Multiple Sclerosis Treatment Landscape and Unmet Needs

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Disclosures

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Multiple Sclerosis Treatment Landscape and Unmet Needs

- Introduction to multiple sclerosis
- Overview of MS therapy landscape
- What to learn from teriflunomide
- Unmet treatment needs in MS

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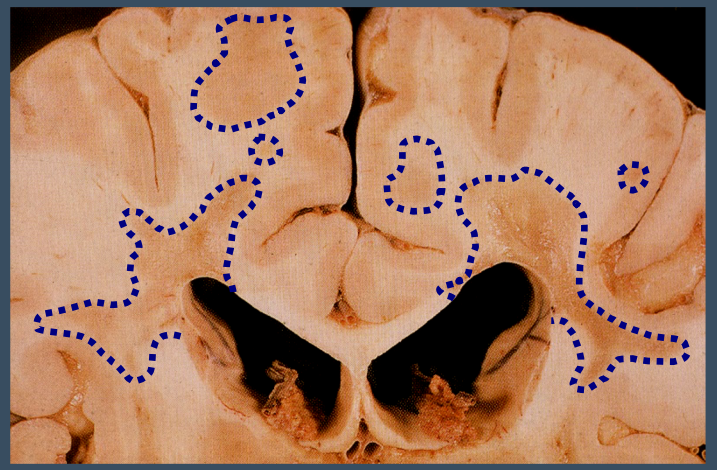
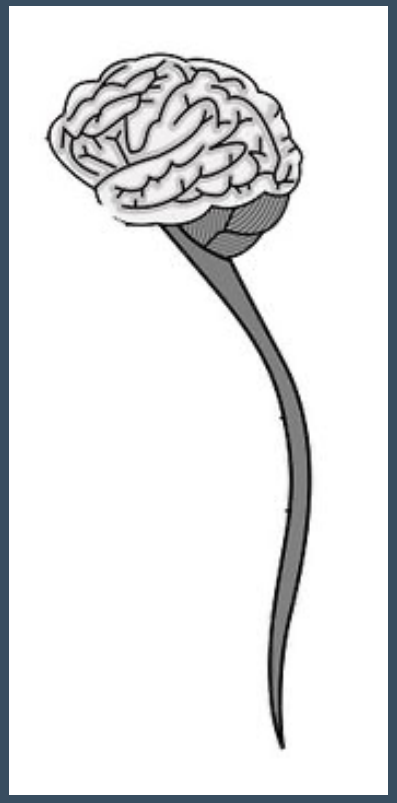
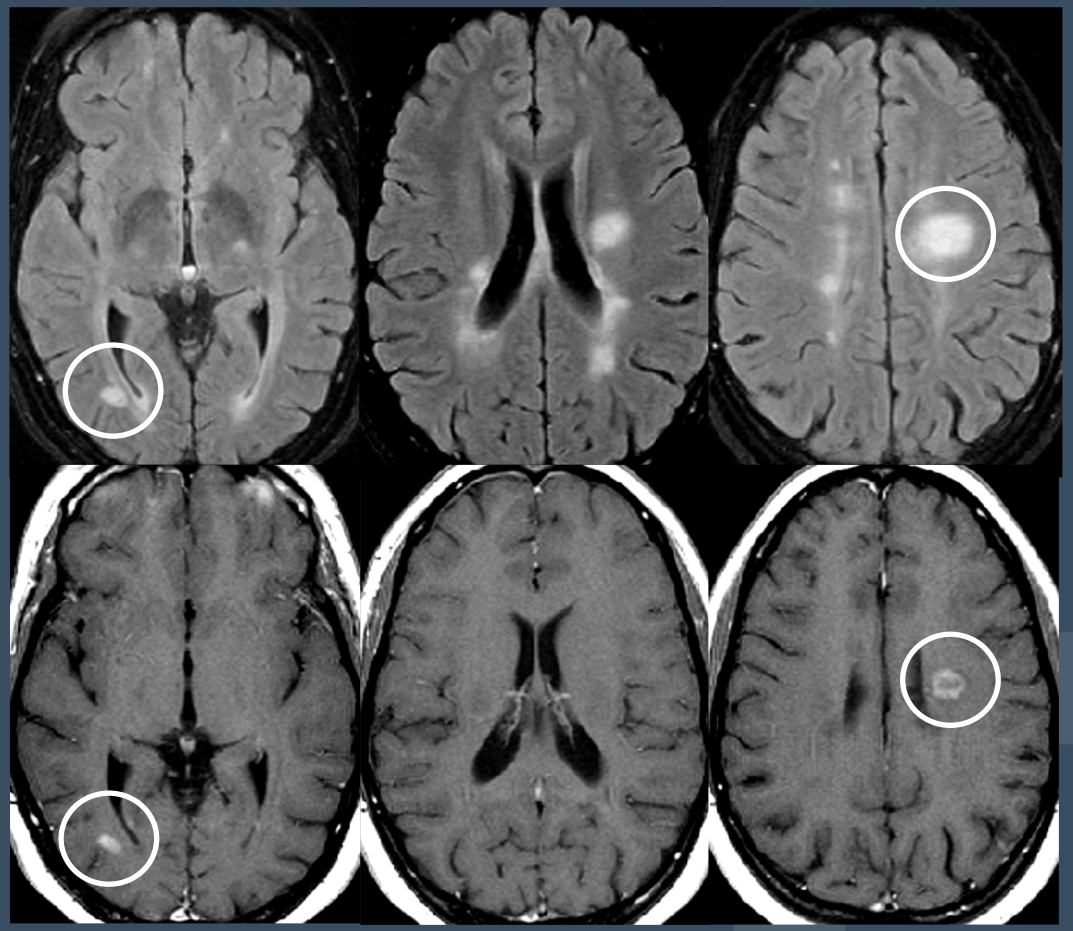
What is Multiple Sclerosis?

- MS = multiple scars
- Immune system attacks the brain and spinal cord







Multiple Sclerosis

- US: 400,000
  - Worldwide: 2.3 million

Multiple Sclerosis

- US: ~~400,000~~ As of March 2019: >900,000 people with MS in US
  - Worldwide: 2.3 million (probably much higher)
- Women more commonly than men (2:1)
- Typical age of onset: 20s - 30s
- Economic costs (US): $20 billion per year

Typical MS Symptoms

Decreased concentration

Anxiety

Double vision

Poor coordination

Bladder urgency

Decreased libido

Pins and needles

Depression

Memory loss

Blurry vision

Erectile dysfunction

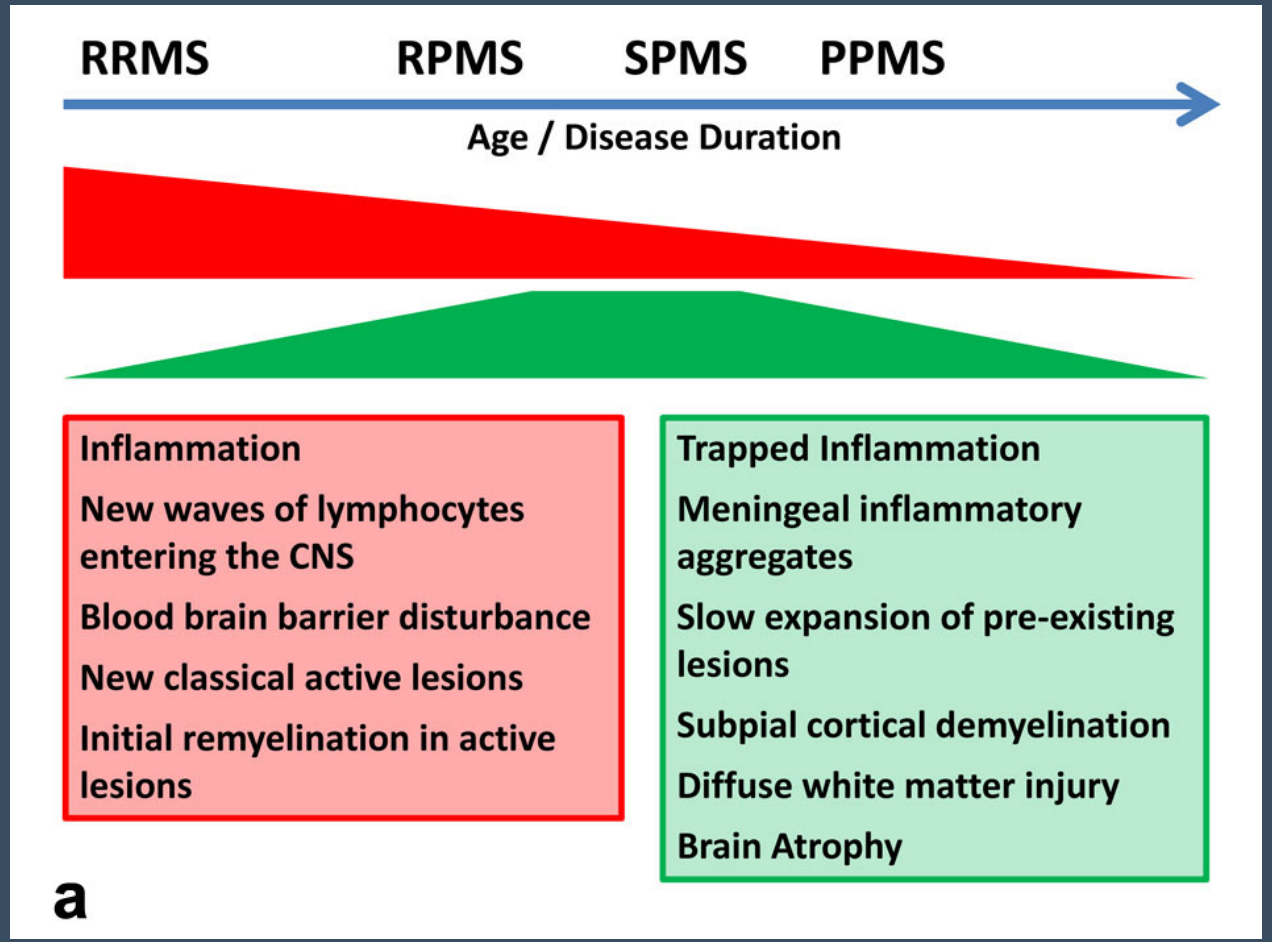
Incontinence

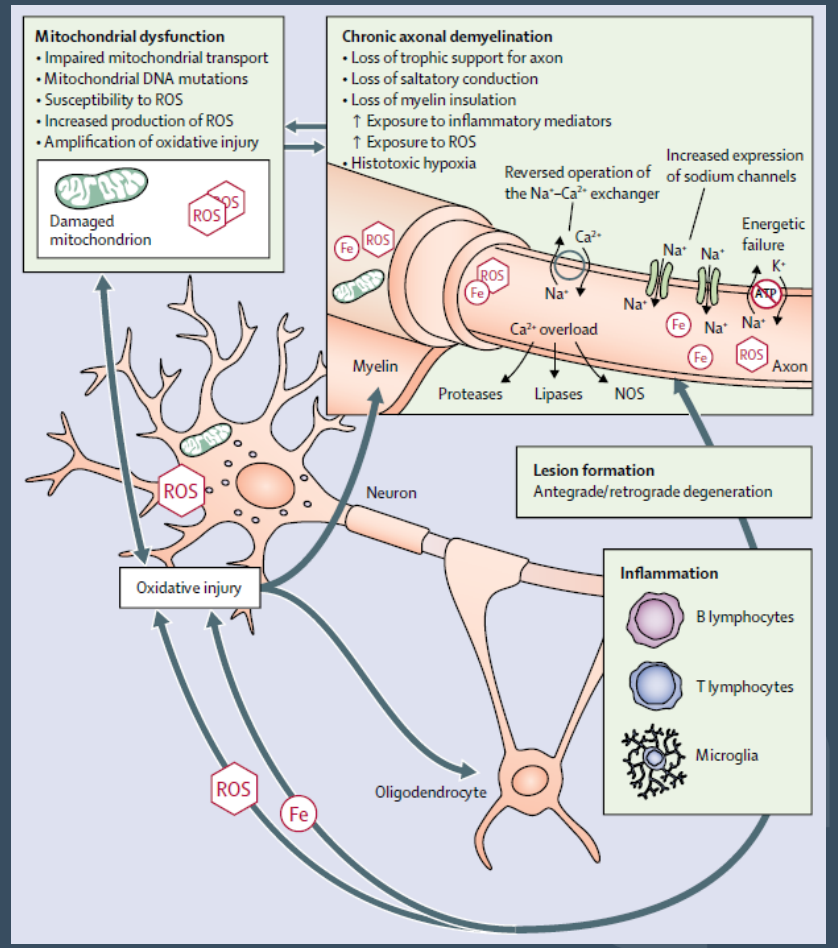
Numbness

Walking problems

Stiffness

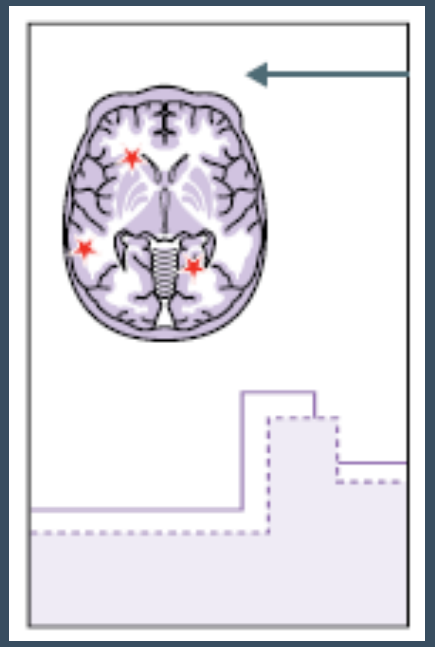
MS pathophysiology





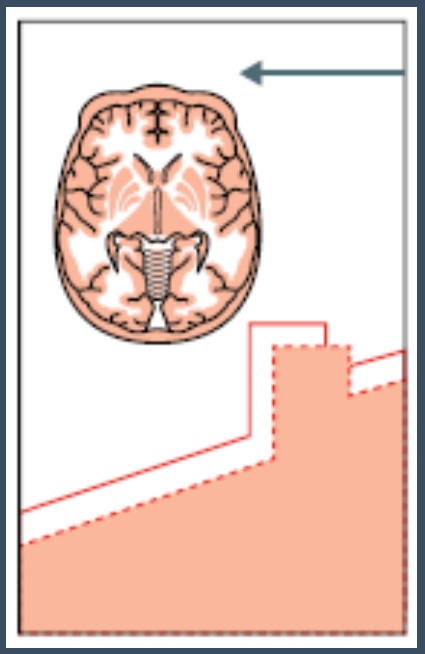
Lassmann Nature Rev. Neurol 2012; Ontaneda Lancet 2017

