



## **New and Emerging Concepts in the Management of Multiple Sclerosis**

Downloadable PDF Slides  
Updated November 2011 (Post-ECTRIMS)

The following slide deck was updated after the 2011 ECTRIMS meeting and may be used as an educational resource for learners who attended the CME/CE presentation “New Frontiers: New and Emerging Concepts in the Management of Multiple Sclerosis”.



## Discussion Topics

- **Pathophysiology**
  - *White matter (WM) plaque, diffuse abnormal WM (DAWM), and grey matter (GM) pathology*
  - *B cell contribution to multiple sclerosis (MS) pathogenesis*
  - *Mitochondrial deoxyribonucleic acid (DNA) in MS*
- **Biomarkers in MS**
  - *Radiologically isolated syndrome*
  - *Biomarkers of therapeutic response*
  - *Anti-JCV antibody (Ab) test*
- **New and emerging therapies for MS**
  - *Current understanding of mechanisms of action*
  - *Updates on efficacy and safety data*

## Pathophysiology



## MS Pathology Beyond the WM Plaque

- **Plaque-centered view (past 100 years)<sup>1</sup>**
  - *Demyelination around small venules*
  - *Inflammatory process*
  - *Axonal injury*
  - *Some remyelination*
- **Modest correlation between lesion load and clinical disability<sup>2</sup>**
- **Recent magnetic resonance imaging (MRI) studies suggest additional pathology may be more indicative of disease severity<sup>1</sup>**
  - *DAWM pathology<sup>1,2</sup>*
  - *GM pathology<sup>1</sup>*

<sup>1</sup>Lassmann H. *Neuroimaging Clin N Am.* 2008;18:563-576.  
<sup>2</sup>Seewann A, et al. *Arch Neurol.* 2009; 66:601-609.



## MS Pathology Beyond the WM Plaque

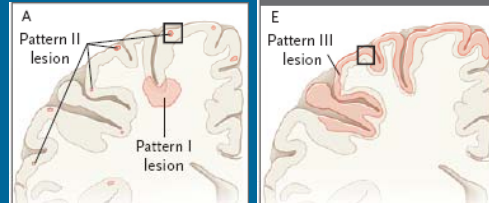
- **DAWM pathology<sup>1</sup>**
  - *As observed postmortem, diffuse (not focal) areas of reduced myelin, axonal loss, and chronic fibrillary gliosis*
  - *Distinct pathology from focal WM lesions, suggesting secondary degenerative process*
- **GM pathology**
  - *GM involved early in disease course<sup>2</sup>*
  - *GM pathology manifests on MRI as lesions, atrophy, abnormal neuronal metabolites, increased diffusivity, and T2-hypointensity<sup>3</sup>*
  - *GM lesions compared to WM lesions: very few lymphocytes (T- and B-cells), less microglial activation, and fewer perivascular cuffs<sup>4</sup>*

<sup>1</sup>Seewann A, et al. *Arch Neurol.* 2009;66:601-609.  
<sup>2</sup>Ceccarelli A, et al. *Mult Scler.* 2010;16:39-44.  
<sup>3</sup>Neema M, et al. *J Neuroimaging.* 2009;19:3-8.  
<sup>4</sup>Dutta R, Trapp BD. *Neurology.* 2007;68(suppl 3):S22-S31.



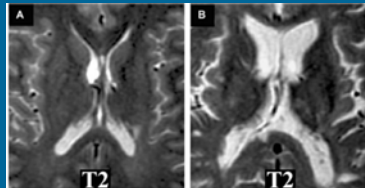
## GM Pathology

- **Cortical demyelination<sup>1</sup>**
  - 3 lesion patterns (observed postmortem)
  - Cortical atrophy is associated with disease progression, physical disability, cognitive dysfunction<sup>2</sup>



Reproduced with permission from Rudick RA, Trapp BD. *N Engl J Med.* 2009;361:1505-1506. Copyright © 2009 Massachusetts Medical Society.

- **Deep GM (basal ganglia, thalamus, brainstem)<sup>3</sup>**



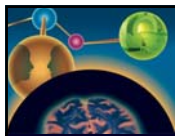
Images courtesy of Mohit Neema, MD (Neema M, et al. *J Neuroimaging.* 2009;19:3-8).

- Deep GM atrophy detected as T2 hypointensity (Figure A) and associated with sustained progression of disability

<sup>1</sup>Rudick RA, Trapp BD. *N Engl J Med.* 2009;361:1505-1506.

<sup>2</sup>Disanto G, et al. *Autoimmune Dis.* 2011;932351.

<sup>3</sup>Neema M, et al. *J Neuroimaging.* 2009;19:3-8.

