WCN 2015

XXII World Congress of Neurology
Santiago - Chile 2015
Changing Neurology Worldwide
Santiago, Chile, October 31 - November 5, 2015

Case-study based therapeutic update of MS

W M Carroll

Dept Neurology Sir Charles Gairdner Hospital, Australian Neuromuscular Research Institute, Centre for Neuromuscular and Neurological Disorders, University of Western Australia, Queen Elizabeth II Medical Centre

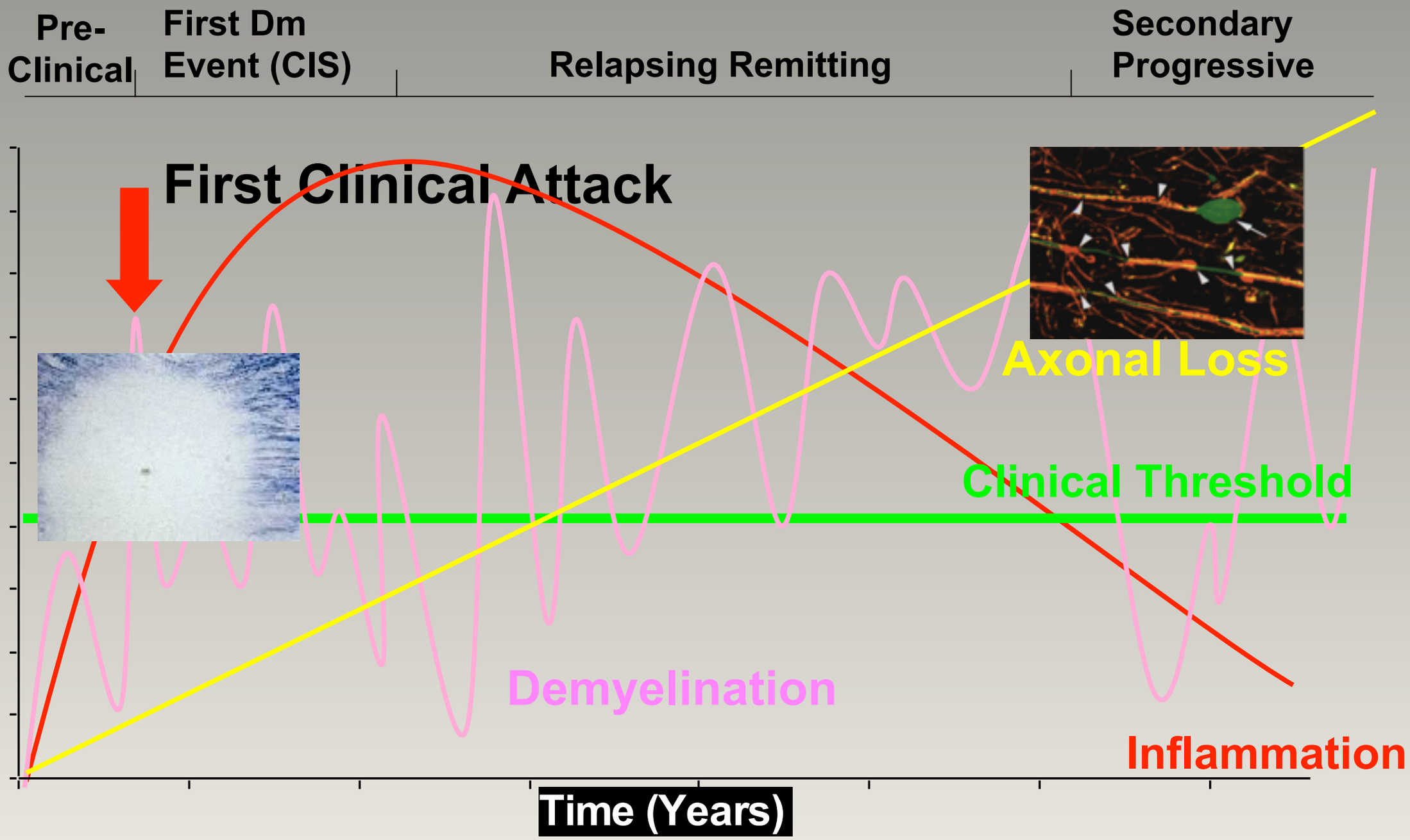
Multiple Sclerosis TC 14

Outline of Update

Goals	Minimise disability Prevent disability Reverse disability
Means	Disease suppression Disease elimination
Measurement	Disease activity Treatment endpoint(s) EDSS-plus etc

Redefining evidence based interpretations of disease activity to permit continuing treatment.

Clinical Course and Pathology



Goals

Minimise, Prevent or Reverse disability

Treat early with most effective agent and most acceptable Risk:Benefit ratio

Disease activity, age of patient, duration of disease, extent and distribution of disability

Usually neurologist selects most effective agent(s)
and patient decides on most acceptable risk:benefit

