

# Current Trials: New Agents, Combination Strategies, and Emerging Concepts in Treatment

Joseph R. Berger, MD

Professor and Chairman

Neurology Department

University of Kentucky College of Medicine

Chief of Department and Head of MS Center

University of Kentucky Medical Center

Lexington, Kentucky

*Fourth Annual MASTER MS Fellowship Program*

**MASTER MS**  
*Fellowship Program*

# Key Points

- The field of MS therapy is changing rapidly
- Newer therapies will likely supplant currently available DMDs
- The newer therapies will have both known and unforeseen complications
- Future treatment options will be far more complex than those currently available to us

# At the Association for Research in Nervous and Mental Disease, December 10–11, 1948

*One should no more tell our patients they have multiple sclerosis than we should tell them they have inoperable cancer...When I have to make the diagnosis of multiple sclerosis, I make it to the relations, not to the patient; and I try to defend the patient from hearing the name because once the name is heard, it is vested with lamentable result.*

Robert Foster Kennedy



# At the Association for Research in Nervous and Mental Disease, December 10–11, 1948



*And I certainly agree with him that the diagnosis should never be told to the patient unless it is absolutely essential to that patient for the arrangement of his life, and that the facts should be explained to the family.*

H. Houston Merritt

# An Advancing Landscape From 5 Compounds Now...

1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003

IFN  $\beta$ -1b

IFN  $\beta$ -1a SC

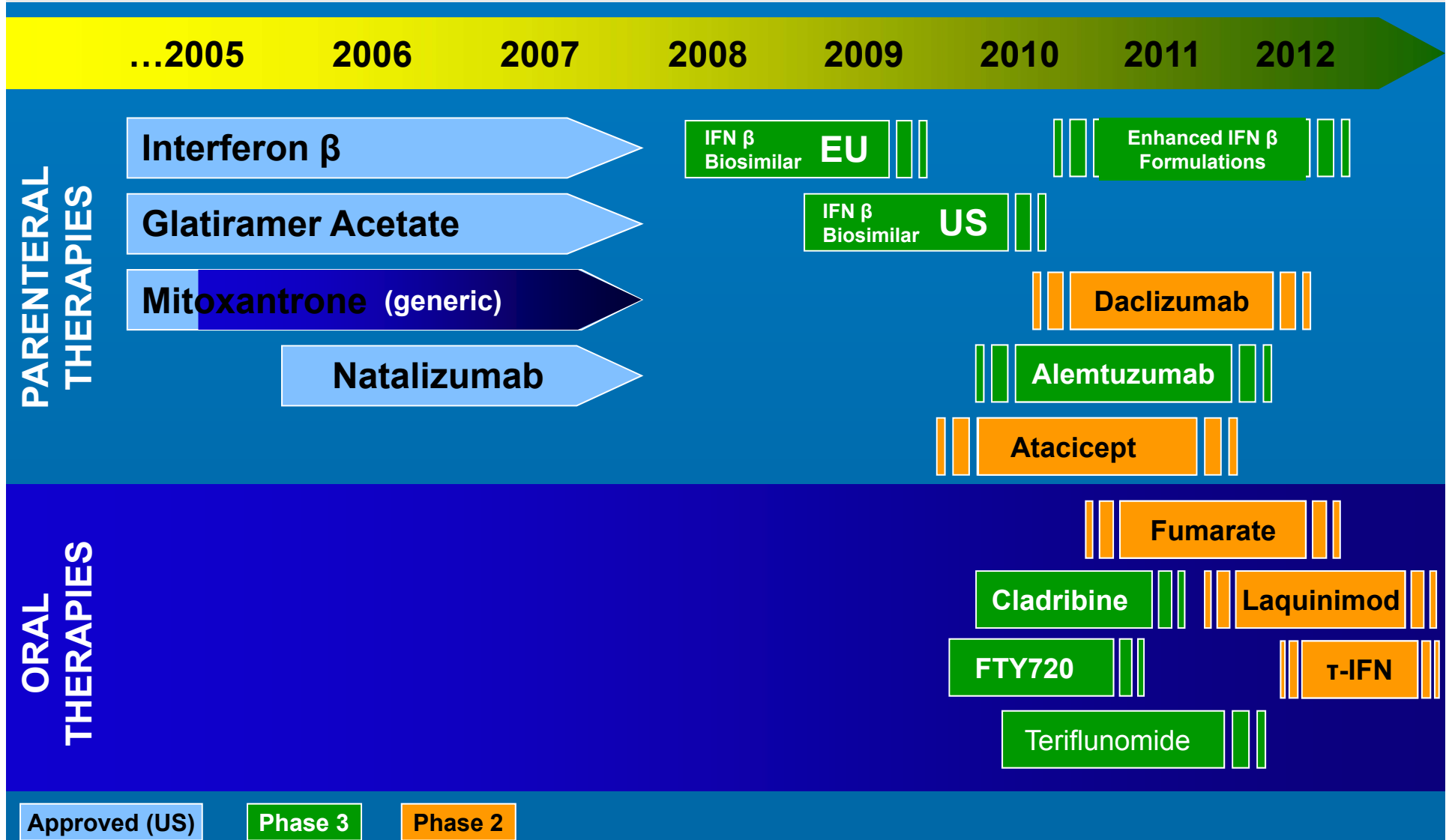
Glatiramer Acetate

IFN  $\beta$ -1a IM

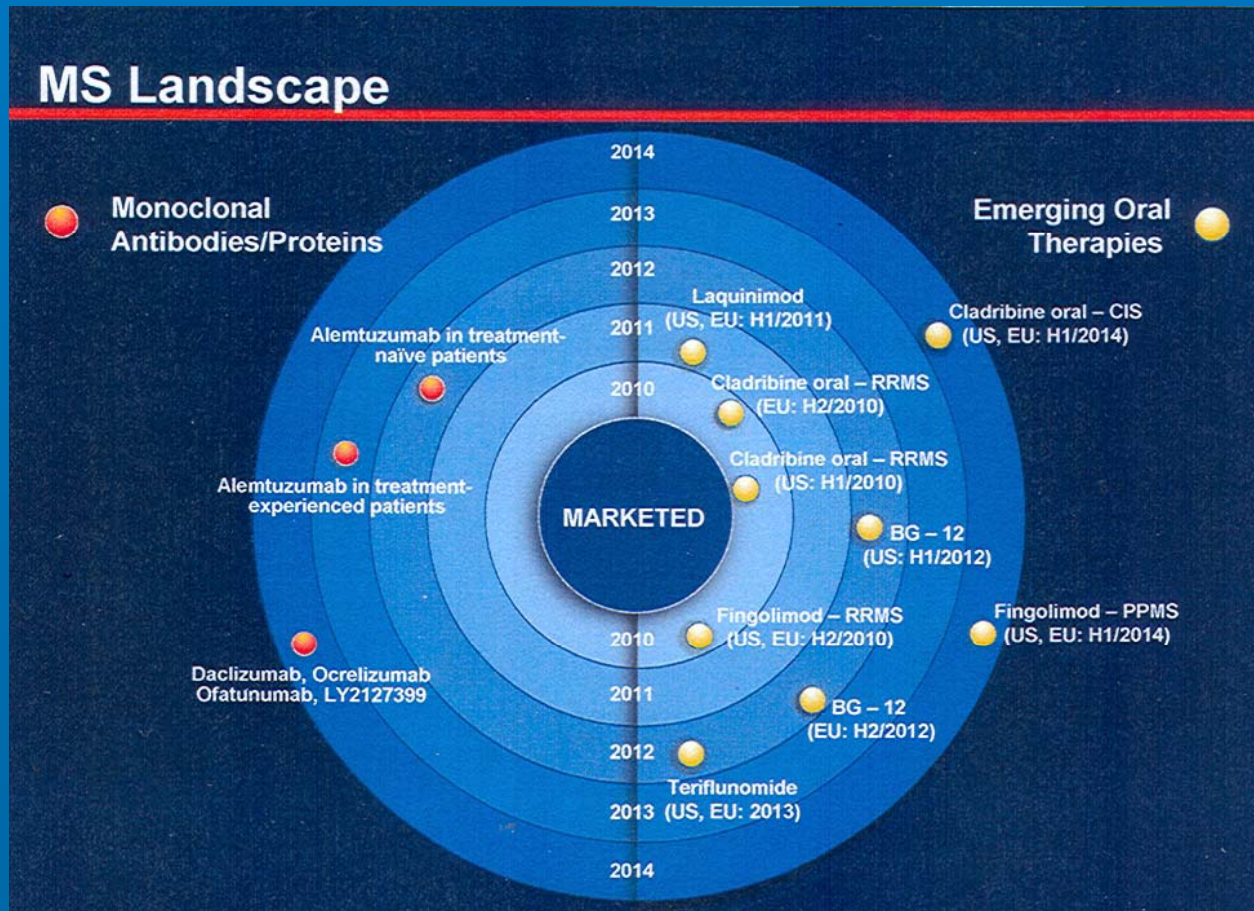
Mitoxantrone

Dates refer to approval for U.S. market

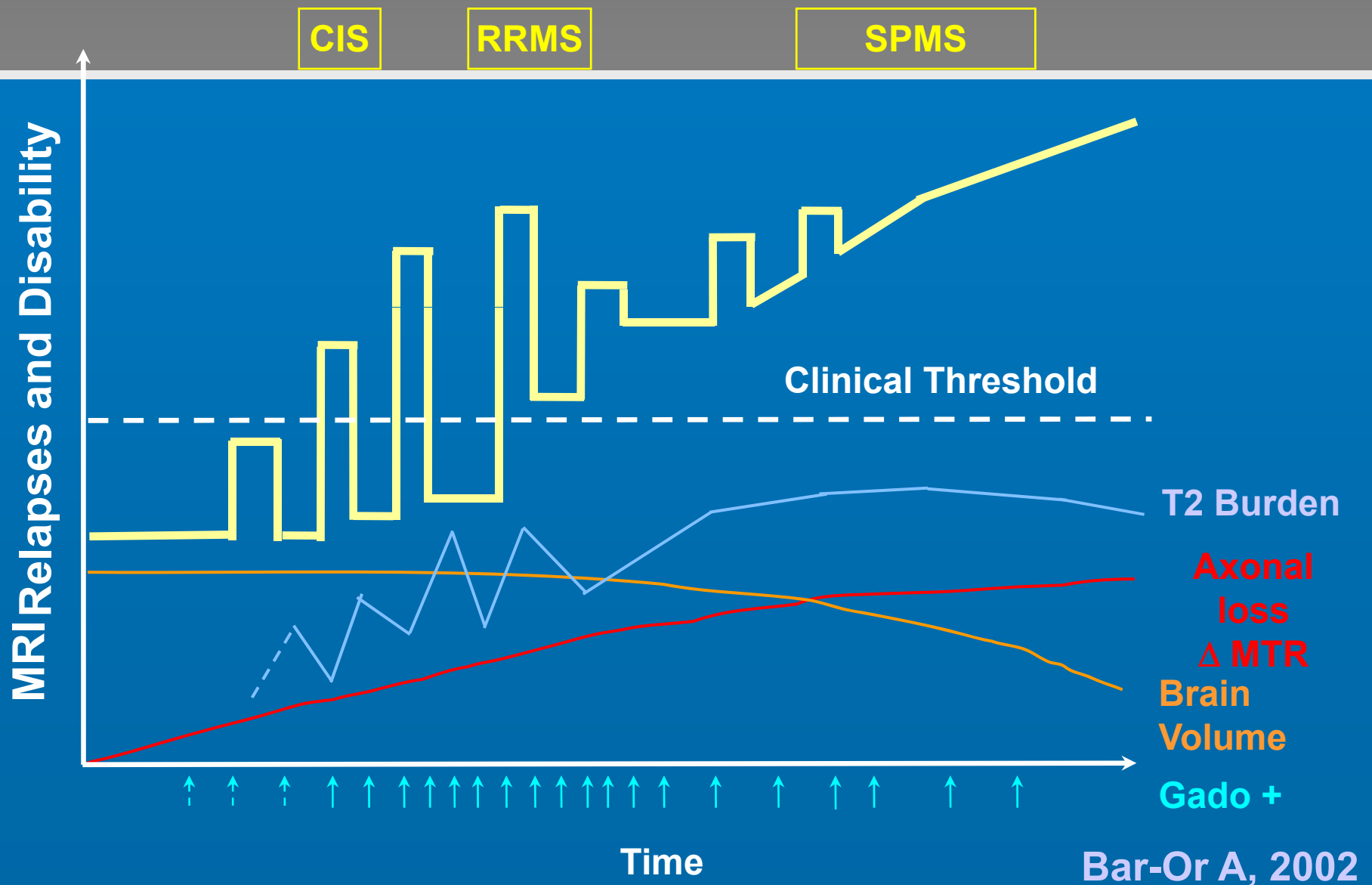
# An Advancing Landscape ...to 12 Compounds by 2012 (?)



