Understanding the JCV and the development of risk stratification

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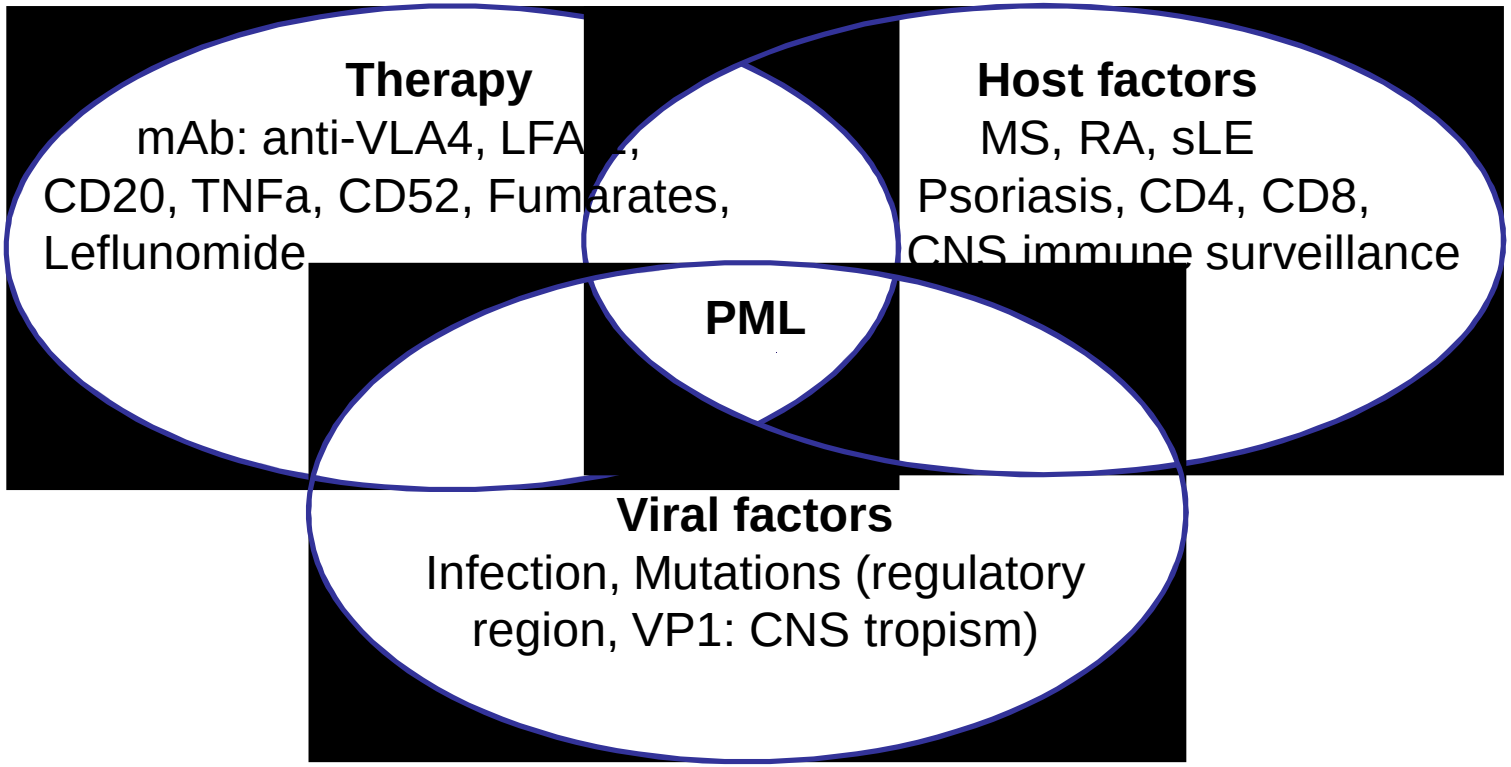
Disclosures

Research support for PML biomarker research

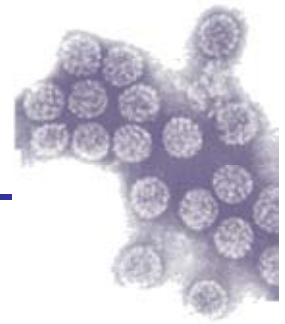
§ BiogenIdec

Understanding JCV, PML…?

§ MS: not known before Natalizumab (VLA-4)



History of JC Virus in PML



1959 Cavanaugh et al.

- inclusion bodies in nuclei of oligodendrocytes

1965 ZuRhein et al.

- EM reveals polyoma-like particles

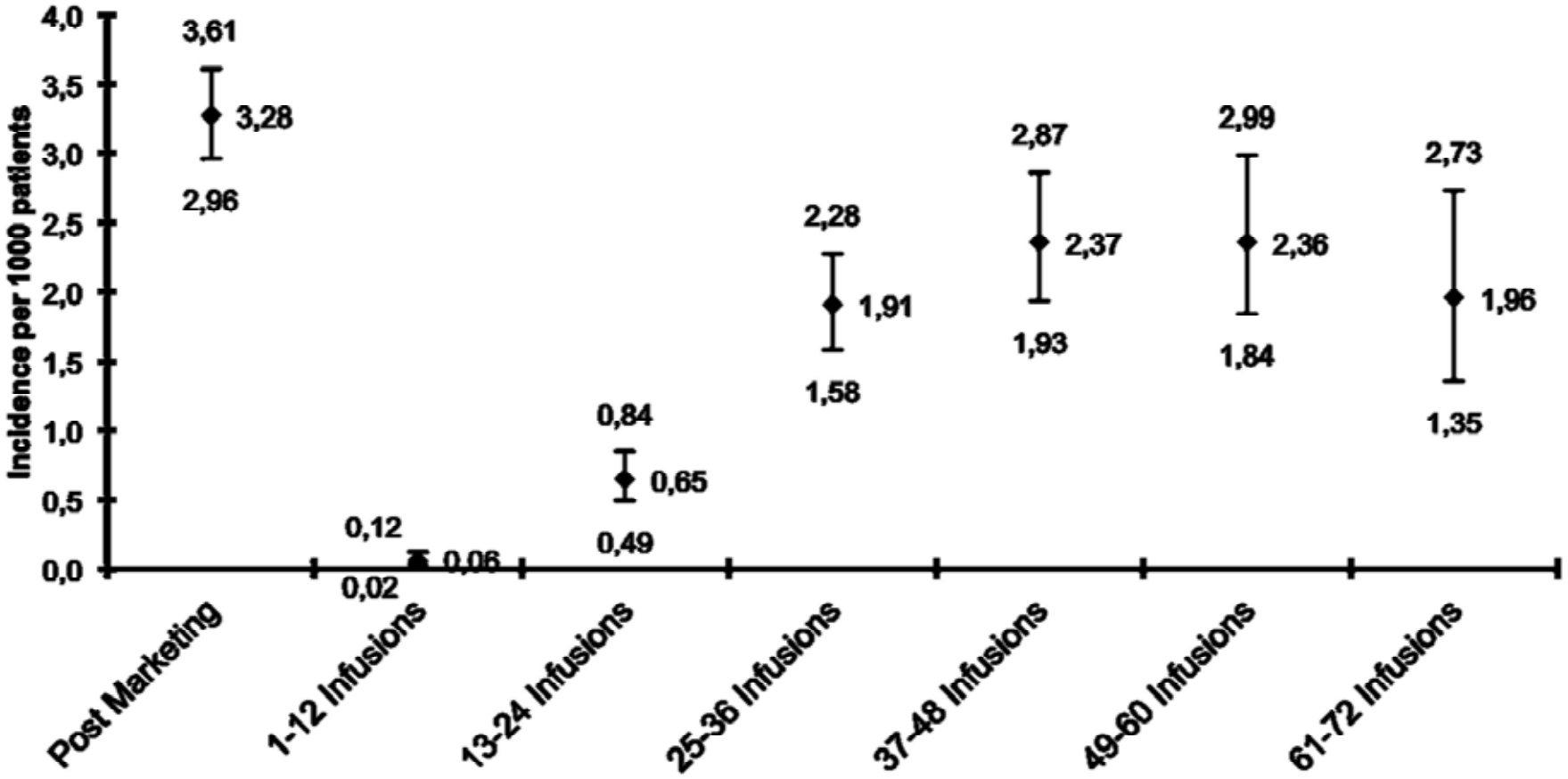
1971 Padgett et al.

- polyomaviruses isolated using glial cell lines

John Cunningham and family

Astrom KE et al., Brain 1958;81:93–111
Cavanagh et al. Lancet 1959;2:524–9.
Zu Rhein et Chou. Science 1965;148:1477–9.
Padhett BL et al., Lancet 1971;1:1257–60.

PML-risk: estimates according to treatment duration



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 July 31, 2013 and 395 confirmed cases as of August 6, 2013. 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.

Take home messages

Natalizumab-PML

- Distinct clinical and MRI presentation
- Early detection is possible, in doubt: STOP Natalizumab
- Aim for rapid immune-reconstitution, be aware of seizures
- IRIS: a double edged sword
- Risk stratification: a moving field