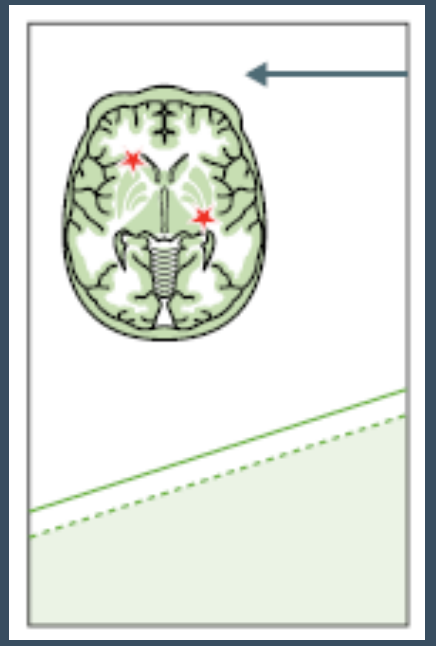
Different Forms of MS



Relapsing remitting

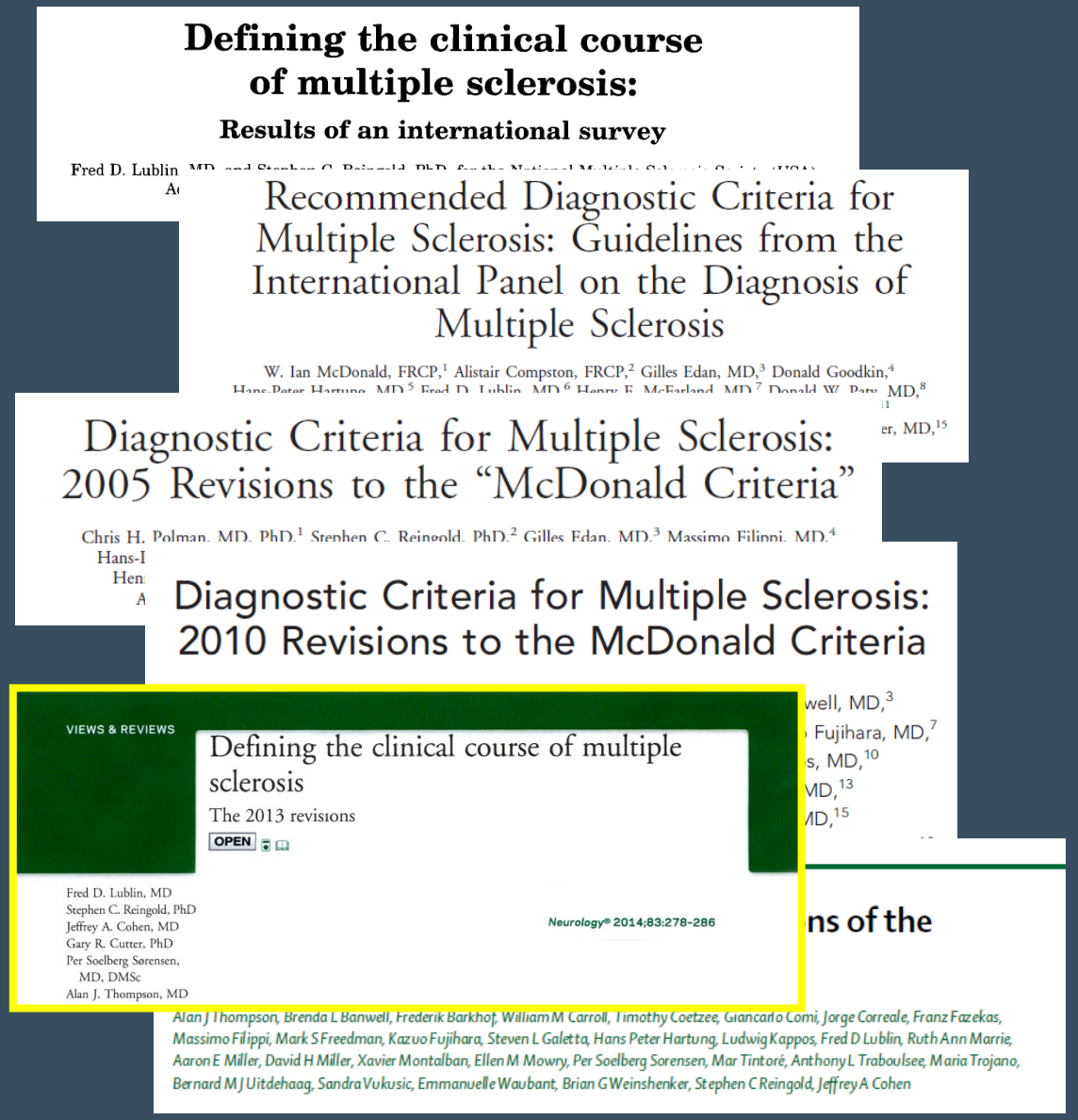
Secondary progressive





Primary Progressive

Diagnostic Criteria



1996: Classified the disease course - RR, SP, PP, PR

2001: Introduced CIS; integrated MRI into diagnostic criteria

2005: Clarified dissemination in time, MRI use, and PPMS criteria

2010: simplified criteria; allowed dx with one episode, and expanded applicability

2013: revised phenotype descriptors to allow concomitant relapsing and progressive aspects of MS

2017: updated utility of CSF; simplified and expanded MRI criteria

Continually integrating new science and insights to characterize disease

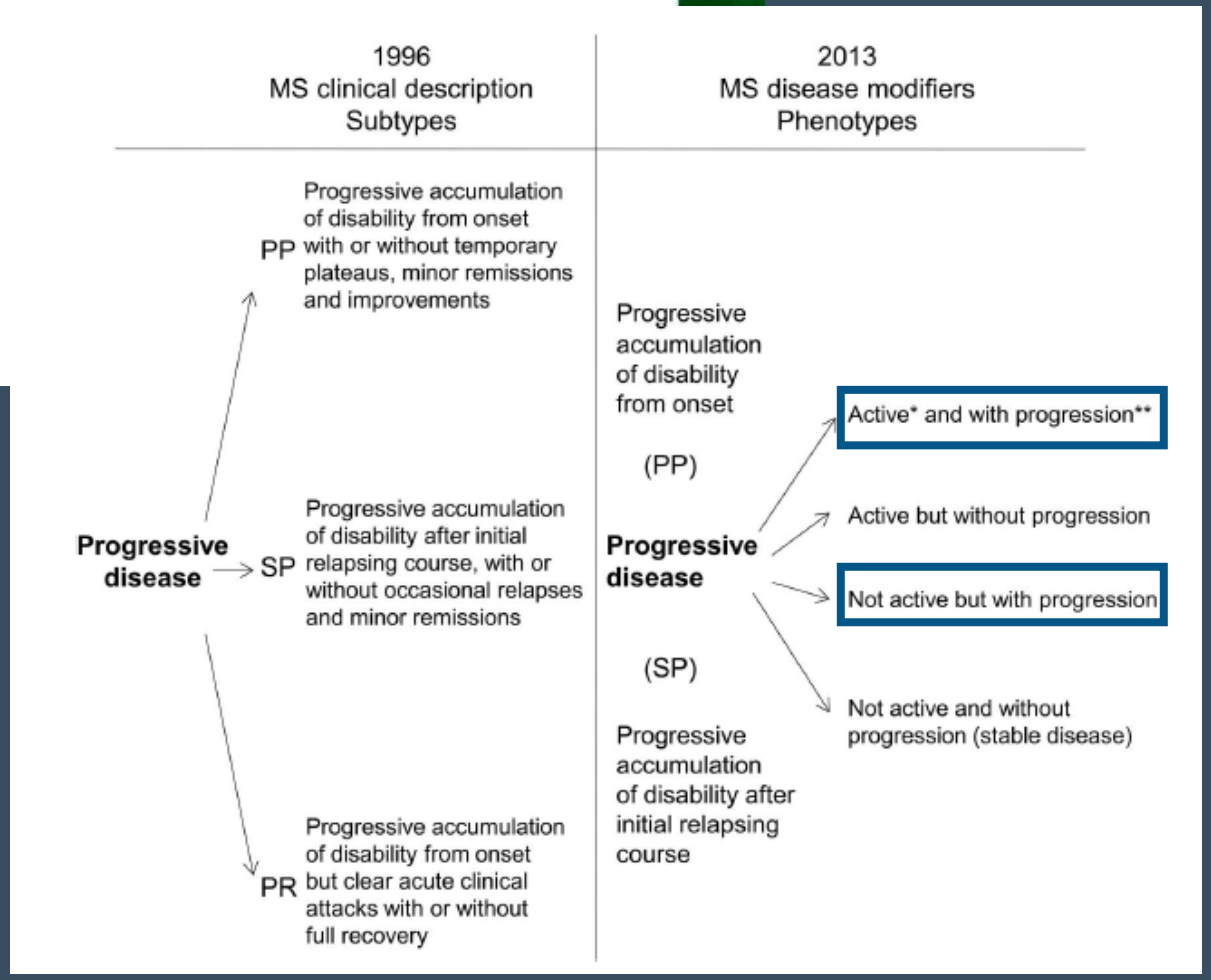
VIEWS & REVIEWS

Defining the clinical course of multiple sclerosis

The 2013 revisions

OPEN

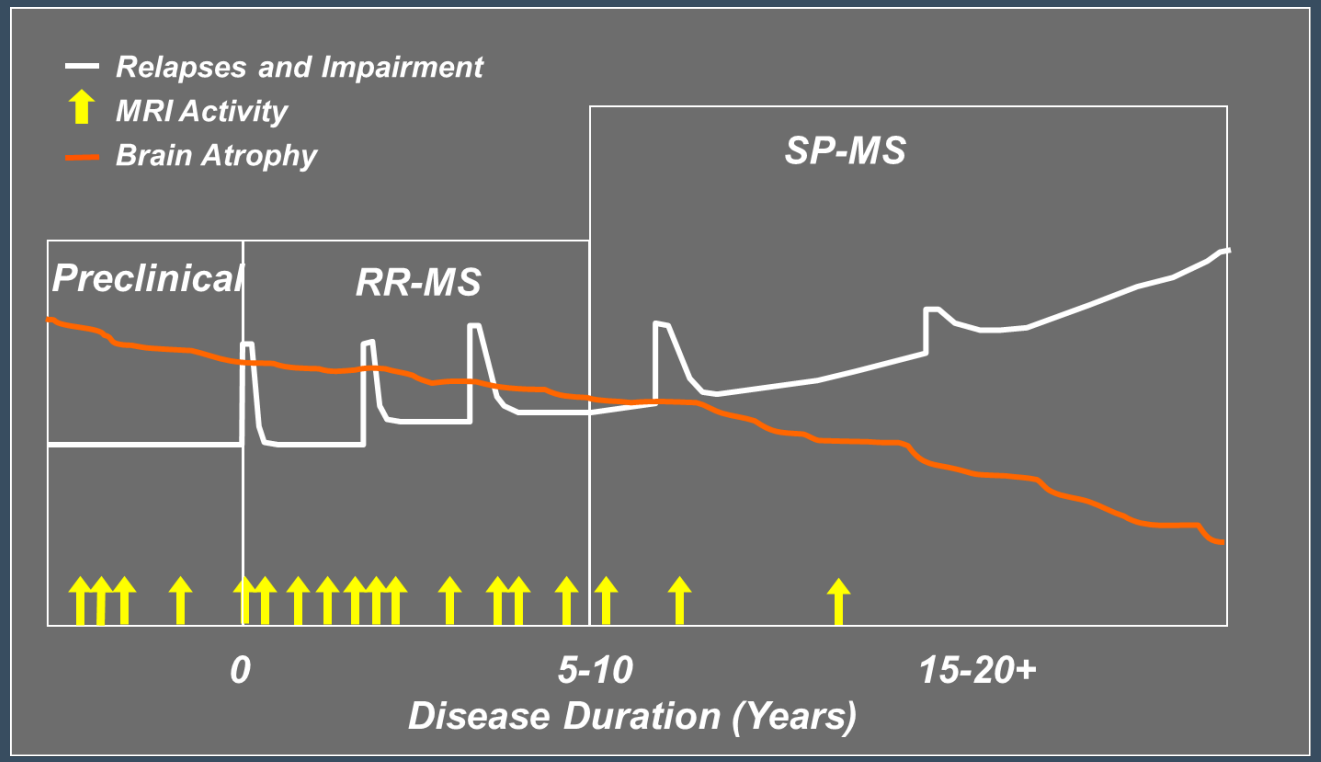
Fred D. Lublin, MD
Stephen C. Reingold, PhD
Jeffrey A. Cohen, MD
Gary R. Cutter, PhD
Per Soelberg Sørensen, MD, DMSc
Alan J. Thompson, MD



Regulators (EMA and FDA) have now divided progressive MS into “active” and “not active,” but left the SPMS and PPMS in place

