Multiple sclerosis in older patients: A patient population with unique needs

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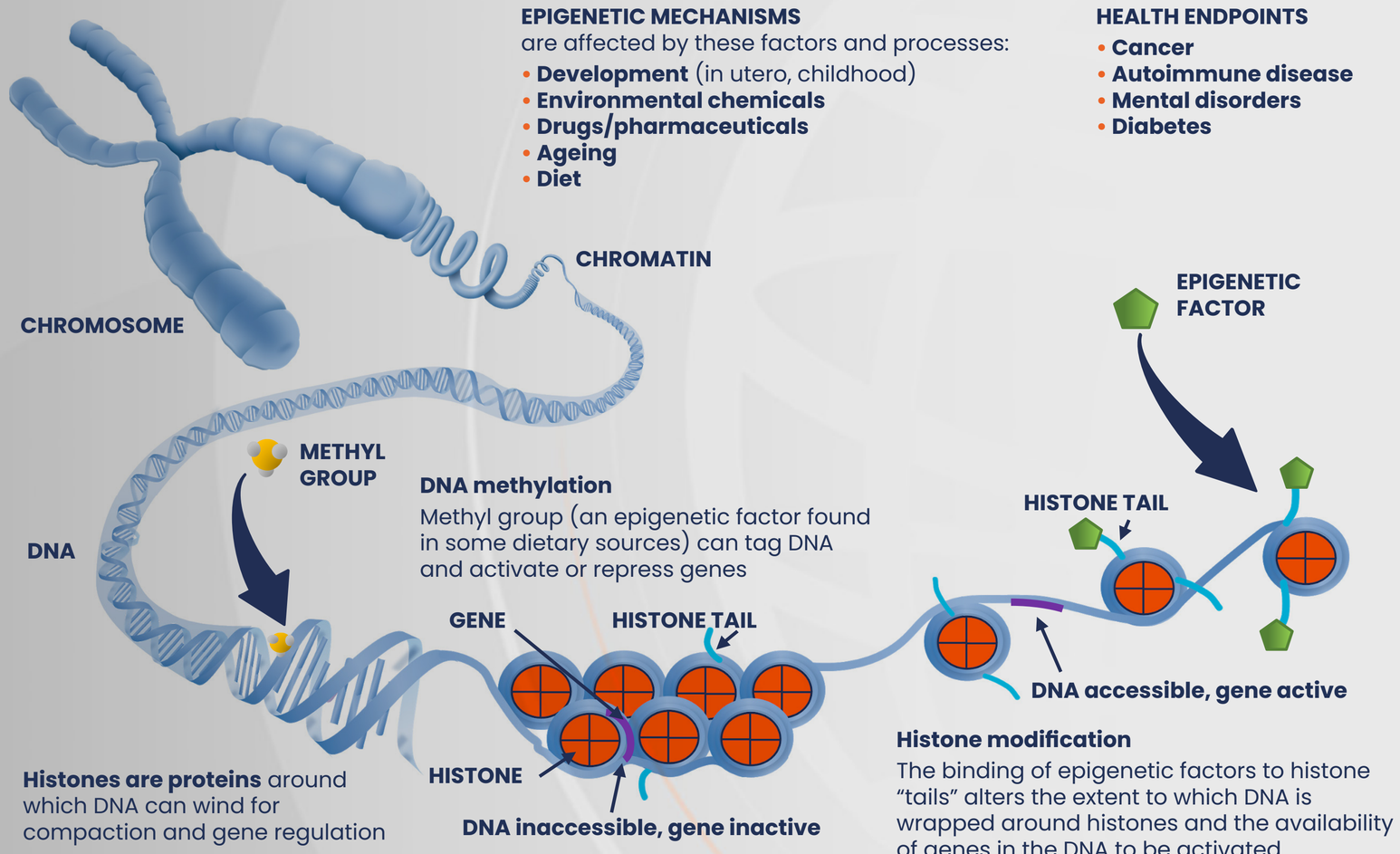
What are immuno- and neuro-senescence and how do they impact older patients with MS?

Biology of senescence[1–4]



1. NIH, National Institute on Aging. Available at: https://permanent.fdlp.gov/gpo46777/biology-of-aging.pdf (accessed March 2021); 2. Calcinotto A, et al. *Physiol Rev.* 2019;99:1047–78; 3. Childs BG, et al. *Nat Med.* 2015;21:1424–35; 4. Morris BJ, et al. *Biochim Biophys Acta Mol Basis Dis.* 2019;1865:1718–44.

Age-related changes affect multiple systems[1–10]

Systems	Potential changes
Nervous	Brain atrophy
Lymphatic/immune	Immunosenescence
Cardiovascular	Atherosclerosis
Endocrine	Increased adiposity
Muscular	Loss of mass; weakness
Digestive	Increased sensitivity, slower transit
Reproductive	Menopause/andropause
Dermatologic	Elastosis
Skeletal	Osteoporosis

1. NIH, National Institute on Aging. Available at: https://permanent.fdlp.gov/gpo46777/biology-of-aging.pdf; 2. Goronzy JJ, Weyand CM. *Nat Immunol.* 2013;14:428–36; 3. Wannamethee SG, et al. *Am J Clin Nutr.* 2007;86:1339–46; 4. Mayo Clinic. Available at: www.mayoclinic.org/healthy-lifestyle/womens-health/in-depth/belly-fat/art-20045809; 5. Goldspink *G. J Aging Res.* 2012;2012:158279; 6. Bitar K, et al. *Neurogastroenterol Motil.* 2011;23:490–501; 7. Mayo Clinic. Available at: www.mayoclinic.org/healthy-lifestyle/mens-health/in-depth/male-menopause/art-20048056; 8. NIH, National Institute on Aging. Available at: https://order.nia.nih.gov/sites/default/files/2018-09/menopause.pdf; 9. Lifshitz OH, Tomecki KJ. Available at: https://teachmemedicine.org/cleveland-clinic-the-aging-skin/; 10. NIH News in Health. Available at: https://newsinhealth.nih.gov/2015/01/osteoporosis-aging (all web links accessed March 2021).

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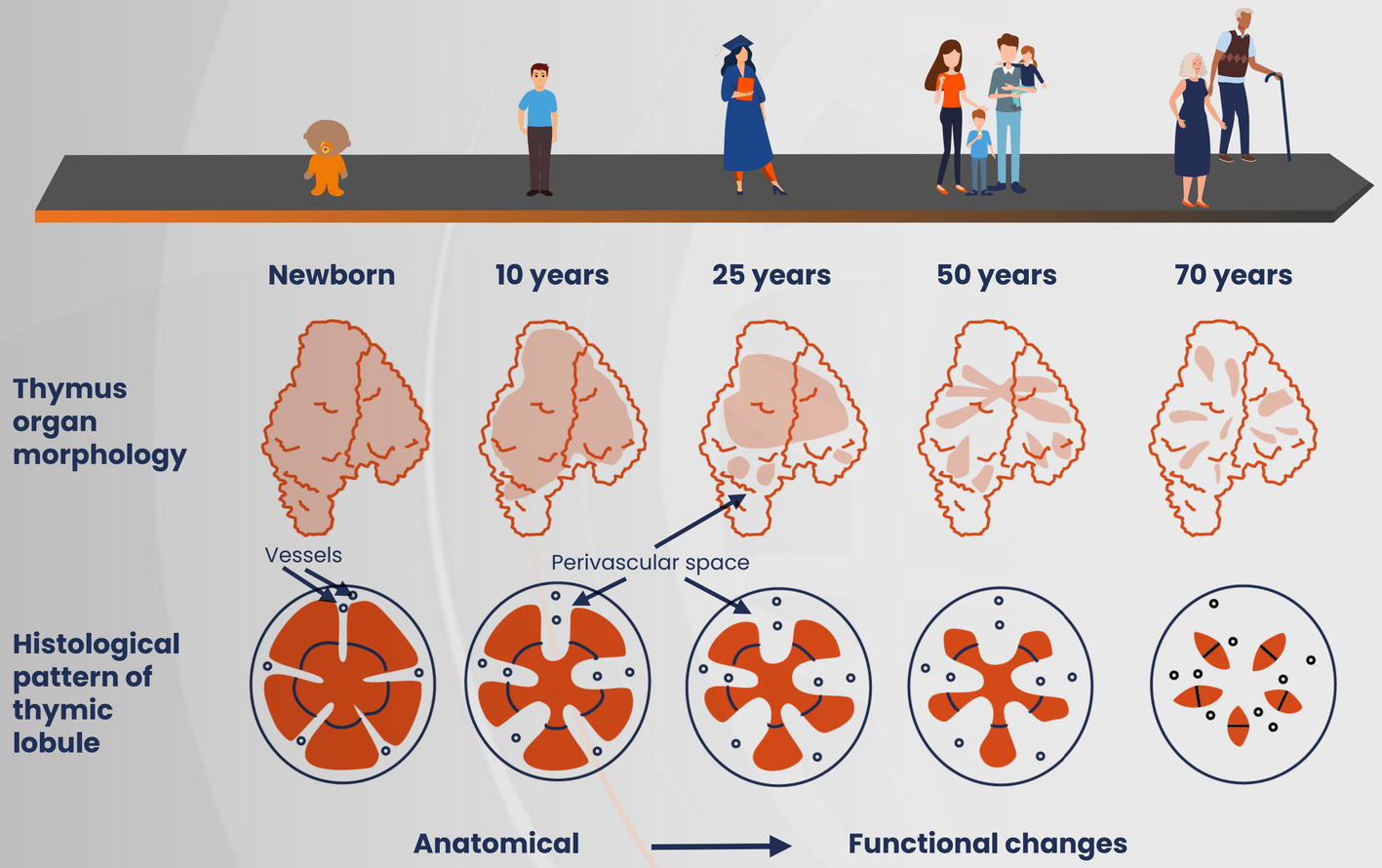
Immunosenescence begins relatively early[1–3]



The decline in immune function begins early in life, rises through midlife, and worsens with age

1. Farber DL, et al. *Nat Rev Immunol.* 2014;14:24–35; 2. Goronzy JJ, Weyand CM. *Nat Immunol.* 2013;14:428–36; 3. Thomas R, et al. *Immun Ageing.* 2020;17:2.

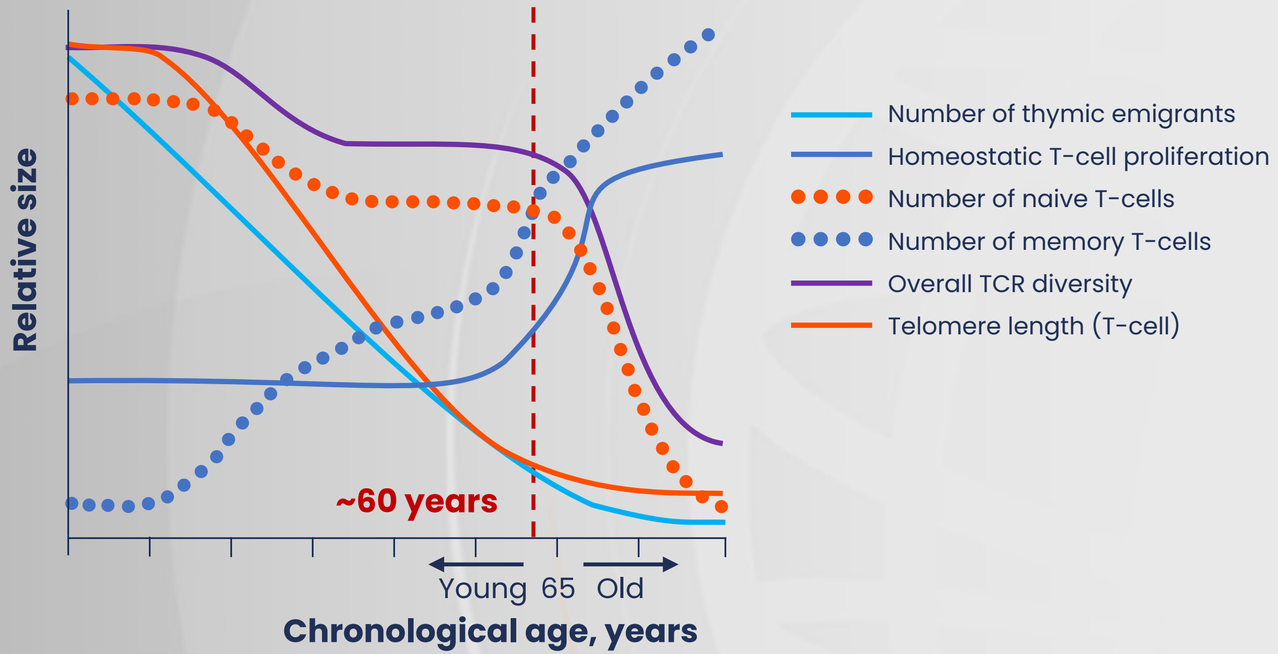
A summary of the main changes in the immune system due to immunosenescence

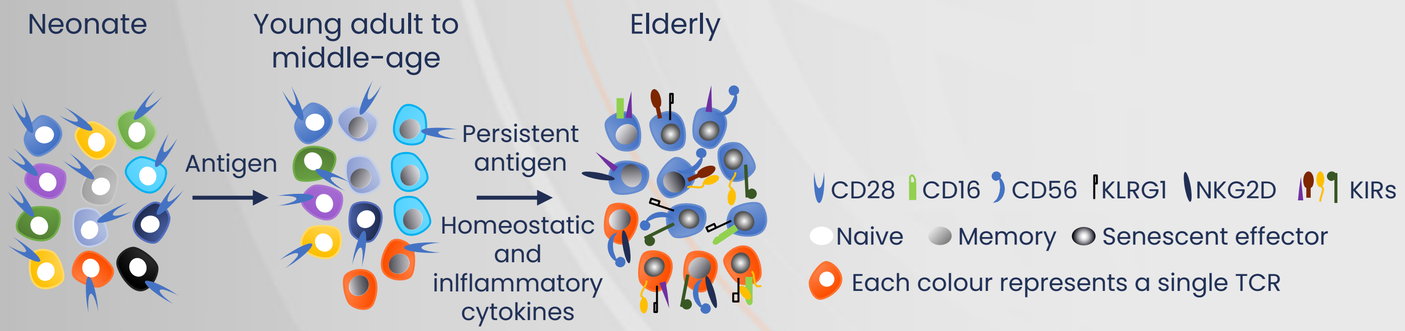
Affected cells	Function affected by ageing
NK cells	Elimination of infected cells/cytotoxicity Products of cytokines
Neutrophil and monocyte/macrophages	Chemotaxis Elimination of pathogen/microbiocidal function Phagocytosis TLR signalling
Dendritic cells	Phagocytosis Antigen presentation
T-cells	Decreased naive T-cells (CD4 and CD8) Increased antigen-experienced T-cells (CD4 and CD8) Decreased T-cell diversity
CD4 T-cells and B-cells	High-affinity antibody responses
B-cells	Decreased naive B-cells Class-switch recombination, somatic hypermutation Reduced repertoire (decreased response to neo-antigen)

NK, natural killer; TLR, Toll-like receptor.

