CURRENT CONCEPTS IN MS—DIAGNOSIS & TREATMENT

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- WWW.COASTALNEUROLGICAL.COM
- UCTV.TV
- www.youtube.com search Parkinson's pathophysiology Dee Silver

OUTLINE OF MS TALK

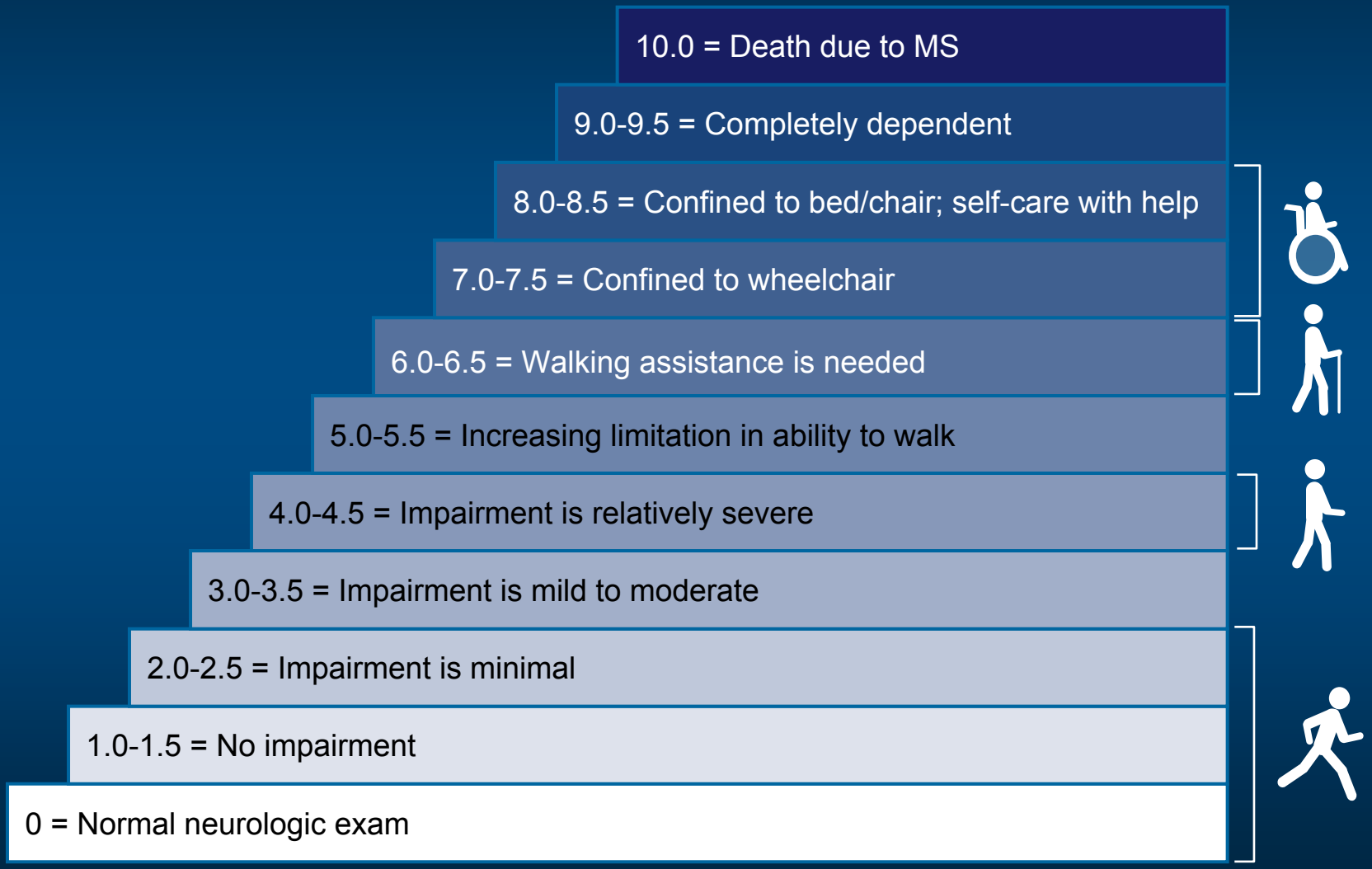
- PART 1
- EPIDEMIOLOGY
- SIGNS AND SYMPTOMS
- PATHOPHYSIOLOGY
- PART 2
- TREATMENT FORMAT
  - DMT (IMMUNOMODULATORS) EFFICACY, SAFETY, TOLERABILITY
  - DMT (IMMUNOSUPPRESORS) EFFICACY, SAFETY, TOLERABILITY
  - ALGORITHMS

FUTURE DRUGS

EPIDEMIOLOGY OF MS

- 500,000 PEOPLE IN US WITH MS
- 3 MILLION IN WORLD (+ MANY OTHERS)
- 2/3 ONSET BETWEEN 20 & 40; AVERAGE AGE OF ONSET IS 24 YEARS
- RATIO FEMALES TO MALES IS 2 TO 1
- CAUCASIANS MORE LIKELY & NORTHERN AREAS & HIGHER IN EUROPEAN DESENT

EDSS: Assessing the course of disease



Kurtzke JF. *Neurology*. 1983;33:1444-1452.

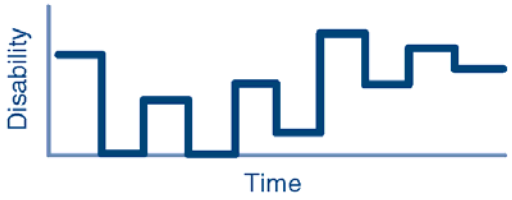
NATURAL HISTORY OF MS

- RELAPSES & REMISSIONS; VARIABLE DEGREE OF RECOVERY (25% WITH 1 POINT INCREASE OF EDSS & 50% WITH .5 INCREASE)
- MRI---FOR EVERY CLINICALLY ASSOCIATED LESION THERE ARE 5 SILENT LESIONS
- MOST GO ON TO SECONDARY PROGRESSIVE MS (SPMS); AVERAGE AFTER ONSET IS 11 TO 19 YEARS.

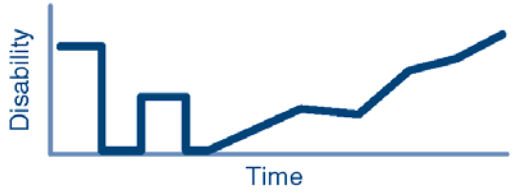
The 4 types of MS[1]

A relapse, or attack, is the period during which your symptoms worsen, or new symptoms occur[2]

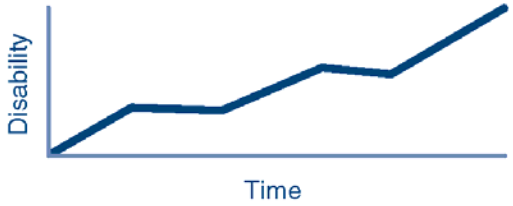
RRMS
Relapsing-remitting MS



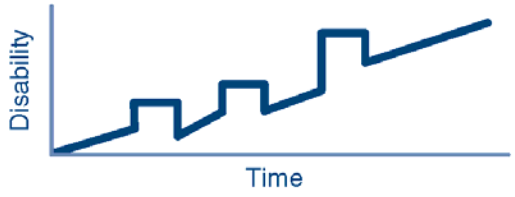
SPMS
Secondary-progressive MS



PPMS
Primary-progressive MS



PRMS
Progressive-relapsing MS



References: 1. Four disease courses of MS. NMSS Web site. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-is-ms/four-disease-courses-of-MS/index.aspx. Accessed January 26, 2010.
2. Exacerbations. NMSS Web site. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/exacerbations/index.aspx. Accessed February 16, 2010.

Diagnostic criteria for clinically definite MS

- The criteria for a diagnosis of MS have evolved over time
- Poser criteria (1983)[1]
  - 2 attacks and evidence of separate lesions
- McDonald criteria (2001, 2005, 2010)[2]
  - Formally incorporated MRI and lesions into the established diagnostic workup that focuses on neurologic history and examination, and paraclinical laboratory examinations
- Over time, changes in diagnostic criteria have incorporated clinical advances and improvements in imaging technology to allow for earlier diagnosis and treatment
- ANY TWO IN SPACE & ANY TWO IN TIME, ANY 2 ANY NEW

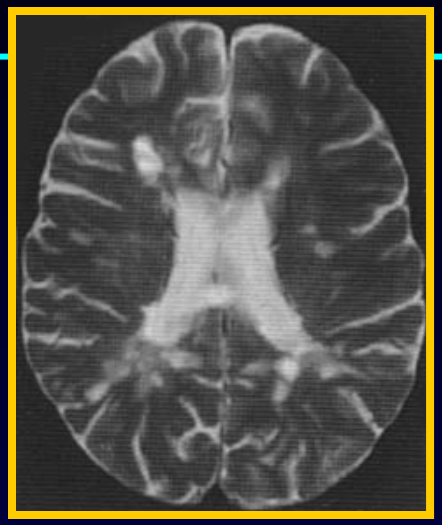
1. Poser criteria. All About Multiple Sclerosis Web site. **2.** Polman CH, et al. *Ann Neurol.* 2005;58(6):840-846.

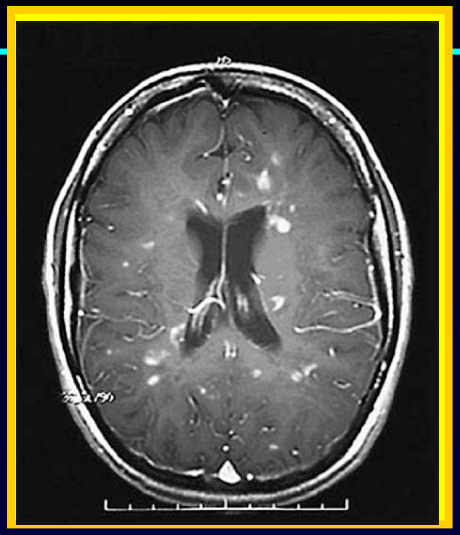
MRI Scan in MS; PERIVENTRICULAR, JUXTACORTICAL, INFRATENTORIAL, GRAY MATTER, SPINAL CORD

- T2 – CSF & LESION WHITE
  - Inflammation/edema
  - Demyelination and/or gliosis
  - Axonal loss
- T1 Non-Enhanced: CSF & LESION BLACK
  - Demyelination and/or gliosis (chronic black holes)
  - Axonal loss – within and outside lesions
- T1 Enhanced: WITH CONTRAST, CSF BLACK, LESION WHITE
  - Predominantly acute inflammation, break down in BBB

Conventional MRI in MS Clinical Practice

T2
BOD*



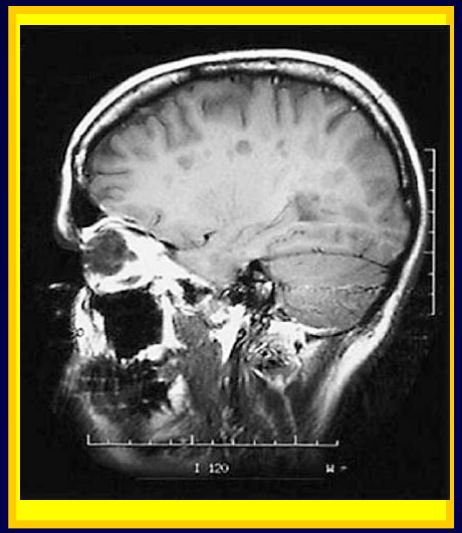


T1/Gd postcontrast
Active Inflammation†

T1 precontrast
Hypointensities†

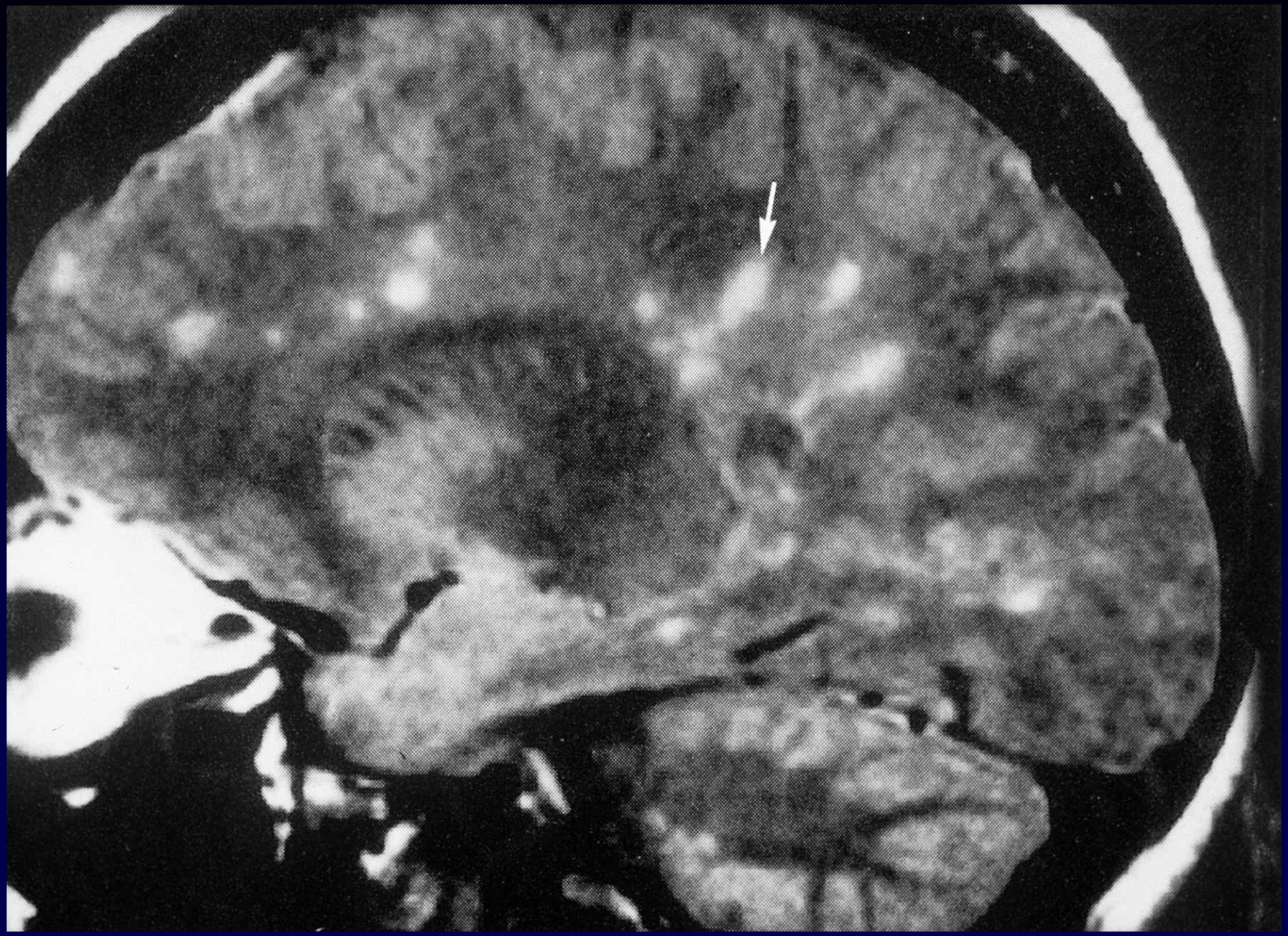
Acute Hypointensities

Chronic Black Holes

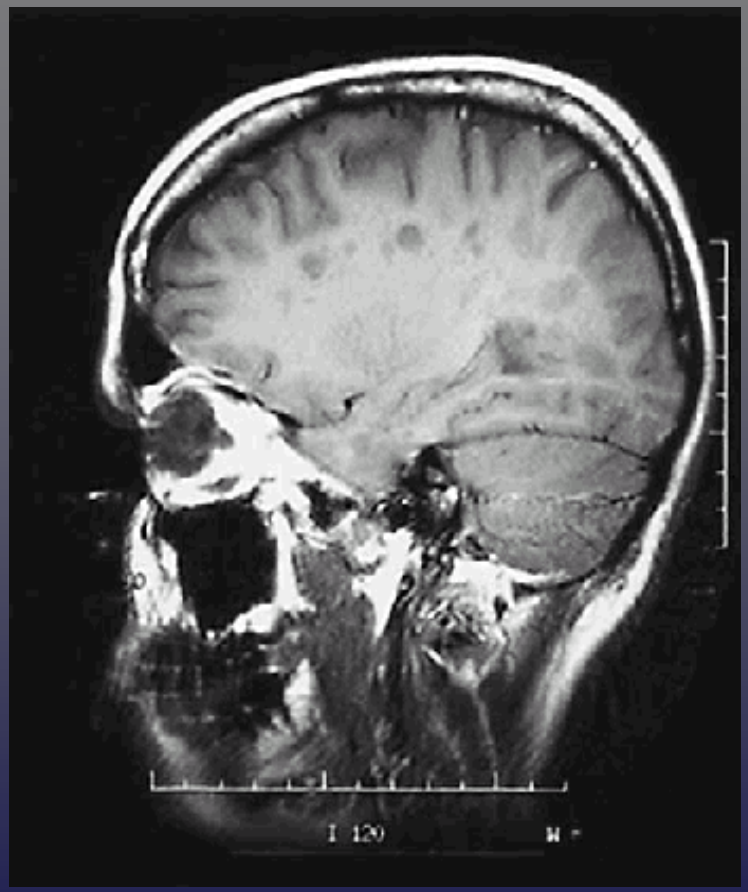


- **Stongest correlation with progression of disability**
- **Correlates with cognition**
- **Represents most severe tissue destruction**

*Reprinted with permission from Miller DH et al. *Magnetic Resonance in Multiple Sclerosis*. Cambridge: Cambridge University Press; 1997. †Noseworthy JH et al. *N Engl J Med*. 2000;343:938-952.

