

SUPPLEMENTARY MATERIALS

LymphoTEC: a Retrospective Real-World Study on Lymphocyte Reconstitution After Lymphopenia in Patients With Multiple Sclerosis Treated With Dimethyl Fumarate in France

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Supplementary Methods

Factors studied for potential association with absolute lymphocyte count (ALC) reconstitution and for occurrence of lymphopenia after dimethyl fumarate (DMF) were age at DMF discontinuation (< 35, 35 to < 45, 45 to < 55 and $\geq$ 55 years), sex (male/female), diabetes (yes/no/unknown), smoking habits (never/current/former/unknown), last ALC under DMF (continuous variables), Expanded Disability Status Scale (EDSS) at DMF discontinuation (0–3.0 [minimal disability], 3.5–9.5 [moderate to severe disability], or unknown), number of relapses in the year before DMF initiation (0, 1, $\geq$ 2), disease duration at DMF discontinuation (stratified [0 to < 3, 3 to < 5, 5 to < 10, $\geq$ 10 years]), treatment before DMF (yes/no), DMF duration in years (0 to < 1, 1 to < 2, 2 to < 3, $\geq$ 3), DMF duration up to lymphopenia in months (continuous variable), DMF duration after lymphopenia in months (0 to < 0.1, 0.1 to < 0.5, 0.1 to < 1.5, $\geq$ 1.5), and grade of lymphopenia at DMF discontinuation (Grades 1, 2, and 3).

For occurrence of lymphopenia after DMF, factors studied were: age at DMF initiation (< 25, 25 to < 35, 35 to < 45, 45 to < 55 and $\geq$ 55 years), sex (male/female), diabetes (yes/no/unknown), smoking habits (never/current/former/unknown), first ALC close to DMF initiation (continuous variable), EDSS (0–3.0 [minimal disability], 3.5–9.5 [moderate to severe disability], or unknown), number of relapses in the last year (1, $\geq$ 2), disease duration at DMF initiation (stratified [0 to < 3, 3 to < 5, 5 to < 10, $\geq$ 10 years]), and treatment before DMF (yes/no).

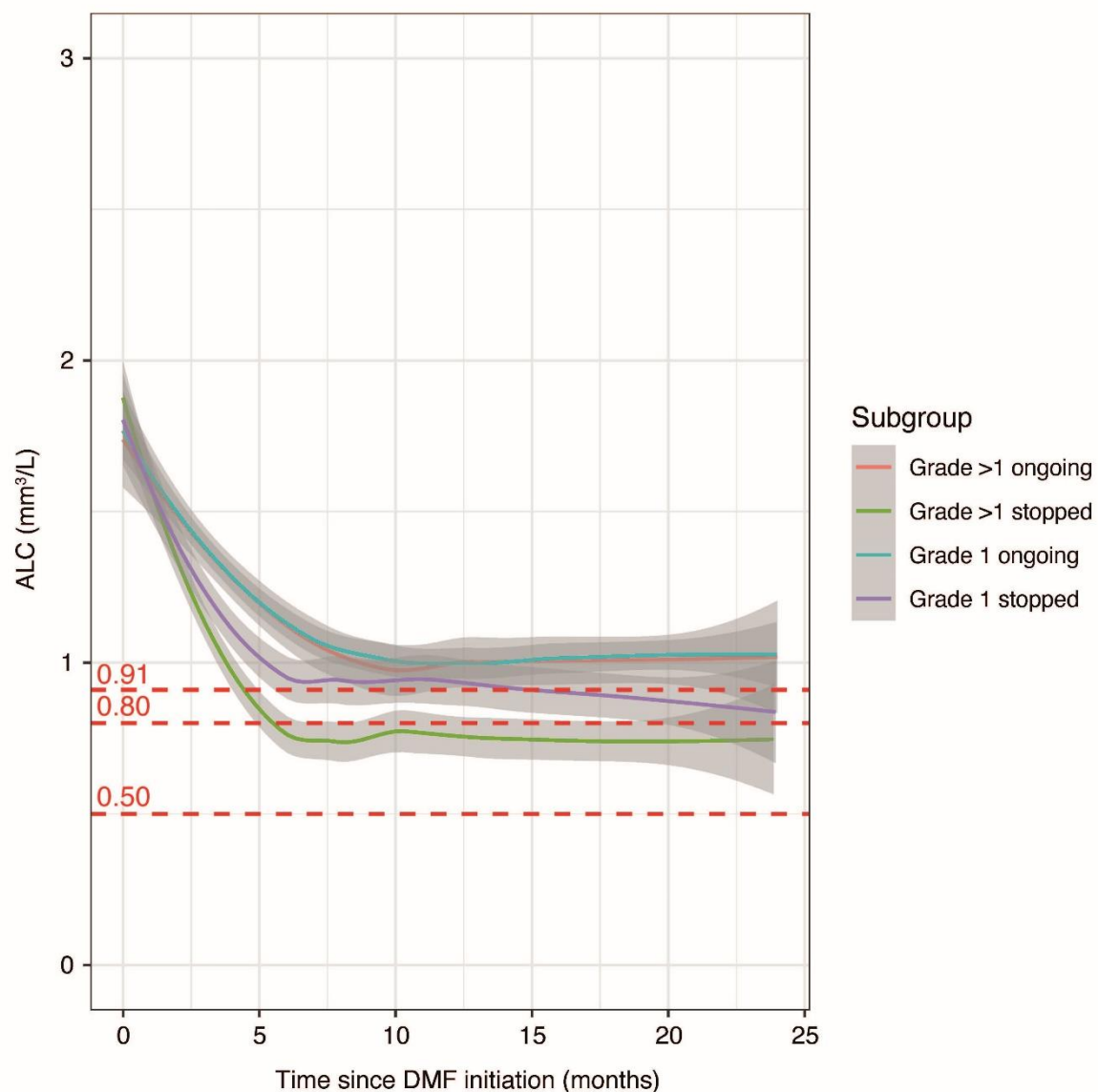
Supplementary Table S1 Lymphopenia by grade after DMF initiation in population A

