DIPARTIMENTO DI NEUROSCIENZE
SALUTE MENTALE E ORGANI DI SENSO
NESMOS

SAPIENZA
UNIVERSITÀ DI ROMA

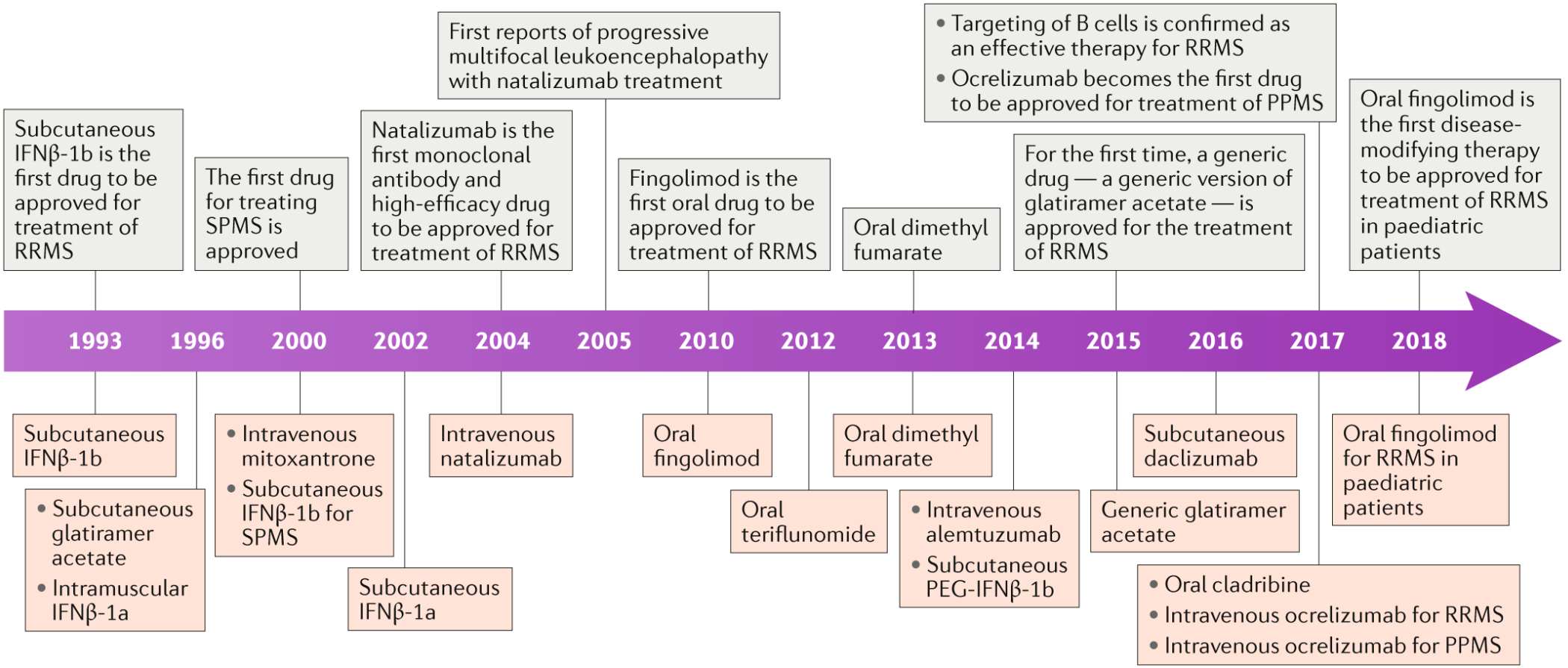
AZIENDA OSPEDALIERA
SANT' ANDREA
FACOLTÀ DI MEDICINA E
PSICOLOGIA

Utilizzo precoce di terapie di seconda linea della Sclerosi Multipla nelle forme remittenti recidivanti: Cons

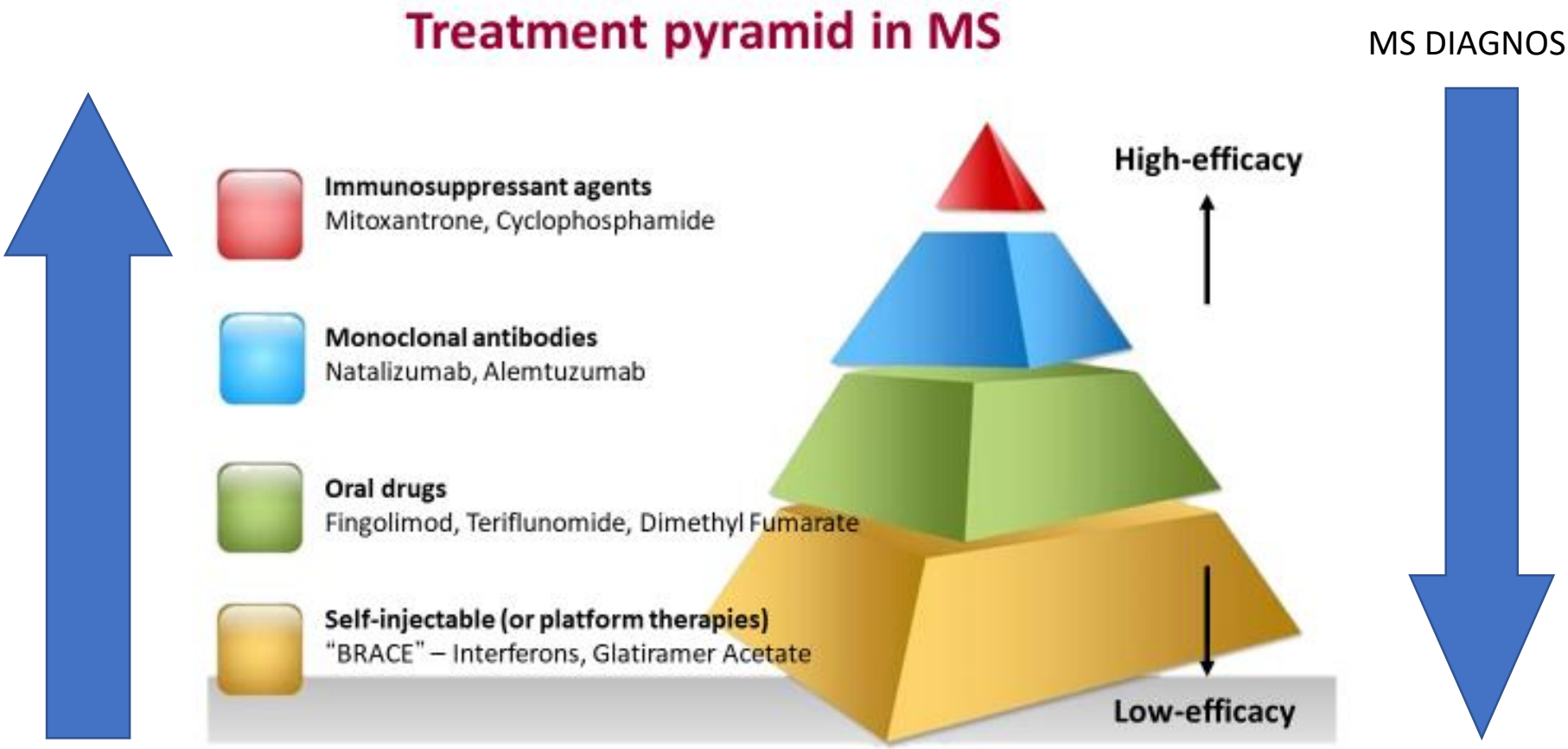
Dott.ssa Roberta Reniè
Medico in Formazione Specialistica