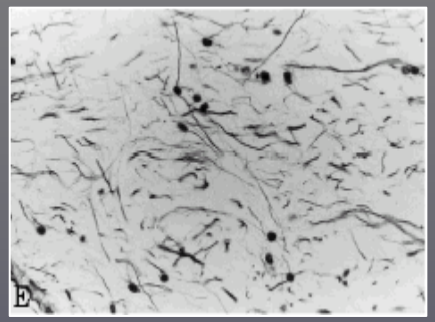


Histopathologic Correlates of Black Holes: T1 Hypointensity Correlates with Axonal Loss



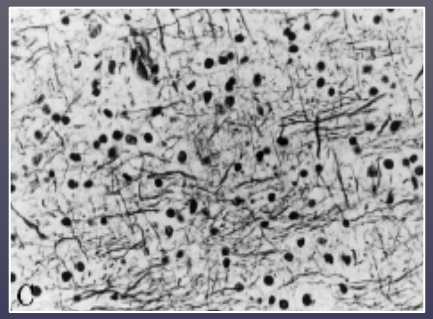
Bodian axonal density

1. **Strongly hypointense**



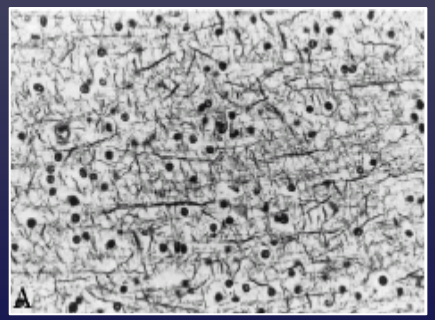
20%

2. **Mildly hypointense**



60%

3. **NAWM**



100%

Reprinted with permission from Noseworthy JH et al. *N Engl J Med*. 2000;343:938-952.

Reprinted with permission from van Waesberghe JH et al. *Ann Neurol*. 1999;46:747-754.

RADIOLOGICAL ISOLATED SYNDROME

- NO SYMPTOMS—OFTEN NOT REALIZED BY PATIENT OR DISCOVERED BY CAREFUL HX
- MRI DONE FOR SOME OTHER SIGN OR SYMPTOM (ER OR OFFICE FOR HEADACHES , TRAUMA, NONSPECIFIC S & S
- MRI—USUALLY T2 LESIONS, MAYBE T1 & RARELY T1 ENHANCED; ANY 2 & ANY NEW

CLINICAL ISOLATED SYNDROME
CIS

- SYMPTOM THAT MAY FIT WITH HISTORY OF MS—ONE CLINICAL EVENT BY HISTORY KNOWN
- MRI FINDINGS IN APPROPIATE AREAS; PERIVENTRICULAR, JUXTACORTICAL, INFRATENTORIAL, GRAY MATTER OR SPINAL CORD
- ANY 2 & ANY NEW

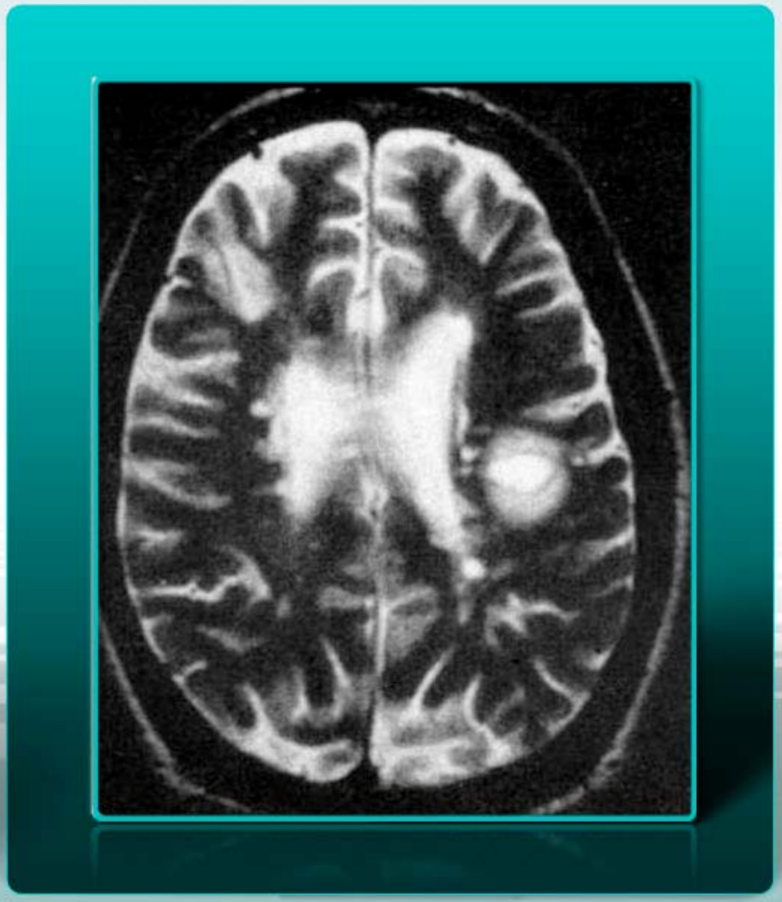
There are many possible symptoms of MS[1]

- Walking problems
- Coordination problems
- Balance problems
- Depression
- Emotional changes
- Dizziness and vertigo
- Sexual dysfunction
- Fatigue
- Pain
- Changes in cognitive function
- Vision problems
- Numbness
- Bowel/bladder dysfunction
- Spasticity

Reference: 1. About MS: symptoms. NMSS Web site. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-MS/symptoms/index.aspx. Accessed February 12, 2010.

Patient Profile

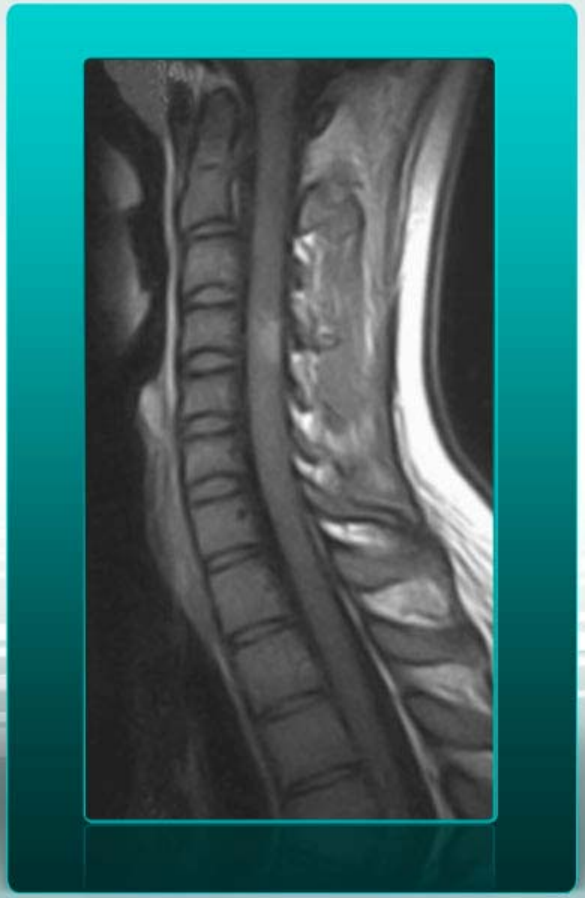
- **21-year-old, right-handed female**
  - Has developed painful vision loss in her left eye
  - Last year, the patient had numbness in her right leg lasting for 3 weeks
    - Confirmed by neurologist who also found increased reflexes in left arm
    - No treatment offered; numbness resolved completely
  - Diagnosed with optic neuritis
  - Abnormal MRI brain scan



Patient Profile

Returning to our patient profile:

- **Treated with steroids, symptoms resolved after 3 weeks**
- **Patient did well until 10 months later, when she developed vertigo, right facial numbness and tingling, and unsteady gait**
  - Repeat MRI brain scan revealed a new pontine lesion; MRI cervical spine scan was normal
  - Started on Avonex® (interferon beta-1a)
- **After 9 months of treatment with Avonex, patient experienced gait disturbance and right-leg paresis**
  - MRI brain scan: 2 new non-enhancing right parietal subcortical lesions
  - MRI cervical spine scan revealed lesion at C4 with faint Gd+



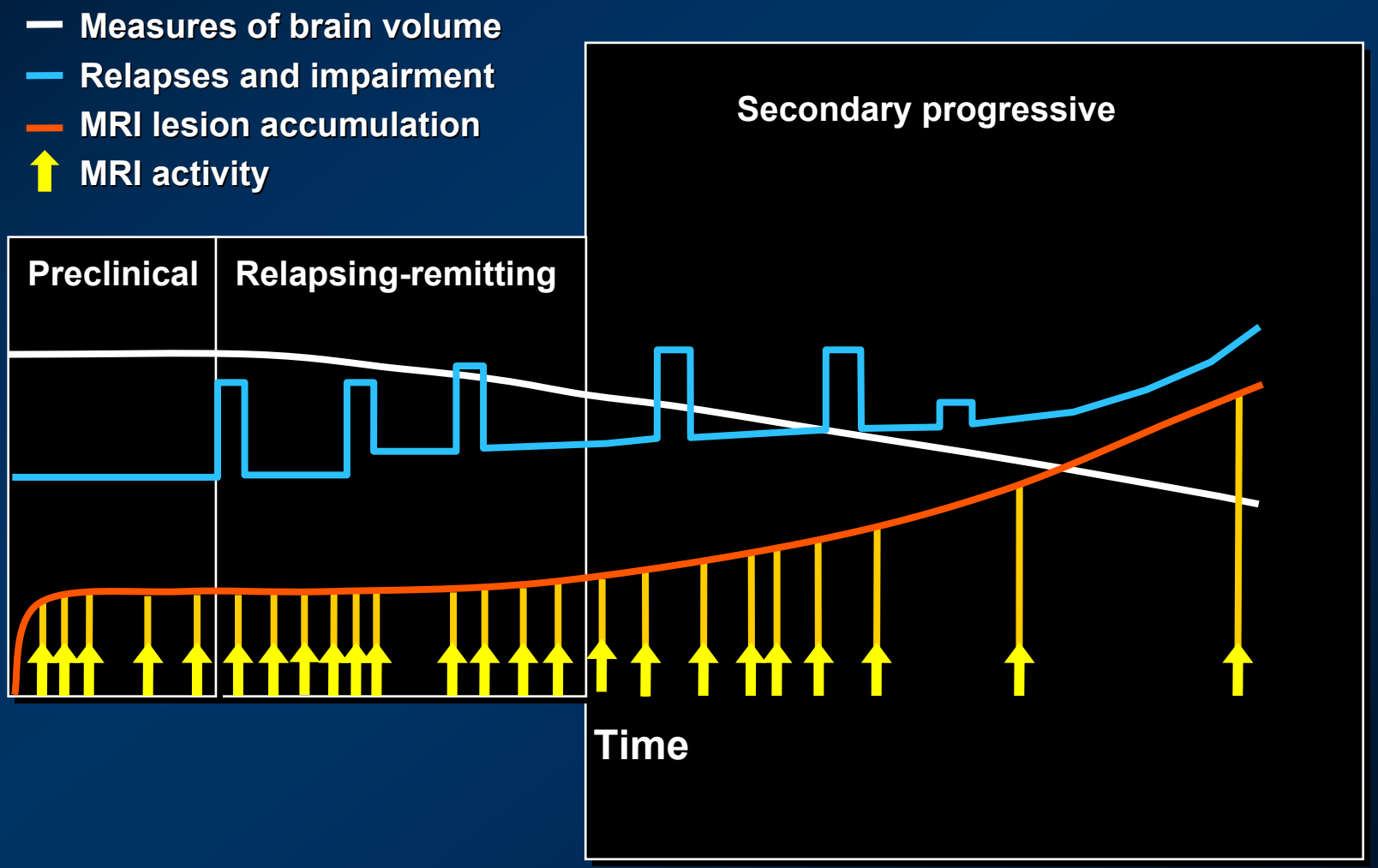
Gd+=gadolinium enhancement.

Avonex is a registered trademark of Biogen Idec.

TREATMENT ALGORITHM

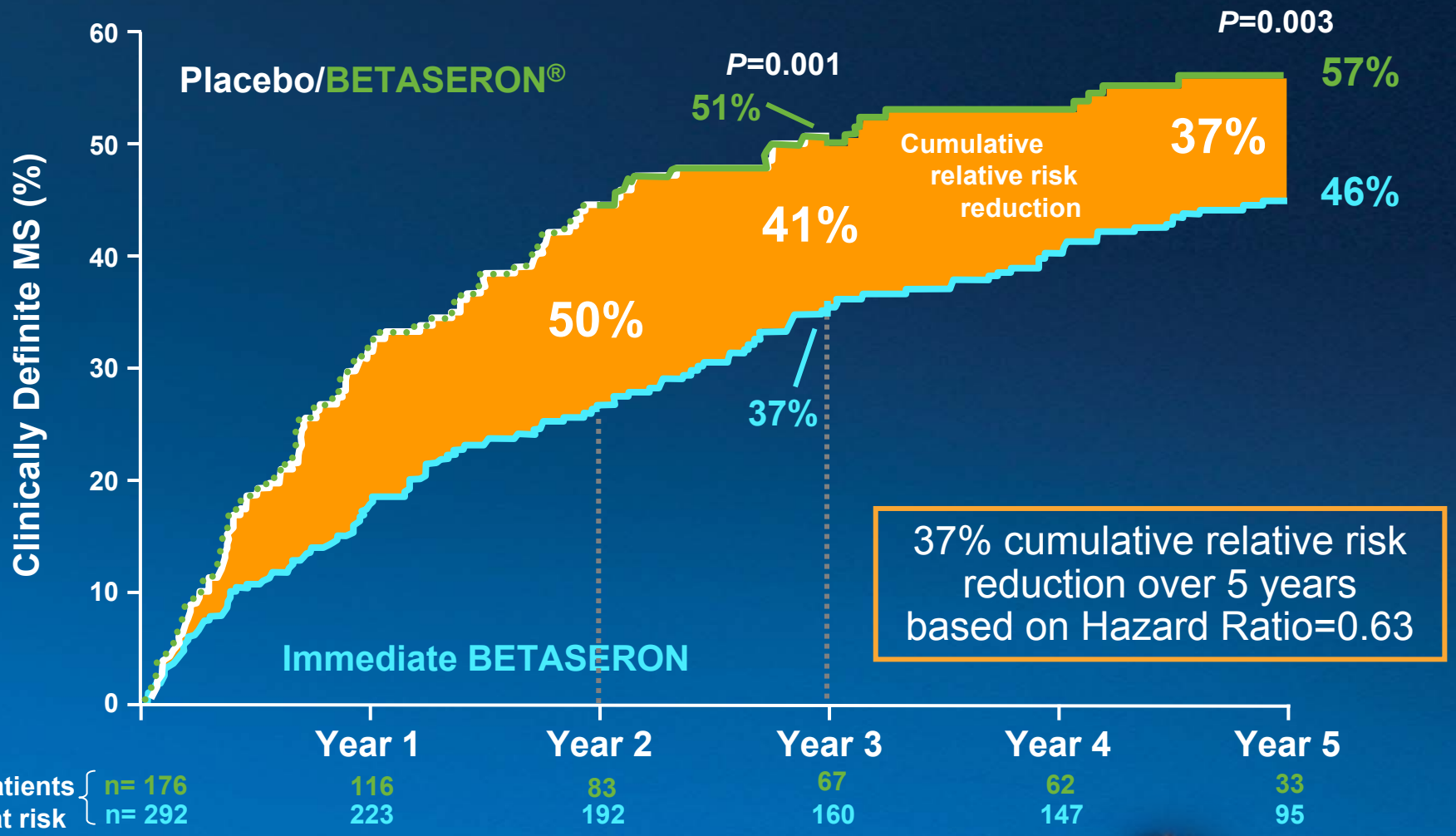
- RIS; DETERMINE CORRECT DX WITH CSF & REPEAT MRI; ? RX IF Gd+ & LOOKS LIKE MS
- CIS; AGGRESSIVE RX WITH DMT'S & CLOSE FOLLOW UP WITH MRI IN 1 YR
- RRMS; DMT'S IMMUNOMODULATORS WITH CLOSE FOLLOW UP & IF RELAPSE & MRI CHANGES (ESPECIALLY IF Gd+) OR NEW # T2 LESIONS ON MRI, CHANGE DMT
- IF RRMS & HIGH BURDEN ON MRI & OR FREQUENT & PROGRESSIVE COURSE, RX WITH NATALIZUMAB, FINGOLIMOD,OR TERIFLUNOMIDE
- USE MP OR ACTHAR IN RELAPSE

Natural History Of MS
Clinical and MRI Measures



Hartung HP et al. *The Lancet* 2002;360:2018-2025.

Time to CDMS
5 Year Results of the Integrated Data-set



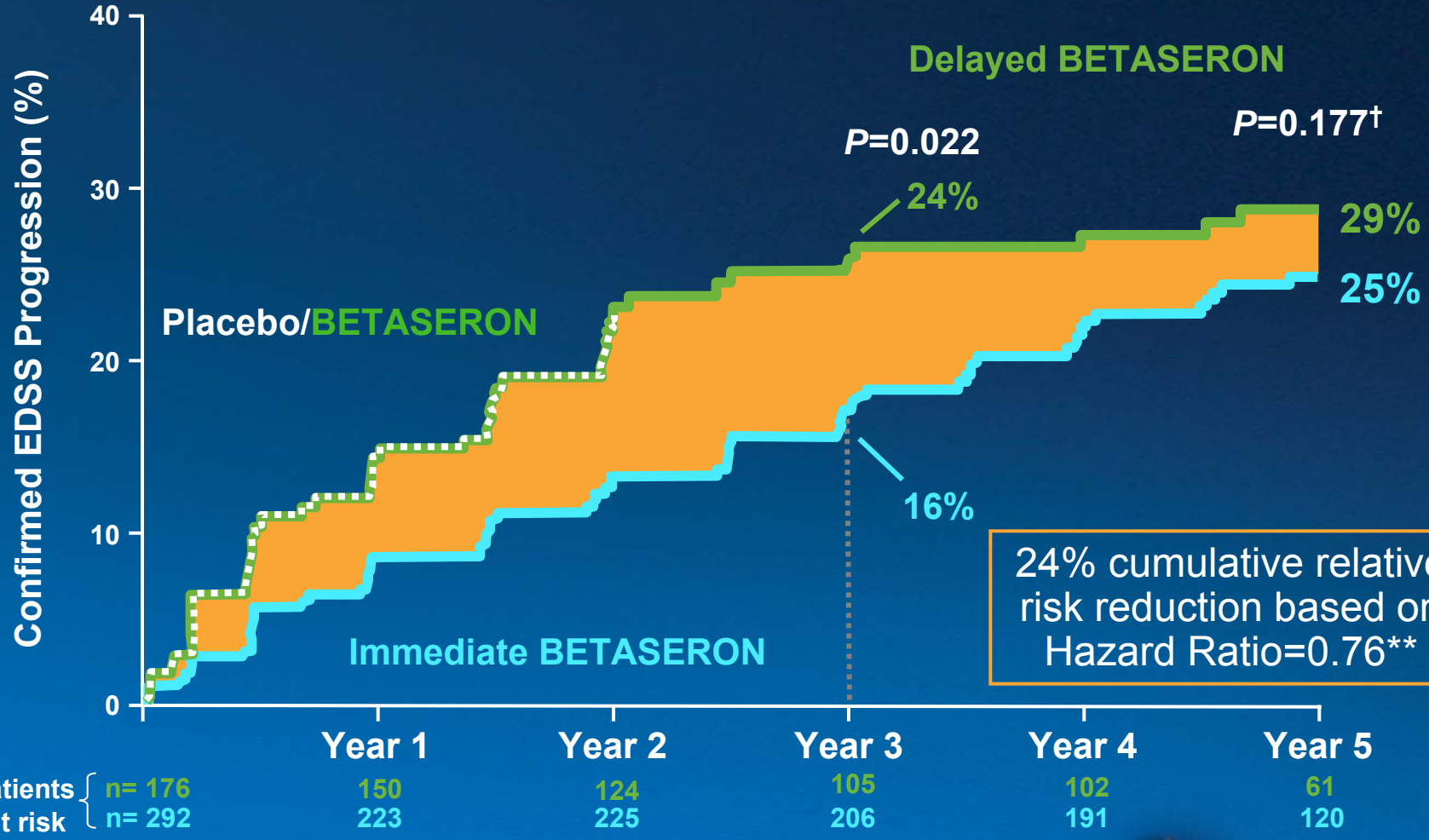
37% cumulative relative risk reduction over 5 years based on Hazard Ratio=0.63

*By proportional hazards regression adjusted for age/gender/steroids/T2-lesions/Gd-lesions

Kappos L, et al. Lancet. 2007;370:389-397; Freedman MS, et al. Poster [P901] ECTRIMS, September, 2008, Montreal, Quebec, Canada.