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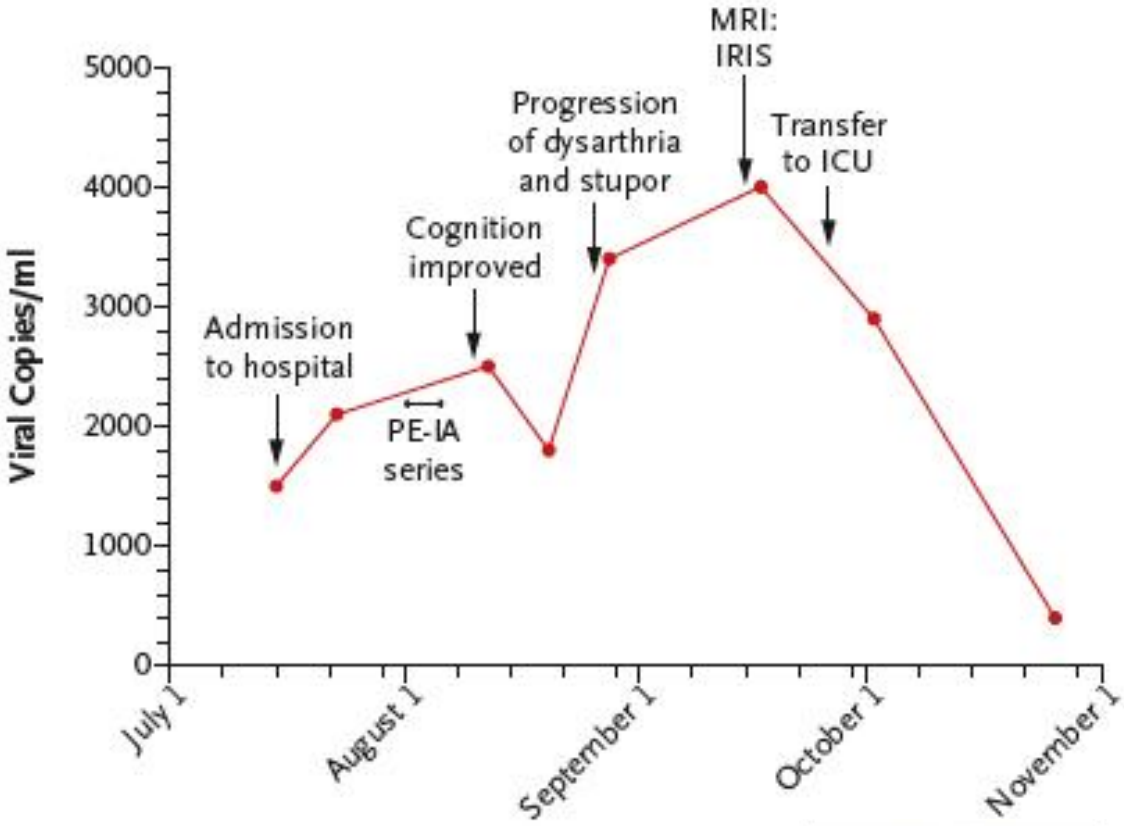
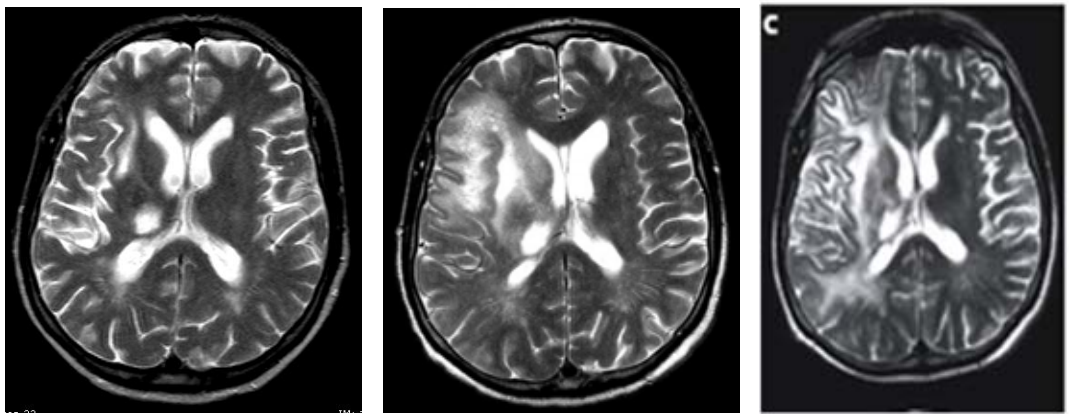
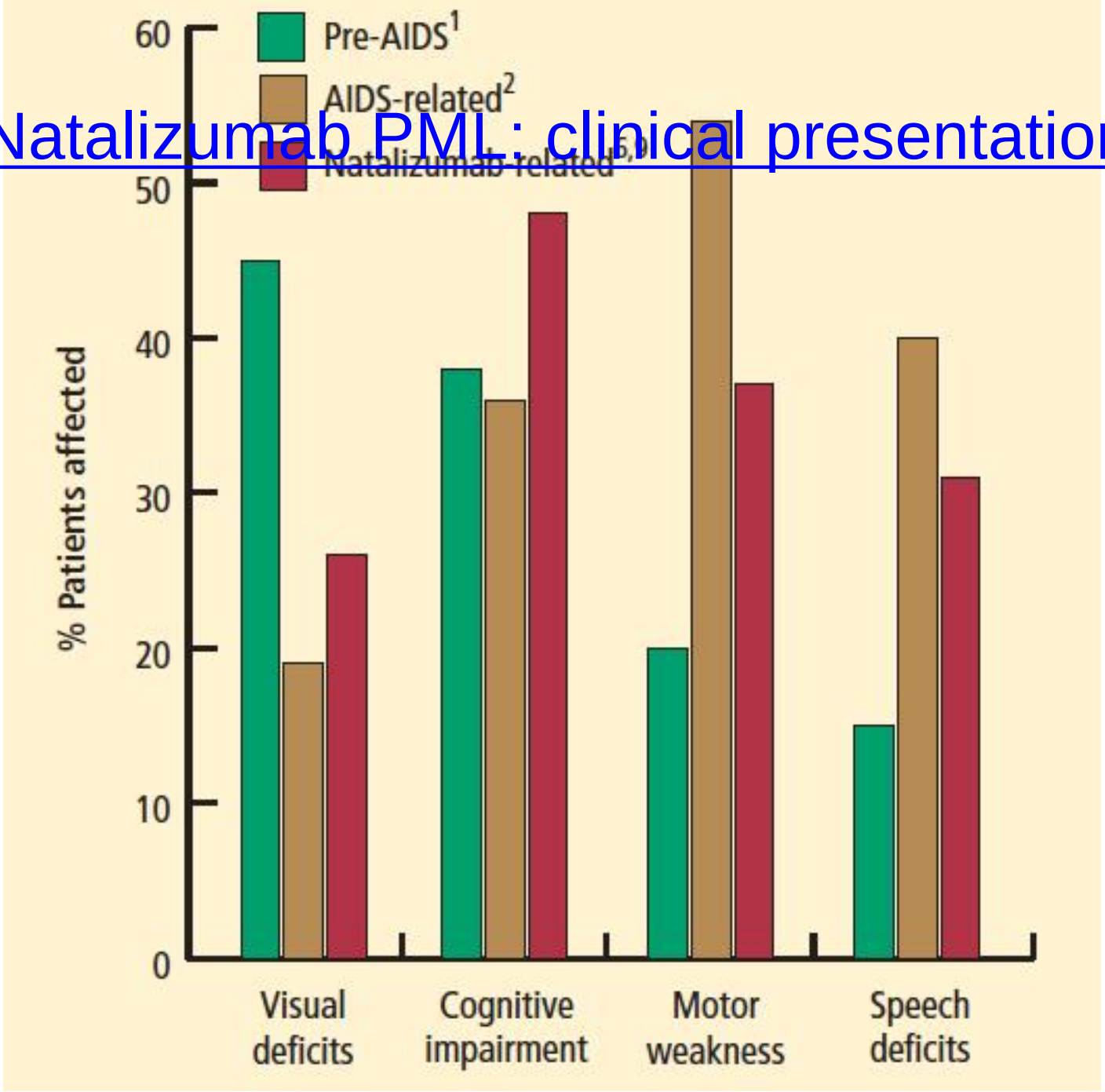
PML: early case in the postmarketing phase





Wenning et al.,
New Engl J Med 2009;
361:1075-80

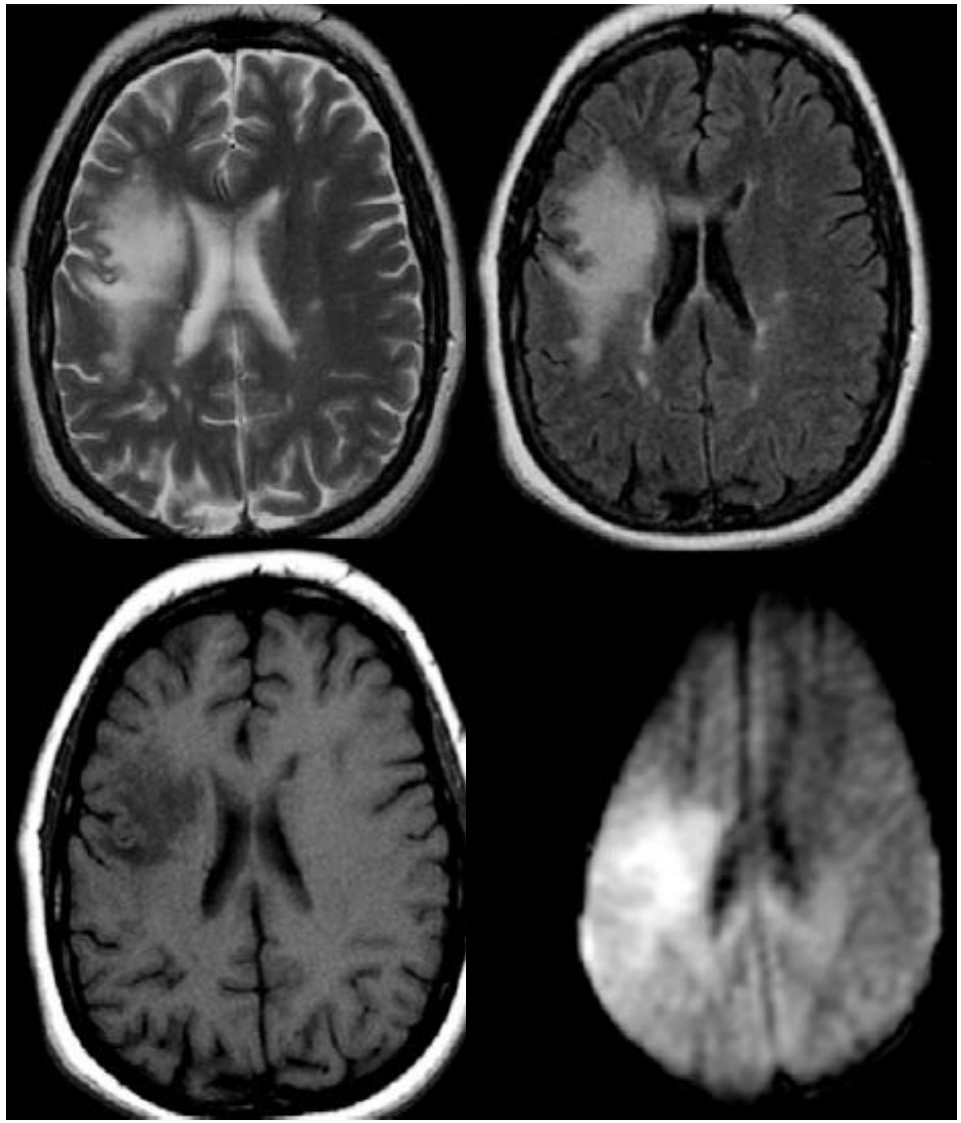
Natalizumab PML : clinical presentation



Berger, Cleveland Clin J 2011;78S2

Natalizumab PML: MRI-pattern

- large >3cm
- subcortical
- T2-hyperintense



- FLAIR hyperintense
- sharp border
  è grey matter
- ill-defined border
  è white matter

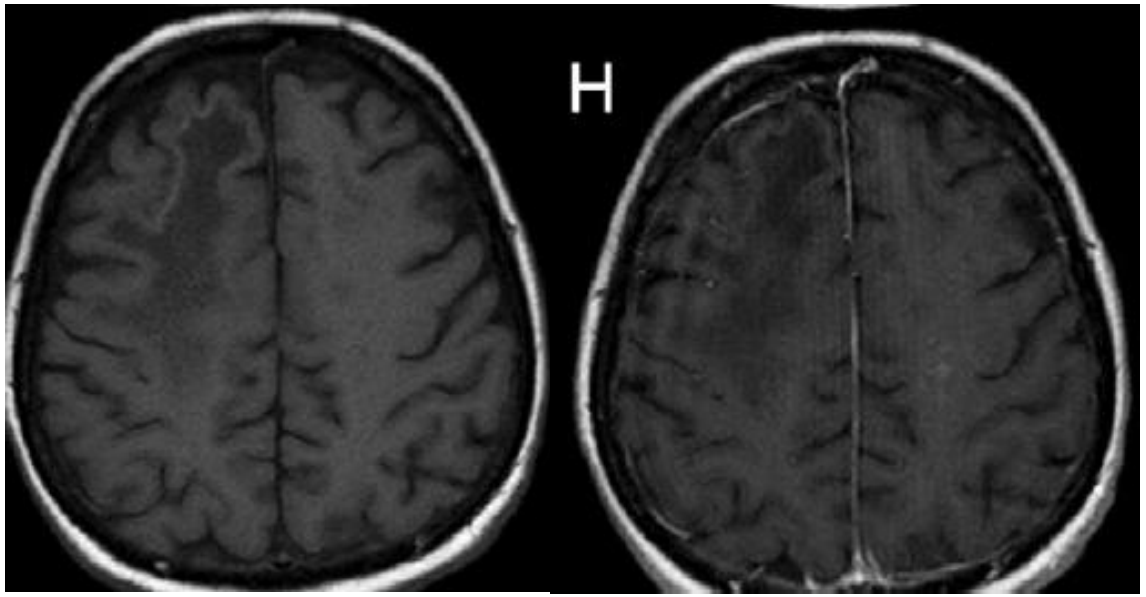
- T1 hypointense

- DWI hyperintense
- Early PML: 41% Gd+

N=22 patients

Yousry et al., Ann Neurol 2012;72:779

Natalizumab PML: MRI pattern



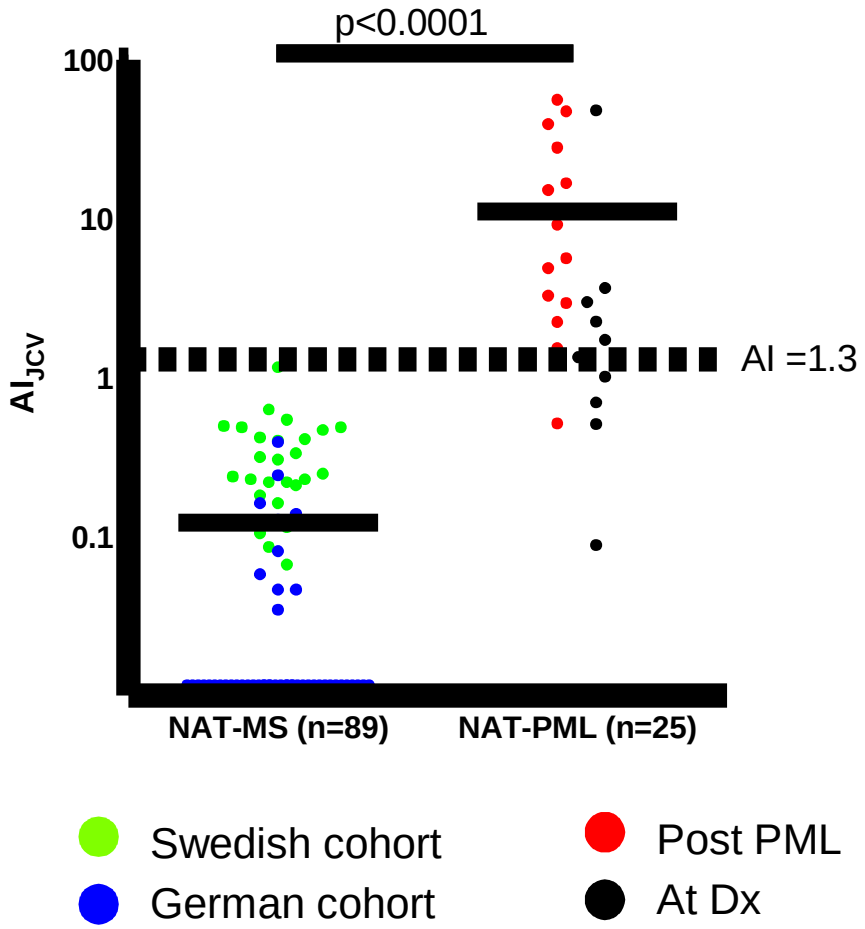
- T1-hyperintensity: during/after PML-IRIS phase, differentiating against PML-phase
- involvement of cortex (50%) and basal ganglia (28%)
- Gd-enhancement: punctate/rimlike

