Clinical development issues in progressive MS

EMA London, 10/17/2013

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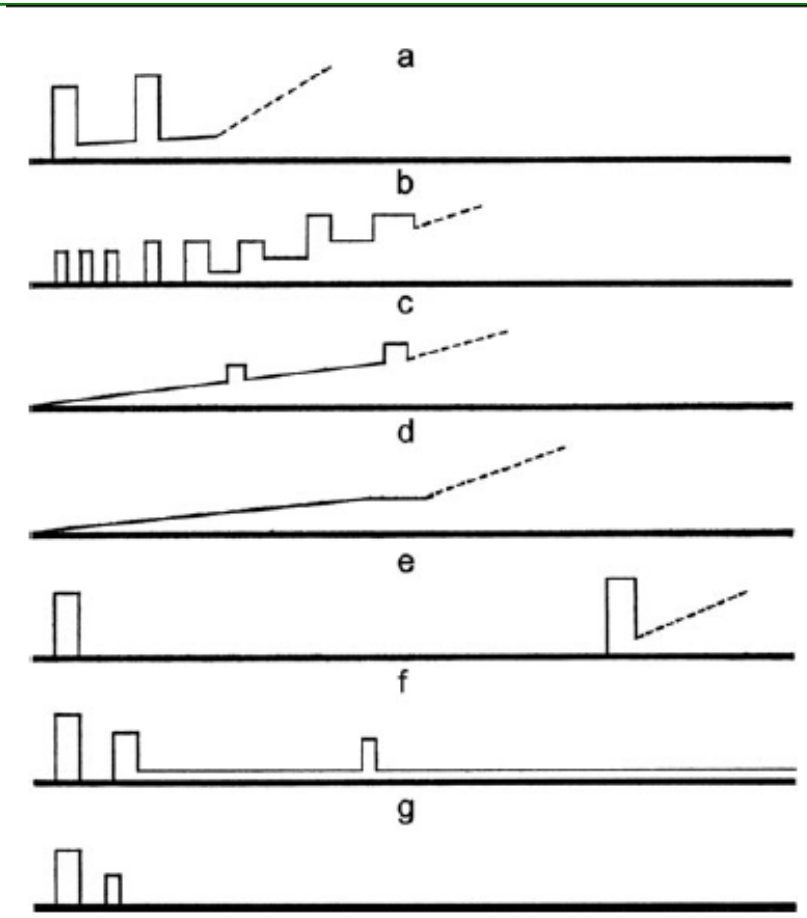
Multiple Sclerosis, Teva Pharmaceuticals R&D

History of MS
Seven original disease courses

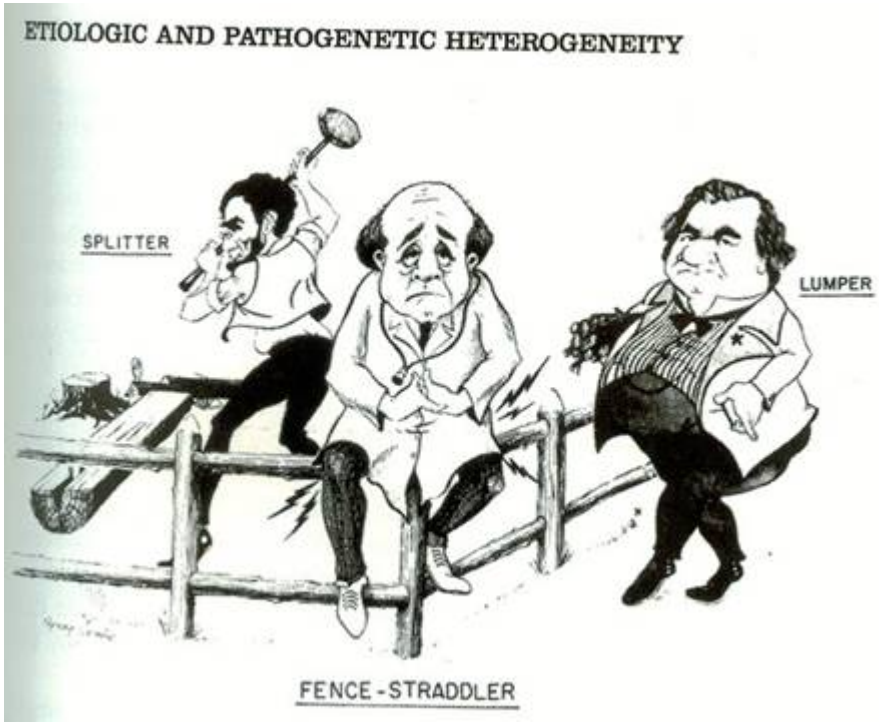


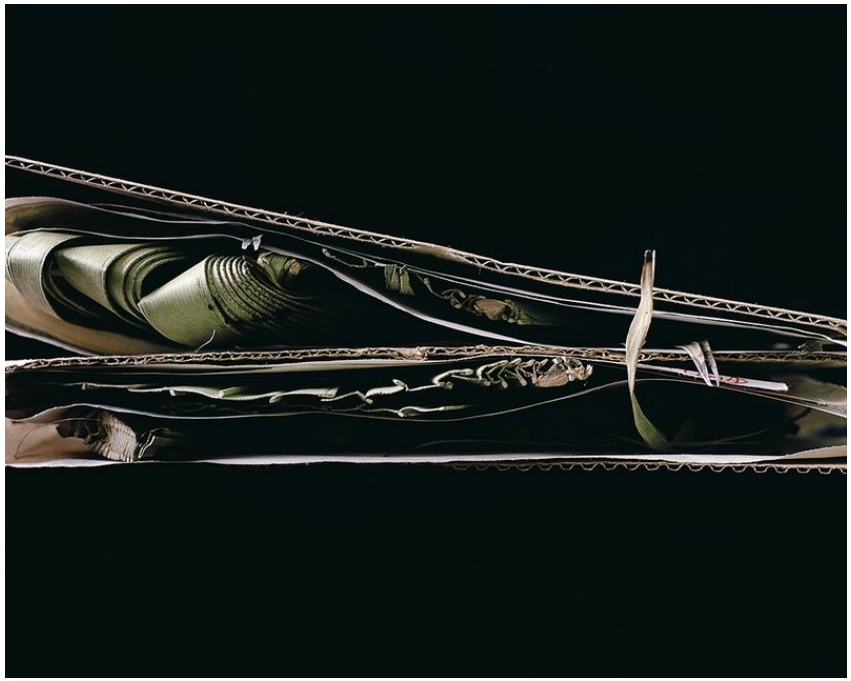
McAlpine D (1972) Multiple sclerosis: a reappraisal. In: McAlpine D, Lumsden CE, Acheson ED (eds) Diagnosis and classification of multiple sclerosis, 2nd ed. Churchill Livingstone, Edinburg

One disease? Seven phenotypes!

(Lublin-Reingold phenotypes, from 4 to 3)

How useful are the existing MS phenotypes in guiding clinical trials in MS?





