Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis

Benjamin Turner, Bruce a C Cree, Ludwig Kappos, Xavier Montalban,
Caroline Papeix, Jerry S Wolinsky, Regine Buffels, Damian Fiore, Hideki
Garren, Jian Han, et al.

HAL Id: hal-04465305
https://hal.sorbonne-universite.fr/hal-04465305

Submitted on 19 Feb 2024

ORIGINAL COMMUNICATION

Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis

Benjamin Turner[1] · Bruce A. C. Cree[2] · Ludwig Kappos[3] · Xavier Montalban[4,5] · Caroline Papeix[6] · Jerry S. Wolinsky[7] · Regine Buffels[8] · Damian Fiore[9] · Hideki Garren[9] · Jian Han[9] · Stephen L. Hauser[2]

Abstract

Objective The efficacy and safety of ocrelizumab, versus interferon (IFN) β-1a, for the treatment of relapsing multiple sclerosis (RMS) from the identically designed OPERA I (NCT01247324) and OPERA II (NCT01412333) phase III studies has been reported; here we present subgroup analyses of efficacy endpoints from the pooled OPERA I and OPERA II populations.

Methods Patients with RMS were randomized to either ocrelizumab 600 mg administered by intravenous infusion every 24 weeks or subcutaneous IFN β-1a 44 μg three times per week throughout the 96-week treatment period. Relapse, disability, and MRI outcomes were analyzed for predefined and post hoc subgroups based on demographic and disease characteristics along with prior treatment using appropriate statistical tests to determine the treatment effect in subgroups and treatment-by-subgroup interactions.

Results The significant treatment benefit of ocrelizumab, versus IFN β-1a, observed in the overall OPERA I and OPERA II pooled populations was maintained across most subgroup strata for all endpoints, including annualized relapse rate, disability progression, and MRI outputs.

Conclusions The treatment effect of ocrelizumab versus IFN β-1a, measured by clinical and MRI outcomes, was maintained across most of the subgroups and strata of interest, and the pattern of treatment benefit across all subgroups was consistent with that from the pooled OPERA studies.

Keywords Relapsing · Multiple sclerosis · Ocrelizumab · Subgroup · Interferon β-1a · Phase 3

Introduction

The efficacy and safety of ocrelizumab, a humanized CD20+ B-cell selective monoclonal antibody, versus high-dose, high-frequency interferon (IFN) β-1a in patients with relapsing multiple sclerosis (RMS), was demonstrated in the phase III OPERA I and OPERA II studies [1]. The identical study designs, comparable baseline demographics and disease characteristics of patients, and the evidence of no interaction between treatment and trial on the primary endpoint (annualized relapse rate [ARR]) between the OPERA I and OPERA II trials [1], permitted pooling of trial data.

Compared with IFN β-1a, treatment with ocrelizumab resulted in a 47% lower ARR (primary endpoint; $p < 0.001$) in the analysis of the pooled OPERA I and OPERA II

✉ Benjamin Turner
Benjamin.Turner@bartsandthelondon.nhs.uk

1 Department of Neurology, The Royal London Hospital, London E1 1BB, UK

2 Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

3 University Hospital Basel, University of Basel, Basel, Switzerland

4 Vall d'Hebron University Hospital, Barcelona, Spain

5 Division of Neurology, St Michael's Hospital, University of Toronto, Toronto, Canada

6 Pitié-Salpêtrière Hospital, Paris, France

7 McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA

8 F. Hoffmann-La Roche Ltd, Basel, Switzerland

9 Genentech, Inc., South San Francisco, CA, USA

intent-to-treat (ITT) population [2]. Similarly, treatment with ocrelizumab was associated with relatively lower rates of disability progression confirmed at 12 weeks (12W-CDP; 40%) and at 24 weeks (24W-CDP; 40%) in the prespecified pooled analysis of both studies. These data were further supported by a significantly greater suppression of development of new areas of inflammation (assessed by MRI of the brain with the use of gadolinium enhancement) and new or newly enlarged plaque formation (as measured by lesions on T2-weighted MRI) [1].

The current analyses were undertaken to understand if the treatment effects of ocrelizumab are consistent across subgroups of patients with different baseline characteristics; to describe the efficacy of ocrelizumab in patient subgroups relating to disability and clinical and MRI disease activity; and to describe the efficacy of ocrelizumab in both treatment-naïve patients and those previously treated with disease-modifying therapy (DMT).

Methods

Trial design and patients

The methodology of the identically designed phase III OPERA I (NCT01247324) and OPERA II (NCT01412333) studies has been reported previously [1]. Patients (aged 18–55 years, McDonald criteria [2010] diagnosis of MS [3], baseline Expanded Disability Status Scale [EDSS] score 0–5.5, ≥ 2 documented clinical relapses within the previous 2 years or one clinical relapse within the year before screening) were randomized (1:1) to treatment with either ocrelizumab 600 mg administered by intravenous infusion every 24 weeks, or subcutaneous IFN β-1a 44 μg three times per week throughout the 96-week treatment period. All patients provided written informed consent.

Statistical analyses

Statistical approaches, including sample size calculations and analyses of primary and secondary endpoints, have been described previously [1].

Subgroup analyses, based on data from the 96-week double-blind treatment period, of the primary (ARR) and secondary endpoints were assessed in the ITT population (all randomized patients [ocrelizumab, $n = 827$; IFN β-1a, $n = 829$]); analyses of no evidence of disease activity (NEDA) were conducted in the modified ITT (mITT) population (ocrelizumab, $n = 761$; IFN β-1a, $n = 759$), where patients withdrawn from the trial for reasons other than efficacy failure or death and who had no evidence of clinical disease activity at the time of treatment discontinuation in the trial were excluded [1].

Prespecified subgroups were: study (OPERA I versus OPERA II), age (< 40 versus ≥ 40 years), sex, BMI (< 25 kg/m^2 versus ≥ 25 kg/m^2), region (USA versus rest of world), baseline EDSS score (< 4 versus ≥ 4), baseline gadolinium-enhancing T1 lesion status (0 versus ≥ 1), and pre-treated patients with active disease (pre-treated for ≥ 1 year with either ≥ 1 relapse in the year prior to randomization or ≥ 1 baseline T1 gadolinium-enhancing lesion) or highly active disease (≥ 1 relapse in the year prior to randomization and ≥ 9 T2 lesions or ≥ 1 T1 gadolinium-enhancing lesion at baseline). Additional post hoc subgroups, included because of their clinical relevance, consisted of: baseline EDSS score (< 2.5 versus ≥ 2.5 [for further evaluation of patients with lower disability at baseline]), prior DMT use within the 2 years prior to study inclusion (yes versus no), prior relapse (≤ 1 versus ≥ 2), and baseline normalized brain volume (≥ 1500 cm^3 versus < 1500 cm^3).

Statistical analyses of endpoint by subgroup

Subgroup-level treatment comparisons were used to determine whether the treatment effects of ocrelizumab and IFN β-1a were the same within each subgroup level. Treatment-by-subgroup interaction tests were used to determine whether the treatment effect of ocrelizumab versus IFN β-1a was the same between the two levels of subgroup. p values < 0.05 from the treatment-by-subgroup interaction test indicate that the treatment effect of ocrelizumab versus IFN β-1a was not the same between the two levels of subgroup.

For ARR, both subgroup-level and treatment-by-subgroup interactions testing were performed using a negative binomial or quasi-Poisson model with the number of relapses as the response variable and log-transformed exposure time as the offset variable in both models. Factors included in subgroup-level tests were treatment, study, region, and baseline EDSS score (< 4.0 versus ≥ 4.0); additional factors in treatment-by-subgroup interaction testing were subgroup and treatment-by-subgroup interaction.

Disability progression, with 12- or 24-week confirmation, subgroup-level, and treatment-by-subgroup interactions testing were performed using Cox proportional hazard models with time to onset of disability progression as the response variable and treatment (ocrelizumab versus IFN β-1a) as a factor, and study, region and baseline EDSS score (< 4.0 versus ≥ 4.0) as adjustments in both models; additional factors in the treatment-by-subgroup interaction testing were subgroups and treatment-by-subgroup interaction.

For the MRI outcomes of T1 gadolinium-enhancing lesions and new/enlarging T2 lesions, subgroup-level and treatment-by-subgroup interactions testing were performed using a negative binomial or quasi-Poisson model with the number of lesions as the response variable, the log-transformed number of MRI scans as the offset variable, and baseline lesion count,

treatment, study, region, and baseline EDSS score (< 4.0 versus ≥ 4.0) as factors in both models; additional factors in the treatment-by-subgroup interaction tests were subgroup and treatment-by-subgroup interaction. For change from baseline brain volume, subgroup and treatment-by-subgroup interaction testing used a mixed-effect model of repeated measures model (unstructured covariance matrix) with percentage change in brain volume as the dependent variable and baseline brain volume, treatment, study, region, baseline EDSS score (< 4.0 versus ≥ 4.0), week, baseline brain volume-by-week, and treatment-by-week as factors in both models; additional factors in the treatment-by-subgroup interaction tests were subgroup and treatment-by-week-by-subgroup.

