Supplemental

Sex impacts Treatment Decisions in Multiple Sclerosis

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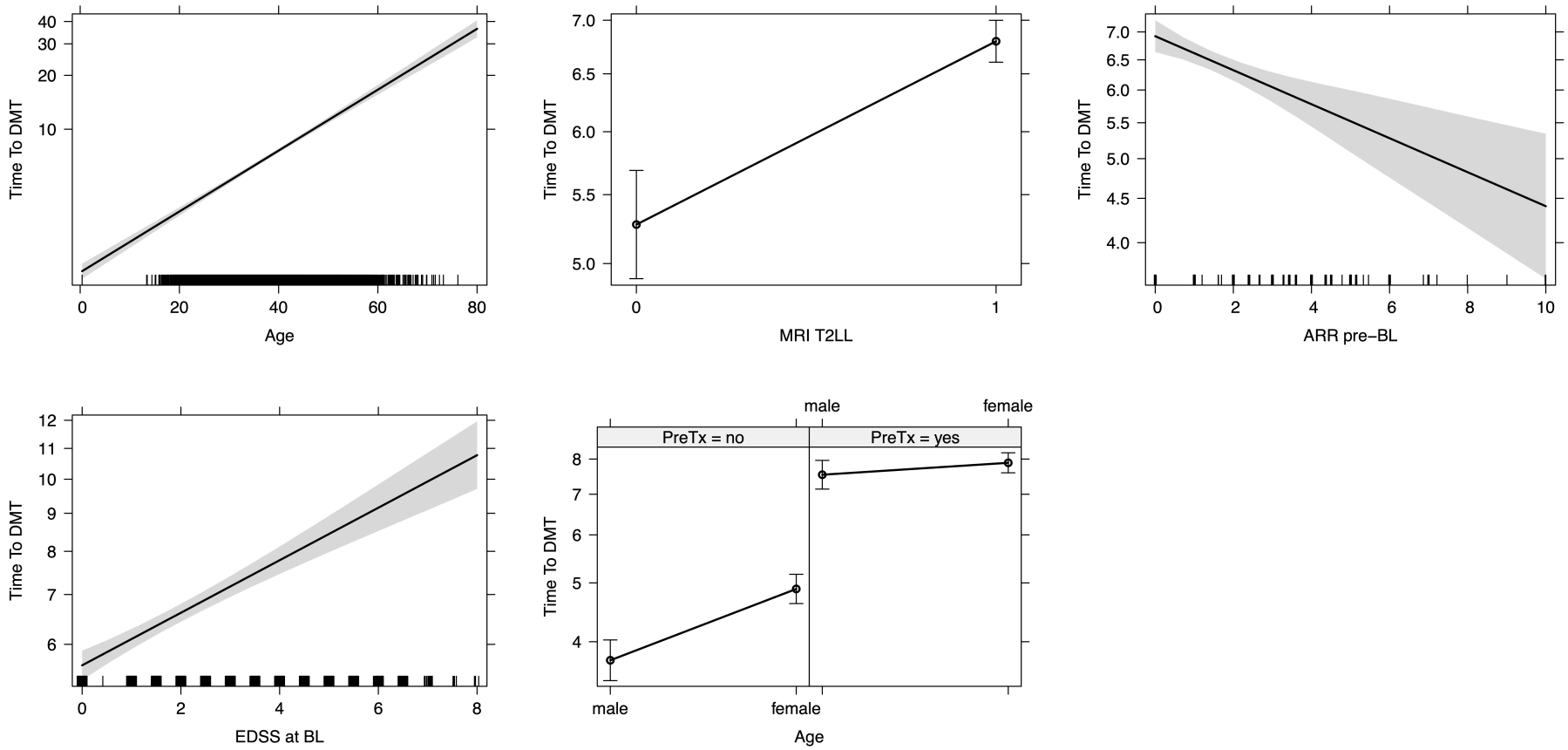
Figure e-1 Time to start of DMT in female and male pwMS depending on different disease activity measures.



Legend:

Pre-treatment included interferon-beta and/ or glatiramer acetate.

