Efficacia, sicurezza e tollerabilità dei Mabs

Nelle malattie autoimmuni del Sistema Nervoso Centrale

Emilio Portaccio

Università di Firenze

Outline

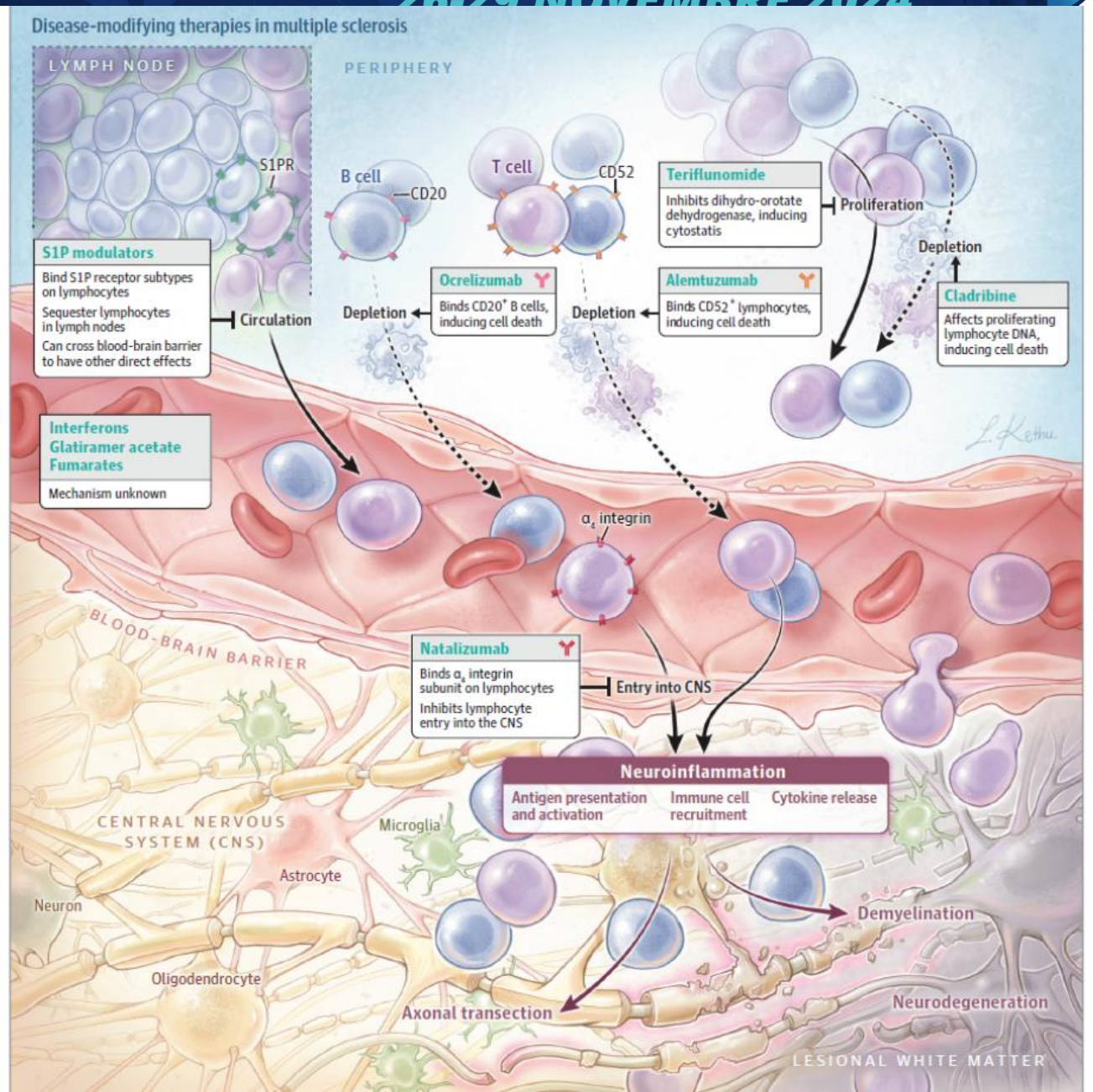
- MAbs in MS and NMOSD: efficacy
- MAbs in MS and NMOSD: safety
- MAbs in CNS disorders: beyond autoimmune diseases