Subgroup-level testing of NEDA or NEDA 24–96 (NEDA rebaselined at Week 24, which provides a representation of steady-state efficacy unconfounded by any initial disease activity carried over from baseline and recent pre-baseline disease state [4]) used the Cochran–Mantel–Haenszel test with treatment and NEDA status as the column/row factors and study, region, and baseline EDSS score (< 4.0 versus ≥ 4.0) as stratification factors. Treatment-by-subgroup interaction used the Breslow–Day test with treatment/NEDA status as the column/row factors and subgroup as the stratification factor.

For subgroup-level analyses, key covariates (i.e., study, region, or baseline EDSS < 4.0 versus ≥ 4.0) were not included as a main effect if the key covariate was used as the subgroup. If the subgroup was EDSS < 2.5 versus ≥ 2.5, then baseline EDSS < 4.0 versus ≥ 4.0 was not included as a main effect.

Analyses of patients who were pre-treated and had active or highly active disease were conducted in a similar way to the subgroup-level analyses described above, with the exception that no treatment-by-subgroup testing was conducted.

Results

Patient disposition, demographic and disease characteristics, and safety findings from the individual OPERA I and OPERA II studies were reported previously [1]. Baseline demographic and disease characteristics between treatment groups in the pooled ITT population were generally comparable (Table 1), and characteristics within the mITT population were generally comparable to those within the ITT population (Supplementary Table S1).

Subgroup analyses

Annualized relapse rate

The significant reduction in ARR observed in the overall pooled analysis of the ITT population with ocrelizumab, relative to IFN β-1a (47% [$p < 0.001$]), was maintained

across the majority of subgroup-levels, including study, region, age, sex, baseline BMI, prior DMT use and prior relapse, baseline EDSS, normalized brain volume, and gadolinium-enhancing T1 lesions; a numerical trend favoring ocrelizumab was observed for the specific subgroup strata of patients aged ≥ 40 years (Fig. 1).

Significant treatment-by-subgroup interactions for ARR were observed between patients aged < 40 versus ≥ 40 years ($p = 0.006$) and patients with or without baseline T1 gadolinium-enhancing lesions ($p < 0.001$). Treatment-by-subgroup interaction p values for all endpoints and subgroups are presented in Supplementary Table S2.

Confirmed disability progression

The significant reductions in disease progression with 12-week confirmation (40% [$p < 0.001$]; Fig. 2) and 24-week confirmation (40% [$p = 0.003$]; Supplementary Fig. S1), relative to IFN β-1a, observed in the overall pooled analysis of the ITT population were maintained across most subgroup-levels.

For 12W-CDP, numerical trends favoring ocrelizumab were observed in the subgroup strata of patients: from the USA, who received prior DMT, with ≥ 2 prior relapses at baseline, with a baseline EDSS score < 2.5, or with a baseline BMI ≥ 25 kg/m^2 (Fig. 2). The pattern of numerical trends favoring ocrelizumab for 24W-CDP was the same as for 12W-CDP with the addition of trends for males and for patients with a baseline normalized brain volume < 1500 cm^3 (Supplementary Fig. S1).

Significant treatment-by-subgroup interactions were observed between patients with a baseline BMI < 25 kg/m^2 versus ≥ 25 kg/m^2 for both 12W-CDP ($p = 0.026$) and 24W-CDP ($p = 0.016$; Fig. 2).

MRI outcomes

The substantial reductions in both the average number of gadolinium-enhancing T1 lesions (94% [$p < 0.001$]; Fig. 3) and the average number of new or newly enlarged hyperintense T2 lesions per scan (80% [$p < 0.001$]; Fig. 4), of ocrelizumab relative to IFN β-1a, observed in the overall pooled analysis of the ITT population were maintained across all subgroup-levels ($p < 0.001$ for both endpoints and all comparisons).

For T1 gadolinium-enhancing lesions, treatment-by-subgroup interactions were observed between patients aged < 40 versus ≥ 40 years ($p = 0.030$) and patients with or without baseline T1 gadolinium-enhancing lesions ($p = 0.001$). With respect to new or newly enlarged hyperintense T2 lesions, treatment-by-subgroup interactions were observed between patients with a baseline EDSS score < 4.0 versus ≥ 4.0

Table 1 Baseline demographic and disease characteristics of the pooled OPERA I and OPERA II intent-to-treat population

Characteristic	IFN β-1a 44 µg (N = 829)	Ocrelizumab 600 mg (N = 827)
Age		
Years, mean (SD)	37.2 (9.2)	37.1 (9.2)
< 40 years, n (%)	484 (58.4)	496 (60.0)
≥ 40 years, n (%)	345 (41.6)	331 (40.0)
Female, n (%)	552 (66.6)	541 (65.4)
Body mass index		
kg/m^2, mean (SD)	26.4 (6.2)	26.2 (5.8)
< 25 kg/m^2, n (%)	413 (50.2)	406 (49.6)
≥ 25 kg/m^2, n (%)	409 (49.8)	412 (50.4)
Time since MS symptom onset, years, mean (SD)	6.5 (6.1)	6.7 (6.2)
Time since RMS diagnosis, years, mean (SD)	3.9 (4.9)	4.0 (4.9)
No DMT in the 2 years before study inclusion, n (%)	606 (73.4)[a,b]	605 (73.3)[a,b]
EDSS score		
Mean (SD)	2.8 (1.3)[c]	2.8 (1.3)
< 2.5, n (%)	329 (39.7)[c]	310 (37.5)
≥ 2.5, n (%)	499 (60.3)[c]	517 (62.5)
< 4.0, n (%)	627 (75.7)[c]	629 (76.1)
≥ 4.0, n (%)	201 (24.3)[c]	198 (23.9)
Number of relapses, mean (SD)		
In the last year, mean (SD)	1.33 (0.69)[d]	1.32 (0.67)[d]
In the last 2 years, mean (SD)	1.76 (0.92)[d]	1.79 (0.91)[d]
≤ 1 relapse, n (%)	584 (70.6)[d]	585 (70.8)[d]
≥ 2 relapses, n (%)	243 (29.4)[d]	241 (29.2)[d]
MRI		
Patients with no T1 gadolinium-enhancing lesions, n (%)	495 (60.2)[e]	485 (59.3)[e]
Patients with ≥ 1 T1 gadolinium-enhancing lesion, n (%)	327 (39.8)[e]	333 (40.7)[e]
Number of T2 lesions, mean (SD)	51 (38)[f]	50 (39)[f]
T2 lesion volume, cm^3, mean (SD)	10.18 (11.8)[f]	10.79 (14.1)[f]
Normalized brain volume, cm^3, mean (SD)	1500 (89)[g]	1502 (88)[g]
Normalized brain volume < 1500 cm^3, n (%)	398 (48.7)[g]	402 (49.0)[g]
Normalized brain volume ≥ 1500 cm^3, n (%)	420 (51.3)[g]	418 (51.0)[g]

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *IFN* interferon, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *OCR* ocrelizumab, *RMS* relapsing multiple sclerosis, *SD* standard deviation

[a]Data include patients who were untreated with any DMT in the 2 years before screening

[b]IFN β-1a n = 826, OCR n = 825

[c]IFN β-1a n = 828

[d]IFN β-1a n = 827, OCR n = 826

[e]IFN β-1a n = 822, OCR n = 818

[f]IFN β-1a n = 824, OCR n = 822

[g]IFN β-1a n = 818, OCR n = 820

($p = 0.007$) and a baseline BMI < 25 kg/m^2 versus ≥ 25 kg/m^2 ($p = 0.043$).

The benefit in change from baseline brain volume observed in the overall pooled analysis of the ITT population with ocrelizumab, relative to IFN β-1a (least square mean difference, 0.31% [$p < 0.001$; Fig. 5]), was maintained across the majority of subgroup-levels; a numerical trend favoring ocrelizumab was observed in patients from the USA. A treatment-by-subgroup interaction was observed between patients with a normalized baseline brain volume < 1500 cm^3 and ≥ 1500 cm^3 ($p = 0.002$).