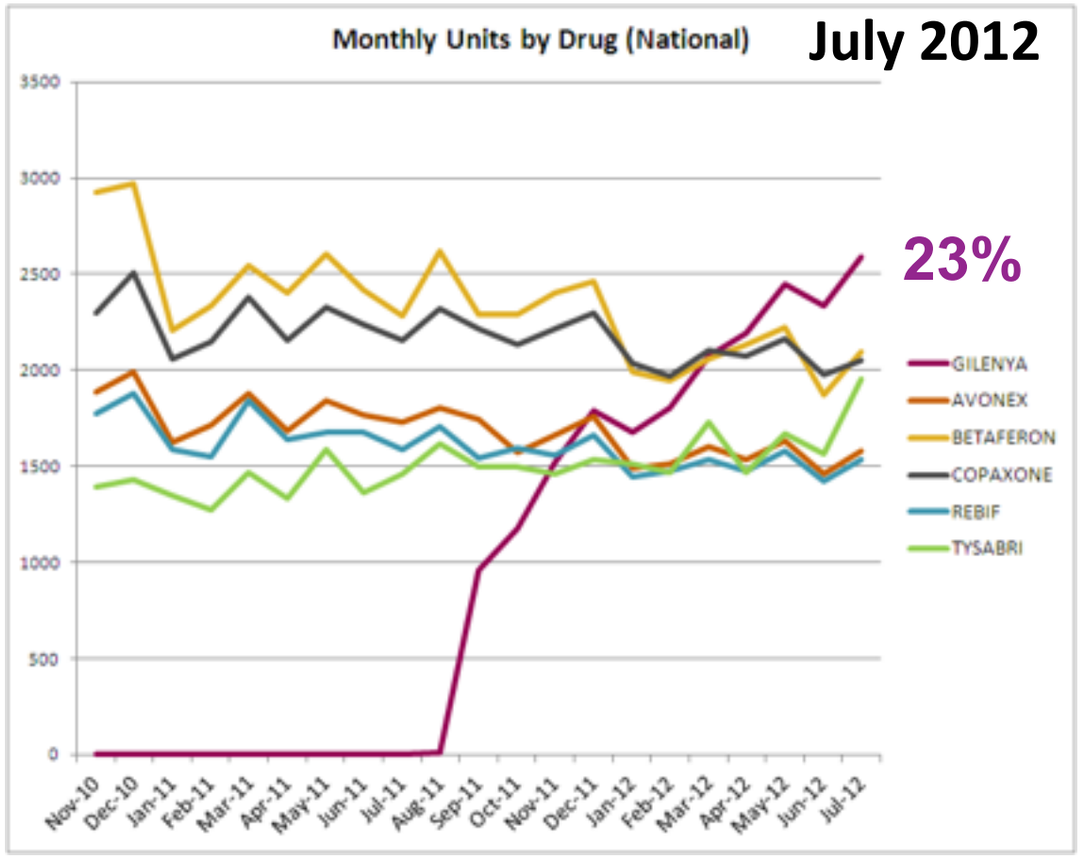
Accessible DMD in Australia

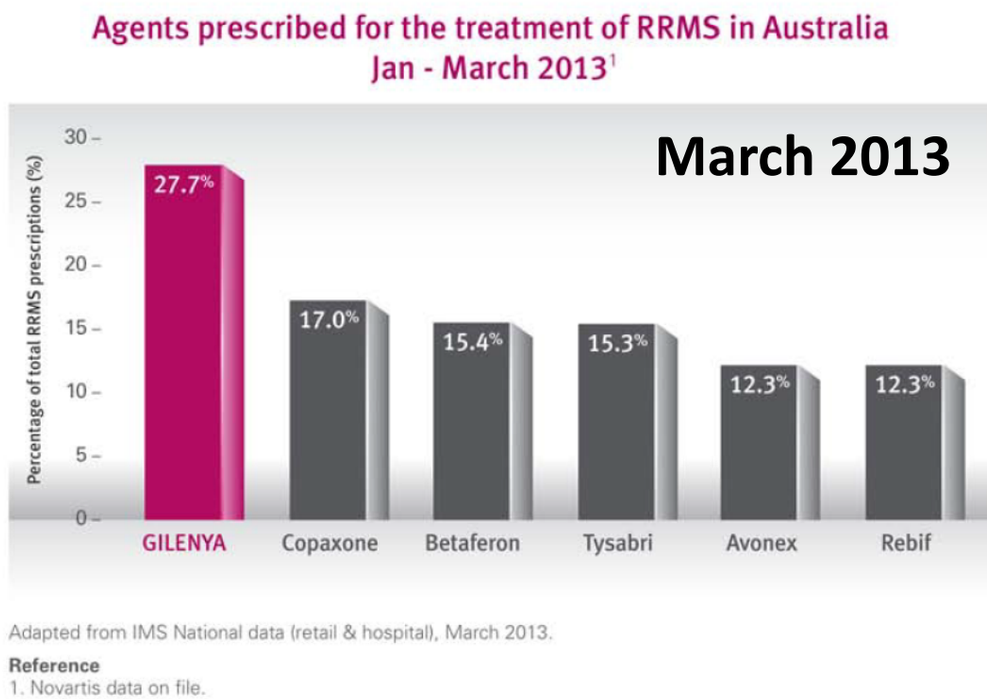
Monoclonals/ Biologics
Natalizumab
Alemtuzumab
Rituximab
Ocrelizumab

Orals
Fingolimod
Difumarate
Teriflunomide

Injectables
Interferon B-1b sc
Interferon B-1a sc
Interferon B-1a im
Glatiramer Acetate

Immunosuppressants
Mitoxantrone
Cladribine

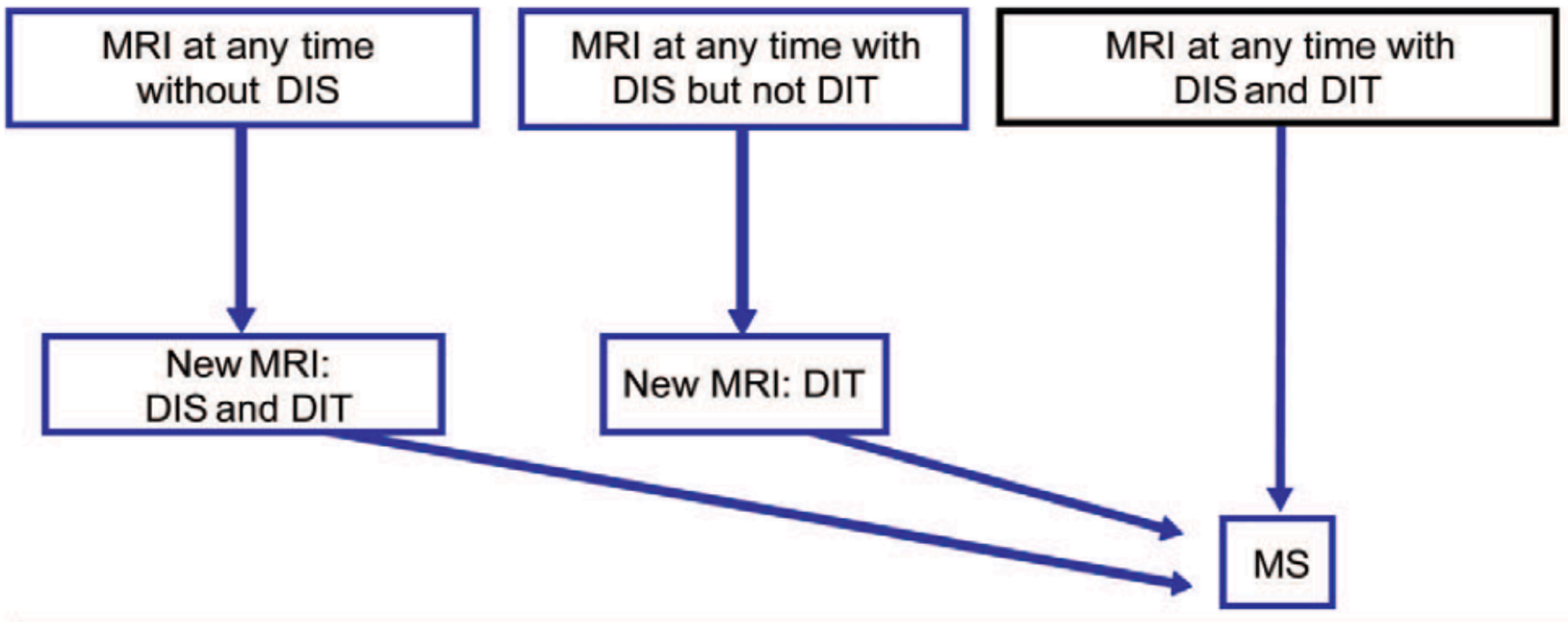




MRI criteria for MS in patients with clinically isolated syndromes

Montabaln X et al Neurology 2010;74:427-434

New proposed diagnostic algorithm in patients with typical clinically isolated syndromes (CIS)



DIS	DIT
≥1 asymptomatic lesion in each of ≥2 characteristic locations: PV, JC, PF, spinal cord	(i) Simultaneous presence of asymptomatic Gd enhancing and non-enhancing lesion(s) at any time (ii) A new T2 and/or Gd-enhancing lesion on follow up MRI irrespective of timing of baseline scan

This algorithm only applies to patients with typical CIS, aged 14 to 50 years and after having performed a complete diagnostic workup. Gd = gadolinium-enhancing lesion; PV = periventricular; JC = juxtacortical; PF = posterior fossa; BS = brainstem; SC = spinal cord; DIS = dissemination in space; DIT = dissemination in time.

2010 Revisions to the McDonald Criteria.

Polman et al (2011) Annals of Neurology Volume 69, 292–302

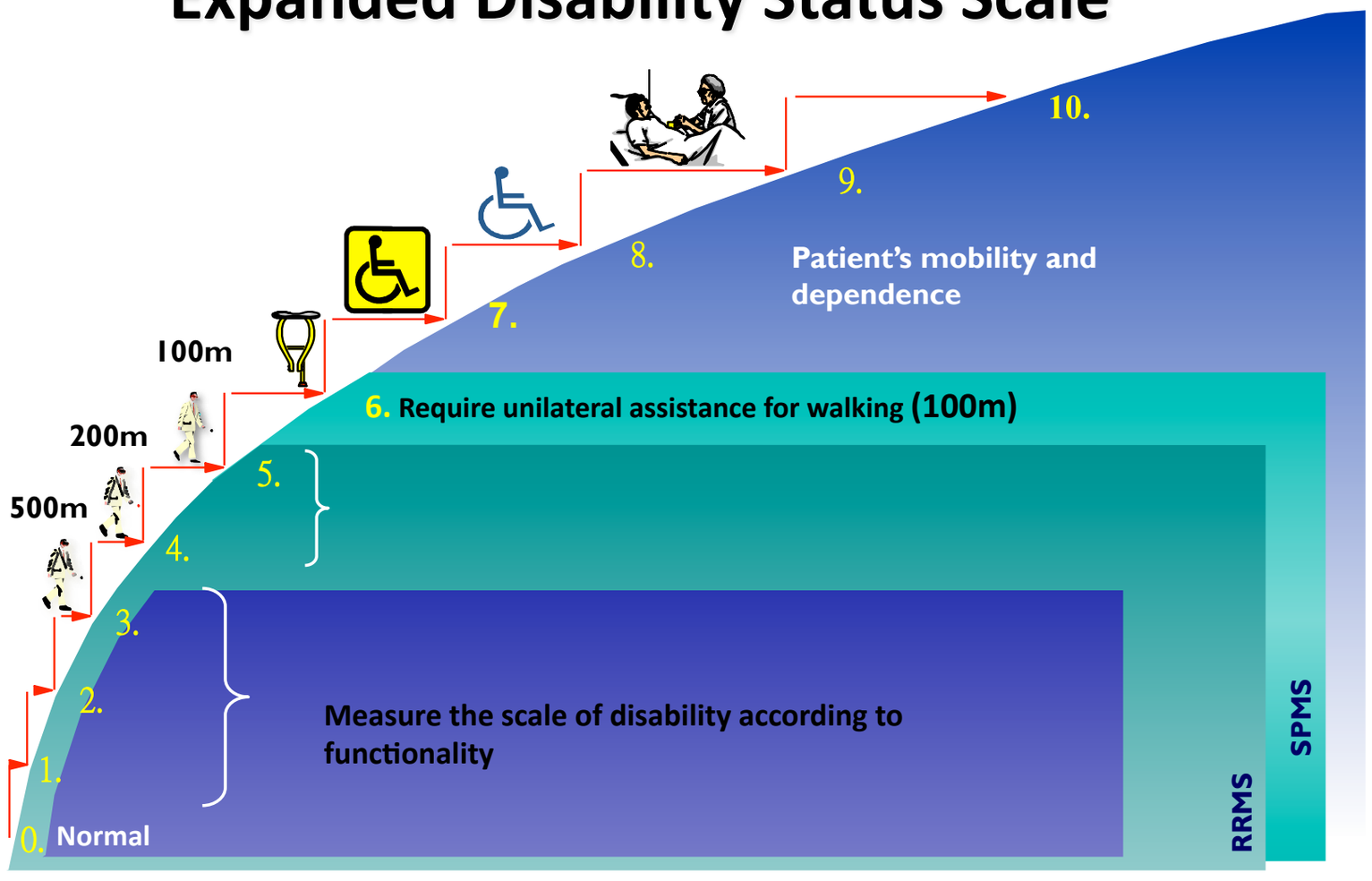
Benign* and Aggressive Disease

Retrospective (Biomarkers required)

