

# Ten Years of Ocrelizumab in Relapsing Multiple Sclerosis

## The OPERA I and II Randomized Clinical Trials

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**IMPORTANCE** Preventing irreversible disability accumulation is a primary treatment goal in multiple sclerosis (MS).

**OBJECTIVE** To assess 10-year safety and efficacy of ocrelizumab (OCR) in patients with relapsing MS (RMS).

**DESIGN, SETTING, AND PARTICIPANTS** In 2 phase 3 multicenter randomized clinical trials (OPERA I and II), patients were randomized to OCR or interferon beta-1a (IFN) throughout a 2-year double-blind period (DBP) and entered an open-label extension (OLE) to receive OCR for up to an additional 8 years. Study periods were August 2011 to December 2022, with clinical cutoff on July 15, 2023. Data analyses were run between March 2023 and May 2026. Patients with RMS, aged 18 to 55 years, with an Expanded Disability Status Scale (EDSS) score of 0 to 5.5, and at least 1 relapse within the year before screening were eligible for inclusion.

**INTERVENTIONS** OCR (600 mg every 24 weeks) or IFN (44 µg 3 times weekly) in the DBP, then OCR during the OLE.

**MAIN OUTCOMES AND MEASURES** Outcomes included time to onset of 48-week confirmed disability progression (CDP) or progression independent of relapse activity (PIRA); time to reach EDSS score of 4.0 and 6.0; relapse rates; and incidence of adverse events (AEs) and serious AEs.

**RESULTS** A total of 1656 patients were randomized, and 1651 patients received either OCR (n = 825) or IFN (n = 826). A total of 1325 patients (80.0%) entered the OLE, of whom 853 (64.4%) completed the studies. A total of 1093 of 1656 patients (66.0%) were female; mean (SD) baseline age was 37.1 (9.2) years vs 37.2 (9.2) years in the OCR vs IFN arms, respectively. Over 10 years, continuous OCR (OCR-OCR) significantly reduced the hazard of 48-week CDP by 24% compared with delayed initiation (IFN-OCR; hazard ratio, 0.76; 95% CI, 0.61-0.95; *P* = .02), with 680 patients (82.2%) receiving OCR-OCR remaining free of 48-week CDP and 712 (86.1%) free of PIRA. OCR-OCR treatment reduced the hazard of progressing to key disability milestones, including EDSS of 4.0 (34%; hazard ratio, 0.66; 95% CI, 0.43-1.03; *P* = .06) and 6.0 (43%; hazard ratio, 0.57; 95% CI, 0.40-0.82; *P* = .002), with 502 (93.3%) and 774 (94.2%) retaining scores less than 4.0 and 6.0, respectively. In patients receiving OCR-OCR, relapse rates decreased from 0.139 at year 1 to 0.016 at year 10. Rates of AEs and SAEs, including serious infections, did not increase over the 8-year OLE.

**CONCLUSIONS AND RELEVANCE** In the OPERA I and II randomized clinical trials, continuous OCR treatment over 10 years provided greater benefit in preserving function than a 2-year delay in initiating OCR, reinforcing the importance of early high-efficacy treatment.

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Preventing irreversible accumulation of disability and preserving patient function is a primary treatment goal for all multiple sclerosis (MS) phenotypes, including patients with relapsing MS (RMS).<sup>1-5</sup> Ocrelizumab was the first anti-CD20 monoclonal antibody approved for treating RMS.<sup>6,7</sup> In the phase 3 OPERA I and II randomized clinical trials, treatment with ocrelizumab resulted in near-complete suppression of magnetic resonance imaging (MRI) activity, about 50% lower relapse activity, and 40% lower disability progression relative to interferon (IFN) beta-1a, while showing a comparable safety profile.<sup>8</sup> These effects on disease activity were sustained over 5 years of follow-up in the open-label extension (OLE) study, with no new safety signals.<sup>9</sup> Importantly, the risk of long-term disability accumulation, including reaching key disability milestones, was lower in patients who initiated ocrelizumab earlier vs those who switched after 2 years from IFN at the start of the OLE.<sup>10</sup> The benefit of early high-efficacy treatment initiation has also been confirmed in the 5-year follow-up of the pivotal trials of the approved anti-CD20 drugs.<sup>11,12</sup> These data highlight the importance of early and sustained treatment with a high-efficacy disease-modifying therapy (DMT) to minimize neurological damage and irreversible accumulation of disability in patients with MS.<sup>3,13-17</sup> To further understand the long-term impact of ocrelizumab treatment in patients with RMS, we present a post hoc analysis assessing the efficacy and safety profile of ocrelizumab from the pooled phase 3 OPERA I and II randomized clinical trials over a period of up to 10 years.

## Methods

### Patients, Trial Design, Protocol Approval and Registration, and Consent

Key eligibility criteria in the OPERA trials included patient age 18 to 55 years, a diagnosis of RMS (2010 revised McDonald criteria),<sup>18</sup> an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 at screening, and 2 or more documented relapses in the 2 years before screening or 1 relapse in the 1 year before screening. At the start of the double-blind controlled treatment period (DBP), patients were randomly assigned (1:1) to receive either intravenous ocrelizumab, 600 mg, every 24 weeks or subcutaneous IFN beta-1a, 44 µg, 3 times weekly (patients in each group also received a matching subcutaneous or intravenous placebo). Patients who completed the 96-week DBP were eligible to enter the 8-year OLE phase, during which all patients received ocrelizumab regardless of their original randomization to ocrelizumab (OCR-OCR) or IFN beta-1a (IFN-OCR). Additional details on the study design and eligibility criteria have been previously described.<sup>8,9</sup> The trial protocols and statistical analysis plan are available in [Supplement 1](#). Race and ethnicity were self-reported by participants.

