Multiple Sclerosis Therapy Consensus Group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper)

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***Abstract*:** Multiple sclerosis is a complex, autoimmune-mediated disease of the central nervous system characterized by inflammatory demyelination and axonal/neuronal damage. The approval of various disease-modifying therapies and our increased understanding of disease mechanisms and evolution in recent years have significantly changed the prognosis and course of the disease. This update of the Multiple Sclerosis Therapy Consensus Group treatment recommendation focuses on the most important recommendations for disease-modifying therapies of multiple sclerosis in 2021. Our recommendations are based on current scientific evidence and apply to those medications approved in wide parts of Europe, particularly German-speaking countries (Germany, Austria, and Switzerland).

Keywords: disease-modifying therapy, guideline, multiple sclerosis, treatment recommendation

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Essential facts at a glance

Multiple sclerosis (MS) is a complex, most likely autoimmune-mediated inflammatory neurodegenerative disease of the central nervous system (CNS), characterized by inflammatory demyelination and axonal/neuronal damage. In Germany, an estimated 250,000 people suffer from MS. In recent years, the approval of various therapies has significantly changed the course and prognosis of the disease. This position statement (white paper) by members of the KKNMS (Competence Network Multiple Sclerosis), members of the BDN (Association of German Neurologists), members of the DGN (German Society of Neurology), and members of the Austrian and Swiss neurological societies describes – based on available evidence – crucial issues and current status of disease-modifying pharmacological therapies for people with MS.

Currently, the distinction between relapsing MS (RMS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) is still the pre-dominant description in regulatory documents. Whereas clinical classification of MS into (1) relapsing and (2) progressive forms, each of which can progress with and without activity [measured both

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clinically and with magnetic resonance imaging (MRI)], is much closer to clinical reality and better matches the underlying pathobiology.

Data from real-world cohort and registry studies gathered in recent years reveal, first, an early therapeutic intervention yields long-term benefits, and second, for patients with disease activity, early treatment with a high-efficacy therapy may have advantages over an escalation approach that favors lower-efficacy therapies for initial treatment.

Presently, two treatment approaches/schools of thought dominate the selection of optimal therapy for (highly) active MS. Both strategies are based on evaluating the individual patient's risk of further MS progression and considering the risk *versus* efficacy of the specific disease-modifying therapies (DMTs).

1. According to the escalation approach, lower-efficacy therapies with a known and relatively safe risk profile are selected for initial treatment. If – despite sufficiently long and regular treatment – disease activity persists/recurs, treatment is escalated to a more potent therapy option.
2. Alternatively, treatment can be initiated with a high-efficacy DMT already at the time of diagnosis, for example, with alemtuzumab, cladribine, natalizumab, ocrelizumab, ofatumumab, or S1P modulators (fingolimod, ozanimod, ponesimod).

Data from observational studies suggest that initial treatment with a high-efficacy DMT may be associated with a lower risk of conversion to SPMS in patients with disease activity.

When starting or switching treatment, it is essential to continuously monitor patients, including a thorough neurological examination and MRI of the brain at regular intervals.

It is advisable to take a 'de-risking approach' and perform a complete laboratory and vaccination status check (currently obligatory for several therapies but not for all) before starting a DMT.

Furthermore, crucial questions regarding the management of MS patients in the COVID pandemic have recently sprung up. In this context, it is necessary to point out that (1) according to current data, MS patients do not *per se* have an increased risk for SARS-CoV-2 infection or a severe course of the disease, while a higher degree of disability due to MS can nevertheless increase the risk for severe COVID-19; (2) the principles behind DMTs and their application are not fundamentally changed by the pandemic; and (3) MS patients are recommended to be vaccinated.

For further guidance on treatment effects and side effects of each drug and information on necessary examinations and laboratory controls before therapy initiation or switch, we refer to the descriptions in the summary of product characteristics (SmPC) of the respective medicines.

Introduction and background

MS is a complex, most likely autoimmune-mediated inflammatory neurodegenerative disease of the CNS. In Germany, an estimated 250,000 people suffer from MS.[1,2] The approval of several DMTs for treating different forms or stages of the disease requires us to update our knowledge base, looking at the benefits and risks of these therapies in the context of high-quality studies.

This position statement (white paper) of the MSTCG (Multiple Sclerosis Therapy Consensus Group) reflects open questions on MS, the disease course, and management under DMTs in 2021, based on available scientific evidence. Our treatment recommendations are primarily applicable in German-speaking countries (regarding regulatory aspects and approvals), while the defined recommendations and treatment approaches are highly relevant for the MS community worldwide. Our knowledge about the disease has expanded in recent years, especially regarding specifics on (early) diagnosis, disease course assessment and prognosis, and options for measurability in the clinical practice. Together with the approval of and experience with various compounds and therapeutic concepts, these advances have shaped the place of pharmacological intervention in modern MS management. Nevertheless, it is not possible to make scientifically sound and concrete recommendations for every situation; for example, there is still insufficient evidence on the use of pharmacotherapy in radiologically isolated syndrome (RIS). Therefore, a deliberative approach tailored to the individual patient and the individual circumstances is still

necessary (and reasonable) instead of categorical, rigid recommendations.

The key issues addressed here relate to the timing and nature of therapeutic interventions and the approach to clinical management of MS under therapy. Our recommendations, including their rationales, represent the current state of MS management and treatment. They are intended to provide practical guidance for clinicians and a scientifically sound foundation for treatment decisions. We include recommendations on the following topics:

- early treatment of patients with clinically isolated syndrome (CIS)
- efficacy of DMTs
- treatment of patients with relapsing as well as progressive disease forms
- monitoring of treatment response
- treatment strategies for inadequate response to therapy
- therapy discontinuation or switch
- long-term effects of DMTs
- treatment in special situations such as pregnancy
- treatment strategies in the context of COVID-19

This MSTCG position statement is an initiative of members of the KKNMS, members of the BDN, members of the DGN, and members of the Austrian and Swiss neurological societies.

The essential core is based on the 2018 ECTRIMS/EAN guideline and its upcoming update while focusing on the care situation in German-speaking countries.[3,4] Several authors of this position statement were involved in writing the 2018 ECTRIMS/EAN guideline. Furthermore, the 2018 US guideline was considered.[5,6]

The first version of this position statement and the main questions were developed by a core team of authors, and consensus recommendations were reconciled in several conferences. The position statement was then further developed with the entire group of authors in an additional reconciliation process, and consent was reached on the core statements. The basis for participation was the disclosure of all conflicts of interest. Our approach was guided by the following subsections, which are considered endpoints or evaluation criteria for DMTs in MS:

a. reducing the risk of relapses or newly occurring relapses
b. reducing the risk of meeting criteria for MS diagnosis in patients with CIS
c. reducing the risk of disability worsening
d. reducing the risk of MRI activity [new/enlarging T2 lesions, gadolinium-enhancing (Gd+) lesions] and CNS atrophy
e. improving health status as experienced/reported by the patient [PROMS – patient-reported outcome measures, including quality of life (QoL)]
f. reducing the risk of cognitive impairment
g. frequency/severity of adverse events
h. reducing the risk of SPMS (in patients with relapsing disease)
i. timing the switch between different DMTs
j. monitoring the phase between two DMTs
k. for pulse therapies: occurrence of disease activity during the first year of treatment (i.e. before administration of another cycle)
l. for pulse therapies: benefit and timing of an additional cycle of treatment
m. reducing the risk of disease activity and disability worsening during and after pregnancy

The evidence strength was graded according to an assessment of the underlying (study) data (grade 1–5, analogous to the system suggested by the Oxford Centre for Evidence-based Medicine. For more detail on classification of types of studies within this system, please see https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009).

All recommendations reflect a consensus within the author group (thus formally >95%).

Based on the data basis, the recommendation strength is graded as follows [analogous to the AWMF (German Association of the Scientific Medical Societies) rules][7]:

1. Grade A: must (strong recommendation)
2. Grade B: should (recommendation)
3. Grade C: may (weak recommendation/expert opinion)
4. Grade D: is feasible (good clinical practice point)

Within the framework of the recommendations, all treatment decisions require a patient/physician

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consensus (keyword: *shared decision making*). Selecting a high-efficacy DMT should involve prior consultation with the patient scrutinizing the following factors:

- individual patient characteristics (especially MS characteristics, expected adherence, age, sex, and aspects of family and life planning)
- existing comorbidities
- previous therapies
- side effects and risk profile of the drug, including the necessary measures for therapy monitoring
- indication for the drug, and possibilities of cost reimbursement

MS diagnosis, course, and prognosis

The McDonald criteria are applied for MS diagnosis and, after initial publication in 2001, have been updated several times, with the most recent version from 2017.[8] While dissemination in time (DIT) and dissemination in space (DIS) remains the core criterion for MS, the major updates relate to (1) oligoclonal bands (OCBs) as an additional criterion for DIT, (2) counting symptomatic lesions for both DIT and DIS, and (3) equivalence of cortical and juxtacortical lesions.[2,9,10] Reported past episodes should be considered if there is a suitable electrophysiological and morphological correlate [e.g. paresthesia, paroxysmal visual disturbances without visually evoked potentials (VEP), optical coherence tomography (OCT), sensory evoked potentials (SEP), MRI correlates]. The diagnosis should be postponed in case of diagnostic uncertainty and a timely re-evaluation planned.

Although the approval texts still distinguish between RMS, RRMS, PPMS, and SPMS, the clinical classification of MS into (1) relapsing and (2) progressive forms, each of which can progress with and without activity (measured both clinically and with MRI), is much closer to clinical reality and better matches the underlying pathobiology.[11]

RIS is diagnosed in clinically asymptomatic patients who do not have a clinically manifest inflammatory demyelinating episode but whose MRI is highly suggestive of inflammatory demyelinating disease and who may, in addition, have a chronic inflammatory cerebrospinal fluid (CSF) syndrome or abnormalities in electrophysiology (under exclusion of other differential diagnoses). Sufficient data on the indication of immunotherapies for treating RIS are lacking. However, there may be cases with persistent and documented paraclinical disease activity in which immunotherapies may be indicated in the individual (off-label therapy). Currently, several studies are ongoing, including studies on dimethyl fumarate and teriflunomide (https://www.clinicaltrials.gov/ct2/results?recrs=&cond=Radiologically+Isolated+Syndrome&term=&cntry=&state=&city=&dist=).

CIS is defined as a monofocal or multifocal first clinical event suggestive of MS in a person not previously diagnosed with MS. Depending on the clinical and diagnostic findings (monofocal *versus* multifocal presentation, OCB+ *versus* OCB–, MRI conspicuous *versus* inconspicuous), there is a risk (high/low) for the transition of isolated symptoms to MS over time.

MS under McDonald criteria can be categorized as relapsing or progressive type.[9] Provided there is only one relapse and no additional clinical or paraclinical activity or progression to date while the criteria for DIT and DIS are still met, diagnosis is no longer CIS but McDonald MS [not further defined as the specific type, that is, RMS, RRMS, or progressive MS (PMS) is not clear].

MS can be assessed as mild/moderate or active/highly active. Indicative for assessment are (1) relapse frequency, (2) MRI findings (lesion load, lesion localization), and (3) regression of relapse(s), disease activity, and disease severity (measured by clinical as well as radiological parameters); also, the patient's age and comorbidities have to be considered.

Activity is determined based on clinical relapses (severity of clinical symptoms/duration/tendency to regress) and MRI activity (contrast-enhancing lesions; new or enlarged T2 lesions).

Progression is determined by an annual or more frequent examination. If no examination results are available, activity is considered 'unknown'. In addition to the Expanded Disability Status Scale (EDSS), standardized instruments for assessing clinical function in patients with MS include the Multiple Sclerosis Functional Composite (MSFC), the Brief International Cognitive Assessment for MS (BICAMS), the 6- and 2-min walk tests, or the timed 25-foot walk test.

If no assessments are available, disease activity and progression are 'unknown'. It is fundamental to note that the classifications are not categorical or static and require continuous review and monitoring.

In RMS, a distinction is often made between RMS and RRMS, with the additional assessment of whether the respective relapses are with or without residual disability.

Residual disability after relapses that do not remit completely is referred to as RAW (relapse-associated worsening). A disability acquired independent of relapses is referred to as PIRA (progression independent of relapse activity).[12]

In PMS, it is possible to determine activity as well as progression. In addition, a distinction is made between PPMS and SPMS. If this is not possible, the assessment PMS remains, with the add-on 'unclear type'.

Disease-modifying pharmacological therapies

Currently, 17 drugs are approved for MS treatment in Germany (for an overview of the respective drugs and their modes of action, see Table 1; for specifics in Switzerland refer to Achtnichts and colleagues).[2,13–18]

Initially, various injectable drugs were approved in the 1990s. They were based on recombinant interferon-beta preparations and, from 2001 onwards, also on the polypeptide glatiramer acetate. Interferon-beta preparations have since been further devolved on toward a pegylated form with a prolonged half-life.[19]

Then, at the beginning of this century, several studies were started on oral drugs such as fingolimod, dimethyl fumarate, and teriflunomide. Instead of a placebo, these trials could include active comparators such as interferon-beta and glatiramer acetate. In recent years, additional studies with class I evidence have been published on the newly developed and more selective S1P receptor modulators ozanimod, ponesimod, and siponimod. By gradually increasing dosing over the first treatment week, initial heart rhythm monitoring could be omitted in most patients.

At the same time, several monoclonal antibodies (mAb) were investigated for parenteral therapy of RMS. The first mAb to be approved was natalizumab in 2006, which in two studies reduced clinical disease activity by nearly 70% and MRI parameters by approximately 90% compared with placebo.[20] This success has been hampered by the emergence of human Polyomavirus HPyV-2 (formerly John Cunningham virus, JCV)-induced progressive multifocal leukoencephalopathy (PML) in more than 800 patients. Regular safety testing is now required and involves determining antibody titer against serum HPyV-2 and cerebral MRI scans to detect suspicious lesions early on (e.g. https://www.ema.europa.eu/en/medicines/human/referrals/tysabri). Natalizumab is also approved in a subcutaneous formulation since March 2021.

