Online Supplement

Table S1
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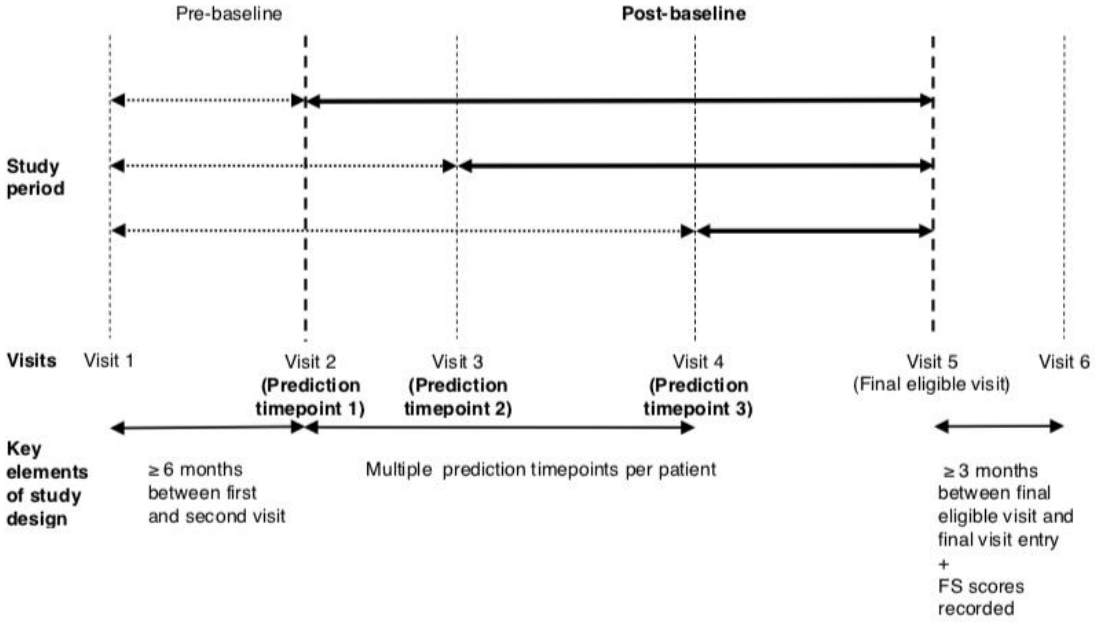
Table S2
Data quality procedure

- Duplicate patient records were removed.
- Centres with <10 patient records were excluded (irrespective of patients' inclusion in the study).
- Patients with missing date of birth were excluded.
- MS onset dates after the MSBase data extract date were removed.
- Patients with missing date of the first clinical presentation of MS were excluded.
- The dates of MS onset and the first recorded MS course were aligned.
- Patients with the age at onset outside the 0-100 range were excluded.
- A logical sequence of the MS courses (e.g. clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS) was assured.
- Entries with the initiation of progressive MS prior to its clinical onset of MS were excluded.
- Visits with missing visit date or the recorded date before the clinical MS onset or after the date of MSBase data extract were removed.
- EDSS scores outside the range of possible EDSS values were removed.
- Duplicate visits were merged.
- MS relapses with missing visit date or the recorded date after the date of MSBase data extract were removed.
- Duplicate MS relapses were merged.
- Relapses occurring within 30 days of each other were merged.
- Visits preceded by relapses were identified and time from the last relapse was calculated for each visit.
- Therapies were labelled as discontinued or continuing.
- Therapies with erroneous date entries were removed (e.g. commencement date > termination date, commencement after the MSBase data extract date, commencement of disease modifying therapy before the year 1980).
- MS disease modifying therapies were identified and labelled.
- Duplicate treatment entries were removed.
- Where multiple disease modifying therapies were recorded simultaneously, treatment end date of the previous therapy was imputed as the commencement date of the following therapy.
- Consecutive entries for certain disease modifying therapies were merged into a continuous treatment entry, given that the gap between the entries did not exceed 190 days for mitoxantrone, 365 days for cladribine, 90 days for other disease modifying therapies.
- The default duration of treatment effect was recorded as 190 days (mitoxantrone), 5 years (alemtuzumab) or 365 days (cladribine) from treatment commencement.

