News on modifying diseases therapies

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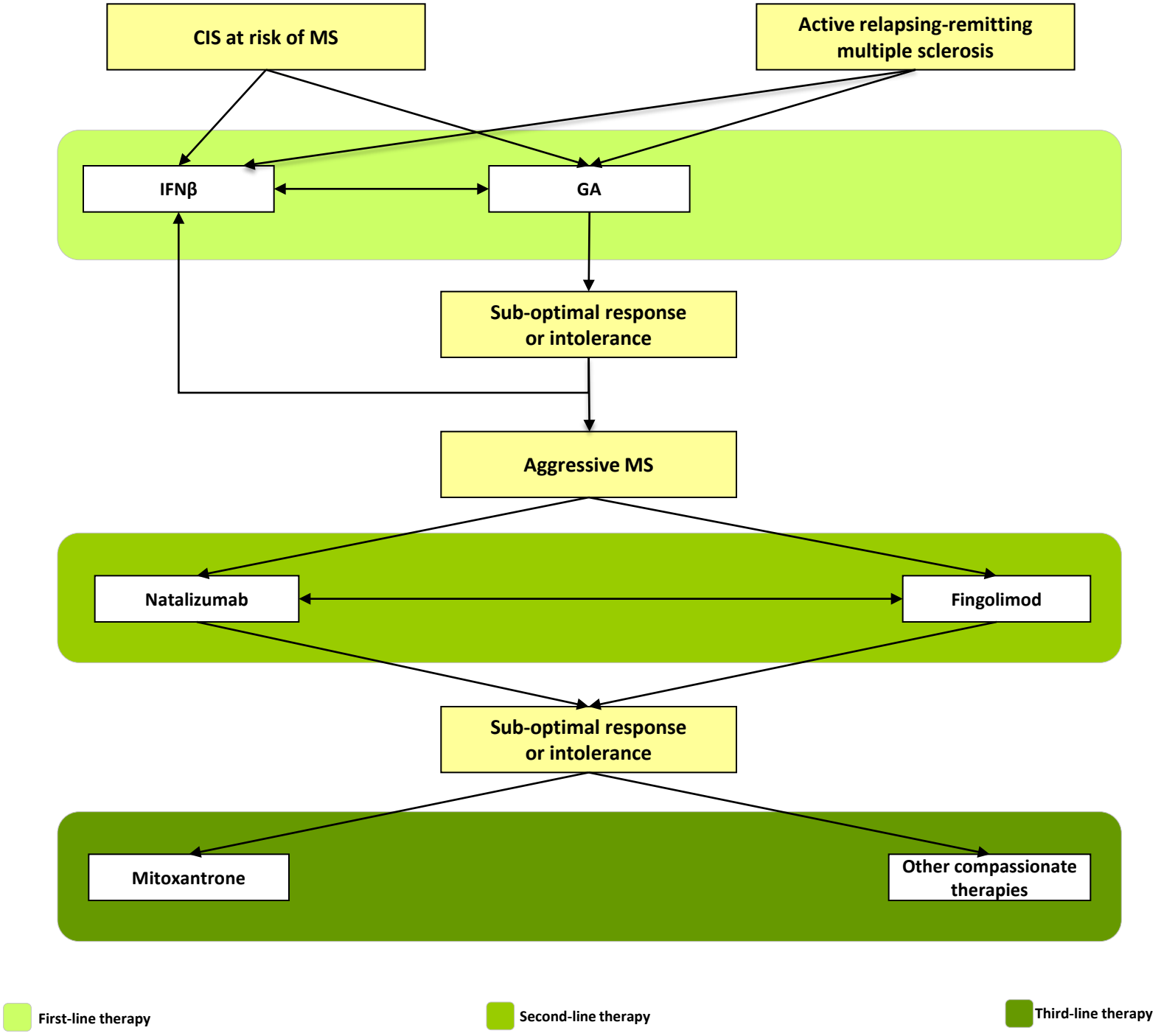
CHU Toulouse France

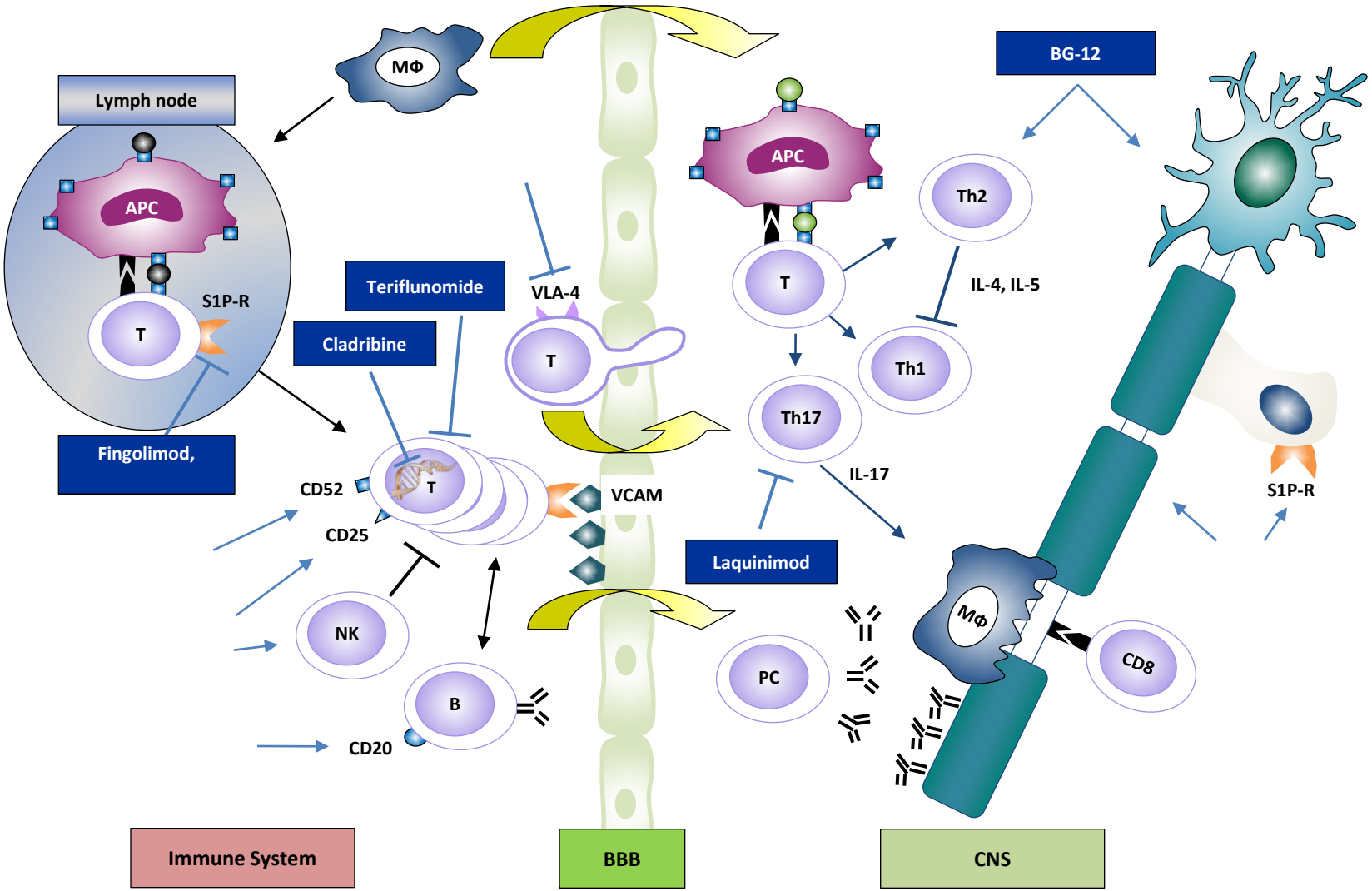
ECTRIMS

- Current treatment strategies
- Future oral treatments
- Future non oral treatments
- Drug safety and risks