In recent years, anti-CD20 antibodies have become established as a further therapeutic option for RMS. Ocrelizumab has been approved since 2018 and was developed from rituximab, which was never formally approved for MS treatment (only off-label use). Ofatumumab, which is administered subcutaneously, received approval in March 2021. Ocrelizumab was also the first compound ever to be approved for PPMS. In the relatively small but well-structured pivotal study, a significant delay in disability progression since the onset of progressive MS, particularly in the first year after initiation of therapy, was achieved in patients under 50 years of age and with short disease duration. This resulted in a theoretical delay of wheelchair use by up to 7 years.[21,22]

Another i.v.-administered antibody, alemtuzumab, was very effective in pivotal trials and is considered a prototype of the so-called immune depletion and repopulation strategies (IDRPs) or immune reconstitution therapies (IRTs).[23] In approximately 50% of patients, there is long-term remission after two treatment cycles without the need for further maintenance therapy. However, a number of infectious and autoimmune side effects limit its use to highly active courses.

Already at the beginning of the last decade, Cladribine, which originated in oncology treatment (hairy cell leukemia), was shown to reduce relapses by more than 50% in RMS patients.[24] This so-called pulse therapy is administered in only two weekly cycles in years 1 and 2. The drug also belongs to the IDRPs.

The MSTCG integrative consensus scheme consisting of all DMTs and their according

Table 1. Important aspects of MS immunotherapy.

	Substance	Indication	Mechanism	Risks for immune system	Other risks	Blood count checks	Other control examinations
Oral	Cladribine	(highly) active RMS	Chlorinated analog of the DNA building block deoxyadenosine, reduces both resting and dividing lymphocytes	(Desired) leukopenia/ lymphopenia, anemia, slightly increased risk of infection	In pivotal trials, higher rate of cancer disease under treatment than under placebo	Every 2–3 months blood count and diff. blood picture, consider infection prophylaxis for grade 3 and 4 lymphopenia. Discontinue medication in second year of treatment if lymphocyte levels are below 800/µl.	Check GOT, GPT, y-GT, bilirubin, CRP, creatinine and U status every 2–3 months; pregnancy test before each treatment cycle. Annual cMRI.
	Dimethyl fumarate	Mild/ moderate RMS	Modulation of cytokine expression, inhibition of immune cell proliferation, Nrf2 activation, possibly lymphocyte apoptosis	Leukopenia/ lymphopenia, rarely neutropenia, risk of infection	Flush symptomatology, gastrointestinal side effects, elevated liver counts	Before therapy blood count and diff. blood picture. During therapy diff. blood picture every 6–8 weeks in the first year of therapy and every 3–6 months thereafter. Discontinue therapy if abs. lymphocytes $<$ 500/µl or leukocytes $<$ 3000/µl, BEWARE of values between 500 and 800/µl	Before therapy: electrolytes; infection status (HBV, HCV, HIV, VZV, TB if applicable); pregnancy test; liver and kidney values; CRP. cMRI $<$ 3 months old. During therapy: no specific other controls, however, as with other immunotherapies, periodic laboratory checks are still recommended. Annual cMRI
	Fingolimod	(highly) active RMS	Functional S1P modulator; retention of lymphocytes in lymphoid organs	(Desired) lymphopenia, herpesvirus infections, VZV reactivation, hemophagocytic syndrome, cryptococcal meningitis, macular edema, vaccine responses slightly reduced, a slightly increased risk of PML and basal cell carcinoma	Cardiac conduction defects at first dosage; elevated liver count, macular edema, isolated skin tumors, hypertension, reduced diffusion capacity, hypercholesterolemia	Before therapy blood count and diff. blood picture. During therapy diff. blood picture after 2 and 4 weeks, and every 3 months thereafter. Discontinue therapy if abs. lymphocytes $<$ 200/µl, therapy restart possible from 600/µl	Before therapy: ECG; infection status (HBV, HCV, HIV, syphilis, VZV, potentially Tbc); pregnancy test; liver transaminases, serum bilirubin; kidney values; CRP. Ophthalmologic, and if necessary dermatologic and pulmonologic examinations. cMRI $<$ 3 months old. During therapy: cardiac monitoring at first dosage; liver count at 2–4 weeks, and every 3–6 months thereafter. Discontinuation of therapy if transaminases $>$ 3$\times$ ULN with elevated bilirubin, or if $>$ 5$\times$ ULN with or without elevated bilirubin, ophthalmologic examination recommended after 3 months, dermatologic examination annually. Annual cMRI.

(Continued)

Table 1. (Continued)

Substance	Indication	Mechanism	Risks for immune system	Other risks	Blood count checks	Other control examinations
Ozanimod	(highly) active RMS	Functional S1P modulator; retention of lymphocytes in lymphoid organs	Leukopenia/ lymphopenia, slightly increased risk for PML (also cases without lymphopenia); risk profile comparable with fingolimod	Cardiac conduction defects at first dosage; elevated liver count, macular edema, isolated skin tumors, hypertension, reduced diffusion capacity, hypercholesterolemia	Before therapy blood count and diff. blood picture. During therapy diff. blood picture after 2 and 4 weeks, and every 3 months thereafter. Discontinue therapy if abs. lymphocytes $<$ 200/µl, therapy restart possible from 600/µl	Before therapy: ECG; infection status (HBV, HCV, HIV, syphilis, VZV, potentially Tbc); pregnancy test; liver transaminases, serum bilirubin; kidney values; CRP. Ophthalmologic, and if necessary dermatologic and pulmonologic examinations. cMRI $<$ 3 months old. During therapy: cardiac monitoring only in case of known or newly detected irregularities on ECG; liver count at 2–4 weeks, and every 3–6 months thereafter. Discontinuation of therapy if transaminases $>$ 3$\times$ ULN with elevated bilirubin, or if $>$ 5$\times$ ULN with or without elevated bilirubin, ophthalmologic examination recommended after 3 months, dermatologic examination annually. Annual cMRI.
Ponesimod	Expected: (highly) active RMS, SPMS with relapses	Functional S1P antagonist; retention of lymphocytes in lymphoid organs	(Desired) lymphopenia; increased risk of infections (upper respiratory tract; urinary tract; herpesvirus infections; cryptococcal meningitis; PML), cutaneous malignancies; risk profile comparable with fingolimod	Cardiac arrhythmias especially with cardiac med. history, liver damage, pulmonary function impairment, arterial hypertension, macular edema, posterior reversible encephalopathy (PRES)	Before therapy blood count and diff. blood picture. During therapy diff. blood picture after 2 and 4 weeks, and every 3 months thereafter. Discontinue therapy if abs. lymphocytes $<$ 200/µl, therapy restart possible from 600/µl	Before therapy: ECG, vaccination status, funduscopy, liver transaminases, serum bilirubin, infection status (HBV, HCV, HIV, VZV, Tbc), pregnancy test, urine status, CRP. Ophthalmologic, and if necessary dermatologic and pulmonologic examinations. cMRI $<$ 3 months old. During therapy: clinical-neurological checks after 1 month, and every 3–6 months thereafter; liver checks incl. serum bilirubin after 1 month, and every 3–6 months thereafter. Discontinuation of therapy if transaminases $>$ 3$\times$ ULN with bilirubin elevation, or if $>$ 5$\times$ ULN with or without bilirubin elevation, ophthalmologic examination recommended after 3 months, dermatologic examination annually. Annual cMRI.

(Continued)

Table 1. (Continued)

Substance	Indication	Mechanism	Risks for immune system	Other risks	Blood count checks	Other control examinations
Siponimod	SPMS with relapses, SPMS without relapses, with MRI activity	Functional S1P modulator; retention of lymphocytes in lymphoid organs	(Desired) lymphopenia, herpesvirus infections, VZV reactivation, hemophagocytic syndrome, cryptococcal meningitis, slightly increased PML risk (same as fingolimod), vaccine responses slightly reduced, slightly increased risk of basal cell carcinoma	Cardiac conduction defects at first dosage; liver elevation, macular edema, isolated skin tumors, hypertension, reduction in diffusion capacity, hypercholesterolemia	Before therapy blood count and diff. blood picture. During therapy diff. blood picture after 2 and 4 weeks, and every 3 months thereafter. At 2-mg dosing and confirmed abs. lymphocytes $<$ 200/µl: dose reduction to 1 mg; at 1-mg dosing and abs. lymphocytes $<$ 200/µl discontinue therapy, therapy restart possible from 600/µl	Before therapy: CYP2 C9 genotyping; ECG, immunization status, funduscopy, vaccination status, liver transaminases, serum bilirubin, infection status (HBV, HCV, HIV, lues, VZV, Tbc), pregnancy test, urine status, CRP. Ophthalmologic, and if necessary dermatologic and pulmonologic examinations. cMRI $<$ 3 months old. During therapy: cardiac monitoring only in case of known or newly detected irregularities on ECG, liver count after 2–4 weeks, and every 3–6 months thereafter. Discontinuation of therapy in case of transaminases $>$ 3$\times$ ULN with bilirubin elevation, or if $>$ 5$\times$ ULN with or without bilirubin elevation, ophthalmological examination after 3 months, and if necessary dermatologic and pulmonologic controls.
Teriflunomide	Mild/ moderate RMS	DHO-DH inhibition, thereby inhibiting the proliferation of activated lymphocytes	Lymphopenia, neutropenia, risk of infection, vaccination response slightly reduced, very rarely pancytopenia/ agranulocytosis	Elevated liver count, hair thinning, peripheral neuropathy, acute renal failure	Before therapy blood count and diff. blood picture. During therapy diff. blood picture every 2 months in the first half year of therapy, and every 3 months thereafter. Discontinuation of therapy if abs. lymphocytes $<$ 200/µl	Before therapy: liver count, pancreas count, kidney count, vaccination status, infection status (HBV, HCV, HIV, lues, VZV, Tbc), CRP, pregnancy test, urine status, blood pressure check. cMRI $<$ 3 months old. During therapy: liver count checks every 4 weeks for the first 6 months, and every 2 months thereafter, discontinuation of therapy if transaminases confirmed above 3$\times$ ULN; check pancreatic enzymes after clinic; blood pressure check every 6 months; if necessary pulmonological checks. Annual cMRI.

(Continued)

Table 1. (Continued)

	Substance	Indication	Mechanism	Risks for immune system	Other risks	Blood count checks	Other control examinations
	(Azathioprine)	Mild/ moderate RMS (second choice)	Purine analog, inhibits DNA/RNA synthesis, rapidly dividing cells are particularly affected, immunosuppressant	Leukopenia/ lymphopenia, rarely neutropenia/ anemia, very rarely thrombotic microangiopathy	Increased risk of malignancy (2-fold after 5 years; 4.4-fold after 10 years), elevated liver count, rarely pancreatitis	During therapy diff. blood picture every 2 weeks initially, over the course every 4–8 weeks, target lymphopenia of 600–1000/µl.	Liver count initially every 2 weeks, over the course every 4–8 weeks. Annual cMRI.
Injection	Glatiramer acetate	Mild/ moderate RMS	Th1/Th2-shift, APC modulation, BDNF production	Reduced CD4/ CD8 ratio in CSF, mild leukocytosis, left shift, PML, slightly increased risk of infection, vaccination response slightly reduced, rarely infusion reactions	Immediate post-injection reaction or flush, elevated liver count	Before therapy blood count and diff. blood picture. During therapy diff. blood picture every 3 months in the first year of therapy.	Before therapy: liver count, kidney count, vaccination status. cMRI < 3 months old. During therapy: liver and kidney count checks every 3 months in the first year of therapy. Annual cMRI.
	β-Interferon	CIS, mild/ moderate RMS, SPMS with relapses	Inhibition of T-cell activation, Treg induction, inhibition of immune cell migration at the BBB	Lymph node swelling, leukocytosis, leukopenia, thrombocytopenia	Elevated liver count, local reactions at injection site, depression; very rarely thyroid dysfunction	Before therapy blood count and diff. blood picture. During therapy diff. blood picture 1 month after therapy initiation, and every 3 months thereafter. Discontinue therapy if leukocytes < 3000/µl or platelets < 75,000/µl	Before therapy: liver count, kidney count, vaccination status. cMRI < 3 months old. During therapy: liver and kidney count checks 1 month after therapy initiation, and every 3 months thereafter. Discontinue therapy if transaminases > 5× ULN. Annual cMRI.
	Ofatumumab	(highly) active RMS, SPMS with relapses	Monoclonal antibody against CD20, causing depletion of the middle B-cell line. Precursors of B cells and mature plasma cells are not eliminated.	(Desired) B-cell lymphopenia, decrease in serum IgM, T cell lymphopenia; increased risk of infections (upper respiratory tract, urinary tract, oral herpes), hepatitis B reactivation, PML	Injection-related reactions	Before therapy blood count and diff. blood picture and immune status. During therapy diff. blood picture and immune status after 3 months, and every 6–12 months thereafter.	Before therapy: IgG and IgM in serum, infection status (HBV, HCV, HIV, lues, VZV, Tbc), pregnancy test, urine status, CRP, vaccination status including pneumococcal vaccination, baseline MRI of the skull with contrast medium < 3 months old. During therapy: IgG in serum and liver and kidney counts every 6 months. Annual cMRI.

(Continued)

Table 1. (Continued)

	Substance	Indication	Mechanism	Risks for immune system	Other risks	Blood count checks	Other control examinations
Infusion	Alemtuzumab	(highly) active RMS	Monoclonal antibody against CD52, causing rapid elimination of CD52 immune cells in circulation, 'ordered' repopulation and thereby immune regulation	(Desired) leukopenia/ lymphopenia, neutropenia, risk of infection	Autoimmune diseases, cardiovascular risks	Before therapy blood count and diff. blood picture. During therapy diff. blood picture monthly for at least 5 years. For platelets < 30% of baseline value or below the lower limit of normal weekly controls, for platelets < 100,000 hematological check.	Before therapy: liver count, kidney count; infection status (HBV, HCV, HIV, lues, VZV, Tbc), pregnancy test, urine status, CRP, vaccination status, baseline MRI of the skull with contrast medium < 3 months old. During therapy: renal parameters (creatinine, GFR, U status, and sediment), CRP, liver values monthly for at least 5 years; TSH every 3 months. Female patients: HPV screening annually. Annual cMRI.
	Natalizumab	(highly) active RMS	Monoclonal antibody against a4b1 integrin, inhibits immune cells binding to endothelial cells via VCAM	(Desired) leukopenia/ lymphopenia, infusion reaction, secondary antibody-mediated autoimmunity (thyroid, ITP, kidney), susceptibility to infection, vaccination response reduced, high risk for PML	Elevated liver counts	Before therapy blood count and diff. blood picture. During therapy diff. blood picture every 3–6 months. JCV antibody status in neg. patients every 6 months, if necessary JCV antibody index and CD62L during follow-up.	Before therapy: liver count, kidney count; baseline MRI of the skull with contrast medium < 3 months old; further recommended: infection status (HBV, HCV, HIV, lues, VZV, Tbc), pregnancy test, urine status, CRP, vaccination status. During therapy: liver count check after 3 and 6 months. Discontinue therapy temporarily if transaminases > 3× ULN. Terminate therapy if transaminases > 5× ULN. JCV-Ab status after 24 months. cMRI every 6 months.
	Ocrelizumab	(highly) active RMS, SPMS with relapses, PPMS with clinical/MRI activity	Monoclonal antibody against CD20, causing depletion of immature and mature B cells. Early precursors of B cells, mature plasma cells, and CD20 negative B cells are not eliminated.	(Desired) B cell lymphopenia, reduction of IgM and potentially IgG in serum, T cell lymphopenia	Upper respiratory tract infection, nasopharyngitis, influenza, herpes infection	Before therapy blood count and diff. blood picture; recommended: immune status. During therapy diff. blood picture every 3 months, immune status 3 months after first dose, and recommended every 6 months thereafter.	Before therapy: IgG and IgM in serum; liver count, kidney count; infection status (HBV, HCV, HIV, lues, VZV, Tbc), pregnancy test, urine status, CRP, vaccination status incl. pneumococcal vaccination; baseline MRI of the skull with contrast medium < 3 months old. During and up to 1 h after infusion: monitoring for infusion reactions. During therapy: Serum IgG and liver, kidney values every 6 months. Annual cMRI.