The trial protocols (ClinicalTrials.gov identifiers: [NCT01247324](#) and [NCT01412333](#)) were approved by the relevant institutional review boards and ethics committees. Patients provided written informed consent. The study followed the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guideline.<sup>19</sup>

## Key Points

**Question** What is the long-term safety and efficacy profile of ocrelizumab in patients with relapsing multiple sclerosis (RMS)?

**Findings** In the OPERA I/II randomized clinical trials including 1656 patients with RMS, treatment with ocrelizumab for up to 10 years led to near-complete and sustained suppression of relapse activity, robust control of progression independent of relapses, and minimal disability accrual. Patients starting ocrelizumab 2 years earlier had significantly greater relapse and disability control compared with patients initially treated with interferon beta-1a, without new or cumulative safety signals emerging over the 10-year follow-up.

**Meaning** Results confirm the long-term clinical benefits and manageable safety profile of ocrelizumab and reinforce the importance of early initiation of high-efficacy treatment in patients with RMS.

## Study Outcomes

Study outcomes are described briefly below, with full details provided in the eMethods in [Supplement 2](#).

### Efficacy End Points

Clinical disability outcomes included 48-week confirmed disability progression (48-week CDP), repeated 48-week CDP, 48-week confirmed progression independent of relapse activity (PIRA), time to EDSS score of 4.0 or greater (in patients with baseline EDSS score ≤3.0), time to walking aid requirement (EDSS score ≥6.0, in patients with baseline EDSS <6.0), and 24- and 48-week confirmed disability improvement (CDI; in patients with baseline EDSS score ≥2.0). Acute outcomes included annualized relapse rate (ARR), proportion relapse free, and no evidence of disease activity (NEDA-3).

### MRI Outcomes

MRI outcomes included T1 gadolinium (Gd)-enhancing, new or enlarging (N/E) T2, and new T1 hypointense lesion counts (so-called black holes), along with percentage changes in whole-brain, cortical gray matter, and white matter volumes.

### Safety Outcomes

Safety end points included adverse events (AEs), serious AEs (SAEs), infusion-related reactions (IRRs), serious infections (SIs), immunoglobulin trajectories, standardized malignancy rates (including comparisons with controls with MS from the Danish MS Registry<sup>20</sup> and with the general population from the National Cancer Institute Surveillance, Epidemiology, and End Results [SEER] Program<sup>21</sup>), and pregnancy outcomes.

### Statistical Analysis

Statistical methods are described briefly below, with full details provided in the eMethods in [Supplement 2](#).

Analyses were performed in the pooled OPERA I and II intention-to-treat (ITT) population. The primary exposure of interest was the treatment sequence group (OCR-OCR vs IFN-OCR). Two-tailed  $\alpha = .05$  was considered significant. Analyses were performed with SAS software version 9.2 or higher (SAS Institute).

### Disability End Points

All disability end points were analyzed as time-to-event outcomes using Kaplan-Meier and Cox proportional hazards models, except for annualized rate of repeated CDP, which was analyzed using a generalized estimating equation (GEE) Poisson regression model. Hazard ratios (HRs) were adjusted by study and stratification factors (baseline EDSS score <4.0 or ≥4.0 and geographical region, which was required for regulatory purposes). Sensitivity analyses for 48-week CDP addressing potential informative censoring bias due to patient discontinuation were performed by stratifying Kaplan-Meier estimates according to completer status and by using inverse probability of censoring weighting (IPCW) models.

### Disease Activity

ARR and NEDA-3 were analyzed using a GEE Poisson regression model. Relapse-free status was assessed via survival analysis. Rate ratios (RRs) were also adjusted by study and stratification factors.

### MRI Outcomes

MRI lesion counts (T1 Gd-enhancing, N/E T2, and new T1 hypointense) were analyzed using negative binomial models adjusted by study, baseline metric values, and stratification factors. Annualized rates of brain atrophy and percentage volume changes were calculated using a mixed-effect model of repeated measures, incorporating baseline volume measurements as covariates, and compared with age- and sex-matched healthy controls<sup>22</sup> and normative data.<sup>23</sup>

### Safety Outcomes

Safety outcomes were analyzed in all ocrelizumab-exposed patients and reported as incidence rates (events per 100 patient-years [PY]) with Poisson-derived 95% confidence intervals. Malignancies (excluding nonmelanoma skin cancer [NMSC]) were adjusted for age and sex for comparison against non-MS and MS controls.<sup>20,21</sup> Major congenital anomalies were classified according to definitions in the European Surveillance of Congenital Anomalies Guide version 1.5,<sup>24</sup> as described previously.<sup>25</sup>

### Subgroup Analyses

Key disability, relapse, NEDA-3, and safety outcomes were also analyzed in treatment-naïve (TN) patients at baseline and in a subgroup of recently diagnosed TN (RDTN) patients defined as having at enrollment a disease duration of 2 years or less since symptom onset.