	IFN β-1a (*N*=829)				OCR (*N*=827)				Rate ratio (95% CI; p)
	Group, *n*	Relapses, *n*	Patient years	Adjusted ARR	Group, *n*	Relapses, *n*	Patient years	Adjusted ARR	
All patients	829	334	1339.16	0.29	827	194	1415.72	0.16	0.54 (95% CI: 0.44–0.66; p<0.001)
Study									
OPERA I	411	166	678.12	0.29	410	96	706.26	0.16	0.54 (95% CI: 0.40–0.72; p<0.001)
OPERA II	418	168	661.04	0.29	417	98	709.45	0.16	0.53 (95% CI: 0.40–0.71; p<0.001)
Region									
ROW	610	254	1013.69	0.29	610	143	1058.03	0.15	0.52 (95% CI: 0.41–0.67; p<0.001)
USA	219	80	325.47	0.29	217	51	357.69	0.17	0.58 (95% CI: 0.39–0.85; p=0.005)
Age, years[a]									
<40	484	212	779.40	0.36	496	103	846.48	0.15	0.41 (95% CI: 0.31–0.55; p<0.001)
≥40	345	122	559.76	0.23	331	91	569.23	0.17	0.76 (95% CI: 0.56–1.03; p=0.073)
Sex									
Female	552	233	887.84	0.30	541	130	920.62	0.16	0.53 (95% CI: 0.41–0.68; p<0.001)
Male	277	101	451.33	0.25	286	64	495.09	0.14	0.56 (95% CI: 0.40–0.80; p=0.001)
Baseline body mass index, kg/m²									
<25	413	171	668.23	0.30	406	98	696.53	0.16	0.52 (95% CI: 0.39–0.70; p<0.001)
≥25	409	160	658.05	0.28	412	94	703.99	0.15	0.55 (95% CI: 0.41–0.73; p<0.001)
Baseline normalized brain volume, cm³									
<1500	398	168	645.88	0.28	402	103	688.08	0.16	0.58 (95% CI: 0.43–0.76; p<0.001)
≥1500	420	165	678.61	0.33	418	91	714.72	0.16	0.49 (95% CI: 0.36–0.67; p<0.001)
Prior disease-modifying therapy use in the 2 years before study inclusion									
No	605	226	995.71	0.28	604	137	1034.43	0.16	0.57 (95% CI: 0.45–0.72; p<0.001)
Yes	224	108	343.46	0.32	223	57	381.29	0.15	0.46 (95% CI: 0.31–0.69; p=0.001)
Prior relapse[b]									
≤1	584	203	942.02	0.24	585	122	1000.77	0.14	0.57 (95% CI: 0.45–0.71; p<0.001)
≥2	243	130	394.84	0.38	241	72	413.87	0.20	0.53 (95% CI: 0.40–0.71; p<0.001)
Baseline Expanded Disability Status Scale score[b]									
<4	627	226	1023.33	0.22	629	118	1081.62	0.11	0.49 (95% CI: 0.40–0.62; p<0.001)
≥4	201	108	315.78	0.35	198	76	334.10	0.23	0.67 (95% CI: 0.50–0.89; p=0.006)
<2.5	329	113	540.27	0.21	310	52	530.56	0.10	0.46 (95% CI: 0.31–0.69; p<0.001)
≥2.5	499	221	798.85	0.29	517	142	885.16	0.16	0.57 (95% CI: 0.45–0.73; p<0.001)
Baseline T1 gadolinium-enhancing lesions, n[a]									
0	495	164	811.56	0.25	485	124	828.95	0.18	0.74 (95% CI: 0.56–0.96; p=0.025)
≥1	327	167	519.59	0.35	333	70	570.93	0.13	0.36 (95% CI: 0.26–0.50; p<0.001)

← Favors OCR　　Favors IFN β-1a →
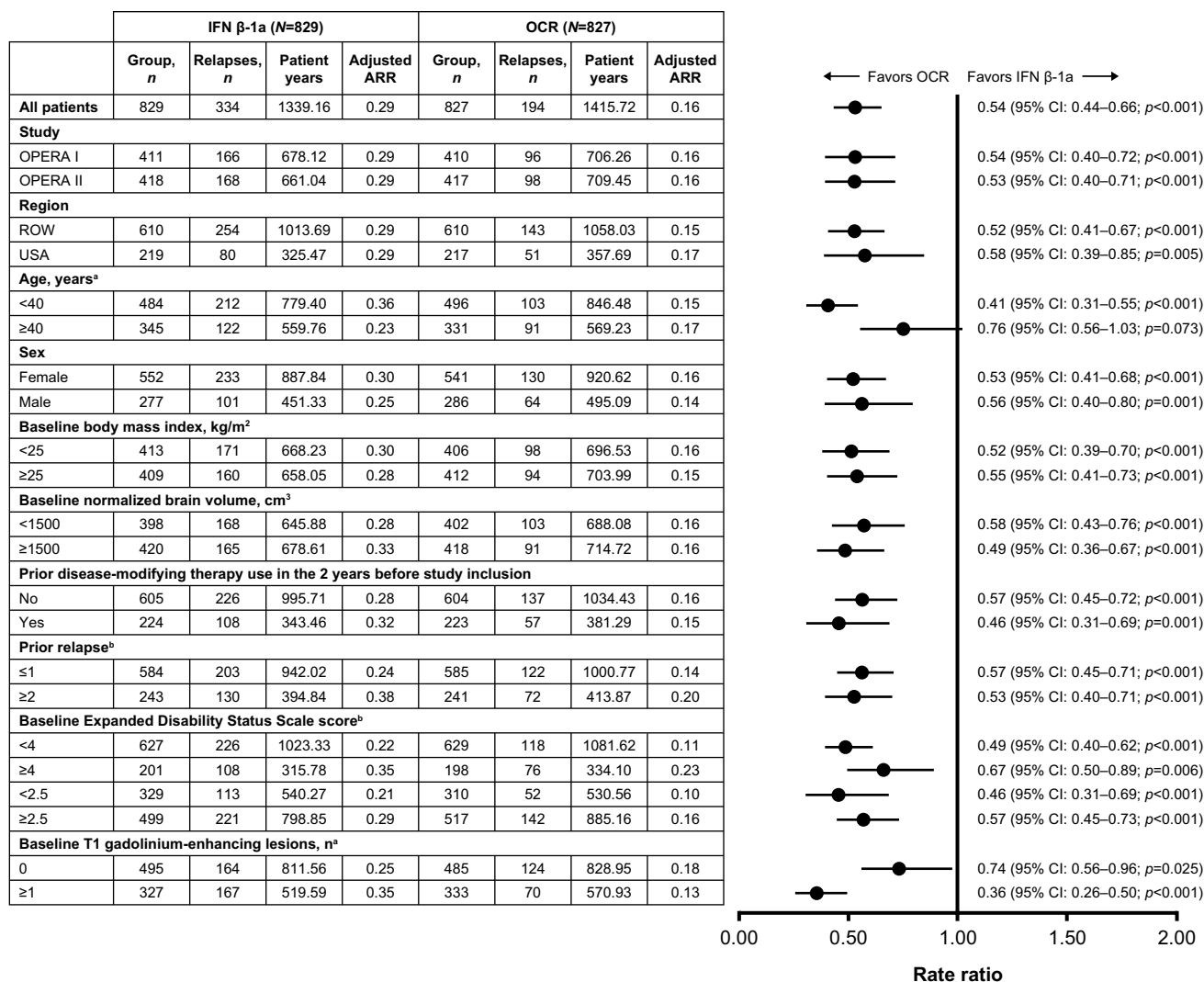
0.00　0.50　1.00　1.50　2.00　**Rate ratio**

Fig. 1 Annualized relapse rate by subgroup in the pooled OPERA I and OPERA II intent-to-treat population. Subgroup-level and treatment-by-subgroup interactions were assessed by the negative binomial method, or quasi-Poisson model if appropriate (where indicated). *ARR* annualized relapse rate, *CI* confidence interval, *IFN* interferon, *OCR* ocrelizumab, *ROW* rest of world. [a]A significant treatment-by-subgroup interaction was observed for age (<40 versus ≥40 years; *p*=0.006) and for baseline T1 gadolinium-enhancing lesion status (0 versus ≥1; *p*<0.001); *p* values <0.05 from the treatment-by-subgroup interaction test indicate that the treatment effect of OCR versus IFN is not the same at each subgroup-level. [b]Estimated by quasi-Poisson model

No evidence of disease activity

The increase in the proportion of patients with NEDA in the overall pooled mITT population with ocrelizumab (75% [*p* < 0.001]), relative to IFN β-1a, was maintained across most subgroup-levels (Fig. 6); a numerical trend favoring ocrelizumab was observed in patients with a baseline EDSS score ≥ 4.0. A treatment-by-subgroup interaction was observed between patients with a baseline EDSS score < 4.0 and ≥ 4.0 (*p* = 0.022).

Similarly, when NEDA was rebaselined to Week 24, the improvement in the proportion of patients with NEDA 24–96 seen in the overall pooled mITT population with ocrelizumab (72% [*p* < 0.001]), relative to IFN β-1a, was maintained across all subgroup-levels (Supplementary Fig. S2). Treatment-by-subgroup interactions were observed between patients with a baseline EDSS score < 4.0 and ≥ 4.0 (*p* = 0.008), patients < 40 and ≥ 40 years old (*p* < 0.001), and those with or without T1 gadolinium-enhancing lesions at baseline (*p* < 0.001).