# Emerging Landscape for MS



# Clinical and MRI Course in MS



# MS Clinical Course Categories

- Relapsing remitting MS (RRMS) -70%
  - recovery between attacks; slow accretion of deficit
  - 0.4-1.1 relapses/year (1.5-2.3/year for first year)
- Secondary progressive (SPMS)
  - relapsing progressive
  - attacks at onset with increasing deficit
- Primary chronic progressive (PCPMS) - 15%
  - slow steady progression
- Acute (malignant) MS
  - polysymptomatic disease at onset that progresses
- Benign MS
  - no significant deficit after 10-15 years

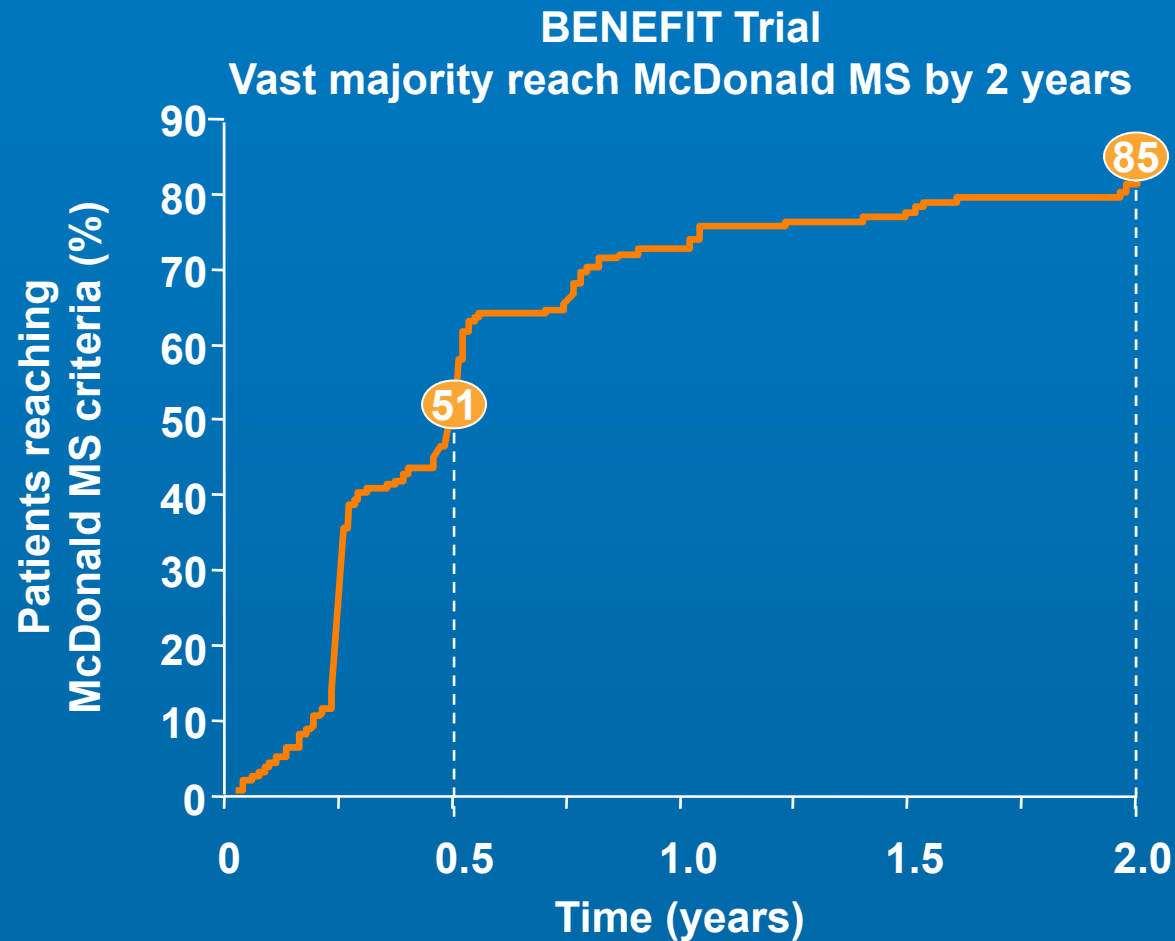
# Clinically Isolated Syndromes

- Isolated involvement of a region of the CNS
  - optic neuritis, brainstem, spinal cord
- Risk of development of MS related to baseline MR and CSF OCBs
  - CIS-MRI+ have 80% likelihood of progression in 10 years v. 20% with MRI–
  - MRI lesion load correlates crudely with disability at 5 years
  - in ON, +CSF OCBs increase likelihood of MS even with MRI–

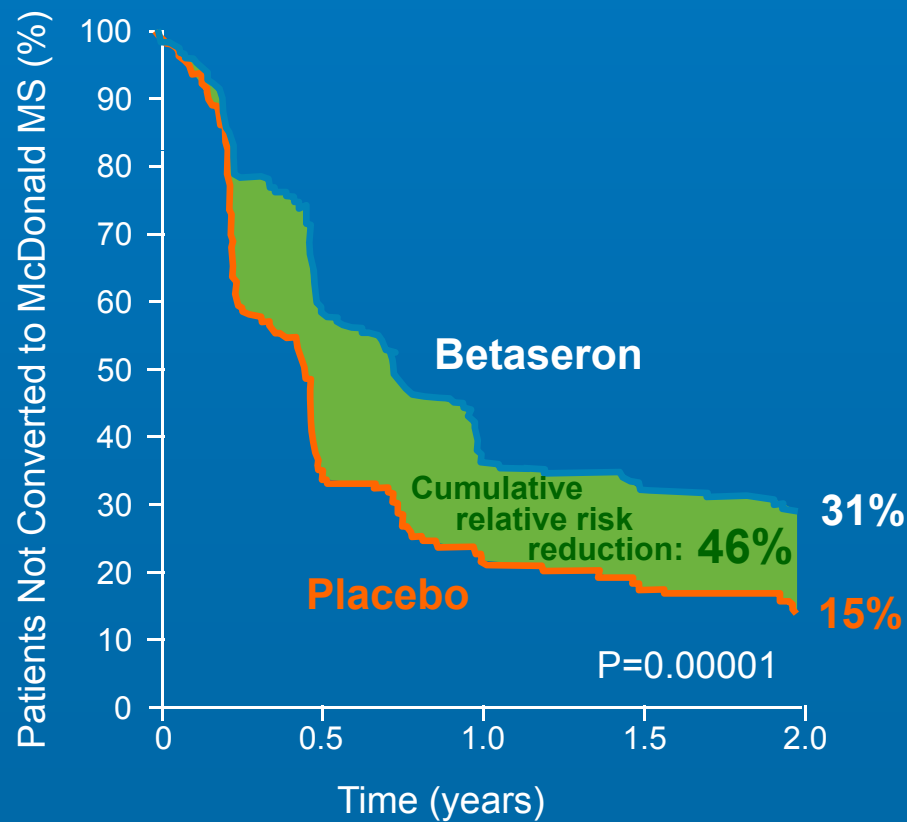
# Risk of Developing MS at 5 Years After Isolated Attack

<u>Type of attack</u>	<u>MRI abnormal</u>	<u>MRI normal</u>
No. pts.	57	32
All cases	72%	6%
O.N.	82%	6%
Brainstem	67%	0%
Sp. cord	59%	9%

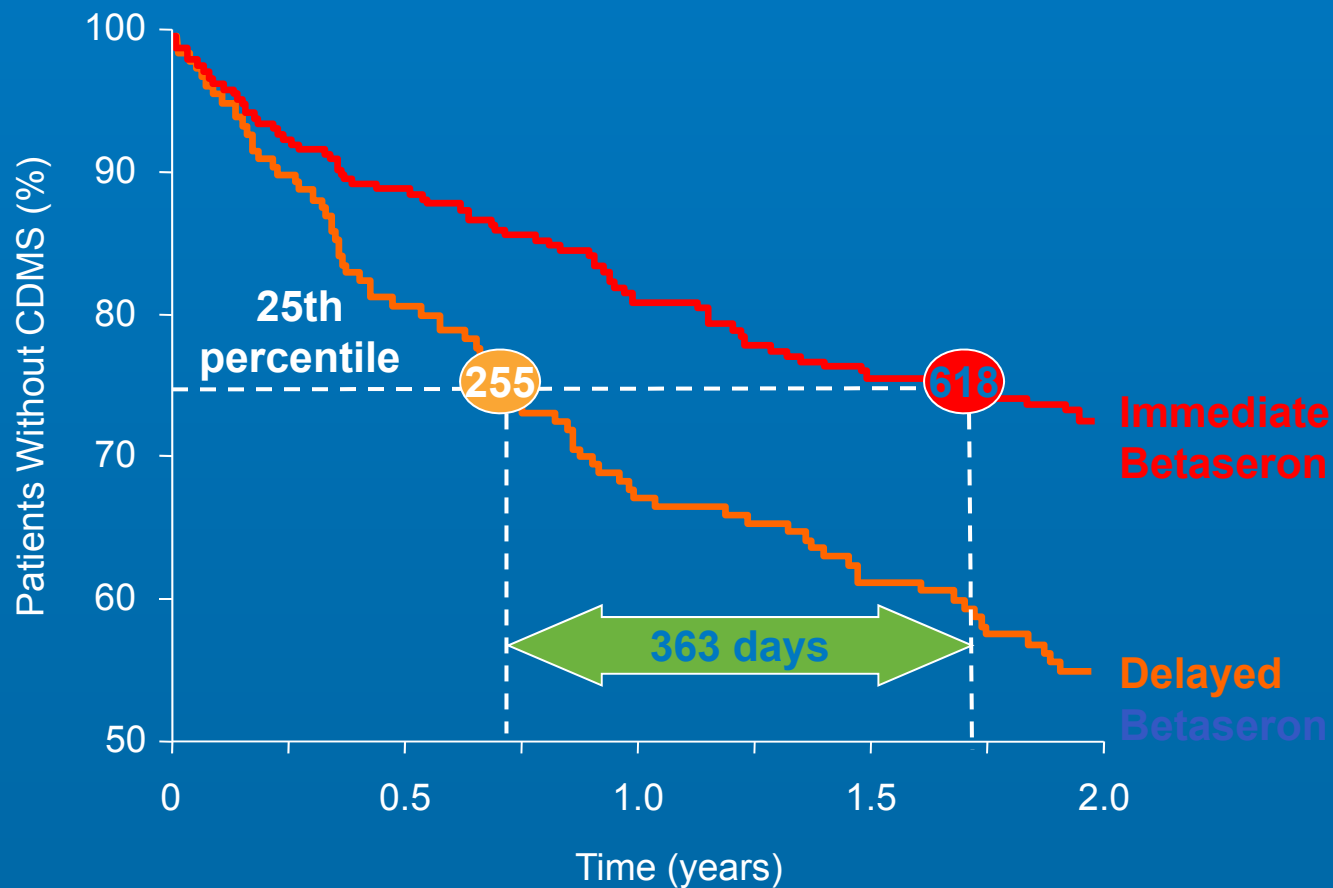
# 85% of Patients in Delayed Treatment Arm Convert to CDMS at 2 years



