Update: PML in MS

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Department of Neurology

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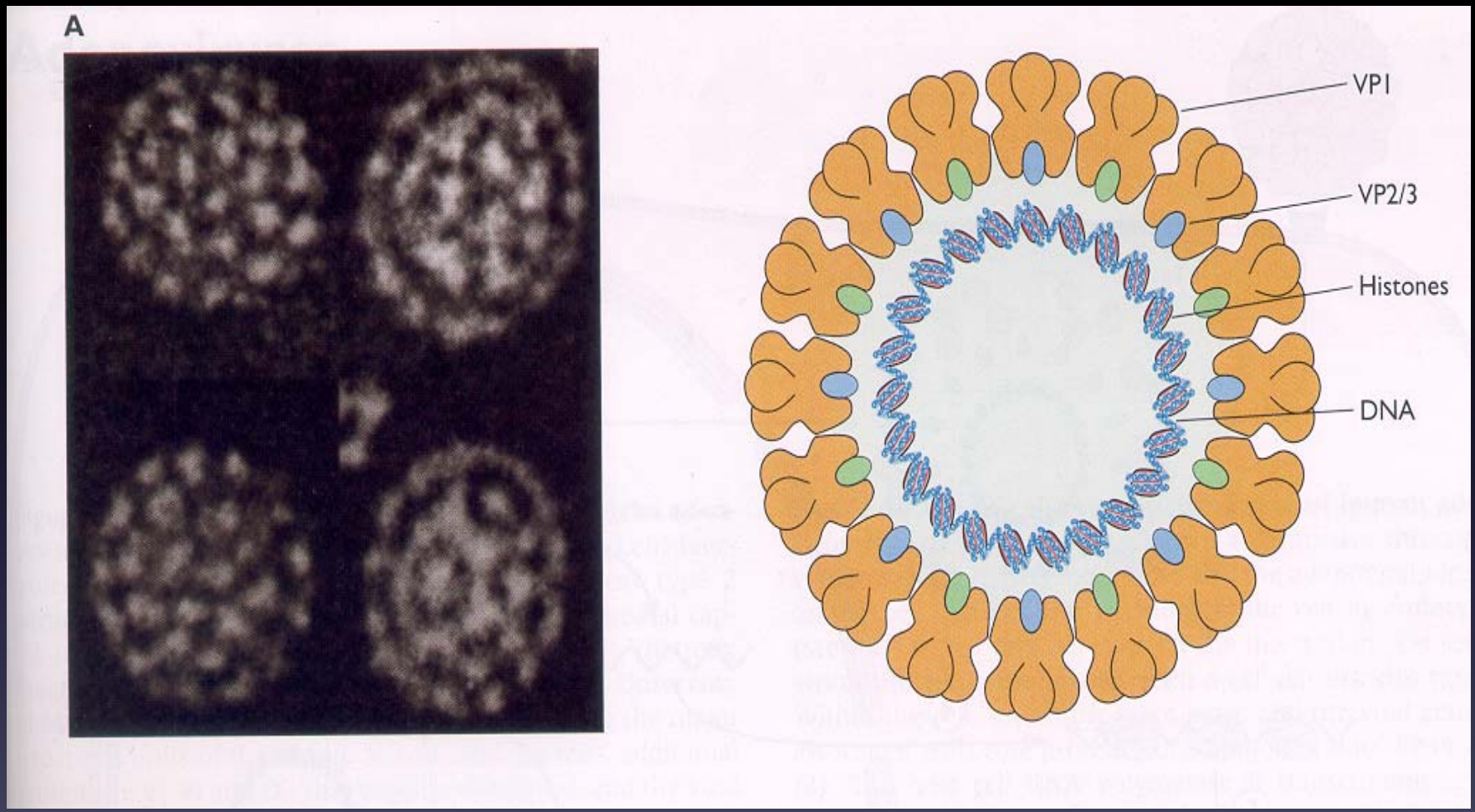
There are no FDA Approved Drugs for Treatment of PML: All Medications Discussed are "Off-Label"

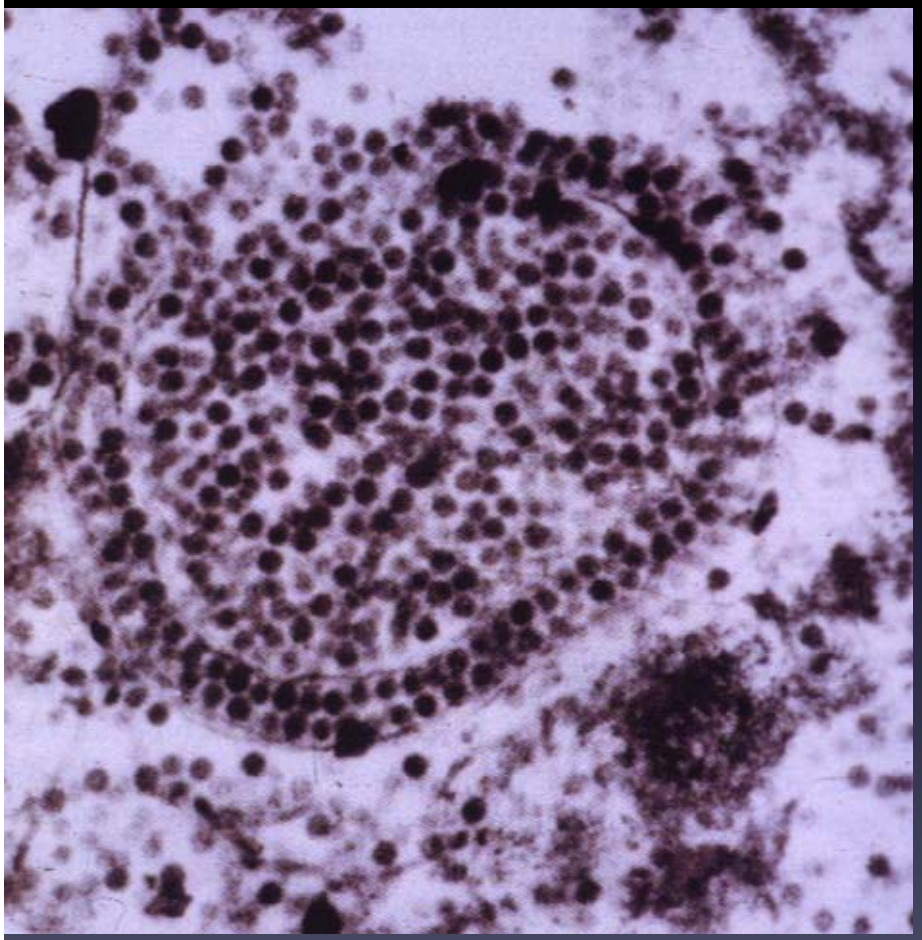
Dr. Tyler has done expert consulting related to PML and JC Virus for: PML Consortium, Genentech, Pfizer, Roche, Jansen, Biogen

JC virus: structure

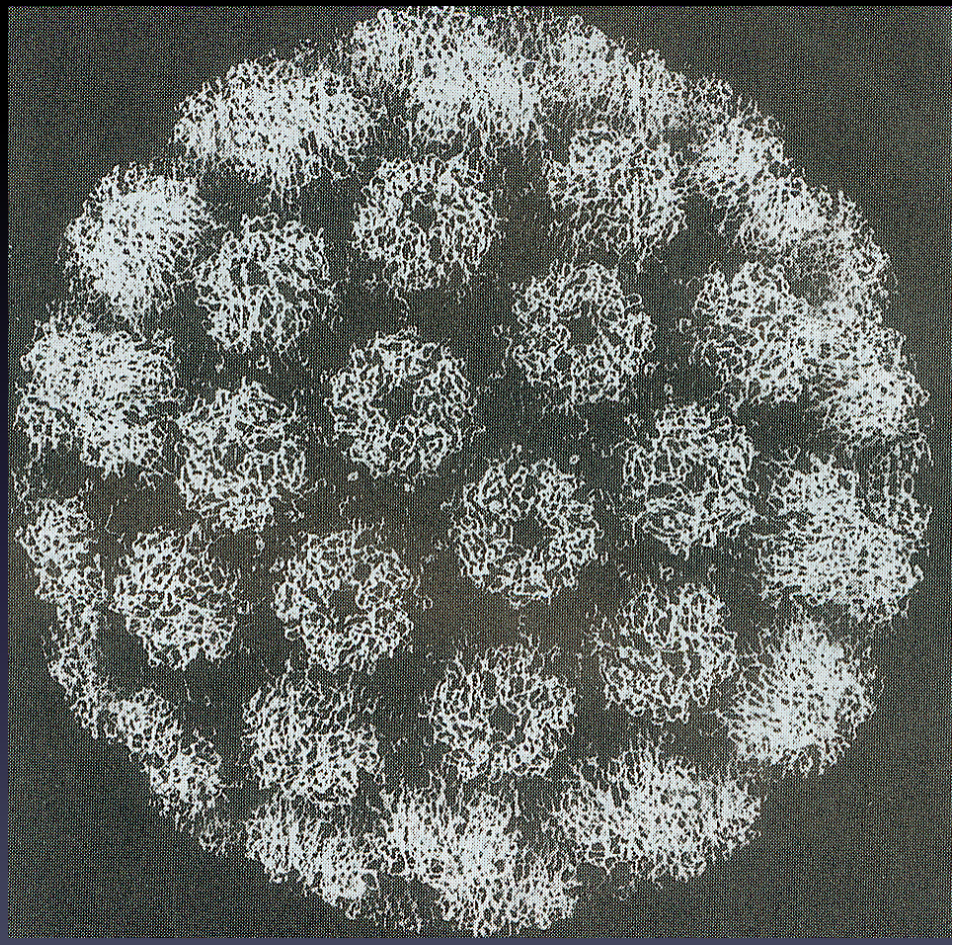


Non-enveloped, icosahedral, ~50nm virions, 72 capsomeres
Circular double-stranded DNA, 5kbp:
Encodes: NCCR, Agnoprotein, VP1, VP2, VP3, T antigen, t antigen

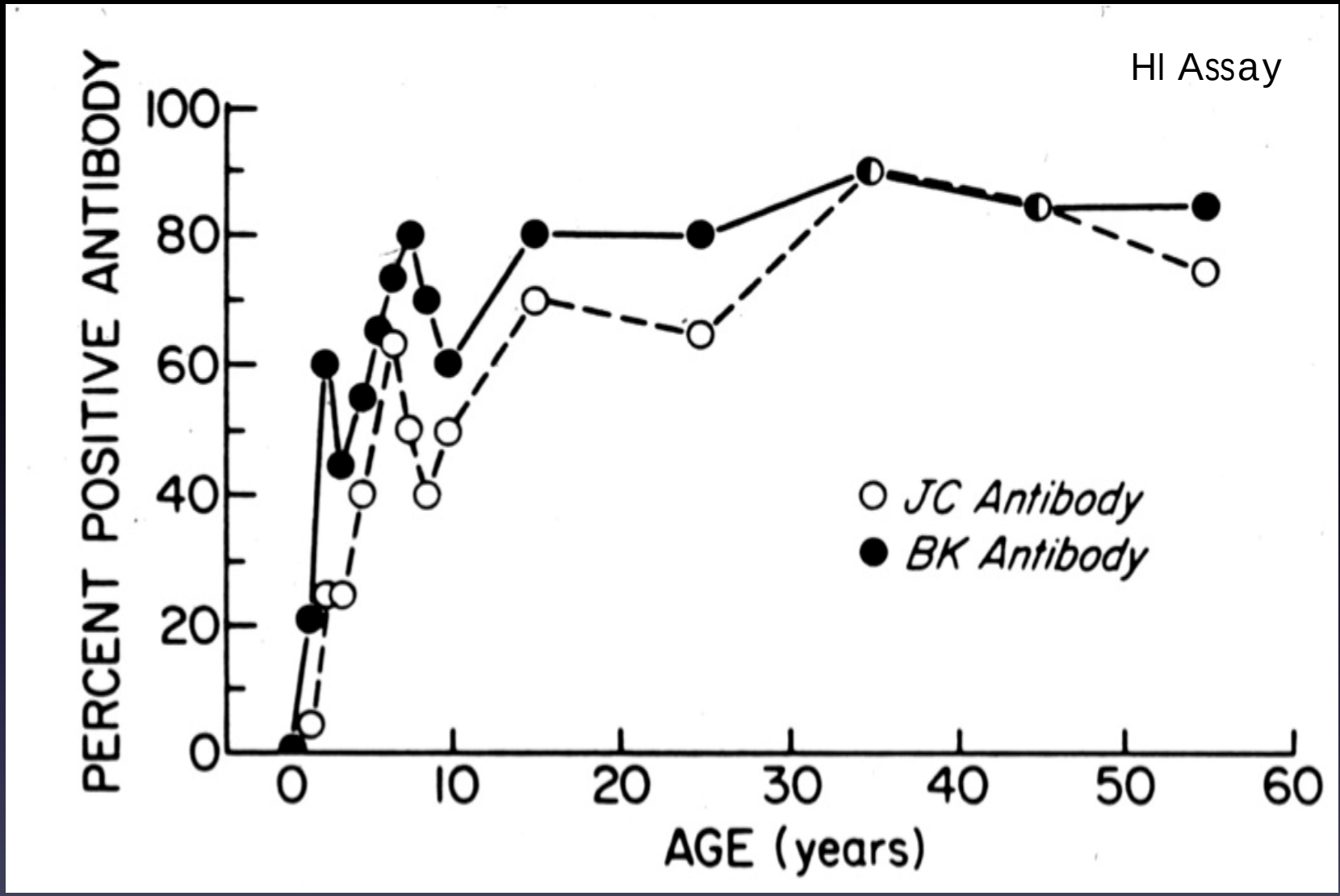
JCV Structure



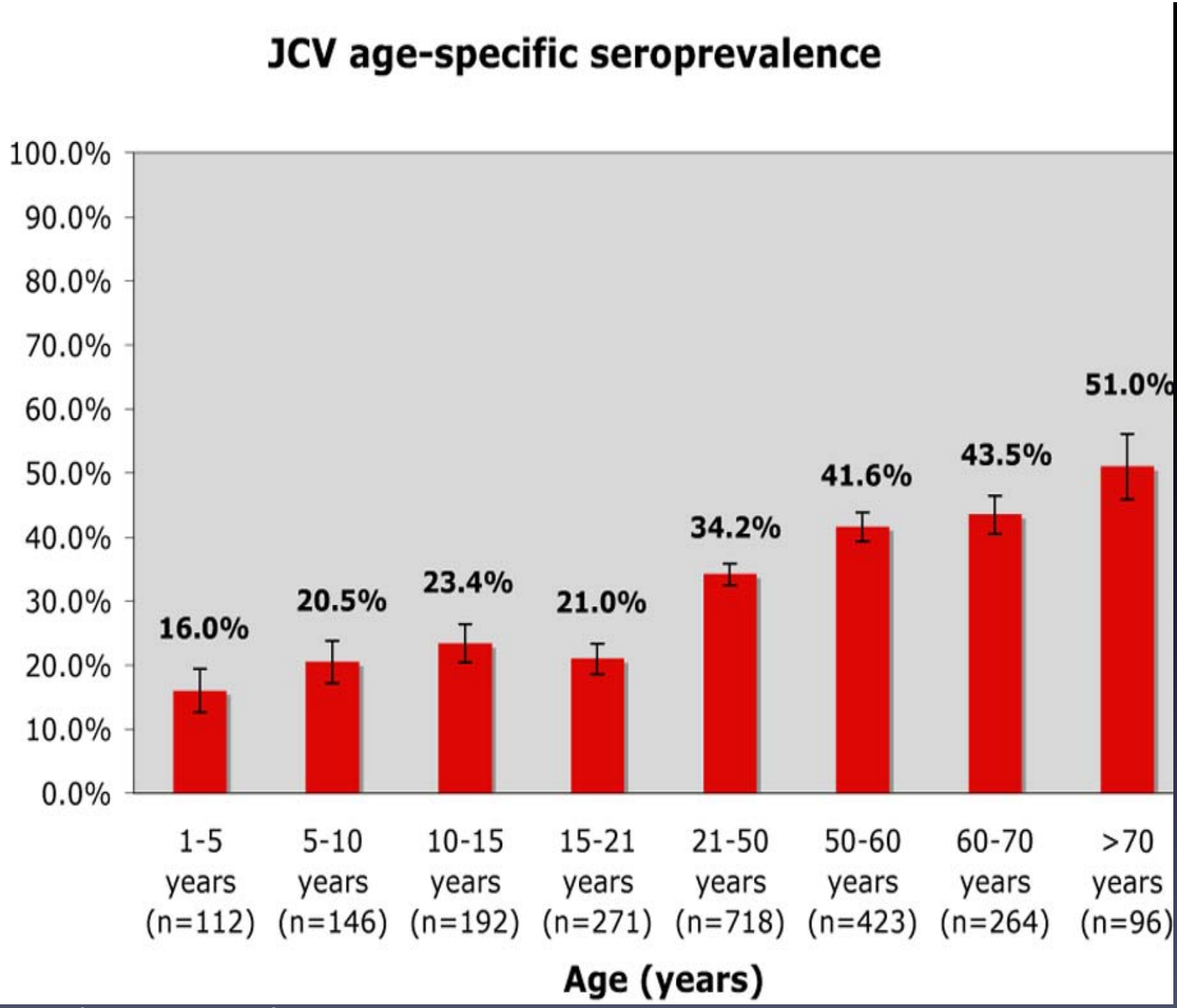
TEM of JCV in Oligodendrocyte nucleus
X100,000 (E. Major)



