Optimizing the management of patients with relapsing forms of MS: An update on diagnosis and emerging treatment options

touch™ NEUROLOGY

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by USF Health and touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by USF Health or touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in USF Health or touchIME activities*
- *USF Health and touchIME accept no responsibility for errors or omissions*

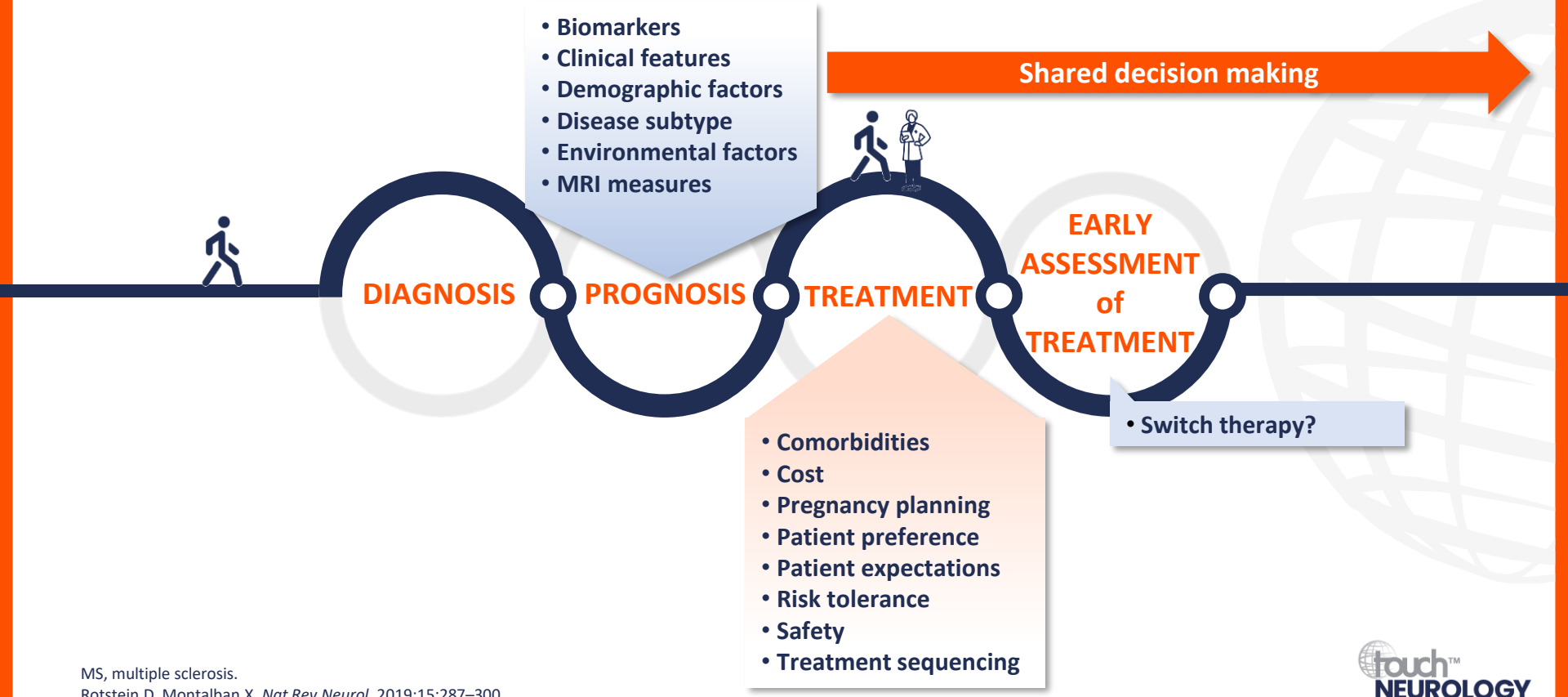
Optimizing the use of DMTs: What are the key considerations for achieving an appropriately personalized treatment strategy?

Prof. Martin Weber

University Medical Center
Göttingen, Germany

touch™ NEUROLOGY

Considerations for the personalized treatment of MS



MS, multiple sclerosis.

