

Supplementary Table 1 Subgroup analyses for EDSS 6		
Subgroups	Adjusted HR (95% CI)	P values for interaction
Age, yrs		
< 42·8	0.27 (0.21 – 0.35)	0·3016
≥42·8	0.23 (0.17 – 0.31)	
Gender		
Female	0.26 (3·12 – 4·90)	0·9837
Male	0.25 (0.18 – 0.36)	
Disease duration, yrs		
< 9·4	0.27 (0.21 – 0.35)	0·5498
≥9·4	0.24 (0.18 – 0.32)	
Disability (EDSS)		
< 2·5	0.25 (0.19 – 0.34)	0·6031
≥2·5	0.24 (0.19 – 0.31)	
The number of relapses in two years before baseline		
= 0	0.25 (0.20 – 0.32)	0·7789
> 0	0.26 (0.19 – 0.35)	
The number of DMTs used before the baseline		
< 0	0.27 (0.22 – 0.34)	0·4944
≥0	0.23 (0.16 – 0.32)	
High-efficacy DMT use during PIRA, yrs		
= 0	0.28 (0.23 – 0.34)	0·0359
= 1	0.16 (0.09 – 0.27)	
Early DMT		
= 0	0.30 (0.24 – 0.38)	0·0329
= 1	0.19 (0.13 – 0.26)	
Early PIRA		
= 0	0.27 (0.22 – 0.34)	0·2603
= 1	0.21 (0.14 – 0.32)	
The proportion of DMT use period		
<0·37	0.28 (0.22 – 0.36)	0·3545
≥0·37	0.23 (0.17 – 0.31)	

Supplementary Table 2 Subgroup analyses for SPMS		
Subgroups	Adjusted HR (95% CI)	P values for interaction
Age, yrs		
< 42·4	0.28 (0.18 – 0.43)	0·6431
≥42·4	0.23 (0.13 – 0.42)	
Gender		
Female	0.26 (0.17 – 0.40)	0.6414
Male	0.21 (0.11 – 0.39)	
Disease duration, yrs		
< 8·8	0.20 (0.12 – 0.34)	0.1364
≥8·8	0.32 (0.20 – 0.50)	
Disability (EDSS)		
< 2·5	0.22 (0.13 – 0.37)	0.5573
≥2·5	0.28 (0.18 – 0.44)	
The number of relapses in two years before baseline		
= 0	0.27 (0.18 – 0.42)	0.4174
> 0	0.21 (0.12 – 0.36)	
The number of DMTs used before the baseline		
< 0	0.23 (0.15 – 0.35)	0.3221
≥0	0.31 (0.18 – 0.54)	
High-efficacy DMT use during PIRA, yrs		
= 0	0.28 (0.20 – 0.40)	0.2071
= 1	0.14 (0.05 – 0.40)	
Early DMT		
= 0	0.29 (0.19 – 0.44)	0.3167
= 1	0.20 (0.11 – 0.36)	
Early PIRA		
= 0	0.28 (0.19 – 0.41)	0.4013
= 1	0.20 (0.10 – 0.41)	
The proportion of DMT use period		
<0·38	0.25 (0.15 – 0.41)	0·7514
≥0·38	0.26 (0.17 – 0.41)	

Supplementary Table 3 Characteristics of the Study Population by PIRA Persistence, and the significant risk factors in the univariate and multivariable analyses for sensitivity analysis 1.

				Univariate		Multivariable	
Risk factors	Total (n=2,100)	Persistent PIRA (n=1,365)	Non-persistent PIRA (n=735)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, per 10 yrs	4.20 (0.99)	4.30 (0.97)	4.00 (0.99)	0.77 (0.72 – 0.84)	<0.0001	0.82 (0.76 – 0.90)	<0.0001
Sex				0.92 (0.79 – 1.08)	0.3343	–	–
Male	609 (29)	404 (30)	205 (28)			–	–
Female	1491 (71)	961 (70)	530 (72)			–	–
High-efficacy DMT use during PIRA [†]	552 (26)	348 (25)	204 (28)	1.16 (0.99 – 1.37)	0.0699	1.20 (1.02 – 1.42)	0.0253
The number of DMTs used before the baseline [‡]	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	1.00 (0.92 – 1.08)	0.9168	–	–
The number of relapses in one year before baseline	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.94 (0.80 – 1.10)	0.4189	–	–
The number of relapses in two years before baseline	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	1.01 (0.93 – 1.10)	0.7894	–	–
Disability (baseline EDSS)	2.5 (2.0 – 3.5)	2.5 (2.0 – 3.5)	2.0 (2.0 – 3.0)	0.69 (0.63 – 0.76)	<0.0001	0.73 (0.67 – 0.80)	<0.0001
Disease duration, yrs	8.6 (5.0 – 14.0)	9.1 (5.3 – 14.6)	7.7 (4.3 – 12.6)	0.98 (0.97 – 0.99)	<0.0001	–	–
the proportion of DMT use period	0.6 (0.3 – 0.8)	0.5 (0.3 – 0.8)	0.6 (0.3 – 0.8)	1.43 (1.12 – 1.83)	0.0046	–	–
Early DMT	1155 (55)	721 (53)	434 (59)	1.25 (1.08 – 1.45)	0.0028	–	–
Early PIRA	529 (25)	314 (23)	215 (29)	1.29 (1.10 – 1.51)	0.0019	–	–
Visual	1131 (54)	755 (55)	376 (51)	0.88 (0.76 – 1.01)	0.0727	0.82 (0.71 – 0.95)	0.007
Brainstem	658 (31)	475 (35)	183 (25)	0.68 (0.57 – 0.80)	<0.0001	0.75 (0.63 – 0.89)	<0.0001
Pyramidal	446 (21)	309 (23)	137 (19)	0.82 (0.68 – 0.99)	0.0392	0.82 (0.68 – 1.00)	0.0447
Cerebellar	960 (46)	614 (45)	346 (47)	1.07 (0.92 – 1.23)	0.3764	–	–
Sensory	545 (26)	377 (28)	168 (23)	0.83 (0.70 – 0.99)	0.0411	–	–
Bowel/Bladder	405 (19)	266 (19)	139 (19)	0.97 (0.81 – 1.17)	0.7655	–	–
Mental	391 (19)	264 (19)	127 (17)	0.92 (0.76 – 1.11)	0.3753	–	–

Values are median (interquartile range), n (%), or mean \pm SD.

[†]Variables with P<0.20 in univariate analyses or those of known clinical relevance were included in multivariable analyses, and only the variables included in the final model were reported in the multivariable columns. Treatment exposures were adjusted as a time-varying variable in all Cox proportional-hazards models.

[‡]High-efficacy DMTs include natalizumab, rituximab, ocrelizumab, ofatumumab, stem cell transplant, alemtuzumab, mitoxantrone, fingolimod, and cladribine.

[§]The baseline was set at the time of PIRA occurrence.

PIRA = Progression Independent Of Relapse Activity; DMT = Disease-Modifying Therapies; EDSS = Expanded Disability Status Scale.

Supplementary Figure 1 Time to non-persistent PIRA

