Physician* Information and Management Guidelines for Multiple Sclerosis patients on TYSABRI Therapy

Version 15: [12th April 2016]

***TYSABRI therapy is to be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions in centres with timely access to MRI**

Table of Contents

1 Introduction

This guidance document has been developed for those physicians initiating and supervising TYSABRI in accordance with the conditions of the Marketing Authorisation of the drug, in order to ensure its safe and effective use. It contains information to be used in conjunction with the TYSABRI Summary of Product Characteristics (SmPC) (Appendix I) and is supported by the Treatment Initiation, Continuation and Discontinuation Forms (Appendix 4).

The physician pack also includes a copy of the Patient Information Leaflet (PIL) and Patient Alert Card (Appendices 2 and 3).

It is recommended that physicians initiating and supervising treatment with TYSABRI should share relevant sections of this document with radiologists involved in the differential diagnosis of PML.

The guidance document focuses primarily on PML, which currently remains the most important adverse reaction affecting patients treated with TYSABRI, and provides practical advice to physicians that is not available through the SmPC.

Other important safety issues associated with TYSABRI, and information about the patient populations suitable for treatment with TYSABRI, are fully described in the SmPC, and physicians should ensure that this guidance document is used together with the SmPC.

2 Opportunistic Infections including Progressive Multifocal Leukoencephalopathy (PML)

Prescribers should be aware of the possibility that PML and other opportunistic infections may occur during TYSABRI therapy and should include them in the differential diagnosis of all infections that occur in TYSABRI treated patients. Cases of PML have also been reported in patients up to 6 months after the last dose of TYSABRI. Patients, their partners and care givers also need to be advised of symptoms that may be indicative of early PML and continue to be vigilant for approximately 6 months following discontinuation (see Section 6.2 and Appendix 3: Alert Card, Appendix 4: Treatment Initiation, Continuation and Discontinuation Forms).

If an opportunistic infection is suspected, dosing with TYSABRI must be suspended until it can be excluded through further evaluations.

2.1 *Definition*

An opportunistic infection is defined as an infection due to an organism that generally does not cause disease, or causes only mild or self-limited disease in people with normally functioning immune systems, but causes more significant disease in people with impaired immunity. Examples include PML, oesophageal candidiasis, systemic fungal infections, *Pneumocystis jiroveci* pneumonia, mycobacterial infections (including atypical mycobacteria, and tuberculosis), chronic intestinal cryptosporidiosis, disseminated viral infections (such as disseminated herpes or cytomegalovirus infections), toxoplasmosis, cryptosporidium infections.

2.2 *Infections Including Opportunistic Infections Associated with TYSABRI*

A case of *Cryptosporidium* diarrhoea was reported in MS clinical trials. In clinical trials in Crohn's Disease, cases of additional opportunistic infections have been reported, some of which were fatal. In these studies concomitant use of other agents including immunosuppressants was common. Occasional reports of other opportunistic infections have been reported with marketed use of TYSABRI.

2.3 *Herpes Infections*

TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. In post-marketing experience, serious, life-threatening, and sometimes fatal cases have been reported in multiple sclerosis patients receiving TYSABRI.

2.4 *Management of Potential Opportunistic Infections*

All TYSABRI treated patients presenting with symptoms of infections should be fully investigated. Early referral to a specialised physician with experience in investigating and managing opportunistic infections should be considered.

In cases of serious infections all efforts must be made to determine the causative organism. If an opportunistic infection is suspected then TYSABRI treatment must be stopped.

2.5 *Progressive Multifocal Leukoencephalopathy (PML)*

2.5.1 Epidemiology

Progressive Multifocal Leukoencephalopathy (PML) is a sub-acute, evolving infectious disease of the Central Nervous System (CNS) caused by the JC Virus (JCV). It has been described since the 1930s and the term was first used in 1958. It was first described as a rare complication of lymphoproliferative diseases in middle-aged and elderly patients (Astrom, 1958). Cases have also been reported as a consequence of immunosuppressant treatment of patients with autoimmune disorders and solid organ transplant recipients.

The incidence of PML increased as a consequence of the HIV pandemic. Its prevalence in patients with AIDS was reported as 5%. The introduction of Highly Active Anti Retroviral Therapy (HAART), whilst not reducing the incidence of PML in HIV patients, has been associated with a reduction in mortality (Koralnik, 2004).

An analysis of the 2-step anti-JCV antibody assay (STRATIFY JCV) in over 6,000 MS patients has demonstrated the prevalence of anti-JCV antibodies to be approximately 55%. Anti-JCV antibody prevalence in the EU was reported as ranging from 48.8% to 69.5% in the EU in a cross sectional study of MS patients irrespective of treatment (Bozic *et al*.. 2014). In the MS population, anti-JCV antibody prevalence increased with age and was lower in women than in men in all cohorts tested. These findings are consistent with those reported in the literature in healthy adults using similar methodologies (Egli 2009; Kean 2009; Knowles 2003). In general, anti-JCV antibody prevalence did not appear to be affected by prior immunosuppressant use, prior exposure to TYSABRI, or duration of TYSABRI exposure.

2.5.2 Aetiology

The disease affects the sub-cortical, white matter (Safak and Khalili, 2003) and is caused by the reactivation of JC virus, a human polyomavirus (Berger *et al*., 1998). The triggers for JCV replication are unknown but may result from confluence of risk factors, one of which is a compromised cellular immune system. This can be the consequence of HIV infection, systemic immunosuppression or the use of anti-neoplastic agents, as well as some malignancies.

2.5.3 Pathology

Replication of JCV in the brain causes a lytic infection of oligodendrocytes resulting in the widespread destruction of myelin. Microscopic lesions develop in the sub-cortical white matter which enlarge and may coalesce with a characteristic pattern on MRI examination.

The presenting symptoms reflect the multifocal pattern of demyelination. Visual, motor and cognitive deterioration are nearly always present in advanced stages of the infection with widespread lesion size, with cortical blindness, marked weaknesses such as hemiparesis and behavioural disturbances common. Other symptoms include sensory deficits, vertigo, and seizures (Berger, 1998). These symptoms, as well as their evolution, can help differentiate the onset of PML from the typical symptoms of a relapse of MS but some overlap may exist.

Besides oligodendrocytes, JCV can also infect cerebellar granule cell neurons resulting in JCV granule cell neuronopathy (GCN). JCV GCN is associated with mutations in the C terminus of the JCV VP1 gene, coding for the major capsid protein. JCV GCN can occur in isolation or in combination with PML. There have been very rare reports of

JCV GCN in patients receiving natalizumab (Agnihotri, 2014; Schippling, 2013). Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome). In JCV GCN, serial MRI of the brain shows severe progressive cerebellar atrophy over several months and JCV DNA is detected in the CSF. Similar to when new neurological symptoms suggestive of PML develop, TYSABRI treatment should be suspended if JCV GCN and/or PML is suspected and permanently discontinued if JCV GCN and/or PML is confirmed.

2.5.4 Diagnosis

The EFNS published guidelines for the diagnosis and management of neurological complications of HIV infection including PML (Portegies, 2004). The diagnostic criteria are reproduced here.

Slowly progressive focal neurological deficits with asymmetrical white matter abnormalities on MRI suggest PML. The lesions are generally subcortical in location with finger like projections toward the cortex, and have no mass effect. The lesions are hypointense on T1W MRI sequences, hyperintense on T2W and FLAIR (fluid-attenutated inversion recovery), hyperintense on DWI (diffusion weighted imaging) and generally do not enhance with contrast.