Triglav TK, Poljak M. *Acta Dermatovenerol Alp Pannonica Adriat.* 2013;22:65–70.

Immunosenescence





KIRs, killer immunoglobulin-like receptor; KLRG1, killer cell lectin-like receptor G1; NKG2D, natural killer group 2 member D; TCR, T-cell receptor.

Vallejo AN. *Trends Mol Med.* 2007;13:94–102.

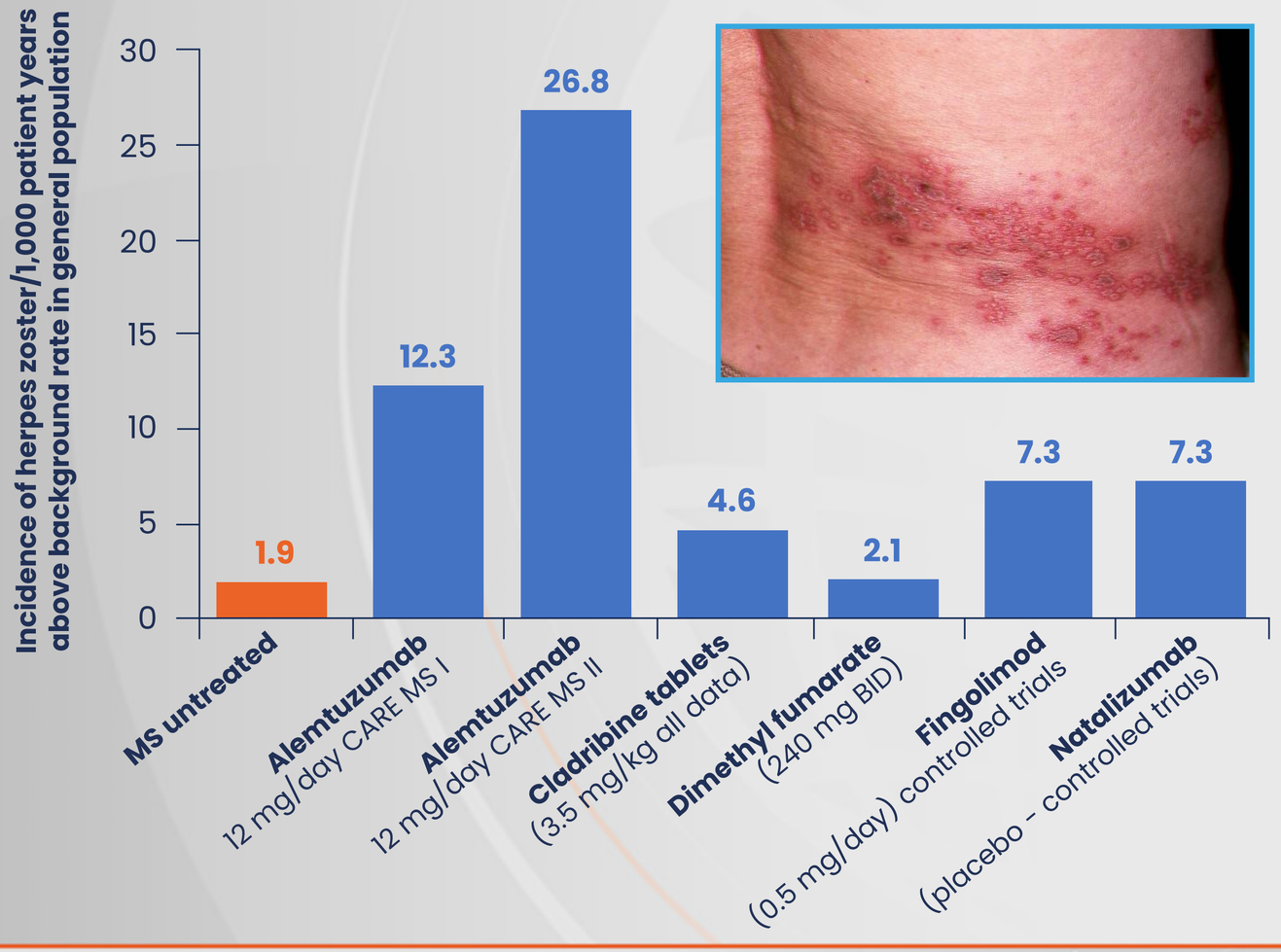
Ageing and lymphocyte changes by DMTs impact PML risk in patients with MS

DMT	Cases of PML	PML patient age (years)
Natalizumab	763 in >181,300 patients	15–73
Fingolimod	19 in >225,000 patients	34–71
Dimethyl fumarate	5 in >270,000 patients	54–66
Ocrelizumab	0 in >40,000 patients	
Teriflunomide	0 in >71,000 patients	
Alemtuzumab	0 in >18,400 patients	

DMT, disease-modifying therapy; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

Mills EA, Mao-Draayer Y. *Mult Scler.* 2018;24:1014–22

Incidence of herpes zoster per 1,000 patient years, across different MS treatments[1,2]



BID, twice a day; MS, multiple sclerosis.

1. Arvin AM, et al. *JAMA Neurol.* 2015;72:31–9; 2. Cook S, et al. *Mult Scler Relat Disord.* 2019;29:157–67.

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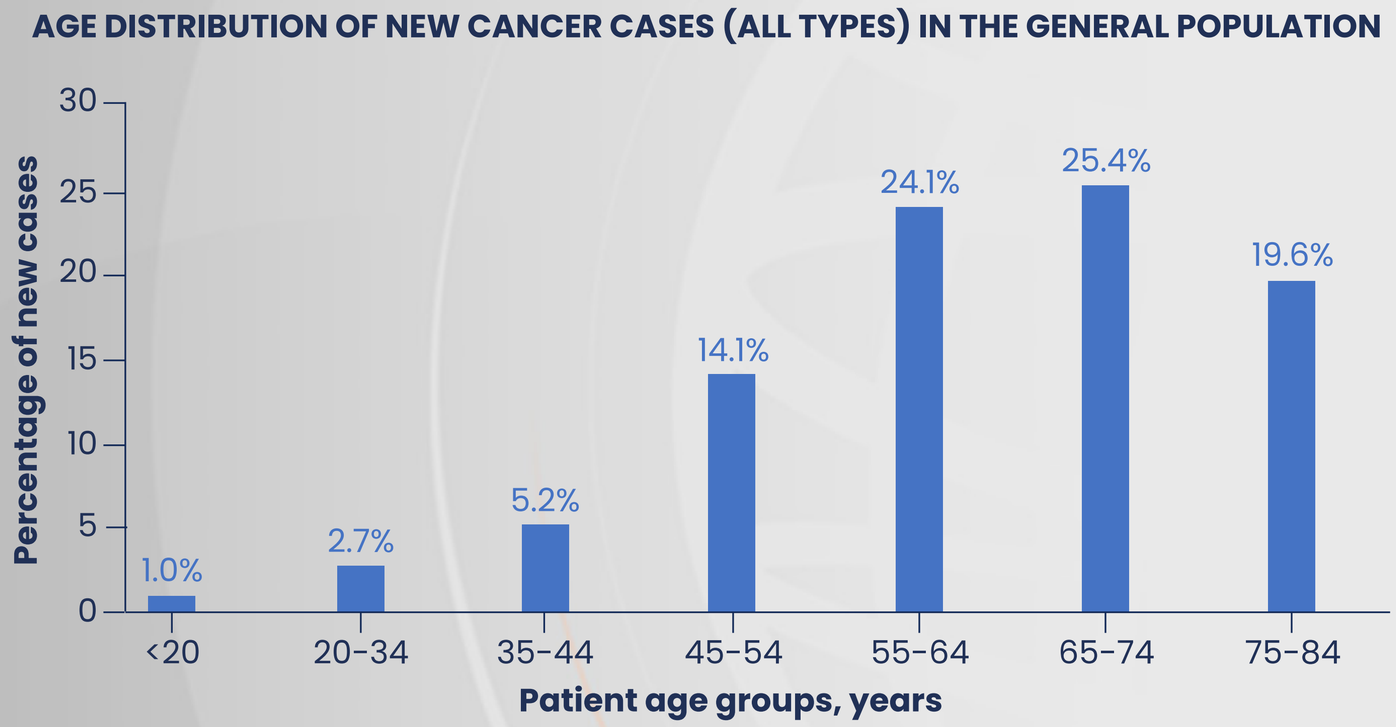
Increased risk for malignancies with ageing



Advancing age is the most important risk factor for cancer overall and for many individual cancer types

NIH National Cancer Institute. Available at: www.cancer.gov/about-cancer/causes-prevention/risk/age (accessed March 2021).

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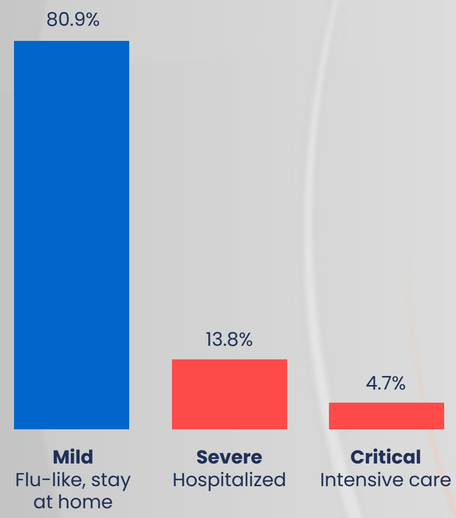
COVID-19: Consider the epidemiology of these risk factors in the general population

The majority of infections are mild

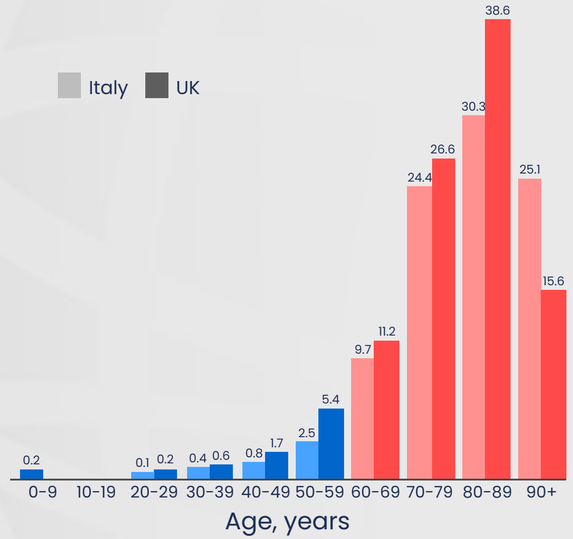
Sources: China Center for Disease Control and Prevention; **N=44,672**



Seriousness of symptoms

Those aged ≥60 are most at risk

Sources: Italian Portal of Epidemiology for Public Health, UK Office of National Statistics; **N=24,923**



Fatality rate (%) by age range

Frailty: older patients are more vulnerable to lung damage, and overall they are less prone to proper screening (e.g. due to poor fever response, dementia, etc.)

COVID-19, coronavirus disease 19.

Information is Beautiful. Available at: https://informationisbeautiful.net/visualizations/covid-19-coronavirus-infographic-datapack/(accessed March 2021).

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COVID-19: Consider these risk factors – Covisep epidemiology in the MS population

Multicentre, retrospective, observational cohort study conducted in MS expert centres and general hospitals

347 patients (mean [SD] age, 44.6 [12.8] years, 249 women; mean [SD] disease duration, 13.5 [10.0] years)

COVID-19 severity, demographics, neurological history, EDSS, comorbidities, COVID-19 characteristics and outcomes

Comorbidity	Cumulative R^2
EDSS	0.20
Age	0.26
Obesity	0.27

Cumulative variability of severe COVID-19

In this MS cohort, disability, age and obesity were identified as the main risk factors for COVID-19 severity

EDSS, Expanded Disability Status Scale; SD, standard deviation.
Louapre C, et al. *JAMA Neurol.* 2020;77:1079–88.