Rotstein D, Montalban X. *Nat Rev Neurol.* 2019;15:287–300.

touch™ NEUROLOGY

Importance of patient-driven treatment in MS

Patient preferences[1]

Primary treatment goals

Slowing disease progression

Managing symptoms

Day-to-day treatment goals

Slowing disease progression

Managing symptoms

Many patients would like to know about their long-term prognosis, but **clinicians need to check patients' preferences and psychological readiness**, over time[2]

Patient-centred care should consider **patients' needs and preferences** to engage patients in treatment decisions[2]

HCPs and patients have different priorities[3]
Practical requirements are important to patients but are often overlooked by HCPs[3]

HCPs must provide **accurate and clear information** to support patients[3]

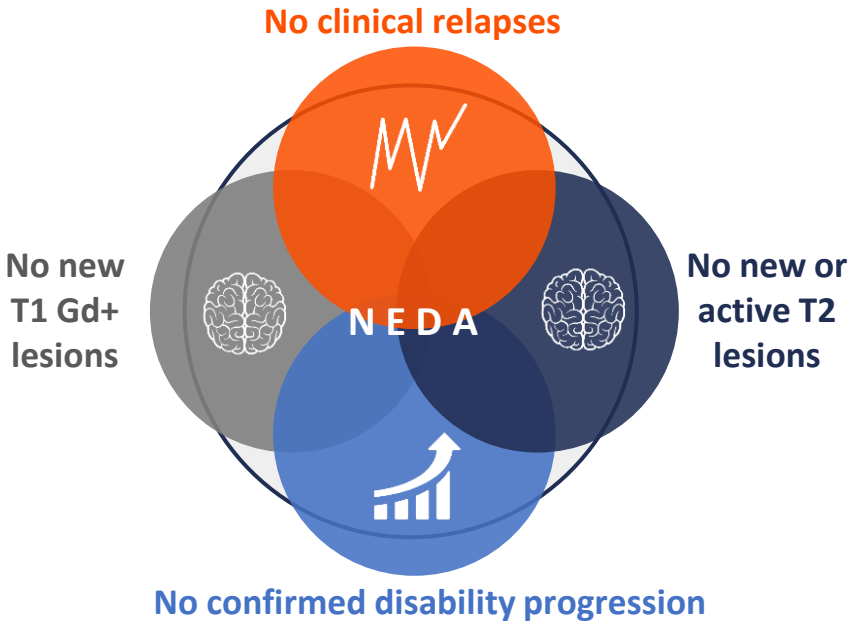
HCP, healthcare professional; MS, multiple sclerosis.

1. Newsome SD, et al. *Mult Scler Relat Disord*. 2022;68:104376; 2. Castillo-Triviño T, et al. *Mult Scler Relat Disord*. 2022:64:103969;
3. Reickmann P, et al. *Mult Scler Relat Disord*. 2018:19:153–60.

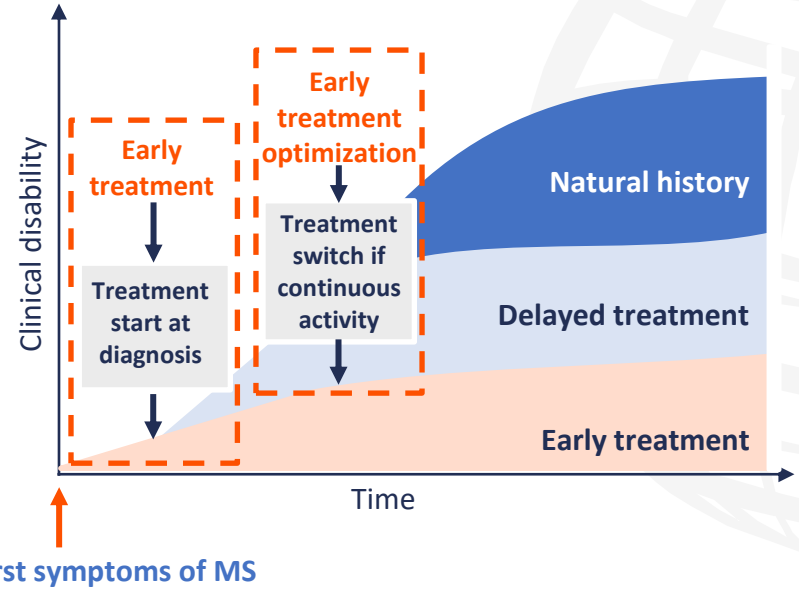
touch™ NEUROLOGY

Clinical targets for patients with MS

Treatment goals[1,2]



'Windows of opportunity'[3]



Gd+, gadolinium enhanced; MS, multiple sclerosis; NEDA, no evident disease actvity.

