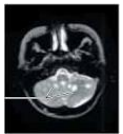

بسم الله الرحمن الرحيم

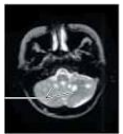
DEFINITION

- ***Multiple sclerosis (MS) is a chronic disease that usually begins in young adults.***
- ***Multiple sclerosis (MS) is the most common disabling neurologic disease in people ages 18 to 60, after trauma.***
- ***The lesions in MS are multiple in time and are multiple in space.***



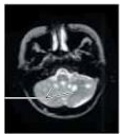
MS pathology

- ***Pathologically, it is characterized by multiple areas of CNS white matter inflammation,demyelination, and glial scarring (sclerosis).***
- ***The lesions are therefore multiple in space.***



Autoimmunity in MS

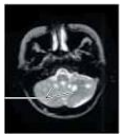
- ***T-cell reactivity is found against several epitopes of myelin basic protein (MBP) and proteolipid protein (PLP).***
- ***Antibody-secreting B cells are also activated in MS. The amount of IgG in the CSF and the rate of IgG synthesis are increased. Because only a few clones of CSF cells are activated, the response is oligoclonal.***



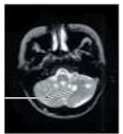
Autoimmunity in MS

- The predominant lymphocytes in MS lesions are T- cells (**CD4 +** cells extend from the periphery of active plaques into adjacent white matter, whereas **CD8+** cells predominate in the perivascular regions).

- A **shift from Th 2** cells(expressing IL-4, IL-5, IL-10, and IL-13), **toward Th 1 cells** (expressing **IFN-gamma**, **TNF**, and **IL-2**) may be characteristic.
- Activated T cells and the **microglia-macrophage**s can contribute to tissue injury.
- Cytokines characteristic of T cells include interleukin-2 (IL-2), interferon-y, and tumor necrosis factor- α (TNF- α) (lymphotoxin). factors released by **macrophages and microglia** include **TNF-α**, **leukotrienes**, **thromboxanes,proteases,** and **complement components.** Many of these immunologically active substances can result in upregulation of adhesion molecules, which can promote or facilitate nonspecific lymphocyte-macrophage migration to the site of immune injury and immune effector-target cell interactions.



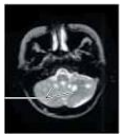
- ***The cytokine called tissue necrosis factor (TNF) is toxic to oligodendroglial cells and myelin and can be found in MS plaques. Furthermore, CSF levels of TNF may correlate with MS disease activity.***



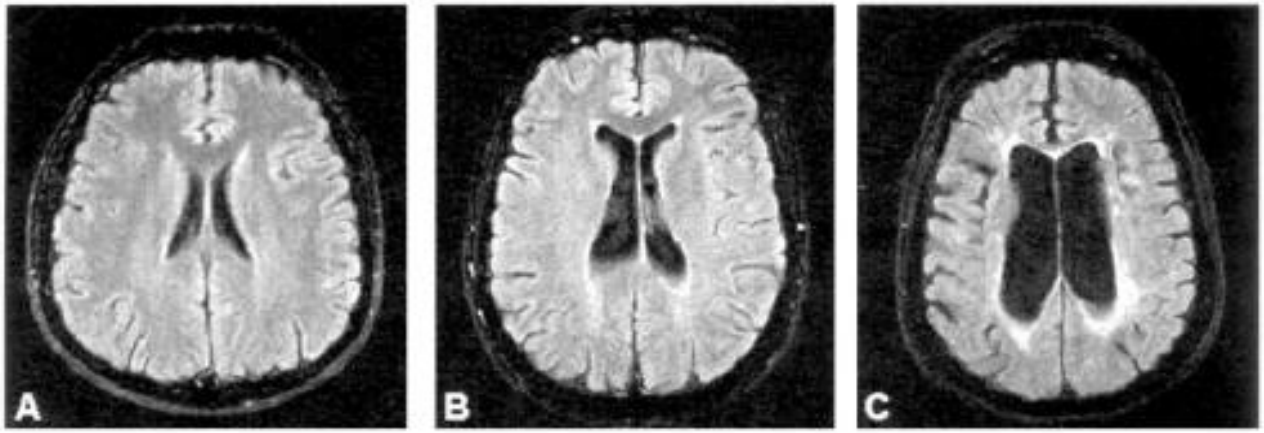
MS course

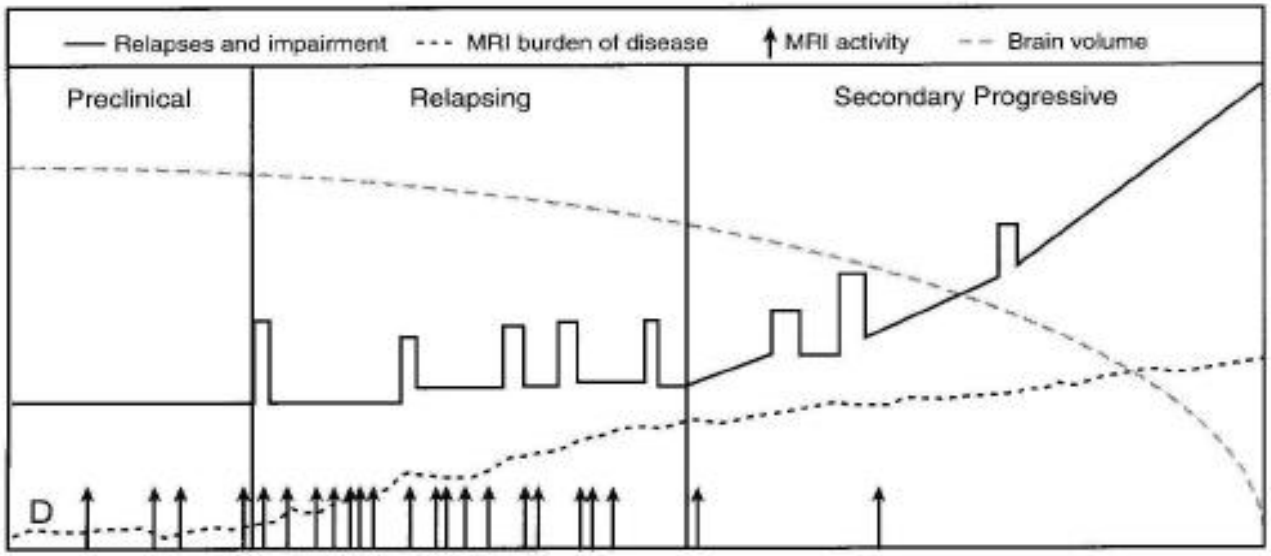
- ***Neuroinflamatory phase***

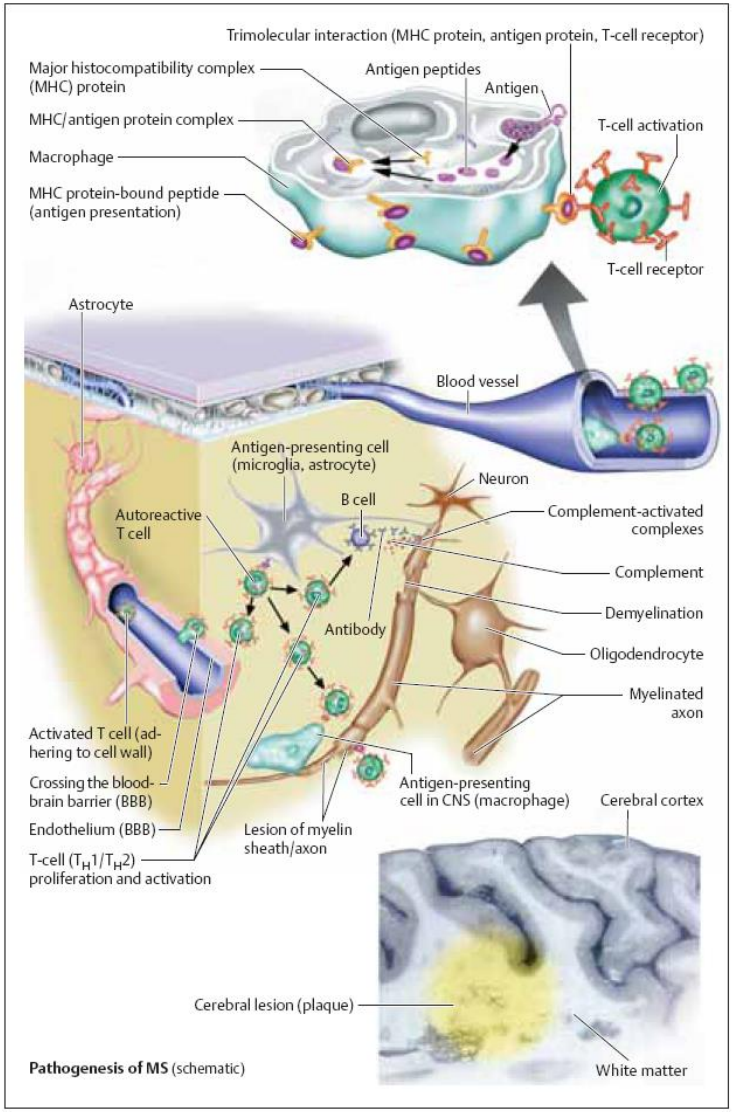
- ***Neurodegeneration phase(axonal damage)***



Changes in MRI with duration of disease







Pathogenesis of MS (schematic)

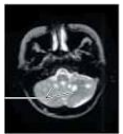
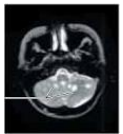


Table 375-6 Two-Year Outcomes for FDA-Approved Therapies for Multiple Sclerosis[a]

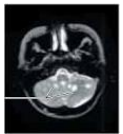
	Clinical Outcomes[b]		MRI Outcomes[c]	
Dose, Route, and Schedule	**Attack Rate, Mean**	**Change in Disease Severity**	**New T2 Lesions[d]**	**Total Burden of Disease**
IFN-β-1b, 250 μg SC qod	-34%e	-29% (ns)	-83%f	-17%e
IFN-β-1a, 30 μg IM qw	-18%g	-37%g	-36%f	-4% (ns)
IFN-β-1a, 44 μg SC tiw	-32%e	-30%g	-78%e	-15%e
GA, 20 mg SC qd	-29%f	-12% (ns)	-38%f	-8%f
MTX, 12 mg/m^2 IV q3mo	-66%e	-75%g	-79%g	nr
NTZ, 300 mg IV qmo	-68%e	-42%[e]	-83%e	-18%e



MS treatment strategies

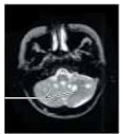
- ***Imunomodulatory and immunosuppressive therapies (Pathological and ethiological)***

- ***Symptomatic therapies(relief symptoms)***

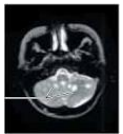


New agents

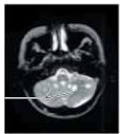
- A large number of agents are under active investigation for MS therapy. Several of these drugs are **parenteral monoclonal** antibodies .Of these, natalizumab is only approved drug, but others such as rituximab (anti-CD20 drug that specifically depletes B cells), alemtuzumab (anti-CD52 drug), and daclizumab (anti–interleukin-2 a receptor drug) are under current investigation.
- **oral therapies** may be near at hand for MS patients. Promising results from phase 2 studies of fingolimod (FTY720), a sphingosine-1-phosphate receptor modulator that results in downregulation of the receptor and sequestration of lymphocytes in peripheral lymph odes, and teriflunomide, a dihydroorotase inhibitor with antiinflammatory properties, have led current phase 3 investigations.Several other oral agents, including cladribine, fumarate (BG12), and laquinimod, are also under active investigation.