	Lymphopenic patients (population A; <i>n</i> = 356)
At first lymphopenia, <i>n</i> (%)	
Grade 1	173 (48.6)
Grade 2	173 (48.6)
Grade 3	10 (2.8)
Maximal grade, ^a <i>n</i> (%)	
Grade 1	100 (28.1)
Grade 2	206 (57.9)
Grade 3	49 (13.8)
Grade 4	1 (0.3)

DMF dimethyl fumarate

^aWorst grade of lymphopenia observed from DMF initiation until the last clinical evaluation or initiation of the next disease-modifying therapy, whichever event occurred first

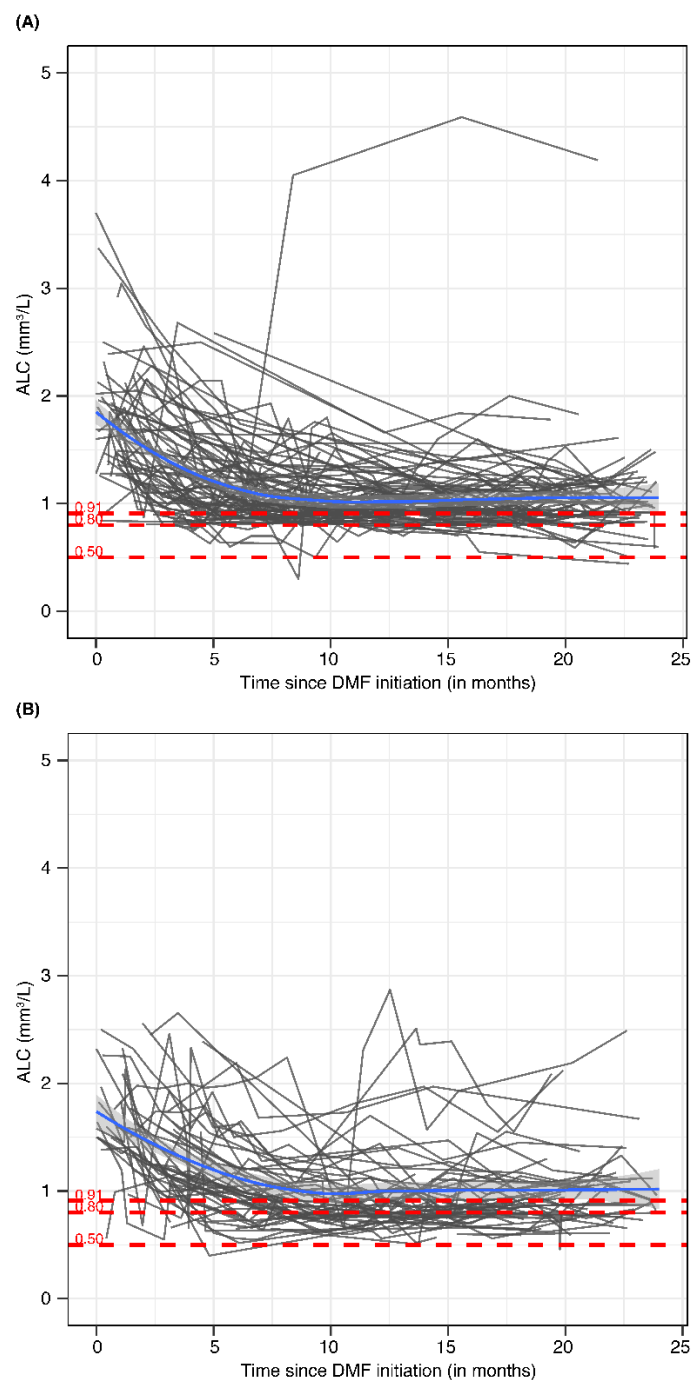
Supplementary Fig. S1 Mean evolution of ALC by grade and DMF status from DMF initiation to last observed ALC on DMF (population A)



Mean evolution approximated by a smoothed function resulting from a nonparametric regression (LOESS regression) are presented in red (Grade > 1, ongoing), in green (Grade > 1, stopped), in turquoise (Grade 1, ongoing), and in purple (Grade 1, stopped) with two-sided 95% confidence interval in gray. The red dashed lines correspond to ALC values (0.5, 0.8, and 0.91 $\times 10^9/L$)