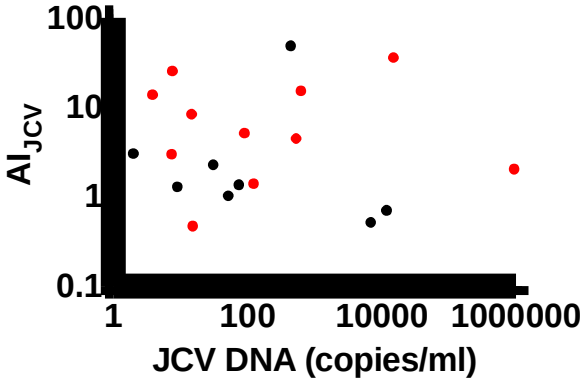
Yousry et al., Ann Neurol 2012;72:779

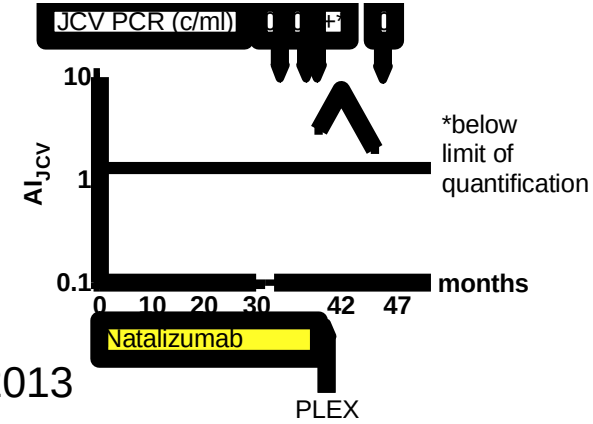
C. Warnke et al. Anti-JCV antibody index in CSF for diagnosis of PML

1) AI_{JCV} increased in Nat-PML (100% Specificity, 63-80% Sensitivity 63-80%)

2) No correlation between CSF JCV DNA and AI_{JCV}: additive diagnostic value







Courtesy of C. Warnke, Düsseldorf, presented at DGN 2013

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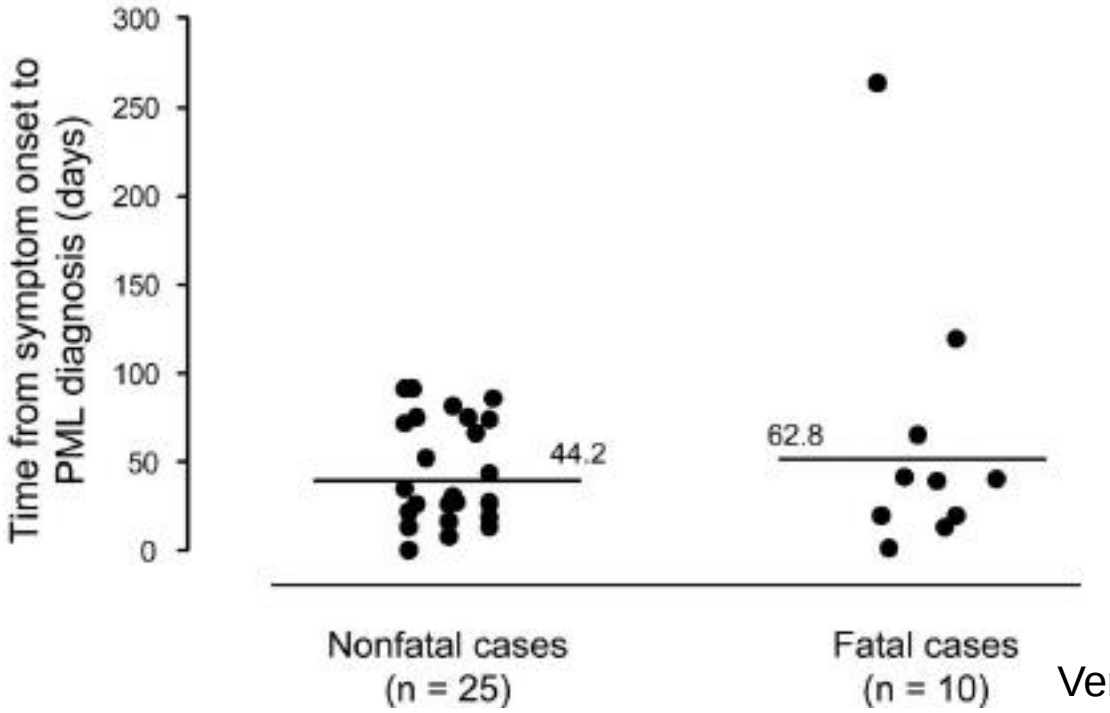
PML: factors associated with prognosis

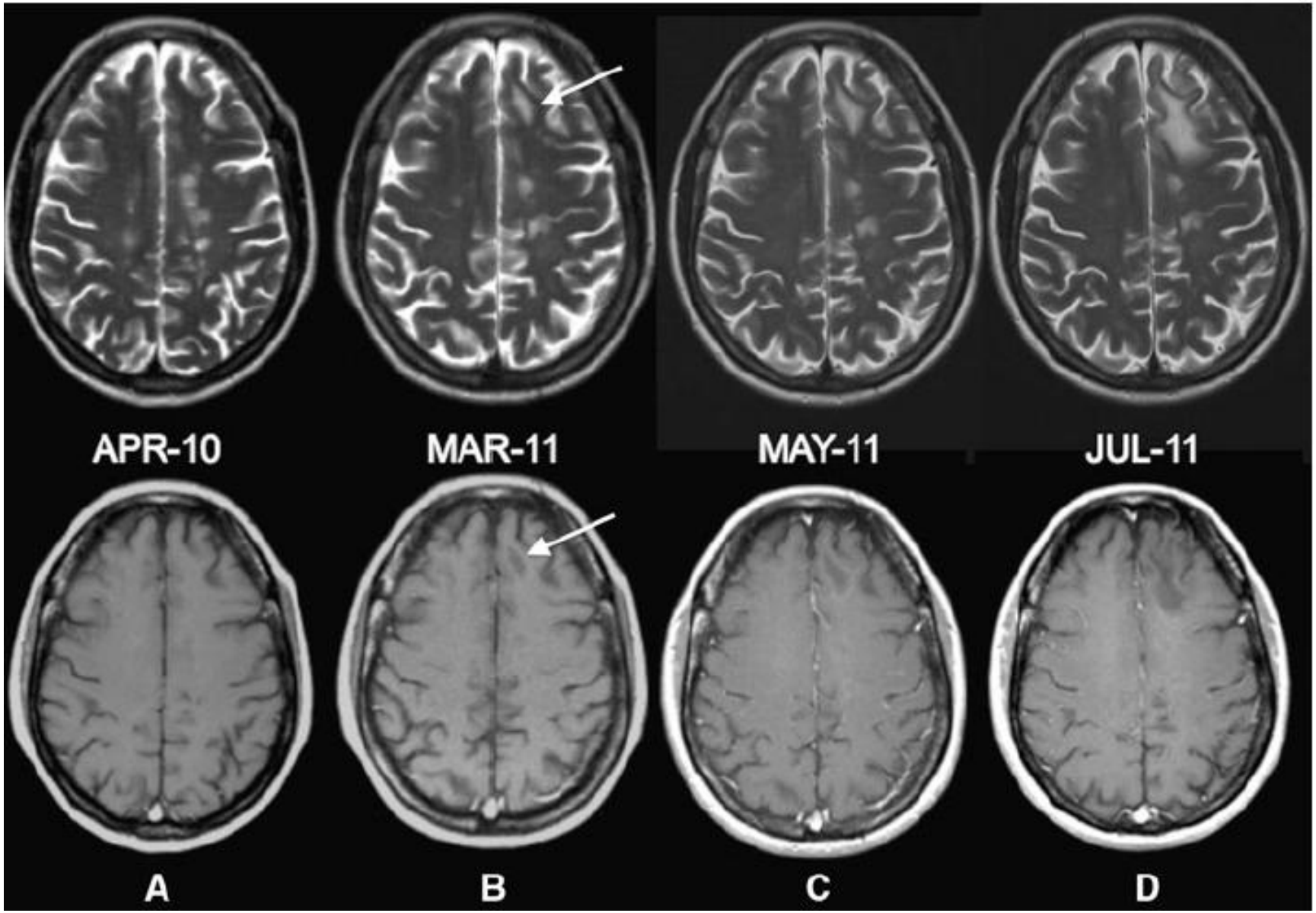
Mortality ?≥20% (HIV: median survival 183 days)

Survivors:

- younger, lower pre-PML EDSS, restricted MRI extension
- but not: Natalizumab exposure, immunosuppressants, CSF viral load



Vermersch et al., Neurology 2011;76:1697



asymptomatic è è

>2a CSF-PCR neg. è PCR positive

Natalizumab Nat continued è è

Ayzenberg et al, J Neurol 2012;76:574

MRI in “preclinical” PML

- MRI-abnormalities may precede clinical/CSF changes
- Especially frontal lesions a-/oligosymptomatic
- Diagnostic value of repeat MRI
- “radiologically suspected PML”: interrupt treatment until proven otherwise
- MRI-sequences: T2, FLAIR, DWI, T1, T1-post Gd

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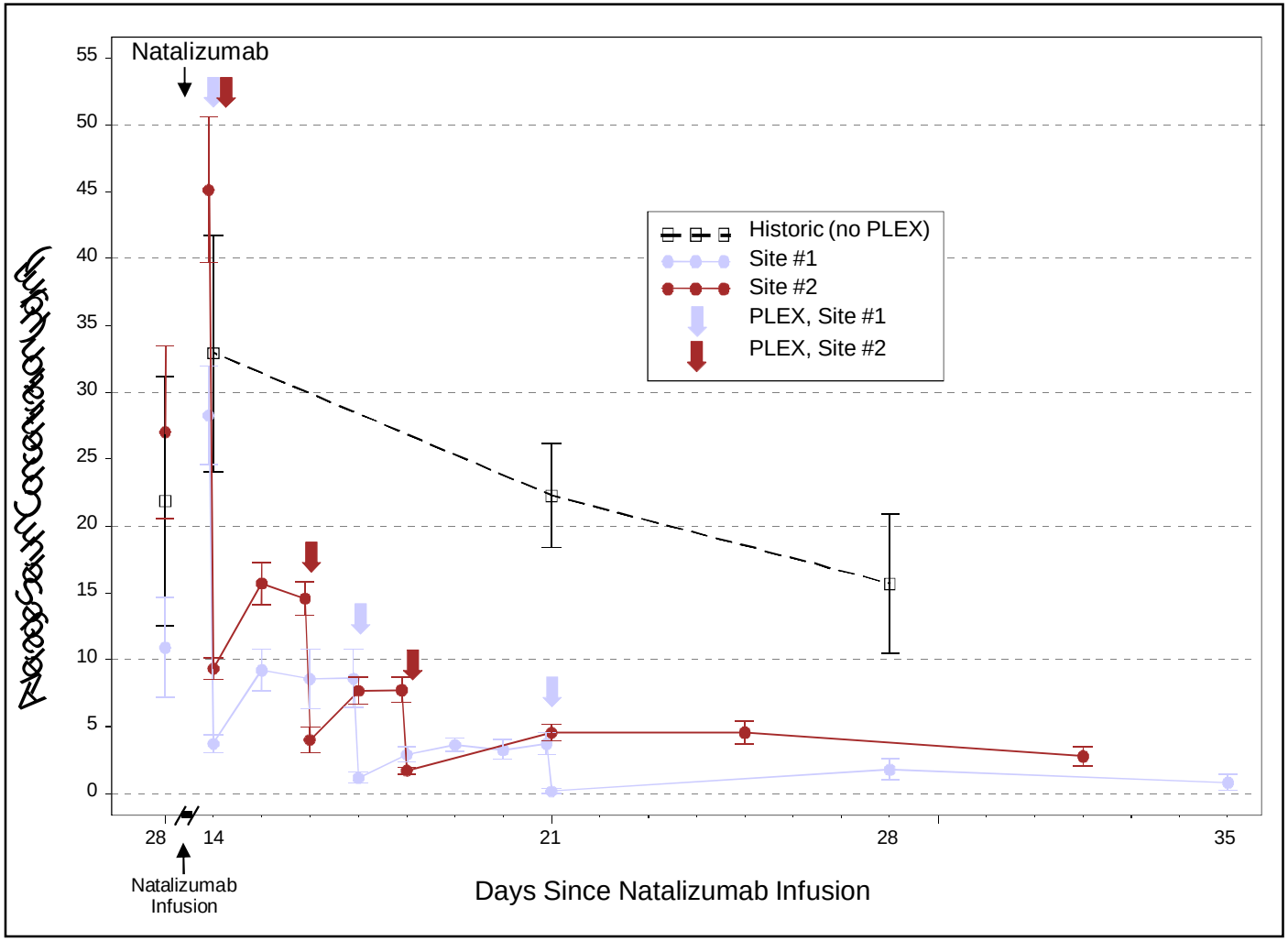
Treatment

No EBM-proven treatment

- ?? Mefloquine, Serotonin 5-OH-tryptamine receptor antagonists, CCR5-antagonists
- ?Nucleoside analogues...
- Failure of clinical studies after successfull pre-clinical studies?
  - CNS-penetration
  - Late treatment initiation
  - Phase of the disease?