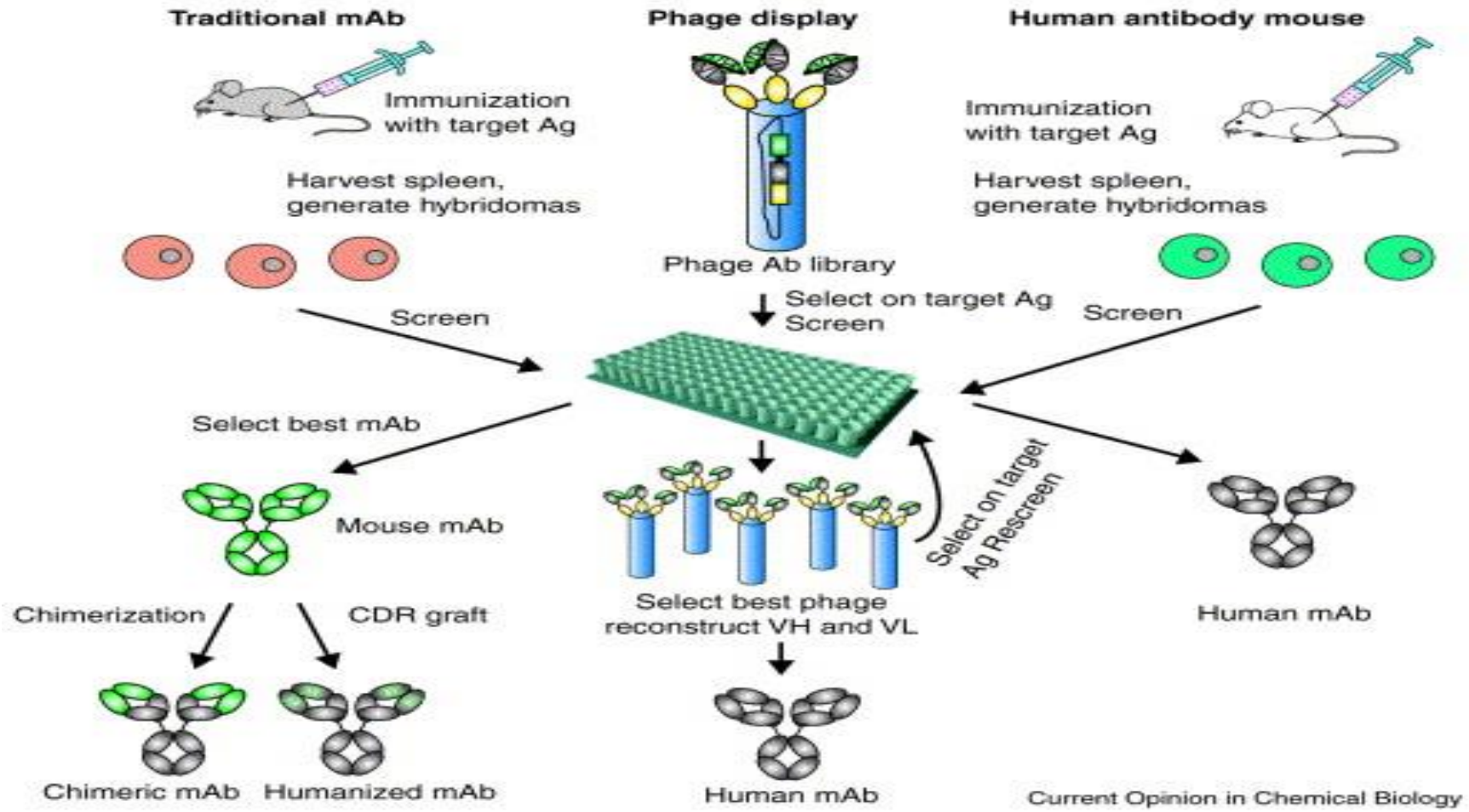
- **Monoclonal antibodies**

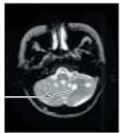


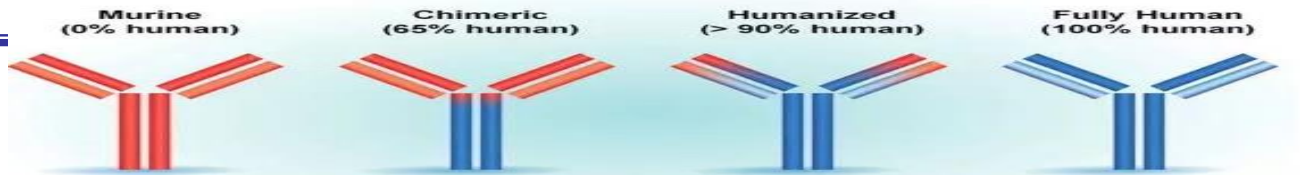
are
identical because they are produced by
one type of
immune cell, all clones of a single parent
cell.

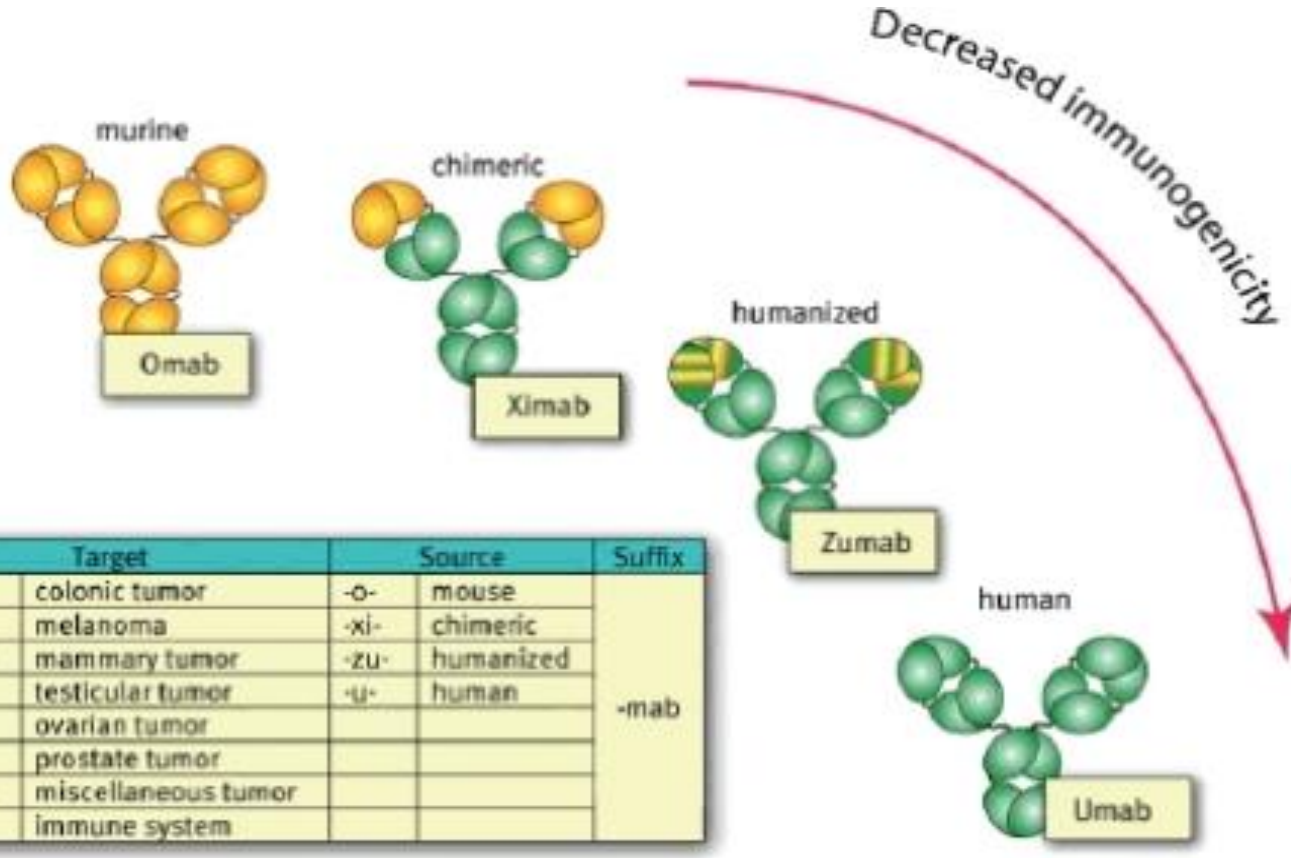


Production of mAB

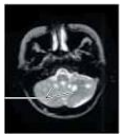




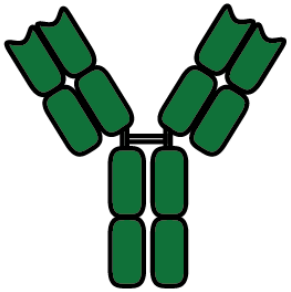
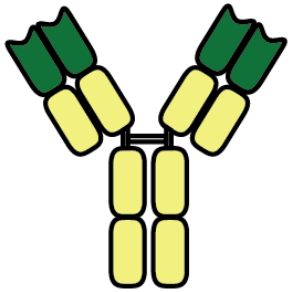
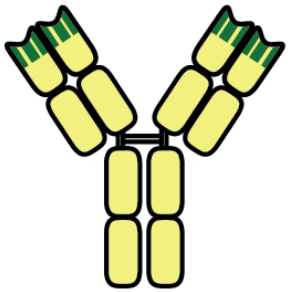
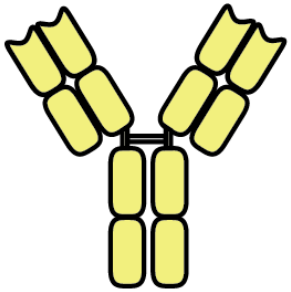