Abbreviations: ARR, annualized relapse rate; BL, baseline; DMT, disease-modifying treatment; moderate-efficacy DMT, mDMT; MRI, magnetic resonance imaging; preTX, pre-treatment; T2LL, T2 lesions load

Table e-1: Demographics and clinical characteristics in pwMS depending on sex (*total cohort*)

	All	**Female**	**Male**
Number	4224	2905	1319
Age (years)	36.5 (28.9 – 45.0)	36.3 (28.7 – 44.7)	37.1 (29.5 – 45.4)
Disease duration (years)	5.9 (2.2 – 11.7)	6.0 (2.3 – 11.9)	5.6 (1.9 – 10.9)
Year of disease onset	2008 (2002-2013)	2007 (2001-2013)	2008 (2003-2013)
Pre-ARR[†,‖]	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)
EDSS[§]	2 (1 – 3)	2 (1 – 3)	2 (1 – 3.5)
MRI T2LL[§] (>9), n (%)[‖]	3738 (88.5)	2567 (88.4)	1171 (88.8)
Pre-treatment[¶], n (%)	2989 (70.8)	2088 (71.9)	901 (68.3)
DMT, n (%)			
Dimethyl fumarate	1045 (24.7)	716 (24.6)	329 (24.9)
Teriflunomide	387 (9.2)	246 (8.5)	141 (10.7)
Fingolimod	1145 (27.1)	792 (27.3)	353 (26.8)
Natalizumab	1490 (35.3)	1058 (36.4)	432 (32.8)
Ocrelizumab	87 (2.1)	44 (1.5)	43 (3.3)
Cladribine	38 (0.9)	29 (1.0)	9 (0.7)
Alemtuzumab	32 (0.8)	20 (0.7)	12 (0.9)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline).
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.
[‖] Missing values: Pre-ARR, n=3; MRT T2LL, n=33.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment, MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-2: Logistic regression analysis identifying predictors of highly effective DMT.

	Coefficient	**SE**	**P value**	**95% CI**		**OR**
Constant	-1.890	0.212	**<0.001**	-2.309	-1.476	0.151
Sex (female, ref: male)	-0.002	0.086	0.979	-0.172	0.166	0.998
Age [years]	-0.043	0.005	**<0.001**	-0.051	-0.034	0.958
Disease duration [years]	0.006	0.007	0.381	-0.007	0.019	1.006
Pre-ARR[†]	1.000	0.053	**<0.001**	0.898	1.106	2.719
EDSS[§]	0.511	0.033	**<0.001**	0.447	0.576	1.666
MRI T2LL[§] (>9, ref: ≤9)	0.740	0.125	**<0.001**	0.496	0.985	2.095
Pre-treatment[¶] (yes, ref: no)	1.571	0.088	**<0.001**	1.400	1.744	4.813

Cox Snell: 0.427

Legend:
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.
[ ] shows units and () indicates reference categories.
Bold p-values hold with Bonferroni-Holm correction.

Abbreviations: ARR, annualized relapse rate; CI, confidence interval; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; OR, Odds ratio; ref, reference; SE, standard error; T2LL, T2 lesions load

Table e-3: Gamma regression analysis identifying predictors of time to DMT.

	Estimate	SE	P value	95% CI		Exp(Estimate)
Constant	-0.456	0.069	**<0.001**	-0.596	-0.316	0.634
Sex (female, ref: male)	0.271	0.048	**<0.001**	0.176	0.365	1.311
Age [years]	0.039	0.001	**<0.001**	0.037	0.042	1.040
Pre-ARR[†]	-0.045	0.011	**<0.001**	-0.067	-0.023	0.956
EDSS[§]	0.081	0.009	**<0.001**	0.064	0.098	1.085
MRI T2LL[§] (>9, ref: ≤9)	0.253	0.040	**<0.001**	0.174	0.332	1.288
Pre-treatment[¶] (yes, ref: no)	0.704	0.048	**<0.001**	0.610	0.797	2.022
Sex : Pre-treatment	-0.225	0.058	**<0.001**	-0.339	-0.112	0.798

Cox Snell: 0.312

Legend:

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.
[ ] shows units and () indicates reference categories.
Bold p-values hold with Bonferroni-Holm correction.

Abbreviations: ARR, annualized relapse rate; CI, confidence interval; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; ref, reference; SE, standard error; T2LL, T2 lesions load
Note: Exp(estimate) gives the factor change in the expected value of y when x changes by 1 unit

Table e-4: Demographics and clinical characteristics in pwMS depending on treatment escalation (*Question 1*).