# Immediate Betaseron Rx ↓ Risk of Progression to CDMS by 46% at 2 years



# Immediate vs Delayed Rx Delays Conversion to CDMS by 1 Year

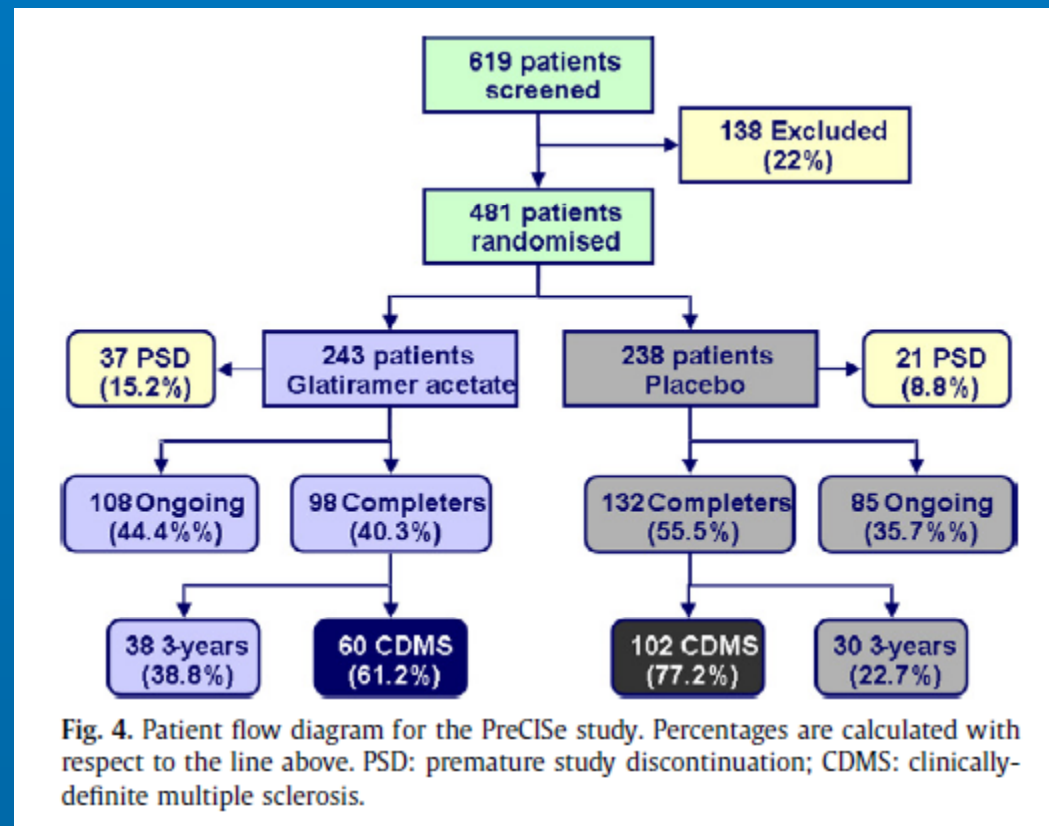


\*At 25<sup>th</sup> percentile

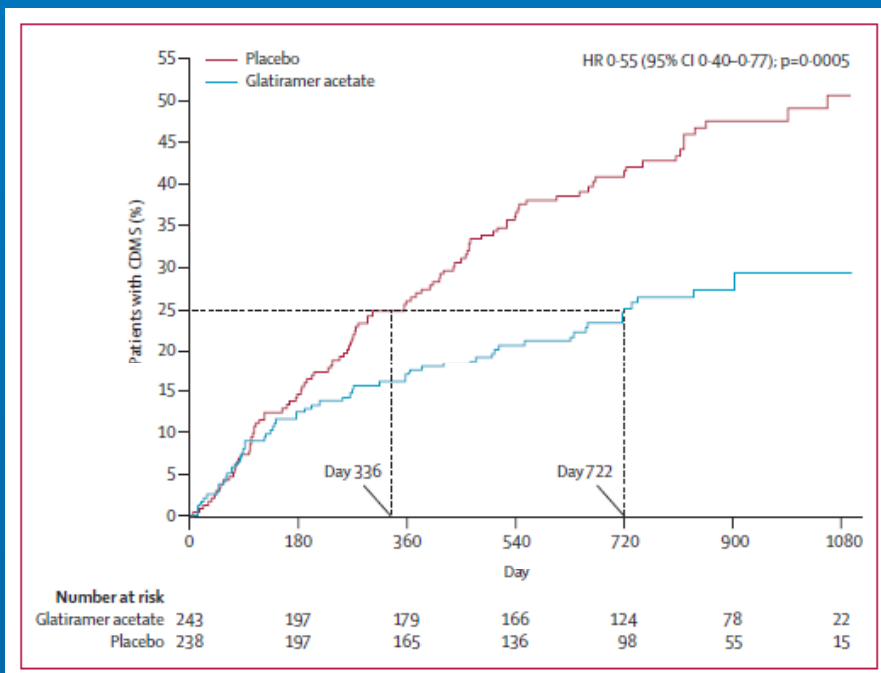
# PRECISE – Copaxone for CIS

- Delay in progression to CDMS
  - GA reduced CDMS by 45% compared to placebo
  - Time for 25% to convert to CDMS was prolonged 115% from 335 days for placebo to 722 days for GA
- Reduction of disease burden
  - ↓ new T2 lesions
  - ↓ T2 lesion burden