1. Beadnall HN, et al. *Ther Adv Neurol Disord*. 2019;12:1756286418823462; 2. Newsome SD, et al. *Neurol Ther*. 2023;doi: 10.1007/s40120-023-00549-7;
3. Ziemssen T, et al. *J Neurol*. 2016;263:1053–65;

touch™ NEUROLOGY

Factors associated with poor outcomes in MS

Demographic and clinical features[1]

- Older age at onset
- Sex (male)
- Social construct of race /ethnicity
- Cardiovascular comorbidities
- Psychiatric comorbidities
- Smoking

Disease-related clinical features[1]

- Number of relapses after onset
- Poor recovery from first relapse
- Brief inter-attack intervals
- Pyramidal, cerebellar, sphincteric and/or cognitive symptoms at onset
- Clinical presentation other than optic neuritis
- Multifocal presentation at onset
- Progression at onset
- Rapidly worsening disability

MRI features[1]

- New T2 lesions over time
- Gadolinium-enhancing lesions at baseline
- Infratentorial lesions at baseline
- Spinal cord lesions at baseline

MRI prognostic biomarkers[2]

- PRL
- Cortical lesions
- Remyelinated lesions
- White matter lesions

Relevance

Laboratory measures[1]

- Presence of cerebrospinal fluid-specific oligoclonal bands

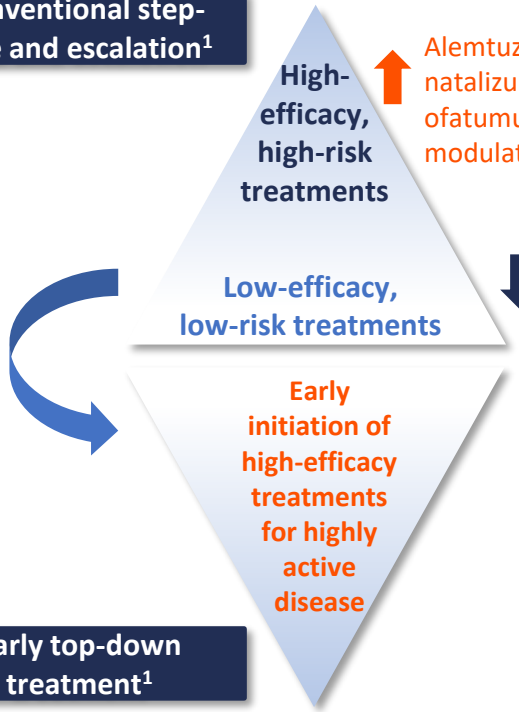
MS, multiple sclerosis; PRL, paramagnetic rim lesions.

1. Espiritu A, Oh J. *Pract Neurol*. 2022;Feb:44–8; 2. Kolb H, et al. *Neuroimage Clin*. 2022;36:103194.

touch™ NEUROLOGY

High- and medium-efficacy DMTs for RMS

Conventional step-care and escalation[1]

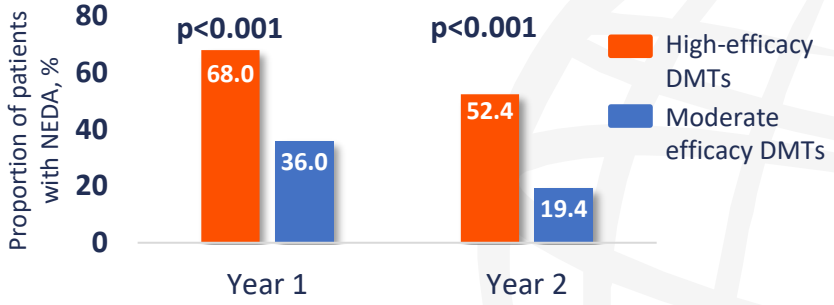


Alemtuzumab, cladribine, natalizumab, ocrelizumab, ofatumumab, rituximab, S1PR modulators[1–3]