Efficacy in pre-treated patients with active or highly active disease

A total of 301 patients were defined as pre-treated with active disease (ocrelizumab, *n* = 153; IFN β-1a, *n* = 148)

	IFN β-1a (N=829)		OCR (N=827)			
	Group, n	Events, n	Group, n	Events, n		
All patients	829	113	827	75		0.60 (95% CI: 0.45–0.81; p<0.001)
Study						
OPERA I	411	50	410	31		0.57 (95% CI: 0.37–0.90; p=0.015)
OPERA II	418	63	417	44		0.63 (95% CI: 0.42–0.92; p=0.018)
Region						
ROW	610	79	610	45		0.53 (95% CI: 0.36–0.76; p<0.001)
USA	219	34	217	30		0.77 (95% CI: 0.47–1.26; p=0.3)
Age, years						
<40	484	53	496	34		0.59 (95% CI: 0.39–0.92; p=0.019)
≥40	345	60	331	41		0.61 (95% CI: 0.41–0.92; p=0.018)
Sex						
Female	552	70	541	48		0.64 (95% CI: 0.44–0.93; p=0.019)
Male	277	43	286	27		0.56 (95% CI: 0.34–0.91; p=0.019)
Baseline body mass index, kg/m² [a]						
<25	413	54	406	23		0.39 (95% CI: 0.24–0.64; p<0.001)
≥25	409	59	412	51		0.81 (95% CI: 0.55–1.18; p=0.3)
Baseline normalized brain volume, cm³						
<1500	398	64	402	43		0.61 (95% CI: 0.41–0.90; p=0.013)
≥1500	420	47	418	32		0.63 (95% CI: 0.40–0.99; p=0.046)
Prior disease-modifying therapy use in the 2 years before study inclusion						
No	605	82	604	53		0.60 (95% CI: 0.42–0.85; p=0.004)
Yes	224	31	223	22		0.61 (95% CI: 0.35–1.06; p=0.080)
Prior relapse						
≤1	584	82	585	52		0.58 (95% CI: 0.41–0.82; p=0.002)
≥2	243	31	241	23		0.67 (95% CI: 0.39–1.16; p=0.2)
Baseline Expanded Disability Status Scale score						
<4	627	87	629	64		0.66 (95% CI: 0.48–0.92; p=0.014)
≥4	201	26	198	11		0.39 (95% CI: 0.19–0.80; p=0.010)
<2.5	329	44	310	37		0.82 (95% CI: 0.53–1.27; p=0.4)
≥2.5	499	69	517	38		0.48 (95% CI: 0.33–0.72; p<0.001)
Baseline T1 gadolinium-enhancing lesions, n						
0	495	65	485	43		0.60 (95% CI: 0.40–0.88; p=0.010)
≥1	327	47	333	32		0.60 (95% CI: 0.38–0.95; p=0.029)

← Favors OCR   Favors IFN β-1a →
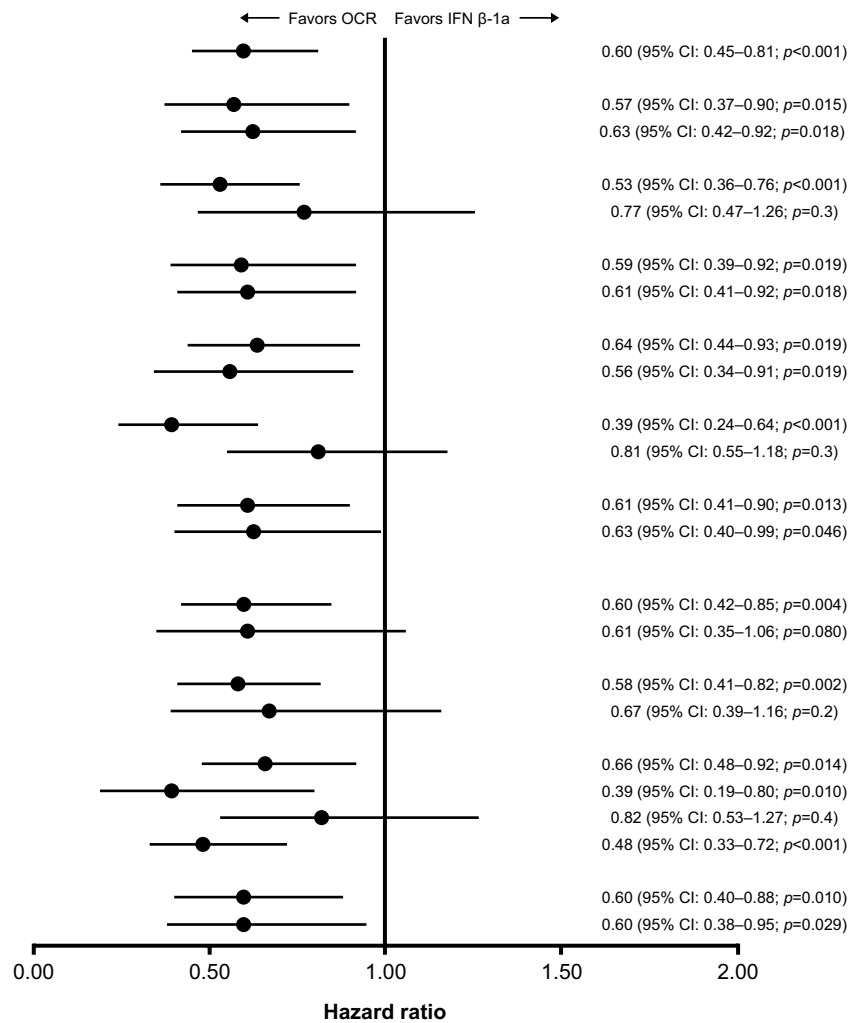
Hazard ratio

Fig. 2 Disease progression confirmed at Week 12 by subgroup in the pooled OPERA I and OPERA II intent-to-treat population. Subgroup-level and treatment-by-subgroup interactions were assessed by the Cox proportional hazards method. *CI* confidence interval, *IFN* interferon, *OCR* ocrelizumab, *ROW* rest of world. [a] A significant treatment-by-subgroup interaction was observed for BMI (< 25 kg/m² versus ≥ 25 kg/m²; $p = 0.026$); p values < 0.05 from the treatment-by-subgroup interaction test indicate that the treatment effect of OCR versus IFN is not the same at each subgroup-level

and 283 patients were defined as pre-treated with highly active disease (ocrelizumab, $n = 143$; IFN β-1a, $n = 140$). Consistent with the reduction in ARR in the overall ITT pooled population (47%; $p < 0.001$), ocrelizumab, relative to IFN β-1a, reduced the ARR in patients who were pre-treated with active disease by 65% ($p < 0.001$) and pre-treated with highly active disease by 68% ($p < 0.001$).

Similar benefits in patients who were pre-treated with active disease or pre-treated with highly active disease were observed for 12W-CDP (54% relative reduction [$p = 0.032$] or a 53% relative reduction [$p = 0.035$], respectively) compared with a 40% reduction ($p < 0.001$) in the overall ITT pooled population; 24W-CDP (51% relative reduction [$p = 0.075$] or a 50% relative reduction [$p = 0.082$], respectively) compared with a 40% reduction ($p = 0.003$) in the overall ITT pooled population; T1 gadolinium-enhancing lesions (98% relative reduction [$p < 0.001$ in both subgroups]) compared with a 94% reduction ($p < 0.001$) in the overall ITT pooled population; and new or enlarging T2 lesions (80% relative reduction [$p < 0.001$ in both subgroups]) compared with an 80% reduction ($p < 0.001$) in the overall ITT pooled population.

For patients who were pre-treated with either active or highly active disease, the statistically significant treatment benefits of ocrelizumab relative to IFN β-1a were

	IFN β-1a (N=829)			OCR (N=827)		
	Group, n	Lesions, n	MRIs, n	Group, n	Lesions, n	MRIs, n
All patients	829	802	2081	827	42	2235
Study						
OPERA I	411	337	1064	410	21	1118
OPERA II	418	465	1017	417	21	1117
Region						
ROW	610	474	1590	610	27	1686
USA	219	328	491	217	15	549
Age, years[a,b]						
<40	484	594	1208	496	24	1331
≥40	345	208	873	331	18	904
Sex						
Female	552	558	1376	541	32	1445
Male	277	244	705	286	10	790
Baseline body mass index, kg/m²						
<25	413	444	1044	406	23	1105
≥25	409	358	1016	412	19	1106
Baseline normalized brain volume, cm³						
<1500	398	388	1001	402	18	1090
≥1500	420	404	1059	418	24	1126
Prior disease-modifying therapy use in the 2 years before study inclusion[b]						
No	605	544	1550	604	31	1632
Yes	224	258	531	223	11	603
Prior relapse[b]						
≤1	584	508	1463	585	19	1575
≥2	243	293	615	241	23	659
Baseline Expanded Disability Status Scale score[b]						
<4	627	673	1597	629	32	1707
≥4	201	129	484	198	10	528
<2.5	329	315	843	310	20	841
≥2.5	499	487	1238	517	22	1394
Baseline T1 gadolinium-enhancing lesions[a]						
0	495	173	1274	485	20	1310
≥1	327	626	801	333	22	905