Conclusions

Normal ageing or senescence is hardwired

- Thymic involution
- Reduced repertoire diversity
- Loss of naive T-cells
- Dysregulated homeostatic proliferation
- Clonal expansion driven by CMV and EBV

Warning of vaccine recall memory

Reduced vaccine responses

Increased susceptibility to infections

Age-related infections and opportunistic infections

- For example, pneumococcal infections
- For example, PML

Higher risk of adverse events

- Infections
- Secondary malignancies

Reduced thymic and bone marrow reserve

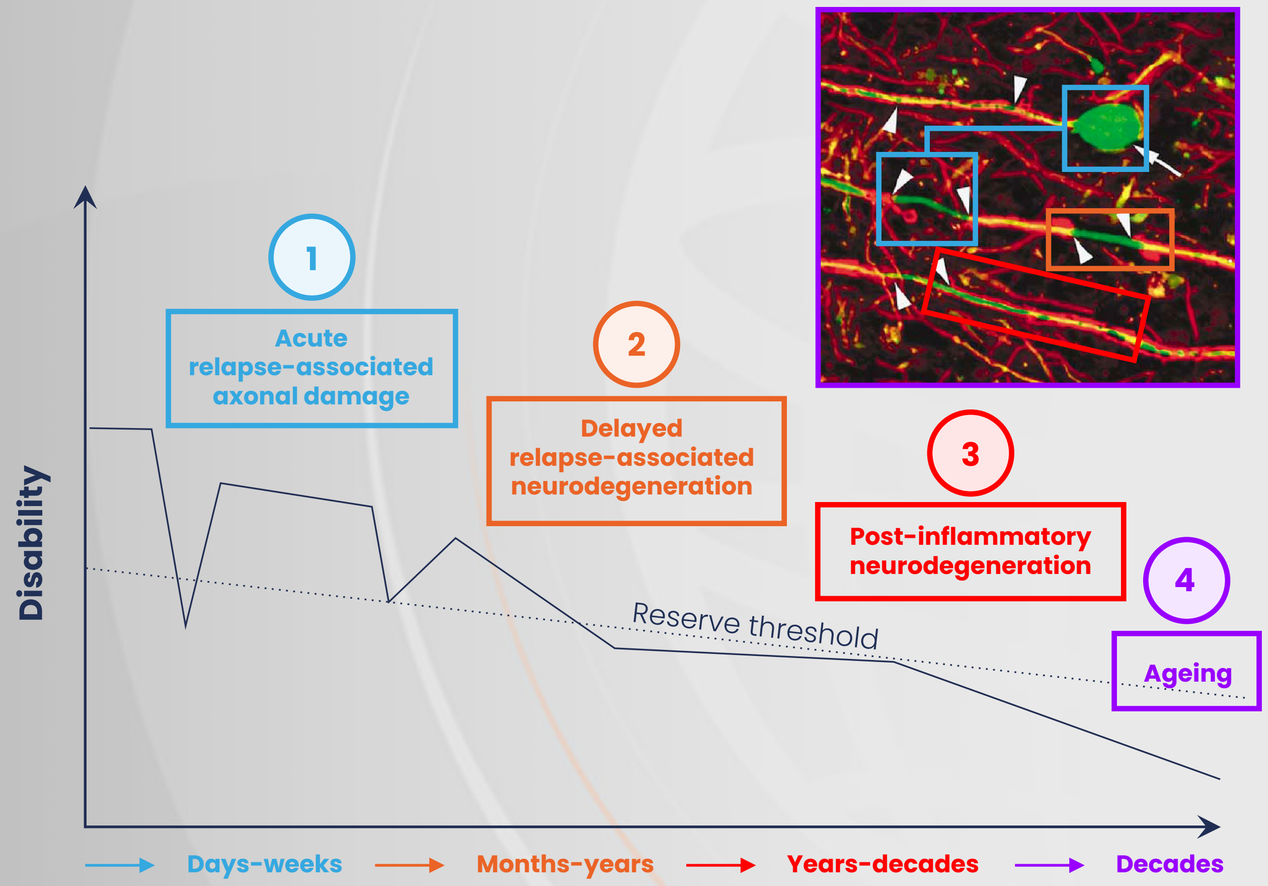
Potential impact on the treatment of MS

- Driver of disease progression
- Reduced therapeutic response to DMTs
- Comorbidities that interact with DMTs

CMV, cytomegalovirus; EBV, Epstein-Barr virus.

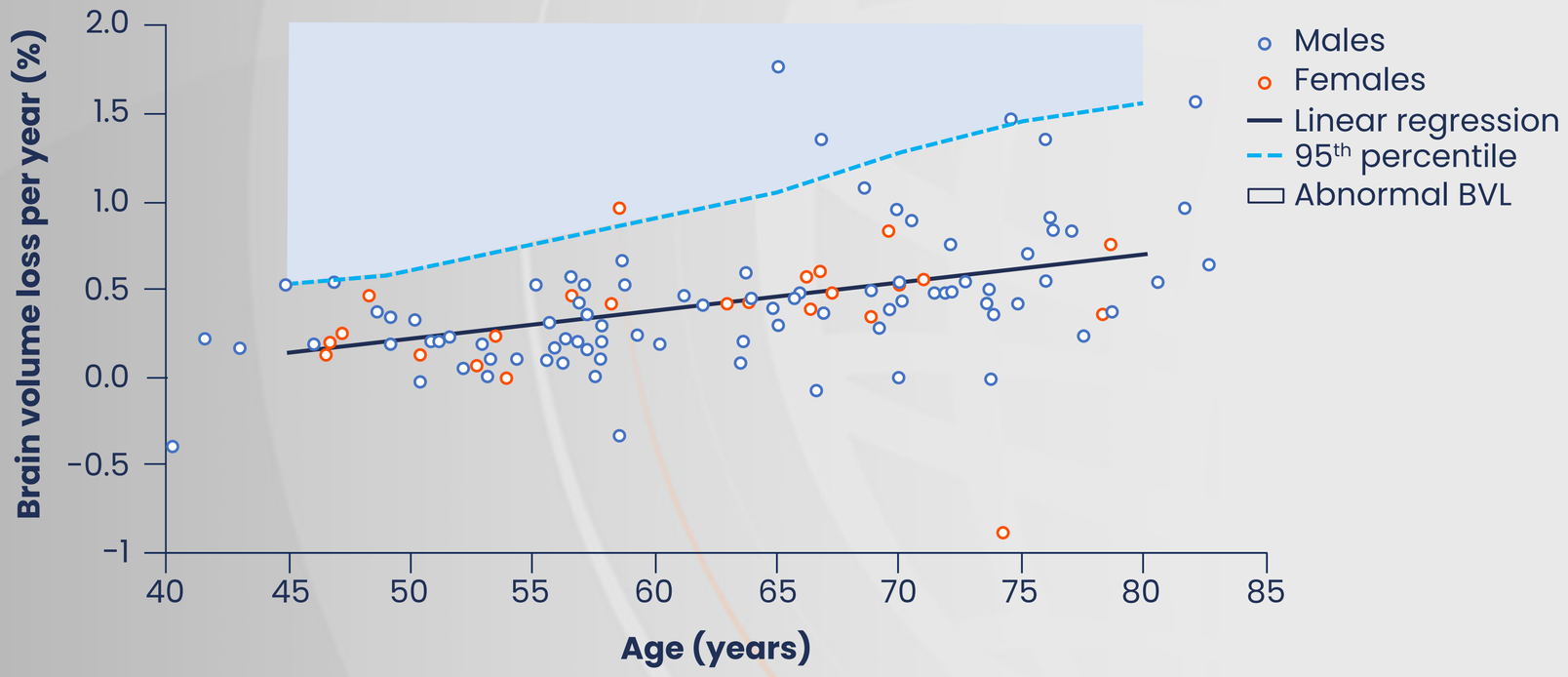
What is the role for DMTs in older patients with MS?

Ageing is one of the mechanisms underpinning MS progression[1,2]



1. Trapp BD, et al. *N Engl J Med.* 1998;338:278–85; 2. Giovannoni G, 2019. Available at: www.multiple-sclerosis-research.org/2019/04/old-age-how-is-it-going-to-affect-me (accessed March 2021).

Estimated brain volume loss using SIENA/FSL: Longitudinal brain volumetry in healthy adults



BVL, brain volume loss; FSL, FMRIB Software Library; SIENA, structural image evaluation, using normalization, of atrophy.
Opfer R, et al. *Neurobiol Aging.* 2017;65:1–6.

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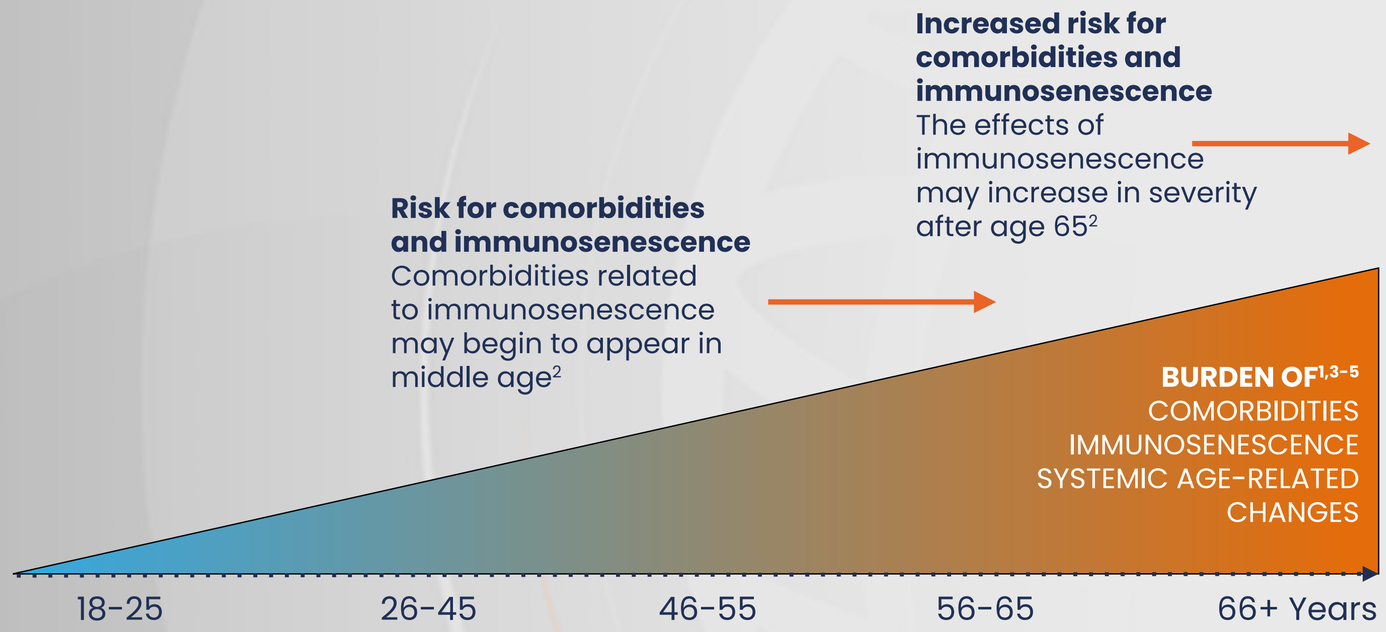
Ageing is a significant factor affecting the course of MS



Generational shift[6-9]
Age of diagnosis is skewing younger
Different generations may have different priorities and approaches to life stage issues that may affect management[1,3-5]

Ageing population[1]
The average age of people with MS is rising, partly due to improved management[1]

1. Sanai SA, et al. *Mult Scler.* 2016;22:717–25; 2. Farber DL, et al. *Nat Rev Immunol.* 2014;14:24–35; 3. Thomas-Vaslin V, et al. In: Kapur S, Portela MB, Eds. *Immunosuppression - Role in Health and Diseases.* InTech. 2012; 4. Marrie RA, et al. *Neurology.* 2016 86:1279–86; 5. Goronzy JJ, Weyand CM. *Nat Immunol.* 2013;14:428–36; 6. National Multiple Sclerosis Society. Available at: www.nationalmssociety.org/What-is-MS/Who-Gets-MS (accessed March 2021); 7. Multiple Sclerosis Association of America. Available at: www.mymsaa.org/ms-information/faqs (accessed March 2021); 8. Rovira A, et al. *Nat Rev Neurol.* 2015;11:471–82; 9. Bar-Or A, Antel JP. *Curr Opin Neurol.* 2016;29:381–87.