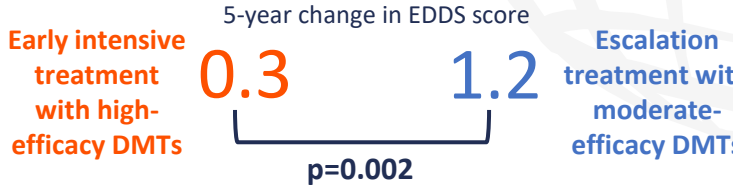
Dimethyl fumarate, glatiramer acetate, beta interferon, teriflunomide[1,3]

Early top-down treatment[1]

NEDA at year 1 and 2 was significantly more likely in patients on high-efficacy DMTs vs moderate-efficacy DMTs[3]



The 5-year change in EDDS score was significantly lower in the early intensive treatment group vs those receiving escalation therapy[4]



DMT, disease-modifying therapy; EDDS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; RMS, relapsing multiple sclerosis; S1PR, sphingosine-1-phosphate receptor.

1. Smith AL. et al. *Arch Dis Child*. 2022;107:216–22; 2. Simpson A, et al. *Curr Treat Options Neurol*. 2021;23:19;
3. Simonsen CS, et al. *Front Neurol*. 2021;12:693017; 4. Harding K, et al. *JAMA Neurol*. 2019;76:536–41.