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

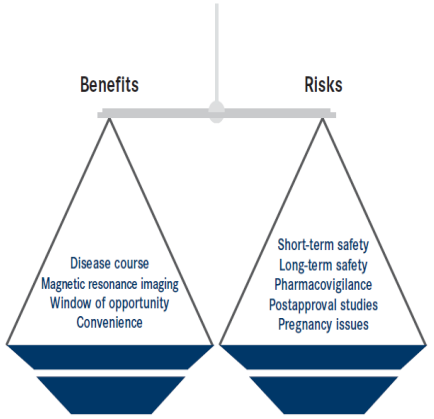

1993
Subcutaneous IFNβ-1b is the first drug to be approved for treatment of RRMS
Subcutaneous IFNβ-1b
1996
• Subcutaneous glatiramer acetate
• Intramuscular IFNβ-1a
2000
The first drug for treating SPMS is approved
• Intravenous mitoxantrone
• Subcutaneous IFNβ-1b for SPMS
2002
Natalizumab is the first monoclonal antibody and high-efficacy drug to be approved for treatment of RRMS
Subcutaneous IFNβ-1a
2004
Intravenous natalizumab
2005
First reports of progressive multifocal leukoencephalopathy with natalizumab treatment
2010
Fingolimod is the first oral drug to be approved for treatment of RRMS
Oral fingolimod
2012
Oral teriflunomide
2013
Oral dimethyl fumarate
Oral dimethyl fumarate
2014
• Intravenous alemtuzumab
• Subcutaneous PEG-IFNβ-1b
2015
For the first time, a generic drug — a generic version of glatiramer acetate — is approved for the treatment of RRMS
Generic glatiramer acetate
2016
Subcutaneous daclizumab
2017
• Targeting of B cells is confirmed as an effective therapy for RRMS
• Ocrelizumab becomes the first drug to be approved for treatment of PPMS
• Oral cladribine
• Intravenous ocrelizumab for RRMS
• Intravenous ocrelizumab for PPMS
2018
Oral fingolimod is the first disease-modifying therapy to be approved for treatment of RRMS in paediatric patients
Oral fingolimod for RRMS in paediatric patients