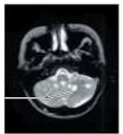


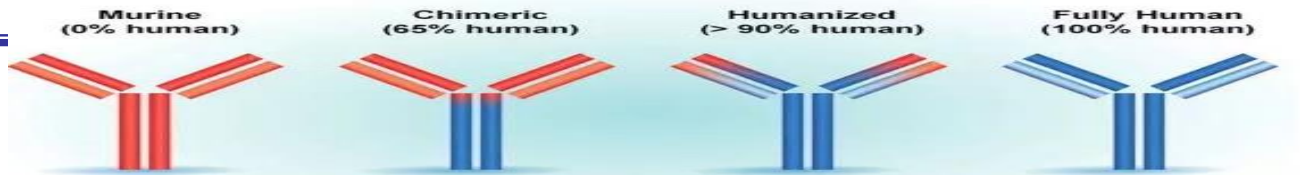
Prefix	Target		Source		Suffix
variable	-co(l)-	colonic tumor	-o-	mouse	-mab
	-me(l)-	melanoma	-xi-	chimeric	
	-ma(r)-	mammary tumor	-zu-	humanized	
	-go(t)-	testicular tumor	-u-	human	
	-go(v)-	ovarian tumor			
	-pr(o)-	prostate tumor			
	-tu(m)-	miscellaneous tumor			
	-li(m)-	immune system			

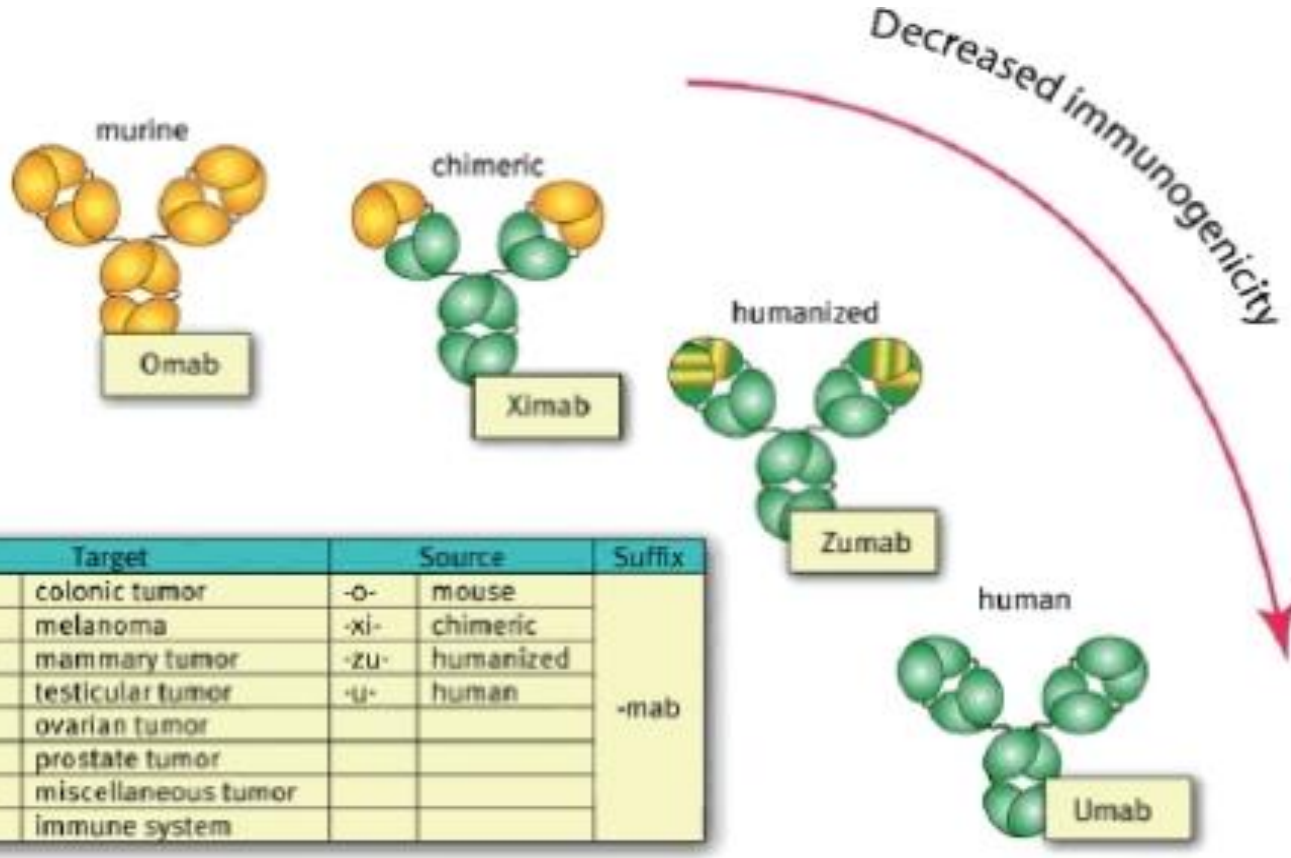


Different types of mABs

Mouse mAb	Chimeric mAb	Humanized mAb	Human mAb
			
-momab	-ximab	-zumab	-mumab
Not evaluated in MS	Rituximab	Alemtuzumab Daclizumab Natalizumab Ocrelizumab	Ofatumumab
Infusion reactions very frequent (>50%)	Infusion reactions frequent (approximately 30%)	Infusion reactions occasional (5%-10%)	Infusion reactions rare (<1%)







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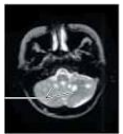
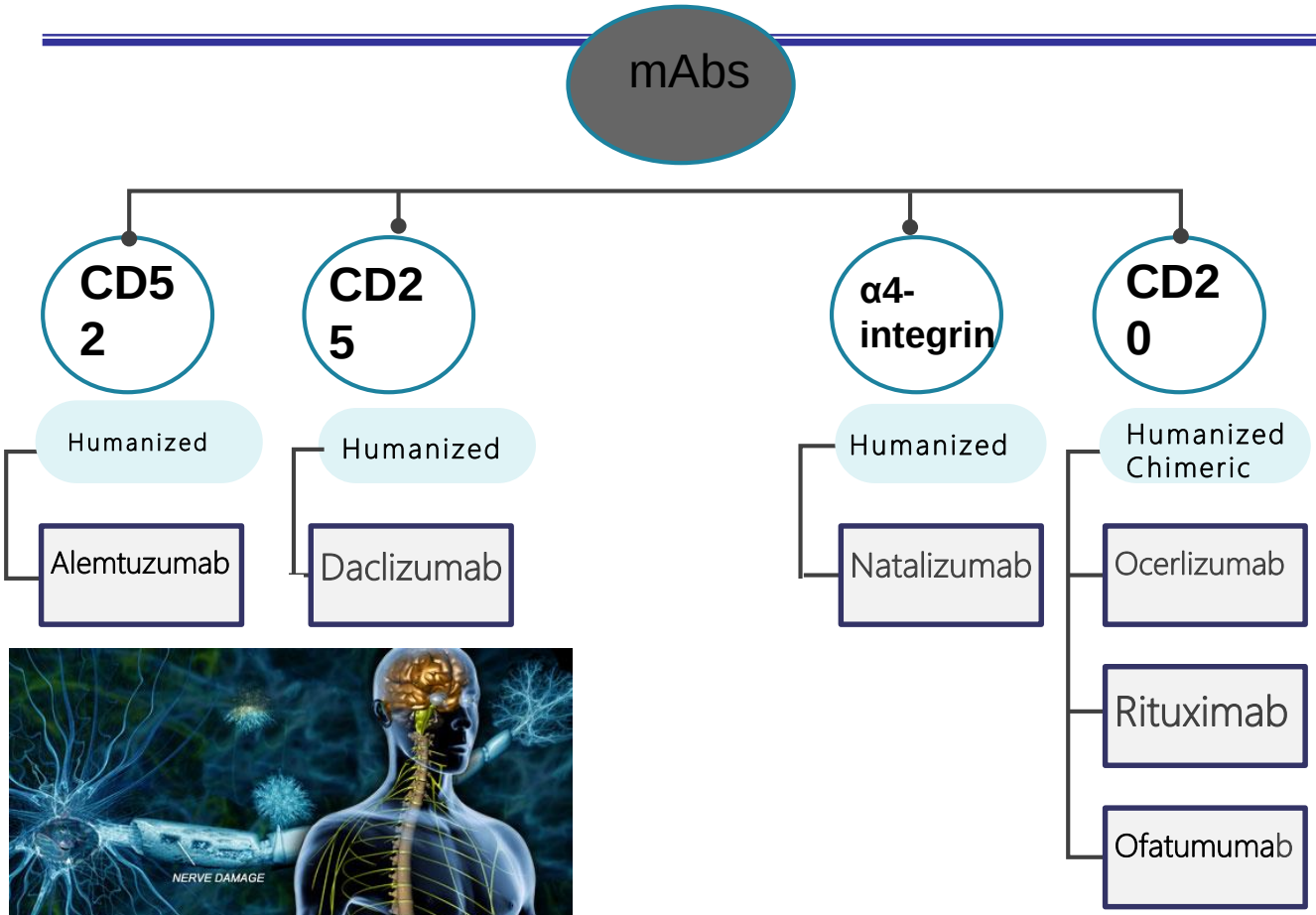
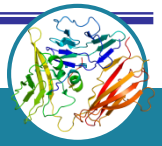
	-me(l)-	melanoma	-xi-	chimeric	
	-ma(r)-	mammary tumor	-zu-	humanized	
	-go(t)-	testicular tumor	-u-	human	
	-go(v)-	ovarian tumor			
	-pr(o)-	prostate tumor			
	-tu(m)-	miscellaneous tumor			
	-li(m)-	immune system			

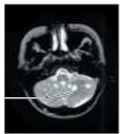


Monoclonal antibodies in MS

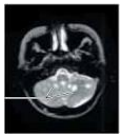




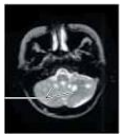
- mAbs for MS have strong immunomodulatory effects
- They are highly selective for their specific target



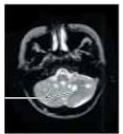
Natalizumab (Tysabri)



- natalizumab reduced the rate of clinical relapses by about 66% (approximately twice as effective as any of the other class of medications for MS) and decreased gadolinium-enhancing brain MRI lesions by over 90%.
- It is given as a monthly infusion at dose of 300 mgs over one hour.

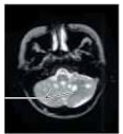


- Volumetric MRI can demonstrate cerebral atrophy even early in the course, when obvious lesions are sparse.
- This atrophy apparently results from axonal and neuronal loss and correlates better with disability than earlier scanning techniques, particularly with cognitive and memory dysfunction.

