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# Natalizumab Safety

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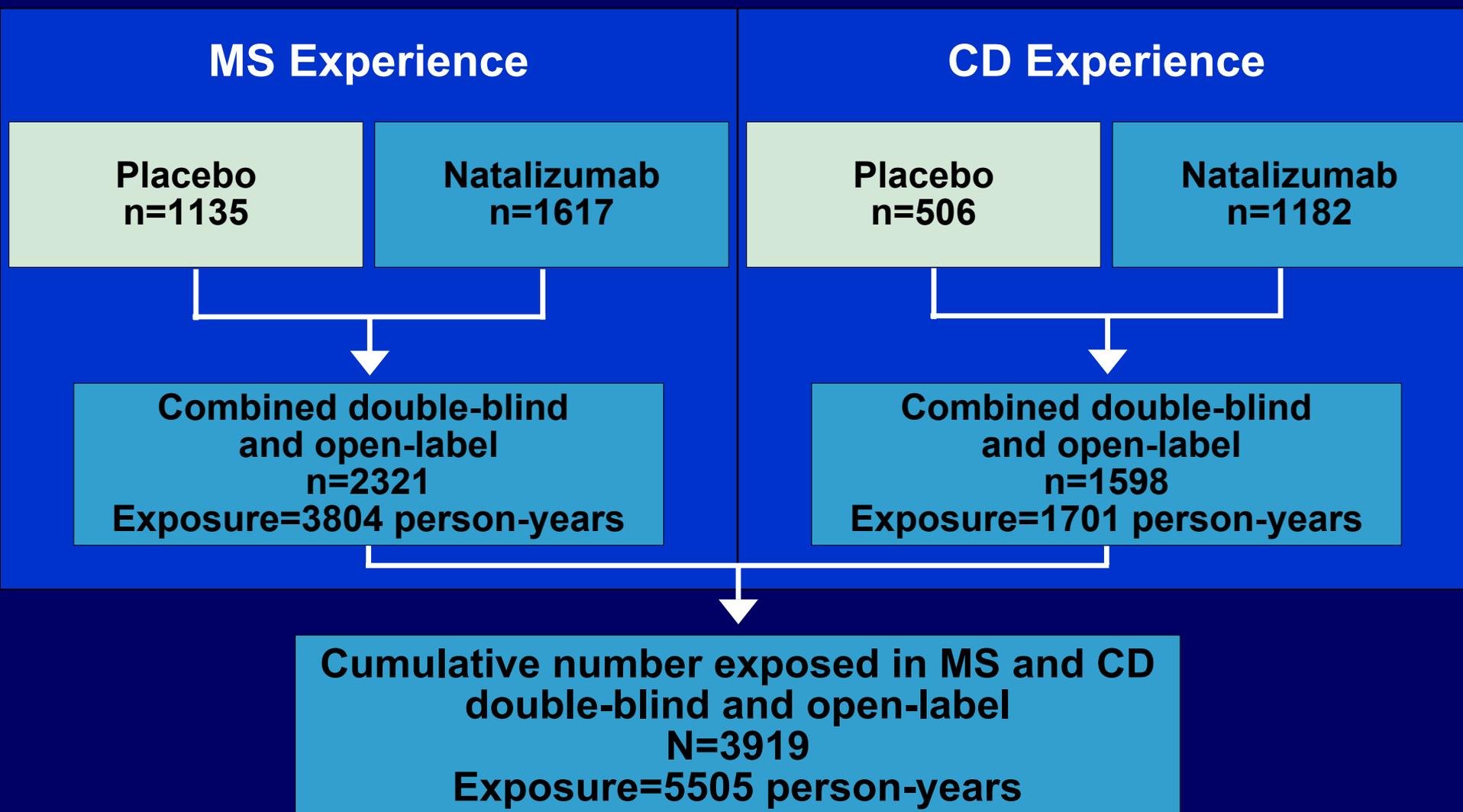
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# Natalizumab Safety

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- ◆ General Safety Overview
- ◆ Infections
- ◆ Progressive Multifocal Leukoencephalopathy (PML)  
Safety Evaluations

# Safety Population



## 2-Year Overview of Adverse Events

### Double-Blind, Placebo-Controlled Trials of MS

	Number (%) of Patients			
	Placebo n=1135		Natalizumab n=1617	
AEs	1104	(97.3)	1552	(96.0)
SAEs	214	(18.9)	251	(15.5)
Non-MS SAEs	131	(11.5)	184	(11.4)
Serious hypersensitivity	2	(0.2)	13	(0.8)
Malignancy	15	(1.3)	11	(0.7)
Deaths	3	(0.3)	2	(0.1)