CIS at risk of MS
Active relapsing-remitting multiple sclerosis
IFNβ
GA
Sub-optimal response or intolerance
Aggressive MS
Natalizumab
Fingolimod
Sub-optimal response or intolerance
Mitoxantrone
Other compassionate therapies
First-line therapy
Second-line therapy
Third-line therapy

Future oral treatments

Molecules in development for Multiple Sclerosis act on multiple pathways and therapeutic targets



APC, antigen presenting cell; BBB, blood/brain barrier; CNS, central nervous system; IFN, interferon; S1P-R, sphingosine 1-phosphate receptor; TNF, tumour necrosis factor

Image adapted from: Linker RA *et al. Trends Pharmacol Sci* 2008

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 17 February 2011
Doc.Ref.: EMA/108602/2011

Assessment report

Gilenya

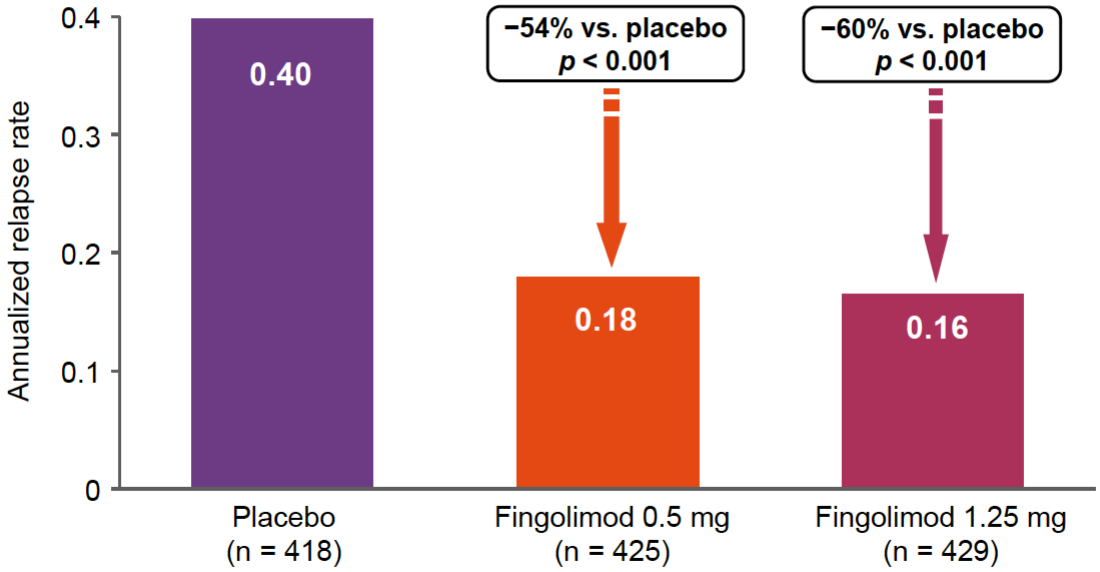
International nonproprietary name: Fingolimod

"Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.

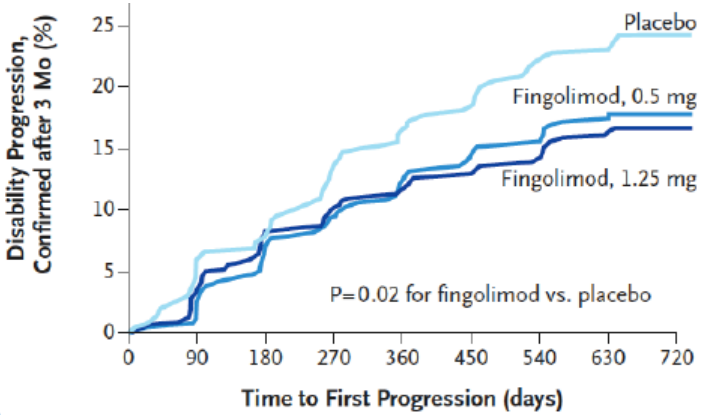
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI".

FREEDOMS:
Primary endpoint – annualized relapse rate

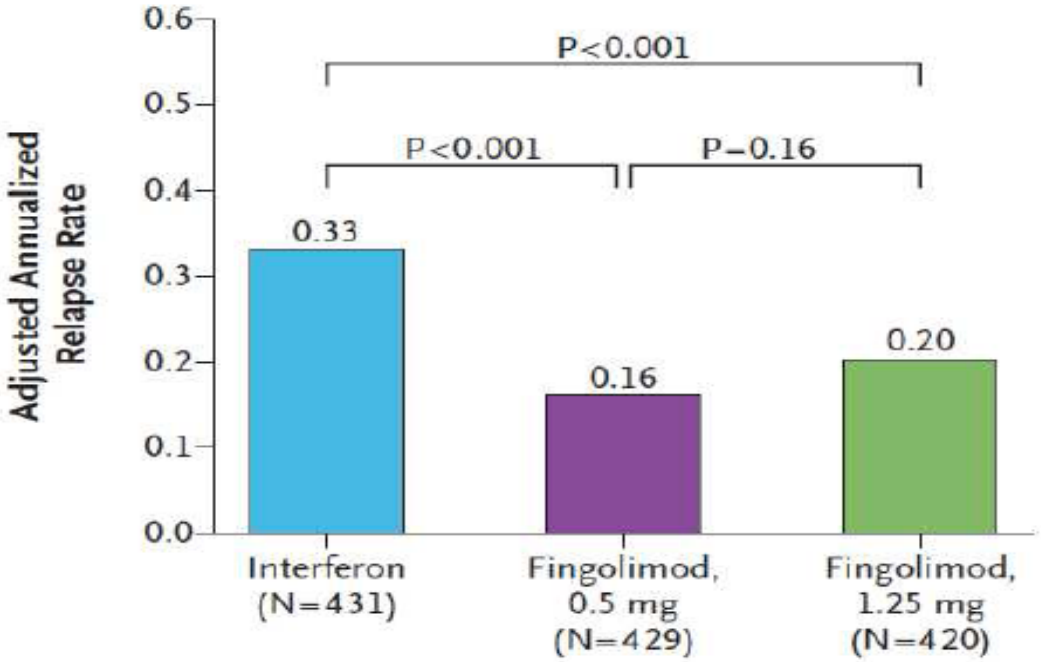


ITT population, Negative binomial regression model adjusted for treatment group, country, number of relapses in previous two years and baseline Expanded Disability Status Scale (EDSS) as covariates

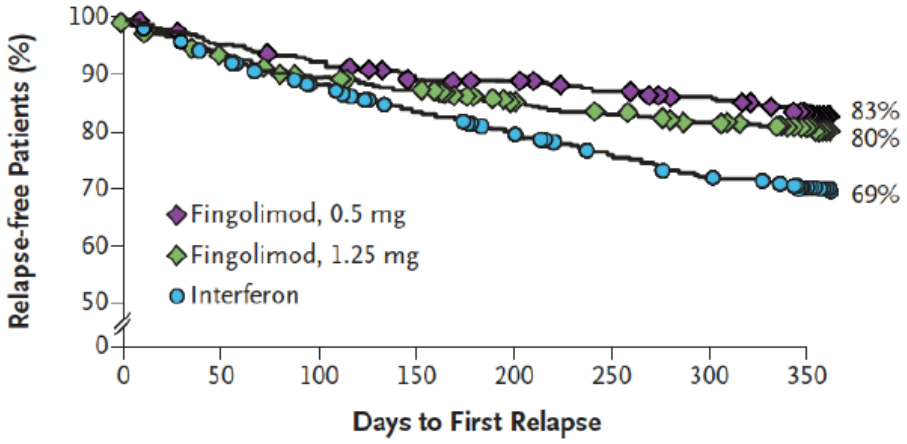
FREEDOMS



No. at Risk									
Fingolimod, 1.25 mg	429	401	373	356	344	332	322	305	165
Fingolimod, 0.5 mg	425	416	388	370	354	340	332	321	152
Placebo	418	391	371	341	320	308	290	279	143