Lublin FD et al. Neurology, 2014;83:1-9

Natural History of Relapsing MS



MS Disease Course

Expanded Disability Status Scale - EDSS

Multiple Sclerosis Treatment Landscape and Unmet Needs

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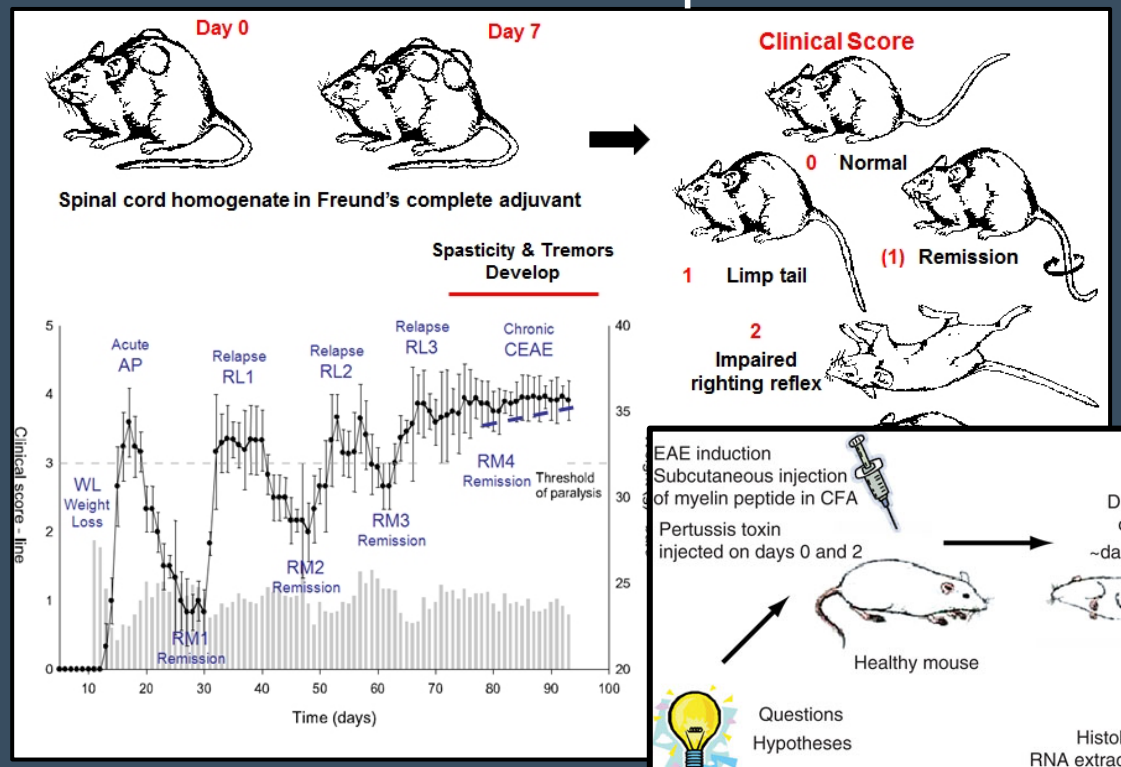
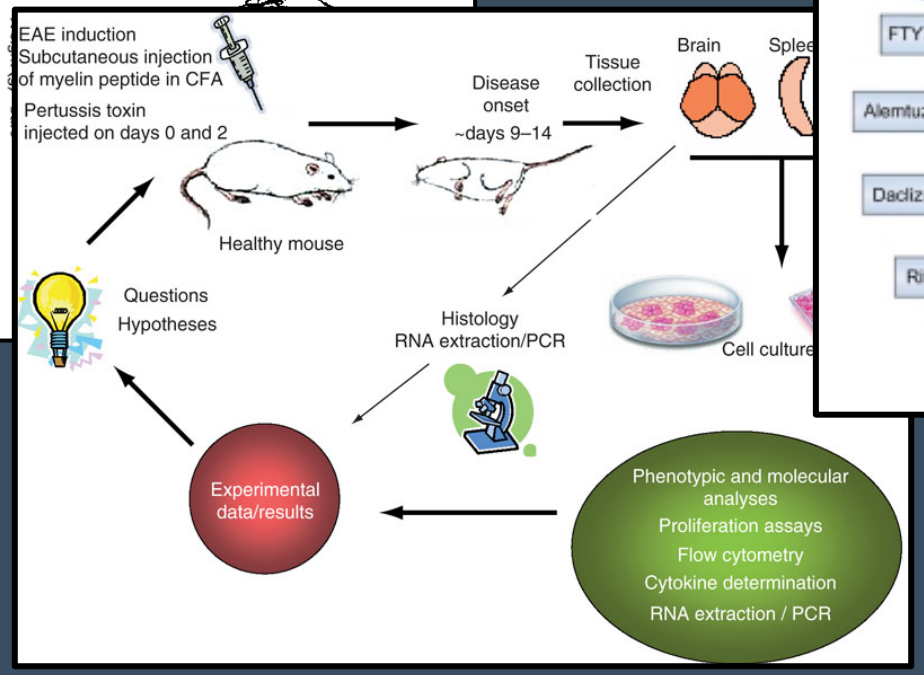
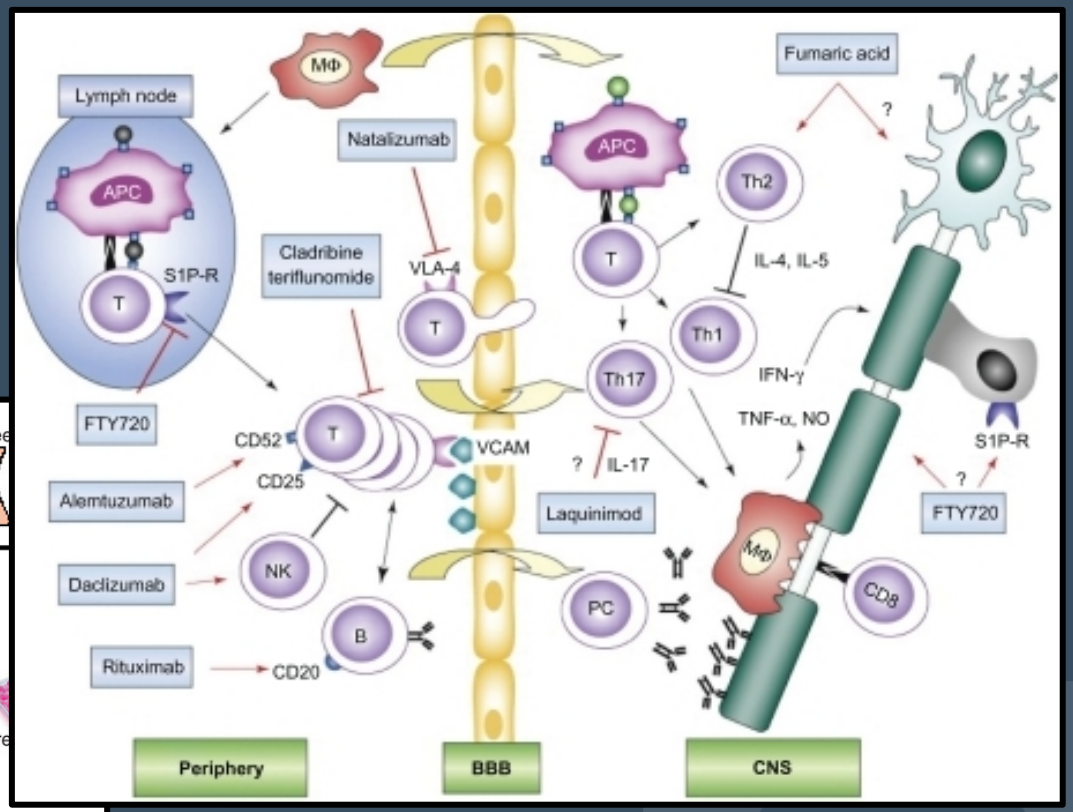
Preclinical models

Experimental Autoimmune Encephalomyelitis







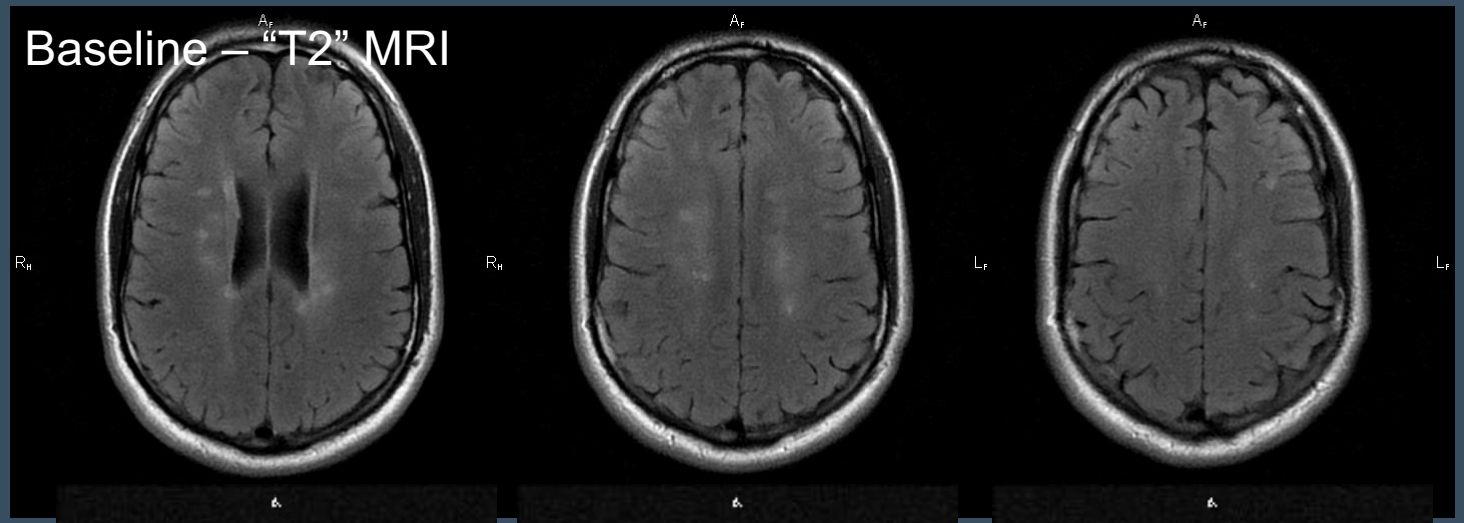
Ignatius et al, Front Immunol 2015
Gran et al, Handbook of Neurochemistry and Molecular Neurobiology, Springer 2008
Barten et al, Drug Des Devel Ther 2010

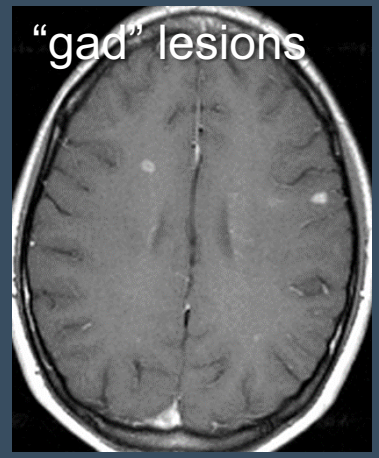
Preclinical models

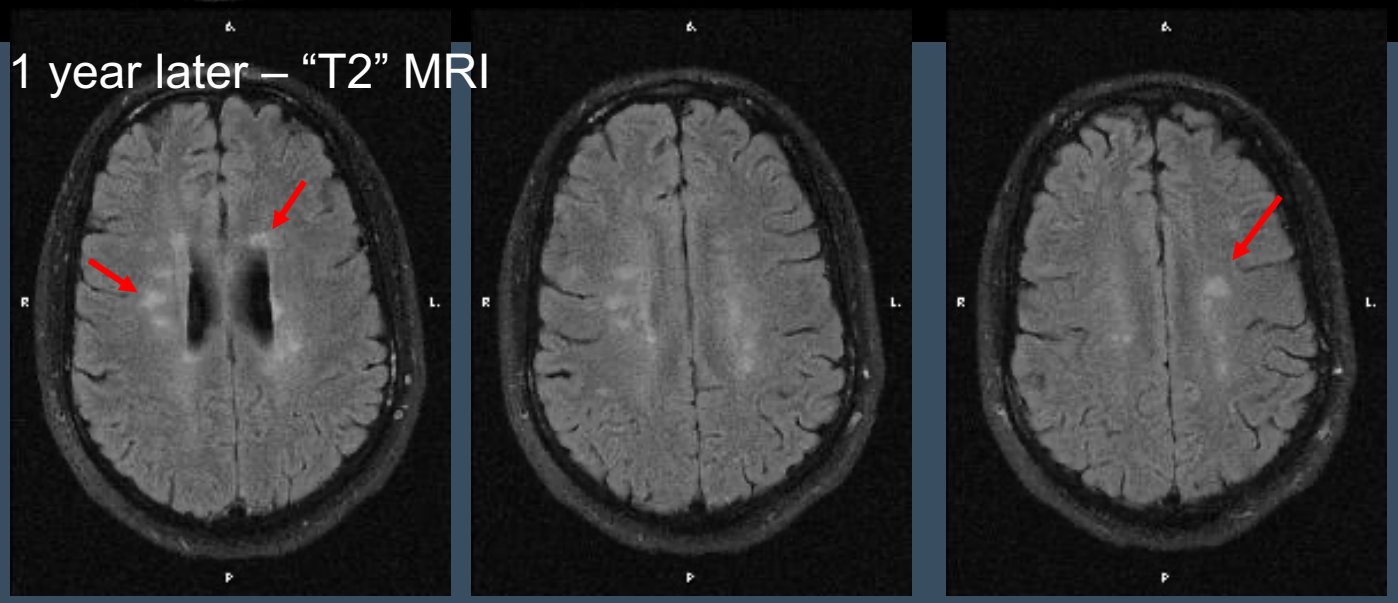
Experimental Autoimmune Encephalomyelitis

- Useful to:
  - Understand basic mechanisms of CNS inflammation
  - Test new potential mechanisms
  - Test new potential therapies
- Limitations:
  - Sometimes finds incorrect answer (anti-TNFα)
  - Hasn’t been helpful with progressive MS

Phase 2 trial metric







T2 and Gad lesions:

- Objective
- Easily detected and counted (software)
- Relatively specific for MS
- Standard primary outcome for phase 2 trial in relapsing MS

Phase 2 trial metric

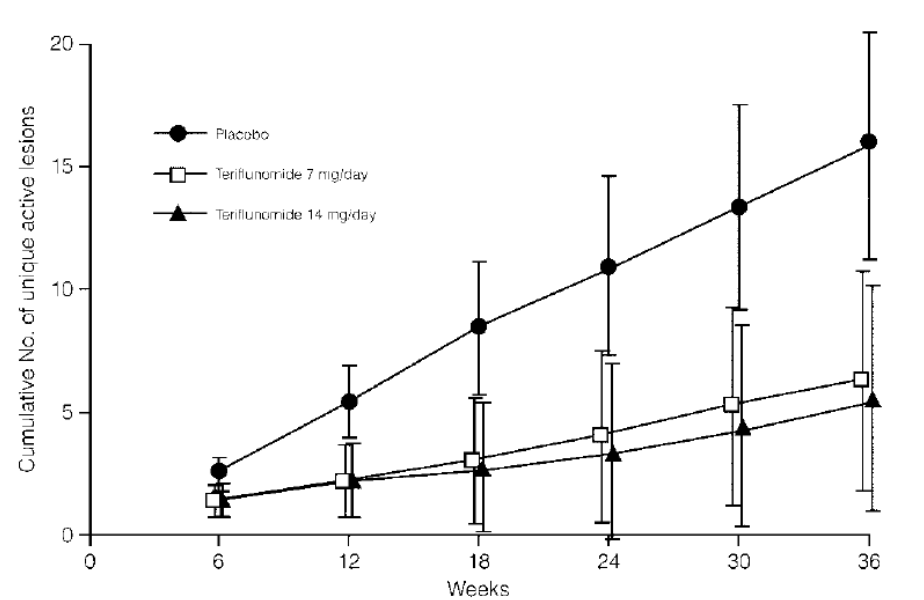
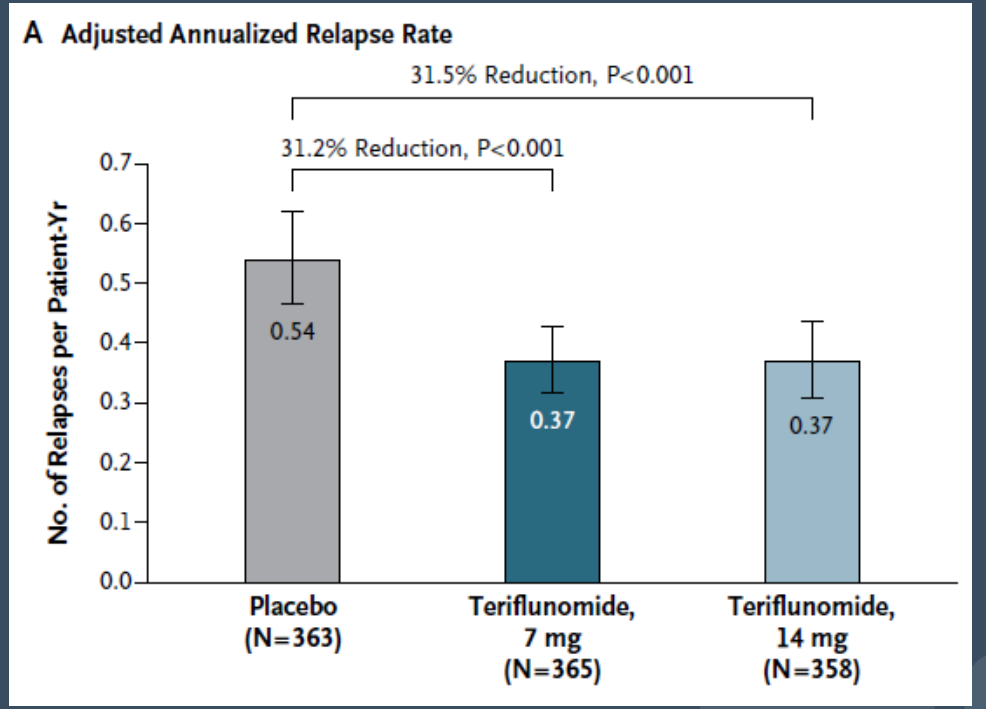


Figure 2. Cumulative mean number of combined unique active lesions adjusted for baseline.