Time to Confirmed Disease Progression*

5-year Results of the Integrated Data-set



*Main analysis without unscheduled visits

**By proportional hazards regression adjusted for T2-lesion volume

Kappos L, et al. *Lancet*. 2007;370:389-397; Freedman MS, et al. Poster [P901] ECTRIMS, September, 2008, Montreal, Quebec, Canada.

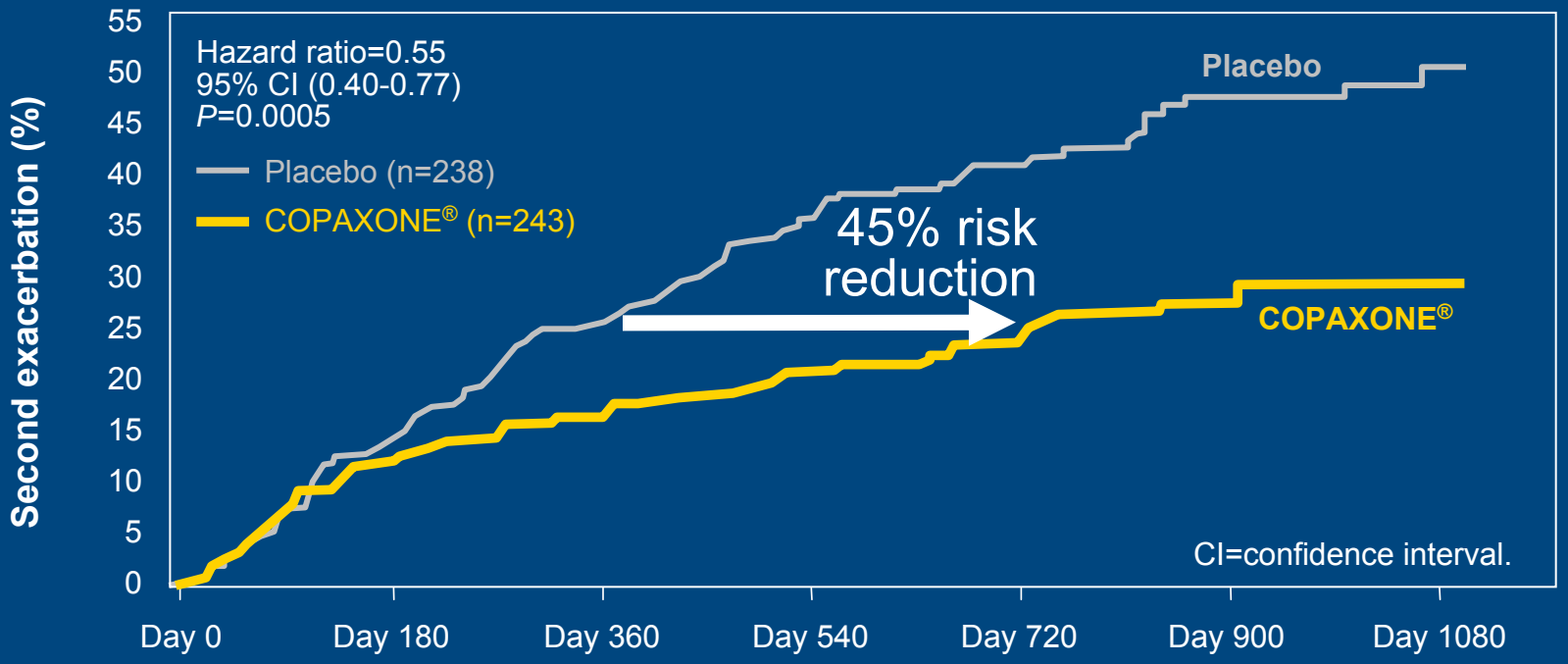
BETASERON® (INTERFERON BETA-1b)

NOT A MOMENT TOO SOON.

†Not statistically significant

PreCISe: Efficacy in clinically isolated syndrome (CIS)

Primary endpoint: COPAXONE® (glatiramer acetate injection) significantly delayed the second clinical event[2,3]

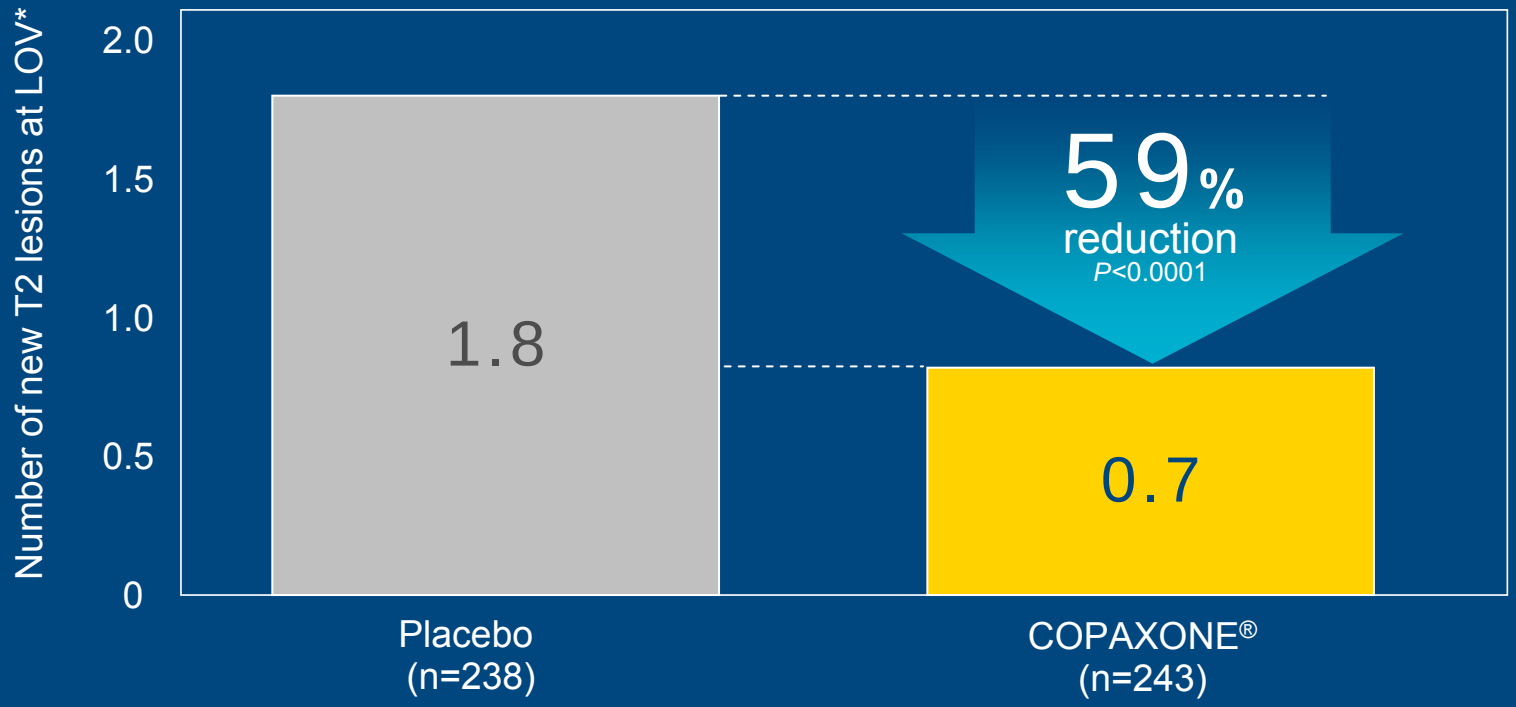


PreCISe: A multicenter, randomized, double-blind, placebo-controlled study in patients presenting with a single, well-defined, unifocal, neurologic event highly suggestive of MS (CIS) and ≥2 T2 lesions, each ≥6 mm in diameter. Patients were randomized to receive either COPAXONE® 20 mg SC daily (n=243) or placebo (n=238). The primary endpoint was time from randomization to second clinical event.[3,4]

2. COPAXONE® PI. **3.** Comi G, Filippi M. AAN 2008. Abstract LBS.003. **4.** Data on file. Teva Neuroscience, Inc.

PreCISe: T2 lesions

Secondary endpoint: COPAXONE® (glatiramer acetate injection) significantly reduced new T2 lesions[2,4]

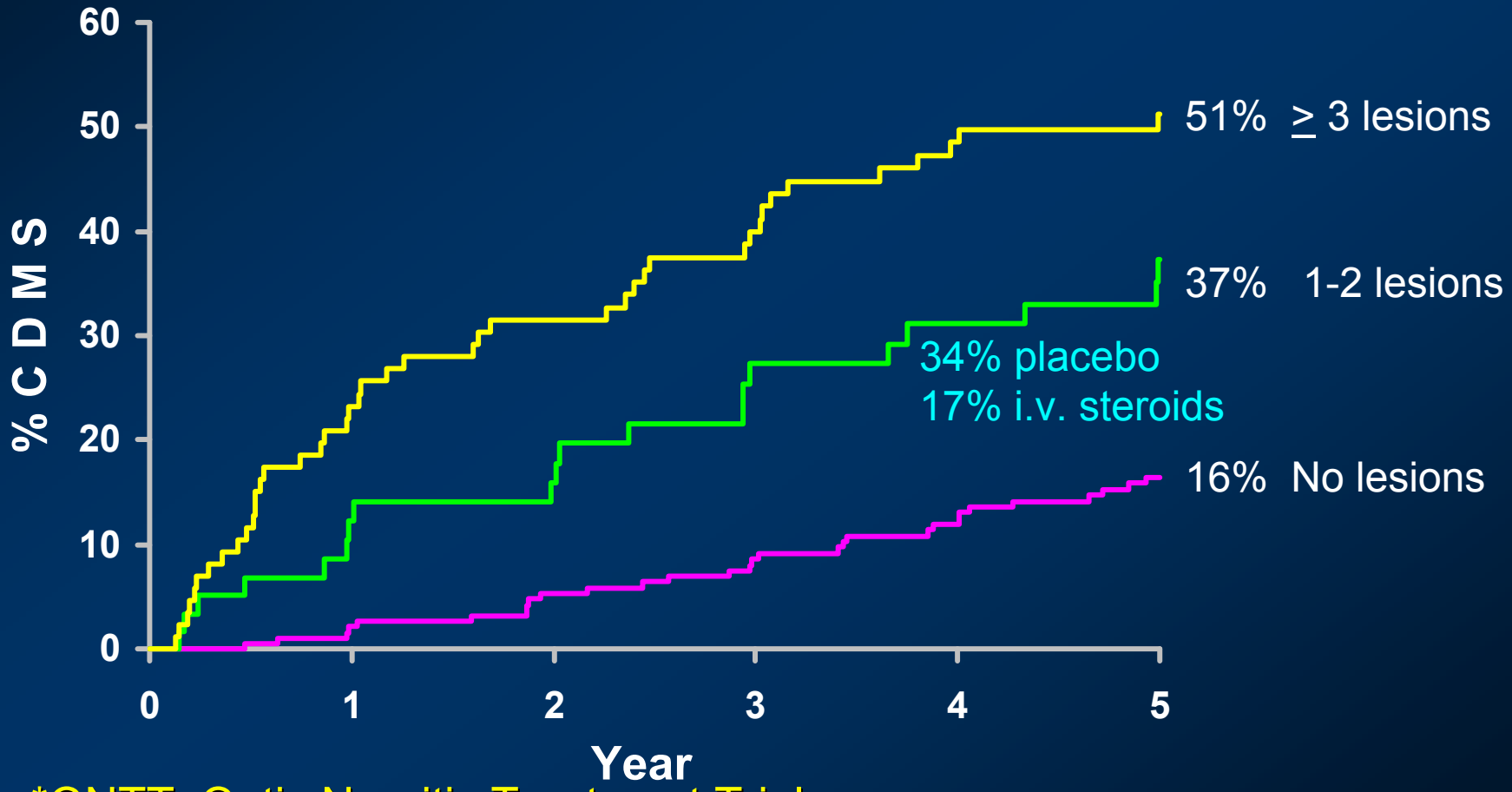


PreCISe: See slide 6 for full study design.

2. COPAXONE® PI. **4.** Data on file. Teva Neuroscience, Inc.

*Last observed value.

MRI Predicts CDMS Development*

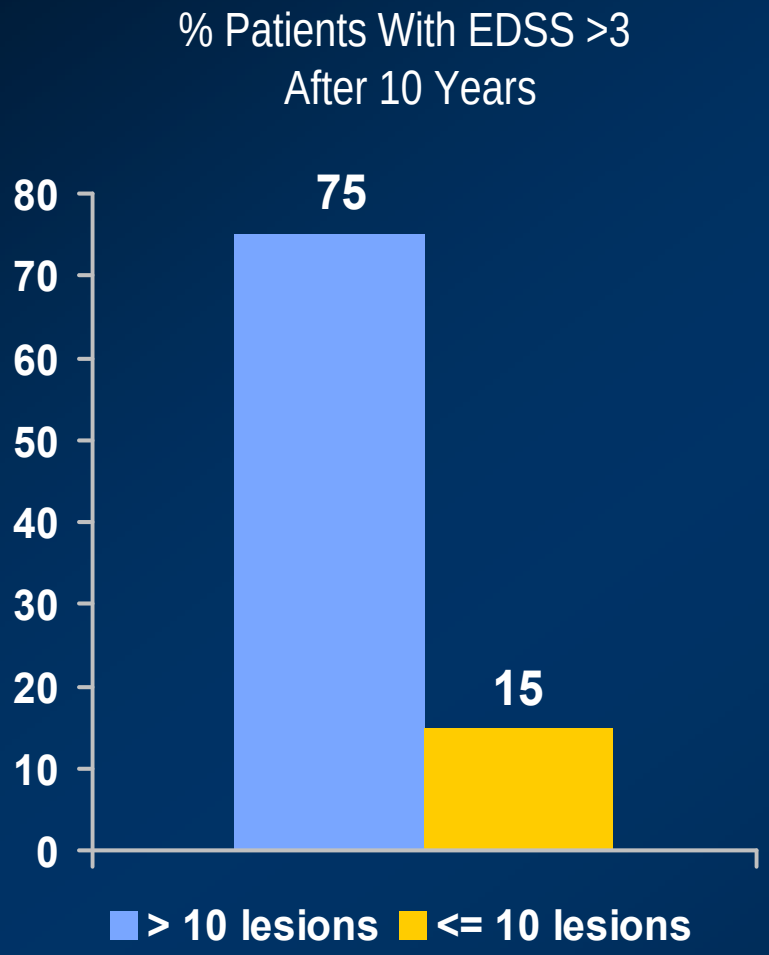


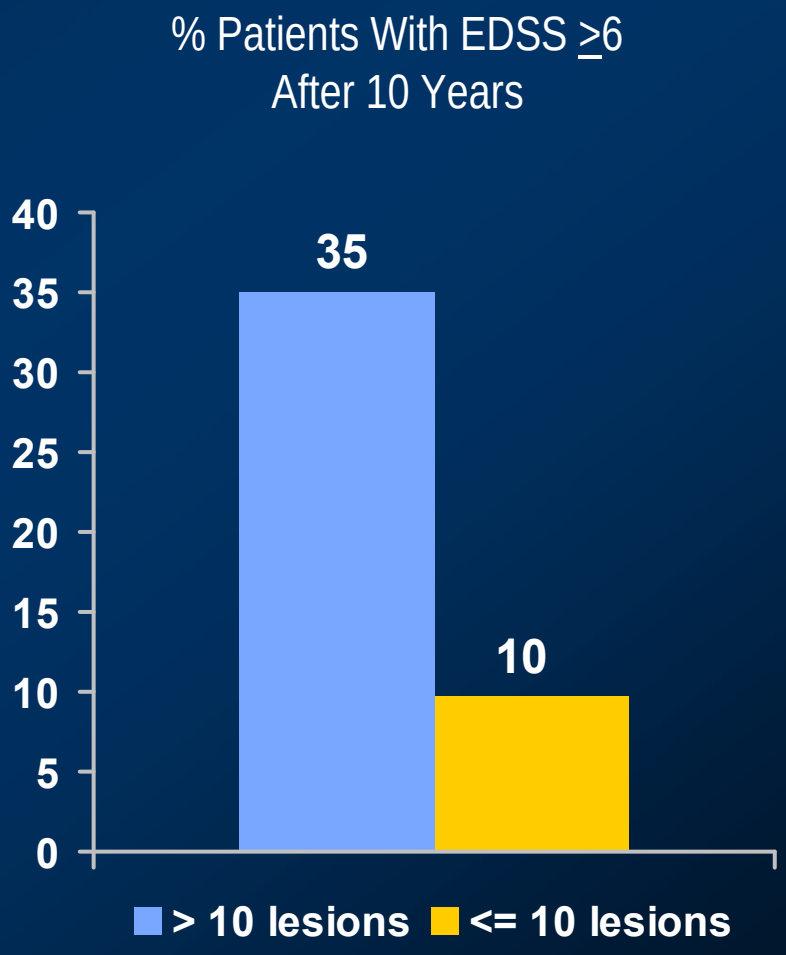
*ONTT: Optic Neuritis Treatment Trial

The exact relationship between MRI findings and the clinical status of patients is unknown