Adjusted Annualized Relapse Rate
0.6
0.5
0.4
0.3
0.2
0.1
0.0
P<0.001
P<0.001
P=0.16
0.33
0.16
0.20
Interferon (N=431)
Fingolimod, 0.5 mg (N=429)
Fingolimod, 1.25 mg (N=420)

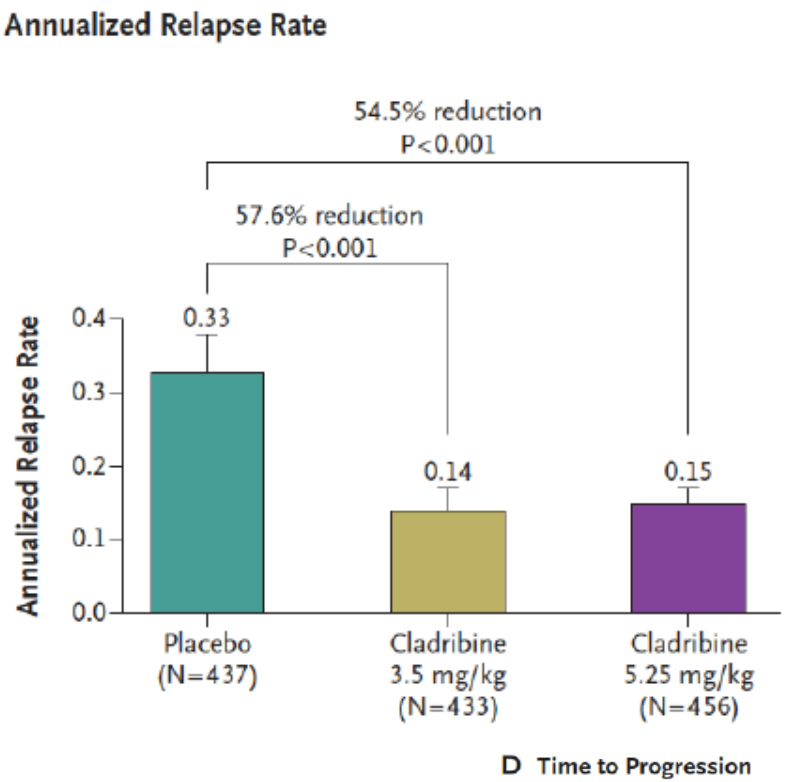
TRANSFORMS


Relapse-free Patients (%)
100
90
80
70
60
50
0
0
50
100
150
200
250
300
350
Days to First Relapse
Fingolimod, 0.5 mg
Fingolimod, 1.25 mg
Interferon
83%
80%
69%

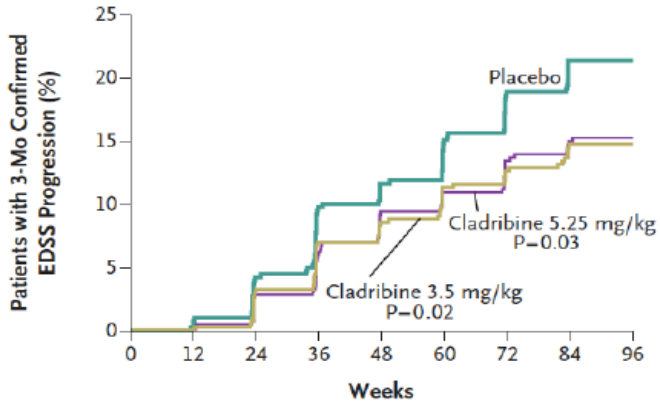
Safety profile

- Uncertainty on safety related to fingolimod biological profile
  - Cardio-vascular disorders, macular edema, respiratory disorders, lymphopenia, liver dysfunction,
  - Infections
  - Neoplasms
  - Teratogenicity
- Registration with risk management plan

Cladribin



CLARITY Trial



No. at Risk									
Placebo	437	424	399	373	355	333	315	304	304
Cladribine 3.5 mg/kg	433	424	407	389	379	364	355	347	347
Cladribine 5.25 mg/kg	456	447	425	404	388	375	363	350	350

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Refusal of the marketing authorisation for Movectro (cladribine)

What were the CHMP's main concerns that led to the refusal?

In September 2010 the CHMP had concerns about the medicine's safety. An increased number of patients with cancer were observed in clinical trials with Movectro compared to the control group. The Committee also noted that the benefits and the most appropriate dosage for treatment had not been fully established in patients who were expected to use the medicine. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Movectro did not outweigh its risks and recommended that it be refused marketing authorisation.

In January 2011, the CHMP's main concerns were not resolved during the re-examination procedure. In particular it was still concerned about Movectro's long term safety, even if the medicine were to be used in the restricted group of patients. Therefore the Committee confirmed its initial negative opinion.

Teriflunomide

TEMSO

1088 patients randomised:

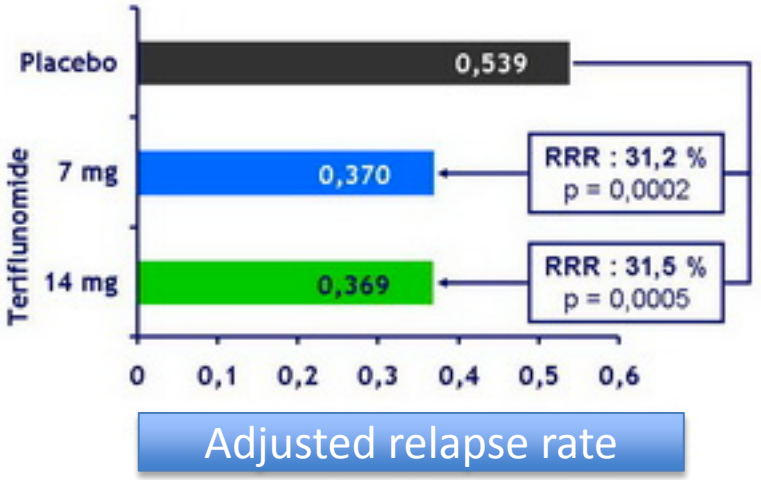
Placebo n = 363
Teriflunomide 7 mg n = 366
Teriflunomide 14 mg n = 359

