Therapies and recent developments

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Ligue française contre la sclérose en plaques Ensemble

Poissy Saint-Germain-en-Laye Centre Hospitalier Intercommunal www.chi-poissy-st-germain.fr

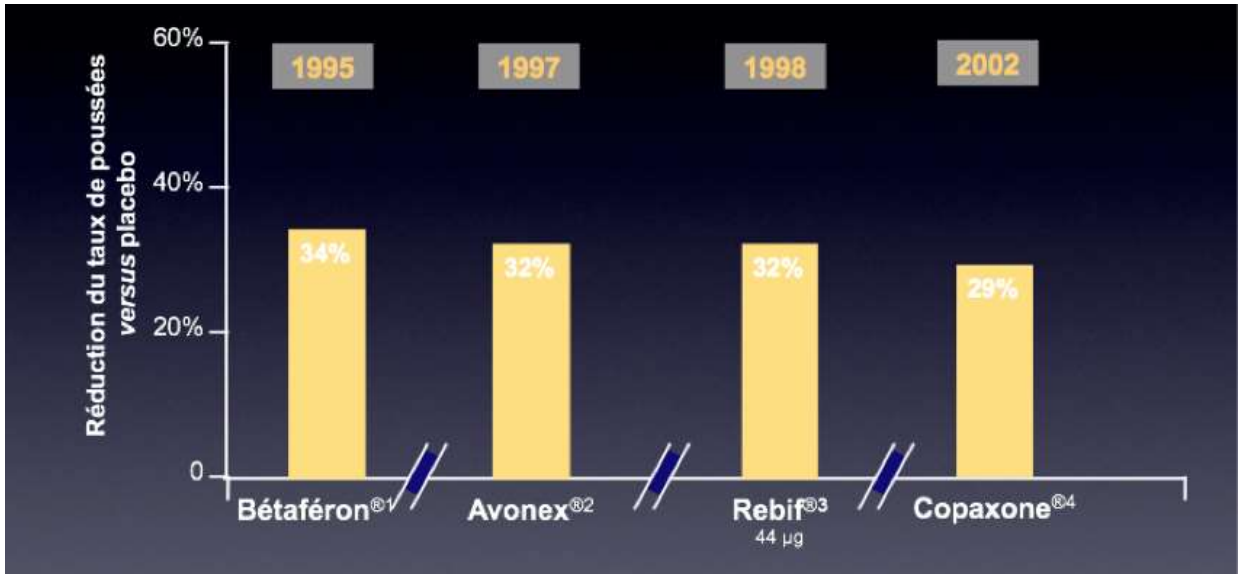
RÉSEAU SEP Ile de France Ouest

Reduction of the annualised relapse rate

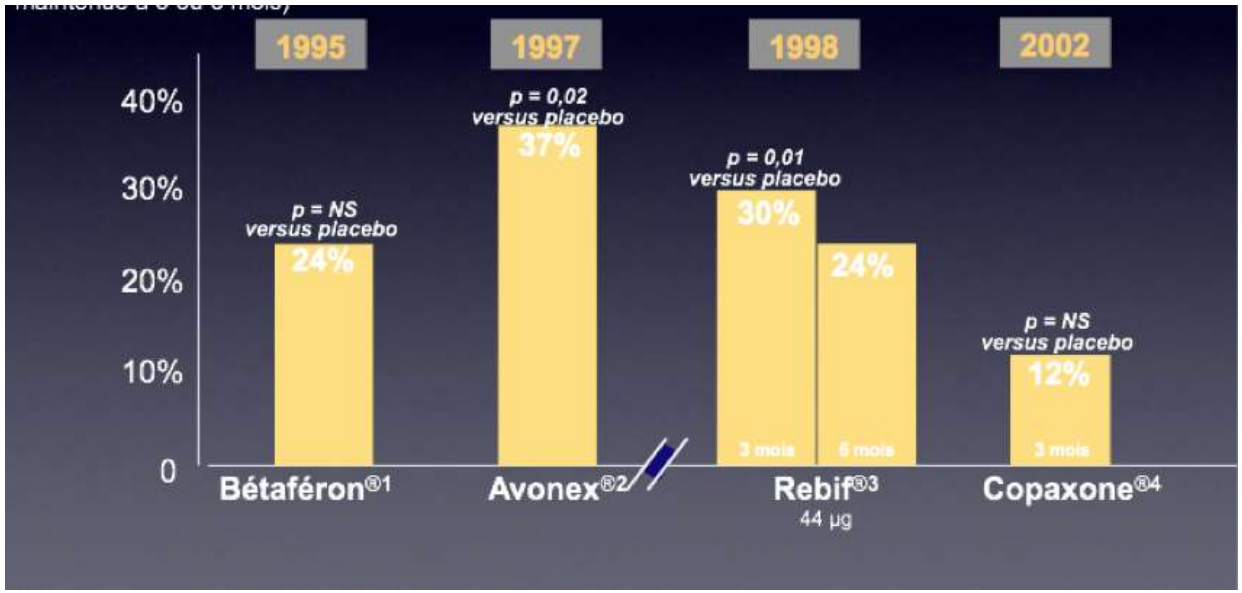
Increase of the number of patient without relapse

Increase the delay between relapse

Results of the pivotal trials



First line treatments reduce the risk of relapse



Moderate impact on the prevention of persisting impairment as measured by EDSS score at 3 or 6 months

A benign profile of side effects

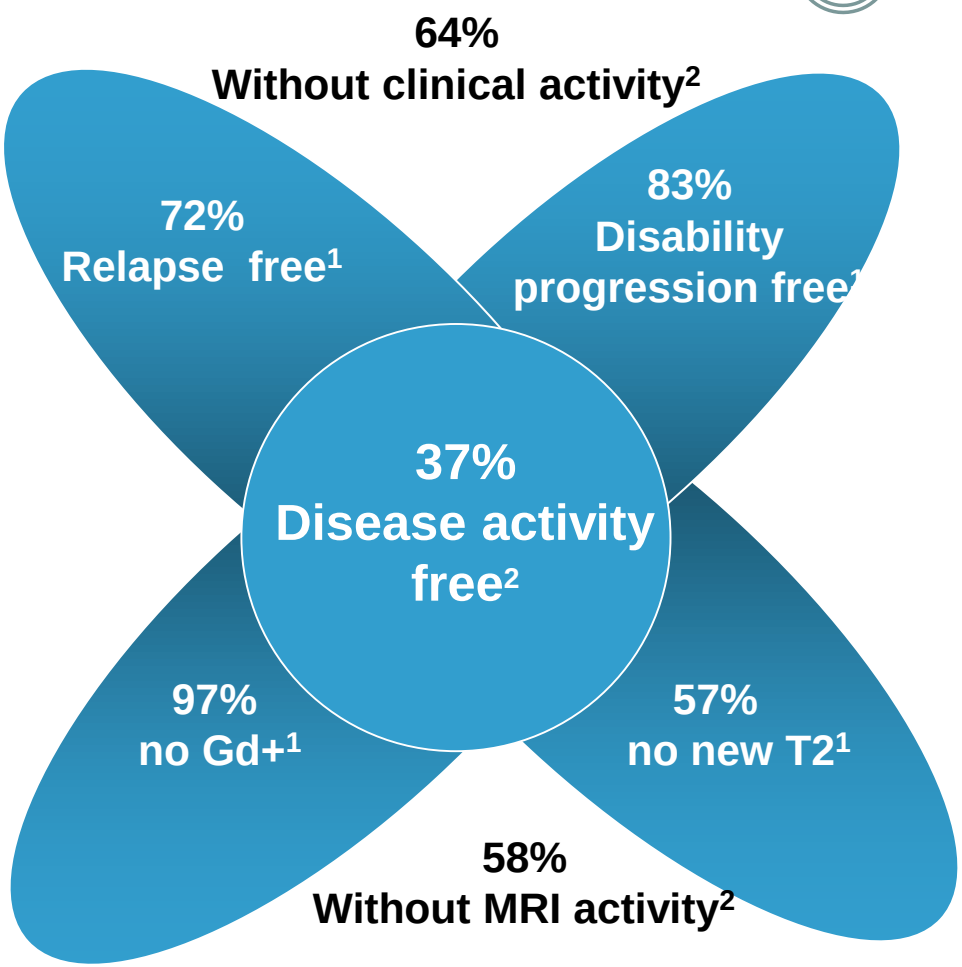
- Interferon :
  - Flu-syndrome
  - Cutaneous reactions
  - fatigue
  - Hepatic
- Glatiramer acetate
  - Cutaneous reactions

- No risk of malignancies or severe infections even after years of exposure
- Interferon might reduce the risk of death

Second line treatments

- Natalizumab (Tysabri)
- Fingolimod (Gilenya)
- Mitoxantrone (Elsep)

Disease activity free



Two years disease activity free[2]		
Placebo	7%	(n=304)
Natalizumab	37%	(n=600)

