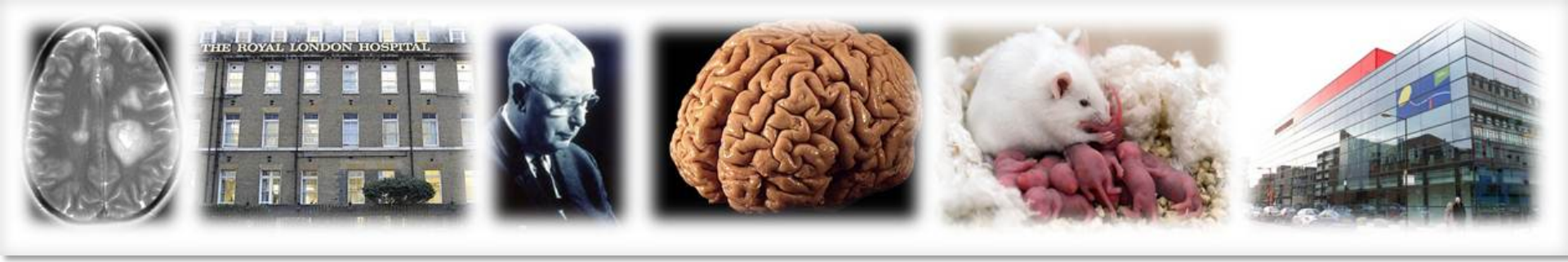
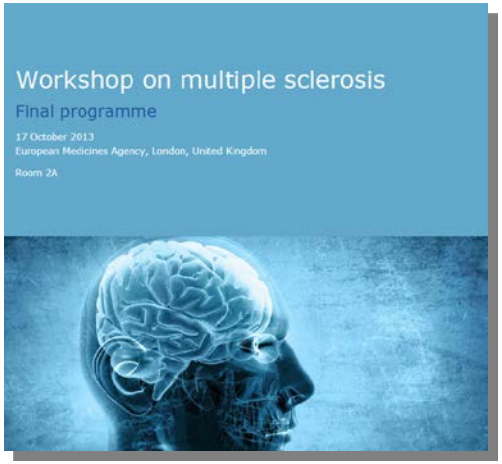



# Treatment guidelines for relapsing MS and the 'two step approach' for disease modifying therapy




Klaus Schmierer, PhD FRCP

Blizard Institute, Barts and The London School of Medicine & Dentistry

Barts Health NHS Trust

# Disclosures

PI of trials sponsored by Novartis & Roche.

Involved in trials sponsored by Biogen, Genzyme, Teva and BIAL.

Speaking honoraria from, and/or in an advisory role for, Novartis, Sanofi-Aventis, Merck-Serono and Merck Inc.

Grant support from HEFCE, Isaac Schapera Trust, National MS Society (US), MS Society of Great Britain & Northern Ireland, Novartis and Barts and The London Charity.

# The suggested TSA

"For products with an anticipated profound effect on the immune system and thus potential serious safety [concerns] a two step procedure is foreseen:

1) Products should be evaluated in comparative superiority study in patients with insufficient responsive to first line treatment

2) If the safety profile is judged to be acceptable, efficacy studies may be extended to a broader multiple sclerosis population."

# Why challenge the TSA?

Because we already have one in the UK!

**And we don't like it**

# Key document

NHS Commissioning Board

**Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS)**

**April 2013**

**Reference : NHSCB/D04/P/a**

EMA (safety & efficacy) > NICE (cost-effectiveness) > CCG (funding)

# Start criteria 2013 Commissioning Board

## Fingolimod

- Patients have *unchanged* or *increased* relapse rate or *ongoing severe* relapses compared with previous year despite Tx with β IFN
- Fingolimod is provided at discounted price as part of patient access scheme

# Challenging the TSA

- Predicting disease course
- Efficacy of DMT
- Side effects/safety of DMT
- Cost of DMT

# Challenging the TSA

- Predicting disease course
- Efficacy of DMT
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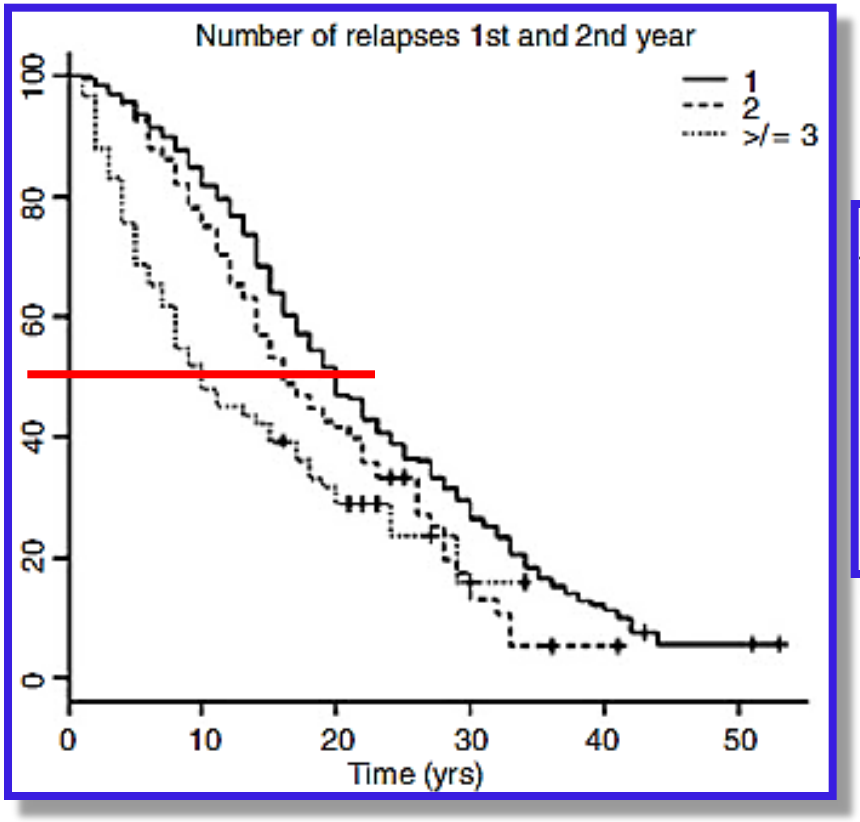
- Cost of DMT

# Relapses and disease progression

Time from disease onset to DSS 6*




| No. of relapses Years 1–2 | Mean years (median) | 95% CI | P-value |
|---|---|---|---|
| | Time from disease onset to DSS 6 | | |
| 1 relapse | 22.7 (20) | 21.1–24.1 | <0.001 |
| 2 relapses | 18.7 (16) | 16.9–20.4 | 0.010 |
| ≥3 relapses[a] | 15.1 (10) | 12.5–16.7 | |
| | Time from onset of progressive phase to DSS 6 | | |
| 1 relapse | 6.1 (4) | 5.2–6.8 | <0.001 |
| 2 relapses | 5.3 (4) | 4.3–6.2 | <0.001 |
| ≥3 relapses[a] | 2.5 (1) | 1.7–3.1 | |

*Requires a walking aid to walk 100m

Scalfari, et al. Brain 2010

# Atrophy mainly affects the limbic system and the deep grey matter at the first stage of multiple sclerosis

JNNP 2010

Bertrand Audoin,[1,2] Wafaa Zaaraoui,[1] Françoise Reuter,[1,2] Audrey Rico,[1,2] Irina Malikova,[1,2] Sylviane Confort-Gouny,[1] Patrick J Cozzone,[1] Jean Pelletier,[1,2] Jean-Philippe Ranjeva[1]