MS DIAGNOSIS



MS DIAGNOSIS

Figure 1. Assessing Benefits and Risks



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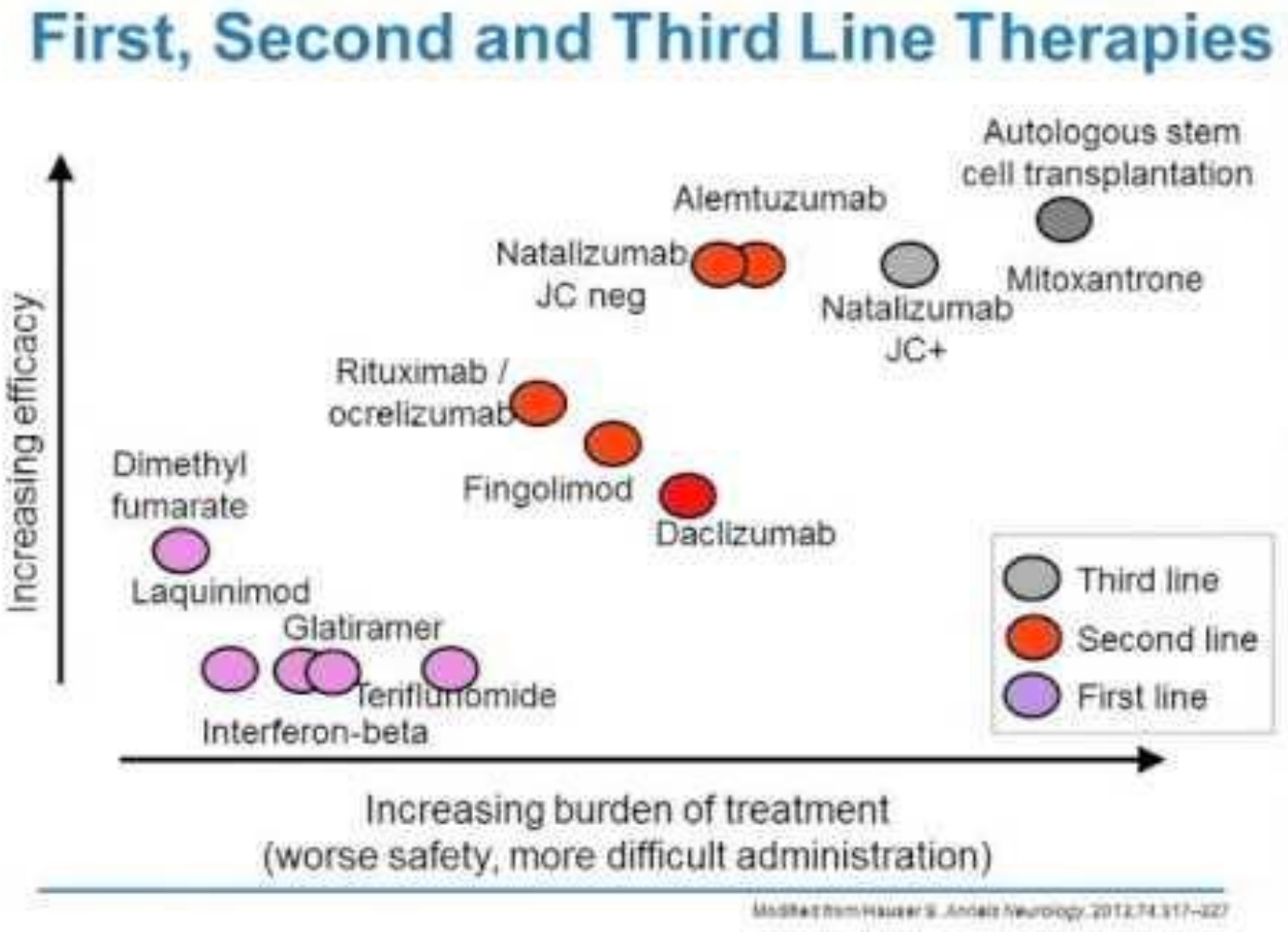


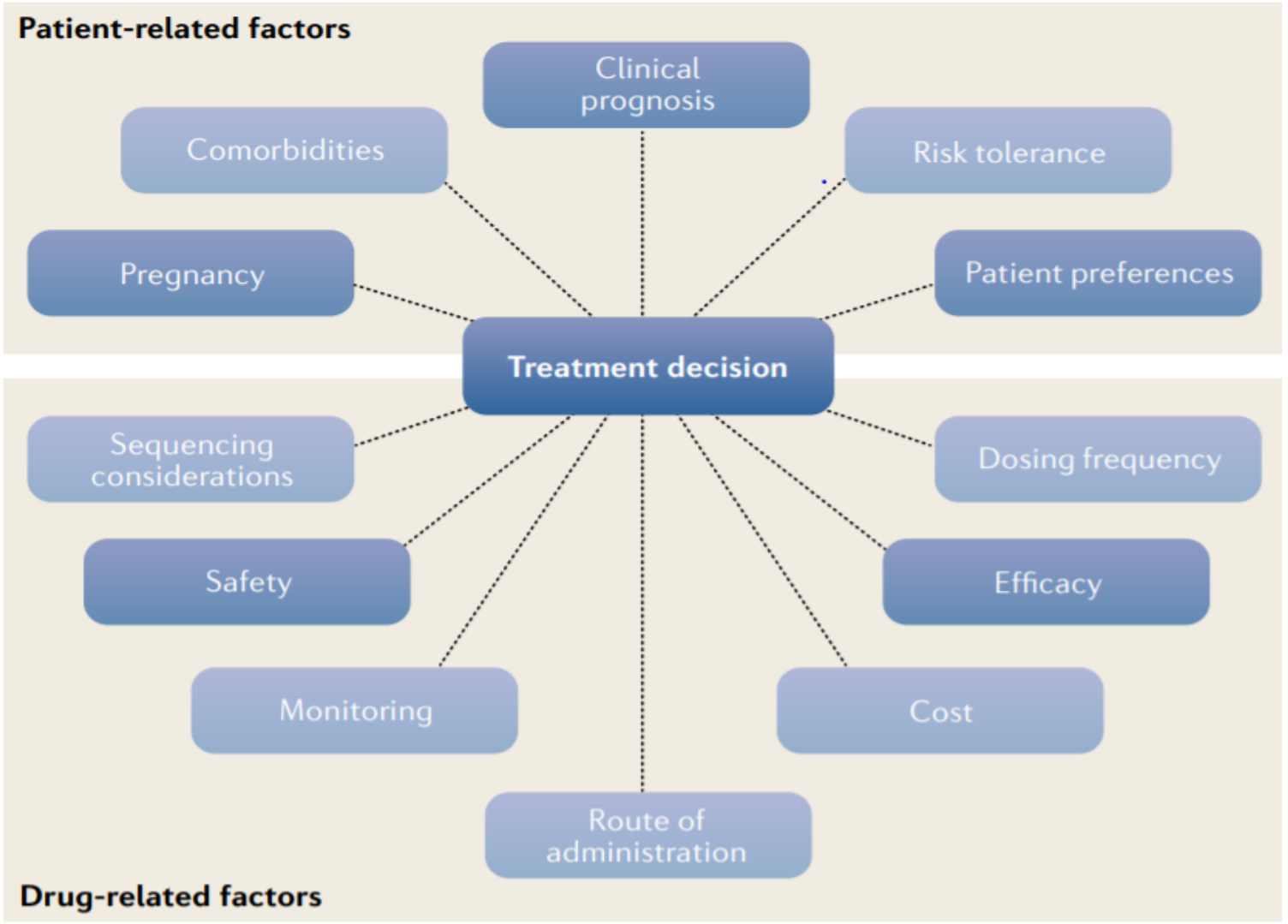


Fig. 2 | **Factors that influence the initial treatment decision for patients with multiple sclerosis.** Patient-related factors (top) and drug-related factors (bottom) are shown. Dark blue indicates factors that are typically most important. These factors should be weighed in a shared discussion between the physician and patient.