Outline

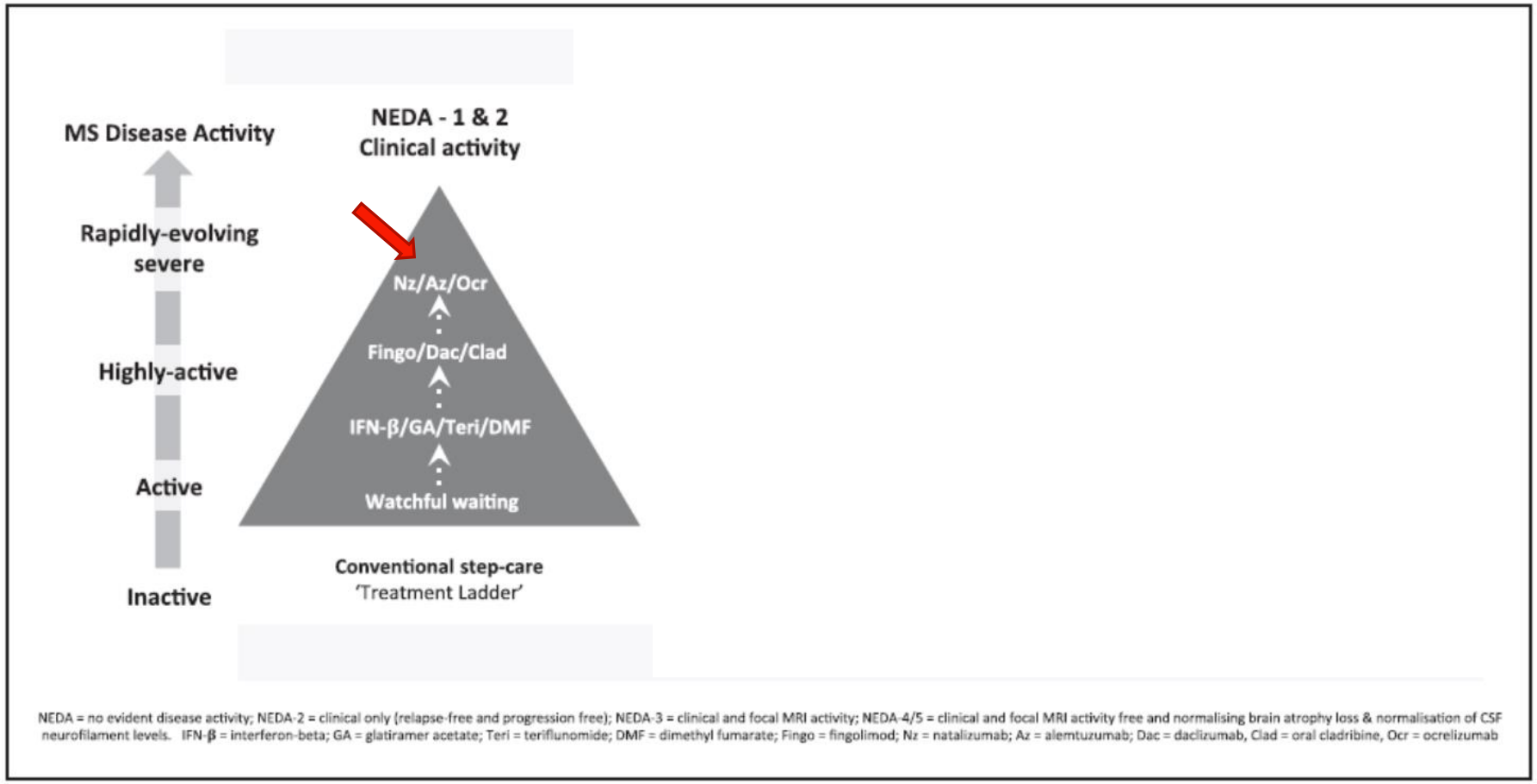
- MAbs in MS and NMOSD: efficacy
- MAbs in MS and NMOSD: safety
- MAbs in CNS disorders: beyond autoimmune diseases

Mabs in MS

- Natalizumab
- Alemtuzumab
- *Anti-CD20* (Ocrelizumab, Ofatumumab, Ublituximab, Rituximab)



MAbs in MS – efficacy



NEDA = no evident disease activity; NEDA-2 = clinical only (relapse-free and progression free); NEDA-3 = clinical and focal MRI activity; NEDA-4/5 = clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. IFN-β = interferon-beta; GA = glatiramer acetate; Teri = teriflunomide; DMF = dimethyl fumarate; Fingo = fingolimod; Nz = natalizumab; Az = alemtuzumab; Dac = daclizumab, Clad = oral cladribine, Ocr = ocrelizumab

Giovannoni G, Curr Opin Neurol 2018

MAbs in MS – efficacy

THERAPEUTIC ADVANCES in
Neurological Disorders

Review

Beyond lines of treatment: embracing early high-efficacy disease-modifying treatments for multiple sclerosis management

Celia Oreja-Guevara, Sergio Martínez-Yélamos, Sara Eichau, Miguel Ángel Llaneza, Jesús Martín-Martínez, Joaquín Peña-Martínez, Virginia Meca-Lallana, Ana María Alonso-Torres, Ester Moral-Torres, Jordi Río, Carmen Calles, Adrián Ares-Luque, Lluís Ramió-Torrentà, María Eugenia Marzo-Sola, José María Prieto, María Luisa Martínez-Ginés, Rafael Arroyo, María Ángeles Otano-Martínez, Luis Brieva-Ruiz, Montserrat Gómez-Gutiérrez, Alfredo Rodríguez-Antigüedad, Victoria Galán Sánchez-Seco, Lucienne Costa-Frossard, Miguel Ángel Hernández-Pérez, Lamberto Landete-Pascual, Montserrat González-Platas and José E. Meca-Lallana

Ther Adv Neurol Disord

2024, Vol. 17: 1–19

DOI: 10.1177/17562864241284372

Correspondence to:
Celia Oreja-Guevara
Department of Neurology, Hospital Clinico San Carlos, IdISSC, C/Prof Martín Lagos, s/n, Moncloa - Aravaca, 28040, Madrid, Spain

Brown J et al JAMA 2019	Harding K et al JAMA Neurol 2019	Buron MD et al. Neurology 2020	He A et al. Lancet Neurol 2020	Iaffaldano P et al. TAND 2021
First DMT: • fingolimod, alemtuzumab, or natalizumab (n=235); • Injectables (n=380)	Early Intensive Therapy (EIT) (n=104) vs Escalation (ESC) (n=488)	Initial treatment with High efficacy DMT (n=194) or medium efficacy DMT (n=194).	Rituximab, Ocrelizumab, MTX, Alemtuzumab, or Natalizumab either 0-2 years (early) (n=213) or >4 years (late) (n=253) after clinical disease onset.	Early Intensive Therapy (EIT) (n=363) vs Escalation (ESC) (n=363)
5.8 years Time to SP conversion (data-driven definition)	Up to 6.9 years (mean for ESC group) 5-year change in EDSS.; time to Sustained Accumulation of Disability (SAD).	4 years Time to 6-month confirmed EDSS worsening and to first relapse	7.8 years EDSS at 6 to 10 years and cumulative hazard of confirmed disability progression	8.5 years Disability trajectories at 10 years by using longitudinal models
MSBase			MSBase	
2019		2020		2021
Initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion to SP than initial treatment with injectables.	Mean 5-year change in EDSS was lower in the EIT group than the ESC group. EIT better than ESC to reduce the risk of reaching SAD.	Initial therapy with high efficacy DMT was associated to a lower risk of confirmed disability worsening and a first relapse.	High-efficacy therapy commenced within 2 years of disease onset is associated with less disability after 6–10 years than when commenced later in the disease course.	EIT strategy is more effective than ESC strategy in controlling disability progression over time.