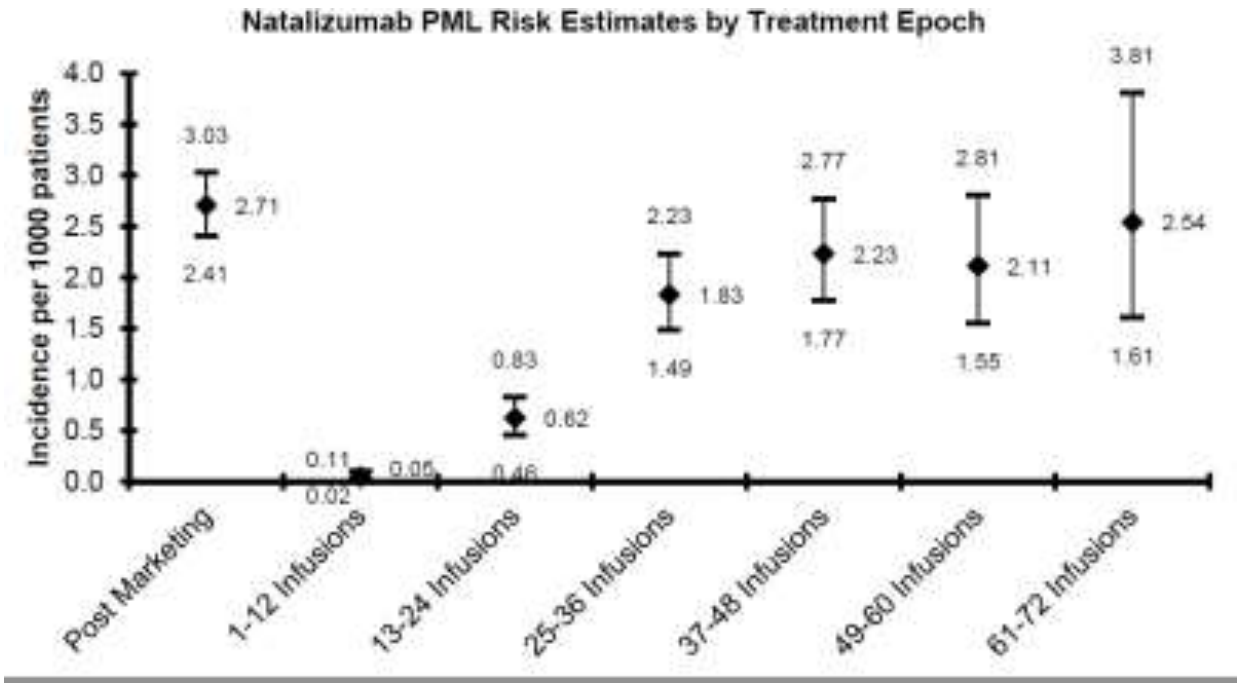
[1]Polman CH, et al. *N Engl J Med*. 2006;354:899-910.
[2]Havrdova E, et al. Presented at: 23rd Congress of the ECTRIMS; October 13, 2007; Prague, CZ.

PML is a viral infection of the Oligodendrocytes

It is secondary to immunosuppression

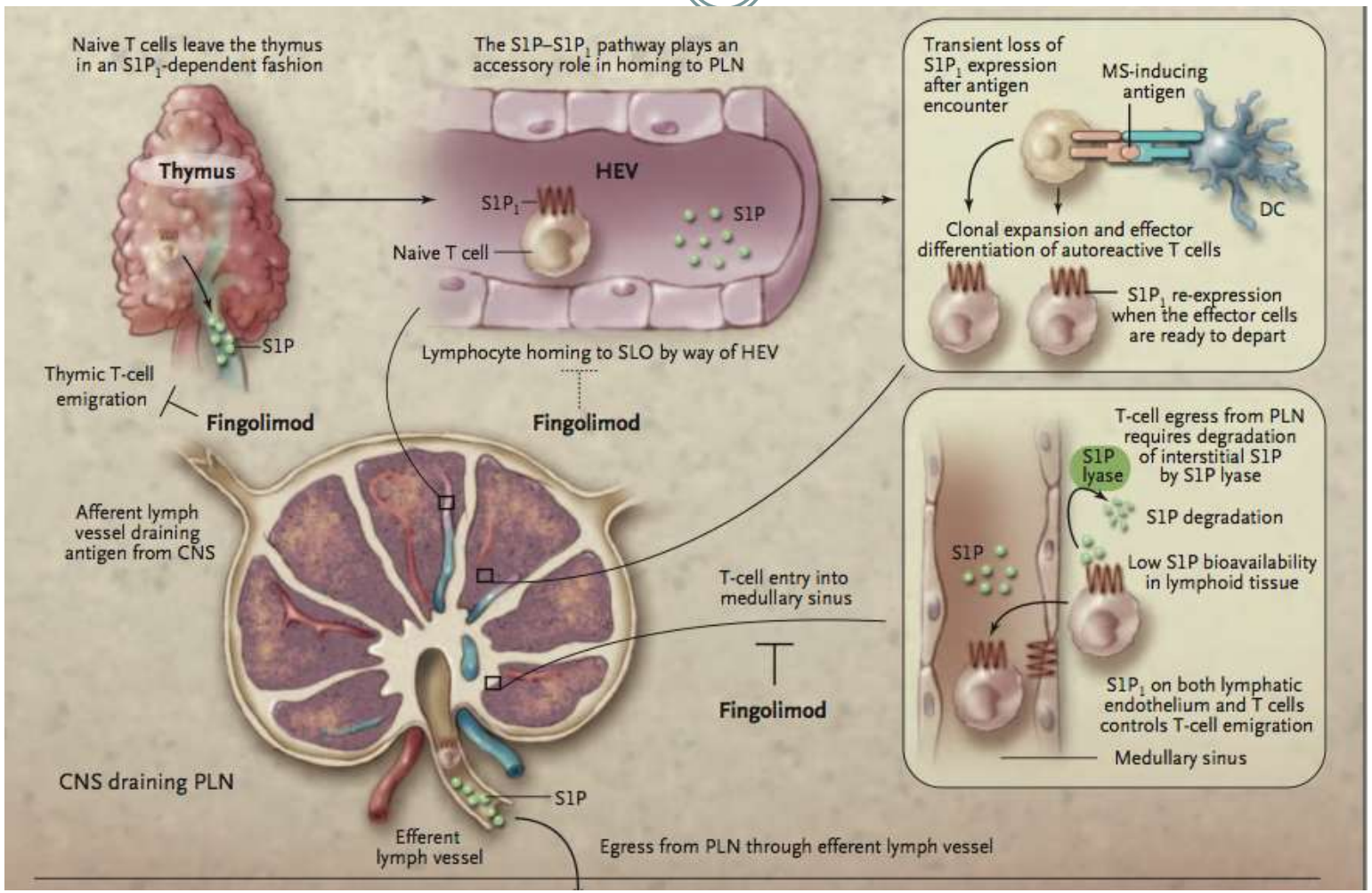
Prognostic is severe with a risk of death (1/5) or severe persisting disability

No treatment

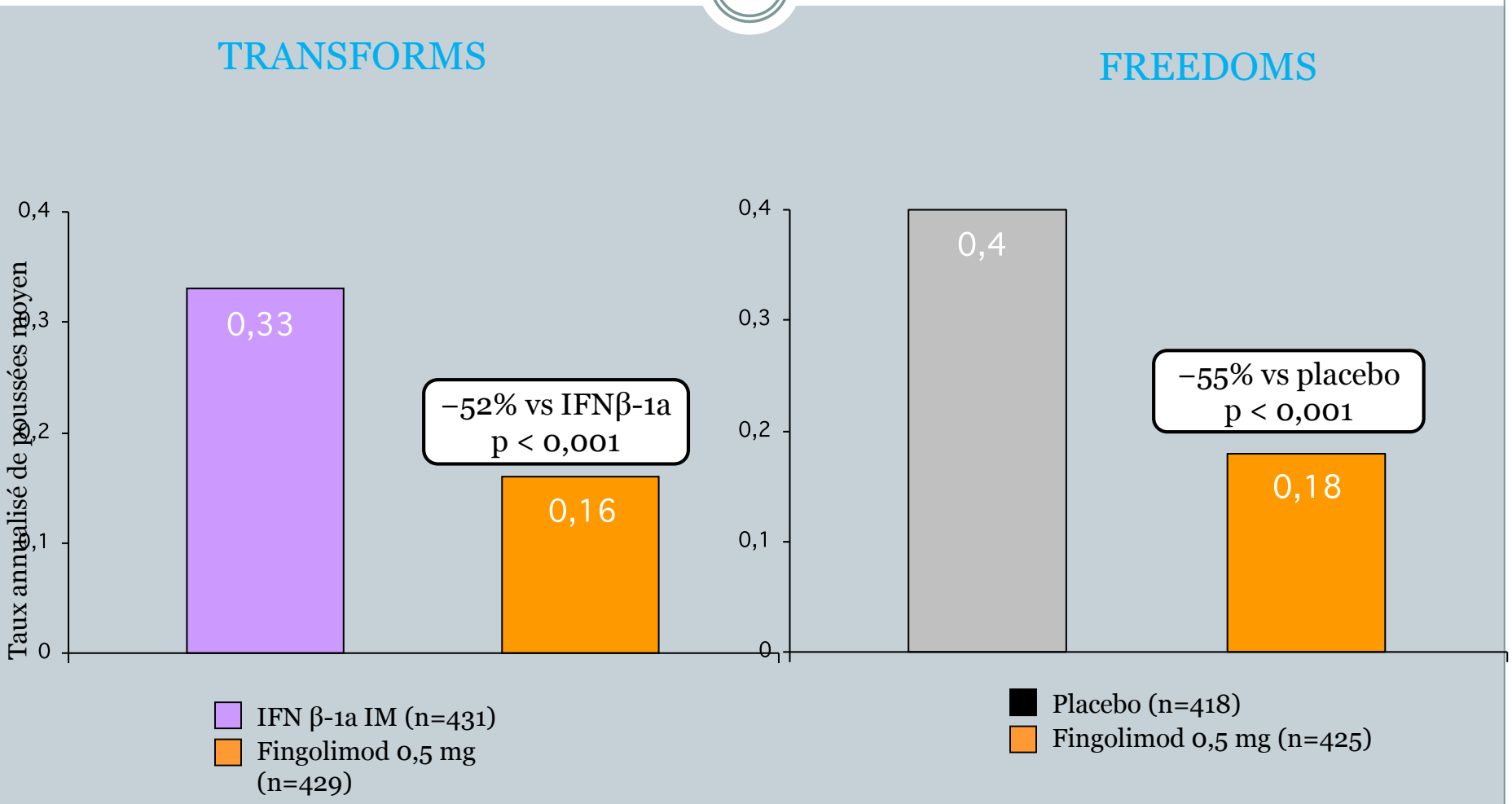


A major risk with Natalizumab : the occurrence of progressive multifocal leucoencephalopathy

Fingolimod, (Gilenya) S1P réceptors agonist Immunosuppressive



Annualized relapse rate in pivotal studies



Population ITT: tous les patients randomisés ayant reçu au moins 1 dose de traitement

Kappos L. et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis N Engl J Med 2010; 362 : 387-401
Cohen J.A. et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis N Engl J Med 2010; 362 : 402-415