EDITORIAL

Potential Benefits of Early Aggressive Treatment in Multiple Sclerosis

Ari J. Green, MD, MCR

"Our doubts are traitors,
and make us lose the good we oft might win,
by fearing to attempt."
William Shakespeare, *Measure for Measure*

"Optimism, not pessimism, is needed in medicine; not, however, the optimism that takes up each new fad to the exclusion of old and tried measures, but the kind that begets hopefulness and confidence."
Minor Comments. *JAMA*. 1901; 36

The brain is arguably the most precious organ in the body. Yet ever, mounting evidence suggests that intervention with immunomodulatory or other immunotherapeutic agents actually bends the arc on the long-term progression of MS.[5-7]

In this week's issue of *JAMA*, Brown et al[8] provide a very important addition to this growing mountain of evidence. They used an extraordinarily large international data set, MSBase, headquartered in Melbourne, Australia. A major advantage of this data set is that it uses a standardized definition of what constitutes secondary progressive disease to compare time to secondary progression for patients taking different MS thera-

One additional obvious conclusion from this work is that, despite the positive effect on progression achieved by immunotherapeutics, we are not yet ready to declare victory. Even over modest time scales, a significant percentage of patients still exhibited progression despite receiving the most robust adaptive immune targeting agents available. Whether com-

Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: A systematic review

Bernd Merkel [a,b], Helmut Butzkueven [a,b], Anthony L. Traboulsee [c], Eva Havrdova [d], Tomas Kalincik [a,b,*]

Table 2
Summary of the relevant outcomes of the studies included in this review, with arrows indicating reported trends: ↑ the outcome measure increased after early high-efficacy treatment, - no differences between early vs. delayed high-efficacy treatment, ↓ the outcome measure decreased after early high-efficacy treatment.

Study reference (name)	Intervention	Study type	Features defining early treatment	Outcome	Trend in early (vs. delayed) high-efficacy treatment[a]
Cohen 2010 [1] (TRANSFORMS)	Fingolimod	Subgroup	No prior exposure to DMTs	ARR	↓
Cohen 2013 [2] (TRANSFORMS)	Fingolimod	Subgroup	Age < 40	ARR	↓
			Previous exposure to DMTs	ARR	-
Barkhof 2014 [3] (TRANSFORMS)	Fingolimod	Subgroup	No prior exposure to DMTs	% brain volume change	↑
			EDSS ≤ 3.5	% brain volume change	↑
			Age < 40	% brain volume change	-
Khatri 2011 [4] (TRANSFORMS ext)	Fingolimod	Extension	Originally randomised to study DMT	ARR	↓
				MRI lesions	↑
				% brain volume change	↑
				Disability progression	-
Kappos 2015 [5] (FREEDOMS ext)	Fingolimod	Extension	Originally randomised to study DMT (1.25 mg)	ARR	↓
				MRI lesions	-
			Originally randomised to study DMT (0.5 mg)	ARR	-
				MRI lesions	↑
Radue2012 [6] (FREEDOMS)	Fingolimod	Subgroup	No prior exposure to DMTs	% brain volume change	↑
			EDSS ≤ 3.5	% brain volume change	-
Izquierdo 2014 [7]	Fingolimod	Extension	Originally randomised to study DMT	ARR	↑
Hutchinson 2009 [8] (AFFIRM, SENTINEL)	Natalizumab	Subgroup	Age < 40	ARR	↓
				Disability progression	↓
			EDSS ≤ 3.5	ARR	↓
				Disability progression	-
Putzki & Maurer 2010 [9]	Natalizumab	Subgroup	Disease duration ≤ 6 years	ARR	↓
Putzki & Buehler 2010 [10]	Natalizumab	Subgroup	Disease duration ≤ 6 years	ARR	↓
Kallweit 2012 [11]	Natalizumab		No prior exposure to DMTs	ARR	–
Butzkueven 2014 [12] (TOP)	Natalizumab		EDSS < 3	ARR	↓
			No prior exposure to DMTs	ARR	↓
Coles 2011 [13] (CAMMS223)	Alemtuzumab		Age < 31	ARR	↓
				Disability progression	↓
				Disability reduction	↑
			Disease duration < 1.3 years	ARR	↓
				Disability progression	↓
				Disability reduction	↑
			EDSS < 2	ARR	-
				Disability progression	↓

ABBIAMO MARKER PROGNOSTICI PER LA SCLEROSI MULTIPLA?

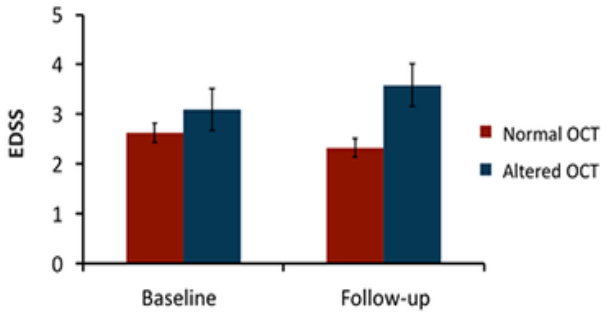
MRI Prognostic Factors

Overall activity[a-c]	• Predicts relapses • Predicts brain atrophy
T2 lesion load[d]	• Predicts relapses and long-term disability
Cortical lesions[e]	• Predicts long-term disability
Spinal cord atrophy[f]	• Predict EDSS
Thalamic atrophy and ventricular size[g]	• Predicts conversion from CIS to clinically definite MS
fMRI[h]	• Correlates with cognitive dysfunction
MT MRI[i]	• Predicts long-term disease evolution

a. Kappos L, et al. *Lancet*. 1999;353:964-969; b. Sormani MP, et al. *Neurology*. 2007;69:1230-1235; c. Paolillo A, et al. *J Neurol*. 2004;251:432-439; d. Fisniku LK, et al. *Brain*. 2008;131:808-817; e. Calabrese M, et al. *Ann Neurol*. 2010;67:376-383; f. Rocca MA, et al. *Neurology*. 2011;76:2096-2102; g. Zivadinov R, et al. *Radiology*. 2013;268:831-841; h. Rocca MA, et al. *AJNR Am J Neuroradiol*. 2010;31:1240-1246; i. Agosta F, et al. *Brain*. 2006;129:2620-2627.