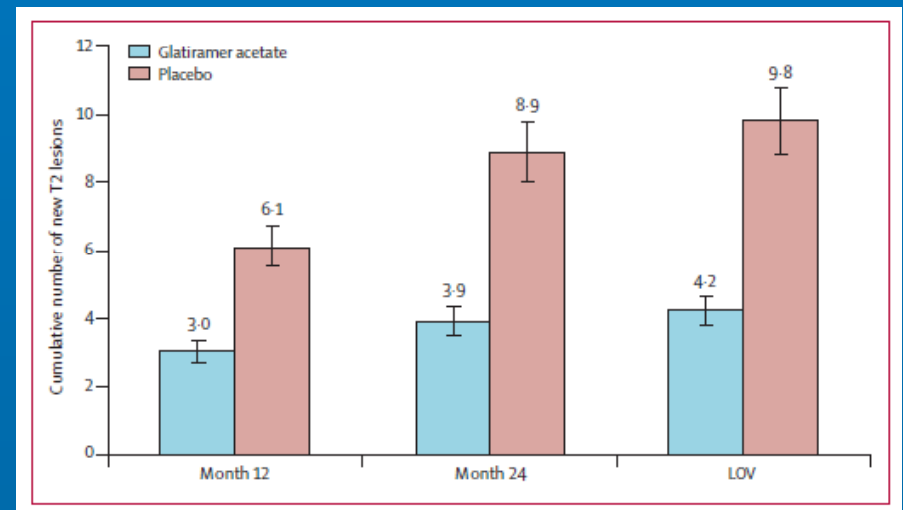
# PRECISE – Copaxone for CIS



# PRECISE Graphs



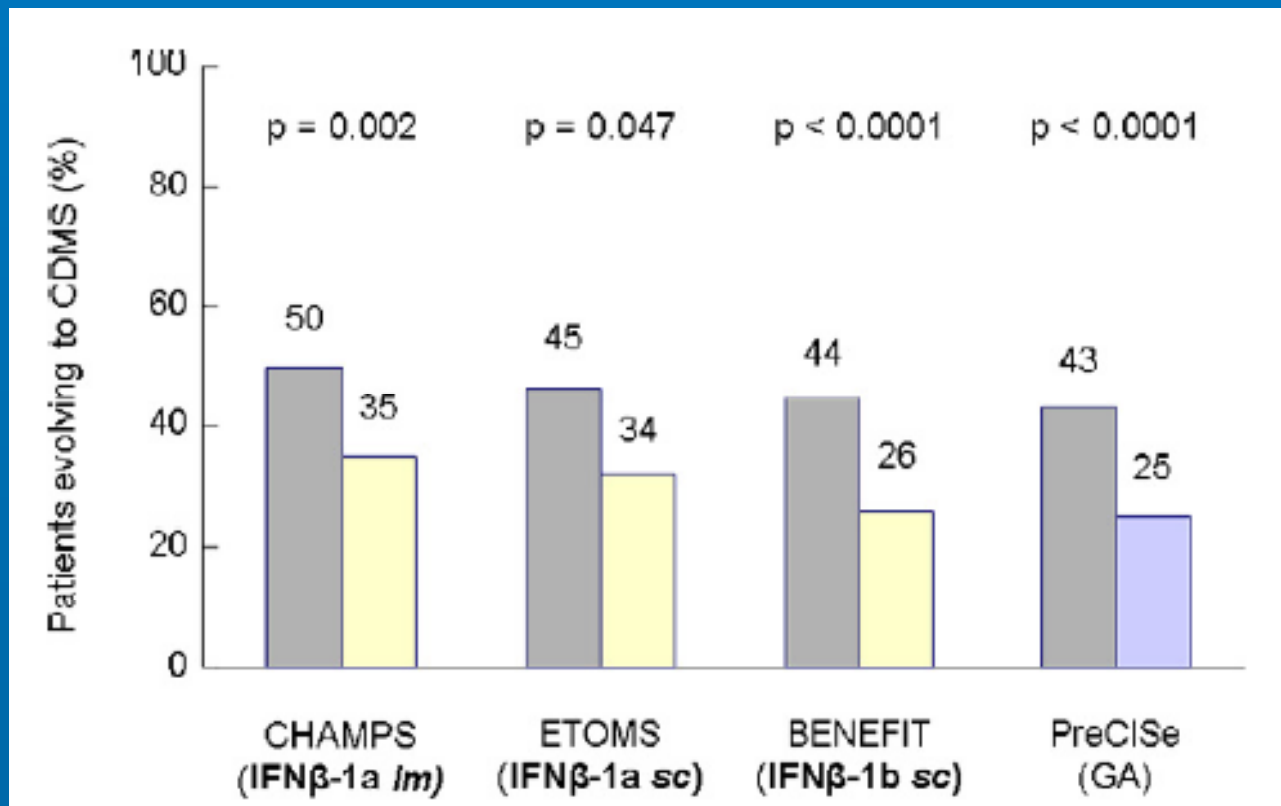
Delay in progression to CDMS



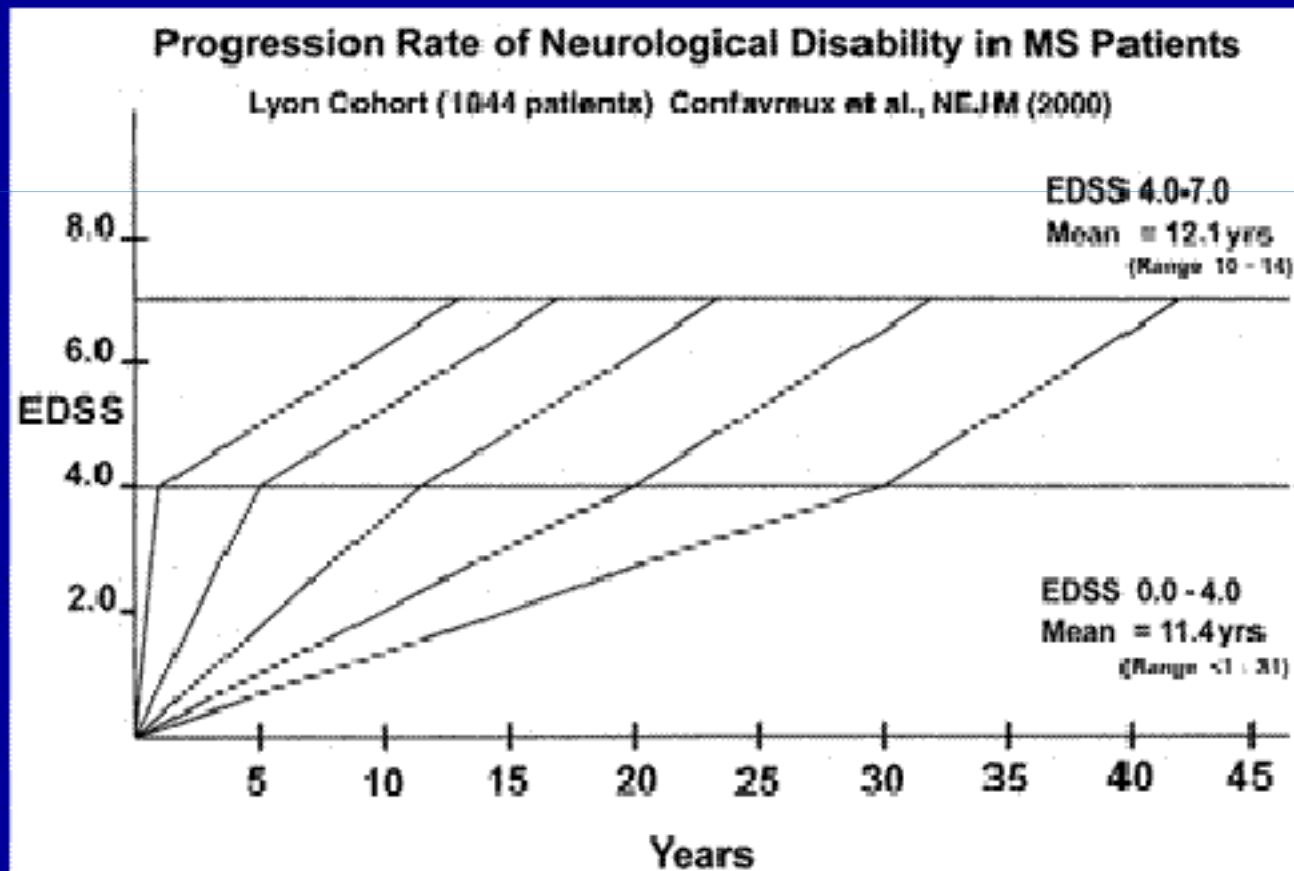
Reduction in cumulative new T2 lesions

# Delay in Progression to CIS

All DMDs have a significant effect



# Progression of Neurological Disability



# The Future of MS Therapy

- Immune-directed therapies
  - Immune ablation with reconstitution
  - Immunosuppression
  - Immunomodulation
  - Suppression of cell entry into CNS
- Neuroprotective therapies
- Myelin repair strategies

# Immune Ablation and Reconstitution

<b>Substance</b>	<b>Proposed Mechanism</b>	<b>Pros</b>	<b>Cons</b>	<b>Phase</b>
Autologous SCT	New maturation of acquired immune system	Profound alteration of T and B cell repertoire	Mortality 5-10%; Immunogenetic predisposition not influenced	II
Allogenic SCT	Alteration of immune genetic predisposition	Alteration of genetic predisposition	Mortality >20%	PC
Genetically engineered SCT	Specific alteration of immune genetic predisposition	Alteration of genetic predisposition	Many unknowns; Unpredictable side effects	PC

# Stem Cell Transplant for MS

- SCT did not work for PPMS and SPMS
  - Abrogation of MRI inflammation
  - Loss of brain volume over 2 years
- Response in RRMS more promising
  - No Rx-related mortality
  - No disease progression
  - Significant improvement
- High-intensity myeloablative regimens with TBI or busulfan had high mortality

# Parenteral Agents

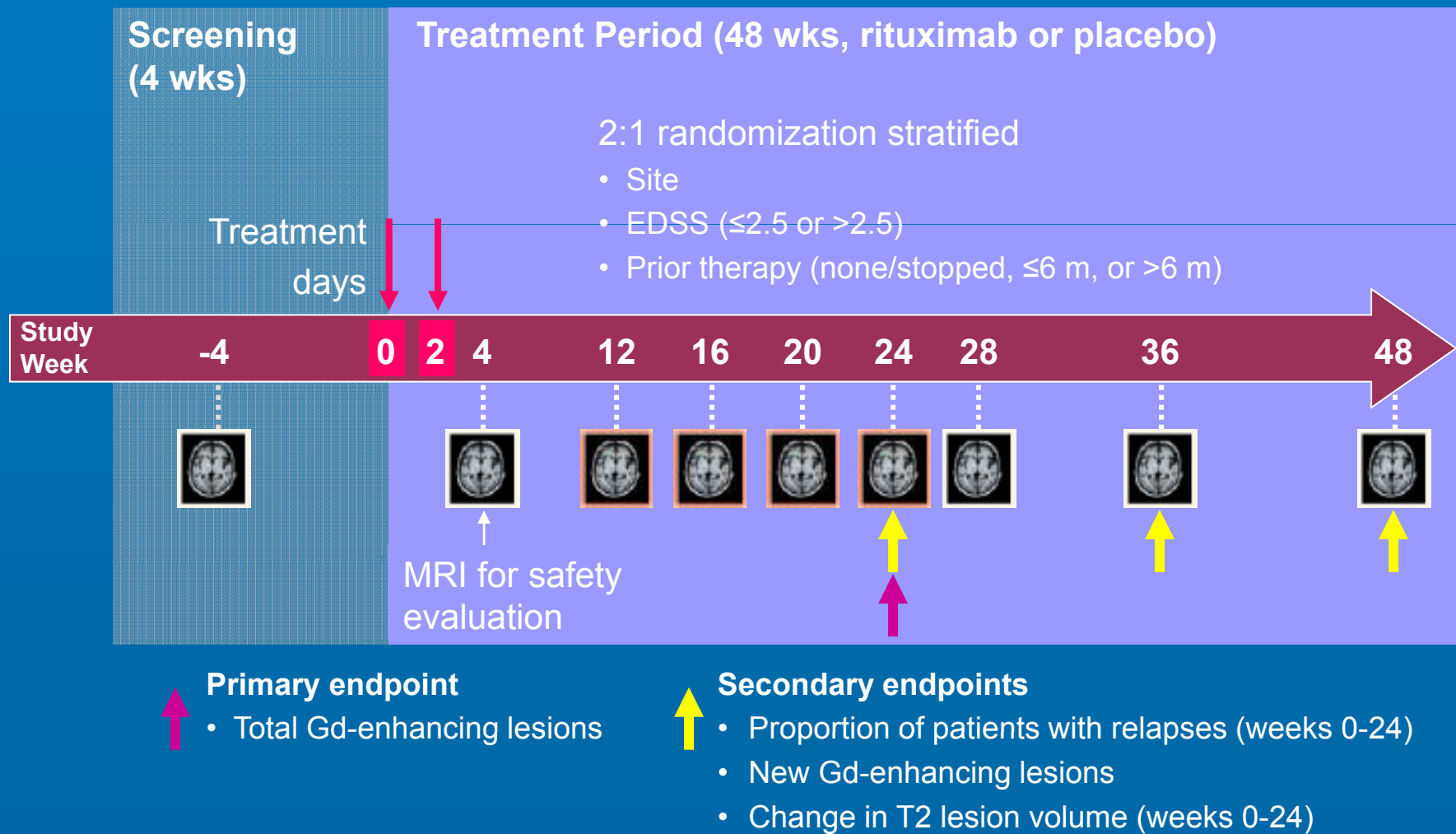
# Rituximab

- Chimeric human/murine monoclonal Ab to CD20
- Depletes circulating B cells
- Approved by FDA for
  - Standard therapy with CHOP for aggressive lymphoma (eg, diffuse B cell-lymphoma [approved 1997])
  - Refractory rheumatoid arthritis in combination with methotrexate (approved 2006)
- >300,000 patients treated with RTX alone or in combination with CHOP

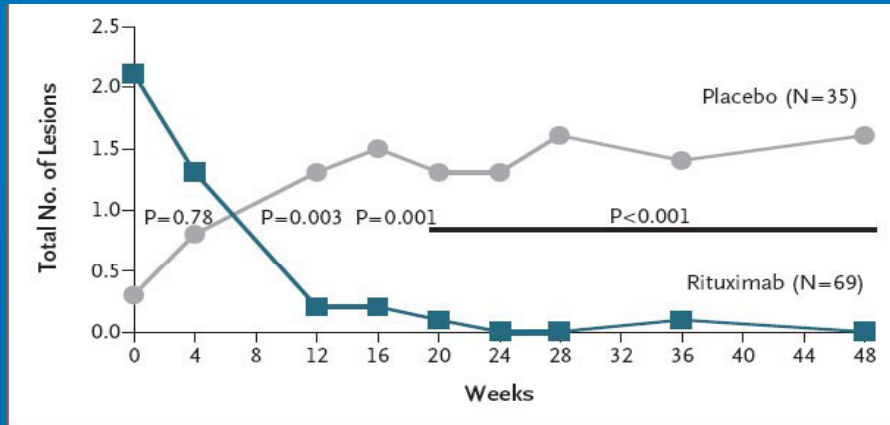
# Rituximab and Multiple Sclerosis

- Initial trial for NMO
- Phase 2 study for RRMS
  - Randomized, 48 weeks, 104 pts with RRMS
  - Rituximab 1 g IV vs placebo on days 1 and 15
  - Gd+ T1 brain lesions at 12, 16, 20, and 24 weeks
    - Rituximab  $0.5 \pm 2.0$ ; placebo  $5.5 \pm 15$  ( $P < 0.0001$ )
  - Relapses at 24 weeks
    - Rituximab 14.5% vs placebo 34.3% ( $P = 0.02$ )
- Current trials
  - HERMES (phase II for RRMS)
  - OLYMPUS (phase II/III for PPMS) – *ineffective*