# Summary of Deaths

## Multiple Sclerosis Placebo-Controlled Experience

<b>Age/Gender</b>	<b>Cause of Death</b>	<b>Infusion</b>	<b>Medications/ Relevant History</b>
38/M	Malignant melanoma	5	Melanoma, lesion present at first dose
49/F	Alcohol intoxication	25	Emotional lability

# Summary of Deaths

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## Multiple Sclerosis Open-Label Experience

Age/Gender	Cause of Death	Infusion	Medications/ Relevant History
46/F	PML	37	IFN $\beta$
5/F	Respiratory distress/MS	10	Last dose 5 months prior
51/F	Seizure, arrhythmia	31	Last dose 6 months prior
27/M	Suicide	31	Last dose 5 months prior

# Summary of Deaths

## Crohn's Disease Cumulative Experience

Age/Gender	Cause of Death	Infusion	Medications/ Relevant History
42/M	Asphyxiation	1	None
67/M	MI, shock	28	Hypertension
49/F	Peritonitis, renal failure	3	Post-op complications
60/M	PML	8	AZA, lymphopenia
69/M	PCP	34	Cirrhosis, ARF, sepsis
73/M	Pulmonary aspergillosis	11	Prednisolone, GI bleed, hospitalization

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## Rheumatoid Arthritis Cumulative Experience

Age/Gender	Cause of Death	Infusion	Medications/ Relevant History
53/F	Intra-op pulmonary hemorrhage	3	Renal stone, <i>E. coli</i> urosepsis
59/F	Rheumatoid lung	1	None

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# Infections

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# Infections

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- ◆ General Overview of Infections
  - Common
  - Serious
  - Risk of infection over time
  - Herpes infections
- ◆ Opportunistic Infections including PML

# Common Infections With Difference Between Natalizumab and Placebo of $\geq 1\%$

Double-Blind, Placebo-Controlled Trials of MS

	Number (%) of Patients	
	Placebo n=1135	Natalizumab n=1617
<b>Total Patients with Infections</b>	<b>839 (73.9)</b>	<b>1192 (73.7)</b>
Influenza	146 (12.9)	225 (13.9)
Pharyngitis	59 (5.2)	125 (7.7)
Gastroenteritis NOS	21 (1.9)	56 (3.5)
Tonsillitis	23 (2.0)	51 (3.2)
Bladder infection NOS	16 (1.4)	38 (2.4)
<b>Rate of Infection per Person-Year</b>	<b>1.50</b>	<b>1.54</b>

# Serious Infections ( $\geq 0.1\%$ in Natalizumab)

Double-Blind, Placebo-Controlled Trials of MS

	Number (%) of Patients	
	Placebo n=1135	Natalizumab n=1617
<b>Total Patients with Serious Infections</b>	<b>26 (2.3)</b>	<b>39 (2.4)</b>
Appendicitis	3 (0.3)	6 (0.4)
Urinary tract infections	5 (0.4)	6 (0.4)
Pneumonia/bronchial infection	3 (0.3)	6 (0.4)
Sinusitis NOS	1 (<0.1)	3 (0.2)
Viral infection NOS	0	3 (0.2)
Infection NOS	1 (<0.1)	2 (0.1)
Urosepsis	1 (<0.1)	2 (0.1)
<b>Rate per 1000 Person-Years</b>	<b>13.1</b>	<b>14.1</b>