Key message:

- **Early initiation of highly effective therapy may provide more benefit than an escalation approach**

Current arguments for early use of heDMTs

The overall safety profile of novel heDMTs was comparable to meDMTs in short-term head-to-head clinical trials. Long-term risk–benefit ratio of heDMTs is uncertain but might be more favorable when initiated at a younger age

Early use of heDMTs have shown greater reductions in clinical and radiological activity and a lower risk of disease progression and disability; meDMTs in patients with active disease or poor prognosis factors are associated with accelerated disability progression

Some patients have disease progression in the following years after diagnosis; increasing availability and understanding of biomarkers enhance the ability to predict the disease course

In general, heDMTs are associated with lower work absenteeism and higher productivity; their early use could result in overall cost-effectiveness and healthcare system sustainability

Classical arguments for the escalation approach

Safety concerns with heDMT should drive decisions on treatment strategy; meDMT have a better safety profile than heDMT, and long-term safety of early heDMT is scarce

Since meDMTs have an acceptable efficacy with low safety concerns, all patients should start with meDMT. HeDMTs should only be used after a suboptimal response to meDMT that justifies taking the risks

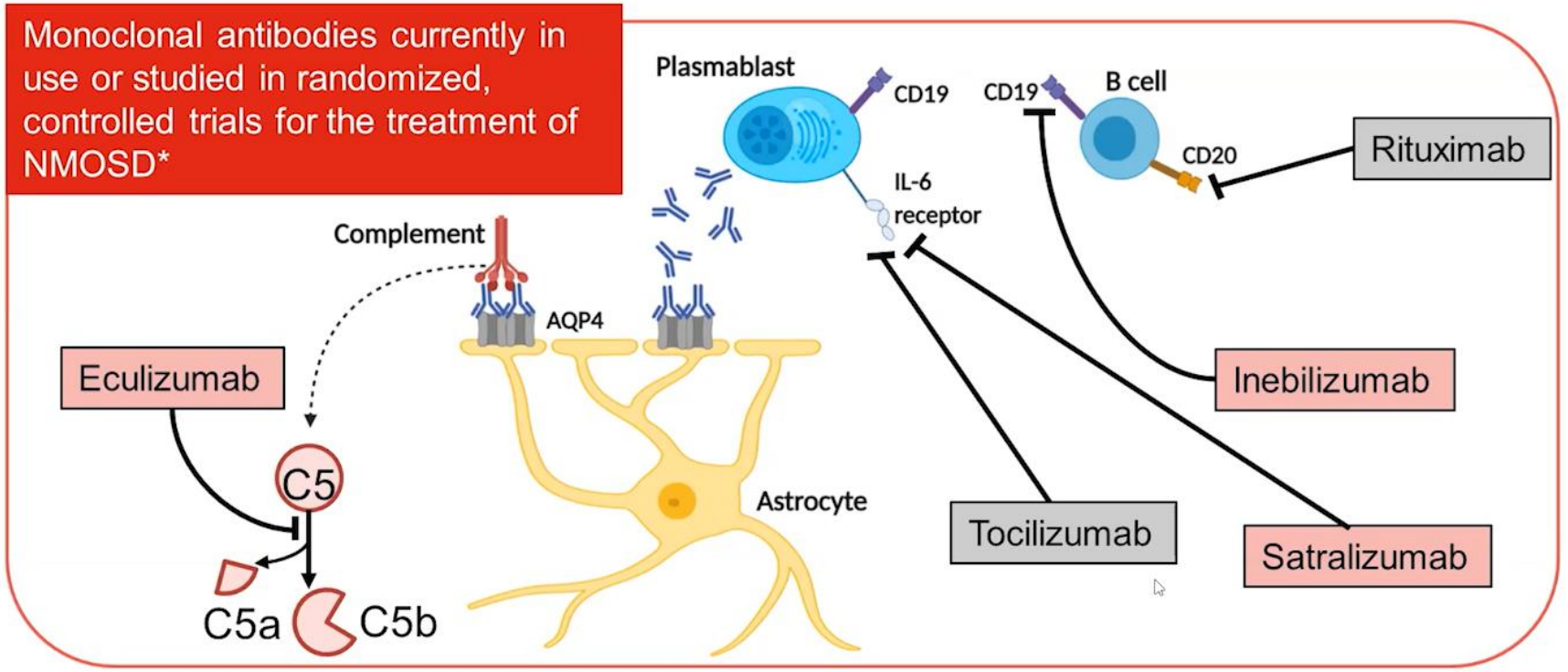
Sometimes predicting whether a patient will experience a severe or benign disease course is difficult; cautious escalation approach to balance efficacy