Detection of JCV DNA in the CSF by PCR strongly supports the diagnosis because it has a sensitivity of 72–100% and a specificity of 92–100% (Cinque *et al.*, 1997). If the CSF-PCR is negative, it is recommended to repeat CSF-PCR. Use of an ultrasensitive PCR JCV DNA test is important (e.g., with a Limit of Detection (LoD) of 10 copies/mL) as many confirmed PML cases have demonstrated a low copy count. Brain biopsy remains the final confirmatory test, but a positive CSF-PCR offers acceptable evidence. MRI is the sensitive paraclinical tool for detection of symptomatic and asymptomatic PML in Tysabri treated patients (Wattjes and Barkhof, 2014). A previous baseline brain MRI scan should be available for use as a reference to help in differentiating between PML and other neurological diseases, e.g., MS lesions.

A detailed diagnostic algorithm has been developed to assist physicians with the assessment of new or worsening neurological symptoms in TYSABRI treated MS patients. This is described in detail in Section 3 of this guidance document.

2.6 *PML in TYSABRI Treated Patients*

During extended pre-registration trials, two cases of PML were reported in MS patients and a full safety evaluation revealed one further case in a clinical trial patient with Crohn's Disease (Yousry, 2006). In the post-marketing setting, the risk of PML has been well characterized over the first 6 years of treatment with the identification of different levels of PML risk in different patient subgroups (see below).

2.7 *PML Risk Factors*

The following risk factors have been associated with development of PML during TYSABRI treatment:

- **The presence of anti-JCV antibodies.** Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. However, PML only occurs in a minority of patients who are anti-JCV positive because JCV infection is only one of several steps required for the development of PML. The anti-JCV antibody assay is of greatest

utility in stratifying PML risk when a positive test result is used in combination with the other identified risk factors described below.

- **Treatment duration**. The risk of PML increases with TYSABRI treatment duration, especially beyond 2 years.
- **Prior immunosuppressant (IS) treatment**. Patients who have a history of treatment with an immunosuppressant prior to starting TYSABRI are also at increased risk of developing PML

Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of TYSABRI therapy, and have received prior immunosuppressant therapy) have a higher risk of PML. In anti-JCV antibody positive TYSABRI treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e. the risk is greater in those with a high antibody index compared to those with a low index). Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with TYSABRI for longer than 2 years.

Irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with TYSABRI and for 6 months following discontinuation of therapy.

The PML Risk Estimates Algorithm (Figure 1) summarizes PML risk by anti-JCV antibody status, prior IS use and duration of treatment (by year of treatment) and stratifies this risk by index value when applicable.

- For anti-JCV antibody negative patients: PML risk estimates are based on post-marketing data from approximately 125,000 TYSABRI exposed patients where the estimated incidence of PML for anti-JCV antibody negative patients is 0.1/1000. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result.

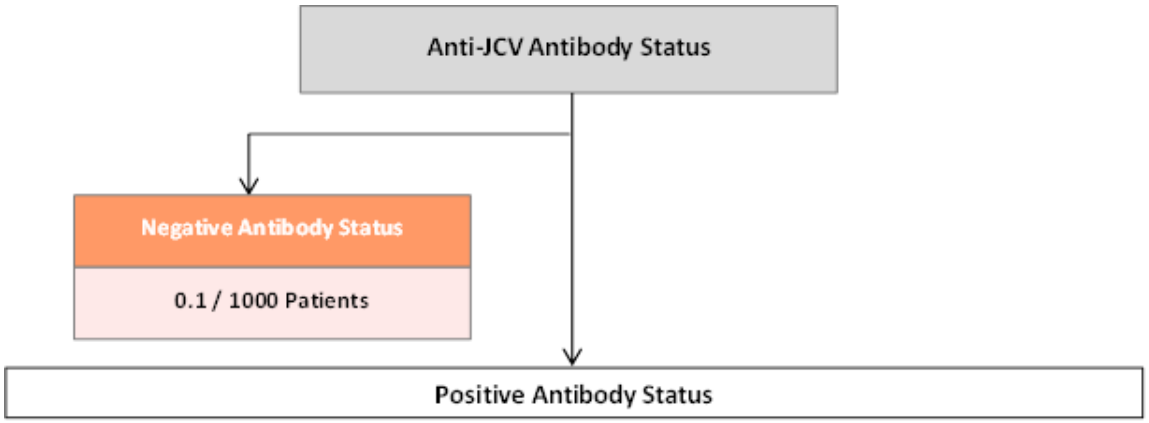
- For anti-JCV antibody positive patients risk estimates were derived using Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical studies. The risk estimates from the Life Table Method are forward-looking in yearly intervals (for example the risk estimate corresponding to the 25-36 month natalizumab exposure period is the PML risk estimated for the next year for patients treated for 24 months with Tysabri).The individual treatment length of each patient is taken into consideration with drop-outs (eg, treatment discontinuation) accounted for.

- For anti-JCV antibody positive patients who have not used prior immunosuppressants: Index can further stratify PML risk in patients treated with Tysabri. A higher anti-JCV antibody index is associated with an increased risk of PML.

- For anti-JCV antibody positive patients who have used IS previously: These patients are at an increased risk of PML, since prior IS use is recognized as an independent risk factor for PML. PML risk estimates for this patient population are based on Tysabri clinical trial data where prior IS use comprised the

following 5 IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide and mycophenolate mofetil. The exact mechanism by which these 5 IS therapies lead to an increased PML risk is unknown. In patients with prior IS current data does not show an association between higher index and PML risk. The underlying biological explanation for this effect is unknown.

Figure 1: PML Risk Estimates Algorithm

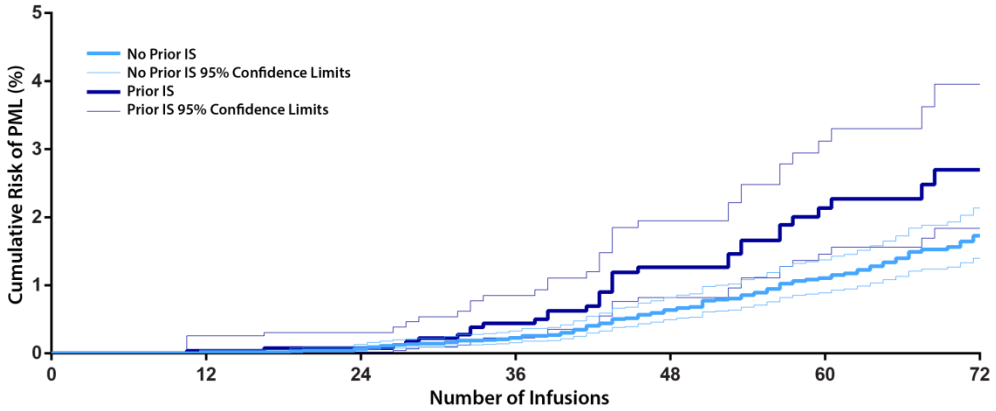


Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with Prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
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

PML risk estimates in anti-JCV antibody positive patients were derived using Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical studies. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of immunosuppressant were derived from combining the overall yearly risk with the antibody index distribution. The risk of PML in anti-JCV antibody negative patients were estimated based on post-marketing data from approximately 125,000 TYSABRI exposed patients.