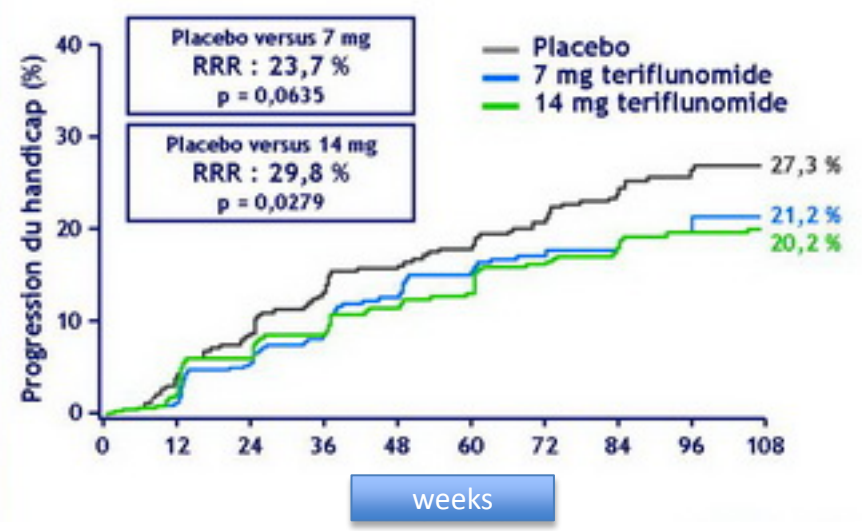
Treatment 2 years

Safety:
No severe adverse event

ECTRIMS 2010

New data confirming the first results presented at AAN 2011

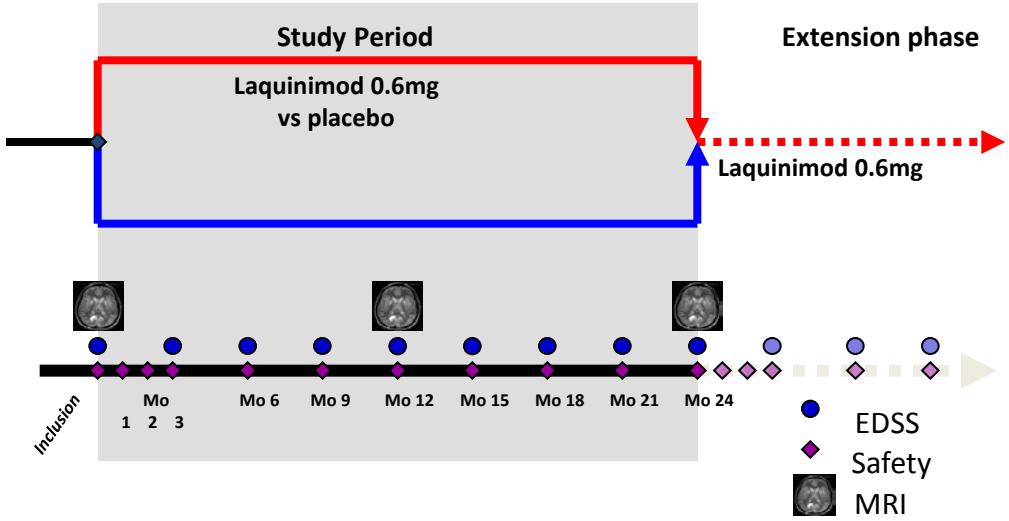




ALLEGRO STUDY DESIGN
LAQUINIMOD vs PLACEBO in RR MS PATIENTS

- **Randomized multicentric double blind study:**
  - Laquinimod 0.6 mg/day : 550 patients
  - Placebo : 556 patients
  - Study duration: 24 months

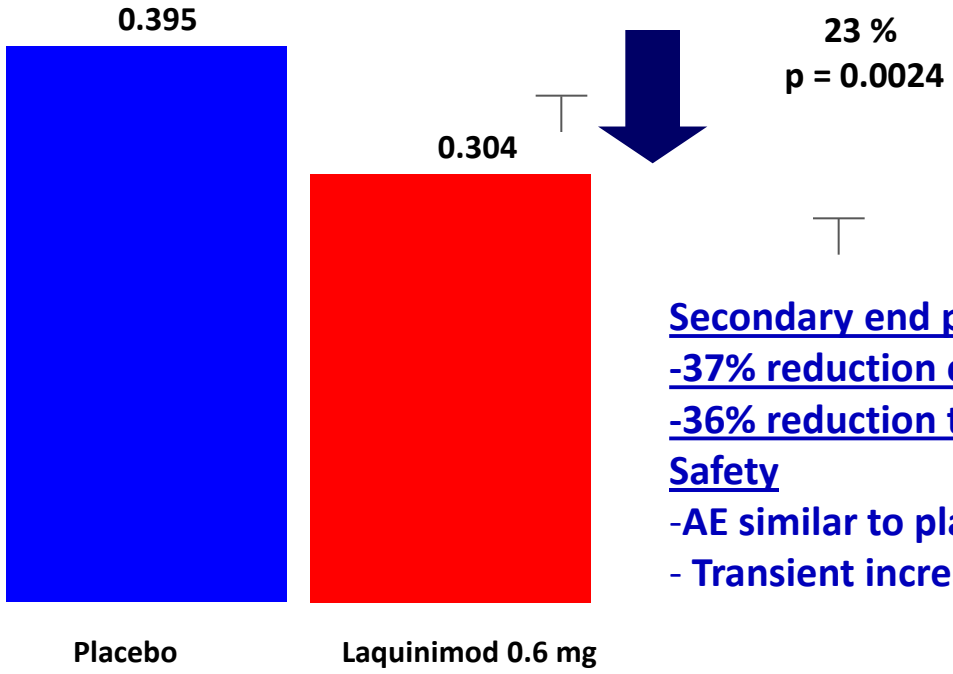
Study design



- **Endpoints**
  - Primary : annualised relapse rate
  - Secondary : sustained progression of disability, (EDSS), (MSFC), cumulative number of Gd + lesions, new T2 lesions, deterioration of brain atrophy

ALLEGRO TRIAL
PHASE III LAQUINIMOD vs PLACEBO

Primary endpoint : annualised relapse rate



Secondary end point
-37% reduction cumulative number of Gd+ lesions
-36% reduction time to sustained progression disability
Safety
-AE similar to placebo
- Transient increase ALAT

Clinical§	Placebo*	BG00012 120 mg once daily	BG00012 120 mg three times daily	BG00012 240 mg three times daily
Weeks 0–24	65	64	64	63
Annualised relapse rate (95% CI)¶	0·65 (0·43–1·01)	0·42 (0·24–0·71)	0·78 (0·52–1·16)	0·44 (0·26–0·76)
p value vs placebo	..	0·196	0·572	0·272
Relapse-free	49 (75%)	53 (83%)	44 (69%)	51 (81%)
p value vs placebo‖	..	0·387	0·437	0·524
Weeks 25–48	59	58	56	52
Annualised relapse rate (95% CI)¶	0·26 (0·13–0·53)	0·24 (0·11–0·50)	0·47 (0·27–0·82)	0·16 (0·07–0·41)
Relapse-free	52 (75%)	50 (86%)	43 (77%)	48 (92%)
Weeks 0–48	59	58	56	52
Annualised relapse rate (95% CI)¶	0·41 (0·26–0·64)	0·29 (0·17–0·50)	0·60 (0·41–0·88)	0·28 (0·16–0·50)
Relapse-free	40 (68%)	44 (76%)	32 (57%)	40 (77%)