## Results

### Patient Demographics, Disease Characteristics, and Disposition

Overall, 1656 patients were randomized (ITT population), with 827 patients in the ocrelizumab arm and 829 in the IFN arm. In total, 1325 patients (80.0%) entered the OLE phase (ITT-OLE population), with a greater proportion of patients from the ocrelizumab arm (OCR-OCR:  $n = 702$  [84.9%]) than the

IFN-OCR arm ( $n = 623$  [75.2%]). A total of 853 patients (51.5%) completed the study, with a median (range) treatment duration of 9.7 (0-11.2) years. A total of 1093 of 1656 patients (66.0%) were female; mean (SD) baseline age was 37.1 (9.2) years vs 37.2 (9.2) years in the ocrelizumab vs IFN arms, respectively. Notably, most patients remained in the study across long-term follow-up, although retention was consistently higher in the OCR-OCR arm compared with the IFN-OCR arm. At year 5, retention was 77.3% in the OCR-OCR group vs 69.3% in the IFN-OCR group. By year 8, retention was 66.7% vs 61.8%, and at year 9, retention remained 63.9% vs 58.8%, respectively; across both arms, more than 1000 patients received treatment for at least 9 years (eFigure 1 in Supplement 2). Details on patient disposition and reasons for discontinuation are shown in eFigure 2 in Supplement 2. Baseline demographics and disease characteristics of the ITT population were well balanced between the 2 treatment groups, and the group of patients who completed the 10-year follow-up was comparable with the ITT population (Table 1). For baseline demographics and disease characteristics of the TN populations, see eTable 1 in Supplement 2.

### Clinical Efficacy Assessments

#### Disability Progression

Over the 10-year period, patients continuously treated with ocrelizumab (OCR-OCR) demonstrated sustained low levels of disability progression across all key milestones compared with those who switched from IFN beta-1a (IFN-OCR). For 48-week CDP (Figure 1A), 680 patients treated with OCR-OCR (82.2%) remained event-free over 10 years. Initial treatment with ocrelizumab resulted in a statistically significant 24% lower hazard of 48-week CDP compared with delayed initiation (HR, 0.76; 95% CI, 0.61-0.95;  $P = .02$ ). This benefit was largely established during the DBP, as progression hazards became similar between arms after switching to open-label ocrelizumab (rebaselined OLE phase: HR, 1.02; 95% CI, 0.81-1.28;  $P = .86$ ) (eFigure 3 in Supplement 2). The mean annual rate of CDP events in the OCR-OCR arm remained consistently low at 0.029% (95% CI, 0.025%-0.034%), equating to approximately 3 events per 100 PY (eFigure 4 in Supplement 2). Regarding PIRA (Figure 1B), 712 OCR-OCR patients (86.1%) remained free from 48-week confirmed progression, corresponding to a numerical 14% lower hazard compared with the IFN-OCR switch group (HR, 0.86; 95% CI, 0.67-1.10;  $P = .24$ ). For disability milestone transitions, among patients with baseline EDSS score of 3.0 or less ( $n = 538$ ), 502 patients (93.3%) in the OCR-OCR group did not progress to EDSS score of 4.0 or higher over 10 years (Figure 1C), representing a numerical 34% hazard reduction (HR, 0.66; 95% CI, 0.43-1.03;  $P = .06$ ). Finally, among patients with baseline EDSS score less than 6.0 ( $n = 822$ ), 774 patients (94.2%) in the OCR-OCR group did not require a walking aid during follow-up (Figure 1D), demonstrating a statistically significant 43% lower hazard of reaching EDSS score of 6.0 or higher compared with the IFN-OCR group (HR, 0.57; 95% CI, 0.40-0.82;  $P = .002$ ).

In sensitivity analyses addressing potential informative censoring bias, progression rates for 48-week CDP were

**Table 1. Patient Demographics and Disease Characteristics at Baseline and Last Known Follow-Up: All Patients and Patients Who Completed the Open-Label Extension**