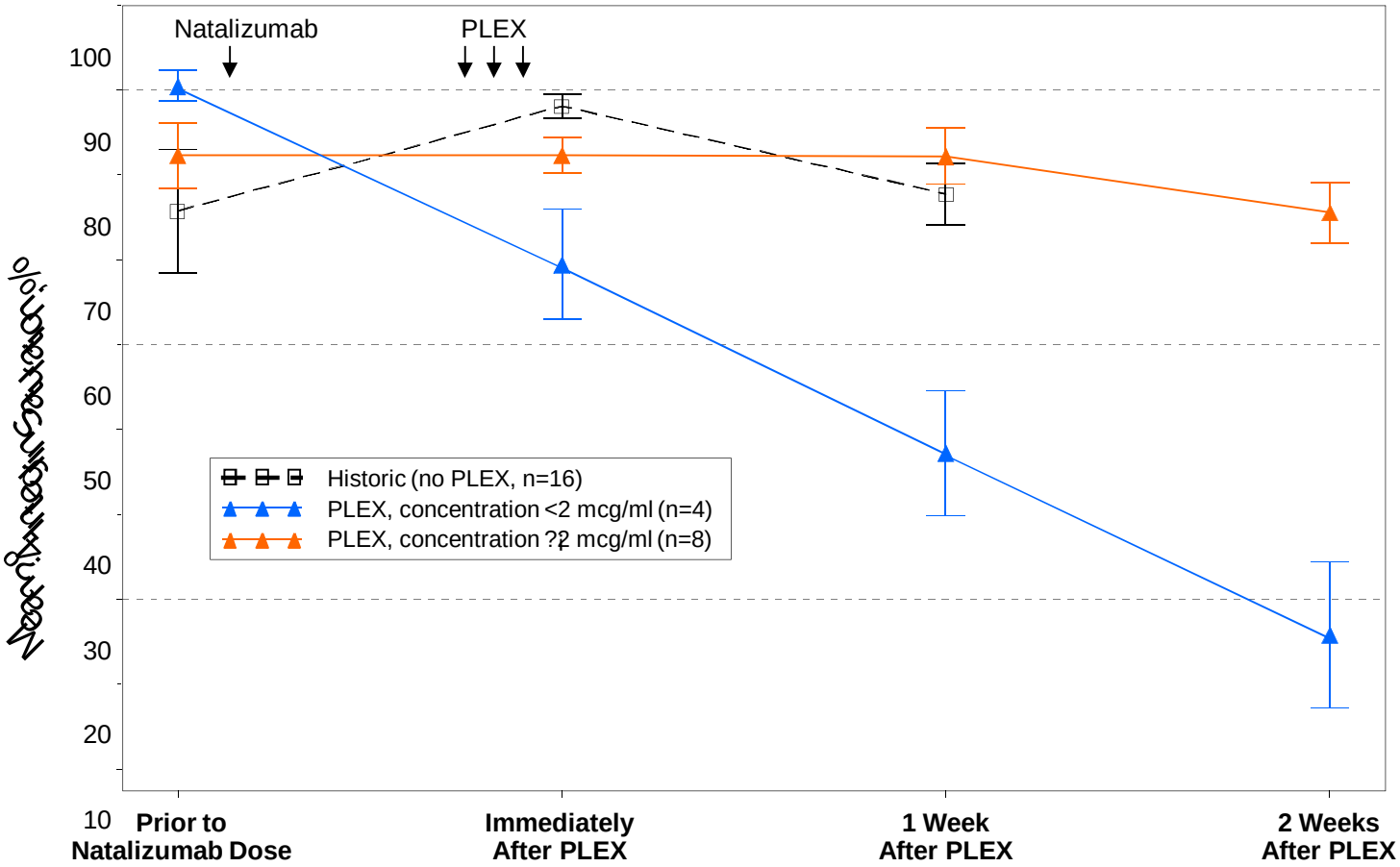
v Immune-reconstitution

Serum Natalizumab concentration before and after PLEX



Khatrie et al., Neurology 2009

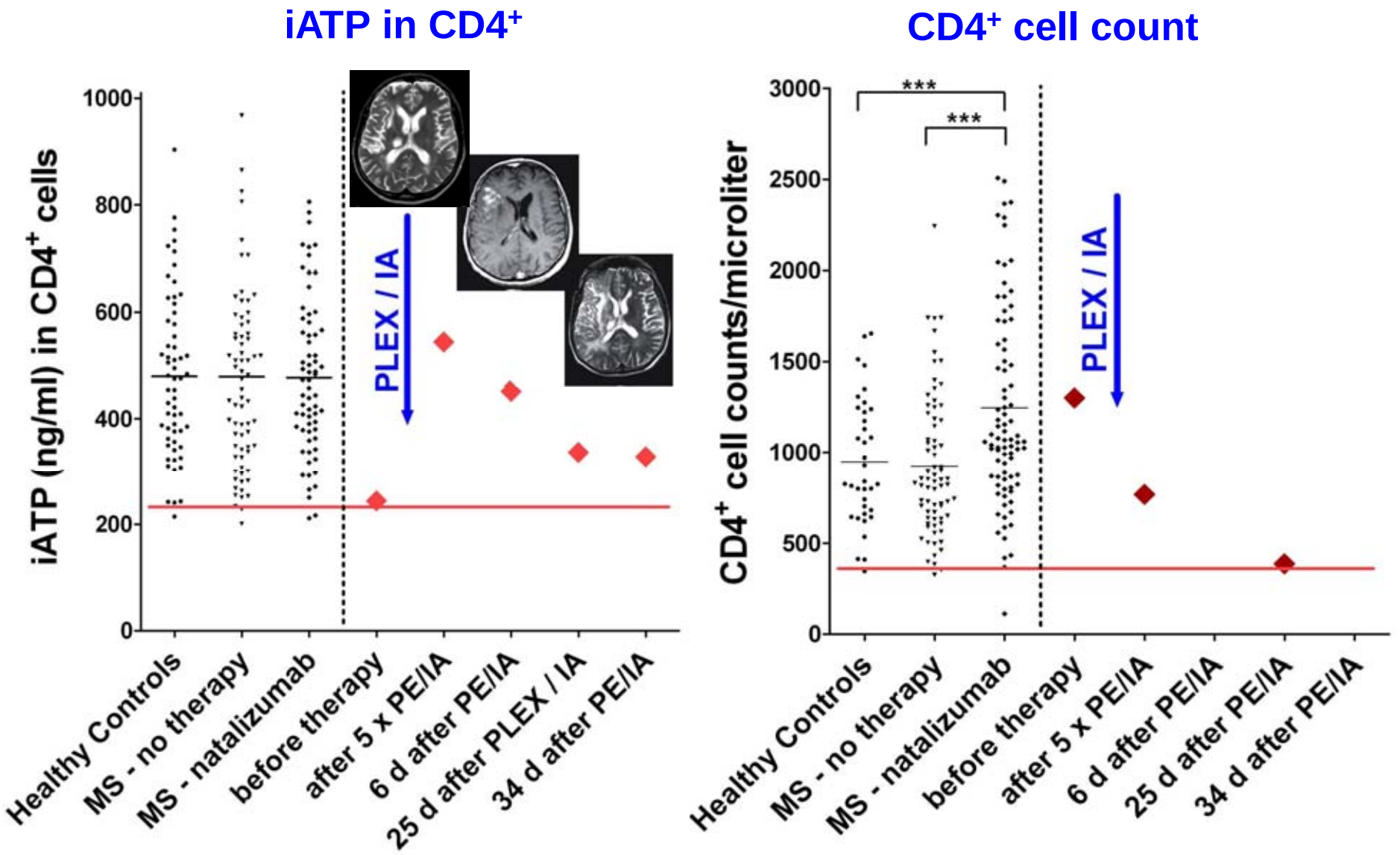
?4-Integrin Saturation Before and After PLEX



Khatri et al., Neurology 2009

When serum natalizumab concentration decreased <1-2 mcg/ml, de-saturation of ?4 integrin was observed.

CD4-cell count vs. –function after PLEX



Haghikia et al., PLOSone 2011

Supportive measures: Bochum experience

- The first 2-4 weeks after PLEX are like ‚honeymoon‘

- Not evidence based: mirtazapine (to block 5HT receptors, >30 mg) and mefloquine 250 mg/week or zidofovir 5 mg/kg (nephrotoxic)

Wenning et al., New Engl J Med 2009; 361:1075-80
Dahlhaus et al., JNNP 2013, 84:1068
Hoepner et al., Ther Advances Neurol Dis 2013, epub ahead of print

Natalizumab PML: Seizures

N=15 (39.5 a, SD 6.9), single center

- 8 of 15 (53%) with seizures
  - Often manifesting as status epilepticus
  - 61 days after diagnosis of PML
  - 5 cases: Gd-enhancement MRI (IRIS)

	PML+Seizure (%)	PML-Seizure (%)	p-value
AED prophylaxis	1 (16.7)	5 (83.3)	
No AED prophylaxis	7 (77.8)	2(22.2)	0.04[1]
Total	8 (53.3)	7 (46.7)	