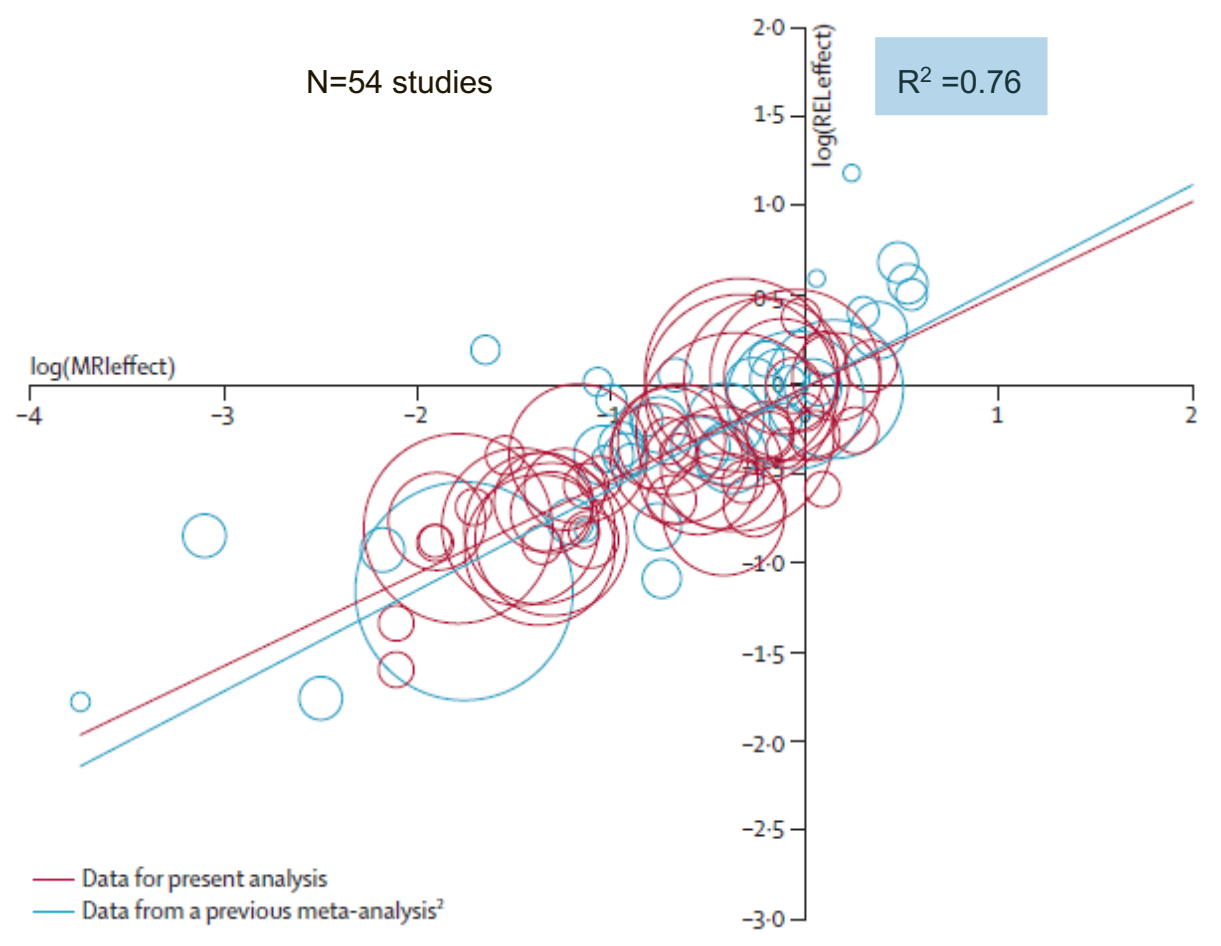
MRI outcome from
Phase II teriflunomide trial

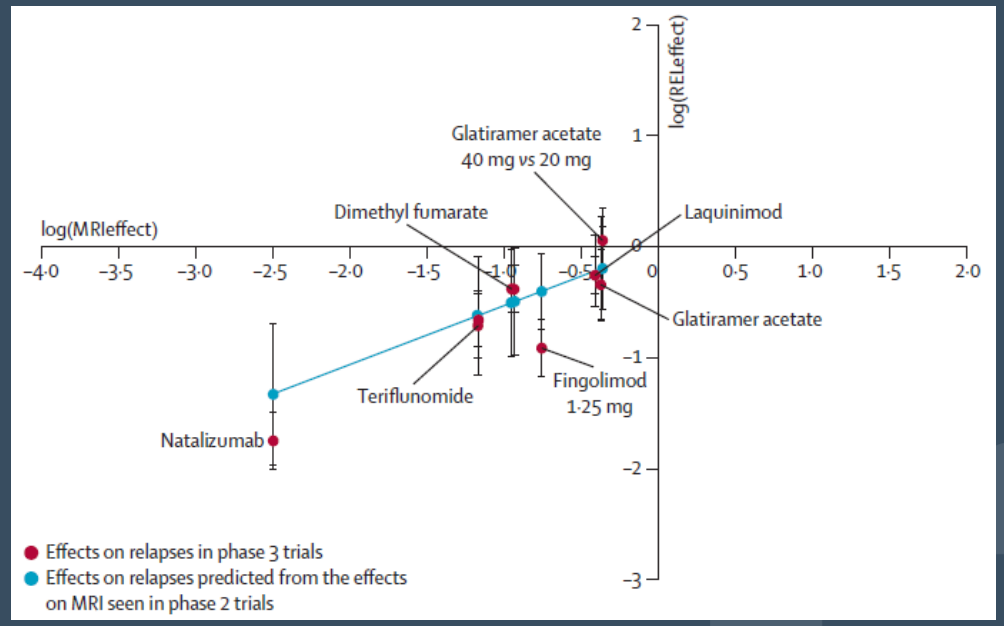


Clinical outcome from
Phase III teriflunomide trial

O'Connor et al, Neurol 2006
O'Connor et al, NEJM 2011

MRI Predicting Relapse Reduction in RRMS





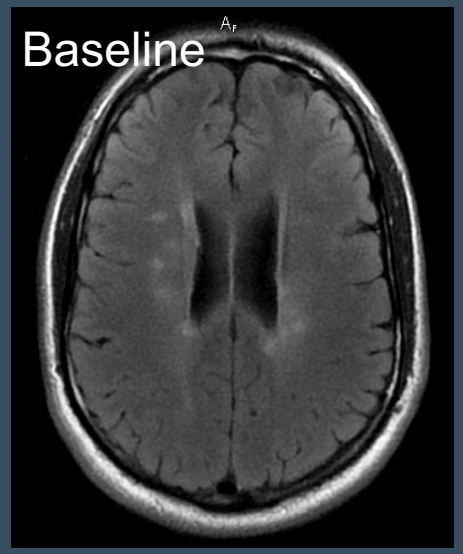
Sormani et al, Lancet Neurol 2013

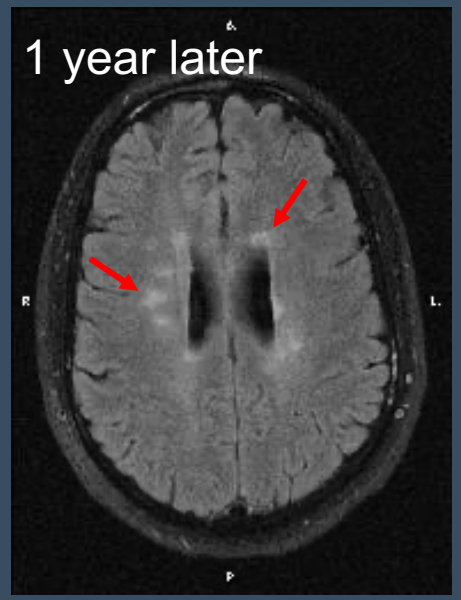
Phase 2 trial metric

- New/enlarging T2 & Gad lesions
  - Standard metric for phase 2 relapsing MS trials
  - Analyzed separately or together (“combined unique”)
  - Never received regulatory acceptance (but don’t need it)
- Equivalent metric for progressive MS is unknown
  - Whole brain atrophy
  - Advanced imaging methods are being tried

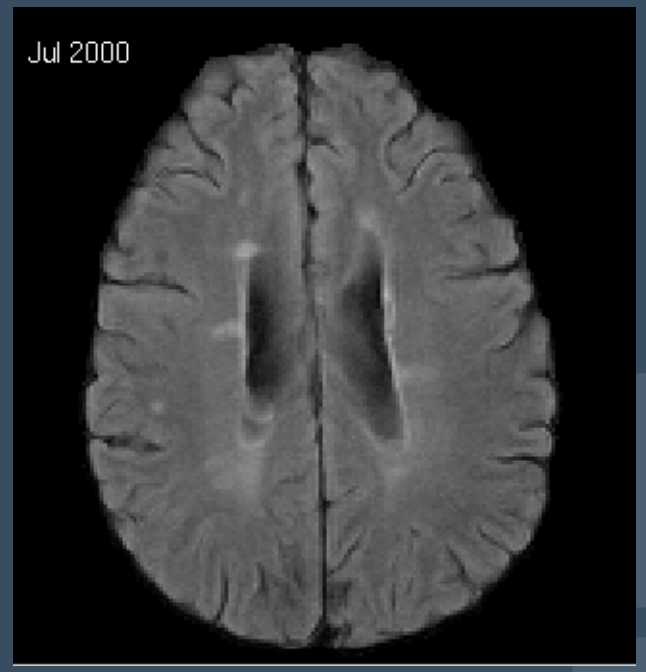
Goal of MS Therapies

- Decrease inflammation
  - Clinical relapses (episodes)
  - New lesions on MRI

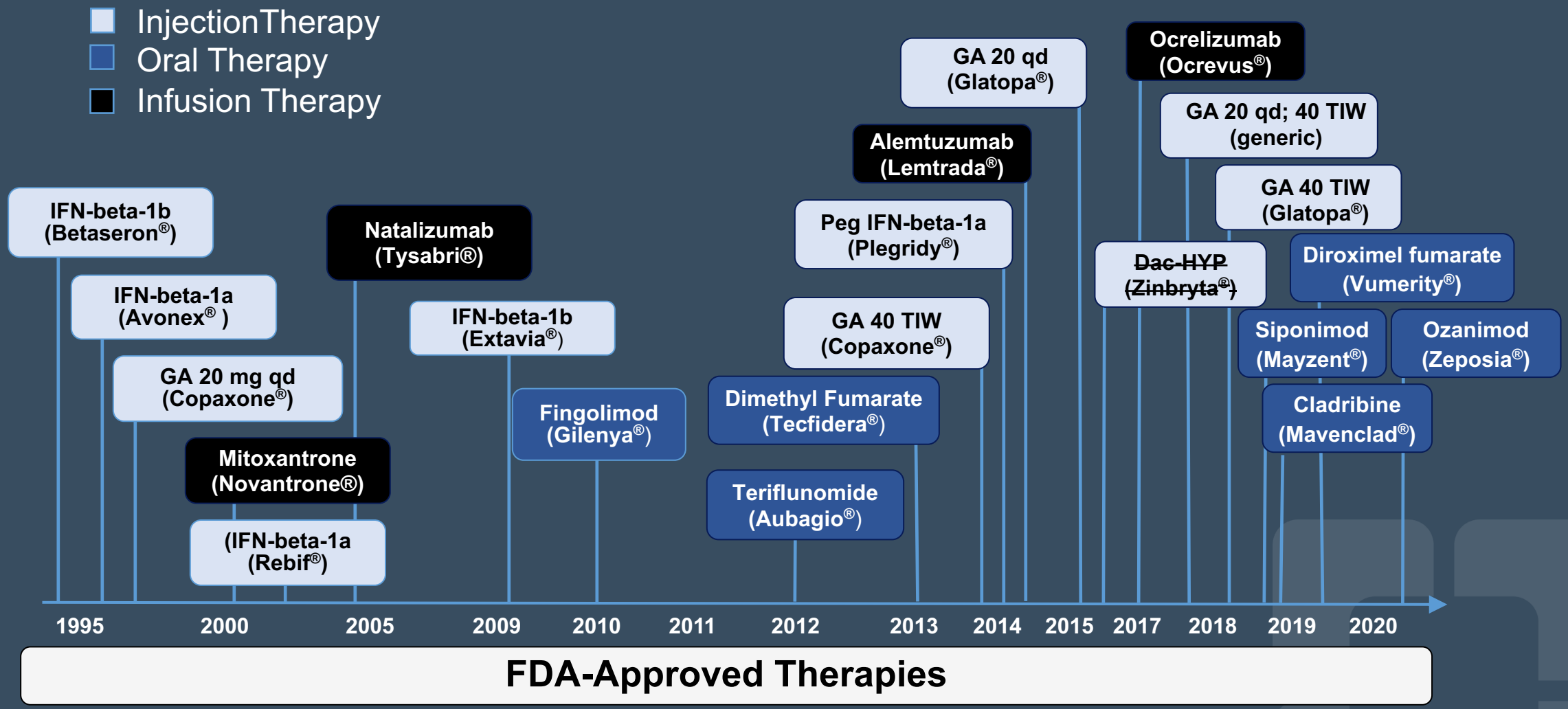




- Decrease permanent injury
  - Accumulation/progression of disability
  - Brain atrophy