touch™ NEUROLOGY

Understanding the role of B cells in MS pathogenesis and progression

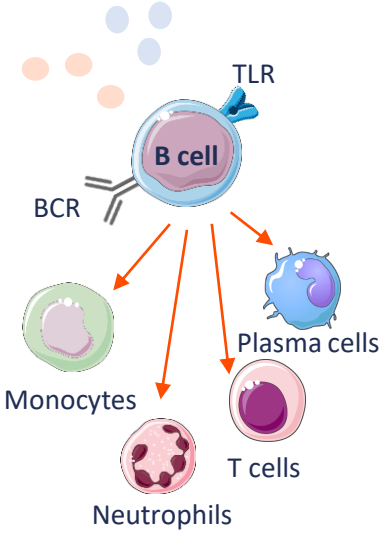
Prof. Martin Weber

University Medical Center
Göttingen, Germany

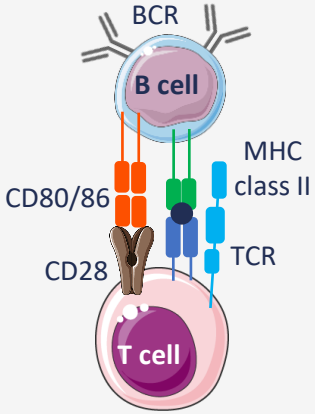
touch™ NEUROLOGY

B cells in the immune pathophysiology and pathology of MS

Interaction with other immune cells

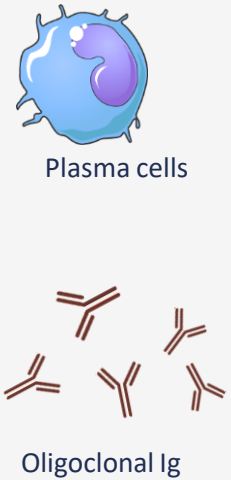


Antigen presentation

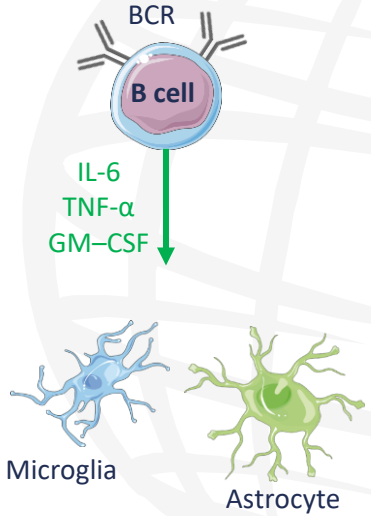


Breg dysfunction

Autoantibody production



Activation of glial cells



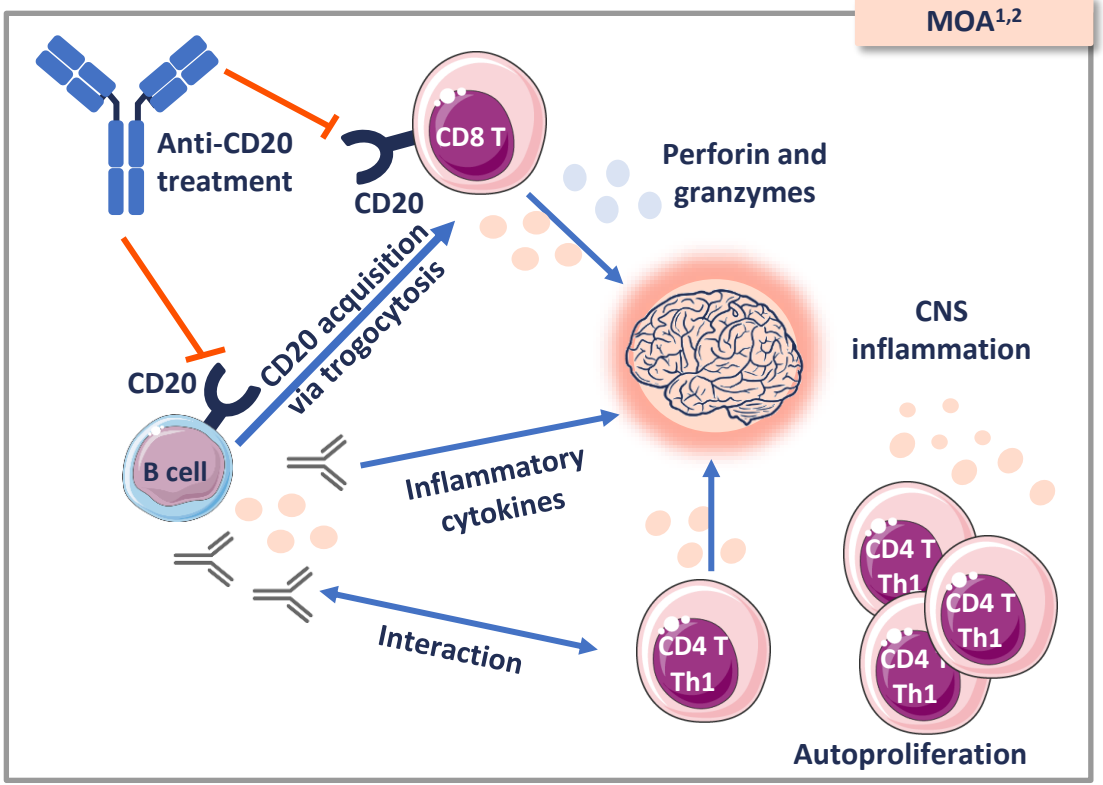
BCR, B-cell receptor; Breg, regulatory B cell; CD, cluster of differentiation; GM-CSF, granulocyte–macrophage colony-stimulating factor; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; MS, multiple sclerosis; PD-L1, programmed death ligand 1; TCR, T-cell receptor; Teff, effector T cell; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; TNF-α, tumour necrosis factor-α.

Margoni M, et al. *J Neurol.* 2022;269:1316–34.

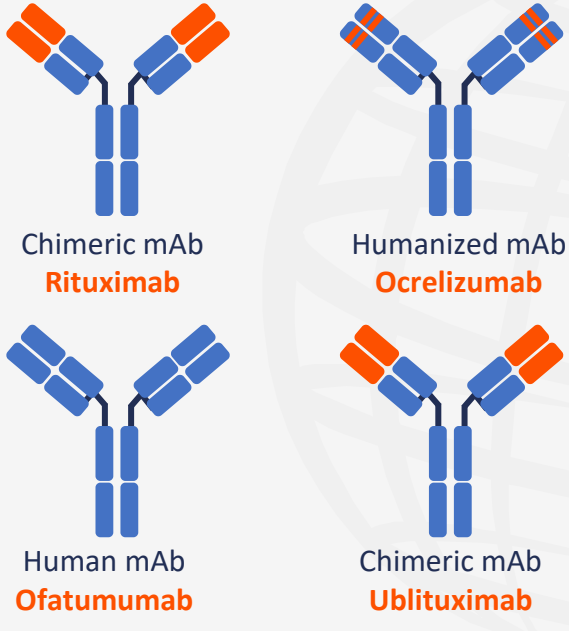
touch™ NEUROLOGY

CD20-targeting treatments

MOA[1,2]



Anti-CD20 monoclonal antibodies[3]



Cell images: Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).
CD, cluster of differentiation; CNS, central nervous system; mAb, monoclonal antibody; MOA, mode of action; Th1, type 1 T-helper cell.