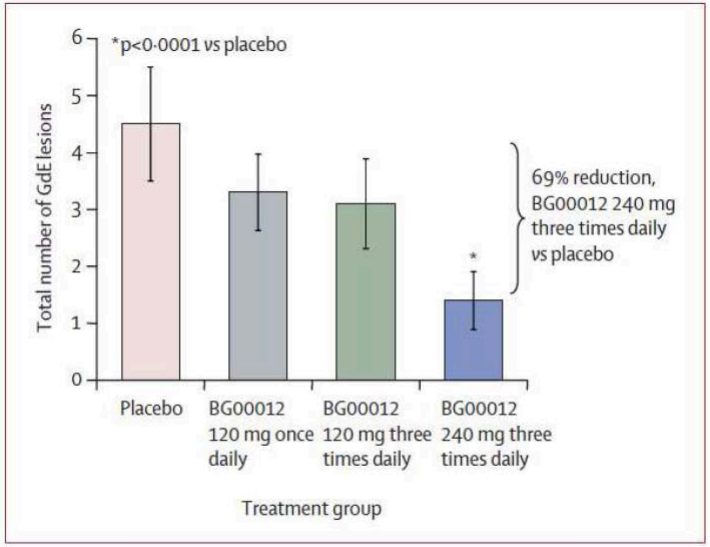


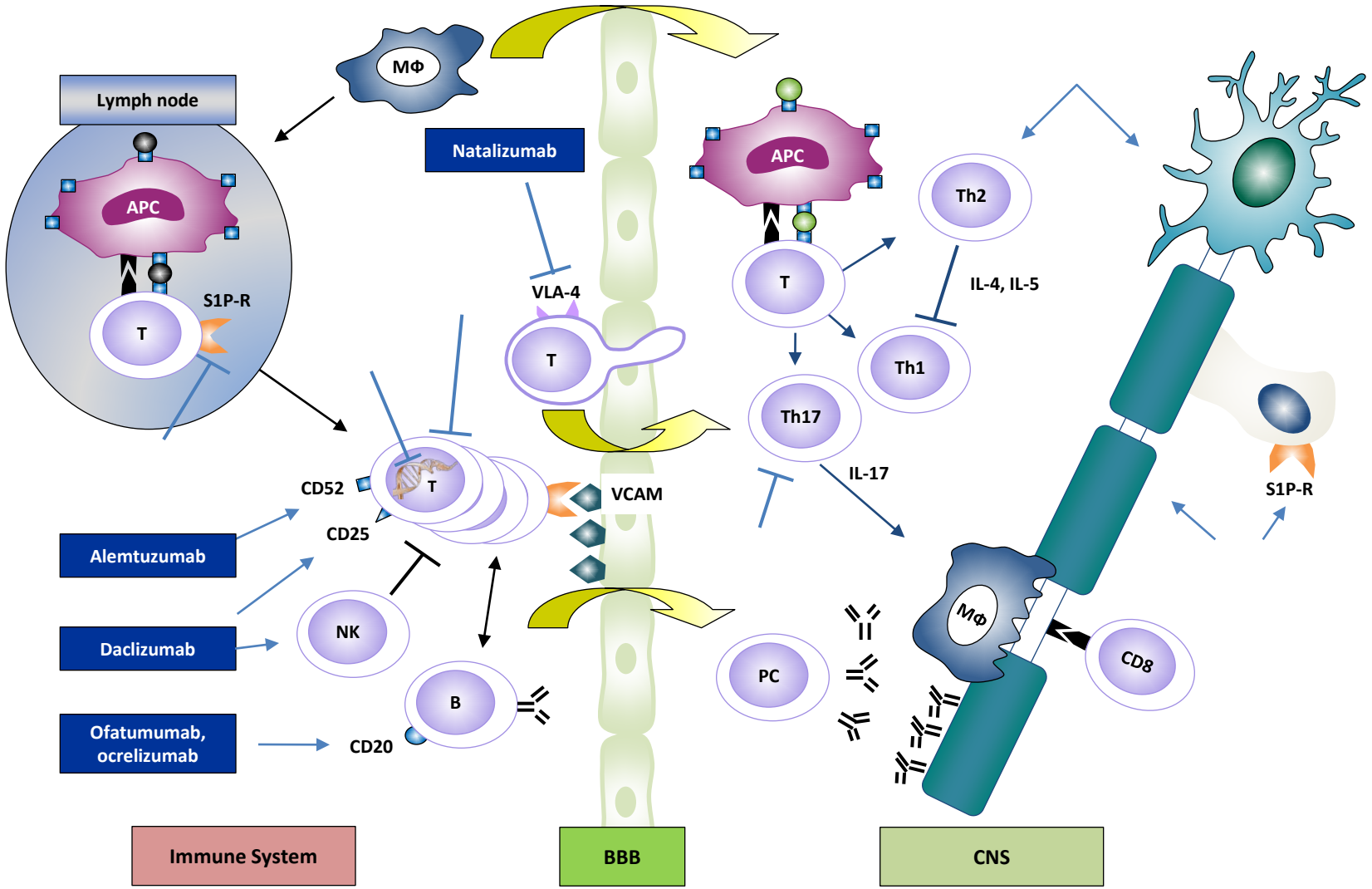
Figure 3: **Mean total number of GdE lesions from scans at weeks 12, 16, 20, and 24 combined**
Vertical bars=SE.

Fumarate (BG12)

Kappos et al Lancet 2008

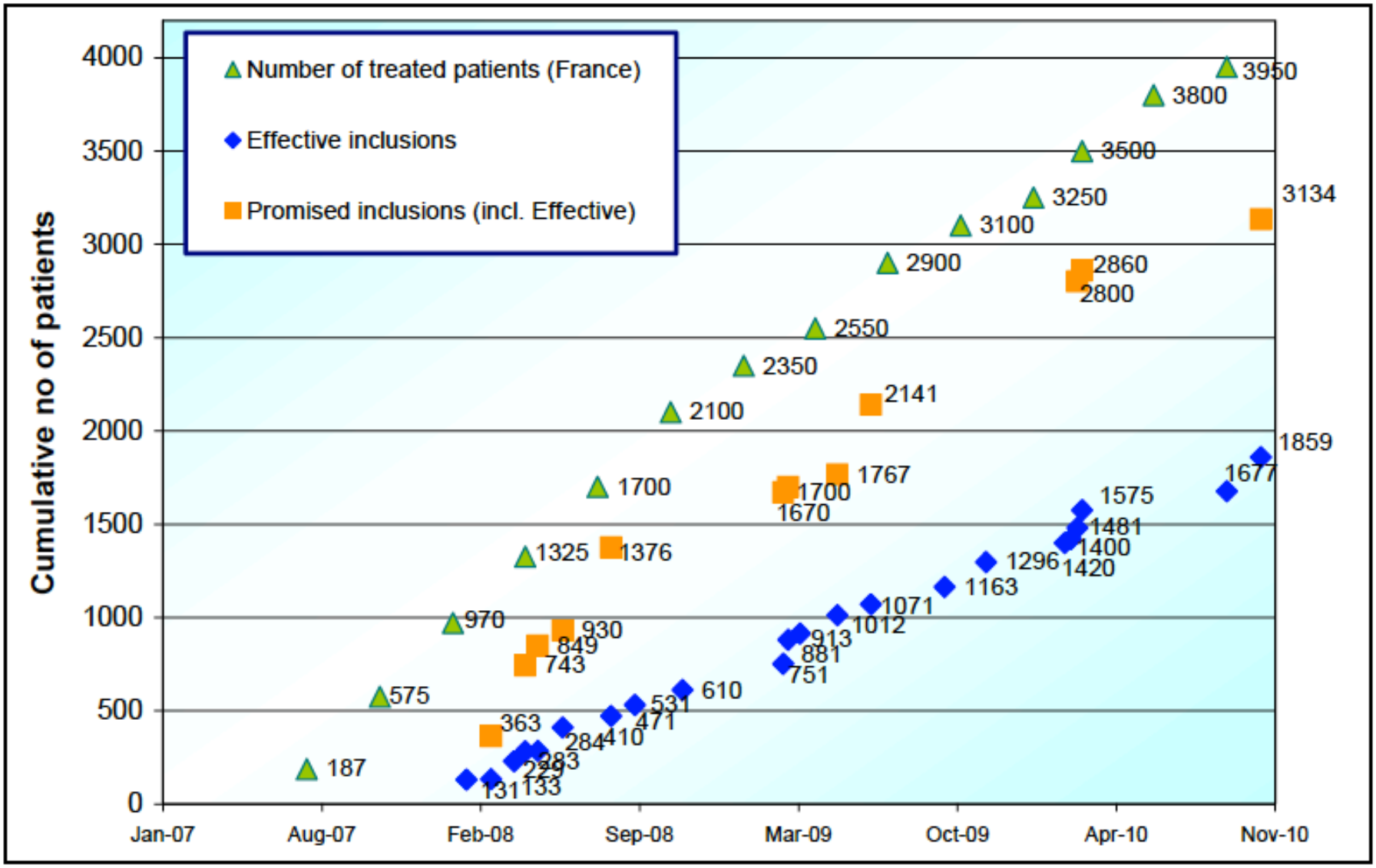
Future non oral treatments

Molecules in development for Multiple Sclerosis act on multiple pathways and therapeutic targets