DMT escalation			
	All	**Escalation**	**No Escalation**
Number	1211	149	1062
Sex (female), n (%)	799 (66.0)	96 (64.4)	703 (66.2)
Age (years)	37.6 (29.9 – 46.1)	35.6 (27.7 – 42.8)	38.2 (30.1 – 46.6)
Disease duration (years)	4.1 (1.1 – 10.5)	3.4 (1.0 – 9.8)	4.3 (1.1 – 10.6)
Year of disease onset	2013 (2006-2016)	2013 (2006-2015)	2013 (2006-2017)
Pre-ARR[†]	1 (0 – 1)	1 (1 – 2)	1 (0 – 1)
EDSS[§]	1.5 (1 – 2)	1.5 (1 – 2)	1.5 (1 – 2)
MRI T2LL[§] (>9), n (%)	998 (82.4)	125 (83.9)	873 (82.2)
Pre-treatment[¶], n (%)	577 (47.6)	75 (50.3)	502 (47.3)
DMT, n (%)			
Dimethyl fumarate	881 (72.7)	99 (66.4)	782 (73.6)
Teriflunomide	330 (27.3)	50 (33.6)	280 (26.4)
Time to DMT escalation (or observation period in pwMS without escalation)	1.99 (0.96 – 3.41)	1.39 (0.71 – 2.45)	2.10 (1.01 – 3.60)
ARR on DMT[‡]	0.21 (0.51)	0.76 (0.90)	0.13 (0.38)
EDSS Progression, n (%)	225 (18.6)	61 (40.9)	164 (15.4)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline). ARR was calculated as the number of relapses divided by the observation period in years.

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate., [‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-5: Demographics and clinical characteristics depending on sex in pwMS escalating or continuing DMT (*Question 1*).

	All	**Female**	**Male**
Number	1211	799	412
Age (years)	37.6 (29.9 – 46.1)	37.9 (30.2 – 46.0)	37.2 (29.6 – 46.3)
Disease duration (years)	4.1 (1.1 – 10.5)	4.6 (1.2 – 11.3)	3.4 (1.0 – 9.1)
Year of disease onset	2013 (2006-2016)	2012 (2006-2016)	2013 (2008-2017)
Pre-ARR[†]	1 (0 – 1)	1 (0 – 1)	1 (1 – 1)
EDSS[§]	1.5 (1 – 2)	1.5 (1 – 2)	1.5 (1 – 2)
MRI T2LL[§] (>9), n (%)	998 (82.4)	656 (82.1)	342 (83.0)
Pre-treatment[¶], n (%)	577 (47.6)	393 (49.2)	184 (44.7)
DMT, n (%)			
Dimethyl fumarate	881 (72.7)	591 (73.9)	290 (70.4)
Teriflunomide	330 (27.3)	208 (26.0)	122 (29.6)
Time to DMT escalation (or observation period in pwMS without escalation)	1.99 (0.96 – 3.41)	1.94 (0.96-3.41)	2.12 (0.98-3.41)
ARR on DMT[‡]	0.21 (0.51)	0.21 (0.52)	0.22 (0.50)
EDSS Progression, n (%)	225 (18.6)	150 (18.8)	75 (18.2)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline).
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.
[‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment, EDSS, Expanded Disability Status Scale, MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-6: Demographics and clinical characteristics in pwMS discontinuing moderate-efficacy DMT (*Question 2*).

mDMT discontinuation			
	All	**Discontinuation**	**No Discontinuation**
Number	862	73	789
Sex (female), n (%)	578 (67.1)	59 (80.8)	519 (65.8)
Age (years)	38.6 (30.4 – 46.8)	35.9 (26.7 – 49.3)	38.8 (31.0 – 46.5)
Disease duration (years)	4.8 (1.3 – 10.9)	5.2 (1.7 – 9.6)	4.8 (1.3 – 10.9)
Year of disease onset	2012 (2006-2015)	2011 (2007-2014)	2012 (2006-2015)
Pre-ARR[†]	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)
EDSS[§]	1.5 (1.0 – 2.0)	2.0 (1.0 – 2.5)	1.5 (1.0 – 2.0)
MRI T2LL[§] (>9), n (%)	719 (83.4)	61 (83.6)	658 (83.4)
Pre-treatment[¶], n (%)	434 (50.3)	43 (58.9)	391 (49.6)
DMT, n (%)			
Dimethyl fumarate	640 (74.2)	58 (79.5)	582 (73.8)
Teriflunomide	222 (25.8)	15 (20.5)	207 (26.2)
Time to DMT discontinuation (or observation period in pwMS without discontinuation)	2.7 (1.8 – 4.0)	2.4 (1.9 – 3.4)	2.7 (1.8 – 4.1)
ARR on DMT[‡]	0.11 (0.26)	0.06 (0.19)	0.12 (0.27)
EDSS progression, n (%)	65 (7.5)	12 (16.4)	53 (6.7)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline). ARR was calculated as the number of relapses divided by the observation period in years.