Additionally, some physicians may find a Kaplan Meier (KM) curve useful to provide a visual representation of cumulative PML risk over time using a time-to-event analysis (Figure 2). In the KM curve, PML risk estimates for a given time point represent the total cumulative risk up to that time point (for example, at the time point of 48 months, the risk estimate on the KM curve represents the total risk up to 48 months, not the risk between 24 months and 48 months). Like Figure 1, data for these analyses were also obtained from the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials and also takes the individual treatment length of each patient into consideration with drop-outs (e.g., treatment discontinuation) into account.

Figure 2: Cumulative PML risk over time for anti-JCV antibody positive patients stratified by prior IS



	Number of Subjects at Risk (a)						
No Prior IS	18,616	16,130	12,925	9,755	6,880	4,379	2,277
Prior IS	3,080	2,671	2,201	1,693	1,159	720	366
	Cumulative Number of PML Cases (b)						
No Prior IS	0	2	10	28	62	89	109
Prior IS	0	1	2	9	21	29	32

NOTE 1: Number of PML cases after 72 infusions: No Prior IS = 11, Prior IS = 4. NOTE 2: For patients with missing data on anti-JCV antibody status and/or prior IS use, multiple imputation methodology us used to impute the status. (a) Average number of subjects who were in the study and did not have the event at the end of the specified time over multiple imputations. (b) Cumulative number of PML cases at the end of the specified time.

SOURCE: TYSABRIMS/PRAC-ART20/POOLED/F-TTPML-KM-PRIORIS-MI5-V2.SAS

2.8 *Recommended Patient monitoring*

Testing for Anti-JCV Antibodies

Serum anti-JCV antibody testing provides supportive information for risk stratification of TYSABRI treatment. Testing for serum anti-JCV antibody prior to initiating TYSABRI therapy or in patients receiving TYSABRI with an unknown antibody status is recommended. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2 year treatment point is recommended to inform on appropriate patient MRI monitoring

In the STRATIFY-1 clinical study approximately 11% of patients changed serostatus from anti-JCV antibody negative to positive per year. Approximately 12-16% serostatus change from antibody negative to positive in the second generation assay was reported in Unilabs real world data over a median duration of 12 months. In the STRATIFY-2 clinical study approximately 6% of patients changed serostatus from anti-JCV antibody positive to negative per year. Patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results. From available longitudinal STRATIFY-2 study, in patients who changed serostatus from positive to negative, the median last index level before testing antibody negative was 0.44 (25th quartile = 0.34; 75th quartile = 0.55), which was close to the cut-off index level of 0.4). Furthermore, findings from another longitudinal study showed that 1 in 13 seropositive patients seroreverted to negative, mostly in patients with a titre of ≤0.6, i.e. also close to the cut-off point for positive/negative.

Patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results.

Testing should only be performed using an appropriate and validated assay e.g. STRATIFY JCV. The anti-JCV antibody assay should not be used to diagnose PML. Anti-JCV antibody testing should not be performed during, or for at least two weeks following, plasma exchange due to the removal of antibodies from the serum.

Recommended MRI monitoring

MRI in the clinical practice of MS has been shown to be a useful tool for patient monitoring. It may assist in differentiating PML lesions from MS plaques in patients that develop new neurological symptoms or signs once on therapy. Recommendations for MRI monitoring is summarized below:

a) **Recent MRI (usually within 3 months) prior to initiation of TYSABRI is recommended. MRI should be performed at least on a yearly basis.** Clinicians should evaluate the yearly MRI in asymptomatic patients on Tysabri for any signs of PML.

b) **More frequent MRI monitoring every 3-6 months using an abbreviated protocol should be considered in patients at a higher risk of PML**. This includes:

- Patients who have all three risk factors for PML (i.e., are-anti-JCV antibody positive **and** have received more than 2 years of TYSABRI therapy, **and** have received prior immunosuppressant therapy)

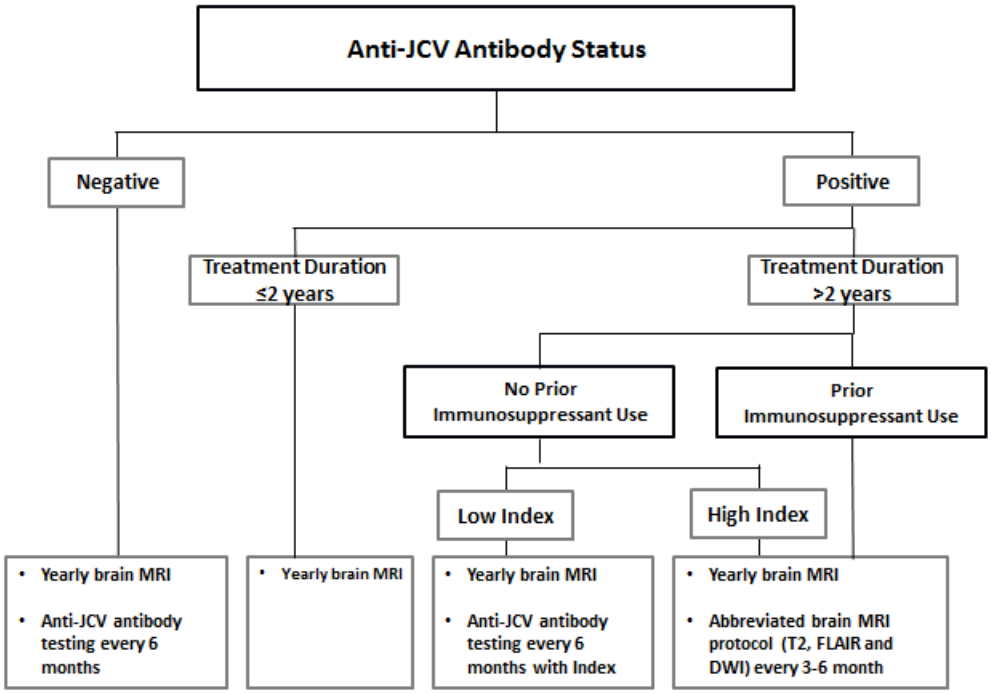
Or

- Patients with a high anti-JCV antibody index who have received more than 2 years of TYSABRI therapy and without prior history of immunosuppressant therapy.

Current evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with TYSABRI for more than 2 years. MRI monitoring decisions should take this evidence into consideration and physician discretion is advised for those patients with index values between 0.9 and 1.5.

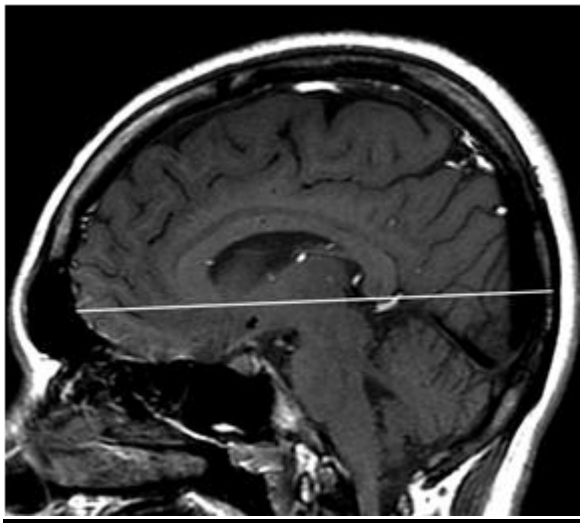
A summary of the recommended monitoring is provided in Figure 3.

