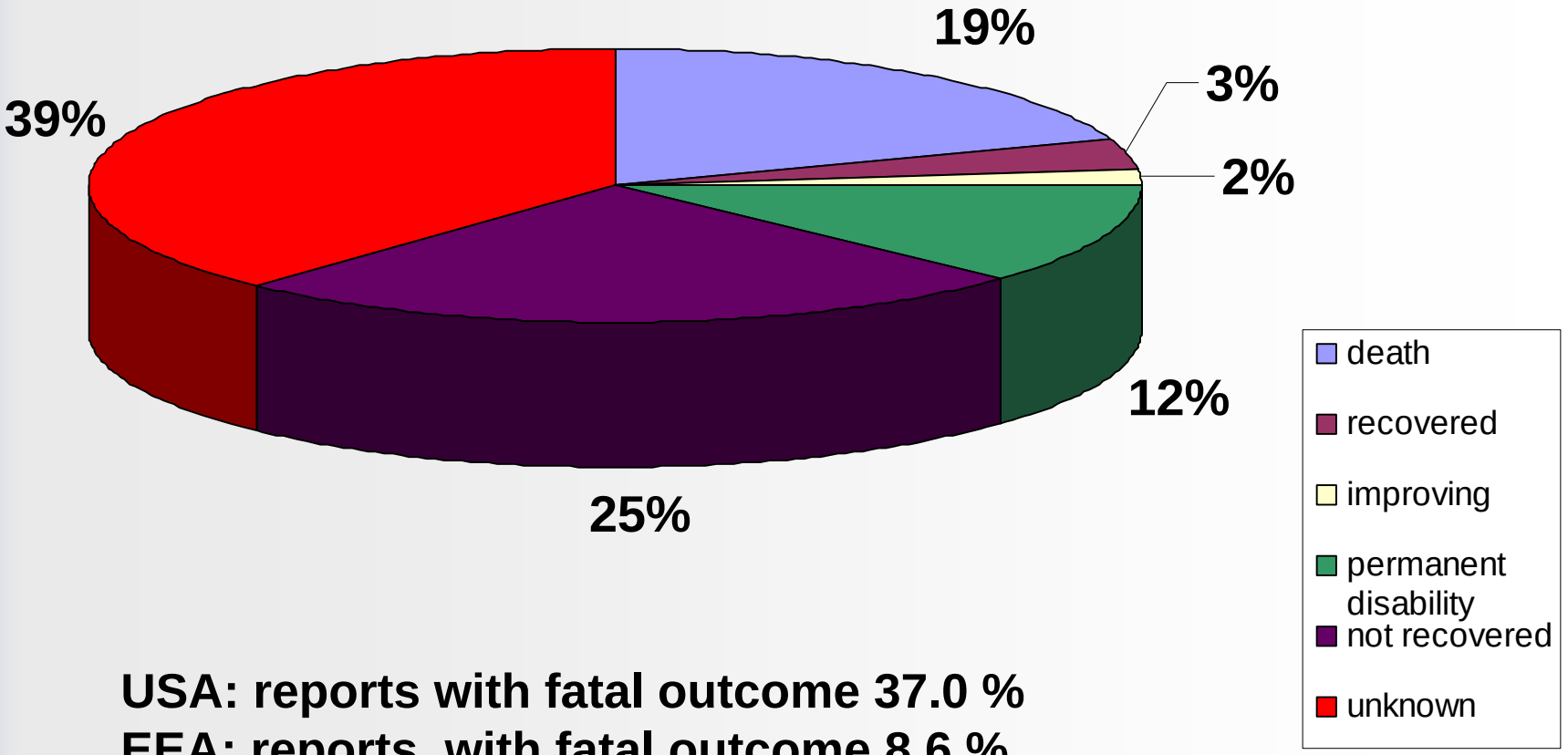
PML First Symptoms (n=144 Patients)



PML First Symptoms (n=144 Patients)

- cognitive/ behavioral/ psychiatric symptoms (70)
  - cognitive impairment (43), behavioral disturbance (8), personality change (8), psychiatric alterations (9), attention deficits (2)
- motor symptoms (47)
  - hemiparesis (24), focal paresis (11), multifocal paresis (4), paresis NOS (2), involuntary movements (3), dysphagia (1), spasticity (1), motor symptoms NOS (1)
- speech difficulties (dysarthria/ aphasia) (38)
- visual disturbance (31)
  - visual disturbance(13), hemianopsia (11), other visual field defects (2), diplopia (3), optic neuritis (2)
- cerebellar symptoms (31)
- sensory symptoms (14)
- seizure (6)
- other symptoms (15), worsening MS (2), unknown symptoms (8)
- no clinical symptoms (4)

PML Outcome (n=144 pts) Based on ICH Criteria



USA: reports with fatal outcome 37.0 %
EEA: reports with fatal outcome 8.6 %

Functional Status of PML Survivors (As of 1-Jun-2011 with 109 PML survivors)