Ø Current algorithm in Bochum: preventive antiepileptic treatment

Hoepner et al., Ther Advances Neurol Dis 2013, epub ahead of print

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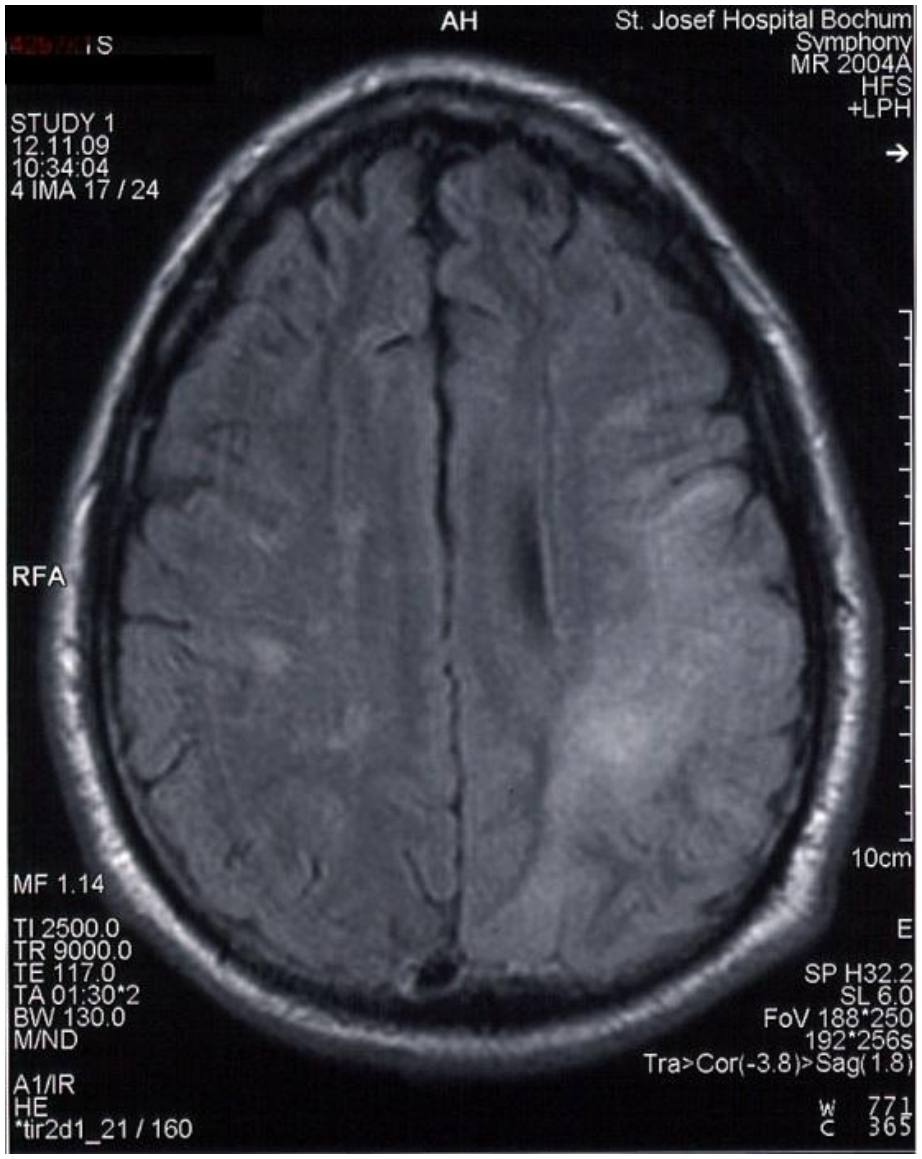
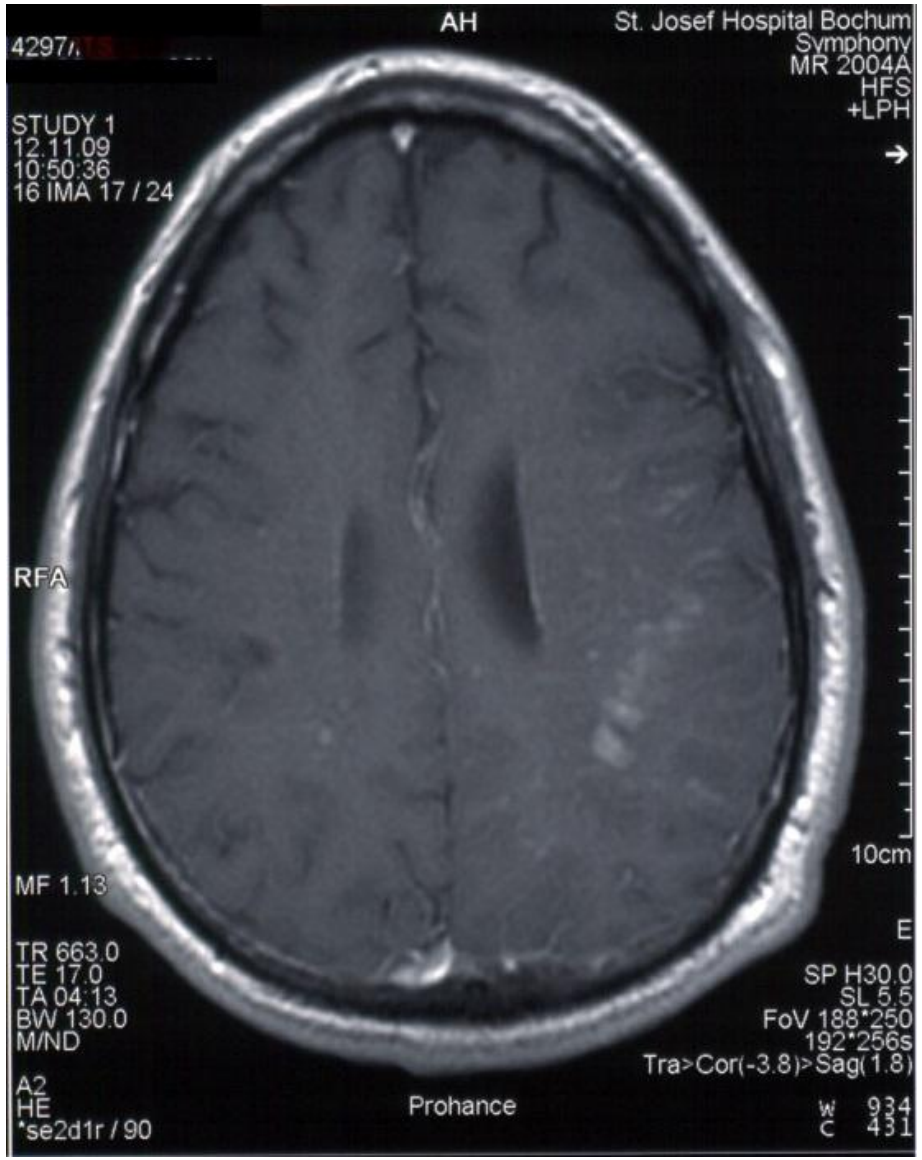
Ca. 4 weeks after PLEX, worsening...





Immune reconstitution inflammatory syndrome

- Often 2-6 weeks after PLEX/IA

Features of PML-IRIS

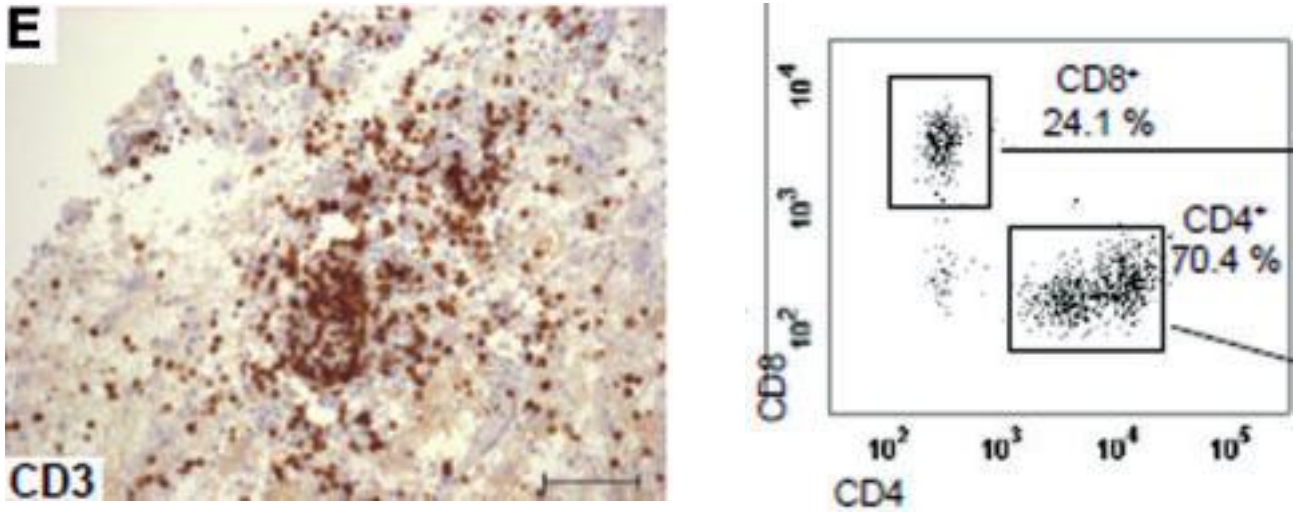
- Paradoxical worsening of clinical or radiographic finding with recovery of the immune system
- New or increased neurologic deficits
- Increase in the number or size of lesions on neuroimaging
- Contrast enhancement of brain lesions
- (Brain edema)
- Concurrent with diagnosis of PML

- v cave: seizures, „early PML-IRIS“
- v No specific biomarker of IRIS

Berger, Cleveland Clin J 2011;78S2

IRIS: $CD4^+/CD8^+$ T-cells

- JCV-specific $CD4^+$ and $CD8^+$ cells: associated with survival, control/elimination of JCV-infected oligodendrocytes

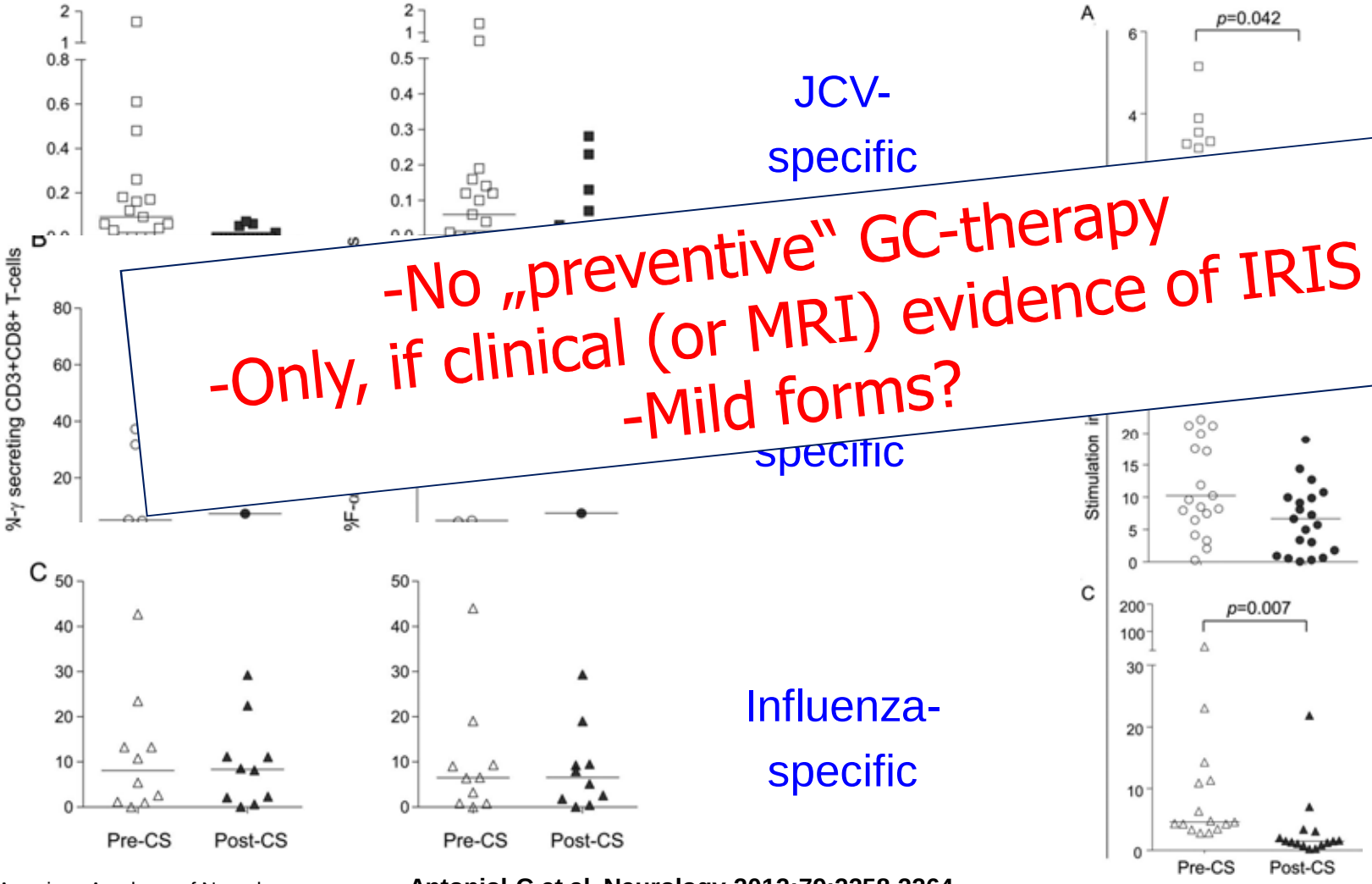


- Bystander damage: Glucocorticosteroids?

Du Pasquier et al., Brain 2004; 127:1970
Aly et al., Brain 2011, 134: 2687

Effects of Glucocorticosteroids on JCV-specific T-cells

IFNγ-secreting TNFα-secreting CD8+ T-cell proliferation (CD4/CD8)



-No „preventive" GC-therapy
-Only, if clinical (or MRI) evidence of IRIS
-Mild forms?

Antoniol C et al. Neurology 2012;79:2258-2264

Functional Status in PML Survivors with at Least 6 Months of Follow-up Time (N=47)

Mild Able to carry on normal activity and to work; no special care needed	100	13% (n=6)	**BOCHUM (15)** 20% (n= 3)
	90		
	80		
Moderate Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	47% (n=22)	67 % (n = 10)
	60		
	50		
Severe Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	**17 of 19 cases of severe disability (89%)**	
	30	40% (n=19)	13 % (n = 2)
	20		
	10	**75-80% survival**	**100 % survival**
	0		

1. Vermersch P et al. *Neurology*. 2011;76:1697-1704.

Dahlhaus S, *et al*. *J Neurol Neurosurg Psychiatry* 2013;**84**:1068–1074.