A Case for Progressive MS (PMS)

- MS is a chronic inflammatory disease at all stages that affects the entire CNS, not simply focal demyelinating plaques
- Many different immunological mechanisms lead to demyelination in MS, subsequent neurodegeneration is associated with activation of microglia and astrocytes
- MS is biologically one disease, when adjusted for age and disability status no differences are found between the phenotypes in epidemiology, age of progression onset, genomics, genetics in familial forms, and MRI brain atrophy rate, as well as T2 lesion load and distribution

- Preventing or delaying disability progression is the recommended primary end point in PMS studies. EDSS measurements are currently the primary endpoint of choice, albeit suboptimal.
- Less relevant are effects on superimposed relapses, and selection of patients based on acute active lesions, as the DMT effects on this axis of the pathology has been well established

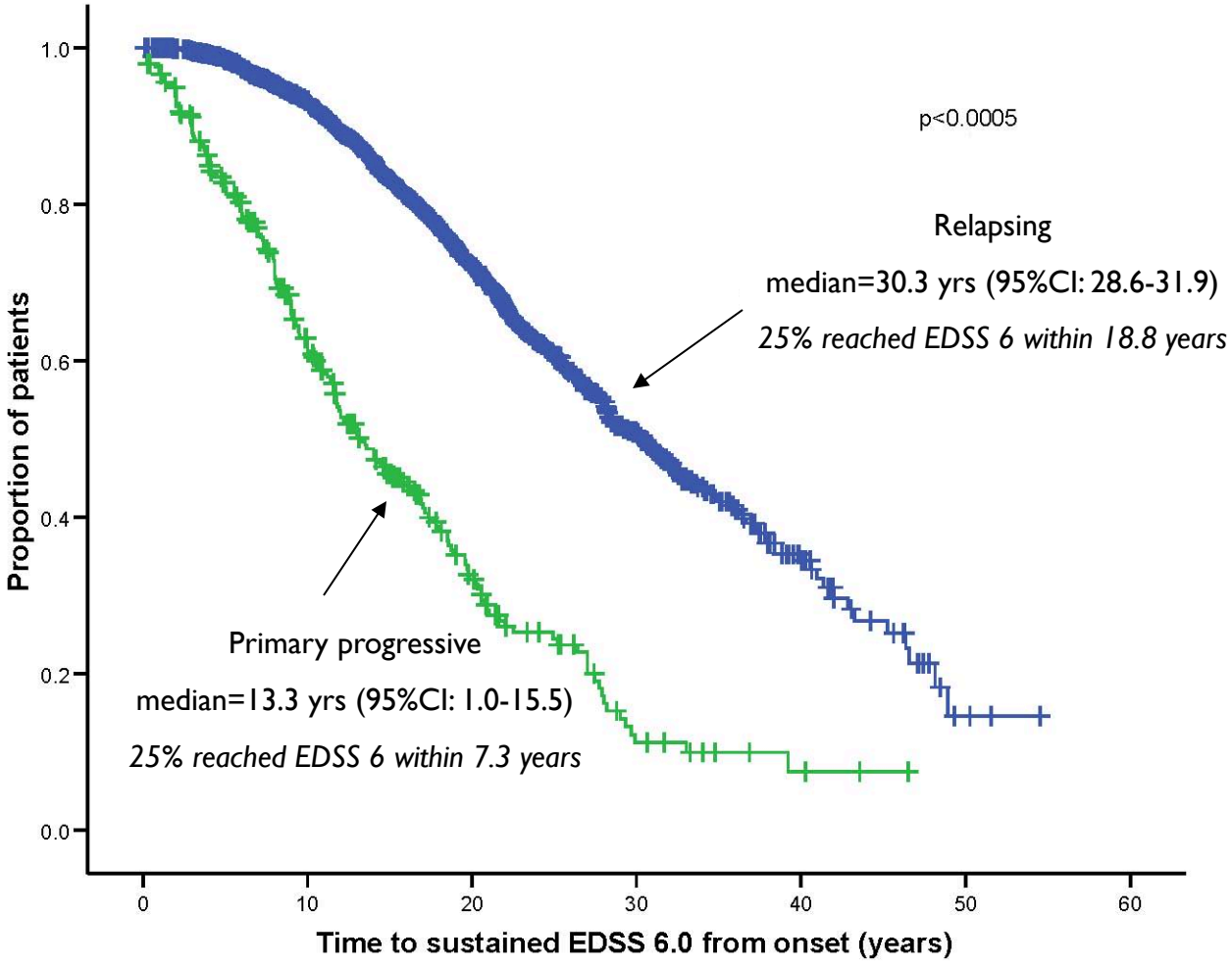
Key TEVA comments on EMA Guidelines

- Current science does not support clearly discernible genetic, pathological or epidemiological clinical features which differentiate RRMS leading to SPMS from PPMS, both are united by age of the patient
- Recommendations:
- To study both phenotypes of PMS for an appropriate DMT (MOA neurodegeneration) in one combined patient population to address the uniform disability progression
- Inclusion by age and EDSS is paramount, OCB (?)
- Primary endpoint: Rate of disability progression
  - Use EDSS and MSFC components
  - Buttressed by MRI markers of neurodegeneration
- RE: RRMS: Primary efficacy parameters
  - Progression should be considered an interchangeable primary endpoint to relapse rate (not necessarily requiring co-primary endpoint).
  - The decision on the appropriate endpoint should be driven by the DMTs mode of action.

CLINICAL COURSE
Natural History
Epidemiology

Kaplan Meier curves:

Time to sustained and confirmed EDSS 6 by disease course



<u>British Columbia</u>

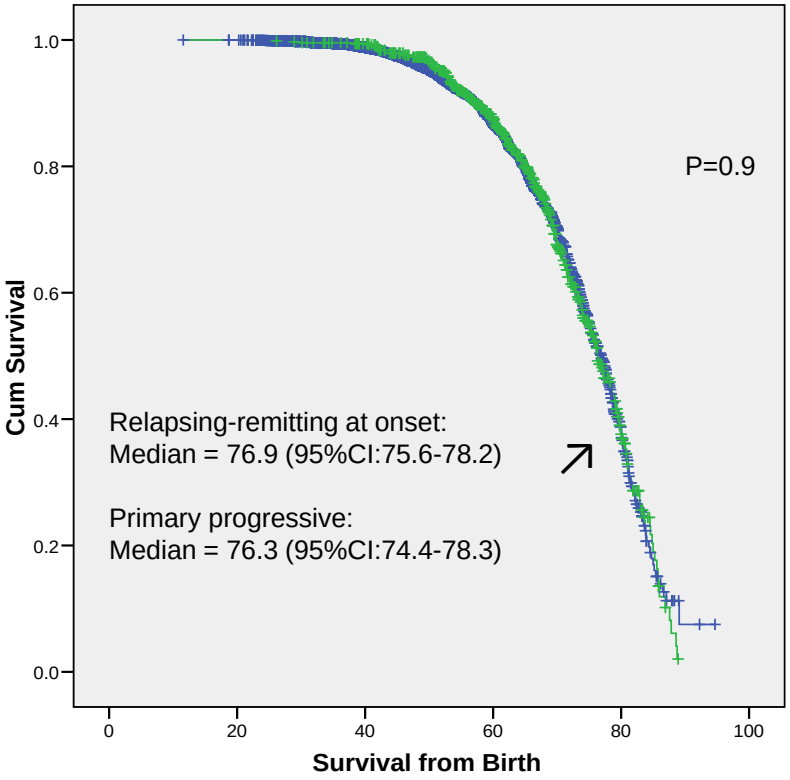
Tremlett et al. Neurology 2006; 66: 172-177