Fingolimod : safety

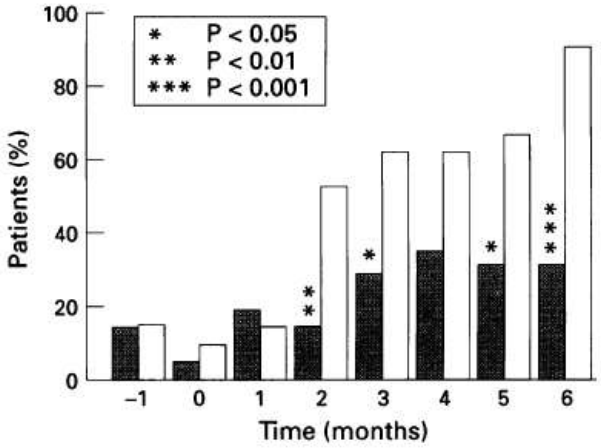
- bradycardia
- Macular oedema
- Hépatitis
- Lymphopénia
- Infections (HSV, VZV)
- hypertension

Mitoxantrone

Journal of Neurology, Neurosurgery, and Psychiatry 1997;62:112–118

Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria

Gilles Edan, David Miller, Michel Clanet, Christian Confavreux, Olivier Lyon-Caen, Catherine Lubetzki, Bruno Brochet, Isabelle Berry, Yan Rolland, Jean-Claude Froment, Vincent Dousset, Emmanuelle Cabanis, Marie-Thérèse Iba-Zizen, Jean-Marc Gandon, H M Lai, Ivan Moseley, Olivier Sabouraud



ARR 1 yr before	EDSS MTX onset	ARR 1 yr after	ARR 2-5 yrs
3.2	↑ 2.2	0.29 (↓ 91%)	0.3 – 0.4

% patients without G+enhancing lesions

Safety :

- Leukaemia
- dose related cardiac toxicity
- aménorrhée

Therapeutic strategy

- Treating early with first line immunomodulator high risk patients :
  - Frequent relapses
  - High lesion load
  - Detectable MRI activity
  - Cognitive impairment
  - Sequelae
- Identifying bad responders :
  - Relapses despite treatment
  - Persistent MRI activity
- Introducing second line immunosuppressive drugs when necessary

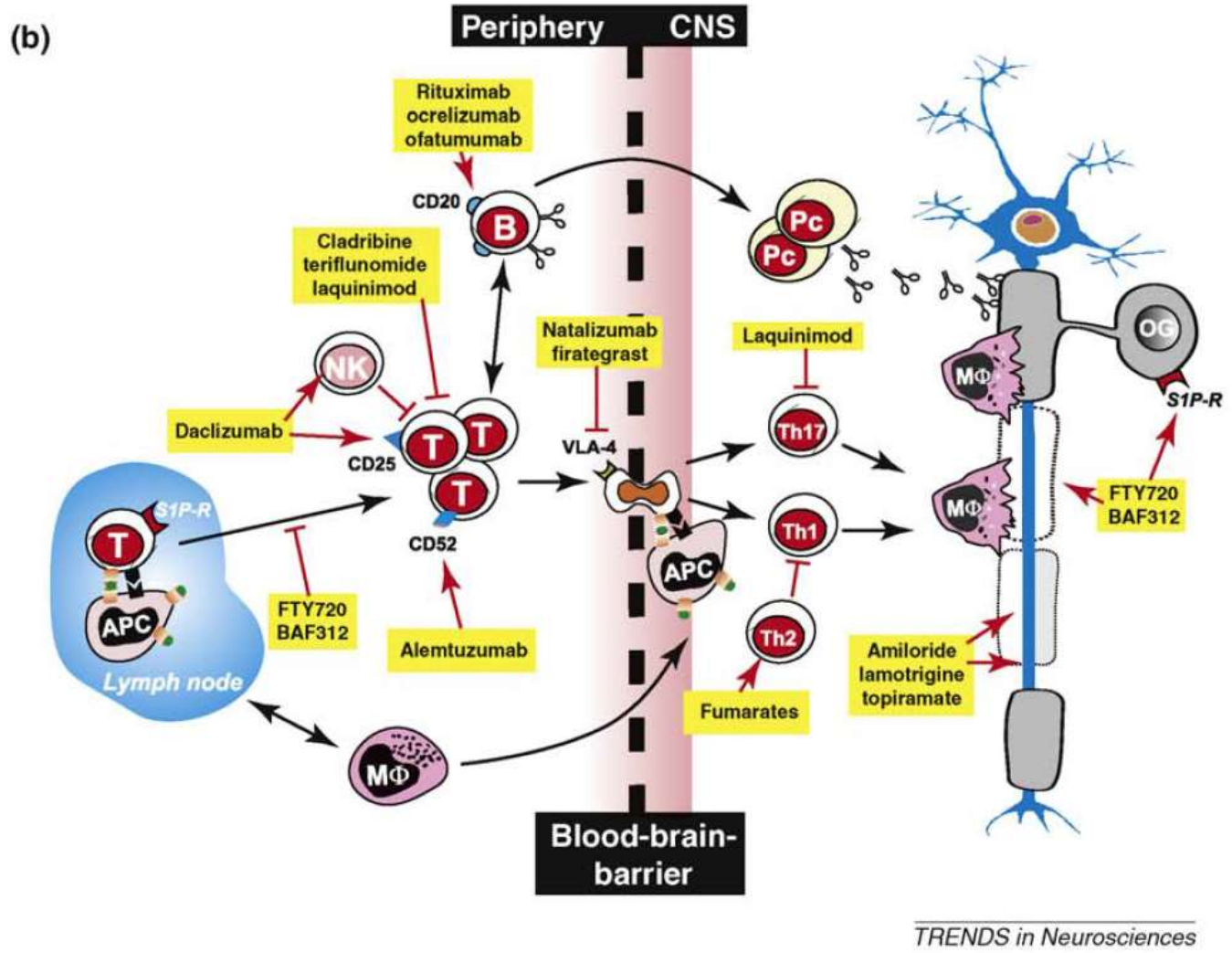
What do we expect from new drugs?

- Higher efficacy :
  - More effective or more specific on inflammation
  - Neuroprotective action (to prevent degenerative process)
  - Promotion of repair or remyelination
  - Efficacy in disease subgroups and in disease phase less amenable to existing treatments
- A good (better) tolerability and safety
  - More convenient administration
  - Low frequency or severity of immediate side effects
  - Low risk of infections or malignancies

Upcoming treatment in MS

- Non specific immunosuppression and immunomodulation
- Selective immunosuppression
  - Leukocyte depletion
  - B lymphocytes depletion
- Immune cell trafficking
- Neuroprotective drugs
- Remyelinating drugs
- Cell stem therapy

Putative modes of action for the drugs in MS



Non specific immunosuppression and immunomodulation

PEG INTERFERON

COPAXONE EOD

TECFIDERA (BG-12) ; BIOGENIDEC

AUBAGIO (TERIFLUNOMIDE) ; GENZYME

LAQUINIMOD (NERVENTRA) TEVA

SIMVASTATIN

Pegylated interferon B-1a : The ADVANCE study

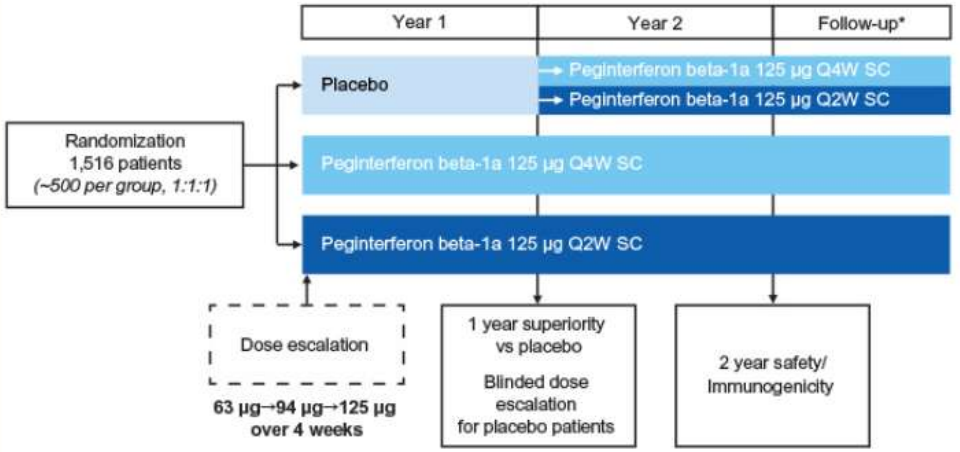
Attachment of poly-ethyleneglycol molecules increases the half-life and reduces the dosing frequency

Efficacy demonstrated over placebo on relapse rate (36%) and disability progression (38%) when administered every two weeks

Injection site reactions in 62% of patients

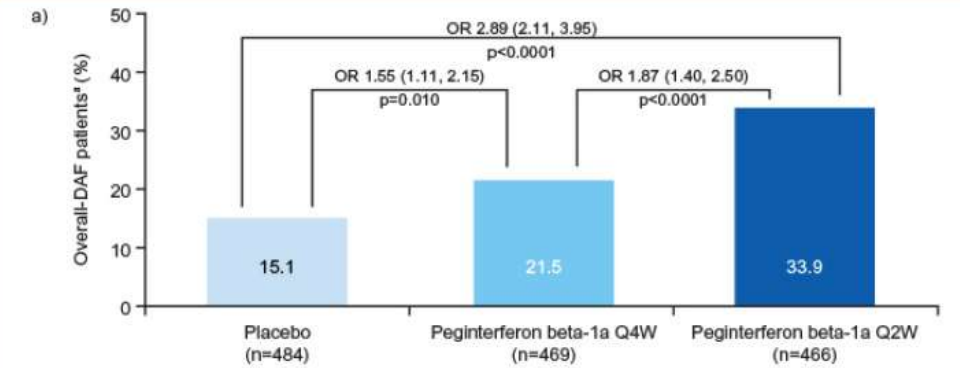
Influenza like illness in 47 % of patients