OCT Alterations Predict Development of Disability

- N = 68 patients without previous optic neuritis and normal or altered baseline OCT followed for 2 years
- Baseline OCT alterations predicted the future development of disability with a NPV of 91.4% and a PPV of 23% (*P* = .003)



Di Maggio G. *Eur J Neurol*. 2015;22(suppl 1):277. Poster P2215.

June 4, 2019

Serum Neurofilament Light Chain as a Prognostic Marker in Multiple Sclerosis

Robert T. Naismith, MD reviewing Kuhle J et al. Neurology 2019 Mar 5

Questi marcatori risultano essere promettenti per la valutazione del rischio di sviluppare disabilità ma al momento non sono validati e necessitano di altri studi con campioni più ampi

Quali sono i principali rischi con le terapie di seconda linea?

Table 2 Major infections associated with approved immunomodulatory and immunosuppressive MS treatments

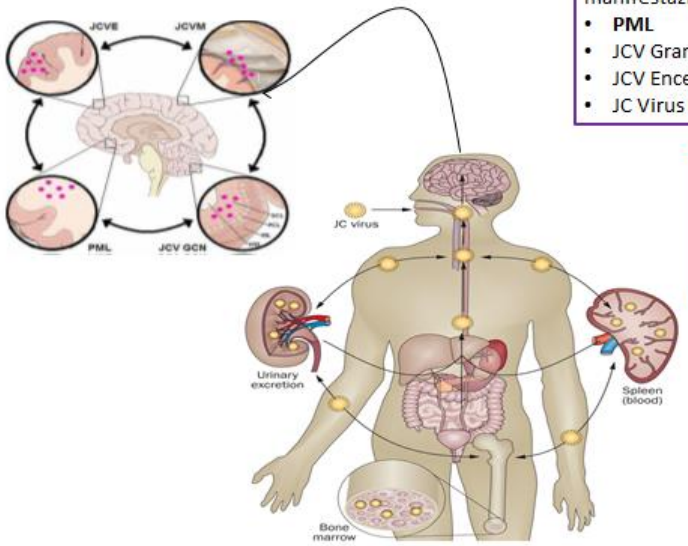
Table 2 | **Major infections associated with approved immunomodulatory and immunosuppressive MS treatments**[225–227]

Drug	Bacterial infections	Viral infections	Fungal infections	Protozoa and parasites
Relapse treatment				
GCS (high-dose pulsed treatment)	• Pyogenic bacteria • Gram-negative rod-shaped bacteria/enterobacteria • Gram-positive rod-shaped bacteria • *Mycobacterium tuberculosis* • Other mycobacteria	• JCV (PML) and HBV reactivation in association with CT • Particular risk of herpesviruses/CMV	• *Pneumocystis jiroveci*, mostly in association with CT • Cryptococcal meningitis	Reported in continuous GCS treatment
Injectable disease-modifying treatments				
• IFN-β1a/b • Peg-IFN-β1a	• No increased risk of infections[52] • Possible increased response against *Mycobacterium avium*[228] • Local infections at injection site possible	• JCV (PML) after intramuscular IFN-β1a monotherapy with combined CVID (+)[54] • Possible antiviral effect on HBV/HCV, no risk of reactivation in chronic viral hepatitis[229–233]	No increased risk of infections[52,234–238]	• NR • Possible protective effect against *Leishmania*[236]
Glatiramer acetate	Local infections at injection site possible	Herpesviruses/CMV (+)	Candidosis +	NR
Oral disease-modifying treatments				
Fingolimod	(+)[18]	• JCV (PML) (+)[239] • Herpesviruses ++	Cryptococcal meningitis/ meningoencephalitis (+)[66,67]	NR
Dimethyl fumarate and fumaric acid esters	(+)	JCV in patients with MS and psoriasis (+)[77,78,83,86] and in patients treated with CT*[78,80–82,240]	NR	NR
Teriflunomide	• Fatal *Klebsiella*-related septicaemia (+)[241] • Gastrointestinal tuberculosis (+)	• JCV (+) • Case reports in patients treated with leflunomide/ CT/PT • Combined CMV + hepatitis C infection (+)	Seen in patients treated with leflunomide or CT	NR
Azathioprine	+	• JCV (+) • Seen in patients treated with CT • Herpesvirus CT/++ • HBV reactivation +[98,242]	Seen in patients treated with CT +	Seen in patients treated with CT +
Intravenous disease-modifying treatments				
Natalizumab	• Gram-negative rod-shaped bacteria/enterobacteriaceae: • *Mycobacterium tuberculosis* (+)[243] atypical mycobacteria[244,245]	• JCV (PML) ++[111,119] • Herpesvirus ++[246–252]	Severe cutaneous *Candida* infection (+)[253]	• Protozoa (+) • Cryptosporidiosis (+)[21,254]
Alemtuzumab	*Listeria* meningitis (+)[125,135,136]	• JCV: not reported for MS • Herpesvirus[133,134]	NR	*Cryptosporidium* infection +[134,255]
Mitoxantrone	+	Herpesvirus ++	+	+

The table includes findings from trials in neurology, haematology and rheumatology. (+), single cases; +, reported association; ++, of particular risk. CMV, cytomegalovirus; CT, under combination therapy; CVID, common variable immunodeficiency syndrome; GCS, glucocorticosteroids; HBV, hepatitis B virus; HCV, hepatitis C virus; JCV, JC virus; MS, multiple sclerosis; NR, no reported risks for MS treatment, or insufficient data; PML, progressive multifocal leukoencephalopathy; PT, immunosuppressive pretreatment. *See main text for details.