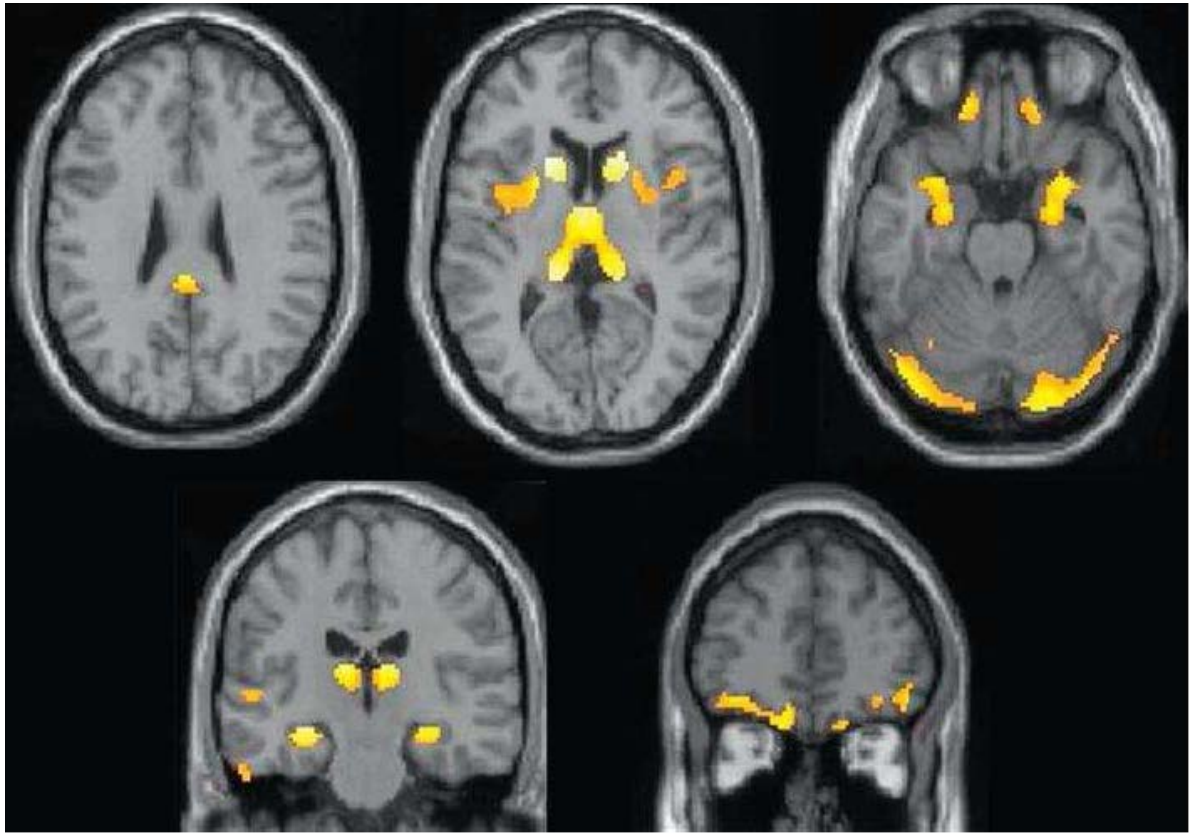
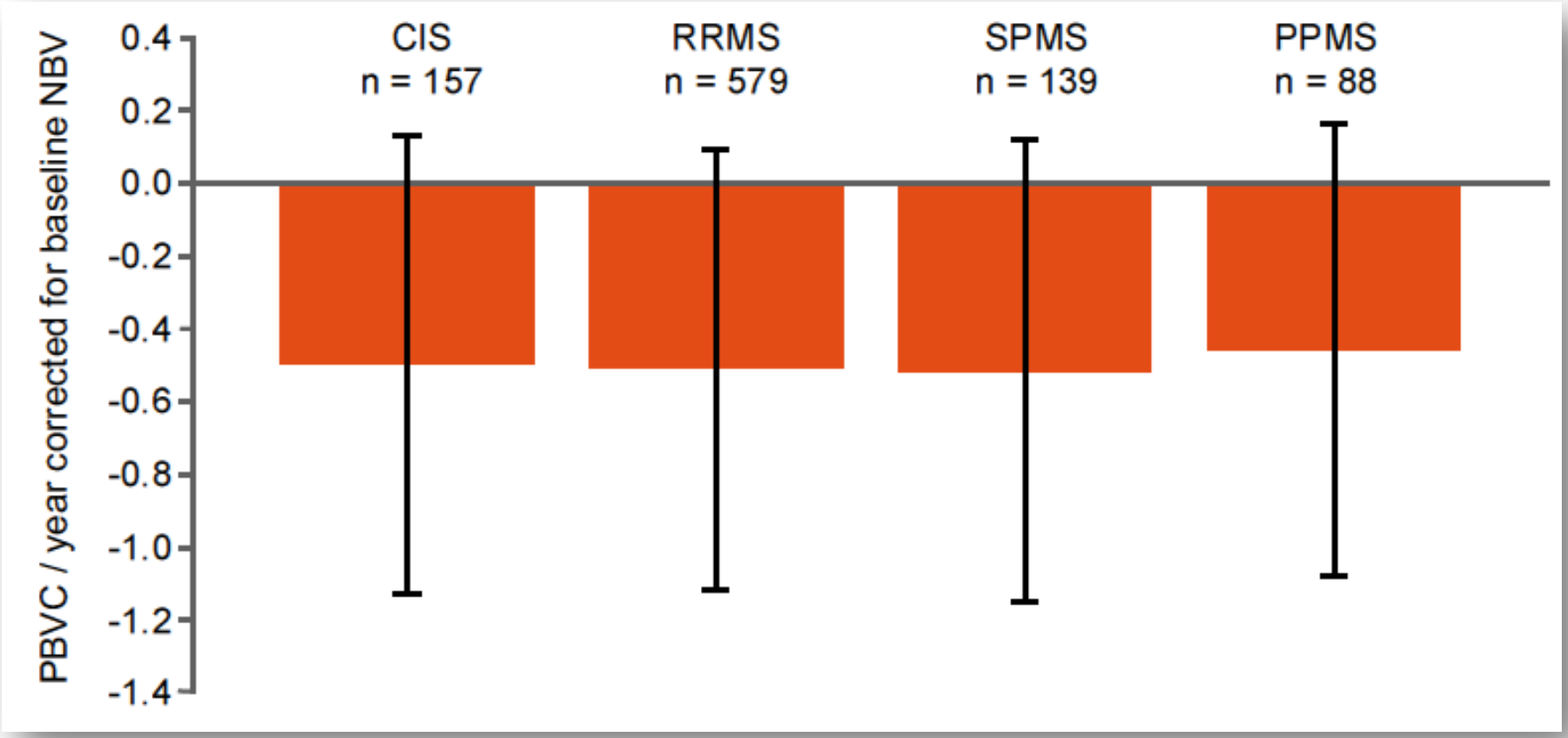