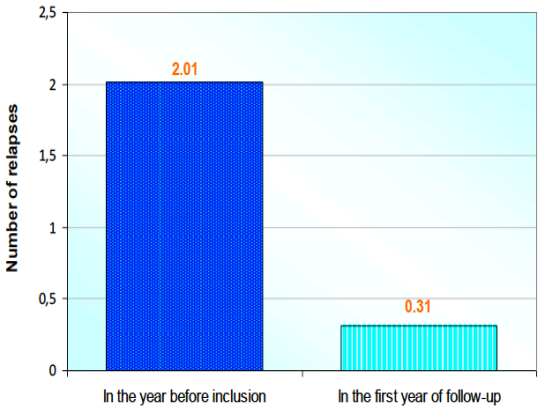


APC, antigen presenting cell; BBB, blood/brain barrier; CNS, central nervous system; IFN, interferon; S1P-R, sphingosine 1-phosphate receptor; TNF, tumour necrosis factor

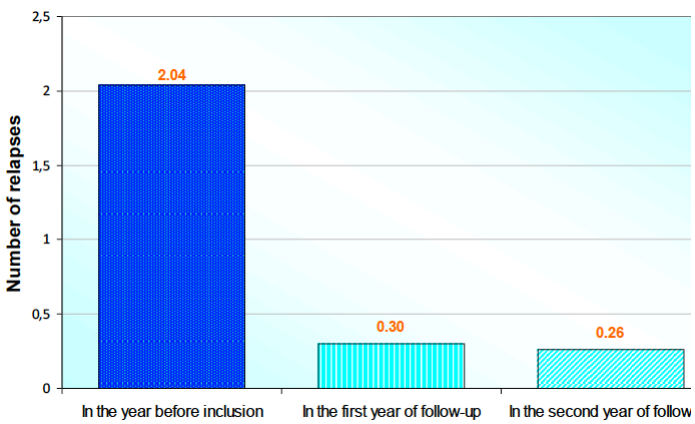
Image adapted from: Linker RA *et al. Trends Pharmacol Sci* 2008