Overall, meDMTs are less expensive than heDMTs, imposing a lower cost to payers

Oreja-Guevara C et al, TAND 2024

Mabs in NMOSD

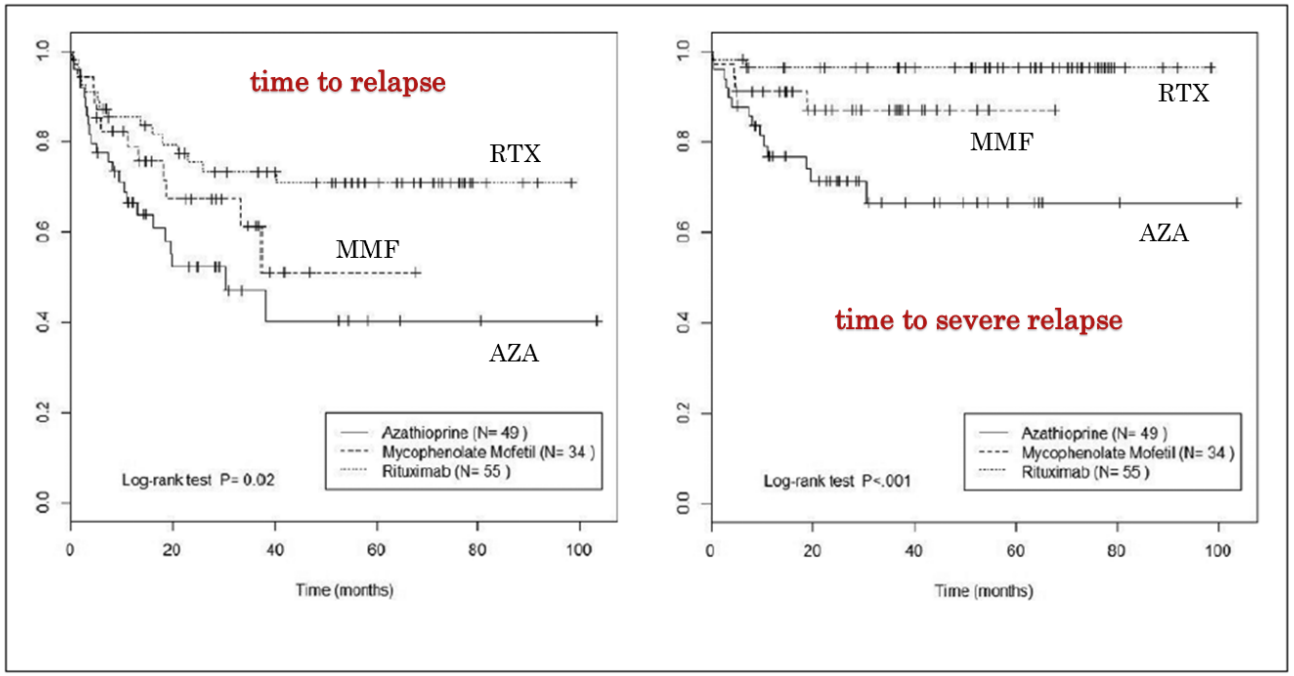
- *Anti-CD20* (Rituximab)
- *Anti-CD19* (**Inebilizumab**)
- *Anti-IL6R* (**Satralizumab**, Tocilizumab)
- *Anti-C5* (**Eculizumab**, **Ravulizumab**)



Adapted from figures in Papadopoulos M et al. *Nat Rev Neurol.* 2014;10:493-506; Pittock SJ, Lucchinetti CF. *Ann N Y Acad Sci.* 2016;1366:20-39; Weinshenker BG, Wingerchuk DM. *Mayo Clin Proc.* 2017;92:663-679.
Illustration created in BioRender.com.