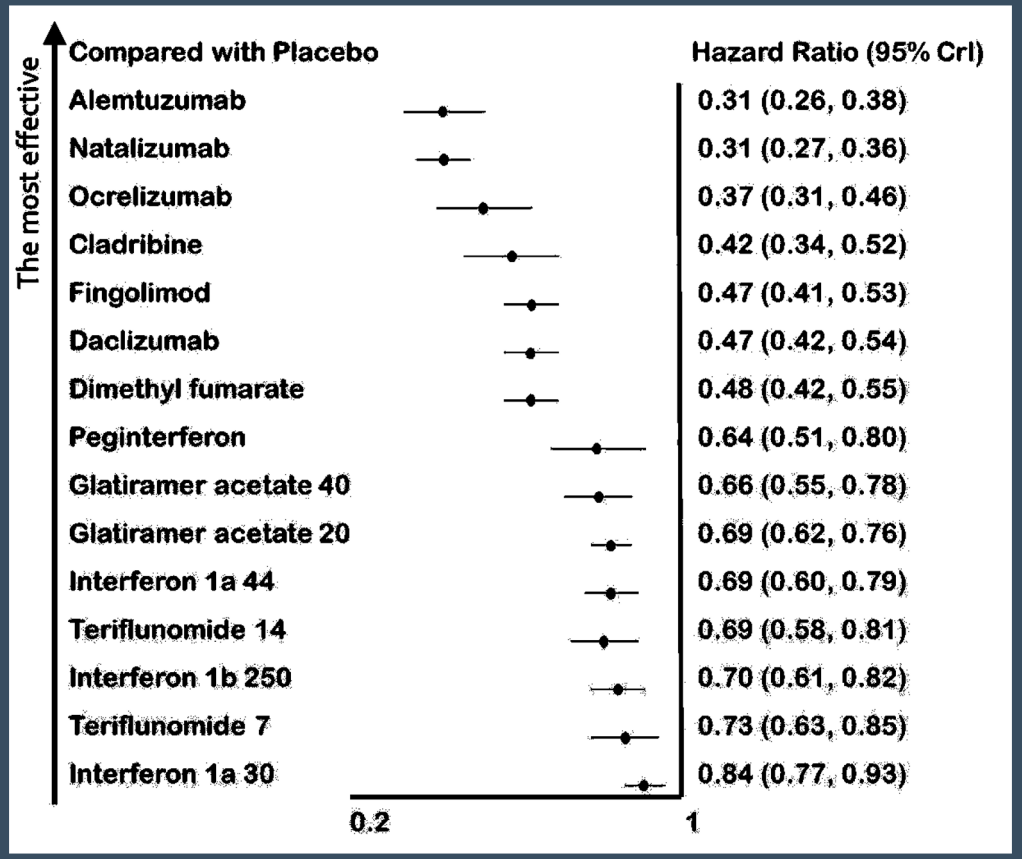


MS Therapy – Embarrassment of Riches

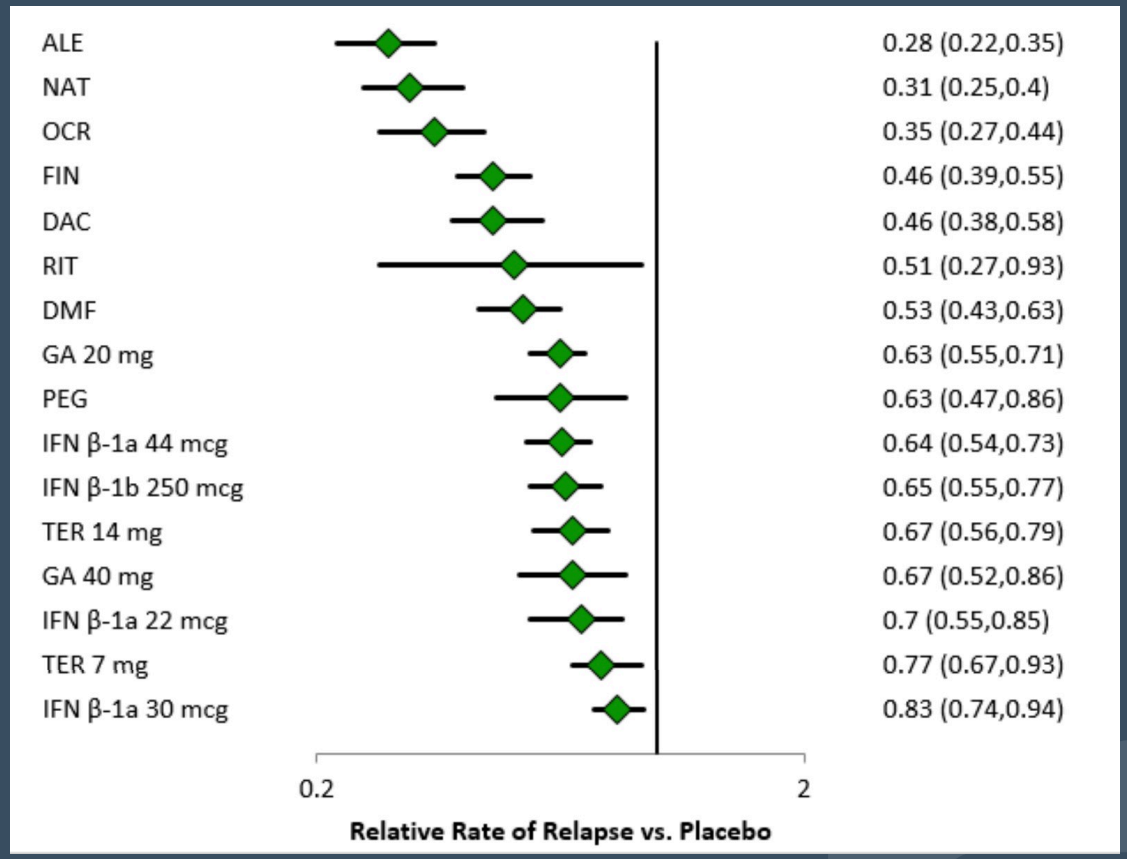


Adapted from Wingerchuk & Weinshenker. BMJ. 2016

DMTs and Annualized Relapse Rate

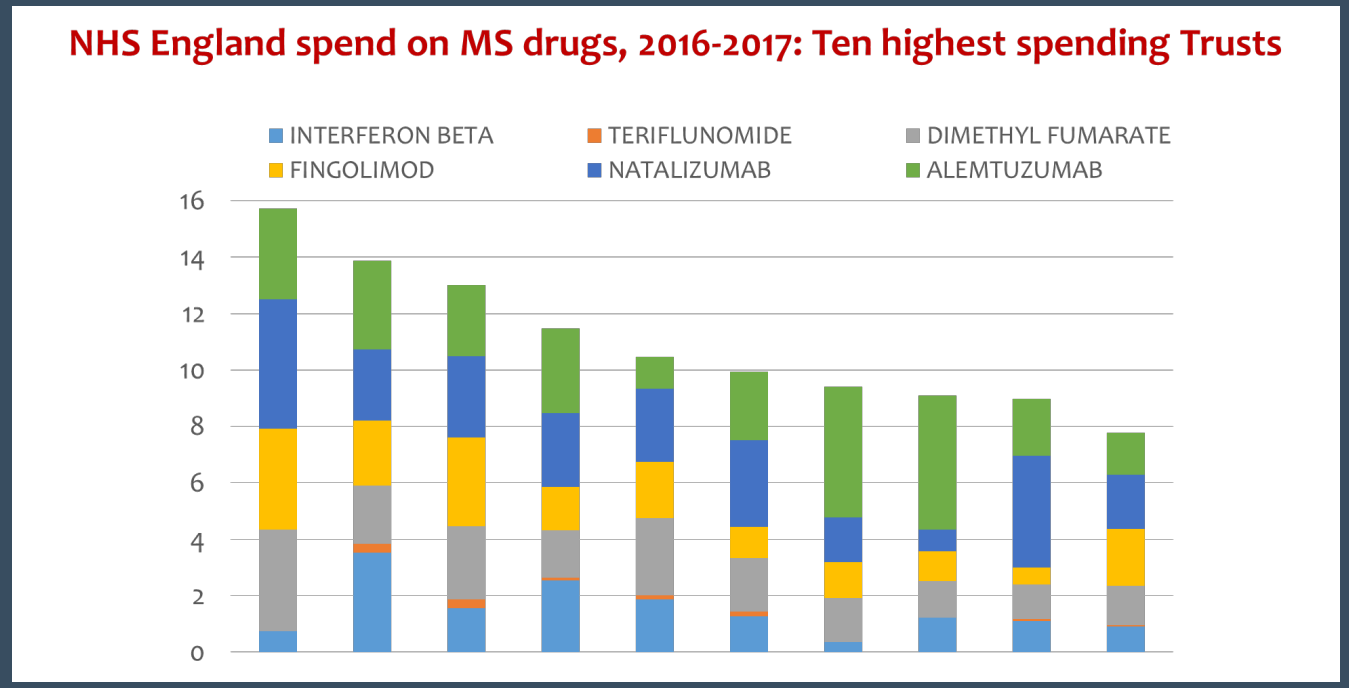


Forest plot of network meta-analysis comparing DMTs with placebo for annualized relapse rate, Horizontal bars: 95% credible intervals.
Lucchetta RC et a. *CNS Drugs.* 2018; 32:813-26.



Forest Plot for Annualized Relapse Rate: relative risk for each drug compared to placebo.
California Institute for Clinical and Economic Review, 2017.

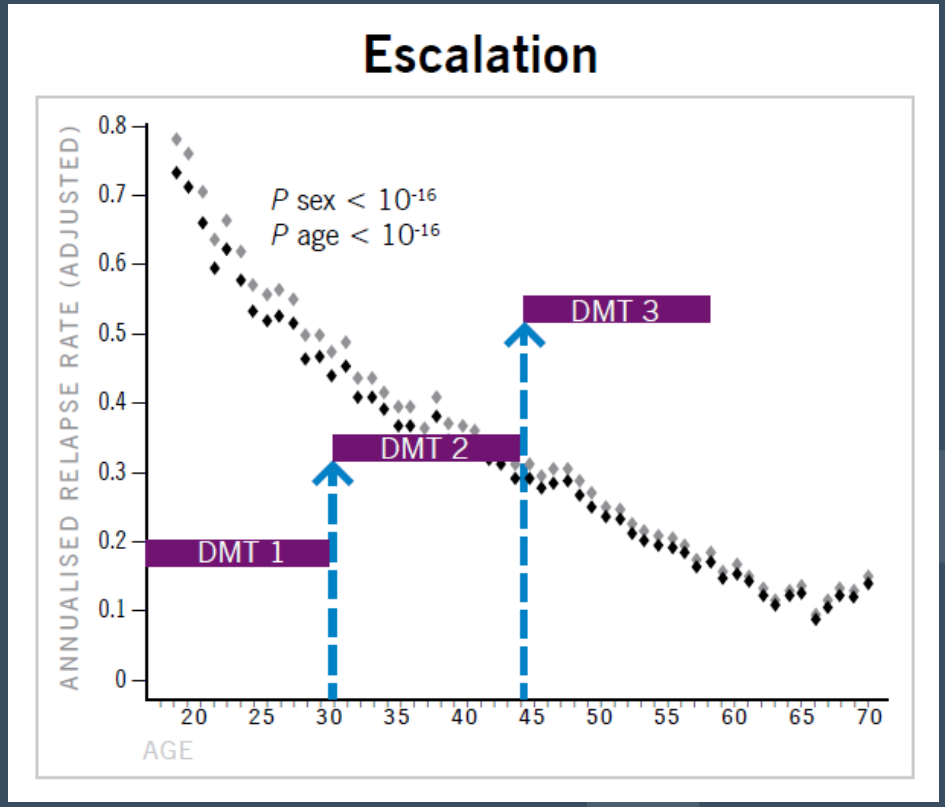
What is the best MS therapy?



Significant Variability

Currently, there are no guidances on which therapy to use when.

Typical treatment approach:



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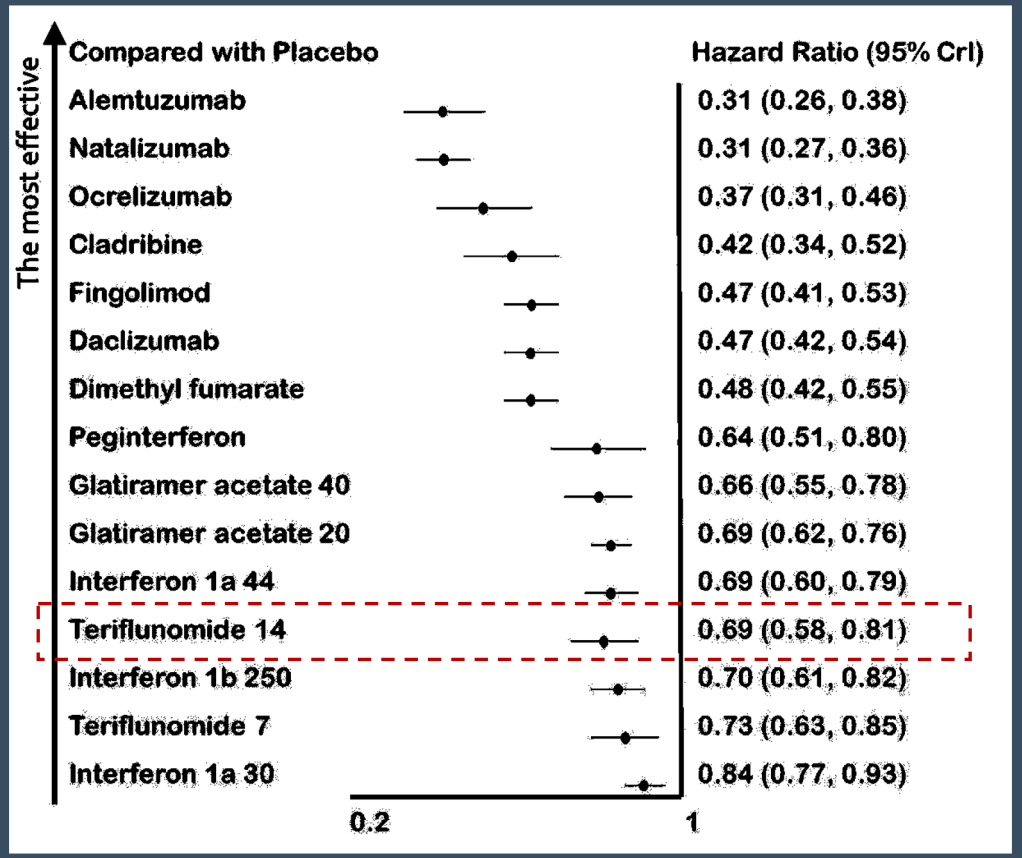
Teriflunomide