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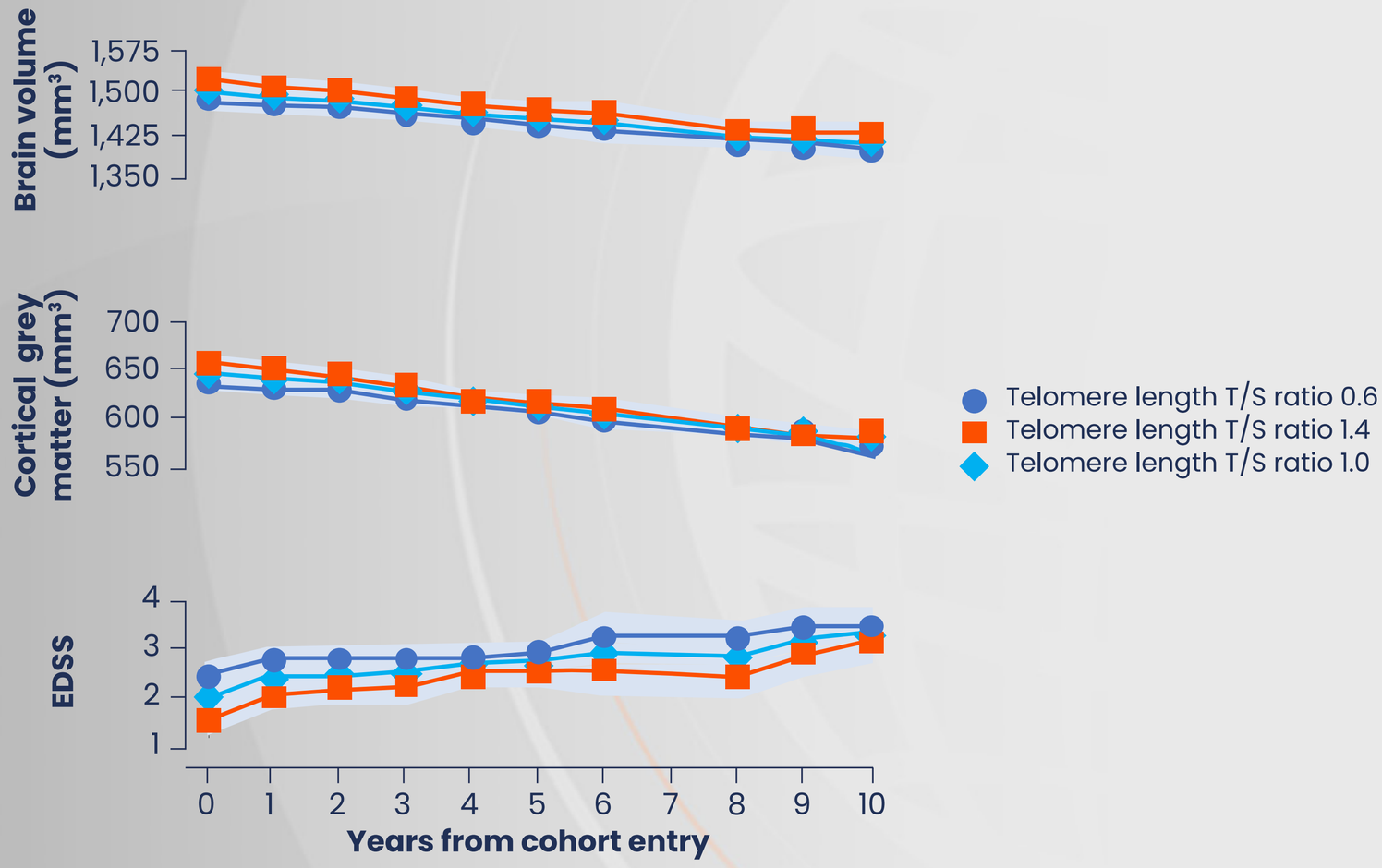
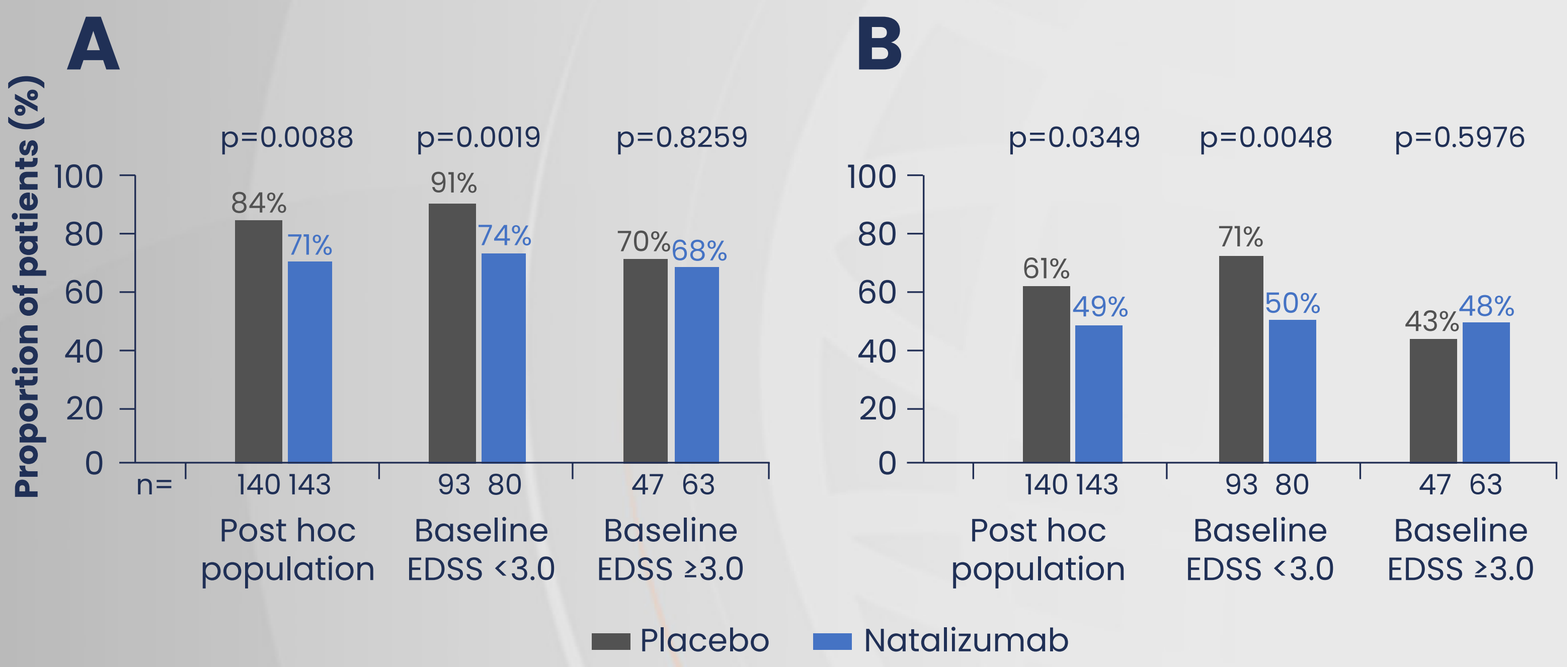
Telomere length is associated with disability progression in MS



EDSS, Expanded Disability Status Scale.

Krysko KM, et al. *Ann Neurol.* 2019;86:671–82.

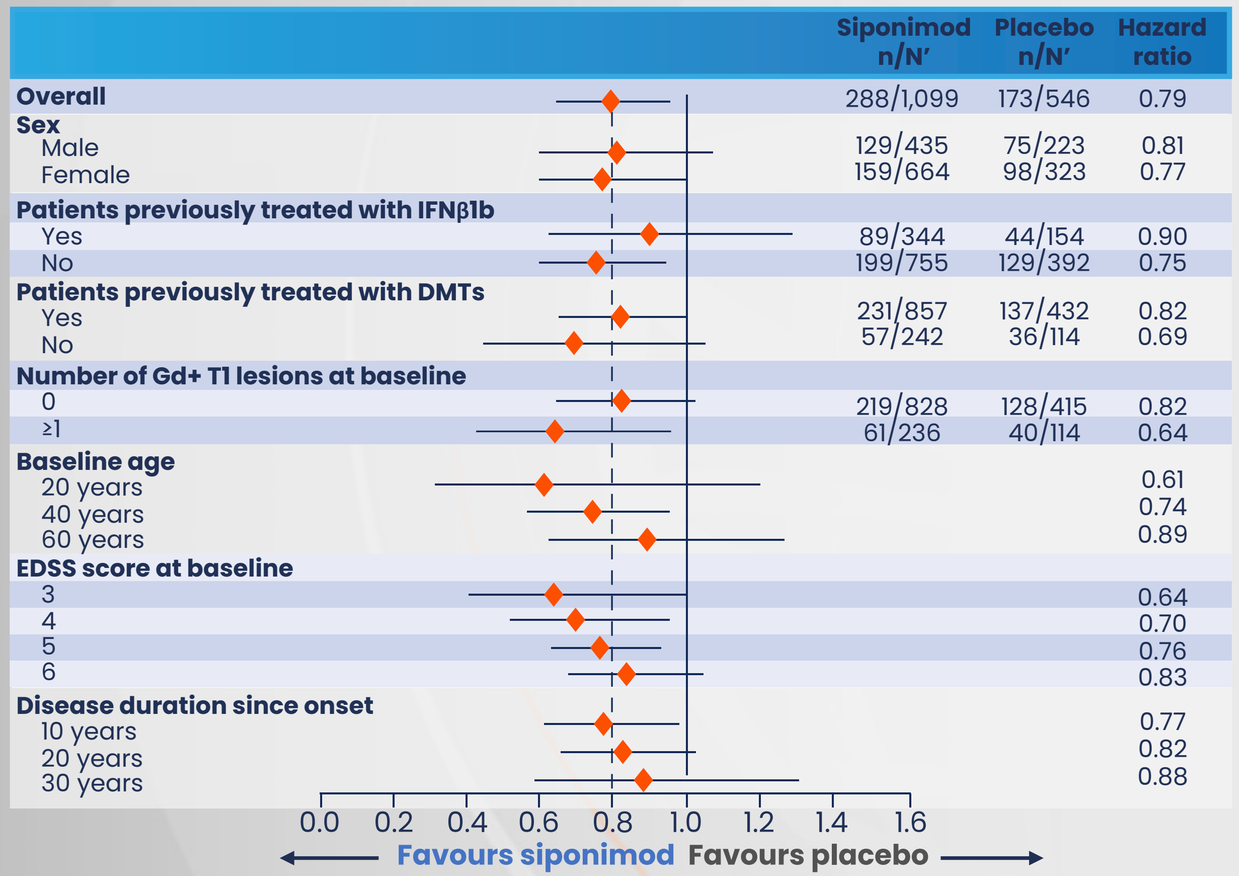
Natalizumab and clinical recovery from relapses



Proportion of patients with ≥0.5-point (A) and ≥1.0-point (B) increase in EDSS score from pre-relapse to relapse (relapse severity)

Lublin FD, et al. *Mult Scler Relat Disord.* 2014;3:705–11.

Siponimod vs placebo in SPMS (EXPAND): A double-blind, randomized, phase III study



EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFNβ1b, interferon beta-1b; SPMS, secondary progressive multiple sclerosis.
Kappos L, et al. *Lancet.* 2018;391:1263–73.

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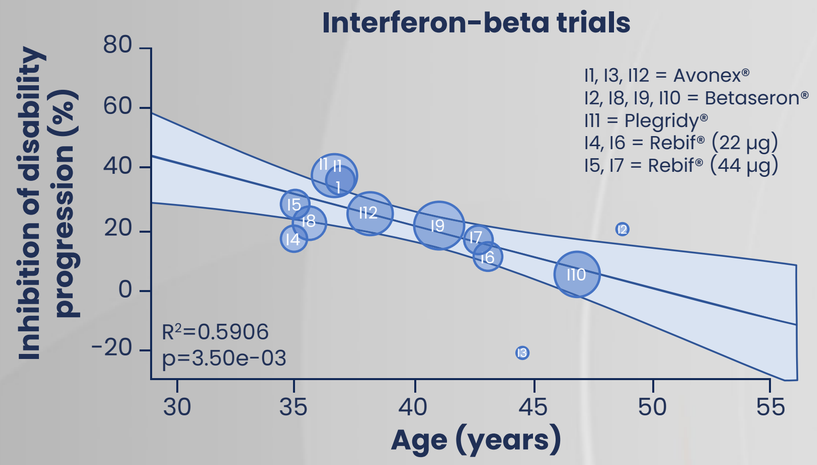
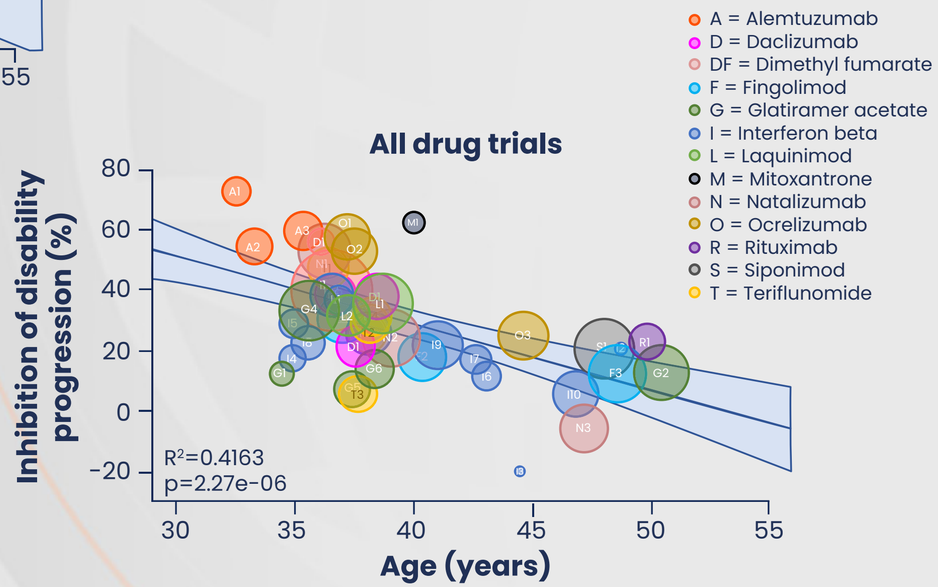
Meta-analysis of the age-dependent efficacy of MS treatments





Weideman AM, et al. *Front Neurol.* 2017;8:577.

