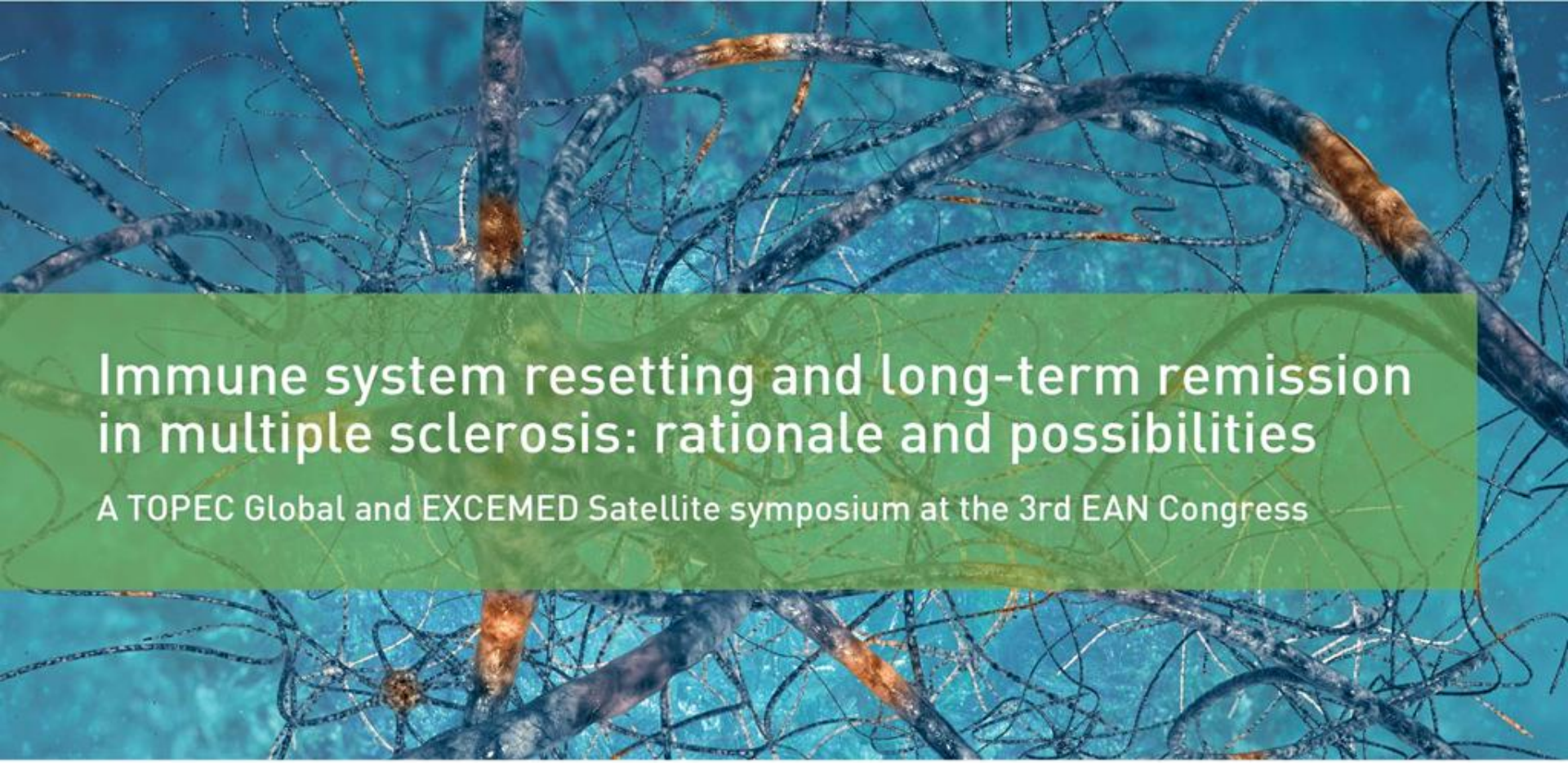


Immune system resetting and long-term remission in multiple sclerosis: rationale and possibilities

A TOPEC Global and EXCEMED Satellite symposium at the 3rd EAN Congress

gna Global Neurology Academy

TOPECGLOBAL

EXCEMED

EAN 2017

Amsterdam June 23-27, 2017

“MS Nowadays-new goals”

Giancarlo Comi

Dept. of Neurology & Institute of Experimental Neurology

Università Vita Salute S.Raffaele, Milano

European Charcot Foundation

Disclosure statement

In the last year , Giancarlo Comi received personal compensation for activities such as consulting, scientific advisory boards or speaking from:

Bayer Schering Pharma, Biogen-Dompè, Biogen Idec, MerckSerono, Novartis, Roche, Sanofi-Aventis, Almirall, Teva, Actelion, Receptors.