(Continued)

Table 1. (Continued)

Substance	Indication	Mechanism	Risks for immune system	Other risks	Blood count checks	Other control examinations
(Mitoxantrone)	SPMS with relapses (second choice)	Topoisomerase II inhibitor, inhibits DNA synthesis, rapidly dividing cells are particularly affected, immunosuppressant	(Desired) neutropenia, decrease in lymphocytes, immunoglobulin M decreased in blood	Nausea, hair loss, cardiotoxicity (dose-dependent), risk of leukemia (not dose-dependent), infertility, jaundice	Before therapy blood count and diff. blood picture. During therapy diff. blood picture before each administration and thereafter weekly for 4 weeks. Discontinue therapy if neutropenia < 1500/ml, dose adjustment if leukopenia < 2000/ml or thrombocytopenia < 50,000/ml for nadir	Before therapy: liver count, kidney count; infection status (HBV, HCV, HIV, lues, VZV, Tbc), pregnancy test, urine status, CRP, vaccination status, baseline MRI of the skull with contrast medium < 3 months old. During therapy: liver and kidney counts, CRP, U status, ECG, TTE (also up to 5 years after end of therapy). Annual cMRI.

APC, antigen-presenting cells; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CIS, clinically isolated syndrome; CRP, C-reactive protein; CSF, cerebrospinal fluid; DHO-DH, dihydroorotate dehydrogenase; ECG, electrocardiogram; GFR, glomerular filtration rate; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; ITP, immune thrombocytopenia; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive MS; RIS, radiologically isolated syndrome; RMS, relapsing MS; RRMS relapsing-remitting MS; SPMS, secondary progressive MS; TSH, thyroid stimulating hormone; TTE, transesophageal/transtracheal echocardiography; ULN, upper limit of normal; VCAM, vascular cell adhesion molecule; VZV, varicella-zoster virus.

indication is outlined in Figure 1. In the following sections, we turn to the key questions and recommendations for MS treatment.

Key questions and recommendations for therapeutic intervention

What is the benefit of DMT in patients with CIS (regardless of whether they meet the criteria for definite MS or not) compared with no treatment?

Review on evidence followed by our recommendations. CIS is defined as a monofocal or multifocal first clinical event suggestive of MS in a person not previously diagnosed with MS. Typical presentations include unilateral optic neuritis (ON), focal brainstem or cerebellar symptomatology, or symptoms of partial transverse myelitis. Symptoms usually develop subacutely and persist for at least 24 h without concurrent fever or infection. If the criteria for local and temporal dissemination are met during the diagnosis (which is increasingly often the case given the high sensitivity of the 2017 diagnostic criteria), CIS marks the presumed first episode of MS (see Box 1).[8,25] If this is not the case, there is a risk (high/low) for the transition of isolated symptoms to MS over time, depending on the clinical and diagnostic findings (monofocal *versus* multifocal presentation, OCB+ *versus* OCB–, MRI conspicuous *versus* inconspicuous). Variants of ON may cause diagnostic difficulties (while other diseases need to be excluded in a careful analysis of the findings):

- ON without cerebral or spinal MRI-lesions with negative OCB → diagnosis: isolated ON and no CIS.
- ON without cerebral or spinal MRI-lesions with positive OCB → diagnosis: CIS, as OCB significantly increases the risk for a second clinical event.
- ON with one MRI-lesion but without OCB → diagnosis: ON, as according to the current definition of CIS/disseminated lesions, ⩾2 MRI-lesions are required.
- ON with one MRI-lesion and positive OCB → diagnosis: CIS.
- ON with ⩾2 MRI-lesions but without positive OCB → diagnosis: CIS.

The Barcelona cohort, a prospective open collection of CIS patients initiated in 1995, is considered a valuable and informative source for

		McDonald MS: Relapsing MS (RMS)			Progressive MS (PMS)	
	CIS	RRMS		SPMS		PPMS
Disease-modifying therapy		(highly-) active[6] first- and second-line therapies	***Pulsed therapies*** • Alemtuzumab • Cladribine • Ocrelizumab ***Continuous therapies*** • Natalizumab[3] • Ofatumumab • S1P-modulators (Fingolimod, Ozanimod, Ponesimod)	**with relapses** • Cladribine • Interferon-b-1b s.c. • Ocrelizumab • Ofatumumab • Ponesimod • Siponimod • (Mitoxantrone[2])	**without relapses, with MRI activity** • Siponimod	**with clinical / MRI activity** • Ocrelizumab
	• Interferon-b-1a i.m. • Interferon-b-1a s.c. • Interferon-b-1b s.c.	mild / moderate	• Dimethyl fumarate • Glatiramer acetate[5] • Interferons[4] • Teriflunomide • (Azathioprine[1])			

Figure 1. Disease-modifying therapy of MS.
Available drugs are listed alphabetically, not by strength or preference. Scheme updated based on the KKNMS Scheme, Aktuelle Neurologie 2014. [1]Azathioprine is formally approved but rarely applied (second choice). [2]Mitoxantrone formally approved here as well as in highly active RRMS but rarely applied due to the unfavorable side-effect profile and the cumulative maximum dose (second choice). [3]Natalizumab: both i.v. and s.c.; especially in case of HPyV-2 (JCV) antibody positivity [HPyV-2 (JCV) Ab ⩾ 0.9 HPyV-2 (JCV) Ab titer] risk stratification is essential due to PML risk! High risk for PML after (a) prior immunosuppression, (b) ⩾18 months of continuous therapy, and with (c) positive HPyV-2 (JCV) Ab status. [4]Interferons: interferon-b-1a i.m., interferon-b-1a s.c., interferon-b-1b s.c., pegylated interferon-b-1a s.c./i.m. [5]Glatiramer acetate includes other glatiramoids. [6]Decisions on type of therapy (as well as therapy concept) depend on the level of disease activity and severity; thus first- and second-line therapies are included here. For explanations on specific multiple sclerosis types, see also Box 1.

assessing future prognoses of patients with CIS. Recently, long-term data were published on 401 CIS patients from this cohort who were enrolled before 2006 and followed up for at least 10 years (mean follow-up 14.4 years).[26] Overall, patients treated early on (median 4 months after a first CIS event) had a significantly lower risk of achieving an EDSS score of 3.0 when compared with patients treated after another relapse (median 36 months after a first CIS event). The risk for future disability accumulation was estimated upon lesion burden in the baseline MRI. Analyses revealed that detecting approximately 20 T2 lesions on the baseline MRI was a valid predictor of aggressive MS progression. Another notable study describes the long-term course of an English CIS cohort over 30 years, prospectively recruited between 1984 and 1987.[27] As this study is often used to argue for a more defensive therapeutic approach after a first demyelinating event, it is important to keep in mind that these patients were recruited at the beginning of the MRI era and the imaging quality at that time is not comparable with today's MRI quality. Nevertheless, this

Box 1. Classification of MS disease courses, including RIS, under consideration of the 2017 updated McDonald criteria for MS, and adapted from Lublin and colleagues and Okuda and colleagues.[8,11,28]

RIS	
CIS	• Monofocal • Multifocal
McDonald MS	• Monofocal • Multifocal

MS, relapsing type – (RMS, RRMS)	• Mild/moderate course
	• Active/highly active course
	  ◦ With activity (MRI/relapses)
	  ◦ Without activity
	  ◦ Activity unknown
	  ◦ With progression
	  ◦ Without progression
	  ◦ Progression unknown
	  ◦ With residual disability
	  ◦ Without residual disability

MS, progressive type – (PMS, PPMS, SPMS)	• Primary progressive course
	• Secondary progressive course
	• Unclear course
	  ◦ With activity (MRI/relapses)
	  ◦ Without relapses, with MRI activity
	  ◦ Without activity
	  ◦ Activity unknown
	  ◦ With progression
	  ◦ Without progression
	  ◦ Progression unknown

CIS, clinically isolated syndrome; MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, primary progressive MS; RIS, radiologically isolated syndrome; RMS, relapsing MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

work was also able to correlate disability accumulation with the level of lesion burden at baseline, particularly in the presence of infratentorial MRI-lesions.

The benefit of immunotherapy for CIS patients (regardless of whether they meet the criteria for definite MS or not) was investigated in five placebo-controlled trials and their respective long-term studies. Three studies (with a total of 1368 patients), comparing interferon preparations with placebo, showed a longer time to next relapse (= clinically definite MS, CDMS) and less lesion increase on MRI for the treatment group.[29–31] Injectable therapeutics reduced relapses in CIS by approximately 40–45%, supporting the importance of anti-inflammatory action in the early stages of MS.

CIS patients who had received a placebo for 2 years were offered interferon in the extension studies. The extension studies on beta-interferon suggest that patients who received placebo in the double-blind phase were disadvantaged regarding the degree of disability for the entire observation period compared with patients treated with beta-interferon from the start.[31] Looking at 3-year follow-up data, patients treated early also took longer to convert to CDMS than placebo patients.[32] This difference persisted at follow-up observations after 5, 8, and 11 years.[33–36] Similarly, a study of glatiramer acetate in CIS patients ($N = 481$) showed delayed conversion to CDMS in the treated group compared with placebo after 3 years; this is also true for studies of teriflunomide and cladribine in CIS patients.[37–39] A systematic review and meta-analysis on three

clinical trials revealed DMT could also attenuate brain atrophy in CIS patients over time.[40] Due to the more sensitive diagnostics for CIS in the revised McDonald criteria, the frequency of CIS diagnosis has decreased in favor of RRMS diagnosis in recent years – with many of the newer agents no longer being studied in this specific setting. However, the mainly retrospective subgroup analyses of all available agents consistently show that early treatment with immunotherapy significantly benefits patients.

Recommendation 1:

- Under exclusion of other differential diagnostic causes, CIS patients (regardless of whether the criteria for DIT and DIS are met) must be offered immunotherapy.
- The choice of immunotherapy should be based on predictive parameters; primarily (1) MRI findings (number and localization of lesions) but also (2) extent of relapse regression, (3) multifocal presentation, and (4) CSF-specific OCB or chronic inflammatory CSF changes.
- For CIS patients with a high lesion burden or infratentorial lesions on diagnostic MRI, immunotherapy should be actively recommended given the presumed unfavorable prognosis. Here, depending on the individual circumstances, high-efficacy therapy can be considered already for initial treatment.
- Treatment of CIS should not be unnecessarily delayed and should not follow an escalation approach in the individual (highly active) case (please note any recommendations for off-label use).

What is the benefit of DMT in patients with RMS compared with no treatment/treatment with another disease-modifying drug?

Review on evidence followed by our recommendations. All placebo-controlled trials on currently available DMTs demonstrated a reduction in disease activity, as measured by relapses and new lesions on MRI compared with their comparator arm. A subset of these studies was also able to demonstrate superiority in terms of reduced disability progression. At the time, studies with interferon preparations were performed in collectives with significantly higher disease activity than nowadays, resulting in a relapse rate reduction of approximately 30%. The first studies with fingolimod showed a wide therapeutic active dosing range (between 0.5 and 5 mg) and, for the first time, a relapse rate reduction of above 50%. The two studies with dimethyl fumarate also provided convincing effects regarding relapse rate reduction. Finally, teriflunomide showed good results in two studies, especially for the stabilization of disability progression. These three preparations initiated the second generation of DMTs, which offered an improved form of application and tolerability, in addition to a partly higher potency. In the clinical practice, secondary factors such as compatibility with family planning (dimethyl fumarate), better acute tolerability (fingolimod, teriflunomide), autoimmunological comorbidities (teriflunomide, dimethyl fumarate), and long-term experience emerged as relevant for treatment decisions.