| Characteristic                                          | No. (%)              |                      |                      |                      |
|---------------------------------------------------------|----------------------|----------------------|----------------------|----------------------|
|                                                         | All patients         |                      | OLE completers       |                      |
|                                                         | OCR-OCR<br>(n = 827) | IFN-OCR<br>(n = 829) | OCR-OCR<br>(n = 438) | IFN-OCR<br>(n = 415) |
| Time receiving treatment, median (range), y             | 9.7 (0.0-11.2)       | 9.7 (0.0-11.1)       | 10.1 (8.7-11.2)      | 10.1 (9.2-11.1)      |
| Age at baseline, mean (SD), y                           | 37.1 (9.2)           | 37.2 (9.2)           | 36.8 (8.8)           | 37.6 (8.7)           |
| Age at last known follow-up, mean (SD), y               | 45.4 (9.9)           | 44.8 (10.1)          | 47.4 (8.8)           | 48.2 (8.7)           |
| Age group, y                                            |                      |                      |                      |                      |
| <40                                                     | 247 (29.9)           | 280 (33.8)           | 90 (20.5)            | 85 (20.5)            |
| 40-59                                                   | 517 (62.5)           | 488 (58.9)           | 309 (70.5)           | 282 (68.0)           |
| ≥60                                                     | 63 (7.6)             | 61 (7.4)             | 39 (8.9)             | 48 (11.6)            |
| Sex                                                     |                      |                      |                      |                      |
| Female                                                  | 541 (65.4)           | 552 (66.6)           | 273 (62.3)           | 258 (62.2)           |
| Male                                                    | 286 (34.6)           | 277 (33.4)           | 165 (36.7)           | 157 (37.8)           |
| Race <sup>a</sup>                                       |                      |                      |                      |                      |
| American Indian or Alaska Native                        | 2 (0.2)              | 4 (0.5)              | 2 (0.5)              | 2 (0.5)              |
| Asian                                                   | 2 (0.2)              | 3 (0.4)              | 2 (0.5)              | 1 (0.2)              |
| Black or African American                               | 41 (5.0)             | 32 (3.9)             | 18 (4.1)             | 8 (1.9)              |
| Native Hawaiian or other Pacific Islander               | 1 (0.1)              | 0                    | 1 (0.2)              | 0                    |
| White                                                   | 743 (89.8)           | 757 (91.3)           | 393 (89.7)           | 384 (92.5)           |
| Other                                                   | 29 (3.5)             | 23 (2.8)             | 19 (4.3)             | 13 (3.1)             |
| Multiple                                                | 9 (1.1)              | 10 (1.2)             | 3 (0.7)              | 7 (1.7)              |
| Previous DMTs                                           |                      |                      |                      |                      |
| Yes                                                     | 224 (27.1)           | 224 (27.0)           | 123 (28.1)           | 101 (24.3)           |
| No                                                      | 603 (72.9)           | 605 (73.0)           | 315 (71.9)           | 314 (75.7)           |
| Time since MS diagnosis, mean (SD), y                   | 4.0 (4.9)            | 3.9 (4.9)            | 3.8 (4.7)            | 4.0 (5.0)            |
| Comorbidities at last known follow-up, No. <sup>b</sup> | 825                  | 623                  | 438                  | 415                  |
| None                                                    | 343 (41.6)           | 148 (23.8)           | 183 (41.8)           | 102 (24.6)           |
| 1                                                       | 241 (29.2)           | 217 (34.8)           | 122 (27.9)           | 139 (33.5)           |
| ≥2                                                      | 241 (29.2)           | 258 (41.4)           | 133 (30.4)           | 174 (41.9)           |
| EDSS at baseline, median (IQR) score                    | 2.5 (2.0-3.5)        | 2.5 (1.8-3.5)        | 2.5 (1.8-3.5)        | 2.5 (1.8-3.5)        |
| <3.0                                                    | 427 (51.6)           | 440 (53.1)           | 248 (56.6)           | 225 (54.2)           |
| 3.0 to 5.5                                              | 395 (47.8)           | 383 (46.2)           | 189 (43.2)           | 189 (45.5)           |
| ≥6.0                                                    | 5 (0.6)              | 5 (0.6)              | 1 (0.2)              | 1 (0.2)              |
| EDSS at last known follow-up, median (range) score      | 3.0 (0-7.5)          | 2.5 (0-8.5)          | 2.5 (0-7.0)          | 2.5 (0-8.0)          |
| No. of relapses in year prior to baseline               | 794                  | 801                  | 426                  | 403                  |
| 1                                                       | 553 (69.6)           | 558 (69.7)           | 295 (69.2)           | 281 (69.7)           |
| 2                                                       | 197 (24.8)           | 197 (24.6)           | 105 (24.6)           | 97 (24.1)            |
| ≥3                                                      | 44 (5.5)             | 46 (5.7)             | 26 (6.1)             | 25 (6.2)             |
| No. of T1 Gd-enhancing lesions, mean (SD)               | 1.8 (4.6)            | 1.9 (5.0)            | 1.8 (4.2)            | 1.7 (4.9)            |
| No. of T2 lesions, mean (SD)                            | 50.1 (38.8)          | 51.0 (37.8)          | 53.2 (41.4)          | 50.7 (36.1)          |
| Brain volume, mean (SD), cm <sup>3</sup>                |                      |                      |                      |                      |
| Whole-brain volume                                      | 1502.4 (88.5)        | 1500.2 (89.3)        | 1499.6 (89.0)        | 1493.0 (86.5)        |
| White matter volume                                     | 795.0 (50.2)         | 794.1 (50.0)         | 794.0 (49.5)         | 792.0 (52.1)         |
| Cortical gray matter volume                             | 563.6 (57.0)         | 561.3 (55.9)         | 561.9 (56.6)         | 557.3 (53.9)         |

Abbreviations:  
DMT, disease-modifying therapy;  
EDSS, Expanded Disability Status Scale; Gd, gadolinium;  
IFN, interferon;  
IFN-OCR, patients switching from interferon to ocrelizumab;  
MS, multiple sclerosis;  
OCR, ocrelizumab;  
OCR-OCR, patients taking continuous ocrelizumab;  
OLE, open-label extension.