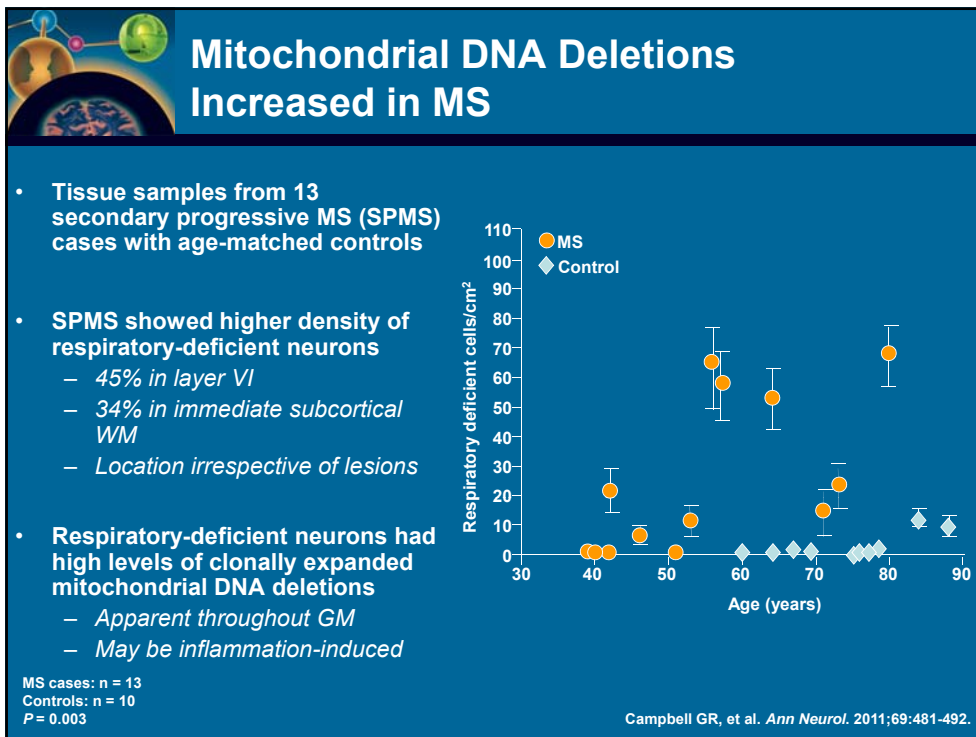
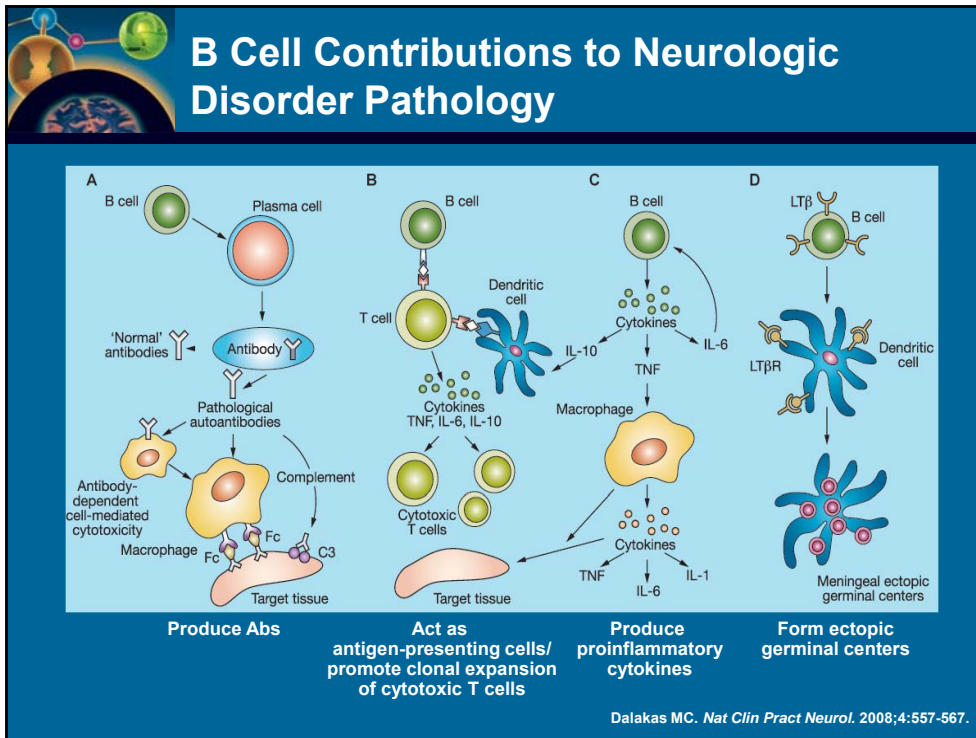


## B cells in MS Pathogenesis

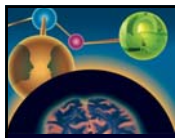
- **Historically, activated, cytotoxic, and immunoregulatory T cells have been key focus in MS<sup>1</sup>**
  - Potentially attributable to early observations of T cells being the main lymphocytic subset within MS plaques
- **B cells traditionally thought to play a secondary T-cell-dependent role<sup>2</sup>**
- **Growing evidence suggests a central role for B cells in MS pathogenesis<sup>1,2</sup>**
  - Fundamental contributions to T cell activation and tissue injury

<sup>1</sup>Dalakas MC. *Nat Clin Pract Neurol.* 2008;4:557-567.

<sup>2</sup>Hartung HP, Kieseier BC. *Ther Adv Neurol Disord.* 2010;3:205-216.



## Biomarkers in MS



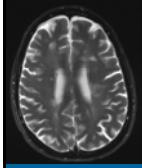
### Personalized Medicine: A Need for Biomarkers in MS

- **Prognostic biomarkers are needed to provide information about short and long-term course of individual patients' disease**
  - *Ongoing efforts to:*
    - Assess treatment versus no treatment
    - Assess risk versus benefit of various treatments per individual
- **Predictive biomarkers are needed to provide information about response to therapy**
  - *Ongoing efforts to:*
    - Identify responders and nonresponders to first-line therapies
    - Identify individuals at risk for adverse events (AEs)
- **Vast majority of biomarker findings currently reside in the discovery stage, with few truly validated**

Villoslada P. *Drug News Perspect.* 2010;23:585-595.

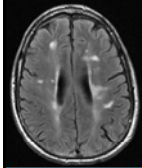


## Radiologically Isolated Syndrome: A Prognostic Biomarker?



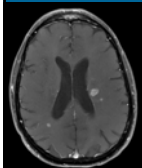
- **Incidental evidence from brain MRI<sup>1</sup>**

- Brain MRI acquired for other indications (eg, headache, head trauma)
- Absence of clinical symptoms of MS



- **Diagnosis and management remain controversial**

- Okuda study: radiologic progression in 59% in 2.7 years; clinical symptoms in 33% in 5.4 years<sup>2,3</sup>
- LeBrun study: radiologic progression in 83% in 2 years; clinical symptoms in 37% in 5 years<sup>3</sup>
- Other conditions may mimic MS radiologically<sup>2</sup>
- Evidence of patients with MS neuropathology, but asymptomatic throughout life<sup>2</sup>
- Neuropsychologic testing may be warranted<sup>2</sup>



Images provided courtesy of Bruce Cree, MD, PhD.

<sup>1</sup>Bermel RA, Fox RJ. *AAN Continuum*. 2010;16:37-57.

<sup>2</sup>Bourdette D, Simon J. *Neurology*. 2009;72:780-781.

<sup>3</sup>Okuda DT, et al. *Neurology*. 2009;72:800-805.



## Controversy Regarding Antimyelin Abs as a Predictor of CDMS

- In 2003, Berger T, et al. reported detection of serum Abs against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP), predicting early conversion to CDMS<sup>1</sup>
- In 2007, Kuhle J, et al. reported no association between antimyelin Abs and progression to MS<sup>2</sup>
- To date, 7 different studies have shown correlations ranging from highly significant to not significant at all<sup>3</sup>
  - All studies employed the same antimyelin immunoblot assay
  - In studies where a lack of association was observed, other prognostic factors, such as presence of oligoclonal bands in cerebrospinal fluid and number of hyperintense lesions on T2-weighted MRI, were positively confirmed

CDMS: clinically definite MS

<sup>1</sup>Berger T, et al. *N Engl J Med*. 2003;349:139-145.