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate., [‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; mDMT, moderate-efficacy DMT; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-7: Demographics and clinical characteristics depending on sex in pwMS stopping or continuing moderate-efficacy DMT (*Question 2*).

	All	**Female**	**Male**
Number	862	578	284
Age (years)	38.6 (30.4 – 46.8)	38.5 (30.2 – 46.2)	38.8 (30.9 – 47.9)
Disease duration (years)	4.8 (1.3 – 10.9)	5.3 (1.5 – 11.3)	4.0 (1.1 – 9.8)
Year of disease onset	2012 (2006-2015)	2011 (2005-2015)	2012 (2007-2016)
Pre-ARR[†]	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)
EDSS[§]	1.5 (1.0 – 2.0)	1.5 (1.0 – 2.0)	1.5 (1.0 – 2.0)
MRI T2LL[§] (>9), n (%)	719 (83.4)	484 (83.7)	235 (82.7)
Pre-treatment[¶], n (%)	434 (50.3)	299 (51.7)	135 (47.5)
DMT, n (%)			
Dimethyl fumarate	640 (74.2)	433 (74.9)	207 (72.9)
Teriflunomide	222 (25.8)	145 (25.1)	77 (27.1)
Time to DMT discontinuation (or observation period in pwMS without discontinuation)	2.7 (1.8 – 4.0)	2.6 (1.7-4.1)	2.8 (2.0-4.0)
ARR on DMT[‡]	0.11 (0.26)	0.12 (0.27)	0.10 (0.24)
EDSS progression, n (%)	65 (7.5)	44 (7.6)	21 (7.4)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline). ARR was calculated as the number of relapses divided by the observation period in years.

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate. [‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; mDMT, moderate-efficacy DMT; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-8: Reasons for discontinuation of moderate-efficacy DMT depending on sex (*Question 2*).

	All	**Female**	**Male**
Family planning	24 (33)	24 (100)	0 (0)
Patient's request	19 (26)	15 (79)	4 (21)
Disease stability	8 (11)	6 (75)	2 (25)
Disease progression	5 (7)	1 (20)	4 (80)
Adverse events	17 (23)	15 (88)	2 (12)

Legend:
Data are shown as number (percentage).

Abbreviations: DMT, disease-modifying treatment

Table e-9: Demographics and clinical characteristics in pwMS depending in treatment de-escalation (*Question 3*).

DMT de-escalation			
	All	**De-escalation**	**No de-escalation**
Number	1836	78	1758
Sex (female), n (%)	1268 (69.1)	48 (61.5)	1220 (69.4)
Age (years)	35.8 (28.3 – 43.4)	34.1 (29.5 – 44.7)	35.8 (28.2 – 43.4)
Disease duration (years)	6.8 (3.2 – 12.3)	7.5 (3.9 – 13.0)	6.8 (3.2 – 12.2)
Year of disease onset	2006 (2000-2010)	2003 (2000-2009)	2006 (2000-2010)
Pre-ARR[†]	2 (1 – 2)	2 (1 – 2)	2 (1 – 2)
EDSS[§]	2.5 (1.5 – 3.5)	2 (1.5 – 3)	2.5 (1.5 – 3.5)
MRI T2LL[§] (>9), n (%)	1696 (92.4)	73 (93.6)	1623 (92.3)
Pre-treatment[¶], n (%)	1573 (85.7)	70 (89.7)	1503 (85.5)
DMT, n (%)			
Fingolimod	829 (45.2)	29 (37.2)	800 (45.5)
Natalizumab	1007 (54.8)	49 (62.8)	958 (54.5)
Time to de-escalation (or observation period in pwMS without de-escalation)	5.53 (3.24 – 7.89)	4.26 (2.21 – 6.84)	5.59 (3.30 – 7.92)
ARR on DMT[‡]	0.16 (0.29)	0.16 (0.26)	0.16 (0.29)
EDSS progression, n (%)	629 (34.3)	20 (25.6)	609 (34.6)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline). ARR was calculated as the number of relapses divided by the observation period in years.

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate., [‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-10: Demographics and clinical characteristics depending on sex in pwMS de-escalating or continuing DMT (*Question 3*).