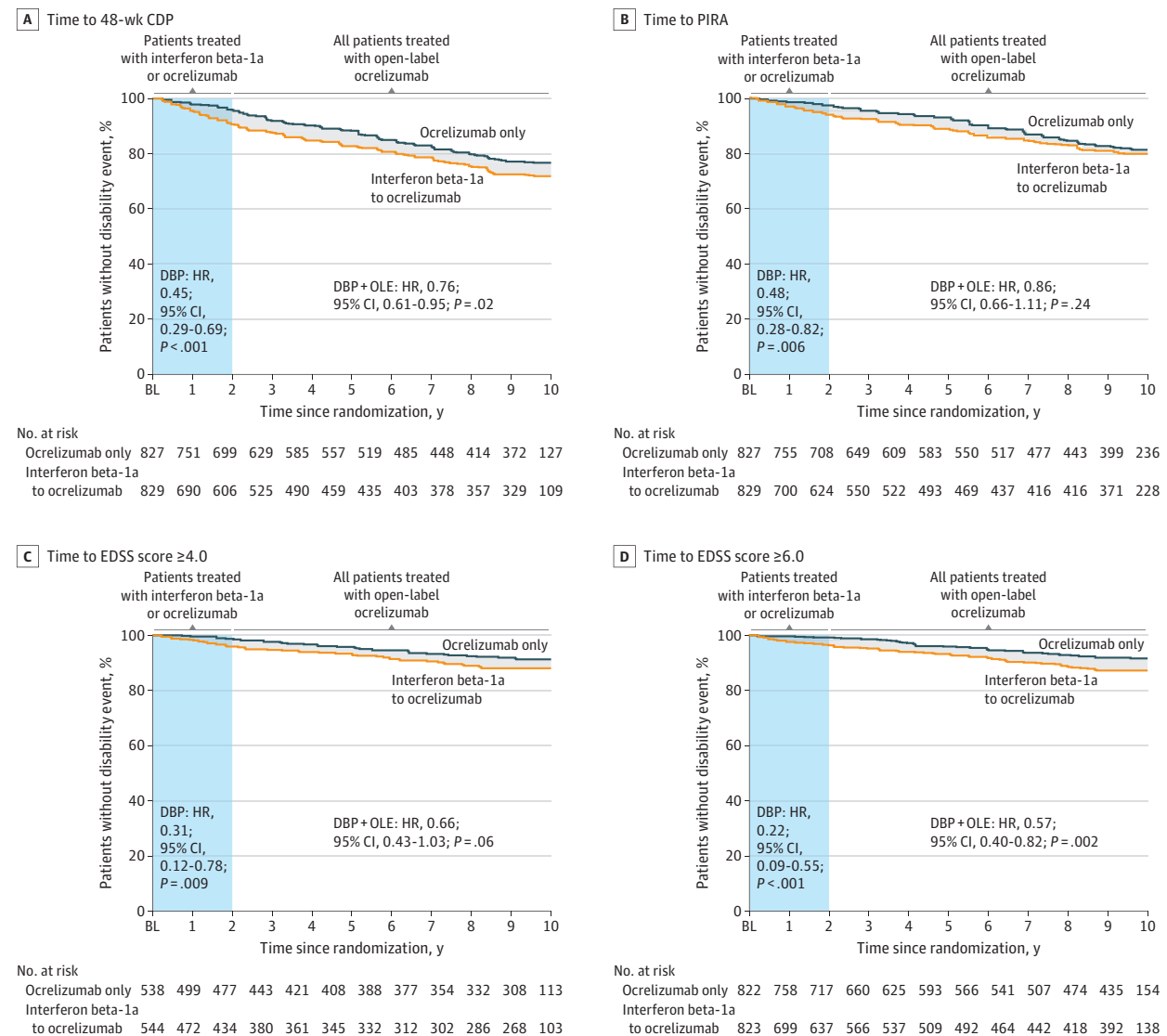
<sup>a</sup> Data were self-reported by patients.

<sup>b</sup> Comorbidities were classified using the Charlson-Deyo and Elixhauser comorbidity indices (eTable 3 in Supplement 2).

only slightly higher among patients who discontinued the study compared with completers in both the OCR-OCR arm (27.7%; 95% CI, 20.6%-34.8%; vs 21.3%; 95% CI, 17.4%-25.1%) and the IFN-OCR arm (eFigure 5 in [Supple-](#)

[ment 2](#)). Furthermore, IPCW-adjusted models yielded consistent results (HR, 0.75; 95% CI, 0.60-0.94) with the primary Cox analysis for 48-week CDP (HR, 0.76; 95% CI, 0.61-0.95).

Figure 1. Kaplan-Meier Plots Showing Time to Onset of Disability Progression



A, Cumulative survival probability according to Kaplan-Meier estimations of experiencing the first 48-week confirmed disability progression (CDP) event. Proportion of patients receiving continuous ocrelizumab (OCR-OCR) without 48-week CDP over 10 years was 82.2% (Kaplan-Meier estimate at year 10, 76.6%). Risk reduction in the double-blind period (DBP) was 55%, and the risk reduction over 10 years was 24%. B, Cumulative survival probability according to Kaplan-Meier estimations of experiencing the first progression independent of relapse activity (PIRA) event. Proportion of OCR-OCR patients without PIRA over 10 years was 86.1% (Kaplan-Meier estimate at year 10, 81.3%). Risk reduction in the DBP was 52% and the average risk reduction over 10 years was 14%. C, Cumulative survival probability according to Kaplan-Meier estimations of experiencing the first time to Expanded Disability Status

(EDSS) score  $\geq 4.0$  event. Proportion of OCR-OCR patients without an EDSS score  $\geq 4.0$  event over 10 years was 93.3% (Kaplan-Meier estimate at year 10, 91.4%). Risk reduction in the DBP was 69% and the risk reduction over 10 years was 34%. D, Cumulative survival probability according to Kaplan-Meier estimations of experiencing the first time to EDSS score  $\geq 6.0$  event. Proportion of OCR-OCR patients without an EDSS score  $\geq 6.0$  event over 10 years was 94.2% (Kaplan-Meier estimate at year 10, 92.1%). Risk reduction in the DBP was 78% and the risk reduction over 10 years was 43%. Kaplan-Meier estimates at year 10 differ from the actual proportion of patients without events over 10 years due to censoring rules. Eleven time points are displayed corresponding to assessments conducted every 48 weeks up to week 528 (year 10). BL indicates baseline; HR, hazard ratio; OLE, open-label extension.

### Disability Improvement

Numerically more patients in the OCR-OCR arm experienced disability improvement over the 10-year period (rates of 48-week CDI at year 10: 26.7% vs 23.1%) compared with the IFN-OCR group (HR, 1.17; 95% CI, 0.91-1.51;  $P = .21$ ) (eFigure 6A in Supplement 2). In 138 (3.6%) and 108 (5.6%) of OCR-OCR and IFN-OCR patients with CDI, respectively, subse-

quent disability progression was observed. Similar trends were observed for 24-week CDI (eFigure 6A in Supplement 2).

### Relapses

Over 10 years, more patients remained relapse free in the OCR-OCR group ( $n = 604$  [73.0%]) compared with the IFN-OCR group ( $n = 524$  [63.2%]), representing a 38% risk reduction (HR,

0.62; 95% CI, 0.52-0.74;  $P < .001$ ). In the 8-year OLE period, 564 patients (80%) were relapse free regardless of the treatment allocation during the DBP. The number of relapses decreased consistently over time, and in year 10, only approximately 1 out of 100 patients experienced a relapse (Figure 2A).