Figure S1
Illustration of study design



Each vertical line represents one visit entry where the minimum dataset and Expanded Disability Status Scale score was recorded. A 'prediction time point' was defined as any visit recorded during the relapsing remitting disease course with: (i) at least one visit entry at least six months prior and, (ii) at least two subsequent visits. At each prediction time point visit, the patient's risk of SPMS was re-evaluated using Cox models. The period between the first visit entry and each prediction time point was called the pre-baseline period (identified with thin arrows). The post-baseline period (identified with bold arrows) was defined as the time between each prediction time point and the final eligible visit (i.e. the last visit that was followed by an additional visit at least three months later). In this example, the patient had 6 recorded visits, and the risk of SPMS was evaluated at 3 of them.
FS: functional system; SPMS: secondary progressive multiple sclerosis

Definitions of the study variables

The age of the patient, disease duration, annualised relapse rate, number of relapses in the previous year, proportion of time on DMTs (pre- and post-baseline), annualised EDSS slope and frequency of visits during the post-baseline period were calculated at each prediction time point.

A relapse was defined as new symptoms or exacerbation of existing symptoms persisting for ≥24 hours, in the absence of concurrent illness/fever, and occurring ≥30 days after a previous relapse (Schumacher et al., Ann N Y Acad Sci 1965;122:552-68). Annualised relapse rate was calculated as the number of previous relapses divided by the duration of the pre-baseline period.

Disability was scored using EDSS by accredited EDSS scorers (Neurostatus certification was required at the participating centres), and scores obtained <30 days after a relapse were excluded. The annualised EDSS slope was calculated using the EDSS scores recorded over the pre-baseline period, fitted by a linear regression model. The date of symptom onset was included as an extra time point in this calculation, and was assigned an EDSS score of 0; this date was included so as to represent the day prior to the reported onset of the first MS symptoms. The annualised EDSS slope was then categorised into descriptions of the gradient: improving (gradient < -0.05 EDSS points per year); stable (gradient between -0.05 and 0.05 inclusive); slow worsening (gradient >0.05 and ≤0.24); and rapid worsening (gradient >0.24). These values were determined as follows: a caliper of 0.05 was chosen around the zero gradient to become the stable category; any negative gradient less than -0.05 was denoted to be an improving course; and the median of the remaining positive values (0.24 EDSS points per year) was used to differentiate slow from rapid worsening. These descriptions collectively were denoted as the annualised disability trajectory.

The time spent on DMT was defined by the treatment start and stop dates. The proportion of time on therapy was calculated as the length of time spent on therapy in the pre- or post-baseline period divided by either the disease duration (pre-baseline) or time between each prediction time point and the SPMS conversion date or the final eligible visit (post-baseline). Due to the relatively small number of patients treated with newer agents, the proportion of time spent on each therapy was not stratified based on efficacy.

Qualitative MRI information (i.e. presence or absence of new or enlarging T2 lesions or contrast-enhancing lesions) was recorded by neurologists in the participating centres. Recent brain MRI activity was defined as the presence of either new or enlarging T2 lesions or contrast-enhancing lesions over the 2 years preceding each prediction time point. To complete the sensitivity analyses, the presence or absence of T2 lesions in the brain over the past 2 years or in the spinal cord at any time, and the presence of oligoclonal bands in the CSF that were not mirrored in the serum at any time, were calculated.

Table S3
Number of included patients per centre (primary analysis)