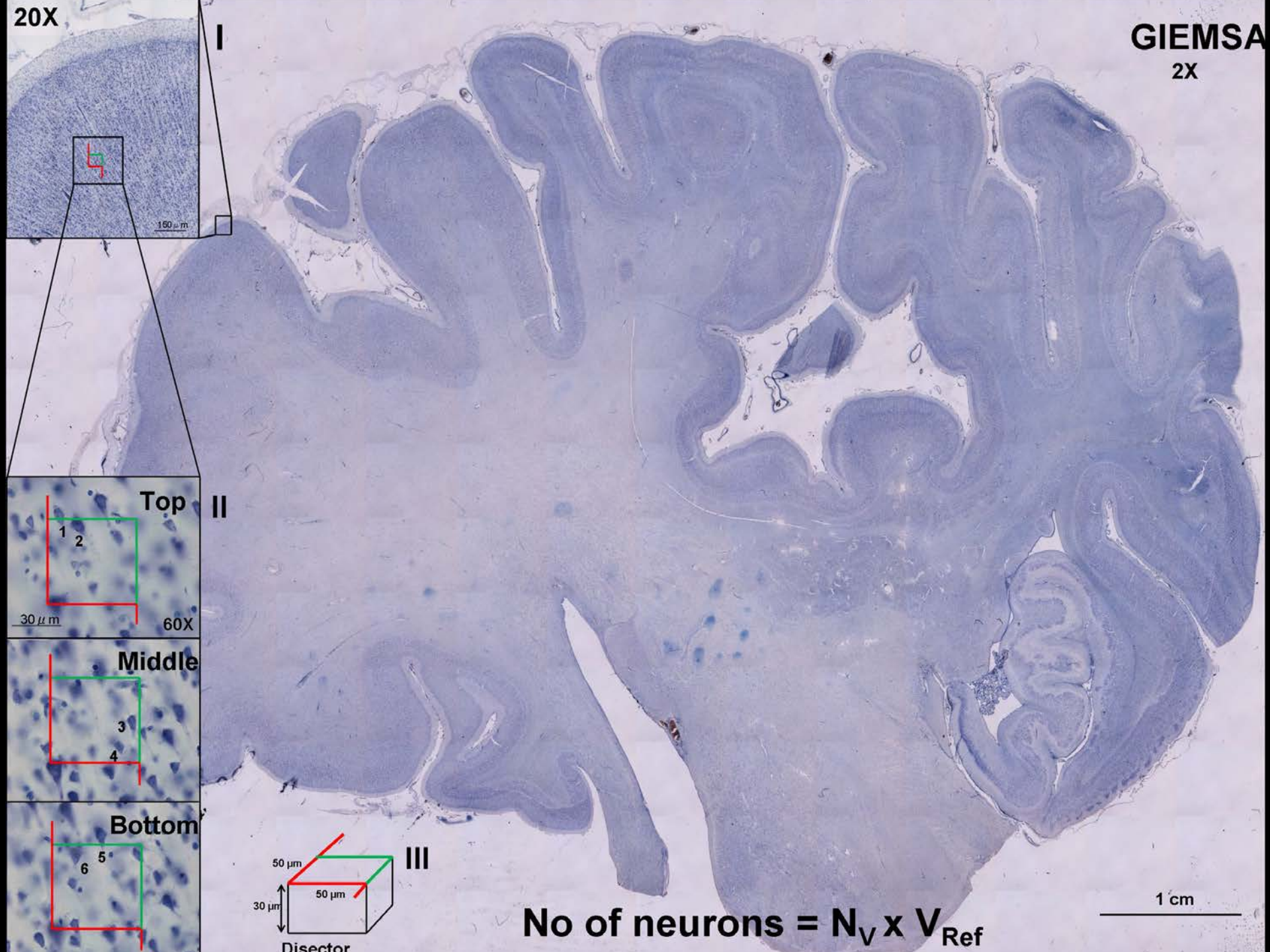
**Figure 2** Regions showing significant grey-matter atrophy in clinically isolated syndrome patients (n=62) compared with controls (n=37) ($p<0.005$, familywise error corrected). Grey-matter atrophy was located in the bilateral thalami, bilateral caudate nuclei, bilateral lenticular nuclei, bilateral insula, bilateral orbitofrontal cortices, bilateral internal temporal regions, posterior cingulate cortex and bilateral cerebellum.

# Brain atrophy occurs across all stages

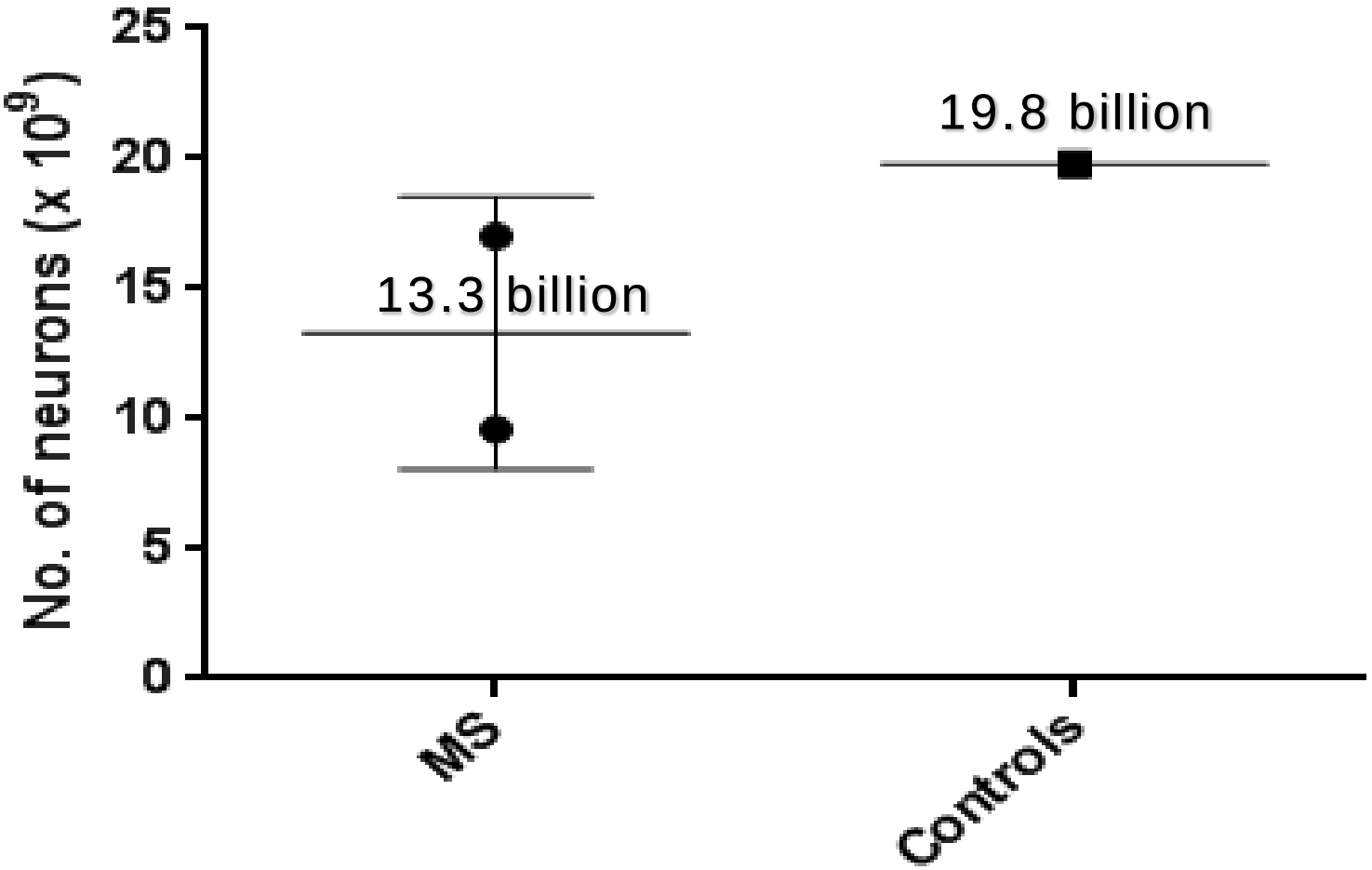
n= 963 pwMS




De Stefano, et al. Neurology 2010


20X
I
150 µm
GIEMSA
2X
Top
II
1
2
30 µm
60X
Middle
3
4
Bottom
5
6
III
50 µm
50 µm
30 µm
Disector
No of neurons = $N_V$ x $V_{Ref}$
1 cm

# Total number of cortical neurons




Carassiti D, et al. ECTRIMS 2013, P425

# The progress of cognitive decline in newly diagnosed MS patients

Hankomäki E, Multanen J, Kinnunen E, Hämäläinen P. The progress of cognitive decline in newly diagnosed MS patients.
Acta Neurol Scand: DOI: 10.1111/ane.12161.


n= 30 MS, n= 37 HC, FU= 6 years

**E. Hankomäki[1,2], J. Multanen[2], E. Kinnunen[2], P. Hämäläinen[3]**

[1]Ludus-Neuropsychology, Helsinki, Finland; [2]Department of Neurology, Hyvinkää hospital, Hyvinkää, Finland; [3]Masku Neurological Rehabilitation Centre, Masku, Finland

Six years after diagnosis no decline in overall cognitive function, *however* significant changes in divided attention (dual task) and information processing speed (SDMT).