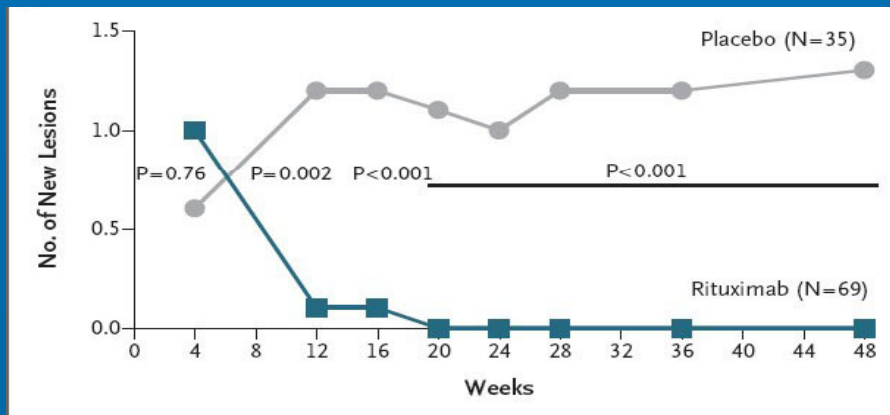
# Rituximab in RRMS



# Rituximab in RRMS (cont)



Mean total Gd-enhancing lesions by week\*



New Gd-enhancing lesions by week\*

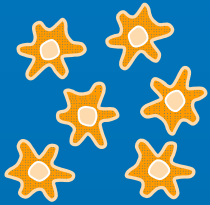
\*Missing values imputed by an average of available data

# Ocrelizumab

- Humanized anti-CD20 monoclonal Ab
- Genentech – comarketed with Biogen
- Other anti-CD20 Abs
  - Rituximab – chimeric
  - Ofatumumab – fully human
- Advantages over rituximab
  - ↓antigenic
  - ↓complement activation than rituximab
  - ↓infusion reactions
- In phase 3 trial for active RA
- Disagreement between companies on proceeding with phase 3 trials for MS

# Anti-B-cell Therapy in Multiple Sclerosis

**BAFF (Blys)**  
B-cell Activating Factor



**BAFF-R**



- Promotes survival and B-cell differentiation
- Potent T cell costimulation and IL2 producer
- Sustains GC, enhances Ig production and survival of plasmablasts

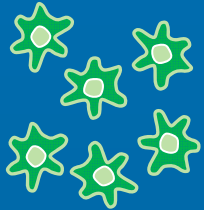
**BCMA**



- Promotes lymphocyte maturation and antibody production

**APRIL**

A Proliferating Inducing Ligand



**TACI**



- Promotes B-cell proliferation
- Strong stimulator of plasma cell survival
- Stimulates IgM production

Produced by monocytes, macrophages, DC, and circulates as a trimer

**B cell**

# Anti-B-cell Therapy in Multiple Sclerosis

**Table 2** Monoclonal antibodies and fusion proteins against B cell targets

Monoclonal antibodies/fusion proteins	Targets on B cells	Action
1. Anti-soluble BAFF (belimumab)	Soluble BAFF	Inhibits binding of BAFF to TACI, BCMA, and BAFF-3
2. Anti-BAFF-receptor IgG fusion protein	Soluble BAFF-R IgG	Inhibits BAFF
3. BAFF (Blys) antagonist	BAFF	Neutralizes Blys
4. BCMA IgG	APRIL	Inhibits mostly APRIL
5. TACI IgG fusion protein (atacept)	Blys and APRIL	Inhibits BAFF and APRIL
6. Anti-lymphotoxin- $\beta$ receptor	Lymphotoxin $\beta$	Blocks the formation of ectopic germinal centers
7. Anti-CD <sub>22</sub> (epratuzumab)	CD <sub>22</sub>	B cell depletion
8. Anti-CD <sub>20</sub> (rituximab, ocrelizumab)	CD <sub>20</sub>	B cell depletion

# Atacicept in Multiple Sclerosis: Phase 2 Clinical Trial

- Copromoted by Merck Serono and ZymoGenetics
- 300 patients will be randomized to 3 doses of the drug and placebo
- Treatment for 36 weeks and follow up to 48 weeks
- Being tested for SLE, lupus nephritis, rheumatoid arthritis, and MS
- Atacicept contains the soluble TACI receptor
- TACI receptors bind to BLYs and APRIL, cytokines of the TNF family
- BLYs and APRIL levels are elevated in SLE, RA, and MS

# Rituximab-associated PML

- Feb 2006: Labeling change by FDA to include PML
- RADAR (Research on Adverse Drug Event and Reports) Project
  - Review from 1997–2008
  - 68 lymphoproliferative disorders
    - Most CLL
    - Incidence rate about 1:20,000
  - 2 SLE (Rx'd <12 mos)
  - 3 RA (Rx'd 18 mos but also on chemoRx)
  - 1 autoimmune pancytopenia (RTX, AZA, steroids)
  - 1 autoimmune hemolytic anemia (RTX and steroids only)
- Others
  - 7 additional lymphoproliferative disorders
  - 1 Wegener's granulomatosis
  - 1 cryoglobulinemia (Rx <12 mos)
  - 1 ITP

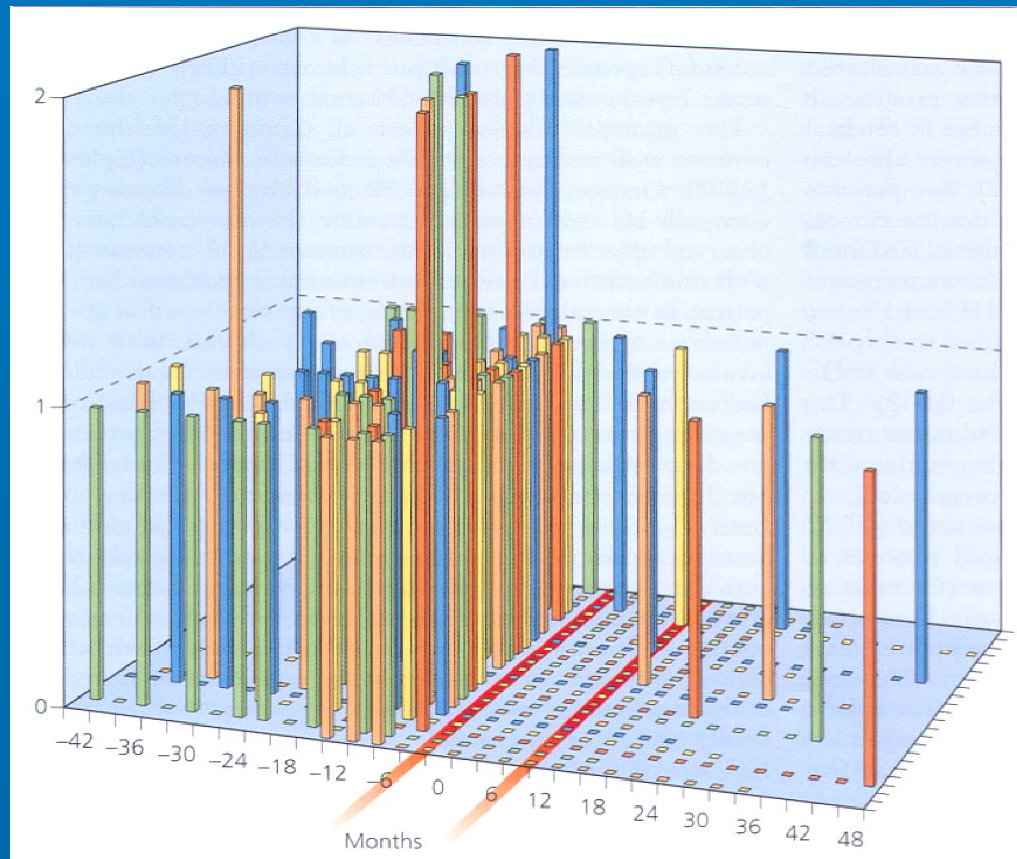
# Alemtuzumab

- Anti-CD52 monoclonal antibody
- In development by Genzyme
- Rapidly developing lymphopenia following pulse treatment
  - 99% of T and B cells gone within 1 hour
  - Prolonged suppression of T cells
    - Total T cells in 66 mos
    - CD3 T cells recovered in 51 months, CD4 in 61 mos, CD8 in 30 mos
  - B cells recover after 3 months

# Alemtuzumab (cont)

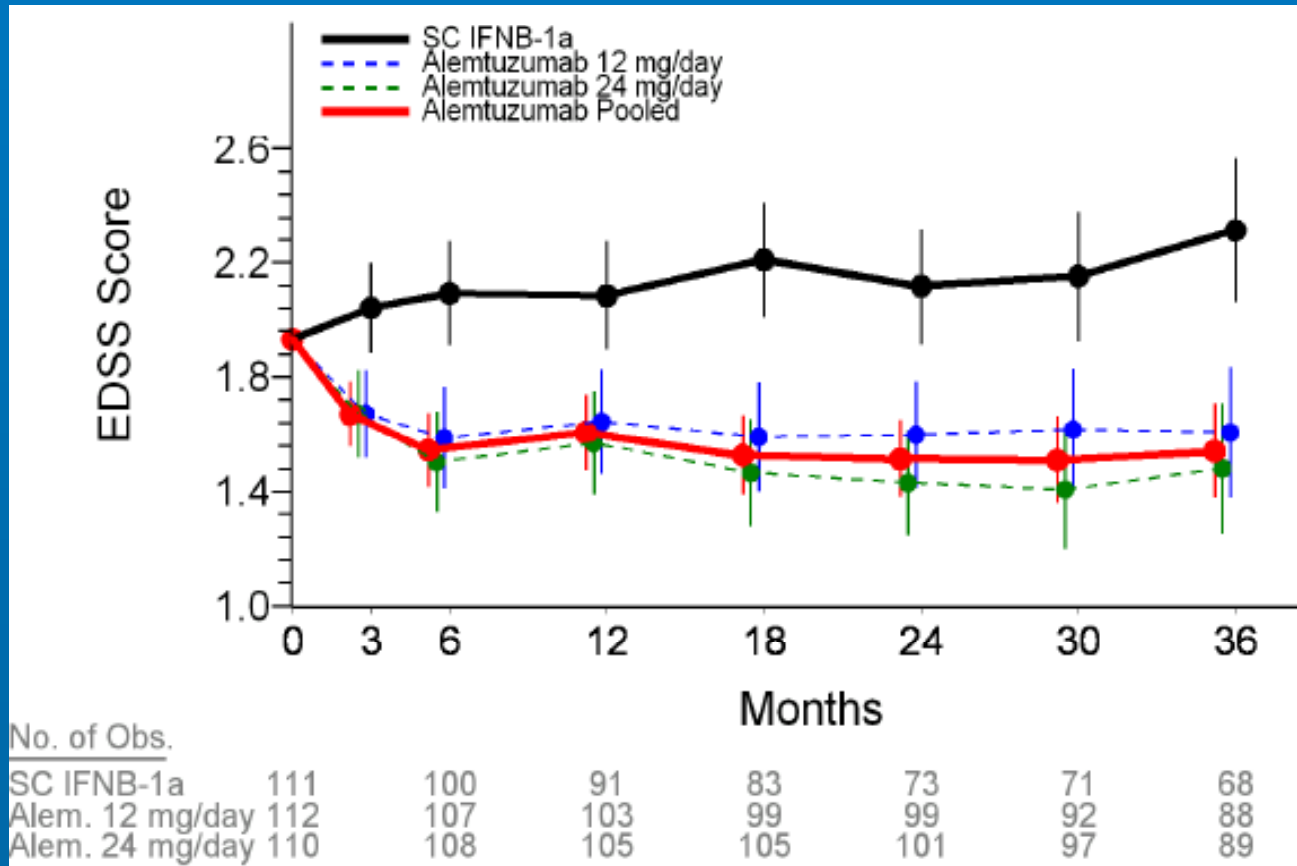
- CAMMS223
  - 334 patients with early active RRMS
  - Randomized to 1:1:1—IFN  $\beta$ -1a 44  $\mu$ g: IV ALM 24 mg/d: IV ALM 12 mg/d
  - 2-year follow-up
  - 88% vs 66%  $\downarrow$  in sustained decline in EDSS
  - Mean EDSS improved with ALM