Long-term follow up

N=15 (39.5 a, SD 6.9), single center, median 21.5 months

- CSF free of JCV DNA: 4.5 months (median, 8/15 patients, 1.5-9 months)
- New Gd-MRI activity: approximately 9 months
- New relapse: approximately 15 months
- Treatment: GLAT, IFN, FTY
- 5 stable without immunotherapy (median 2 years after PML diagnosis)

Dahlhaus et al., JNNP 2013; 84:1068

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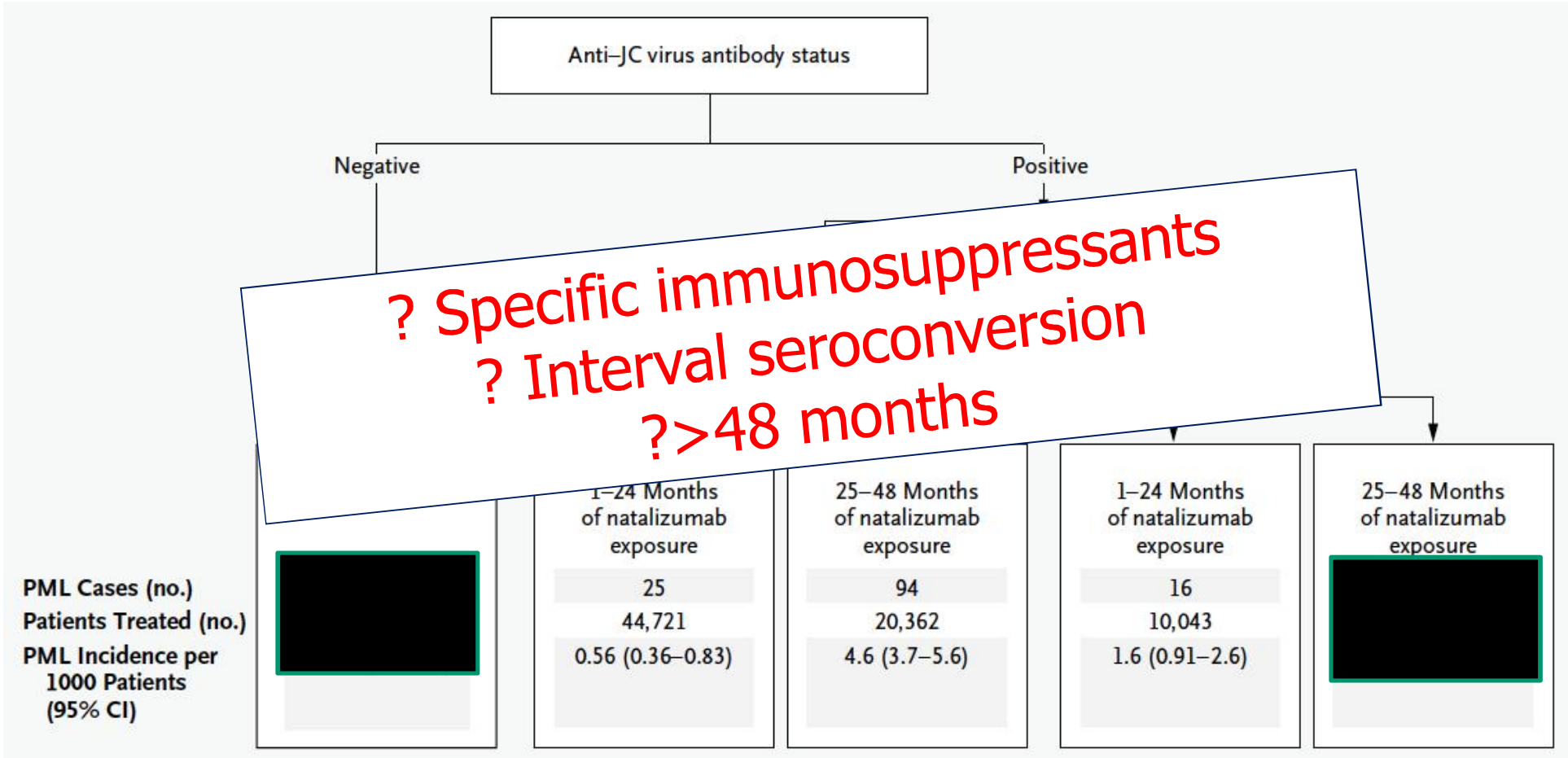
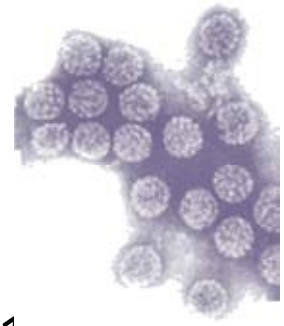
Current risk stratification strategy



Blomgren et al., NEJM 2012

PML-risk stratification: Anti-JC-Virus Antibodies

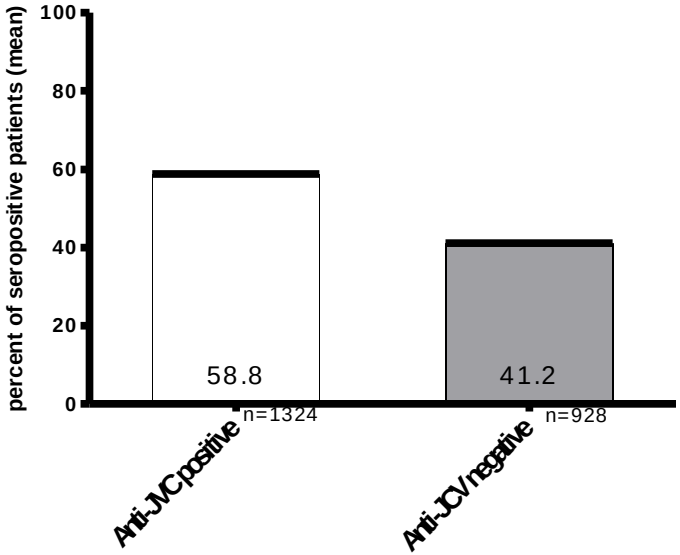


Generation 1 Assay (Stratify™)

– Anti-JCV antibodies in all (n=17) PML-patients, 16 - 18 months prior to diagnosis è High-negative predictive value

Gorelik et al, Ann Neurol 2010

Bochum cohort (anti-Tysabri antibody biobank)



N=2.782 samples, 2.253 patients

– 58.8% seropositive

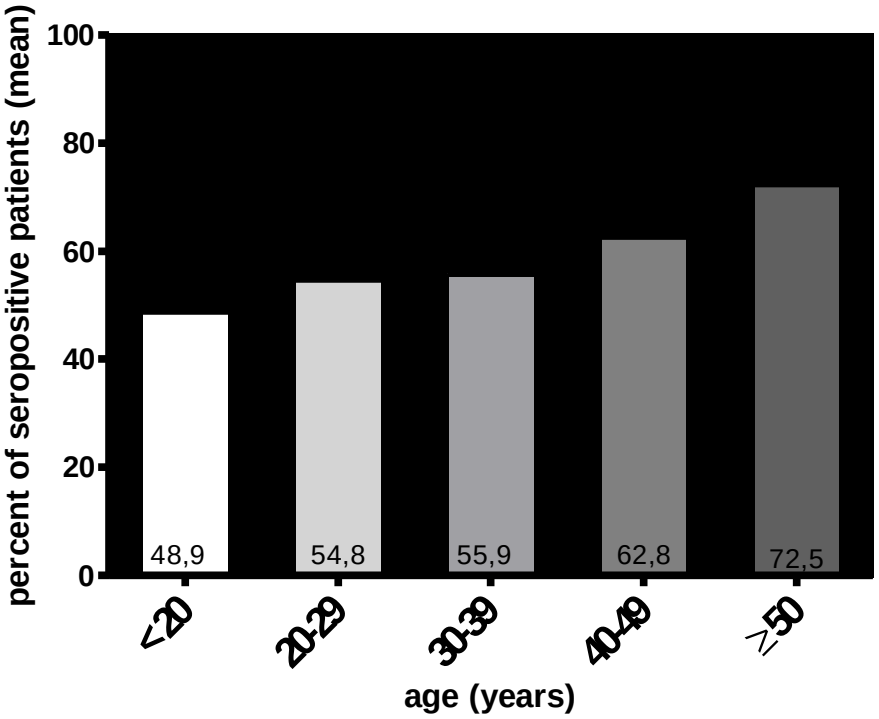
– M (64.4)>F (56.2) seropositive

– Independent from: disease/ treatment duration

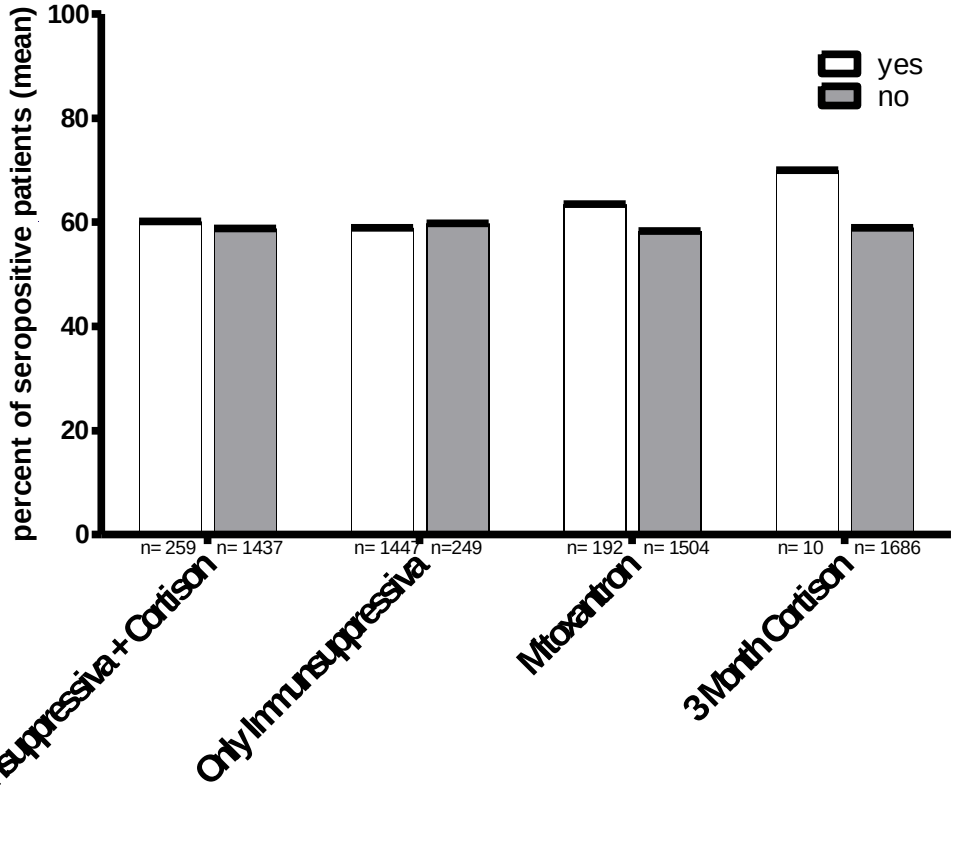
Trampe et al., Neurology 2012

JCV-antibodies: age-dependent but independent of pretreatment

Age



Immunosuppressants



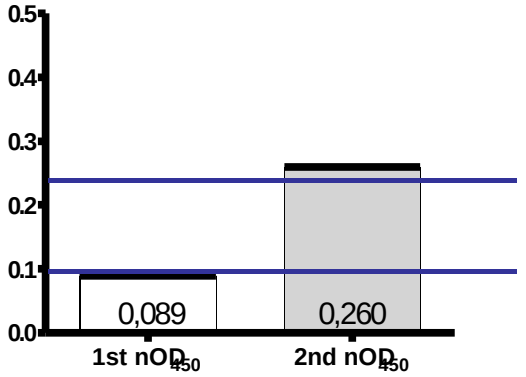
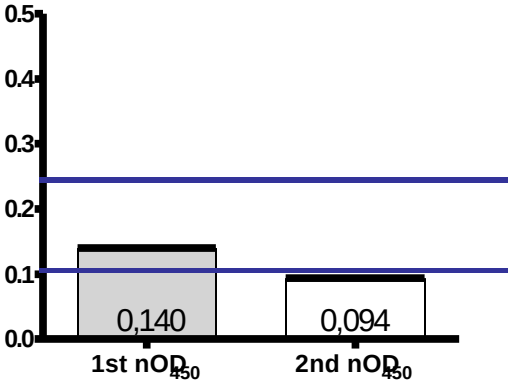
Trampe et al, Neurology 2012

JCV-antibodies in pre-PML sera: Bochum cohort (generation 1 assay)