# Serious Infections

## Post-Marketing Experience\*

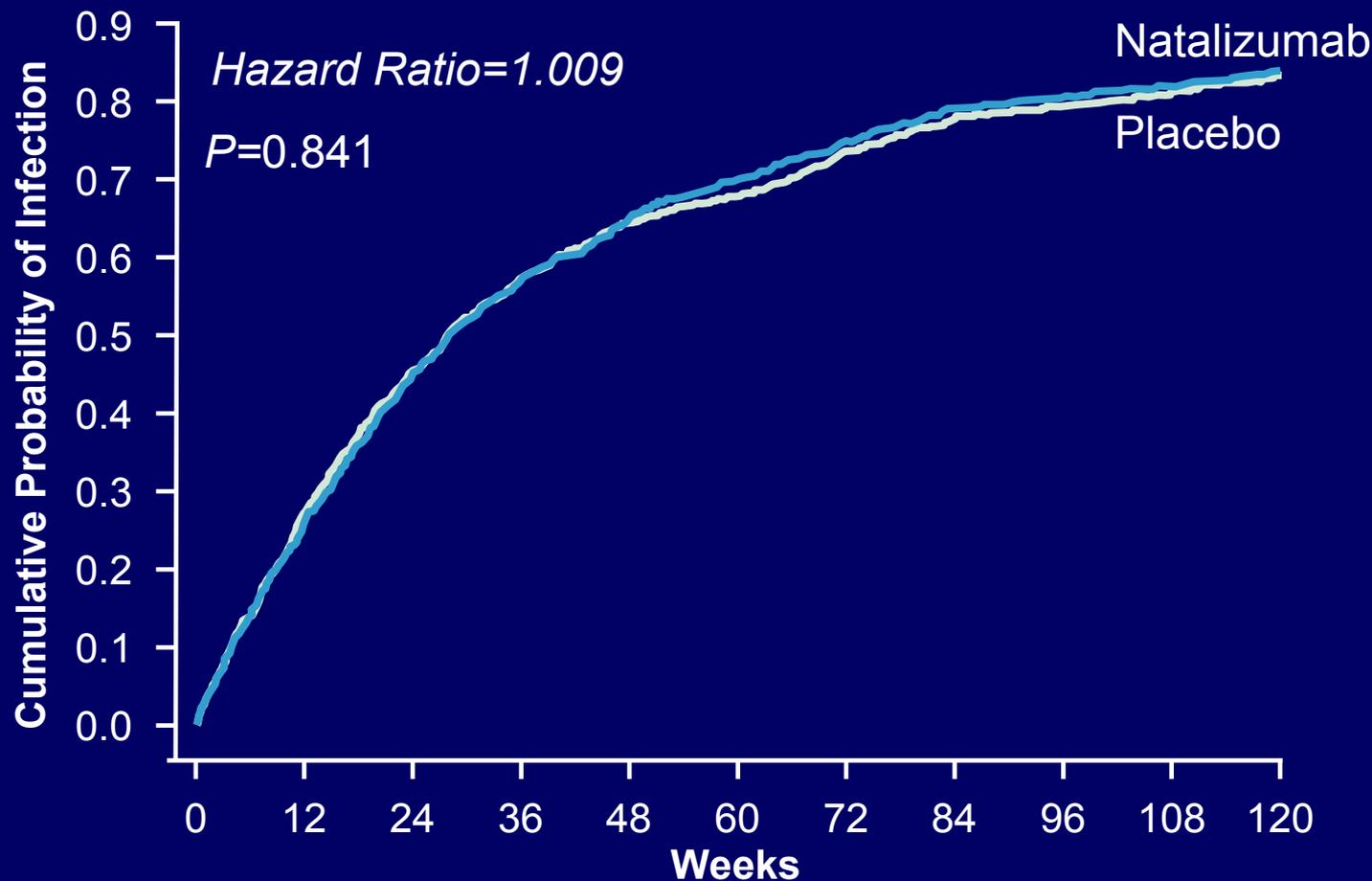
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- ◆ Approximately 7000 patients received 1 or more natalizumab infusions
- ◆ Serious infections reported in 16 patients (0.2%)
  - Pneumonia, UTI most common
- ◆ 2 reports of serious herpes infections
  - 1 fatal encephalitis 3 months after 1 dose
  - 1 HSV meningitis following first dose with recovery
- ◆ No opportunistic infections, including PML

\*Through 1 June 2005

# Risk of Infection

## Double-blind, Placebo-Controlled Trials of MS



Placebo	1135	1115	1023	936	902	837	822	805	795	788	617
Natalizumab	1617	1579	1412	1328	1298	1169	1154	1139	1129	1115	898

# Herpes Family Viruses

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- ◆ Reactivation can be a marker of altered cell-mediated immunity
  - Latent DNA virus
  - Reactivation leads to clinical manifestations
  - Tropism for the nervous system
- ◆ High rate of sporadic infection

# Incidence and Rate of Herpes Infections

## Double-Blind, Placebo-Controlled Trials of MS

	Number (%) of Patients	
	Placebo n=1135	Natalizumab n=1617
<b>Total Patients with Herpes Infections</b>	<b>69 (6.1)</b>	<b>116 (7.2)</b>
Herpes simplex	53 (4.7)	80 (4.9)
Herpes zoster	16 (1.4)	33 (2.0)
Herpes infection NOS	4 (0.4)	5 (0.3)
CMV hepatitis	0	1 (<0.1)
Mononucleosis	0	1 (<0.1)
CMV infection	1 (<0.1)	0
HSV ophthalmic	1 (<0.1)	0
<b>Rate per 1000 Person-Years</b>	<b>58</b>	<b>67</b>