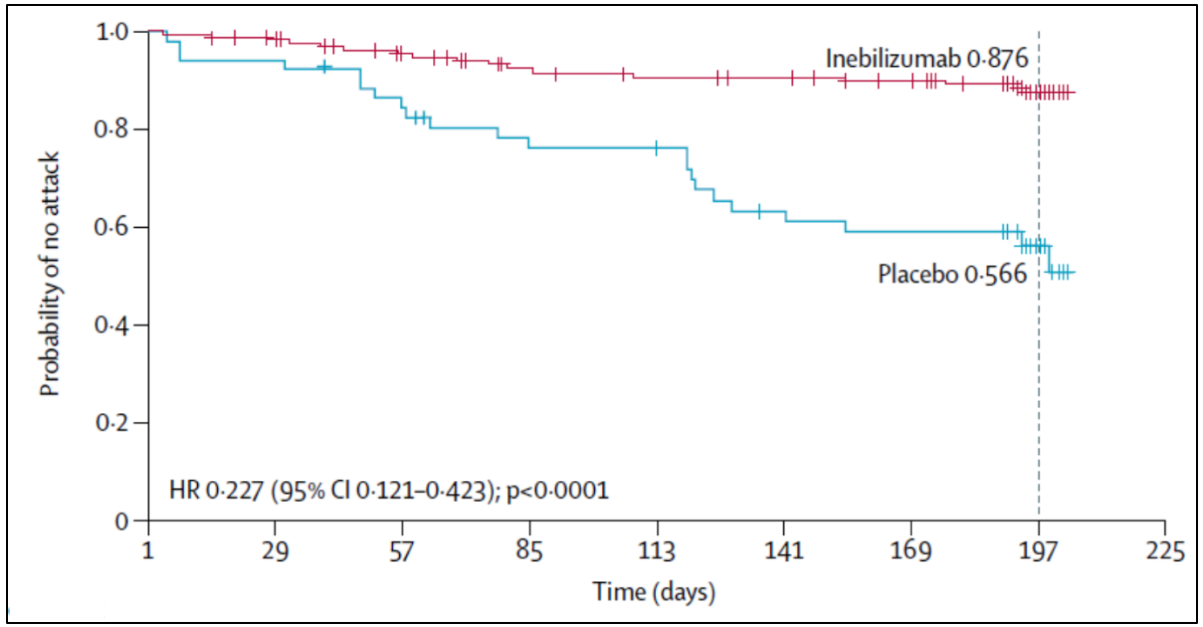
MAbs in NMOSD – efficacy

RITUXIMAB



Hye Jeon et al, MSJ 2016

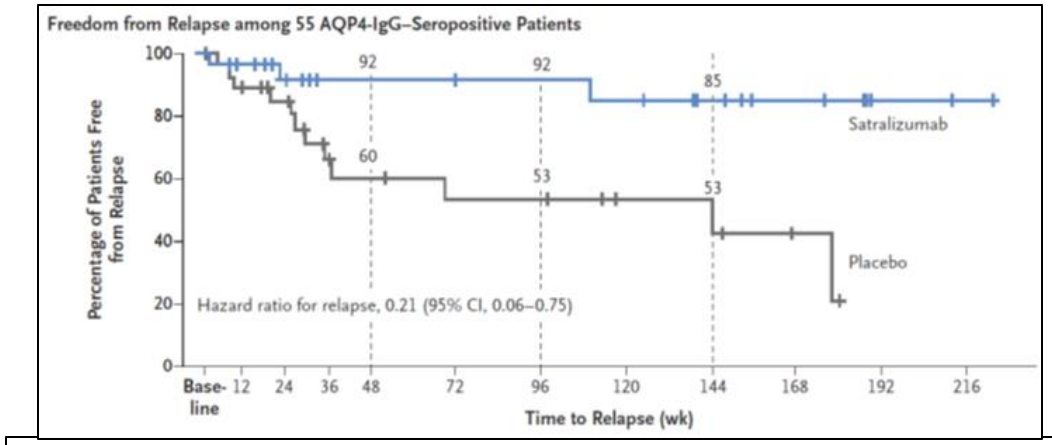
INEBILIZUMAB

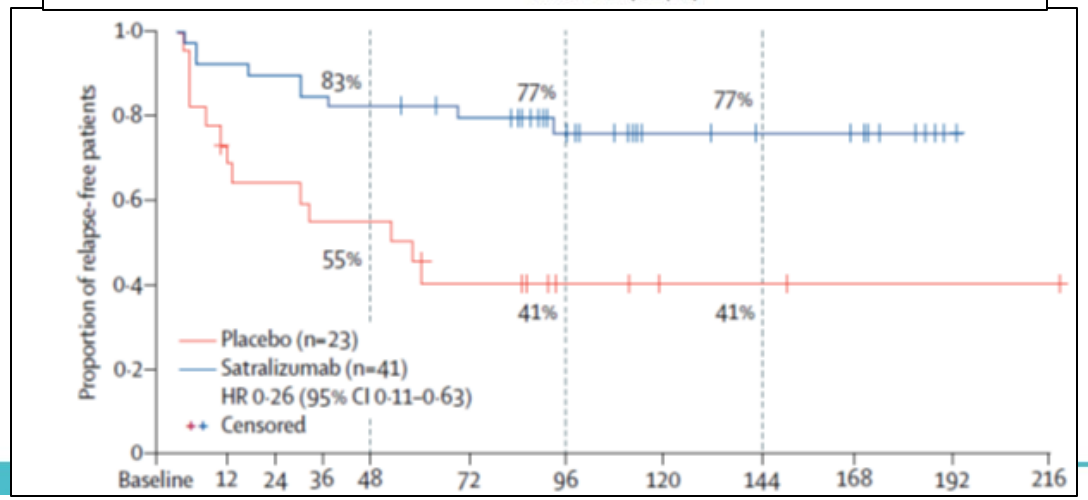


Cree B et al, Lancet 2019

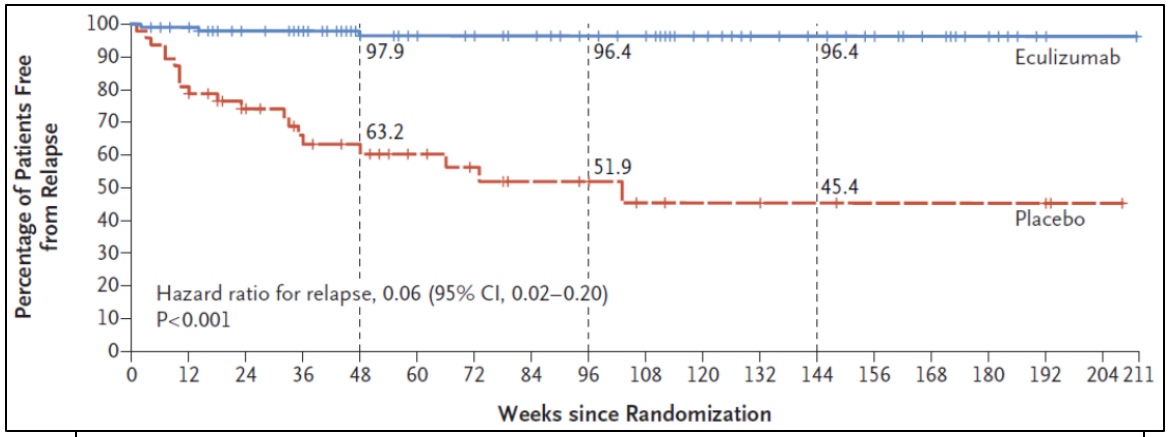
MAbs in NMOSD – efficacy

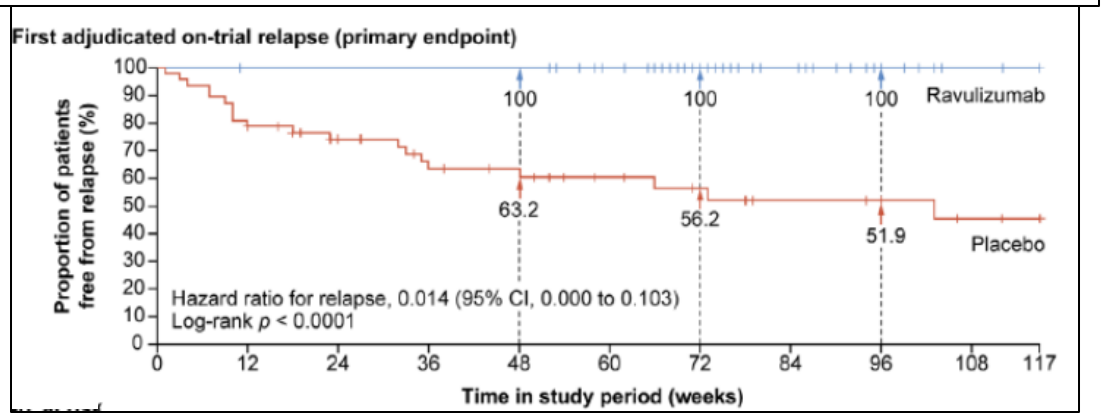