	All	**Female**	**Male**
Number	1836	1268	568
Age (years)	35.8 (28.3 – 43.4)	36.3 (28.4 – 43.7)	34.4 (28.0 – 42.9)
Disease duration (years)	6.8 (3.2 – 12.3)	7.2 (3.2 – 12.9)	6.1 (3.0 – 11.0)
Year of disease onset	2006 (2000-2010)	2005 (1999-2010)	2006 (2002-2010)
Pre-ARR[†]	2 (1 – 2)	2 (1 – 2)	2 (1 – 2)
EDSS[§]	2.5 (1.5 – 3.5)	2 (1.5 – 3.5)	2.5 (1.5 – 3.5)
MRI T2LL[§] (>9), n (%)	1696 (92.4)	1172 (92.4)	524 (92.3)
Pre-treatment[¶], n (%)	1573 (85.7)	1087 (85.7)	486 (85.6)
DMT, n (%)			
Fingolimod	829 (45.2)	564 (44.5)	265 (46.7)
Natalizumab	1007 (54.8)	704 (55.5)	303 (53.3)
Time to de-escalation (or observation period in pwMS without de-escalation)	5.53 (3.24 – 7.89)	5.58 (3.20-7.97)	5.51 (3.33-7.55)
ARR on DMT[‡]	0.16 (0.29)	0.17 (0.31)	0.14 (0.24)
EDSS progression, n (%)	629 (34.3)	429 (33.8)	200 (35.2)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline). ARR was calculated as the number of relapses divided by the observation period in years.

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate. [‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-11: Demographics and clinical characteristics in pwMS discontinuing high-efficacy DMT (*Question 4*).

hDMT discontinuation			
	All	**Discontinuation**	**No Discontinuation**
Number	1941	231	1710
Sex (female), n (%)	1370 (70.6)	186 (80.5)	1184 (69.2)
Age (years)	35.7 (28.2 – 43.6)	33.9 (28.0 – 43.8)	35.8 (28.2 – 43.5)
Disease duration (years)	6.8 (3.1 – 12.2)	6.6 (2.9 – 10.9)	6.8 (3.2 – 12.3)
Year of disease onset	2006 (2000-2010)	2005 (2000-2009)	2006 (2000-2010)
Pre-ARR[†]	2 (1 – 2)	2 (1 – 3)	2 (1 – 2)
EDSS[§]	2.5 (1.5 – 3.5)	2.5 (1.5 – 4.0)	2.3 (1.5 – 3.5)
MRI T2LL[§] (>9), n (%)	1796 (92.5)	217 (93.9)	1579 (92.3)
Pre-treatment[¶], n (%)	1660 (85.5)	197 (85.3)	1463 (85.6)
DMT, n (%)			
Natalizumab	1074 (55.3)	158 (68.4)	916 (53.6)
Fingolimod	867 (44.7)	73 (31.6)	794 (46.4)
Time to DMT discontinuation (or observation period in pwMS without discontinuation)	5.36 (3.08 – 7.72)	2.92 (1.95 – 5.09)	5.63 (3.32 – 7.92)
ARR on DMT[‡]	0.18 (0.34)	0.33 (0.59)	0.16 (0.29)
EDSS progression, n (%)	318 (16.4)	71 (30.7)	247 (14.4)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline). ARR was calculated as the number of relapses divided by the observation period in years.

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate., [‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment, EDSS, Expanded Disability Status Scale; hDMT, high-efficacy DMT; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-12: Demographics and clinical characteristics depending on sex in pwMS stopping or continuing high-efficacy DMT (*Question 4*).

	All	**Female**	**Male**
Number	1941	1370	571
Age (years)	35.7 (28.2 – 43.6)	35.9 (28.3 – 43.5)	34.7 (28.0 – 43.8)
Disease duration (years)	6.8 (3.1 – 12.2)	7.1 (3.2 – 12.7)	6.2 (3.0 – 11.0)
Year of disease onset	2006 (2000-2010)	2005 (1999-2010)	2006 (2002-2010)
Pre-ARR[†]	2 (1 – 2)	2 (1 – 2)	2 (1 – 2)
EDSS[§]	2.5 (1.5 – 3.5)	2.0 (1.5 – 3.5)	2.5 (1.5 – 3.5)
MRI T2LL[§] (>9), n (%)	1796 (92.5)	1268 (92.6)	528 (92.5)
Pre-treatment[¶], n (%)	1660 (85.5)	1171 (85.5)	489 (85.6)
DMT, n (%)			
Natalizumab	1074 (55.3)	767 (56.0)	307 (53.8)
Fingolimod	867 (44.7)	603 (44.0)	264 (46.2)
Time to DMT discontinuation (or observation period in pwMS without discontinuation)	5.36 (3.08 – 7.72)	5.28 (2.97-7.74)	5.46 (3.34-7.52)
ARR on DMT[‡]	0.18 (0.34)	0.19 (0.37)	0.15 (0.26)
EDSS progression, n (%)	318 (16.4)	216 (15.8)	102 (17.9)

Legend:
Data are shown as median (IQR) unless otherwise specified. Disease duration was the time between symptom onset and inclusion into registry, i.e. DMT start (baseline). ARR was calculated as the number of relapses divided by the observation period in years.