- Orally available compound with daily administration
- Reasonably well tolerated
- Mechanism of action: blocks dihydro-orotate dehydrogenase (DHODH)
  - Inhibits pyrimidine (DNA) synthesis
  - Inhibits T-cell and B-cell proliferation

DMTs and Annualized Relapse Rate



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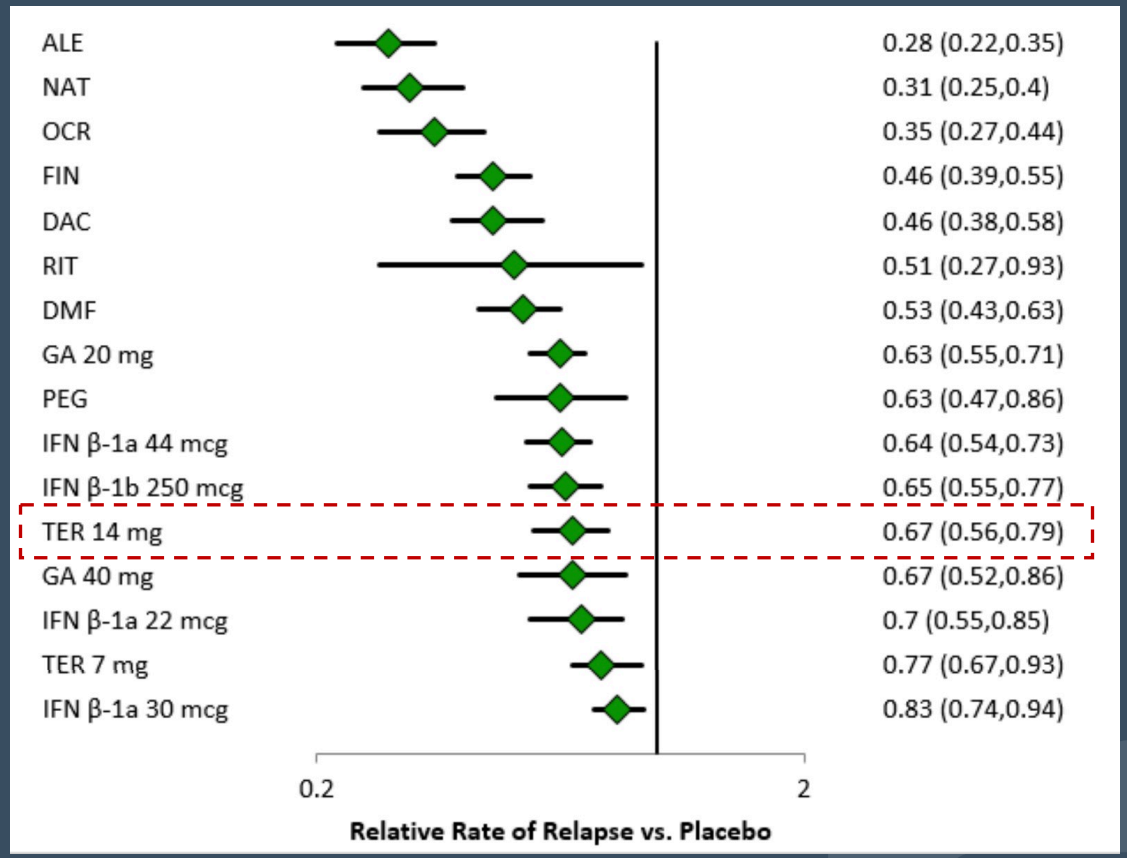
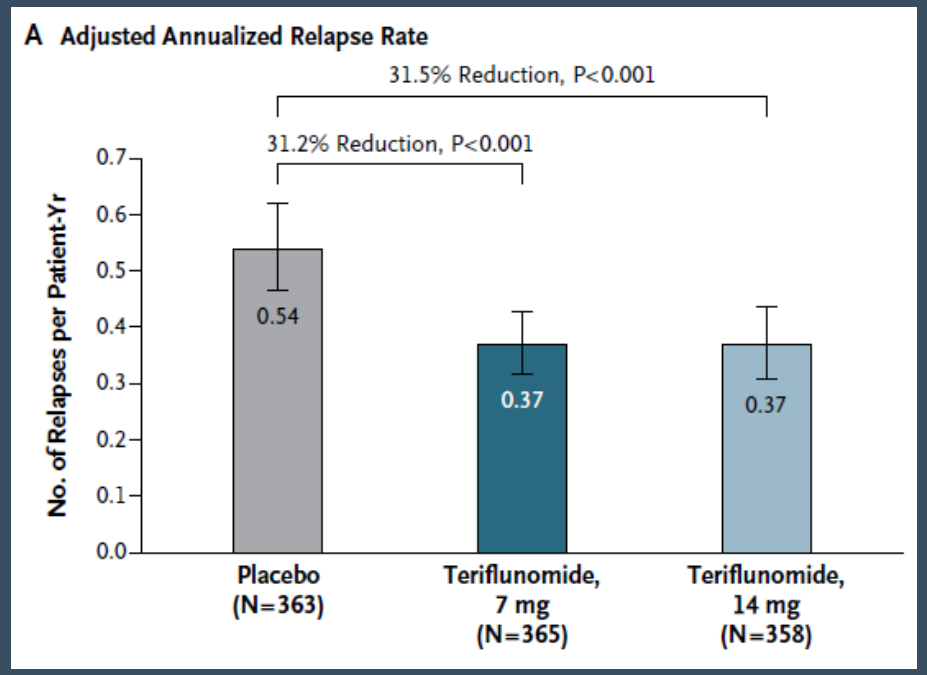
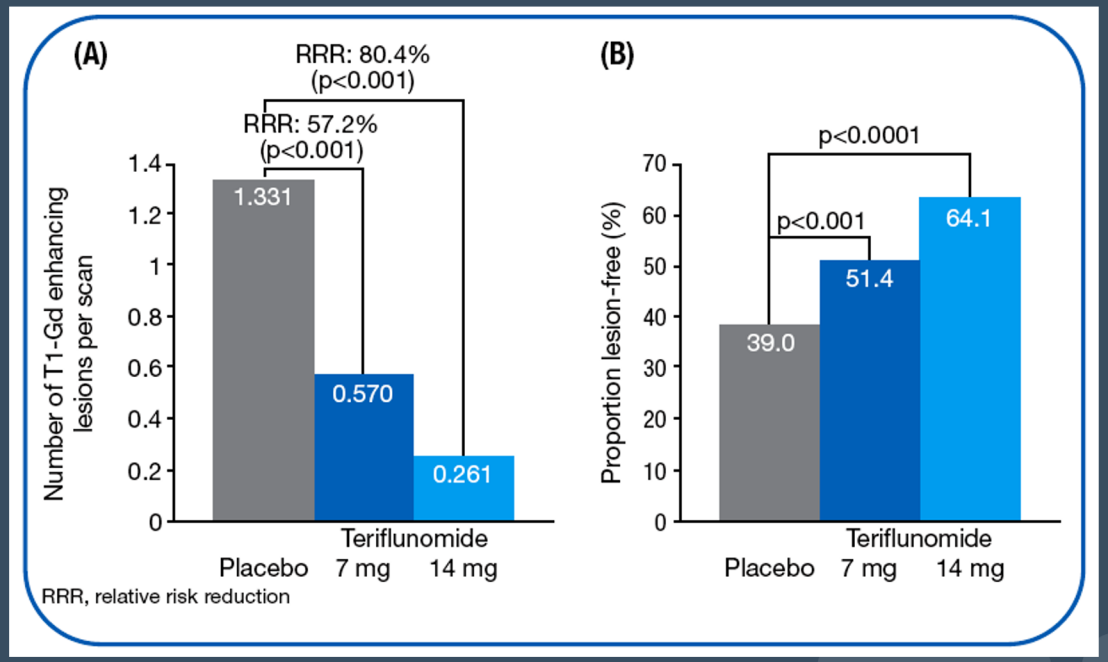


Forest Plot for Annualized Relapse Rate: relative risk for each drug compared to placebo.
California Institute for Clinical and Economic Review, 2017.

Teriflunomide
TEMSO Trial

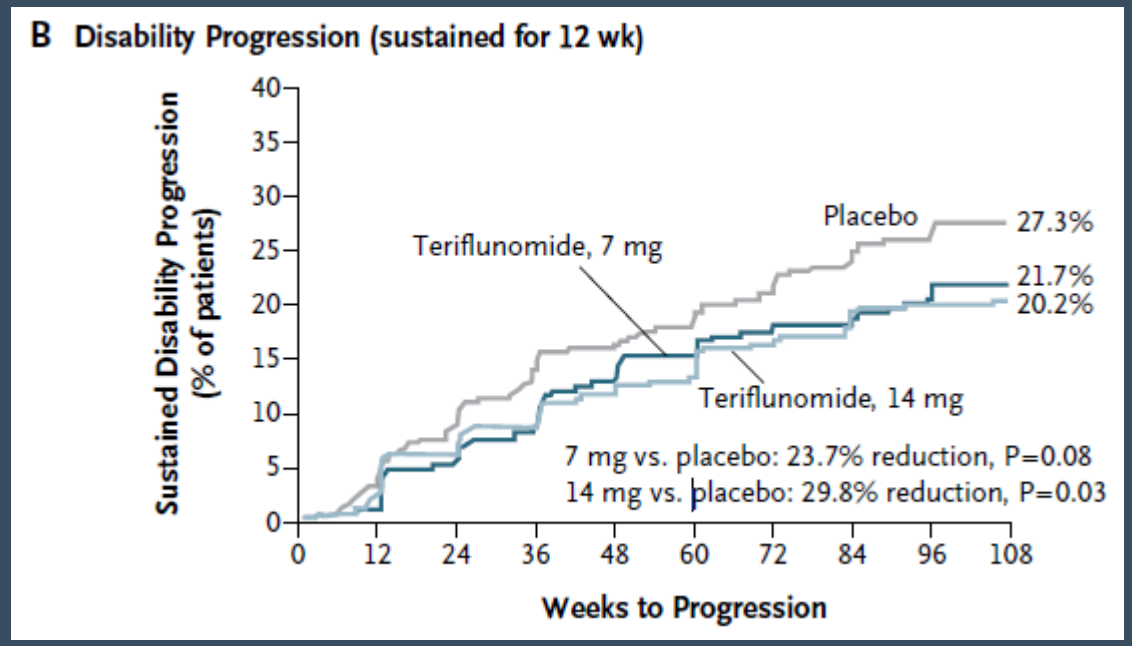


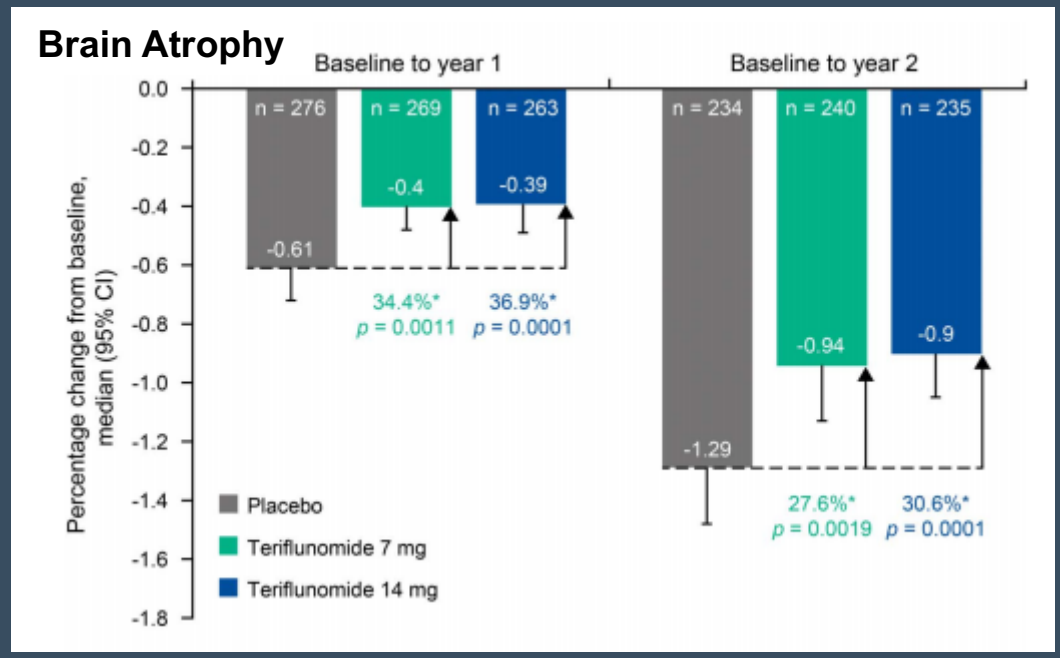


Solid MRI benefits and reasonable relapse rate reduction

O'Connor et al, NEJM 2011

Teriflunomide
TEMSO Trial



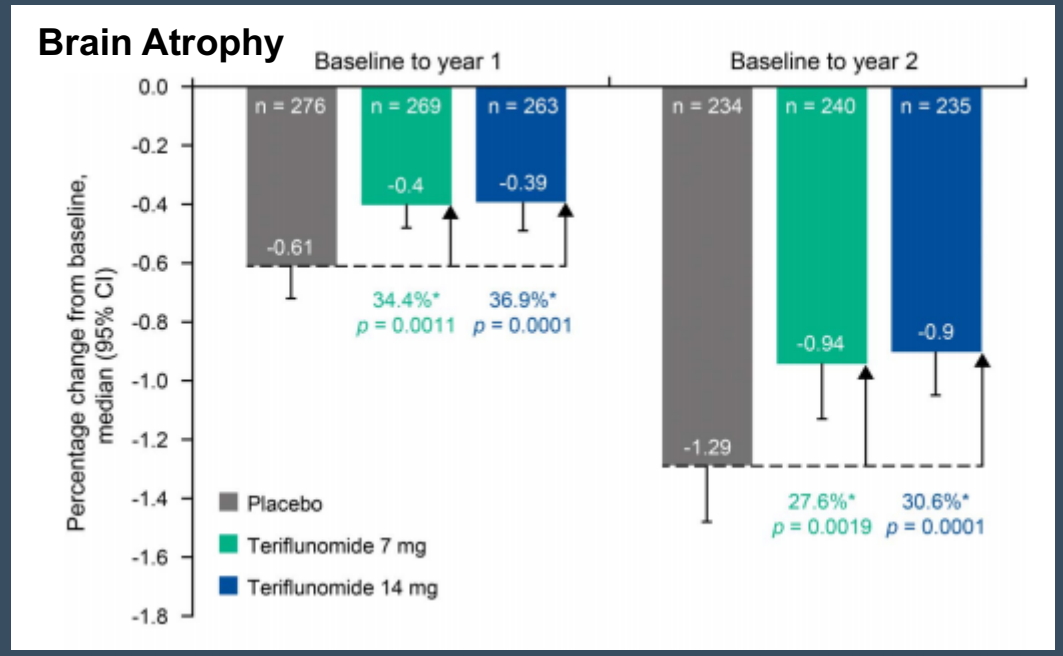


- Surprisingly large benefits in slowing progression of disability and atrophy
- Similar disability benefits in other Ph3 - TOWER (no MRI was done)