ALC absolute lymphocyte count, DMF dimethyl fumarate, LOESS locally estimated scatterplot smoothing

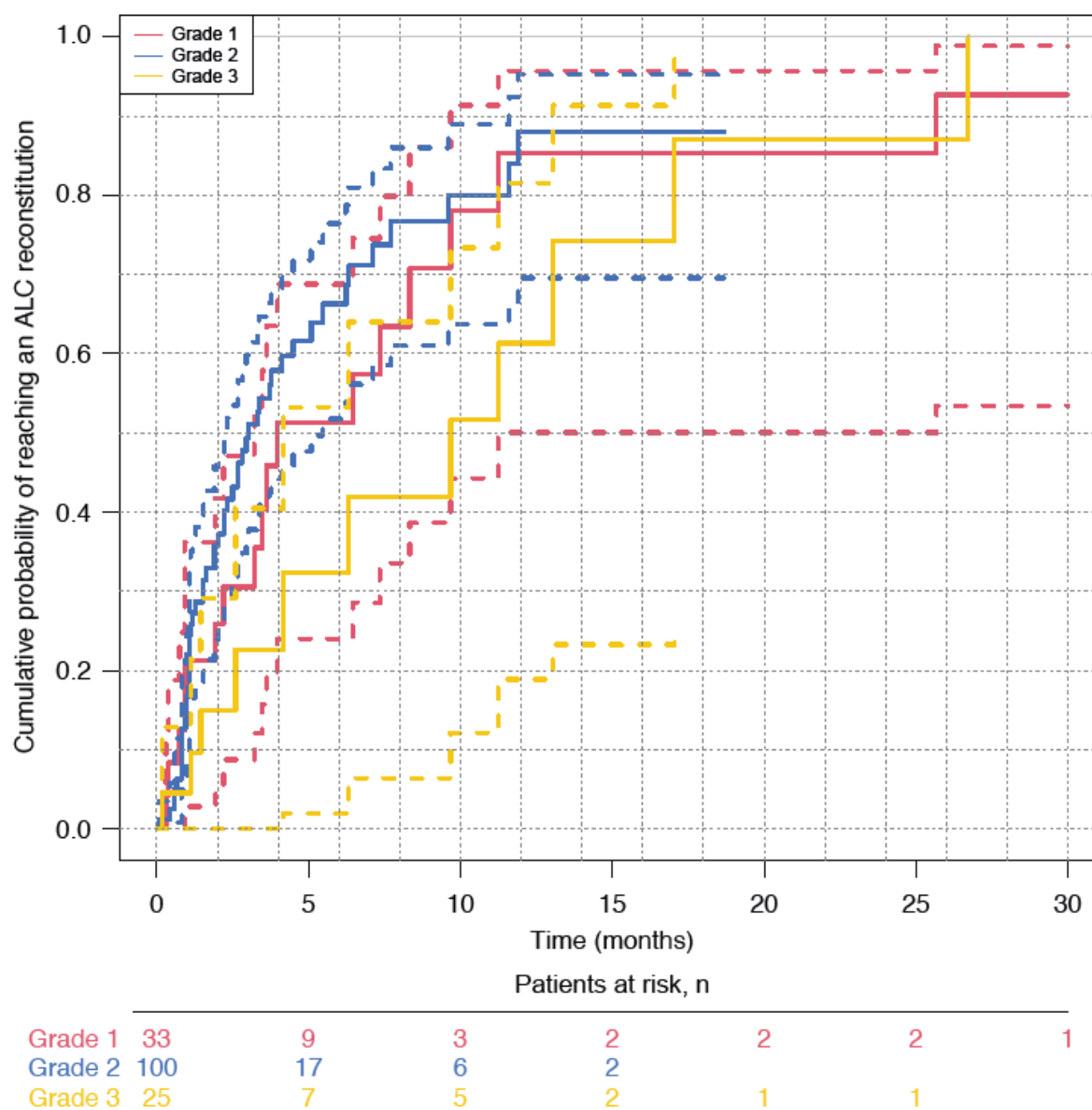
Supplementary Fig. S2. Individual ALC counts from DMF initiation to the last observed ALC in patients who remained on DMF and had (A) first lymphopenia of Grade 1 or (B) first lymphopenia of Grade > 1 (population A)



Individual ALCs are displayed as black lines, mean evolution approximated by a smoothed function resulting from a nonparametric regression (Loess regression) is presented in blue with its 2-sided 95% CI in grey. The red dotted lines correspond to ALC values (0.5, 0.8 and 0.91 $\times 10^9/\text{L}$).

ALC absolute lymphocyte count, DMF dimethyl fumarate; LOESS locally estimated scatterplot smoothing

Supplementary Fig. S3 Cumulative probability of the first ALC reconstitution after DMF discontinuation (population B)



Kaplan-Meier estimation stratified by grade of lymphopenia. Data were censored at the DMT initiation after DMF discontinuation or at the last ALC value, whichever event occurred first.
 ALC absolute lymphocyte count, DMF dimethyl fumarate, DMT disease-modifying therapy