

Supplementary Table 2. Serious adverse events related to high efficacy DMTs.

Treatment	Adverse events
Dimethyl fumarate	<ul style="list-style-type: none"> - PML risk Class II¹
Fingolimod	<ul style="list-style-type: none"> - PML risk Class II¹ - Herpetic infections² - Other opportunistic infections³ - Skin cancer, lymphomas
Cladribine	<ul style="list-style-type: none"> - PML risk unknown, probably class III in MS^{1,4} - Herpetic infections² - Tuberculosis reactivation - Cancer: more frequent in the cladribine arm than in the placebo arm, but similar to the general population
Natalizumab	<ul style="list-style-type: none"> - PML risk Class I¹ - PML-IRIS⁵ - Herpetic infections
Alemtuzumab	<ul style="list-style-type: none"> - PML risk Class III?^{1,6} - Herpetic infections², including CMV - Tuberculosis reactivation - Lysteria meningitis - Other opportunistic infections - HPV and cervical dysplasia - Cardiovascular (stroke, heart infarction, arterial dissection)⁷ - Liver injury⁸ - Secondary autoimmunity⁸
Ocrelizumab/rituximab	<ul style="list-style-type: none"> - PML risk Class III for rituximab¹, carry-over from natalizumab/fingolimod to ocrelizumab⁹ - Hepatitis B reactivation

	<ul style="list-style-type: none"> - Hypogammaglobulinemia - Cancer: more common in ocrelizumab arm than in control arms, but similar to the general population (breast cancer) - Neutropenia¹⁰
aHSCT	<ul style="list-style-type: none"> - Opportunistic infections - Secondary autoimmunity¹¹

Abbreviations: PML: progressive multifocal leukoencephalopathy; MS: multiple sclerosis; IRIS: immune reconstitution inflammatory syndrome; HPV: human papillomavirus.

References, supplemental material:

1. Berger JR. Classifying PML risk with disease modifying therapies. *Mult Scler Relat Disord* 2017; 12: 59-63.
2. Faissner S and Gold R. Efficacy and Safety of the Newer Multiple Sclerosis Drugs Approved Since 2010. *CNS Drugs* 2018; 32(3): 269-287.
3. Winkelmann A, Loebermann M, Reisinger EC, et al. Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol* 2016; 12(4): 217-233.
4. Berghoff M, Schanzer A, Hildebrandt GC, et al. Development of progressive multifocal leukoencephalopathy in a patient with non-Hodgkin lymphoma 13 years after treatment with cladribine. *Leuk Lymphoma* 2013; 54(6): 1340-1342.
5. Tan IL, McArthur JC, Clifford DB, et al. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. *Neurology* 2011; 77(11): 1061-1067.
6. Gerevini S, Capra R, Bertoli D, et al. Immune profiling of a patient with alemtuzumab-associated progressive multifocal leukoencephalopathy. *Mult Scler* 2019; 1352458519832259.
7. McCall B. Alemtuzumab to be restricted pending review, says EMA. *Lancet* 2019; 393(10182): 1683.
8. Soleimani B, Murray K and Hunt D. Established and Emerging Immunological Complications of Biological Therapeutics in Multiple Sclerosis. *Drug Saf* 2019; 42(8): 941-956.
9. Kadish R, Robertson D and Sweeney M. Fatal leukoencephalopathy in a patient with multiple sclerosis following treatment with ocrelizumab (P5.353). *Neurology* 2018; 90(15 (Supplement)): P5.353.
10. Cohen BA. Late-onset neutropenia following ocrelizumab therapy for multiple sclerosis. *Neurology* 2019; 92(9): 435-436.
11. Loh Y, Oyama Y, Statkute L, et al. Development of a secondary autoimmune disorder after hematopoietic stem cell transplantation for autoimmune diseases: role of conditioning regimen used. *Blood* 2007; 109(6): 2643-2548.