SV40 at 3.4 A Resolution (S. Harrison)
40-50nm, non-enveloped, icosahedral

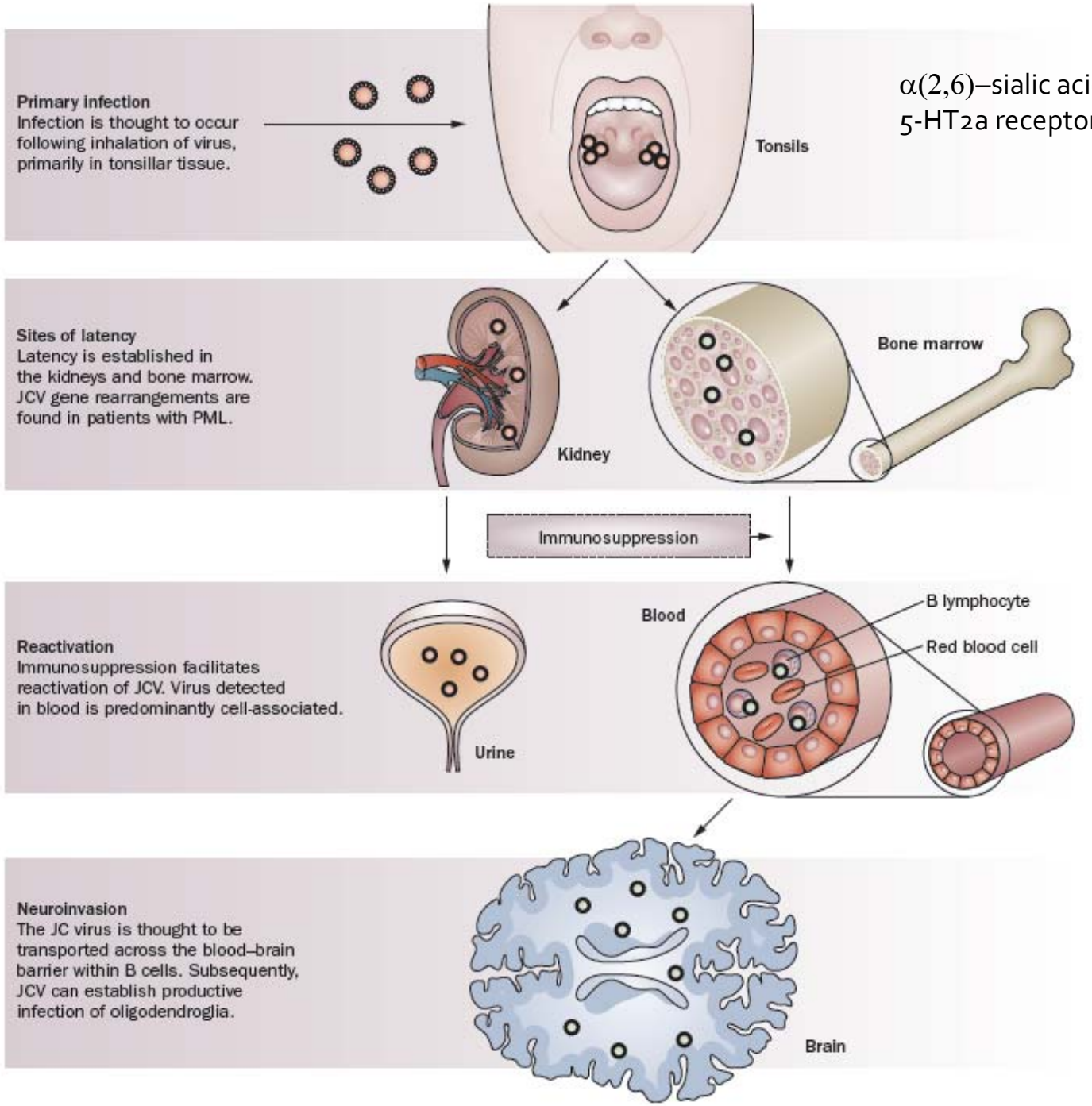


Taguchi F et al., Mol Immunol 26:1057, '82



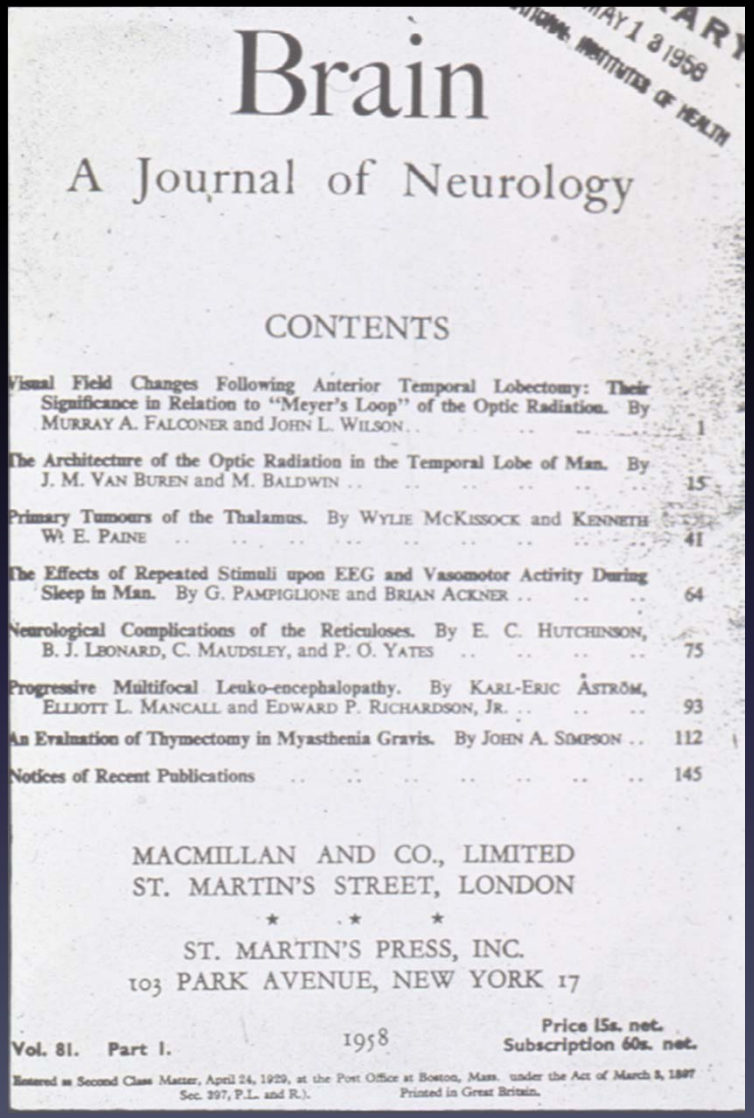
Kean J et al. , PLoS Pathogens 5:e1000363,'09

Brew et al. Nat Rev Neurol 6:667, 2010



$\alpha(2,6)$–sialic acid
5-HT2a receptor

PML – Initial Description



Brain

A Journal of Neurology

CONTENTS

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ST. MARTIN'S PRESS, INC.
103 PARK AVENUE, NEW YORK 17

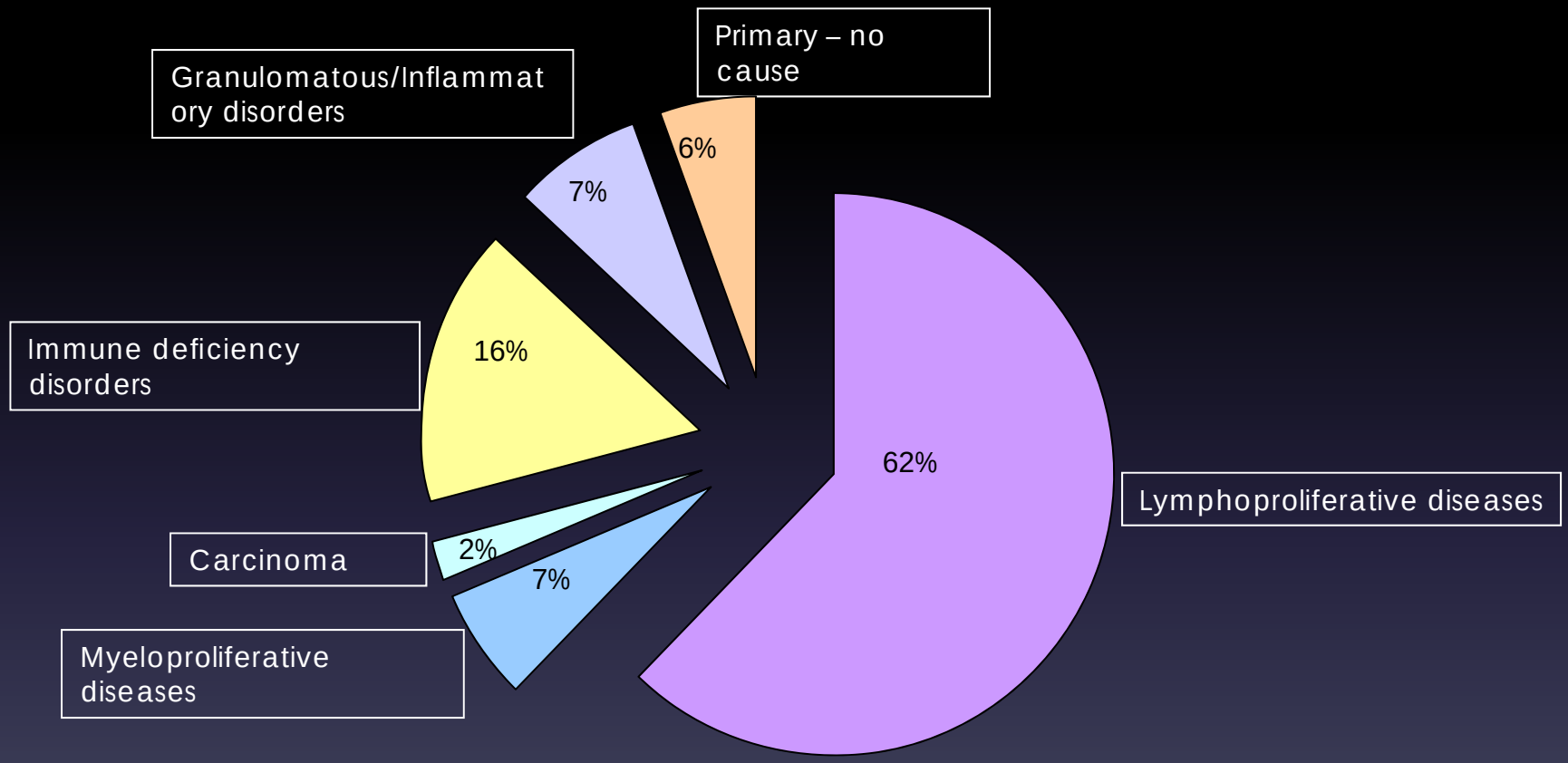
Vol. 81. Part 1. 1958 Price 15s. net. Subscription 60s. net.

Entered as Second Class Matter, April 24, 1929, at the Post Office at Boston, Mass. under the Act of March 3, 1897 Sec. 397, P.L. and R.). Printed in Great Britain.

- "In the course of regular post-mortem examinations of the brains of patients coming to autopsy at the MGH, my attention has been called in recent years to an unusual disorder of the cerebral white matter with distinctive features unfamiliar to me and my colleagues from our own experience or that of others."

(EPR NEJM 265:815, 1961)

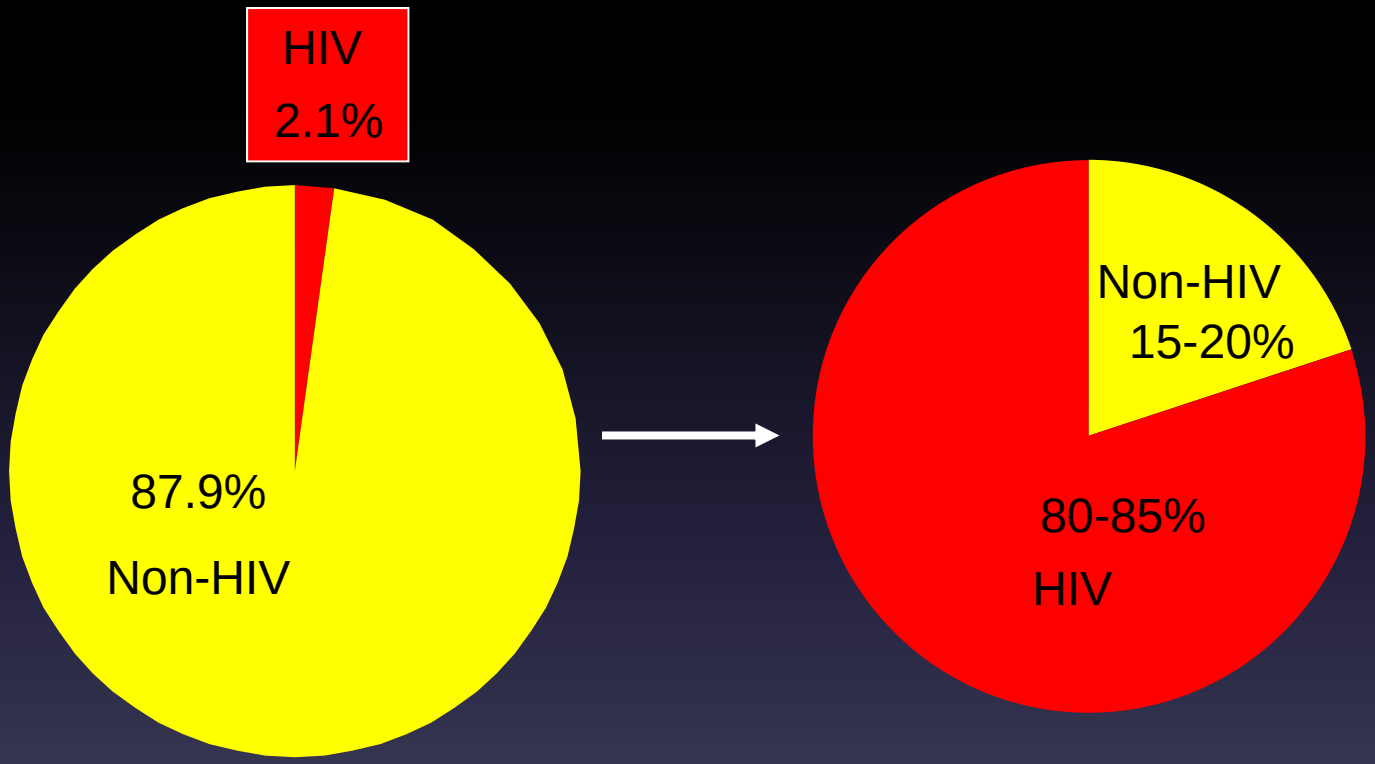
Illnesses associated with PML 1984



230 cases published and unpublished cases (1958-1984)
69 pathologically confirmed and 40 virologically and pathologically confirmed