Hartung, H.-P. *et al.* (2016) Disease-modifying therapies and infectious risks in multiple sclerosis
Nat. Rev. Neurol. doi:10.1038/nrneurol.2016.21

Patogenesi PML



Infezione primaria asintomatica
Riattivazione negli immunocompromessi determina
manifestazioni neurologiche:

- **PML**
- JCV Granule Cell Neuronopathy
- JCV Encephalopathy
- JC Virus Meningitis

N casi PML / Esposizione a farmaci

- Natalizumab (749 casi/~180.000 esposti)°
- Fingolimod (19 casi/~225.000 esposti)°
- Dimetil fumarato (5 casi/~311.000 esposti)*

° Dati aggiornati al nov 2017
* Dati aggiornati al 2018

Anti-JCV Antibody Status

Negative Antibody Status
0.1 / 1000 patients

Positive Antibody Status

Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Alemtuzumab Safety

Common AEs in Trials	Incidence	Risk Management Strategy
Infusion reactions • Rash, headache, nausea, pyrexia, transient cardiac disturbances	Most patients (~3% serious)	Corticosteroids prior to dosing first 3 days of each course; antihistamines prior to each dose and as needed
Infections • Oral herpes, UTI, URI, nasopharyngitis, sinusitis, influenza, bronchitis, noninvasive fungal	71% (most mild to moderate)	Oral herpes prophylaxis on day 1 and continued for 1 mo after each course
Autoimmune AEs	–	Before starting and monthly until 48 mo after last infusion
• Thyroid disorders	34%	Thyroid function test
• ITP	1% serious	Monthly CBC, symptom survey
• Nephropathies/anti-GBM	0.3%	Serum creatinine, urinalysis

Hartung H, et al. *Mult Scler*. 2015;2:22-34.

Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing

Share

Press release 12/04/2019

EMA has started a review of the multiple sclerosis medicine Lemtrada (alemtuzumab) following new reports of immune-mediated conditions (caused by the body's defence system not working properly) and problems with the heart and blood vessels with the medicine, including fatal cases.

As a temporary measure while the review is ongoing, Lemtrada should only be started in adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least two disease-modifying therapies (a type of multiple sclerosis medicine) or where other disease-modifying therapies cannot be used. Patients being treated with Lemtrada who are benefitting from it may continue treatment in consultation with their doctor.

In addition to the restriction, EMA's safety committee (PRAC) has recommended an update of the product information for Lemtrada to inform patients and healthcare professionals about cases of:

- immune-mediated conditions, including autoimmune hepatitis (with damage to the liver) and haemophagocytic lymphohistiocytosis (overactivation of the immune system which may affect different parts of the body);
- problems with the heart and blood vessels occurring within 1–3 days of receiving the medicine, including bleeding in the lungs, heart attack, stroke, cervicocephalic arterial dissection (tears in the lining of the arteries in the head and neck);
- severe neutropenia (low levels of neutrophils, a type of white blood cell that fights infections).

REBOUND DOPO SOSPENSIONE DELLA TERAPIA

Table 1. Summary of the most representative studies that showed a rebound phenomenon after cessation of natalizumab treatment.

	Number of patients included	Definition of rebound	Percentage of patients with rebound activity	Risk factors
West et al. 2010	68 patients who stopped NAT treatment compared to 16 patients who continued NAT treatment	Severe relapse defined by an increase of 3 points in EDSS and a large number of Gd+ lesions	10%	No risk factors identified
Kerbrat et al. 2011	27 patients who had been treated with NAT for at least 6 months	Clinical relapse and at least 20 Gd-enhancing lesions on MRI.	15%	Tendency toward higher pre-NAT ARR and MRI activity
Sorensen et al. 2014	375 patients who had been treated with NAT for at least 24 weeks.	Increase of ARR to levels higher than pretreatment.	22%	Higher ARR during NAT treatment and anti-NAT antibodies.
Salhofer-Polanyi et al. 2014	201 patients who had been treated with NAT for 24.5 months	Clinical worsening beyond pretreatment levels measured by mean change scores of ARR and EDSS	11.9%	Low pre-NAT ARR, longer treatment gap after its withdrawal, and poor treatment response to NAT

EDSS, Expanded Disability Status Scale; NAT, Natalizumab; ARR, annualized relapse rate; MRI, magnetic resonance imaging.

Table 1 – Multiple sclerosis patients with disease reactivation following fingolimod withdrawal.

Gender	Age (years)	Reason for discontinuation	Time to first relapse (months)	Lymphocyte recovery	Multiple new lesions (>10)	Treatment during relapse	DMT after relapse	References
F	47	SPMS	5	N/S	Yes	MP	None	[3]
F	30	Genital herpes	3	N/S	Yes	MP	Natalizumab	[3]
M	53	Completion of RCT	3	N/S	No	MP	None (PPMS)	[4]
M	60	Completion of RCT	4	N/S	No	MP plus oral taper	None (PPMS)	[4]
F	~35	Breast cancer	1.5	Yes	Yes	MP, rituximab	Rituximab	[14]
F	~30	Planned pregnancy	1.5	Yes	No (9)	MP	Fingolimod	[14]
F	~28	Planned pregnancy	1	Yes	Yes	MP plus oral taper	Rituximab	[14]
F	~45	Adverse effects	1.5	Yes	Yes	MP and dexamethasone, rituximab	Dimethyl fumarate	[14]
F	~35	Patient decision	1.5	No	Yes	MP	Fingolimod	[14]
F	20	Lymphopenia	3	No	Yes	MP plus oral taper	Dimethyl fumarate	[20]
F	41	SAH	3	No	Yes	MP, PE	Fingolimod	[20]
F	30	Increased transaminases	3	No	Yes	MP, PE	Dimethyl fumarate	[20]
M	53	Melanoma	3	Yes	Yes	MP	Natalizumab	[8]
F	31	Planned pregnancy	2	N/S	N/S	MP	N/S	[9]
F	44	Lymphopenia	3	Yes	No	MP, intrathecal triamcinolone	Dimethyl fumarate	[30]
F	36	Angina pectoris	2	Yes	No	MP	Dimethyl fumarate	[30]
F	29	Viral neuritis	4	No	Yes	MP plus oral taper	Interferon-beta	[33]
F	36	Lymphopenia	2	Yes	Yes	MP	Glatiramer acetate	[34]
F	19	Lack of efficacy	2	Yes	Yes	MP, PE	Cyclophosphamide	[34]
F	33	Patient decision	3	Yes	Yes	MP	Cyclophosphamide	[36]
F	31	Planned pregnancy	3	N/S	Yes	MP	None, relapse during pregnancy	[37]
F	36	Lymphopenia	2	Yes	Yes	MP plus oral taper	N/S	[38]
F	32	Lymphopenia	1	Yes	Yes	MP, immune adsorption	Natalizumab	[39]