Figure 3: Recommended Patient Monitoring



Standard brain MRI protocol (for baseline and routine annual scans for all patients):

- ***Scanner field strength >1.0 T, slice thickness <5 mm with no gap and with whole brain coverage***
- ***Axial images prescribed from the subcallosal line (Fig 4)***



Full MRI Protocol
Sagittal and axial 2D FLAIR or 3D FLAIR
Axial FSE PD/T2
Axial DWI
Axial T1W spin echo pre and post contrast
Gd injection 0.1 mmol/kg over 30 seconds
5-minute delay after contrast injection

More frequent MRIs in higher risk patients should be performed using an abbreviated protocol. (FLAIR/T2-weighted and diffusion weighted imaging [DWI]).

Abbreviated MRI protocol (screening MRI) for safety monitoring in high risk patients
Sagittal and axial 2D FLAIR
Axial FSE PD/T2W
Axial DWI

If MRI lesions are suggestive of PML, a full MRI protocol with contrast enhancement should be performed.

When MRI lesions suggestive for PML are detected, the MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-IRIS, particularly during follow up. It is also recommended that upon request for follow-up MRI, treating physicians inform radiologists that PML or other opportunistic infections are being considered in the differential diagnosis.

3 Diagnosis of PML

Including clinical and MRI differentiation between PML and MS symptoms/lesions.

3.1 *General Principles*

The following points should be considered when undertaking the clinical management of MS patients on TYSABRI therapy.

- All TYSABRI treated patients should have regular clinical follow-up to allow for early detection of changes in neurological status. If any new neurological symptoms in patients treated with TYSABRI develop, PML should always be considered as a diagnosis.

- Patients, their partners and care givers need to be advised of symptoms that may be indicative of early PML (see Section 6.2 and Appendix 3: Alert Card, Appendix 4: Treatment Initiation and Continuation Forms) and be counseled on the need to be vigilant for these symptoms while on TYSABRI treatment, and also for approximately 6 months after the last dose of TYSABRI (PML has also been reported up to 6 months following the last dose of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation).

- **In all cases where further investigation of change in neurological status or change in brain MRI is indicated, TYSABRI must be suspended and not restarted until non MS pathology has been confidently excluded. Suspension of TYSABRI therapy, for short duration (days or weeks), is not expected to compromise therapeutic efficacy based on the pharmacodynamics of the drug.**

- The decision to suspend TYSABRI at any stage may be based on the initial clinical presentation, MRI findings, the evolution of symptoms or signs and/or the response to corticosteroid treatment.

- **TYSABRI should be permanently discontinued if PML is confirmed.**

- **TYSABRI dosing should only be restarted when the diagnosis of PML is excluded (if necessary, by repeating clinical, MRI and laboratory investigations if suspicion of PML remains).**

3.2 *Clinical Differentiation between PML and MS Relapse*

The following guidance and algorithm (Figure 4) describes a suggested approach to the clinical assessment of new or worsening neurological symptoms in MS patients treated with TYSABRI.

New or recurrent neurological symptoms should prompt careful evaluation in order to assess the underlying pathology e.g. MS or PML. It is important to note that presence of new onset neurologic symptoms are not required to diagnose PML in the setting of MRI findings consistent with PML and the presence of JC virus in the central nervous system (CSF or in brain tissue). Cases of asymptomatic PML have been reported. In both high and low risk asymptomatic patients, any new suspected lesion at recommended MRI evaluation for monitoring PML risk should be carefully evaluated,

particularly when an abbreviated protocol has been performed (see following section MRI Differentiation between PML and MS relapse). Table 1 highlights the clinical features that help differentiate MS from PML. It should be noted that the table is not all inclusive and there may be a great deal of overlap between symptoms of the two conditions. Physicians should be aware that the clinical picture of PML or other opportunistic infections can be difficult to distinguish from MS, especially early in the evolution. The history and pattern of previous and current symptoms and signs are important to note and will facilitate the management of TYSABRI treated patients.

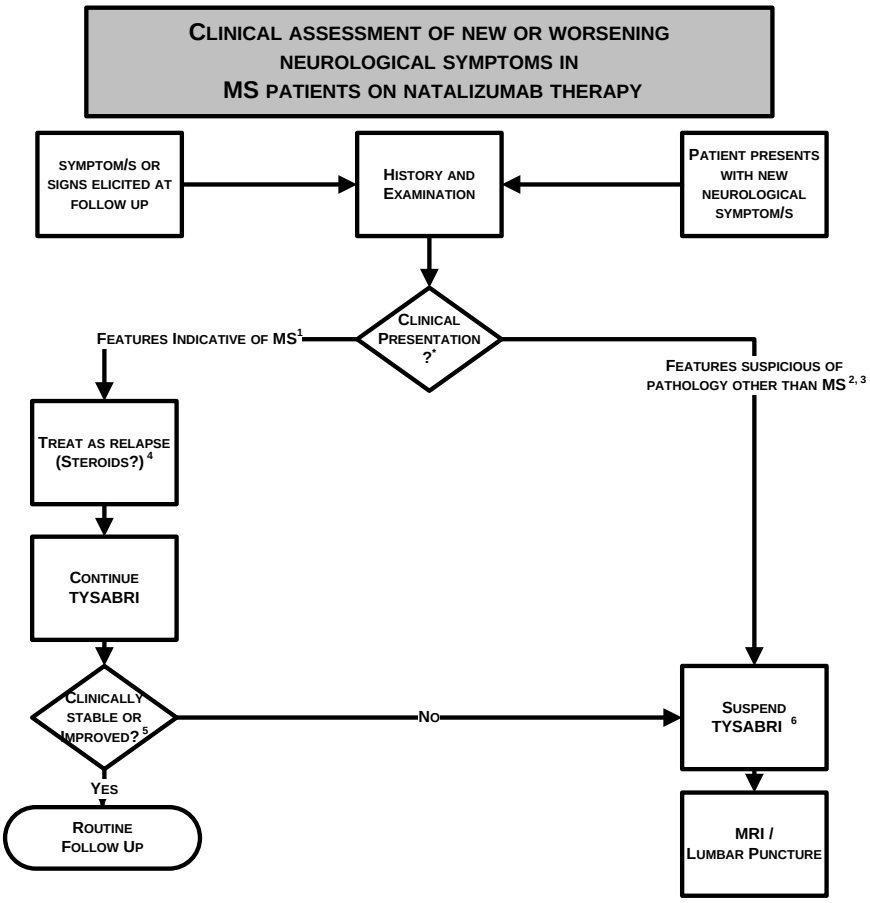
Table 1. Clinical Features of MS and PML

	Features Indicative of :	
	MS [1]	**PML [2]**
Onset	Acute	Sub-acute
Evolution	• Over hours to days • Normally stabilise • Resolve spontaneously even without therapy	• Over weeks • Progressive
Clinical Presentation	• Diplopia • Paraesthesia • Paraparesis • Optic Neuritis • Myelopathy	• Aphasia • Behavioural or cognitive changes and neuropsychological alteration • Retrochiasmal visual deficits • Hemiparesis • Seizures • Ataxia (for GCN)

Reference: Kappos *et al.*, 2011

If the clinical presentation cannot exclude PML, further investigations including MRI evaluation (Figure 5, Table 2) and / or lumbar puncture and cerebrospinal fluid (CSF) evaluation (Figure 6) should be undertaken as soon as possible. A definitive diagnosis of PML should only be made on the basis of a clinical presentation or MRI findings and the identification of JC viral DNA in the central nervous system (CNS).