Brooks & Walker, Neurol. Clin. '84

AIDS associated PML 1983 v 2003

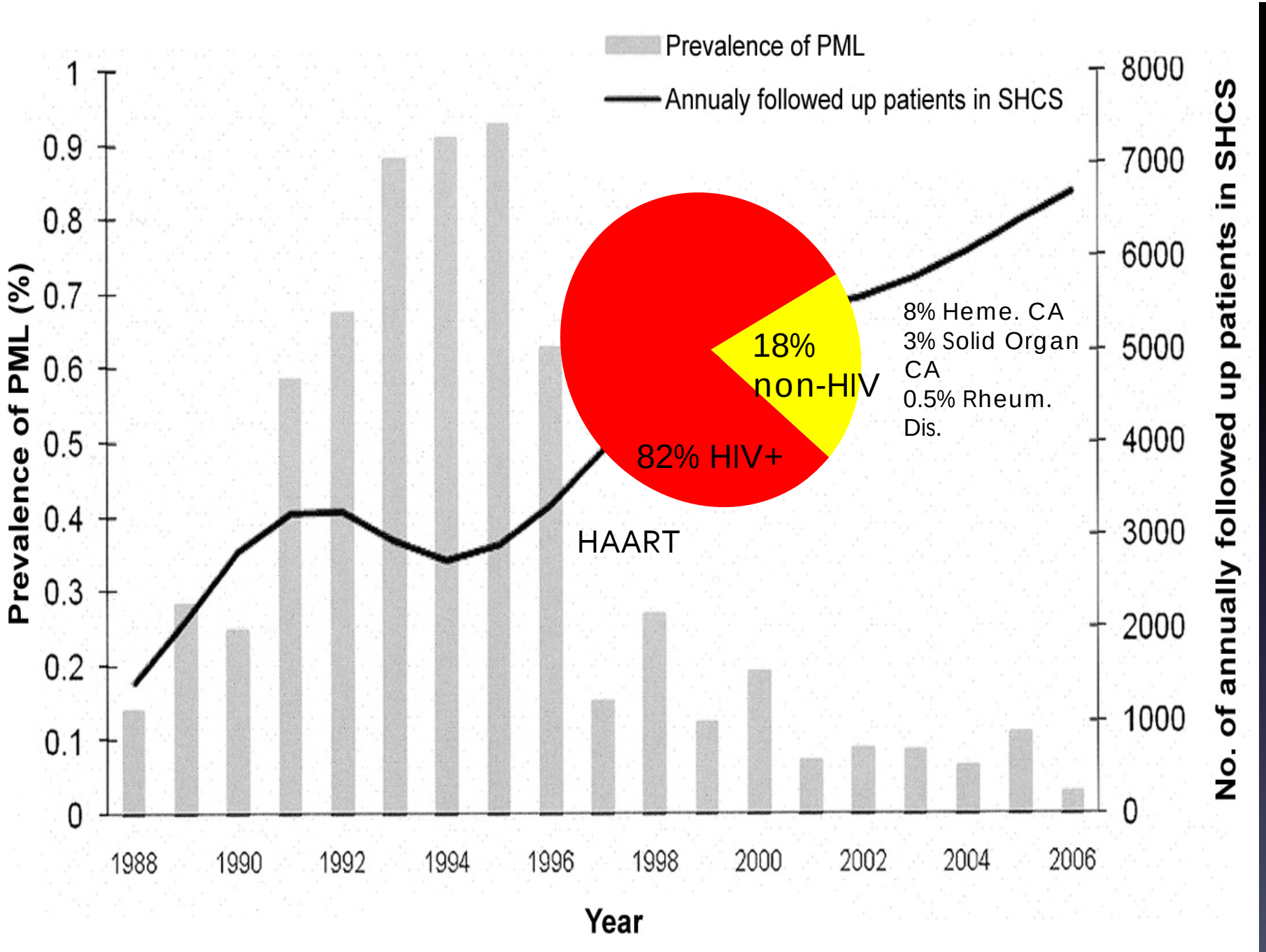


Brooks and Walker 1958-1984

0.15 per million incidence

Berger 2000-2003

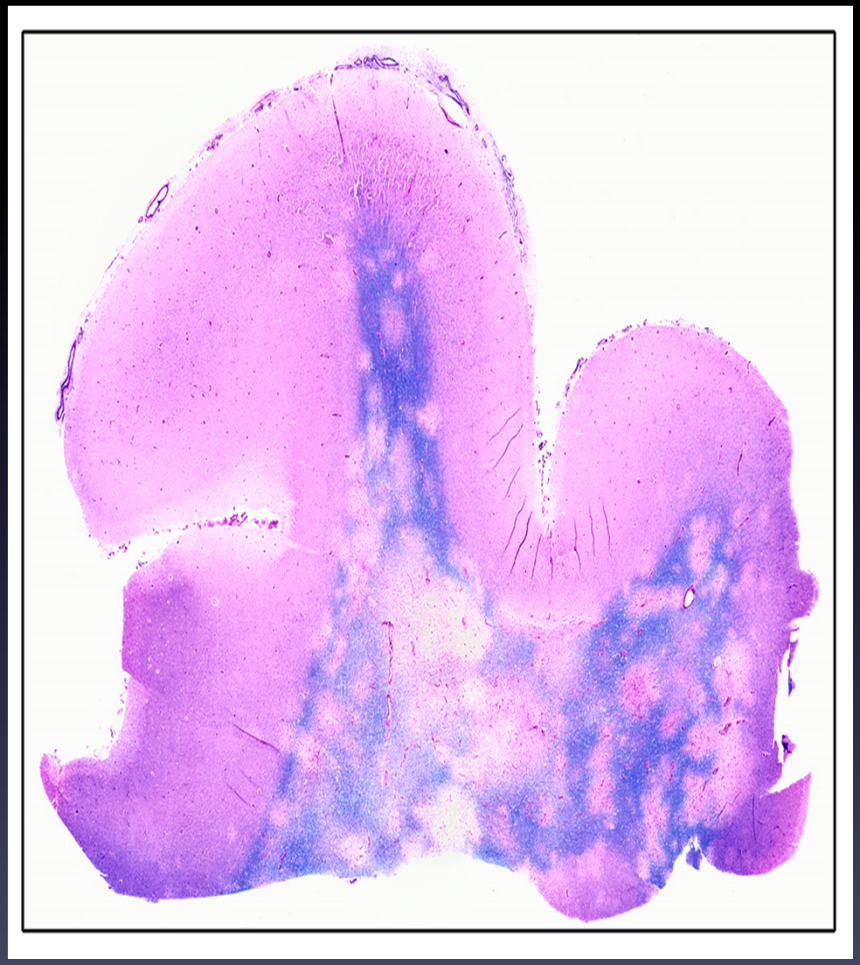
o.6 per million incidence



Khanna N et al. CID 48:1459, '09

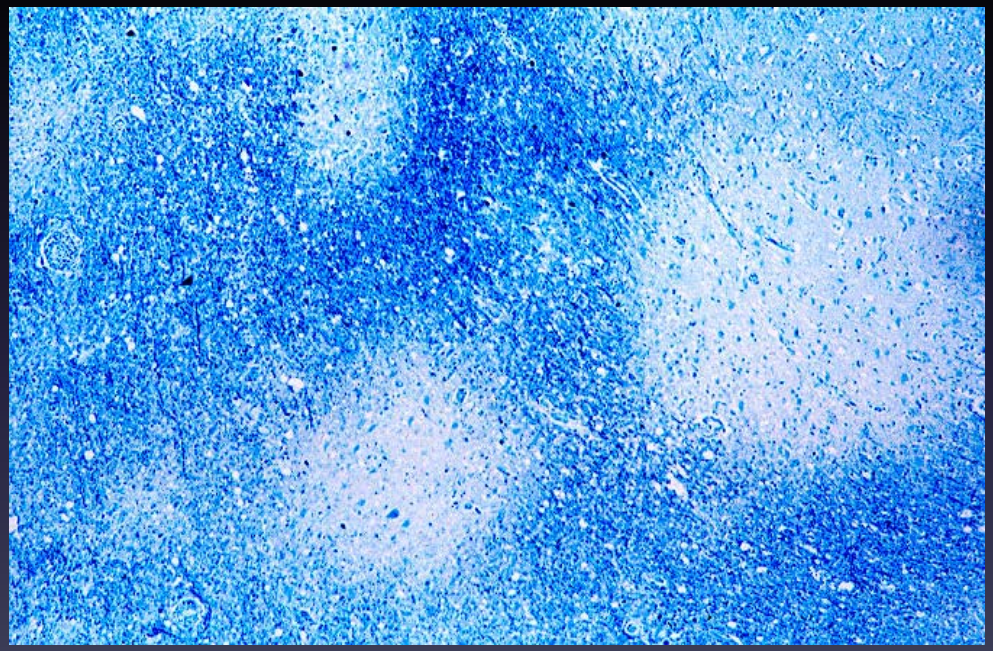
Molloy ES Arth Rheum 60:3761, '09

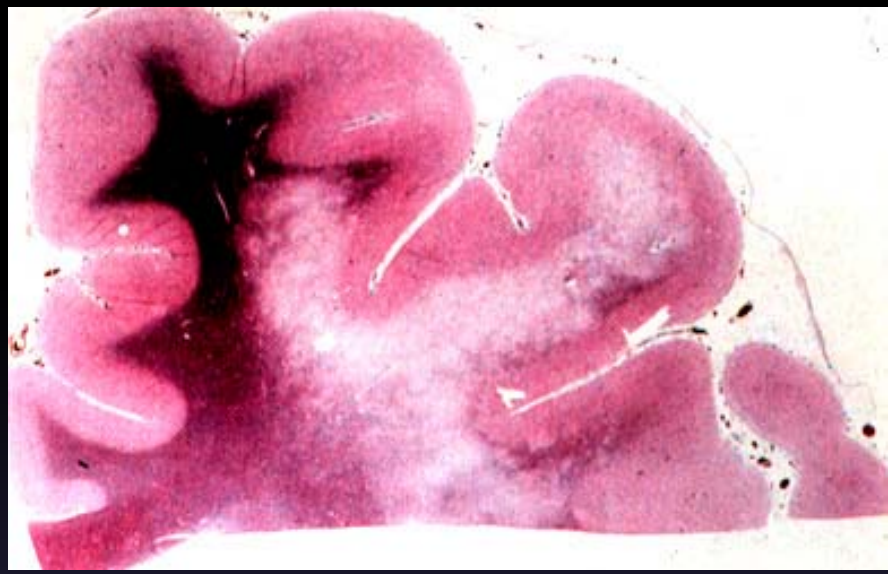
Demyelination: Usually Multifocal
LFB Myelin Stain

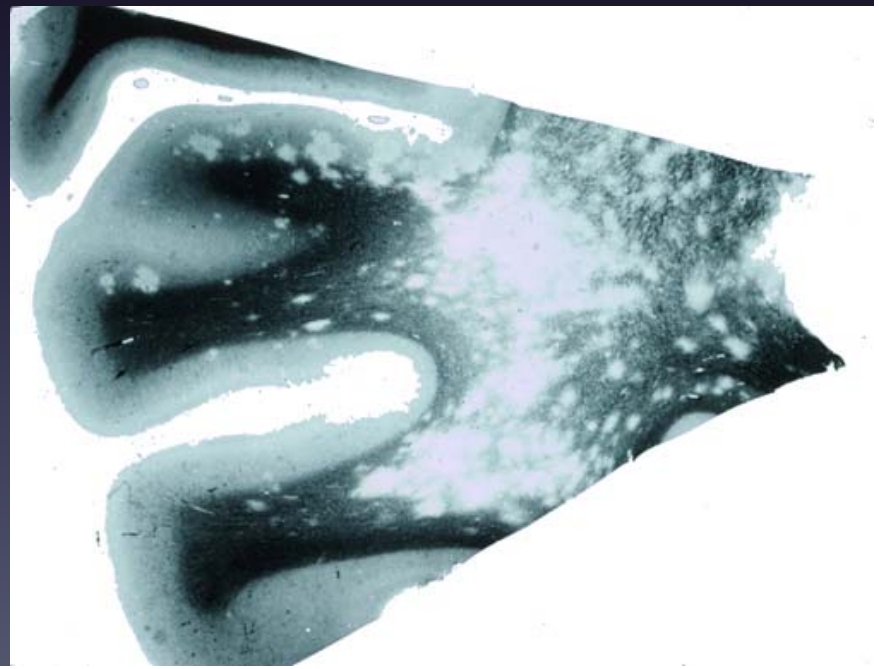


Demyelination in PML

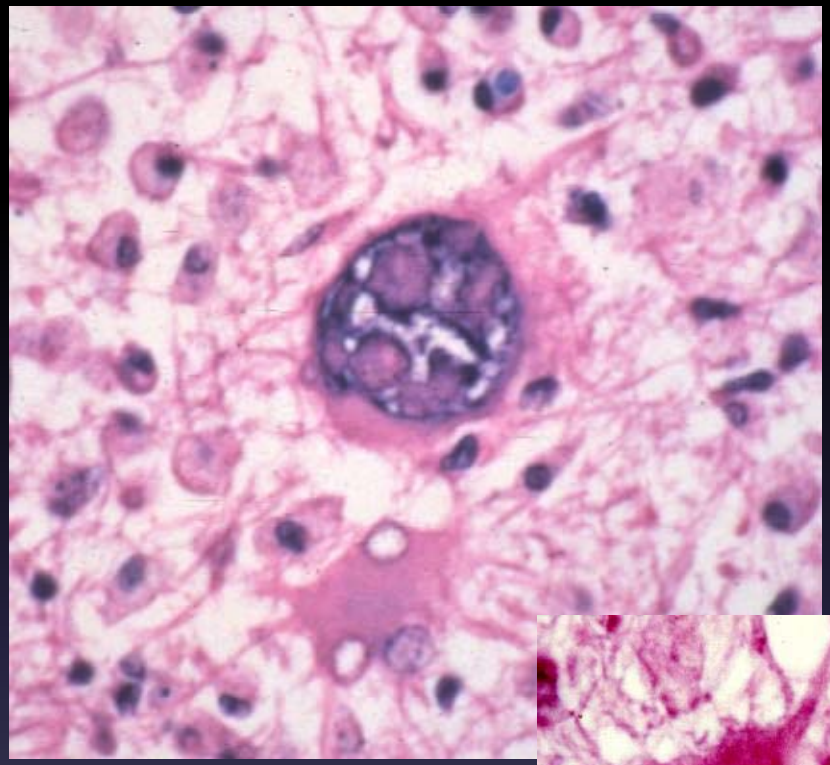
Typically multifocal
Size variable 1mm-to several cm's
No mass, classically no inflammation