Arch Neurol 1993 Aug;50(8):841-6

Early MRI Events Correlate with Disease Progression

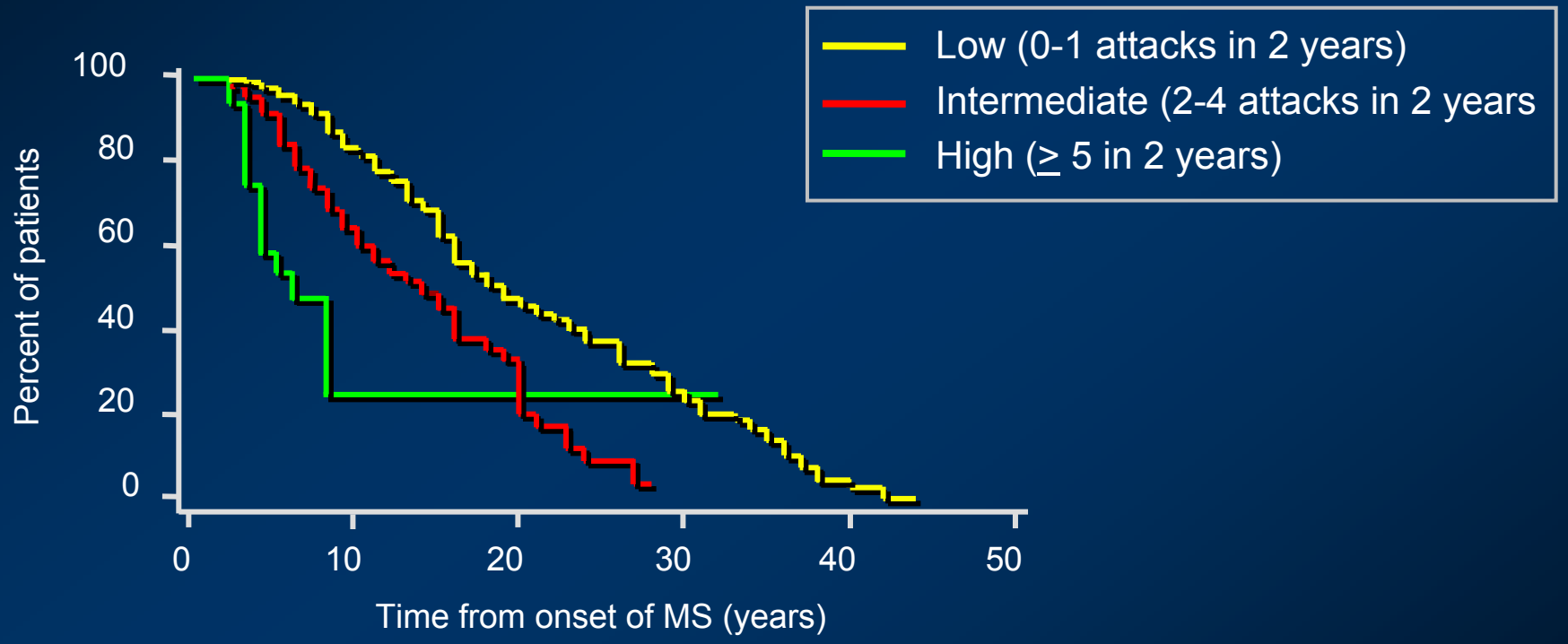




The exact relationship between MRI findings and the clinical status of patients is unknown

Brex et al, N. Engl. J. Med, 346, 158-164
O'Riordan, et al. Brain. 1998.

Early Relapses Affect Long-term Disability

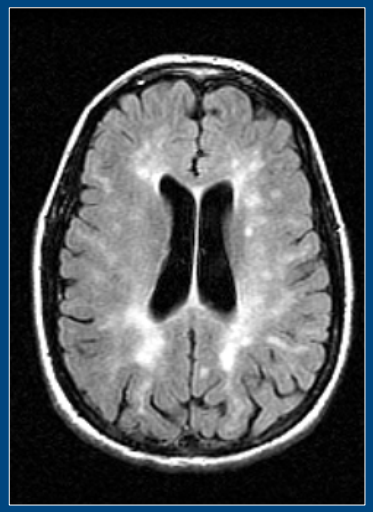


Actuarial analysis of disability: percentage of patients not having reached DSS 6: difference between the groups significant ($P<0.0001$).

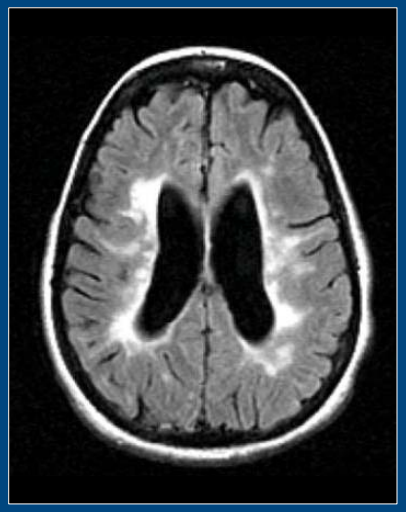
Weinshenker BG, et al. Brain. 1989;112:1422.

Brain atrophy: A long-term MRI metric

- Change in EDSS[18]

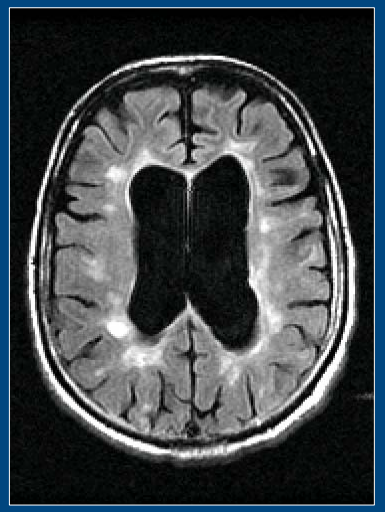


10-year disease duration;
EDSS 2.5



15-year disease duration;
EDSS 4.0

PBVC=6.2% (10-15 years)



20-year disease duration;
EDSS 6.5

PBVC=13.2% (10-20 years)

PBVC=7% (15-20 years)

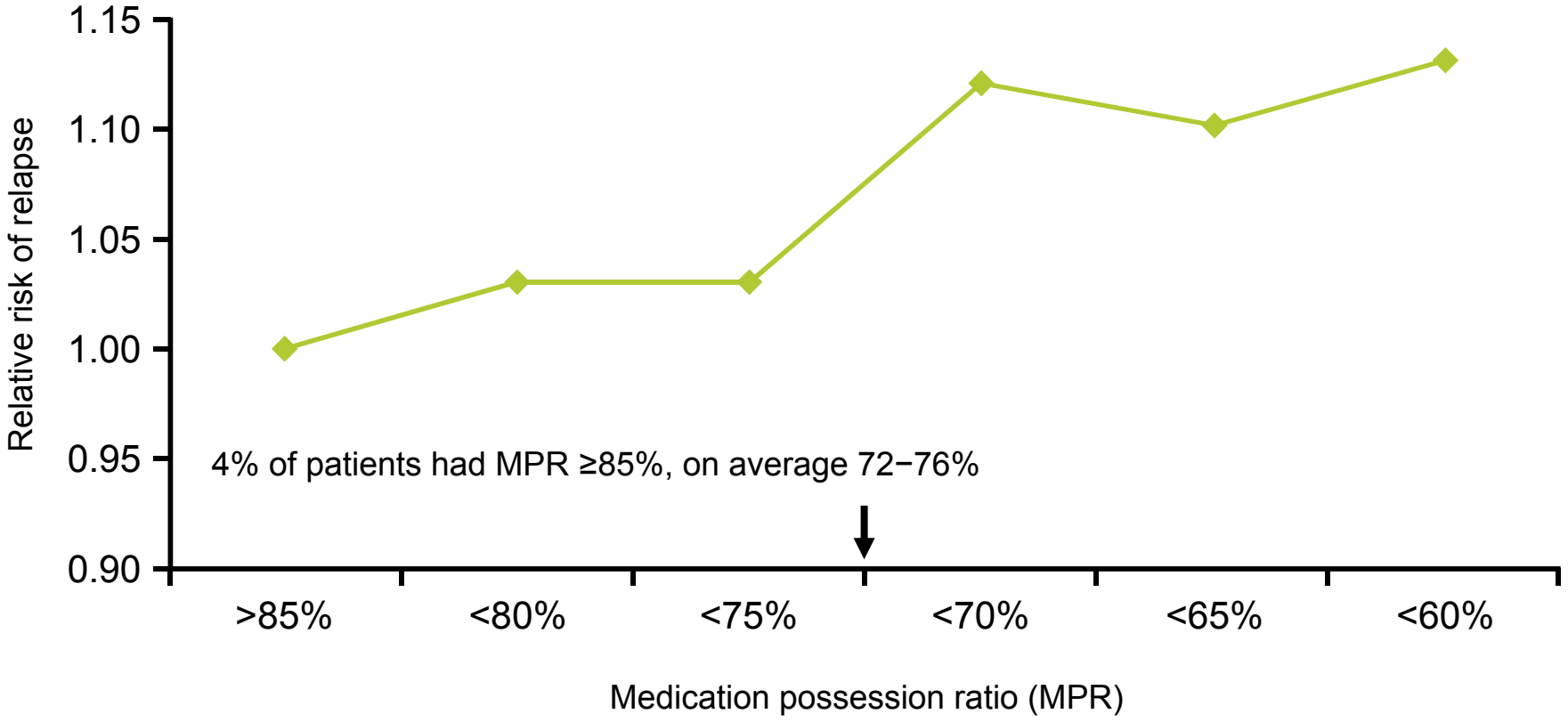
- Cognitive impairment[18]
- Fatigue[19]

Brain atrophy images courtesy of R. Zivadinov. Unpublished data.

18. Barkhof F. *J Neurol*. 2004;251(suppl 4):IV/6-IV/12. **19.** Tedeschi G, et al. *J Neurol Sci*. 2007;263:15-19.

Association Between Non-adherence and Relapse

Non-experimental, retrospective analysis of pharmacy and medical claims data
(includes all licensed IFNβ drugs excluding Extavia®)



N=1606, 2006−2008
IFNβ: interferon-beta
Steinberg SC, et al. *Clin Drug Investig.* 2010;30:89-100.

Suggested Indications of a Suboptimal Response

Indications

- >1 relapse per year or lack of improvement from baseline[1]
- Incomplete recovery from relapses[1]
- Poly-regional neurologic involvement[1]
- Involvement of brainstem or spinal cord lesions[1]
- Loss of neurologic function that disrupts daily activities[1]
- Persistent IFNβ or natalizumab Nabs[2]
- Patient factors that influence response (non-adherence, ethnicity)[3-5]

Measures to verify changes

- Established scores (eg, EDSS)[6]
- Repeat MRI scans[2]
- Rule out other causes (eg, urinary tract infection)[7]
- Nab test for patients currently on IFNβ or natalizumab therapy[2]

Collective results inform the prescriber/patient decision to continue or modify DMT therapy[6]

1. Cohen B, et al. *Neurology.* 2004;63:S33-40; 2. Rudick R, et al. *Lancet Neurol.* 2009;8:545-59; 3. Steinberg SC, et al. *Clin Drug Investig.* 2010;30:89-100.
4. Cree B, et al. *Arch Neurol.* 2011;68:464-8; 5. Cree B, et al. *Arch Neurol.* 2005;62:1681-3; 6. Rieckmann P, et al. *Ther Adv Neurol Dis.* 2008;1:181-92;
7. Rantell A. *Br J Nurs.* 2009;18:920-5.

Use of MRI in MS

- MRI findings may predict relapse rate[1*]
- Surrogates of disability: MRI activity and relapse[2†]
  - IFNβ treatment reduced the risk of EDSS worsening by 31%
  - 1-year MRI activity and relapses independently accounted for >60% of the treatment effect
- Further data are needed to validate MRI as a surrogate of disability[3]
  - EDSS can be considered insensitive
  - Need to differentiate between surrogacy and correlation in literature

MRI predictors of relapse[1*]

Predictor	Relapse rate *P* value
Baseline, before treatment	
Presence of Gd+ lesions	0.032
Number of relapses in last 2 years	<0.0001
Baseline T2 lesions, volume	0.010
Black hole lesion volume	0.030
Within 1 year of IFNβ treatment	
New MRI lesions	0.003

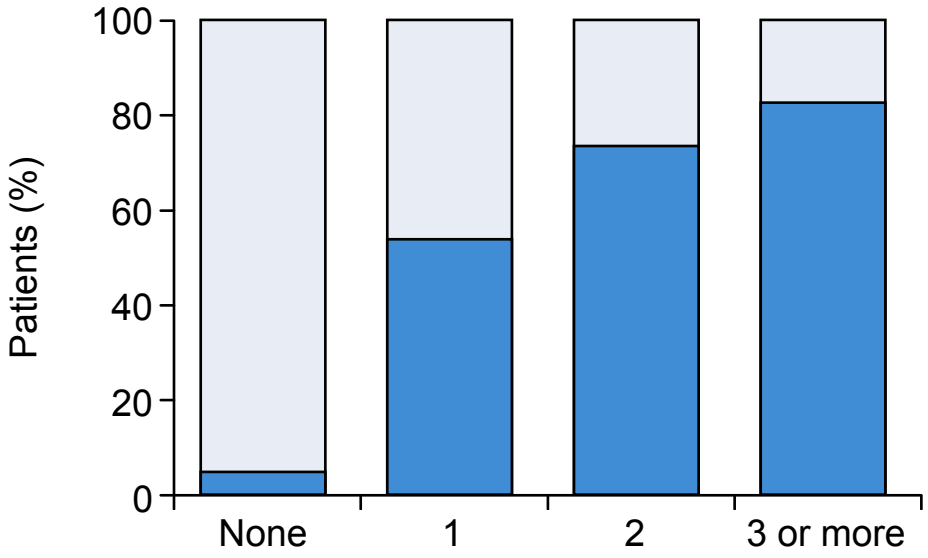
*Patients (N=857) treated with IFNβ-1b, parameters obtained before and within the first year of treatment
†Defined as EDSS increase ≥1 point over 2 years; Combination of 1-year MRI lesion activity and relapses accounted for 100% of the treatment effect on EDSS
1. Hartung HP, et al. Presented at the American Academy of Neurology, 2012; 2. Sormani M, et al. *Neurology.* 2011;177;1684-90; 3. Ebers G, et al. *Neurology.* 2012:1367 [Letter to the editor in response to Sormani M, et al 2011].

Predictors of Poor Treatment Response

- New lesions on T2-weighted MRI after 1 year of IFNβ[1]

- Short-term disease activity[2*]
  - T2-weighted lesions, Gd+ lesions
  - Relapses

Percentage of patients defined as "Responders" and "Poor Responders"[1]



Responders	228	24	12	10
Poor responders	11	28	33	48

*Over first 2 years of IFNβ

1. Prosperini L, et al. *Eur J Neurol.* 2009;11:1202-9; 2.Bermel R, et al. Presented at the 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis. Poster no. P1011: 2011.

MRI Measures to Assess Suboptimal Response

Selected features of MRI measures used in MS and associated pathology[1]

- T2 weighting:
  - New lesions: inflammation, demyelination
  - Enlarging T2 lesions: increasing inflammation, demyelination
  - Chronic lesions: non-specific (eg, demyelination, scarring, tissue destruction)
- T1 weighting:
  - Acute hypointense lesions (black holes): edema associated with inflammation
  - Chronic hypointense lesions: tissue destruction with demyelination and axon loss
- Gd+ enhanced T1 weighting: disruption of the blood-brain barrier
- Magnetization transfer: myelin changes
- MRS
  - NAAP peak: axon integrity
  - Lipid peak: demyelination
- Changes in brain atrophy: brain atrophy that is not specific for cell type

MRS: magnetic resonance spectroscopy; NAAP: *N*-acetylaspartate

Cohen B, et al. *Neurology.* 2004;63:S33-40.

CSF Biomarkers of MS Activity (Oligoclonal Bands)

- B-cell activation presenting as OCB production[1]
  - Predicts conversion from CIS to MS
  - Correlates with MRI activity, relapse onset, and disability progression

- Presence of OCB at disease onset predicts a more aggressive disease course (EDSS score reaching 4; *P*=0.02)[2*]

- Elevated NFL proteins are associated with conversion to more severe MS[3]

*Relapsing-onset patients included relapsing-remitting and secondary progressive MS.
CSF: cerebrospinal fluid; OCB: oligoclonal bands; CIS: clinically isolated syndrome; NFL: neurofilament light
1. Disanto G, et al. *Neurology.* 2012;78:823-32; 2. Sola P, et al. *Mult Scler.* 2010;17:303-11; 3. Salzer J, et al. *Mult Scler.* 2010;16:287-92.

Additional Recommendations to Improve Patient Participation (INDIVIDUAL RESPONSIBILITY & EDUCATION)

- Schedule frequent office visits, particularly during the first year of treatment, to help ensure tolerance and adherence[1,2]
- Improve patient–prescriber and patient–nurse interactions[3]:
  - Understand and identify barriers to adherence
  - Maintain communication
  - Educate resources
  - Improve QoL
  - Schedule manageable visits
- Provide a working definition of relapse during DMT therapy[1]
- Help define realistic expectations (cure versus relieving symptoms)[4]

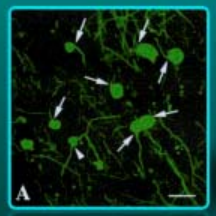
1. Rieckmann P, et al. *Ther Adv Neurol Discord.* 2008;1:181-92; 2. Rio J, et al. *Mult Scler.* 2005;11:306-9; 3. Lugaresi A, et al. *Patient Prefer Adherence.* 2012;6:143-52; 4. Perrin-Ross A, et al. *Neurology.* 2008;71:S21-S23.