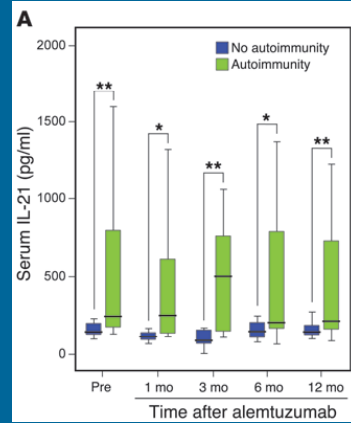
<sup>2</sup>Kuhle J, et al. *N Engl J Med*. 2007;356:371-378.

<sup>3</sup>Berger T, Reindl M. *N Engl J Med*. 2007;356:1888-1889.



## Predicting Autoimmunity With Alemtuzumab

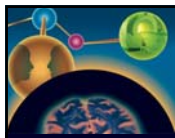
- Alemtuzumab treatment results in rapid, profound, prolonged lymphopenia
  - *Thyroid autoimmunity occurs in 20%-30% of patients*
- Autoimmunity patients have higher levels of T cell cycling, driven by genetically higher levels of IL-21
  - *Higher IL-21 levels exist pretreatment*
- By increasing cell cycling, IL-21 may increase the probability of generating self-reactive T-cells
- IL-21 could serve as a potential biomarker for risk of autoimmunity after alemtuzumab treatment



Nonautoimmune: n = 15  
Autoimmune: n = 15

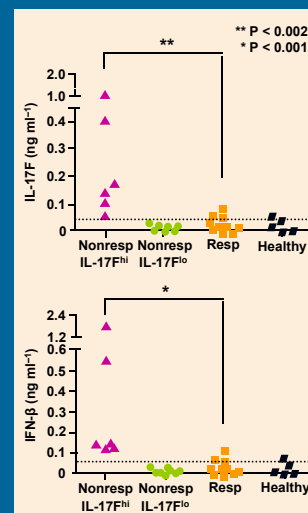
Reprinted from Jones JL, et al. *J Clin Invest.* 2009;119:2052-2061. Copyright © 2009 American Society for Clinical Investigation.

Jones JL, et al. *J Clin Invest.* 2009;119:2052-2061.



## Predicting IFN-β Response

- Well-known: 30%-50% of MS patients do not respond to IFN-β therapy
- In EAE mouse model:
  - $T_H1$ -induced EAE mice benefit from IFN-β
  - $T_H17$ -induced EAE mice worsen with IFN-β
    - $T_H17$  cells produce IL-17F
- A subset of relapsing-remitting MS (RRMS) patients have high levels of IL-17F and endogenous IFN-β
  - *These patients are potentially of a  $T_H17$ -like phenotype*
- High IL-17F concentration in serum was associated with lack of response to IFN-β
  - *Worse disease with more relapses*

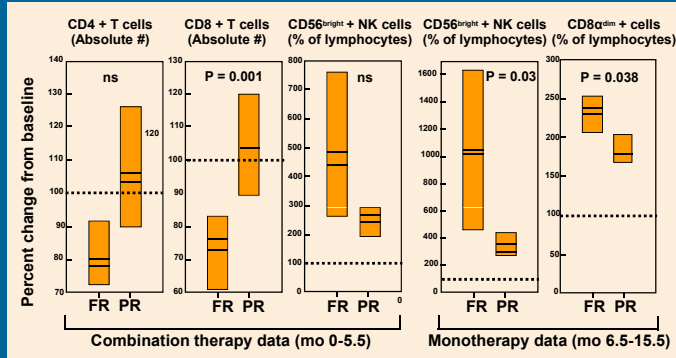


Axtell RC, et al. *Nat Med.* 2010;16:406-412.



## Predicting Daclizumab Response

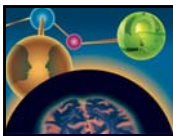
- Daclizumab suppresses MS-associated brain inflammation<sup>1</sup>
- Daclizumab is associated with a selective expansion of CD56<sup>bright</sup> natural killer cells and contraction of CD4<sup>+</sup> and CD8<sup>+</sup> T cells<sup>1</sup>



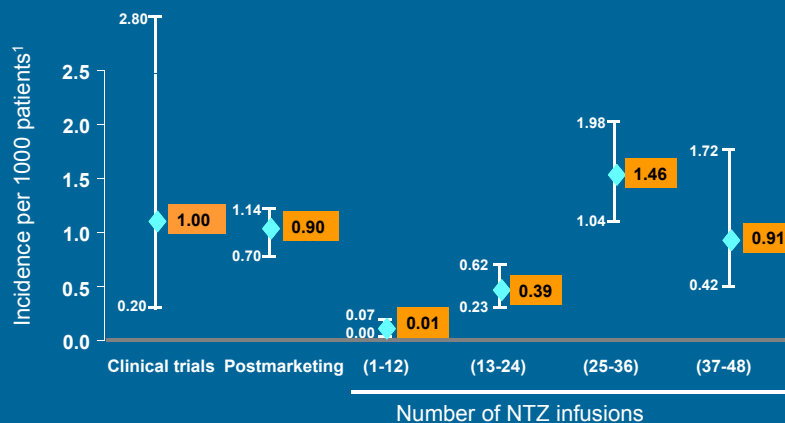
Data suggests extent of  $\Delta$  in CD8<sup>+</sup> and CD56<sup>bright</sup> NK cell counts early in daclizumab therapy may identify patients unlikely to have a full therapeutic response<sup>2</sup>

FR: full responders: n = 8  
PR: partial responders: n = 7

Bielekova B, et al. *Proc Natl Acad Sci U S A*. 2006;103:5941-5946.  
Bielekova B, et al. *Arch Neurol*. 2009;66:483-489.



## NTZ: Estimated Incidence of PML by Treatment Epoch



133 cases of PML have been documented in patients treated with NTZ as of June 2011.<sup>2</sup>

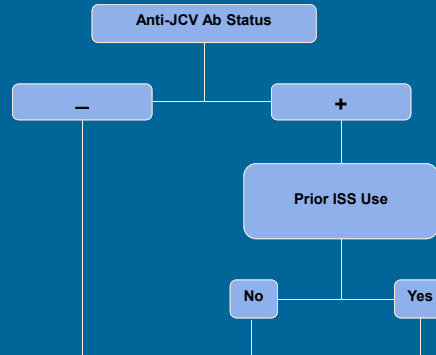
NTZ: natalizumab  
PML: progressive multifocal leukoencephalopathy

<sup>1</sup>Vermersch P, et al. European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2010; Gothenburg, Sweden. Abstract 112.  
<sup>2</sup>National MS Society. <http://www.nationalmssociety.org/news/news-detail/index.aspx?nid=2308>. Accessed July 14, 2011.