Figure 1: ADVANCE study design



*12-week safety follow-up period for those subjects who do not enter an extension study (ATTAIN);
Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

Figure 6: Proportions of a) overall-DAF, and b) clinical-DAF patients at Week 48



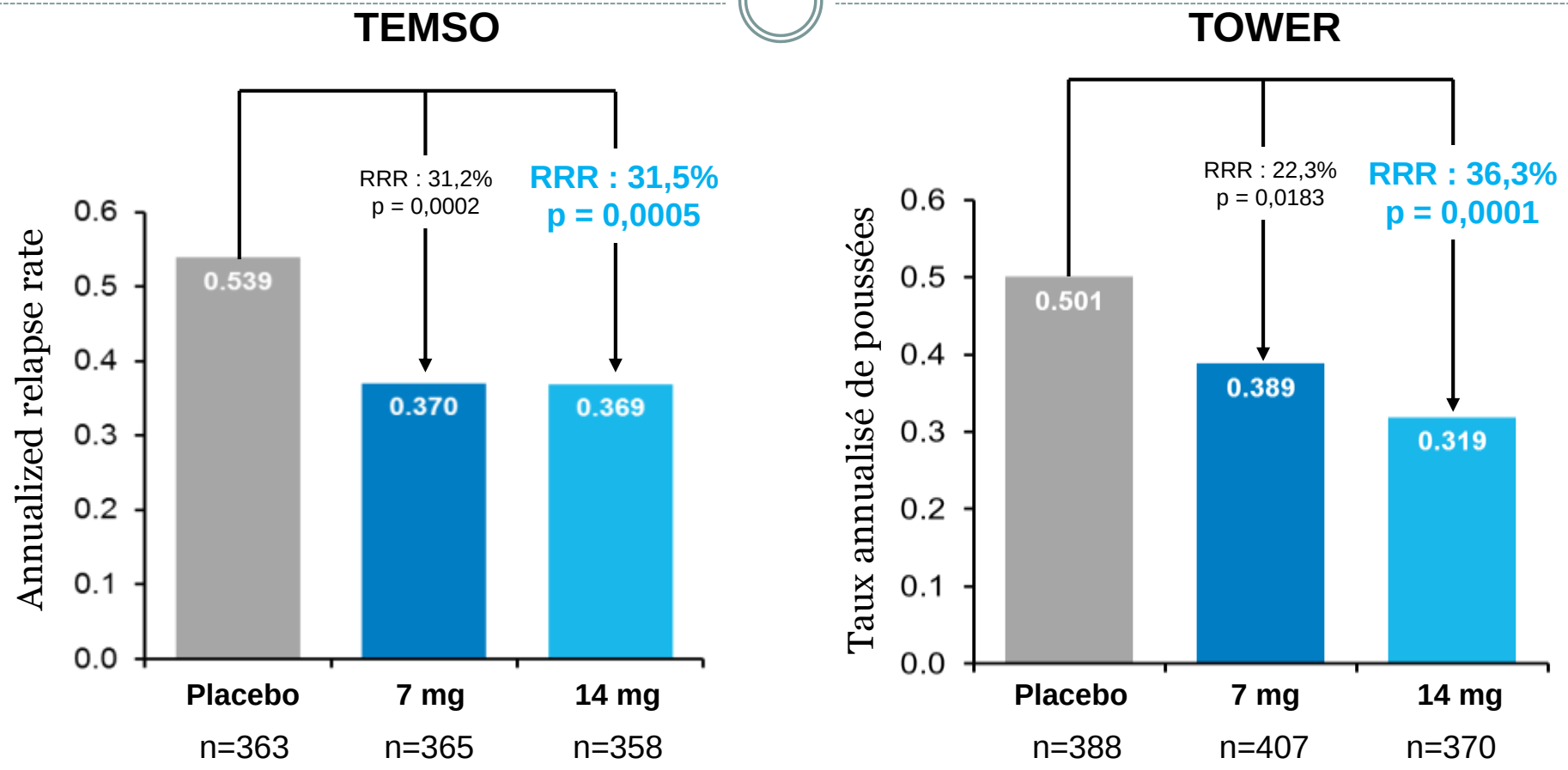
Glatiramer acetate injection every other days

Table 6: Study 5 Efficacy and MRI Results

	COPAXONE 40 mg/mL (n=943)	Placebo (n=461)	P-Value
Clinical Endpoints			
Number of confirmed relapses during the 12-month placebo-controlled phase			
Adjusted Mean Estimates Relative risk reduction	0.331 34%	0.505	<0.0001

		COPAXONE 40 mg/mL (n=943)	Placebo (n=461)
General Disorders And Administration Site Conditions	Injection Site Erythema	22%	2%
	Injection Site Pain	10%	2%
	Injection Site Mass	6%	0%
	Injection Site Pruritus	6%	0%
	Injection Site Edema	6%	0%

Teriflunomide (AUBAGIO) significantly reduced the relapse rate



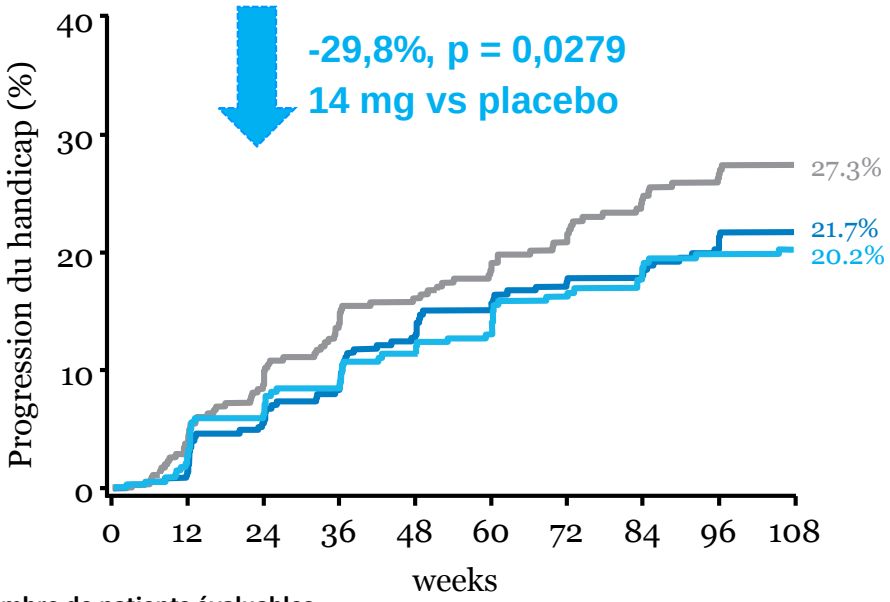
In a phase III sudy (TENERE) there was no difference between Teriflunomide and interferon B-1a in relapse rate

Freedman M, et al. ACTRIMS, 2013 (P5).

And the risk of permanent disability

+ 1 point ou + 0,5 if EDSS > 5,5

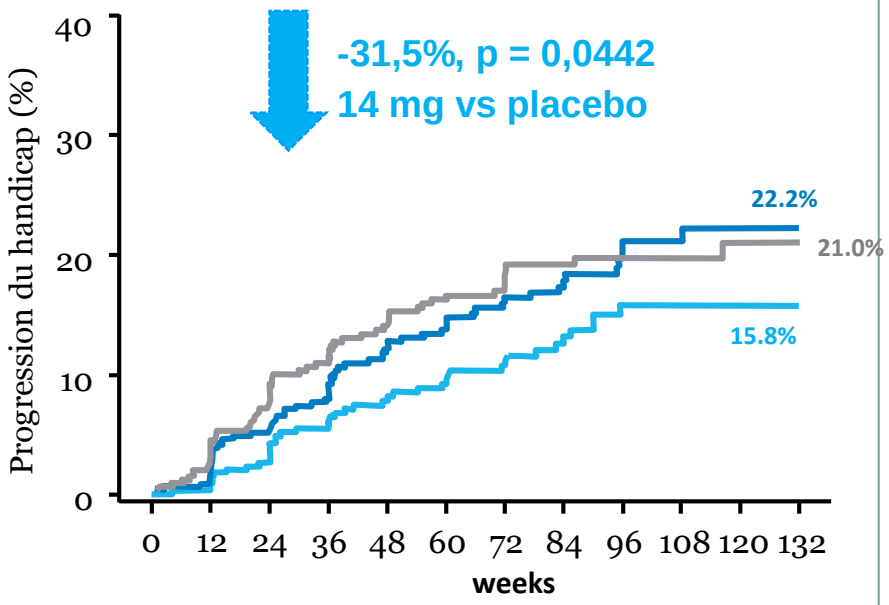
TEMSO[1]



Nombre de patients évaluables

Placebo	363	336	306	279	258	242	224	211	200	160
7 mg	365	343	309	290	266	252	238	234	224	178
14 mg	358	329	302	285	262	251	234	227	217	175

TOWER[2]