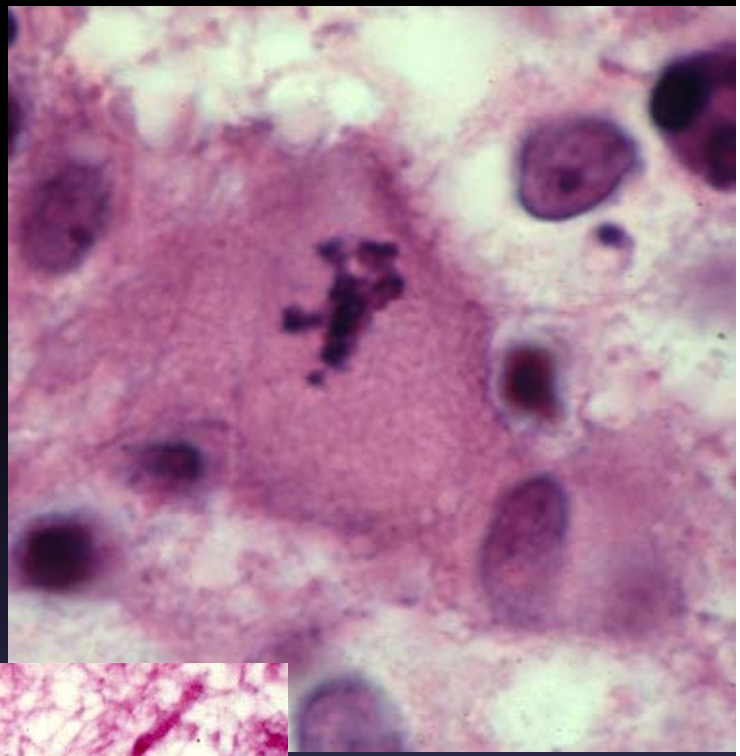


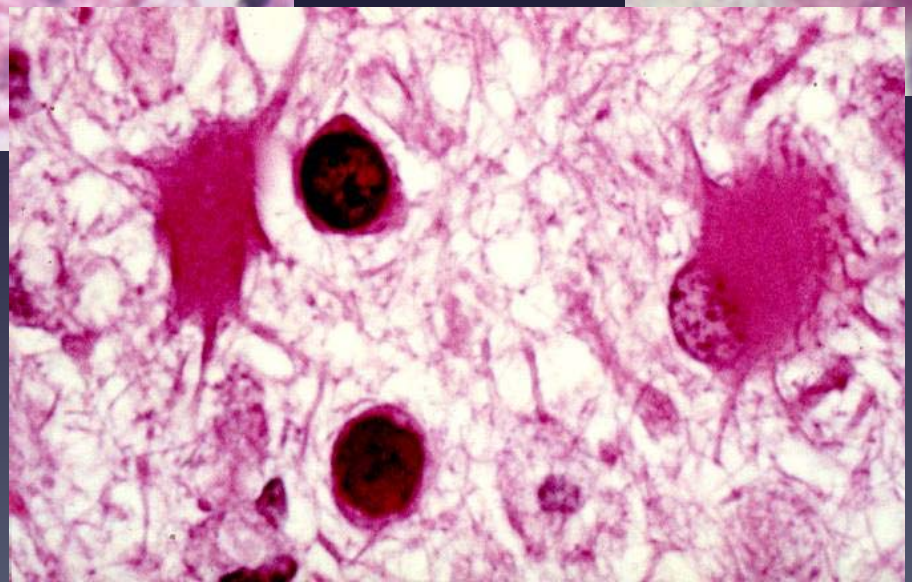


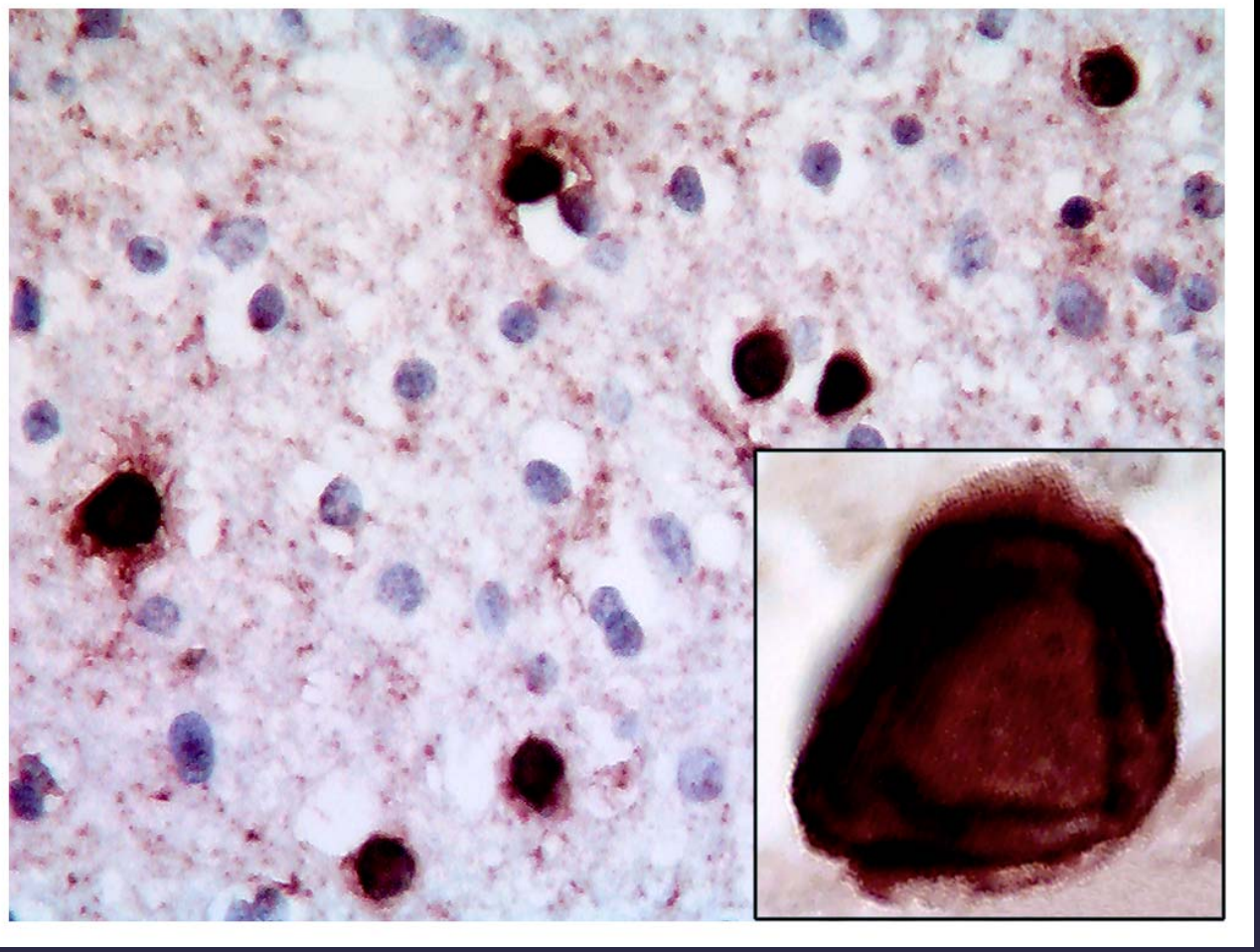


Bizarre Enlarged Astrocytes in PML



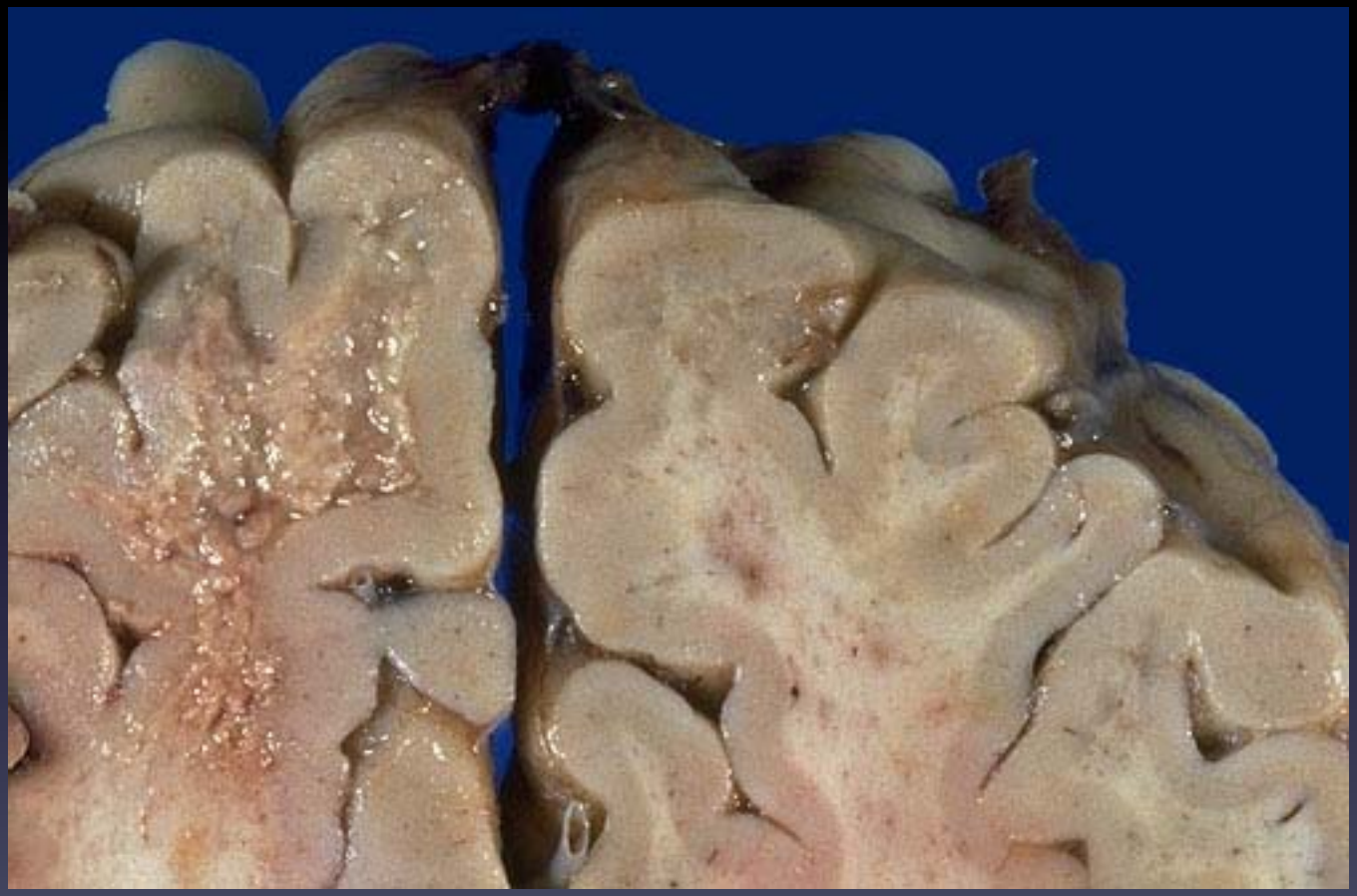






ISH+ signal for JCV DNA intranuclear inclusion bearing oligos

Gross Pathology



Symptoms and Signs of PML

[109 confirmed cases, Brooks & Walker, 1984]

	At Onset	+ At Diagnosis	TOTAL
Motor weakness	20%	75%	95%
Visual deficits	45%	13%	58%
Mental deficits	38%	20%	58%
Incoordination	10%	19%	29%
Speech	15%	10%	25%
Sensory deficits	5%	5%	10%
Sz	3%	7%	10%
HA	5%	0%	5%
Vertigo	4%	0%	4%

PML symptom	% PML cases with symptom
Cognitive/behavioral	49%
Motor (eg: hemiparesis)	37%
Speech (eg: dysarthria, aphasia)	31%
Visual (eg: hemianopsia)	26%
Cerebellar (eg: ataxia)	17%
Seizure (eg: focal motor, generalized)	17%
Sensory (eg: paresthesia)	3%

Source: Biogen Idec, First 35 Tysabri-PML Cases

Table 1 PML clinical symptoms and signs in association with different predisposing causes

PML by predisposing cause	No. of patients in each study	Cognitive and behavioral, %	Motor weakness, %	Gait abnormality and incoordination, %	Sensory loss, %	Speech or language disorder, %	Visual deficits, %	Headache, %	Seizures, %
PML in the pre-AIDS era[60]	230	36	33	13		17	34	7	5
AIDS-associated PML[23]	154	36	42	35	19	40	19	32	9
Natalizumab-associated PML[35]	42	54	45		7	24	41		14

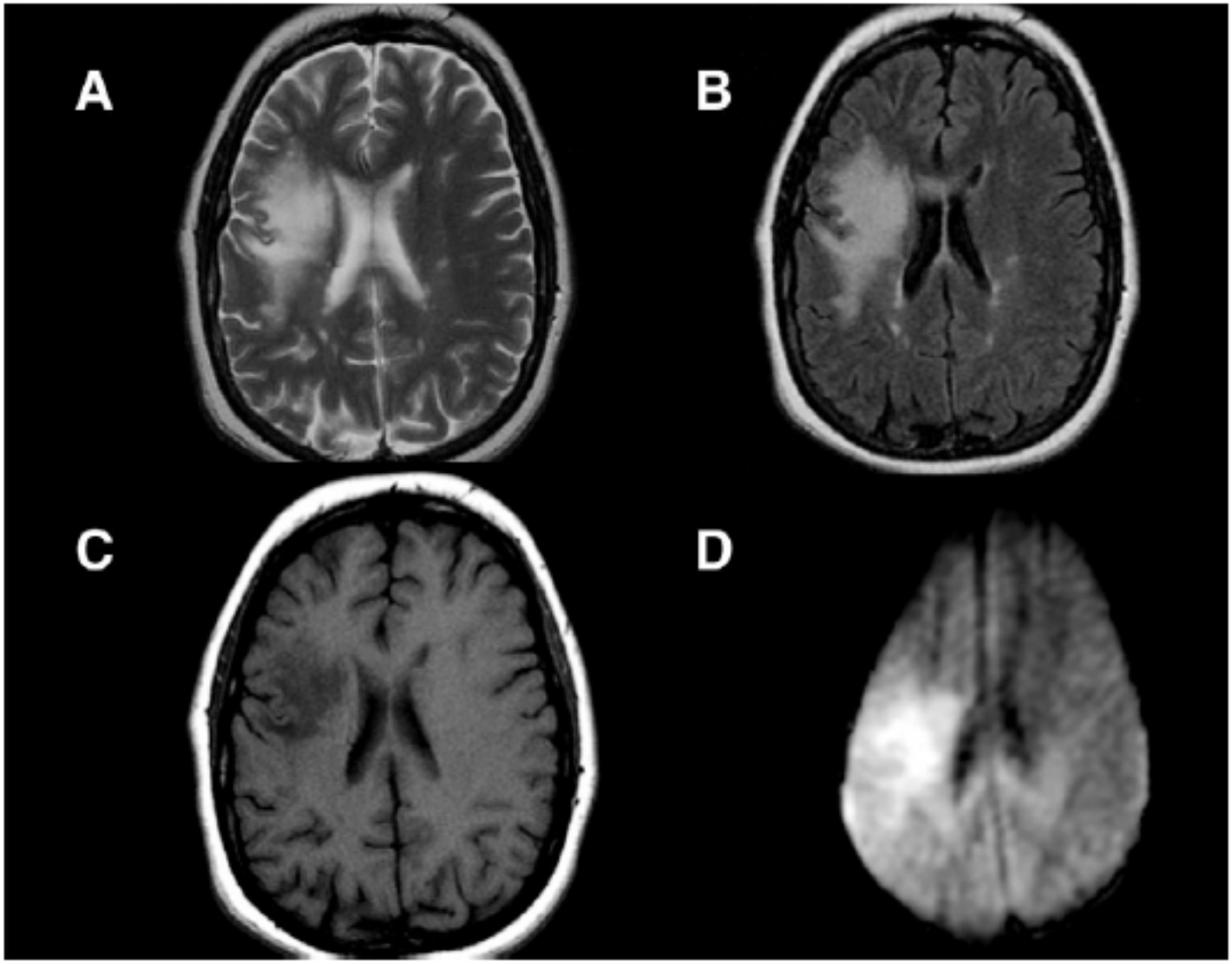
Berger et al. Neurology 80:1430, 2013

TABLE 1: Recommendations for the Diagnosis of Early PML in Natalizumab-Treated Multiple Sclerosis Patients

Features	Characteristics
Location	[a]Subcortical location is the prime site, thereby involving U-fibers; cortex and basal ganglia are often involved; often bilateral
Size	Usually >3cm
Borders	Sharp toward the gray matter, ill defined toward the white matter
Mode of extension	Lesions increase in size and new lesions appear
Mass effect	No mass effect in small or large lesions
T2W images	Always hyperintense
T1W images	[a]Typically hypointense; no reversion of signal intensity; hyperintensity is suggestive of PML-IRIS
FLAIR	Always hyperintense; better appreciated than on T2W images
DW images	[a]Always hyperintense; in larger lesion there is a hyperintense rim at the lesion's edge
Perilesional	[a]Small, punctate T2-hyperintense lesions in the immediate vicinity of the main lesion are often present
Enhancement	Frequent enhancement, punctate and/or rimlike
Atrophy	No atrophy in the early phase

[a]Features especially helpful in the identification of small PML lesions.
DW = diffusion-weighted; FLAIR = fluid-attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy; T1W = T1-weighted; T2W = T2-weighted.

Yousry et al. Ann Neurol 72:779, 2012



A: T_2
B: FLAIR
C: T_1
D:DWI

Yousry et al Ann N 72:779, 2012

CSF

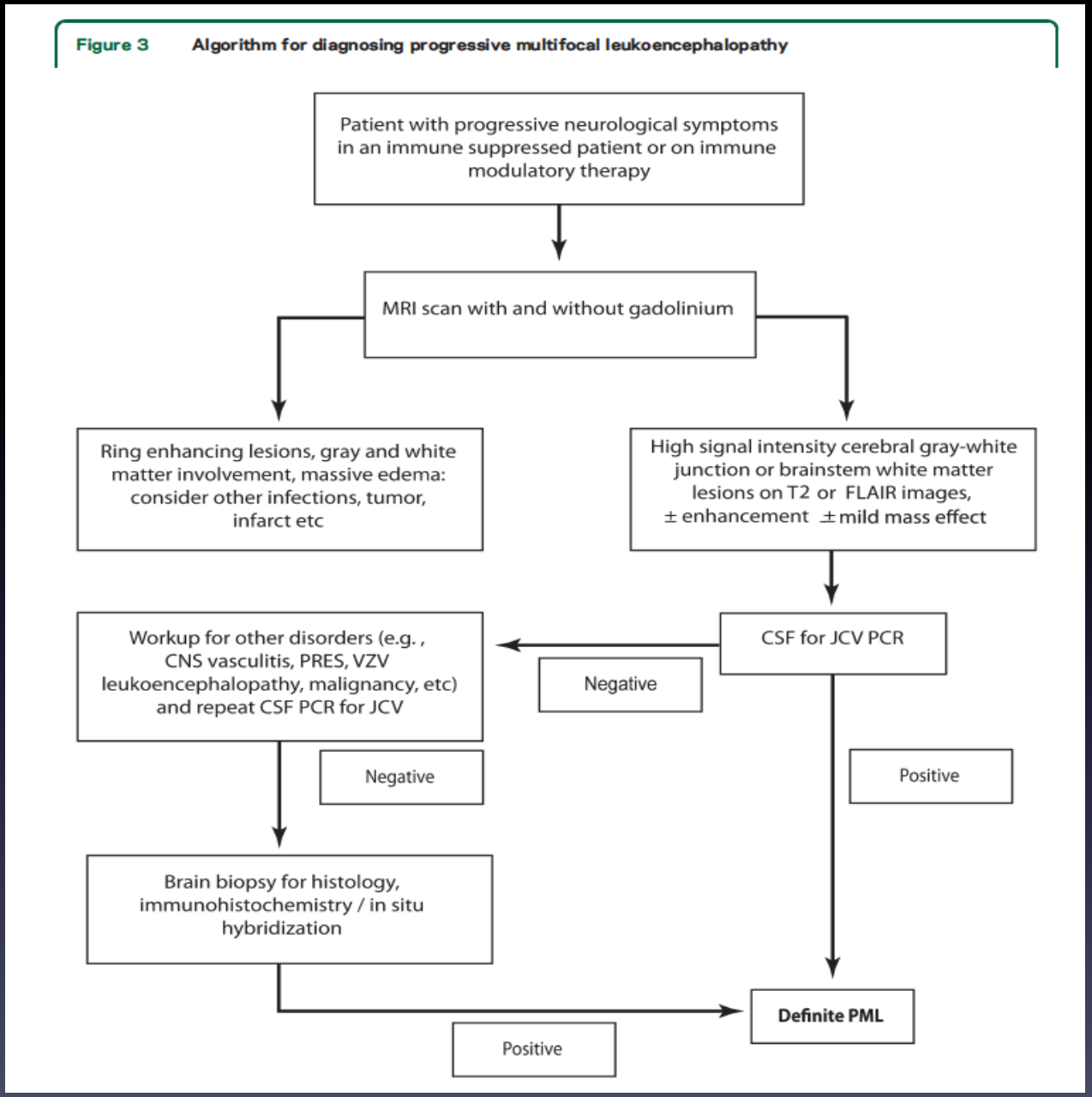
- Mild or no pleocytosis : mean 8 cells/ul, median 2 cells, rare>20)
- Sltly Elevated protein (55%): mean 67 mg/dl, rarely>200 mg/dl
- Normal glucose (>85%)
- PCR is ~95-100% specific but sensitivity variable depending on viral load (~70-90%? to >95%) and assay sensitivity
  - NINDS (E. Major) 10 DNA copies/ul vs. Commercial ~200 copies/ul
- Brain biopsy is 'gold standard'-
  - specificity 100%
  - sensitivity 90-95%

Table 2 Establishing the diagnosis with clinical, radiographic, and laboratory data[a]

Certainty of PML diagnosis	Compatible clinical features	Compatible imaging findings	CSF PCR for JC virus
Definite	+	+	+
Probable	+	−	+
	−	+	+
Possible	+	+	−/ND
	−	−	+
Not PML	−	−	−
	+	−	−
	−	+	−

Abbreviations: ND = not done or equivocal result; PML = progressive multifocal leukoencephalopathy.
[a] + = Positive; − = negative.