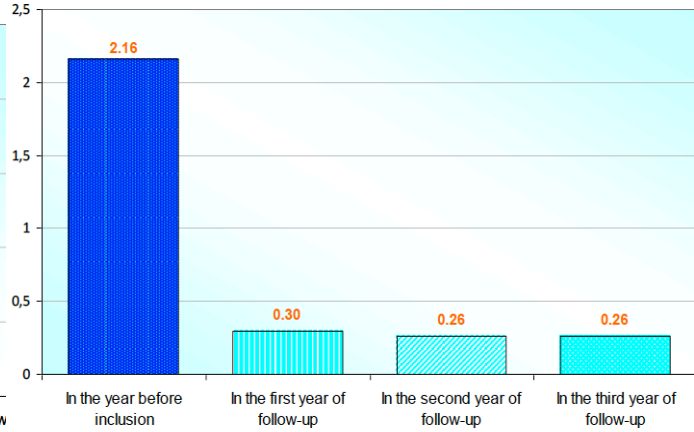
TYSEDMUS: TOTAL NUMBER OF INCLUSIONS



1051 patients

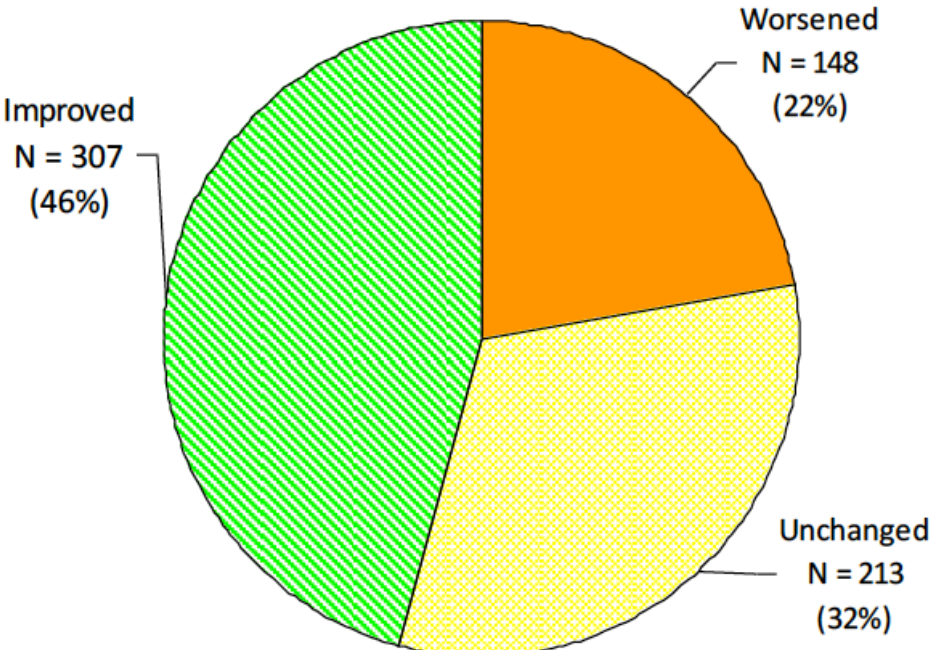


565 patients

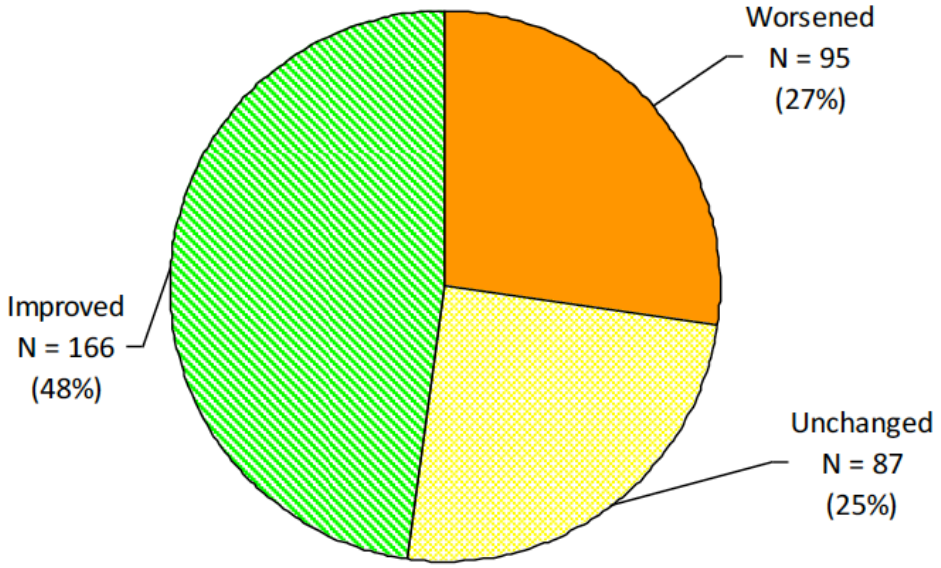


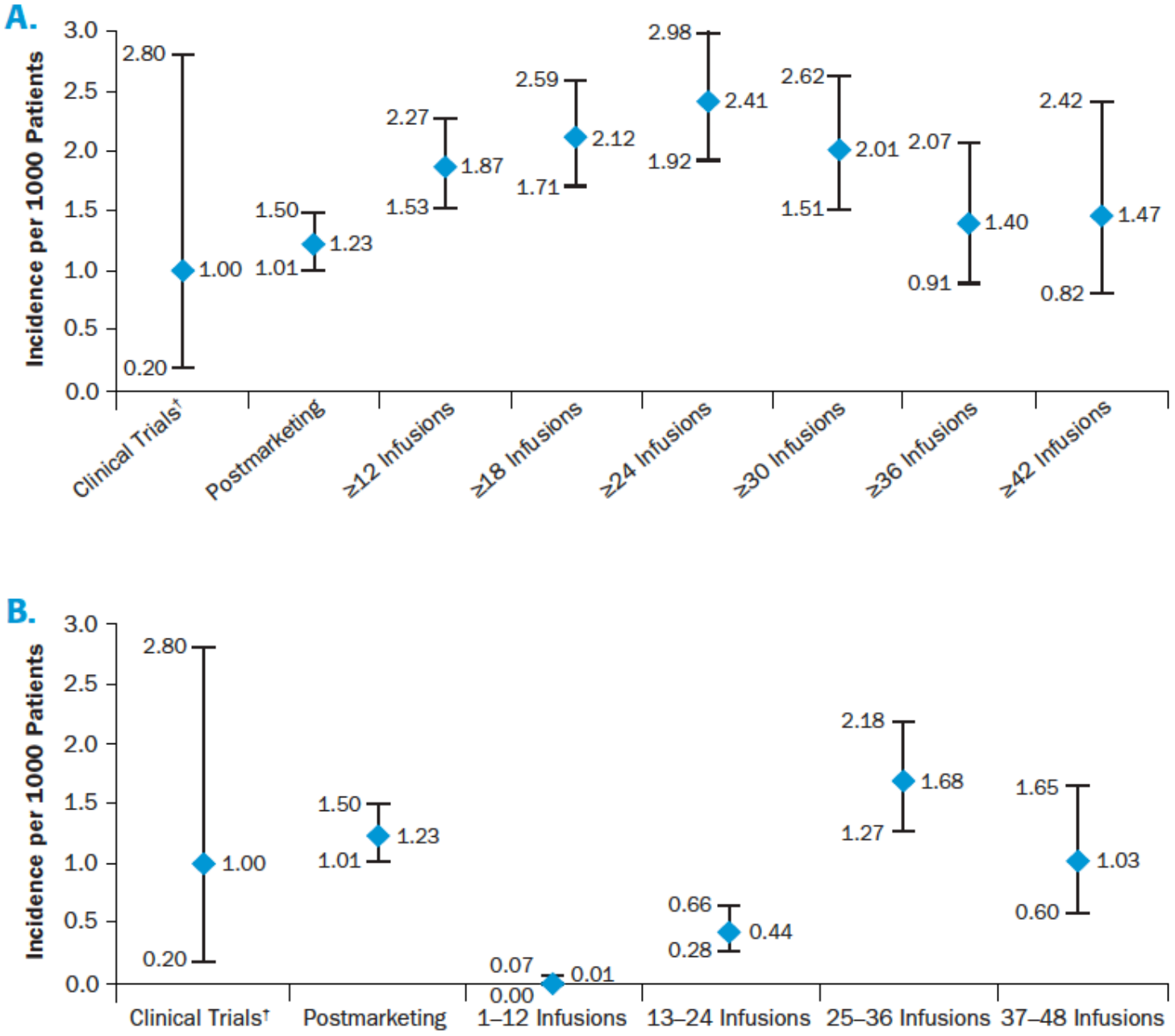
86 patients

EDSS after 1 year 668 patients



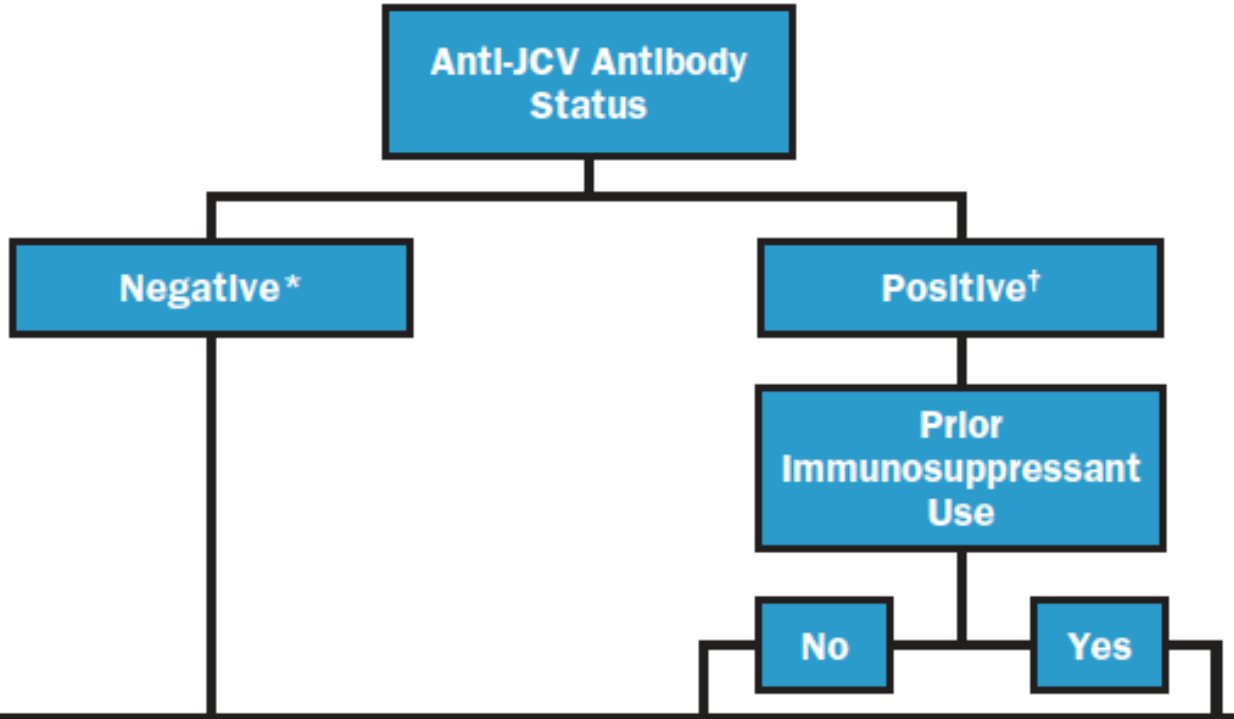
EDSS after 2 years 348 patients





PML Update 4 2011

Natalizumab risk stratification

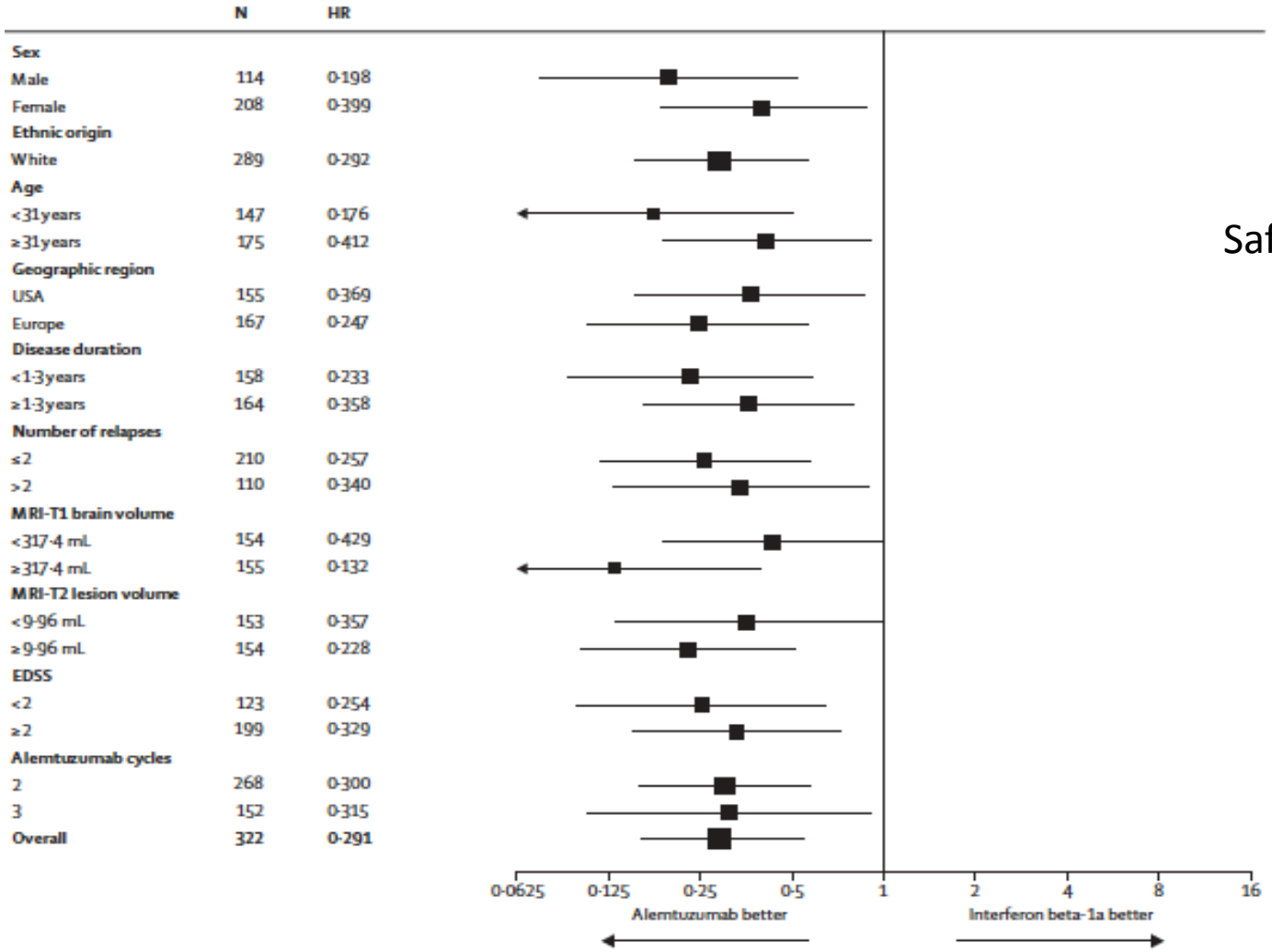


Natalizumab Exposure	Anti-JCV Antibody Negative	Anti-JCV Antibody Positive with No Prior Immunosuppressant Use	Anti-JCV Antibody Positive with Prior Immunosuppressant Use
0–2 Years	≤0.11/1000 (95% CI: 0–0.59)	0.35/1000 (95% CI: 0.19–0.60)	1.2/1000 (95% CI: 0.58–2.2)
>2 Years		2.8/1000 (95% CI: 2.0–3.8)	8.1/1000 (95% CI: 5.4–11.6)

Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes

Alasdair J Coles, Edward Fox, Anton Vladic, Suzanne K Gazda, Vesna Brinar, Krzysztof W Selmaj, Ann Doan-Do Bass, Daniel R Wynn, David H Margolin, Stephen L Lake, Susan Moran, Jeffrey Palmer, M Shelton Smith, D Alastair S Compston

Lancet Neurology 2011



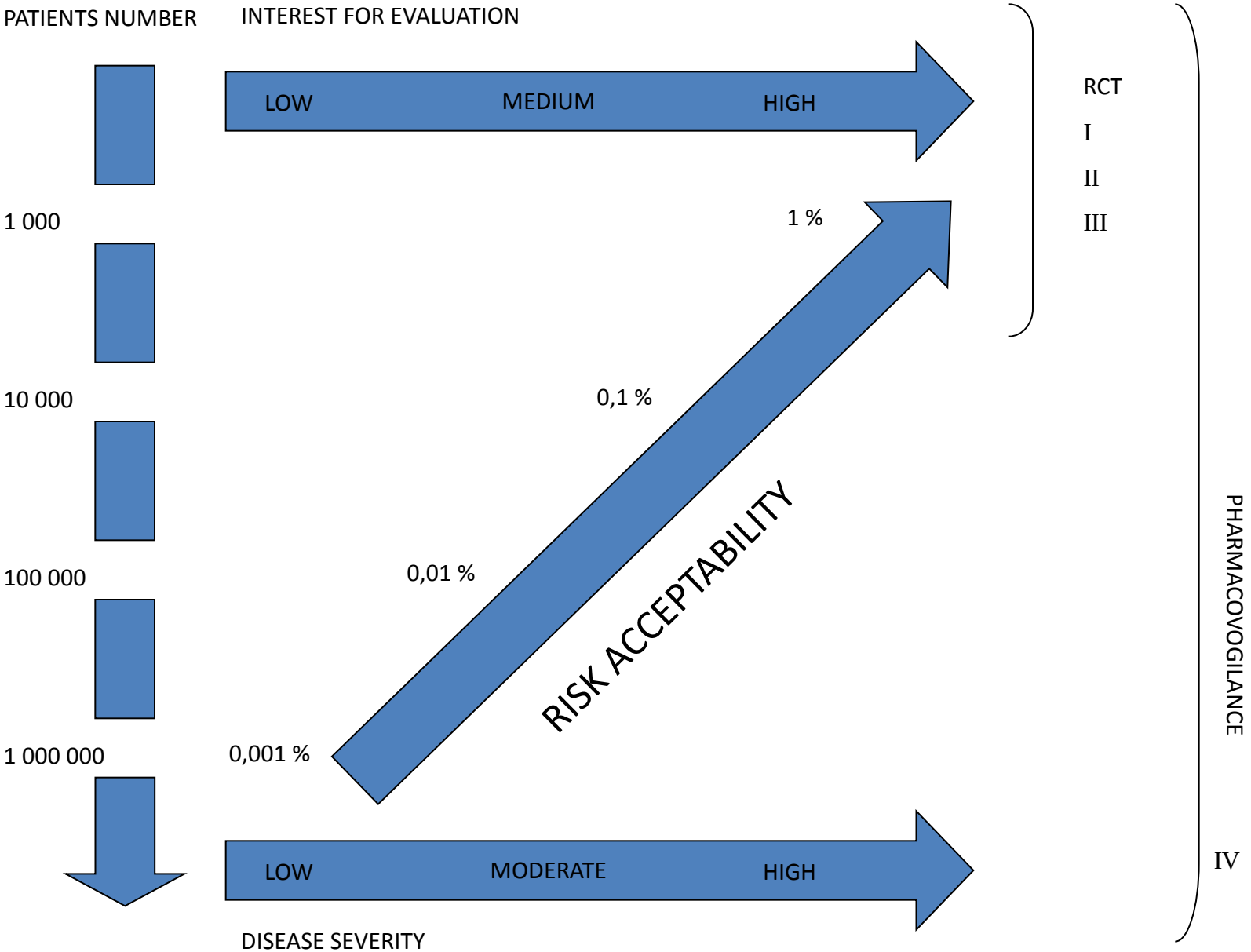
Safety ?

- Allergic reactions
- Infections
- Autoimmune diseas.
- Malignant diseas.

Drug Safety and risks

Intrinsic risks of immunosuppression