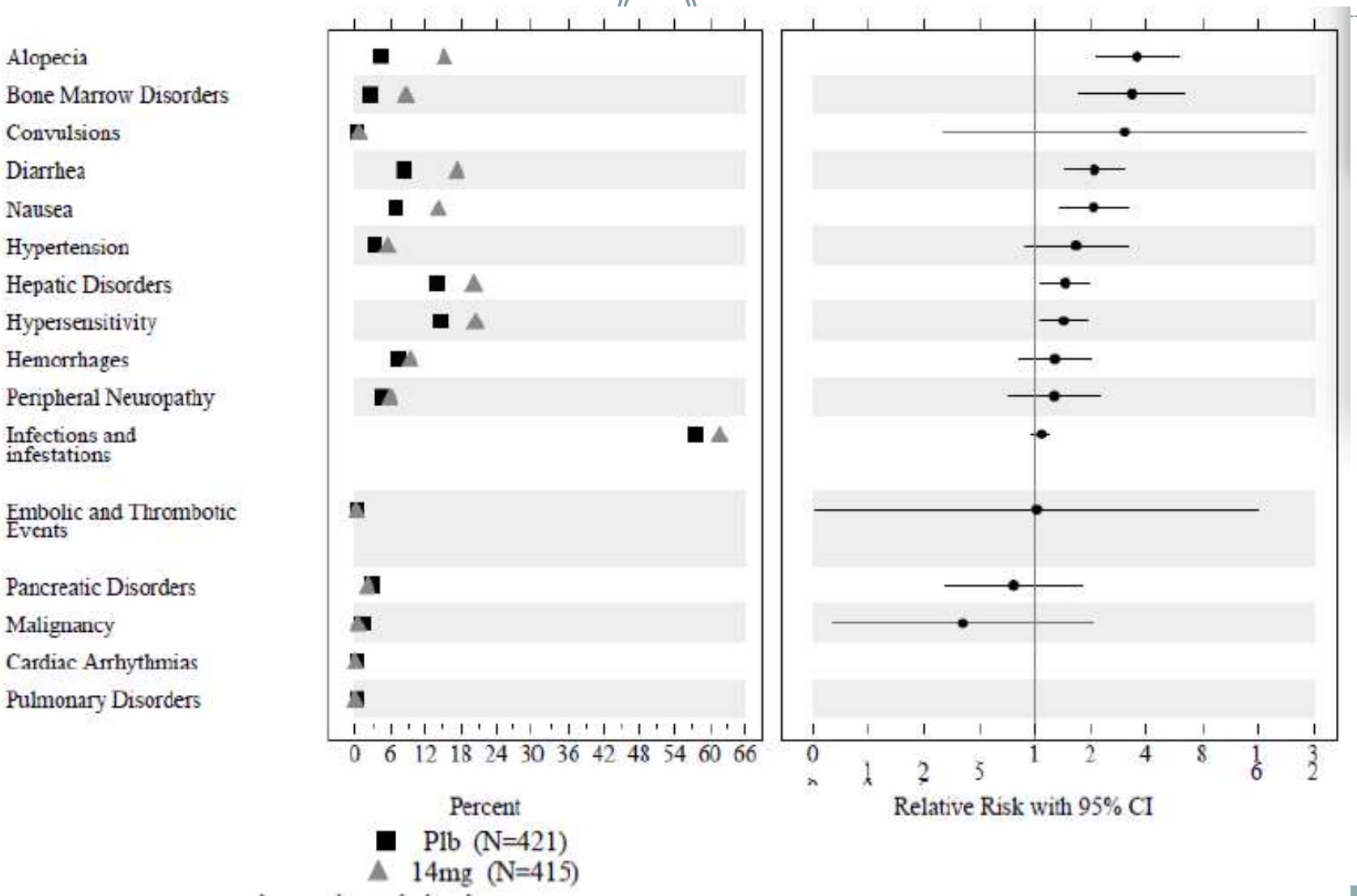


Placebo	388	354	325	295	271	241	195	156	128	83	57	33
7 mg	406	375	337	314	286	248	202	163	114	77	61	38
14 mg	370	340	310	286	267	245	211	162	124	87	63	40

Placebo Teriflunomide 7 mg Teriflunomide 14 mg

1. O'Connor et al. N Engl J Med 2011;365:1293-303; 2. Confavreux et al. Lancet Neurol 2014 Jan 22 [Epub ahead of print]

Adverse events of special interest



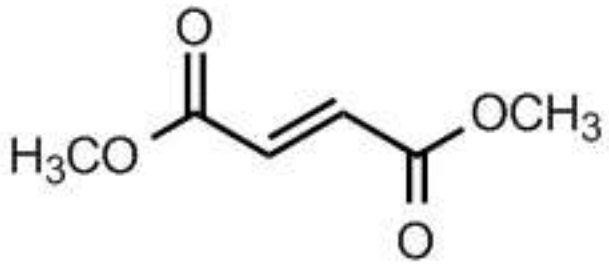
Pregnancy outcomes from the teriflunomide clinical development programme

Embryolethality and teratogenicity observed in animal studies

Table 1. Pregnancy Outcomes in Female Patients

	Pregnancy outcome, n			
Treatment	Live birth	Induced abortion	Spontaneous abortion	Ongoing pregnancy
Teriflunomide	21	28	13	7
Placebo	2	6	1	0
Interferon beta	2	0	0	0
Screen failure	0	1	0	0

All newborns born from mothers or fathers exposed to Teriflunomide had no structural or functional abnormalities at birth



dimethyl fumarate (BG-12)

Anti-inflammatory and neuroprotective agent

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 20, 2012 VOL. 367 NO. 12

Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis

Robert J. Fox, M.D., David H. Miller, M.D., J. Theodore Phillips, M.D., Ph.D., Michael Hutchinson, F.R.C.P., Eva Havrdova, M.D., Mariko Kita, M.D., Minhua Yang, M.S., Kartik Raghupathi, M.S., Mark Novas, M.D., Marianne T. Sweetser, M.D., Ph.D., Vissia Viglietta, M.D., Ph.D., and Katherine T. Dawson, M.D., for the CONFIRM Study Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

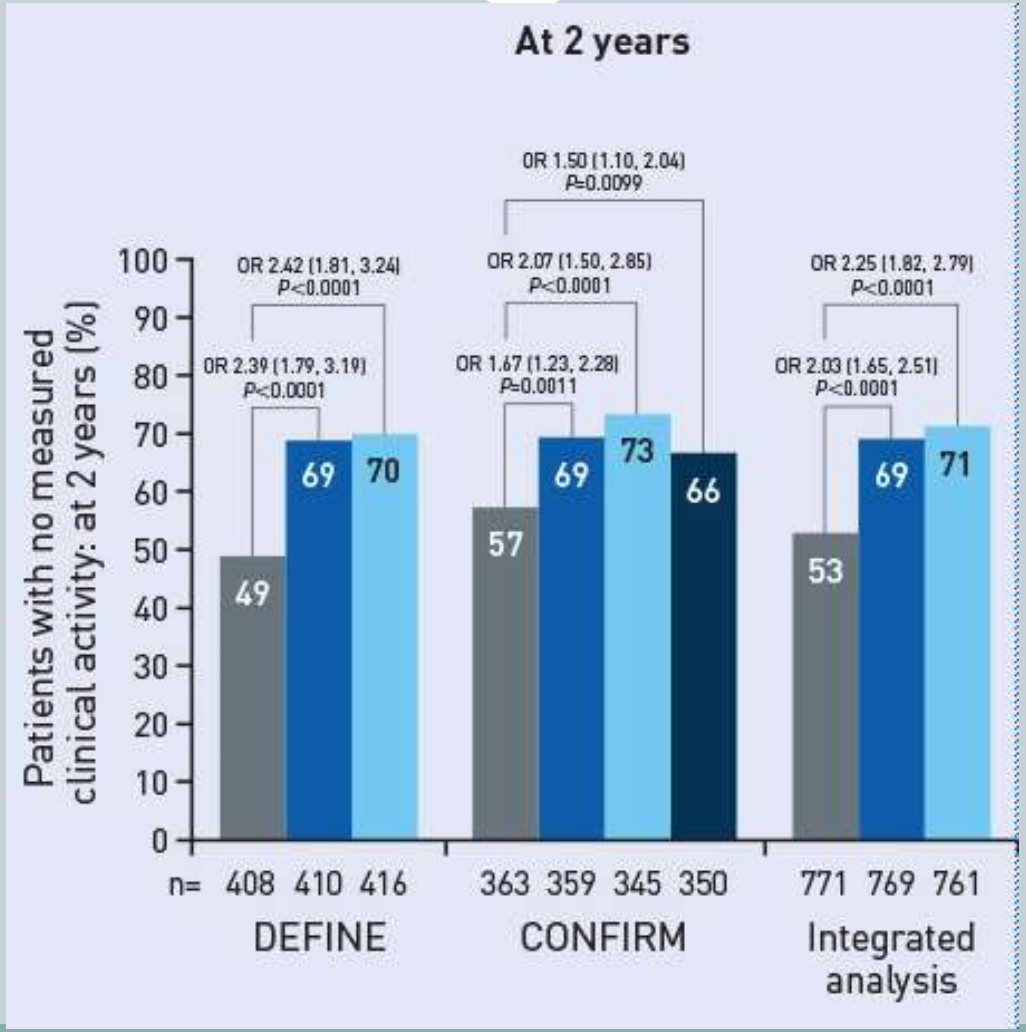
ORIGINAL ARTICLE

Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis

Ralf Gold, M.D., Ludwig Kappos, M.D., Douglas L. Arnold, M.D., Amit Bar-Or, M.D., Gavin Giovannoni, M.D., Krzysztof Selmaj, M.D., Carlo Tornatore, M.D., Marianne T. Sweetser, M.D., Ph.D., Minhua Yang, M.S., Sarah I. Sheikh, M.D., and Katherine T. Dawson, M.D., for the DEFINE Study Investigators*