n=2837

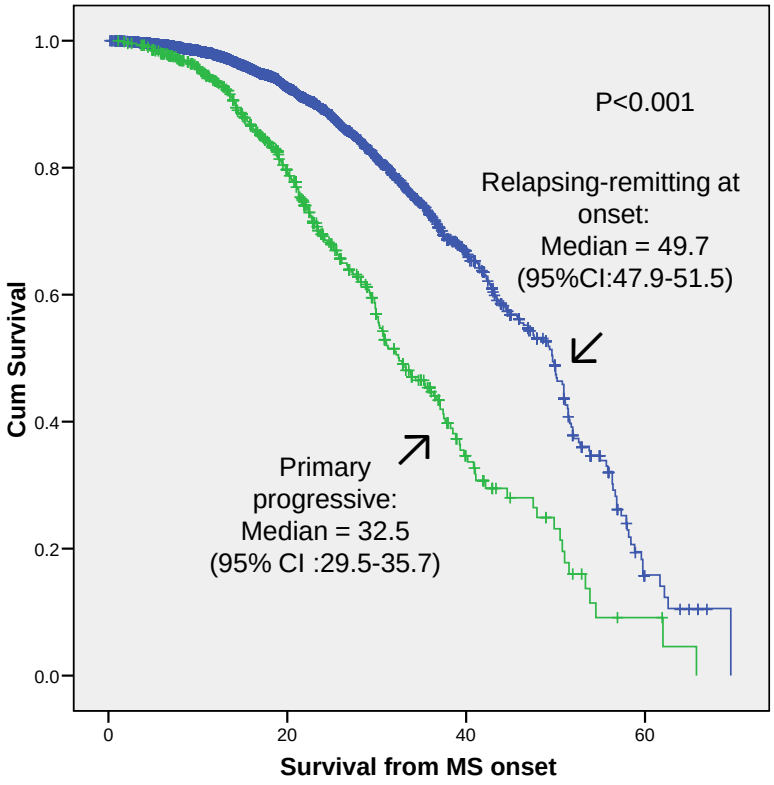
KM Survival curves by clinical course:

From birth or from onset of MS

From Birth (Identical)

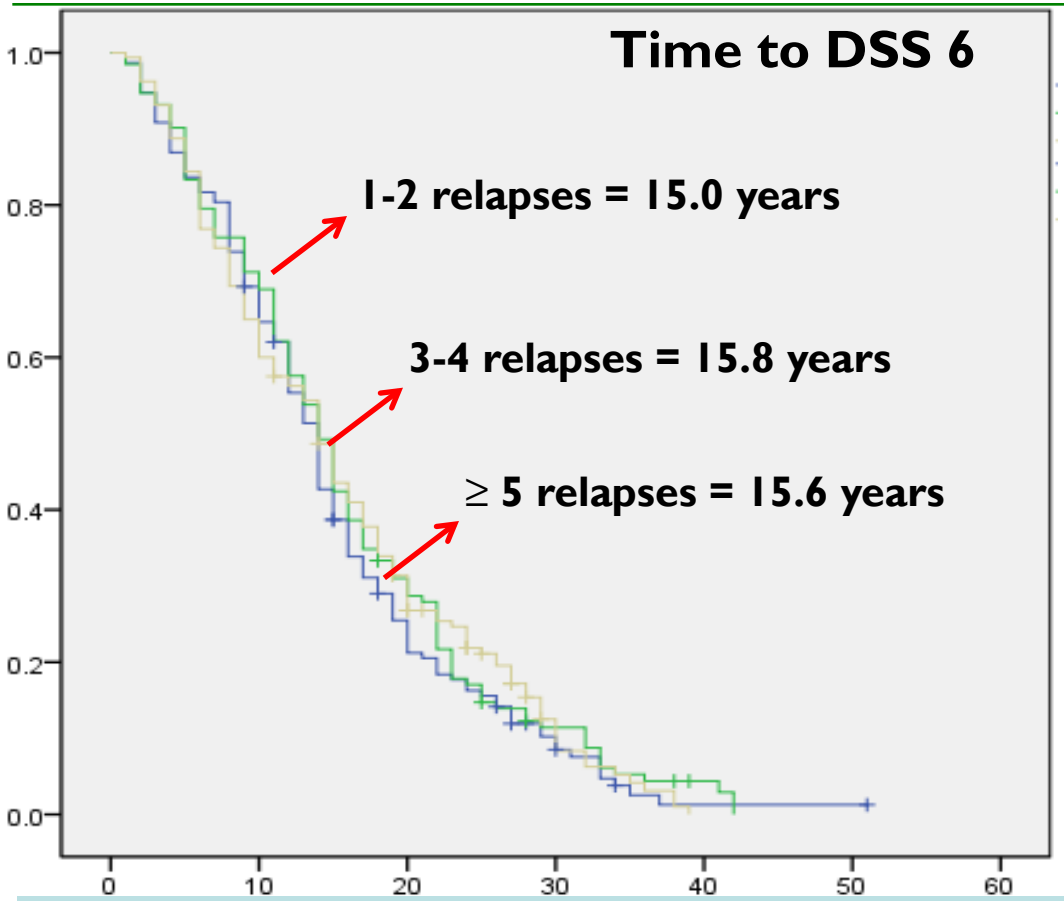


From Onset (RR is skipped?, time delayed)



Same disease different phenotypes

Total Relapses during RR phase



Risk of reaching DSS 6

Num of relapses	HR (p = 0.76)
1	0.99
2	0.98
3	0.98
4	0.97
5	0.97

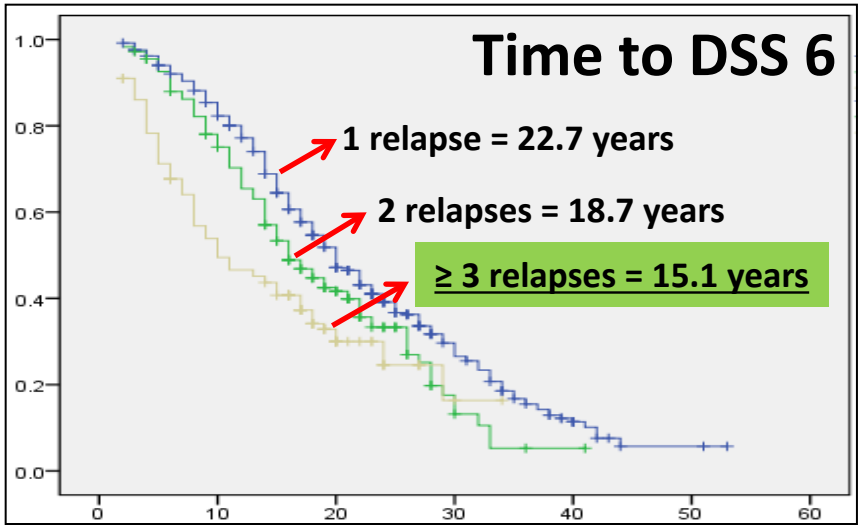
HR =Hazard ratio

Can't assume relapse suppression will make a difference for time to EDSS 6-8 but this is what has been assumed!

Relapses ← **? Causal or concomitant ?** → **Late outcome**

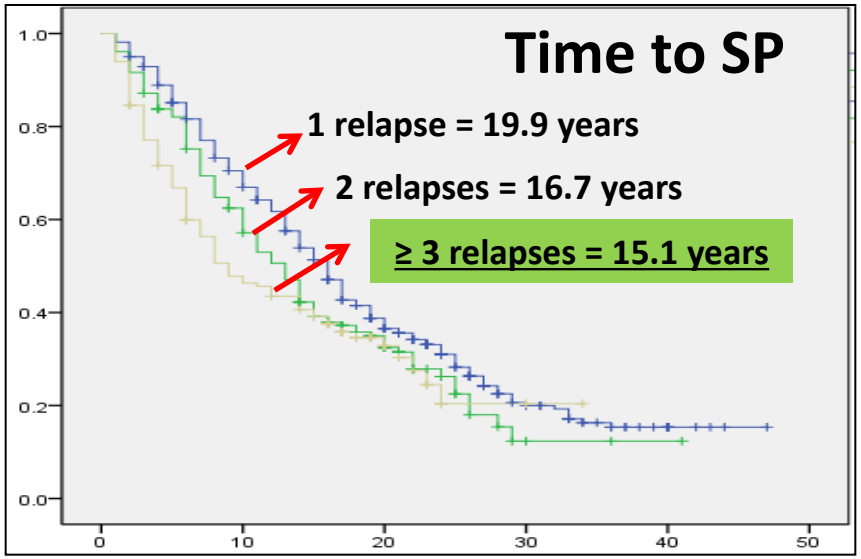
(Scalfari et al. 2010)