SATRALIZUMAB





ECULIZUMAB e RAVULIZUMAB





Traboulsee A et al, Lancet Neurol 2020; Yamamura T et al., NEJM 2019

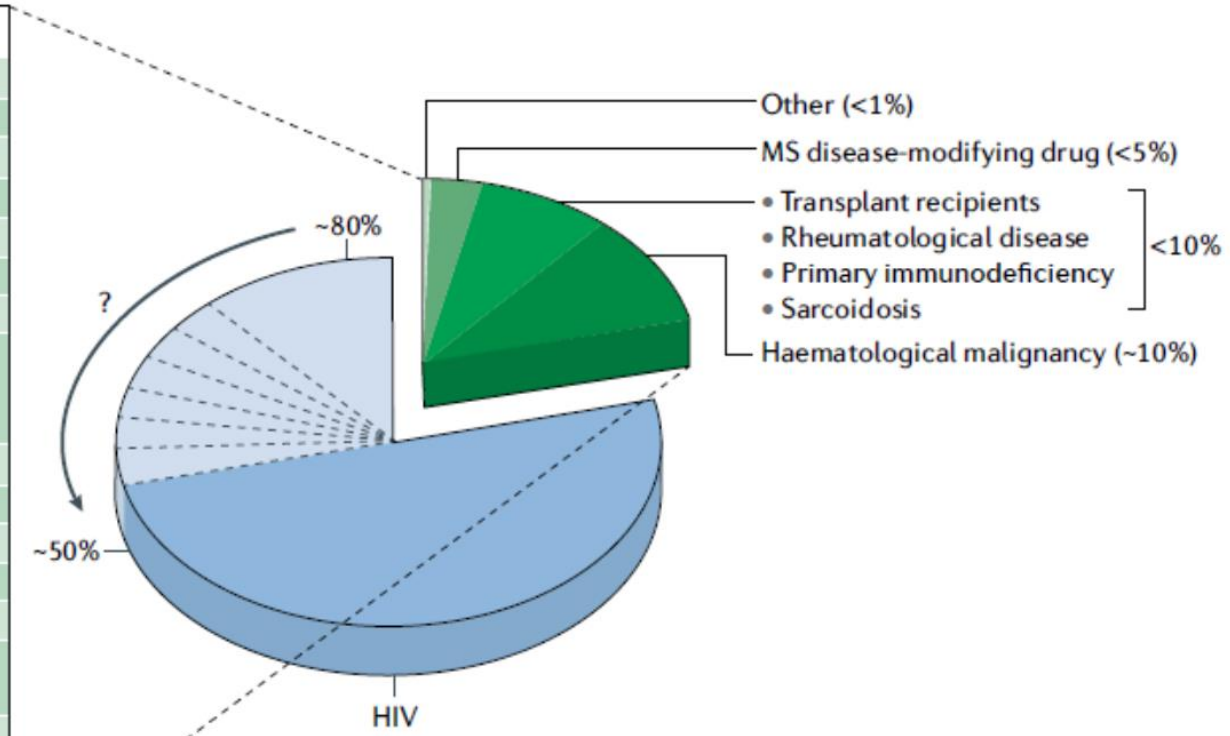
Pittock S et al, NEJM 2019; Pittock S et al. Ann Neurol 2023

Outline

- MAbs in MS and NMOSD: efficacy
- MAbs in MS and NMOSD: safety
- MAbs in CNS disorders: beyond autoimmune diseases