In randomized direct and indirect comparison studies, the drugs alemtuzumab, fingolimod, ozanimod, ponesimod, natalizumab (in a combination study with interferon-beta *versus* natalizumab alone), ocrelizumab, and ofatumumab were superior to the respective comparators in terms of relapse frequency and MRI parameters. In contrast, differences in disability progression were not as clear in these studies, although evident in some. For all preparations, there is strong evidence for a significant reduction of inflammatory activity. A systematic review and meta-analysis on four randomized-controlled trials showed DMT to delay the rate of brain volume loss in RRMS patients.[41]

The various preparations differ in their therapeutic efficacy, measured by the relative reduction of relapse activity/frequency. In addition, they can be divided into continuous immunotherapies and pulsed therapies according to their mode of action. Continuous therapies have several possible modes of action, ranging from immunomodulation to alteration of immune cell migration. Pulsed therapies (alemtuzumab, cladribine, ocrelizumab) act by depleting immune cells, with effects over a longer time (months to years).[23] A common feature of all therapies is that they primarily act on the peripheral adaptive immune system, thereby preventing damage within the CNS. CNS damage that has already occurred can only be influenced to a small extent by these therapies.[42,43] However, in addition to affecting acute inflammatory activity due to relapses, these therapies may also reduce further deterioration of neurological function that occurs independently of

relapses. This PIRA may even be the central driver of neurological decline during the relapsing phase.[12,44]

Recommendation 2:

- Initiation of DMT in RRMS is necessary to reach the treatment goal of reducing inflammatory activity in the form of disease flares and new lesions in MRI. The overriding focus is to preserve the so-called cerebral reserve. In addition, various studies (registry studies, open-label extension studies) indicate the positive influence of these therapies on the longer term risk of disability and secondary progression.
- In general, patients diagnosed with MS must be offered immunotherapy provided that therapy conduct is supported by (1) an adequate infrastructure; (2) an adequate disease assessment; (3) continuous monitoring of the disease and the therapy; and (4) knowledge, recognition, and treatment of therapeutic side effects. The entire spectrum of DMTs approved for RMS can be offered (i.e. alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate/glatiramoids, interferon beta-1a, interferon beta-1b, pegylated interferon beta-1a, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide; reserve medications: azathioprine, mitoxantrone).
- Selecting the optimal therapy is based on the current knowledge of the respective mechanism of action and follows two main treatment approaches. Both strategies are based on evaluating the individual patient's risk of further MS progression and considering the risk *versus* efficacy of the specific DMT.
  I. According to the escalation approach, lower-efficacy therapies with a known and relatively safe risk profile are selected for initial treatment. If further disease activity is evidenced (clinically or via MRI), treatment is escalated to a more potent therapy option.
  II. Alternatively, treatment can be initiated with a high-efficacy DMT already at the time of diagnosis. For example, with alemtuzumab, cladribine, natalizumab, ocrelizumab, ofatumumab, or S1P modulators (fingolimod, ozanimod, ponesimod).
- The immunotherapy must be selected based on main MS parameters (prognosis, disease activity, and disease severity), primarily on (1) relapse frequency, (2) MRI findings (lesion burden, lesion localization), and (3) regression of relapse(s), disease activity, and disease severity (measured by clinical and radiological parameters); In addition, the patient's age, sex, comorbidities, presence of CSF-specific OCB or chronic inflammatory CSF changes, and especially the safety profile of DMT are to be considered.
- The definition of (highly) active RMS should adhere to the following: $\geqslant$1 relapse within the last 12 months, $\geqslant$2 relapses in the last 24 months, OR $\geqslant$3 new T2 lesions or $\geqslant$1 new Gd+ lesion in a follow-up MRI (contrast agent can be omitted if recent and high-quality follow-up images are available) in the last 12 months.

What is the benefit of DMT in patients with progressive MS (PPMS or SPMS) compared with no treatment?

Review on evidence followed by our recommendations. The development of DMTs for treating progressive MS (PPMS/SPMS) has been less successful than for RMS. It is now generally accepted that treatment is more effective if started early in the disease course rather than later. One of the likely reasons is a neurodegenerative component in the pathophysiology of MS that is not (or no longer) responsive to immunotherapy and has its primary site of action not directly in the CNS. Interferon beta 1-b, mitoxantrone, and siponimod are approved for SPMS. Siponimod is approved for the active disease, as defined by additional relapses or MRI activity. In data from the pivotal trial conducted explicitly in SPMS patients, a better response is seen in younger patients with inflammatory activity.[45] For SPMS with relapse activity, other DMTs are also formally approved under the RMS label, although no dedicated studies for patients with SPMS exist. As it is well demonstrated that DMTs reduce relapse rates, treatment is reasonable in SPMS patients with relapse or RMS activity, even though long-term observational data are currently unavailable.

Uncertainties may arise further down the line when patients with initially active SPMS have

been treated and no longer have relapses. Various experts, including the authors of the North American guideline, recommend discontinuing therapy when there is pure progression without relapse.[5] However, it is unclear whether the DMT suppresses relapse activity despite not affecting progression, meaning that patients would continue to benefit from the relapse rate reduction provided by DMT. If therapy is discontinued in SPMS patients, close monitoring of subsequential inflammatory activity is essential.

For PPMS, ocrelizumab is the only currently approved treatment. Here, too, the pivotal study indicates better efficacy in younger patients with shorter disease duration.[46] Even if the effect in PPMS is comparatively small as measured by the EDSS, at least younger patients benefit from therapy with ocrelizumab, especially as there is no approved alternative. There are no data from controlled trials in older patients (>55 years) with a longer disease course (>15 years) and a higher degree of disability (EDSS score > 6.5). Nevertheless, according to the authors' assessment, therapeutic nihilism should not be practiced here. In particular, when patients are at risk of losing physical independence, a therapeutic attempt is justified. For the patients' QoL, this attempt can be decisive.

For treating progressive MS, intrathecal steroids (antispasmodic and anti-inflammatory) and cyclic methylprednisolone pulse therapies (as individual treatment approaches) continue to be selected – mainly in the context of symptomatic therapy optimization. Some clinical data exist on this, as well as experience from the real-world context (e.g. current data from the DMSG registry), even if no evidence-based studies are available.[47–50]

Recommendation 3:

- Patients with progressive MS benefit from DMT, especially in the early stages of the disease, and must be treated when clinical and imaging activity is present. In individual cases, therapy should also be considered in later disease stages or after longer disease duration if vital functions are at risk of being lost. The age of the patient should be included in the risk-benefit assessment.
- Before starting therapy, the therapy goals must be discussed and, in the following, continuously reviewed. In case of unchanged disease progression after therapy initiation, insufficient response to therapy must be assumed. However, in addition to the endpoints MRI activity, relapse rate, and overall disability, it is critical to also look for changes within relevant functional systems included in the EDSS (e.g. upper extremity function), as well as improvements in QoL as perceived by the patient and a reduced risk for cognitive impairment.
- As changes in the progressive forms are often slow and fluctuations are also part of the disease picture, positive and negative changes should be confirmed (ideally after 3 or 6 months).
- In progressive disease courses, decisions regarding treatment efficacy should ideally be possible within 2 years. If DMT is not effective, discontinuation of therapy should be discussed with the patient.

What is the benefit of early treatment with a DMT versus *no therapy in MS patients?*

Review on evidence followed by our recommendations. It is generally agreed that DMTs have a better effect early in the course of MS. Recent registry data indicate that later initiation of DMT leads to more extensive disability in the longer term.[51–53]

In addition to preventing acute episodes of the disease, prophylactic therapy may reduce the risk of long-term neurologic deterioration or secondary progression. Due to the slow course of MS, this therapeutic goal cannot be investigated in randomized trials. However, from registry data generated in recent years, we can infer that DMTs do indeed reduce the risk for long-term neurologic deterioration.[52–58] The long-term benefits of therapy strongly depend on how early DMT is started.[59]

Due to the great heterogeneity of the clinical MS course, the further individual patient's course is extremely difficult to predict. Although the term 'benign MS' has been abandoned eventually, there may be courses that do not lead to any (significant) disability after 30 years – even without therapy. While in overall analyses 15–20% of patients do not accumulate measurable disability in the longer term, there are no reliable or

accepted predictors for a course without substantial disability.[60]

Recommendation 4:

- DMT in MS must be started as early as possible after diagnosis to avoid further/future disability. In individual cases, a wait-and-see approach with regular neurological and imaging checks may also be considered in patients with very low lesion burden and complete remission of mild clinical symptoms.
- The superiority of immediate therapy after a first clinical event (CIS) *versus* early treatment (<3–6 months after the first clinical event) appears to be minimal.

In MS patients, what is the advantage of early onset of high-efficacy DMTs compared with late onset?

Review on evidence followed by our recommendations. Choosing the first DMT in MS patients is challenging. The choice must occur on an individual patient level and take into account several factors: clinical symptoms, MRI activity, the efficacy of the therapeutic agent, side effects of the therapeutic agent, handling, route of administration, and the patient's life circumstances and family situation. A general rule applies: the more potent the DMT, the higher the potential risk of severe side effects. The so-called escalation regimen, in which therapy is always started with a less effective drug and switched to a high-efficacy DMT if disease activity persists, was initially advocated when only a few DMTs were available.[61] With the availability of multiple high-efficacy DMTs, including depleting therapies, the hit-hard-and-early concept was postulated, recommending using high-efficacy DMT at disease onset, in analogy to, for example, rheumatology. Controlled trials that might demonstrate the superiority of one of these therapeutic approaches have now been initiated, but results will not be available for several years. Retrospective registry studies already suggest that in patients with disease activity, early use of high-efficacy DMT compared with lower-efficacy DMT may delay subsequent disability progression or transition to SPMS.[52,55] The underlying reason may be in concordance with delaying therapy initiation early in the disease: persistent clinical or subclinical disease activity under less effective therapy may cause irreversible neurological deficits and allow the activation of signaling pathways associated with progressive disease progression that could have been otherwise prevented.

High-efficacy therapies are not suitable for every patient and require an individual risk-benefit assessment. Depleting or IRTs, including autologous hematopoietic stem cell transplantation, have a special position in this regard. They cause profound changes in the immune system. Thus, on one hand, they show a higher risk of severe side effects and notably increased risk of infection in the first months after a therapy pulse. On the other hand, a proportion of patients profit from disease stabilization and therapeutic effects persisting years beyond the end of therapy, inducing long-lasting therapy-free disease stability.[23,62–64] Substance-specific risk reduction strategies need to be applied. In comparison, conventional immunotherapies require continuous therapy with cumulative risks over time, counting toward the individual risk-benefit balance.

Recommendation 5:

- Considering the disease course in the long-term, there is an advantage of using high-efficacy *versus* lower-efficacy DMTs from the beginning. This treatment strategy is supported by registry data, although prospective studies are lacking. Due to a possible increased risk for severe side effects and in consideration of individual life circumstances, the use of high-efficacy DMTs at the beginning of the disease should be decided individually and following the patient's wishes.
- Different therapy concepts exist within the group of high-efficacy DMTs. (1) Sustained therapy: efficacy relatively immediate with application and accompanied by reversibility after discontinuation: natalizumab and S1P receptor modulators (as well as ocrelizumab and ofatumumab with limitation due to the mechanism of action), *versus* (2) pulsed therapy: efficacy due to immune depletion and repopulation significantly beyond the half-life of the drug, possibly also permanent therapy-free disease stability: alemtuzumab and cladribine (and possibly ocrelizumab, with severe limitation due to mechanism of action).

Which examinations and parameters predict poor response to DMT in MS patients?

Review on evidence followed by our recommendations. After an adequate treatment period with a DMT, the occurrence of new relapses, new lesions on MRI, or a confirmed disability increase in the last 12 months characterizes an active disease course and insufficient or suboptimal treatment response. However, because DMTs need time to take full effect and the incidence of potential side effects varies widely, treatment and monitoring periods vary in both pivotal and real-world studies. In a retrospective cohort analysis, the time from therapy initiation to onset of effect on relapse rate reduction was described as approximately 3–4 months (12–30 weeks), which is consistent with long-term clinical experience.[65,66] Especially, a relapse or MRI activity within the first 4–8 weeks after therapy initiation requires an individual decision whether this can be tolerated until the full onset of DMT action or whether, due to disease severity, a direct switch to a more potent therapy is necessary.

MRI examination of the brain and clinical parameters serve the evaluation of DMT response in MS patients.[66–68] Attention needs to be paid to standardized implementation and sufficient imaging quality, with assessments conducted by an experienced investigator. Evaluation algorithms may help analyze the images but are not yet sufficiently validated and not generally available in practice.

In addition, if inadequate therapy response is suspected, medication adherence on the part of the patient should be ensured. Further details on individual DMTs and their monitoring are described in the SmPCs. For safety monitoring of high-efficacy DMTs, a cerebral MRI scan should be performed annually. To monitor treatment safety in patients at high risk of developing natalizumab-associated PML [anti-HPyV-2 (JCV) antibody positive and treatment duration of 18 months or more], more frequent MRI examinations at 3–6 monthly intervals are necessary. For patients at high risk of PML who switch DMT, a recent MRI (no older than three 3 months) should be available before starting the new DMT, and preclinical PML should also be ruled out by polymerase chain reaction (PCR) of the CSF.

According to European consensus publications, definite treatment failures are those patients with ⩾3 new T2 lesions and 1 relapse or ⩾2 relapses independent of MRI activity in 6–12 months despite DMT; and according to an American consensus, those patients with ⩾1 relapse, ⩾2 new MRI-lesions, or increase in disability over 1 year.[5,66,68,69] Clearly enlarged T2 lesions also count as new MRI-lesions.[3]

It is recommended that DMT-treated patients undergo a standardized cerebral MRI examination within 6 months after treatment initiation, as well as an MRI examination after 12 months, which is ideally compared with a reference image 3–6 months after treatment initiation to assess treatment response.[66] If highly active disease processes are apparent or new symptoms or severe side effects occur, imaging may need to be repeated earlier. Several centers recommend a so-called re-baselining 3 months after therapy initiation, under the notion that therapy initiation often occurs after an activity event, and the actual baseline can be better defined after 3 months. The primary parameter for evaluation is the number of new or enlarging T2 lesions. Gd administration is not mandatory for follow-up evaluation. However, if an acute event is suspected (e.g. suspected clinical relapse), contrast administration is still recommended. There is insufficient evidence for further MRI checks at standardized intervals beyond the MRI at 12 months after the initial reference image; checks should therefore be determined individually. However, an annual interval for paraclinical controls is suggested for documentation of the course and assessment of dynamics, activity, or progression.

To what extent and for which clinical decisions the determination of serum neurofilament light chains (sNfLs) can serve as a surrogate marker will become clear in the coming years. Currently, longitudinal measurements seem to be helpful to distinguish a stable disease from active progression even without MRI.[70,71] Other markers, such as cerebral atrophy (MRI), cervical/spinal atrophy (MRI), or retinal atrophy (OCT), have not yet found their way into routine use. Measurements of subclinical pathological neurophysiological parameters (e.g. VEP, SEP, MEP) have been shown to be associated with a poor prognosis and also poor response to DMT.[72] To what extent and for which clinical decisions the determination

of sNfLs can serve as a surrogate marker will become clear in the coming years.[73]

So far, there is insufficient evidence for the performance of regular spinal MRI examinations to assess MS progression. A spinal MRI at the time of diagnosis is widely recommended to obtain a baseline assessment for future use on one hand and to be able to include any spinal lesions as a negative prognostic factor in treatment decisions, on the other hand. Due to the lack of sufficiently standardized methods, the same line of argumentation holds for the regular use of brain atrophy as a progression marker.[66,74]

Recommendation 6:

- The goal of MS therapy is the best possible disease control and the best possible QoL for the patient. In practice, disease control must be measured by clinical parameters (especially relapses, disability) and MRI activity (so-called NEDA concept, 'no evidence of disease activity'). Various assessments (patient-based, physician-based) are available for measuring QoL.
- In DMT-treated patients, therapeutic success should be monitored by a clinical assessment every 3 months and by comparison of a standardized cerebral MRI within 3–6 months after treatment initiation (evaluated as so-called re-baselining) and with an MRI 12 months after treatment initiation and thereafter at annual intervals. Non-response to therapy may be assessed after 6–9 months at the earliest (see also specifics of pulsed therapies).
- A DMT switch must be considered in case of disability-relevant relapses, rapid disability progression, or severe side effects (safety, tolerability).
- The switch from a DMT for a mild/moderate disease course to a DMT for a (highly) active course should be made if there is $\geqslant$1 relevant relapse, or $\geqslant$2–3 new or enlarged MRI-lesions confirmed by experts, or an increase in disability $\geqslant$0.5–1 EDSS point (confirmed after 3–6 months) within 1 year (this is a so-called 'vertical switch').
- A DMT switch within the same efficacy range may be appropriate in case of side effects (tolerability, safety) or minor disease activity (this is a so-called 'horizontal switch').