NEW Goals: Outline

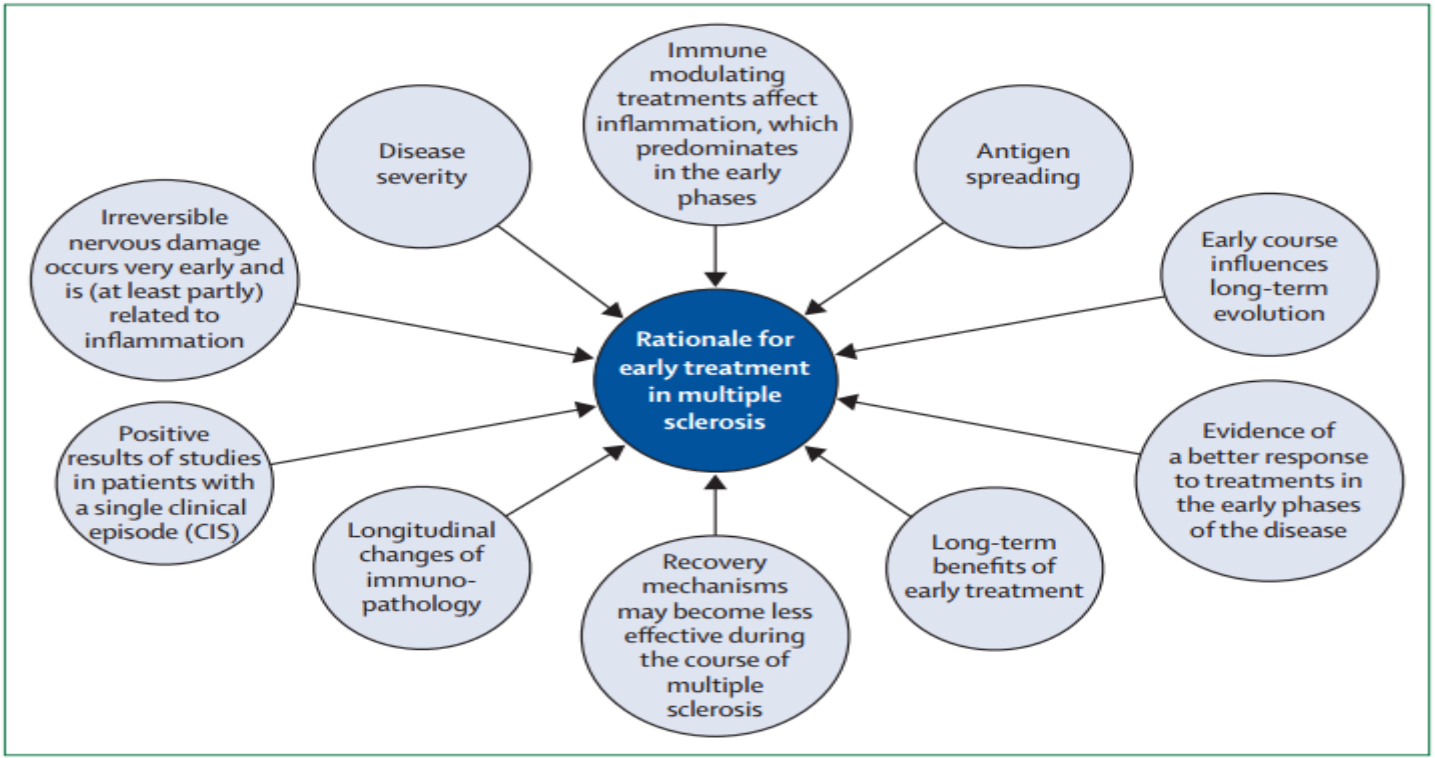
Early treatment

Individualized treatment

Induction strategy

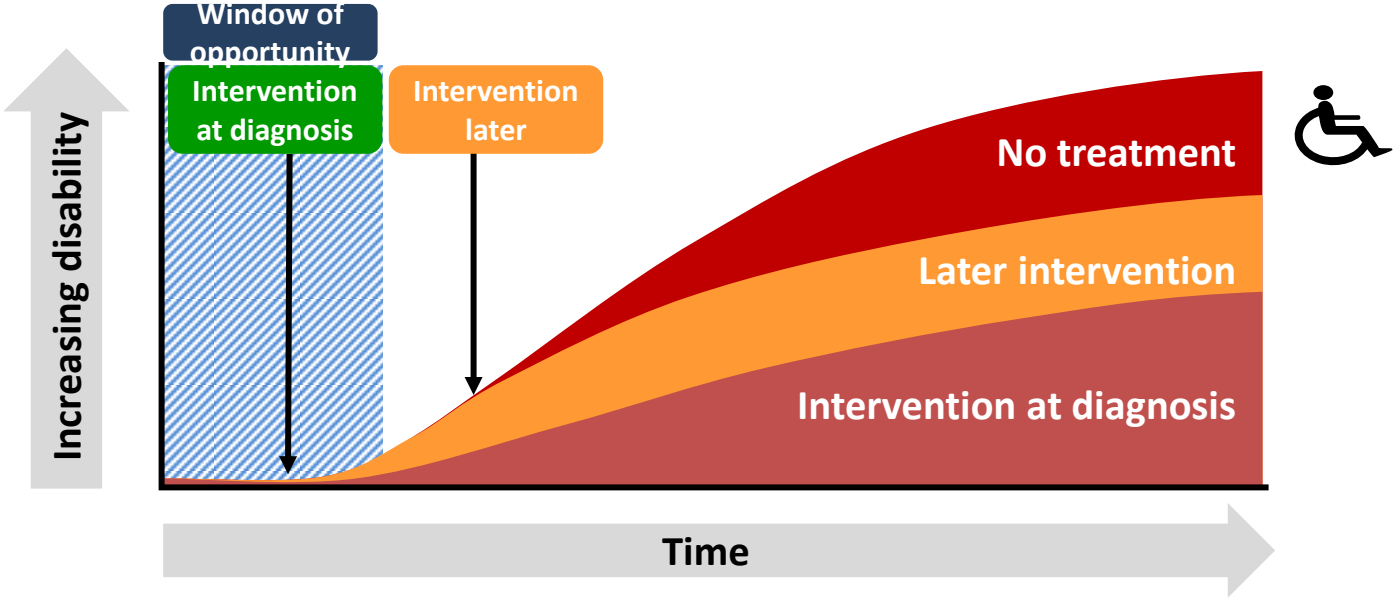
Multiple **S**clerosis **C**are **U**nit

Rationale for early therapy in multiple sclerosis



Comi, Lancet 2016

Window of opportunity – earlier treatment modify the course of disease

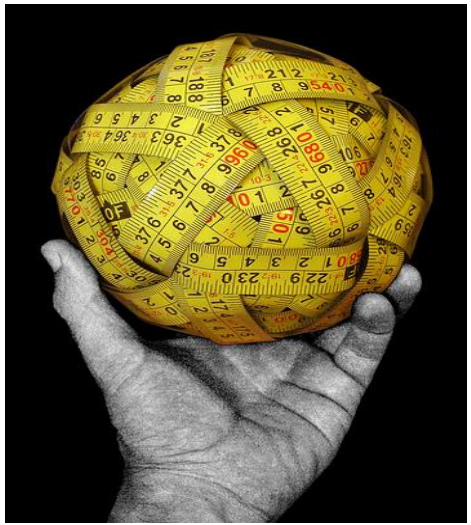


Early treatment initiation and prompt intervention on break-through disease is critical to optimise disability outcomes

Bases for individualised treatment in MS

- **Complexity and heterogeneity of MS**
  - Polygenic inheritance
  - Multifaced gene-gene and gene-environment interaction
- **Large intraindividual variability of MS courses**
  - Early long term prognostic factors
  - Short term prognostic factors
- **Treatments with different mechanisms of action and different efficacy/safety profile**
- **Interindividual variability of the response to treatments**
  - Clinical and MRI predictors
  - Pharmacogenomics
- **Multiple treatment algorithms**
  - Induction/Escalation
  - Combination

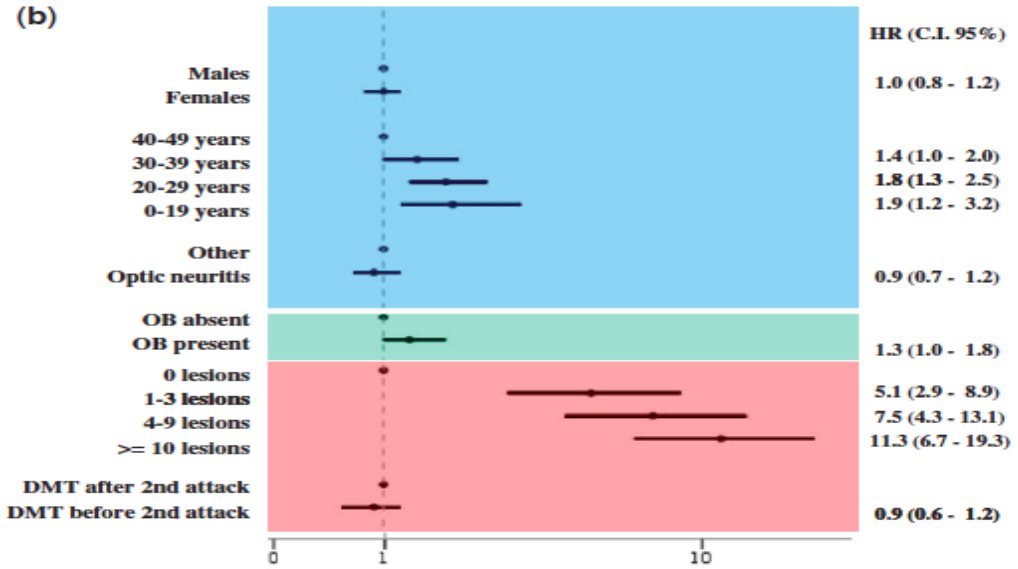
Prognostic factors in MS



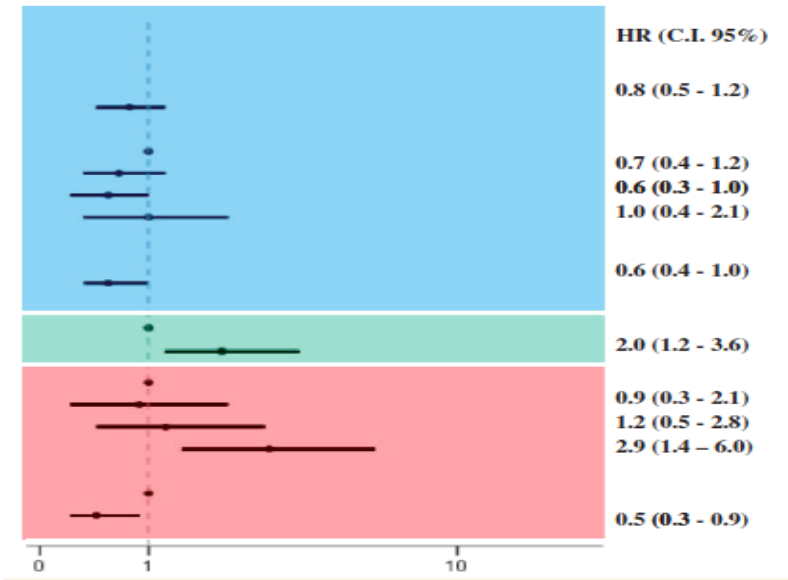
- Clinical
- MR Imaging
- Neurophysiological
- Biological

Barcelona CIS cohort: Multivariate analysis at baseline

Risk of conversion to CDMS



Risk of reaching EDSS ≥3.0



DMT =IFNβ/glatiramer acetate
HR=hazard ratio; OCB=oligoclonal bands.

Tintoré M et al. Brain 2015

DOI: 10.1111/ane.12761

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

Multiple biomarkers improve the prediction of multiple sclerosis in clinically isolated syndromes

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Funding information
This research was partially funded by a Grant by the Italian Ministry of Health (RF 2011-02349698)

Objectives: Since its introduction, MRI had a major impact on the early and more precise diagnosis of multiple sclerosis (MS), and the 2010 diagnostic criteria even allow a diagnosis to be made just after a single attack if stringent MRI criteria are met. Several other clinical and paraclinical markers have been reported to be associated with an increased risk of MS independently of MRI in patients with clinically isolated syndromes (CIS), but the incremental usefulness of adding them to the current criteria has not been evaluated. In this study, we determined whether multiple biomarkers improved the prediction of MS in patients with CIS in a real-world clinical practice.