Figure 4. Clinical Assessment



[1] See Table 1

[2] See Table 1

[3] Clinicians should consider other non-MS pathology in addition to PML especially opportunistic infections

[4] Relapses should be managed according to usual clinical practice. A single, short course of steroids can be considered in cases where PML is unlikely on clinical grounds. Lack of response to steroids should be a trigger for further investigation.

[5] Clinical findings should be compared with those recorded at clinical presentation* of this episode

[6] If non MS pathology is suspected at clinical presentation or during follow up **ALL future infusions** should be postponed until PML or other opportunistic infections have been definitively excluded

Reference: Kappos *et al.*, 2011

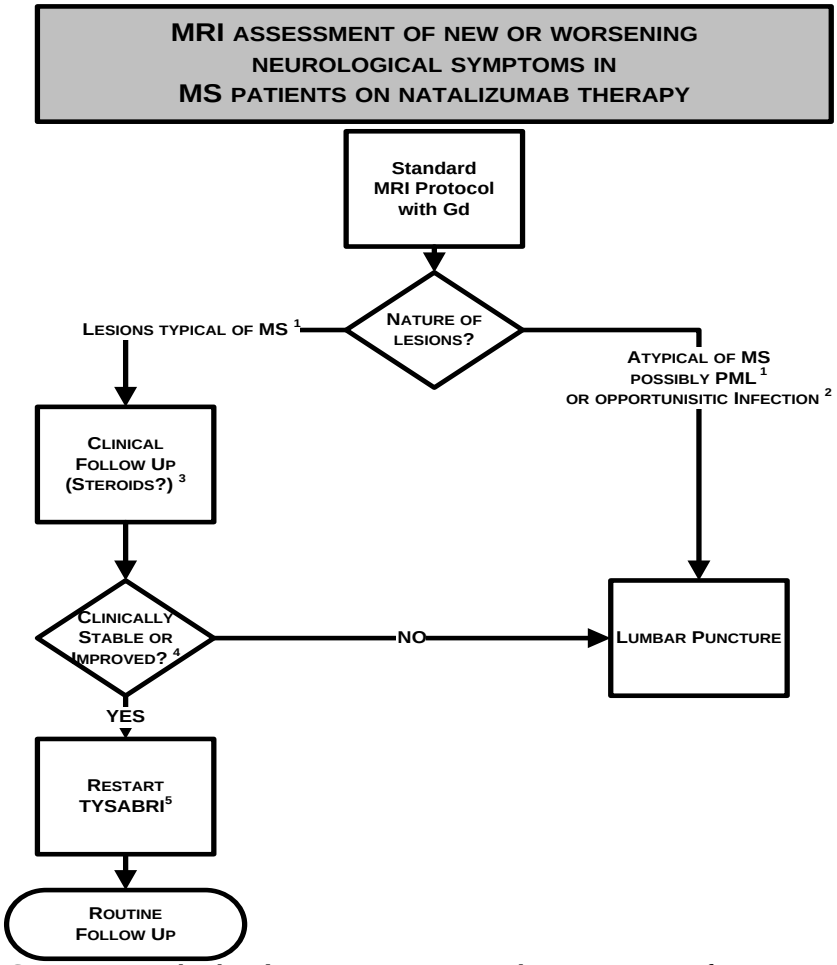
3.3 *MRI Differentiation between PML and MS Relapse*

A standardized MRI protocol preferably with and without contrast for the follow-up of patients on TYSABRI is proposed to obtain the best possible images for clinical decision making to assist with clinical decision-making (Yousry *et al*., 2006, Yousry 2012). FLAIR is the most sensitive sequence for detection of PML (Wattjes *et al.*. Nat. Rev. Neurol. 2015). Diffusion-weighted imaging sequences may also be helpful in distinguishing new lesions from chronic MS plaques and MRI changes from a previous scan (Wattjes *et al.*, 2015; Mader *et al.*, 2003). The MRI sequence parameters for each scanner should be selected for good representation of CNS anatomy and visualisation of MS lesions. Consistent use of the standard MRI protocol will help recognition of early alterations on MRI (Table 2).

Further information on the differentiation between PML and MS may be found at www.ms-pml.org or may be requested by sending an email to safeguardAC@vumc.nl

Figure 5. MRI Assessment (See Section 3.1) TYSABRI must be suspended and not restarted until non MS pathology has been confidently excluded.

If PML is suspected based on a clinical presentation and an MRI is not readily available, laboratory investigations e.g. lumbar puncture to exclude PML should not be delayed.



[1] See Table 2 Comparison with a baseline scan may assist with interpretation of MRI appearances

[2] Clinicians should consider other non-MS pathology in addition to PML especially opportunistic infections

[3] Relapses should be managed according to usual clinical practice. A single, short course of steroids can be considered in cases where PML is unlikely on clinical grounds. Lack of response to steroids should be a trigger for further investigation.

[4] Clinical findings should be compared with those recorded at clinical presentation of this episode

[5] Resumption of TYSABRI therapy must only be considered once **PML or other opportunistic infections have been definitively excluded** on the basis of clinical findings and/or further investigations.

Reference: Kappos et al, 2011

Table 2. Features Visualised on MRI
To be considered in the differential diagnosis of MS and PML.

Feature	Multiple Sclerosis	PML
Lesion location	Focal, periventricular or deep white matter. Lesions occur in all areas of the brain , optic nerves and spinal cord.	Asymetetric , focal or multifocal . Subcortical or diffuse white matter. cortical grey matter, and deep gray matter , brainstem, middle cerebellar peduncles, .. PML is not seen in spinal cord or optic nerves
Lesion shape and lesion borders	Ovoid or flame shape; sharp borders, often perilesional edema	Irregular shape, finger-like projections toward the cortex. Ill-defined border toward the white matter, sharp border toward the grey matter.
Mode of extension	Initial enlargement over days or weeks and decrease in size within months.	Progressive increase in size.
Mass effect	Large acute lesions may have mass effect.	No mass effect
T2-weighted images	Homogeneous hyperintensity with surrounding edema	Diffuse hyperintensity often with , punctate microcystic inclusions. Perilesional nodules in the vicinity of the primary lesion. (milky way galaxy)
T1-weighted images	Acute lesions: hypointense or isointense. Increasing signal intensity over. time	Isointense to hypointense at onset, with decreasing signal intensity over time
FLAIR images	Hyperintense, sharply delineated.	Hyperintense .Most sensitive sequence for detection of PML.
Contrast enhancement in acute lesions	homogeneous nodular , ring or open ring enhancement conforms to shape and size of the lesion. ,resolution over 1-2 months. .	43% of lesions show enhancement at the time of presentation patchy or nodular appearance. .Enhancement does not conform to size or shape of the lesion Increased enhancement with IRIS
DWI	Acute lesions hyperintense. Chronic lesions isointense..	Acute lesions hyperintense. Distinguishes new PML lesions within areas of chronic WM disease. No restriction on ADC
Atrophy	Diffuse atrophy with progressive MS disease	Post PML-IRIS –encephalomalacia and diffuse brain atrophy in the affected areas.