1. Ochs J, et al. *Sci Transl Med. 2022*;14: eabi4632; 2.Heming M, Wiendl H. *Proc Natl Acad Sci USA*. 2023;120:e2221544120; 2. Margoni M, et al. *J Neurol*. 2022;269:1316–34.

touch™ NEUROLOGY

CD20-targeting treatments: Key efficacy data

Agent	Rituximab[1]	Ocrelizumab[2]	Ofatumumab[3]	Ublituximab[4]
Study	**HERMES** Phase II NCT00097188	**OPERA I and II** Phase III NCT01247324 and NCT01412333	**ASCLEPIOS I and II** Phase III NCT02792218 and NCT02792231	**ULTIMATE I and II** Phase III NCT03277261 and NCT03277248
Population	RRMS (N=104)	RMS (N=1656)	RMS (N= 1882)	RMS (N=1094)
Primary endpoint 1	Total count of Gd+ lesions (mean ±SD)	Annualized relapse rate	Annualized relapse rate	Annualized relapse rate
Primary outcomes	**Rituximab vs placebo** 0.5±2.0 vs 5.5±15.0 (p<0.001)	**Ocrelizumab vs IFN-β-1a** **OPERA I:** 0.16 vs 0.29 (p<0.001) **OPERA II**: 0.16 vs 0.29 (p<0.001)	**Ofatumumab vs teriflunmide** **ASCLEPIOS I:** 0.11 vs 0.22 (p<0.001) **ASCLEPIOS II:** 0.10 vs 0.25 (p<0.001)	**Ublituximab vs teriflunomide** **ULTIMATE I:** 0.08 vs 0.19 (p<0.001) **ULTIMATE II:** 0.09 vs 0.18 (p=0.002)
Secondary endpoint 2	Proportion of patients with relapses	Disability progression	Disability worsening	Number of Gd+ lesions on MRI
Secondary outcomes	At 48 weeks 20.3% vs 40.0% (p=0.04)	At 24 weeks 6.9% vs 10.5% (HR 0.60, p=0.003)	At 6 months 8.1% vs 12.0% (HR 1.35, p=0.09)	**ULTIMATE I:** 0.02 vs 0.49 (p<0.001) **ULTIMATE II**: 0.01 vs 0.25 (p<0.001)

CD, cluster of differentiation; Gd+, gadolinium enhancing; HR, hazard ratio; IFN, interferon; MRI, magnetic resonance imaging; MS, multiple sclerosis; RMS, relapsing MS; RRMS, relapsing-remitting MS; SD, standard deviation.

1. Hauser SL, et al. *N Engl J Med*. 2008;358:676–88; 2. Hauser SL, et al. *N Engl J Med*. 2017;376:221–34; 3. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57; 4. Steinman L, et al. *N Engl J Med*. 2022;387:704–14.

CD20-targeting treatments: Adverse events*

Agent	Rituximab[1]	Ocrelizumab[2]	Ofatumumab[3]	Ublituximab[4]
	Infusion-associated adverse events		Injection-related reactions	Infusion-associated adverse events
	Chills	Nasopharyngitis	Nasopharyngitis	Headache
	Headache	Upper respiratory tract infection	Headache	Nasopharyngitis
	Nausea	Headache	Injection-site reactions	Pyrexia

*Top four most frequent adverse events. CD, cluster of differentiation.

1. Hauser SL, et al. *N Engl J Med*. 2008;358:676–88; 2. Hauser SL, et al. *N Engl J Med*. 2017;376:221–34; 3. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57; 4. Steinman L, et al. *N Engl J Med*. 2022;387:704–14.

touch™ NEUROLOGY

Possible adverse events after anti-CD20 therapy

CD, cluster of differentiation.