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate. [‡] Mean (SD) is shown.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; T2LL, T2 lesions load

Table e-13: Reasons for discontinuation of high-efficacy DMT depending on sex (*Question 4*).

	All	**Female**	**Male**
Family planning	74 (32)	74 (100)	0 (0)
JCV positivity	32 (14)	25 (78)	7 (22)
Patient's request	43 (19)	31 (72)	12 (28)
Disease stability	3 (1)	2 (67)	1 (33)
Disease progression	31 (13)	21 (68)	10 (32)
Adverse events	31 (13)	23 (74)	8 (26)
PML	7 (3)	6 (86)	1 (14)
Neutralizing antibodies	1 (0.4)	1 (100)	0 (0)
Other	9 (4)	3 (33)	6 (67)

Legend:
Data are shown as number (percentage).

Abbreviations: DMT, disease-modifying treatment; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy

Table e-14: Cox regression analysis in a subgroup of pwMS excluding females with family planning for identifying predictors of early moderate-efficacy DMT discontinuation.

	Coefficient	**SE**	**P value**
Sex (female, ref: male)	0.736	0.421	0.081
Age [years]	0.098	0.030	**<0.001**
Disease duration [years]	-0.039	0.022	0.075
Pre-ARR[†]	-0.176	0.213	0.410
EDSS[§]	0.059	0.111	0.595
MRI T2LL[§] (>9, ref: ≤9)	-0.184	0.404	0.649
Pre-treatment[¶] (yes, ref: no)	0.219	0.314	0.487
DMT (DMF, ref: TER)	0.734	0.350	0.036
ARR on DMT	-1.674	1.019	0.100
EDSS progression (yes, ref: no)	0.970	0.381	0.012
Sex : Age	-0.062	0.032	0.052

Legend:
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.
[ ] shows units and () indicates reference categories.
Bold p-values hold with Bonferroni-Holm correction.

Abbreviations: ARR, annualized relapse rate; DMF, dimethyl fumarate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; SE, standard error; T2LL, T2 lesions load; TER, teriflunomide

Table e-15: Cox regression analysis in the subgroup of pwMS excluding females with family planning for identifying predictors of early high-efficacy DMT discontinuation.

	Coefficient	**SE**	**P value**
Sex (female, ref: male)	0.040	0.181	0.825
Age [years]	0.028	0.009	0.003
Disease duration [years]	-0.008	0.013	0.539
Pre-ARR[†]	0.010	0.071	0.885
EDSS[§]	0.226	0.055	**<0.001**
MRI T2LL[§] (>9, ref: ≤9)	0.220	0.391	0.573
Pre-treatment[¶] (yes, ref: no)	-0.215	0.240	0.370
DMT (NTZ, ref: FTY)	0.204	0.200	0.309
ARR on DMT[#]	0.044	0.339	0.897
EDSS progression (yes, ref: no)	0.717	0.173	**<0.001**

Legend:

[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.
[#] Additionally, interaction between the variable "ARR on DMT" and different "reasons for DMT stop" (adverse events and patient request) was considered due to confounding.
[ ] shows units and () indicates reference categories.
Bold p-values hold with Bonferroni-Holm correction.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; FTY, fingolimod; MRI, magnetic resonance imaging; NTZ, natalizumab; ref, reference; SE, standard error; T2LL, T2 lesions load

Table e-16: Sensitivity analysis in pwMS escalating or continuing DMT (*Question 1*) according to start of DMT.

	Whole cohort			**After 2015**
	Coefficient	**95%-CI**		**Coefficient**
Age [years]	-0.021	-0.041	-0.001	-0.024
EDSS[§]	0.144	0.003	0.286	0.139
ARR on DMT	2.117	1.779	2.455	2.013
Sex : ARR on DMT	-0.708	-1.073	-0.344	-0.636
EDSS progression (yes, ref: no)	0.417	0.069	0.765	0.515
MRI activity during DMT (yes, ref: no)	3.166	2.546	3.786	3.286

Legend:
For this sensitivity analysis, the cohort of patients were used when inclusion into the AMSTR was after January, 1st 2015. For patients before 2015, separate analysis is not shown due to sample size limits.
Absolute numbers of events (DMT escalation from TER or DMF) was low before 2015, as both DMT have been approved not before 2013 and 2014, respectively. Note that the percentage of events (DMT escalation) was similar before/ after January, 1st 2015: 17/112 (15%) vs. 132/1099 (12%).
§ This variable was assessed at baseline.
[ ] shows units and () indicates reference categories.