Early relapses (Y1+Y2) meaningful association



Risk of reaching DSS 6

Num of relapses	HR (p < 0.001)
1	1.23
2	1.51
3	1.85
4	2.27
5	2.79



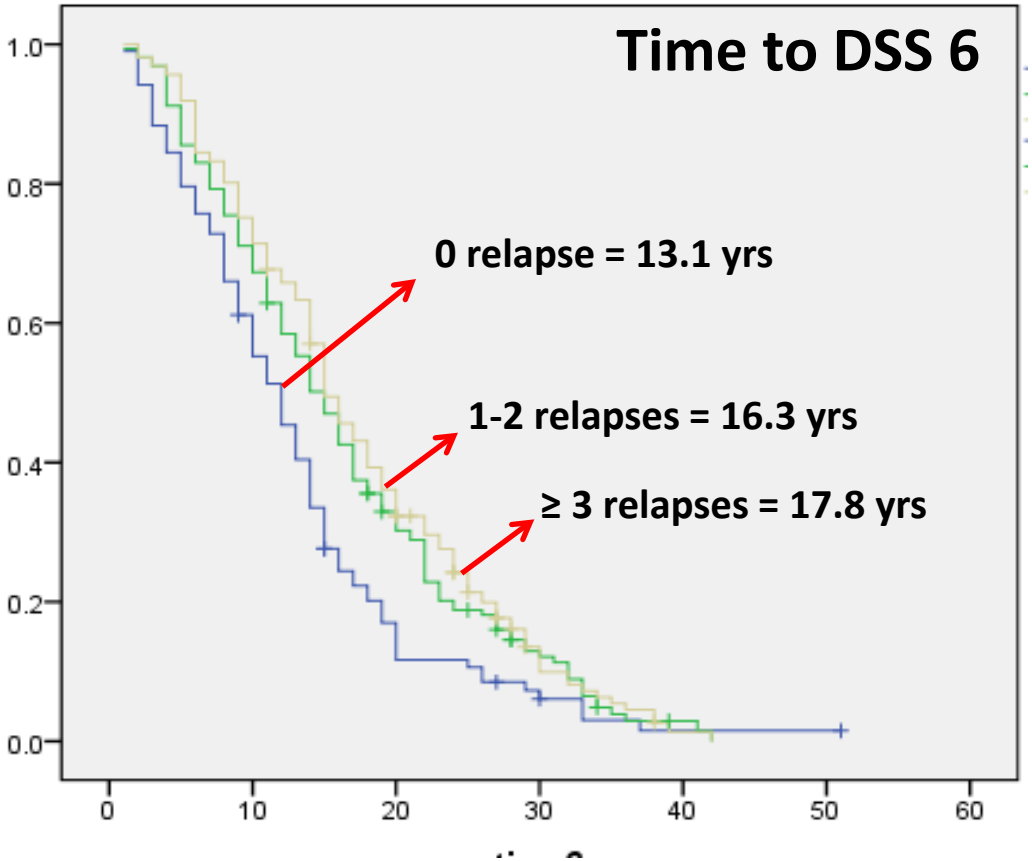
Risk of reaching SP

Num of relapses	HR (p < 0.001)
1	1.25
2	1.56
3	1.94
4	2.42
5	3.02

(Scalfari et al. 2010)

Relapses Y3 - onset SP assoc. with better outcome

These are the relapses enumerated in clinical trials



Risk of reaching DSS 6

Num of relapses	HR (p = 0.01)
1	0.94
2	0.89
3	0.85
4	0.80
5	0.76

(Scalfari et al. 2010)

This is slightly bigger effect than y1y2 associating with more rapid disability

Analysis of disease activities in SPMS and PPMS

Comparison of Disease Activity in SPMS and PPMS in the Context of Multicenter Clinical Trials

Rotem Orbach[1,3¶], Zhenming Zhao[2¶], Yong-Cheng Wang[2], Gilmore O'Neill[1], Diego Cadavid[1*]

1 MS Clinical Development Group, Biogen Idec, Cambridge, Massachusetts, United States of America, **2** Biostatistics, Biogen Idec, Cambridge, Massachusetts, United States of America, **3** Multiple Sclerosis Center at Sheba Medical Center, Tel-Hashomer, Israel

- 101 variables were analyzed from two multicenter clinical studies (IMPACT and OLYMPUS)

- Only two variables were observed to differ
- 9 hole PEG and one EDSS sensory measure