Summary

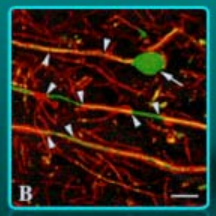
- A suboptimal response to DMT may contribute to changes in relapse rate/severity, MRI activity, and disability
- Patient factors such as adherence and individual risk should be considered when assessing treatment response
- Work for individual responsibility & patient & family education
- Patients may not always display or complain of clinical symptoms but may have other markers, such as changes in MRI, indicative of disease activity
- A variety of patient and clinical factors can contribute to suboptimal response; this underlies the importance of a well-defined treatment plan with routine follow-up

Pathology of MS Is Continuous and Usually Leads to Permanent Disability

- Inflammatory activity and demyelination occur from the onset of MS[1]
- Repeated inflammatory injury leads to irreversible axonal damage due to formation of demyelinated plaques[1,2]
- Disease pathology is continuous, even during periods of apparent remission[3]
- Axonal transection is abundantly seen in active and chronic active lesions in patients as early as 2 weeks to 27 years from disease onset. Aggressive early treatment should therefore be considered.[2]



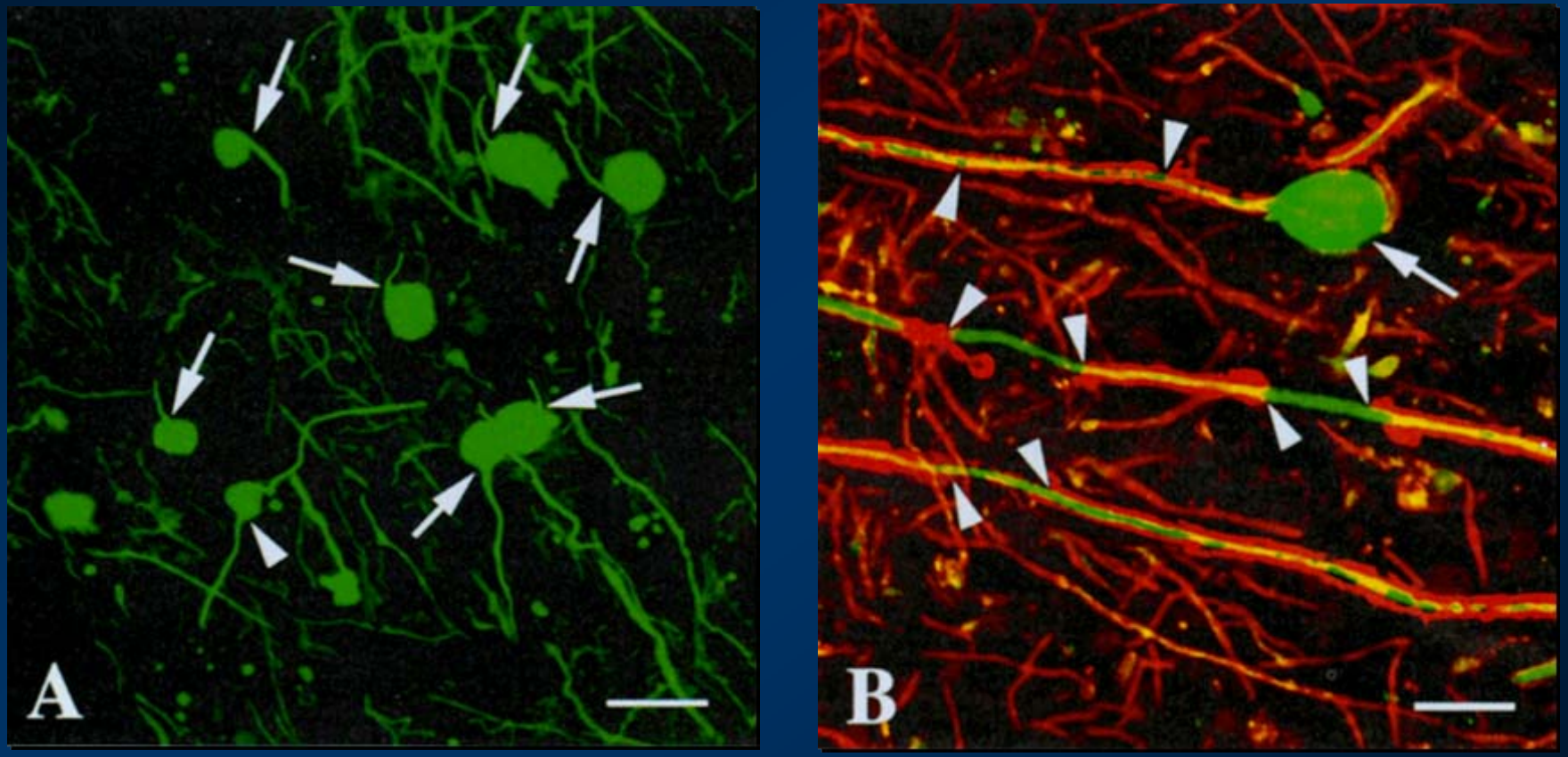
Transection of axons (arrows)



Demyelination (arrowheads)

1. Riekmann P. *Int MS J*. 2005;1242-51. 2. Trapp BD et al. *N Engl J Med*. 1998;338:278-285. 3. Vrecko DE. *Efficient Designs of Multiple Sclerosis Clinical Trials*. British Columbia, Canada: Simon Fraser University; 2007.

Axons are Transected in MS Plaques



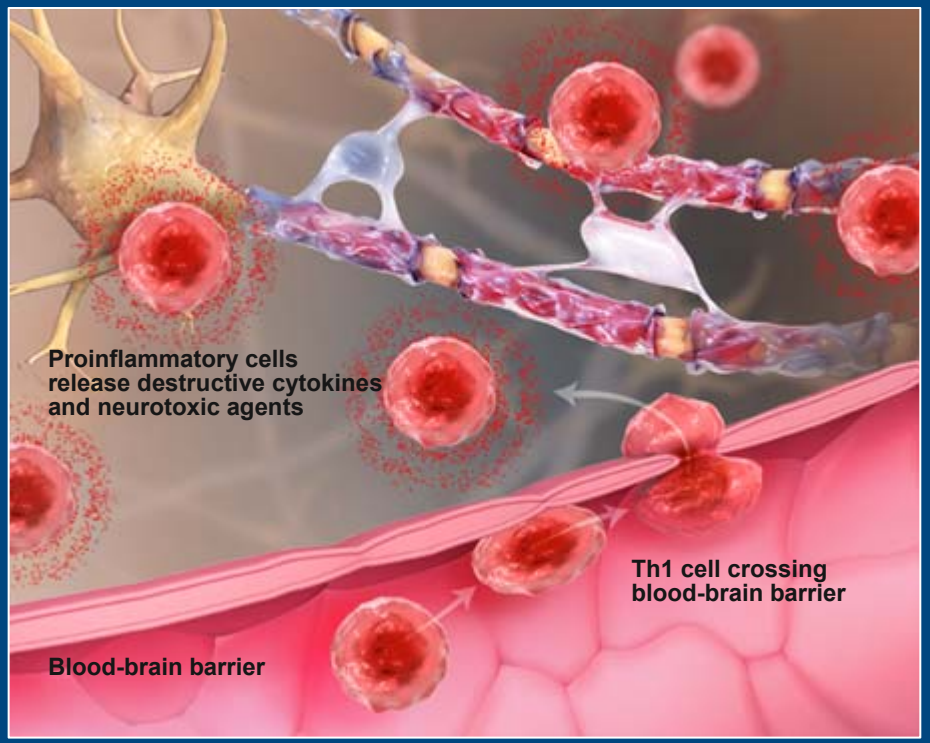
SMI-32 (non-phosphorylated neurofilament)
-demyelinated axons and swellings MBP intact axons

Trapp BD, et al. *N Engl J Med.* 1998;338:278-285.

HISTORY OF MS DRUG RELEASE

- BETASERON—1993
- AVONEX—1996
- COPAXONE—1997
- REBIFF—2002
- NAVANTRONE--2006
- TYSABRI--2010
- ESTAVIA--2009
- GILENYA—2011
- AUBAGIO—2012

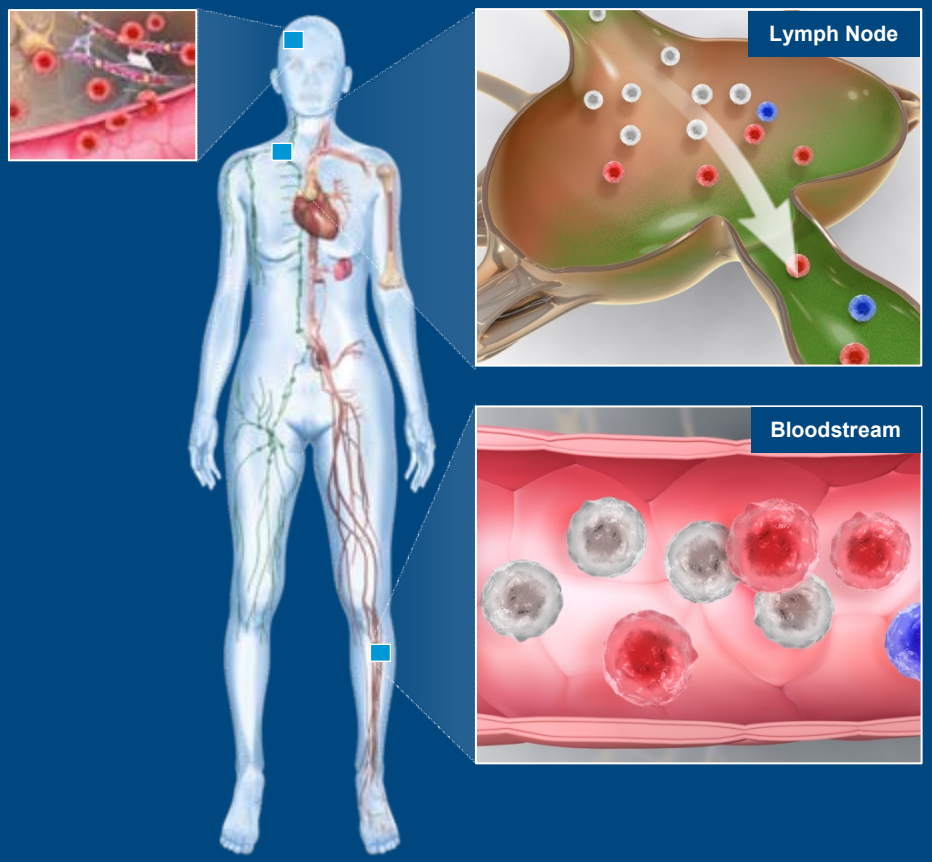
The pathophysiology of MS[1-4]



MS-specific proinflammatory immune cells cross from the bloodstream into the central nervous system (CNS) secreting proinflammatory cytokines, and eventually destroy myelin and facilitate neuronal death.

1. Ziemssen T. *J Neurol*. 2005;252(Suppl 5):V/38-V/45. **2.** Yong VW, et al. *Neurology.* 2007;68(22 Suppl 3):S32-S37. **3.** Dhib-Jalbut S. *Neurology.* 2007;68(22 Suppl 3):S13-S21. **4.** Tzartos JS, et al. *Am J Pathol.* 2008;172(1):146-155.

Impact on the immune system in MS: Expanding our view beyond the CNS[1-6]

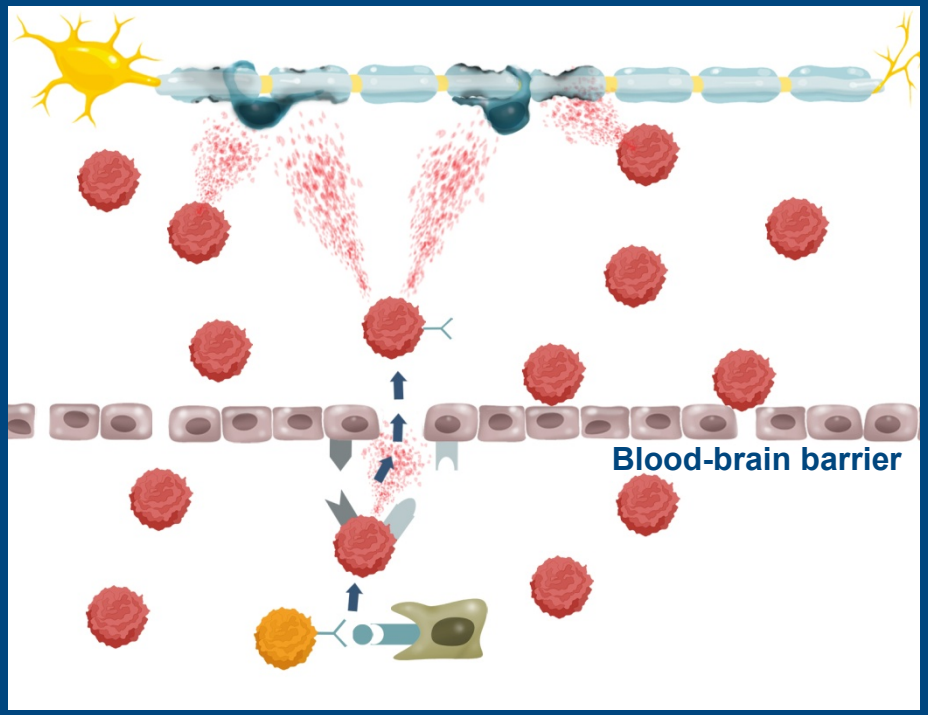


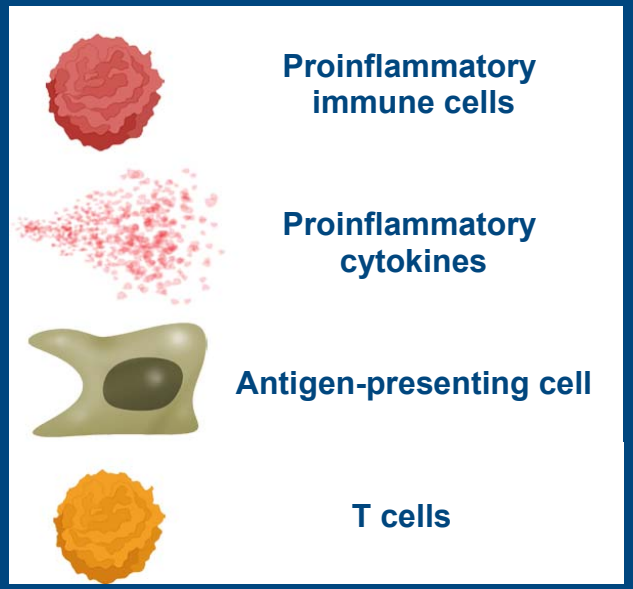
- MS is a debilitating autoimmune disease characterized by both inflammation and axonal degeneration[1]
- In order to regulate CNS damage, treatment of MS is focused on restoring immune system balance[2-5]
- It is important to expand our view to consider treatment impact on the overall immune response

Proinflammatory Th1 cells (MS-specific)
Anti-inflammatory Th2 cells (MS-specific)
Naïve T cells

1. Kasper LH, et al. *Neurology.* 2010;74(Suppl 1):S2-S8. **2.** Ziemssen T. *J Neurol*. 2005;252(Suppl 5):V/38-V/45. **3.** Yong VW, et al. *Neurology.* 2007;68(22 Suppl 3):S32-S37. **4.** Dhib-Jalbut S. *Neurology.* 2007;68(22 Suppl 3):S13-S21. **5.** Tzartos JS, et al. *Am J Pathol.* 2008;172(1):146-155. **6.** Itano AA, et al. *Nat Immunol.* 2003;4(8):733-739.

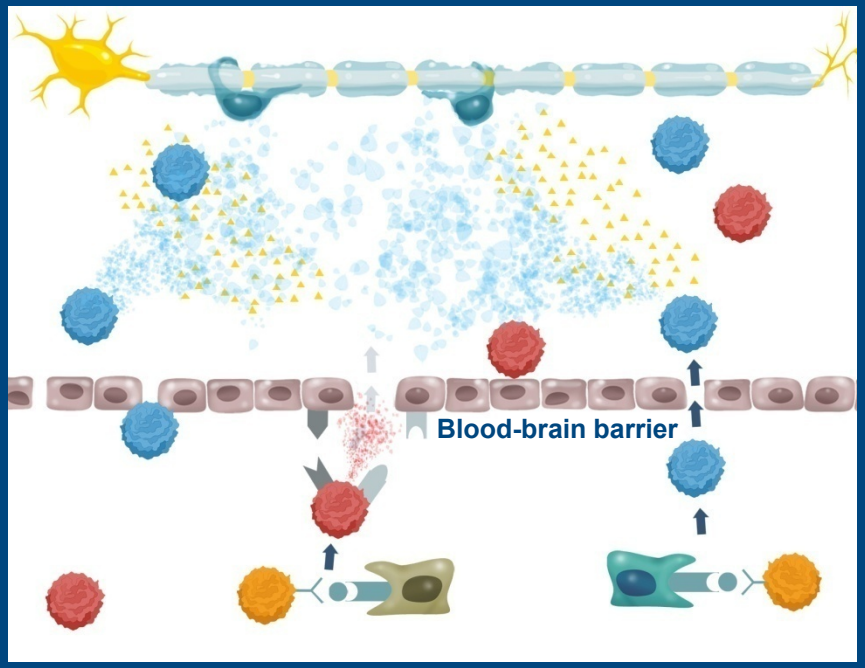
MS: Immune dysfunction[1-4]

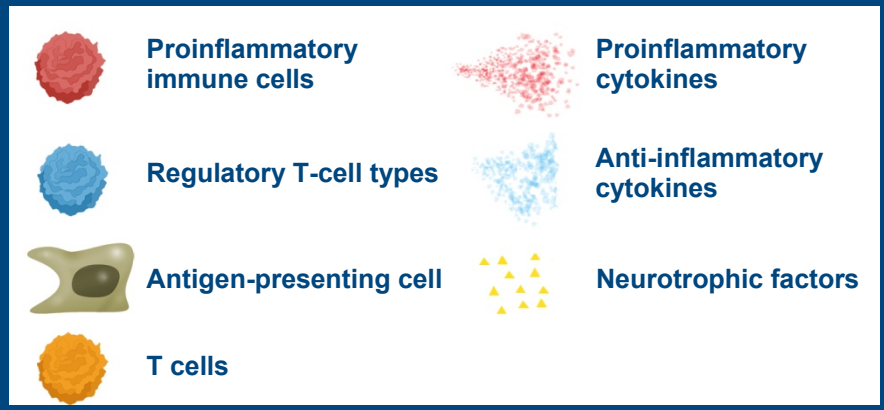




1. Ziemssen T. *J Neurol*. 2005;252:V/38-V/45. **2.** Yong VW, et al. *Neurology.* 2007;68:S32-S37. **3.** Dhib-Jalbut S. *Neurology.* 2007;68:S13-S21.
4. Tzartos JS, et al. *Am J Pathol.* 2008;172:146-155.