Abbreviations: ARR, annualized relapse rate; CI, confidence interval; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.

Table e-17: Sensitivity analysis in pwMS discontinuing moderate-efficacy DMT (*Question 2*) according to start of DMT.

	Whole cohort			**After 2015**
	Coefficient	**95%-CI**		**Coefficient**
Sex (female, ref: male)	1.214	0,421	2,007	1.303
Age [years]	0.087	0,032	0,142	0.057
ARR on DMT	-1.674	-3,287	-0,060	-1.312
EDSS progression (yes, ref: no)	0.773	0,131	1,416	0.833
Sex : Age	-0.112	-0,170	-0,055	-0.090

Legend:
For this sensitivity analysis, the cohort of patients were used when inclusion into the AMSTR was after January, 1st 2015. For patients before 2015, separate analysis is not shown due to sample size limits.
Absolute numbers of events (discontinuation of TER or DMF) was low before 2015, as both DMT have been approved not before 2013 and 2014, respectively. Note that the percentage of events (DMT discontinuation) was similar before/ after January, 1st 2015: 10/95 (11%) vs. 63/767 (8%).
[ ] shows units and () indicates reference categories.

Abbreviations: ARR, annualized relapse rate; CI, confidence interval; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale.

Table e-18: Sensitivity analysis in pwMS de-escalating or continuing high-efficacy DMT (*Question 3*) according to start of DMT.

	Whole cohort			**Before 2015**
	Coefficient	**95%-CI**		**Coefficient**
EDSS progression (yes, ref: no)	-0.719	-1.240	-0.197	-0.653

Legend:
For this sensitivity analysis, the cohort of patients were used when inclusion into the AMSTR was before January, 1st 2015. For patients after 2015, separate analysis is not shown due to sample size limits.
Note that the percentage of events (DMT de-escalation) was similar before/ after January, 1st 2015: 67/1318 (5%) vs. 11/518 (2%)
() indicates reference categories.

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale.

Table e-19: Sensitivity analysis in pwMS discontinuing high-efficacy DMT (*Question 4*) according to start of DMT.

	Whole cohort			**Before 2015**
	Coefficient	**95%-CI**		**Coefficient**
Sex (female, ref: male)	0.542	0.211	0.873	0.648
EDSS[§]	0.163	0.070	0.255	0.185
ARR on DMT	-0.958	-1.697	-0.217	-0.549
EDSS progression (yes, ref: no)	0.634	0.337	0.932	0.686

Legend:
For this sensitivity analysis, the cohort of patients were used when inclusion into the AMSTR was before January, 1st 2015. For patients after 2015, separate analysis is not shown due to sample size limits.
Note that the percentage of events (DMT escalation) was lower after January, 1st 2015: 37/542 (7%) vs. 194/1399 (14%).
() indicates reference categories.

Abbreviations: ARR, annualized relapse rate; CI, confidence interval; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale

Table e-20: A posteriori power analyses for the multivariable Cox regression identifying predictors of DMT escalation (*Question 1*).

	Coefficient	**HR**	**Sig.**	**A posteriori power**	**Sample size for a power of 0.8**
Sex (female, ref: male)	0.446	1.562		0.8	1340
Age [years]	-0.021	0.979	*		
Disease duration [years]	-0.025	0.975		0.6	2162
Pre-ARR[†]	0.004	1.004		effect size of this co-variable not clinically relevant	
EDSS[§]	0.144	1.155	*		
MRI T2LL[§] (>9, ref: ≤9)	-0.021	0.979		effect size of this co-variable not clinically relevant	
Pre-treatment[¶] (yes, ref: no)	0.017	1.017		effect size of this co-variable not clinically relevant	
DMT (DMF, ref: TER)	-0.043	0.958		effect size of this co-variable not clinically relevant	
ARR on DMT	2.117	8.309	***		
Sex : ARR on DMT	-0.708	0.493	***		
EDSS progression (yes, ref: no)	0.417	1.517			
MRI activity during DMT (yes, ref: no)	3.166	23.709	***		

Legend:
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.

*, **, *** shows statistical significance at a p value <0.05, <0.01 and <0.001.
[ ] shows units and () indicates reference categories.
":" denotes interaction effects between variables.