Berger J et al. Neurology 80:1430, 2013



Berger et al. Neurology 80:1430, 2013

Rx in PML

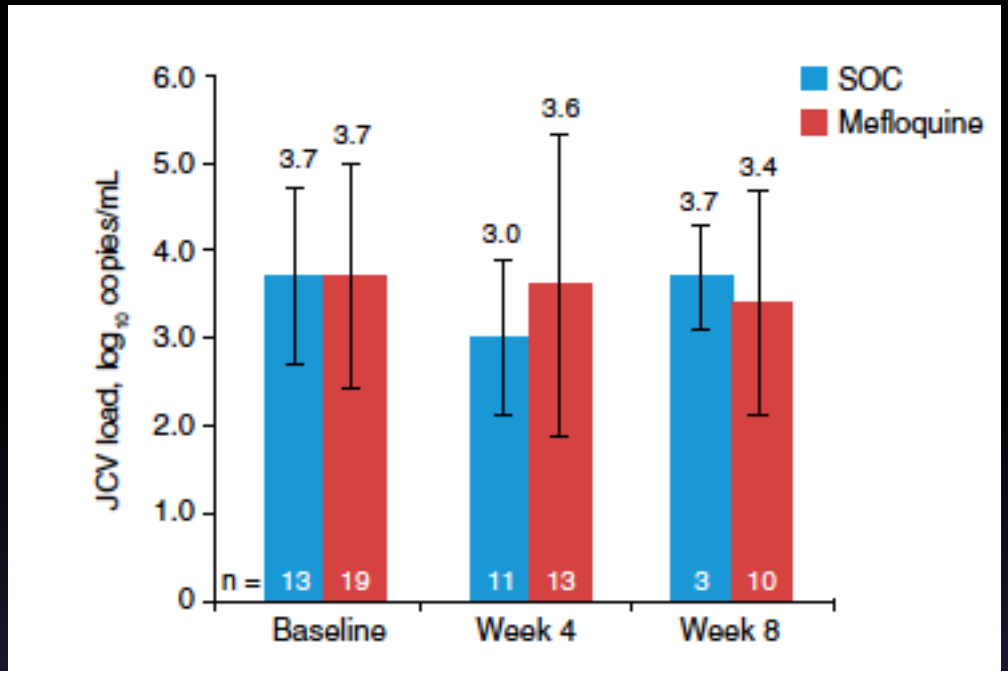
Table 1 | Summary of reported therapeutic trials for progressive multifocal leukoencephalopathy[123]

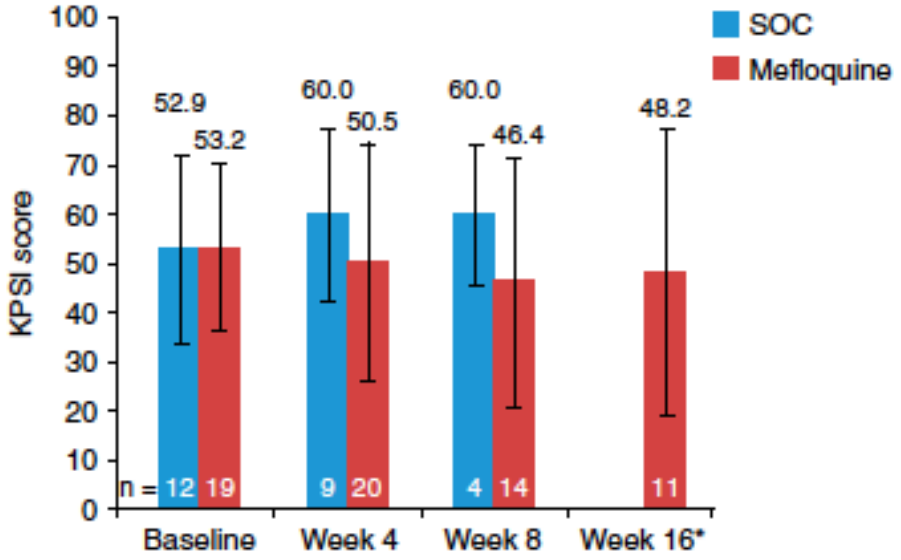
Therapy	Total number of patients	Randomized controlled clinical trial?	Number of patients treated with a single therapy*	Number of patients reported to have responded positively to treatment with a single therapy
Cytarabine[93,124–126]	162	Yes in one series	117	26
Cidofovir[96,124,127–134]	225	No	18	9
Interferon α[95,97]	>33	No	27	25
Interferon β[123,135]	2	No	1	0
Topotecan[136]	11	Yes	11 (3 weeks of antiretroviral therapy)	3
Interleukin 2[103–105,137]	4	No	3	3
Selective serotonin uptake inhibitors[99,100]	2	No	2	2

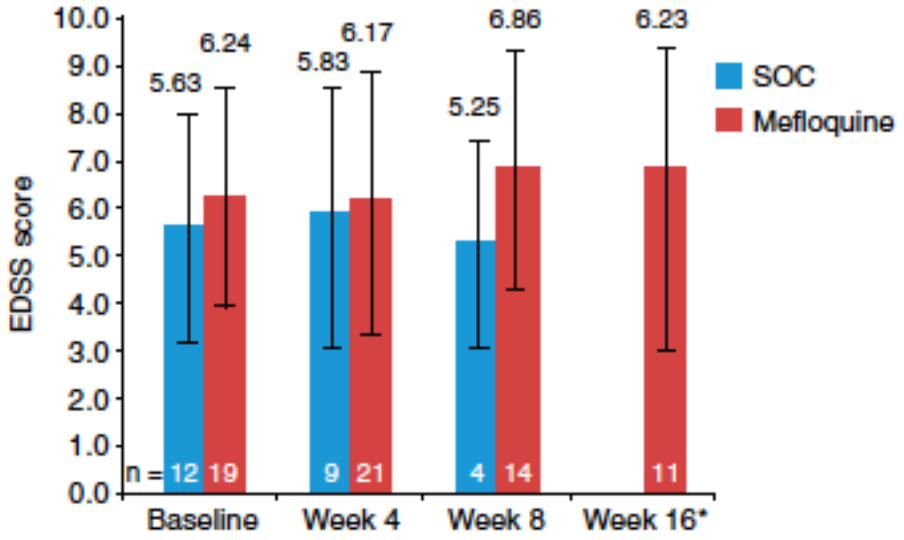
*Reduction of immunosuppression was considered to be a single agent.

Brew et al. Nat Rev Neurol 6:667, 2010

No Effect of Mefloquine in PML







Clifford D et al. J Neurovirol 19:351, 2013

Neurology 85:104, 2015

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CLINICAL AND IMMUNOLOGIC EFFECTS OF MARAVIROC IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) is a rare but generally fatal disease due to JC virus (JCV) reactivation, mainly occurring in immunosuppressed patients.[1] Therapeutic options are limited to blocking glial cell infection by mirtazapine or restoring cell-mediated immunity to acquire viral control.[2]

Maraviroc (MVC), a chemokine receptor type 5 (CCR5) blocker, effectively suppresses plasma HIV RNA in HIV-1-infected patients and possible immunologic effects, such as enhancement of CD4+ T-cell reconstitution, have been attributed to MVC therapy.[3]

PML has been described in patients with CD4+ T-cell lymphocytopenia, either idiopathic or otherwise induced, as in sarcoidosis.[1] Similar to HIV-positive patients, these patients have low CD4+ T-cell counts and an activated immune system. This led us to postulate that interfering in the CCR5 pathway via MVC might enhance CD4+ T-cell recovery by immunomodulating properties, aiming for immune control of the JCV infection. Here, we describe 3 immunocompromised HIV-negative patients diagnosed with PML who were treated off-label with MVC and showed long-term clinical improvement.

Case Report/Case Series

Treatment of Progressive Multifocal Leukoencephalopathy With Interleukin 7

Karl B. Alstadhaug, MD, PhD; Thérèse Croughs, MD; Stian Henriksen, MSc; Céline Leboeuf, PhD; Irini Sereti, MD, MHS; Hans H. Hirsch, MD, MSc; Christine Hanssen Rinaldo, PhD

IMPORTANCE No reliable treatment options are known for progressive multifocal leukoencephalopathy with underlying immunodeficiency. We describe successful compassionate use of recombinant human interleukin 7 in a patient with idiopathic $CD4^+$ T-cell lymphocytopenia.

OBSERVATIONS After the diagnoses of progressive multifocal leukoencephalopathy and idiopathic $CD4^+$ T-cell lymphocytopenia were established, a 61-year-old man was treated with recombinant human interleukin 7 on November 1, 2012. Except for an episode of epilepsia partialis continua on January 16, 2013, a gradual clinical improvement was observed until March. Abnormalities shown on magnetic resonance imaging regressed; JC virus DNA in plasma, likely originating from the brain based on sequencing data, cleared; and increases in peripheral $CD4^+$ T cells and JC virus intrathecal antibodies were observed. One year after treatment, the $CD4^+$ T-cell count returned to baseline and the clinical improvement waned, possibly due to the patient's complex epilepsy. On the latest evaluation on January 14, 2014, the patient's condition was unchanged, with no signs of ongoing central nervous system infection.

CONCLUSIONS AND RELEVANCE The present case argues strongly for proof of the treatment concept. However, deeper insight into the JC virus and its pathogenesis and the immune response during central nervous system infection as well as further clinical studies are needed before recombinant human interleukin 7 can be recommended for the treatment of other cases of immunodeficiency and progressive multifocal leukoencephalopathy.

JAMA Neurol. 2014;71(8):1030-1035. doi:10.1001/jamaneurol.2014.825
Published online June 30, 2014.

Video at jamaneurology.c

Supplemental content at jamaneurology.com

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Bone Marrow Transplantation (2011) 46, 987–992

www.nature.com/bmt

ORIGINAL ARTICLE

Polyomavirus JC-targeted T-cell therapy for progressive multiple leukoencephalopathy in a hematopoietic cell transplantation recipient

A Balduzzi[1], G Lucchini[1], HH Hirsch[2,3], S Basso[4], M Cioni[4], A Rovelli[1], A Zincone[5], M Grimaldi[6], P Corti[1], S Bonanomi[1], A Biondi[1], F Locatelli[7,8], E Biagi[1] and P Comoli[4]

Progressive multifocal leukoencephalopathy (PML) associated with polyomavirus JC (JCV) infection has been reported to be usually fatal in allogeneic hematopoietic SCT (HSCT) recipients. We present the case of a 19-year-old HSCT patient diagnosed with JCV-associated PML after prolonged immunosuppression for severe GVHD. No short-term neurological improvement was observed after antiviral treatment and discontinuation of immunosuppressive therapy. Donor-derived JCV Ag-specific CTLs were generated *in vitro* after stimulation with 15-mer peptides derived from VP1 and large T viral proteins. After adoptive CTL infusion, virus-specific cytotoxic cells were shown in the peripheral blood, JCV-DNA was cleared in the cerebrospinal fluid and the patient showed remarkable improvement. Adoptive T-lymphocyte therapy with JCV-specific CTLs was feasible and had no side effects. This case suggests that adoptive transfer of JCV-targeted CTLs may contribute to restore JCV-specific immune competence and control PML in transplanted patients.

RESEARCH ARTICLE

INFECTIOUS DISEASE

Broadly neutralizing human monoclonal JC polyomavirus VP1–specific antibodies as candidate therapeutics for progressive multifocal leukoencephalopathy

Ivan Jelcic,[1]* Benoit Combaluzier,[2]* Ilijas Jelcic,[1] Wolfgang Faigle,[1] Luzia Senn,[2] Brenda J. Reinhart,[1] Luisa Ströh,[3] Roger M. Nitsch,[2,4] Thilo Stehle,[3,5] Mireia Sospedra,[1] Jan Grimm,[2†‡] Roland Martin[1†‡]

In immunocompromised individuals, JC polyomavirus (JCPyV) may mutate and gain access to the central nervous system resulting in progressive multifocal leukoencephalopathy (PML), an often fatal opportunistic infection for which no treatments are currently available. Despite recent progress, the contribution of JCPyV-specific humoral immunity to controlling asymptomatic infection throughout life and to eliminating JCPyV from the brain is poorly understood. We examined antibody responses against JCPyV major capsid protein VP1 (viral protein 1) variants in the serum and cerebrospinal fluid (CSF) of healthy donors (HDs), JCPyV-positive multiple sclerosis patients treated with the anti–VLA-4 monoclonal antibody natalizumab (NAT), and patients with NAT-associated PML. Before and during PML, CSF antibody responses against JCPyV VP1 variants show "recognition holes"; however, upon immune reconstitution, CSF antibody titers rise, then recognize PML-associated JCPyV VP1 variants, and may be involved in elimination of the virus. We therefore reasoned that the memory B cell repertoire of individuals who recovered from PML could be a source for the molecular cloning of broadly neutralizing antibodies for passive immunization. We generated a series of memory B cell–derived JCPyV VP1–specific human monoclonal antibodies from HDs and a patient with NAT-associated PML–immune reconstitution inflammatory syndrome (IRIS). These antibodies exhibited diverse binding affinity, cross-reactivity with the closely related BK polyomavirus, recognition of PML-causing VP1 variants, and JCPyV neutralization. Almost all antibodies with exquisite specificity for JCPyV, neutralizing activity, recognition of all tested JCPyV PML variants, and high affinity were derived from one patient who had recovered from PML. These antibodies are promising drug candidates for the development of a treatment of PML.

Published Ahead of Print on February 22, 2017 as 10.1212/WNL.0000000000003740

No evidence of beneficial effects of plasmapheresis in natalizumab-associated PML

Landi et al.

	PLEX+	PLEX-	
Final outcome, n (%)	93	25	0.48
Improved	19 (21)	7 (28)	
Stable	15 (16)	4 (16)	
Worsened	30 (32)	10 (40)	
Death	29 (31)	4 (16)	

NEJM Vol. 353:
362, 369, 375
July 28, 2005

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis

B.K. Kleinschmidt-DeMasters, M.D., and Kenneth L. Tyler, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab

Annette Langer-Gould, M.D., Scott W. Atlas, M.D., Ari J. Green, M.D.,
Andrew W. Bollen, M.D., and Daniel Pelletier, M.D.

BRIEF REPORT

Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease

Gert Van Assche, M.D., Ph.D., Marc Van Ranst, M.D., Ph.D.,
Raf Sciot, M.D., Ph.D., Bénédicte Dubois, M.D., Ph.D.,
Séverine Vermeire, M.D., Ph.D., Maja Noman, M.D.,
Jannick Verbeeck, M.Sc., Karel Geboes, M.D., Ph.D.,
Wim Robberecht, M.D., Ph.D., and Paul Rutgeerts, M.D., Ph.D.

Risk:
1 case per 1000 pts
(95% CI 0.2-2.8)
3116 pts
Mean 17.9 doses
Yousry TA et al.
NEJM 354:924, '06

FDA News

FOR IMMEDIATE RELEASE
P05-07
February 28, 2005

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Issues Public Health Advisory on Tysabri, a New Drug for MS

The Food and Drug Administration (FDA) today issued a public health advisory to inform patients and health care providers about the suspended marketing of Tysabri (nataluzimab) while the agency and the manufacturer evaluate two serious adverse events reported with its use.

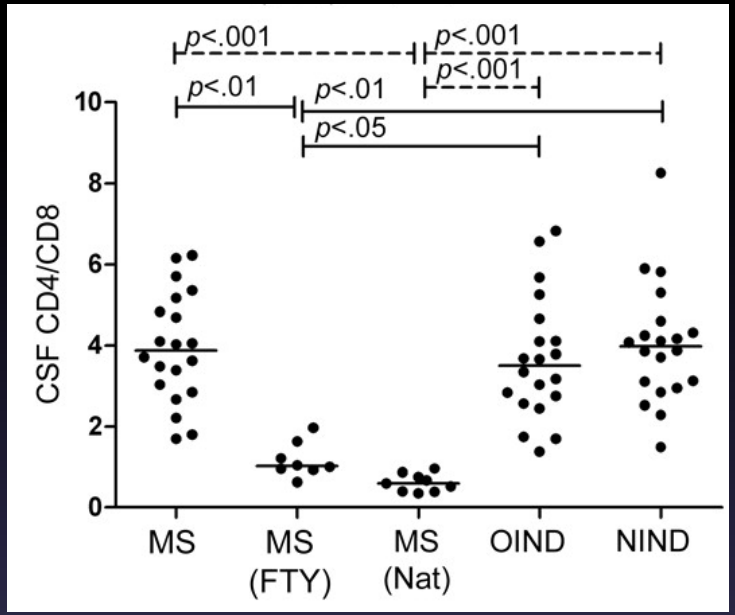
Tysabri, which received accelerated approval from FDA in November 2004, is an innovative treatment that represents a new approach to treating patients with relapsing forms of multiple sclerosis (MS).

"FDA worked with the company to make sure this information, even though preliminary, was given to physicians and patients as soon as possible and supports their decision to voluntarily suspend marketing as well as the use of the product in clinical trials. At the same time, FDA continues to believe Tysabri offers great hope to MS patients," said Steven Galson, M.D., MPH, Acting Director, FDA's Center for Drug Evaluation and Research (CDER). "Patients being treated with Tysabri should contact their physician to discuss appropriate alternative treatments while these reports are being evaluated," added Dr. Galson.

FDA received a report from Biogen Idec, the manufacturer of Tysabri, of one confirmed fatal case and one possible case of progressive multifocal leukoencephalopathy (PML) in patients receiving Tysabri for MS. FDA was given preliminary information about these cases by Biogen, Idec on February 18, 2005. Details became available to FDA the next week.

Treatment With Immunomodulatory Drugs Results in Altered T-Cell Populations

- Decreased CD4+/CD8+ T-cell ratios in CSF following MS Rx
  - Natalizumab[1,2]
  - Fingolimod[2]
- Decreased numbers of CD3+ T-cells in the blood and CSF
  - Rituxan[3,4]



Kowarik M et al. *Neurology.* 2011;76:1214.

1. Stuve O et al, *Arch Neurol*. 2006;63:1383. **2.** Kowarik M et al. *Neurology*. 2011;76:1214. **3.** Cross A et al. *J Neuroimmunol.* 2006;180:63-70. **4.** Piccio L et al, *Arch Neurol*. 2010;67:707-14.

FDA AERS: ? PML Risk of new biologics and targeted CA therapeutics PRR (95% CI), 49 new drugs:

- Brentuximab vedotin (Adcetris){CD30} 24.5 (14.8-40.6)
- Ofatumumab (Arzerra){CD20} 16.3 (9.6-27.4)
- Alemtuzumab (Campath, Lemtrada) {CD52} 9.9 (6-16.4)
- Obinutuzumab (Gazyva){CD20} 7.4 (2.4-22.8)
- Ibrutinib (Imbruvica){Bruton TK inhib.} 5.6 (3-10.5)
- Belimumab (Benlysta){Blys stim.} 4.5 (2.3-9)
- Idelalisib (Zydelig){PI3K inhib.} 4.1 (1.3-12.6)

Raisch et al. Exp Op. Drug Safety 15:1003, 2016

PML in a Patient without Severe Lymphocytopenia Receiving Dimethyl Fumarate

Nieuwkamp DJ et al. NEJM 372:1474, 2015.