(Reference: Kappos 2011; Yousry 2012, Wattjes 2014)

Laboratory Differentiation of PML from MS Relapse

This algorithm suggests how laboratory investigations can be integrated with clinical and MRI assessments in patients treated with TYSABRI (Figure 6).

The detection of JCV DNA by PCR in the cerebrospinal fluid of a symptomatic or asymptomatic patient with MRI findings consistent with PML confirms the diagnosis of PML. However, a negative JCV PCR result should not exclude a possible diagnosis of PML. Depending on the clinical presentation and the availability of MRI resources the analysis of CSF may well be conducted early. If JCV DNA is not detected in CSF and if clinical and/or suspicion of PML remains high, a repeat lumbar puncture should be performed. Brain biopsy to detect JCV should be considered if JCV DNA is not detected in CSF on repeat testing, especially if the result is based on an assay with a Limit of Detection (LoD) that is higher than the recommended 10 copies/mL (see below), and clinical and MRI suspicion remains high.

CSF analysis for JCV DNA

CSF samples should be analysed as quickly as possible to facilitate the diagnosis of PML.

Assays should be based on quantitative real time PCR methodology to maximize sensitivity and specificity for detection and it is recommended to use an assay with a Limit of Detection (LoD) of at least 10 copies/mL. This level of detection is diagnostically relevant since PML has been confirmed in patients with low copy numbers in the CSF.

If continued clinical or MRI-based suspicion of PML persists despite a local or reference laboratory result being negative (i.e. not detected) for JCV DNA by PCR, and especially if the result is based on an assay with a LoD that is less sensitive than the recommended 10 copies/mL, a further test for JCV DNA (the same CSF sample or a fresh aliquot) is recommended.

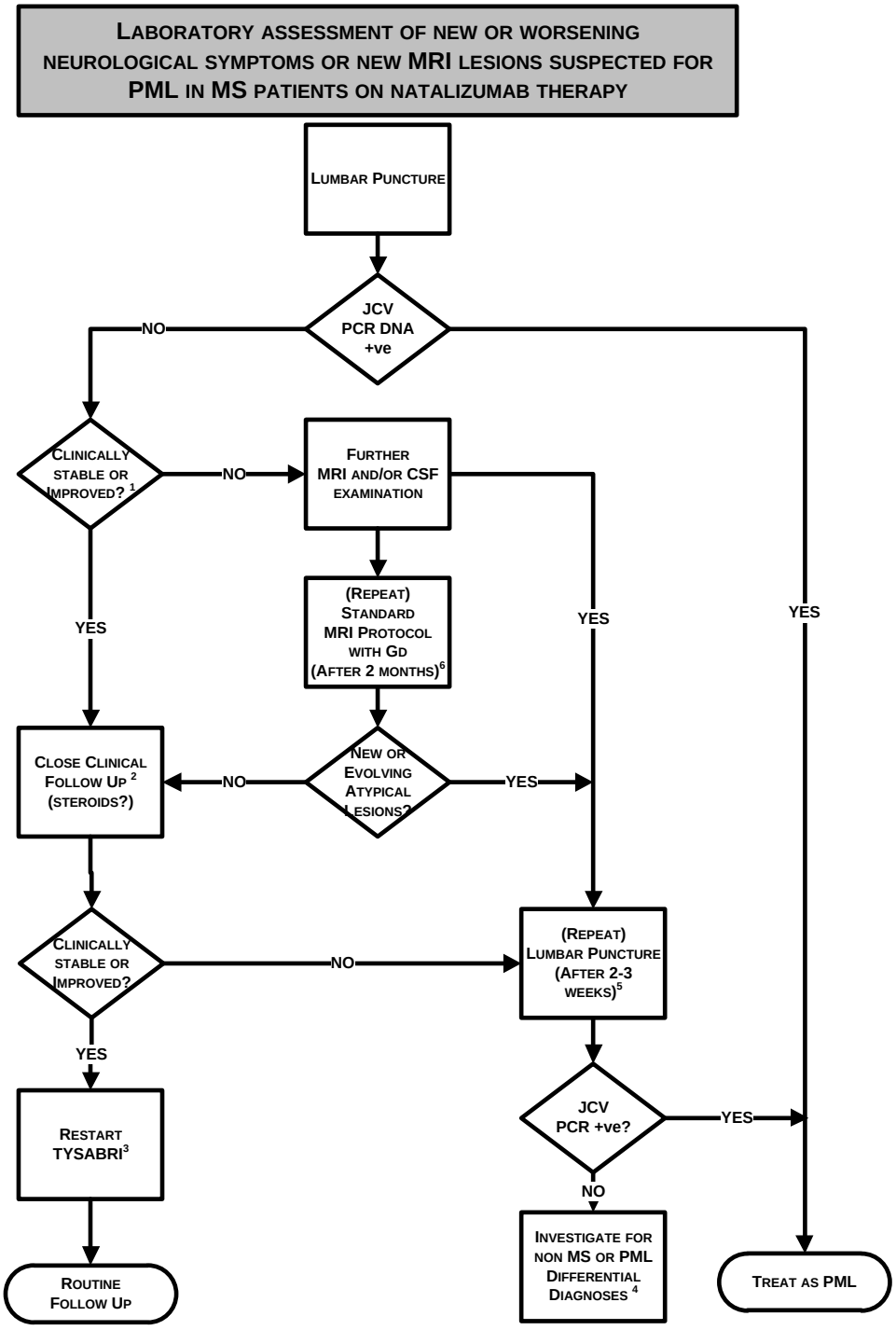
The Marketing Authorisation Holder (MAH) is not in a position to certify any laboratory. However, the MAH is aware of two central laboratories (Focus Diagnostics, Cypress, California and Unilabs, Copenhagen, Denmark) that offer a real time PCR assay specific for detection of JCV DNA in the cerebrospinal fluid.

The real-time assay at Unilabs was developed and qualified at the Translational Sciences department within the MAH and transferred to Unilabs for validation and clinical use. The real-time assay at Unilabs has a LoD of 10 copies/ml. A head-to-head comparison of the sensitivity of the assays performed at Unilabs and NIH (National Institute of Health in the USA) has not been carried out. However, the two sensitivity assessments have been described as similar in the literature published by the NIH as similar viral standards and controls have been used in development of the assay.

Reference testing laboratories are Unilabs, Denmark.
Helpline: +45 3374 3077 (Opening Hours 08:00-16:30 CET)
Email: helpdesk@unilabs.com

Details of the procedure for the collection, handling and transport of samples to the central facility are available from Medical Affairs in your country.

Figure 6. Laboratory Differentiation (See Section 3.1, TYSABRI must be suspended and not restarted until non MS pathology has been confidently excluded).



[1] Clinical findings should be compared with those recorded at clinical presentation of this episode

[2] Close clinical follow would be at least bi-weekly assessments.Relapses should be managed according to usual clinical practice. A single, short course of steroids can be considered in cases where PML is unlikely on clinical grounds. Lack of response to steroids should be a trigger for further investigation.

[3] Resumption of TYSABRI therapy must only be considered once PML or other opportunistic infection has been excluded on the basis of clinical findings and/or further investigations.