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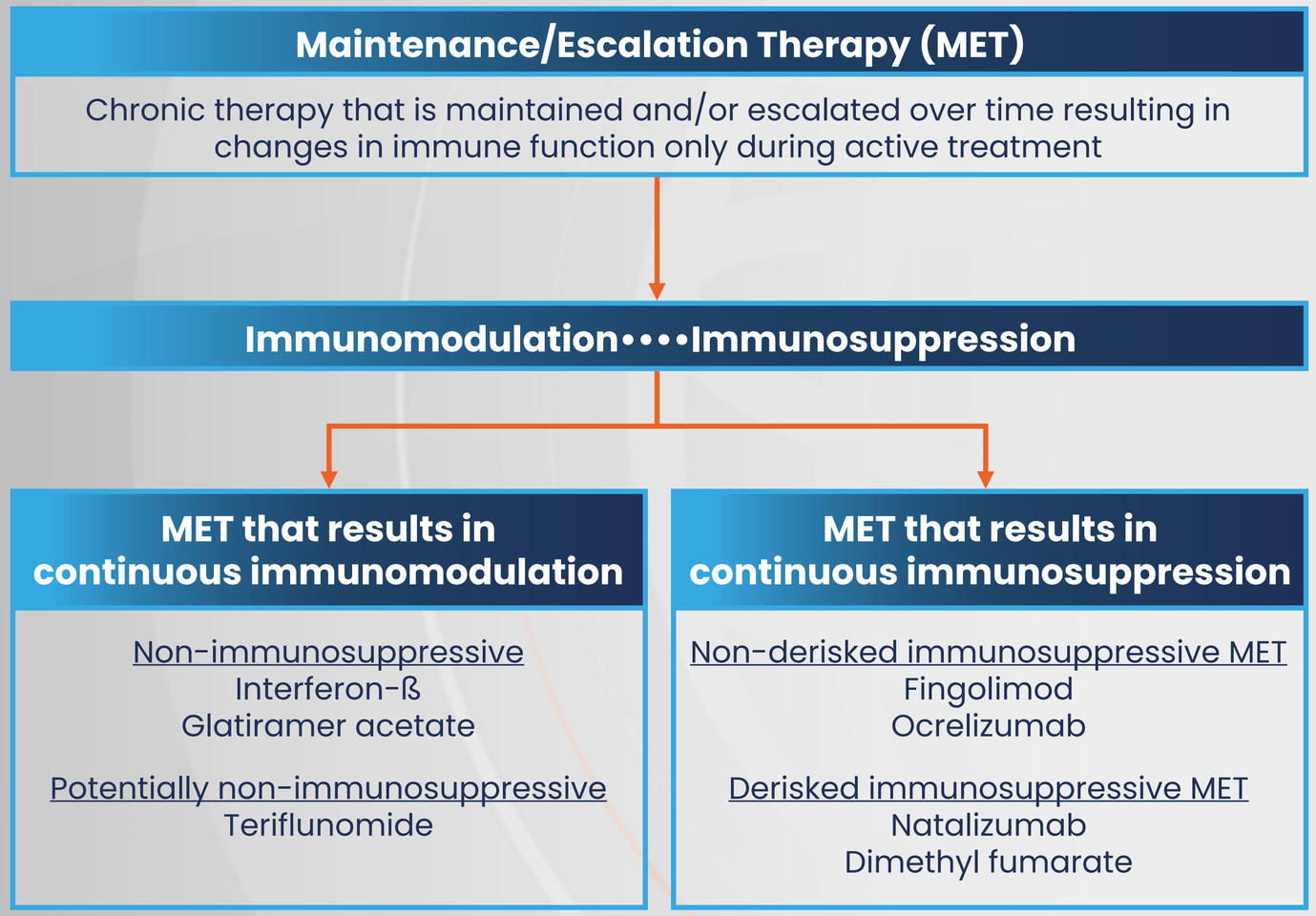
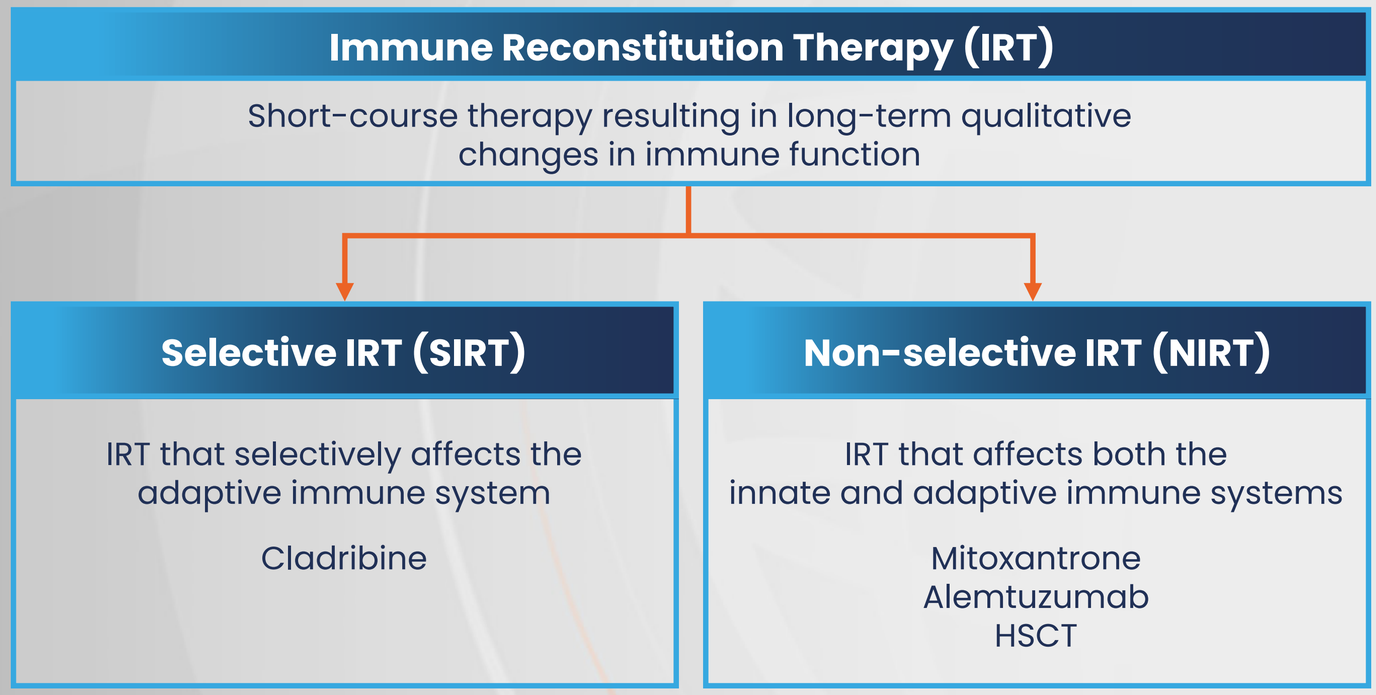
Classification of DMTs for relapsing forms of MS



Giovannoni G. *Curr Opin Neurol.* 2018;31:233–43.

Classification of DMTs for relapsing forms of MS

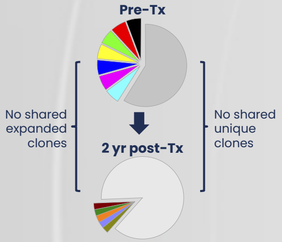


HSCT, haematopoietic stem cell transplantation.
Giovannoni G. *Curr Opin Neurol*. 2018;31:233–43.

Thymic output generates a new and diverse TCR repertoire after ASCT in patients with MS

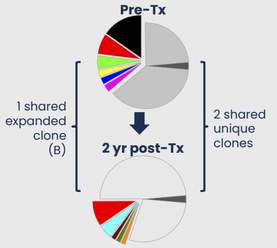
Patient 1, CD4+, TCRBV1 (TRB09*)

Pre-Tx	A	TRBV9*01,	TRBJ2-2*01,	TRBD2*02	CASSVGEGLNTGELFF
	B	TRBV9*02,	TRBJ1-1*01,		CAGTSSNTEAFF
	C	TRBV9*01,	TRBJ1-3*01,	TRBD2*02	CASSSGGLPGNTIYF
	D	TRBV9*01,	TRBJ1-2*01,	TRBD2*01	CASNPSGGGGVYGYTF
	E	TRBV9*02,	TRBJ2-2*01,	TRBD1*01	CASSVHGTGNTGELFF
	F	TRBV9*01,	TRBJ2-5*01,	TRBD1*01	CASSAEAPGRGSNQPQHF
	G	TRBV9*01,	TRBJ2-6*01,	TRBD1*01	CASSPNDRLSSGANVLTF
		Unique sequences (n = 19; 55.9%)			
2 yr post-Tx	H	TRBV9*03,	TRBJ2-1*01,	TRBD2*01	CASSVDGASSYNEQFF
	I	TRBV9*01,	TRBJ2-1*01,	TRBD1*01	CASSLRGELYNEQFF
	J	TRBV9*03,	TRBJ2-1*01,	TRBD1*01	CASSASTAMGTEAFF
	K	TRBV9*03,	TRBJ2-6*02,		CASSVVAYNSPLHF
	L	TRBV9*03,	TRBJ2-7*01,	TRBD2*01	CASRNTSPPYEQYF
		Unique sequences (n = 62; 86.1%)			



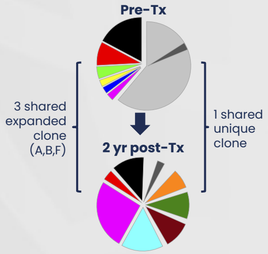
Patient 1, CD4+, TCRBV17 (TRB19*)

Pre-Tx	A	TRBV19*03,	TRBJ2-1*01,	TRBD2*01	CASSSGDQMRQFF
	B	TRBV19*01,	TRBJ1-2*01,		CASSIDLQTSYFYTFGSG
	C	TRBV19*03,	TRBJ2-1*01,	TRBD2*02	CASSIGEGNEQFF
	D	TRBV19*03,	TRBJ1-1*01,	TRBD1*01	CQTSSWVGGKGEAFF
	E	TRBV19*03,	TRBJ2-7*01,	TRBD1*01	CASRDSSGGAYEQYE
	F	TRBV19*02,	TRBJ2-5*01,	TRBD1*01	CASSTSGGPSNQPQHF
		Unique sequences (n = 43; 61.4%)			
2 yr post-Tx	B	TRBV19*03,	TRBJ1-2*01,		CASSIDLQTSYGYTFGSG
	G	TRBV19*02,	TRBJ1-5*01,		CASSIDANNQPQHF
	H	TRBV19*03,	TRBJ2-7*01,	TRBD1*01	CASSQRGATYEQYF
	I	TRBV19*01,	TRBJ1-2*01,		CASSIDLNAGARHGYTFGSG
	J	TRBV19*01,	TRBJ1-2*01,		CASPVPAFREQFFGPG
		Unique sequences (n = 59; 80.8%)			



Patient 5, CD8+, TCRBV21 (TRB11*)

Pre-Tx	A	TRBV11-1*01,	TRBJ2-2*01,	TRBD1*01	CASSLAANYGYTF
	B	TRBV11-3*04,	TRBJ1-2*01,	TRBD2*01	CASSLAANYGYTF
	C	TRBV11-2*01,	TRBJ2-5*01,	TRBD2*01	CASSFSGGAETQYF
	D	TRBV11-1*01,	TRBJ2-1*01,	TRBD2*01	CASSPSGGVYNEQFF
	E	TRBV11-1*01,	TRBJ2-1*01,	TRBD2*01	CASLVGGLSYNEQFF
	F	TRBV11-2*01,	TRBJ2-1*01,	TRBD1*01	CASSLVPTGPNSYNEQFF
		Unique sequences (n = 37; 60.7%)			
2 yr post-Tx	A	TRBV11-1*01,	TRBJ1-2*01,	TRBD2*01	CASSLAANYGYTF
	B	TRBV11-3*01,	TRBJ2-2*01,	TRBD2*01	CASSLAANYGYTF
	F	TRBV11-2*01,	TRBJ2-1*01,	TRBD1*01	CASSLVPTGPNSYNEQFF
	G	TRBV11-2*01,	TRBJ2-7*01,	TRBD1*01	CASSLEQGALYEQYF
	H	TRBV11-3*01,	TRBJ2-1*01,	TRBD1*01	CASSLVPTGPNSYNEQFF
	I	TRBV11-3*04,	TRBJ2-1*01,	TRBD1*01	CASSLVPTGPNSYNEQFF
	J	TRBV11-3*04,	TRBJ2-7*01,	TRBD1*01	CASSLEQGALYEQYF
		Unique sequences (n = 62; 86.1%)			



ASCT, autologous stem cell transplant; TCR, T-cell receptor.
Muraro PA, et al. *J Exp Med.* 2005;201:805–16.

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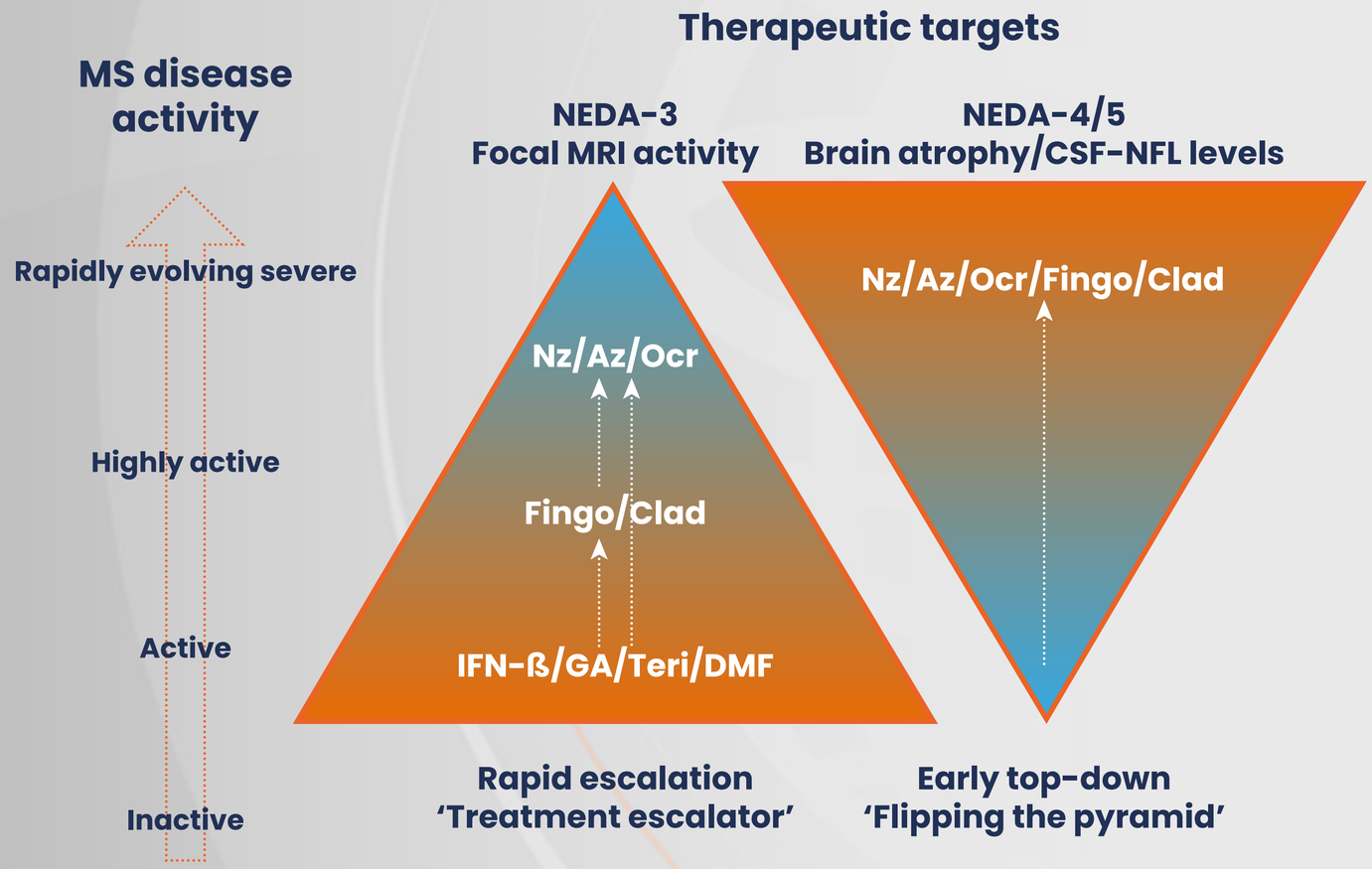
Different therapeutic approaches to the use of DMTs in the treatment of relapsing forms of MS



Az, alemtuzumab; Clad, oral cladribine; Dac, daclizumab; DMF, dimethyl fumarate; Fingo, fingolimod; GA, glatiramer acetate; IFN-β, interferon-beta; 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 normalizing brain atrophy loss and normalization of CSF neurofilament levels; Nz, natalizumab; Ocr, ocrelizumab; Teri, teriflunomide.