# The paradigm shift: Treat early

- Early active therapy for people with MS, as practiced in rheumatology
- Potent immunomodulatory agents for early treatment are desired
- Immune system rebooters vs. reversible immunomodulators (β-IFN, GLAT, Natalizumab, Fingolimod, Dimethyl-Fumarate, Teriflunomide, …)

## Evidence from monoclonal antibody therapy

**Relapsing SPMS** | **Relapsing Remitting MS**

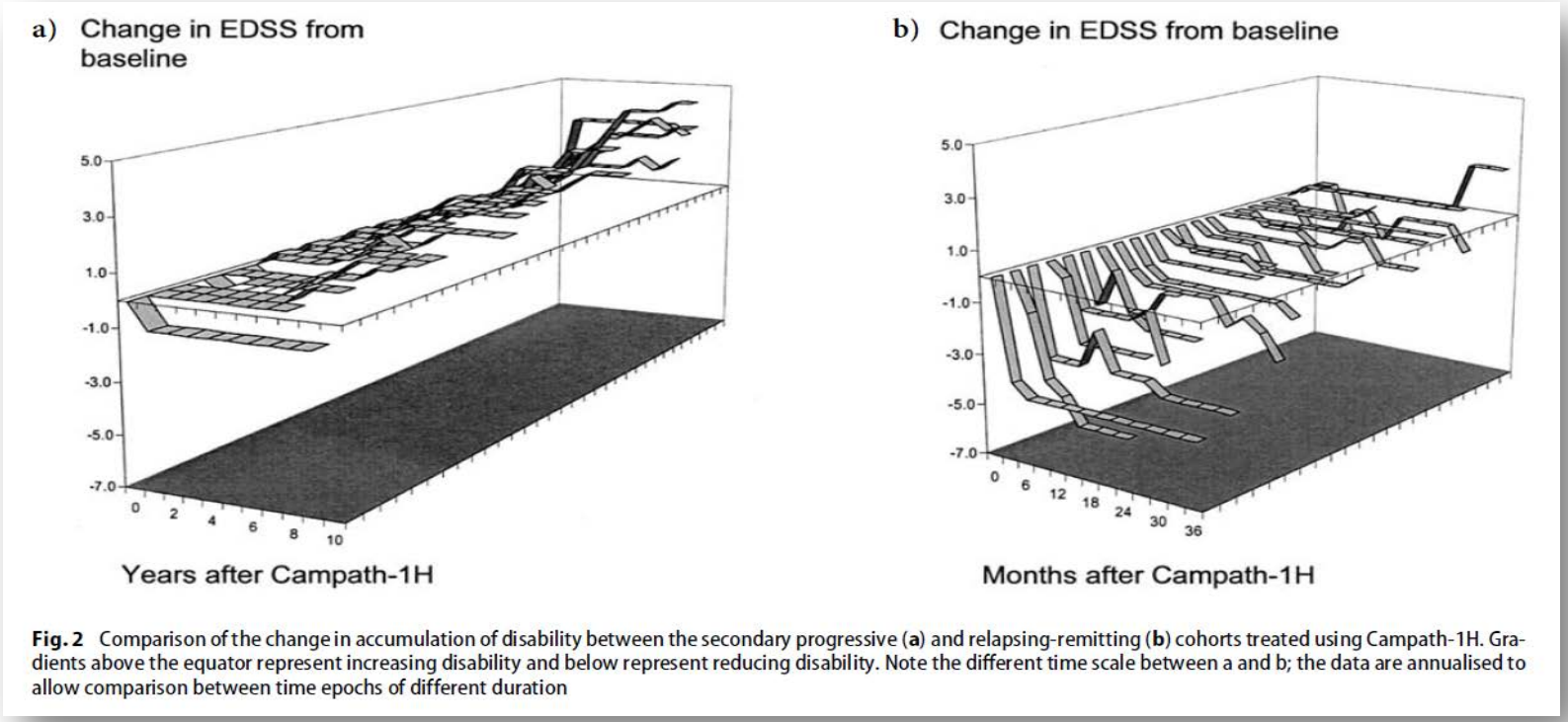
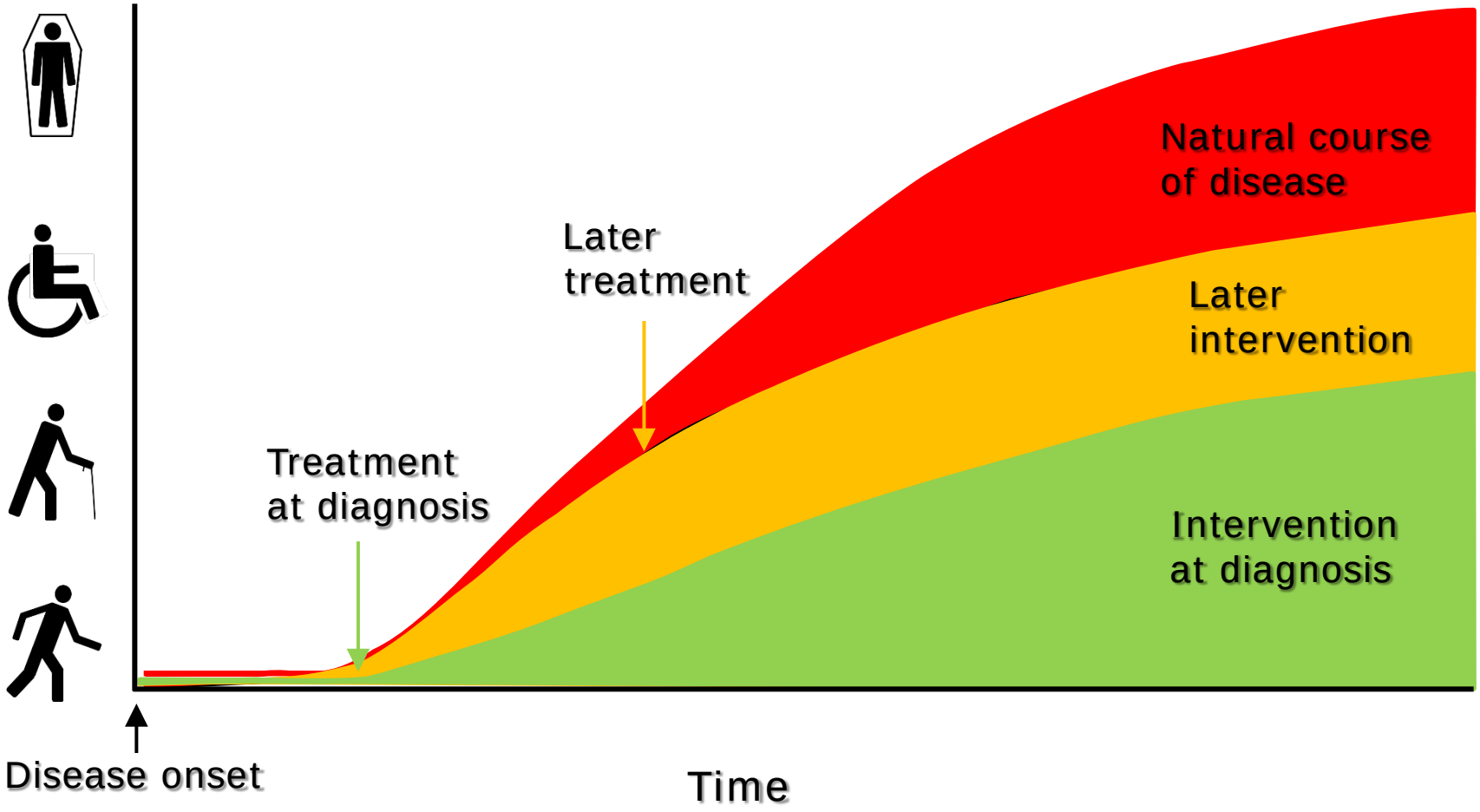



**Fig. 2** Comparison of the change in accumulation of disability between the secondary progressive (**a**) and relapsing-remitting (**b**) cohorts treated using Campath-1H. Gradients above the equator represent increasing disability and below represent reducing disability. Note the different time scale between a and b; the data are annualised to allow comparison between time epochs of different duration