biogen idec

Proportion of patients without clinical activity at 2 years

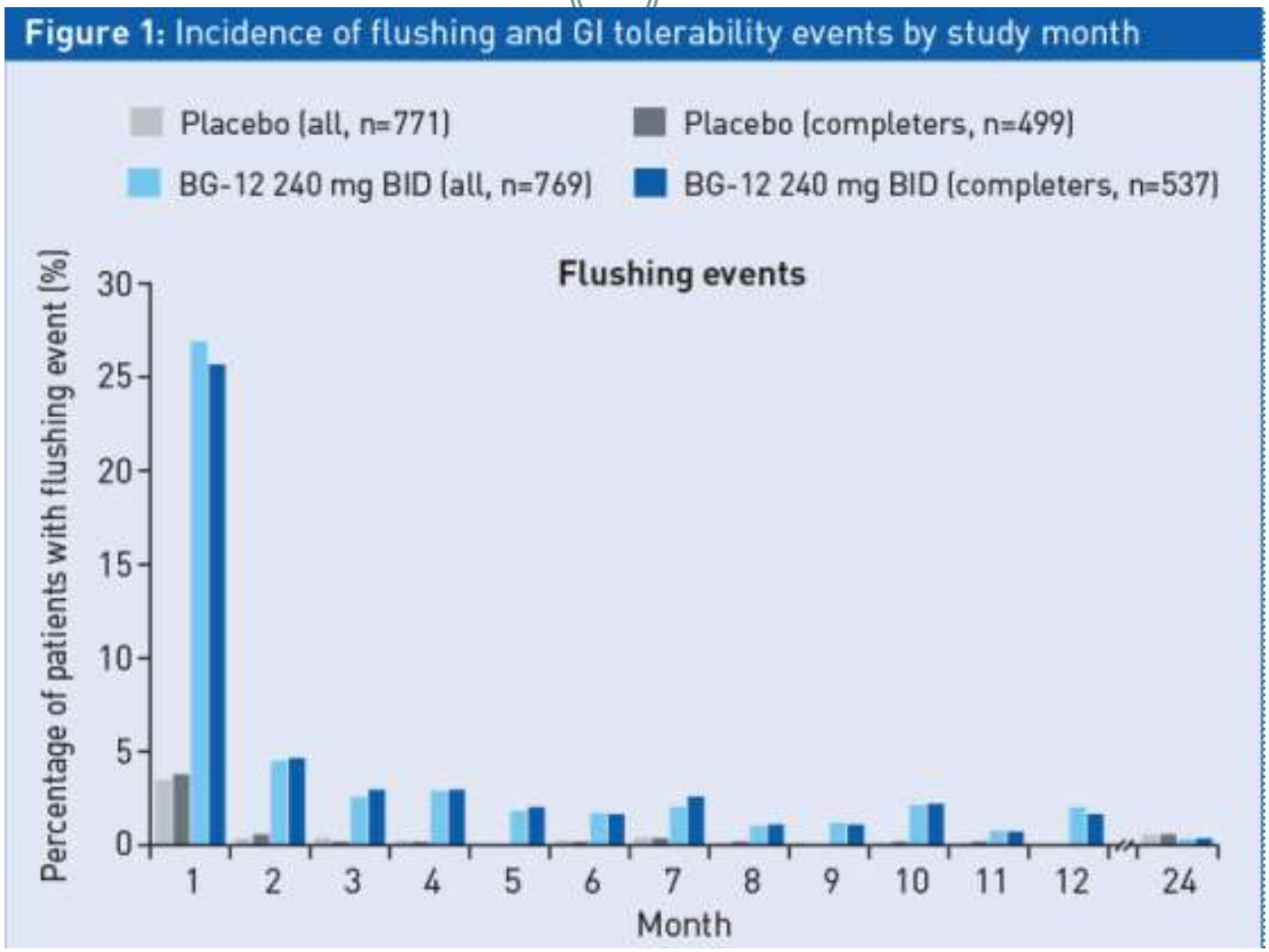


Side effects

Table 3. Adverse and Serious Adverse Events.*

Adverse Event	Placebo (N = 408)	Twice-Daily BG-12 (N = 410)	Thrice-Daily BG-12 (N = 416)
	number of patients (percent)		
Any adverse event	387 (95)	395 (96)	396 (95)
Most frequently reported adverse events†			
Flushing	20 (5)	154 (38)	132 (32)
Multiple sclerosis relapse	189 (46)	111 (27)	114 (27)
Diarrhea	55 (13)	62 (15)	78 (19)
Nausea	38 (9)	53 (13)	54 (13)
Upper abdominal pain	28 (7)	40 (10)	52 (12)
Proteinuria	34 (8)	38 (9)	50 (12)
Abdominal pain	22 (5)	46 (11)	37 (9)
Pruritus	19 (5)	42 (10)	34 (8)
Vomiting	24 (6)	40 (10)	30 (7)

Incidence of flushing event by study months



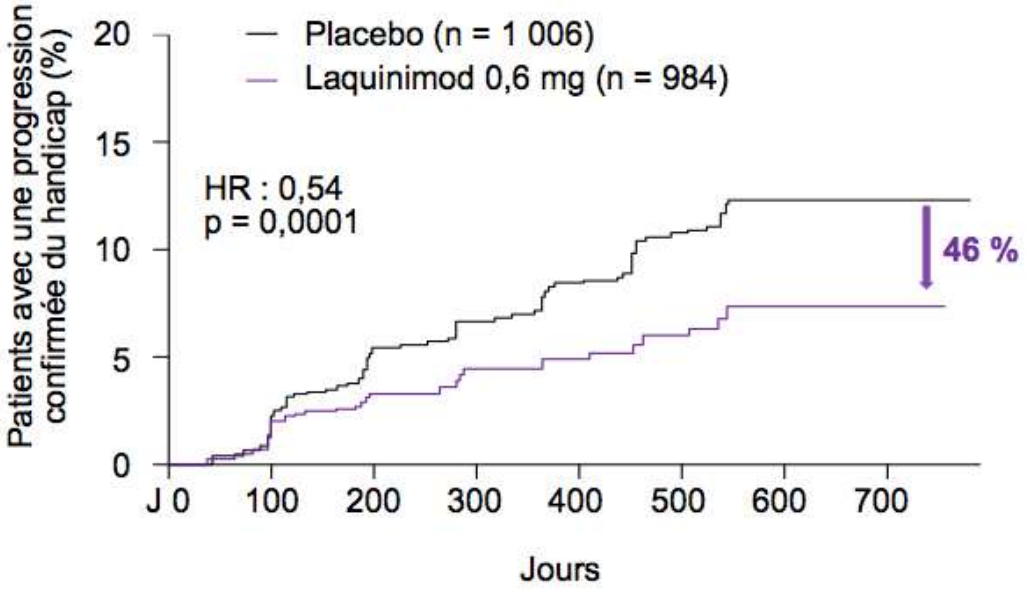
Long term risk ?

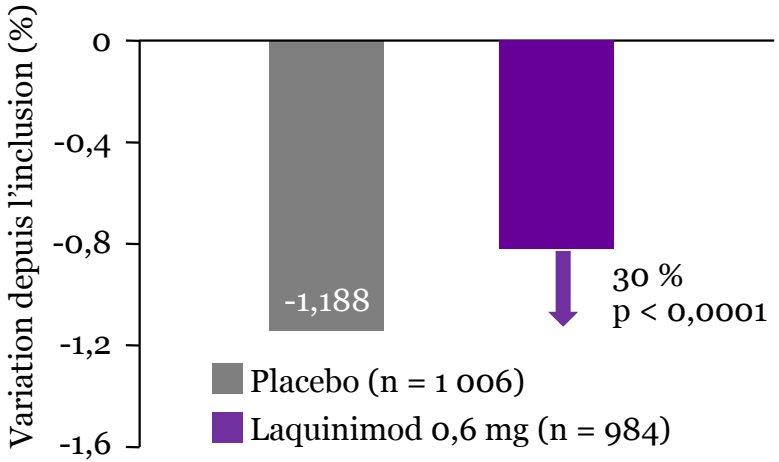
PML in a Patient Treated with Fumaric Acid

PML in a Patient Treated with Dimethyl Fumarate from a Compounding Pharmacy

Laquinimod
ALLEGRO and BRAVO *studies*

- Reduction of the risk of clinical impairment
- Brain atrophy

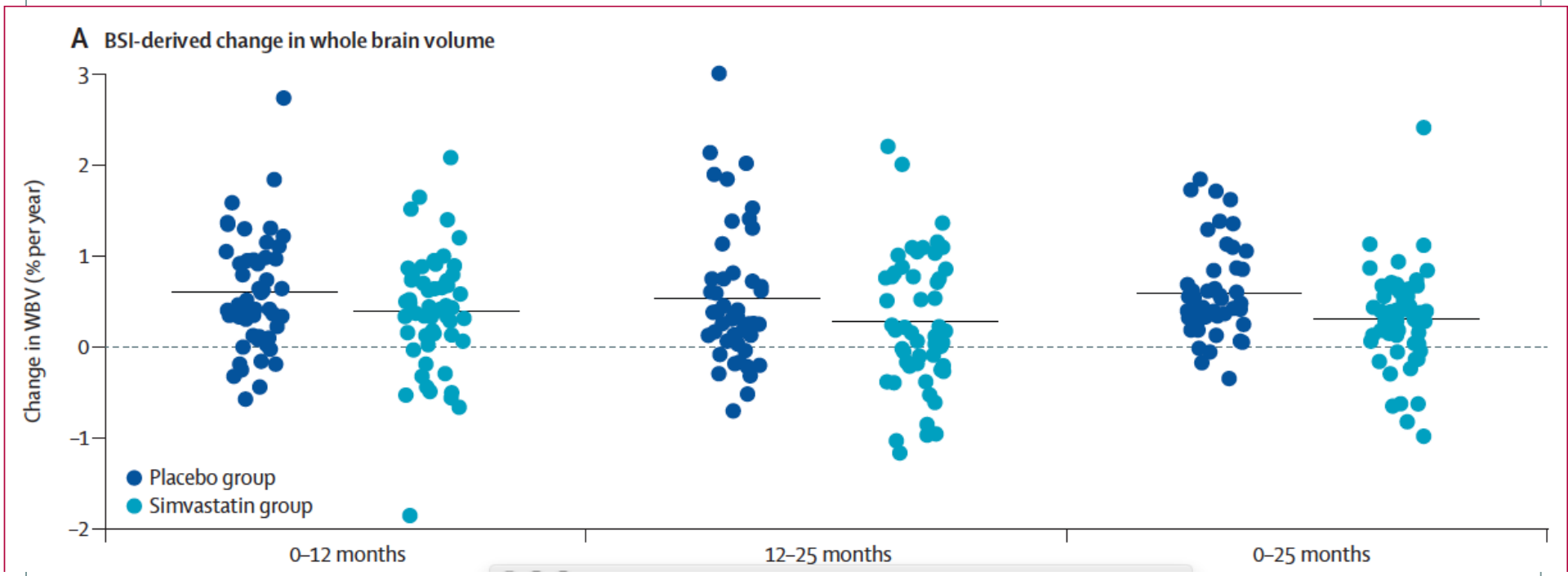




AAN 2012 – D'après Vollmer T et al., Abstr. S01.007, actualisé

Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial

Jeremy Chataway, Nadine Schuerer, Ali Alsanousi, Dennis Chan, David MacManus, Kelvin Hunter, Val Anderson, Charles R M Bangham, Shona Clegg, Casper Nielsen, Nick C Fox, David Wilkie, Jennifer M Nicholas, Virginia L Calder, John Greenwood, Chris Frost, Richard Nicholas