Presumed MOA of COPAXONE® (glatiramer acetate injection): Immunomodulation[36,37]



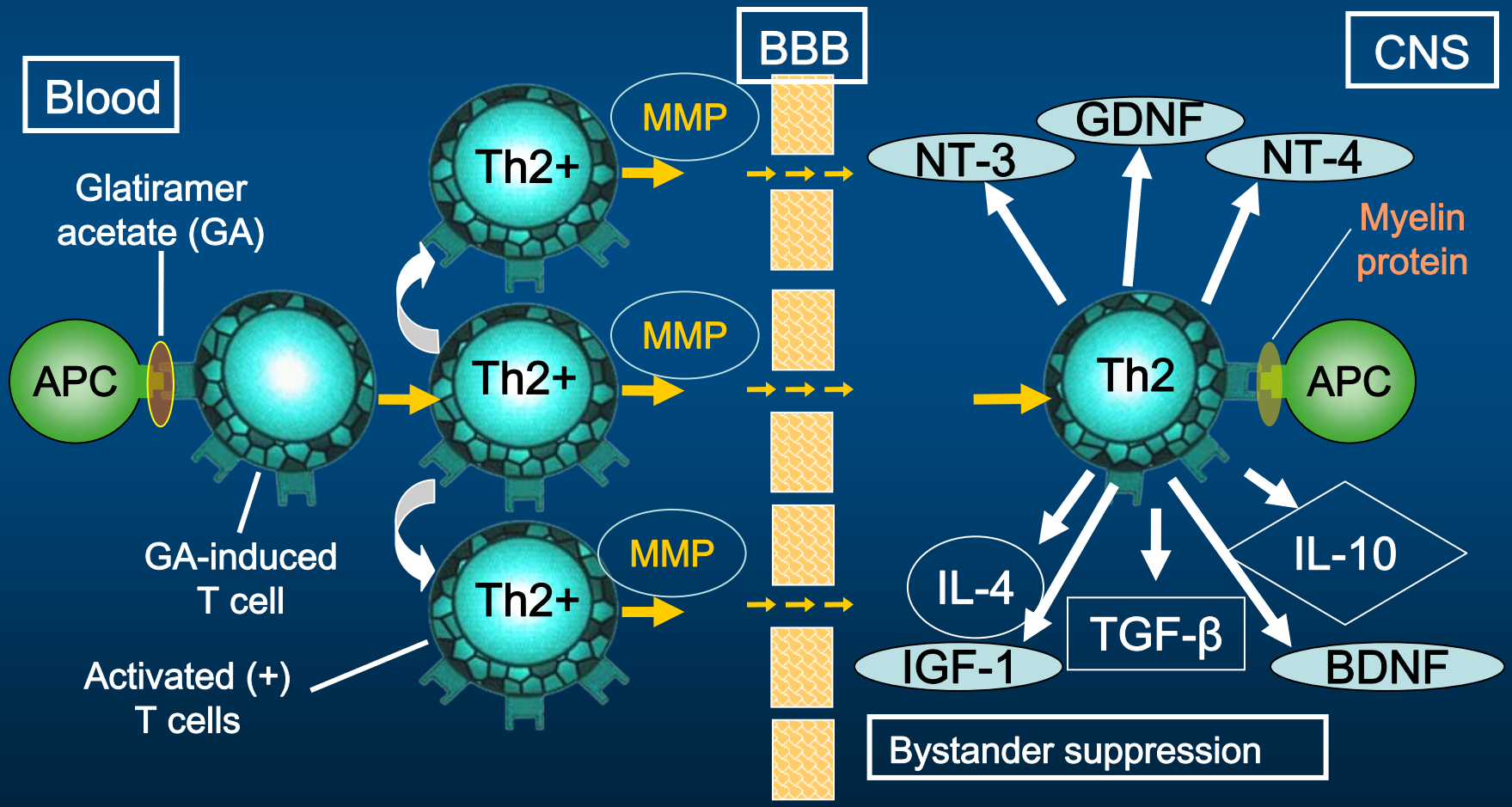


- Induces a population of regulatory T-cell types (Th2,Treg)
- Anti-inflammatory cytokines and neurotrophic factors are released
- May prevent nerve damage and lead to remyelination*

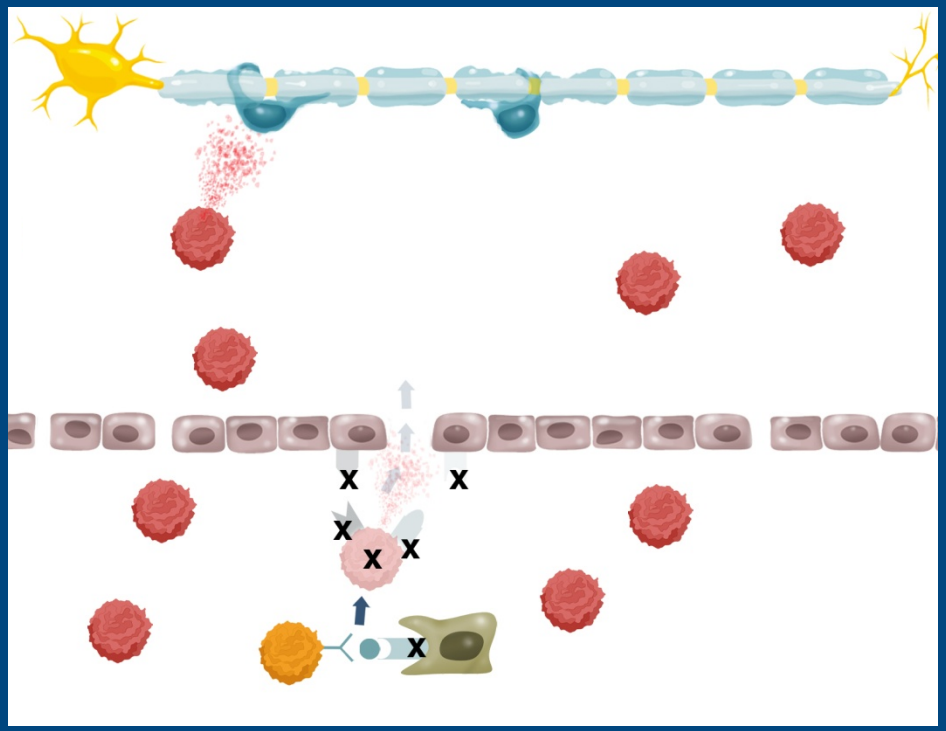
* It is not known if these effects play an important role in the observed clinical activity of COPAXONE® in MS. T cells derived from MS patients receiving therapy with COPAXONE® have been shown to produce neurotrophic factors, including brain-derived neurotrophic factor, and to prevent nerve damage and enhance in situ remyelination and repair in animal models.

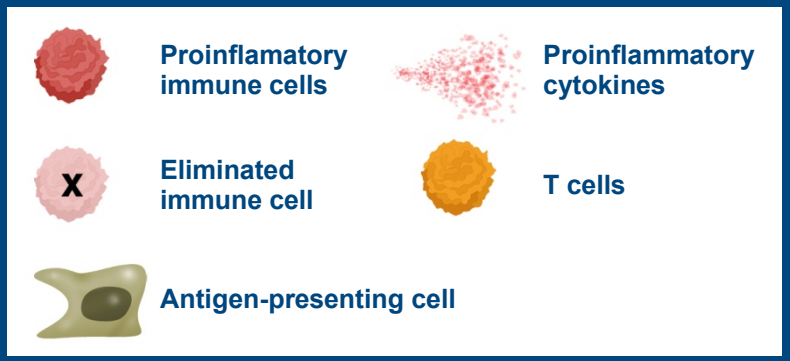
36. Weber MS, et al. *Neurotherapeutics.* 2007;4:647-653.
37. Aharoni R, et al. *Proc Natl Acad Sci U S A.* 2008;105:11358-11363.

Glatiramer acetate-induced Cytokines and Neurotrophic Factors



Presumed MOA of IFNβ: Immunomodulation[38]

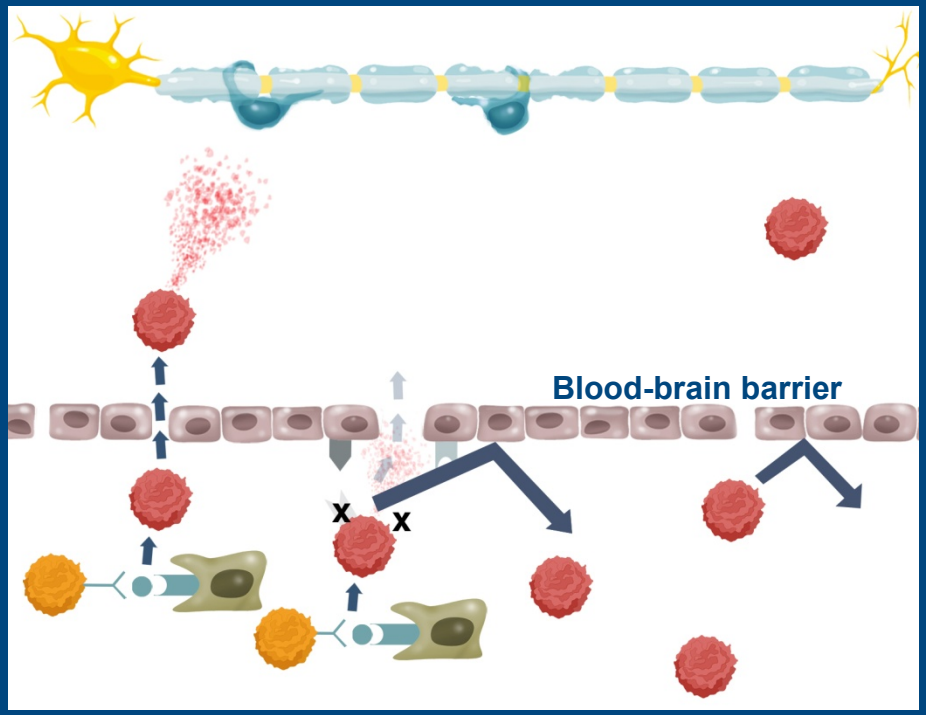


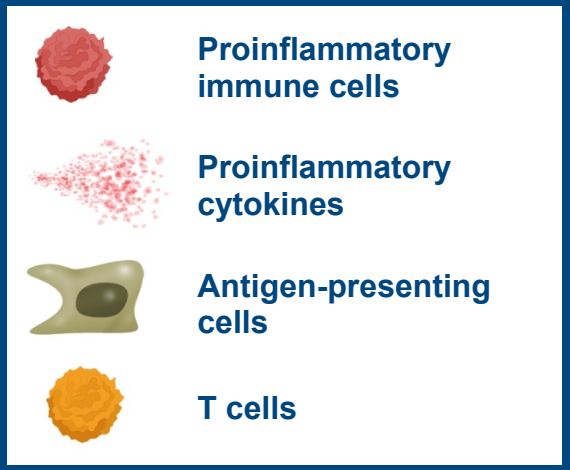


- Reduces proinflammatory cytokine levels
- Reduces lymphocyte trafficking into the central nervous system (CNS)

38. Betaseron® prescribing information. Bayer HealthCare Pharmaceuticals Inc.

Presumed MOA of Natalizumab: Reduction of cell trafficking[19]

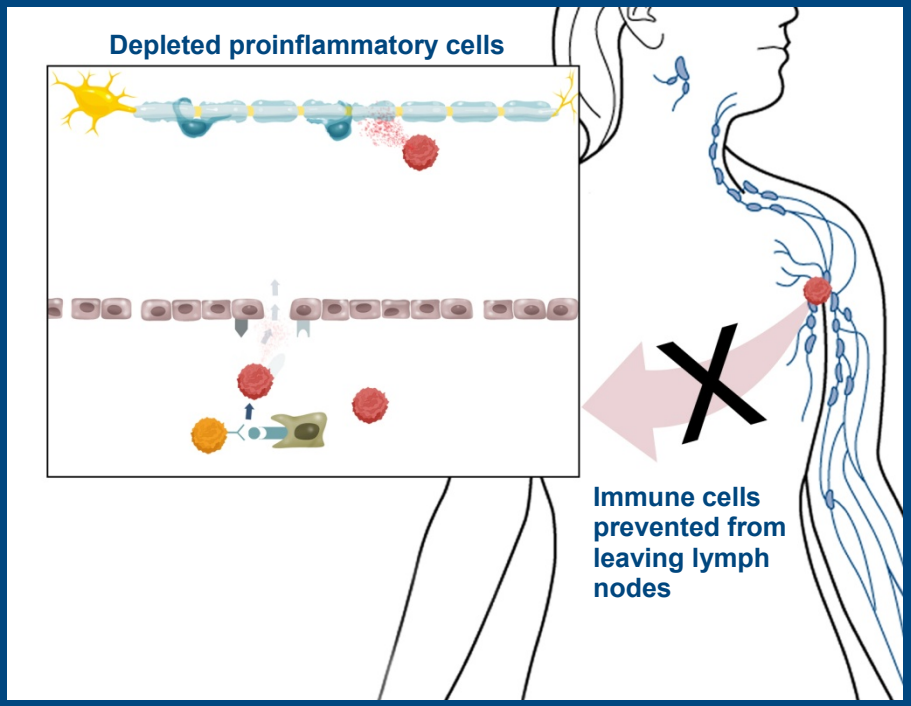


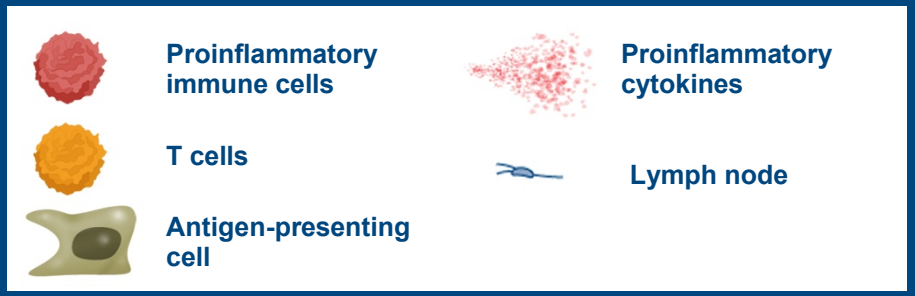


- Inhibits the α4-mediated adhesion of leukocytes to vascular cell adhesion molecule-1
- Strongly reduces proinflammatory cell recruitment to the CNS

19. Tysabri® (natalizumab) prescribing information. Biogen Idec Inc.

Presumed MOA of Fingolimod (FTY720): Immune cell sequestration[24,44]

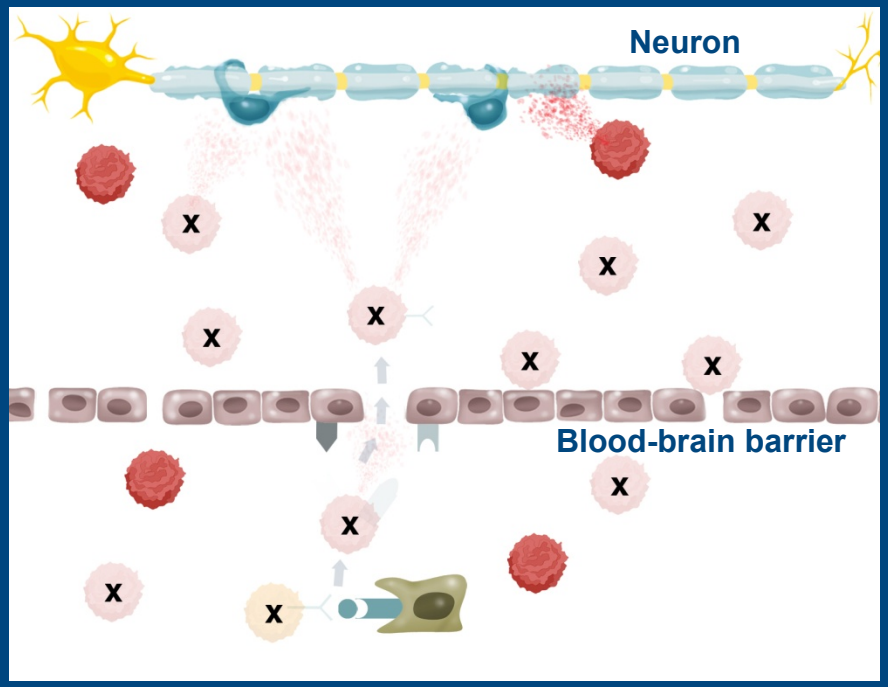


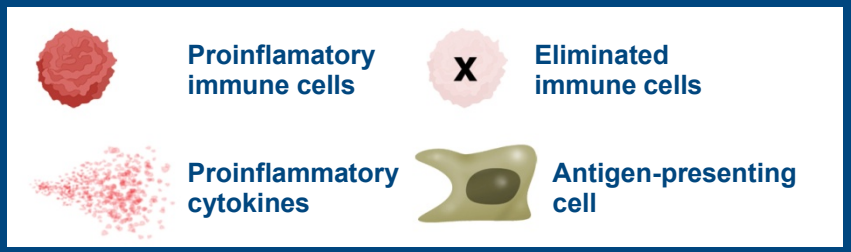


- Believed to modulate sphingosine 1-phosphate receptors on lymphocytes
- Prevents lymphocytes from leaving the lymph nodes and entering the bloodstream and CNS compartment
- Still allows memory effector cells (lymphocytes) to be in plasma; lymphocytes may go to 70% of baseline

24. Mundel T. FTY_AAN May 1, 2009. **44.** Lopez-Diego RS, et al. *Nat Rev Drug Discovery*. 2008;7:909-920.

Presumed MOA of oral Cladribine: Immune cell ablation[39-43]





- **Believed to be cytotoxic to proinflammatory immune cells**
  - Passively crosses immune cell membrane and accumulates inside cell
  - Inhibits DNA synthesis and repair
  - Reduces number of blood-cell types implicated in the pathogenesis of MS