For MS patients on DMT and with poor response to treatment, what is the benefit of switching to higher-efficacy DMTs (vertical switch) versus *similar efficacy DMTs (horizontal switch)?*
Review on evidence followed by our recommendations. Treatment of MS with DMT is based on the following therapeutic concept:

1. Initiation of a DMT early in the disease course, that is, after diagnosis (see recommendation 4).
2. As all DMTs are primarily anti-inflammatory, the therapeutic concept follows the pathogenetic concept according to which effective prevention of inflammatory disease activity (based on clinical and MRI outcome criteria) also contributes to the prevention of further/future irreversible disease progression or individual disability.[75,76]
3. The efficacy of DMTs is monitored clinically (regarding further relapses and disability increase measured by the EDSS, FSS, or MSFC, as appropriate) and radiologically (new or enlarging MRI T2 lesions) in line with NEDA concept.[77] Any medical monitoring should necessitate further meaningful action.
4. If the selected DMT does not have the desired therapeutic effect, that is, explicit evidence exists for clinical and radiological disease activity (see recommendation 6), the therapeutic goal of 'no disease activity' failed. If a moderate DMT is ineffective, switching to a high-efficacy DMT is the logical and coherent consequence following points 1, 2, and 3.

The existing literature offers no uniform definition of treatment failure for a (moderate-efficacy) DMT. Regardless, in addition to the intuitive view of treatment failure (= any degree of new disease activity despite existing therapy), there is now a consensus on the assessment of definitive treatment failure.[5,66,68,69]

Older studies have looked at the effects of immediate *versus* delayed switching from a moderate-efficacy DMT with treatment failure to a high-efficacy DMT. All studies consistently revealed an advantage when switching to alemtuzumab, fingolimod, or natalizumab compared with glatiramer acetate or interferon preparations.[78–87]

In all phase III registration studies of high-efficacy DMTs, the baseline demographic data of the included study populations show that a substantial proportion of up to 75% of the study participants had been pre-treated with a moderate-efficacy DMT.[20,24,88–91] Insufficient efficacy of a prior DMT cannot be assumed in all study participants (because, for example, side effects could also motivate a therapy switch/clinical trial participation). If considered in conjunction with the inclusion criteria for these studies, however, which all required some disease activity in the 12 months before study entry (average of 1.3–1.7 relapses), a substantial proportion of patients will have had continued disease activity despite receiving a moderate-efficacy DMT.

In addition, all phase III pivotal studies of high-efficacy DMTs (compared with placebo or active comparator groups in their respective core studies and followed by preplanned long-term observational studies) revealed that the switch from placebo/active comparator to a more potent DMT resulted in a level of efficacy comparable with that in the study population receiving high-efficacy DMT from baseline.[81,91–93] Another outcome uniformly evident in the observational studies is the disability accumulated in the placebo/active comparator groups during the core study was not reversible, that is, the accumulated neurological impairment could not be compensated.

Finally, in a recent publication, therapy with a high-efficacy DMT had a significantly lower risk of RAW and PIRA than a moderate-efficacy DMT.[12]

Although the concept of 'no evidence of disease activity' (NEDA) has relevance in scientific assessments as well as treatment concepts and therapy targets, it is not (yet) accepted as an endpoint for, for example, U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) approvals, or GBA (German Joint Federal Committee) procedures. Various reservations are held against the NEDA concept. Under the study conditions, MRI turns out to be 10× more sensitive compared with the criteria and therefore dominates the calculation. However, the MRI endpoints are only partly transferable to clinical reality regarding the frequency of examinations and standardization of assessments. Therefore, there are proponents of a purely clinical NEDA definition (so-called NEDA2), defined by relapses and disability progression.[77] In addition, it is questioned what level of control of relapse activity and severity and disability stabilization can realistically be achieved and whether paraclinical activity in itself and if so which kind, justifies changing the treatment regimen; and also, how closely singular measurement points correlate with future disease progression (see also background to recommendation 6). Reference is made to the current lack of parameters to predict individual risk for relapses, disability progression, or other disease manifestations such as cognitive impairment.

In accordance with the European guideline (ECTRIMS/EAN 2018) and most international professional societies, the authors of this position statement point out the major achievement of modern MS therapy in this context: Through the use of high-efficacy DMT, the long-term stabilization of the disease can be achieved – possibly with a reduction in disease severity – if the inflammatory process is stopped as early and as completely as possible. Here, the known and potentially unknown (long-term) risks of DMTs must be weighed against the benefits. Currently though, benefit-risk considerations are often at the forefront of discussions. However, in the authors' opinion, MS and its control should be weighted as the main priority, while the possibilities of active risk reduction (de-risking) and safety monitoring should be positively considered when assessing therapy risks. If there were a highly effective therapy without the risk of side effects, there would be little argument for withholding it from patients; this sets a critical anchor for the discussion, namely, the influence of safety aspects in debates and decisions about therapy concepts.

Recommendation 7:

- MS patients on DMT for mild/moderate forms and with clinical and radiological signs indicating poor response to current treatment (see recommendation 6) should switch to a high-efficacy DMT without delay.
- The high-efficacy DMT is chosen in consultation with the patient based on the following factors:
  a. individual patient characteristics (especially MS characteristics, expected adherence, age, sex, and aspects of family and life planning)
  b. existing comorbidities.

c. side effects and risk profile of the DMT, including the necessary measures for therapy monitoring
d. indication for the drug, and possibilities of cost reimbursement

Does discontinuation of treatment with a high-efficacy DMT increase the risk for a rebound of disease activity in patients with RRMS?

Review on evidence followed by our recommendations. Several studies and reports describe the further development of MS and clinical and paraclinical disease activity after discontinuing DMT. The course after discontinuation depends on various factors such as disease severity in the individual patient, disease duration, comorbidities, and the type of DMT. While pulsed immunotherapies tend to stabilize disease over the longer term, maintenance therapies suggest a more rapid return of disease activity after cessation. The therapy sequence is also essential.[94–96] In addition, there are immunopathogenic factors (genetics, environment, lifestyle).

Another factor to consider is differences in washout periods, that is, the times between discontinuation of a substance and initiation of follow-up treatment (typically from 1 to 6 months). Special consideration in this context is given to drugs that affect leukocyte migration.[97,98] For them, in addition to the expected recurrence of disease activity due to discontinuation, various reports describe a rebound, meaning a return of disease activity to a level exceeding that before the start of therapy. Although numerous studies describe this effect for fingolimod and natalizumab, rebound does not occur in every individual after discontinuing these therapies. However, an appropriate follow-up treatment should always be administered after these therapies to prevent the potential recurrence of disease activity.[97,98]

Recommendation 8:

- Discontinuation or suspension of a medication for the therapy of (highly) active MS, either based on suboptimal efficacy or safety concerns, must be accompanied by a clear follow-up concept.
- The following factors should be considered when selecting a follow-up medication:
  1. disease activity (clinical and MRI): the higher the disease activity, the larger the need for immediate initiation of a new therapy
  2. disease severity
  3. half-life as well as biological activity of the previous medication [differentiation between so-called maintenance therapies (Natalizumab, S1P modulators, partly Ocrelizumab) and pulsed therapies (Alemtuzumab, Cladribine, partly Ocrelizumab)]
  4. the risk of 'carry-over' PML (see recommendation 10) should be reduced as much as possible, and clinical, MRI, and liquid diagnostic parameters [detection of HPyV-2 (JCV) DNA by PCR] should be used to determine the baseline or pre-conversion status
- The risk of recurrence of disease activity or rebound (especially after leukocyte migration therapies such as natalizumab or S1P receptor modulators) should be considered and can be expected 2–6 months after discontinuation of these agents.

If RRMS patients remain stable on DMT for an extended period, is treatment continuation beneficial compared with a treatment stop?

Review on evidence followed by our recommendations. The scientific data on this clinically highly relevant question are scarce. The only available data result from retrospective observational studies mostly on older injectable MS therapeutics and comprising relatively small cohorts. A prospective paper from the Global MS Database describes that while relapse rates remain stable after discontinuation of injectable MS therapies, disease progression is significantly accelerated.[99] These results are consistent with smaller retrospective observations. So if treatment is well tolerated and safe, patients should be motivated to continue.

Special consideration must be given to agents inhibiting leukocyte migration (S1P receptor modulators fingolimod, ozanimod, ponesimod, siponimod, and natalizumab).[97,98] Here, discontinuation without a concept for follow-up treatment should be the exception (challenging situations arise, for example, in the context of pregnancy, lactation, or surgery).

IRTs (alemtuzumab, cladribine, within limitation ocrelizumab) are special cases in the sense that disease remission without further or follow-up treatment is part of the therapeutic concept.[23] The cohorts of the pivotal studies of alemtuzumab

(CARE MS I and II) have been followed up in very controlled conditions.[63,100] These data show that about 50% of patients are stable for many years without the need for follow-up treatment, including the possibility of treating recurrent disease activity again with CD52 depletion (with the prospect of achieving re-stabilization). CLARITY Extension data are available for cladribine. Here, after only two cycles of depletion, a group of patients showed long-lasting disease stability in the absence of further DMT.[100] Only a few controlled studies currently exist for the discontinuation of B-cell depleting drugs. However, a reversible mechanism of action, and therefore ultimately a return of disease activity, can be expected due to the B-cell dominance of the depletion principle. Established prognostic or diagnostic markers (such as the dynamics of depleting *versus* repopulating immune cell types) that would indicate durable remission for a specified group do not exist for MS. Hence, also IRTs require established guidelines for monitoring and appropriate action plans for recurring disease activity.

Evidence and practical examples for recommending a 'de-escalation of treatment' (meaning switching to a lower-efficacy DMT from a higher-efficacy DMT) are generally low, despite pathophysiological rationale and arguments. Assuming that the sensitivity of the disease toward a lower-efficacy DMT might be different following pulsed immune therapy, the concept of de-escalation could be an option hereafter, maybe in general or after a return of disease activity (i.e. induction followed by maintenance).[23,100] Currently, however, there is very little controlled evidence for a de-escalation approach.

More attention is now being paid to disease activity in relation to age, effects of therapy relating to age, and phenomena of immune senescence *versus* immunocompetence in old age.[101,102] Roughly, the inflammatory activity and the effect of immunotherapy, especially the influence on progression, decrease with age. When weighing the therapeutic goals and benefit-risk profile, considering disease activity becomes more important, especially at a higher age (>55).

Recommendation 9:

- MS patients who are stable on a given DMT, receive clinical and radiological monitoring, and are without any safety or tolerability issues, must continue therapy.
- Discontinuing or pausing treatment is associated with the risk of recurrence of disease activity and progression, depending on the mechanism of action (see also recommendation 8).
- Discontinuing or pausing treatment at a patient's explicit request (without planned follow-up therapy) may be done if adhering to clear guidelines for clinical and imaging monitoring.

Which strategy is recommended for patients who are scheduled to switch DMT?

Review on evidence followed by our recommendations. Even with the availability of different DMTs, the heterogeneity of MS presents a challenge for therapy selection. The goal is to select the therapy that best meets the individual patient's needs, taking into account efficacy, an acceptable benefit-risk ratio, and a relatively straightforward application.[103] In the absence of predictive biomarkers, stepwise and often time-consuming optimizations are necessary, possibly resulting in multiple therapy switches.[104] Reasons for switching a DMT may include lack of efficacy, adverse events (intolerance, safety), and insufficient treatment adherence.

A recently published multicenter retrospective Italian study analyzed data from 2954 patients with RRMS diagnosed between 2010 and 2017.[105] Here, 48% of patients had switched therapy at least once in 3 years. Insufficient efficacy was the main reason for switching. Switching was observed more frequently in patients treated with first-line injectable therapeutics than in patients treated with second-line therapies such as fingolimod or natalizumab. An analysis of 595 German MS patients, with a mean age of 41.6 years, revealed that more than 60% of patients had ⩾1 relapse within 12 months before switching.[106] Here, the main reasons for switching DMT were the failure of current therapy (53.9%), patient request (22.4%), and adverse events (19.0%). However, despite the demonstrated need for optimization, only 43.5% of patients were subsequently switched to a high-efficacy DMT, although the physicians in charge sought the switch to result in clinical optimization and had positive expectations regarding the outcome. These data demonstrate the still hesitant approach to switching to a high-efficacy DMT, which is likely due to the safety profile of these agents.

Accordingly, patient safety-oriented monitoring should be in place when switching DMTs, with the goal of not generating safety problems through a particular therapy sequence.[16]

Recommendation 10:

- The switch from dimethyl fumarate, glatiramer acetate/glatiramoids, and interferon preparations to another DMT should be carried out without a washout interval. However – especially with dimethyl fumarate – it is recommended to check the differential blood count and, if necessary, to wait until the blood count has recovered before switching in the case of lymphopenia.
- For substances that regularly lead to lymphopenias, such as alemtuzumab, cladribine, or S1P receptor modulators, the lymphopenia should have largely regressed before switching if the patient's clinical condition permits a pause in therapy (benefit-risk analysis).
- When switching from natalizumab to another high-efficacy therapy, the risk of 'carry-over' PML must be considered. Therefore, a careful neuroradiological diagnosis must be performed before switching. In high-risk patients, CSF analysis for HPyV-2 (JCV) DNA should be performed (for further details and discussion on PML risk, see the section 'Which therapeutic strategy should be selected to minimize the risk of PML for MS patients treated with DMTs?').
- The potential effect duration of DMTs should be considered when switching, especially if laboratory values or other factors dictate a break in therapy. Recurrence of disease activity can be severe for MS patients and is possible as early as 6 weeks after cessation of treatment for natalizumab and within the first 3 months for S1P receptor modulators.