(*Everyone's hope)

Aggressive Disease

- Rapid accumulation of disability
- ≥ 2 relapses in the past 12 months
  and/or
- ≥ 2 points progressive increase in EDSS in the past 12 months
- Other pointers; failure to recover fully from relapse, T1 black holes



Adapted from Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33:1444-1452

Evidence favours early treatment

The human experiments

CIS studies BENEFIT etc
21yr Long Term Follow-up

Alemtuzumab CAMMS 223, CARE-MS I and II, 5 yr EXTENSION

Natalizumab AFFIRM, SENTINEL & STRATA (5 yr extension)

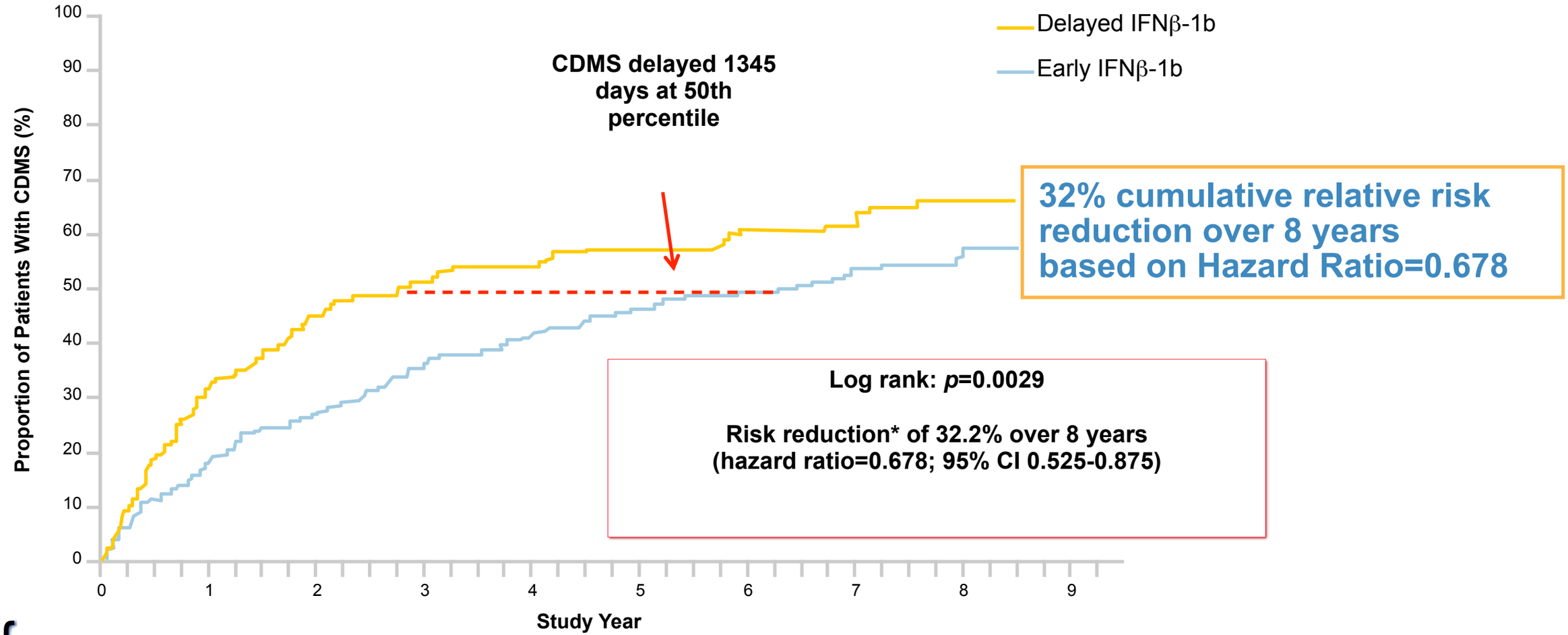
Ocrelizumab OPERAI/II ORATORIO*

All demonstrate the same effect.
Earlier treatment equates to potentially better outcome

* Primary Progressive MS

BENEFIT trial

Early Treatment Reduced the Risk of CDMS Over 8yrs



Number at Risk*											
Delayed IFNβ-1b	n=	176	116	84	68	63	49	41	40	15	0
Early IFNβ-1b	n=	292	224	194	165	152	124	86	74	29	0

BENEFIT trial at 11 yrs: Cognitive Function

Foley FW et al for BENEFIT Study Group. ECTRIMS 2015

All patients asked to complete a Cognitive Assessment including PASAT3 (longitudinal since baseline) and SDMT (cross sectional)

278 of the original 468

223 PASAT3, 211 SDMT & 223 Cognitive fatigue *

*standard 90s PASAT time divided into 30s intervals

- Early treatment group had higher mean PASAT 3 scores at yr 11 and throughout study
- Early 52.9 vs late 52.0 p=007 (no time x treatment interaction effects as these emerged early in trial and persisted)
- No cross sectional differences in the SDMT at Yr 11. Median score 53 for both early and late groups. Comparable to other RRMS groups.
- No evidence of Cognitive fatigue in either group