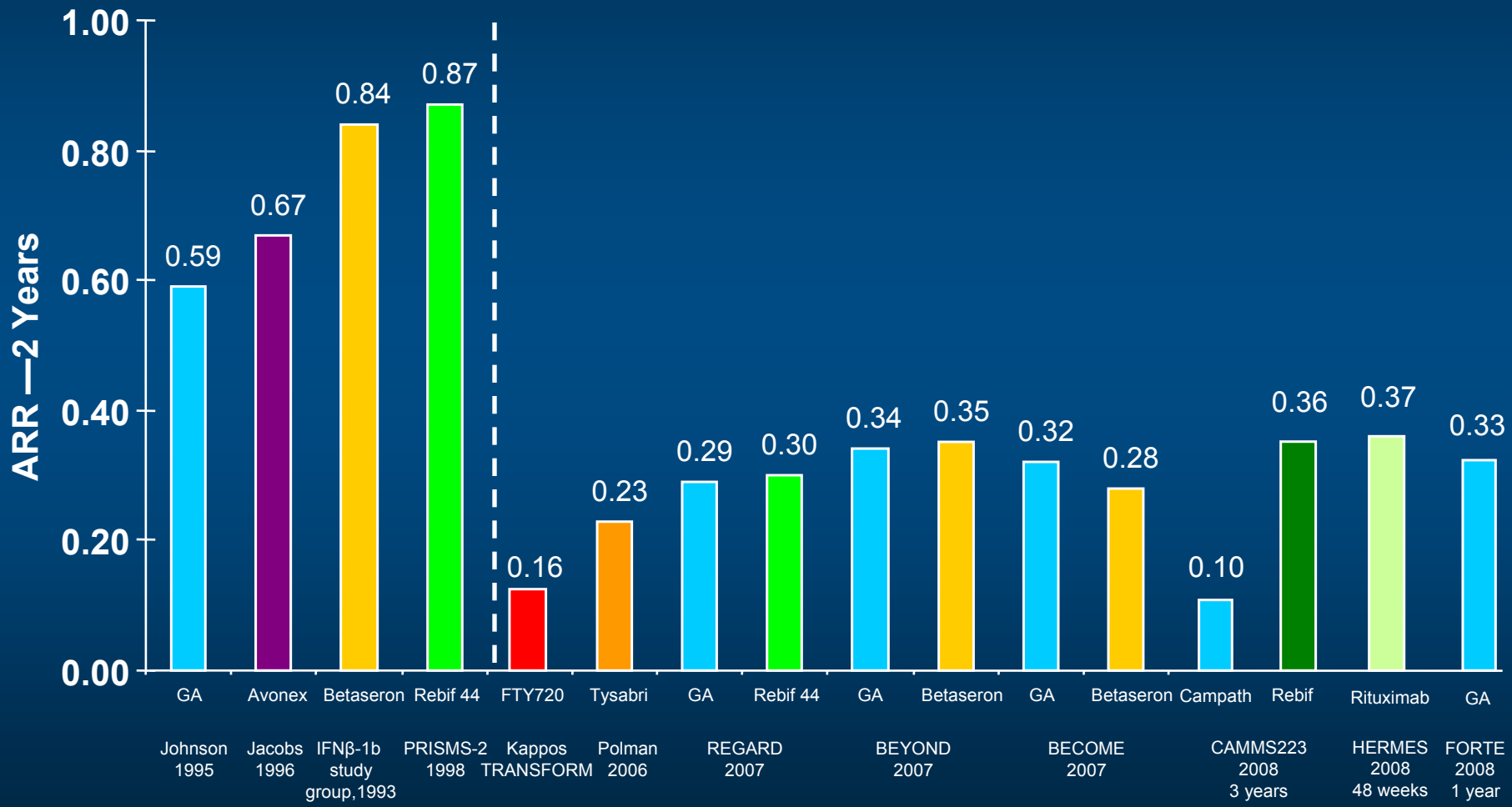
39. Romine JS, et al. *Proc Assoc Am Physicians*. 1999;111:35-44. **40.** Cladribine (Mylinax). Multiple Sclerosis Resource Center Web site. **41.** Beutler E, et al. *Proc Natl Acad Sci U S A.* 1996;93:1716-1720. **42.** Understanding Cancer and Related Topics. National Cancer Institute. **43.** Swan JB, et al. *J Clin Invest.* 2007;117:1137-1146.

PIVATOL TRIALS

- TRIALS STARTED IN LATE 1980'S—COMPLETED IN MID 1990'S
- MOST MS PATIENTS HAD DISEASE FOR 5 TO 7 YRS—HENCE DISEASE BURDEN SIGNIFICANT
- DEMYELINATION & AXONAL LOSS
- NATURAL HISTORY WAS ARR OF 1.7

Trends Across Clinical Trials:

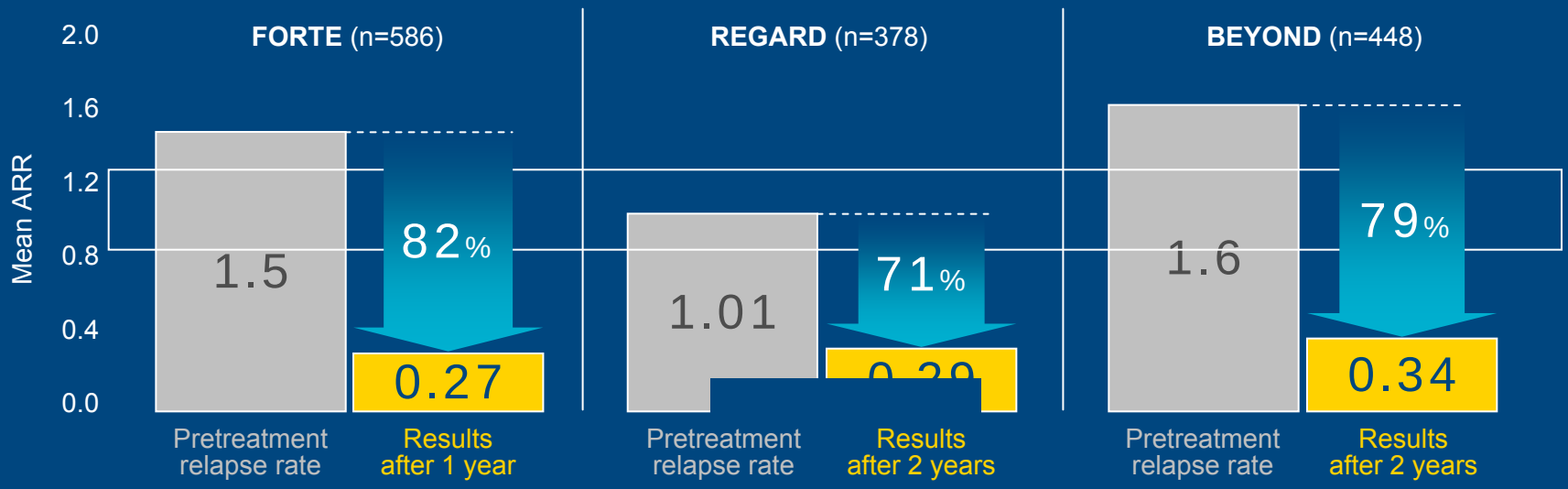
Annual Relapse Rate



ARR=annualized relapse rate.

Recent studies: Relapse rates

ARR in patients treated with COPAXONE® (glatiramer acetate injection) 20 mg qd[4,13,16]



- During a double-blind, placebo-controlled pivotal trial, COPAXONE® reduced relapses by 29% vs placebo over 2 years (1.19 vs 1.68; *P*=0.055) in patients with RRMS diagnosed using Poser criteria[8]

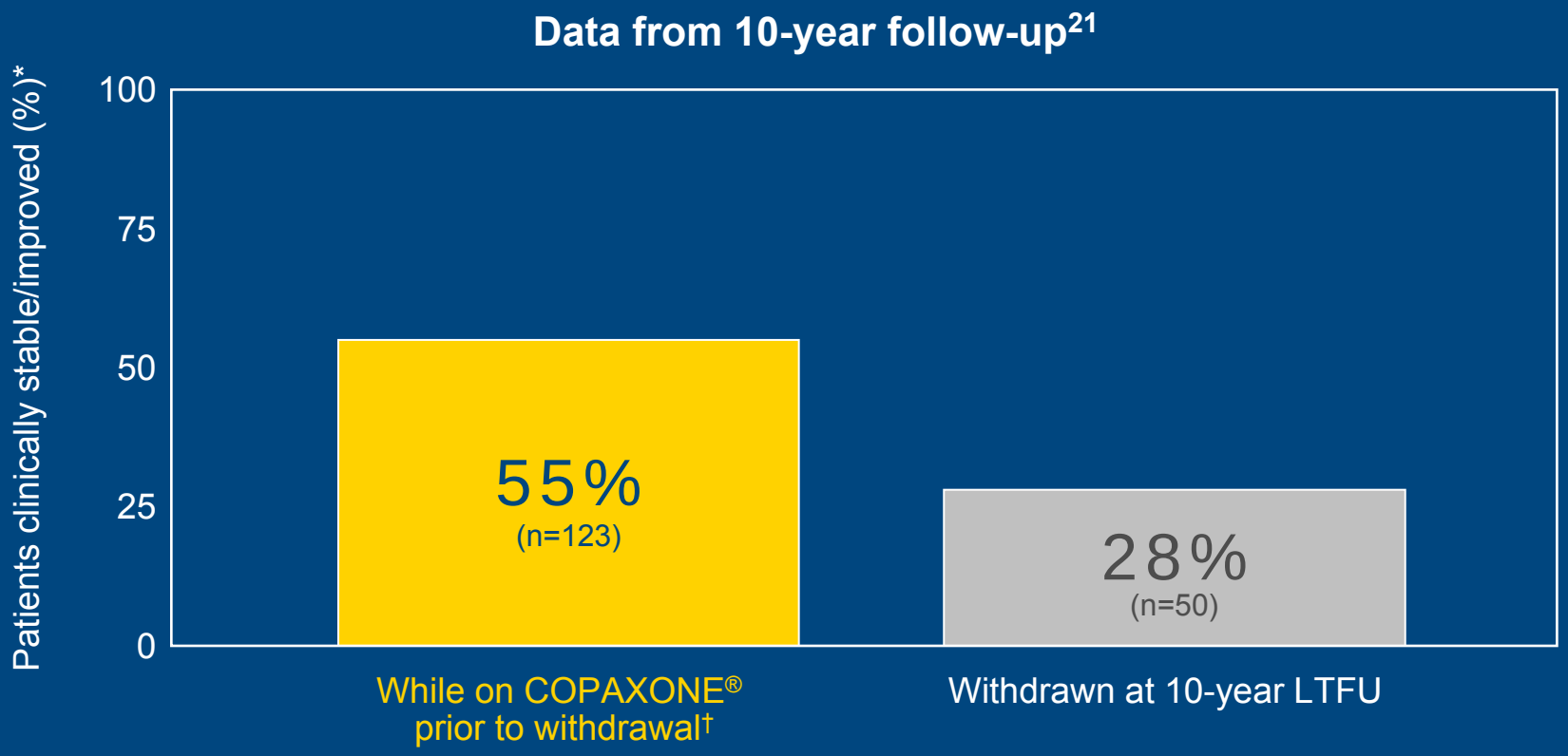
FORTE: Randomized, double-blind study designed to assess the efficacy, safety, and tolerability of COPAXONE® 40 mg SC daily compared with the currently approved COPAXONE® 20 mg SC daily in 1155 patients with McDonald-diagnosed RRMS. The 40-mg dose did not demonstrate increased efficacy in rate of confirmed relapses as the primary endpoint. COPAXONE® 40 mg SC is not an FDA-approved dose for the treatment of RRMS.

REGARD: See full study design on slide 12.

BEYOND: See full study design on slide 13.

4. Data on file. Teva Neuroscience, Inc. **8.** Johnson KP, et al. *Neurology*. 1995;45:1268-1276. **13.** Mikol DD, et al. *Lancet Neurol.* 2008;7:903-914. **16.** FORTE press release. Teva Neuroscience, Inc. July 7, 2008.

After discontinuing COPAXONE® (glatiramer acetate injection), withdrawn patients worsened



Pivotal trial and open-label follow-up: See full study design on slide 19.

COPAXONE® exposure (years; mean ± SD): 4.26 ± 3.13.

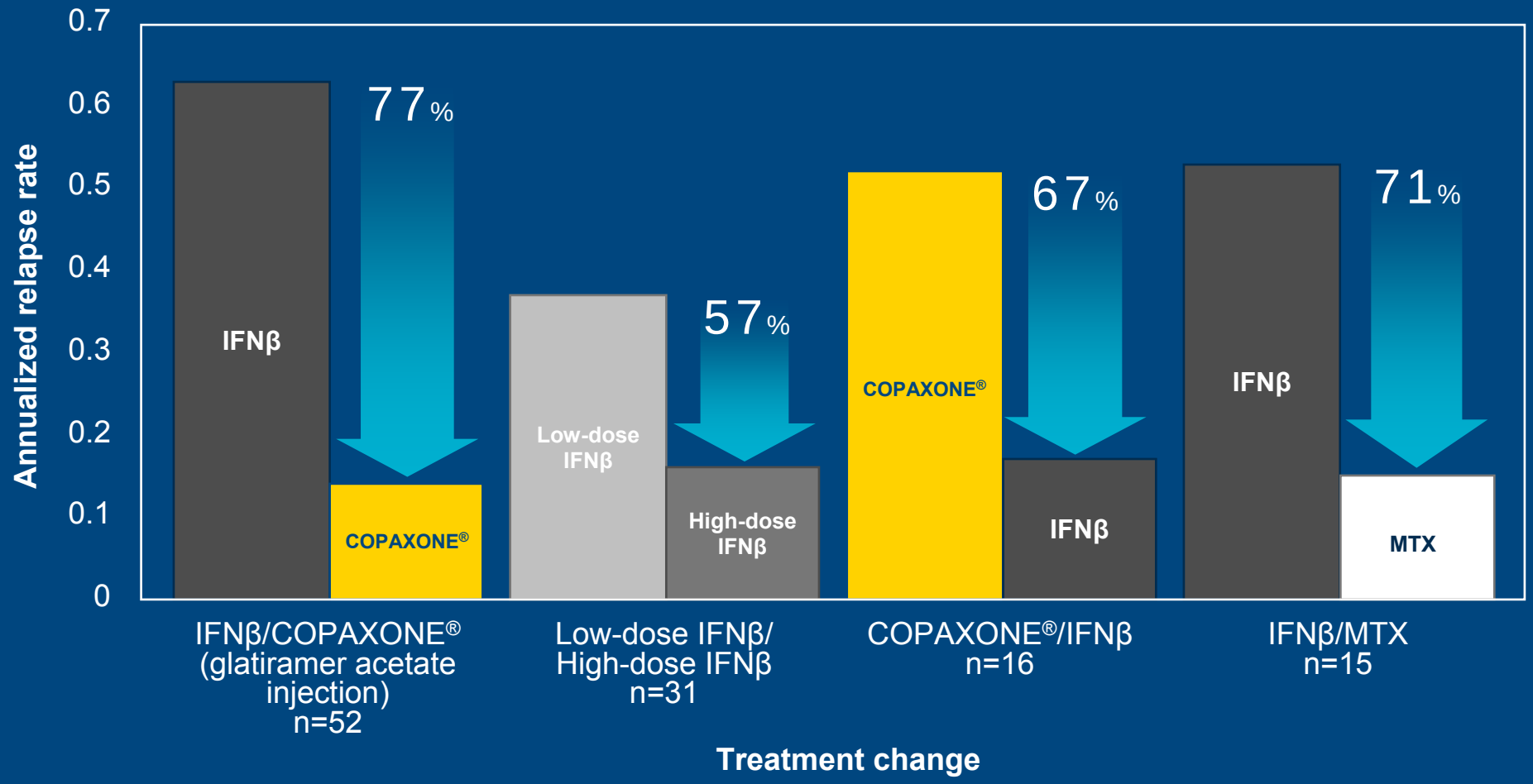
The labeling for COPAXONE® does not include an indication for slowing progression of disability.

*EDSS increase ≤0.5 points.

†One patient received 1 dose and never returned for evaluation.

21. Ford CC, et al. *Mult Scler*. 2006;12:309-320.

Carrá: Relapse rate reduction following change in therapy[7,11]



7. Carrá A, et al. *Eur J Neurol*. 2008;15:386-393.
11. COPAXONE® PI.

Copaxone® (glatiramer acetate injection): PEPTIDE COPOLYMER (MIMICS MBP) Safety information

Copaxone® is associated with

- Immediate postinjection reactions
- Injection-site reactions
- Lipoatrophy

Copaxone® is NOT associated with

- Immunosuppression/serious infections*
  - —Pneumonia
  - —Urinary tract infections
- PML*
- IFNβ-related flu-like symptoms
- Depression*
- Severe hepatic injury*
- NAbs
- Anaphylaxis*

*Copaxone® has no warnings or precautions for these serious adverse events.

Copaxone® is pregnancy category B

No evidence of risk in humans. Animal studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Copaxone® (glatiramer acetate injection) prescribing information. Teva Neuroscience, Inc.

High-dose Interferon-β: Safety Information

High-dose Interferon-β® is associated with

- Injection-site reactions
- IFNβ-related flu-like symptoms
- Depression*
- Severe hepatic injury (Rebif® [IFNβ-1a] only)*
- Anaphylaxis*
- NAbs

*High-dose IFNβ has warnings or precautions for these serious adverse events.

High-dose Interferon-β is not associated with

- Immunosuppression/serious infections
  - Pneumonia
  - Urinary tract infections
- IPIRs
- Lipoatrophy
- PML

High-dose Interferon-β is pregnancy category C

Evidence suggests a possible risk in humans. Animal studies have demonstrated potential hazards to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Betaseron® (IFNβ-1b) prescribing information. Bayer Healthcare Pharmaceuticals Inc. Rebif® (IFNβ-1a) prescribing information. EMD Serono Inc.

Tysabri® (natalizumab): Safety Information

Tysabri® is associated with

- Progressive multifocal leukoencephalopathy (PML)*
- Immunosuppression/serious infections*
  - Pneumonia
  - Urinary tract infections
- Clinically significant hepatic injury*
- Anaphylaxis*
- Neutralizing antibodies (NAbs)*

*Tysabri® (natalizumab) has warnings or precautions for these serious adverse events.