Forest plot. ← Favors OCR　Favors IFN β-1a →

- All patients: 0.06 (95% CI: 0.04–0.08; p<0.001)
- OPERA I: 0.06 (95% CI: 0.03–0.10; p<0.001)
- OPERA II: 0.05 (95% CI: 0.03–0.09; p<0.001)
- ROW: 0.06 (95% CI: 0.03–0.09; p<0.001)
- USA: 0.05 (95% CI: 0.02–0.10; p<0.001)
- <40: 0.04 (95% CI: 0.03–0.06; p<0.001)
- ≥40: 0.08 (95% CI: 0.05–0.13; p<0.001)
- Female: 0.07 (95% CI: 0.04–0.11; p<0.001)
- Male: 0.04 (95% CI: 0.02–0.07; p<0.001)
- <25: 0.05 (95% CI: 0.03–0.09; p<0.001)
- ≥25: 0.05 (95% CI: 0.03–0.08; p<0.001)
- <1500: 0.04 (95% CI: 0.02–0.07; p<0.001)
- ≥1500: 0.06 (95% CI: 0.03–0.10; p<0.001)
- No: 0.05 (95% CI: 0.04–0.08; p<0.001)
- Yes: 0.03 (95% CI: 0.02–0.06; p<0.001)
- ≤1: 0.04 (95% CI: 0.02–0.06; p<0.001)
- ≥2: 0.06 (95% CI: 0.04–0.10; p<0.001)
- <4: 0.04 (95% CI: 0.03–0.06; p<0.001)
- ≥4: 0.08 (95% CI: 0.04–0.14; p<0.001)
- <2.5: 0.07 (95% CI: 0.03–0.12; p<0.001)
- ≥2.5: 0.05 (95% CI: 0.03–0.08; p<0.001)
- 0: 0.11 (95% CI: 0.06–0.21; p<0.001)
- ≥1: 0.03 (95% CI: 0.02–0.05; p<0.001)
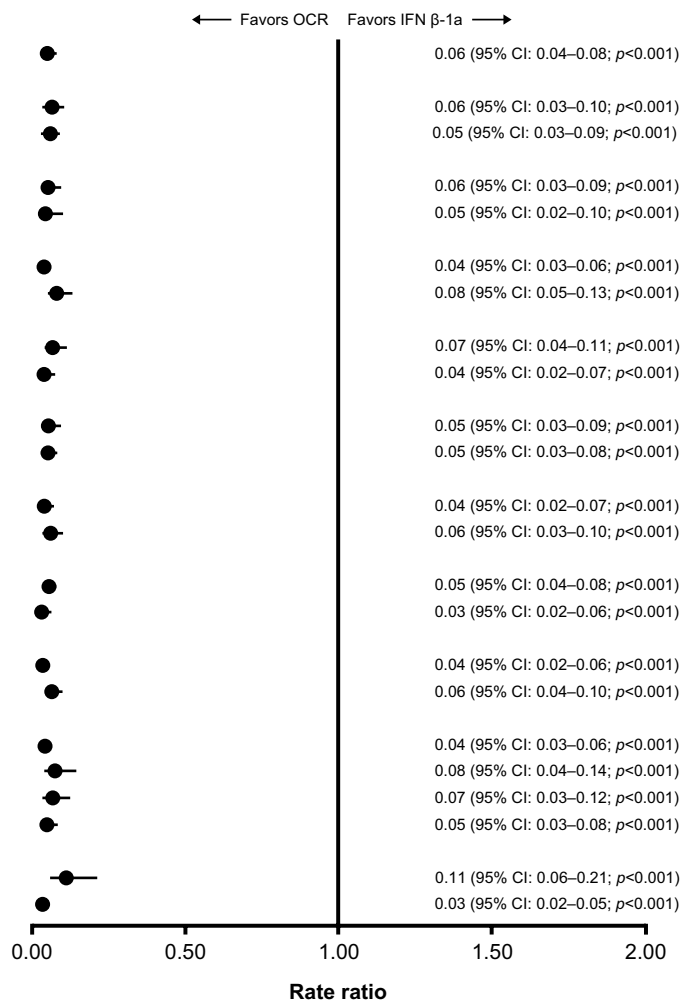
Rate ratio: 0.00　0.50　1.00　1.50　2.00

Fig. 3 T1 gadolinium-enhancing lesions by subgroup in the pooled OPERA I and OPERA II intent-to-treat population. Subgroup-level and treatment-by-subgroup interactions were assessed by the negative binomial method, or quasi-Poisson model if appropriate (where indicated). *CI* confidence interval, *IFN* interferon, *MRI* magnetic resonance imaging, *OCR* ocrelizumab, *ROW* rest of world. [a]A significant treatment-by-subgroup interaction was observed for age (<40 versus ≥40 years; $p=0.030$) and for baseline T1 gadolinium-enhancing lesion status (0 versus ≥1; $p=0.001$); p values <0.05 from the treatment-by-subgroup interaction test indicate that the treatment effect of OCR versus IFN is not the same at each subgroup-level. [b]Estimated by quasi-Poisson model

demonstrated for all endpoints except for 24W-CDP, which comprised a relatively smaller number of patients.

Discussion

In the OPERA I and OPERA II studies, ocrelizumab, relative to IFN β-1a, was associated with significantly better outcomes in terms of ARR, disability progression, suppression of new inflammatory lesions in the brain (T1 gadolinium-enhancing lesions), and new or newly enlarged plaque formation (new/enlarging T2 lesions) [1]. The subgroup analyses presented here demonstrate that the significant treatment benefits of ocrelizumab, relative to IFN β-1a, are maintained across most baseline-, clinically, and radiologically defined subgroups, although the magnitude of the treatment benefit of ocrelizumab over IFN β-1a may be greater in one of the two levels of subgroup. Treatment-by-subgroup interactions were observed for some endpoints over particular subgroups; however, all showed a benefit (significant or numerical) of ocrelizumab over IFN β-1a at each of the two levels of subgroup.

OPERA I and OPERA II were not powered to detect statistically significant effects for all subgroup analyses, including those predefined and with pre-planned pooling (12W-CDP or 24W-CDP), or to test for heterogeneity between subgroups. Additionally, post hoc analyses of

	IFN β-1a (N=829)			OCR (N=827)		
	Group, n	Lesions, n	MRIs, n	Group, n	Lesions, n	MRIs, n
All patients	829	4019	2091	827	810	2246
Study						
OPERA I	411	1916	1066	410	430	1123
OPERA II	418	2103	1025	417	380	1123
Region						
ROW	610	2821	1595	610	595	1690
USA	219	1198	496	217	215	556
Age, years						
<40	484	3064	1216	496	615	1340
≥40	345	955	875	331	195	906
Sex						
Female	552	2281	1384	541	484	1457
Male	277	1738	707	286	326	789
Baseline body mass index, kg/m²ᵃ						
<25	413	2181	1047	406	514	1107
≥25	409	1825	1023	412	290	1115
Baseline normalized brain volume, cm³						
<1500	398	1855	1004	402	317	1095
≥1500	420	2125	1066	418	492	1133
Prior disease-modifying therapy use in the 2 years before study inclusion						
No	605	2709	1557	604	567	1641
Yes	224	1310	534	223	243	605
Prior relapse						
≤1	584	2636	1469	585	532	1584
≥2	243	1381	619	241	278	661
Baseline Expanded Disability Status Scale scoreᵃ						
<4	627	3225	1604	629	546	1719
≥4	201	794	487	198	264	527
<2.5	329	1738	849	310	285	844
≥2.5	499	2281	1242	517	525	1402
Baseline T1 gadolinium-enhancing lesions, n						
0	495	945	1277	485	195	1313
≥1	327	3070	804	333	612	910