## Risk Stratification for PML on NTZ

- PML risk in NTZ-treated patients quantified and stratified by:
  - NTZ treatment duration
  - Prior ISS use
  - Anti-JCV Ab status
- Patients with all 3 risk factors have greatest risk for developing PML
- Anti-JCV Ab negative patients have significantly lower risk

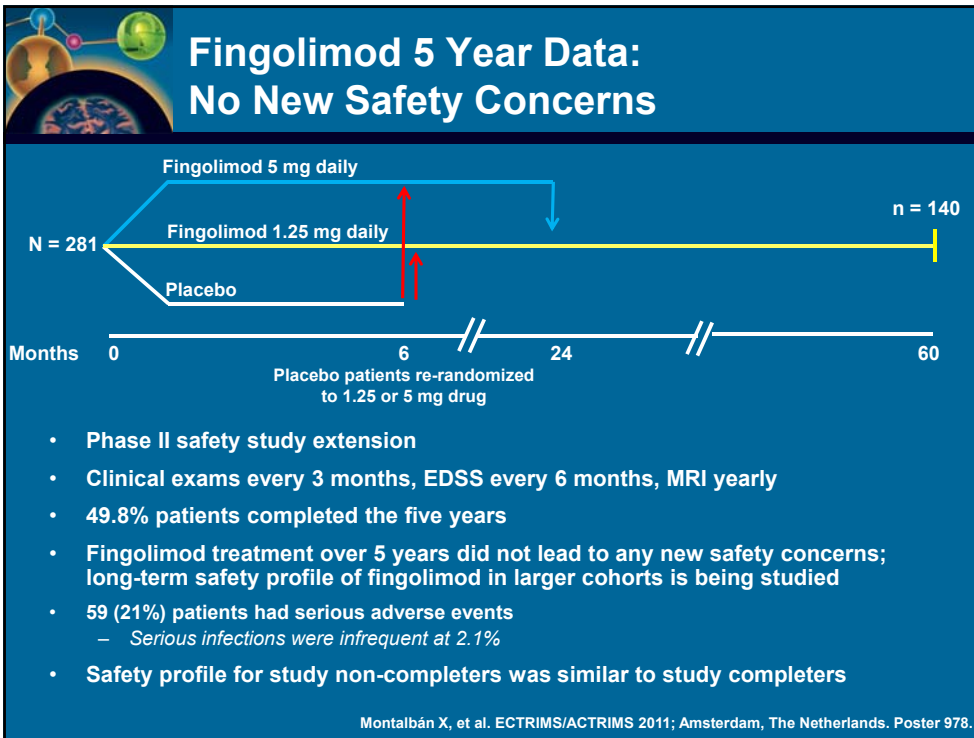
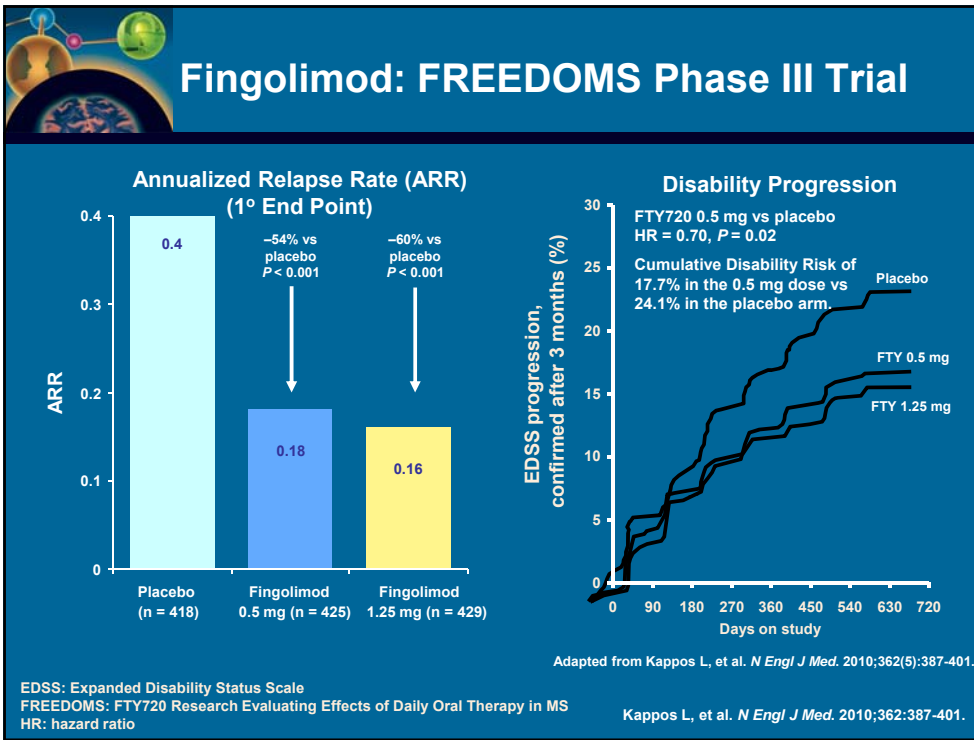


NTZ Exposure	Anti-JCV Ab -	Anti-JCV Ab +, No Prior ISS Use	Anti-JCV Ab +, Prior ISS Use
0-2 Years	≤ 0.11/1000 (95% CI: 0-0.59)	0.35/1000 (95% CI:0.19-0.60)	1.2/1000 (95% CI: 0.58-2.2)
> 2 Years		2.8/1000 (95% CI:2.0-3.8)	8.1/1000 (95% CI: 5.4-11.6)

ISS: immunosuppressant

Sandrock A, et al. American Academy of Neurology (AAN) 2011; Honolulu, HI. P03.248.

## New and Emerging MS Therapies



## Teriflunomide\*: TEMSO Efficacy 2-Year Clinical Outcomes

- **Teriflunomide<sup>1</sup>**
  - Parent compound used in treatment of RA (leflunomide)
  - Inhibits pyrimidine synthesis
    - Reversibly inhibits dihydro-orotate dehydrogenase, key enzyme in *de novo* pyrimidine synthesis
  - Inhibits T cell division
    - Alters tyrosine kinase activation of calcium mobilization
  - Inhibits EAE
- **TEMSO (108-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study)<sup>1,2</sup>**

Treatment	ARR	Reduction vs Placebo	P-value
Placebo	0.54	-	-
Teriflunomide 7 mg	0.37	31.2%	0.0002
Teriflunomide 14 mg	0.37	31.5%	0.0005

Treatment	Progression (%)	Reduction vs Placebo	P-value
Placebo	27.3	-	-
Teriflunomide 7 mg	21.7	23.7%	0.084
Teriflunomide 14 mg	20.2	29.8%	0.028

\*Investigational agent

<sup>1</sup>Tallantyre E, et al. *Int MS J*. 2008;15:62-68.  
<sup>2</sup>O' Connor P, et al. ECTRIMS 2010; Gothenburg, Sweden. Abstract 79.