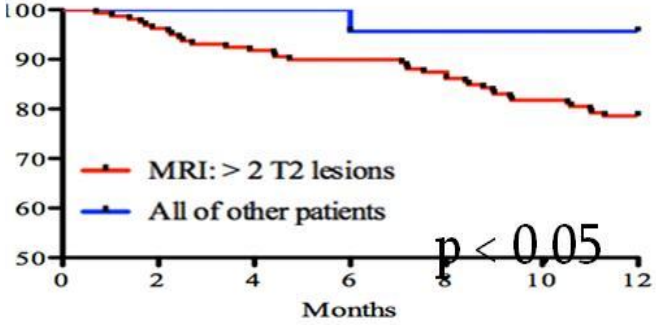
Materials and methods: This was a retrospective study involving patients with CIS admitted to our department between 2000 and 2013. We evaluated baseline clinical, MRI, neurophysiological, and cerebrospinal fluid (CSF) data.

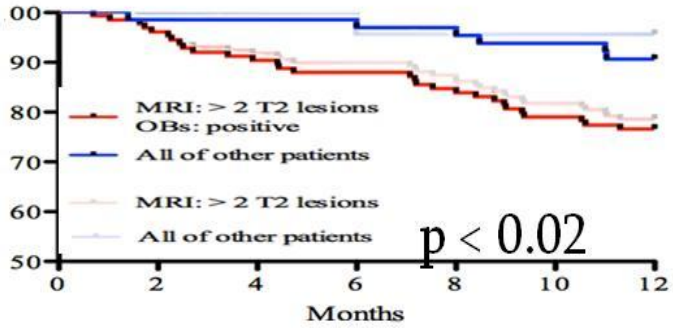
Results: During follow-up (median, 7.2 years), 127 of 243 participants (mean age, 31.6 years) developed MS. Cox proportional-hazards models adjusted for established MRI criteria, age at onset, number of T1 lesions, and presence of CSF oligoclonal bands significantly predicted the risk of developing MS at 2 and 5 years. The use of multiple biomarkers led to 29% net reclassification improvement at 2 years ($P<.001$) and 30% at 5 years ($P<.001$).

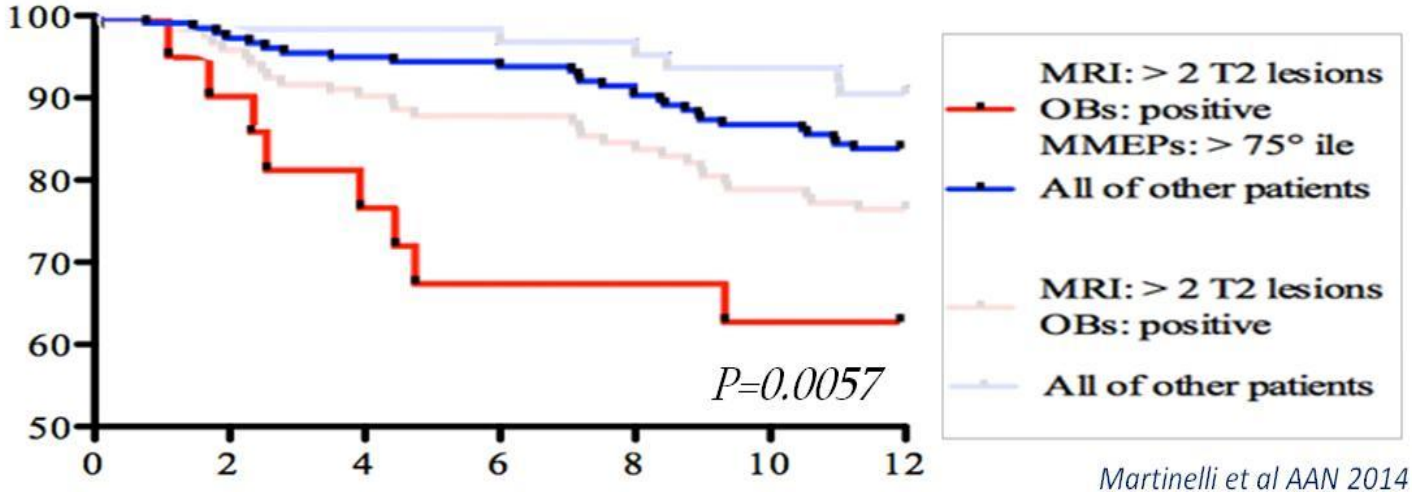
Conclusions: The simultaneous addition of several biomarkers significantly improved the risk stratification for MS in patients with CIS beyond that of a model based only on established MRI criteria.