Further confirmation of early treatment benefit of RRMS

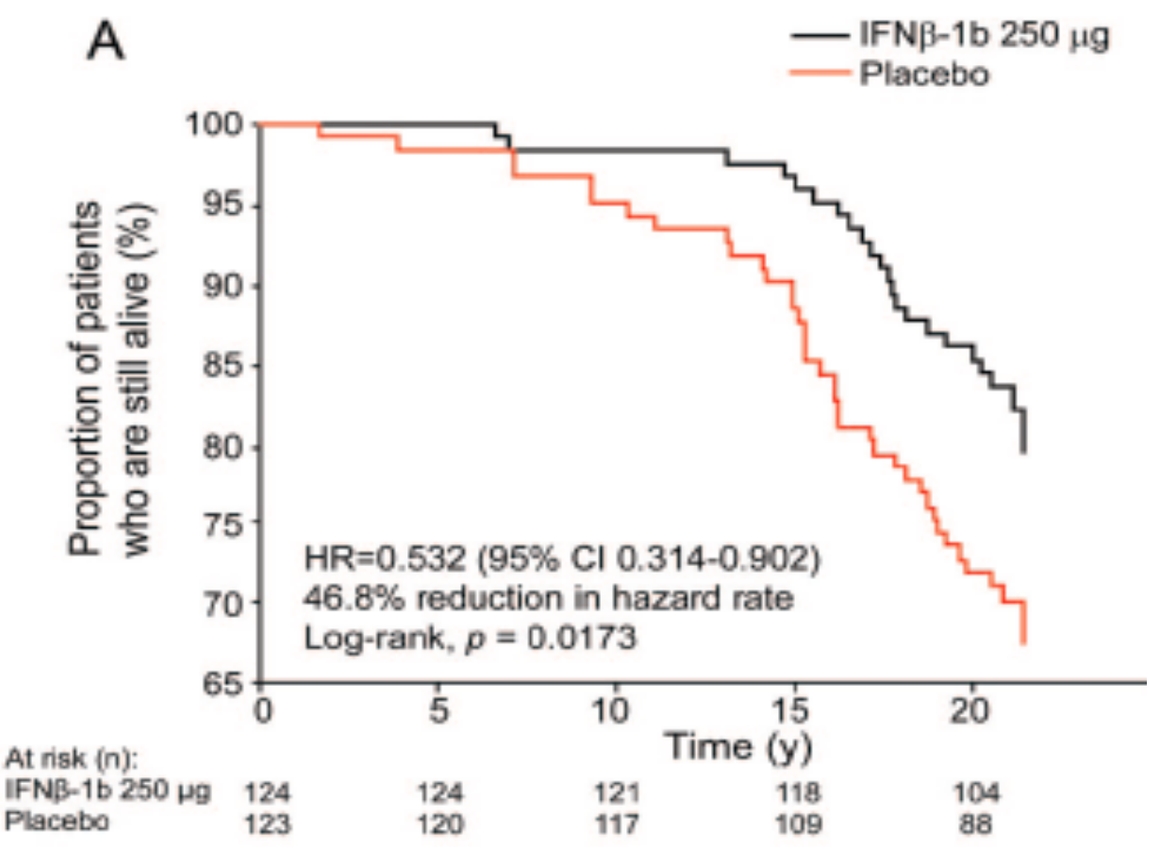
Also matched by ARR and EDSS data

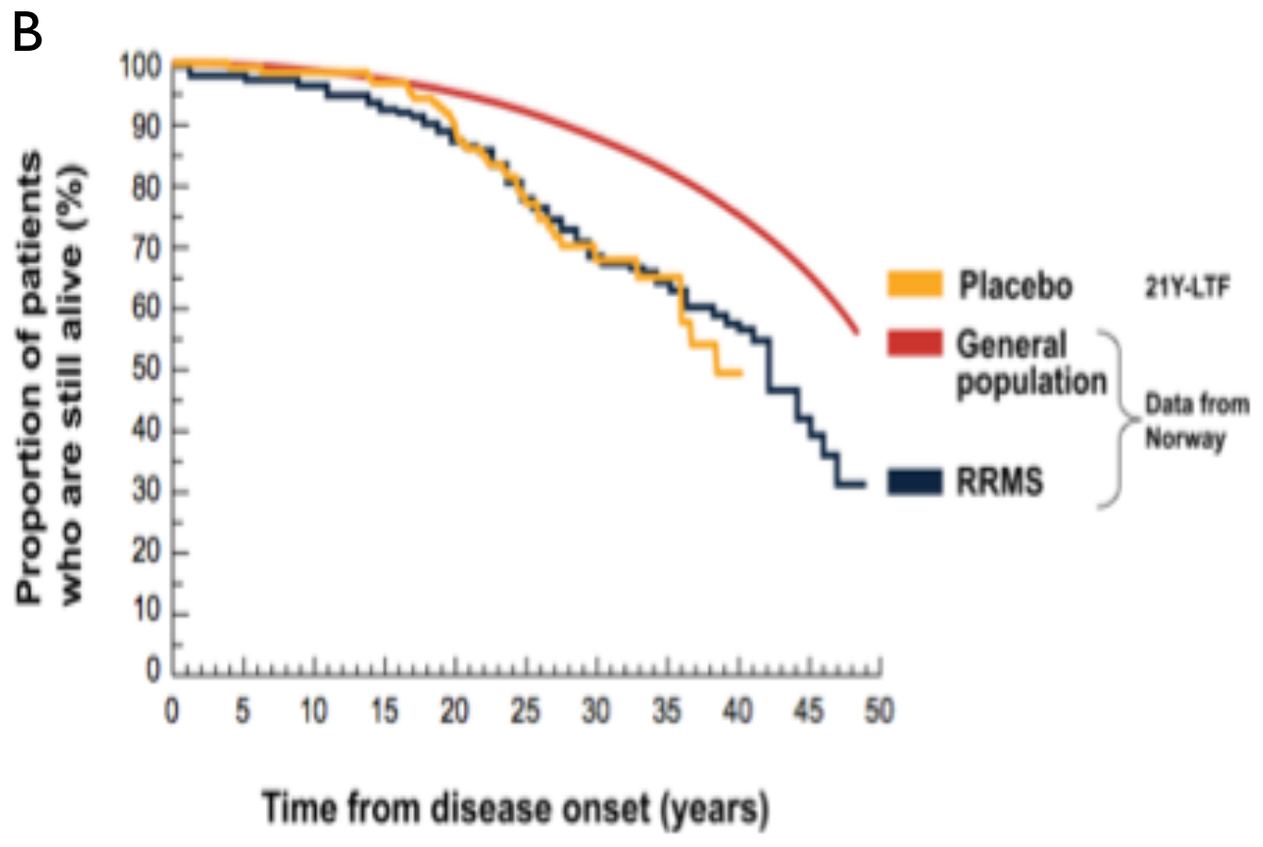
Survival in MS

A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial

Goodin et al., Neurology 2012

- **evidence that reducing disease activity using a modestly effective therapy EARLY in the disease affects survival**
- **98.4% follow-up for 21 years of the original IFNB-1b RRMS pivotal study**
- **risk of death from all causes reduced by 47% in the actively treated arms (with 5 years more of active treatment with IFNβ-1b)**



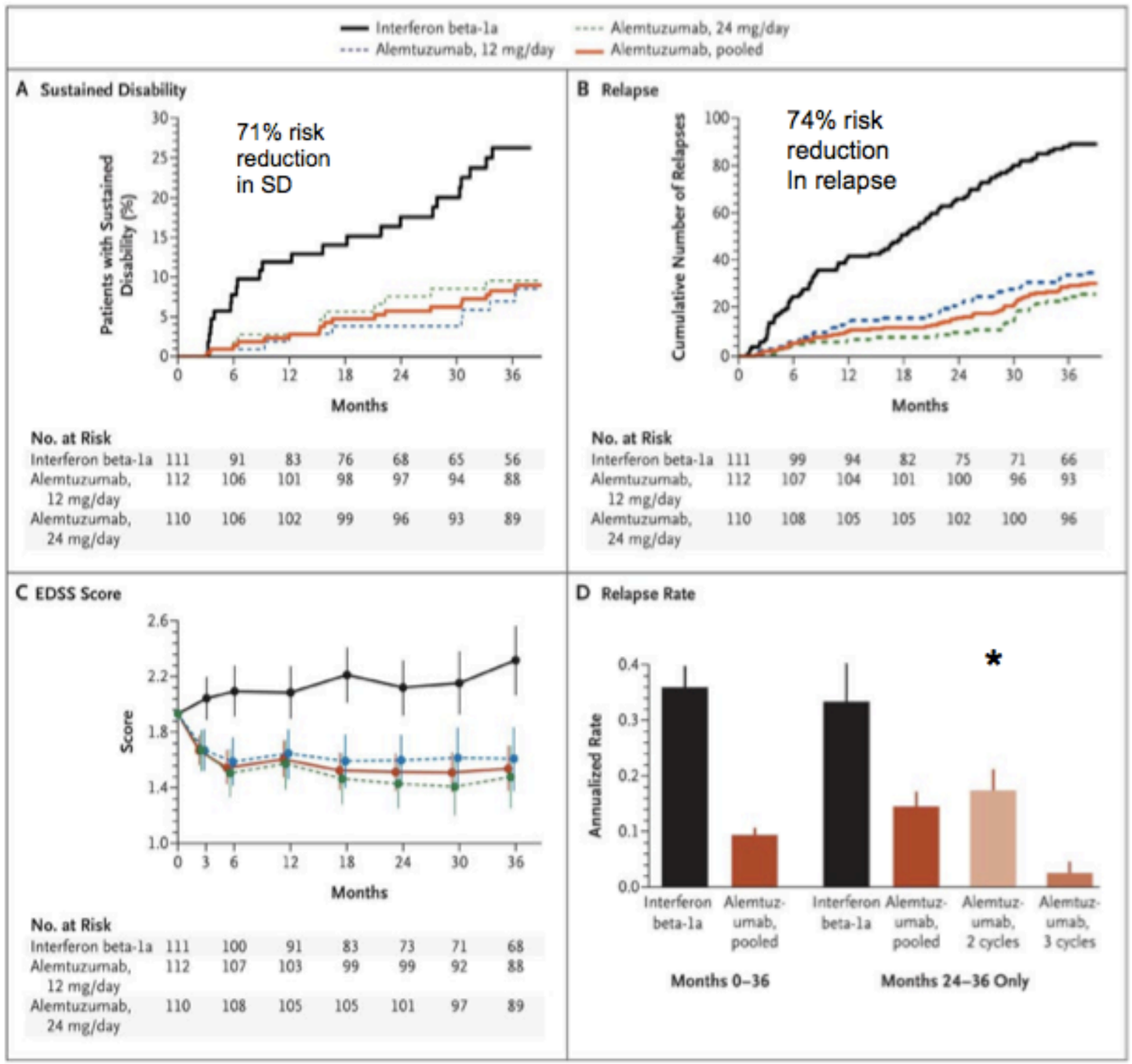


ALEMTUZUMAB

Anti CD52 mAb (targeting T and B cells; B > T). Daily infusion with HDMP for 5 days once a year