Centre	Country	Patients
Hospital Fernandez, Capital Federal, Argentina	Argentina	71
INEBA - Institute of Neuroscience Buenos Aires, Buenos Aires, Argentina	Argentina	72
Instituto de Neurociencias Cordoba, Cordoba, Argentina	Argentina	2
Hospital Italiano, Buenos Aires, Argentina	Argentina	75
Sanatorio Allende, Cordoba, Argentina	Argentina	11
University of Western Australia, Nedlands, Australia	Australia	12
Brain and Mind Centre, Sydney, Australia	Australia	71
University of Melbourne, Melbourne, Australia	Australia	468
University Newcastle, Newcastle, Australia	Australia	310
Geelong Hospital, Geelong, Australia	Australia	29
St Vincents Hospital, Fitzroy, Melbourne, Australia	Australia	25
Monash Medical Centre, Melbourne, Australia	Australia	70
Liverpool Hospital, Sydney, Australia	Australia	25
Box Hill Hospital, Melbourne, Australia	Australia	445
Westmead Hospital, Sydney, Australia	Australia	84
Flinders University, Adelaide, Australia	Australia	159
University of Queensland, Brisbane, Australia	Australia	171
Townsville Hospital, Townsville, Australia	Australia	10
Royal Hobart Hospital, Hobart, Australia	Australia	17
The Alfred, Melbourne, Australia	Australia	54
Austin Health, Melbourne, Australia	Australia	14
Concord Repatriation General Hospital, Sydney, Australia	Australia	7
Royal Brisbane and Women's Hospital, Brisbane, Australia	Australia	18
Cliniques Universitaires Saint-Luc, Brussels, Belgium	Belgium	260
AZ Alma Ziekenhuis, Sijsele - Damme, Belgium	Belgium	10
Universitary Hospital Ghent, Ghent, Belgium	Belgium	6
Rehabilitation and MS-Centre Overpelt and Hasselt University, Hasselt, Belgium	Belgium	93
Universidade Metropolitana de Santos, Santos, Brazil	Brazil	39
CSSS Saint-Jérôme, Saint-Jerome, Canada	Canada	97
Jewish General Hospital, Montreal, Canada	Canada	59
Hopital Notre Dame, Montreal, Canada	Canada	1042
CISSS Chaudière-Appalache, Levis, Canada	Canada	600
Neuro Rive-Sud, Quebec, Canada	Canada	643
CIREN, Havana, Cuba	Cuba	94
General University Hospital and Charles University in Prague, Prague, Czech Republicech Republic	Czech Republic	1457
Nemocnice Jihlava, Jihlava, Czech Republicech Republic	Czech Republic	133
Kommunehospitalet, Arhus C, Denmark	Denmark	111
Hospital Universitario Virgen de Valme, Seville, Spain	Spain	146
Hospital Universitario Donostia, San Sebastián, Spain	Spain	64
Hospital Clinico San Carlos, Madrid, Spain	Spain	111
Hospital General Universitario de Alicante, Alicante, Spain	Spain	11
Hospital Universitario Virgen Macarena, Sevilla, Spain	Spain	825
Hospital de Galdakao-Usansolo, Galdakao, Spain	Spain	108
Hospital Germans Trias i Pujol, Badalona, Spain	Spain	218
Hospital Universitario de la Ribera, Alzira, Spain	Spain	21
Hospital Ramon y Cajal, Madrid, Spain	Spain	1
MS Clinic, Hopital Tenon, Paris, France	France	15
The Walton Centre for Neurology and Neurosurgery, Liverpool, United Kingdom	United Kingdom	1

Craigavon Area Hospital, Craigavon, United Kingdom	United Kingdom	30
Royal Victoria Hospital, Belfast, United Kingdom	United Kingdom	6
South East Trust, Belfast, United Kingdom	United Kingdom	43
Veszprém Megyei Csolnoky Ferenc Kórház zrt., Veszprem, Hungary	Hungary	8
Jahn Ferenc Teaching Hospital, Budapest, Hungary	Hungary	33
Semmelweis University Budapest, Budapest, Hungary	Hungary	9
University of Debrecen, Debrecen, Hungary	Hungary	18
Péterfy Sandor Hospital, Budapest, Hungary	Hungary	10
Josa András Hospital, Nyiregyhaza, Hungary	Hungary	6
Petz A. County Hospital , Gyor, Hungary	Hungary	6
Szent Imre Hospital, Budapest, Hungary	Hungary	7
University of Szeged, Szeged, Hungary	Hungary	9
St Vincent's University Hospital, Dublin, Ireland	Ireland	3
Assaf Harofeh Medical Center, Beer-Yaakov, Israel	Israel	75
Bombay Hospital Institute of Medical Sciences, Mumbai, India	India	27
PGIMER, Chandigarh, India	India	1
Isfahan University of Medical Sciences, Isfahan, Iran	Iran	16
University “G. d’Annunzio ”, Chieti, It	Italy	934
Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy	Italy	304
University of Bari, Bari, Italy	Italy	1102
University of Florence, Florence, Italy	Italy	109
C. Mondino National Neurological Institute, Pavia, Italy	Italy	274
Ospedali Riuniti di Salerno, Salerno, Italy	Italy	198
University of Parma, Parma, Italy	Italy	219
Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy	Italy	186
Azienda Ospedaliera Universitaria, Modena, Italy	Italy	575
Ospedale P. A. Micone, Genova, Italy	Italy	160
Amiri Hospital, Kuwait City, Kuwait	Kuwait	443
American University of Beirut Medical Center, Beirut, Lebanon	Lebanon	36
Clinical Centar-Neurology, Skopje, Macedonia	Macedonia	4
Clinic of Neurology Clinical Center, Skopje, Macedonia	Macedonia	22
Mater Dei Hospital, Balzan, Malta	Malta	22
HOSPItalyAL KUALA LUMPUR, Kuala Lumpur, Malaysia	Malaysia	1
University Hospital Nijmegen, Nijmegen, Netherlands	Netherlands	144
Francicus Ziekenhuis, Roosendaal, Netherlands	Netherlands	62
Zuyderland Ziekenhuis, Sittard, Netherlands	Netherlands	392
Groene Hart Ziekenhuis, Gouda, Netherlands	Netherlands	108
Hospital São João, Porto, Portugal	Portugal	191
Central Military Emergency University Hospital, Bucharest, Romania	Romania	8
King Fahad Specialist Hospital-Dammam, Khobar, Saudi Arabia	Saudi Arabia	19
Razi Hospital, Manouba, Tunisia	Tunisia	96
KTU Medical Faculty Farabi Hospital, Trabzon, Turkey	Turkey	339
19 Mayis University, Samsun, Turkey	Turkey	439
Hacettepe University, Ankara, Turkey	Turkey	14
Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey	Turkey	23
Dokuz Eylul University, Konak/Izmir, Turkey	Turkey	232
Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey	Turkey	132
Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey	Turkey	213
New York University Langone Medical Center, New York, United States	United States	24
TOTAL		**15717**