Which long-term therapeutic approach is optimal for patients last treated with alemtuzumab or cladribine?

Review on evidence followed by our recommendations. A special situation occurs under depleting therapies with immune cells reconstitution.[23,107] Although the underlying mechanisms are not fully understood, the depletion following alemtuzumab or cladribine treatment will lead to a long-lasting biological effect that persists beyond the phase of lymphocyte reduction. The basic idea is that the immune system is reconstituted with less autoimmune potential after depletion. Both therapies are administered over 2 years only, with two and four treatment cycles, respectively. Long-term observations show that 50–60% of patients require no further therapy for 5 years after being treated with alemtuzumab or cladribine and remain essentially free of relapses and disability progression.[63,64] Reports exist of patients with more than 10 years of sustained disease stability. In this group of patients, the long-term therapeutic approach is relatively simple: if clinical stability is achieved, there is no need for further immunotherapy initially, and only clinical progression needs to be followed up.

However, sustained disease stability is not observed in all patients. If disease activity recurs already during therapy, no studies are available to determine the most favorable course of action. For alemtuzumab, data are available which indicate a third (and in theory even a fourth and fifth) therapy cycle to lead to a renewed stabilization of disease activity without increasing the risk of therapeutic side effects; while side effects do remain at the same level, leaving a continuous risk.[63,108] In principle, all other types of follow-up treatments are conceivable, while there is the concern of insufficient efficacy with moderate-efficacy therapies, as patients previously treated with alemtuzumab or cladribine are often patients with highly active disease forms. If choosing high-efficacy DMTs for follow-up treatment, the risk of a serious adverse event could be increased, primarily because of the long-lasting biological effect (not half-life) of alemtuzumab and cladribine. Also, the sequential use of these two therapeutics is not recommended because the summation of the respective long-lasting effects on the immune system is unpredictable. However, other DMTs can be chosen for follow-up treatment, subject to relatively close monitoring regarding potential severe side effects. Even if follow-up therapies are (and often need to be) implemented in clinical practice, there are no systematically collected data on sequential treatment after alemtuzumab or cladribine.

The situation is even more difficult if there is renewed disease activity in the first treatment year

with alemtuzumab or cladribine. In individual cases, paradoxical disease activation has been apparent after alemtuzumab.[95,109] On the contrary, disease activity in the first year of alemtuzumab treatment is not entirely uncommon, especially after pretreatment with natalizumab or S1P receptor modulators.[96] In the CareMS trials, a particularly impressive treatment effect was seen in the second year in patients with incomplete early response, indicating that partial early disease activity does not equate to treatment failure. Hence, if disease activity is partially reduced (incomplete early response), it would be reasonable or justifiable to continue treatment in the second year to follow the long-term therapeutic approach. Patients with unabated or even increased disease activity (primary non-response or paradoxical disease exacerbation) may require an early therapy switch. Here, only high-efficacy DMTs can be selected for follow-up treatment because the disease activity occurred under a highly potent drug. Switching from cladribine to alemtuzumab or *vice versa* seems inadvisable due to the unclear consequences for immunocompetence (see above). Thus, anti-CD20 antibodies, natalizumab, or S1P-receptor modulators should be primarily considered for an early treatment switch, whereby the respective previous therapies are taken into account in the individual decision.

Recommendation 11:

- If disease activity recurs after completed alemtuzumab treatment, a third therapy cycle should be considered, under the premise that disease activity was significantly reduced after the first two cycles, and therapy response or disease control can thus be assumed.
- If disease activity recurs after completed cladribine treatment, a third therapy cycle, analogous to alemtuzumab, may be considered (currently off-label for cladribine in the third and fourth year), although no sufficient data are available to support this approach.
- Switching from alemtuzumab to cladribine or *vice versa* should be well justified due to the low predictability of sequential combined effects on the immune system. All other approved DMTs may be administered under close monitoring if disease activity occurs.
- If disease activity occurs under alemtuzumab or cladribine in the first treatment year, this should, on one hand, be interpreted in the context of previous therapy and disease history (pre-existing activity/severity). On the other hand, the effect of treatment should be waited for, and treatment should be continued into the second year to follow the long-term therapeutic approach. If, however, disease activity is clearly unabated or even paradoxically increased after the first therapy cycle compared with the status before therapy initiation, the switch to another high-efficacy DMT should be made.

Which therapeutic strategy should be selected to minimize the risk of PML for MS patients treated with DMTs?

Review on evidence followed by our recommendations. All DMTs have a theoretical risk of immunological side effects due to their impact on the immune system, particularly as none of the available therapies selectively or specifically target MS.

Several recent studies have addressed the risk for infections and immunological side effects of DMTs.[110] As largely immunological safety concerns limit the widespread use of high-efficacy therapies, a primary goal of DMT monitoring is the prevention, early detection, and management of side effects, especially infections.[16] The risk of PML due to HPyV-2 (JCV) is particularly prominent in the context of DMTs.[111–113] While treatment with natalizumab undoubtedly carries the highest risk of treatment-associated PML, it is not the only agent for which PML cases have been described. Currently, drugs with high risk (>1:1000: natalizumab), intermediate risk (1:1000–1:50,000: dimethyl fumarate, fingolimod, ozanimod, siponimod), and low risk [<1:50,000: alemtuzumab, cladribine, glatiramer acetate/glatiramoids, interferons, ocrelizumab, (rituximab) teriflunomide] are distinguished.[16,111,112]

Regarding risk stratification for PML under natalizumab, the past years have provided essential insights: A stratification according to the parameters (1) duration of therapy, (2) previous immunosuppression, and (3) presence of anti-HPyV-2 (JCV) antibodies (Ab) and their quantity (HPyV-2 (JCV) index) can be applied to calculate

the risk of developing PML (ranking from <1:10 to >1:10,000).[113–115] Some other markers are in development but so far unavailable for application (e.g. CD62L titers, lipid-specific IgM bands). The risk for PML ultimately increases with the duration of therapy, that is, with each natalizumab infusion. Therefore, patients on natalizumab therapy need to be closely and continuously monitored, and in the case of negative HPyV-2 (JCV) Ab status, monitoring by ELISA is recommended every 6 months. HPyV-2 (JCV)-Ab positive patients with an index of ⩾0.9 should generally not be treated with natalizumab for longer than 18 months. Exceptions are feasible if therapies are closely monitored clinically (every 3 months) and by MRI (every 3–6 months), with a systematic program in place to detect symptoms of PML. The MRI assessment requires diffusion-weighted imaging (DWI) and post-contrast sequences.[66]

Under natalizumab treatment, the risk of seroconversion appears to be slightly higher than in the average population and MS patients in general (2–10%/year).[116–118]

Extended Interval Dosing (EID) has recently been advocated as another measure to mitigate PML risk, mainly based on analyses from the TOUCH registry.[119] This retrospective analysis found that EID over an average of 6 weeks resulted in a significantly lower PML risk than therapy over the initially approved interval of 4 weeks. The authors classify the result as class III evidence as they are based on retrospective data analysis. Data from a prospective study addressing the efficacy of a 6-week *versus* 4-week dosing interval (NOVA study) are available in preliminary form and, not unexpectedly, suggest maintenance of efficacy even with EID.[120] Presently, a safe recommendation cannot be derived, although the study and the possibility of EID are also mentioned in the SmPC for natalizumab. Another currently unclear point is how the newly approved subcutaneous application form for natalizumab can be classified regarding the PML risk.

For dimethyl fumarate, monitoring of leukocyte levels and absolute lymphocyte counts is required to prospectively avoid safety risks, including PML. Dimethyl fumarate significantly reduces lymphocyte and leukocyte counts in approximately 10% of patients, and the drug should be discontinued at confirmed counts of <500/µl. In the range of persistent second-degree lymphopenia (500–800/µl), close monitoring is advised, as PML cases have occurred with lymphocyte levels in the second-degree range. Here, based on immune senescence processes, patient age is likely a relevant cofactor in the development of PML. Overall, the risk of PML associated with dimethyl fumarate is approximately 1:45,000.

The PML risk during fingolimod therapy is just below 1:10,000 (which does not include the 'carry-over' PML cases from natalizumab to fingolimod). Nevertheless, there are no actual measures or specific laboratory values to stratify PML risk, except for the lymphocyte threshold of 200/µl, which should not be continuously out of range. However, the number of peripheral lymphocytes might not correlate with the risk of PML, especially because the rate of general infections does not seem to correlate with the number of lymphocytes either. Based on the underlying mechanism of action, it is likely that other S1P receptor modulators carry a risk of PML, in addition to other class-specific immunologic side effects.

For the other drugs (alemtuzumab, cladribine, ocrelizumab, ofatumumab, teriflunomide), the current view is that although there is in principle a PML risk, it is too low to suggest true risk stratification. In particular, age seems to be a main predisposing factor (further indicated by the two PML cases that have occurred under ocrelizumab so far – as of April 2021).

Recommendation 12:

- Natalizumab is associated with a high risk of developing PML if (1) HPyV-2 (JCV)-Ab status is positive (⩾0.9) and (2) treatment duration is ⩾18 months. And, regardless of HPyV-2 (JCV)-Ab status, (3) prior immunosuppression is a risk factor that should be considered alongside treatment duration.
- If stable, patients at low risk of PML [HPyV-2 (JCV)-Ab negative, HPyV-2 (JCV)-Ab titer ⩽ 0.9] must be monitored for treatment safety and receive regular, at least annual, clinical, and paraclinical (MRI) examinations. Also, serum HPyV-2 (JCV)-Ab titer checks must be performed every 6 months.

- For patients at high risk of PML [HPyV-2 (JCV)-Ab titer ⩾ 0.9 and treatment duration with natalizumab > 18 months, previous immunosuppression], more frequent MRI controls (every 3–6 months) must be performed if therapy is continued. In parallel, higher frequency clinical controls (⩽ every 3 months) must also be done. Here, the selection of short MRI protocols with specific PML sequences is possible.
- For patients at high risk of PML who switch drugs, or for patients with a potential for increased disease activity after discontinuation of therapy – as after switching from natalizumab to fingolimod – a cerebral MRI and, if necessary, CSF testing [HPyV-2 (JCV) PCR] must be performed, particularly at the time of discontinuation of current treatment and after initiation of a new treatment, to reliably rule out 'carry-over' PML and to assess the situation at the end of therapy or after therapy initiation.
- To avoid immunological side effects – including opportunistic infections such as PML – leukocytes and especially absolute lymphocytes should be monitored under dimethyl fumarate in the first year in particular. If the count is persistently below 500/µl, the drug must be discontinued. In case of values persistently between 500 and 800 µl – even beyond the first year – increased vigilance measures must be put in place (higher frequency clinical and MRI monitoring). The risk appears to increase with patient age (⩾55 years).
- There are no risk stratification parameters for PML risk under fingolimod (and presumably other S1P modulators) other than higher patient age (⩾55 years).

For MS patients on DMT, which treatment changes become necessary when planning a pregnancy or in case of an unplanned pregnancy? And which type of therapy is recommended post-natal when breastfeeding?

Review on evidence followed by our recommendations. With the increasing incidence of MS in women, therapy during and after pregnancy is a highly relevant topic. A good review on this matter is included in Montalban and colleagues.[3] As, naturally, there are no prospective studies, the most comprehensive experience regarding MS treatment and pregnancy is with DMTs with long-standing approval: Glatiramer acetate and interferon-beta preparations are generally approved during pregnancy, although a physician should assess the benefit of therapy continuation.[121,122] Also, in highly active forms of MS, the patient will usually be advised to first target disease stabilization before a planned conception. Should an unplanned pregnancy occur in a patient with a highly active disease, therapy continuation with natalizumab may be considered. The therapy should then be interrupted from the 32nd week of gestation until delivery, as prolonged treatment can lead to blood count changes in the newborn.

Naturally, there are concerns with immunosuppressive DMTs that interfere with DNA replication or target molecules critically involved in intrauterine development. If a conception occurs under teriflunomide treatment, the drug must be forcibly eliminated by cholestyramine. Based on experience with fingolimod, a conception under S1P modulators must be avoided because of the risk of severe malformations. Differentiation between substances with short (siponimod, ponesimod) *versus* long elimination times (fingolimod, ozanimod) may be relevant here. The use of cladribine is prohibited during pregnancy.

Depleting antibodies can only be used during pregnancy after a strict benefit-risk assessment. There is no known risk of malformation with the latter, but immunological effects in the child may occur, particularly in the last trimester. Due to the long duration of immunological action, cladribine and alemtuzumab (especially after a complete treatment cycle), as well as anti-CD20 antibodies, are suitable candidates to attempt conception during the therapy-free periods (see recommendations).

It should be pointed out that there is a large post-marketing experience with the widely used oral DMT dimethyl fumarate and that no teratogenic effects have been observed.[123]

Recommendation 13:

- Patients must be informed that, except for interferons and glatiramer acetate, DMTs have no approval during pregnancy.
- The same applies post-natal when breastfeeding, during which only interferons have been approved so far.

- For patients with highly active disease, control of disease activity should be a priority, and postponement of a planned conception is advised.
- For planned or unplanned pregnancies in patients with highly active disease, natalizumab may be given up to week 32, considering the individual benefit-risk profile.
- Administration of dimethyl fumarate may be possible up until conception.
- Treatment with immunodepleting DMTs (alemtuzumab, cladribine) may be an alternative therapeutic option compatible with family planning, provided that the interval from last administration to conception is ⩾4 months (alemtuzumab) or ⩾6 months (cladribine; applicable for both(!) sexes).
- From knowledge gathered in clinical practice, it is feasible to plan a conception ⩾4 months after treatment with ocrelizumab (good clinical practice point).
- For women at high risk for disease activity, interferons or glatiramer acetate must be considered as a therapeutic option until the onset of and if necessary during pregnancy.
- In principle, immunotherapy should be resumed after delivery, taking into account the requirements and restrictions during the period of breastfeeding.

Which treatment strategy is recommended for MS patients in the current epidemiological context of COVID-19?