# Incidence and Rate of Herpes Infections

## Placebo-Controlled Monotherapy and Combination Trials of MS

	Monotherapy		Combination	
	Placebo n=498	Natalizumab n=973	Placebo n=637	Natalizumab n=644
<b>Incidence (%)</b>	<b>6.0</b>	<b>6.4</b>	<b>6.1</b>	<b>8.4</b>
<b>Exposure (person-years)</b>	<b>787</b>	<b>1590</b>	<b>1274</b>	<b>1320</b>
<b>Rate (per 1000 person-years)</b>	<b>70</b>	<b>67</b>	<b>50</b>	<b>67</b>

# Summary of Herpes Infections

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- ◆ Slight increase (1.1%) in herpes infections in natalizumab-treated patients
  - Primarily with combination treatment
  - No serious or disseminated herpes infections in MS trials
  
- ◆ Similar observation in CD trials (increase of 0.5%)
  - 5 serious events in CD trials
    - 2 with onset pre-dosing
    - All recovered

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# Opportunistic Infections

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# PML in Natalizumab-Treated Patients

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- ◆ A total of 3 confirmed cases of PML
  - 2 in MS patients (1 fatal): both receiving IFN $\beta$  concurrently
  - 1 in a CD patient (fatal): originally diagnosed as astrocytoma, pre-existing lymphopenia due to immunosuppression
- ◆ Exposure ranged from 8 to 37 infusions
- ◆ All presented with behavioral changes

# Incidence of Opportunistic Infections

## Placebo-Controlled and Cumulative MS Experience

	Placebo-Controlled		Cumulative Experience N=2283
	Placebo n=1135	Natalizumab n=1617	
Number (%) Patients with OIs	0	2 (0.12)	<b>3 (0.13)</b>
Exposure (person-years)	2060	2910	<b>3804</b>
Rate (per 1000 person-years)			<b>0.8</b>
PML	0	1 (0.06)	<b>2 (0.09)</b>
Cryptosporidial gastroenteritis	0	1 (0.06)	<b>1 (0.04)</b>

# Incidence of Opportunistic Infections

## Placebo-Controlled and Cumulative CD Experience

	Placebo-Controlled		Cumulative Experience N=1598
	Placebo n=506	Natalizumab n=1182	
Number (%) Patients with OIs	0	1 (0.08)	<b>5 (0.31)</b>
Exposure (person-years)	180	425	<b>1701</b>
Rate (per 1000 person-years)			<b>2.9</b>

# Summary of Opportunistic Infections

## Cumulative CD Experience

Age/Gender	Infection Type	Infusion	Medications/ Relevant History	Outcome
60/M	PML	8	AZA / lymphopenia	Death
69/M	PCP	34	Cirrhosis, ARF, sepsis	Death
73/M	Pulmonary aspergillosis	11	Prednisolone / GI bleed, prolonged hospitalization	Death
33/F	CMV colitis	1	AZA	Recovered
65/F	MAC infection	8	Prednisone / <i>S. aureus</i> pneumonia	Recovered
32/M	Lung abscess	13	AZA	Recovered
62/F	<i>Burkholderia cepacia</i> pneumonia	3	Tobacco use, CHF	Recovered
20/M	Presumed TB	25	Prednisone, AZA, last dose 6 months prior	On treatment

## Opportunistic Infections

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- ◆ Natalizumab treatment associated with an increased risk of PML
  - Incidence estimate: 1/1000 (95% CI: 0.2 to 2.8/1000)
- ◆ May be increased risk of other opportunistic infections
  - 1 non-PML infection in MS patients
  - Remaining in CD patients with pre-existing co-morbidity, immunocompromise

# Overall Safety Summary

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- ◆ AEs and SAEs balanced between groups
  - Hypersensitivity consistent with approved labeling
  - No increase in malignancy
- ◆ No increase in incidence or rate of common or serious infections
- ◆ Herpes infections may be slightly increased on natalizumab treatment
- ◆ PML and other opportunistic infections occurred on natalizumab treatment
  - Seen mostly in patients with CD, significant co-morbidity or use of immunomodulators or immunosuppressants