### MRI Lesion Activity

Treatment with ocrelizumab led to rapid and near-complete suppression of MRI activity, evident from week 24 for T1 Gd-enhancing lesions and weeks 24 to 48 for N/E T2 lesions; this control was maintained throughout the study (eFigure 7A and B in Supplement 2). In patients switching from IFN to ocrelizumab (IFN-OCR), a similar suppression was observed after switching, and from the first OLE year onward, no difference was seen between the 2 arms (eFigure e7A and B in Supplement 2). Importantly, treatment with ocrelizumab also resulted in near-complete suppression of new T1 hypointense lesions; this suppression was maintained throughout the study, including in IFN-OCR patients in the OLE (eFigure 7C in Supplement 2).

### NEDA-3

Over 10 years of treatment, 485 of 827 patients (58.6%) treated with OCR-OCR showed NEDA compared with 315 of 829 patients (38.0%) treated with IFN-OCR, representing a 51.6% risk reduction (RR, 0.48; 95% CI, 0.41-0.55;  $P < .001$ ). Throughout the study, the proportion of OCR-OCR patients achieving NEDA-3 remained above 84% each year, whereas for IFN-OCR patients, this was observed only from year 2 onward in the OLE (Figure 2B).

### Brain Atrophy

Whole-brain volume loss from baseline to year 10 (Figure 2C) was numerically lower in the OCR-OCR group (−3.38%; 95% CI, −3.59% to −3.18%) compared with the IFN-OCR group (−3.62%; 95% CI, −3.82% to −3.41%); this difference was significant up to year 8 (difference in adjusted means, 0.24%;  $P = .004$ ). During the OLE, both groups receiving ocrelizumab showed stable and comparable annualized atrophy rates (eFigure 8A in Supplement 2). Similar trends were seen for white matter atrophy and cortical gray matter atrophy (eFigure 8B and C in Supplement 2).

Annual rates of whole-brain atrophy appeared to be similar to normal brain aging, as described in a normative dataset of individuals with similar age ranges and scanned in MRI scanners with similar field strength (1.5 T) and processing methodology (SIENA<sup>22</sup>) to those used in the OPERA trials (Figure 2C).

### Subgroup Analyses in TN and RDTN Patients

Among TN patients continuously treated with ocrelizumab ( $n = 603$ ), 101 (83.3%) remained free from 48-week CDP and 525 (87.1%) remained free from 48-week PIRA over 10 years (eFigure 9A and B in Supplement 2). By year 10, 15 (26%) experienced disability improvement (48-week CDI) (eFigure 6B in Supplement 2). Overall, 367 (60.9%) achieved 10-year NEDA-3, with annual NEDA-3 rates remaining greater than 84% throughout follow-up (eFigure 10A in Supplement 2). Relapses declined consistently, reaching an ARR of approxi-

mately 0.01 (1 relapse per 100 PY) at year 10 (eFigure 10B in Supplement 2).

In the RDTN OCR-OCR subgroup ( $n = 375$ ), 63 patients (82.4%) remained free from 48-week CDP and 322 (85.9%) were free from 48-week PIRA (eFigure 9C and D in Supplement 2). By year 10, 11 (29.0%) achieved 48-week disability improvement (eFigure 6C in Supplement 2). Ten-year NEDA-3 was achieved by 234 patients (62.4%), with yearly rates remaining higher than 86% (eFigure 10C in Supplement 2). Relapse control was equally robust, with an ARR of 0.007 (1 relapse per 143 PY) at year 10 (eFigure 10D in Supplement 2).

### Safety

In total, 1448 patients (OCR-OCR,  $n = 825$ ; IFN-OCR,  $n = 623$ ) received 1 or more ocrelizumab infusion (cumulative exposure of 10 813.5 PY). Safety data reported here exclude COVID-19 events unless specified (data inclusive of COVID-19 are provided in eTable 2 in Supplement 2).

### AEs

The cumulative rate of AEs was 194 per 100 PY (95% CI, 191-196) and did not increase over the follow-up period, reflecting lower AE rates during the OLE relative to the DBP (Table 2). Rates of SAEs (6.3 per 100 PY; 95% CI, 5.8-6.8), including the rates of SIs and fatalities, remained stable over the 10-year period (Table 2). Rates of AEs, SAEs, and fatalities, including COVID-19 infections, can be found in eTable 2 in Supplement 2.

### Treatment Modification and Discontinuation

AEs leading to dose modification or interruption occurred in less than 0.5% of patients ( $n = 103$ ), primarily IRRs. Approximately 1% of patients discontinued ocrelizumab annually due to AEs (1.26 per 100 PY; 95% CI, 1.06-1.49), most commonly due to IRRs and urinary tract infections (UTIs).