Review on evidence followed by our recommendations. The SARS-CoV-2 pandemic in 2020 has opened up the question to what extent DMTs affect the response of the immune system to new (viral) antigens. Currently, this question cannot be answered, but data available from registry studies allow a first positioning, following on from basic recommendations that were given in the early phase of the pandemic regarding the interconnection of MS, infections, and handling of immunotherapy.[124]

Thus, data from more than 300 patients in the French COVISEP registry were evaluated for their SARS-CoV-2 infection outcome under different DMTs.[125] The authors could demonstrate an increased risk of severe COVID-19 progression in MS patients in relation to age and disability severity score (EDSS). Multivariate regression analysis confirmed older age, higher EDSS, previous cardiac disease, and obesity as risk factors for severe progression – that is, risk factors similar to those in the general population not affected by MS. No differences in COVID-19 progression were found between patient groups with different DMTs in this evaluation. Less favorable courses were more likely in untreated patients; it must be taken into account, however, that the group of untreated patients included more older MS patients with progressive courses.

In contrast, an evaluation of the Italian Musc-19 registry showed, while the overall safety of DMTs was good (even after adjusting data for age and disease progression), the risk for severe COVID-19 increased in the subgroup of patients treated with anti-CD20 mAb and after corticosteroid therapy. Similar conclusions were drawn from data of the so-called Global Data Sharing Initiative, a worldwide data collection of MS patients with COVID-19, which examined the endpoints of hospitalization, ICU admission, ventilation, and death.[126] As in other registry studies, reaching these endpoints was associated with older age, a progressive MS course, and EDSS scores of >6. In addition to the higher risk for untreated patients, the authors found a higher risk for severe COVID-19 progression in patients treated with B-cell-depleting therapy. However, when looking closely at the data, this finding did not apply to the fatal outcome of the infection; here, there was no significant difference between anti-CD20 and other MS therapies. A North American registry analyzed 1626 patients and was able to show that a higher degree of disability was associated with worse COVID-19 progression; this was also true for older age, cardiovascular comorbidities, and recent treatment with corticosteroids and rituximab.[127]

In addition to questions on DMTs, the Corona pandemic has necessitated a reflection on the optimal vaccination strategy for MS patients (e.g. see the MS International federation in which members of the MSTCG are active: https://www.msif.org/news/2020/02/10/the-coronavirus-and-ms-what-you-need-to-know/). As vaccination has just started, sufficient data for MS patients do not yet exist. Therefore, recommendations have to be derived from the general experience with vaccinations during immunosuppressive therapy.[128] In principle, inactivated vaccines can be administered safely, and preferably vaccination should be completed 2–4 weeks before the start of

immunosuppressive therapy. Live vaccines are generally contraindicated in patients receiving immunosuppressive treatment or require a careful benefit-risk assessment. The interval between live vaccination and initiation of immunosuppressive therapy should be at least 6 weeks. As a result, the vaccination status of MS patients should always be checked, and vaccinations potentially refreshed in line with the appropriate guidelines before initiating therapy. Often a check is neglected, however, or vaccination cannot occur prior to MS treatment due to organizational demands, as currently with the SARS-CoV-2 vaccination. Vaccination under a respective therapy needs optimal timing: some DMTs downregulate immune system response, and vaccination may not lead to the desired and sufficient protective immunity. This problem is minor with certain DMTs, such as dimethyl fumarate, glatiramer acetate/glatiramoids, interferon preparations, natalizumab, or teriflunomide, while it is probably more severe with cladribine, fingolimod, or ozanimod. Problems may arise with DMTs causing a depletion of B cells critical for the vaccination response (alemtuzumab, ocrelizumab, ofatumumab). In this context, the immunological memory against SARS-CoV-2 measured after 6 months showed no apparent correlation between T-lymphocytes and B-cell responses, and immunity protection is mediated not only by antibody formation but also by T-lymphocytes (CD4 and in particular CD8).[129] Hence, the measurement of antibody formation is ultimately not the sole information required for expected protection against infection or a more severe disease course.

Few studies on the effects of other vaccines under DMTs have already been conducted.[130–132] Some drugs were found to have a principally reduced vaccine response, while the majority of responses were sufficient for vaccine protection. Of particular interest here is the study of vaccination response 12 weeks after ocrelizumab administration (VELOCE).[131] The positive response rate to a tetanus vaccine at 8 weeks was 23.9% in the ocrelizumab group *versus* 54.5% in the control group (with positive response rate defined as ⩾4-fold increase in antibody titer due to vaccination – while serum protection was achieved by all subjects in the ocrelizumab and control groups). The positive response rate to ⩾5 serotypes of polyvalent pneumococcal vaccine at 4 weeks was 71.6% in the ocrelizumab group and 100% in the control group. The positive response rates to a vaccine against five influenza strains at 4 weeks ranged from 55.6–80.0% in the ocrelizumab group and 75.0–97.0% in the control group. Virtually no antibody responses were detectable against a true neoantigen such as keyhole limpet hemocyanin.

Recommendation 14:

- Based on the data available to date, comorbidities and MS with severe disability pose an increased risk for severe COVID-19, but not MS disease in itself or treatment with DMTs. Only data on CD20 antibodies show the risk of a potentially more severe course under treatment. Thus, there is no reason to withhold or delay therapy for younger and otherwise healthy MS patients due to the pandemic. The selection of a drug should continue to be based solely on the activity and severity of MS.
- However, in older MS patients with a higher degree of disability and pre-existing internal, especially cardiovascular, diseases, the disease activity in trajectory to age should be reflected more intensively in the context of the pandemic, especially for progressive MS, to check whether MS therapy/B-cell-depleting immunotherapy is indicated. Corticosteroid therapy may increase the risk for more severe courses, which should be considered for patients with regular corticosteroid pulses.
- In principle, MS patients must be vaccinated – this includes vaccination against SARS-CoV-2 and applies to all currently available (conceptually inactivated) vaccines (mRNA, adenovirus vector). Vaccination should also be given under DMT as there is a reasonable prospect of achieving a sufficient vaccine response even with ongoing DMT. In this context, no special timing is required for vaccination. For ocrelizumab, data exist on vaccination 3 months after therapy administration, so this time window may be followed if possible. If this is not possible, vaccination against SARS-CoV-2 may be given whenever possible and considering the benefit-risk balance. Otherwise, the respective national vaccination guidelines must be followed. Data on verifying the vaccination response by measuring antibodies are currently insufficient, and this is also not recommended by the manufacturers.

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References

1. Petersen G, Wittmann R, Arndt V, *et al.* Epidemiologie der Multiplen Sklerose in Deutschland. *Nervenarzt* 2014; 85: 990–998.
2. Wiendl H, Korsukewitz C and Kieseier BC. *Multiple Sklerose: Klinik, Diagnostik und Therapie*. 2nd ed. Stuttgart: Kohlhammer Verlag, 2021.
3. Montalban X, Gold R, Thompson AJ, *et al.* ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Eur J Neurol* 2018; 25: 215–237.
4. Montalban X, Gold R, Thompson AJ, *et al.* ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler* 2018; 24: 96–120.
5. Rae-Grant A, Day GS, Marrie RA, *et al.* Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology* 2018; 90: 777–788.

6. Bittner S and Zipp F. AAN unveils new guidelines for MS disease-modifying therapy. *Nat Rev Neurol* 2018; 14: 384–386.
7. German Association of the Scientific Medical Societies (AWMF). *Standing guidelines commission. AWMF guidance manual and rules for guideline development*. 1st ed. Frankfurt: AWMF, 2012.
8. Thompson AJ, Banwell BL, Barkhof F, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
9. Thompson AJ, Baranzini SE, Geurts J, *et al*. Multiple sclerosis. *Lancet* 2018; 391: 1622–1636.
10. Zipp F, Oh J, Fragoso YD, *et al*. Implementing the 2017 McDonald criteria for the diagnosis of multiple sclerosis. *Nat Rev Neurol* 2019; 15: 441–445.
11. Lublin FD, Reingold SC, Cohen JA, *et al*. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278–286.
12. Kappos L, Wolinsky JS, Giovannoni G, *et al*. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol* 2020; 77: 1132–1140.
13. Faissner S, Plemel JR, Gold R, *et al*. Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. *Nat Rev Drug Discov* 2019; 18: 905–922.
14. Filippi M, Bar-Or A, Piehl F, *et al*. Multiple sclerosis. *Nat Rev Dis Primers* 2018; 4: 43.
15. Graetz C, Groppa S, Zipp F, *et al*. Preservation of neuronal function as measured by clinical and MRI endpoints in relapsing-remitting multiple sclerosis: how effective are current treatment strategies. *Expert Rev Neurother* 2018; 18: 203–219.
16. Klotz L, Havla J, Schwab N, *et al*. Risks and risk management in modern multiple sclerosis immunotherapeutic treatment. *Ther Adv Neurol Disord* 2019; 12: 1–31.
17. McGinley MP, Goldschmidt CH and Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. *JAMA* 2021; 325: 765–779.
18. Achtnichts L, Chan A, Czaplinski A, *et al*. Specific aspects of immunotherapy for multiple sclerosis in Switzerland: a structured commentary. *Clin Transl Neurosci* 2019; 3: 1.
19. Kolb-Mäurer A, Sunderkötter C, Kukowski B, *et al*. An update on Peginterferon beta-1a Management in Multiple Sclerosis: results from an interdisciplinary Board of German and Austrian Neurologists and dermatologists. *BMC Neurol* 2019; 19: 1–10.
20. Polman CH, O'Connor PW, Havrdova E, *et al*. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 899–910.
21. Wolinsky JS, Arnold DL, Brochet B, *et al*. Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2020; 19: 998–1009.
22. Butzkueven H, Spelman T, Horakova D, *et al*. Risk of requiring a wheelchair in primary progressive multiple sclerosis: data from the ORATORIO trial and the MSBase registry. *Eur J Neurol*. Epub ahead of print 16 March 2021. DOI: 10.1111/ene.14824.
23. Lünemann JD, Ruck T, Muraro PA, *et al*. Immune reconstitution therapies: concepts for durable remission in multiple sclerosis. *Nat Rev Neurol* 2020; 16: 56–62.
24. Giovannoni G, Comi G, Cook S, *et al*. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 416–426.
25. Dalla Costa G, Martinelli V, Sangalli F, *et al*. Prognostic value of serum neurofilaments in patients with clinically isolated syndromes. *Neurology* 2019; 92: e733–e741.
26. Tintore M, Arrambide G, Otero-Romero S, *et al*. The long-term outcomes of CIS patients in the Barcelona inception cohort: looking back to recognize aggressive MS. *Mult Scler* 2020; 26: 1658–1669.
27. Chung KK, Altmann D, Barkhof F, *et al*. A 30-year clinical and magnetic resonance imaging observational study of multiple sclerosis and clinically isolated syndromes. *Ann Neurol* 2020; 87: 63–74.
28. Okuda DT, Mowry EM, Beheshtian A, *et al*. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology* 2009; 72: 800–805.
29. Comi G, De Stefano N, Freedman MS, *et al*. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive

of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. *Lancet Neurol* 2012; 11: 33–41.

30. Jacobs LD, Beck RW, Simon JH, *et al.* Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000; 343: 898–904.
31. Kappos L, Polman CH, Freedman MS, *et al.* Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006; 67: 1242–1249.
32. Kappos L, Freedman MS, Polman CH, *et al.* Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet* 2007; 370: 389–397.
33. Kappos L, Freedman MS, Polman CH, *et al.* Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. *Lancet Neurol* 2009; 8: 987–997.
34. Kinkel RP, Kollman C, O'Connor P, *et al.* IM interferon β-1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology* 2006; 66: 678–684.
35. Edan G, Kappos L, Montalbán X, *et al.* Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. *J Neurol Neurosurg Psychiatry* 2014; 85: 1183–1189.
36. Kappos L, Edan G, Freedman MS, *et al.* The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. *Neurology* 2016; 87: 978–987.
37. Comi G, Martinelli V, Rodegher M, *et al.* Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1503–1511.
38. Miller AE, Wolinsky JS, Kappos L, *et al.* Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; 13: 977–986.
39. Leist TP, Comi G, Cree BA, *et al.* Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. *Lancet Neurol* 2014; 13: 257–267.
40. Tsivgoulis G, Katsanos AH, Grigoriadis N, *et al.* The effect of disease-modifying therapies on brain atrophy in patients with clinically isolated syndrome: a systematic review and meta-analysis. *Ther Adv Neurol Disord* 2015; 8: 193–202.
41. Tsivgoulis G, Katsanos AH, Grigoriadis N, *et al.* The effect of disease modifying therapies on brain atrophy in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. *PLoS ONE* 2015; 10: e0116511.
42. Fox EJ, Wynn D, Coles AJ, *et al.* Alemtuzumab improves neurological functional systems in treatment-naive relapsing-remitting multiple sclerosis patients. *J Neurol Sci* 2016; 363: 188–194.
43. Phillips JT, Giovannoni G, Lublin FD, *et al.* Sustained improvement in Expanded Disability Status Scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis. *Mult Scler* 2011; 17: 970–979.
44. von Wyl V, Benkert P, Moser A, *et al.* Disability progression in relapse-free multiple sclerosis patients on fingolimod versus interferon-beta/glatiramer acetate. *Mult Scler* 2021; 27: 439–448.
45. Kappos L, Bar-Or A, Cree B, *et al.* Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018; 391: 1263–1273.
46. Montalban X, Hauser SL, Kappos L, *et al.* Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017; 376: 209–220.
47. Rommer PS, Kamin F, Abu-Mugheisib M, *et al.* Long-term effects of repeated cycles of intrathecal triamcinolone acetonide on spasticity in MS patients. *CNS Neurosci Ther* 2016; 22: 74–79.
48. Kamin F, Rommer PS, Abu-Mugheisib M, *et al.* Effects of intrathecal triamincinolone-acetonide treatment in MS patients with therapy-resistant spasticity. *Spinal Cord* 2015; 53: 109–113.
49. Ellenberger D, Eichstädt K, Flachenecker P, *et al.* Decreasing longitudinal use of glucocorticosteroids in multiple sclerosis. *Mult Scler Relat Disord* 2018; 25: 173–174.
50. Rommer PS, Buckow K, Ellenberger D, *et al.* Patients' characteristics influencing the longitudinal utilization of steroids in multiple sclerosis – an observational study. *Eur J Clin Invest* 2015; 45: 587–593.

51. Chalmer TA, Baggesen LM, Nørgaard M, *et al.* Early versus later treatment start in multiple sclerosis: a register-based cohort study. *Eur J Neurol* 2018; 25: 1262–1e110.

52. He A, Merkel B, Brown JWL, *et al.* Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol* 2020; 19: 307–316.

53. Kavaliunas A, Manouchehrinia A, Stawiarz L, *et al.* Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler* 2017; 23: 1233–1240.