Conclusion: SP and PP are phenotypic variation of same disease

Orbach et al, 2012, Plos ONE 7(10) e45409

PPMS and SPMS

Same progression from onset of progressive phase

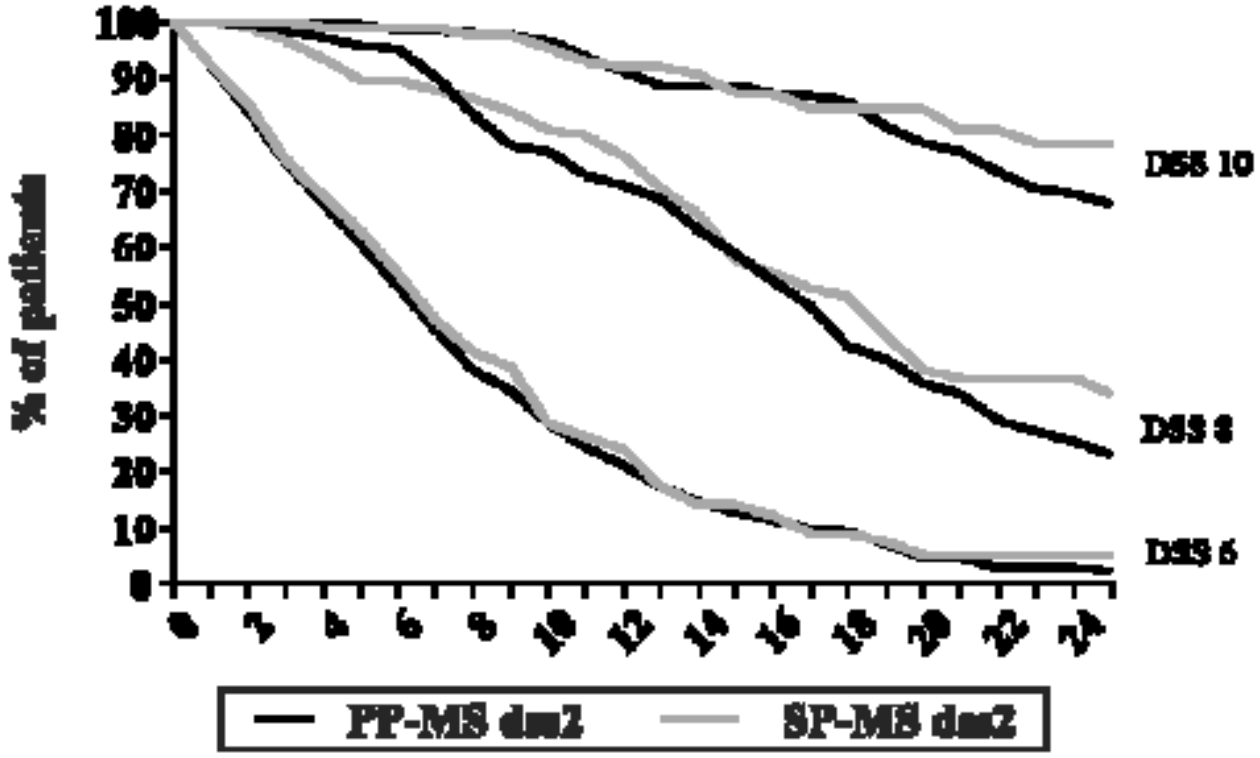


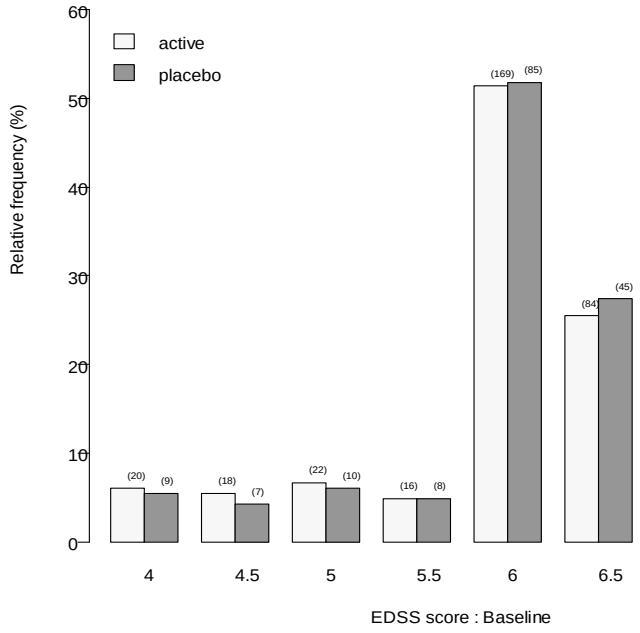
Figure 3 *Time to DSS 6/8/10 – years from onset of progressive MS.*

Rice GPA, Kremenchutzky M, Cottrell DA, Baskerville J, Ebers GC. Observations from the natural history cohort of London, Ontario. In Fililppi M, Comi G eds. Topics in neuroscieince: primary progressive multiple sclerosis. Milano: Springer Verlag Italia, 2002

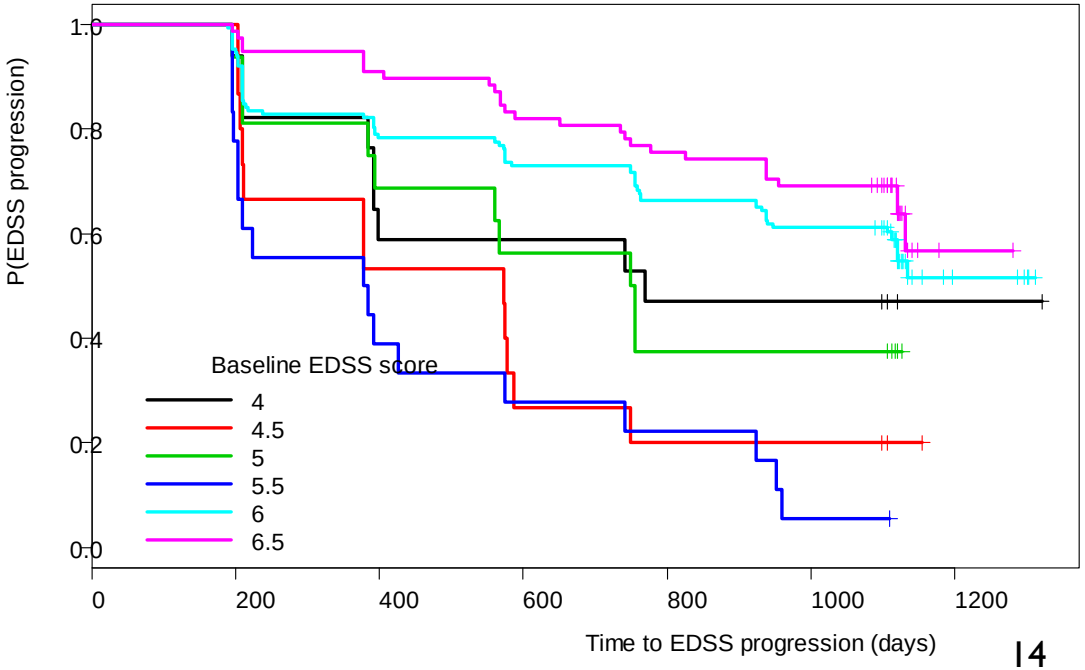
The Role of Age and EDSS in PMS Trials

Careful balance between age and EDSS inclusions is needed to avoid potential skewed distributions and imbalances in higher age and disability strata lowering trial population assay sensitivity

Frequencies and relative frequencies of baseline EDSS scores in each treatment group. The number of participants is given above each bar.



CUPID Trialists 2013



Genetics and phenotypes

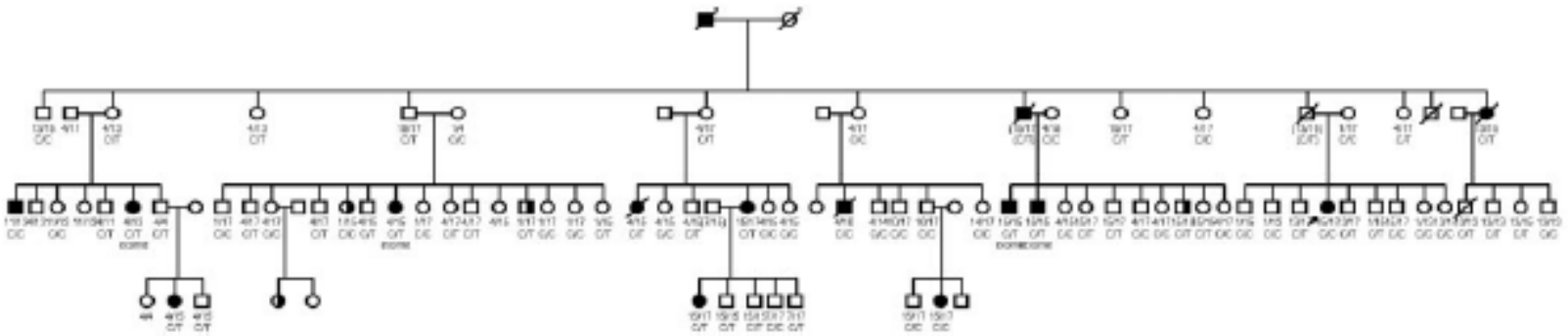
Same genes different phenotypes

Cumulative genetic risk from genetic studies and from familial studies have not identified differences between the MS phenotypes in these pedigrees!