TEMSO: Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients With MS

## Teriflunomide\*: TEMSO Safety and Discontinuations

AEs	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Any AE	87.5%	89.1%	90.8%
Serious AE	12.8%	14.1%	15.9%
Discontinuation AE	8.1%	9.8%	10.9%
Serious Hepatic Disorders	2.5%	1.9%	2.5%
ALT > 3 Times Upper Limit Normal	6.7%	6.3%	6.7%
Serious Infections	2.2%	1.6%	2.5%

n = 1088 patients randomized to teriflunomide (7 mg or 14 mg daily) or placebo  
 73.2% of patients completed treatment<sup>1</sup>  
 Leflunomide is pregnancy category X<sup>2</sup>

\*Investigational agent

<sup>1</sup>O' Connor P, et al. ECTRIMS 2010; Gothenburg, Sweden. Abstract 79.  
<sup>2</sup>[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020905s022lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020905s022lbl.pdf). Accessed August 10, 2011.



## Laquinimod\*: Background and Mechanism of Action

- **Parent compound: linomide<sup>1, 2</sup>**
  - *Laquinimod more potent against MS symptoms and has less side-effects*
- **Laquinimod suppresses development of experimental autoimmune encephalomyelitis<sup>1</sup>**
- **Laquinimod reduces demyelination, inflammation, axonal damage, and oligodendroglial pathology in the murine cuprizone model<sup>3</sup>**
- **In experimental models of human cells, laquinimod:**
  - *Restricts inflammatory gene expression in reactive astrogliosis<sup>4</sup>*
  - *Promotes tightness of endothelial cells of the blood brain barrier (BBB) and restricts T cell migration across the BBB<sup>5</sup>*
  - *Modulates dendritic cell cytokine production and T helper cell priming capacity<sup>6</sup>*

<sup>1</sup>Rammohan KW, Shoemaker J. *Neurology*. 2010;74(suppl 1):S47-S53.

<sup>2</sup>Tan IL, et al. *Mult Scler*. 2000;6:99-104.

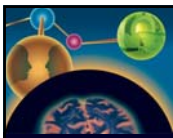
<sup>3</sup>Wegner C, et al. ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Poster 736.

<sup>4</sup>Pham T, et al. ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Poster 489.

<sup>5</sup>Kebir H, et al. ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Poster 441.

<sup>6</sup>Masri L, et al. ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Poster 939.

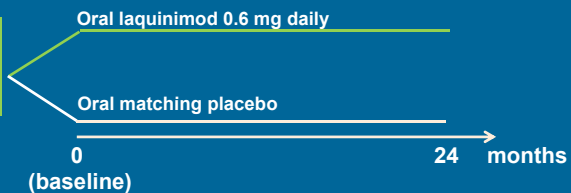
\*Investigational agent



## Laquinimod\*: Phase III Studies

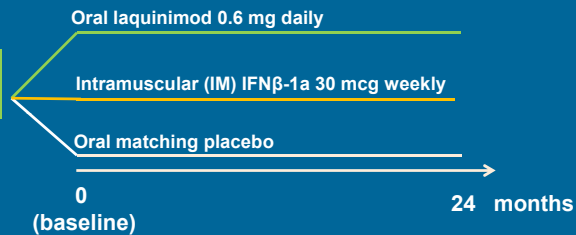
### ALLEGRO – Assessment of Oral Laquinimod in Preventing Progression of MS

- Double-blind treatment
- End points: relapses, EDSS, MRI (black holes, brain volume), MS functional composite (MSFC)



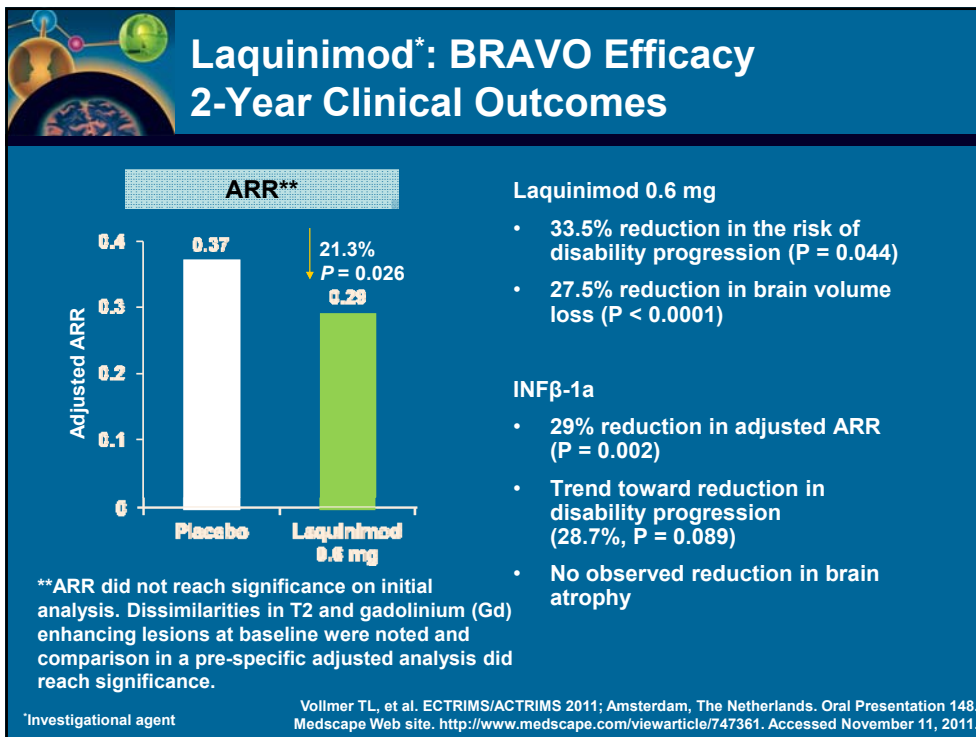
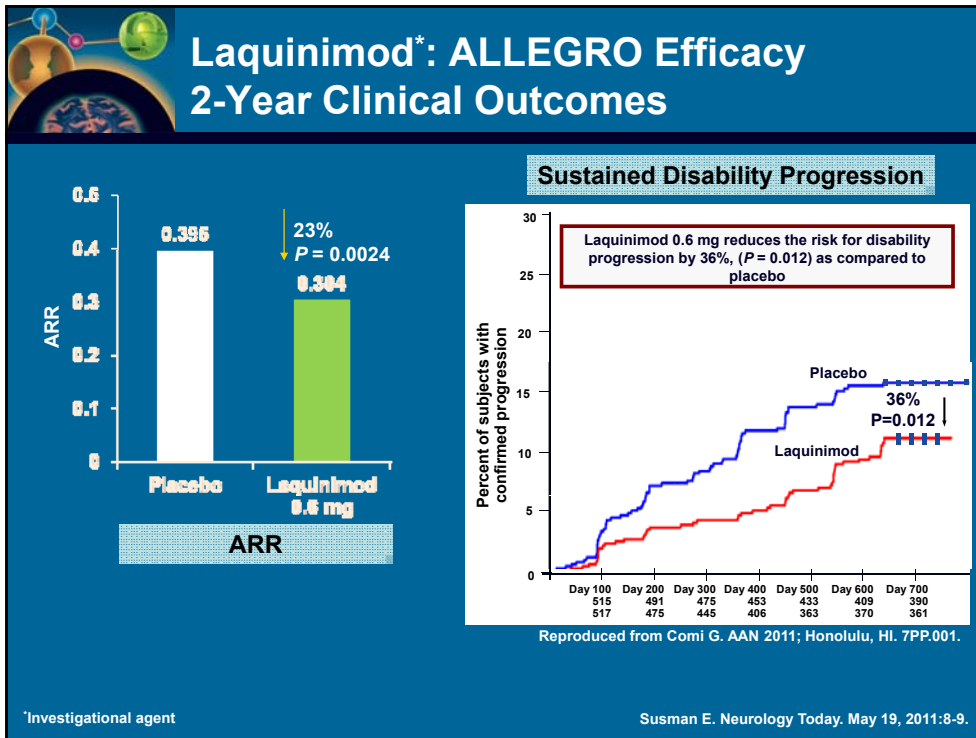
### BRAVO – Benefit-Risk of IFN-β1a and Laquinimod