Forest plot (← Favors OCR Favors IFN β-1a →), Rate ratio axis from 0.00 to 2.00:
- All patients: 0.20 (95% CI: 0.16–0.24; p<0.001)
- OPERA I: 0.23 (95% CI: 0.17–0.30; p<0.001)
- OPERA II: 0.17 (95% CI: 0.13–0.23; p<0.001)
- ROW: 0.20 (95% CI: 0.16–0.26; p<0.001)
- USA: 0.19 (95% CI: 0.13–0.27; p<0.001)
- <40: 0.18 (95% CI: 0.14–0.23; p<0.001)
- ≥40: 0.23 (95% CI: 0.16–0.33; p<0.001)
- Female: 0.20 (95% CI: 0.16–0.26; p<0.001)
- Male: 0.18 (95% CI: 0.13–0.25; p<0.001)
- <25: 0.22 (95% CI: 0.17–0.30; p<0.001)
- ≥25: 0.15 (95% CI: 0.12–0.20; p<0.001)
- <1500: 0.18 (95% CI: 0.14–0.24; p<0.001)
- ≥1500: 0.20 (95% CI: 0.15–0.25; p<0.001)
- No: 0.21 (95% CI: 0.17–0.27; p<0.001)
- Yes: 0.16 (95% CI: 0.11–0.23; p<0.001)
- ≤1: 0.19 (95% CI: 0.15–0.25; p<0.001)
- ≥2: 0.20 (95% CI: 0.14–0.28; p<0.001)
- <4: 0.17 (95% CI: 0.14–0.21; p<0.001)
- ≥4: 0.32 (95% CI: 0.21–0.50; p<0.001)
- <2.5: 0.17 (95% CI: 0.12–0.22; p<0.001)
- ≥2.5: 0.22 (95% CI: 0.17–0.28; p<0.001)
- 0: 0.21 (95% CI: 0.16–0.29; p<0.001)
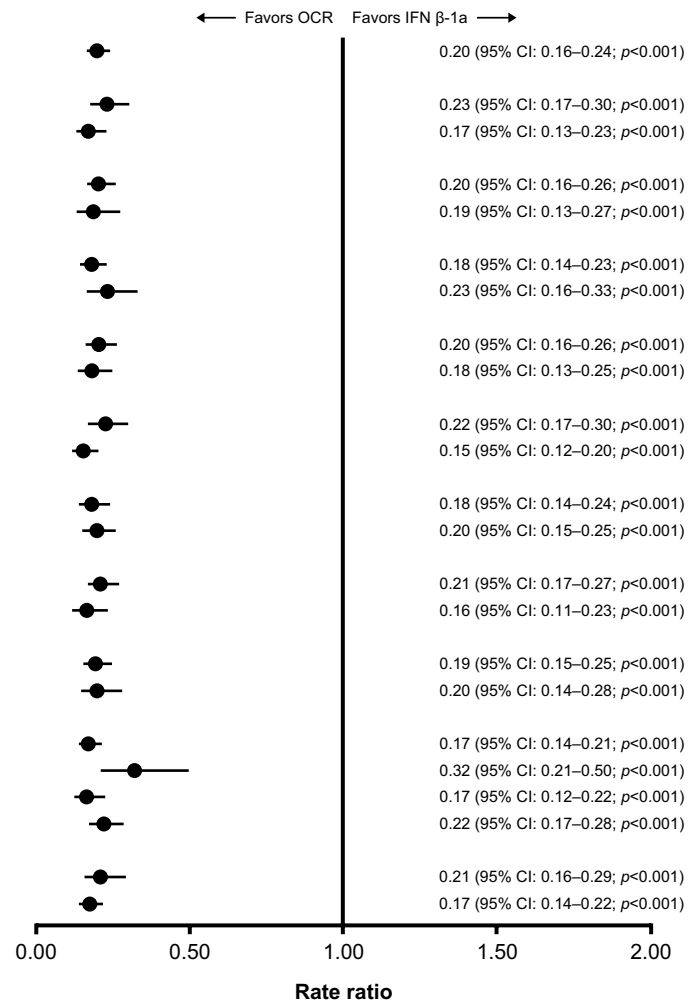- ≥1: 0.17 (95% CI: 0.14–0.22; p<0.001)

Fig. 4 New/enlarging T2 lesions by subgroup in the pooled OPERA I and OPERA II intent-to-treat population. Subgroup-level and treatment-by-subgroup interactions were assessed by the negative binomial method, or quasi-Poisson model if appropriate (where indicated). *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *IFN* interferon, *MRI* magnetic resonance imaging, *OCR* ocrelizumab, *ROW* rest of world. ᵃA significant treatment-by-subgroup interaction was observed for baseline BMI (<25 versus ≥25 kg/m²; $p = 0.043$) and baseline EDSS score (<4.0 versus ≥4.0; $p = 0.007$); p values <0.05 from the treatment-by-subgroup interaction test indicate that the treatment effect of OCR versus IFN is not the same at each subgroup-level

subgroups can be difficult to interpret. Within this analysis most outcomes and subgroups were predefined; only NEDA 24–96 and brain volume change from baseline for outcomes, and the subgroups baseline EDSS score <2.5 versus ≥2.5, prior DMT use yes versus no, those with ≤1 or ≥2 prior relapses, and those with a baseline normalized brain volume of <1500 cm³ or ≥1500 cm³, were post hoc considerations.

Consequently, given the relatively smaller numbers of subjects in some of the subgroups, findings in these subgroups should be interpreted with caution. Further studies with an expanded data set with improved assessment techniques would be required to address these points.

For ARR, gadolinium-enhancing T1 lesions, and NEDA rebaselined at Week 24, significant subgroup interactions suggested that patients who were younger and those with indicators of active inflammatory disease appeared to gain a greater treatment benefit with ocrelizumab, relative to IFN β-1a, than patients who were older and those without markers of active inflammatory disease. These findings are consistent with treatment benefit of other DMTs, which has previously been suggested to be higher in younger than in older patients on the basis of higher disease activity in younger populations with MS [5]. Subgroup analyses performed for other DMTs using either placebo or an active comparator, e.g., fingolimod [6, 7], cladribine [8], teriflunomide [9], dimethyl fumarate [10–12],
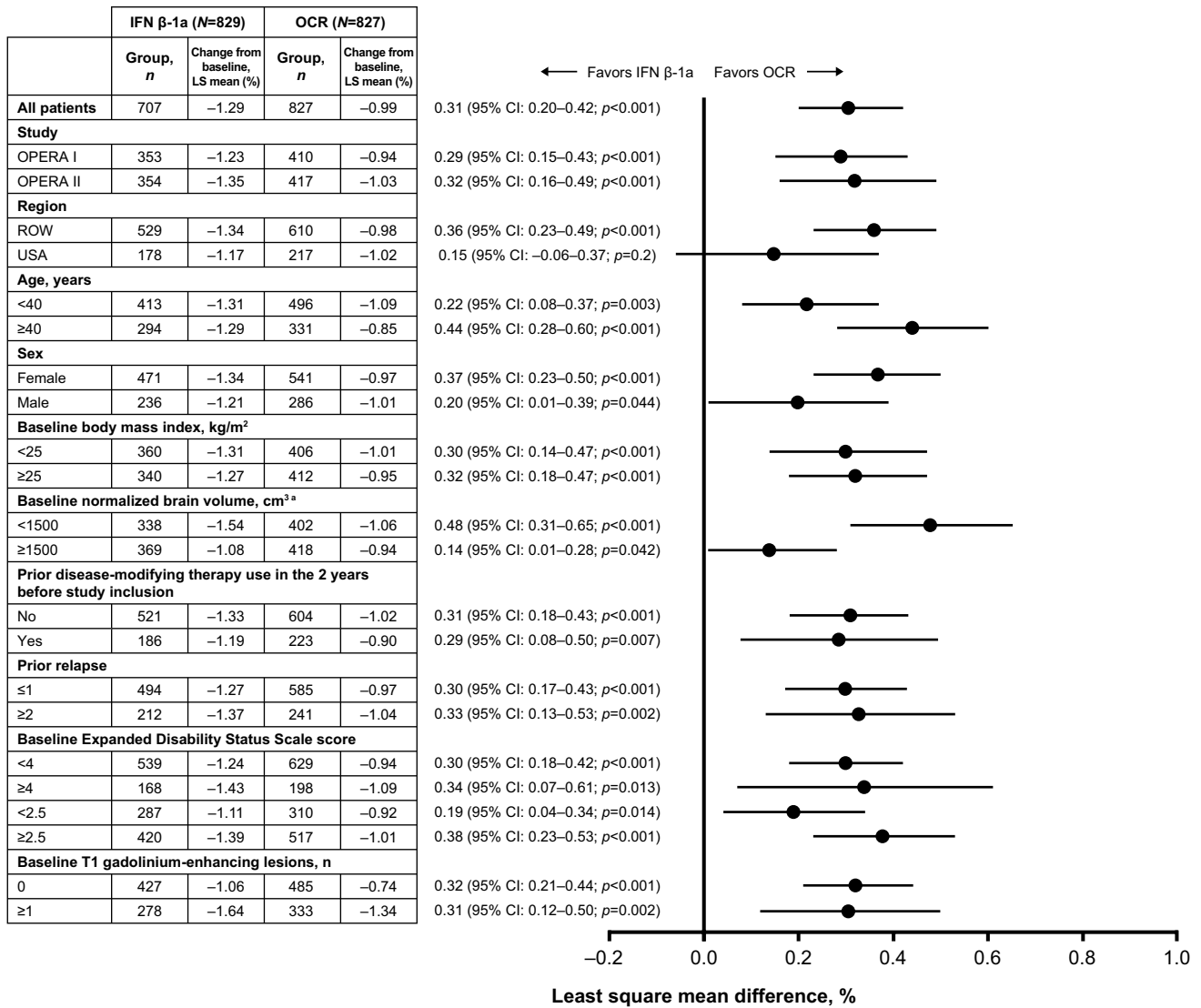
	IFN β-1a (N=829)		OCR (N=827)		
	Group, n	Change from baseline, LS mean (%)	Group, n	Change from baseline, LS mean (%)	
All patients	707	−1.29	827	−0.99	0.31 (95% CI: 0.20–0.42; p<0.001)
Study					
OPERA I	353	−1.23	410	−0.94	0.29 (95% CI: 0.15–0.43; p<0.001)
OPERA II	354	−1.35	417	−1.03	0.32 (95% CI: 0.16–0.49; p<0.001)
Region					
ROW	529	−1.34	610	−0.98	0.36 (95% CI: 0.23–0.49; p<0.001)
USA	178	−1.17	217	−1.02	0.15 (95% CI: −0.06–0.37; p=0.2)
Age, years					
<40	413	−1.31	496	−1.09	0.22 (95% CI: 0.08–0.37; p=0.003)
≥40	294	−1.29	331	−0.85	0.44 (95% CI: 0.28–0.60; p<0.001)
Sex					
Female	471	−1.34	541	−0.97	0.37 (95% CI: 0.23–0.50; p<0.001)
Male	236	−1.21	286	−1.01	0.20 (95% CI: 0.01–0.39; p=0.044)
Baseline body mass index, kg/m²					
<25	360	−1.31	406	−1.01	0.30 (95% CI: 0.14–0.47; p<0.001)
≥25	340	−1.27	412	−0.95	0.32 (95% CI: 0.18–0.47; p<0.001)
Baseline normalized brain volume, cm³ ᵃ					
<1500	338	−1.54	402	−1.06	0.48 (95% CI: 0.31–0.65; p<0.001)
≥1500	369	−1.08	418	−0.94	0.14 (95% CI: 0.01–0.28; p=0.042)
Prior disease-modifying therapy use in the 2 years before study inclusion					
No	521	−1.33	604	−1.02	0.31 (95% CI: 0.18–0.43; p<0.001)
Yes	186	−1.19	223	−0.90	0.29 (95% CI: 0.08–0.50; p=0.007)
Prior relapse					
≤1	494	−1.27	585	−0.97	0.30 (95% CI: 0.17–0.43; p<0.001)
≥2	212	−1.37	241	−1.04	0.33 (95% CI: 0.13–0.53; p=0.002)
Baseline Expanded Disability Status Scale score					
<4	539	−1.24	629	−0.94	0.30 (95% CI: 0.18–0.42; p<0.001)
≥4	168	−1.43	198	−1.09	0.34 (95% CI: 0.07–0.61; p=0.013)
<2.5	287	−1.11	310	−0.92	0.19 (95% CI: 0.04–0.34; p=0.014)
≥2.5	420	−1.39	517	−1.01	0.38 (95% CI: 0.23–0.53; p<0.001)
Baseline T1 gadolinium-enhancing lesions, n					
0	427	−1.06	485	−0.74	0.32 (95% CI: 0.21–0.44; p<0.001)
≥1	278	−1.64	333	−1.34	0.31 (95% CI: 0.12–0.50; p=0.002)