- Malignant diseases infections related
  - EBV, HHV-8, H Papillomavirus, HBV, HCV, *Helicobacter*
  - Lympho-proliferative diseases, Kaposi sarcoma, anogenital, liver and stomach cancers
- Infections
- Immune dysregulations
- Cardiovascular and metabolic risks


PATIENTS NUMBER
INTEREST FOR EVALUATION
LOW
MEDIUM
HIGH
RCT
I
II
III
1 000
1 %
10 000
0,1 %
100 000
0,01 %
RISK ACCEPTABILITY
1 000 000
0,001 %
LOW
MODERATE
HIGH
DISEASE SEVERITY
PHARMACOVOGILANCE
IV

Factors in shared decision making

- Objective and clear communication on treatment risks
- Patients risk attitudes **(Prosser LA et al Med Decis. Mak. 2002)**
  - Risk-seeking patients are more likely to choose risky treatments compared to risk-aversive patients
  - Risk perception for the disease
- Patient's trust in their physicians **(Kraetschmer M et al Health Exp. 2005)**

Summary

- Escalation therapy is the current treatment strategy in early MS
- Oral treatments are arising which could change significantly the current treatment options
- Monoclonal antibodies are powerful agents for treating aggressive RR MS
- Safety profile of these new agents are uncertain and stringent risks management plans are required
- Objectivity and transparency are basic requirements for optimized shared-decision making between patients and neurologists