EPs and conversion to CDMS over 1 year

225 CIS *(from consecutive pts undergoing CSF examination)*

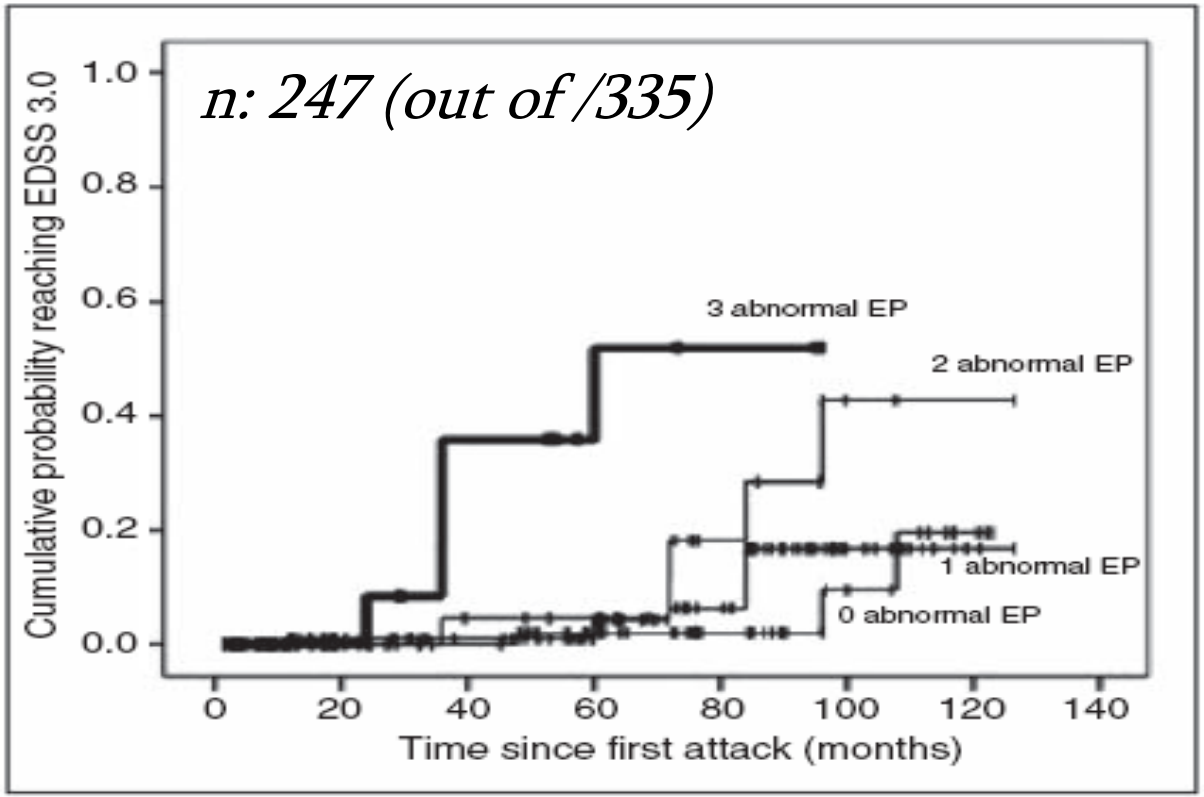






Martinelli et al AAN 2014

CIS: EPs & progression rate - time to EDSS 3.0



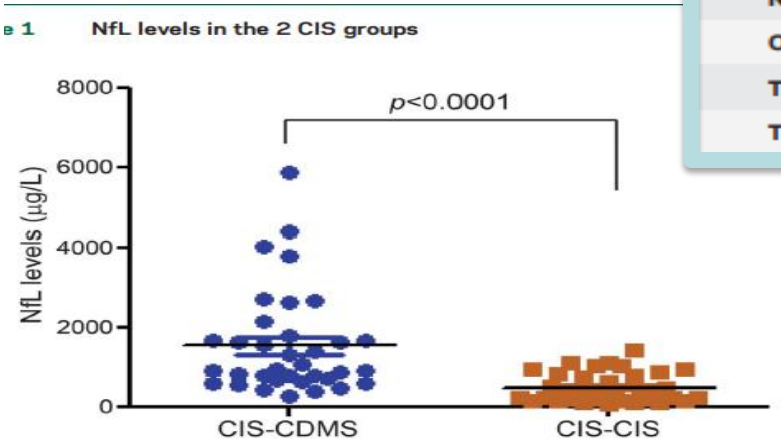
SEPs
VEPs
BAEPs

no MEPs

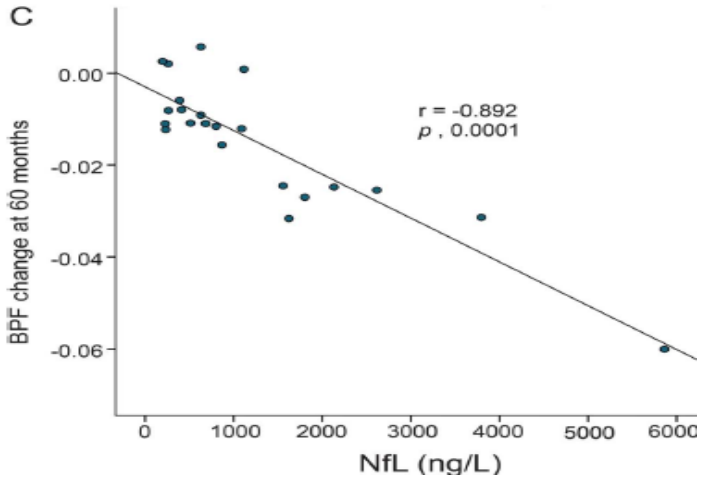
Pelayo, Montalban et al. MSJ 2010

CSF Neurofilament light levels

	p Value	HR/aHR[a]	95% CI
Conversion to CDMS			
Multivariate analysis[d]			
NfL-100	0.040	1.005	1.000-1.011
OCBs	0.048	2.597	1.009-6.683
T2 lesions 1-3	0.071	7.225	0.843-61.920
T2 lesions ≥4	0.022	11.469	1.432-91.868



NfL levels appear to be independent predictors for conversion to CDMS and correlate with MR inflammation variables and atrophy



G Arrambide et al Neurology 2016

Predictivity of the response to DMTs

- Clinical and demographic
- MRI
- Eps
- Laboratory
- Pharmacogenomic

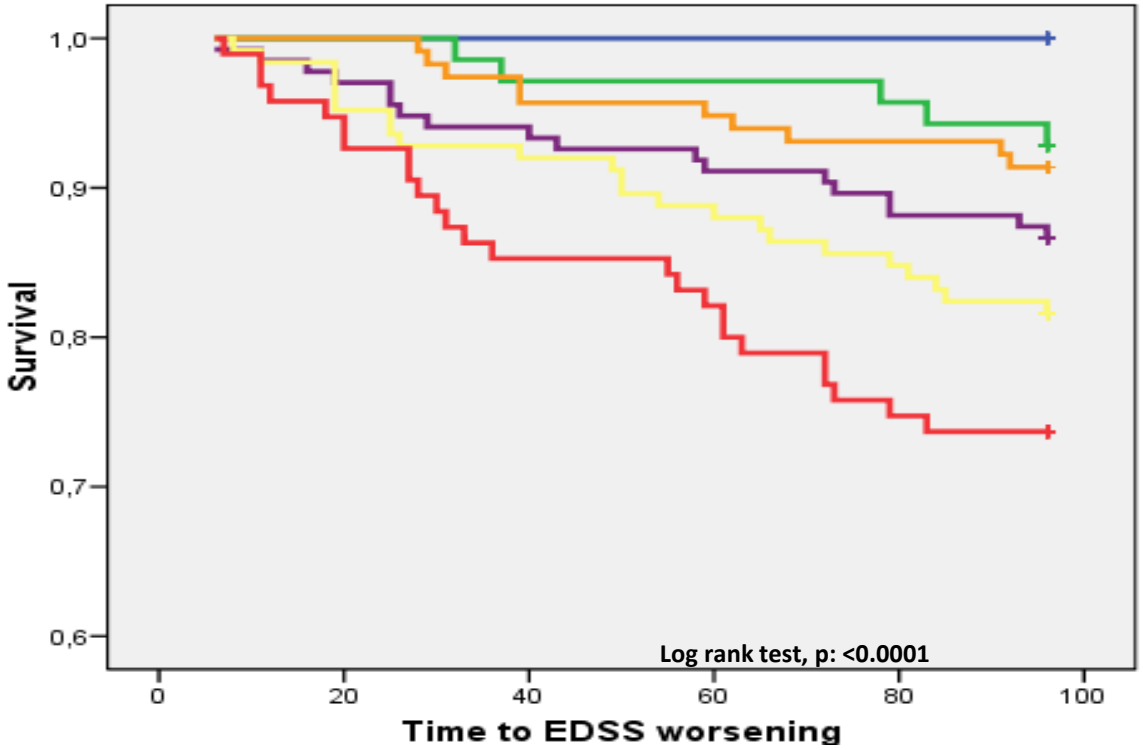
Baseline predictive score of disability worsening at 8 years in patients treated with injectables

Criterion	
Age onset	
≤ 28 years	**0**
> 28 years	**2**
Delay treatment after diagnosis	
≤ 12 months	**0**
> 12 months	**1**
Relapse 1 year pre-DMT	
< 2 relapse	**0**
≥ 2 relapses	**1**
Baseline EDSS	
< 2	**0**
≥ 2	**1**
Baseline T2 lesions	
≤ 9	**0**
>9	**1**
Baseline T1 Gd+ lesions	
≤ 2	**0**
≥ 2	**1**

Patients free from disability worsening according to baseline score

***Worsening:** 6 months confirmed EDSS ≥ 2 points if entry EDSS ≤ 3

6 months confirmed EDSS ≥ 1 point if entry EDSS > 3



Score 0
Score 1
Score 2
Score 3
Score 4
Score ≥ 5

Score	Tot pts (561)	Disability worsening
0	20	0%
1	70	7%
2	116	9%
3	135	13%
4	125	18%
≥ 5	95	26%

Romeo 2015

Annals of NEUROLOGY

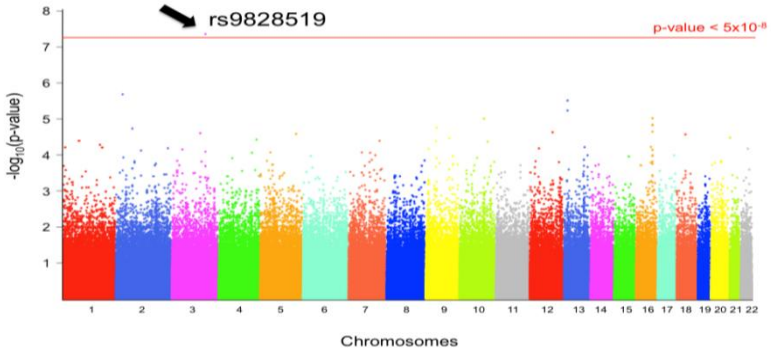
Esposito et al, 2015

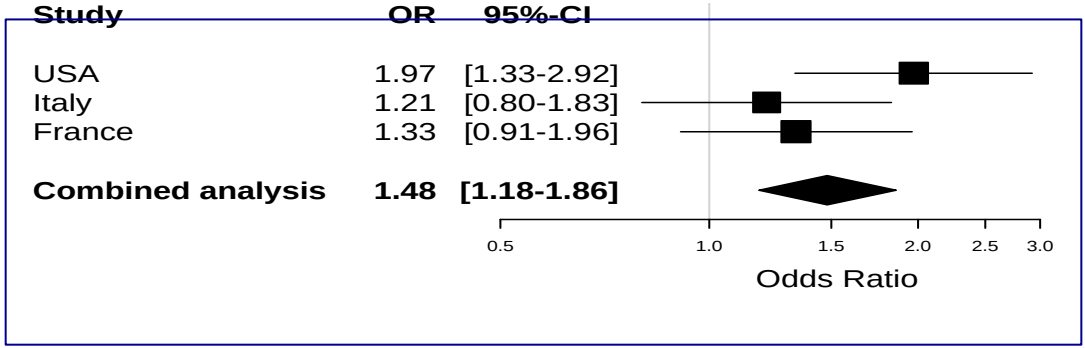
A pharmacogenetic study implicates SLC9A9 in multiple sclerosis disease activity

We investigated the genetic basis of inter-individual differences in response to IFNβ by studying ~1,000 MS patients classified in responders and non-responders

A genome-wide association study performed in Italian MS patients identified a genetic variant, the rs9828519^{G} allele, associated with increased risk of non-response to IFNβ ($P_{discovery}$=4.43x10^{-8})