Coles et al., J Neurol 2006

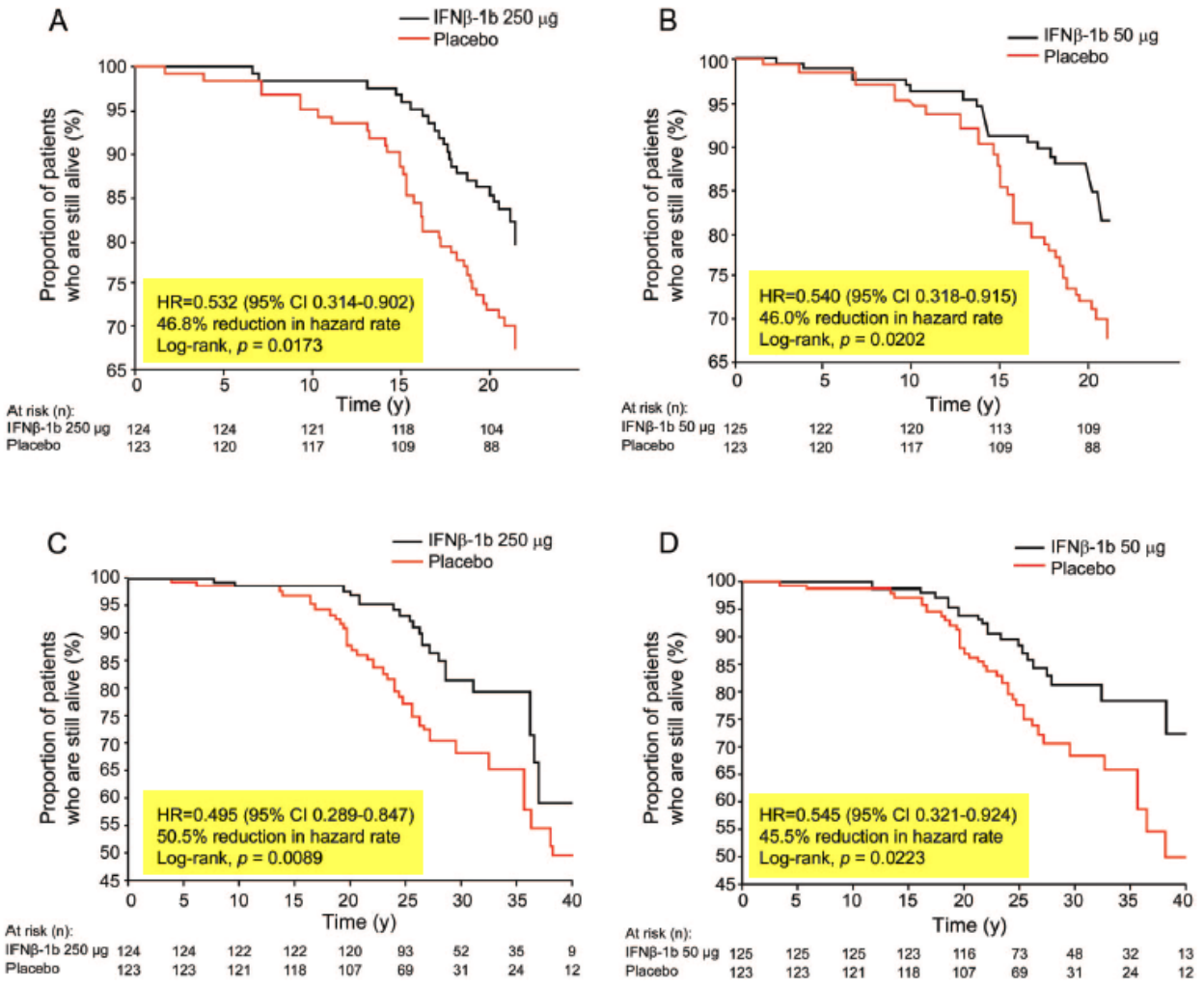
# Treat early


Natural course of disease
Later treatment
Later intervention
Treatment at diagnosis
Intervention at diagnosis
Disease onset
Time

# Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFN-β1b trial

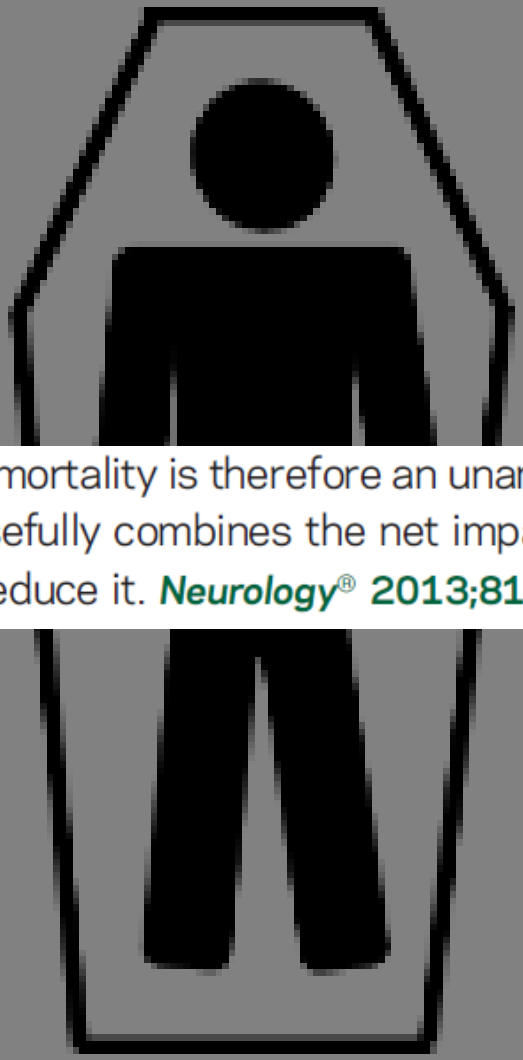
Randomization > death

Onset > death




Survival from pivotal randomized controlled trial randomization over 21 years is shown for interferon β-1b (IFNβ-1b) 250 μg vs placebo (A) and IFNβ-1b 50 μg vs placebo (B). Time from onset of clinical symptoms to death is shown for IFNβ-1b 250 μg vs placebo (C) and IFNβ-1b 50 μg vs placebo (D). Hazard ratios (HRs) and 95% confidence intervals (CIs) are estimated using Cox proportional hazard models without stratification.

Goodin et al. Neurology 2012;78:1315-1322.



Notwithstanding its long latency, mortality is therefore an unambiguously valid long-term outcome in randomized controlled trials. It usefully combines the net impact of treatment efficacy on longevity and adverse events, which may reduce it. ***Neurology*® 2013;81:184-192**

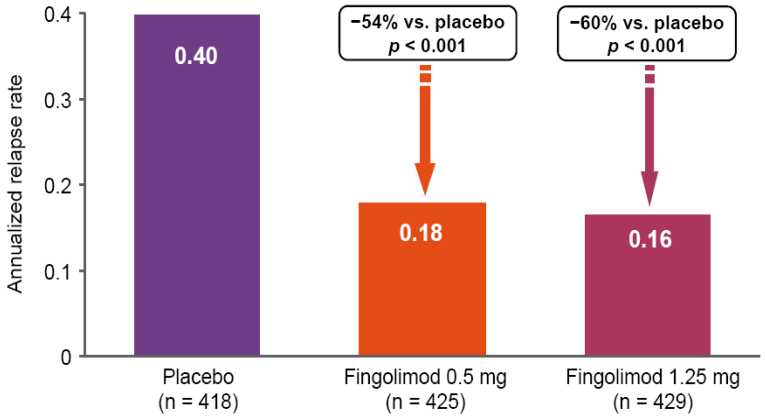
Scalfari, et al. Neurology 2013

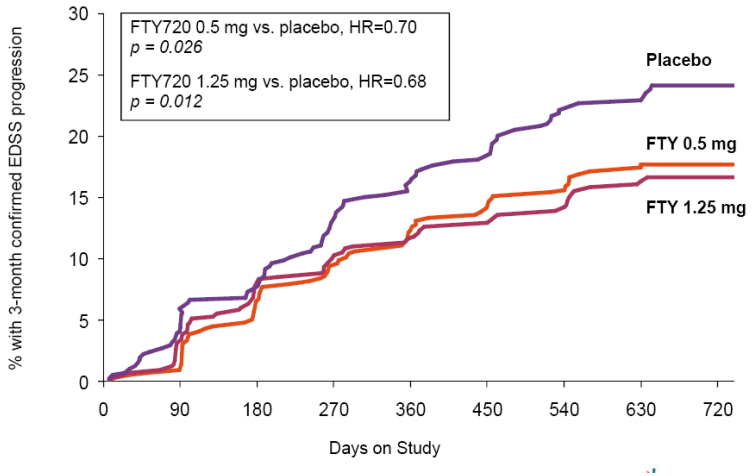
# Challenging the TSA

- Predicting disease course
- Efficacy of DMT
- Side effects/safety of DMT
- Cost of DMT