- Double-blind for oral, rater-blinded for IFN-β1a
- End points: relapses, EDSS, MRI (T1/T2/black holes, brain volume), MSFC



\*Investigational agent  
 ALLEGRO: Safety and Efficacy of Orally Administered Laquinimod Versus Placebo for Treatment of RRMS  
 BRAVO: Laquinimod Double Blind Placebo Controlled Study in RRMS Patients With a Rater Blinded Reference Arm of IFN-β1a

ClinicalTrials Web site. <http://clinicaltrials.gov/ct2/home>. Accessed July 14, 2011.





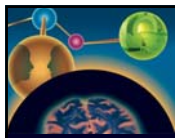
## Laquinimod\*: ALLEGRO and BRAVO Safety Results

ALLEGRO Safety Results		
AE	Placebo (n = 556), n (%)	Laquinimod 0.6 mg (n = 550), n (%)
Death	3 (0.5)	0 (0)
Serious AE	90 (16.2)	122 (22.2)
Pericarditis, pleural effusion	1 (0.2)	0 (0)
Appendicitis	1 (0.2)	5 (0.9)
Herpes infections	20 (3.6)	17 (3.1)
Embolism and thrombosis	2 (0.4)	3 (0.5)
Neoplasms	6 (1.1)	8 (1.5)

- No evidence of immunosuppression or opportunistic infection were seen in patients who received laquinimod
- BRAVO safety results were similar to those of ALLEGRO, with no signal of immunosuppression

\*Investigational agent

Susman E. Neurology Today. May 19, 2011:8-9.  
Vollmer TL, et al.ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Oral Presentation 148.



## Dimethyl Fumarate\*: Background and Mechanism of Action

- Fumaric acid esters are used for the treatment of plaque psoriasis in Europe<sup>1</sup>
- Dimethyl fumarate is suggested to have dual anti-inflammatory and neuroprotective effects
  - Increases production of anti-inflammatory cytokines and inhibits expression of pro-inflammatory cytokines<sup>1</sup>
  - Thought to induce Th-1 to Th-2 shift<sup>1</sup>
  - Suppresses inflammation in macrophages via Nrf2-dependent and independent pathways in vitro<sup>2</sup>
  - Reduces malonate-induced lesion volume in rat striatum<sup>3</sup>

\*Investigational agent

<sup>1</sup>Fox R.J. *European Neurological Review*. 2008;3:99-103.  
<sup>2</sup>Bista P, et al.ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Poster 314.  
<sup>3</sup>Arnold H, et al.ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Poster 958.

## Dimethyl Fumarate\*: Phase III Studies

**DEFINE – Efficacy and Safety of Oral Dimethyl Fumarate in RRMS<sup>1</sup>**

- Double-blind treatment
- End points: relapses, MRI (T2 lesions, Gd+ lesions), EDSS, MSFC

Oral dimethyl fumarate 240 mg twice daily

Oral dimethyl fumarate 240 mg thrice daily

Matching placebo

0 (baseline) 24 months

**CONFIRM – Efficacy and Safety of Oral Dimethyl Fumarate with GA in RRMS<sup>1,2</sup>**

- Rater-blinded, double blinded for dimethyl fumarate and placebo
- End points: relapses, MRI (T2 lesions, T1 lesions, Gd+ lesions), EDSS, MSFC

Oral dimethyl fumarate 240 mg twice daily

Oral dimethyl fumarate 240 mg thrice daily

Subcutaneous (SC) GA 20mg once daily

Matching placebo

0 (baseline) 24 months

\*Investigational agent  
 DEFINE: Determination of the Efficacy and Safety of Oral Fumarate in RRMS  
 CONFIRM: Comparator and an Oral Fumarate in RRMS

<sup>1</sup>ClinicalTrials Web site. <http://clinicaltrials.gov/ct2/home>. Accessed July 14, 2011.  
<sup>2</sup>Fox R. *European Neurological Review*. 2008;3:99-103.