CAMMS 223

Coles et al. N Engl J Med 2008;359:1786-8(



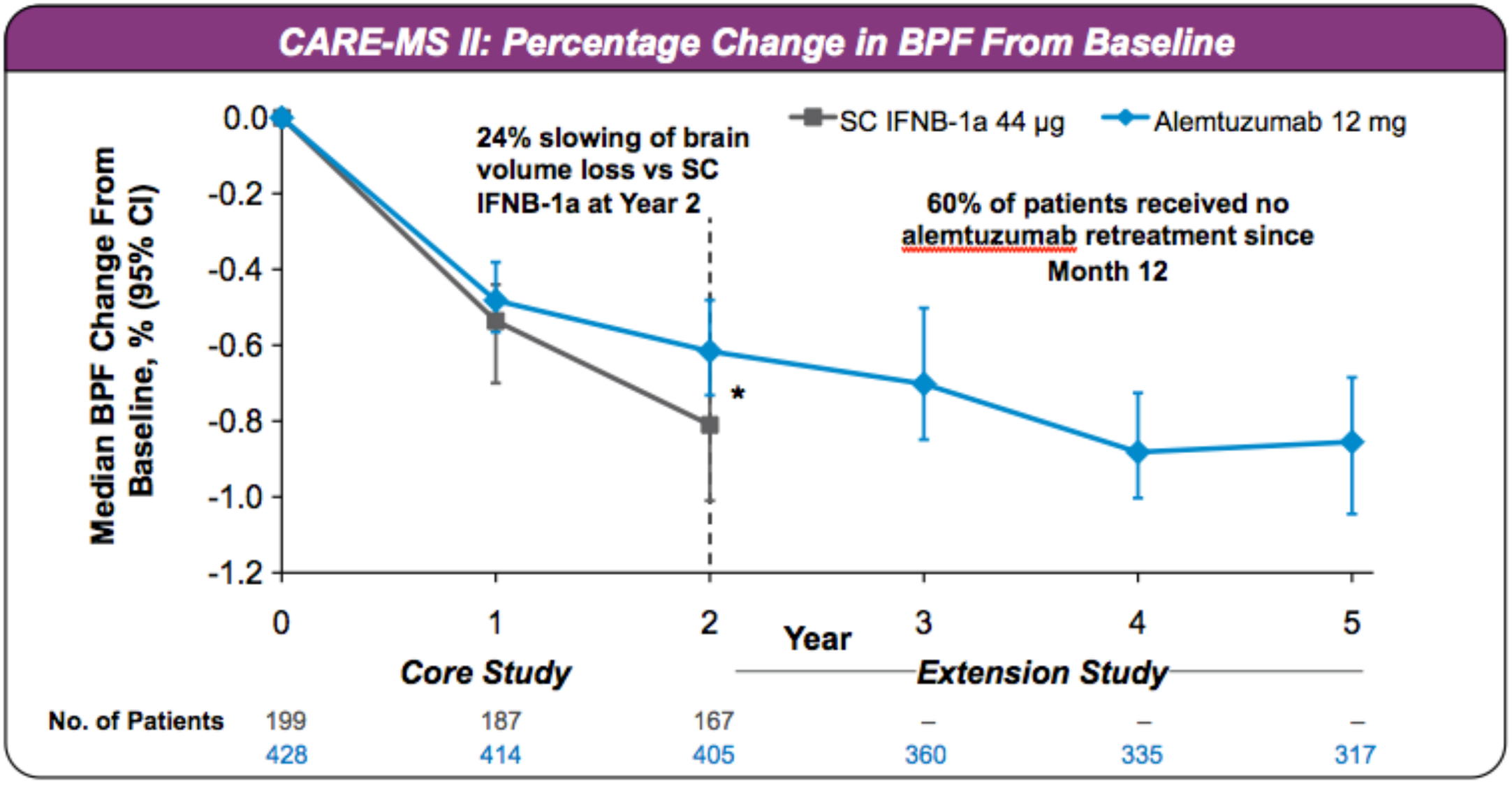
Alemtuzumab vs IFN B-1a in Early RRMS

Efficacy Outcome Measures (disability & relapse) at 36mo

*Note: 72% of Alemtuzumab pts did not receive 3rd dose

The NEW ENGLAND JOURNAL of MEDICINE

Slowing Brain Volume Loss Through 5 Years in CARE-MS II Alemtuzumab-Treated Patients



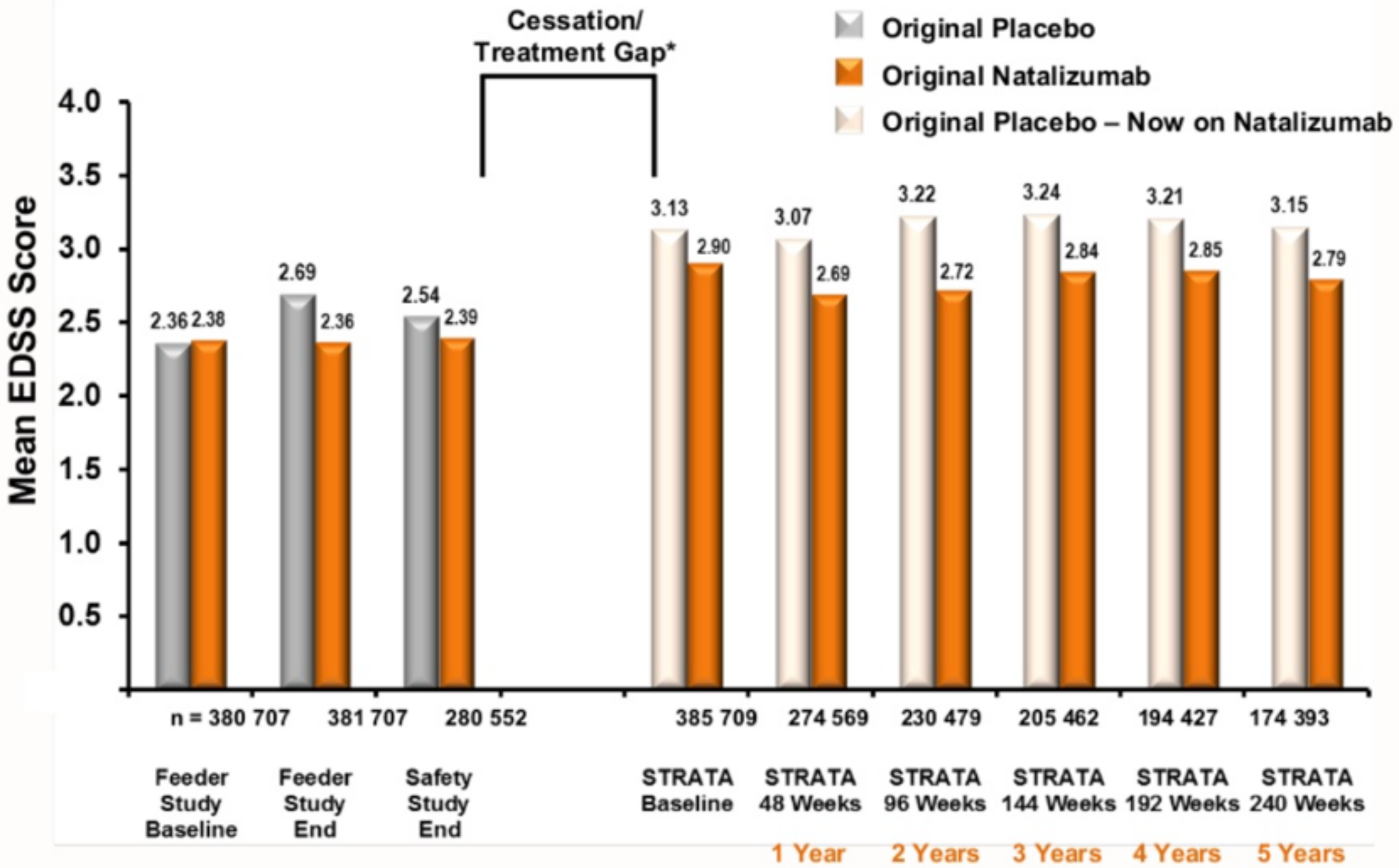
*Alemtuzumab vs SC IFNB-1a, *P*<0.0001

Alemtuzumab slowed the reduction in brain volume by 24% versus SC IFNB-1a at the end of the core CARE-MS II study

The slowing of brain volume loss in alemtuzumab patients was maintained through 5 years

NATALIZUMAB

STRATA: Patients Had Stable EDSS Scores for up to 5 years (Patients in PhaseIII and extension studies)



*$P<0.0001$

Kappos L et al. Presented at ECTRIMS; October 10–13, 2012; Lyon, France P520.