54. Beiki O, Frumento P, Bottai M, *et al.* Changes in the risk of reaching multiple sclerosis disability milestones in recent decades: a nationwide population-based cohort study in Sweden. *JAMA Neurol* 2019; 76: 665–671.

55. Brown JWL, Coles A, Horakova D, *et al.* Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA* 2019; 321: 175–187.

56. Harding K, Williams O, Willis M, *et al.* Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. *JAMA Neurol* 2019; 76: 536–541.

57. Jokubaitis VG, Spelman T, Kalincik T, *et al.* Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Ann Neurol* 2016; 80: 89–100.

58. Kalincik T, Diouf I, Sharmin S, *et al.* Effect of disease-modifying therapy on disability in relapsing-remitting multiple sclerosis over 15 years. *Neurology* 2021; 96: e783–e797.

59. Amato MP, Fonderico M, Portaccio E, *et al.* Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis. *Brain* 2020; 143: 3013–3024.

60. Reynders T, D'haeseleer M, De Keyser J, *et al.* Definition, prevalence and predictive factors of benign multiple sclerosis. *Eneurologicalsci* 2017; 7: 37–43.

61. Multiple Sklerose-Therapie-Konsensus-Gruppe (MSTKG). Immunmodulatorische Stufentherapie der multiplen Sklerose, 1. Ergänzung: Dezember 2000. *Nervenarzt* 2001; 72: 150–157.

62. Burt RK, Balabanov R, Burman J, *et al.* Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. *JAMA* 2019; 321: 165–174.

63. Coles AJ, Cohen JA, Fox EJ, *et al.* Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. *Neurology* 2017; 89: 1117–1126.

64. Patti F, Visconti A, Capacchione A, *et al.* Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS). *Ther Adv Neurol Disord* 2020; 13: 1–10.

65. Roos I, Leray E, Frascoli F, *et al.* Delay from treatment start to full effect of immunotherapies for multiple sclerosis. *Brain* 2020; 143: 2742–2756.

66. Wattjes MP, Ciccarelli O, Reich DS, *et al.* MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in multiple sclerosis. *Lancet Neurol* 2021; 20: 653–670.

67. Gasperini C, Prosperini L, Tintoré M, *et al.* Unraveling treatment response in multiple sclerosis: a clinical and MRI challenge. *Neurology* 2019; 92: 180–192.

68. Wattjes MP, Rovira Miller ÀD, Yousry TA, *et al.* Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis – establishing disease prognosis and monitoring patients. *Nat Rev Neurol* 2015; 11: 597–606.

69. Trojano M, Tintore M, Montalban X, *et al.* Treatment decisions in multiple sclerosis – insights from real-world observational studies. *Nat Rev Neurol* 2017; 13: 105–118.

70. Bittner S, Steffen F, Uphaus T, *et al.* Clinical implications of serum neurofilament in newly diagnosed MS patients: a longitudinal multicentre cohort study. *eBioMedicine* 2020; 56: 102807.

71. Akgün K, Kretschmann N, Haase R, *et al.* Profiling individual clinical responses by high-frequency serum neurofilament assessment in MS. *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e555.

72. Leocani L, Rocca MA and Comi G. MRI and neurophysiological measures to predict course, disability and treatment response in multiple sclerosis. *Curr Opin Neurol* 2016; 29: 243–253.

73. Bittner S, Oh J, Kubala Havrdová E, *et al.* The potential of serum neurofilament as biomarker for multiple sclerosis. *Brain* 2021; 1: awab241.

74. Sastre-Garriga J, Pareto D, Battaglini M, *et al.* MAGNIMS consensus recommendations on the use of brain and spinal cord atrophy measures in clinical practice. *Nat Rev Neurol* 2020; 16: 171–182.

75. Novotna M, Soldán MMP, Abou Zeid N, *et al.* Poor early relapse recovery affects onset of progressive disease course in multiple sclerosis. *Neurology* 2015; 85: 722–729.

76. Ontaneda D, Tallantyre E, Kalincik T, *et al.* Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. *Lancet Neurol* 2019; 18: 973–980.

77. Lu G, Beadnall HN, Barton J, *et al.* The evolution of 'No Evidence of Disease Activity' in multiple sclerosis. *Mult Scler Relat Disord* 2018; 20: 231–238.

78. Bergvall N, Makin C, Lahoz R, *et al.* Relapse rates in patients with multiple sclerosis switching from interferon to fingolimod or glatiramer acetate: a US claims database study. *PLoS ONE* 2014; 9: e88472.

79. Braune S, Lang M and Bergmann A. Efficacy of fingolimod is superior to injectable disease modifying therapies in second-line therapy of relapsing remitting multiple sclerosis. *J Neurol* 2016; 263: 327–333.

80. Cohen JA, Barkhof F, Comi G, *et al.* Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. *J Neurol* 2013; 260: 2023–2032.

81. Coles A, Fox E, Vladic A, *et al.* Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012; 78: 1069–1078.

82. Fox E, Edwards K, Burch G, *et al.* Outcomes of switching directly to oral fingolimod from injectable therapies: results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis. *Mult Scler Relat Disord* 2014; 3: 607–619.

83. He A, Spelman T, Jokubaitis V, *et al.* Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. *JAMA Neurol* 2015; 72: 405–413.

84. Prosperini L, Giannì C, Leonardi L, *et al.* Escalation to natalizumab or switching among immunomodulators in relapsing multiple sclerosis. *Mult Scler* 2012; 18: 64–71.

85. Río J, Tintoré M, Sastre-Garriga J, *et al.* Change in the clinical activity of multiple sclerosis after treatment switch for suboptimal response. *Eur J Neurol* 2012; 19: 899–904.

86. Spelman T, Kalincik T, Zhang A, *et al.* Comparative efficacy of switching to natalizumab in active multiple sclerosis. *Ann Clin Transl Neurol* 2015; 2: 373–387.

87. Vermersch P, Eralinna JP, Nicholas R, *et al.* Efficacy and safety of ocrelizumab in patients with relapsing-remitting multiple sclerosis with a suboptimal response to previous disease-modifying therapies (1-year interim results). *Mult Scler Relat Disord* 2020; 405: 310.

88. Coles AJ, Twyman CL, Arnold DL, *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829–1839.

89. Cohen JA, Barkhof F, Comi G, *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 402–415.

90. Hauser SL, Bar-Or A, Comi G, *et al.* Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017; 376: 221–234.

91. Hauser SL, Kappos L, Arnold DL, *et al.* Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. *Neurology* 2020; 95: e1854–e1867.

92. Butzkueven H, Kappos L, Wiendl H, *et al.* Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). *J Neurol Neurosurg Psychiatry* 2020; 91: 660–668.

93. Gold R, Arnold DL, Bar-Or A, *et al.* Safety and efficacy of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: 9 years' follow-up of DEFINE, CONFIRM, and ENDORSE. *Ther Adv Neurol Disord* 2020; 13: 1–17.

94. Lohmann L, Janoschka C, Schulte-Mecklenbeck A, *et al.* Immune cell profiling during switching from Natalizumab to Fingolimod reveals differential effects on systemic immune-regulatory networks and on trafficking of non-T cell populations into the cerebrospinal fluid – results from the ToFingo successor study. *Front Immunol* 2018; 9: 1560.

95. Wiendl H, Calabresi PA and Meuth SG. Defining response profiles after alemtuzumab: rare paradoxical disease exacerbation. *Neurology* 2018; 90: 309–311.

96. Pfeuffer S, Ruck T, Pul R, *et al.* Impact of previous disease-modifying treatment on effectiveness and safety outcomes, among patients with multiple sclerosis treated with alemtuzumab. *J Neurol Neurosurg Psychiatr.* Epub ahead of print 12 March 2021. DOI: 10.1136/jnnp-2020.

97. Barry B, Erwin AA, Stevens J, *et al*. Fingolimod rebound: a review of the clinical experience and management considerations. *Neurol Ther* 2019; 8: 241–250.

98. Prosperini L, Kinkel RP, Miravalle AA, *et al*. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. *Ther Adv Neurol Disord* 2019; 12: 1–17.

99. Kister I, Spelman T, Alroughani R, *et al*. Discontinuing disease-modifying therapy in MS after a prolonged relapse-free period: a propensity score-matched study. *J Neurol Neurosurg Psychiatr* 2016; 87: 1133–1137.

100. Wiendl H, Bourdette D and Ciccarelli O. Can immune reprogramming with alemtuzumab induce permanent remission in multiple sclerosis? *Neurology* 2017; 89: 1098–1100.

101. Zhang Y, Gonzalez Caldito N, Shirani A, *et al*. Aging and efficacy of disease-modifying therapies in multiple sclerosis: a meta-analysis of clinical trials. *Ther Adv Neurol Disord* 2020; 13: 1–10.

102. Dahlke F, Arnold DL, Aarden P, *et al*. Characterisation of MS phenotypes across the age span using a novel data set integrating 34 clinical trials (NO.MS cohort): age is a key contributor to presentation. *Mult Scler*. Epub ahead of print 28 January 2021. DOI: 10.1177/1352458520988637.

103. Grand'Maison F, Yeung M, Morrow SA, *et al*. Sequencing of disease-modifying therapies for relapsing–remitting multiple sclerosis: a theoretical approach to optimizing treatment. *Curr Med Res Opin* 2018; 34: 1419–1430.

104. Miller AE. Switching or discontinuing disease-modifying therapies for multiple sclerosis. *Continuum* 2016; 22: 851–863.

105. Saccà F, Lanzillo R, Signori A, *et al*. Determinants of therapy switch in multiple sclerosis treatment-naive patients: a real-life study. *Mult Scler* 2019; 25: 1263–1272.

106. Mäurer M, Tiel-Wilck K, Oehm E, *et al*. Reasons to switch: a noninterventional study evaluating immunotherapy switches in a large German multicentre cohort of patients with relapsing-remitting multiple sclerosis. *Ther Adv Neurol Disord* 2019; 12: 1–12.

107. Muraro PA, Martin R, Mancardi GL, *et al*. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. *Nat Rev Neurol* 2017; 13: 391.

108. Tuohy O, Costelloe L, Hill-Cawthorne G, *et al*. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatry* 2015; 86: 208–215.

109. Haghikia A, Dendrou CA, Schneider R, *et al*. Severe B-cell-mediated CNS disease secondary to alemtuzumab therapy. *Lancet Neurol* 2017; 16: 104–106.

110. Luna G, Alping P, Burman J, *et al*. Infection risks among patients with multiple sclerosis treated with Fingolimod, Natalizumab, Rituximab, and Injectable therapies. *JAMA Neurol* 2020; 77: 184–191.

111. Berger JR. Classifying PML risk with disease modifying therapies. *Mult Scler Relat Disord* 2017; 12: 59–63.

112. Koralnik IJ. Overview of the cellular immunity against JC virus in progressive multifocal leukoencephalopathy. *J Neurovirol* 2002; 8: 59–65.

113. Schwab N, Schneider-Hohendorf T, Melzer N, *et al*. Natalizumab-associated PML: challenges with incidence, resulting risk, and risk stratification. *Neurology* 2017; 88: 1197–1205.

114. Ho P-R, Koendgen H, Campbell N, *et al*. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017; 16: 925–933.

115. Plavina T, Subramanyam M, Bloomgren G, *et al*. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2014; 76: 802–812.

116. Schwab N, Schneider-Hohendorf T and Wiendl H. CD62L is not a reliable biomarker for predicting PML risk in natalizumab-treated R-MS patients. *Neurology* 2016; 87: 958–959.

117. Schwab N, Schneider-Hohendorf T, Hoyt T, *et al*. Anti-JCV serology during natalizumab treatment: review and meta-analysis of 17 independent patient cohorts analyzing anti-John Cunningham polyoma virus sero-conversion rates under natalizumab treatment and differences between technical and biological sero-converters. *Mult Scler* 2018; 24: 563–573.

118. Trampe AK, Hemmelmann C, Stroet A, *et al*. Anti-JC virus antibodies in a large German natalizumab-treated multiple sclerosis cohort. *Neurology* 2012; 78: 1736–1742.

119. Ryerson LZ, Foley J, Chang I, *et al*. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology* 2019; 93: e1452–e1462.

120. Campbell N, Cohen J, Wiendl H, *et al.* Evaluating the efficacy and safety of 6-week extended interval dosing of natalizumab via a prospective, controlled, randomized, open-label, rater-blinded phase 3b study. *Neurology* 2019; 92: P32095.

121. Hellwig K, Geissbuehler Y, Sabidó M, *et al.* Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. *J Neurol* 2020; 267: 1715–1723.

122. Hakkarainen KM, Juuti R, Burkill S, *et al.* Pregnancy outcomes after exposure to interferon beta: a register-based cohort study among women with MS in Finland and Sweden. *Ther Adv Neurol Disord* 2020; 13: 1–15.

123. Thöne J, Thiel S, Gold R, *et al.* Treatment of multiple sclerosis during pregnancy – safety considerations. *Expert Opin Drug Saf* 2017; 16: 523–534.

124. Korsukewitz C, Reddel SW, Bar-Or A, *et al.* Neurological immunotherapy in the era of COVID-19 – looking for consensus in the literature. *Nat Rev Neurol* 2020; 16: 493–505.

125. Louapre C, Collongues N, Stankoff B, *et al.* Clinical characteristics and outcomes in patients with coronavirus disease 2019 multiple sclerosis. *JAMA Neurol* 2020; 77: 1079–1088.

126. Peeters LM, Parciak T, Walton C, *et al.* COVID-19 in people with multiple sclerosis: a global data sharing initiative. *Mult Scler* 2020; 26: 1157–1162.

127. Salter A, Fox RJ, Newsome SD, *et al.* Outcomes and risk factors associated with SARS-CoV-2 infection in a North American Registry of patients with multiple sclerosis. *JAMA Neurol* 2021; 78: 699–708.

128. Wagner N, Assmus F, Arendt G, *et al.* Impfen bei Immundefizienz. *Bundesgesundheitsbl* 2019; 62: 494–515.

129. Dan JM, Mateus J, Kato Y, *et al.* Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science* 2021; 371: eabf4063.

130. Bar-Or A, Freedman MS, Kremenchutzky M, *et al.* Teriflunomide effect on immune response to influenza vaccine in patients with multiple sclerosis. *Neurology* 2013; 81: 552–558.

131. Bar-Or A, Calkwood JC, Chognot C, *et al.* Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. *Neurology* 2020; 95: e1999–e2008.

132. Kappos L, Mehling M, Arroyo R, *et al.* Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. *Neurology* 2015; 84: 872–879.