Fig. 5 Change from baseline brain volume (%) by subgroup in the pooled OPERA I and OPERA II intent-to-treat population. Subgroup-level and treatment-by-subgroup interactions were assessed by the mixed-effect model of repeated measures model. *CI* confidence interval, *IFN* interferon, *LS* least square, *OCR* ocrelizumab, *ROW* rest of world. ᵃA significant treatment-by-subgroup interaction was observed for normalized baseline brain volume (<1500 cm³ and ≥1500 cm³; p=0.002); p values <0.05 from the treatment-by-subgroup interaction test indicate that the treatment effect of OCR versus IFN is not the same at each subgroup-level

alemtuzumab [13], and natalizumab [14, 15], also found that efficacy was highest in younger patients with more active disease.

Consistent effects across endpoints were seen for other subgroups of interest. There were no significant sex-based subgroup interactions and the same positive trends of treatment benefit with ocrelizumab were reported in female and male patients. The treatment benefit of ocrelizumab, relative to IFN β-1a, was comparable across endpoints in patients with active or highly active disease who were pre-treated with DMT, while prior treatment per se did not impact the magnitude of the beneficial effect of ocrelizumab. Across other endpoints, the magnitude of

ocrelizumab's treatment benefit on brain atrophy was greater in patients with lower baseline brain volume, which may be related to differential rates of atrophy in the patient subgroups defined by brain volume thresholds. For NEDA (Weeks 0–96) and new or enlarging T2 lesion endpoints, the treatment benefit of ocrelizumab was greater in patients with lower measures of disability at baseline. For both 12W-CDP and 24W-CDP, significant treatment-by-subgroup interactions for BMI indicate that the magnitude of ocrelizumab treatment benefit is greater in lighter patients versus heavier, consistent with lower ocrelizumab exposure in heavier patients (BMI > 25 kg/m² versus < 25 kg/m²). Analyses have shown that patients
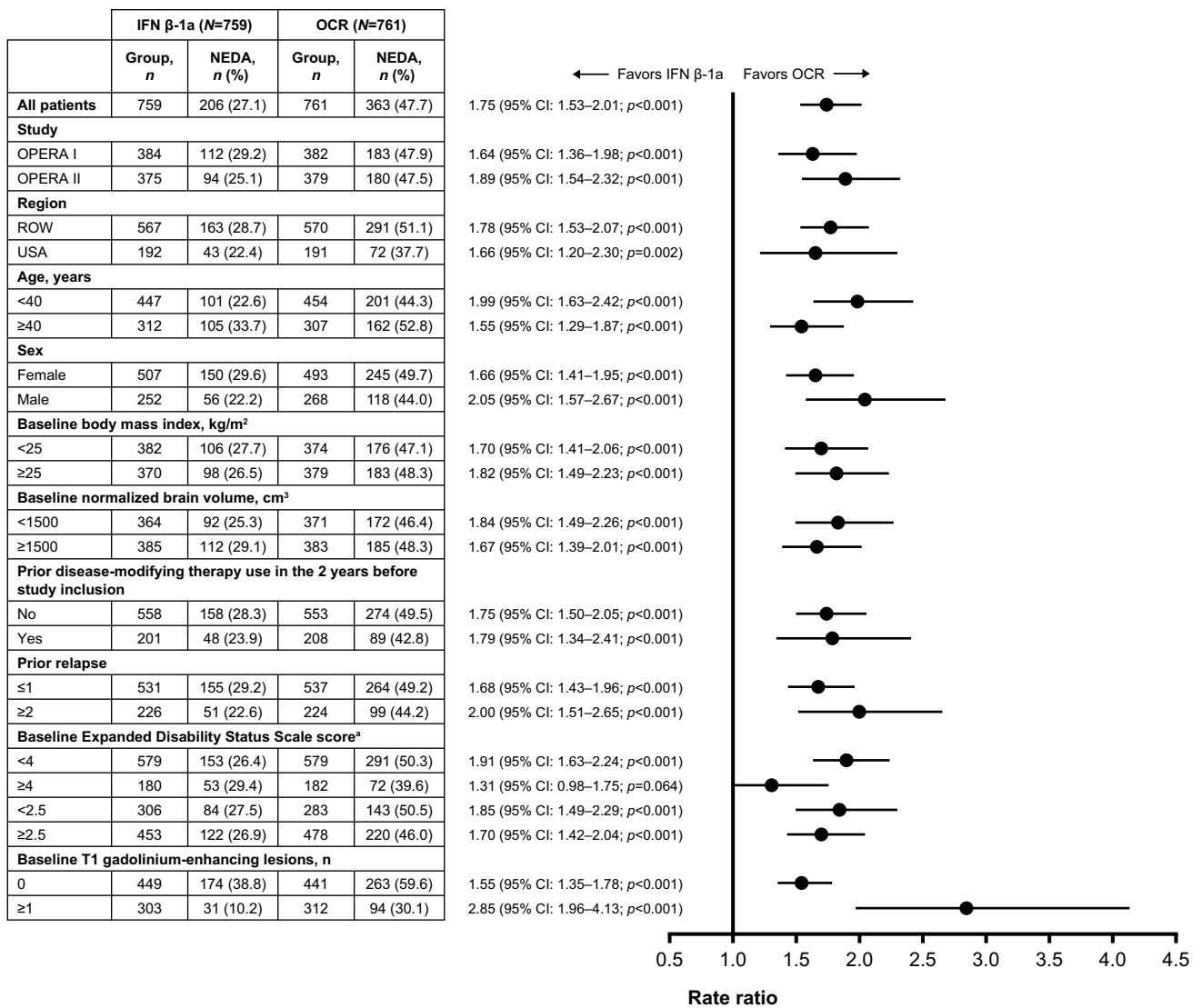
	IFN β-1a (N=759)		OCR (N=761)		
	Group, n	NEDA, n (%)	Group, n	NEDA, n (%)	
All patients	759	206 (27.1)	761	363 (47.7)	1.75 (95% CI: 1.53–2.01; p<0.001)
Study					
OPERA I	384	112 (29.2)	382	183 (47.9)	1.64 (95% CI: 1.36–1.98; p<0.001)
OPERA II	375	94 (25.1)	379	180 (47.5)	1.89 (95% CI: 1.54–2.32; p<0.001)
Region					
ROW	567	163 (28.7)	570	291 (51.1)	1.78 (95% CI: 1.53–2.07; p<0.001)
USA	192	43 (22.4)	191	72 (37.7)	1.66 (95% CI: 1.20–2.30; p=0.002)
Age, years					
<40	447	101 (22.6)	454	201 (44.3)	1.99 (95% CI: 1.63–2.42; p<0.001)
≥40	312	105 (33.7)	307	162 (52.8)	1.55 (95% CI: 1.29–1.87; p<0.001)
Sex					
Female	507	150 (29.6)	493	245 (49.7)	1.66 (95% CI: 1.41–1.95; p<0.001)
Male	252	56 (22.2)	268	118 (44.0)	2.05 (95% CI: 1.57–2.67; p<0.001)
Baseline body mass index, kg/m²					
<25	382	106 (27.7)	374	176 (47.1)	1.70 (95% CI: 1.41–2.06; p<0.001)
≥25	370	98 (26.5)	379	183 (48.3)	1.82 (95% CI: 1.49–2.23; p<0.001)
Baseline normalized brain volume, cm³					
<1500	364	92 (25.3)	371	172 (46.4)	1.84 (95% CI: 1.49–2.26; p<0.001)
≥1500	385	112 (29.1)	383	185 (48.3)	1.67 (95% CI: 1.39–2.01; p<0.001)
Prior disease-modifying therapy use in the 2 years before study inclusion					
No	558	158 (28.3)	553	274 (49.5)	1.75 (95% CI: 1.50–2.05; p<0.001)
Yes	201	48 (23.9)	208	89 (42.8)	1.79 (95% CI: 1.34–2.41; p<0.001)
Prior relapse					
≤1	531	155 (29.2)	537	264 (49.2)	1.68 (95% CI: 1.43–1.96; p<0.001)
≥2	226	51 (22.6)	224	99 (44.2)	2.00 (95% CI: 1.51–2.65; p<0.001)
Baseline Expanded Disability Status Scale score[a]					
<4	579	153 (26.4)	579	291 (50.3)	1.91 (95% CI: 1.63–2.24; p<0.001)
≥4	180	53 (29.4)	182	72 (39.6)	1.31 (95% CI: 0.98–1.75; p=0.064)
<2.5	306	84 (27.5)	283	143 (50.5)	1.85 (95% CI: 1.49–2.29; p<0.001)
≥2.5	453	122 (26.9)	478	220 (46.0)	1.70 (95% CI: 1.42–2.04; p<0.001)
Baseline T1 gadolinium-enhancing lesions, n					
0	449	174 (38.8)	441	263 (59.6)	1.55 (95% CI: 1.35–1.78; p<0.001)
≥1	303	31 (10.2)	312	94 (30.1)	2.85 (95% CI: 1.96–4.13; p<0.001)