Efficacy and Safety of Ocrelizumab in Relapsing Multiple Sclerosis - Results of the Phase III Double Blind IFNB-1a controlled OPERA I and II Studies

S L Hauser et al on behalf of the
OPERA I and II clinical investigators
ECTRIMS 2015. Platform #190

- Compared with IFNB-1a, ocrelizumab significantly reduced
  - ARR
  - 12 and 24 week Confirmed Disability Progression
  - T1 Gd+ enhancing lesions
  - New and/or enlarging T2 lesions

- In exploratory analyses compared to IFNB-1a, ocrelizumab:
  - Reduced Brain Volume loss
  - Increased proportion of patients with NEDA

- Overall in Opera I and II, ocrelizumab had a similar safety profile with IFNB-1a over 96 weeks

- Opera I and II showed that targeting B-cells with ocrelizumab is a potential therapeutic approach in relapsing MS

Common sense favours zero tolerance to disease activity and to aim for NEDA (No Evidence of Disease Activity)

Potential benefits of NEDA

1. Reduced acute brain & cord injury - relapse
2. Reduced later axonal attrition - sublethal axonal and oligodendrocyte injury and delayed degeneration
3. Reduced CNS colonization by ectopic lymphoid tissue*
4. NAWM develops spreading microglial activation*
5. Overall greater axonal preservation, clinical function (ambulation and cognition) and QOL

* potential contribution to progressive phase

- Achieving NEDA reduces the probability of experiencing subsequent clinical and MRI disease activity

- NEDA-4 status has advantages over NEDA-3 in predicting subsequent disability and structural damage as expressed by BVL or up to 7 yrs

  (Note: NEDA-3 at one year was more closely correlated with relapses and new and enlarging T2 lesions)

- Overall these findings support the use of NEDA-4 as a more comprehensive and balanced measure for predicting long term disease evolution in RRMS

Goal

Minimise, Prevent or Reverse disability

Means to do so

Elimination or Suppression

(Finger on the STOP or PAUSE button)

Elimination or Suppression

ALZ 70% "cure."

Immune reconstitution
Thyroid 36%
ITP 1.6%
GMB disease 0.3%

Accept current Risk Benefit

NTZ Best suppression PML Stratify*

Wait for better Risk Benefit

OCZ, FGL] Next best suppression

* JCV Serology, duration, prior IS, JCV index/titre, CD4+ CD62L+ (L-selectin)

2. Case. 41yo F “Suppression”

- 1997. L monoc Uhthoffs phen (ON), dysequillibrium and Lhermitte’s phen.

- 2000. Exercise-diplopia, MRI worse, numerous calloso-septal plaques.
IFNB-1b but ceased in favour of IVF pregnancy

- 2002. CS daughter. IFNB-1b. MRI “cystic” black holes

- 2003. Thermolability with polocrosse, tennis and walking >1km.
MRI multiple new lesions

- 2006. Second daughter. Worsening leg function, no longer running, numb feet
Worsening cognition but completed Dip Ed.
School Landcare coordinator.
Wildflower business.
Extensive spinal and cranial MRI changes with more lesions.
MxA-responder. IFNB-1b.

Natalizumab versus Fingolimod

Braune et al *J Neurol* 2013 no difference between the two drugs over one year
Kalincik et al *Ann Neurol* 2015 higher relapse rates with fingolimod.

Danish Study. Koch Henriksen et al

All previously untreated Danish patients starting treatment after 2011 and who had received treatment for >6months were propensity score matched by logistic regression.

1211 RRMS . 531 NTZ and 670 FGL .
Before PSM FGL < NTZ for RR
After exclusion of unmatched 884 remained.
On Rx ARR 0.31 NTZ and 0.30 FGL

NO DIFFERENCE IN RELAPSE RATE (No MRI Data)

Both controlled for:
gender,
number of relapses in the previous year,
presence of GD+ lesions,
EDSS scores
hospitalizations

French Study. Laplaud et al

RRMS patients from 27 specialized treatment centres
prospective data NTZ 326
FGL 303

At two years (multivariate model)

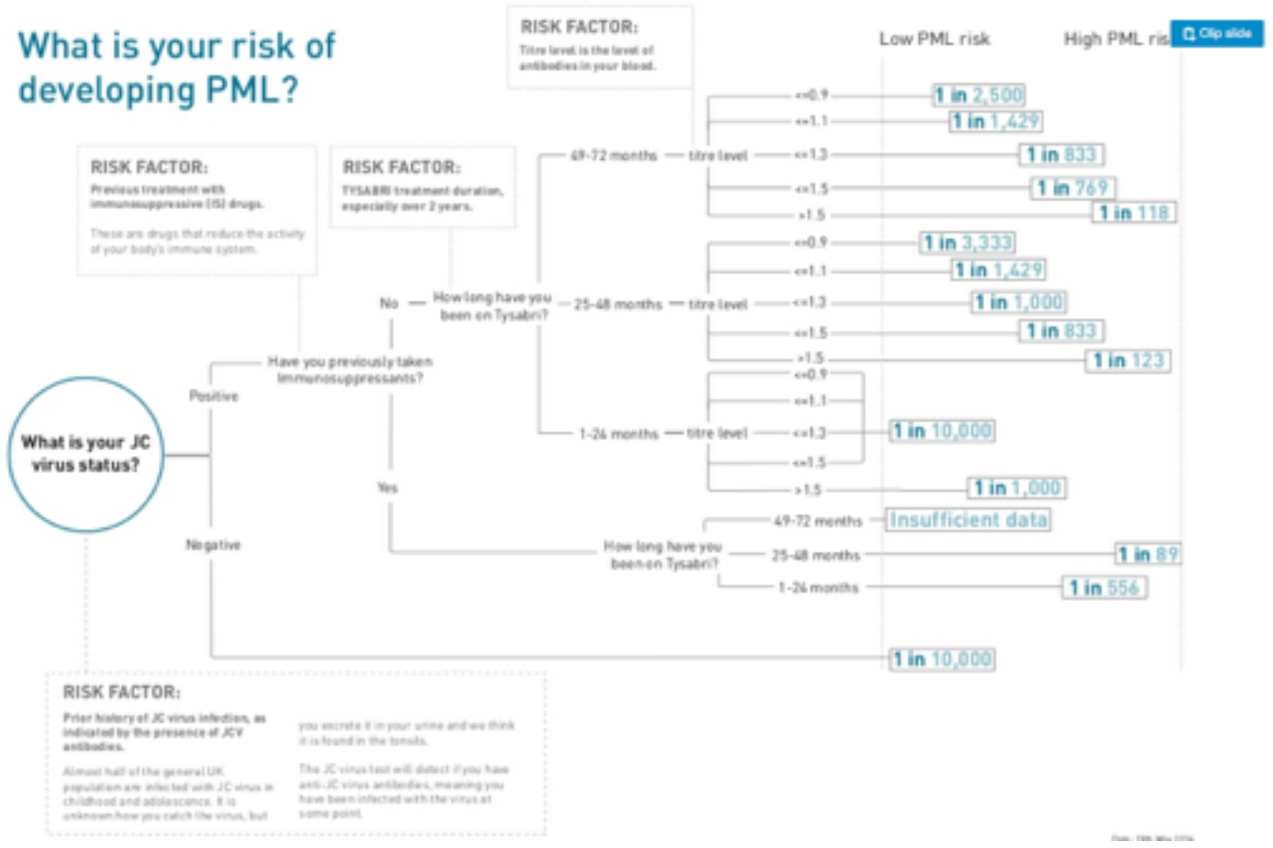
Risk of relapse,
New Gd+ lesions
New T2 lesions

FGL > NTZ

Class IV evidence that natalizumab has better efficacy than fingolimod over two years.

PML Risk

Current practice
Stratify Algorithm



Alternative approach
to rebalance Risk:Benefit

Ryerson LJ et al ECTRIMS 2015

Protection

Cohorts

Standard Interval Dosing (SID)
4w +/- 2d

Extended Interval Dosing (EID)
4w+3d - 8w+5d

PML Cases

SID
4 cases
1052 JCV+
patient yrs

EID
0 cases
1090
patient yrs

Post marketing
incidence
2.5cases per
1000 JCV+
patient yrs

Efficacy

No difference in clinical and imaging findings

Post marketing incidence: 566 cases over 415,207patient years NTZ exposure.
Assuming 55% population JCV+: 415,207x0.55 = 228,364 patient years exposure

Measurement

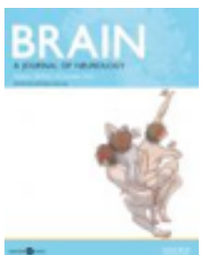
1. More sensitive measures of Disease activity
   Clinical: e.g. EDSS-plus
   MRI: Grey matter atrophy, PBVL, Cortical lesions

2. CIS conversion to CDMS
   MRI T2 lesion load
   CSF Chitinase 3-Like1 (CHI3L1), Nf Light chain

3. Treatment endpoint(s) are there any?

Rationale for EDSS-Plus.... Primary Composite Endpoint of Disability Progression.....ASCEND Phase 3 Study of Natalizumab for SPMS...A Post Hoc Analysis of IMPACT Study Data (P7.240)