Age, at fingolimod discontinuation; DMT, disease modifying therapy; F, female; M, male, MP, intravenous methylprednisolone; N/S, not specified; PE, plasma exchange; SAH, subarachnoid hemorrhage; SPMS, secondary progressive multiple sclerosis; UTI, urinary tract infection.

GRAVIDANZA

TABLE 8-1 Multiple Sclerosis Medications in Pregnancy

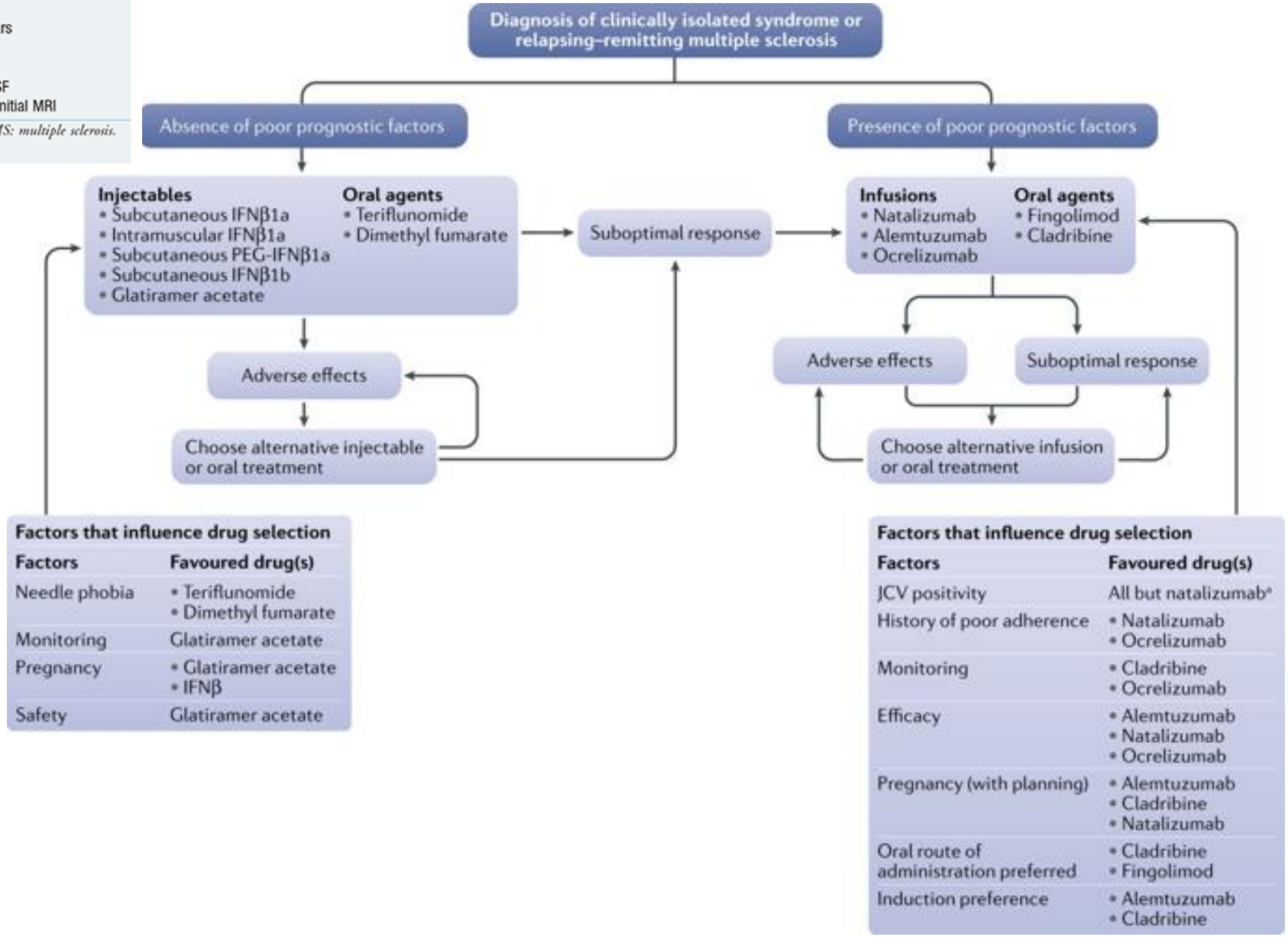
Drug	Pregnancy Category	Last Dose Before Conception	Evidence of Embryolethality or Teratogenicity in Animal Studies?	Data in Exposed Humans
Interferons	C	2 months	Embryolethality: Yes Teratogenic risk: No	No evidence for spontaneous abortion or birth defects
Glatiramer acetate	B	1–2 months, although some neurologists continue through pregnancy	Embryolethality: No Teratogenic risk: No	No evidence for spontaneous abortion or birth defects
Fingolimod	C	2 months	Embryolethality: Yes Teratogenic risk: Yes	Reports of birth defects although no pattern
Dimethyl fumarate	C	A few days or weeks before conception (half-life is very short)	Embryolethality: Yes Teratogenic risk: No	No evidence for spontaneous abortion or birth defects
Teriflunomide	X	Should be washed out with elimination procedure	Embryolethality: Yes Teratogenic risk: Yes	No evidence for spontaneous abortion or birth defects
Natalizumab	C	2 months	Embryolethality: Yes Teratogenic risk: No	Possibly increased risk of spontaneous abortion versus general population but same as other multiple sclerosis controls
Alemtuzumab	C	4 months	Embryolethality: Yes Teratogenic risk: No	No evidence for spontaneous abortion or birth defects; thyroid monitoring is necessary for mother throughout pregnancy
Rituximab	C	Manufacturer recommends 12 months	Embryolethality: No Teratogenic risk: No	Risk of B-cell depletion and other hematologic issues

Pro vs Cons?