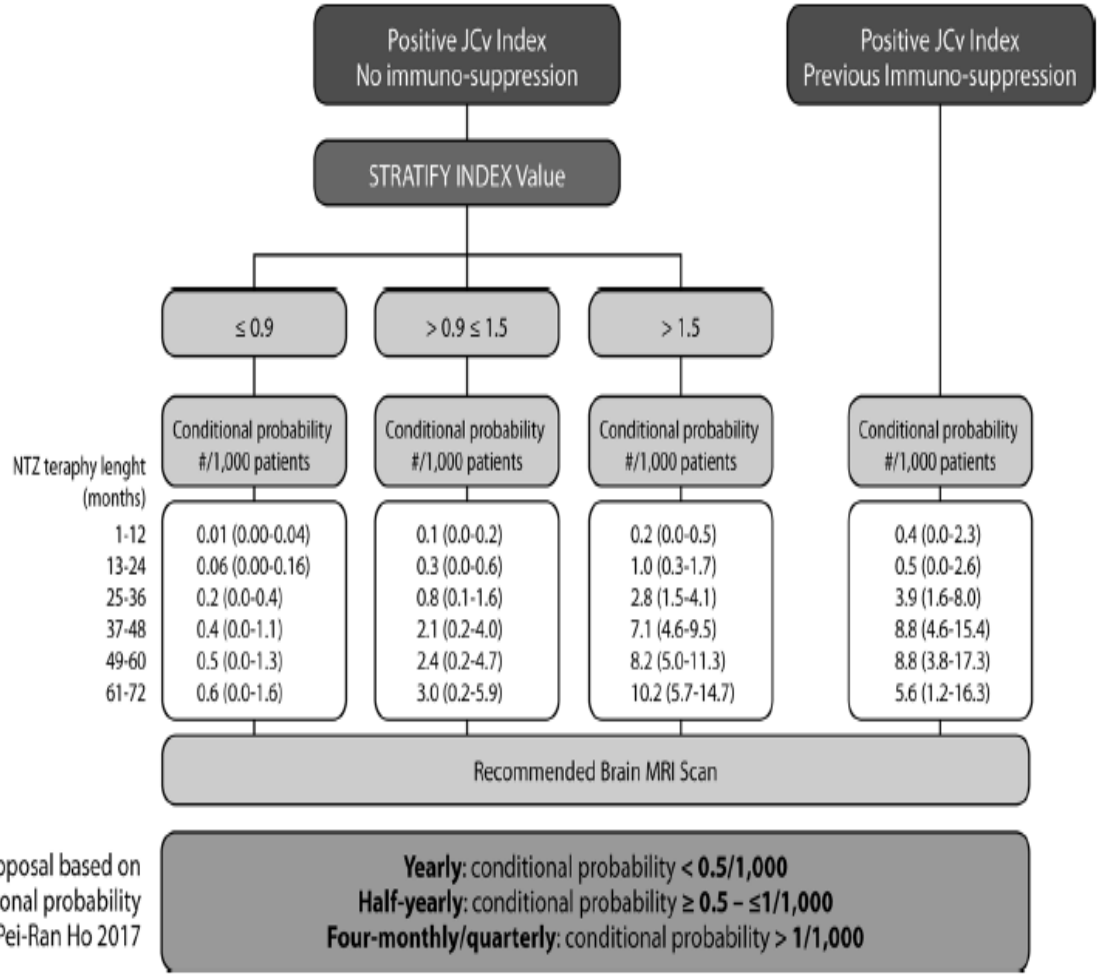
PML risk – natalizumab

Drug	Indications
Belatacept	Kidney transplantation
Belimumab	SLE
Brentuximab vedotin	Hodgkin lymphoma
Cyclosporine	Transplantation
Dimethyl fumarate	RRMS
Efalizumab	Psoriasis
Fingolimod	RRMS
Ibrutinib	CLL, mantle cell lymphoma, marginal zone lymphoma, WM, cGVHD
Mycophenolate mofetil	Transplantation
Natalizumab	RRMS
Obinutuzumab	CLL
Ocrelizumab	RRMS, PPMS
Ofatumumab	CLL
Rituximab	CLL, non-Hodgkin lymphoma, RA, WG, MPA
Ruxolitinib	Myelofibrosis
Sirolimus	Transplantation
Tacrolimus	Transplantation
Vedolizumab	UC, Crohn's disease



Cortese I et al, Nat Rev Neurol 2021

PML risk – natalizumab



Moiola L et al, MSJ 2020

MAbs in MS and NMOSD safety – anti-CD20/CD19

- Risk of HBV reactivation
- Increased incidence of infections in hypogammaglobulinemia
- Very low risk of PML
- Worse COVID-19 course

MAbs in MS and NMOSD safety – anti-IL6R

- Increased incidence of infections
- Hematological alterations (neutropenia, low platelet count)

MAbs in MS and NMOSD safety – anti-C5

- Risk of severe meningococcal meningitis
- Vaccination/prophylaxis

Outline

- MAbs in MS and NMOSD: efficacy
- MAbs in MS and NMOSD: safety
- MAbs in CNS disorders: beyond autoimmune diseases