Giovannoni G. *Curr Opin Neurol.* 2018;31:233–43.

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Conclusions

Ageing or senescence contribute to MS worsening

- Reduce brain reserve
- Early ageing

Biomarkers of senescence are associated with MS-related disability

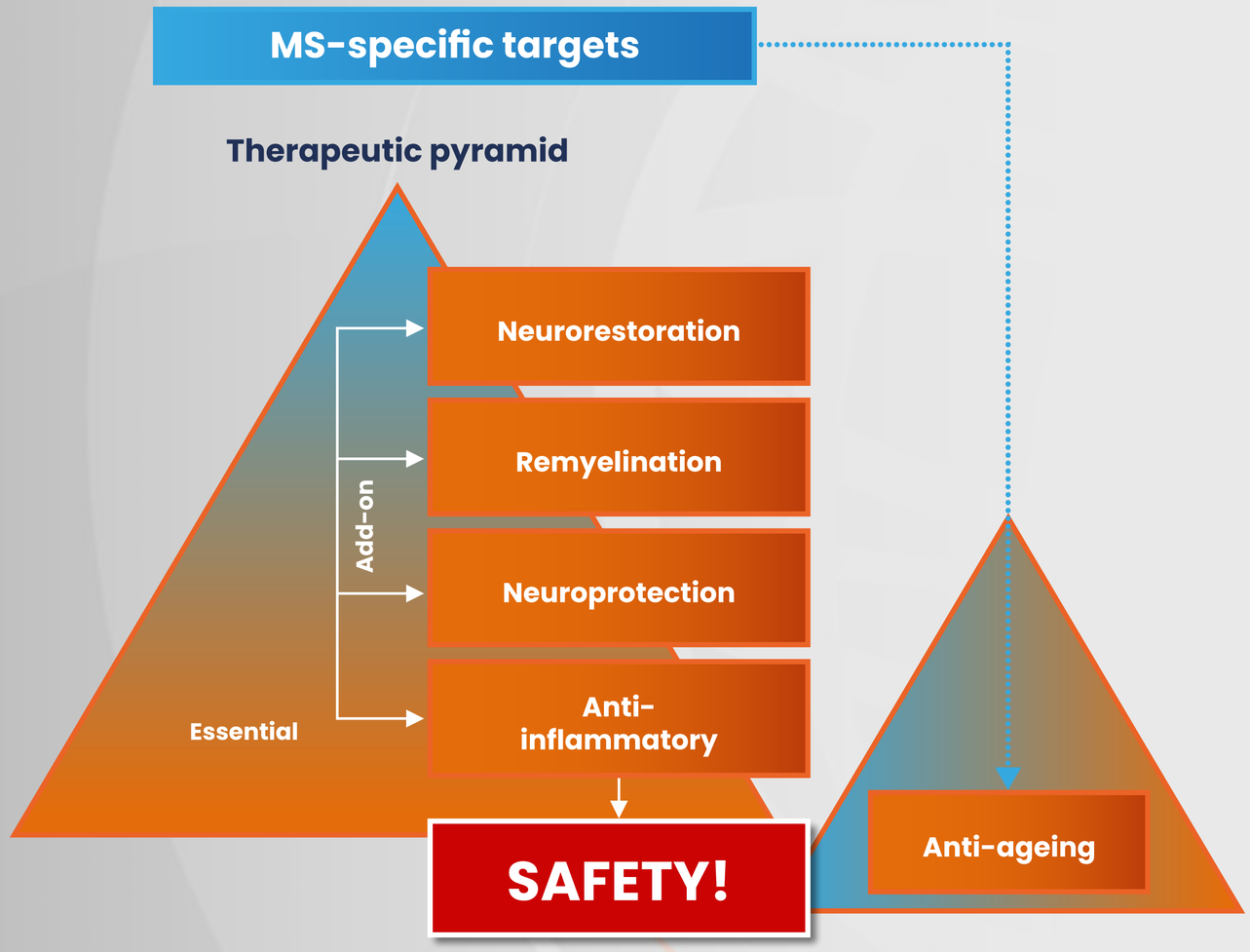
MS-related disease activity may speed up ageing

Ageing is associated with a reduced therapeutic response of DMTs

Although the principles of treating MS are similar in young and older patients, other factors, e.g. safety, need to be considered when adopting a specific therapeutic strategy or choosing a specific DMT

How will practice change in the near future for older patients with MS?

Addressing the unmet need: A holistic therapeutic strategy



Giovannoni G. *Curr Opin Neurol.* 2018;31:233–43.

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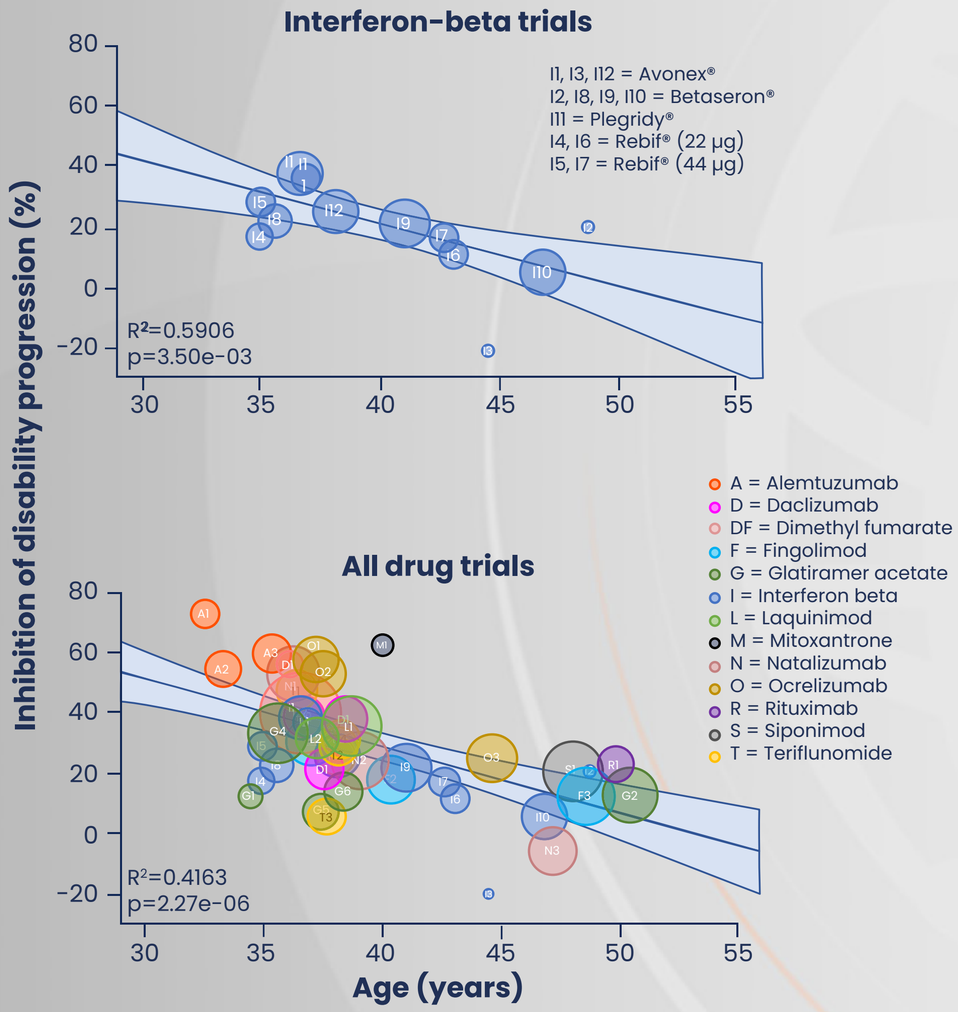
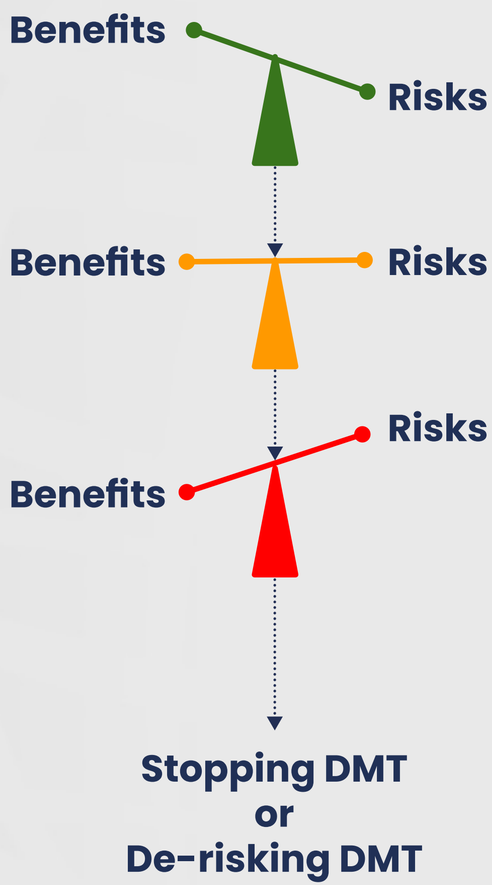
Meta-analysis of the age-dependent efficacy of MS treatments





Weideman AM, et al. *Front Neurol.* 2017;8:598.

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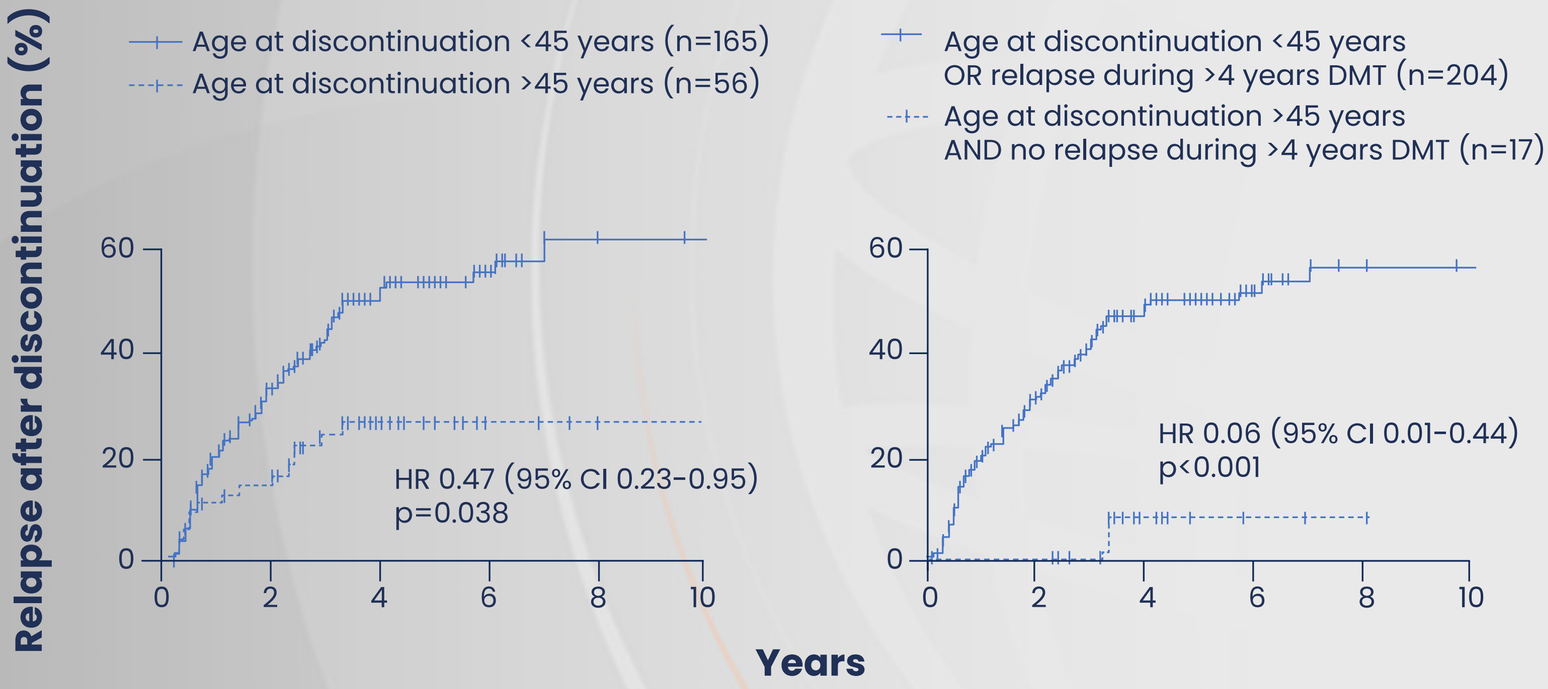
Discontinuation of DMTs in MS



CI, confidence interval; HR, hazard ratio.
Bsteh G, et al. *Mult Scler.* 2017;23:1241–8.