# Alemtuzumab (cont)



94% reduction  
in RR in 22  
patients

# Reduction in EDSS Score with Alemtuzumab



# Alemtuzumab (cont)

- CARE-MS Trial
  - Phase 3 for treatment-naive patients
  - Comparing efficacy and safety to IFN  $\beta$ -1a SC
  - 2-year follow-up
  - Primary endpoints: EDSS and annualized relapse rate
- Care MS2 Trial
  - Phase 3
  - Previously treated patients with breakthrough

# Alemtuzumab (cont)

- MS
  - No ↑ in opportunistic infection to date
  - ↑ in humorally mediated autoimmune disease
    - Idiopathic thrombocytopenic purpura (ITP) (3%)
    - Graves' disease (20%)
    - Anti GBM disease
- Lymphoproliferative disease with SCT
  - Almost 2X risk of CMV reactivation
  - 50% greater risk of opportunistic infection
  - 1 CLL pt with PML 3 mos after alemtuzumab

# Daclizumab

- Humanized monoclonal IgG1 Ab to  $\alpha$  chain of IL-2 receptor (IL-2R $\alpha$ )
- Anti-CD 25 antibody
- Developed by Biogen
- Approved for renal allograft rejection
- MOA
  - IL-2R $\alpha$  expressed on activated T, B, NK cells and monocytes
  - IL-2R $\alpha$  involved in clonal expansion of autoreactive T cells
  - IL-2 and  $\gamma$ -IFN secreted by Th1 cells responsible for CMI

# Daclizumab (cont)

- Uncontrolled trials in MS
  - Well tolerated
  - EDSS stabilized or improved
  - Maybe safe to used with IFN- $\beta$
- CHOICE Trial
  - RDBPC add on in 230 patients with RRMS
  - 3 Rx arms with 2 doses of DAC and PLC
  - Decrease in Gd+ lesions with higher dose
  - No difference in relapse rate
  - 5.2% with grade 3 infections (no grade 4)
- SELECT Trial - ongoing

# MBP 8298 (Dirucotide)

- Developed by BioMS Medical
- DR2 MHC haplotype ↑ susceptibility to MS
  - 50–70% of MS v 20-30% of normals
  - T cell epitope in center of MBP is target
  - Most frequent target of autoAbs in CSF
- MBP8298 – synthetic 17 amino acid peptide mimics myelin target residues 85-96
- Injection results in sustained ↑ Ab to MBP
- Phase 2 trial
  - 500 mg IV q 6 months v PL in 32 patients
  - No change in EDSS except in subgroup with DR2 and/or DR4
- Phase 3 Trial in PPMS and SPMS
  - 510 patients at 60 sites

# Oral Agents

# Cladribine

- Synthetic purine nucleoside analogue<sup>1</sup>
- Merck-Serono developing for MS
- Causes preferential and sustained lymphocyte depletion<sup>2</sup>
  - Greater effect on CD4<sup>+</sup> than CD8<sup>+</sup> T-cells<sup>2</sup>
  - Relative sparing of other haematological and immune cells, including B-cells<sup>3</sup>
- Reduces levels of proinflammatory cytokines and chemokines<sup>4,5</sup>
- Crosses the BBB<sup>6</sup>
- Investigated for treatment of MS and other autoimmune diseases<sup>7</sup>

BBB, blood–brain barrier; MS, multiple sclerosis

<sup>1</sup>Carson DA et al. *Blood*. 1983;62:737–43; <sup>2</sup>Beutler E et al. *Proc Natl Acad Sci USA*. 1996;93:1716–20;

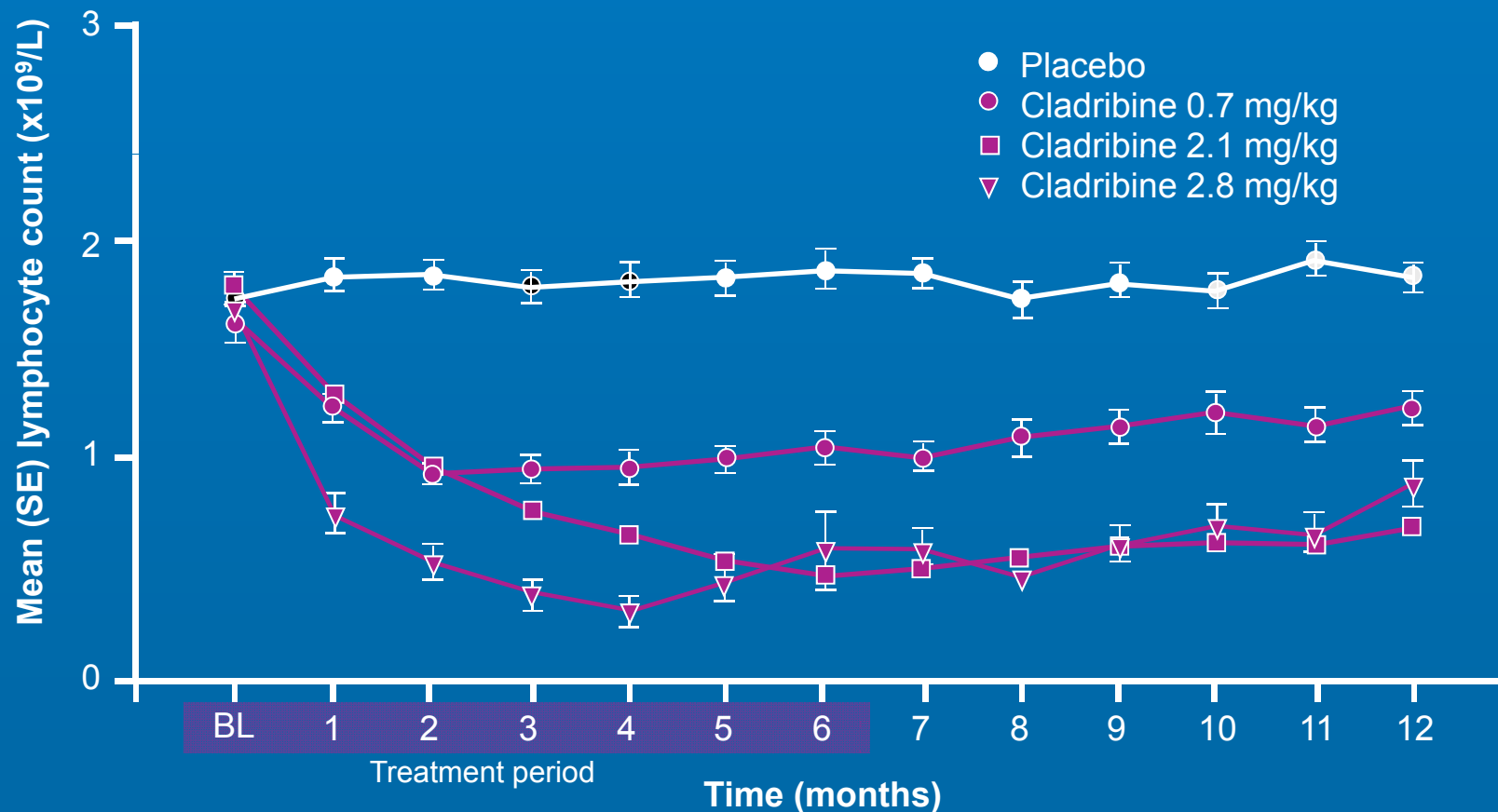
<sup>3</sup>Rice GP et al. *Neurology*. 2000;54:1145–55; <sup>4</sup>Szczucinski A et al. *Acta Neurol Scand*. 2007;115:137–46;

<sup>5</sup>Bartosik-Psujek H et al. *Acta Neurol Scand*. 2004;109:390–2; <sup>6</sup>Liliemark J. *Clin Pharmacokinet*. 1997;32:120–31;

<sup>7</sup>Beutler E et al. *Semin Haematol*. 1996;33:45–52.

# Cladribine and Lymphocytes

## Lymphocyte depletion is dose-dependent



BL, baseline; SE, standard error

Cook S. *Mult Scler.* 2007;13:S7-273,P807.