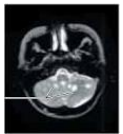


RRMS

- Natalizumab is best positioned as
- a second-line treatment for RRMS patients with persistently active inflammatory disease but could be used as an initial therapy for a patient presenting with a particularly aggressive initial course.
- Mitoxantrone should be reserved for RRMS patients who are worsening rapidly despite initial therapies.



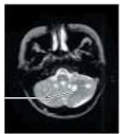
- Natalizumab (Tysabri) is a IgG4k **monoclonal antibody** against a4b1 and a4b7 **integrins**, adhesion molecules expressed on the surface of all leukocytes except neutrophils. It inhibits a4-mediated leukocyte adhesion to the vascular cell adhesion molecule (VCAM)-1 receptor on activated vascular endothelial cells and interferes with the trafficking of activated T lymphocytes across the blood-brain barrier.
- Monthly 300-mg IV doses of natalizumab reduced the number of Gd-enhancing lesions by 80- 92% and the clinical relapse rate by >50%(66 -68%) compared with placebo.
- The risk of PML is estimated to be 0.1% over 18 months of therapy.
- a 2-year, mitoxantrone, 5mg/m2 mitoxantrone, 12 mg/m2 for worsening RRMS and SPMS , decreasing relapse rates and progression of disability,



Dosing :

Multiple sclerosis, relapsing: Note: In high-risk populations or in countries with high tuberculosis burden, screen for latent infections (eg, hepatitis, tuberculosis) prior to initiating therapy. For patients who screen positive for latent infections, consult infectious disease or other appropriate specialists (eg, liver specialists) regarding treatment options before initiating therapy.

IV: 300 mg infused over 1 hour every 4 weeks. **Note:** Limited evidence suggests extended interval infusion (administration every 5 to 8 weeks) may be associated with a lower risk of progressive multifocal leukoencephalopathy and similar efficacy



Adverse Reactions
>10%:

Dermatologic: Skin rash (6% to 12%)

Gastrointestinal: Abdominal distress (11%), gastroenteritis (11%; cryptosporidial gastroenteritis: <1%), nausea (17%)

Genitourinary: Urinary tract infection (3% to 21%)

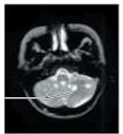
Infection: Influenza (12%)

Nervous system: Depression (19%), fatigue (10% to 27%), headache (32% to 38%)

Neuromuscular & skeletal: Arthralgia (8% to 19%), back pain (12%), limb pain (16%)

Respiratory: Flu-like symptoms (5% to 11%), lower respiratory tract infection (17%), upper respiratory tract infection (22%)

Miscellaneous: Infusion related reaction (11% to 24%; severe infusion related reaction: <1%)



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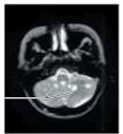
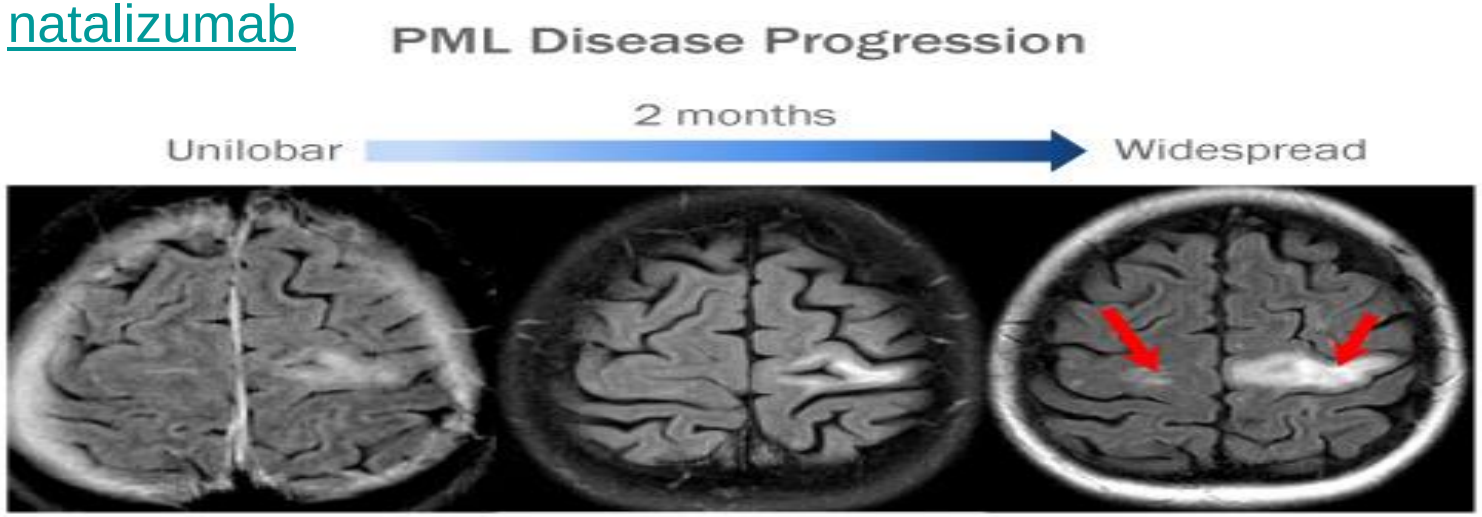


Progressive multifocal leukoencephalopathy (PML)

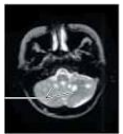
- ~~is a severe demyelinating disease of the central nervous system~~ that is caused by reactivation of the polyomavirus JC (JC virus)
- JC virus can reactivate, spread to the brain, and induce a lytic infection of oligodendrocytes, which are the CNS myelin-producing cells
- There is an increased risk of PML associated with the use of natalizumab