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**PML**

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# Overview of PML

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- ◆ Rare, progressive infection of the CNS
  - Often fatal within 6 months of diagnosis
- ◆ Lytic infection of oligodendrocytes by JC virus, a human polyomavirus
- ◆ Primarily affects immunocompromised individuals
  - Hematologic malignancies
  - HIV
  - Organ transplantation

# Cause of PML: JC Virus

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- ◆ Double-stranded DNA virus
- ◆ Infects healthy individuals at an early age
  - Reported seroprevalence ranges from 30 to 80%
- ◆ Sites of latency: kidney, bone marrow, lymphoid tissues
- ◆ Pathogenesis likely multi-step process
  - Activation from latency
  - DNA rearrangement
  - Interaction with immune system
  - Migration from sites of latency into CNS

# Diagnosis of PML

## ◆ Typical features of PML

### – Clinical

- Tempo: Subacute
- Location: Sub-cortical, cerebellum

### – MRI

- Non-enhancing
- No mass effect
- Subcortical

### – CSF

- JCV DNA detectable

## ◆ Differentiation from MS

### – Clinical

- Tempo: Acute
- Location: Optic nerve, spinal cord, sub-cortical, cerebellum

### – MRI

- Gd-enhancement
- Edema, mass effect
- Periventricular

### – CSF

- JCV DNA negative

No proven means of monitoring or predicting PML onset

# Treatment of PML

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- ◆ Antiviral agents not effective
- ◆ Immune reconstitution most effective treatment
  - HIV experience with HAART<sup>1</sup>
    - Introduction of HAART at diagnosis reduces mortality by half
    - Mild symptoms at treatment initiation associated with improved prognosis
  - Transplantation<sup>2</sup>
    - Reduction of immunosuppression at presentation improves survival
    - Survival reported in one-third of patients in case series
- ◆ Early recognition, immune reconstitution, may improve outcome

<sup>1</sup>Clifford et al 1999; Geschwind et al 2001; Antinori et al 2003; Berenguer et al 2003

<sup>2</sup>Crowder et al 2005; Shitrit et al 2005

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# PML Safety Evaluations

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# PML Safety Evaluations

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- ◆ All dosing suspended 28 February 2005
- ◆ Evaluated patients from trials of MS, CD, and RA
- ◆ Objectives
  - Determine if additional patients had undiagnosed PML or other atypical infections
  - Determine prevalence of JC virus in CSF
  - Assess utility of plasma testing for predicting PML

# Methods

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- ◆ All patients required to see neurologist as soon as possible for clinical examination and MRI
- ◆ CSF collection for JCV DNA analyses strongly encouraged
  - Required for suspect cases
- ◆ Plasma collected for exploratory analyses
- ◆ CSF and plasma controls obtained from Karolinska Institute
- ◆ Study monitored by an Independent Adjudication Committee (IAC)

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# Evaluation Results

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# Participation and Results

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- ◆ 3826 patients eligible for the evaluation
- ◆ 91% of natalizumab-treated patients participated
  - Vital status confirmed in >99%
- ◆ No new cases of PML

# MRI Analyses

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- ◆ ~3000 MRI scans reviewed by reader centers
- ◆ MRI scan very useful to exclude PML diagnosis in patients with MS symptoms
  - Single MRI scan usually sufficient; rescan sometimes required
  - Baseline brain MRI scan important

## CSF Analyses

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- ◆ 800 CSF samples evaluated for JC viral DNA by PCR
  - 396 from natalizumab-treated patients
  - 411 from neurologic controls from Karolinska Institute
  - No JC viral DNA detected
- ◆ JC viral DNA detected in patients with PML
- ◆ CSF testing very specific for diagnosis

# Plasma Analyses

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- ◆ Plasma collected from 2370 patients for exploratory analyses
  - 5 (0.2%) with detectable JC viral DNA
    - No clinical or radiographic changes
    - 3 in placebo group
- ◆ Stored serum samples from the 3 PML patients analyzed
  - JC viral DNA *not* detected in 2 of 3 prior to symptom onset
- ◆ Presence of viremia not necessarily associated with PML and absence does not exclude it

## Options for PML Monitoring

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- ◆ Clinical vigilance
  - Monthly patient checklists/neurologic questionnaires
  - Low threshold to prompt physician assessments
- ◆ JC viral DNA in plasma
  - Sensitivity, predictive value unclear
- ◆ MRI
  - Sensitive, not specific in MS, helpful diagnostically
  - No practical frequency as PML screening test
- ◆ CSF
  - Tends to be negative in early disease
  - Invasive