# CLARITY Trial

## Cladribine Tablets Treating MS Orally

- 96-week randomized, PLC-controlled, double-blind, international trial
- 1326 RRMS patients enrolled 1:1:1 in low-dose, high-dose, and placebo groups
- Once-daily treatment given 2 or 4 times per year
  - Low-dose: two, 4-day treatment courses
  - High-dose: four, 10-day treatment courses

# CLARITY Trial (cont)

- Primary endpoint was relapse rate
- Secondary endpoints
  - Relapse-free
  - Disability progression at 96 weeks
- 90% of patients on drug completed trial
- Two-year results
  - 58% reduction of exacerbation in the low-dose group
  - 55% RR of exacerbations in the high-dose group
- Adverse events were comparable to placebo
  - Lymphopenia more common

# Other Cladribine Trials

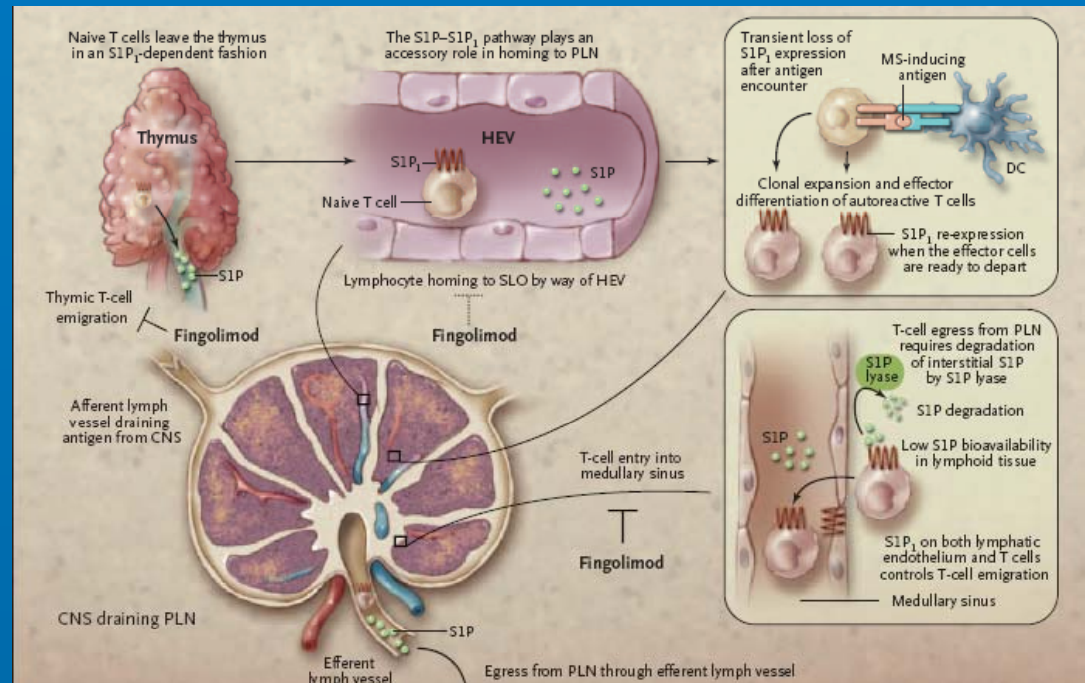
- CLARITY extension study
- ORACLE MS (Oral Cladribine in Early MS)
  - 2-year phase 3
  - Cladribine as monoRx in patients at risk
- ONWARD (Oral Cladribine Added on to Rebif)
  - Designed for breakthrough disease

# Fingolimod—FTY 720

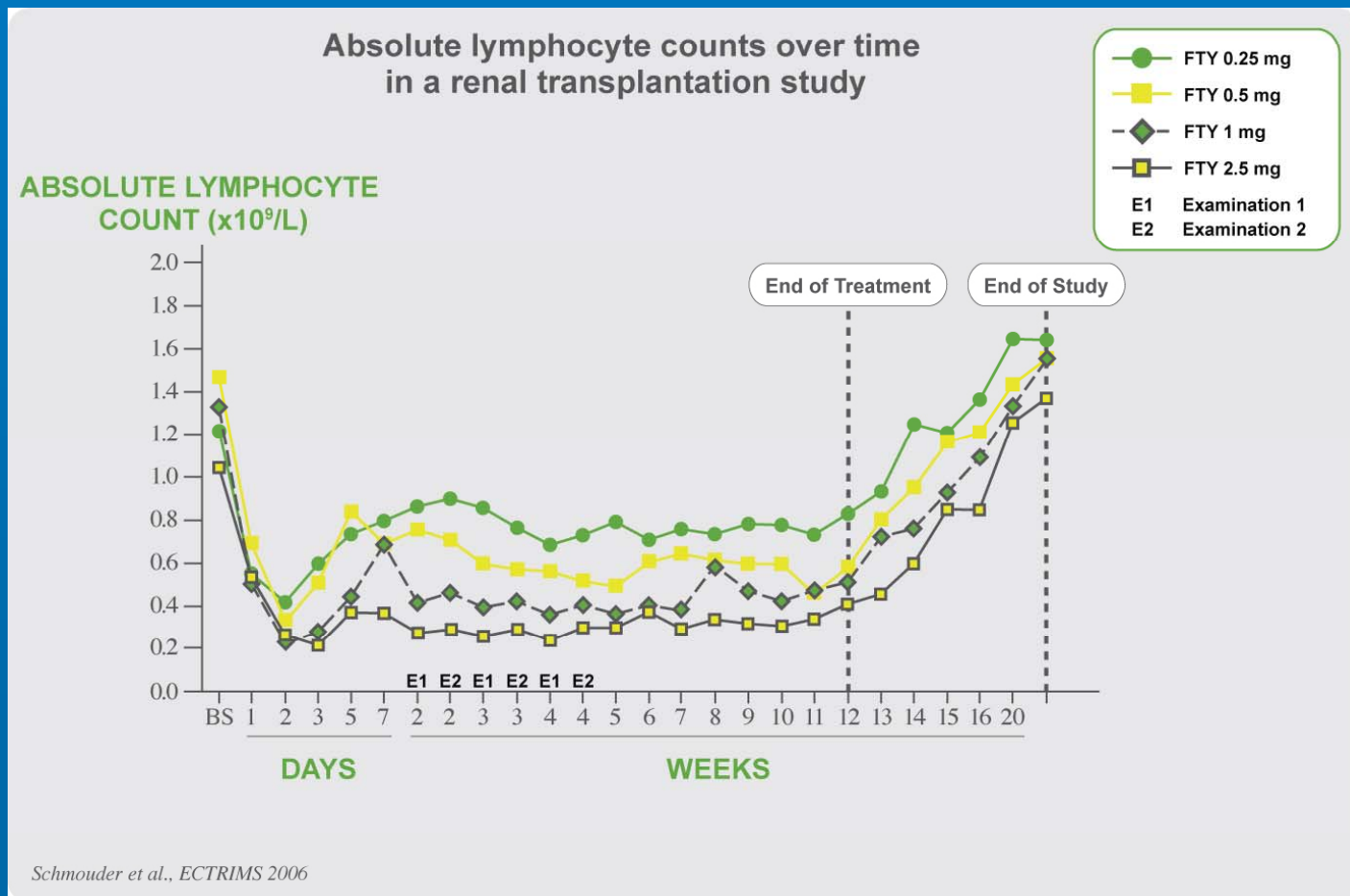
- Immunosuppressant (developed by Novartis)
- Transplant rejection and autoimmune disease
- Sphingosine 1 phosphate receptor superagonist
- S1P regulates a wide variety of cellular functions
  - Includes cell motility and cytoskeletal rearrangements
- S1P released by platelets, immune and nonimmune cells during inflammation
- FTY-720 internalizes S1P receptor

# Fingolimod—FTY 720 (cont)

- Homing of lymphocytes (LC) to different compartments depends on chemokine system
- LC egress from thymus and secondary lymphatic organs (SLO) depends on S1P1
  - Regulated expression of S1P1 controls timing of LC exit from SLO



# Reduction of Blood Lymphocyte Counts by FTY720 Is Reversible



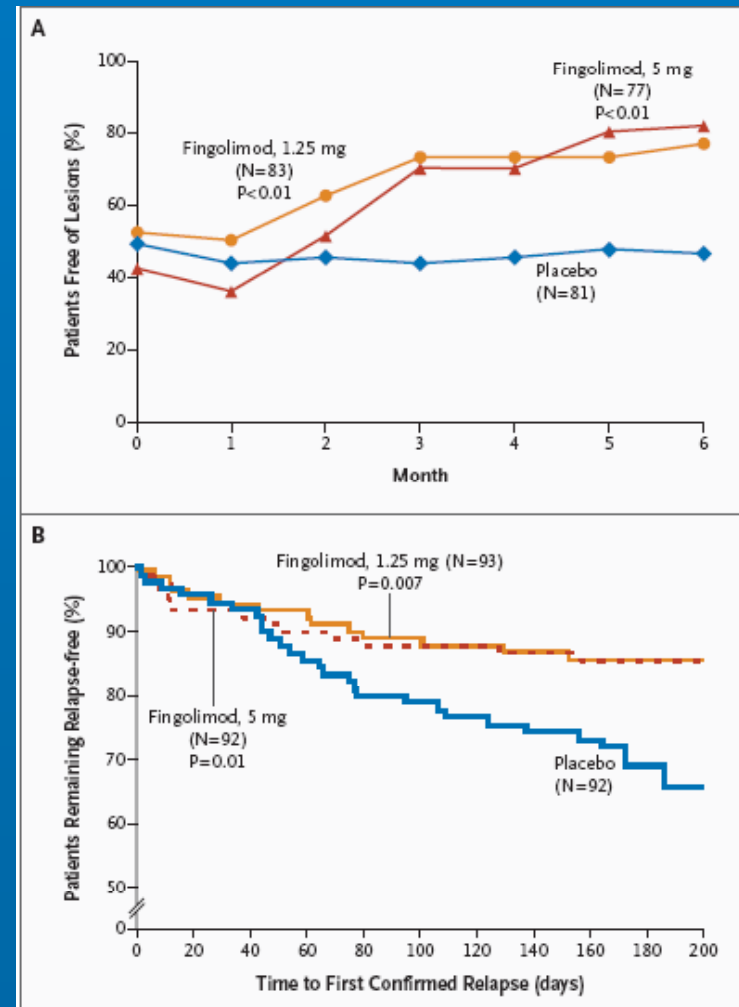
# FTY 720—MS Trials: Phase 2 Trial

- Study design
  - 281 pts, active relapsing MS
  - 3 arms: FTY720 (5.0mg, n=94) vs FTY720 (1.25mg, n=94) vs PCB (n=93)
  - 6 months of Rx followed by 6 months' extension
- 6-month results
  - ↓Gd+ lesion volume, new T2 lesions, T2 volume  $\Delta$
  - ↑ time to first relapse
  - Well-tolerated with good safety profile
- 12-month results
  - 89% in extension phase; re-randomized to active dose
  - 6- or 12-month treatment groups
  - Similar proportions free of Gd+ lesions at 12 months

# Fingolimod (FTY 720) (cont)

## ● Phase 2 trial

- 6-month study in 281 patients
- (PL vs 1.25 mg/d vs 5 mg/d)
- ↓ T1 Gd+ and T2 lesion volume
- Mean total of Gd+
  - 1.25: ↓ 43% v PL ( $P<0.001$ )
  - 5: ↓ 61% v PL ( $P<0.006$ )
- ↓ Relapse rate
  - 1.25: ↓ 55% v PL ( $P=0.009$ )
  - 5: ↓ 53% v PL ( $P=0.01$ )



# FTY 720—MS Trials: Phase 3 Trials

- TRANSFORMS
  - Trial Assessing Injectable Interferon vs FTY 720 Oral in RRMS
- Design
  - 1292 patients
  - Comparison FTY 720 vs Interferon- $\beta$ -1a IM (Avonex)
  - Randomized, double-blind controlled trial
  - 1:1:1 (0.5 mg vs 1.25 mg FTY720 vs IFN  $\beta$ -1a IM)
  - Primary efficacy endpoint: Relapse rate at 1 year
  - One-year study data
    - IFN  $\beta$ -1a IM 0.33 relapses vs 0.16 FTY 0.5 mg (52% reduction)  $p < 0.001$
    - IFN  $\beta$ -1a IM 0.33 relapses vs 0.20 FTY 1.25 mg (38% reduction)  $p < 0.001$
    - Adverse effects: UURI, dyspnea, diarrhea, nausea