	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 5	Pat. 6	Pat. 7	Pat. 8	Pat. 9	Pat. 10
Gender (F/M)	F	F	F	F	M	F	F	F	F	F
Sample collection prior to PML diagnosis (months)	2.9	a) 29.5 b) 25.8	20.6	17.7	37.6	a) 33.6 b) 24.5	a) 26.3 b) 2 c) 0	19.2	0	a) 35.3 b) 31.7
Age at PML diagnosis	35	40	35	45	42	44	58	30	34	41
No. of natalizumab infusions at PML diagnosis	31	29	n.a.	24	n.a.	39	31	30	27	37
Immunosuppressive pretreatment (yes/no)	yes	no	no	no	no	no	no	yes	no	no
Anti-JCV-antibodies (detected/not detected)	detected	a) detected b) detected	detected	detected	detected	a) detected b) detected	a) detected b) detected c) detected	detected	detected	a) detected b) detected

Trampe et al., Neurology 2012

Anti JCV-antibodies: Seroconversion (generation 1 assay)

Anti-JCV First analysis	Anti-JCV Last analysis	nOD_{450} (median)
negative	19/194 initially negative patients tested positive **?á9.8% in 7.7 months**	
positive	13/276 initially positive patients tested negative **?á4.7% in 7.9 months**	

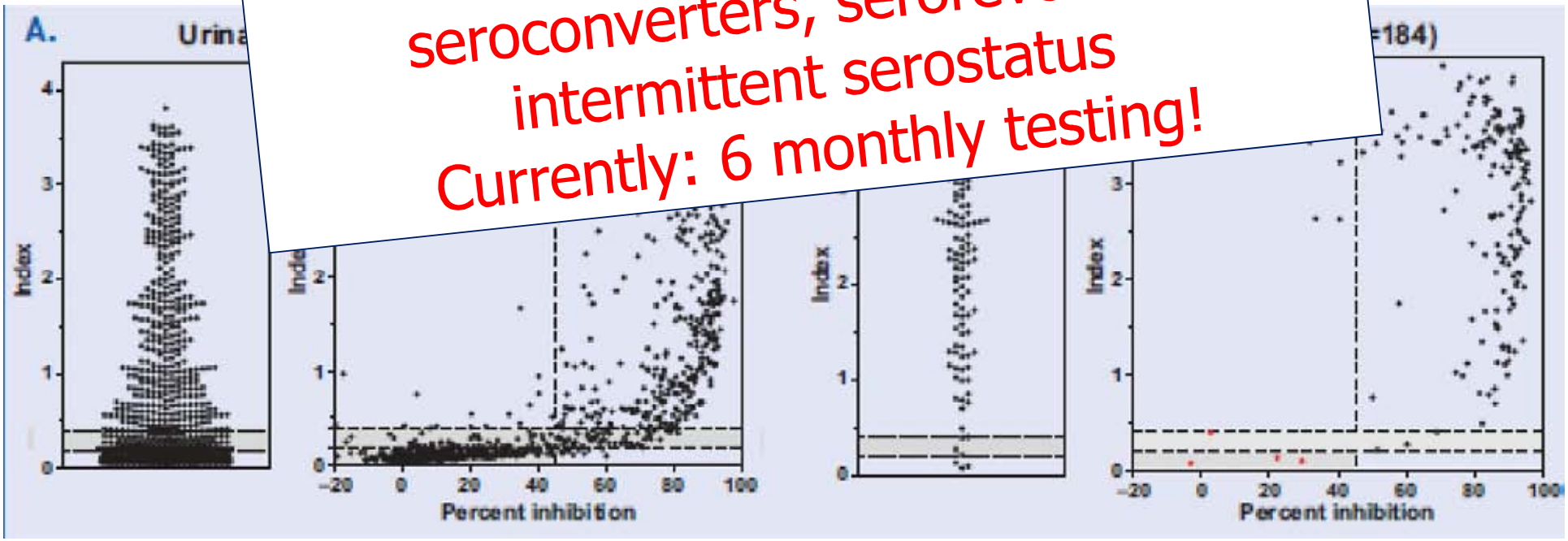
Trampe et al, Neurology 2012

Second generation ELISA

- Technical improvements: e.g. precoated plates, purification of antigen è cross-reactivity, low titre range

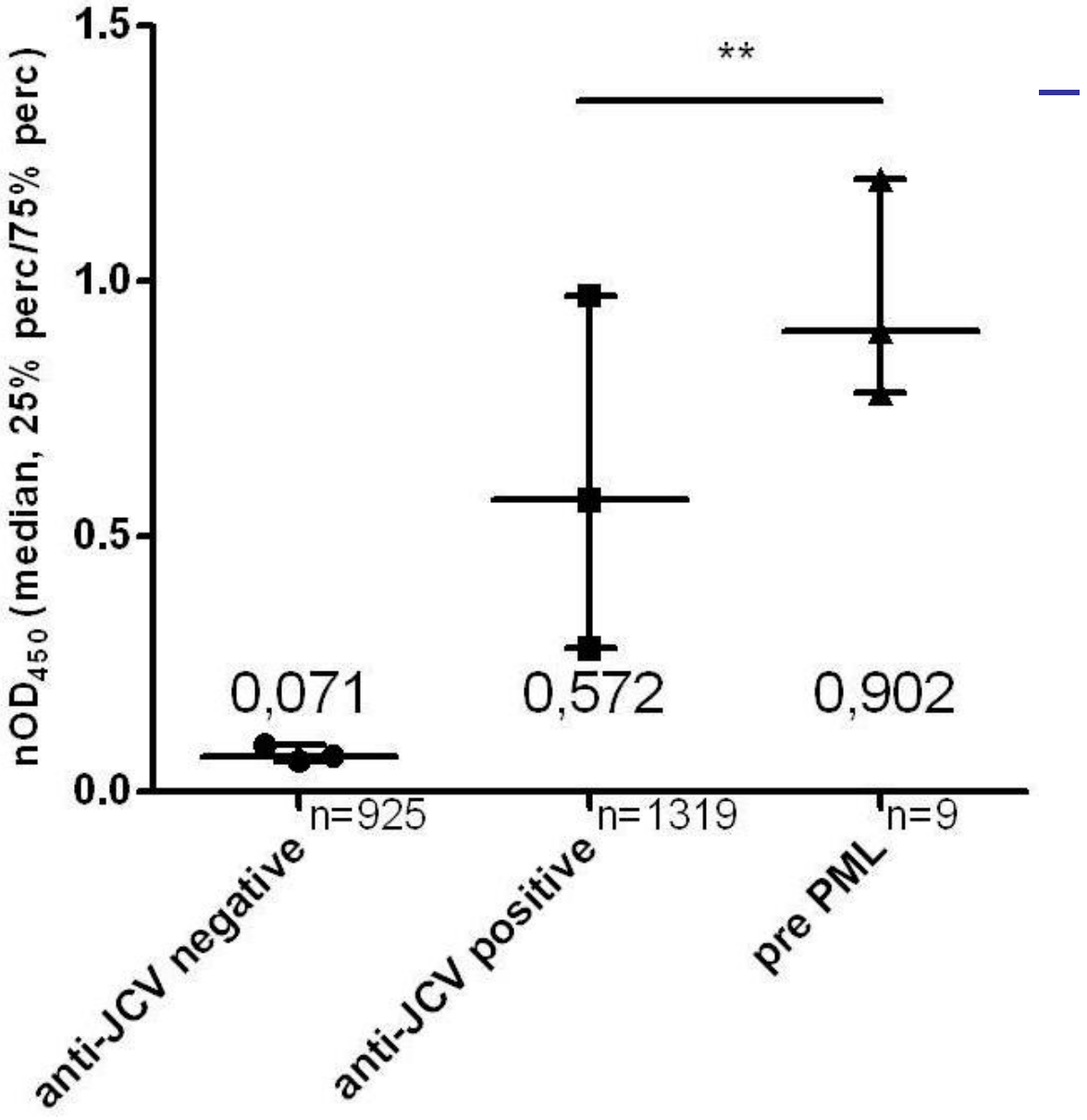
- Same material: Gen2 assay: 57.4%, Gen1 assay 54.7%
- 64 pre-PML samples: 63 positi… .5 month…

? Independent reproduction:
seroconverters, seroreverters,
intermittent serostatus
Currently: 6 monthly testing!