Tysabri® is not associated with

- Depression
- Injection-site reactions
- IFNβ-related flu-like symptoms
- Immediate postinjection reactions (IPIRs)
- Lipoatrophy

Tysabri® is pregnancy category C

Evidence suggests a possible risk in humans. Animal studies have demonstrated potential hazards to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Tysabri® (natalizumab) prescribing information. Biogen Idec Inc.

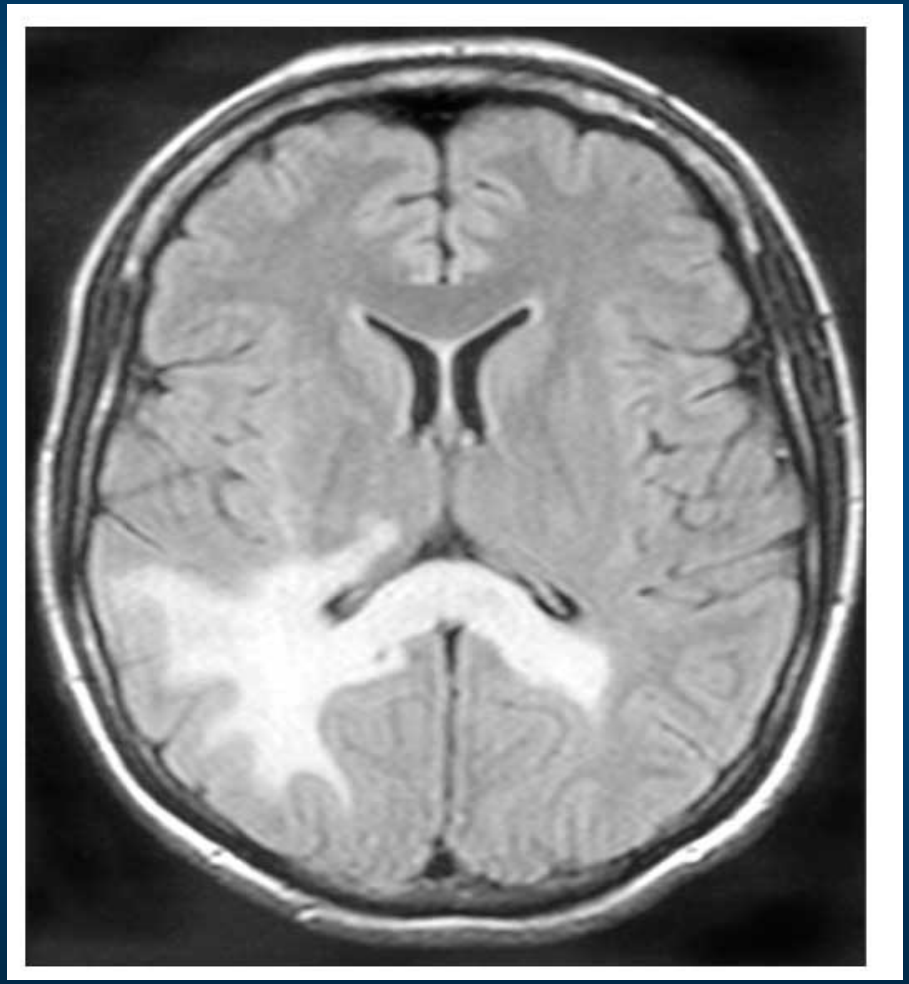
NATALIZUMAB (TYSABRI) AFFIRM

- 942 PATIENTS, 2 TO 1, INFUSION EVERY 4 WEEKS UP TO 116 WEEKS
- ARR AT 2 YRS; P 0.67 & N 0.22 (67% LESS)
- Gd+ LESIONS AT 2 YEARS; DOWN 92%
- 42% LESS INCREASED PHYSICAL DISABILITY SUSTAINED FOR 12 WEEK
- NO RELAPSES AT 2 YRS; N 67% VS P41%
- FREE OF Gd+ LESIONS; N 97% VS P 72%
- NO NEW NO ENLARGING T2: N 57% VS P 15%

NATALIZUMAB (TYSABRI)

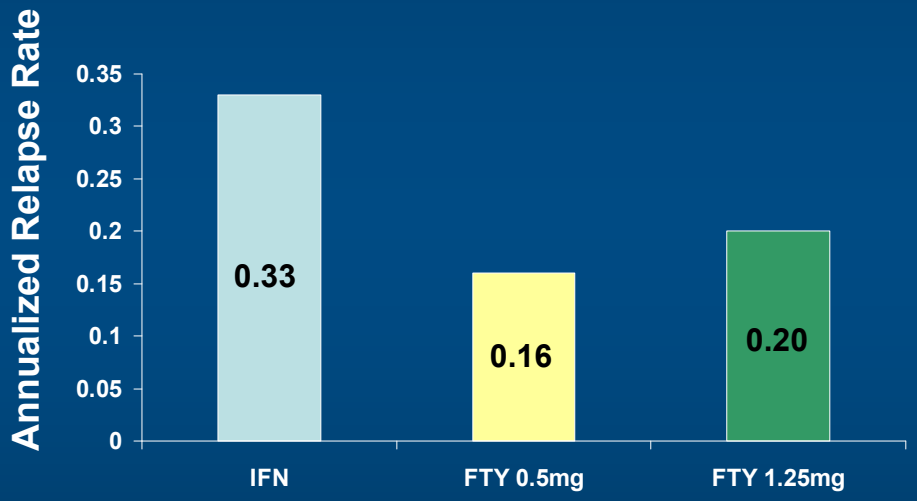
- 104,300 PATIENT EXPOSURES
- PML 285 CASES; 62 DIED, SURVIVAL RATE 78%; 1/3 MILD, 1/3 M; 1/3 SEVERE
- 3 RISK FACTORS; + JCV, PRIOR IMMUNO SUPPRESSANT MEDS, > 24 MONTHS RX,
- ANTI-JCV ANTIBODY TITER @ 6 MONTHS
- PML S&S; CHANGE IN SPEECH & BEHAVIOR, MRI CHANGES(40% Gd+)
- EXCLUSION REQUIRES NEGATIVE JCV DNA IN CSF & NO PROGRESSION; REPEAT CSF QUANITATIVE PCR ASSAY FOR JCV DNA

MRI & PML



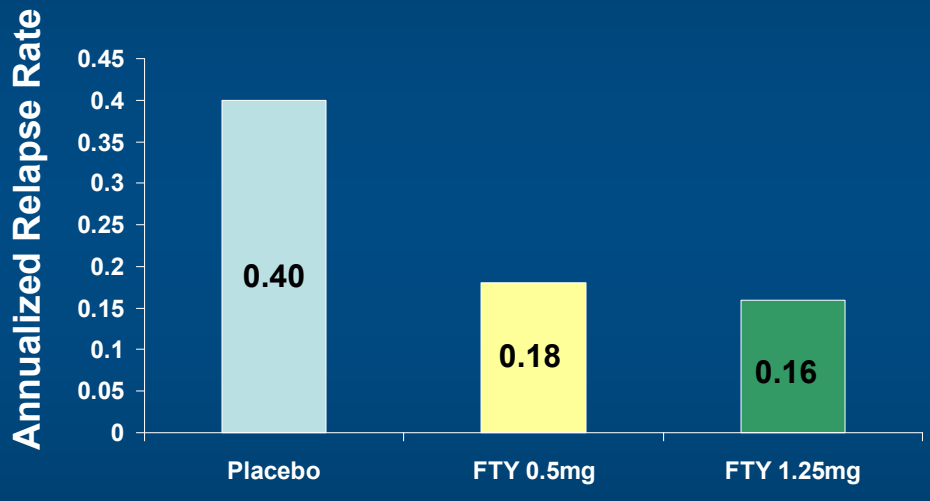
Fingolimod Efficacy: ARR

TRANSFORMS



P<0.001 for both doses vs IFN; values represent reductions in ARR of 52% and 38% vs IFNb-1a

FREEDOMS



P<0.001 for both doses vs placebo; values represent reductions in ARR of 54% and 60% vs PBO

Adapted from Kappos L, et al. NEJM. 2010; 362(5):387-401 and Cohen J, et al. NEJM. 2010; 362(5):402-415.

FINGOLIMOD--FREEDOMS

- 1272 PATIENTS, 2 YRS, ORAL, P VS 0.5MG, 1.25MG
- DATA COMPARED TO 0.5 MG
- REDUCED ARR BY 54% FOR 0.5 MG
- RELAPSE FREE, P 46% VS F 70%, 52% REDUCTION
- # T2 LESIONS REDUCED, P 9.8 VS N 2.5, ABSOLUTE REDUCTION WAS 7.3 LESIONS
- 30% REDUCTION IS CONFIRMED PHYSICAL DISABILITY AT 3 MONTHS

FINGOLIMOD--TRANSFORMS

- 1292 PATIENTS, 1 YR, ORAL INTERFERON BETA-1a IM, 0.5MG, 1.25MG
- DATA COMPARED TO 0.5MG
- ARR, P 0.33 VS F 0.16, 52% REDUCTION
- RELAPSE FREE, P 70% VS F 83%, 19% REDUCTION
- T2 LESIONS REDUCED, P 2.6 VS F 1.6,

FINGOLIMOD(GILENYA) PRECAUTIONS

- CARDIAC—LOW HEART RATE(MONITOR FOR 6 HOURS), LOW BP; LUNGS---SOB; LIVER; ELEVATED ENZYMES,EKG BASE LINE, THEN DAY OF AND AT 6 HOURS (QTc INTERVAL)
- MACULAR EDEMA—1 IN 500, VISUAL LOSS; MONITOR BEFORE & AT 3 MONTHS; HIGHER RISK IN DIABETICS & UVEITIS
- INFECTIONS---2 DEATHS IN HIGHER DOSE(1.25); NEED HX OF CP OR GET VZV VACCINATION & WAIT ONE MONTH.
- WBC LOWER; AFTER DC NORMAL IN 1 TO 2 MONTHS
- CATEGORY C FOR PREGNANCY
- AE---HA, FLU LIKE S & S, BRONCHITIS, BACK PAIN, DIARRHEA
- DEATHS; 30 REASON UNCERTAIN

TERIFLUNOMIDE (AUBAGIO)--TEMSO

- FDA APPROVED ON 9/12/12, AVAILABLE 10/1/12
- 1088 PT IN STUDY, ORAL, P VS 7MG &14MG (MORE ROBUST EFFICACY WITH 14MG, SIMILAR AE'S)
- ANNUALIZED RELAPSE RATE (ARR)
  - AT 2YR: P 0.54 VS 0.37 FOR 7MG & 14MG, REDUCED BY 31%
  - AT 5 YR EXTENSION: 0.234 FOR 7MG AND 0.206 FOR 14MG
- 3-MONTH SUSTAINED DISABILITY PROGRESSION:
  - AT 2YR: P 27.3% VS 20.2% FOR 14MG, REDUCED BY 30%

O'Conner P. et. al. NEJM 2011; 365-1293-303

TERIFLUNOMIDE (AUBAGIO) - TEMSO

- TOTAL LESION VOLUME (T1 HYPOINTENSE PLUS T2 HYERINTENSE):
  - 69% RELATIVE RISK REDUCTION BY 14MG VS PLACEBO
- T1 GD-ENHANCING LESIONS:
  - 80% RELATIVE RISK REDUCTION BY 14MG VS PLACEBO

O'Conner P. et. al. NEJM 2011; 365-1293-303

TERIFLUNOMIDE (AUBAGIO) - TEMSO

- SIMILAR AE'S, SERIOUS AE'S, AND AE'S LEADING TO RX DISCONTINUATION FOR PLACEBO VS TERIFLUNOMIDE
- PREGNANCY CATEGORY X: BASED ON ANIMAL DATA
  - PREGNANCY REGISTRY: 12 LIVE BIRTHS ON TERI, ALL HEALTHY WITH NO STRUCTURAL OR FUNCTIONAL DEFECTS
- COMMON AE'S:
  - DIARRHEA: P 9% , 15% 7MG, 18% 14MG (1 PT D/C IN EACH T ARM)
  - NAUSEA: P 7% , 9% 7MG, 14% 14MG (1 PT D/C IN 7MG)
  - INCREASED ALT: P 7% , 12% 7MG, 14% 14MG
    - ALT>3X ULN SIMILAR FOR P VS T; SIMILAR D/C RATE
  - HAIR THINING: P 3% VS 10-13% T (WITH 1% D/C ON T). PEAK 3-6MO. CAN RECOVER SPONTANEOUSLY EVEN WHILE ON RX, 94% RECOVER WITH OUT SEQUELAE, 2% RECOVER WITH SEQUELAE

O'Conner P. et. al. NEJM 2011; 365-1293-303

TERIFLUNOMIDE (AUBAGIO) - TENERE

- 324 PTS, INFβ-1A (REBIF 44MCG TIW) VS TERIFLUNOMIDE 7MG & 14MG
- PRIMARY ENDPOINT (TIME TO FAILURE = CONFIRMED RELAPSE OR PERMENANT RX D/C)
  - 37.8% FOR 14MG VS 42.3% FOR REBIF (NS)
- ARR: 0.26 FOR 14MG VS 0.22 FOR REBIF (NS)
- TREATMENT D/C DUE TO AE:
  - 10.9% FOR 14MG VS 21.8% FOR REBIF
- ALT INCREASED: 10.9% FOR 14MG VS 30.7% REBIF

Vermersch P et. al. Presented at CMSC/ACTRIMS 2012.

BG-12 (DIMETHYL FUMARATE) DEFINE 2 YR VS P; NOT APPROVED BY FDA YET

- 1237 PATIENTS, ORAL, 240MG 2 X'S(BID) OR 3 X'S(TID) A DAY
- ARR REDUCED FOR 2X'S WAS BY 53%, FOR 3X'S WAS BY 48%
- REDUCED RISK OF RELAPSE FOR 2X'S WAS 49%, FOR 3X'S WAS 50 %
- Gd+ LESIONS REDUCED FOR 2X'S WAS90%, FOR 3X'S WAS73%
- T2 NEW OR ENLARGING LESIONS REDUCED FOR2X'S WAS 85%, FOR 3X'S WAS 74%
- T1 NEW HYPOTENSE REDUCED FOR 2X'S WAS 72 %, 3X'S WAS 63%
- REDUCED DISABILITY PROGRESSION FOR 2X'S BY 38%

, FOR 3X'S WAS 34 %; FREE OF Gd+ LESIONS

- AE—FLUSHING,HEADACHE, DIARRHEA, FATIGUE,NAUSEA, NASOHPARYNGITIS (NO ICREASED INFECTIONS)
- PREGNANCY CATEGORY ?

BG-12 (DIMETHYL FUMARATE) CONFIRM—2 YEAR TO P & WITH GA

- ARR REDUCED FOR 2 X'S WAS 44%, 3X'S WAS 51%, & GA WAS 29%
- % OF PATIENTS THAT RELAPSED FOR 2X'S WAS 34%, 3X'S WAS 45% & GA WAS 29%
- REDUCED DISABILITY PROGRESSION FOR 2X'S WAS 21%, 3X'S WAS 24% & FOR GA WAS 7%
- T2 NEW OR ENLARGING REDUCED FOR 2X'S WAS 71%, FOR 3X'S WAS 73 % & GA WAS 54%
- T1 NEW HYPOINTENSE REDUCED FOR 2X'S WAS 57%, 3X'S WAS 73% & FOR GA WAS 41%

BG-12 DIMETHYL FUMARATE (MECHANISM OF ACTION?)

- ORAL
- ACTIVATES THE Nrf2 PATHWAY WHICH ? REDUCES THE IMPACT OF INFLAMMATORY CELL ON CNS
- INDUCES DIRECT CYTOPROTECTIVE RESPONSES IN CELLS & BALANCES THE PROINFLAMMATORY & OXIDATIVE STATE

TREATMENT ALGORITHM

- RIS; DETERMINE CORRECT DX WITH CSF & REPEAT MRI; ? RX IF Gd+ & LOOKS LIKE MS
- CIS; AGGRESSIVE DMA'S & CLOSE FOLLOW UP WITH MRI IN 1 YR
- RRMS; DMA'S IMMUNOMODULATORS WITH CLOSE FOLLOW UP & IF RELAPSE & MRI CHANGES (ESPECIALLY IF Gd+) OR NEW ?# T2 LESIONS ON MRI, CHANGE DMT
- IF RRMS & HIGH BURDEN ON MRI & OR FREQUENT & PROGRESSIVE COURSE, RX WITH NATALIZUMAB OR FINGOLIMOD, OR TRIFLUNOMIDE
- USE MP OR ACTHAR AS INDICATED

RESCUE RX FOR ACUTE RELAPSE

- M P 1000MG IV FOR 3 TO 5 DAYS
- ORAL PREDNISONE—60 TO 100MGS FOR 5 TO 7 DAYS
  - 30 TO 40% OF RXED RELAPSECASES ARE NOT IMPROVED WITH THE ABOVE RESCUE RX.
- ACTHAR—GEL; 80 TO 120 UNITS SUBQ OR IM SELF ADMINISTERED DAILY FOR 2 TO 3 WEEKS OR LESS—BINDS TO MELANOCORTIN RECEPTORS IN BRAIN—SUPPRESSES CYTOKINES

FUTURE DRUGS PHASE 3 TRIALS

- ALEMTUZUMAL—MONOCLONAL ANTIBODY; TARGETS CD52 ANTIGEN AND B & T CELLS
  - CNS INFECTIONS, INFUSION REACTIONS
- LAQUINIMOD—ORAL, SHIFTS TH1 CELLS TO TH2
  - AE—GBS, RA
- MORE MONOCLONAL ANTIBODIES
- STEM CELLS
- OTHER AVAILABLE DRUGS; AMPURA (10MG BID); NEUDEXTA (10 MG BID FOR PBA); ACEI
- EXERCISE; MAY SLOW PROGRESSION OF MS

OUTLINE OF MS TALK

- PART 1
- EPIDEMIOLOGY
- SIGNS AND SYMPTOMS
- PATHOPHYSIOLOGY
- PART 2
- TREATMENT FORMAT
  - DMT (IMMUNOMODULATORS) EFFICACY, SAFETY, TOLERABILITY
  - DMT (IMMUNOSUPPRESORS) EFFICACY, SAFETY, TOLERABILITY
  - ALGORITHMS

FUTURE DRUGS