TO THE EDITOR: Fumaric acid esters, which are prescribed for the treatment of psoriasis and multiple sclerosis, are considered to have a favorable risk profile. However, treatment-related progressive multifocal leukoencephalopathy (PML) has been described in association with long-lasting, severe lymphocytopenia (<500 lymphocytes per cubic millimeter).[1-3] This has led to the recommendation that lymphocyte counts should be monitored in patients receiving these drugs in order to prevent opportunistic infections such as PML.[4] Here, we report a case of fatal PML after treatment with compounded dimethyl fumarate (DMF) in a patient without severe lymphocyto-

respectively, in June 2014 (Fig. 1). Analysis of the cerebrospinal fluid showed normal levels of leukocytes, protein, and glucose. The patient was seronegative for the human immunodeficiency virus. At that time, a diagnosis of PML was considered. However, testing of the cerebrospinal fluid for JC virus DNA on polymerase-chain-reaction (PCR) assay was negative. Treatment with DMF was discontinued, and the patient received the diagnosis of atypical ischemic stroke.

Owing to progressive hemiparesis and somnolence, she was transferred to our hospital on August 14, 2014. Follow-up MRI showed a rapid

ination of lesions sugges-

FDA Drug Safety Communication: FDA warns about case of rare brain infection PML with MS drug Tecfidera (dimethyl fumarate)

[11-25-2014]

5 Tecfidera MS PML Cases
Lymphopenia (<500/mm^3)
Duration of Rx (yrs)
Age >50
~230,000 pts Rx'd (1/2017)
~1:46,000

~200x < natalizumab

FDA Drug Safety Communication: FDA warns about cases of rare brain infection with MS drug Gilenya (fingolimod) in two patients with no prior exposure to immunosuppressant drugs

This information is an update to the FDA Drug Safety Communication: FDA investigating rare brain infection in patient taking Gilenya (fingolimod) issued on **August 29, 2013 (/Drugs/DrugSafety/ucm366529.htm)**.

Safety Announcement

[8-4-2015] The U.S. Food and Drug Administration is warning that a case of definite progressive multifocal leukoencephalopathy (PML) and a case of probable PML have been reported in patients taking Gilenya (fingolimod) for multiple sclerosis (MS). These are the first cases of PML reported in patients taking Gilenya who had not been previously treated with an immunosuppressant drug for MS or any other medical condition. As a result, information about these recent cases is being added to the drug label.

9 Cases
8/9 >2.5 yrs on Rx
1/9 ~1.5 yrs
Age >49 in 8/9 (1=32)
1:18,000 to 1:8500
35-80x <natalizumab

Drug Risk Categories

- Class I (High)
  - Natalizumab (0.1%-1%)
  - Efalizumab (3/166: 1.8%)
- Class II (Low/Infrequent)
  - Rituximab (1/30,000 in RA)
  - Mycophenylate Mofetil
  - Brentuximab
  - Belimumab (2/18,000)
- Class III (Unknown)

  Alemtuzumab (no Cases in PML some in CLL Rx)

  Fumaric Acid (4+ with fumarate, 1+ with dimethylfumarate in MS)

  Fingolimod (3 Cases)

  TNF alpha blockers (etanercept, infliximab)

  Cyclophosphomide

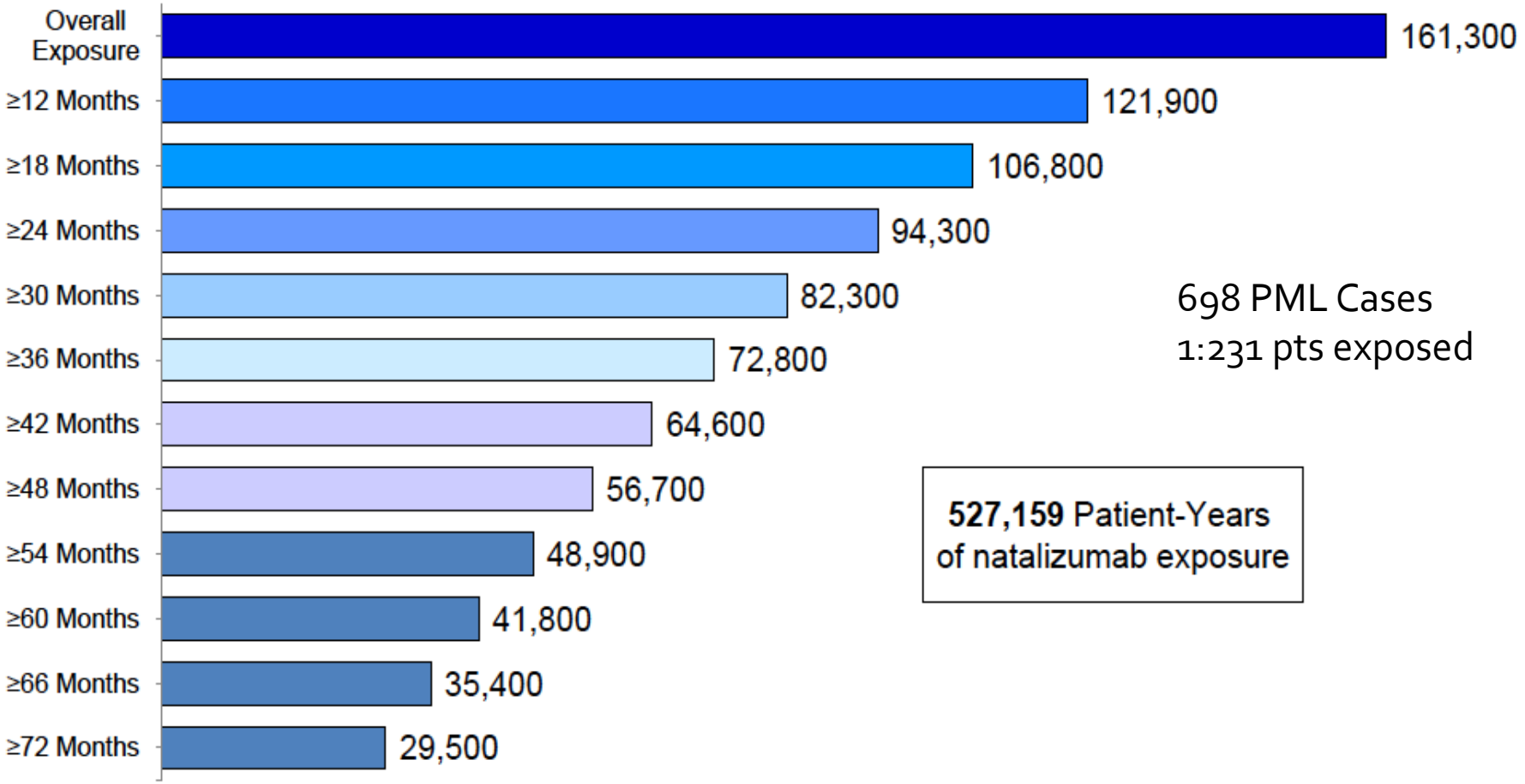
  Azathioprine

  Methotrexate

Chahin & Berger , J Neurovirol 21:623, (Dec) 2015

Use of Natalizumab in the Postmarketing Setting*

Worldwide postmarketing data from 23 Nov 2004 to 30 Sept 2016



698 PML Cases
1:231 pts exposed

527,159 Patient-Years of natalizumab exposure

*Postmarketing data includes patients exposed since 23 November 2004. This excludes approximately 5,100 patients exposed in clinical trials; 2,200 exposed for ≥12 months; 1,900 exposed for ≥18 months; 1,700 exposed for ≥24 months; 1,300 were exposed ≥30 months; 1,000 were exposed ≥36 months; 700 were exposed ≥42 months; and 700 were exposed for ≥48 months. Exposures are estimates and may not fully reflect treatment interruptions that are used in certain patients.

Biogen. Dec. 2016

PML Incidence & Confirmed Cases

- As of November 30, 2016, the global overall incidence of PML in natalizumab-treated patients is: 4.18 per 1000 patients (95% CI 3.88 to 4.51 per 1000 patients)
- As of December 1, 2016 there have been 698 confirmed PML cases (695 MS, 3 CD), (194 US, 438 EEA, 66 ROW)
  - 77% of patients were alive with varying levels of disability*
- As of December 1, 2016, the duration of natalizumab dosing prior to PML diagnosis ranged from 8 to 118 doses
  - Mean duration of natalizumab dosing at time of PML diagnosis was approximately 48 months

Biogen: Tysabri Postmarketing Safety Update. TY-US-0113(11). Dec. 2016

Table 1. Characteristics of 336 Confirmed Post-Marketing TYSABRI-Associated PML Cases by PML Outcome

Characteristic	All (N=336)	Survivors (n=254)	Nonsurvivors (n=82)	p value
Age at diagnosis, years	(n=332)	(n=252)	(n=80)	
Mean (SD)	45.0 (9.6)	43.5 (9.2)	49.5 (9.7)	<0.0001
Median (range)	45 (15–73)	44 (15–71)	50 (24–73)	
Gender, female, n (%)	237 (71)	182 (72)	55 (67)	0.4322
Geography, n (%)				
USA	119 (35)	70 (59)	49 (41)	<0.0001[b]
EU/ROW	217 (65)	184 (85)	33 (15)	
Duration of MS, years	(n=116)	(n=90)	(n=26)	
Mean (SD)	14.1 (8.2)	13.3 (7.7)	16.7 (9.1)	0.0909
Median (range)	12 (1–51)	12 (1–51)	15 (6–38)	
Natalizumab exposure, months				
Mean (SD)	38.6 (14.0)	39.2 (14.0)	36.7 (13.8)	0.1045
Median (range)	38 (8–74)	40 (8–74)	34 (14–72)	
JC viral load, copies/mL	(n=285)	(n=216)	(n=69)	
Mean (SD)	185,797 (893,482)	91,587 (469,668)	480,715 (1,587,521)	<0.0001
Median (range)	500 (1–10,243,280)	386 (1–4,831,575)	2076 (10–10,243,280)	
Time from symptom onset to diagnosis, days	(n=328)	(n=246)	(n=82)	
Mean (SD)	44.2 (51.9)	41.3 (44.5)	52.9 (69.2)	0.2623
Median (range)	27 (0–368)	26 (0–216)	29 (0–368)	
EDSS score, pre-PML	(n=123)	(n=101)	(n=22)	
Mean (SD)	3.9 (1.8)	3.7 (1.8)	5.0 (1.7)	0.0028
Median (range)	3.75 (0–8)	3.5 (0–7)	5.0 (2–8)	
KPS score, pre-PML	(n=84)	(n=72)	(n=12)	
Mean (SD)	79.7 (13.2)	81.2 (12.4)	70.8 (15.1)	0.0117
Median (range)	80 (40–100)	80 (40–100)	70 (40–100)	
Prior immunosuppressant use[a], n (%)	91 (27)	68 (27)	23 (28)	

[a] Mitoxantrone, methotrexate, azathioprine, cyclophosphamide, or mycophenolate

[b] p value is for comparison of survival rate between USA and EU/ROW. All other p values are for comparison between survivors and nonsurvivors

SD standard deviation

Biogen. M-TY-US-00196. Jun 2016

Estimated United States Incidence of PML Stratified by Risk Factor

Anti-JCV Antibody Negative	TYSABRI Exposure†	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
<1/1,000	1-24 months	<1/1,000	1/1,000
	25-48 months	3/1,000	12/1,000
	49-72 months	6/1,000	13/1,000

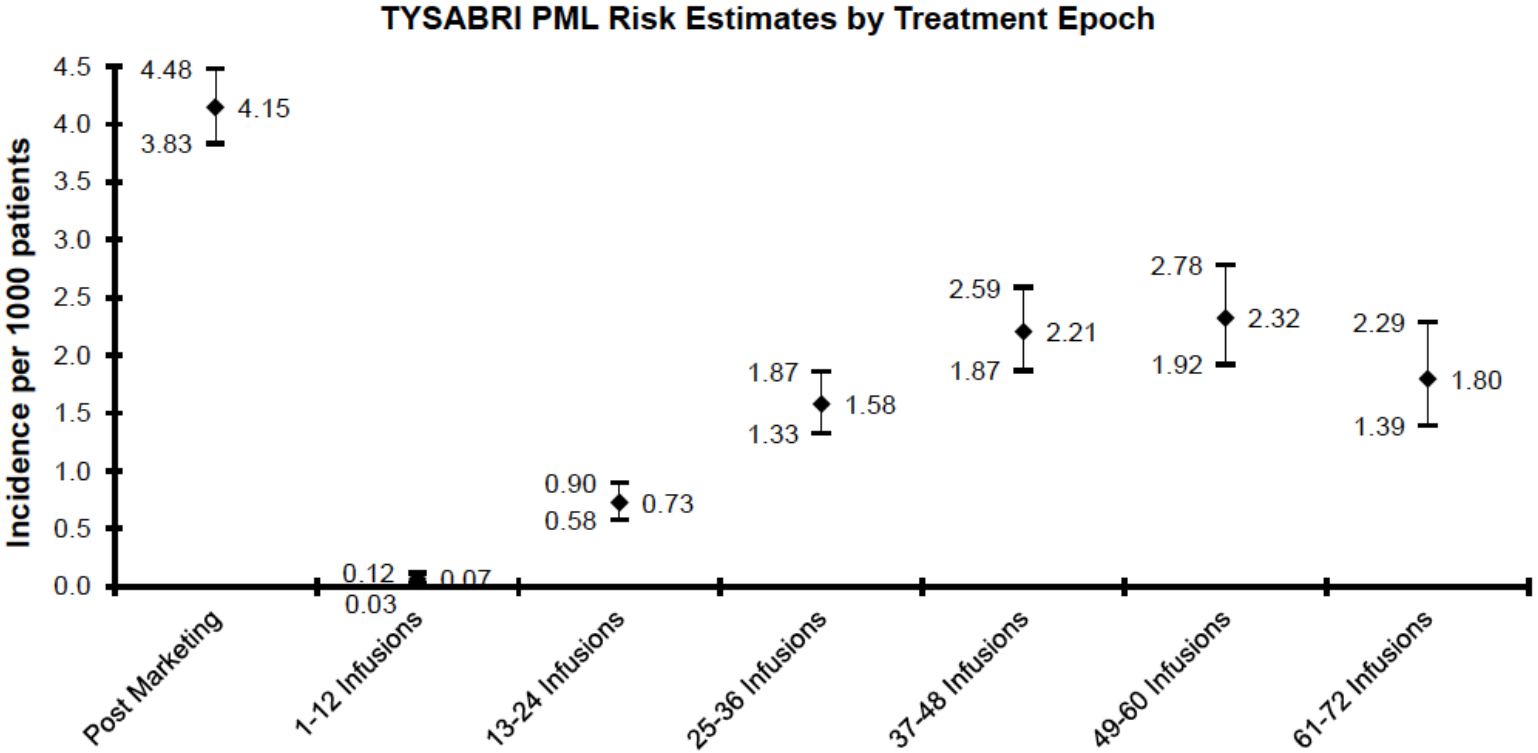
Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.

†Data beyond 6 years of treatment are limited.

The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.

Biogen: Tysabri Postmarketing Safety Update. TY-US-0113(11) & 0102(11). Dec. 2016

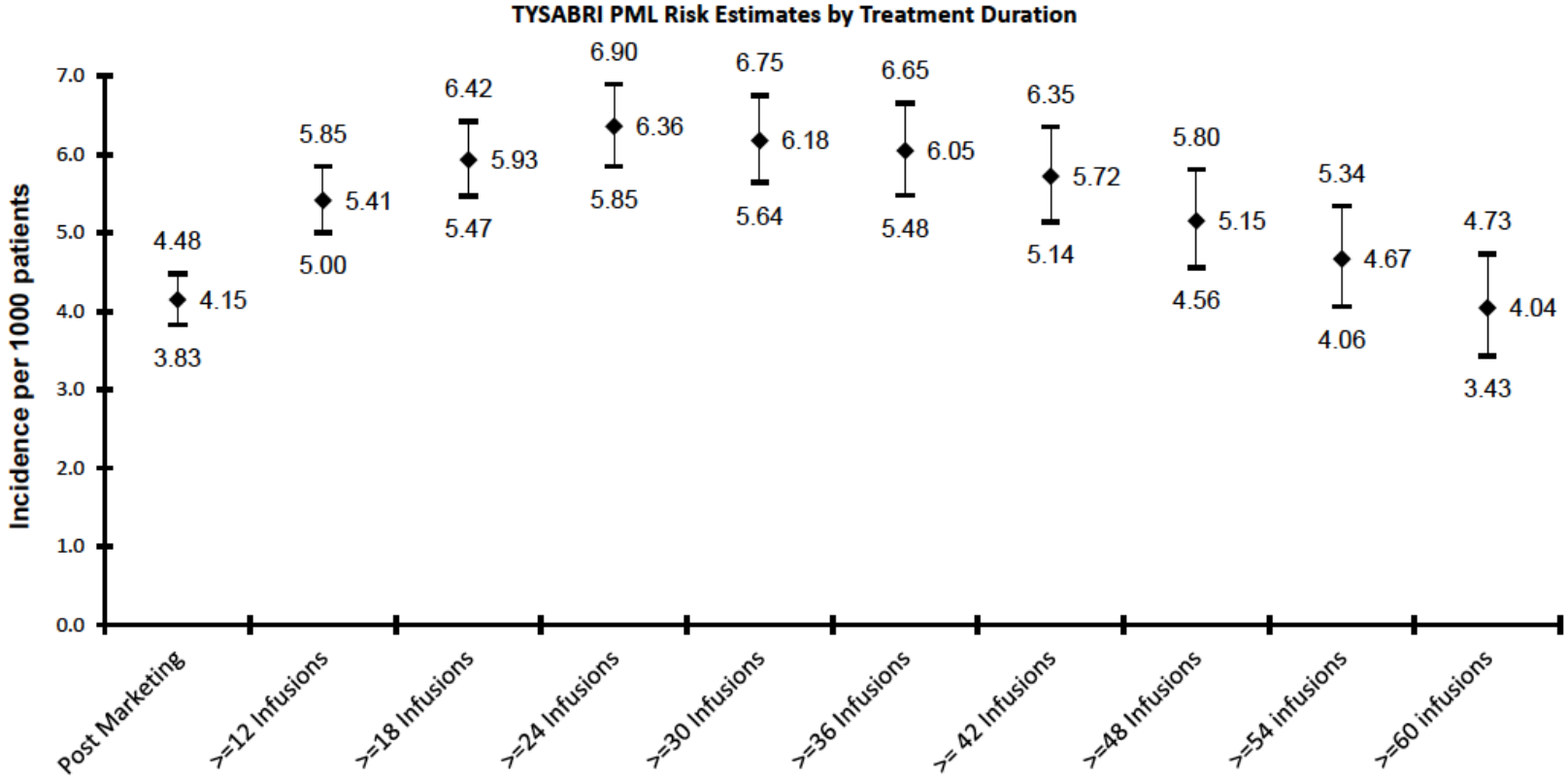
Global Natalizumab PML Risk Estimates by Treatment Epoch: March 2016



Due to the consistency of the incidence over time, this figure will be updated annually after the March 2016 Safety Update.
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 postmarketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.
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, data on file.