Table 1. Indicators of Poor Prognosis in MS

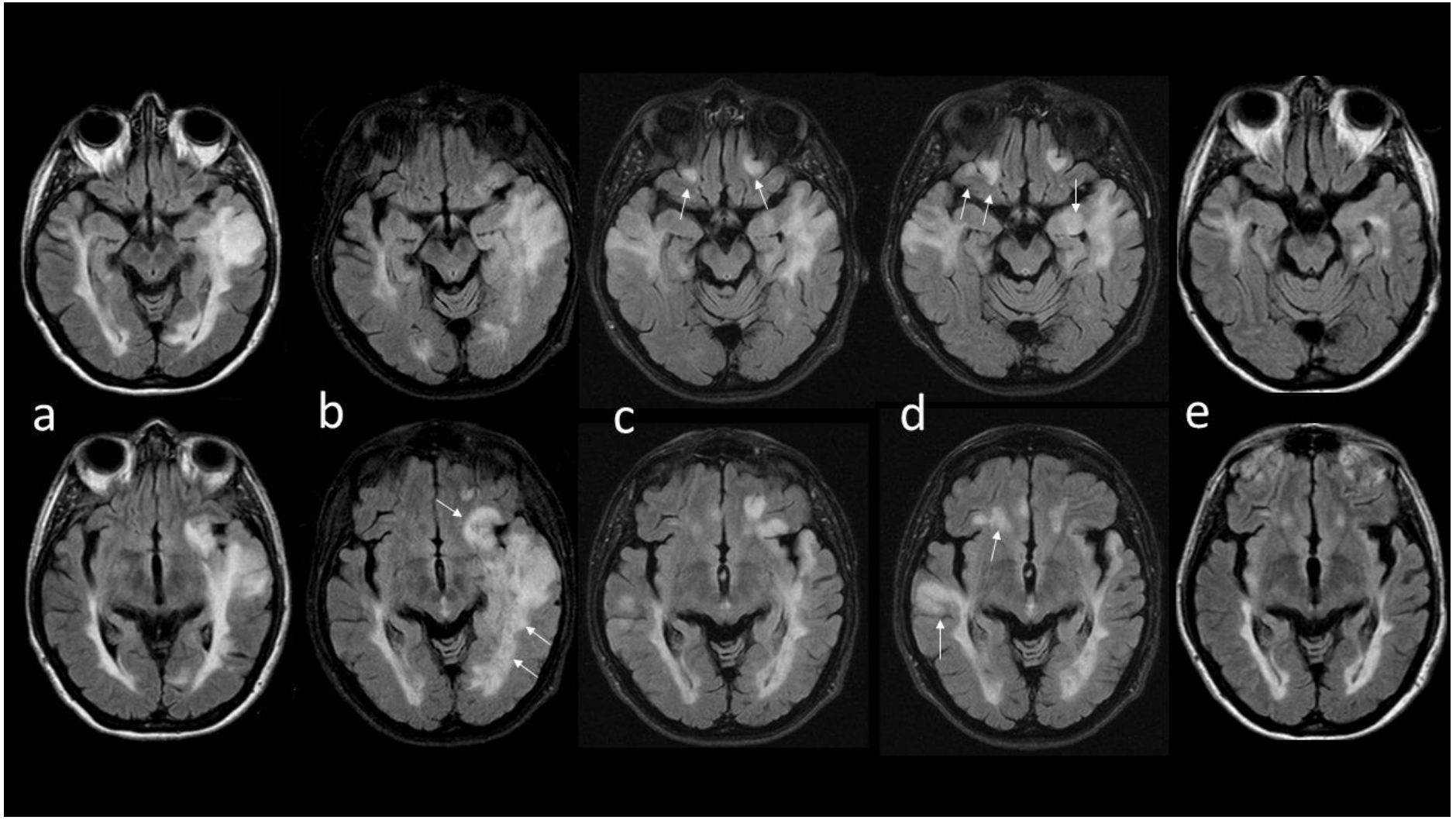
Male gender
Age >40 years at onset
Ethnic origin (Asian or African-American)
Motor, cerebellar, or sphincter symptoms or symptoms from various brain areas on initial presentation
Incomplete recovery from initial attacks
Frequent attacks during early years of disease
Short interval between first two attacks
Rapid progression of disability in early years
Progressive disease from time of onset
Cognitive impairment at onset
Oligoclonal immunoglobulins present in CSF
Multifocal lesions or Gd enhancement on initial MRI

CSF: cerebrospinal fluid; Gd: gadolinium; MS: multiple sclerosis.
Source: Reference 1.



TAKE HOME MESSAGE:

- Al momento le Evidenze Scientifiche riguardo l'effetto dell'utilizzo precoce delle terapie di seconda linea nella Sclerosi Multipla sono conflittuali.
- Visto il peggior profilo di sicurezza di queste terapie è necessaria una selezione appropriata del paziente
- Sono necessari quindi ulteriori Studi atti a identificare e validare marcatori prognostici per l'identificazione precoce dell'andamento della patologia
- La decisione terapeutica deve essere sempre condivisa con le necessità e le richieste del paziente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