[4] Clinicians should consider other non-MS pathology in addition to PML especially opportunistic infections, or consider brain biopsy to confirm/discount presence of JCV

[5] Accelerate retesting if aggressive clinical symptoms persist.

[6] Or earlier if required.

4 Management of PML

Overall, the use of antiviral agents, such as cidofovir and cytarabine, to treat PML has proven ineffective in improving the outcome in patients with PML (Hall 1998; Aksamit 2001; Marra 2002; Gasnault 2001).

Immune reconstitution (restoration of normal immune function) appears to be the most effective treatment with evidence stemming from two areas of study. The first is in HIV where if PML occurs in an untreated patient, introduction of HAART can reverse the disease and improve outcome. Secondly, when PML occurs in transplant patients, if immune suppression can be reduced, outcome may be improved.

The data available suggests that early PML recognition and intervention may improve outcome (Antinori *et al.*, 2003; Berenguer *et al.*, 2003; Clifford *et al.*, 1999; Crowder *et al.*, 2005; Geschwind *et al.*, 2001; Shitrit *et al.*, 2005). It is possible that the earlier recognition of PML and discontinuation of TYSABRI allows immune reconstitution which contributed to the survival of the MS patient reported by Langer-Gould and colleagues (2005). The effect of plasma exchange (PLEX) on TYSABRI clearance and pharmacodynamics was evaluated in a study of 12 MS patients. An estimate of the total drug removal after 3 plasma exchanges (over a 5-8 day interval) was approximately 70-80% (Khatri *et al.*, 2009). This compares to approximately 40% reduction observed by drug discontinuation alone (without plasma exchange) over a similar period of observation. These data also suggest that additional plasma exchanges (up to a total of 5 over a 10 day period) may be required to more consistently reduce TYSABRI concentrations to below sub-therapeutic levels. This may be helpful to restore immunocompetence more quickly and therefore possibly control the JC virus infection. The clinical usefulness of plasma exchange or immunoadsorption to remove TYSABRI and accelerate immune reconstitution is unknown. A review of further cases together with an assessment of the long-term clinical status of patients post-PLEX or immunoadsorption is required before any robust conclusions can be made on clinical usefulness of this intervention. In addition, physicians do need to be aware of one consequence of immune reconstitution to assist with recovery from PML. IRIS (see below) with clinical associated deterioration may occur before improvement is seen. This clinical condition has been observed in the majority of post-marketing PML cases to date.

4.1 *Immune Reconstitution Inflammatory Syndrome (IRIS)*

Clinical neurologic deterioration in patients with PML and/or JCV GCN may be caused by JCV-mediated destruction of CNS tissue, or upon restoration of immune function, by an intracerebral immune inflammatory reaction known as immune reconstitution inflammatory syndrome (IRIS). IRIS is generally suspected when patients with PML exhibit signs of clinical worsening usually, but not always, accompanied by gadolinium enhancement of PML lesions with or without mass effect on brain MRI. The clinical worsening is a result of local inflammatory reaction, including oedema, and manifests as a worsening of neurological symptoms including hemiparesis, ataxia, speech abnormalities, visual disturbance, cognitive/behavioural changes and seizure (dependent on the site of IRIS). Severe sequelae can occur including coma and death. Although JC viral load in the CSF might be expected to decline in the setting of IRIS, it is also possible that due to the breakdown of the blood brain barrier (BBB) and release of JCV from cells lysed during IRIS, it can be increased.

In HIV patients, IRIS usually occurs within 2 to 3 months of initiation of HAART. In patients treated with TYSABRI, IRIS has occurred within days to several weeks after TYSABRI removal by plasma exchange (PLEX) or immunoabsorption (IA). Although

the inflammatory reaction following immune reconstitution may be a necessary step to remove JCV-infected cells, it may become necessary to treat the active immune reaction to prevent potential damage caused by IRIS (Talan 2009; Elston and Thacker 2009) and can be life-threatening and may therefore require management in an intensive care unit. Therefore, following PLEX or IA, periodic clinical monitoring of patients, including MRI monitoring, may be useful for the early detection of IRIS. The diagnosis and management of IRIS is a controversial issue and there is no consensus concerning its treatment. However, it has recently been suggested that corticosteroids may be useful to treat IRIS, particularly in patients with severe to life-threatening IRIS (Tan *et al.*, 2009, Clifford *et al.*, 2010). The following steroid regimens have been reported for the treatment of IRIS in the literature:

1) Oral prednisone 1.5 mg/kg/d x 2 wks with taper over 2 months

2) Intravenous methylprednisolone (1 g/d for 3 or 5 d) with oral taper over 2 months

If further deterioration occurs during steroid taper and this is judged to be due to continuing or new inflammatory reactions a further course of higher dose steroids may be necessary.

Prophylactic steroid treatment is currently not recommended. As scientific and medical knowledge, including both diagnostic criteria and management of IRIS is rapidly evolving, please contact Medical Affairs in your country for the most up-to-date information on treatment recommendations.

5 Prognosis

Early diagnosis, clinical and MRI monitoring, stopping TYSABRI therapy, and the use of plasma exchange (PLEX) may have improved the outcome of PML in affected TYSABRI patients.

Of the 582 confirmed postmarketing PML cases reported globally as of 07 August 2015, 173 cases were from clinical or observational studies, and 409 cases were reported spontaneously. The survival rate for confirmed postmarketing patients with PML is 77% (448 of 582 patients are alive), and the mortality rate is 23% (134 of 582 patients died).

Asymptomatic PML (with a comparison to symptomatic PML)

Cases of asymptomatic PML, have been reported that were initially suspected based on MRI findings and later confirmed by positive JCV DNA in the CSF. As of 04 June 2015, 62 of 566 confirmed PML cases (10.9%) were clinically asymptomatic at the time of PML diagnosis and were initially identified by MRI. Follow-up was available for 48 of the 62 cases (77.4%) with a mean and median duration of follow-up of 12.4 and 11.8 months (range 1 to 33.6 months). At the time of last follow-up, 95% (59/62) of patients were alive and three had a fatal outcome. At the time of the analysis, 63% (39/62) of patients with asymptomatic onset had at least 6 months of follow-up data available. Of the 48 patients for whom follow-up information was available, the majority (70.8%; 34/48) remained free from clinical symptoms, while 29.1% (14/48) became symptomatic subsequent to PML diagnosis. For the patients who became symptomatic, the median time from first suspect MRI to the onset of symptoms was 17 days (mean 32.2 days, range 1-151).

Asymptomatic PML patients had a shorter time from suspicion of PML to diagnosis of PML compared to symptomatic PML patients (median of 28 days versus 53 days). In addition, asymptomatic PML patients had more localized PML on brain MRI at time of suspicion compared to symptomatic PML patients. There was a higher proportion of

asymptomatic PML patients that had unilobar PML lesions on MRI at the time of diagnosis compared to symptomatic PML patients (60% versus 37%). Conversely, 16% of asymptomatic patients had widespread PML on MRI compared to 40% of symptomatic patients.

Asymptomatic patients appear to have less accrual of disability overtime as reflected by lower EDSS scores and higher Karnofsky scores after PML diagnosis compared to symptomatic patients (symptomatic patients did, however, have a slightly higher level of disability pre-PML compared to asymptomatic patients). Asymptomatic PML patients also had a higher survival rate compared to symptomatic patients (95% versus 74%).