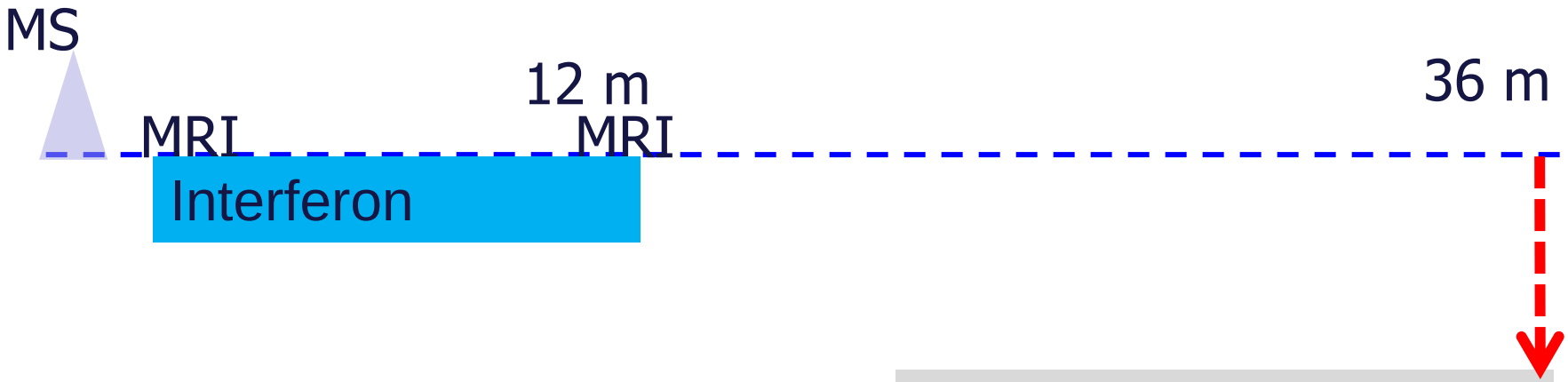
Replication studies performed in 3 independent cohorts confirmed the association ($P_{replication}$=7.78x10^{-4})





Assessing response to interferon beta

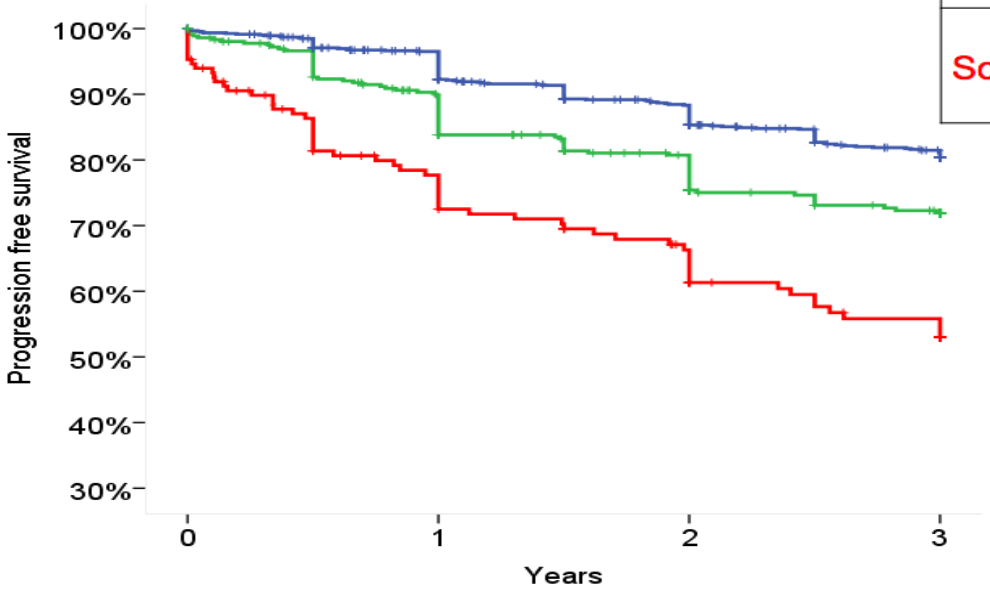
A MAGNIMS study



Sormani 2016

MAGNIMS score

Score=0	new T2 lesions <3 & Relapses=0
Score=1	new T2 lesions <3 & Relapses=1 new T2 lesions ≥3 & Relapses=0
Score=2	new T2 lesions ≥3 & Relapses=1 Relapses≥2



Score=0, n=849, 66%

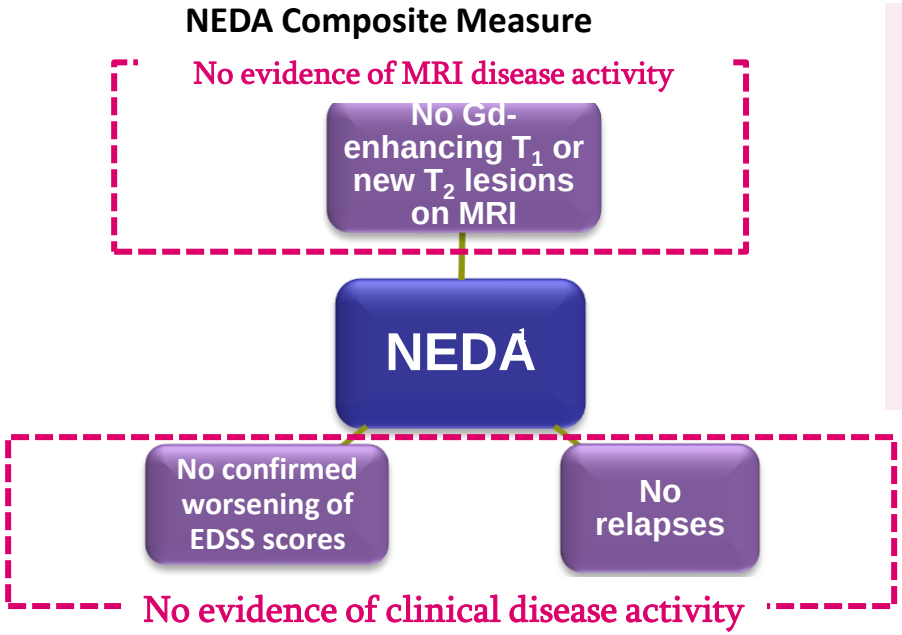
Score=1, n=301, 24%

Score=2, n=130, 10%

Score 0 vs scores 1 or 2: PPV= 34%, NPV=81%, sensitivity=49%, specificity=73%, global accuracy=66%.