Follow-up Time from PML Diagnosis	No. of Survivors at Follow-up Time and Karnowsky reported	Functional Status of Survivors		
		Mild Disability Karnowsky 80-100	Moderate Disability Karnowsky 50 - 70	Severe Disability Karnowsky 10 - 40
≥ 6 Months	47	6 (13 %)	22 (47 %)	19 (40 %)
≥ 9 Months	18	3 (17 %)	9 (50 %)	6 (33 %)

Karnowsky score pre-PML n=7 pts, average change attributed to PML was 26
Data provided by MAH

Immune Reconstitution Inflammatory Syndrome (IRIS), Wenning W, NEJM, 361:1075-1080

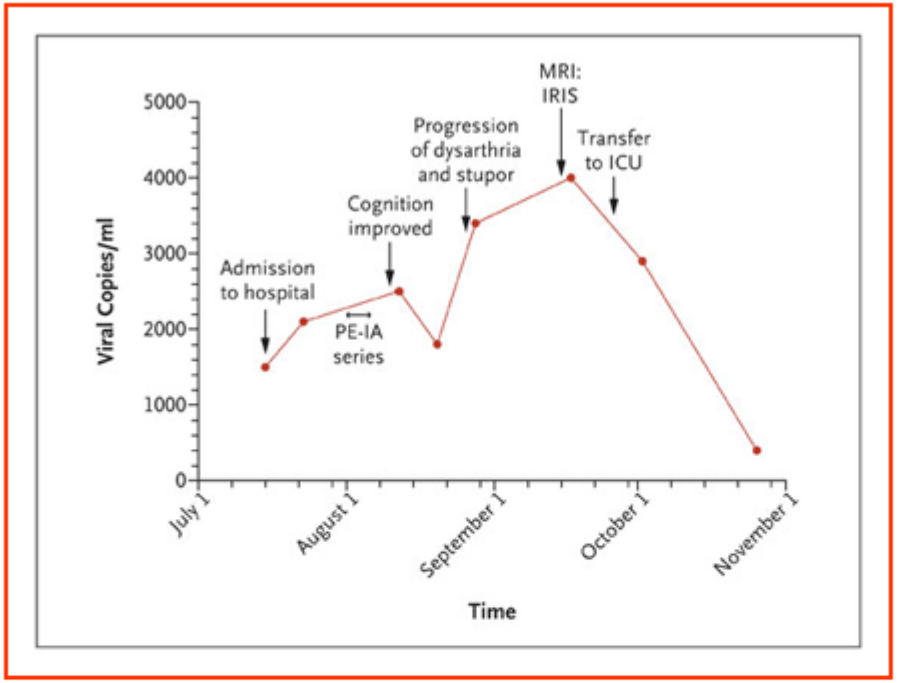


Figure 2. The Course of Disease According to Diagnostic Procedures, Including Longitudinal Testing of Cerebrospinal Fluid for JC Virus DNA, and Therapeutic Approaches.

ICU denotes intensive care unit, IRIS immune reconstitution inflammatory syndrome, and PE-IA plasma exchange and immunoadsorption.

- **Reconstitution of the immune system may result in clinical worsening and pathological inflammation**
- **The majority of Tysabri PML patients developed IRIS**
- **IRIS spectrum consistent with HIV but occurred earlier and more frequently**
- **No consensus guideline on treatment of PML-associated IRIS, corticosteroids used most commonly**

Factors Likely to Increase PML Risk

- Duration of Tysabri therapy
  - PML in MS pts. treated > 24 months is significant higher, however increase may occur earlier (USA)
  - PML risk beyond 3-4 years of treatment is currently unclear
- Prior immunosuppressant use
  - Stratification for severity + duration of MS, type of IS, patient age
- Presence of anti-JCV antibodies
  - False positive and negative JCV antibody assay results

EEA SPC update: PML risk up to 9 in 1000 patients treated

Possible Risk Factors for Mortality from PML

- **Time interval between first symptoms and diagnosis of PML**
- **Larger extent of PML involvement on brain MRI at time of diagnosis**
- **Older age**

Key Elements for Risk Benefit Analysis

- Evaluation of PML incidence beyond 3-4 years of Tysabri treatment for different risk groups
  - Consistent case definition of PML
- Monitoring long term outcome of PML and IRIS
  - Re-evaluation of follow-up (Karnowsky score?)
- Identification of patient groups who benefit most from Tysabri
  - Understand apparent differences of incidence and clinical course of PML between USA and EEA

Risk Minimisation Activities

Early diagnosis of PML

- **High clinical vigilance**
  - **Education of physicians, patients and family members**
- **Validated, sensitive PCR**
  - **Detection threshold as low as possible (< 50 copies/ml?)**
  - **International standard**
  - **Reference labs in all countries**
- **Adherence to the standardised MRI protocol**
  - **MRI ≥ 1 per year**

Evaluation of antibody testing for risk mitigation

- **Sensitivity and specificity of the assay to be determined**

Optimisation of PML and IRIS treatment

- **Evaluation of different treatment options**