All phenotypes were encountered

In a pseudo-dominant MS Pedigree containing TYK2 mutation

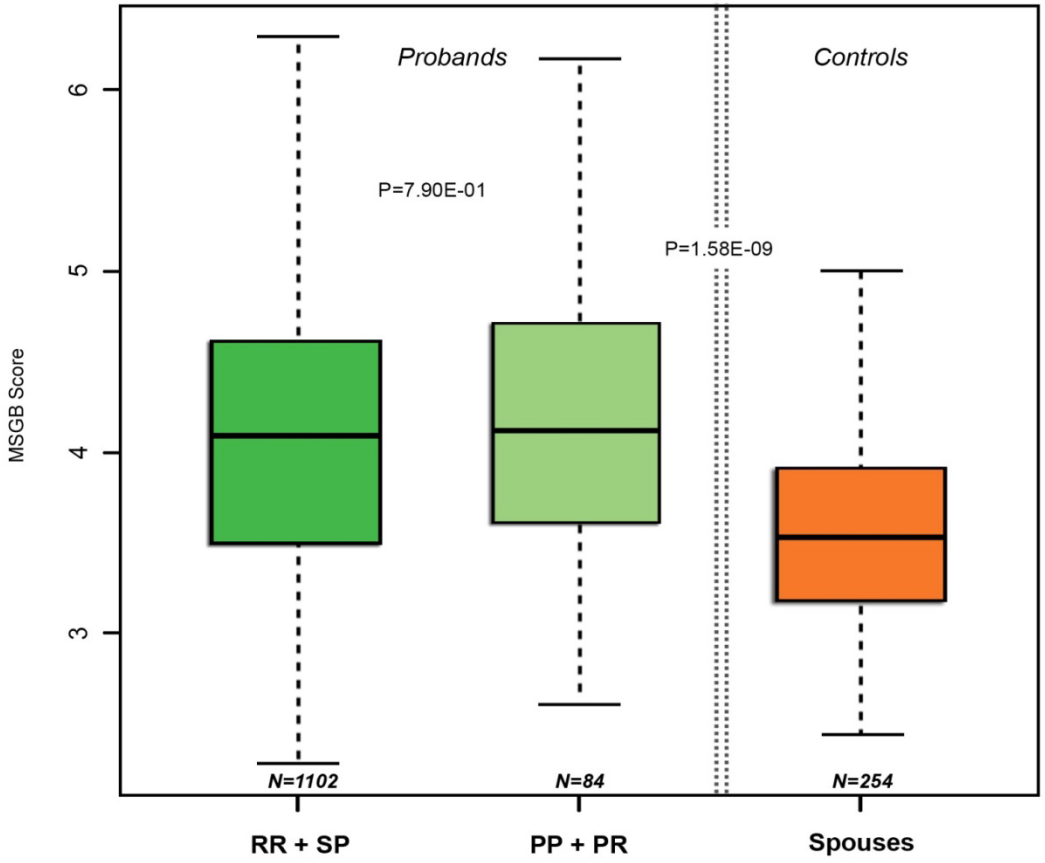
Figure 1 Pedigree in family with high prevalence of multiple sclerosis



Dyment et al Neurology 2012

Cumulative Genetic Risk for MS

Relapsing and Primary Progressive Subtypes Identical



Gourraud et al. *Ann Neurol* 69:65, 2011

MRI findings by MS disease stages

	PP MS	SP MS	RR MS
Brain			
Gd enhancement[a]			
T1	+	++	+++
Black holes[b]			
T1	++	+++	+
Atrophy[b]			
Whole brain	+++	++	+
Grey matter	+++	++	+
Magnetization transfer imaging	+++	+++	++
Diffusion tensor imaging	++	++	+
Proton magnetic resonance spectroscopy	+++	+++	++
Cortical lesions[c] (frequency/extent[a])			
Double-inversion recovery	++	++	+
Spinal cord			
Lesion load			
T2	+++	+++	++
Atrophy[c]	+++	+++	+