Sormani 2016

Evolving Measures: NEDA (No Evidence of Disease Activity) in MS

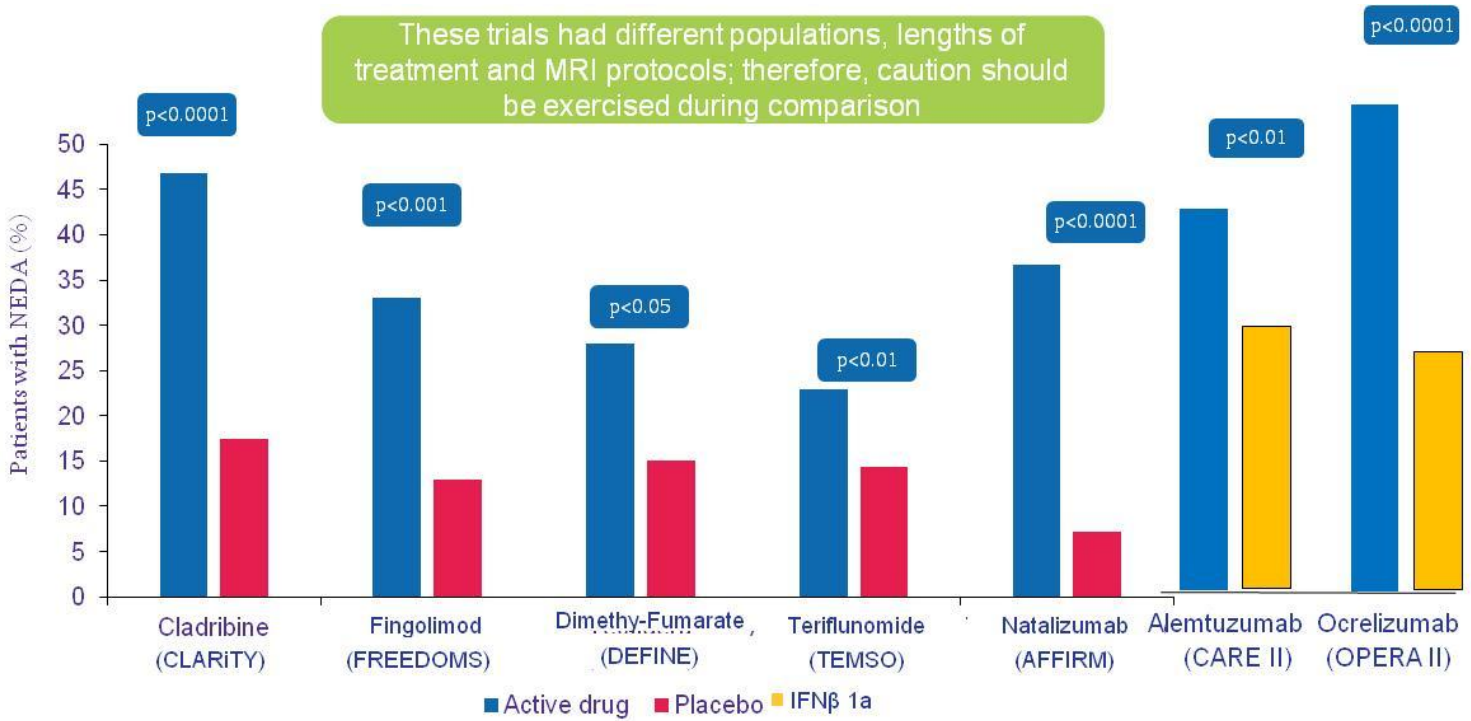


NEDA may be influenced by:

- Baseline characteristics
- Study design
- Assessment timing or criteria (eg, 3-month vs 6-month)
- Timing for re-baseline of patients

Treating to target: NEDA establishes a zero tolerance for ongoing measurable disease activity

Proportion of patients achieving NEDA with DMDs



NEDA, no evidence of disease activity. CLARITY. Giovannoni G et al. Lancet Neurol 2011;10:329-37; FREEDOMS. Bevan CJ, Cree BAC. JAMA Neurol 2014;71:269-70; DEFINE. Giovannoni G et al. Neurology 2012;78 (PD5.005); TEMSO. Freedman M et al. Neurology 2012;78 (PD5.007); AFFIRM. Havrdova E et al. Lancet Neurol 2009;8:254-60; Coles et a, Lancet 2012

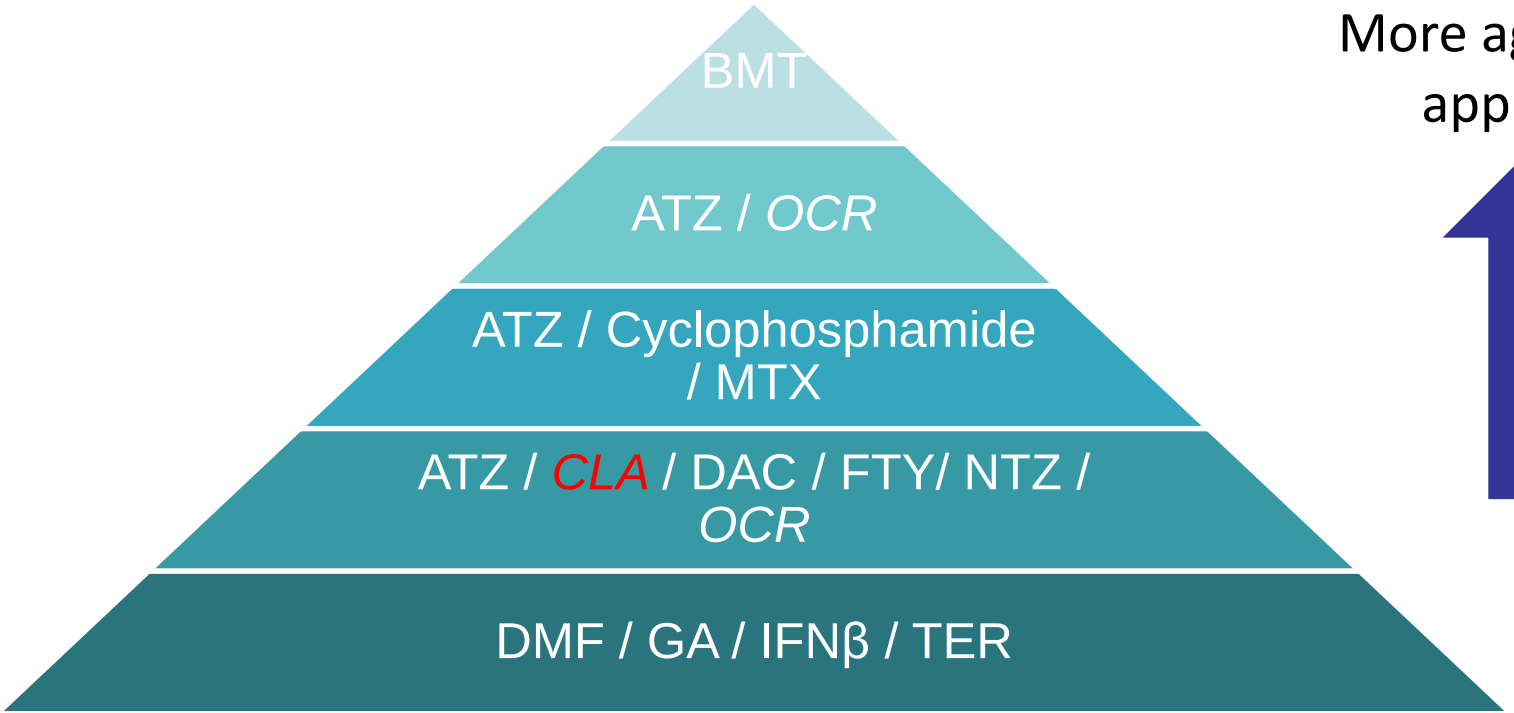
Treatment Algorithms

ESCALATION
(safety first)

INDUCTION
(efficacy first)