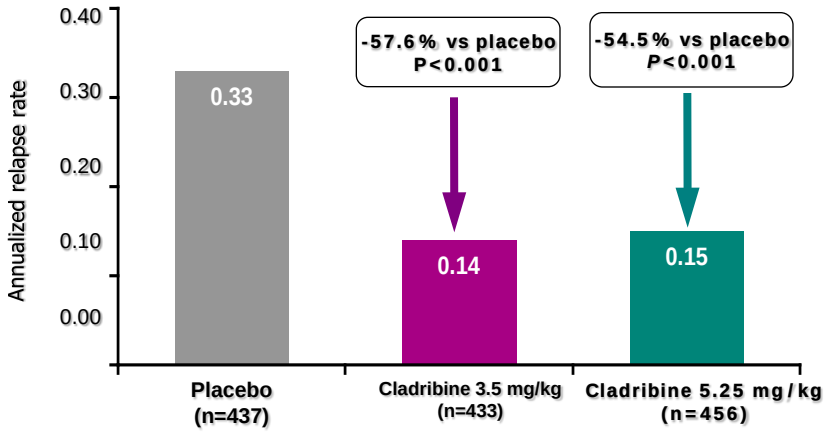
# Results of pivotal trials of oral drugs in relapsing MS

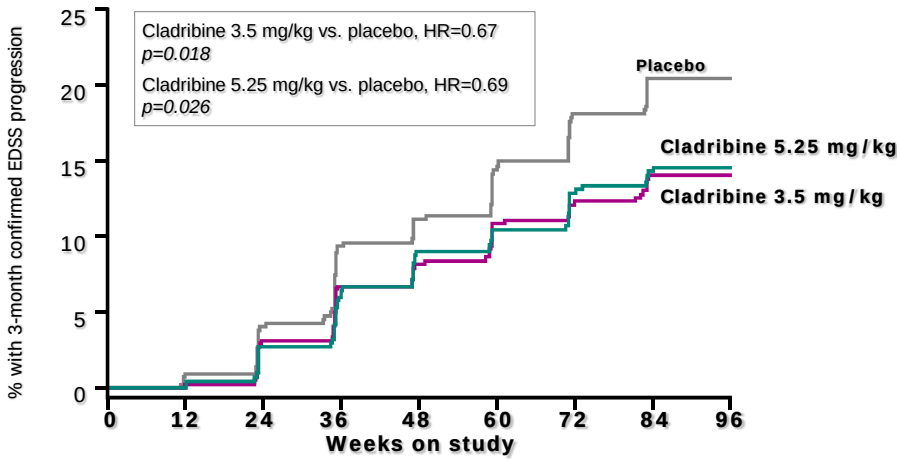
## Fingolimod vs. placebo (n=1272)



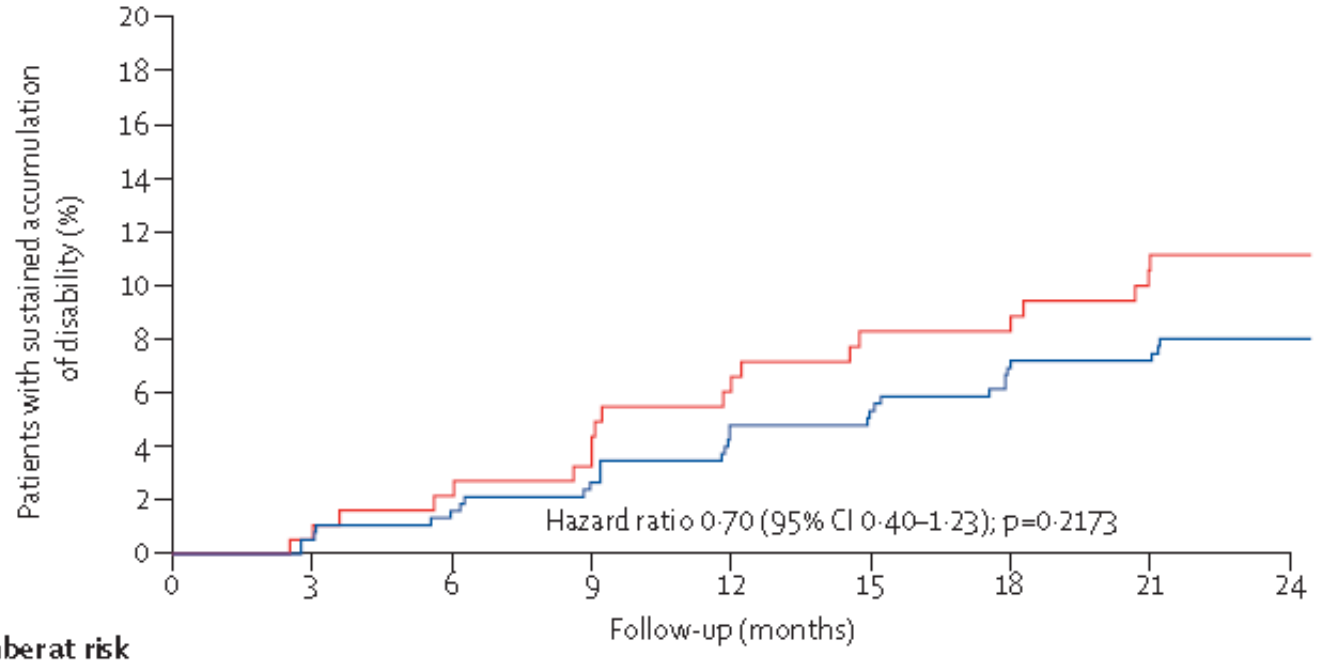




## Cladribine vs. placebo (n=1326)



# ‘Imperfections’ of current DMTs




Cohen, et al. Lancet 2012

PRESS RELEASE

genzyme
A SANOFI COMPANY

**European Commission Approves Genzyme’s Multiple Sclerosis Treatment Lemtrada™ (alemtuzumab)**

*- Follows Recent European Commission Approval of Multiple Sclerosis Treatment Aubagio® (teriflunomide)*

*- Approvals Set the Stage for Launches Throughout EU and Strongly Position Genzyme as a Committed Partner to the MS Community*

Is there an assumption that DMTs currently available are sufficiently efficacious AND safe such that no further drugs are needed in the early stages of RMS?