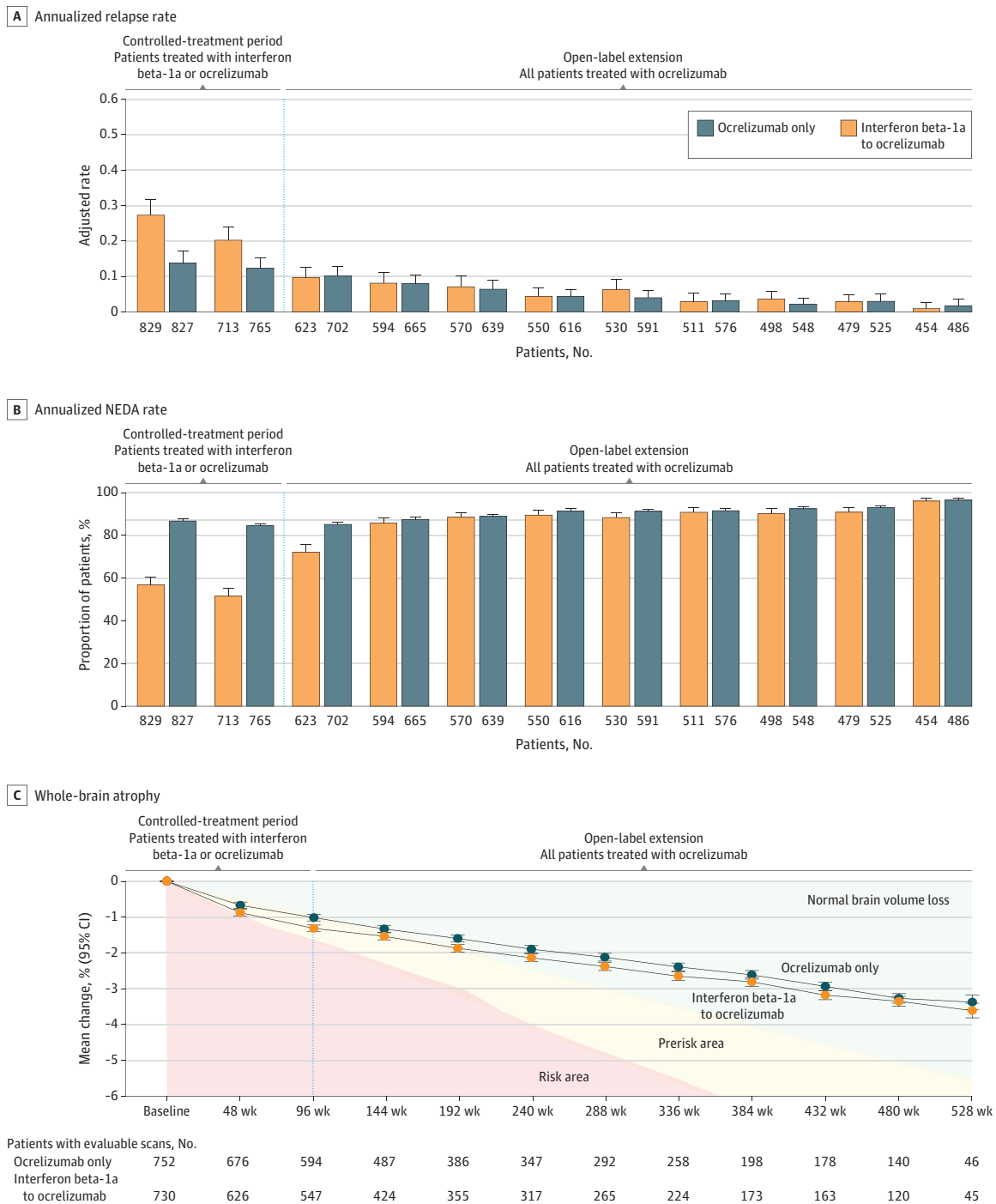
### Infusion-Related Reactions

Incidence of IRRs was highest with the first infusion (349/1448 [24.1%]; OCR-OCR: 27.5%; IFN-OCR: 19.6%). The frequency of IRRs decreased with subsequent dosing, with IRRs observed in less than 3% of patients at each infusion after year 2 in the OLE. Among patients experiencing IRRs ( $n = 514$ ), most were mild (58.2%) or moderate (36.0%), 5.6% were severe, and life-threatening (episode of bronchospasm) in 1 patient; severity also decreased with subsequent dosing (eFigure 11 in Supplement 2). Frequently observed IRR symptoms included pruritus, rash, throat irritation, and flushing, mostly occurring during the infusion, a pattern that remained consistent over time.

### Infections and SIs

Cumulative infection rates were 66.0 per 100 PY (95% CI, 64.5-67.6) over the 10-year period compared with 84.5 per 100 PY (95% CI, 79.9-89.4) during the 2-year DBP in OCR-OCR patients. UTIs and respiratory tract infections were most common. Cumulative SI rates (1.8 per 100 PY) remained consistent with the DBP rates (OCR: 0.8 per 100 PY; IFN: 1.8 per 100 PY) (Table 2) and generally stable, with limited year-on-year variation (Figure 3A; values including COVID-19 reported in

**Figure 2. Bar and Line Graphs Showing Relapse Rate, Disease Activity, and Brain Volume Change During the Double-Blind Period and Open-Label Extension**



No evidence of disease activity (NEDA-3) status was defined as the combined absence from relapses, 48-week confirmed disability progression (CDP), and magnetic resonance imaging (MRI) activity (T1 gadolinium-enhancing lesions and new or enlarging [N/E] T2 lesions). A rebaselining approach was used, with relapses and CDP rebaselined at week 12 and MRI metrics rebaselined at week 24 (time of first postbaseline scan). For annualized NEDA rates, rebaselining was also applied at the beginning of each year. Error bars represent 95% confidence intervals. In panel C, colored background areas represent normative data for brain atrophy derived from a MAGNIMS multicenter cohort

of healthy controls (Battaglini and colleagues<sup>22</sup>). According to Battaglini and colleagues,<sup>22</sup> normal brain volume loss (green) is defined as values <80th percentile; prerisk area (yellow) as values between 80th and 95th percentiles; and risk area (red) as values >95th percentile. Normative percentiles were derived from brain imaging performed in 1.5T scanners, as most patients in OPERA were scanned in 1.5T scanners. Normative percentiles from 30- to 40-year-olds were used for years 0 to 4, and rates from 40- to 50-year-olds were used for years 5 to 10 for alignment with the median age of patients in OPERA throughout the 10-year period.