O'Connor et al, NEJM 2011
Radue et al, Neurol 2017

Teriflunomide
TEMSO Trial

Endpoints	Study 1: WA21092 (OPERA I)		Study 2: WA21093 (OPERA II)	
	Ocrevus 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrevus 600 mg (n=417)	IFN 44 mcg (n=418)
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	0.016	0.286	0.021	0.416
Relative reduction	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan	0.323	1.413	0.325	1.904
Relative reduction	77% (p<0.0001)		83% (p<0.0001)	
Percentage change in brain volume from Week 24 to week 96	-0.572	-0.741	-0.638	-0.750
Relative reduction in brain volume loss	22.8% (p=0.0042)[6]		14.9% (p=0.0900)	

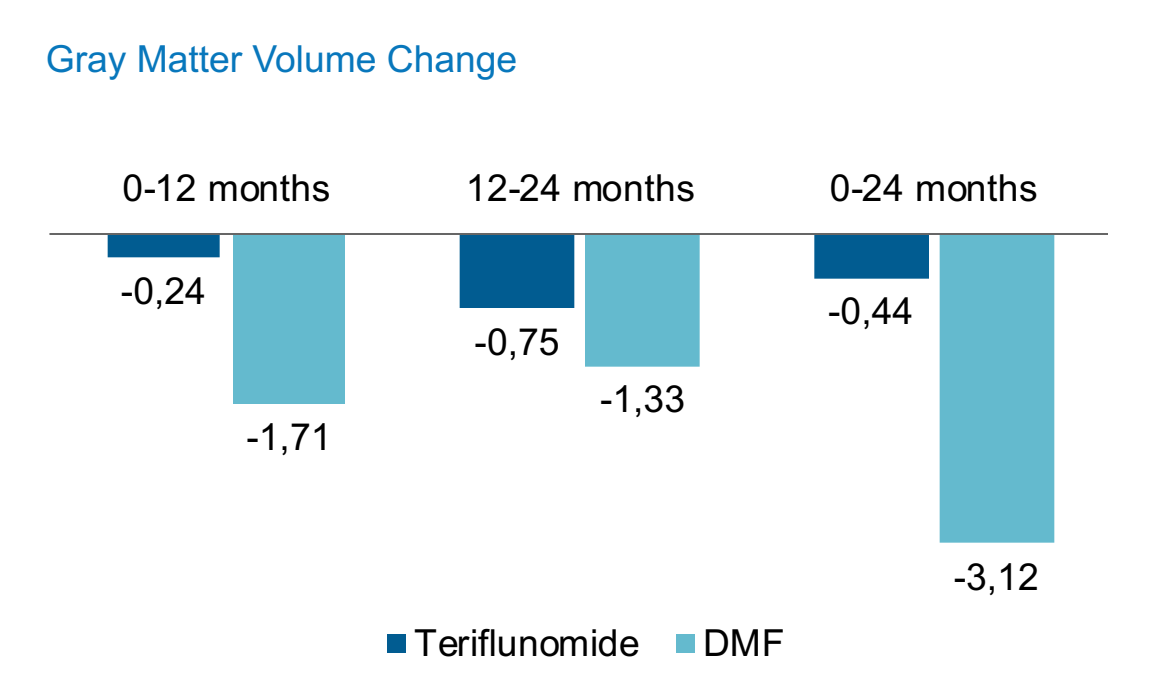


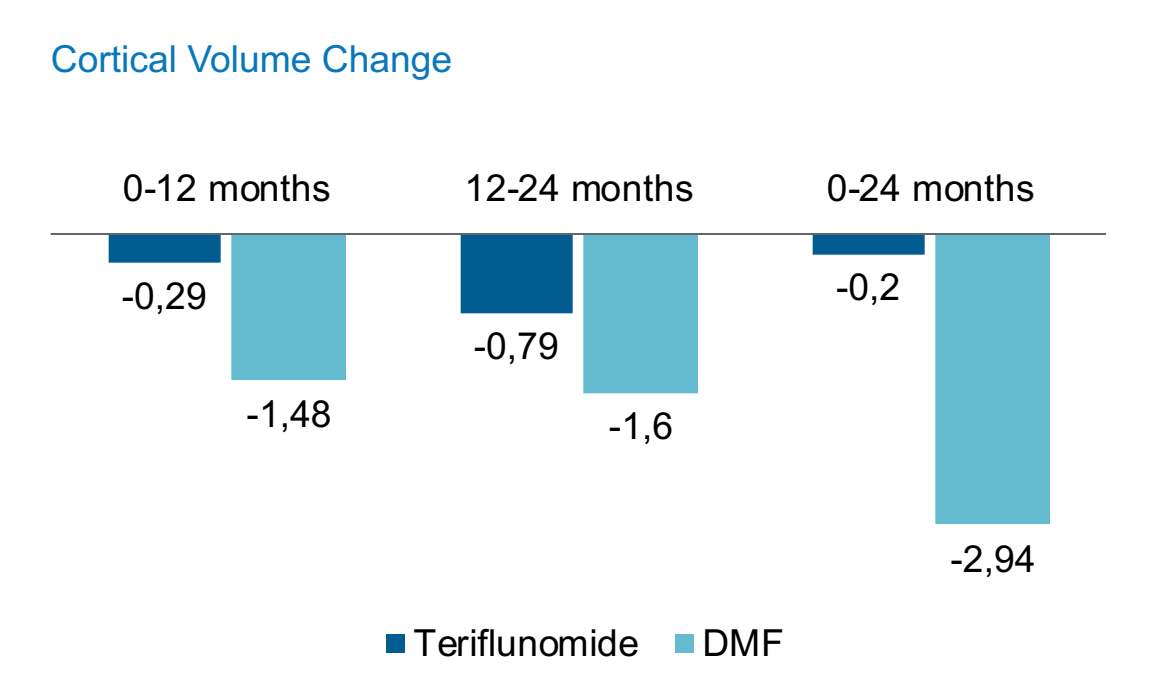
- Teriflunomide's slowed atrophy compares favorably to ocrelizumab

Ocrelizumab EMA SmPC, 2-2018

Radue et al, Neurol 2017

Teriflunomide vs. Dimethylformamide: Gray Matter and Cortical Atrophy



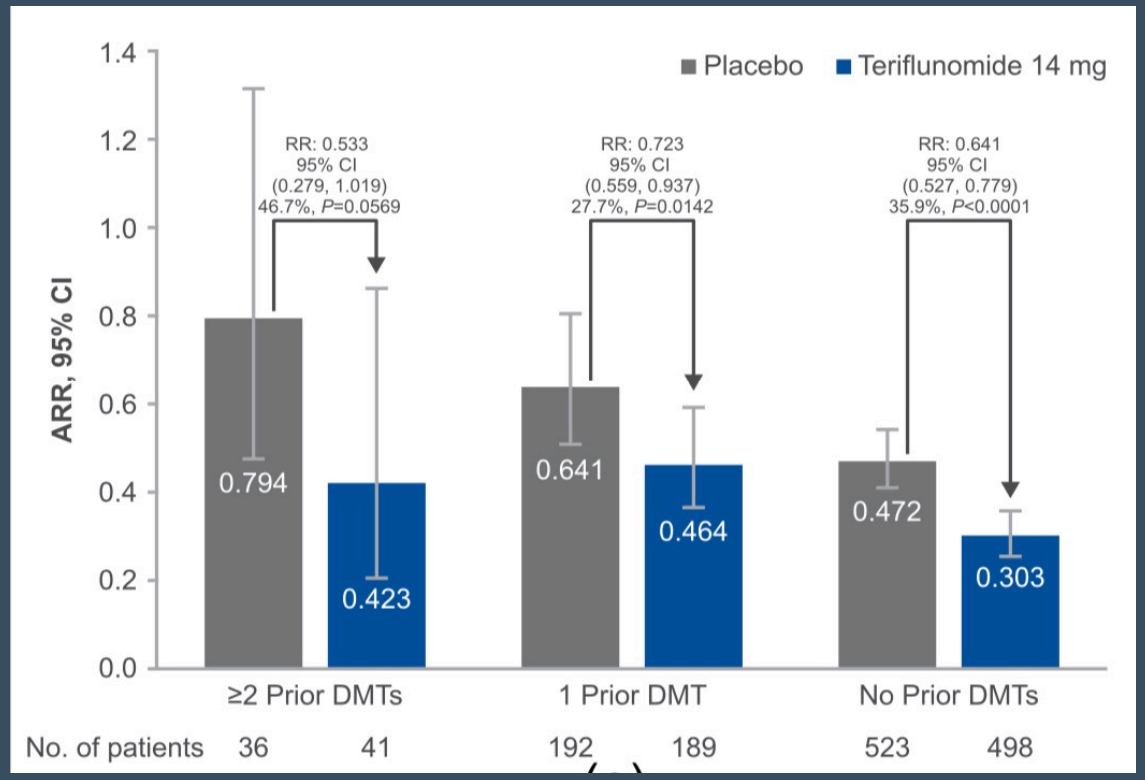


Teriflunomide's atrophy slowing is favorable to dimethyl fumarate

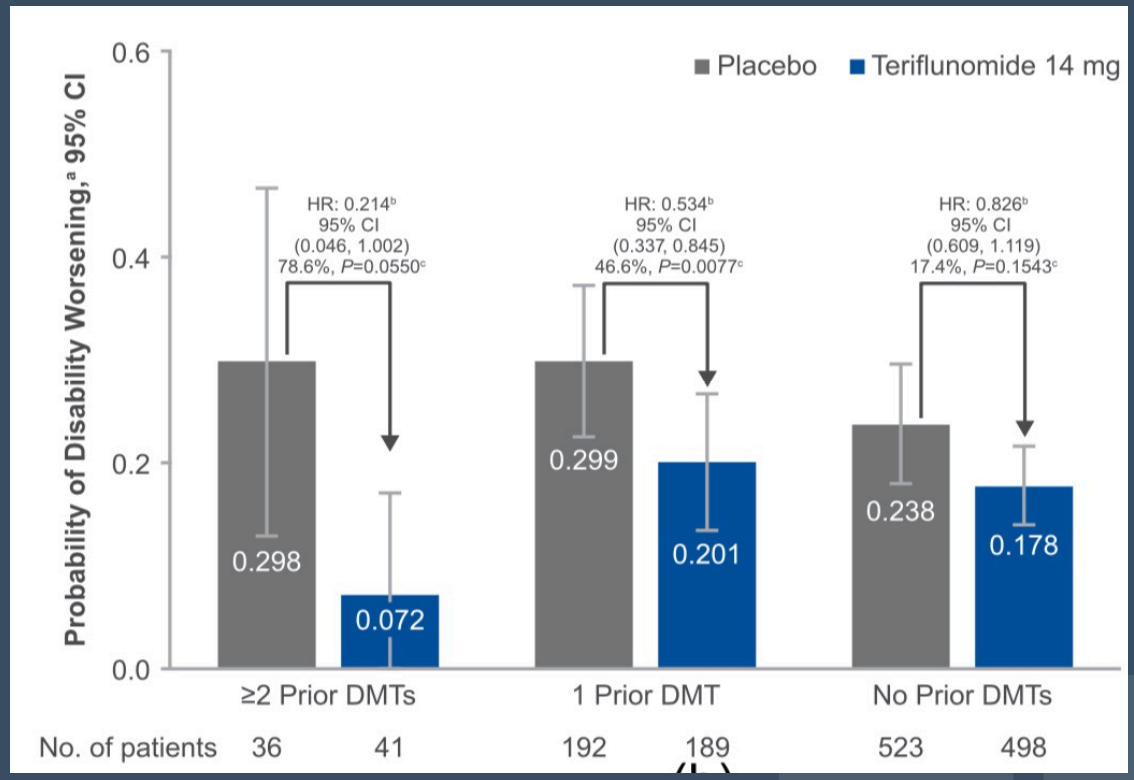
Zivadinov et al, J Clin Med. 2019

Prior treatment and teriflunomide efficacy

Post-hoc analysis from pooled TEMSO and TOWER datasets (2,251 patients)



Relapse rate by prior treatment



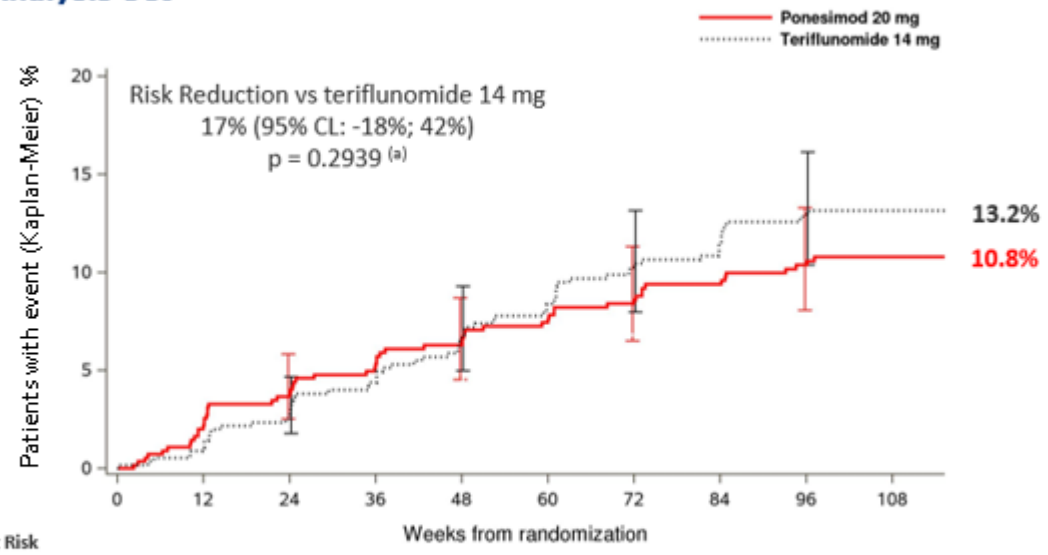
Disability worsening by prior treatment

Teriflunomide provides strong efficacy even after use of multiple prior DMTs

Freedman M et al. *Mult Scler.* 2018

Teriflunomide compared to S1P ponesimod

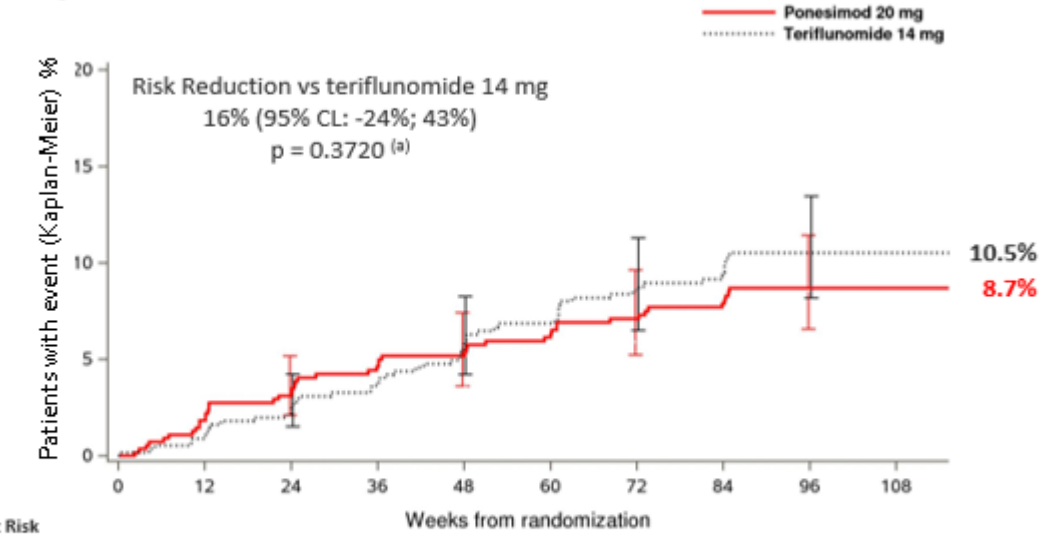
Time to 12-week Confirmed Disability Accumulation
Full Analysis Set



Number at Risk										
Ponesimod 20 mg	567	533	517	503	492	480	469	458	449	315
Teriflunomide 14 mg	566	548	528	513	491	481	467	460	439	290

(a) Non-significant result: Formal testing procedure stopped. Stratified log-rank test p-value and stratified Cox regression risk reduction estimate displayed.