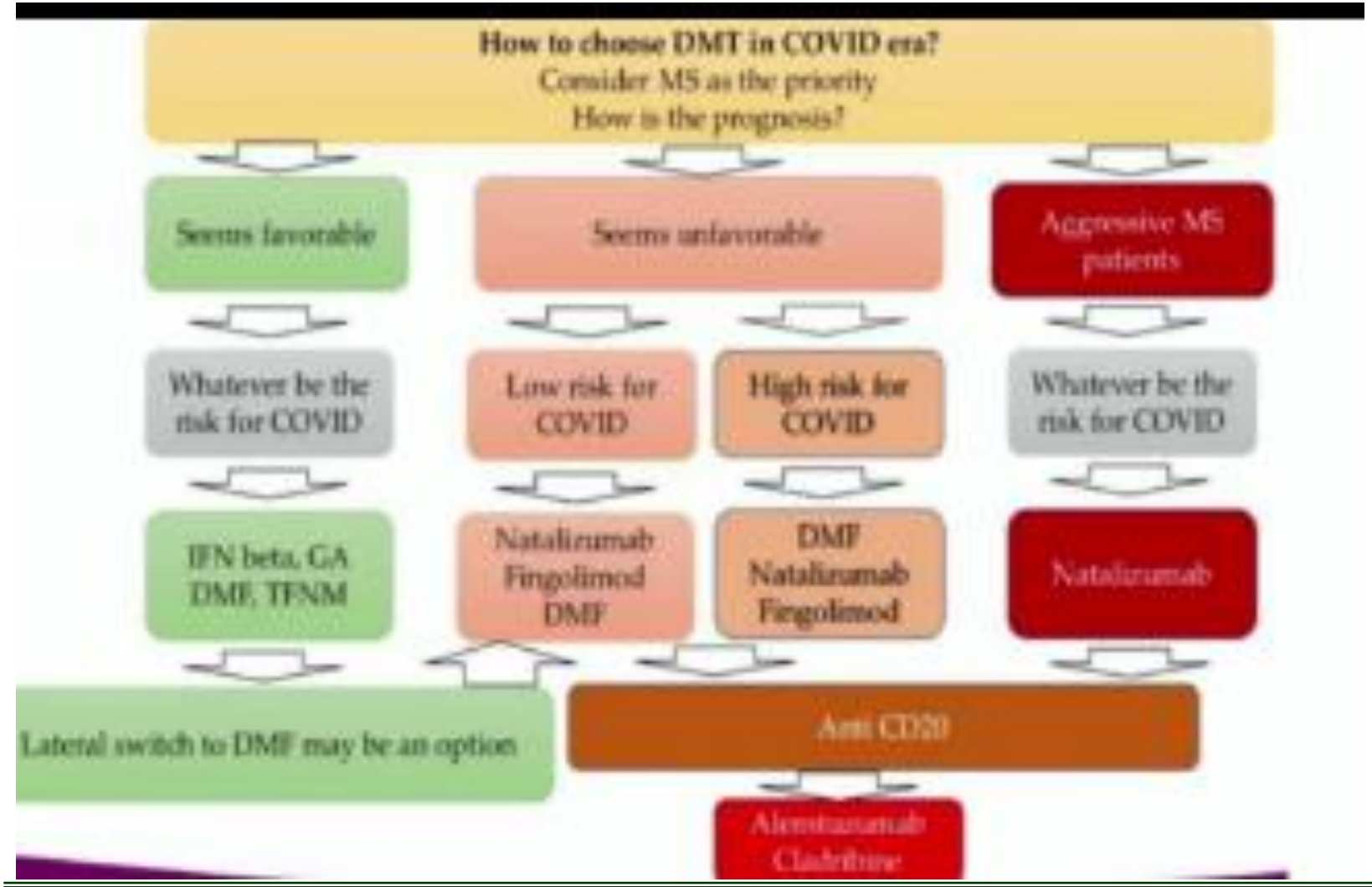


Family Planning
SmPC Information Summary DMTs in Highly Active Segment

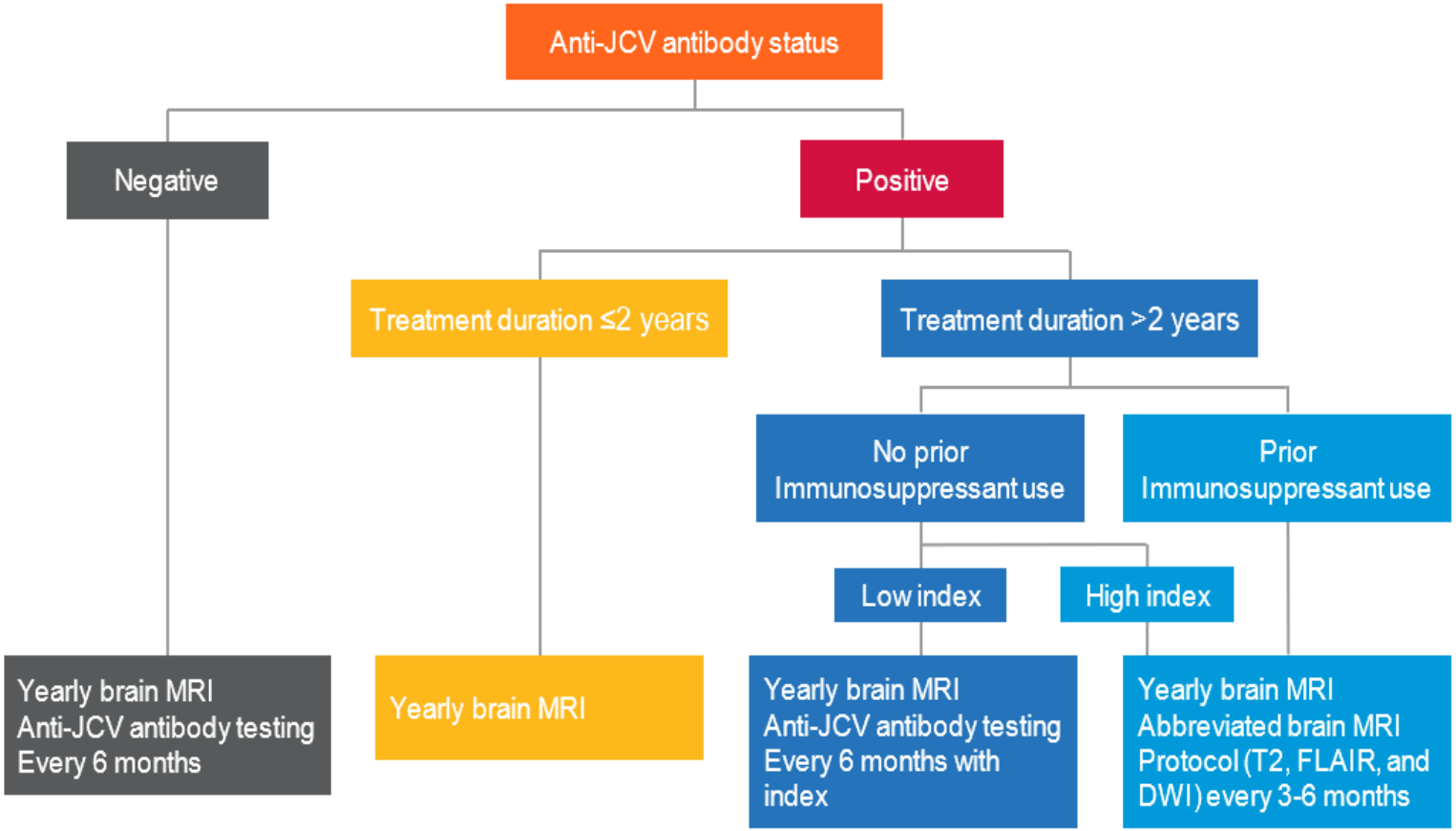
DMT	Effect on fertility	Contraception during treatment	Contraception after last dose	Treatment during pregnancy	Breastfeeding during treatment
TYSABRI[1]	No	No	No	Benefit-risk assessment	Not recommended
Fingolimod[2]	No	Yes	Yes, + 2 months	Contraindicated	Contraindicated
Alemtuzumab[3]	No data	Yes	Yes, + 4 months	Benefit-risk assessment	Benefit-risk assessment
Cladribine[4]	Yes	Yes*	Yes, + 6 months	Contraindicated	Contraindicated
Ocrelizumab[5]	No	Yes	Yes, +12 months	Benefit-risk assessment	Not recommended

* Both male and female patients must use effective contraception during cladribine treatment and for at least 6 months after the last dose.




How to choose DMT in COVID era?
Consider MS as the priority
How is the prognosis?
Seems favorable
Seems unfavorable
Aggressive MS patients
Whatever be the risk for COVID
Low risk for COVID
High risk for COVID
Whatever be the risk for COVID
IFN beta, GA
DMF, TFNM
Natalizumab
Fingolimod
DMF
DMF
Natalizumab
Fingolimod
Natalizumab
Lateral switch to DMF may be an option
Anti CD20
Alemtuzumab
Cladribine

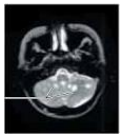
Recommended MRI monitoring based on PML risk



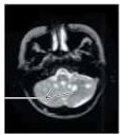
DWI, diffusion-weighted imaging; **FLAIR**, fluid-attenuated inversion recovery; **JCV**, John Cunningham virus; **MRI**, magnetic resonance imaging; **PML**, progressive multifocal leucoencephalopathy.

Physician Information and Management Guidelines for Patients With Multiple Sclerosis Receiving TYSABRI Therapy, Version 18, February 2020.

TYSABRI (natalizumab)



A recent analysis of the TOUCH registry demonstrated a **94% reduction** (95% CI: 78–99% [HR: 0.06; 95% CI: 0.01–0.22]) in the risk of PML in JCV positive patients on Q6W compared to those on Q4W*



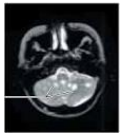
MENACTRIMS Guidelines on vaccination in patients with MS

Select points copied from the MENACTRIMS Guidelines

Timing of COVID-19 Vaccine in Patients Treated with DMTs

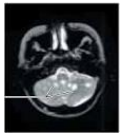
Disease-Modifying Therapy (DMT)	Wait Prior To Initiating Treatment	Wait After Last Dose Given
Interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate, natalizumab	Do not delay	Do not delay
Fingolimod, siponimod, ozanimod	2-4 weeks	Do not delay
Alemtuzumab	4 weeks	6 months
Cladribine	2-4 weeks	Do not delay
Ocrelizumab, rituximab	2-4 weeks	Limited data available (until B cell recovery ≈7-9 months)
Ofatumumab	2-4 weeks	Do not delay

MENACTRIMS Practice Guideline for COVID-19 Vaccination in Patients with Multiple Sclerosis ; Bassem I Yamouta , Magd Zakariab , Jihad Inshasic , Mohammad Al-Jumahd , Maya Zeineddinea , Maurice Dahdalehe , Saeed Bohlegaf ,



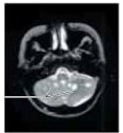
PML associated with Natalizumab Update

- As of August 31, 2018, the global overall incidence of PML in natalizumab-treated patients is: 4.17 per 1000 patients (95% CI 3.88 to 4.47 per 1000 patients)
- As of September 5, 2018 there have been 795 confirmed PML cases (792 MS, 3 CD), (218 US, 497 EEA, 80 ROW)
  - 76% of patients were alive with varying levels of disability*
- As of September 5, 2018, the duration of natalizumab dosing prior to PML diagnosis ranged from 8 to 144 doses.
  - Mean duration of natalizumab dosing at time of PML diagnosis was approximately 50 months.

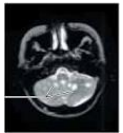


How to assess patient before starting treatment?

- Clinical Hx focusing on current or prior unusual or severe infections
  - CBC & diff; focusing on lymph count
  - HIV screening
- Other recommended tests
  - Detailed Hx & PE and EDSS
  - Brain MRI, unless available from the previous 6 months
  - LFTs
  - Pregnancy test
  - JCV Ab status
  - PPD
  - Screening for malignancy for high risk patients.



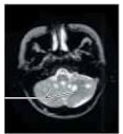
- JCV seronegative patients may continue NTZ while they do not seroconvert.
- JCV positive patients with prior immunosuppression (whatever the index) are better to stop NTZ after 2 years of treatment. Here the index has no value for decision.
- JCV positive patients with index<0.9 could continue NTZ with low risk for 6 years.
- JCV positive patients with index of 0.9-1.5 could continue NTZ with low risk for 3 years.
- JCV positive patients with index>1.5 could continue NTZ with low risk for 2 years.

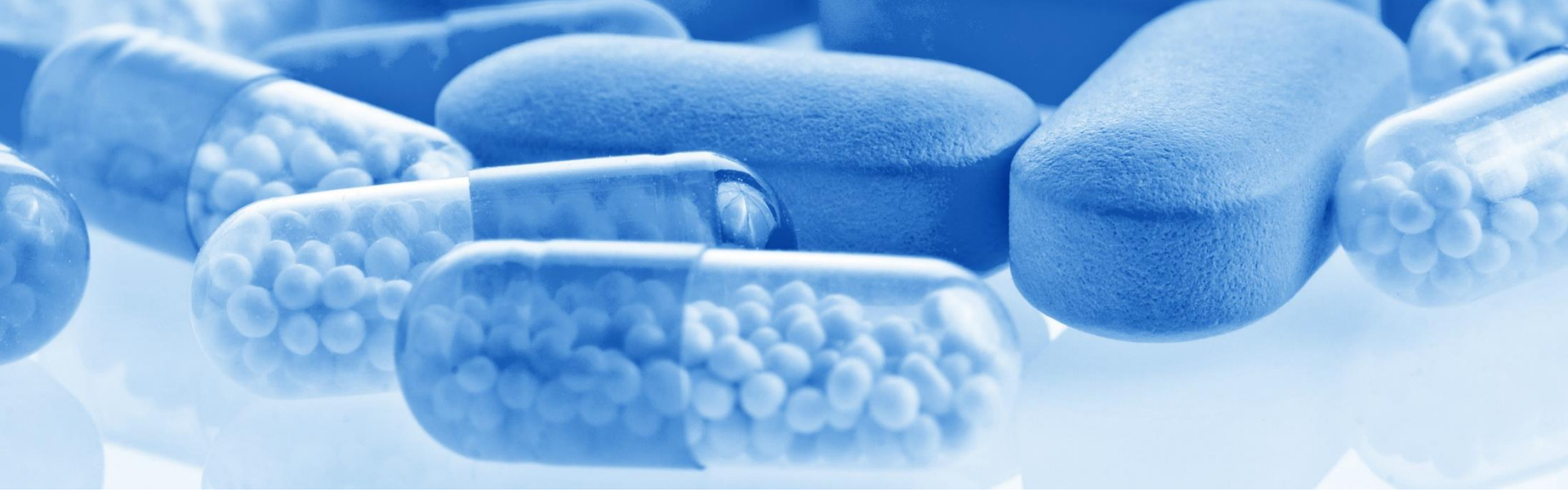


Natalizumab overview

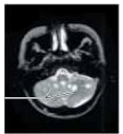
Drug	Indications	Possible Side effects	Some Potential Interactions	Precautions and Contraindications
Natalizumab	• Multiple sclerosis (Relapsing forms) **Additional (in USA)** • Crohn's disease	• Headache • Fatigue • UTI • Flu-like syndrome • Urticaria • Nausea/vomiting • Abdominal pain • PML • Increase in LFTs • Vertigo • Arthralgia	• Live vaccines • Denosumab • Immunosuppressants • Pimecrolimus	**Precautions:** • Immunosuppressed • Hepatic disease • Depression • Pregnancy / lactation • Abrupt cessation may lead to rebound phenomenon • Treatment beyond 24 months increases the risk of PML **Contraindications:** • Hypersensitivity