6 PML diagnosed after discontinuation of Natalizumab

While the majority of cases of PML have occurred during treatment with Tysabri, there have been reports of cases identified more than four weeks after the last infusion. Of the 566 confirmed cases of PML reported as of 4 June 2015 PML onset was known for 98% (555). Seventy-four (13%) had PML onset more than 4 weeks after the last infusion of Tysabri. Eight of these patients (11%) were asymptomatic and initial suspicion of PML was based on MRI findings. Nine patients (12%) died and 65 (88%) were alive at the time of the analysis. TYSABRI exposure ranged from 8 to 90 months (mean 43 and median 42.5), with the majority of the patients (81%; 60/74) having received >24 months of treatment. The time between the last TYSABRI infusion and the onset of PML ranged from 1 to 6 months, with a mean and median of 2.1 and 1.8 months, respectively; the majority of cases (88%; 65/74) occurred within 3 months of the last infusion of TYSABRI.

Since PML has been reported following the discontinuation of Tysabri in patients who did not have findings suggestive of PML at the time of discontinuation, patients and physician should be alert for any new signs or symptoms that may be suggestive of PML and patients should continue with the same MRI monitoring protocol associated with their level of risk for PML for approximately 6 months following discontinuation, taking into account the switch to other MS disease-modifying treatments that are associated with a potential or identified risk of PML.

7 Adverse Reactions associated with infusions

7.1 *Hypersensitivity*

In 2-year controlled clinical trials in MS patients, hypersensitivity reactions occurred in up to 4% of patients. Anaphylactic/anaphylactoid reactions occurred in less than 1% of patients receiving TYSABRI. All patients recovered without sequelae.

Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion.

The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to TYSABRI following an initial short exposure (one or two infusions) and an extended period (three months or more) without treatment. However, the risk of hypersensitivity reactions should be considered for every infusion administered.

7.2 *Managing Infusion Hypersensitivity Reactions in Clinical Practice*

Resources for the management of hypersensitivity reactions should be available.

After dilution, the infusion is to be administered over approximately 1 hour and patients are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions. In the case of hypersensitivity during the infusion (e.g. urticaria with or without associated systemic symptoms, anaphylaxis), administration of the drug should be stopped immediately, and vascular access maintained for emergency treatment and fluid support. Immediate hypersensitivity reactions should be treated according to the severity of the reaction and the facility's Standard Operating Procedure. Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with TYSABRI.

7.3 *Other Adverse Reactions Associated with Infusions*

In 2-year controlled clinical trials in MS patients, an infusion-related event was defined as an adverse event occurring during the infusion or within 1 hour of the completion of the infusion. These occurred in 23.1% of MS patients treated with TYSABRI (placebo: 18.7%). Infusion reactions also occurred more frequently in patients re-exposed to TYSABRI following an initial short exposure (one or two infusions) and an extended period (three months or more) without treatment. In addition to hypersensitivity reactions reported, events reported more commonly with TYSABRI than with placebo included dizziness, nausea, urticaria and rigors. These events were usually mild in severity, resolved at the end of the infusions and did not require interruption of treatment. If individual symptoms are problematic symptomatic treatment may be helpful but there are no data available concerning this.

7.4 *Anti-Natalizumab Antibodies in Clinical Practice*

After approximately 6 months of therapy, persistent antibodies should be considered if there is either reduced efficacy or persistence of adverse events related to infusions (patients that experience a hypersensitivity reaction should be discontinued). In these cases, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in the efficacy of TYSABRI and an increased incidence of hypersensitivity reactions. Patients who have received an initial short exposure to TYSABRI (1-2 infusions) and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon redosing. Therefore, the presence of anti-natalizumab antibodies should be evaluated and if these remain positive in a confirmatory test after at least six weeks, the patient should not receive further treatment with TYSABRI.

Anti natalizumab antibody tests may obtained at:
Florian Deisenhammer MD, MSc
Professor of Neurology
Neuroimmunology Laboratory
Innsbruck Medical University
Innrain 66, 2nd floor
6020 Innsbruck, Austria
Tel: +43 512 504 24264
Fax: +43 512 504 24266

8 Educational guidance

Physicians need to inform patients about the benefits and risks of TYSABRI and provide them with a Patient Alert Card (see Appendix 3) prior to initiation of therapy and continue to counsel patients on the risk of PML on a regular basis thereafter. Due to this increased risk of developing PML with increasing treatment duration, the benefits and risks of TYSABRI treatment should be individually reconsidered by the specialist physician and the patient. The patient should be re-informed about the risks of PML with TYSABRI after 24 months, and should be instructed together with their caregivers on early signs and symptoms of PML. Patients who are discontinuing TYSABRI treatment should also be informed that cases of PML have occurred in patients up to 6-months after the last does of TYSABRI. In this situation, the same monitoring protocol should be continued for approximately six months following discontinuation of TYSABRI. Template treatment initiation, continuation and discontinuation forms are provided in Appendix 4.

8.1 *Informing Patients about Benefits and Risks*

The Patient Information Leaflet (PIL) that is contained in each pack of TYSABRI, explains both benefits and risks in language designed specifically for patients to understand (this has been confirmed by MS patient readability testing). An example is included as parts of this pack (Appendix 2) so that the physician can become familiar with the PIL prior to counseling patients about TYSABRI therapy.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment (see Section 5.1, Hypersensitivity).

Physicians should counsel pregnant women on the use of TYSABRI during pregnancy taking into account the patient's clinical condition. This benefit-risk discussion should also cover the possible return of disease activity after stopping TYSABRI and the monitoring of newborns for potential haematological abnormalities for patients exposed to TYSABRI in the third trimester.

Call for reporting

▼

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and sent by post or email to:
P: ADR reporting/ 203, level 3 Rue D'Argens Gzira GZR 1368, Malta
E: postlicensing.medicinesauthority@gov.mt

In addition a locally agreed template for a treatment initiation information sheet and a treatment continuation sheet at 24 months of treatment and a discontinuation form describing specifically the risk of PML with TYSABRI treatment and the importance of monitoring for PML are provided in appendix 4. These should be provided to patients

before initiation of treatment, after 24 months of treatment, and following discontinuation to ensure that patients are fully informed about the risk of PML.

8.2 *Alert Card*

The Alert Card must be issued to patients.

It reminds patients that because of the risks of PML associated with TYSABRI they must contact their doctor if they believe either their MS is getting worse or they or their family members notice new symptoms such as changes in mood, behaviour, memory, motor weakness, speech and communication difficulties. Partners and care givers should also be made aware of the information provided in the Alert Card. The Alert Card, includes a recommendation for patients to retain the card for a period of 6 months following the last dose of TYSABRI treatment since signs and symptoms suggestive of PML may occur up to 6 months after discontinuation and patients and their caregivers should report any suspect changes in neurological status during this time.

The card contains a space to provide contact information so that they can report these concerns. Their doctor must complete this section when issuing the card.

Alert Cards are included as part of the Physician pack. Additional cards can be ordered from the local company office, contact details are contained in the pack.

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10 Appendices

Appendix 1. Summary of Product Characteristics (SmPC)

Appendix 2. Patient Information Leaflet (PIL)

Appendix 3. Patient Alert Card

Appendix 4. Treatment Initiation, Continuation and Discontinuation Forms

To be inserted when finalised