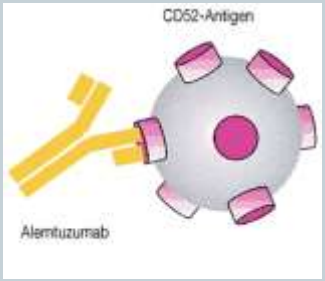
Selective immunosuppression

- LEMTRADA (ALEMTUZUMAB) ; GENZYME
- DACLIZUMAB
- OFATUMUMAB
- OCRELIZUMAB
- RITUXIMAB
- SECUKINUMAB

Lemtrada (alemtuzumab Genzyme)

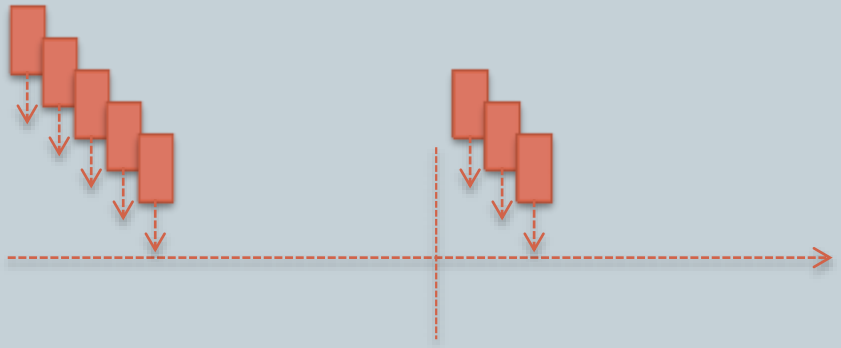
Mode of action

- Monoclonal antibody
- Depletion of the blood lymphocytes count
- Immunosuppressive



Administration

12 mg/day for 5 days



Y1 Y2

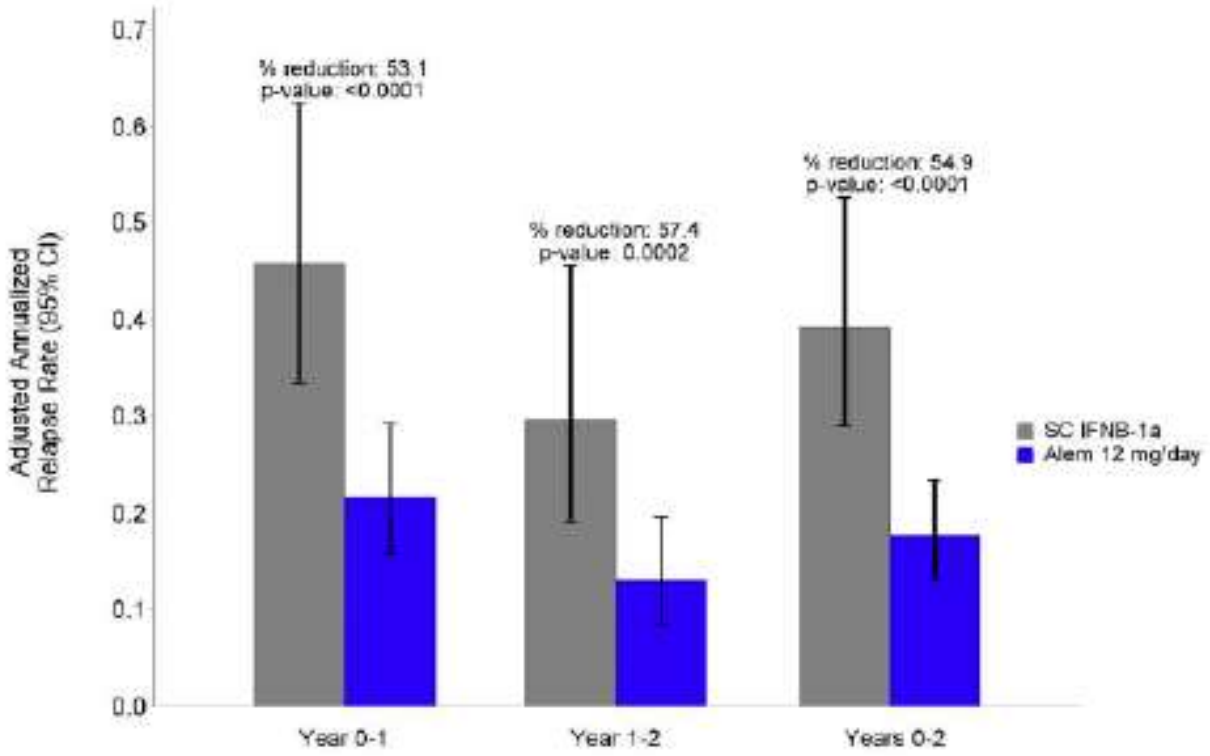
12 mg/day for 3 days

LEMTRADA is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features

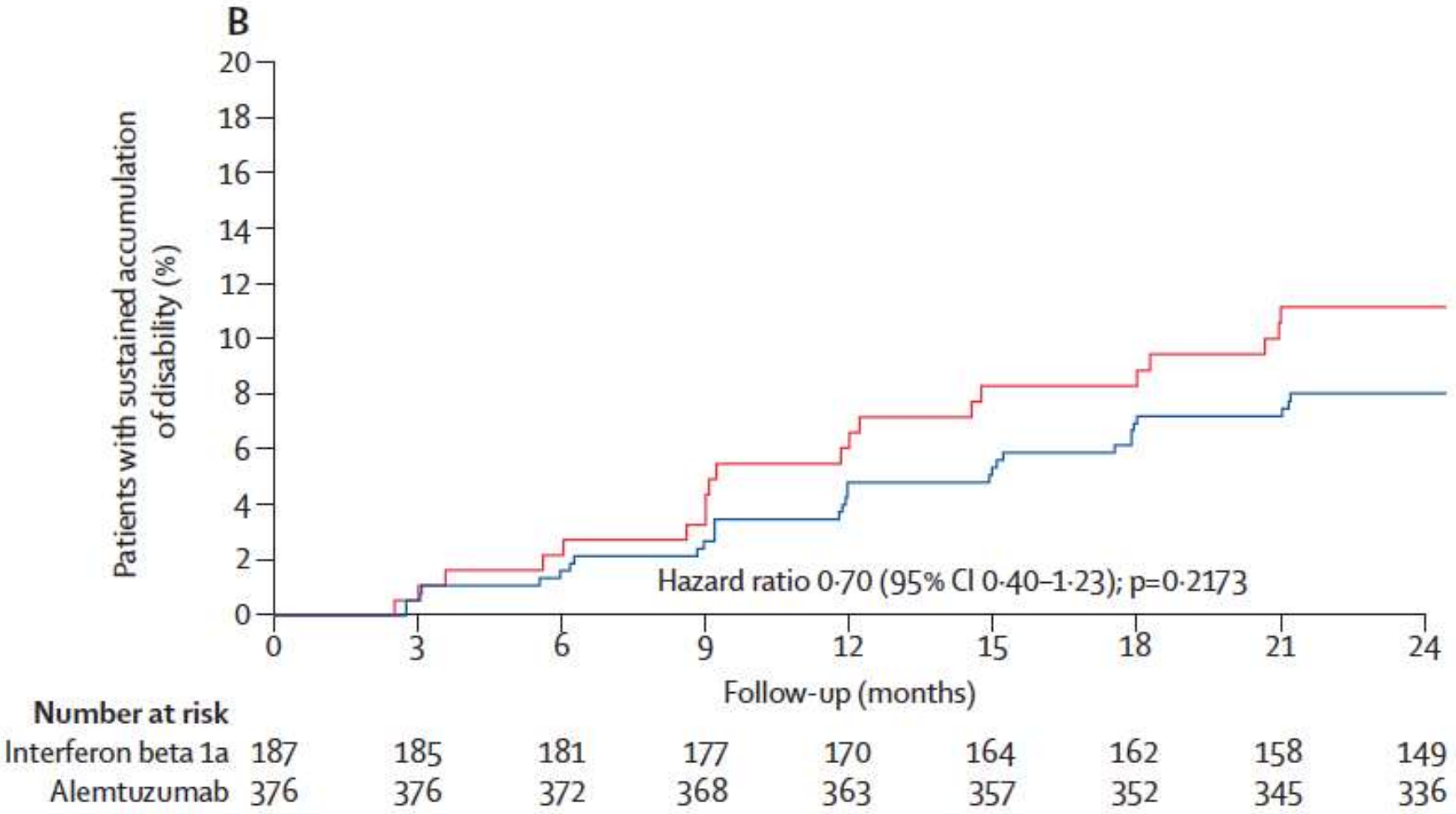
Two phase III studies compared the efficacy of Alemtuzumab to Interferon b-1a

Compared with IFNB-1a, alemtuzumab reduced the relapse rate by 53% in Year 1 and 57% in Year 2 Figure 5.