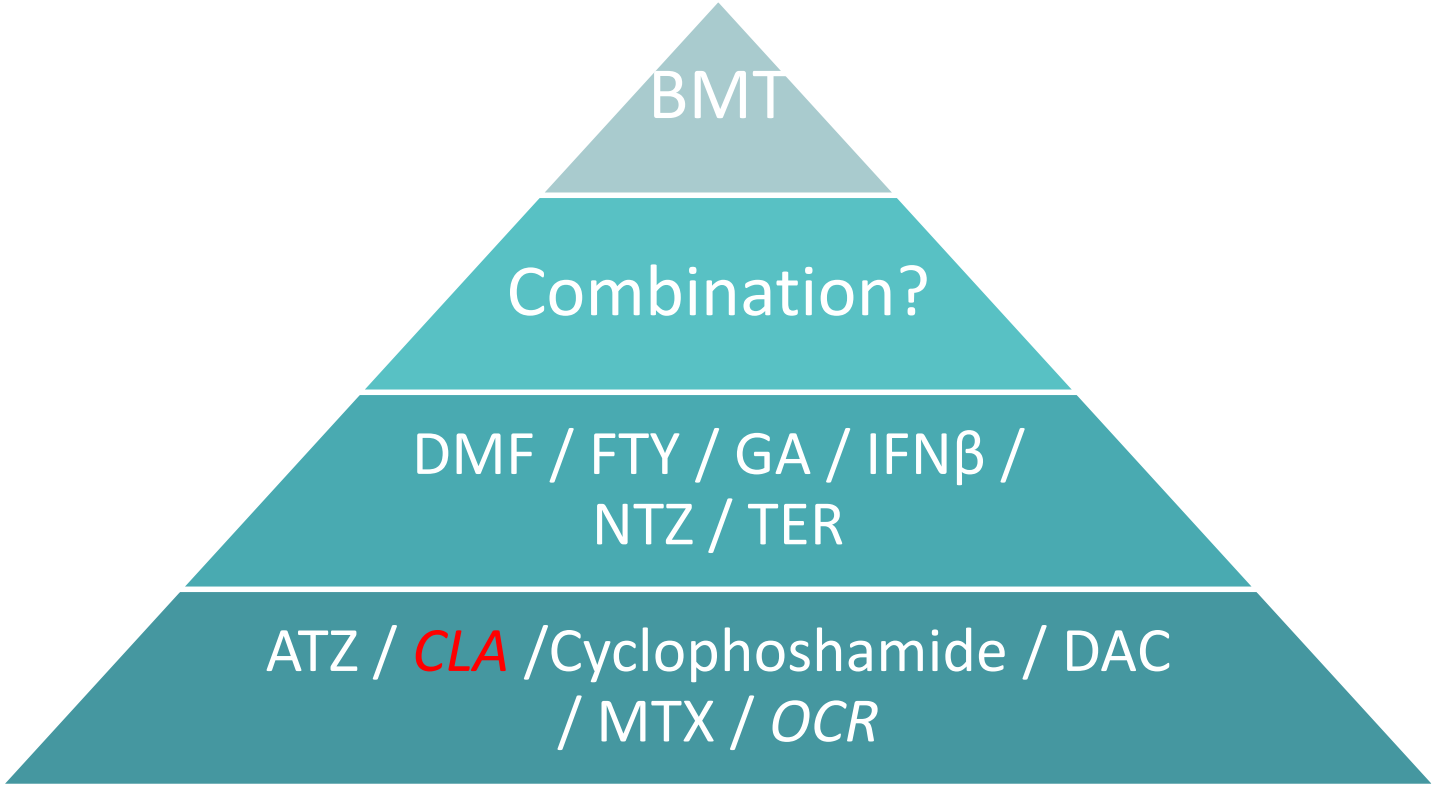
COMBINATION

Treatment algorithm: escalation



More aggressive approach

Treatment algorithm: induction



FDA News Release

FDA approves new drug to treat multiple sclerosis

First drug approved for Primary Progressive MS

For Immediate Release March 29, 2017

Release

Español

On March 28, the U.S. Food and Drug Administration approved Ocrevus (ocrelizumab) to treat adult patients with relapsing forms of multiple sclerosis (MS) and primary progressive multiple sclerosis (PPMS). This is the first drug approved by the FDA for PPMS. Ocrevus is an intravenous infusion given by a health care professional.

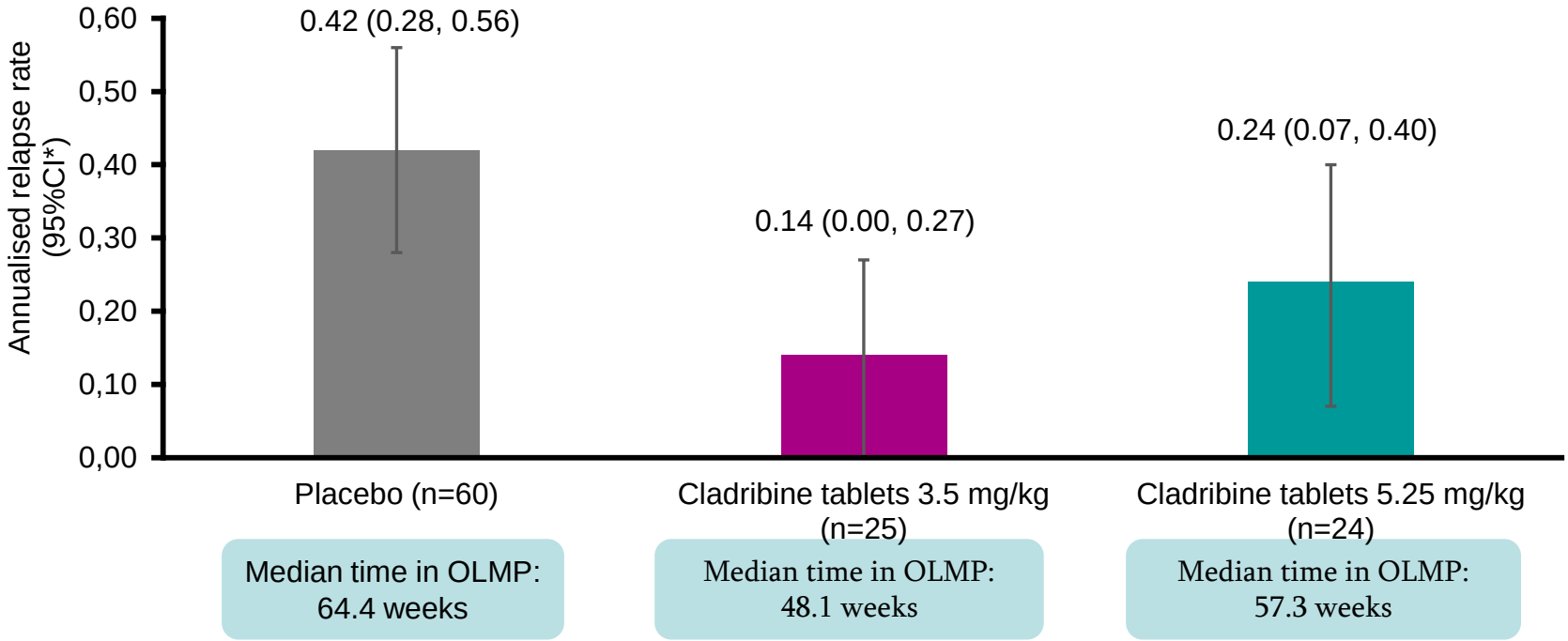
Cladribine Tablets Receives Positive CHMP Opinion for Treatment of Relapsing Forms of Multiple Sclerosis

Mavenclad (Cladribine tablets) has received a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)

SHARE

23 JUN 2017 | DARMSTADT, GERMANY

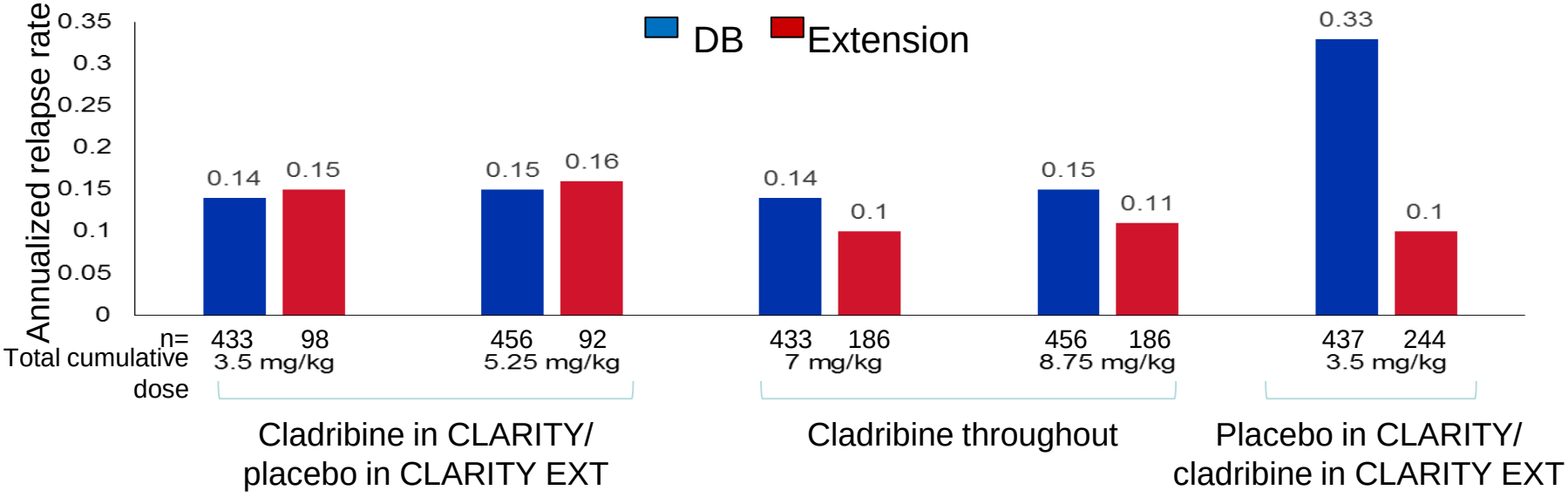
ORACLE: ARR during the open-label period