Mikol D et al *Neurology vol. 84 Suppl. P7. 240*



Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes

Ester Cantó, et al DOI: http://dx.doi.org/10.1093/brain/awv017 918-931 First published online: 14 February 2015

Progressive MS

2010

1 year of disease progression and

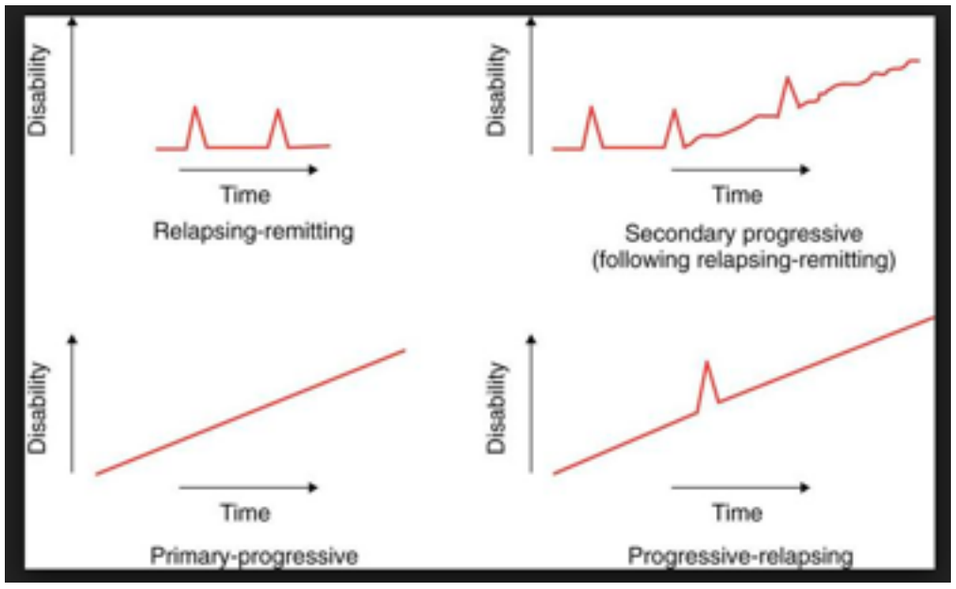
To harmonize MRI criteria within the diagnostic criteria for all forms of MS,

2 / 3 MRI or CSF findings be maintained but adoption of the new MAGNIMS brain imaging criterion for DIS

≥1 T2 lesions in at least 1 area characteristic for MS [periventricular, juxtacortical, or infratentorial]

≥2 T2 lesions in the cord

positive CSF (OCB, IgG index)



2013
MS disease modifiers
Phenotypes

Progressive accumulation of disability from onset

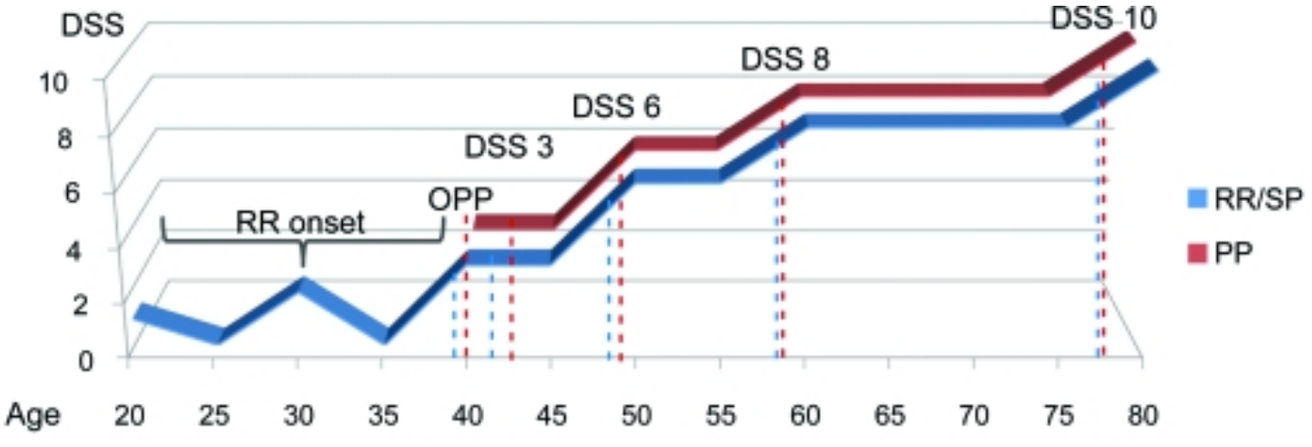
(PP)

Progressive disease

(SP)

- Active* and with progression**
- Active but without progression
- Not active but with progression
- Not active and without progression (stable disease)

Progressive accumulation of disability after initial relapsing course



Age at	OPP	*p*	DSS 3	*p*	DSS 6	*p*	DSS 8	*p*	DSS 10	*p*
RR/SP	40.2 (39)	0.09	41.6 (41)	0.82	49.7 (48)	0.05	59.2 (58)	0.44	76.1 (78)	0.63
PP	38.6 (40)		42.3 (43)		48.0 (49)		58.4 (58)		73.8 (78)	

p values obtained through Log Rank test

"Progression"? What does it mean?

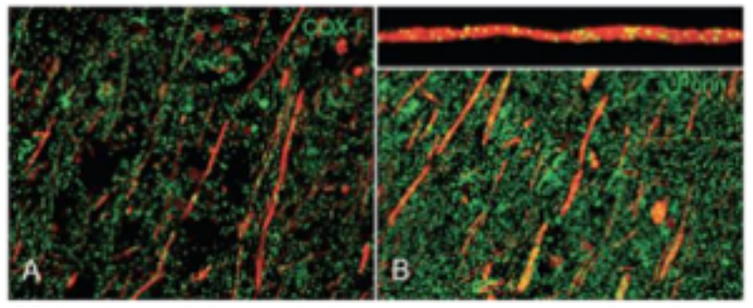
Clinical - accumulation of disability
- slow change over time
- with (SPMS) or without preceding relapses (PPMS)

Imaging – gradual tissue loss (atrophy/shrinkage)
– gradual accumulation/expansion of lesions
(increasing awareness of cortical and central grey matter involvement)

Pathology - axonal damage/loss
- neuronal loss/atrophy

Possible pathological correlates of disease progression

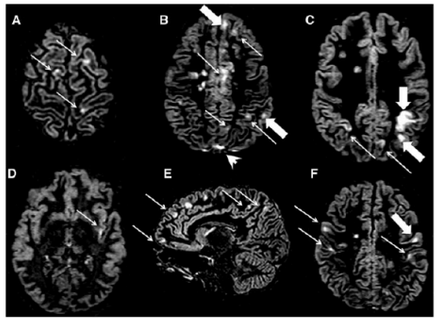
- Slowly expanding pre-existing lesions
- Persistent microglial activation
- Compartmentalized inflammation
- B cell/antibody involvement (EBV)
- Remyelination failure
- Mitochondrial dysfunction
- Axonal/neuronal loss
- Cortical/grey matter involvement
- Changes in the NAWM



Mitochondria and disease progression in multiple sclerosis

D. Mahad,* H. Lassmann,† and D. Turnbull*

Neuropathol Appl Neurobiol. 2008; 34(6): 577–589.

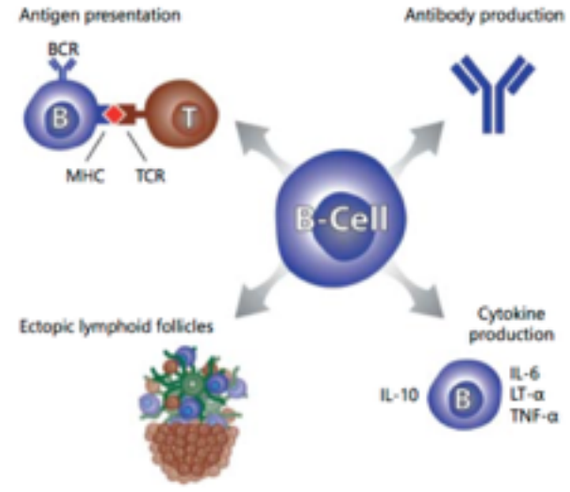


BRAIN
A JOURNAL OF NEUROLOGY

Cortical lesion load associates with progression of disability in multiple sclerosis

Massimiliano Calabrese,[1] Valentina Poretto,[1] Alice Favaretto,[1] Sara Alessio,[1] Valentina Bernardi,[1] Chiara Romualdi,[2] Francesca Rinaldi,[1] Paola Perini[1] and Paolo Gallo[1]