Time to 24-week Confirmed Disability Accumulation
Full Analysis Set



Number at Risk										
Ponesimod 20 mg	567	534	519	506	497	486	475	464	451	318
Teriflunomide 14 mg	566	549	530	517	495	488	475	468	446	297

(a) Exploratory, not formally tested. Stratified log-rank test p-value and stratified Cox regression risk reduction estimate displayed.

Kappos L et al. *ECTRIMS 2019*; Stockholm. Abstract 93

Comparative Disability Effects: Teriflunomide vs. Fingolimod and Dimethyl fumarate

	Dimethyl fumarate 240 mg bid			Fingolimod 0.5 mg qd		Teriflunomide 14 mg qd		
	DEFINE (N=818)[a] (Gold, 2012)	**CONFIRM (N=722)**[a] (Fox, 2012)	**DEFINE+ CONFIRM pooled (N=1540)**[a] (Fox, 2013)	**FREEDOMS N=843** (Kappos, 2010)	**FREEDOMS II N=713** (Calabresi, 2014)	**TEMSO (N=721)**[a] (O'Connor, 2011)	**TOWER (N=758)**[a] (Confavreux, 2014)	**TEMSO + TOWER pooled (N=1479)**[a] (Kappos, 2013)
Proportion of patients with CDW[b]								
Placebo	0.27	0.17	0.222	0.241	0.290	0.273	0.197	0.240
Intervention	0.16	0.13	0.146	0.177	0.253	0.202	0.158	0.179
Hazard ratio	0.62	0.79	0.68	0.70	0.83	0.70	0.68	0.695
Relative risk reduction (%)	38	21	32	30[c]	17[c]	29.8	32	30.5
P value vs placebo, %	p=0.005	p=0.25	p=0.0034	p=0.02	p=0.227	p=0.03	p=0.0442	p=0.003
Hazard ratio	0.62	0.79	0.680	0.70	0.83	0.70	0.68	0.695
P value vs placebo	p=0.005	p=0.25	p=0.0034	p=0.02	p=0.227	p=0.0279	p=0.0442	p=0.0029
NNT								

bid=twice daily; CDW=confirmed disability worsening; NNT=number needed to treat; qd=once daily.

[a] The total number of patients includes those randomized and treated with dimethyl fumarate 240 mg bid, fingolimod 0.5 mg qd, or teriflunomide 14 mg qd, and the respective placebo groups in each study;

[b] 3-month CDW at 2 years;

[c] relative reduction vs placebo derived from hazard ratios reported in cited source.

Teriflunomide had consistent disability slowing in both Phase 3 trials

Freedman MS et al. MSARD. 2016

Real-World Evidence - MS Base Registry

- RRMS patients with ≥3-month treatment persistence and disability follow-up in MSBase registry
  - 614 on teriflunomide
  - 782 on dimethyl fumarate
  - 2332 on fingolimod
- Followed over 2.5 years and matched using propensity scores
- Outcome: Hazard of disability accumulation; hazard of disability improvement
- **Results: no differences in disability accumulation (p≥0.59) or improvement (p≥0.14) were found between therapies**

Kalincik T. *J Neurol Neurosurg Psychiatry.* 2019; 90:458-68

PML Risk

Unlike many other MS therapies, Teriflunomide has low risk fo PML

Berger, MS and Related Dis 2017

J.R. Berger

Table 1
A PML risk stratification table for disease modifying therapies.

Therapeutic Agent	Treated condition predisposes to PML?
Class I – high potential risk of PML	**No**
Natalizumab	MS and Crohn's disease
Class II – low potential risk of PML	**No**
Dimethyl fumarate	MS and psoriasis
Fingolimod	MS
Class III – no or very low potential risk of PML	**Yes**
Alemtuzumab	Hematological malignancies, transplantation
Rituximab	Lymphoproliferative disorders, rheumatoid arthritis, ANCA-associated vasculitis, SLE
Mitoxantrone	Non-Hodgkins lymphoma and leukemia
Teriflunomide	No PML observed with teriflunomide but with related leflunomide
Daclizumab	No PML observed with MS or as prophylaxis for renal transplant

Teriflunomide's unexpected success

Given it's modest anti-inflammatory effect, why has teriflunomide been so commercially successful?

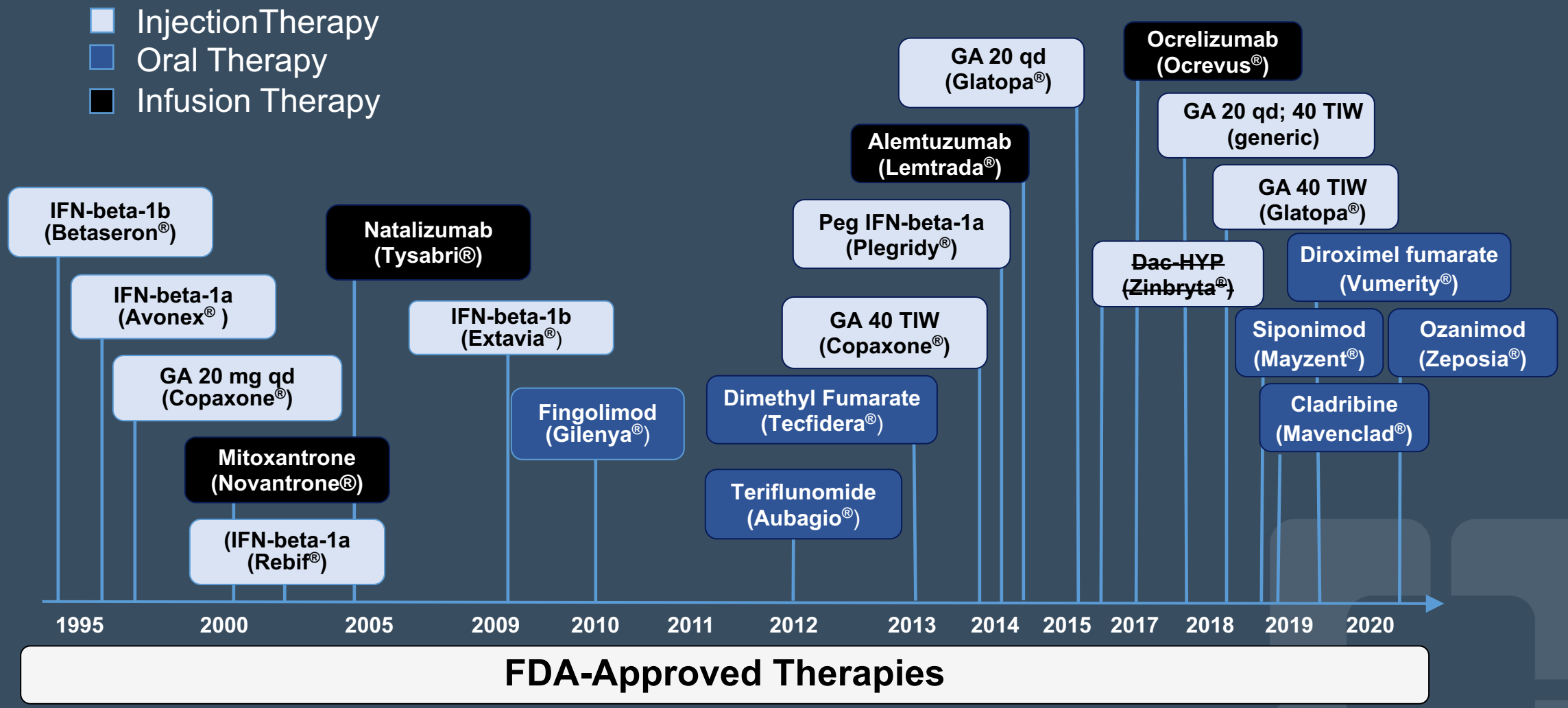
Possible explanations:

- Oral daily administration
- Low risk -> easier patient conversations
  - Essentially no PML risk
- Minimal pre-testing
- Reasonably well-tolerated
- Consistent disability & atrophy slowing

Multiple Sclerosis Treatment Landscape and Medical Needs

- Introduction to multiple sclerosis
- Overview of MS therapy landscape
- What to learn from teriflunomide
- Unmet treatment needs in MS

MS Therapy – Do We Need More?



Adapted from Wingerchuk & Weinshenker. BMJ. 2016

MS Therapies – Current Short-Comings

Injectibles – interferon-β1 and glatiramer acetate

- Uncomfortable administration
- Side-effects: flulike (IFNβ1) and rash (glatiramer acetate)
- Modest anti-inflammatory effects
- Essentially no new-starts except for glatiramer acetate

Orals – S1Ps, fumarates

- Pre-testing: blood tests; EKG first-dose monitoring (fingolimod);
- Risk discussion: cardiac (S1Ps) PML – small but non-zero; no risk stratification (S1Ps)
- Less disability slowing than inflammation would suggest

MS Therapies – Current Short-Comings

Infusions – natalizumab, anti-CD20s

- Frequent infusions (natalizumab)
- Risk discussion: PML (natalizumab>anti-CD20s); infections (anti-CD20s)
- Very long pharmacodynamics – 3-6 months (natalizumab); 6-12 months (anti-CD20s)
- Less disability slowing than inflammation would suggest

MS Therapies – Current Short-Comings

Teriflunomide

- Side-effects
- High treatment discontinuation rate

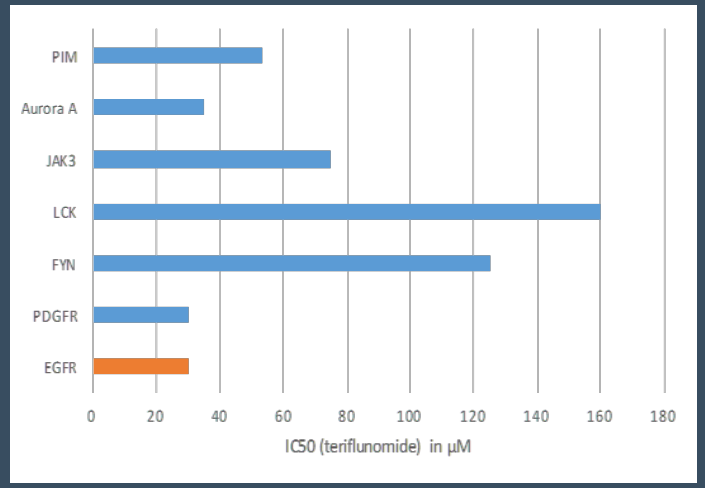
Adverse Event	AUBAGIO 14 mg (n=1002)	AUBAGIO 7 mg (n=1045)	Placebo (n=997)
Headache	16%	18%	15%
ALT increased*	15%	13%	9%
Diarrhea	14%	13%	8%
Alopecia†	13%	10%	5%
Nausea	11%	8%	7%

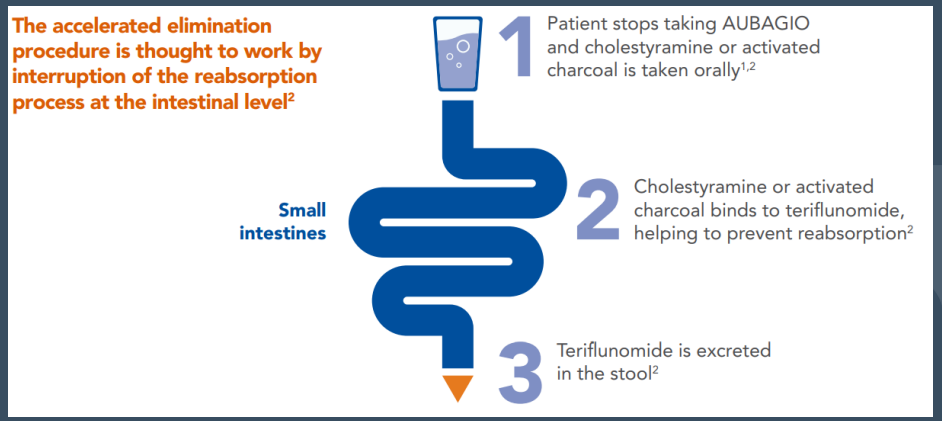
Trial	Discontinuation rate
NCT01487086	16.1% (7 mg or 14 mg)
TEMSO	24.9% (7 mg) 26.5% (14 mg)
TOWER	32.9% (7 mg) 34.1% (14 mg)
TENERE	18.3% (7 mg) 19.8% (14 mg)

MS Therapies – Current Short-Comings

Teriflunomide

- Side-effects
- High treatment discontinuation rate
- Intensive monitoring: monthly labs for six months; intermittent BP check
- Many off-target effects - non-selective inhibitor of numerous protein kinases
- Pregnancy counseling
- Long half-life (16 days) and high accumulation, which requires long wash-out or accelerated clearance





Conclusion

Despite many therapies approved (and nearing approval) for relapsing forms of MS, there remains ample opportunity for a

- safe
- oral
- well-tolerated
- moderately-effective anti-inflammatory, with
- neuroprotective properties beyond what would be expected by reducing inflammation