Table S4
List of disease modifying therapies included in the analysis

Disease modifying therapy	Number of patients
Rebif	2463
Natalizumab	2325
Fingolimod	2059
Avonex	1699
Copaxone	1529
Betaferon-Extavia	1485
Tecfidera	838
Mitoxantrone	578
Teriflunomide	324
Copaxone 40	125
Rituximab	68
Plegridy	52
Alemtuzumab	26
Cladribine	25
ASCT	20
Ocrelizumab	4
Siponimod	3
Total	**13623**

NB: If a patient was treated with more than one disease modifying therapy, only the highest efficacy agent was included in this table.

Table S5
Demographic of excluded cohort (n= 28,732)

	Count (%)	Mean (sd)	Median (quartiles)
Age, years		39.3 (12.8)	38.3 (29.6 , 48.3)
Sex, female	20 189 (70%)		
MS duration, years		7.6 (8.7)	4.4 (1.0, 11.3)
EDSS at first visit		2.8 (2.1)	2.0 (1.5 , 4.0)

NB:
1,048 patients had no visit data recorded
1,580 patients had no EDSS data recorded

Table S6: Effect of various factors on risk of secondary progressive multiple sclerosis – univariate analysis.

Variable	Hazard ratio	95% confidence interval	p value
DEMOGRAPHIC FEATURES			
Sex			
Female	Reference		
Male	1.15	0.98 - 1.33	0.079
Current age (years)	1.04	1.03 - 1.04	<0.001
Age of symptom onset (years)	1.02	1.01 - 1.03	0.034
Disease duration (years)	1.04	1.03 - 1.04	<0.001
CLINICAL FEATURES			
Disability, EDSS	1.44	1.40 - 1.48	<0.001
Annualised relapse rate	0.92	0.82 - 1.03	0.158
Relapses previous year	1.15	1.10 - 1.20	<0.001
Annualised EDSS slope	1.56	1.48 - 1.64	<0.001
Annualised disability trajectory[a]			
Stable	Reference		
Improving	0.52	0.34 - 0.82	<0.001
Slow worsening	3.45	2.64 - 4.51	<0.001
Rapid worsening	5.86	4.44 – 7.74	<0.001
Onset symptoms: Visual	0.90	0.77 - 1.06	0.212
Onset symptoms: Spinal cord	0.88	0.75 - 1.04	0.131
Onset symptoms: Brainstem	0.91	0.77 - 1.07	0.243
Onset symptoms: Supratentorial	1.10	0.95 - 1.27	0.226
Onset symptoms: Polysymptomatic	0.84	0.68 - 1.04	0.105
Proportion of time on therapy[b]	0.47	0.38 - 0.59	<0.001

Fitted with a univariate Cox regression model. Of the 15, 717 patients included in this analysis, 1,546 (10%) became secondarily progressive. Where $p \leq 0.20$, variables were included in the multivariable model (Fig. 3).

[a]'Annualised disability trajectory' is the annualised EDSS slope categorised into descriptions of the gradient: stable (gradient -0.05 - 0.05 EDSS steps per year), improving (<-0.05), slow worsening (0.05 – 0.24), rapid worsening (>0.24).
[b]'Proportion of time on therapy' is the length of time spent on any disease modifying therapy in the pre-baseline period divided by the disease duration.

Onset symptoms were treated as individual variables in the univariate analysis, with the hazard associated with the presence of the onset symptom being compared to the hazard of the absence of the symptom. Patients with multiple onset symptoms were counted both in the phenotype of the symptoms they experienced, and again in the polysymptomatic group.

EDSS: expanded disability status scale.