## Dimethyl Fumarate\*: DEFINE Efficacy Endpoints

Treatment	ARR	Reduction vs Placebo	P-value
Placebo	0.36	-	-
BG-12 BID	0.17	53%	P < 0.0001
BG-12 TID	0.19	48%	P < 0.0001

**BG-12 BID**

- 49% reduced risk of relapse (P < 0.0001)
- 38% reduced risk of disability progression (P < 0.01)
- 85% and 94% reduction in mean # of new or newly enlarging T2 and Gd+ lesions respectively (P < 0.001 for both)

**BG-12 TID**

- 50% reduced risk of relapse (P < 0.0001)
- 34% reduced risk of disability progression (P = 0.05)
- 74% and 72% reduction in mean # of new or newly enlarging T2 and Gd+ lesions respectively (P < 0.001 for both)

\*Investigational agent

Gold R, et al. ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Oral Presentation 95.  
 Arnold D, et al. ECTRIMS/ACTRIMS; 2011 Amsterdam, The Netherlands. Poster 831.



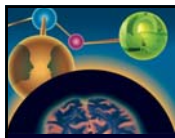
## Dimethyl Fumarate\*: DEFINE Safety Results

	Placebo (n = 408)	BG-12 BID (n = 410)	BG-12 TID (n = 416)
Discontinuations due to AEs	13%	16%	16%
Severe AEs	17%	16%	17%
Flushing	5%	38%	32%
MS relapse	46%	27%	27%

- Incidence of infections and infestations and severe infections and infestations were similar across groups
  - No opportunistic infections observed in BG-12 treatment arms

\*Investigational agent

Selmaj K, et al. ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Poster 994.



## Alemtuzumab\* : Background and Mechanism of Action

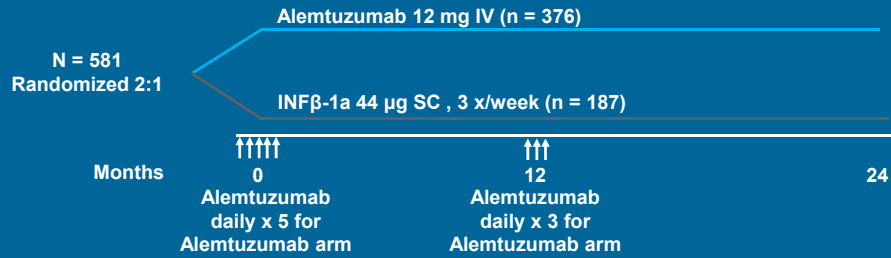
- Alemtuzumab is a monoclonal humanized Ab directed against CD52 antigen (anti-CD52 Ab)<sup>1</sup>
- CD52 is a cell surface glycoprotein. The function of the CD52 antigen is unknown.<sup>1,2</sup>
  - Widely expressed on T cells and B cells (not plasma cells), monocytes, and eosinophils
- Alemtuzumab binding to CD52 causes<sup>1</sup>:
  - Rapid targeted depletion of CD52-expressing cells
  - Depletion of B cells, T cells, monocytes
    - Long-term depletion of CD4+ (median 61 months in SPMS trial) and CD8+ T cells (30 months), resulting in prolonged lymphopenia and reduced inflammation in the central nervous system

\*Investigational agent

<sup>1</sup>Klotz L, et al. *Clin Immunol.* 2011;Epub ahead of print.  
<sup>2</sup>Khan O. *US Neurology.* 2010;6:82-90.

# Alemtuzumab\*: CARE-MS 1 Study Design

## CARE-MS 1: Comparison of Alemtuzumab and Refib Efficacy in MS

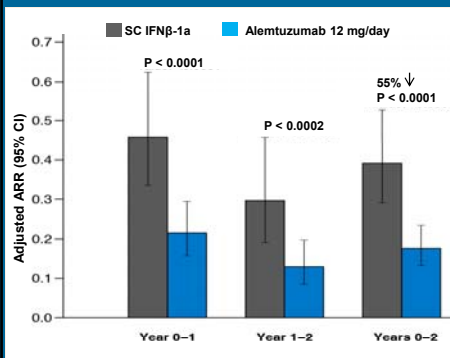


- Both treatment arms received 1 gram methylprednisolone once daily x 3 days at Months 0 and 12
- EDSS performed quarterly and MRI annually
- 97.6% of alemtuzumab patients and 92.5% of IFNβ -1a patients completed the study

\*Investigational agent

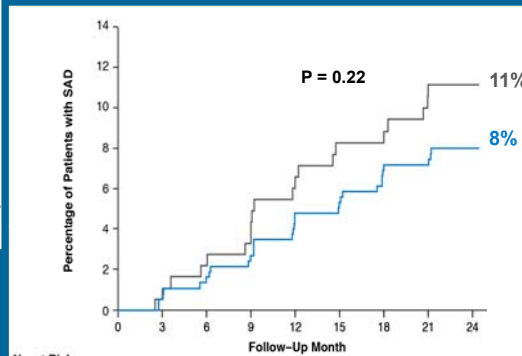
Coles AJ, et al.ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Oral Presentation 151.