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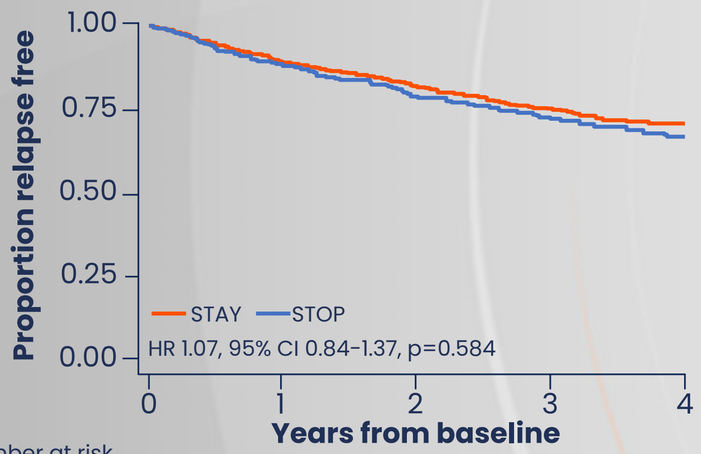
DMTs in MS after a prolonged relapse-free period

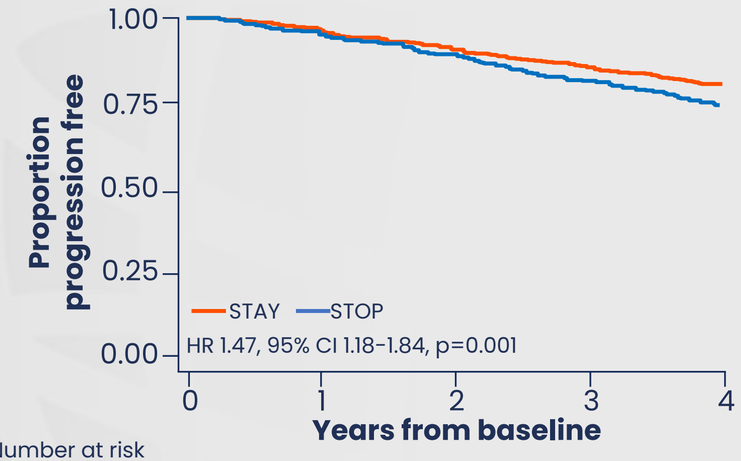
First relapse



Number at risk

STAY 852	594	448	344	98
STOP 426	297	224	172	49

Confirmed disability progression



Number at risk

STAY 828	797	747	685	456
STOP 391	371	338	296	185

Kister I, et al. *J Neurol Neurosurg Psychiatry.* 2016;87:1133–7.

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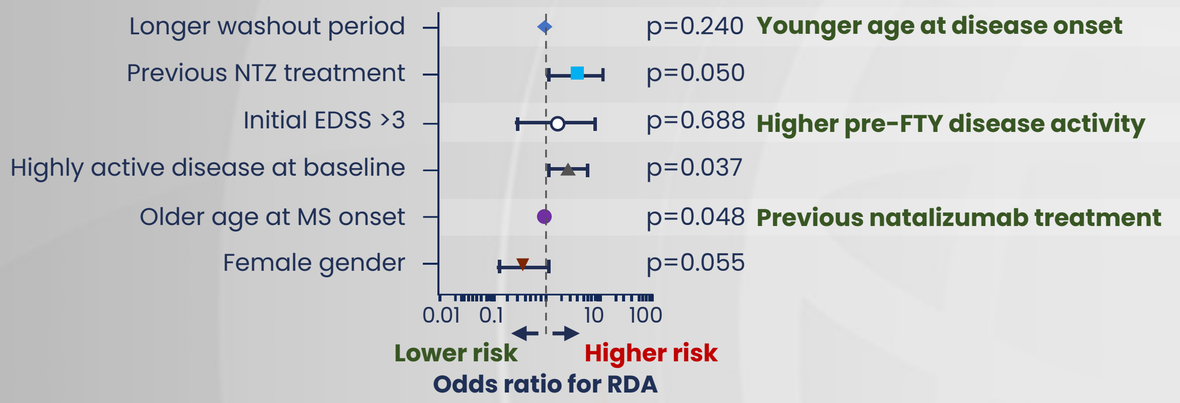
Incidence of recurrence of disease activity after fingolimod discontinuation in older patients

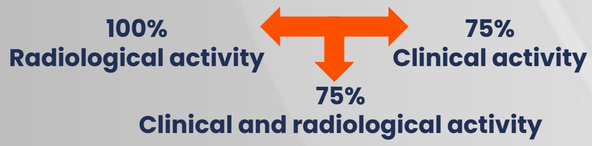
WHICH PATIENTS experience RDA?

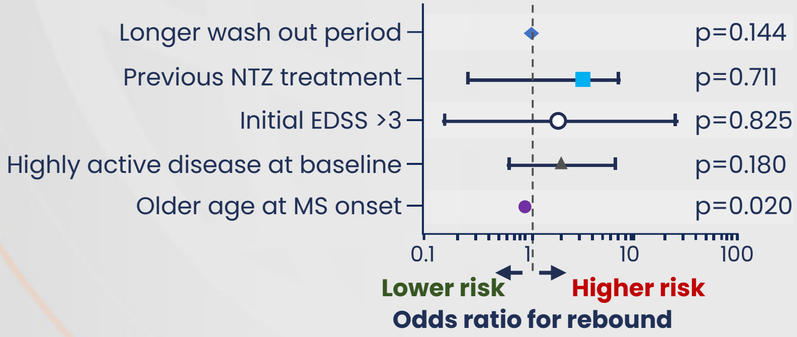


12.5% of patients experienced rebound disease activity

WHICH PATIENTS experience rebound?

- **62.5%** of patients previously stable on treatment
- **37.5%** of patients had no DMT at rebound
- **MRI activity** rather than clinical relapses pre-FTY correlated with rebound





EDSS, Expanded Disability Status Scale; FTY, fingolimod; MRI, magnetic resonance imaging; NTZ, natalizumab; RDA, recurrence of disease activity.
Pantazou V, et al. MSVirtual2020 ePoster P0092. Available at: https://library.msvirtual2020.org/ (accessed March 2021).

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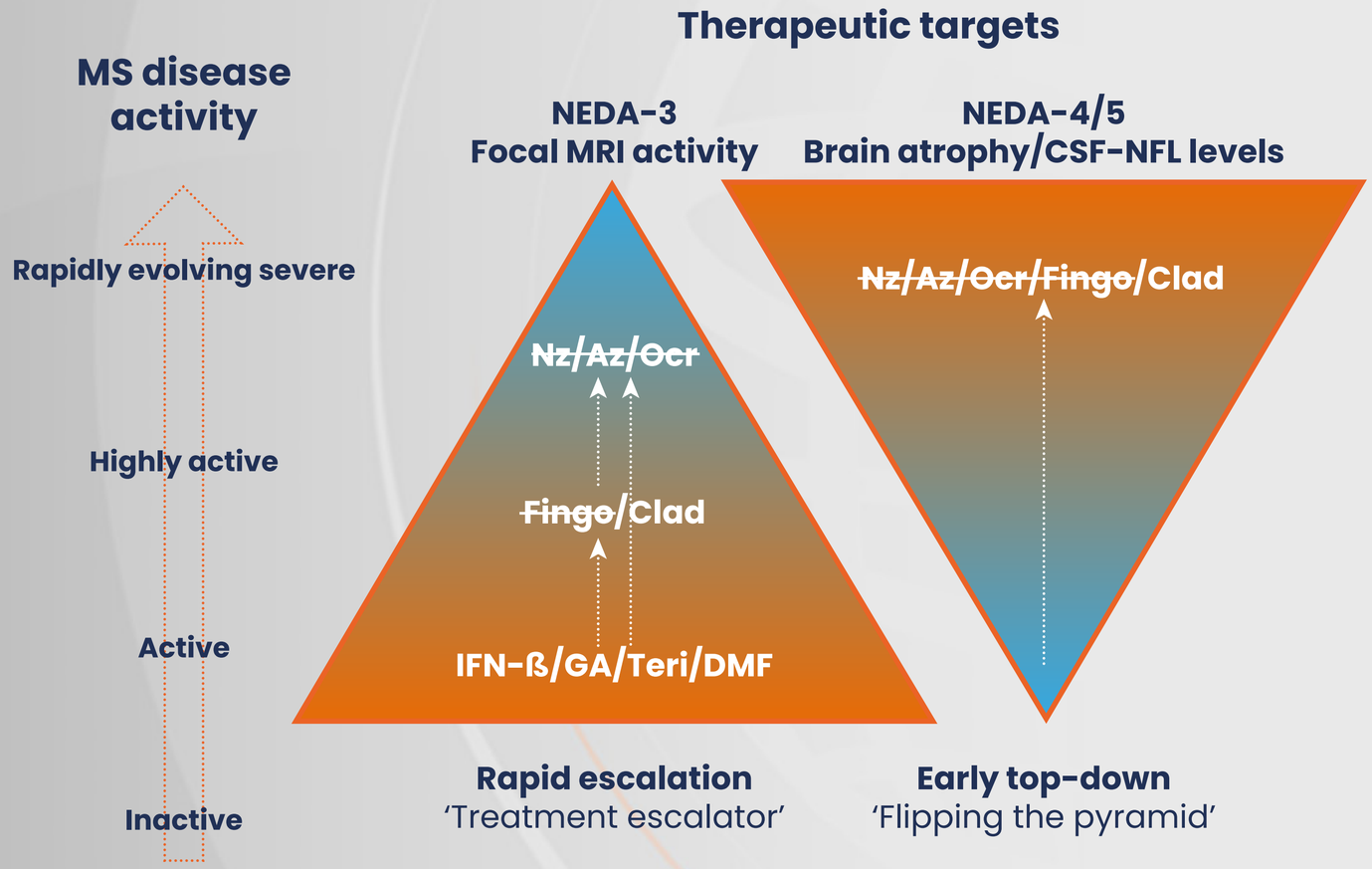
Different therapeutic approaches to the use of DMTs in the treatment of relapsing forms of MS



Az, alemtuzumab; Clad, oral cladribine; Dac, daclizumab; DMF, dimethyl fumarate; Fingo, fingolimod; GA, glatiramer acetate; IFN-β, interferon-beta; 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 normalizing brain atrophy loss and normalization of CSF neurofilament levels; Nz, natalizumab; Ocr, ocrelizumab; Teri, teriflunomide.

Giovannoni G. *Curr Opin Neurol.* 2018;31:233–43.

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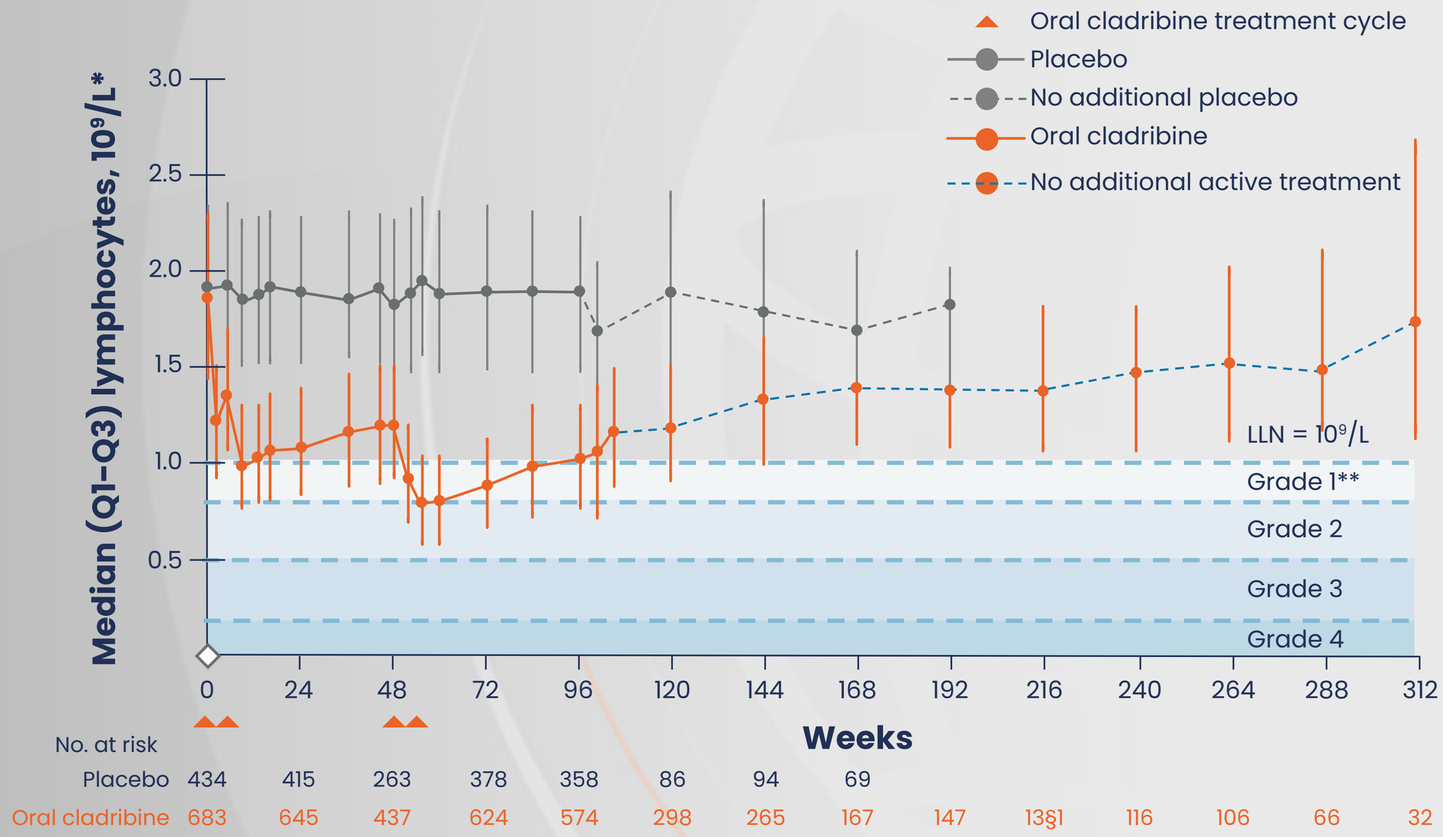
Oral cladribine is associated with a reduction in lymphocyte count



*Pooled data from CLARITY, CLARITY EXT, and PREMIERE. **Grade 1: < lower limit of normal (LLN)–800/mm³; grade 2: <800–500/mm³; grade 3: <500–200/mm³; grade 4: <200/mm³.
Giovannoni G. *Neurotherapeutics.* 2017;14:874–87.