De Séze J, et al. *Front Immunol*. 2023;14:1004795.

touch™ NEUROLOGY

A critical assessment of available and emerging B-cell–targeted therapeutic agents

Prof. Martin Weber

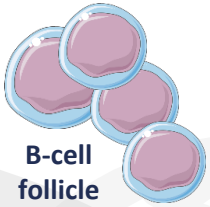
University Medical Center
Göttingen, Germany

touch™ NEUROLOGY

BTK inhibition

Central nervous system

BTK activation is increased in microglia and its inhibition reduces microglial cytokine production



B-cell follicle

Neuron

Demyelination

BTK inhibition decreases integrin and chemokine expression, reducing immune cell infiltration across the BBB

Increased BTK expression has been shown in around MS lesions

MS lesion

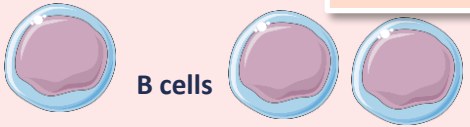
Microglia

BTK inhibition limits B-cell activation downstream of the BCR and their capacity to stimulate and present antigens to T cells

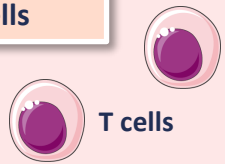
BTK inhibition reduces signalling through Toll-like receptor and inflammasome-related pathways in immune cells

Blood–brain barrier

Peripheral blood

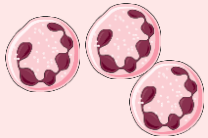


B cells



T cells

Monocytes



Macrophages

Cell images: Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).
BBB, blood–brain barrier; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; MS, multiple sclerosis.
Schneider R, Oh J. *Curr Neurol Neurosci Rep*. 2022;22:721–34.

touch™ NEUROLOGY

Efficacy data for emerging agents

Agent	Evobrutinib[1]	Tolebrutinib[2]	Fenebrutinib[3]
Study	**Phase II** NCT02975349	**Phase IIb** NCT03889639	**FENopta** **Phase II** NCT05119569
Population	RMS (N=267)	RMS (N=130)	RMS (N=106)
Primary endpoint 1	Total count of Gd+ lesions during week 12 through 24 (mean±SD)	Number of new Gd+ lesions at week 12	New Gd+ lesions at week 12
Primary outcomes	**Evobrutinib (75 mg QD) vs PBO** 1.69±4.69 vs 3.85±5.44 (p=0.002)	**Tolebrutininib (60 mg) vs PBO** 0.13±0.43 vs 1.03±2.50	**Fenebrutinib (200 mg BID) vs PBO** 20.6% vs 39.4% (90% relative reduction)
Secondary endpoint 2	Unadjusted annualized relapse rate	Number of new or enlarging T2 lesions	NET2 lesions at week 12
Secondary outcomes	At 24 weeks 0.13 vs 0.37	89% (95% CI 68–96%) relative reduction in the mean±SD number of new or enlarging T2 lesions vs PBO	28.6% vs 48.5% (95% relative reduction)

BID, twice daily; CI, confidence interval; Gd+, gadolinium enhancing; MS, multiple sclerosis ; NET2, new/enlarging T2; PBO, placebo; QD, once a day; RMS, relapsing MS, RRMS, relapsing remitting MS; SD, standard deviation.

1. Montalban X, et al. *N Engl J Med*. 2019;380:2406–17; 2. Reich DS, et al. *Lancet Neurol*. 2021;20:729–38; 3. Bar-Or A, et al. Presented at: ECTRIMS 2023, Milan, Italy. 11–13 Oct 2023. Late breaking oral Abstr. O187.

touch™ NEUROLOGY

Safety data for emerging agents*

Agent	Evobrutinib[1]	Tolebrutinib[2]	Fenebrutinib[3]
	Nasopharyngitis	Headache	Abnormal liver enzymes
	Increase in ALT	Upper respiratory tract infection	Urinary tract infection
	Increase in AST	Nasopharyngitis	Headache

*Top three most commonly reported adverse events.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
1. Montalban X, et al. *N Engl J Med*. 2019;380:2406–17; 2. Reich DS, et al. *Lancet Neurol*. 2021;20:729–38; 3. Bar-Or A, et al. Presented at ECTRIMS 2023, Milan, Italy. 11–13 Oct 2023. Late breaking oral Abstr. O187.

touch™ NEUROLOGY