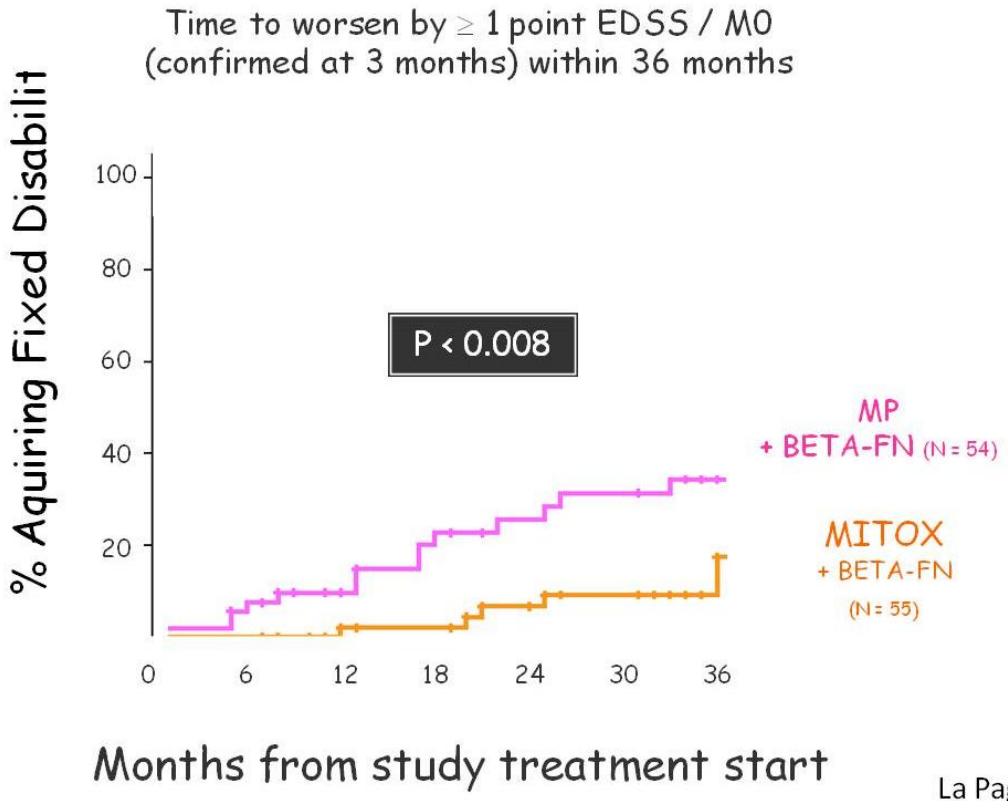
*Two sided 95% confidence interval. ARR has been normalised by duration in the OLMP (total number of relapses/total time in the OLMP in days) x 365.25.
All patients started open-label treatment with IFN β-1a in the OLMP.
ARR, annualised relapse rate; IFN, interferon; OLMP, open-label maintenance period

CLARITY EXT demonstrates the durable efficacy of cladribine and reconfirms the efficacy outcomes of the CLARITY study over 2 years

- The clinical benefits of cladribine 3.5 mg/kg in Years 1 and 2 may be maintained for up to 4 years without further active treatment in Years 3 and 4; 72% of such patients remained relapse-free at the end of Year 4

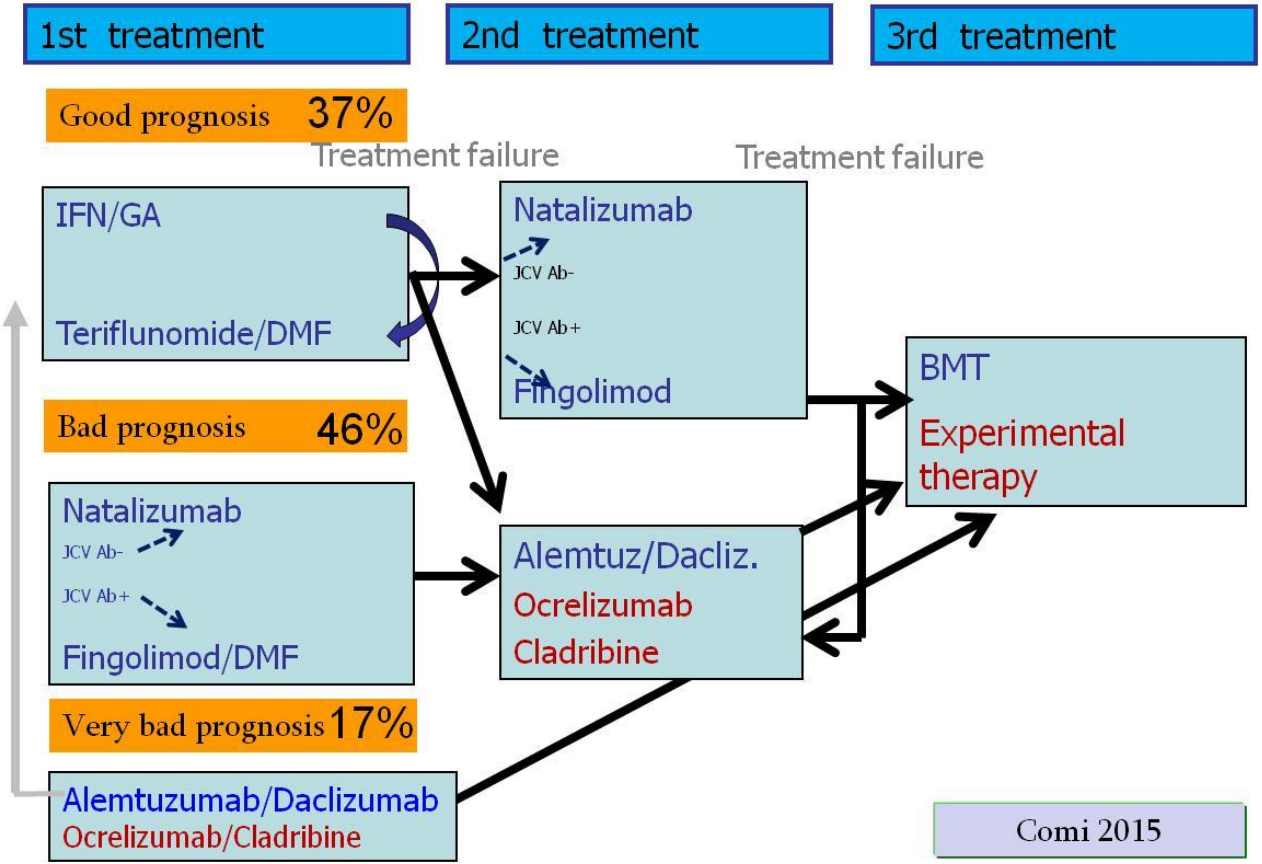


Induction with mitoxantrone followed by BETA IFN vs BETA IFN



La Page 2011

Algorithm for Treatment of Relapsing MS



CellPress

eventually favor changes in white adipocyte phenotype.

[1]Key Laboratory of Agro-ecological Processes in Subtropical Region, Institute of Subtropical Agriculture, Chinese Academy of Sciences; Hunan Provincial Engineering Research Center for Healthy Livestock and Poultry Production; Scientific Observing and Experimental Station of Animal Nutrition and Feed Science in South-Central, Ministry of Agriculture, Changsha 410125, China
[2]University of Chinese Academy of Sciences, Beijing 100039, China
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[4]Animal Nutrition and Human Health Laboratory, School of Biology, Hunan Normal University, Changsha 410018, China
[5]College of Animal Science, South China Agricultural

Forum

Progressive MS Alliance Industry Forum: Maximizing Collective Impact To Enable Drug Development

P. Zaratin,[1,*] G. Comi,[2] T. Coetzee,[3] K. Ramsey,[3] K. Smith,[3] A. Thompson,[4] and M. Panzara[5]

of people living with MS have decided to work together to promote innovation and scientific progress regardless of geographic boundaries. The initial commitment of MS Societies will be €22 million over the next 4 years to sustain a long-term Progressive MS Research Program. The collaboration, formally known as the International Progressive MS Alliance (www.progressivemsalliance.org/), was established in 2012 with the express call to expedite the development of disease-modifying and symptoms-management therapies for people living with progressive MS. Within this framework, collaboration with the pharmaceutical and biotechnol-

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

ean

ECTRIMS-EAN Clinical Practice Guideline on Pharmacological Management of Multiple Sclerosis

General recommendations

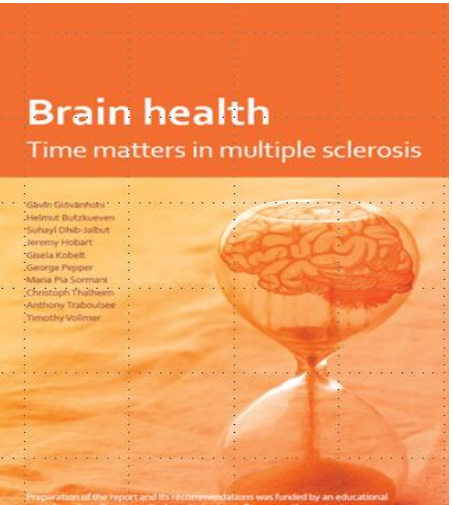
- The entire spectrum of disease modifying drugs should only be prescribed in centres where there is an adequate infrastructure to provide:
  - proper monitoring of patients
  - comprehensive assessment
  - detection of side effects and ability to promptly address them.

ECF has started an action to promote in Europe Multiple Sclerosis Care Unit

as the standard of treatment for MS

In collaboration with:

ECTRIMS – EAN – IFMS – MS Platform



&

MS in the 21st Century

Diagnostic and Treatment Practices for Multiple Sclerosis

ParadigMS
www.paradigms.foundation


ENS