Biogen. TY-US-0113(11) & 0102(11). Dec. 2016

Global Cumulative Natalizumab PML Risk Estimates by Treatment Duration: March 2016



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The incidence for each time period is calculated as the number of PML cases divided by the number of patients exposed to natalizumab (e.g., for ≥24 infusions all PML cases diagnosed with exposure of 24 infusions or more divided by the total number of patients exposed to at least 24 infusions). Biogen, data on file.

Biogen. TY-US-0113(11) & 0102(11). Dec. 2016

PML and Anti-JC Virus Antibody

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Bloomgren G et al. *N Engl J Med*. 2012;366:1870-1880.

Table 3. Estimated Incidence of PML According to Anti–JC Virus Antibody Status.

Variable	Positive for Anti–JC Virus Antibodies	Negative for Anti–JC Virus Antibodies	Total	P Value	Relative Risk of PML with Positive Status (95% CI)
Primary analysis*				<0.001	∞ (14.4–∞)
No. of PML cases	54	0	54		
Total patients treated	13,950	11,414	25,364		
Incidence per 1000 patients (95% CI)	3.87 (2.91–5.05)	0 (0.00–0.32)	2.13 (1.60–2.78)		
Sensitivity analysis I†				<0.001	44.2 (7.63–1784)
No. of PML cases	54	1	55		
Total patients treated	14,209	11,625	25,834		
Incidence per 1000 patients (95% CI)	3.80 (2.86–4.96)	0.09 (0.00–0.48)	2.13 (1.60–2.77)		
Sensitivity analysis II‡				<0.001	44.2 (7.64–1788)
No. of PML cases	54	1	55		
Total patients treated	8670	7094	15,764		
Incidence per 1000 patients (95% CI)	6.23 (4.68–8.12)	0.14 (0.00–0.79)	3.49 (2.63–4.54)		

* The primary analysis was based on the overall incidence of PML of 2.129 cases per 1000 patients who received natalizumab therapy for at least 1 month. All 54 cases of PML occurred in patients who were positive for anti–JC virus antibodies before the diagnosis of PML.

† Sensitivity analysis I was an analysis that was based on the assumption of one hypothetical patient with PML who was negative for anti–JC virus antibodies; this assumption was made in order to derive a conservative estimate of the incidence of PML.

‡ Sensitivity analysis II was an analysis that was based on the assumption of one hypothetical patient with PML who was negative for anti–JC virus antibodies. In addition, this analysis assumed that patients received natalizumab therapy for at least 18 months, since 53 of the 54 patients with PML received natalizumab for at least 18 months.

Biogen Tysabri Safety Update, 2016

276/278 natalizumab-PML MS patients (99%) Anti-JCV Ab+ ≥ 6 months prior to PML diagnosis. Two negative at -8m and -9m.

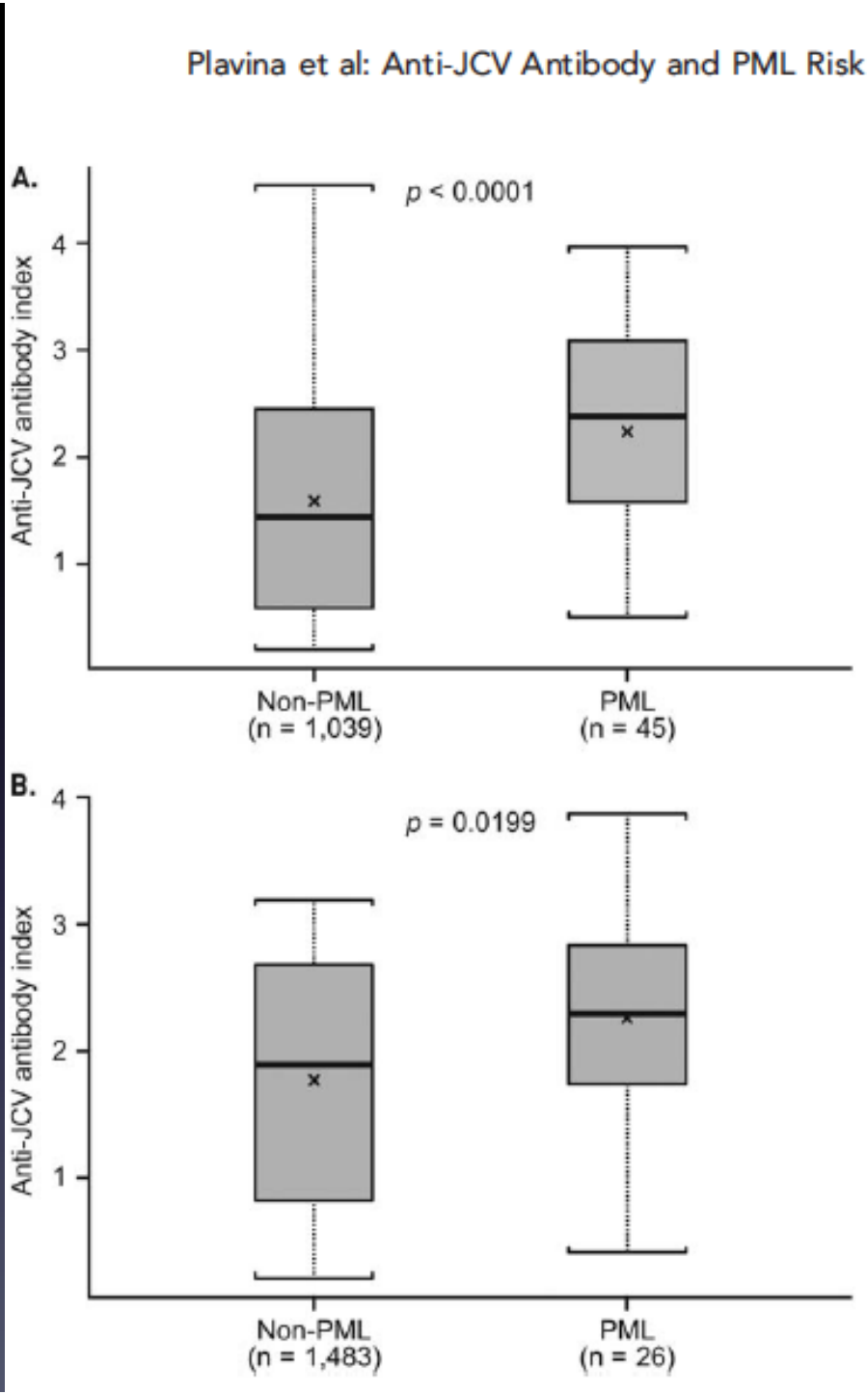
Marie-Sarah Gagne Brosseau, MD
Gary Stobbe, MD
Annette Wundes, MD

NATALIZUMAB-RELATED PML 2 WEEKS AFTER NEGATIVE ANTI-JCV ANTIBODY ASSAY

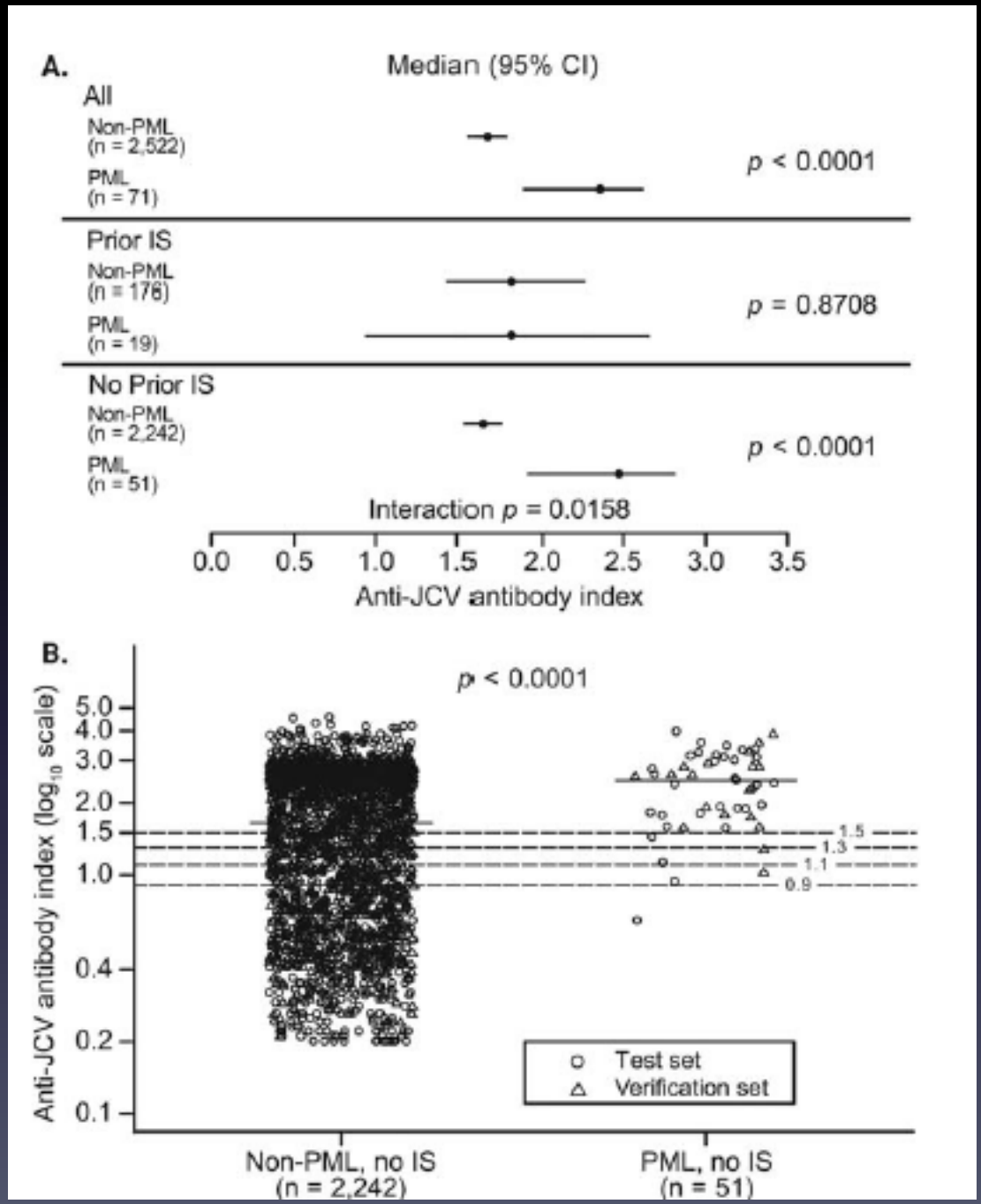
Progressive multifocal leukoencephalopathy (PML) is a serious complication of natalizumab pharmacotherapy, caused by the JC virus (JCV), against which 60% of adults have detectable serum antibodies.[1] The most common symptoms of PML are cognitive impairment, motor dysfunction, visual abnormalities, and speech deficit.[2] Although the mortality rate of 23%[3] in natalizumab-associated cases is lower compared to PML from other causes, most survivors have a poor functional outcome.[4] As of March 3, 2015, Biogen had reported 541 cases of natalizumab-related PML. Of 278 cases with available data, only 2 were negative for anti-JCV antibody; these 2 patients had tests dating from 8 and 9 months prior to diagnosis.[3]

We report a case of PML in a patient receiving natalizumab who had repeated negative anti-JCV antibody testing until 2 weeks prior to onset of symptoms.

Neurology 86:484, 2016



Plavina T et al. Ann N 76:802, 2014



Plavina T et al. Ann N 76:802, 2014

Table 1: Proportions of anti-JCV antibody positive non-PML and PML patients with no prior IS use by index threshold

Index threshold	Percentage non-PML below	95% CI	Percentage PML below	95% CI	OR	*P* value
≤0.7	21.1	19.5–22.7	0.6	0.1–3.9	45.6	<0.001
≤0.9	28.2	26.5–30.1	1.7	0.2–10.9	22.9	0.002
≤1.1	33.6	31.8–35.6	4.4	1.4–12.9	11.1	<0.001
≤1.3	37.9	36.0–39.9	7.5	3.0–17.6	7.5	<0.001
≤1.5	42.9	41.0–44.9	10.1	4.5–21.2	6.7	<0.001

Data for patients with no prior IS use: 2242 non-PML patients and 51 patients using all available anti-JCV antibody index data at least 6 months prior to PML diagnosis. A total of 5547 samples were analyzed by repeated measures with predicted probabilities, ORs, and *P* values estimated from generalized estimating equations with a logit link. An exchangeable correlation structure was assumed.
CI=confidence interval.

Plavina T et al., [Biogen Idec] Abstract DX51. ACTRIMS. May 29-June 1, 2013, Orlando FL

PML Risk Estimates by Index Threshold in Anti-JCV Antibody Positive Patients With No Prior Immunosuppressant Use

Anti-JCV Antibody Index	PML Risk Estimates per 1,000 Anti-JCV Antibody Positive Patients by Natalizumab Treatment Duration (No Prior IS Use)		
	1–24 Months (95% CI)	25–48 Months (95% CI)	49–72 Months (95% CI)
≤0.9	0.1 (0–0.41)	0.3 (0.04–1.13)	0.4 (0.01–2.15)
≤1.1	0.1 (0–0.34)	0.7 (0.21–1.53)	0.7 (0.08–2.34)
≤1.3	0.1 (0.01–0.39)	1.0 (0.48–1.98)	1.2 (0.31–2.94)
≤1.5	0.1 (0.03–0.42)	1.2 (0.64–2.15)	1.3 (0.41–2.96)
>1.5	1.0 (0.64–1.41)	8.1 (6.64–9.8)	8.5 (6.22–11.38)

Ticho B et al. [Biogen Idec] Abstr. #O228. European Neurol. June 9, 2013. Society Barcelona, Spain

Prior Use of Immunosuppressants in Natalizumab Rx'd MS Patients

Table 1. Prior Use of Immunosuppressants among Patients with Multiple Sclerosis Treated with Natalizumab.*

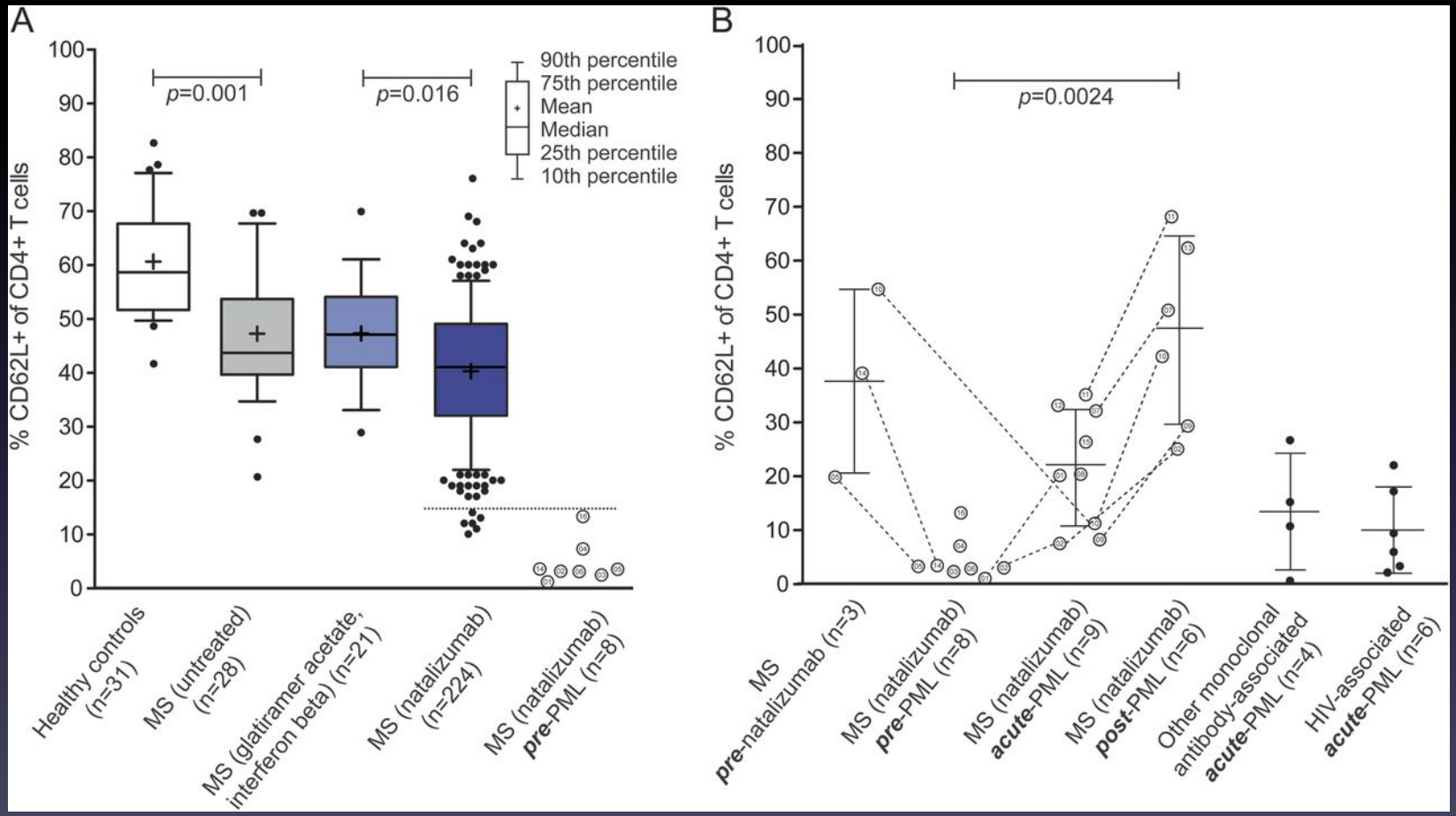
Variable	Confirmed PML Cases in Postmarketing Setting among Patients with Prior Use of Immunosuppressants (N=68)	Patients in TYGRIS Study with Prior Use of Immunosuppressants (N=792)
Immunosuppressant used — no. (%)†		
Mitoxantrone	38 (56)	344 (43)
Methotrexate	9 (13)	45 (6)
Azathioprine	11 (16)	133 (17)
Cyclophosphamide	14 (21)	71 (9)
Mycophenolate mofetil	6 (9)	48 (6)
Other	8 (12)	201 (25)
Duration of prior immunosuppressant use — mo		
Mean	19.9	10.1
Median	12.5	9
Range	0.03–204.0	<1–24
Washout period between immunosuppressant and natalizumab — mo		
Mean	25.8	8.5
Median	17.2	7
Range	0.5–95.4	<1–24

* Included are data from natalizumab-treated patients with progressive multifocal leukoencephalopathy (PML) identified in the postmarketing setting and from natalizumab-treated patients enrolled in the Tysabri Global Observational Program in Safety (TYGRIS) study. Although data on any use of immunosuppressants (i.e., any use vs. no use during the patient's lifetime) before the initiation of natalizumab therapy were collected in the TYGRIS study, the dates of natalizumab treatment (which were used in the calculation of the duration of immunosuppressant use and the length of the wash-out period) were recorded only for immunosuppressants used in the 24 months preceding the initiation of natalizumab therapy.