Figure 5 – Annualised relapse rate (ARR) by time interval: Full analysis set



30% reduction of the risk of sustained disability



Alemtuzumab : adverse events

- Infusion-associated reactions
- Infections
- Auto-immune diseases
  - Thyroiditis
  - nephropathies
  - Immune thrombocytopenia

Humanised monoclonal antibody which depletes circulating B lymphocytes

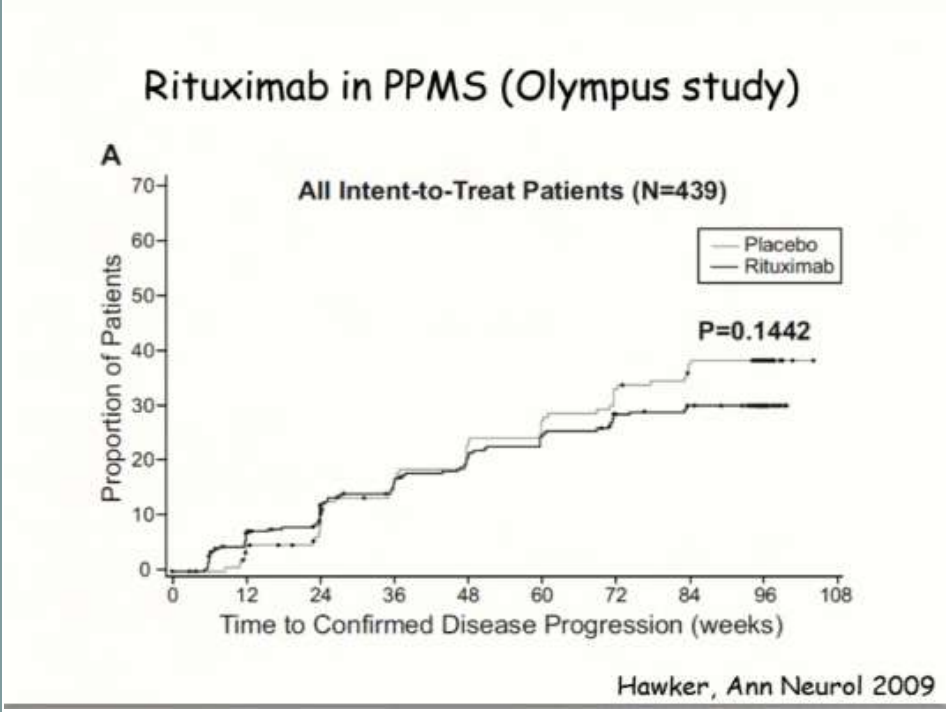
Binds to CD20 like Rituximab

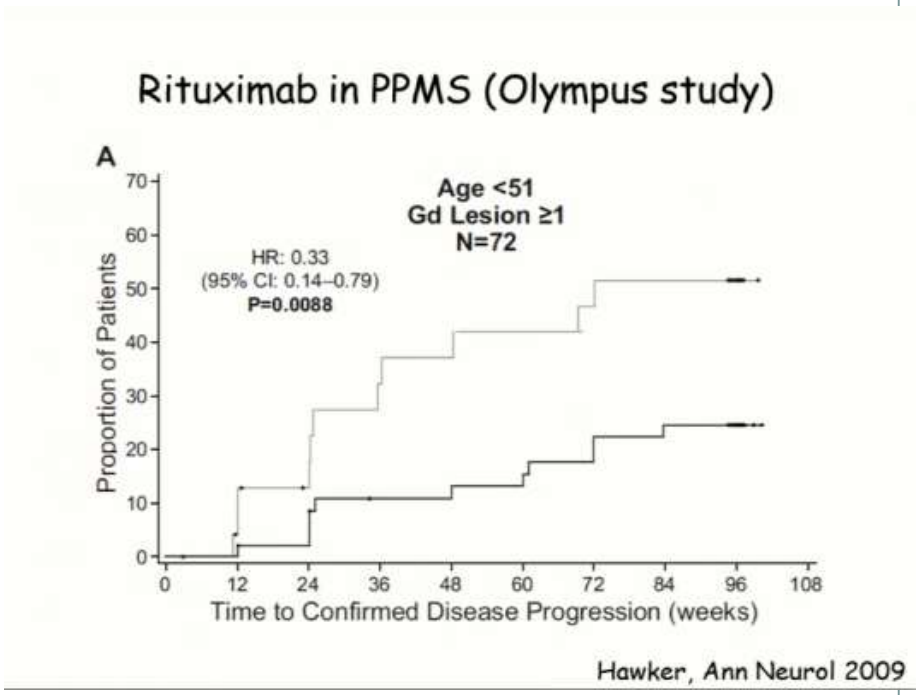
Two phases II studies showed an effect on MRI and relapse rate

Study
A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Patients With Relapsing Sclerosis **Condition:** Multiple Sclerosis, Relapsing-Remitting **Interventions:** Drug: ocrelizumab; Drug: Rebif; Drug: ocrelizumab placebo; Drug: Rebif
A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Patients With Relapsing Sclerosis **Condition:** Multiple Sclerosis, Relapsing-Remitting **Interventions:** Drug: ocrelizumab; Drug: Rebif; Drug: ocrelizumab placebo; Drug: Rebif
A Study of Ocrelizumab in Patients With Primary Progressive Multiple Sclerosis **Condition:** Multiple Sclerosis, Primary Progressive **Interventions:** Drug: ocrelizumab; Drug: Placebo; Drug: methylprednisolone
A Study of the Efficacy and Safety of Ocrelizumab in Patients With Relapsing-Remitting Multiple S **Condition:** Multiple Sclerosis, Relapsing-Remitting **Interventions:** Drug: ocrelizumab; Drug: placebo; Drug: methylprednisolone; Drug: inte
Assessment of Ocrelizumab (OCR) Treatment Effects on Functional Impairment of MS Patients En Phase III Orchestra Programme Using Multimodal Evoked Potentials (EP) and Highresolution Electroencephalography (EEG)

Ocrelizumab

Rituximab in PP-MS : OLYMPUS study





Neuroprotective drugs

AMILORIDE
LAMOTRIGINE
TOPIRAMATE
RILUZOLE

Remyelination

ANTI-LINGO 1 ANTIBODY

Anti-LINGO1

- LINGO1 : inhibitor of oligodendrocyte differentiation and myelination
- In vitro studies : anti-LINGO1 promotes oligodendrocyte differentiation and myelination
- Animal studies : reduction of disease severity and evidence of remyelination
- Phase 1 completed : no serious adverse events
- Phase 2 is ongoing in optic neuritis

Cell therapy in MS

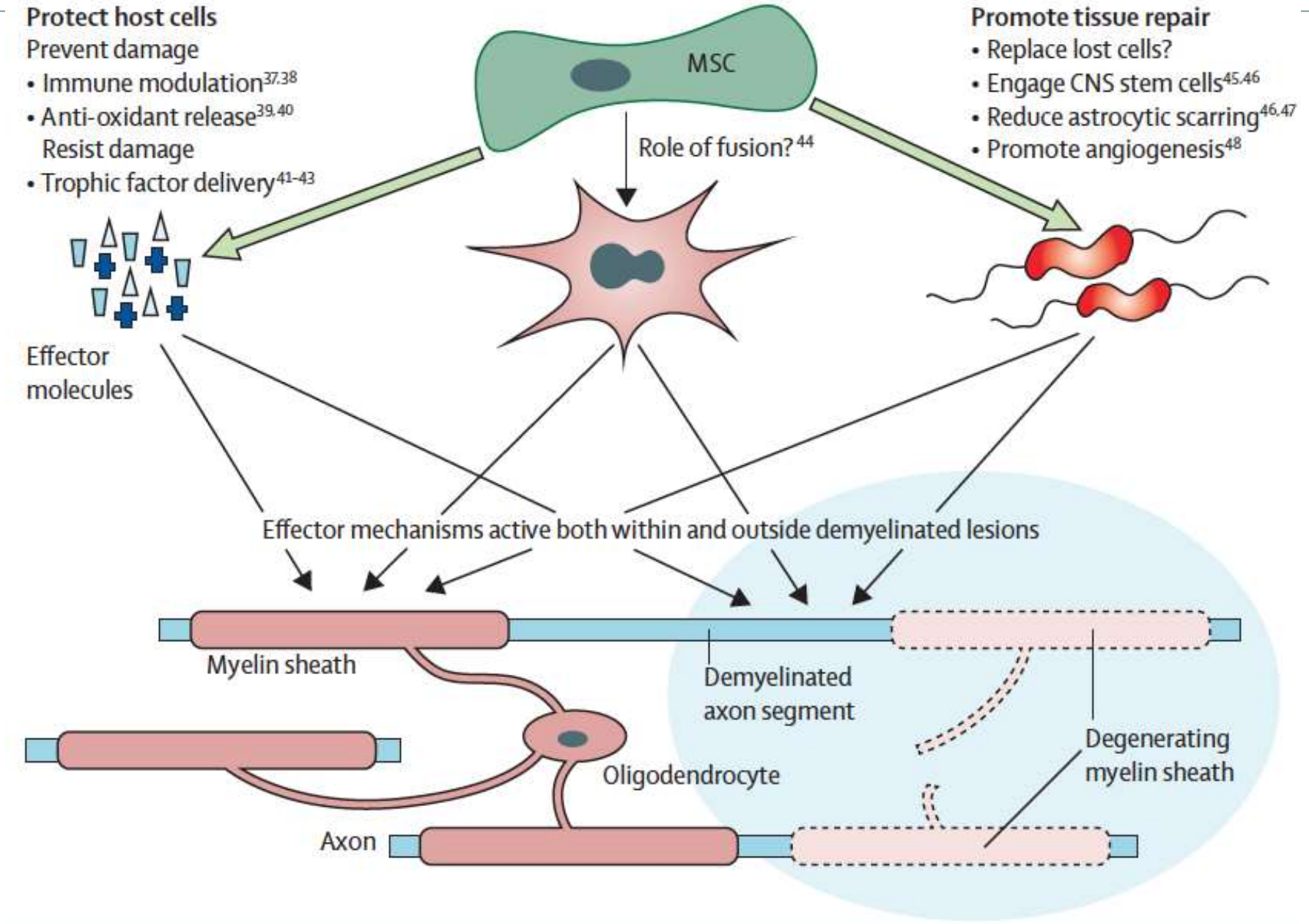


Figure 2: **Potential mechanisms of bone-marrow-cell-mediated repair**
MSC=mesenchymal stem cell.

PREVENTION

Prévention

tobacco	• Increases the risk and the severity of MS
Salt	• Increases the severity of MS
weight	• Increases the risk of MS
D Vitamin	• Increases the risk of MS and (perhaps) the severity; supplémentation?

Summary and conclusions

- New treatments with different mode of actions are upcoming for RR and progressive MS
- New strategies should be proposed to improve the rate of responder and minimize the adverse events
- Identifying early bad responders is a challenging issue
- Long term registries to evaluate safety are mandatory
- Prevention of MS in high risk people is a new field of research
- Cell therapy might be the next revolution in MS treatment