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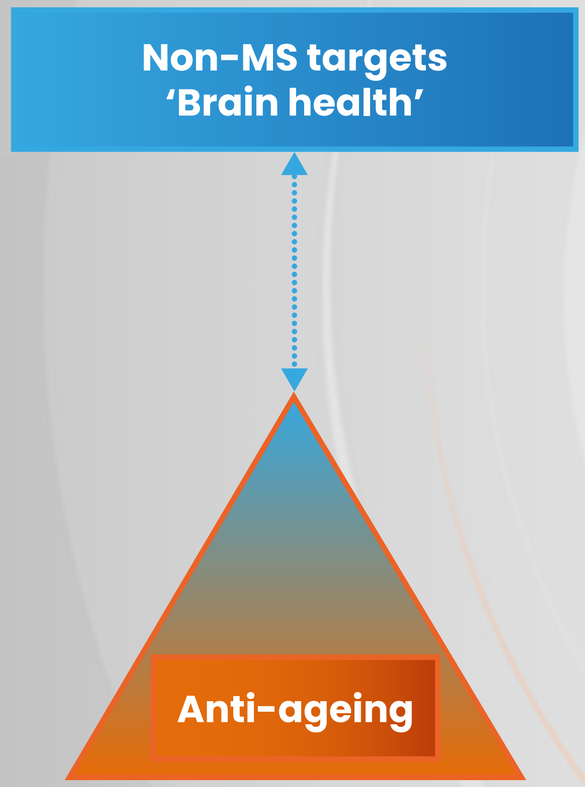
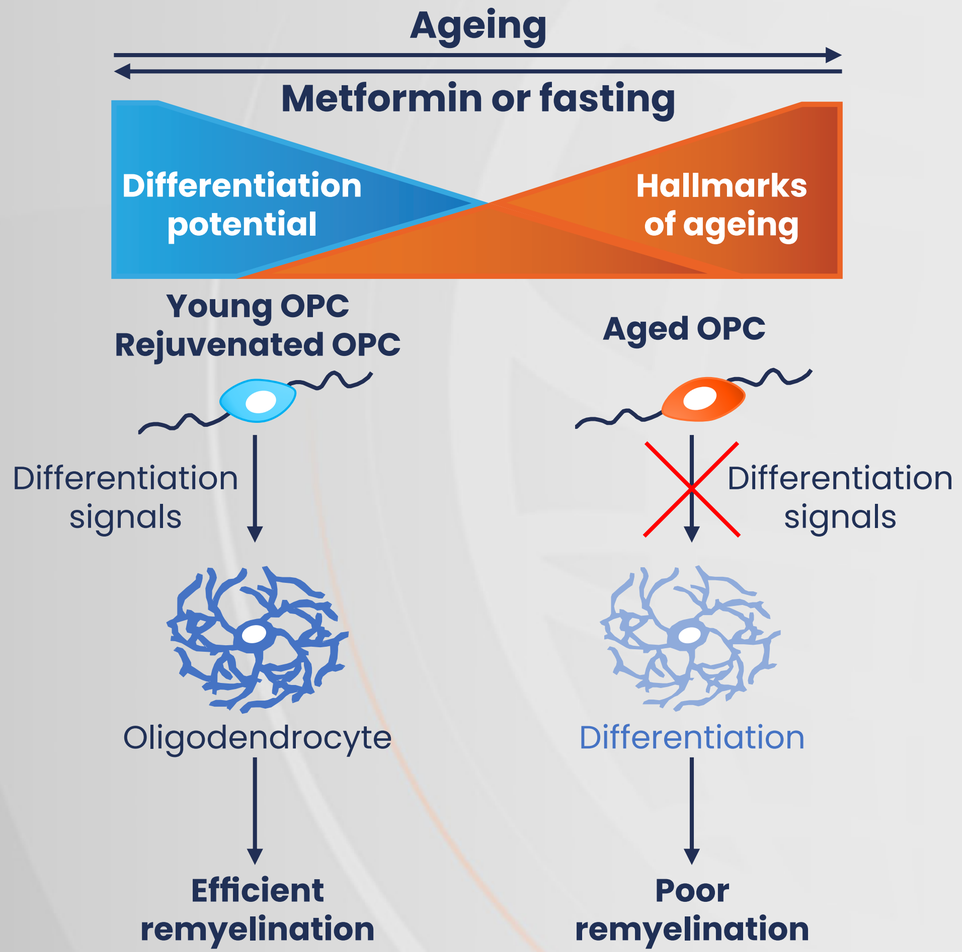
Addressing the unmet need: A holistic therapeutic strategy



- **Smoking**
- **Exercise**
- **Diet**
  - Reduce brain reserve
  - Early ageing
- **Sleep**
- **Comorbidities**
- **Infections**
  - UTIs
  - Periodontitis
  - Sinusitis
  - Respiratory
- **Concomitant medications**
  - Anticholinergics
- **Drugs**
  - Metformin
- **Social determinants of health**
  - Social isolation
  - Social capital
- **HRT**
- **Wellness**

HRT, hormone-replacement therapy; UTIs, urinary tract infections.
Giovannoni G. *Curr Opin Neurol.* 2018;31:233–43.

Metformin restores CNS remyelination capacity by rejuvenating aged stem cells



OPC, oligodendrocyte progenitor cells.
Neumann B, et al. *Cell Stem Cell.* 2019; 25:473–85.

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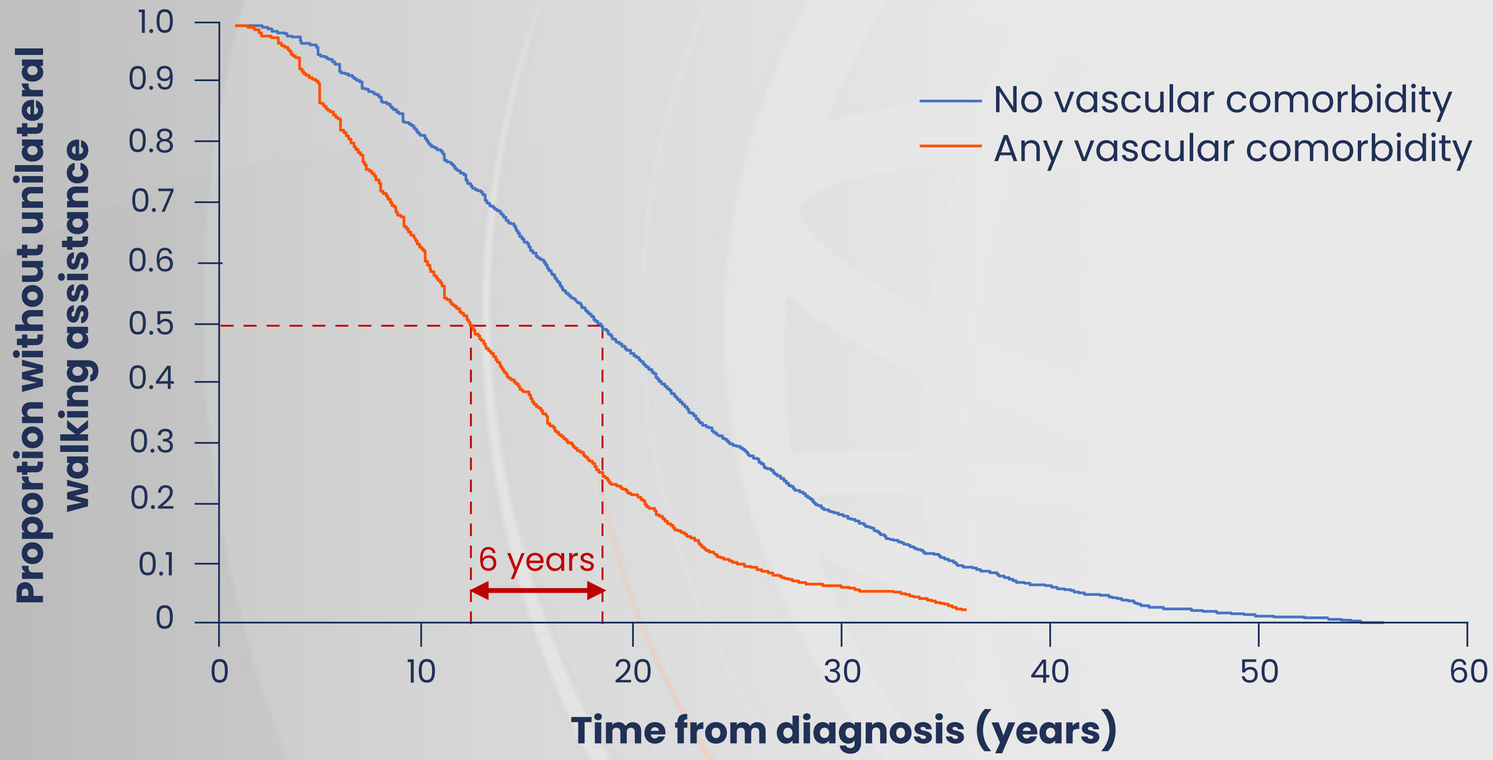
Vascular comorbidity accelerates disability progression



Marrie RA, et al. *Neurology*. 2010;74:1041–7.

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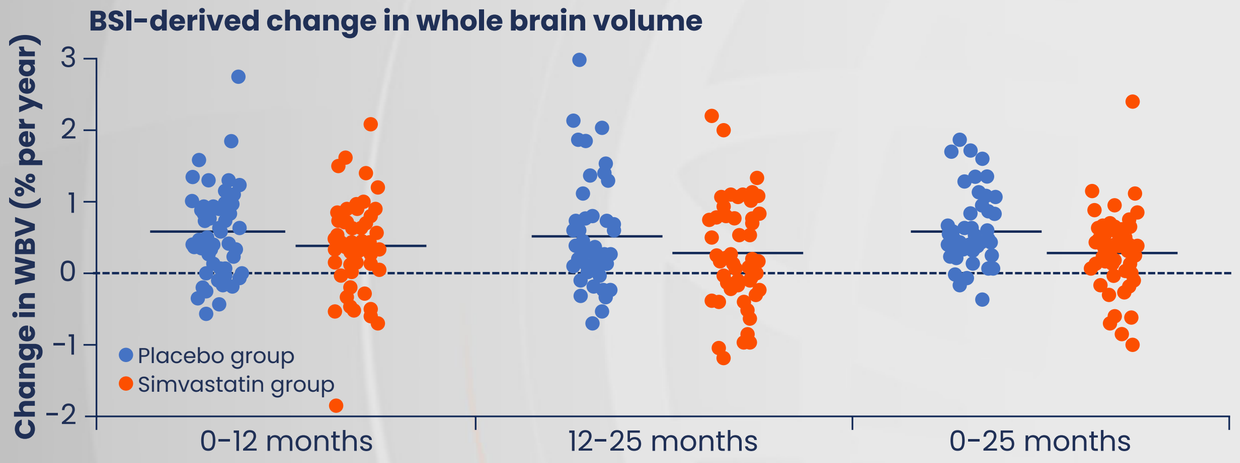
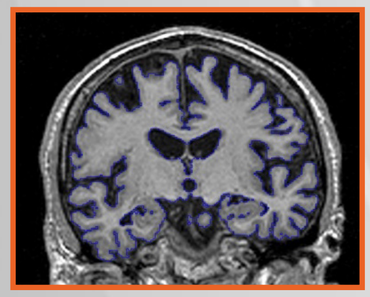
Comorbidities[1,2]

High-dose simvastatin in SPMS: MS-STAT trial





BSI (Boundary Shift Integral)

SPMS, secondary progressive multiple sclerosis; WBV, whole brain volume.

1. Chataway J, et al. *Lancet.* 2014;383:2213–21; 2. Chataway J. Trials in Secondary Progressive MS. Presented at MS Trust Annual Conference, 3–5 November 2013.

Conclusions

Immunosenescence is a natural aspect of ageing and has implications for the management of MS

- Stopping and/or derisking immunosuppressive DMTs
  - Risk of rebound and recurrent disease activity
- Hyper-pharmacovigilance
  - Infections and secondary malignancies
- Annual vaccination

Holistic approach to MS treatment

- Lifestyle and wellness including diet
- Anti-ageing strategies

Proactive approach to screening and managing comorbidities and other factors that impact on MS outcomes

Urgent need to develop an evidence base to deal with these issues that arise with managing MS in the elderly