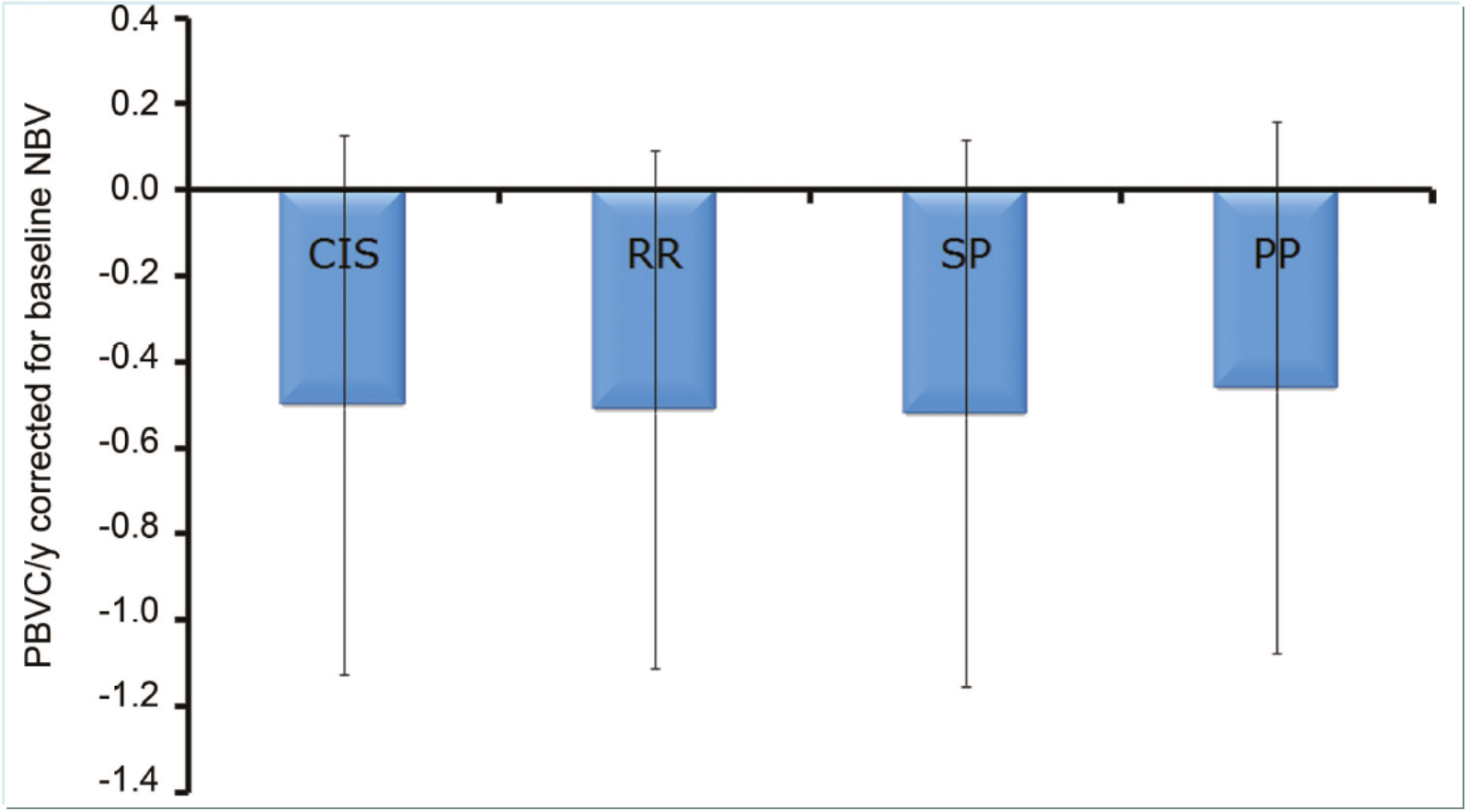
(not matched for age) *Relapse related*

Disability progression

Ambulation/Disability progression

Antel et al, 2012, Act Neuropathol. 123, 627-638

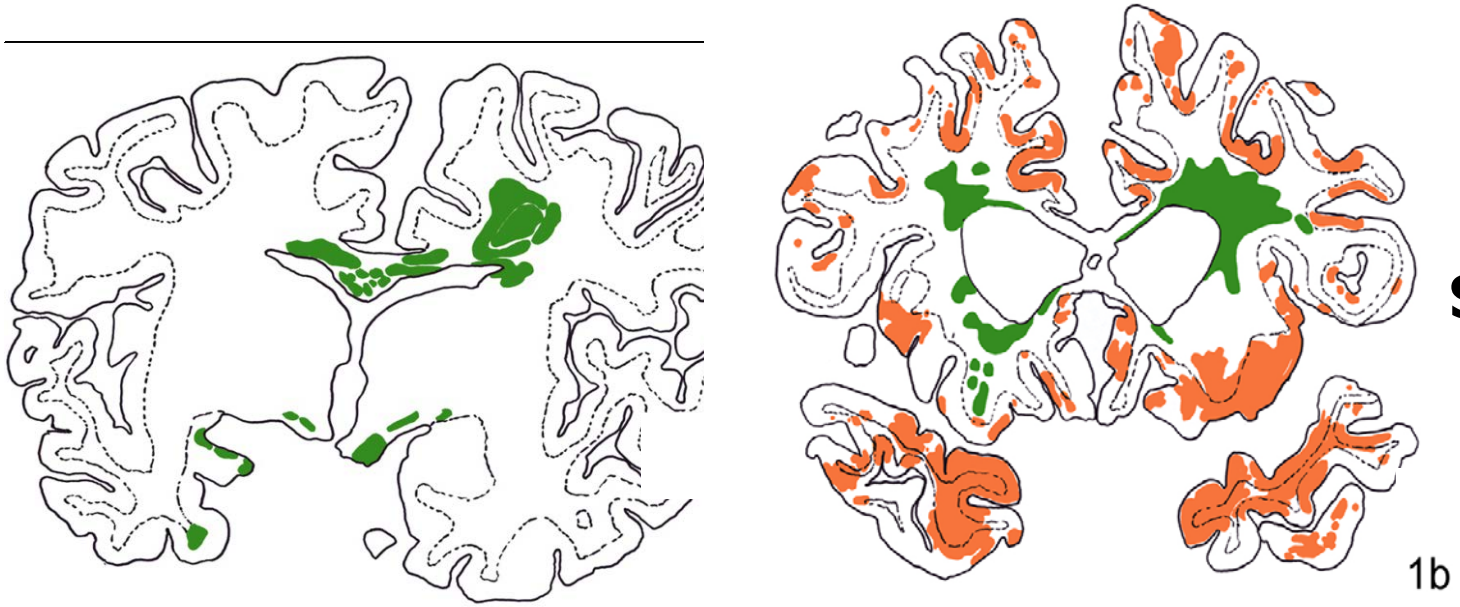
Brain atrophy occurs early and continues throughout the course of MS



From De Stefano, Neurology 2010

Extensive Cortical Demyelination in PMS

RRMS



SPMS/ PPMS

	Cortical lesion area forebrain (%)	White matter lesion area (%)
RRMS	2.96	10.3
PPMS	12.54	6.54
SPMS	13.29	24.13

Kutzelnigg et al., Brain 2005

Microglial activation is common feature in PMS

Table 1 Quantitative differences in pathological features between different subgroups of multiple sclerosis values

	AMS	RRMS	SPMS	PPMS	Controls	Alzheimer's disease	*P*-value group comparison	*P*-value pooled course
Number of cases	11	6	20	14	15	15		
Mean age (years); range	45.27 (28–68)	50.5 (20–67)	46.4 (28–61)	53.9 (28–75)	74.6 (46–89)	79.7 (60–92)		
Female/male ratio	1.75	1	1.44	1.33	1.14	1		
Disease duration (months)	**1.5 (0.2–7)**	120 (48–156)	**192 (72–408)**	**198 (30–411)**	0	n.a.	**$P < 0.001$**	**$P < 0.001$**
WML area forebrain (%)	22.66 (0–85.05)	10.3(1.01–53.25)	24.13 (2.79–60.36)	6.54 (0.46 –76.54)	0	Atrophy	$P = 0.06$	$P = 0.78$
Cortical lesion area forebrain (%)	0 (0–3.93)	2.96 (0–14.14)	**13.29 (0–68.63)**	**12.54 (0–38.68)**	0	Plaques + tangles	**$P < 0.001$**	**$P < 0.001$**
Active WMLs (%)	**100 (90–100)**	**11.44 (0–100)**	0 (0–50)	0 (0–56.25)	0	n.a.	**$P < 0.001$**	**$P < 0.001$**
Slowly expanding WMLs (%)	0 (0)	**10.42 (0–100)**	**14.29 (0–53.85)**	**12.5 (0–50)**	0	n.a.	**$P < 0.001$**	**$P < 0.004$**
Inactive WMLs (%)	0 (0–10)	35.3 (0–85.71)	**85.71 (12.5–100)**	**77.78 (14.29–100)**	0	n.a.	**$P < 0.001$**	**$P < 0.001$**
Inflammatory infiltrates meninges (per 100 mm)	0.56 (0.196–2.793)	0.42 (0–0.824)	0.86 (0–4.752)	0.64 (0–4.506)	0	0	$P = 0.58$	$P = 0.3$
Perivascular inflammatory infiltrates NAWM (per mm^2)	0.04 (0.015–0.12)	0.05 (0.03–0.21)	**0.27 (0.015–0.79)**	**0.13 (0.015–0.88)**	0	0.009 (0.0–0.03)	**$P < 0.001$**	**$P < 0.004$**
Microglia activation NAWM	1.5 (1–4)	2 (2–4)	**4 (2–5)**	**4 (2–5)**	1 (1)	2 (1–4)	**$P < 0.001$**	**$P < 0.001$**
Axonal spheroids NAWM (per mm^2)	2.69 (0–7)	4.67 (1.65–7.5)	**10.25 (0–35.06)**	**16.8 (2.5–81.5)**	0.5 (0–5.75)	3.775 (0.78–7.8)	**$P < 0.001$**	**$P < 0.001$**

These values represent medians, the range for values are given in brackets; n.a.: not applicable.
Values in bold indicate those contributing to the significant differences.

Multiple sclerosis begins as a focal inflammatory disease of the CNS, which gives rise to circumscribed demyelinated plaques in the white matter.
With chronicity, (PPMS) diffuse inflammation accumulates throughout the whole brain, and is associated with slowly progressive axonal injury in the NAWM and cortical demyelination.

Histopathological findings in different MS disease stages

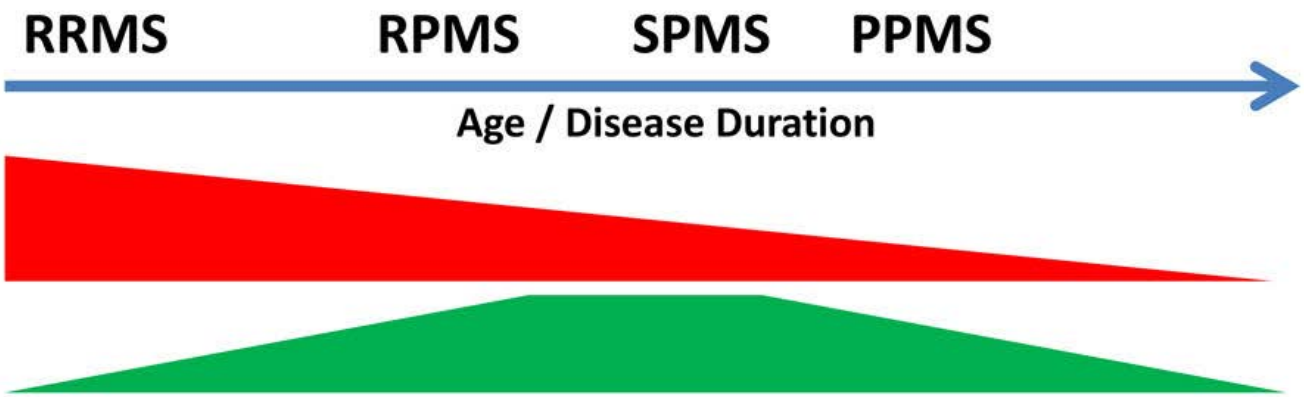
If any, the differences between SP and PP are quantitative not qualitative