B-Cell targeted therapy in Progressive MS

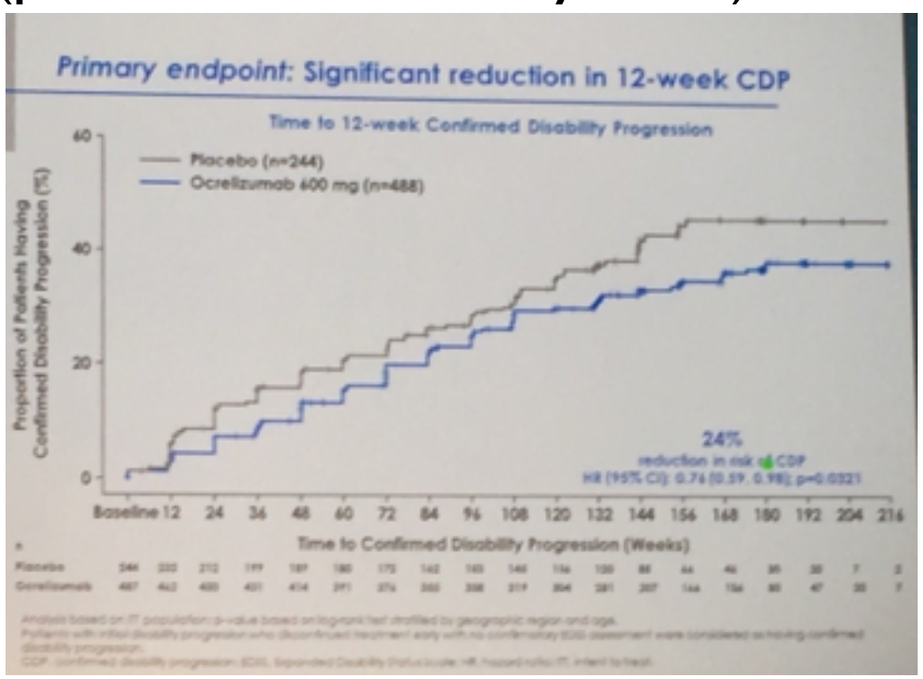


Olympus Rituximab

Failed to meet primary endpoint.
Showed an effect in post hoc analysis of patients <51yrs
and those with Gd+ lesions (reduced HR compared to placebo for both groups)

Oratorio Ocrelizumab

Attained primary endpoint - reduced confirmed disability progression (CPD) at 12wks by 24% p=0321
Reduced CPD at 24wks by 25% p=0.0365
T25-FW decreased by 29% over 120wks
T2 lesion volume decreased by 3.4% over 120wks (placebo increased by 7.4%)
BVL reduced by 17.5% cf placebo over 120wks



Note.
Young age mean 44,45yrs
Short disease duration 6.1, 6.7yrs
Short time from diagnosis 2.8, 2.9yrs
Numbers with Gd+ lesions 24.7, 27.5%

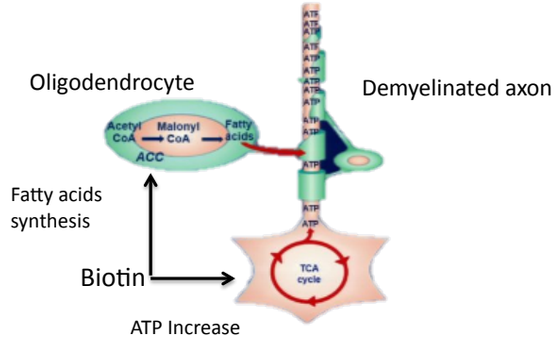
ECTRIMS 2015

Other treatments

SPMS
Simvastatin reduced rate of brain atrophy by 43% pa over 2yrs

Neuroprotection
Lamotrigine
Phenytoin
AntiLINGO

MS SMART Amiloride,Riluzole,Fluoxetine
SPRINT Ibudilast
Biotin (MD1003)



Biotin targets two mechanisms that may underpin progressive MS

INTERNATIONAL
PROGRESSIVE MS ALLIANCE

CONNECT TO END PROGRESSIVE MS

MANAGING MEMBERS:

MS RESEARCH AUSTRALIA

MS Multiple Sclerosis Society of Canada

SCLEROSI MULTIPLA fondazione italiana

MS Multiple Sclerosis Society

ms international federation

MS National Multiple Sclerosis Society

MEMBERS:

Nationale Belgische Multiple Sclerose Liga vzw
Ligue Nationale Belge de la Sclérose en Plaques wbl

Sclerose foreningen

dmsg Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V.

Esclerosis Múltiple España

stichting MS research

Mission:
To expedite the development of effective disease modifying and symptom management therapies for progressive forms of MS

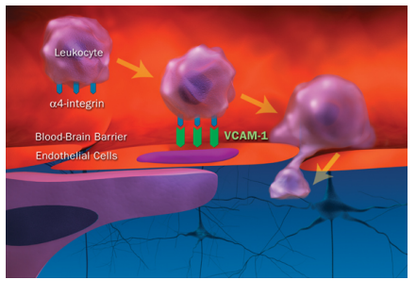
Medication

MOA

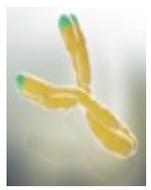
Monitoring

Natalizumab

Humanized mAb targets 4 integrin on leucocytes
prevents encephalitogenic wbc traversing BBB
(impairs T-cell reactivation and B cell proliferation)



300mg ivi/month
LFT,FBP,JCV serology
4-6monthly MRI



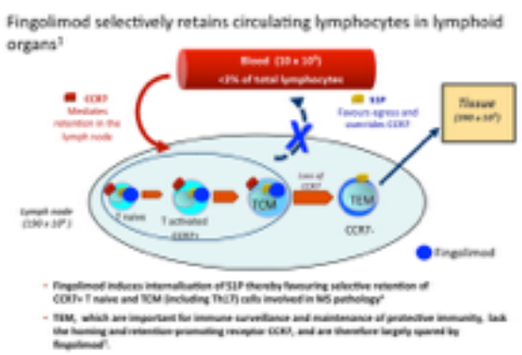
Alemtuzumab

Anti CD52 mAb (targeting T and
B cells; B > T). Daily infusion with
HDMP for 5 days once a year

12mg ivi for 5 days
with HDMP. Repeated
for 3 days at 1yr
6 monthly MRI

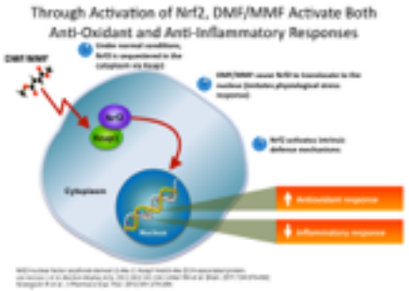
Fingolimod

prevents T lymphocytes
egress from LN

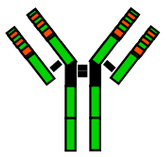


0.5mg od
LFT,FBP,
OCT maculae
MRI 6 monthly

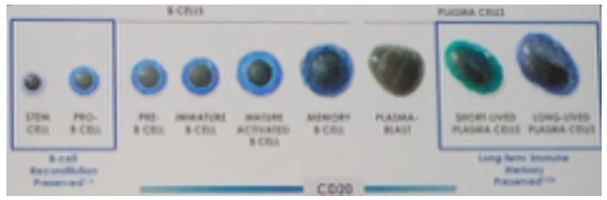
Tecfidera
(BG12)



240mg bd po.
LFT,FBP
MRI 6 monthly

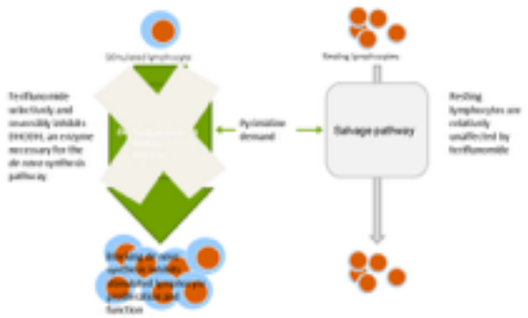


Ocrelizumab



600mg ivi 6 monthly
LFT, FBP & MRI
6 monthly

Teriflunomide



14mg od po
LFT,FBP & MRI
6monthly

Redefining the evidence base to guide use

1. Advent of highly effective treatments has pushed out the duration of "early disease"

eg. Case on NTZ for 7 years - plus pretreatment time makes need for CARE MS 2 criteria to guide use of Alemtuzumab necessary

2. Progression has more than one cause.

eg. Case whose LL disability is progressing with increasing paresis/ spasticity but who has relatively little intracranial disease evident may not be precluded from Alemtuzumab/NTZ
LL signs likely have an "hypoxic" cause not an inflammatory cause.
Hence need to protect remainder of CNS not abandon it