Abbreviations: ARR, annualized relapse rate; DMF, dimethyl fumarate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MRI, magnetic resonance imaging; Sig., Significance; T2LL, T2 lesions load; TER, teriflunomide

Table e-21: A posteriori power analyses for the multivariable Cox regression identifying predictors of moderate-efficacy DMT discontinuation (*Question 2*).

	Coefficient	**HR**	**Sig.**	**A posteriori power**	**Sample size for a power of 0.8**
Sex (female, ref: male)	1.214	3.366	**		
Age [years]	0.087	1.091	**		
Disease duration [years]	-0.031	0.970		0.5	2032
DMT (DMF, ref: TER)	0.617	1.853		0.7	1115
Pre-ARR[†]	-0.027	0.973		effect size of this co-variable not clinically relevant	
EDSS[§]	0.132	1.141		0.4	3179
MRI T2LL[§] (>9, ref: ≤9)	-0.032	0.968		effect size of this co-variable not clinically relevant	
Pre-treatment[¶] (yes, ref: no)	0.337	1.400		0.4	2959
ARR on DMT	-1.674	0.188	*		
EDSS progression (yes, ref: no)	0.773	2.167	*		
Sex : Age	-0.112	0.894	***		

Legend:
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.

*, **, *** shows statistical significance at a p value <0.05, <0.01 and <0.001.
[ ] shows units and () indicates reference categories.
":" denotes interaction effects between variables.

Abbreviations: ARR, annualized relapse rate; DMF, dimethyl fumarate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; Sig., Significance; T2LL, T2 lesions load; TER, teriflunomide

Table e-22: A posteriori power analyses for the multivariable Cox regression identifying predictors of DMT de-escalation (*Question 3*).

	Coefficient	**HR**	**Sig.**	**A posteriori power**	**Sample size for a power of 0.8**
Sex (female, ref: male)	-0.385	0.680		0.5	4648
Age [years]	0.014	1.014		effect size of this co-variable not clinically relevant	
Disease duration [years]	0.008	1.008		effect size of this co-variable not clinically relevant	
Pre-ARR[†]	-0.060	0.942		effect size of this co-variable not clinically relevant	
EDSS[§]	-0.069	0.933		effect size of this co-variable not clinically relevant	
MRI T2LL[§] (>9, ref: ≤9)	0.076	1.079		effect size of this co-variable not clinically relevant	
Pre-treatment[¶] (yes, ref: no)	0.119	1.126		effect size of this co-variable not clinically relevant	
DMT (NTZ, ref: FTY)	-0.058	0.943		effect size of this co-variable not clinically relevant	
ARR on DMT	0.292	1.339		effect size of this co-variable not clinically relevant	
EDSS progression (yes, ref: no)	-0.719	0.487	**		

Legend:
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.

*, **, *** shows statistical significance at a p value <0.05, <0.01 and <0.001.
[ ] shows units and () indicates reference categories.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; FTY, fingolimod; HR, hazard ratio; MRI, magnetic resonance imaging; NTZ, natalizumab; pwMS, people with multiple sclerosis; Sig., Significance; T2LL, T2 lesions load

Table e-23: A posteriori power analyses for the multivariable Cox regression identifying predictors of high-efficacy DMT discontinuation (*Question 4*).

	Coefficient	**HR**	**Sig.**	**A posteriori power**	**Sample size for a power of 0.8**
Sex (female, ref: male)	0.542	1.719	**		
Age [years]	0.001	1.001		effect size of this co-variable not clinically relevant	
Disease duration [years]	-0.021	0.979		0.6	3709
Pre-ARR[†]	-0.034	0.966		effect size of this co-variable not clinically relevant	
EDSS[§]	0.163	1.176	***		
MRI T2LL[§] (>9, ref: ≤9)	0.030	1.031		effect size of this co-variable not clinically relevant	
Pre-treatment[¶] (yes, ref: no)	-0.235	0.791		0.3	7807
DMT (NTZ, ref: FTY)	-0.009	0.991		effect size of this co-variable not clinically relevant	
ARR on DMT	-0.957	0.384	*		
EDSS progression (yes, ref: no)	0.634	1.886	***		

Legend:
[§] These variables were assessed at baseline. [†] ARR was determined in the 12 months prior to baseline. [¶] Pre-treatment included interferon-beta and/ or glatiramer acetate.

*, **, *** shows statistical significance at a p value <0.05, <0.01 and <0.001.
[ ] shows units and () indicates reference categories.

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; FTY, fingolimod; HR, hazard ratio; MRI, magnetic resonance imaging; NTZ, natalizumab; pwMS, people with multiple sclerosis; Sig., Significance; T2LL, T2 lesions load