PML: Progressive multifocal leukoencephalopathy; **TNF:** Tumor necrosis factor; **UTI:** Urinary tract infection

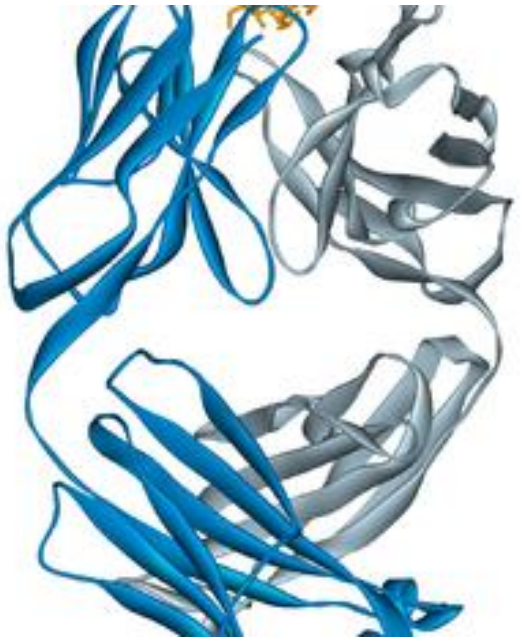


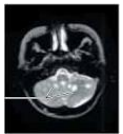


Alemtuzumab



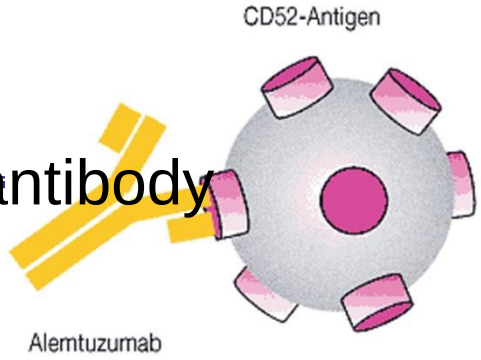
LEMTRADA®
alemtuzumab 12mg IV



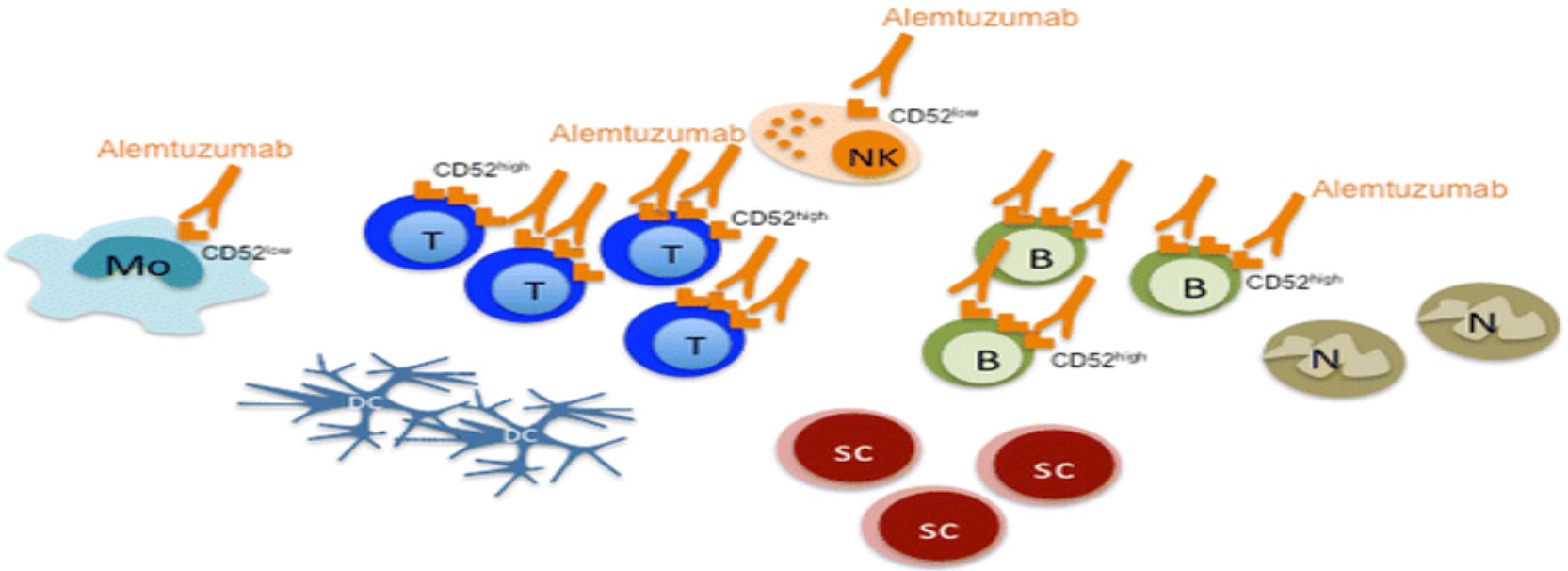


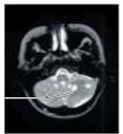
Almetezumab

It is ~~a humanized anti-CD52 IgG1 monoclonal antibody~~



CD52 is present on T and B lymphocytes as well as macrophages, NK cells and some granulocytes





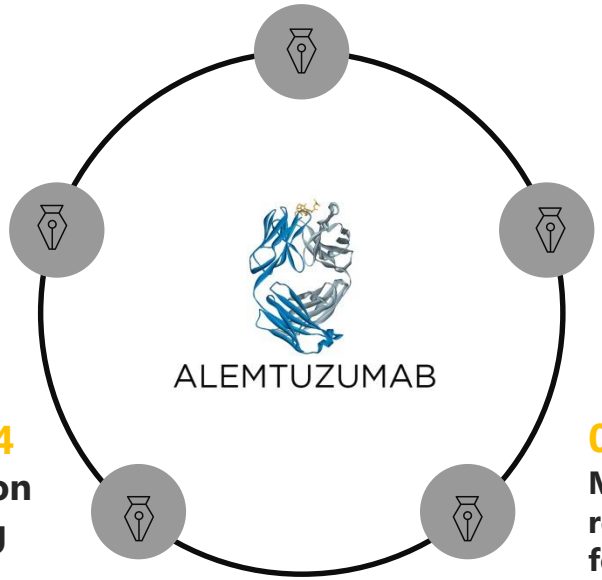
Alemtuzumab

01

Treatment of patients with relapsing forms of multiple sclerosis (MS), generally reserved for patients who have had an inadequate response to 2 or more medications indicated for the treatment of MS.

05

- **Pre-medicate with corticosteroids (methylprednisolone 1000 mg or equivalent) for first 3 days of each treatment course**
- **Observe for at least 2 hours after each infusion**



02

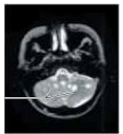
Dosage Forms:
Lemtrada: 12 mg/1.2 mL (1.2mL)

04

Administer by IV infusion over 4 hours (beginning within 8 hours after dilution)

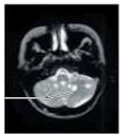
03

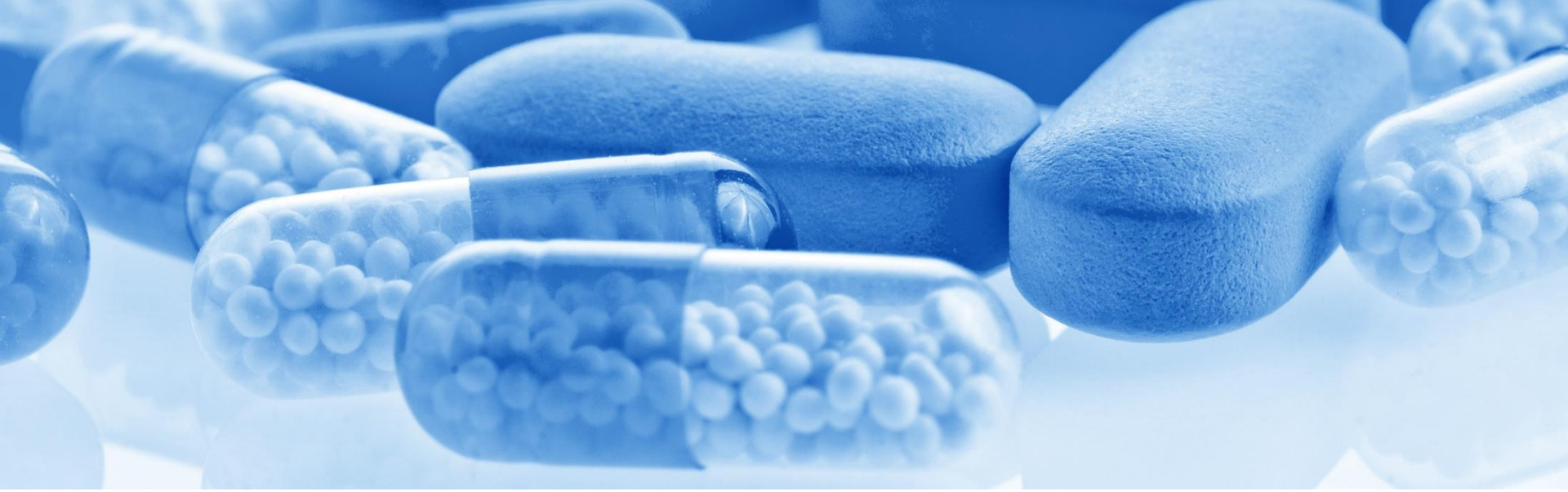
Multiple sclerosis, relapsing: Lemtrada: IV: 12 mg daily for 5 consecutive days (total 60 mg), followed 12 months later by 12 mg daily for 3 consecutive days (total 36 mg); total duration of therapy: 24 months.