# Alemtuzumab\*: CARE-MS 1 2-Year Efficacy Endpoint Results



ARR

## Time to 6 month SAD

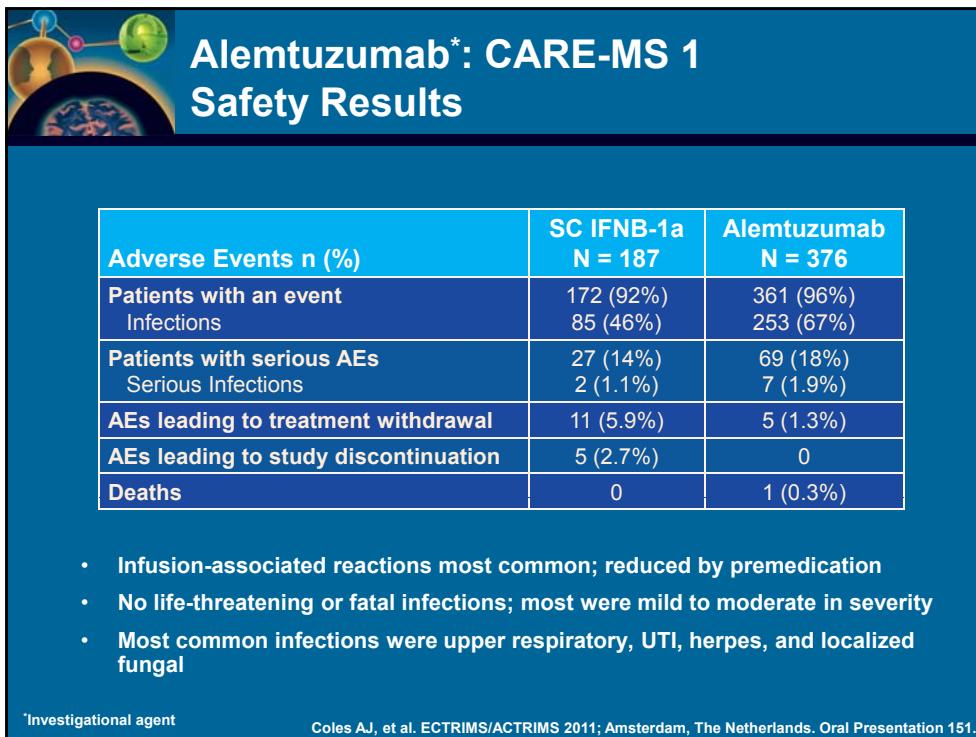
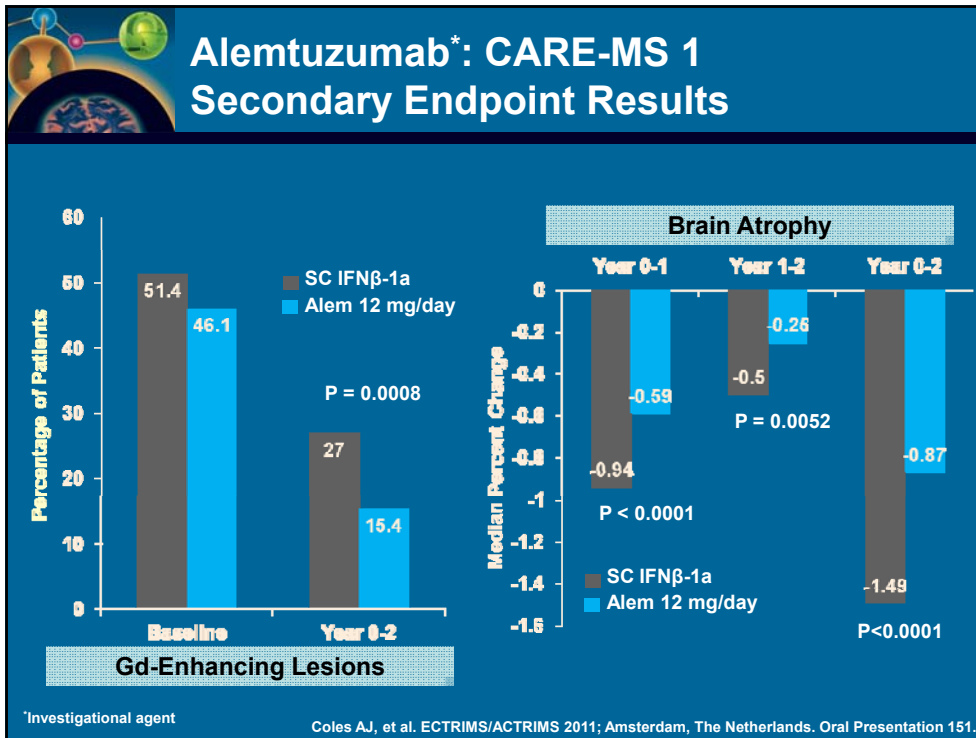


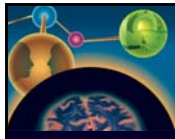
No. at Risk	0	3	6	9	12	15	18	21	24
SC IFNβ-1a	187	185	181	177	170	164	162	158	149
Alem 12 mg/day	376	376	372	368	363	357	352	345	336

\*Investigational agent

SAD = sustained accumulation of disability

Coles AJ, et al.ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Oral Presentation 151. Reproduced permission of Omar Khan, MD.

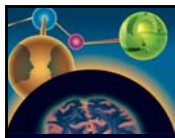




## Higher Vitamin D is Associated With Fewer T2 and Gd-Enhancing Lesions

- 469 subjects with clinically isolated syndrome or RRMS evaluated annually for 5 years by clinical evaluations, brain MRI, and blood draws
- Annual vitamin D (25-hydroxyvitamin D3) levels evaluated for association with subsequent development of:
  - New T2-weighted lesions
  - New Gd enhancing T1-weighted lesions
  - Clinical relapse of MS
- Each 10 ng/mL higher vitamin D level was associated with:
  - 15% lower risk of developing a new T2 lesion ( $P = 0.004$ )
  - 32% lower risk of developing a new Gd-enhancing lesion ( $P = 0.002$ )
- Higher vitamin D levels were associated with lower relapse rate ( $P$  not significant)

Mowry E, et al.ECTRIMS/ACTRIMS 2011; Amsterdam, The Netherlands. Oral Presentation 129.



## Estimated Study Completion Dates for Phase III Trials of Emerging MS Therapies

Therapy	2008	2009/2010	2011	2012+
Fingolimod	TRANSFORMS versus IFN-β1a	FREEDOMS-1 RRMS versus placebo	FREEDOMS-2 RRMS versus placebo	INFORMS PPMS versus placebo 2014
Dimethyl Fumarate			DEFINE RRMS versus placebo	CONFIRM versus placebo and versus IFN-β1a
Laquinimod		ALLEGRO RRMS versus placebo		BRAVO versus IFN-β1a versus placebo
Teriflunomide		TEMPO RRMS versus placebo		TENERE versus IFN-β1a TOWER RRMS 2012
Alemtuzumab			MS-CARE I versus IFN-β1a	MS-CARE II versus IFN-β1a Early 2012
Daclizumab				RRMS Trial versus IFN-β1a 2014
Ocrelizumab				RRMS Trial 2014
Glatiramer acetate versus IFNβ-1a				COMBI-RX January 2010

mipeline.wordpress.com lists: 15 phase III, 54 phase II, 25 phase I, and 71 preclinical trials

ClinicalTrials Web site. <http://clinicaltrials.gov/ct2/home>. Accessed July 14, 2011.



## Take Home Points

- DAWM and GM pathology may shed more light on MS severity compared to WM plaque
- Along with T cells, B cells play a central and complex role in MS immunopathogenesis
- Ongoing biomarker investigations shed light on stratifying patients for appropriate therapy
- New and emerging agents offer opportunities for more individualized MS management



## Products Discussed in This Presentation

<b>Generic Name</b>	<b>Brand Name</b>
Alemtuzumab	Lemtrada®
Cladribine	Litak®, Mevecto®
Dimethyl Fumarate	Investigational
Fingolimod	Gilenya™
Glatiramer Acetate	Copaxone®
IM Interferon $\beta$ -1a	Avonex®
SC Inteferon $\beta$ -1a	Rebif®
Laquinimod	Investigational
Natalizumab	Tysabri®
Ofatumumab	Investigational
Ocrelizumab	Investigational
Rituximab	Rituxan®
Teriflunomide	Investigational