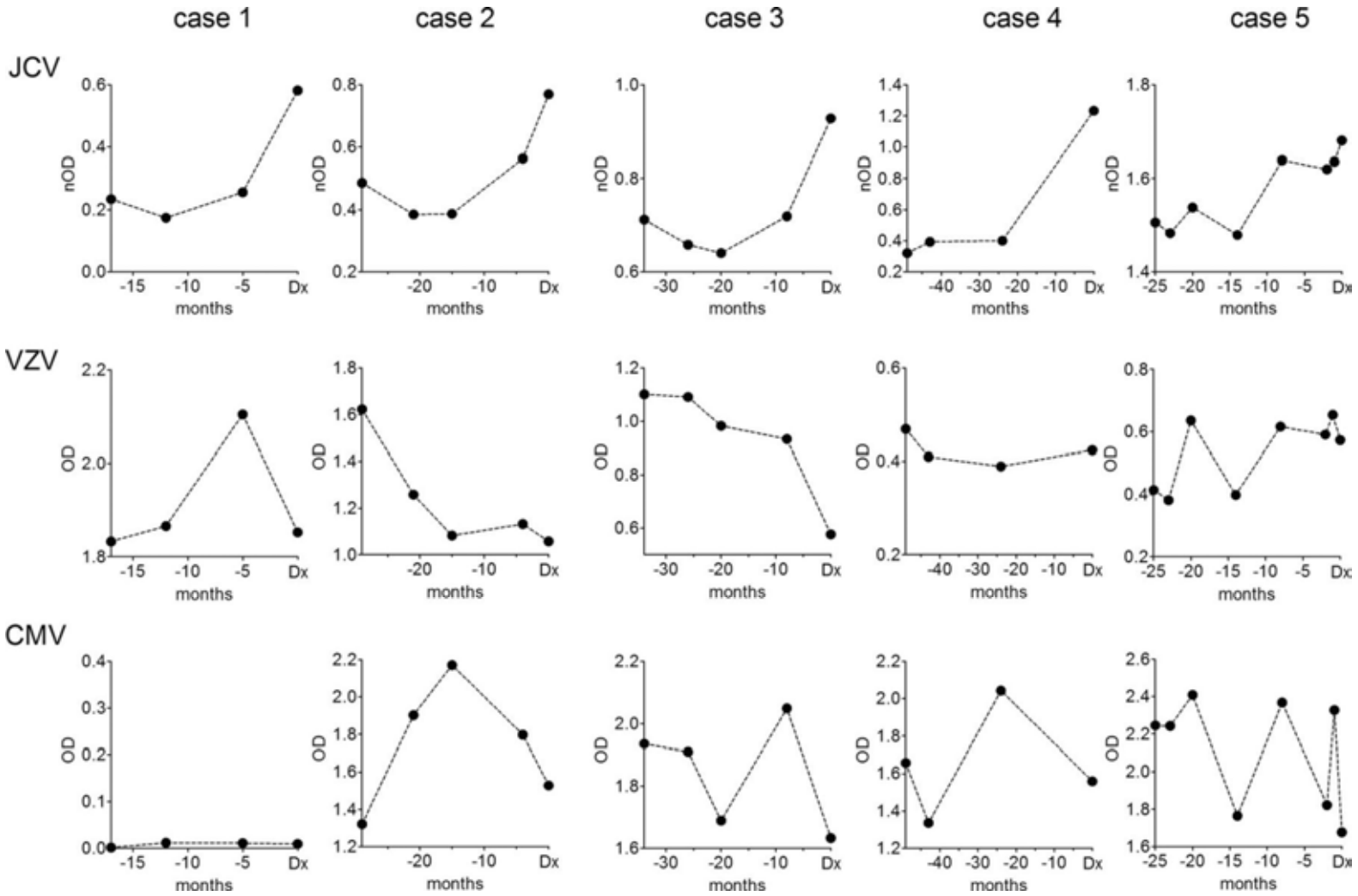
Lee et al, J Clin Virol 2013:57:141

High anti-JCV-antibody titers in Pre-PML sera



Trampe et al, Neurology 2012

JCV-antibody reactivity in pre-PML sera: Swedish cohort

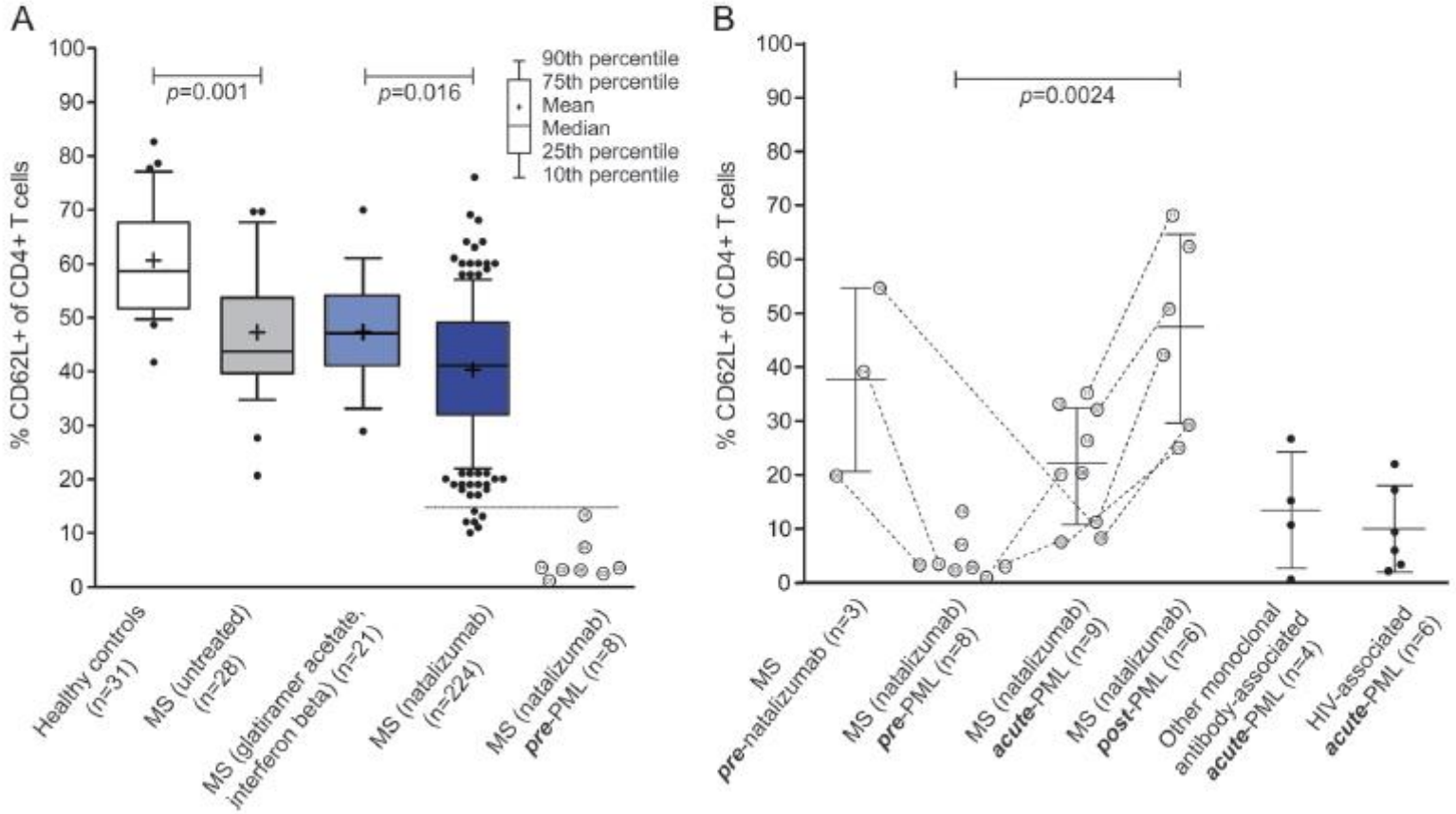


Warnke C et al. J Neurol Neurosurg Psychiatry
doi:10.1136/jnnp-2012-304332

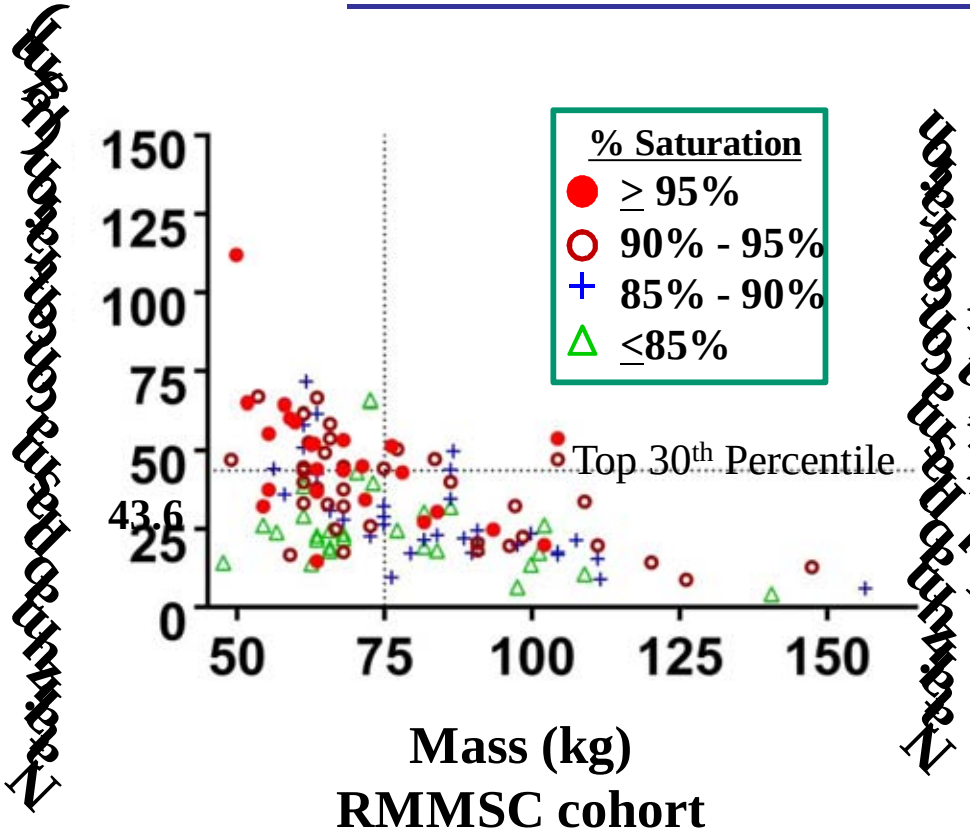
L-Selectin is a possible biomarker for individual PML risk in natalizumab-treated MS patients

Schwab / Wiendl Neurology 2013: 81: 1-7

Figure 1 Surface expression of CD62L and its correlation to progressive multifocal leukoencephalopathy development in multiple sclerosis patients receiving natalizumab therapy



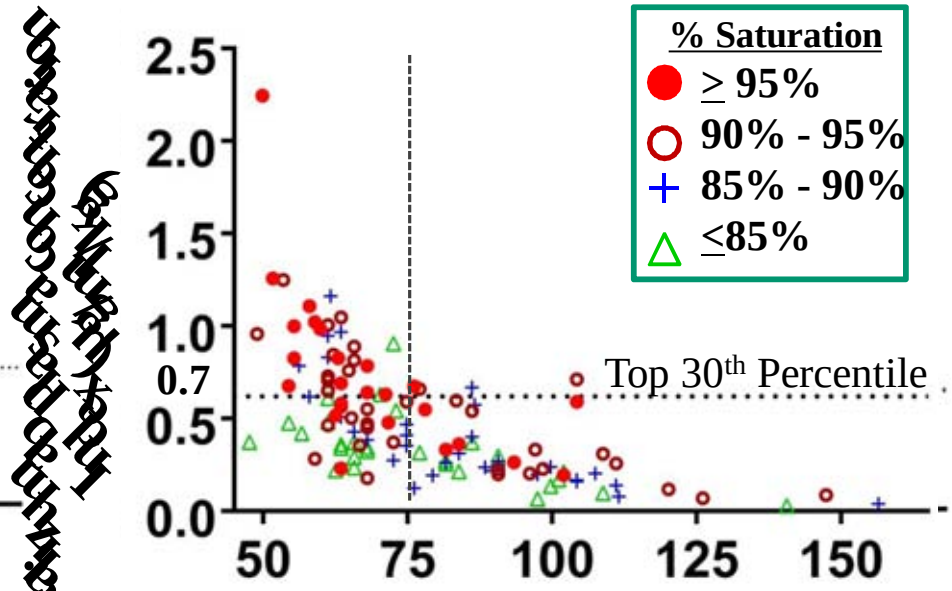
High Saturators Cluster with high Concentration, Low Body Weight



Mass (kg)

RMMSC cohort

n=122 (28-30 day infusion cycle)



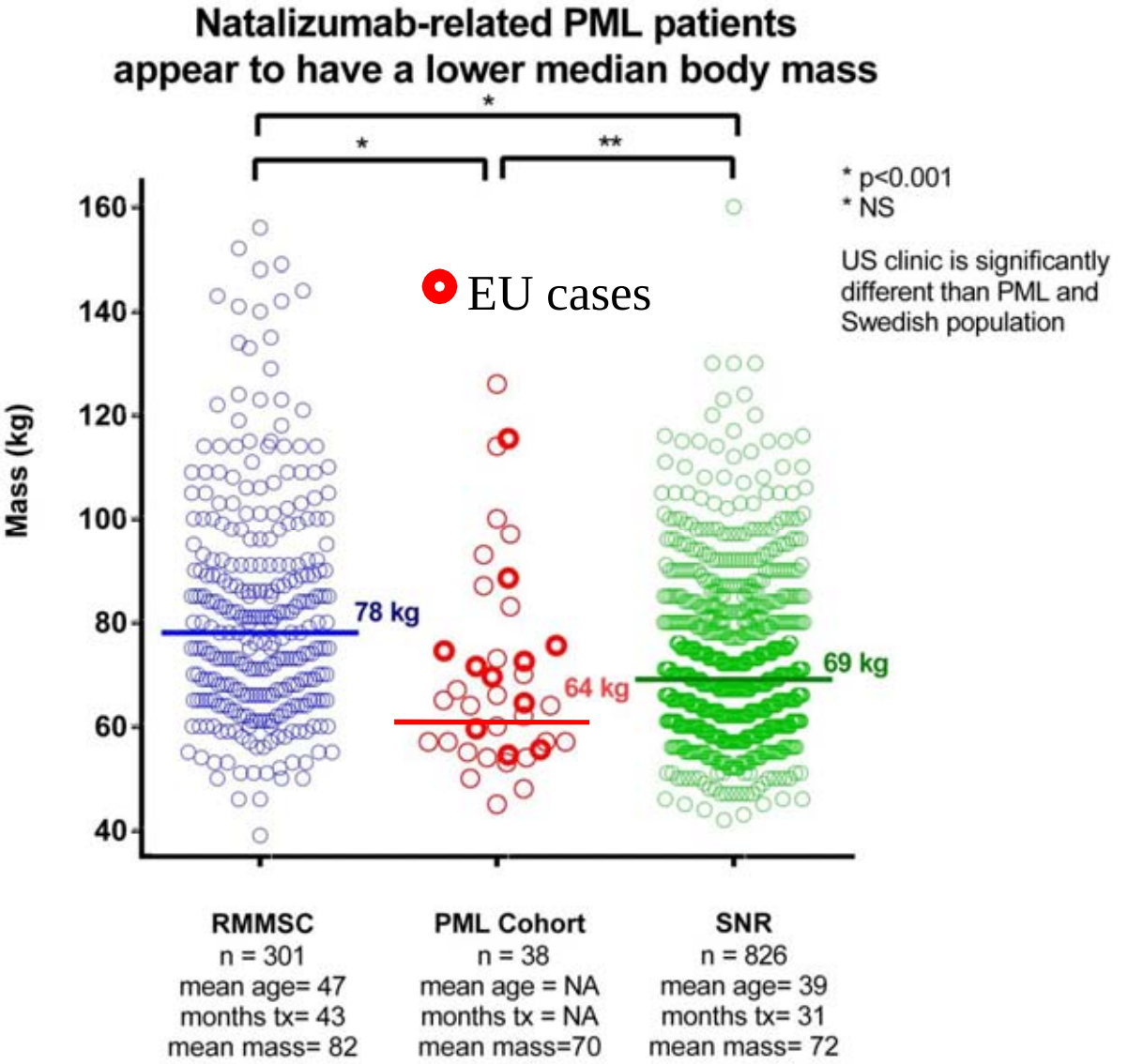
Mass (kg)

RMMSC cohort

n=122 (28-30 day infusion cycle)

Courtesy of J. Foley, presented at AAN 2013

Could body weight differences partially explain the US/EU paradox?



Courtesy of J. Foley, presented at AAN 2013

Biomarkers: lost in translation?

- Prospective validation for a low-event sADR (ethical, logistic concerns)
- Feasibility of biomarker (stability, technique)
- Approval/incorporation into guidelines
- Translation into clinical practice (complexity of data)

Summary

- Early diagnosis: impact on prognosis
- although not evidence based, immune-reconstitution and supportive treatment
- IRIS: no prophylactic treatment
- current 3-parameter risk stratification, repeat serology every 6 months
- future developments: Ab-index, adhesion molecules, body mass index

è prospective validation warranted