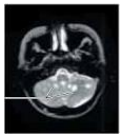
Adverse Reactions
>10%:

Dermatologic: Pruritus (14%), skin rash (53%), urticaria (16%)
Endocrine & metabolic: Thyroid disease (13% to 37%)
Gastrointestinal: Diarrhea (12%), nausea (21%)
Genitourinary: Urinary tract infection (19%)
Hematologic & oncologic: Lymphocytopenia (100%)
Immunologic: Antibody development (neutralizing: 5% to 94%; anti-alemtuzumab: 29% to 83%; no significant effect on drug efficacy)
Infection: Fungal infection (12% to 13%; including oral candidiasis, vulvovaginal candidiasis), herpes virus infection (16%), infection (71%; serious infection: 3%)
Local: Infusion-related reaction (92%)
Nervous system: Fatigue (18%), headache (52%), insomnia (16%)
Neuromuscular & skeletal: Arthralgia (12%), back pain (12%), limb pain (12%)
Respiratory: Nasopharyngitis (25%), oropharyngeal pain (11%), sinusitis (11%), upper respiratory tract infection (16%)
Miscellaneous: Fever (29%)

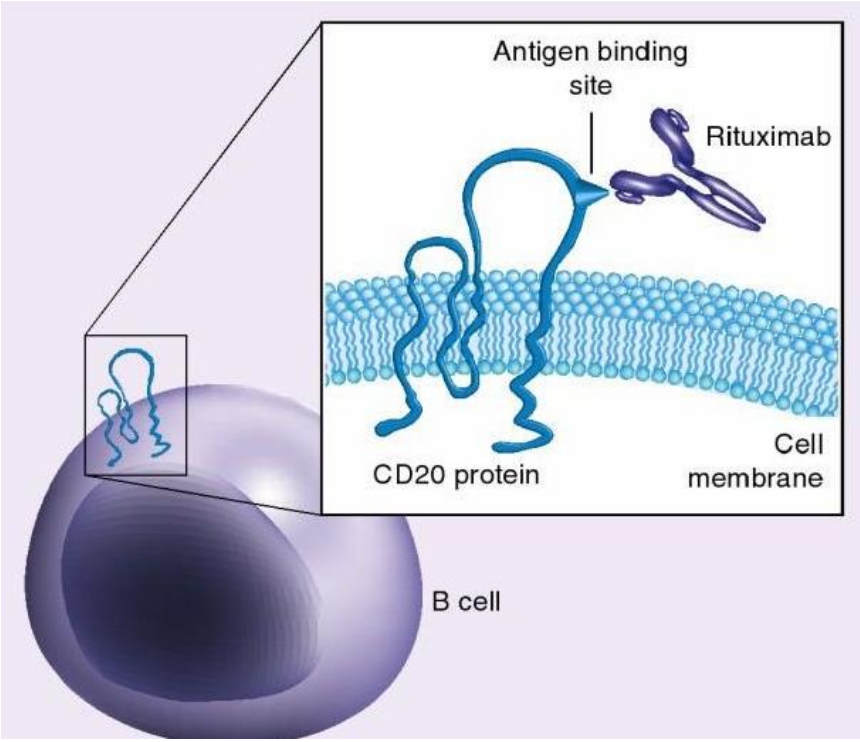


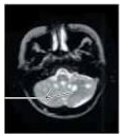


Rituximab

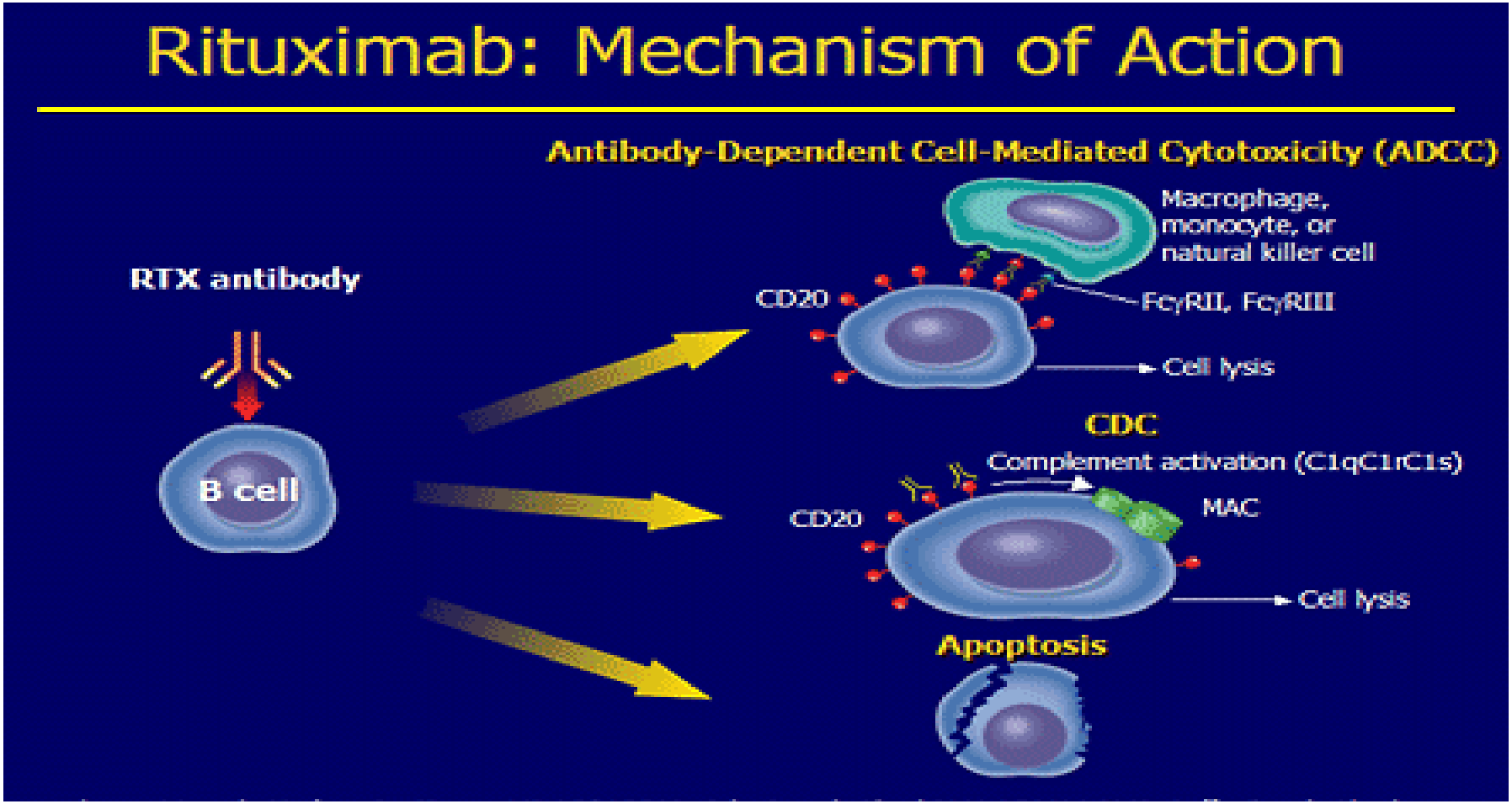


- Rituximab Anti-CD20 Monoclonal antibody
- Chimeric/ murine/ Human mAb



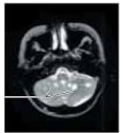


Rituximab: Mechanism of Action



Emerging therapies for MS

- Rituximab
  - Intravenous infusion
  - Monoclonal antibody
  - Approved for non-Hodgkin lymphoma and refractory RA.
  - Causes rapid depletion of B cells for 4-12 months
  - Reduction of contrast enhancing lesions in MRI and relapse rate
  - Side effects: infusion reactions, nausea, infections, and there have been cases of PML described.

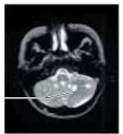


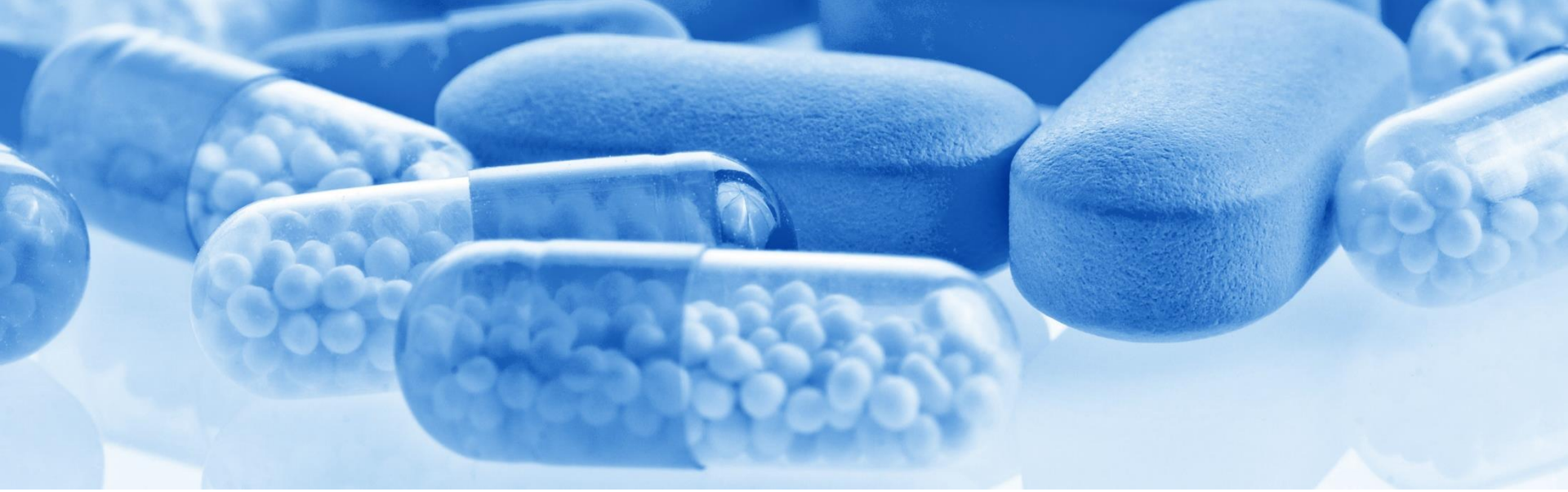
Rituximab's Clinical Trials

- One of these studies reported that rituximab resulted in a 91% reduction in Gd (gadolinium)-enhancing lesions when compared to placebo within a group of individuals with relapsing-remitting MS. Results from this study also indicated that individuals taking rituximab had a lower percentage of relapses than those on placebo.[7]

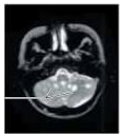
- OLYMPUS study, reported that participants with primary-progressive MS experienced a significant improvement in the time to progression while taking rituximab when compared to placebo.