# FTY 720—MS Trials: Phase 3 Trials (cont)

- FREEDOMS
  - FTY720 Research Evaluating Effects of Daily Oral Therapy in MS)
- Design
  - 2000 patients over 24 months
  - 2-year DB randomized 3-arm trial in 1100 RRMS pts FTY720; 2 doses 0.5 mg and 1.25 mg qd vs placebo or IFN  $\beta$ -1a IM
  - Secondary endpoint – MRI burden of disease
  - Started 1st quarter 2006
  - Centers outside the US started recruitment earlier
  - Expected to be completed in 2009-2010

# Fingolimod (FTY 720) (cont)

- Adverse effects reported from earlier studies
  - Somnolence in 10%
  - Leukopenia in 2% of 1.25 and 5% of 5
  - Decrease in FEV1
  - Transient bradycardia after infusion
  - PRES (1 patient)

# Fumaric Acid (BG-12)

- Derived from plant—fumitory
- Used in Rx of skin diseases since 17th century
- Efficacy in psoriasis demonstrated in 1959
- Developed in MS by Biogen IDEC
- Inhibits T-cell activity by inhibiting apoptosis of activated lymphocytes
- Shifts cytokine profile from  $T_h1 \rightarrow T_h2$
- Possible neuroprotective effect as well

# Fumaric Acid (BG-12) (cont)

- 24-week phase 2b trial
  - PL v 120 mg/d v 360 mg/d v 720 mg/d
  - High dose (720 mg/d) vs PL at wks 12–24:
    - 69% ↓ Gd+ lesions
    - 48% ↓ new T2 lesions
    - 32% ↓ relapse rate
  - No difference between 120 and 360 and PL
  - AEs: flushing and nasopharyngitis
- Two large phase 3 trials underway

# Fumaric Acid (BG-12) (cont)

## **DEFINE Study**

- 1011 patients will be randomized 1:1:1: in a DBRC 3 arm study
- BG12 240 mg bid
- BG 12 240 mg tid
- Placebo

## **CONFIRM study**

- 1232 patients will be randomized in a 1:1:1:1 4 arm comparator trial
- Glatiramer
- Placebo
- BG 12 240 mg bid
- BG 12 240 mg tid

# Laquinimod (ABR-215062)

- Derived from roquinimex (linomide) which suppressed Gd+ in MS
- Developed by Teva Pharmaceuticals and Active Biotech
- Causes shift from Th1 to Th2 profile
- Reduces migration of m $\theta$  across BBB
- Activity is independent of IFN- $\beta$
- Combination with IFN- $\beta$  may be synergistic

# Laquinimod (ABR-215062) (cont)

- Phase 2 trial
  - 209 patients between ages 18 and 65
  - Oral dose of 0.1 mg/d v 0.3 mg/d v PL
  - Active lesions at 24 weeks
    - 5.24 in LQM 0.3 v 9.44 PL ( $P<0.05$ )
    - Only active lesions at baseline contributed to effect
  - No difference in EDSS, MSFC, or SF-36 scores
  - Well tolerated

# Laquinimod (ABR-215062) (cont)

- Phase 2b trial
  - 306 patients between ages 18 and 65
  - Oral dose of 0.3 mg/d v 0.6 mg/d vs PL
  - Active lesions at 36 weeks
    - 10.53 LQM 0.6 vs 16.86 in LQM 0.3 vs 15.77 PL
    - 40% ↓ cumulative Gd+ v PL ( $P=0.0048$ )
  - Trends only observed for RR, relapse-free, and time to first relapse
  - ↑ LFTs dose-dependent and transient

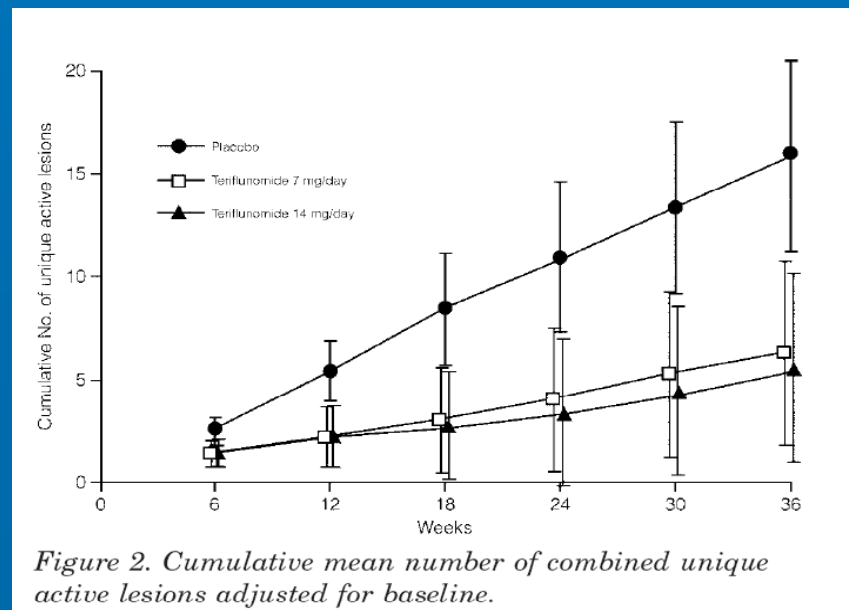
# Teriflunomide

- Active metabolite of leflunomide used in treatment of RA
- Developed by Sanofi-Aventis
- Inhibits pyrimidine synthesis by binding dihydrorotate dehydrogenase
- Inhibits T-cell division
- Suppresses EAE

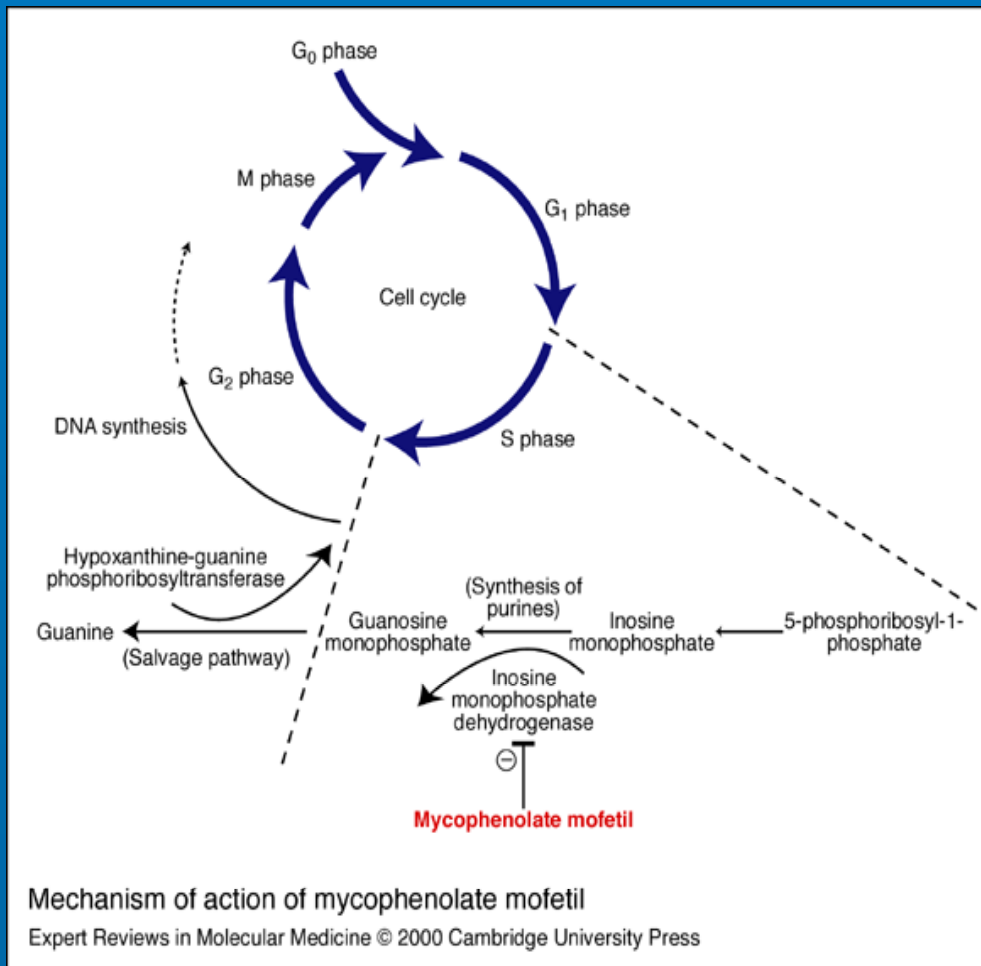
# Teriflunomide (cont)

- Phase 2 trial
  - TF 7 mg/d v 14 mg/d v PL
  - 179 patients randomized
  - 36-week trial
  - ↓ T1 CE lesions (61% 7 mg and 62% 14 mg)
  - ↓ T2 new or enlarging (72% 7 mg and 53% 14 mg)
  - Higher dose favored for T2 lesion volume

- Well-tolerated
  - SAEs: ↑ LFTs, ↓ WBC, rhabdomyolysis



# Mycophenolate Mofetil



- Developed by Aspreva Pharmaceuticals
- Inhibits B- and T-cell proliferation
- Inhibits inosine monophosphate dehydrogenase in the S phase of DNA synthesis
- Lymphocytes are chiefly dependent on de novo synthesis of purines

# Combination Therapies

# Combination Therapies

- Many studies regarded as pilot studies
  - Small numbers
  - Uncontrolled
  - Retrospective
  - Variable doses and regimes (>1 IFN)
- Demonstrate safety but not efficacy
- Widespread adoption of combination therapy will require better-designed trials

# Combination Therapies (cont)

- Recently reported
  - GA and any IFN- $\beta$ 
    - Psychological but no other impact
  - GA and IVMP
    - $\downarrow$  CE lesions
  - GA and natalizumab
    - ? safe
  - IFN  $\beta$ 1-a IM and doxycycline
    - $\downarrow$  CE lesions,  $\downarrow$  relapse rate; better EDSS
  - Daclizumab and IFN- $\beta$ 
    - $\downarrow$  CE lesions,  $\downarrow$  relapse rate

Ytterberg C et al. *Acta Neurol Scand*. 2007;116:96-99. De Stefano N et al. *J Neurol Sci*. 2008;266:44-50. Minagar A et al. *Arch Neurol*. 2008;65:199-204. Rose. *Neurology*. 2007;69:785-789; Kaufman M et al. 60th AAN Annual Meeting, April 12–19, 2008. Chicago, IL.; Goodman A, et al. *Neurology* 2009;72:806-812.

# Combination Therapies (cont)

- Two large studies awaiting results
  - GA and IFN  $\beta$ 1-a IM weekly vs GA vs IFN  $\beta$ 1-a IM (CombiRx)
  - Induction with mitoxantrone
    - 3 monthly doses followed by 2 doses 3 months apart overlapping with GA
- One combination ineffective
  - Natalizumab and IFN  $\beta$ 1-a IM weekly (SENTINEL)

A physician has two sleeves, one containing a diagnostic and the other a therapeutic armamentarium; these sleeves should rarely be emptied in one move; keep some techniques in reserve; time your maneuvers to best serve the status and special needs of your patient.

Albert Richard Lamb, M.D. 1881 - 1959