# Challenging the TSA

- Predicting disease course
- Efficacy of DMT
- Side effects/safety of DMT
- Cost of DMT

# Adverse effects of highly effective DMTs

- Potentially fatal infections (natalizumab, fingolimod)
- Gastro-intestinal, flushing (DMF), PML (fumaderm)
- Hair loss, liver toxicity, teratogenecity, (teriflunomide)
- 20-30% secondary autoimmunity (alemtuzumab)
- Lymphopenia, ?malignancies

J Neurol (2009) 256:554–562
DOI 10.1007/s00415-009-0084-2

ORIGINAL COMMUNICATION

n= 651 pwMS

F. Reed Johnson
George Van Houtven
Semra Özdemir
Steve Hass
Jeff White
Gordon Francis
David W. Miller
J. Theodore Phillips

# Multiple sclerosis patients' benefit-risk preferences: Serious adverse event risks versus treatment efficacy

Maximum acceptable annual risk (MAR)

| Benefit | PML | Liver Failure | Leukemia |
|---|---|---|---|
| | Mean (Lower Bound, Upper Bound) | Mean (Lower Bound, Upper Bound) | Mean (Lower Bound, Upper Bound) |
| Slow Progression Benefit* | 0.31 % (0.26, 0.36) | 0.30 % (0.23, 0.36) | 0.35 % (0.25, 0.44) |
| Clinically Relevant Benefit** | 0.38 % (0.32, 0.43) | 0.39 % (0.32, 0.46) | 0.48 % (0.39, 0.58) |
| Largest Tested Benefit*** | 0.74 % (0.68, 0.79) | 1.02 % (0.92, 1.13) | 1.08 % (0.99, 1.18) |

* Number of relapses in the next 5 years reduced from 4 to 1, time until next disability progression increased from 5 years to 8 years
** Number of relapses in the next 5 years reduced from 4 to 1, time until next disability progression increased from 3 years to 5 years
*** Number of relapses in the next 5 years reduced from 4 to 0, time until next disability progression increased from 1 year to 8 years

# Adherence to injectable DMTs

## Discontinuation rates (β-IFN): 17% - 46%

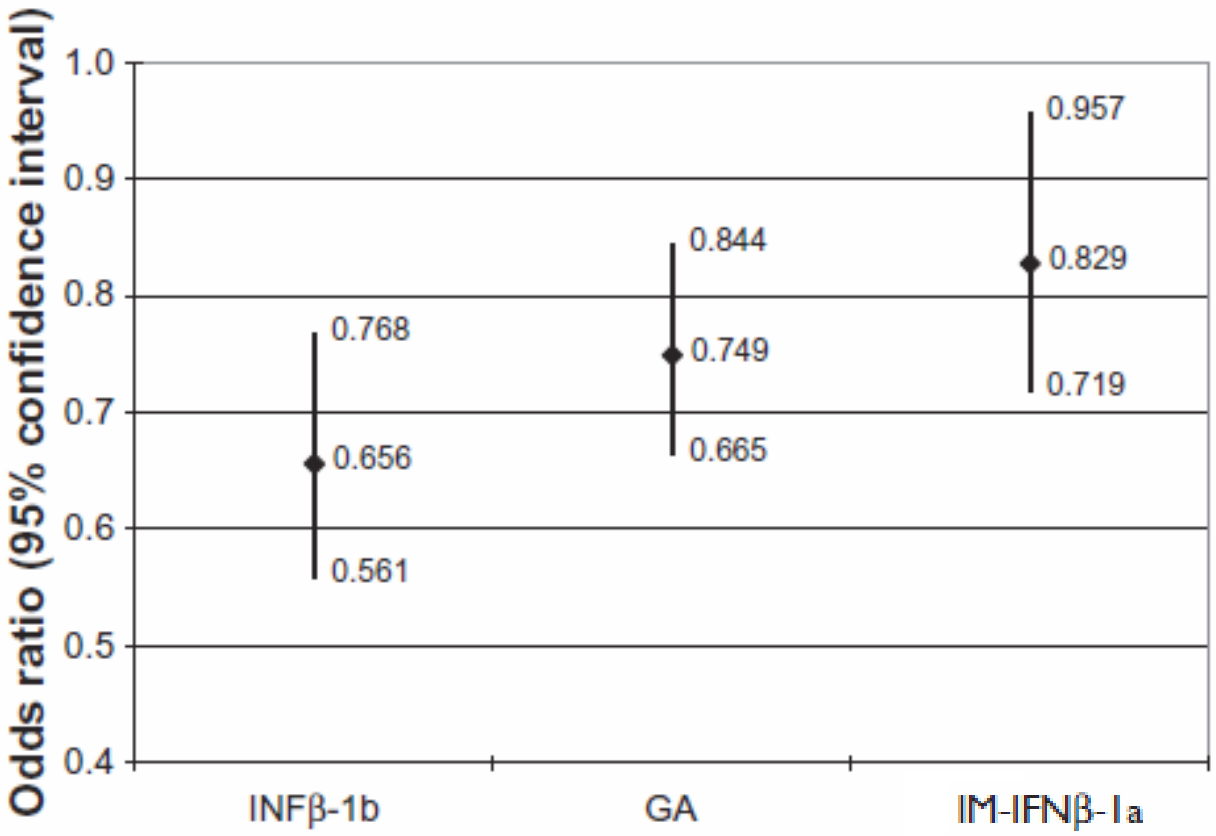



**Figure 2** Regression-adjusted odds ratios of adherence compared with IM-IFNβ-1a: all patients.

Pozilli C, et al. J Neurol Sci 2011; Halpern R, et al. Patient Prefer Adherence 2011

# Key document

NHS
Commissioning Board

**Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS)**

**April 2013**

**Reference : NHSCB/D04/P/a**

# Start criteria 2013 NHS Commissioning Board

## Natalizumab

- ≥ 2 *disabling* relapses over past year
- ≥ 1 $Gd^+$ lesions or increase in $T_2$ lesion load compared to previous MRI unless comparator MRI unavailable or assessment of Gd enhancement unreliable as patient treated with steroids at time of scan
- Either no previous DMD or receiving β IFN

# AAN guideline – natalizumab

...natalizumab be reserved for use in pwRRMS who have failed other therapies either through continued disease activity *or medication intolerance*, or who have a particularly aggressive initial disease course...

Goodin, et al. Neurology 2008

# Start criteria 2013 Commissioning Board

## Fingolimod

- Patients have *unchanged* or *increased* relapse rate or *ongoing severe* relapses compared with previous year despite Tx with β IFN
- Fingolimod is provided at discounted price as part of patient access scheme

Neurology Clinical Practice

# US practice – fingolimod

- Approved as 1st line Tx for pwRRMS
- Option when Tx response is poor *or* *intolerable side effects* on IFN or GA
- particularly in pwRRMS seropositive for JC virus

Hyland & Cohen, Neurol Clin Pract 2011

# Challenging the TSA

- Predicting disease course
- Efficacy of DMT
- Side effects/safety of DMT
- Cost of DMT

# The cost of MS

| Country | Total Direct Medical Cost (2007 Int'l Dollars) | Total Direct Non-Medical Cost (2007 Int'l Dollars) | Total Indirect Costs (2007 Int'l Dollars) | Total Cost (2007 Int'l Dollars) |
|---|---|---|---|---|
| Australia | $18,809 | $16,167 | $6,890 | $41,866 |
| Austria | $20,738 | $10,010 | $17,569 | $48,317 |
| Belgium | $13,746 | $10,108 | $13,267 | $37,121 |
| Canada | $3,162 | $2,421 | $15,932 | $21,514 |
| France | $6,078 | $4,718 | $5,582 | $16,378 |
| Germany | $20,246 | $6,986 | $19,946 | $47,178 |
| Italy | $13,001 | $19,225 | $13,237 | $45,462 |
| Netherlands | $9,845 | $8,910 | $15,849 | $34,605 |
| Norway | $10,995 | $12,472 | $31,023 | $54,489 |
| Poland | $3,495 | $2,713 | $11,423 | $17,631 |
| Spain | $15,973 | $16,498 | $11,544 | $44,015 |
| Sweden | $15,431 | $21,607 | $17,427 | $54,465 |
| Switzerland | $10,211 | $13,365 | $14,473 | $38,048 |
| → United Kingdom | $10,969 | $19,858 | $17,995 | $48,822 |
| United States | $23,975 | $7,844 | $18,888 | $50,707 |
| Weighted average[a] | $13,198 | $11,383 | $16,755 | $41,335 |

[a] Weighted by prevalence of MS in each country.