MAbs in CNS disorders: beyond autoimmune diseases

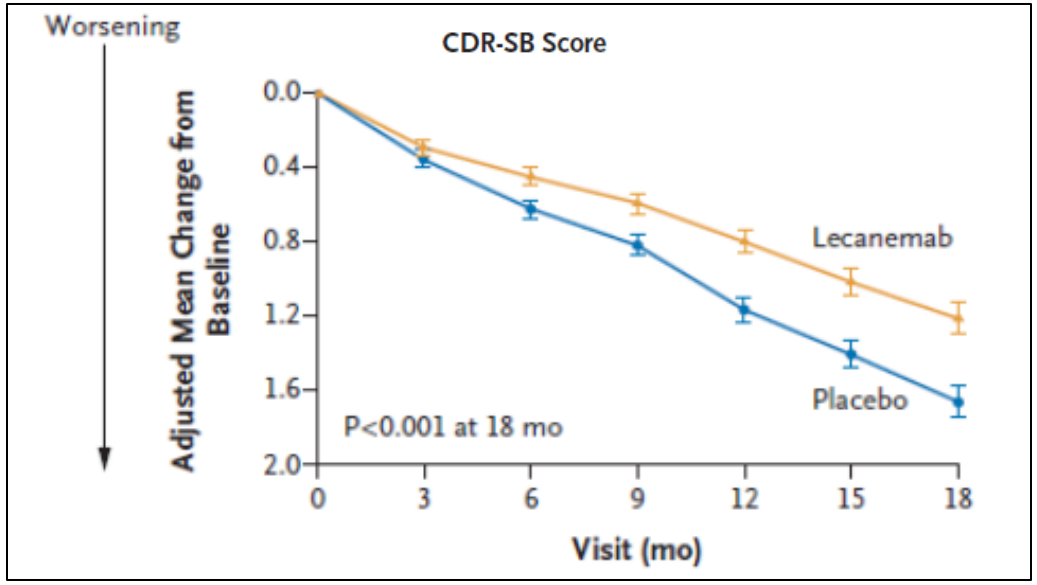
Alzheimer Disease

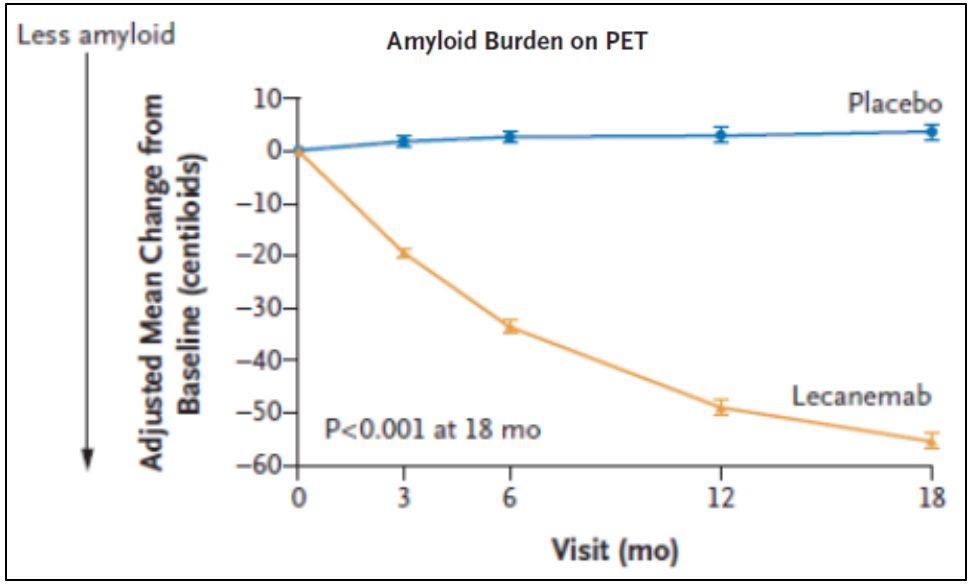
- Bapineuzumab
- Solanezumab
- Gantenerumab
- Crenezumab
- Aducanumab
- Lecanemab

Parkinson Disease

- Cinpanemab
- Prasinezumab
- UCB7853
- LU AF82422
- PRX002
- TAK-341/MEDI1341

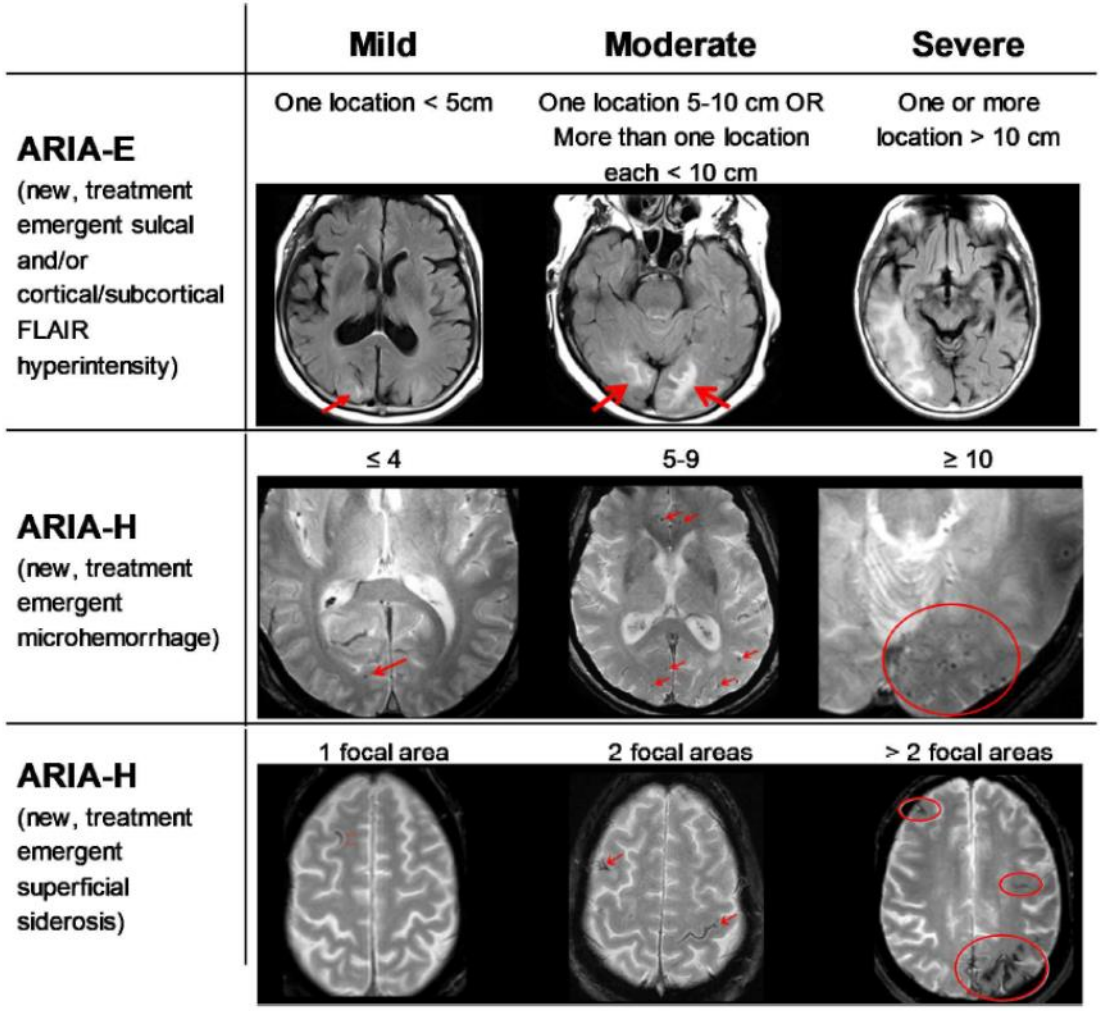
MAbs in AD – Lecanemab efficacy





Van Dyck CH et al, NEMJ 2023

MAbs in AD – Lecanemab safety



Event	Lecanemab (N=898)	Placebo (N=897)
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)

Van Dyck CH et al, NEMJ 2023; Cogswell P et al., AJNR 2024

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 November 2024
EMA/CHMP/530551/2024
Committee for Medicinal Products for Human Use (CHMP)

Lecanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology

Grazie per l'attenzione!