- Furthermore, the OLYMPUS study reported that there was a significantly lower volume of T2 brain lesions on MRI for all participants with primary-progressive MS taking rituximab when compared to placebo

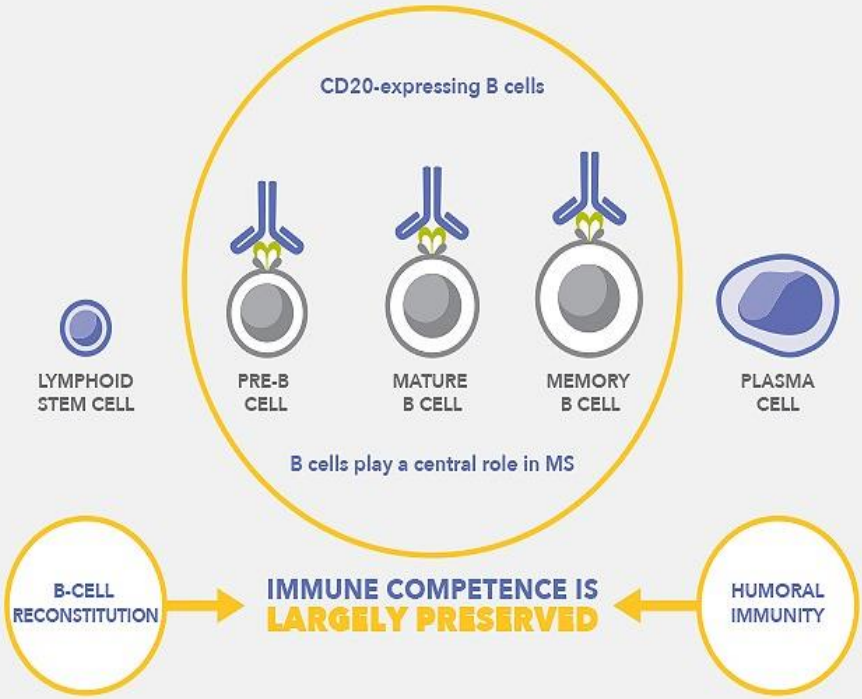


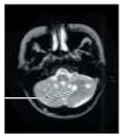


Ocrelizumab



OCREVUS® is a recombinant humanised monoclonal antibody[1]
that selectively targets and depletes CD20-expressing B cells





Ocrelizumab

Ocrelizumab is a humanised monoclonal antibody Directing against CD20

01

02

approved for relapsing or primary progressive forms of multiple sclerosis

03

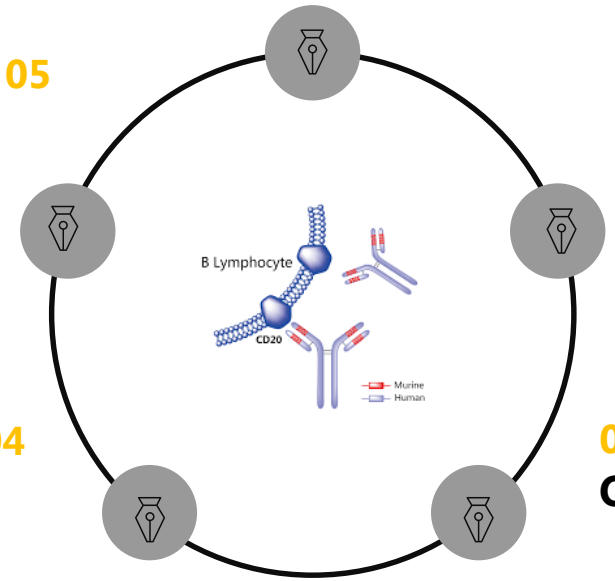
Ocrevus: 300 mg/10 mL (10 mL)

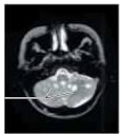
04

IV: 300 mg on day 1, followed by 300 mg 2 weeks later; subsequent doses of 600 mg are administered once every 6 months (beginning 6 months after the first 300 mg dose)

05

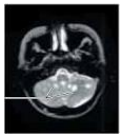
Premedicate with methylprednisolone (100 mg IV) 30 minutes prior to each infusion, and an antihistamine (eg, diphenhydramine) 30 to 60 minutes prior each infusion; may also consider premedication with acetaminophen. Assess for infection; delay administration for active infection.

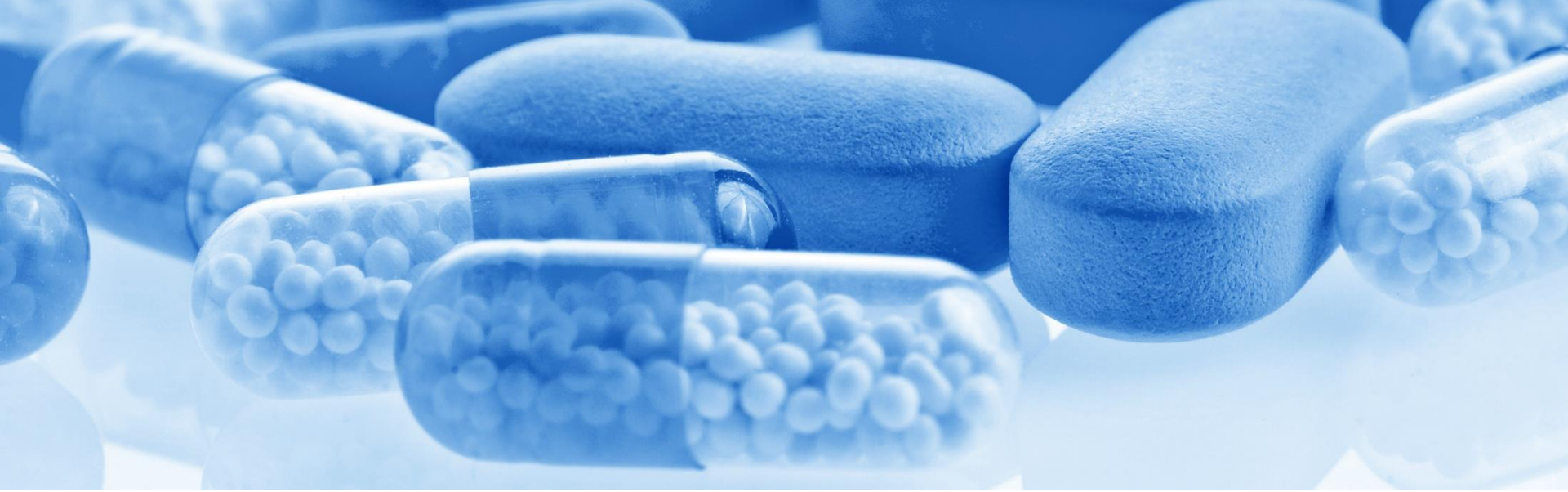




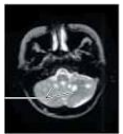
Ocrelizumab in RRMS

- In a phase 2 clinical trial Ocrelizumab
  - Strong clinical and radiographic efficacy compared with placebo
  - Superior efficacy (based on MRI measures only) to first-line DMA for RRMS
- Probably be useful in patients with treatment-refractory or very active disease.
- Ocrelizumab might be less immunogenic and more effective than rituximab in RRMS

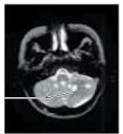




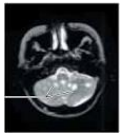
Comparis



Alemtuzumab	Natalizumab	Rituximab	Ocrelizumab
			
Reserve for patients who have inadequate response to ≥2 other druges	[redacted]	off-label for **multiple sclerosis**	[redacted]
Relapsing forms **IV.** **Premedication**	**Relapsing forms** **IV.**	**Relapsing forms** **IV.**	**Relapsing or Primary progressive** **IV.** **Premedication**



- The magnitude of ARR reduction varied between 15%-36% for all interferon-beta products, glatiramer acetate and teriflunomide, and from **50%-69%** for **alemtuzumab**, dimethyl fumarate, fingolimod and **natalizumab**.



Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Alexander Rae-Grant, MD, Gregory S. Day, MD, MSc, Ruth Ann Marrie, MD, PhD, Alejandro Rabinstein, MD, Bruce A.C. Cree, MD, PhD, MAS, Gary S. Gronseth, MD, Michael Haboubi, DO, June Halper, MSN, APN-C, MSCN, Jonathan P. Hosey, MD, David E. Jones, MD, Robert Lisak, MD, Daniel Pelletier, MD, Sonja Potrebic, MD, PhD, Cynthia Sitcov, Rick Sommers, LMSW, Julie Stachowiak, PhD, Thomas S.D. Getchius, Shannon A. Merillat, MLIS, and Tamara Pringsheim, MD, MSc

Correspondence
American Academy of Neurology
guidelines@aan.com

Neurology® 2018;90:789-800. doi:10.1212/WNL.0000000000005345

Abstract

Objective

To review evidence on starting, switching, and stopping disease-modifying therapies (DMTs) for multiple sclerosis (MS) in clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and progressive MS forms.

Methods

Relevant, peer-reviewed research articles, systematic reviews, and abstracts were identified (MEDLINE, CENTRAL, EMBASE searched from inception to November 2016). Studies were rated using the therapeutic classification scheme. Prior published Cochrane reviews were also used.

Results

Twenty Cochrane reviews and an additional 73 full-text articles were selected for data extraction through an updated systematic review (completed November 2016). For people with RRMS, many DMTs are superior to placebo (annualized relapses rates [ARRs], new disease activity [new MRI T2 lesion burden], and in-study disease progression) (see summary and full text publications). For people with RRMS who experienced a relapse on interferon-β (IFN-β) or glatiramer acetate, alemtuzumab is more effective than IFN-β-1a 44 μg subcutaneous 3 times per week in reducing the ARR. For people with primary progressive MS, ocrelizumab is probably more effective than placebo (in-study disease progression). DMTs for MS have varying adverse effects. In people with CIS, glatiramer acetate and IFN-β-1a subcutaneous 3 times per week are more effective than placebo in decreasing risk of conversion to MS. Cladribine, immunoglob-

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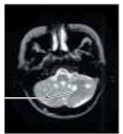
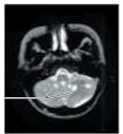
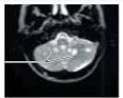




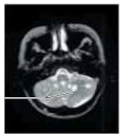
PML

Class I – high potential risk of PML	Natalizumab			
Class II – low potential risk of PML	Dimethyl fumarate	Fingolimod		
Class III – no or very low potential risk of PML	Alemtuzumab	Rituximab	Teriflunomide	Daclizumab



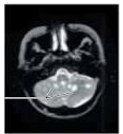
MRI

MRI	Risk of new or enlarging T2 lesions		Reducing the volume or number of T2 lesions	
High confidence	Natalizumab	Ocrelizumab	Natalizumab	
Moderate confidence	Alemtuzumab		Rituximab	Alemtuzumab



Factors to consider when sequencing to high efficacy DMTs

	Desirable factors	Undesirable factors
Natalizumab	• Rapid onset of efficacy • Reversible immune effects	• Increased risk of PML if exposure is more than 24 months • opportunistic infections • Need for contraception
Alemtuzumab	• Treatment may not be necessary for many years after the second treatment course • Pregnancy can be planned between cycles	• Secondary autoimmune disorders • Unknown effects of resetting the immune system make transitioning to other DMTs difficult
Ocrelizumab	• Rapid onset of efficacy	• Unknown effects of long-term Bcell depletion • No long-term safety data • Need for contraception



Thanks for your attention