† Patients may have received more than one type of prior immunosuppressant therapy.

Bloomgren G et al. *N Engl J Med.* 2012;366:1870-1880.

Surface Expression of CD62L on CD4+ T-cells in Blood and Its Correlation to PML Development in MS Patients



1. Schwab N et al. *Neurology* 2013;81:865-871. **2.** ECTRIMS 2013: Schneider T et al., #232, Dynamic biomarkers for clinical efficacy and individual PML prevention under natalizumab therapy.

CD62L is not a reliable biomarker for predicting PML risk in natalizumab-treated R-MS patients

OPEN

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ABSTRACT

Objective: To assess if the percentage of $CD3^+CD4^+CD62L^+$ cells in cryopreserved peripheral blood mononuclear cells (PBMCs) (here termed %CD62L) can predict risk of developing progressive multifocal leukoencephalopathy (PML) and better inform the physician for benefit-risk assessment of natalizumab treatment decisions in a global setting.

Methods: Cryopreserved PBMCs from 21 natalizumab-treated patients who developed PML and 104 matched natalizumab-treated patients with multiple sclerosis (MS) without PML collected as a part of Biogen clinical trials were retrospectively examined for CD3, CD4, CCR7, CD45RA, and CD62L by flow cytometry.

Results: In this cohort, %CD62L in natalizumab-treated patients did not predict PML risk. Natalizumab-treated patients with MS without PML showed highly variable %CD62L upon serial sampling. In the STRATA study, the distribution of %CD62L in samples collected more than 6 months before a PML diagnosis, at diagnosis, and in natalizumab-treated patients without PML overlapped. No statistical threshold for risk could be determined. In addition, we demonstrated that lymphocyte viability strongly affects %CD62L, supporting previous reports that %CD62L is inherently unstable following cryopreservation and is sensitive to sample collection.

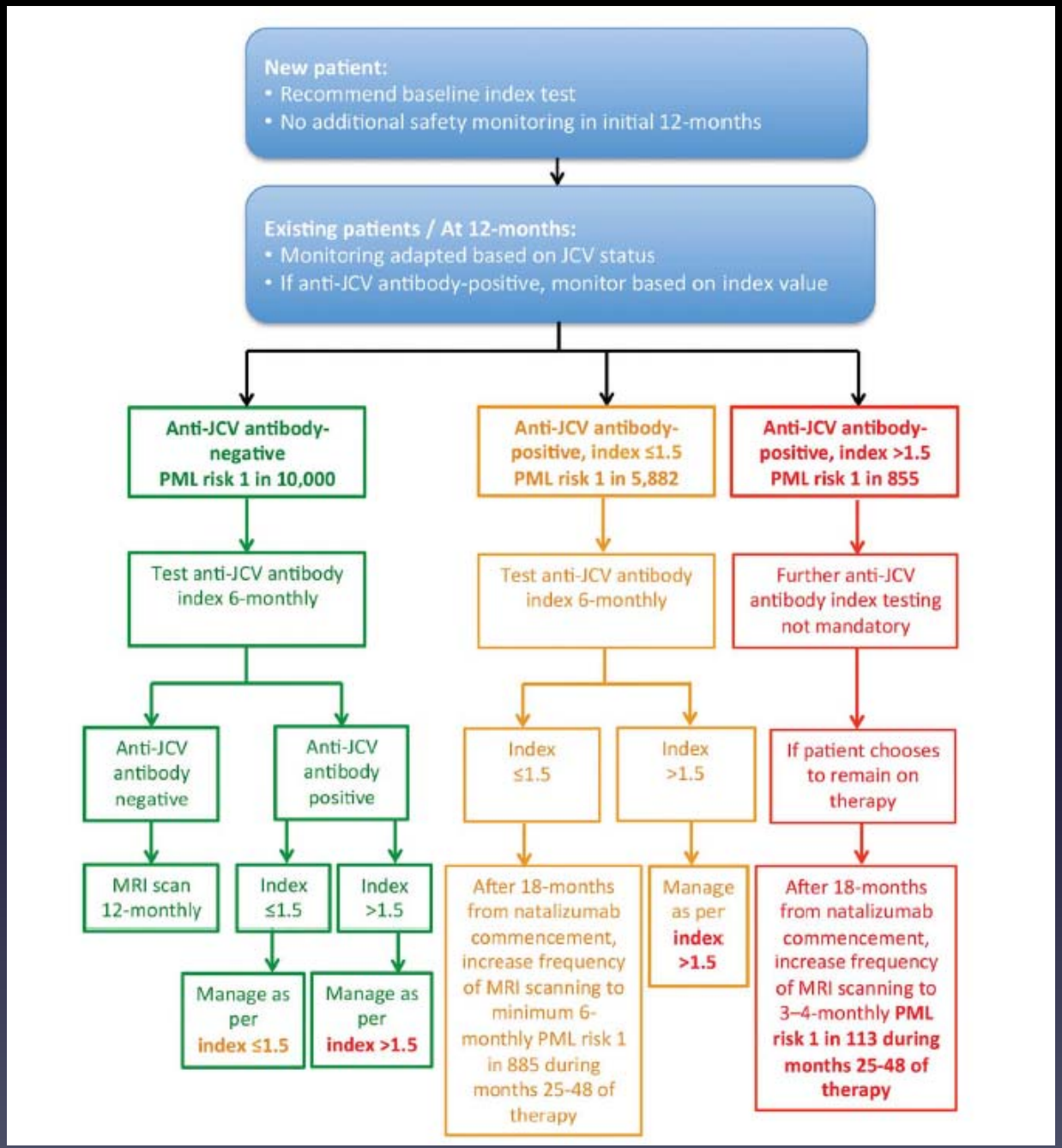
Conclusion: Data from this well-controlled cohort of natalizumab-treated patients indicate that %CD62L is not a biomarker of PML risk. *Neurology®* 2016;86:375–381

Villar LM et al. Ann Neurol 77:447, 2015

Lipid-Specific Immunoglobulin M Bands in Cerebrospinal Fluid Are Associated with a Reduced Risk of Developing Progressive Multifocal Leukoencephalopathy during Treatment with Natalizumab

***Presence of CSF IgM Lipid-Specific Bands may be associated with lower PML risk**
Likely specific for phosphatidycholine?

Bands found in 1/24 (4%) with PML and 224/343 (65%) not PML
OR of Decr Risk 45.9 (5.9-339, p<0.0001)
Anti-JCV+ and IgM Lipid OCB+ + JCV Ab- (OR 1.55, 0.09-25, NS)



McGuigan C et al. J N NS P 87:117, 2016

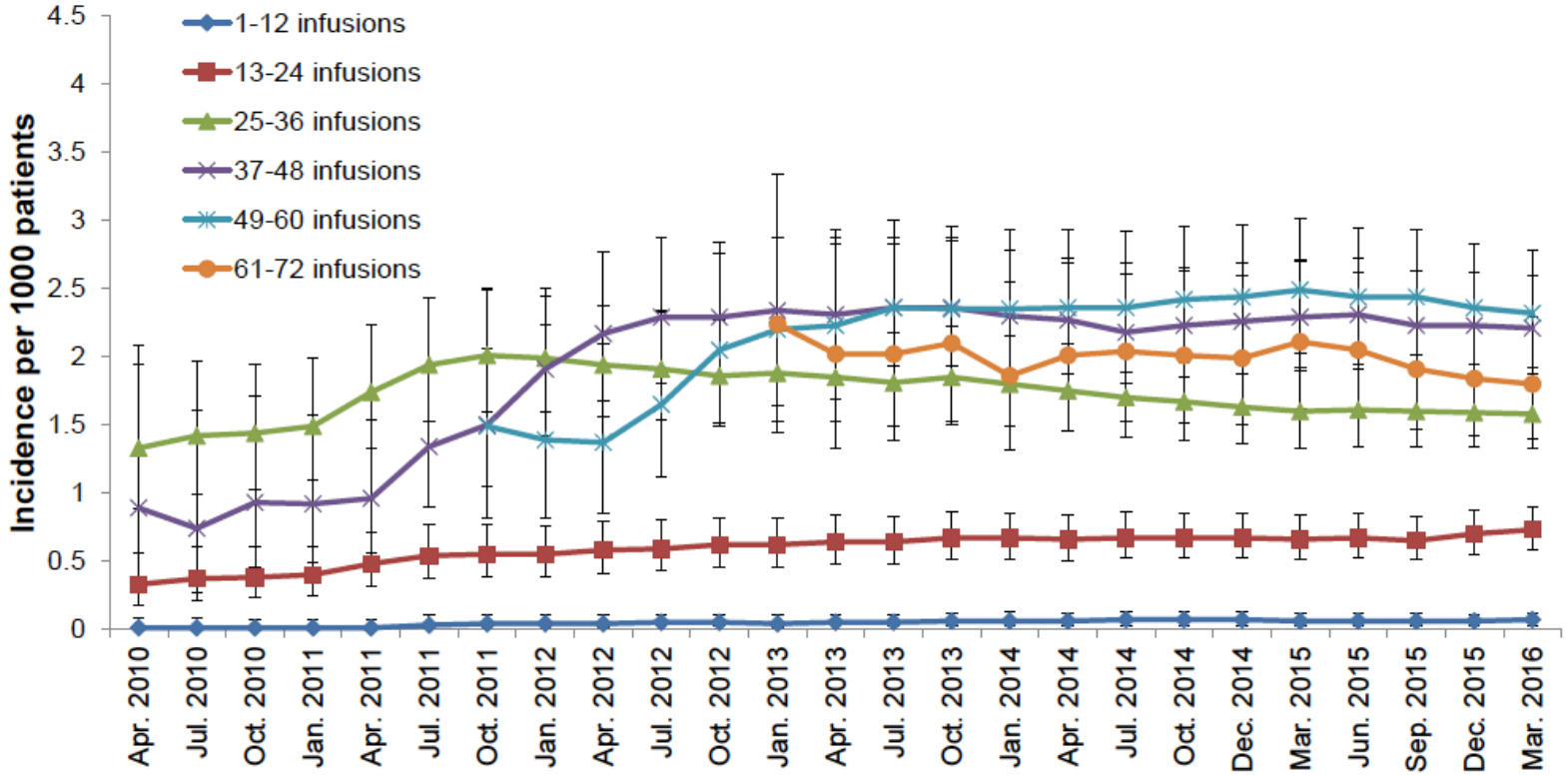
Table 2. Characteristics of Brain MRI at the Time of PML Diagnosis, by PML Outcome

PML extension at diagnosis	All (N=296)	Survivors (n=223)	Nonsurvivors (n=73)	Survival (%)
Unilobar, n (%)[a]	115 (39)	91 (41)	24 (33)	79
Widespread, n (%)[b]	108 (36)	71 (32)	37 (51)	66

[a] Unilobar lesions were confined to one lobe

[b] Widespread lesions involved two or more noncontiguous lobes and/or lesions present in both hemispheres

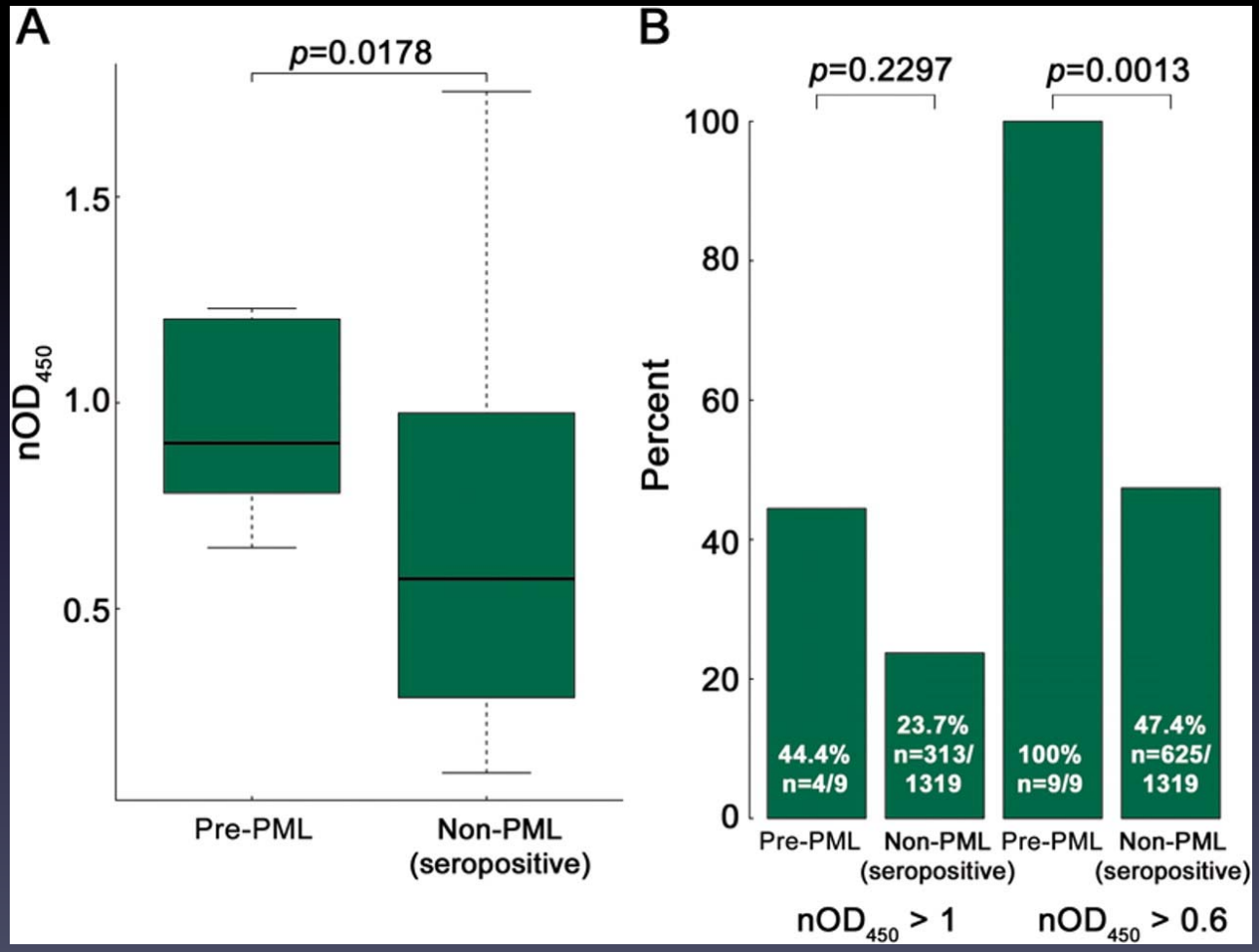
Estimated Global PML Risk by Treatment Epoch (Apr 2010 – Mar 2016)



Due to the consistency of the incidence over time, this figure will be updated annually after the March 2016 Safety Update.
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 and confirmed cases of PML. Data are from the specified month as indicated. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to natalizumab at each time point (e.g., for 25 to 36 infusions the number of 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 , data on file.

Biogen. TY-US-0113(11) & 0102(11). Dec. 2016

Anti-JC Virus (JCV) Ab Levels in Sera From Natalizumab-Treated Patients Who Subsequently Developed PML (Pre-PML) Compared With Those in Anti-JCV Antibody-Positive Patients Who Did Not Develop PML (Non-PML)



Trampe A et al. *Neurology.* 2012:78:1736.