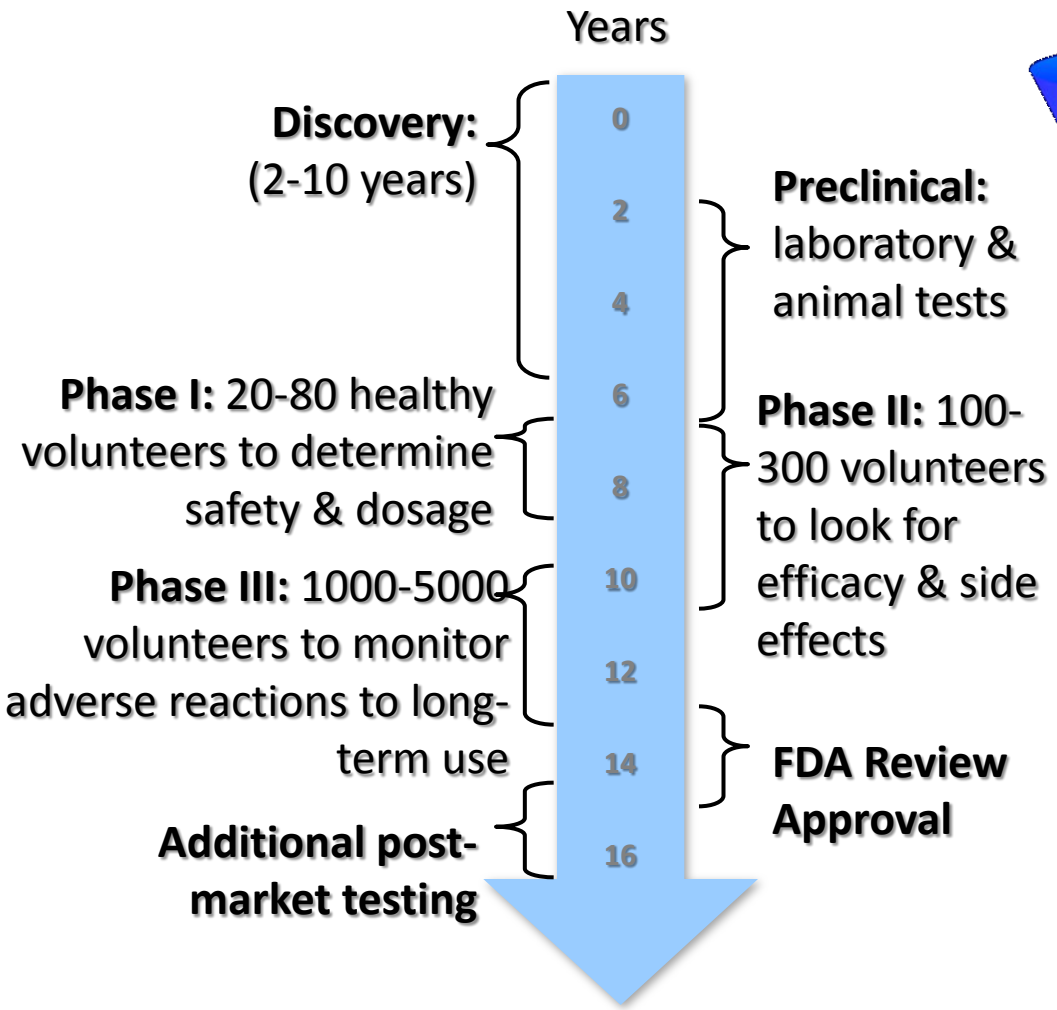
MSIF: Global economic impact of multiple sclerosis, 2010.

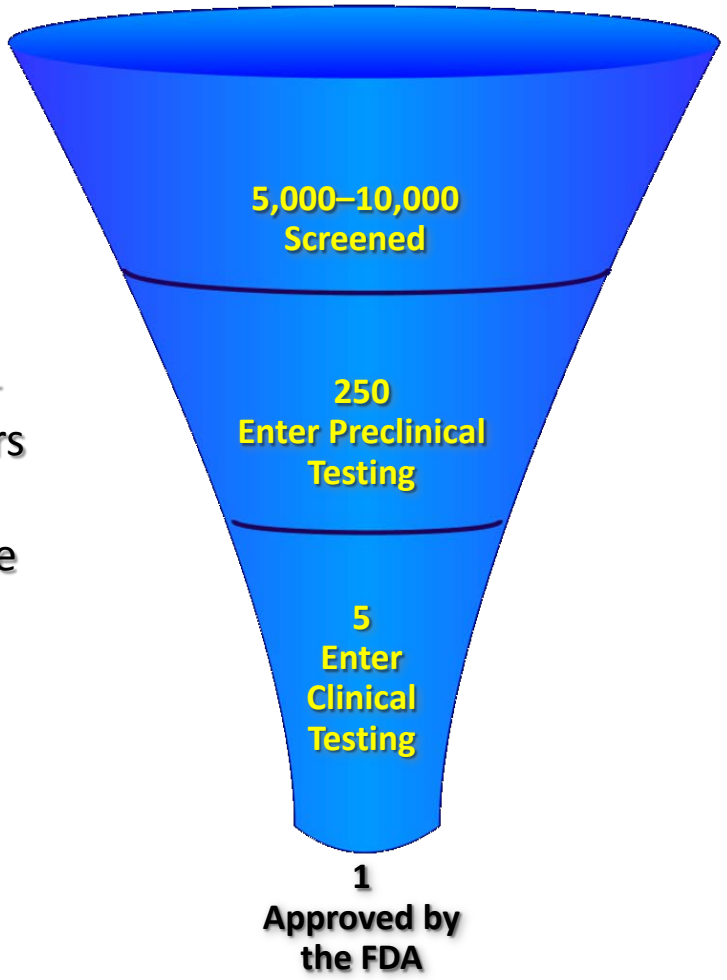
# The cost of MS

- Over 10,000 pwRMS in the UK are currently on disease modifying treatments (DMTs)
- Annual cost, including enabling activities such as employing MS nurses: >£50m
- Current annual cost of DMTs (drug only) in the UK:
  - Glatiramer acetate (Copaxone) £6,800
  - Interferon β-1b (Betaferon) £7,200
  - Interferon β-1a (Avonex) £8,500
  - Interferon β-1a (Rebif) £10,500
  - Natalizumab (Tysabri) £14,690
  - Fingolimod (Gilenya) £19,162 (BNF)

Raftery, BMJ 2010

# ‘Big Pharma’ Model




Source: DiMasi et al. 2003, Tufts

**Net Cost: $802 million invested over 15 years**

# The business of MS

Industry Overview

Equity | United States | Biotechnology
28 February 2013

Bank of America Merrill Lynch

Biotechnology

## Multiple sclerosis primer

"No disruptive MS products in late stage development"

### MS market to nearly double by 2018

In this industry report, we provide a detailed market history, commercial outlook, and development review for multiple sclerosis (MS) drugs.[1] We estimate that global sales of MS therapies in 2012 were $13.7B, growing at an 11% CAGR over the last three years, driven primarily by well above industry average US price increases. Introduction of new oral therapies to date has not led to increased numbers of patients treated, but instead has caused steady market share erosion of older injectable interferon therapies. As we look forward, we expect continued steady market share shifts from interferons to oral therapy, and we predict a modest deceleration in market growth as US pricing strength moderates. Our global MS market est of $23B in 2018 is an 8% CAGR. Our new MS market model predicts share shifts from 2012 to 2018 as follows: BIIB 33% to 48%, TEVA 29% to 21%, NVS 9% to 10%, SNY 0% to 9%, Bayer 11% to 3%, Merck KGa 18% to 9%. Biggest risks to our projections include: (1) collapsing of MS drug pricing, from potential generic Copaxone entry or oral generics in 2018-2019; (2) unexpected safety issues for Tecfidera; (3) market hesitancy to ascribe Avonex long term safety to Peg-Avonex.

2012: $13.7Bill

2018: $23Bill

# Conclusions

- All current DMTs work best when used early in pwRMS
- New generation drugs are an improvement compared to current DMTs, and adverse effects are manageable *despite* some of them having a *"profound effect on the immune system and thus potential serious safety issues"*
- Nevertheless – or precisely for that reason – the evidence is not in favour of a TSA for trials of new DMTs
- New drugs should rather be tested in head-to-head studies or multi-arm design trials (Chataway)
- Not only severe and/or longterm side effects should be considered, but also adverse effects with significant impact on the *current* life of pwRMS
- A TSA would delay development of new DMTs for pwMS and lead to a further rise in cost. Whilst this may cause some problems for 'Big Pharma' it would certainly destroy attempts at repurposing of potentially effective and yet affordable drugs