Table 2 Summary of histopathological findings in differ courses

	PP MS	SP MS	RR MS
Inflammation			
Perivascular cuffing intralesional	+	++	Nd
NAWM	++	++	+
Meningeal follicle-like structures	Absent	Present	Nd
Demyelination			
Cerebral white matter	+	++	+
Cortical	++	++	+
Axonal damage			
NAWM (APP)	++	++	+
Reduced axonal density (lesion)	++	+	Nd
Remyelination	++	+	++

Antel et al, 2012, Act Neuropathol. 123, 627-638

Differences in inflammation: RRMS and SPMS



Inflammation

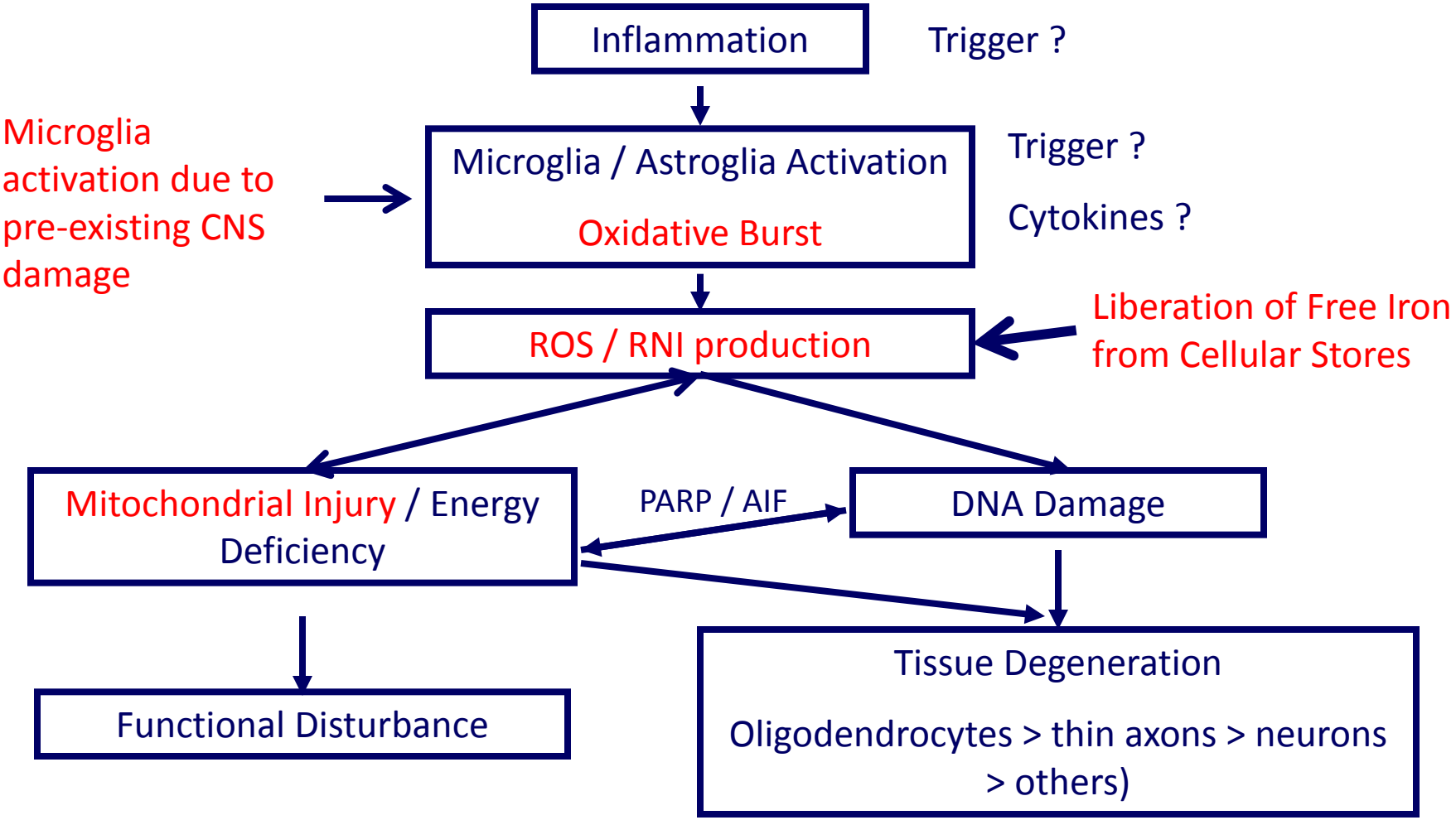
- New waves of lymphocytes entering the CNS
- Blood brain barrier disturbance
- New classical active lesions
- Initial remyelination in active lesions

Trapped Inflammation

- Meningeal inflammatory aggregates
- Slow expansion of pre-existing lesions
- Subpial cortical demyelination
- Diffuse white matter injury
- Brain Atrophy

Lassmann H, et al. *Nat Rev Neurol* 2012;8(11):647–656

Neurodegeneration in MS



Duration of disease and age are accompanied
by a change in the pattern of inflammation in the brain

Inflammation with activated microglia and astrocytes
persists in the CNS behind a repaired, largely intact BBB
requiring potentially a different DMT MOA compared to RRMS

Biological and epidemiological comparisons suggest MS is one disease

- No Genetic Differences
  - Lundstrom W et. al. No influence on disease progression of non-HLA susceptibility genes in MS. *J of Neuroimmunology* 237 (2011)98-100
  - Baranzini S et. al. Genome wide association analysis of susceptibility and clinical phenotype in MS. Human Molecular Genetics 18 (2009) 767-778
  - Harding K et. Al. Genotype-Phenotype correlation for non-HLA disease associated risk alleles in MS. Neuroscience Letters 526 (2012) 15-19
  - International MS Genetics Consortium Risk Alleles for MS Identified by a Genome wide study. NEJM 357 (2007) 851-862
- No Familial Differences
  - Ebers GC. Natural history of primary progressive multiple sclerosis in *Multiple Sclerosis* 2004; 10:S8-S15
- No Pathological Differences
  - Lassmann H Relapsing-remitting and primary progressive MS have the same cause(s)—the neuropathologist's view:1 in *Multiple Sclerosis Journal* 2013 19(3) 266-267
  - Kuhlmann T Relapsing-remitting and primary progressive MS have the same cause(s)—the neuropathologist's view:2 in *Multiple Sclerosis Journal* 2013 19(3) 266-267

Current tools for measuring progression in MS are suboptimal; yet …

Disability and Biomarker Measurements in PMS
EDSS alone may not be ideal

Measures of progression

- EDSS including individual MSFC (replacing PASAT with SDMT)
- 25 FTTW, The 9-HPT, SDMT to be considered
- MRI advanced techniques (MTR, DTI) OCT, neurophysiological measures

Biomarkers

- CSF neurofiliments
- CSF b-tubulin III
- Proteins released by microglia
- Epigenetics
  - miRNA profiles (e.g. miR -155,-338,-491

EDSS progression allowing for individual MSFC components contributing to progression definition is currently the primary end point for two year PMS studies

Suggested Key Enrolment Criteria for PMS Clinical Studies

- Confirmed and documented PMS diagnosis as defined by the revised McDonald criteria (Ann Neurol 2011: 69:292-302)
  - OCB ?
- Evidence of clinical disability progression (retrospectively or prospectively determined) for two years prior
- No relapses in the last two years and progression
- Age 25- 55 years
- EDSS 2-6.5 with stratification
- No Gd+ at baseline (?)
- Normal organ function

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