Fig. 6 Subgroup analyses of the proportion of patients with NEDA in the pooled OPERA I and OPERA II mITT population. Subgroup-level testing used the Cochran–Mantel–Haenszel test and treatment-by-subgroup interactions were assessed by the Breslow–Day test. *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *IFN* interferon, *mITT* modified intent-to-treat, *NEDA* no evidence of disease activity, *OCR* ocrelizumab, *ROW* rest of world. [a]A significant treatment-by-subgroup interaction was observed for baseline EDSS score (<4.0 versus ≥4.0; p=0.022); p values <0.05 from the treatment-by-subgroup interaction test indicate that the treatment effect of OCR versus IFN is not the same at each subgroup-level

with a higher ocrelizumab exposure had a greater benefit on 12W-CDP and 24W-CDP. Therefore, it might be possible that in the BMI subgroups the ocrelizumab exposure had an influence on confirmed disability progression results. However, a contradictory significant treatment-by-subgroup interaction between BMI strata was observed (p = 0.043) for the endpoint of new or enlarging T2 lesion endpoints, indicating a higher magnitude of ocrelizumab treatment benefit in heavier versus lighter patients; however, this finding requires further study before clinical meaningfulness can be confirmed. Subgroup analyses of other studies with MS DMTs have demonstrated an interaction between age and disability progression, with lower levels of progression in younger patients; this was not observed in the current study.

In conclusion, the treatment benefit of ocrelizumab versus IFN β-1a, measured by clinical and MRI outcomes, was maintained across almost all the subgroups and strata of interest, and the pattern of treatment benefit across all subgroups was consistent with that from the pooled OPERA studies. The results show that RMS patients with a wide range of demographic and clinical characteristics benefit more from treatment with ocrelizumab than from IFN β-1a.

Data sharing statement

Compliance with ethical standards

Conflicts of interest B. Turner has received honoraria, travel grants and been a member of advisory boards for Biogen, Merck Serono, Novartis, Sanofi Genzyme, and Roche. C. Papeix has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, and has participated in advisory boards in the past years with Biogen, MedDay, Merck Serono, Novartis, Roche, and Sanofi Genzyme. B. Cree has received personal compensation for consulting from AbbVie, Akili, Biogen, EMD Serono, GeNeuro, Novartis, and Sanofi Genzyme. L. Kappos's institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for Prof. Kappos's activities as principal investigator and member or chair of planning and steering committees or advisory boards in trials sponsored by Actelion, Addex, Almirall, Bayer HealthCare Pharmaceuticals, CSL Behring, Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharma, Pfizer, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Santhera, Siemens, Teva, UCB, and XenoPort; license fees for Neurostatus products; and research grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, the Gianni Rubatto Foundation, the Novartis Research Foundation and the Roche Research Foundation. X. Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva, and Trophos. J.S. Wolinsky has served on advisory boards, data monitoring or steering committees, has consulting agreements, or received speaker honoraria from the following entities: AbbVie, AcademicCME, Actelion, ACTRIMS, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, CMSC, ECTRIMS, EMS Serono, Forward Pharma A/S, France Foundation, GeNeuro, MA's Communications, Masters MS, MedDay Pharmaceuticals, McDonnell Boehnen Hulbert & Berghoff, Novartis Pharmaceuticals, Otsuka, PlatformQ Health Education, PRIME, PTC Therapeutics, Roche Genentech, Sanofi Genzyme, Strategic Consultants International, Takeda, Teva Pharmaceuticals, and WebMD; royalties are received for out-licensed monoclonal antibodies through UTHealth from Millipore

Corporation. R. Buffels is an employee of F. Hoffmann-La Roche Ltd. H. Garren is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. D. Fiore is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. J. Han is an employee of Genentech, Inc. S.L. Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Symbiotix, Bionure, Alector, and Molecular Stethoscope; he has also received travel reimbursement from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

Ethical standards This trial was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki.

Informed consent All patients provided written informed consent.

References

1. Hauser SL, Bar-Or A, Comi G et al (2017) Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 376:221–234
2. Papeix C, Cree B, Turner B et al (2017) Subgroup analyses of annualised relapse rates in patients with relapsing multiple sclerosis who received ocrelizumab or interferon beta-1a in the phase III OPERA I and OPERA II studies. In: 7th Joint European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Meeting; 25–28 October 2017; Paris, France. Poster P687
3. Polman CH, Reingold SC, Banwell B et al (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69:292–302
4. Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M (2015) Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult Scler Relat Disord 4:329–333
5. Tremlett H, Paty D, Devonshire V (2006) Disability progression in multiple sclerosis is slower than previously reported. Neurology 66:172–177
6. Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, Agoropoulou C, Häring DA, Francis G, Kappos L, FREEDOMS Study Group (2012) Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol 11:420–428
7. Derfuss T, Ontaneda D, Nicholas J, Meng X, Hawker K (2016) Relapse rates in patients with multiple sclerosis treated with fingolimod: subgroup analyses of pooled data from three phase 3 trials. Mult Scler Relat Disord 8:124–130
8. Giovannoni G, Cook S, Rammohan K, Rieckmann P, Sørensen PS, Vermersch P, Hamlett A, Viglietta V, Greenberg S, CLARITY Study Group (2011) Sustained disease-activity-free status in patients with relapsing–remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol 10:329–337

9. Miller AE, O'Connor P, Wolinsky JS et al (2012) Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. Mult Scler 18:1625–1632

10. Bar-Or A, Gold R, Kappos L, Arnold DL, Giovannoni G, Selmaj K, O'Gorman J, Stephan M, Dawson KT (2013) Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the DEFINE study. J Neurol 260:2297–2305

11. Hutchinson M, Fox RJ, Miller DH et al (2013) Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing–remitting multiple sclerosis: subgroup analyses of the CONFIRM study. J Neurol 260:2286–2296

12. Kappos L, Gold R, Miller DH et al (2012) Effect of BG-12 on contrast-enhanced lesions in patients with relapsing–remitting multiple sclerosis: subgroup analyses from the phase 2b study. Mult Scler 18:314–321

13. Coles AJ, Twyman CL, Arnold DL et al (2012) Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380:1829–1839

14. Hutchinson M, Kappos L, Calabresi PA et al (2009) The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol 256:405–415

15. van Pesch V, Bartholomé E, Bissay V et al (2014) Safety and efficacy of natalizumab in Belgian multiple sclerosis patients: subgroup analysis of the natalizumab observational program. Acta Neurol Belg 114:167–178