Table 2. Rates of Adverse Events (AEs), Excluding COVID-19 Infections, During the Double-Blind Period (DBP) and Open-Label Extension (OLE)<sup>a</sup>

| AE                                 | Rate per 100 PY (95% CI) |                   |                                        |
|------------------------------------|--------------------------|-------------------|----------------------------------------|
|                                    | DBP <sup>b</sup>         |                   |                                        |
|                                    | IFN (n = 826)            | OCR (n = 825)     | DBP + OLE, OCR (n = 1488) <sup>c</sup> |
| Any AE                             | 296 (287-305)            | 290 (281-299)     | 194 (191-196)                          |
| AEs leading to discontinuation     | 3.93 (2.96-5.12)         | 2.35 (1.63-3.28)  | 1.26 (1.06-1.49)                       |
| Serious AEs                        | 6.29 (5.05-7.75)         | 5.39 (4.26-6.72)  | 6.29 (5.82-6.78)                       |
| Infections and infestations        | 67.8 (63.5-72.2)         | 84.5 (79.9-89.4)  | 66.0 (64.5-67.6)                       |
| Urinary tract infections           | 9.7 (8.1-11.4)           | 11.6 (9.9-13.5)   | 11.0 (10.4-11.6)                       |
| Upper respiratory tract infections | 9.4 (7.8-11.1)           | 13.3 (11.5-15.3)  | 10.7 (10.1-11.3)                       |
| Nasopharyngitis                    | 8.3 (6.9-9.9)            | 13.0 (11.2-15.0)  | 8.7 (8.1-9.2)                          |
| Bronchitis                         | 2.2 (1.5-3.1)            | 3.5 (2.6-4.6)     | 3.1 (2.7-3.4)                          |
| Influenza                          | 3.3 (2.4-4.4)            | 3.1 (2.3-4.2)     | 2.1 (1.9-2.4)                          |
| Serious infections <sup>d</sup>    | 1.79 (1.16-2.64)         | 0.83 (0.43-1.45)  | 1.76 (1.52-2.03)                       |
| Pneumonia                          | 0.14 (0.02-0.52)         | 0.07 (0.002-0.39) | 0.43 (0.31-0.57)                       |
| Urinary tract infections           | 0.14 (0.02-0.52)         | 0 (NE)            | 0.13 (0.07-0.22)                       |
| Infusion-related reactions         | 7.9 (6.5-9.5)            | 34.9 (31.9-38.1)  | 11.2 (10.5-11.8)                       |
| Malignancies <sup>e</sup>          | 0.14 (0.02-0.52)         | 0.28 (0.08-0.71)  | 0.44 (0.33-0.59)                       |
| Excluding NMSC <sup>f</sup>        | NA                       | NA                | 0.29 (0.33-0.59)                       |
| Fatalities <sup>g</sup>            | 0.14 (0.02-0.52)         | 0.07 (0-0.38)     | 0.08 (0.04-0.16)                       |

Abbreviations: IFN, interferon; NA, not available; NE, not estimable; NMSC, nonmelanoma skin cancer; OCR, ocrelizumab; PY, patient-year.

<sup>a</sup> COVID-19-related AEs were excluded from this analysis, but patients continued to contribute to the incidence of all other AEs (see eTable 2 in Supplement 2 for COVID-19 analysis). AEs were classified according to MedDRA versions 18.0 and 25.1. Multiple occurrences of the same AE in 1 patient are counted multiple times, except for malignancies.

<sup>b</sup> Data as of April to July 2015.

<sup>c</sup> Includes patients who received any dose of OCR during the DBP and OLE phase, including patients originally randomized to comparator (IFN) who switched to open-label OCR treatment (data as of March 2023).

<sup>d</sup> Serious infections are defined using AEs falling into the Medical Dictionary for Regulatory Activities (MedDRA) system organ class "infections and

infestations," using the query "Is the event non-serious or serious?" from the AE case report form.<sup>28,29</sup>

<sup>e</sup> Malignancies are identified using AEs falling into the standard MedDRA query "malignant tumors (narrow)" (malignancy listings are provided in eTable 6 in Supplement 2) and are reported as incidence rate per 100 PY of first malignancy.

<sup>f</sup> In the DBP, 1 case of NMSC was observed in the IFN group and none were observed in the OCR group.

<sup>g</sup> Nine deaths (excluding COVID-19, see eTable 2 in Supplement 2 for additional details) were reported as suicide (n = 3) and 1 event each of respiratory failure, tracheal stenosis, myocardial infarction, enterococcal infection, esophageal adenocarcinoma, and death of cause unknown.

eFigure 12 in Supplement 2).<sup>30,31</sup> Lower respiratory infections (mostly pneumonia), UTIs, gastrointestinal, and skin infections were most common (eTable 4 in Supplement 2). Five serious herpes virus cases were observed (1 genital herpes simplex, 1 herpes simplex, 1 herpes simplex meningitis, and 2 herpes zoster); all recovered, and only 1 patient discontinued treatment. No cases of cryptococcosis, listeriosis, aspergillosis, toxoplasmosis, cytomegalovirus, or progressive multifocal leukoencephalopathy were observed. For additional information on all SIs, including COVID-19 infection rates, see eTables 2 and 4 in Supplement 2. Most infections (97.5%) and SIs (88.9%) resolved, allowing 97.6% of patients to remain receiving ocrelizumab (Figure 3B). For additional information on infections and SIs in the subgroups of TN patients, see eFigure 13 in Supplement 2.

### Immunoglobulins

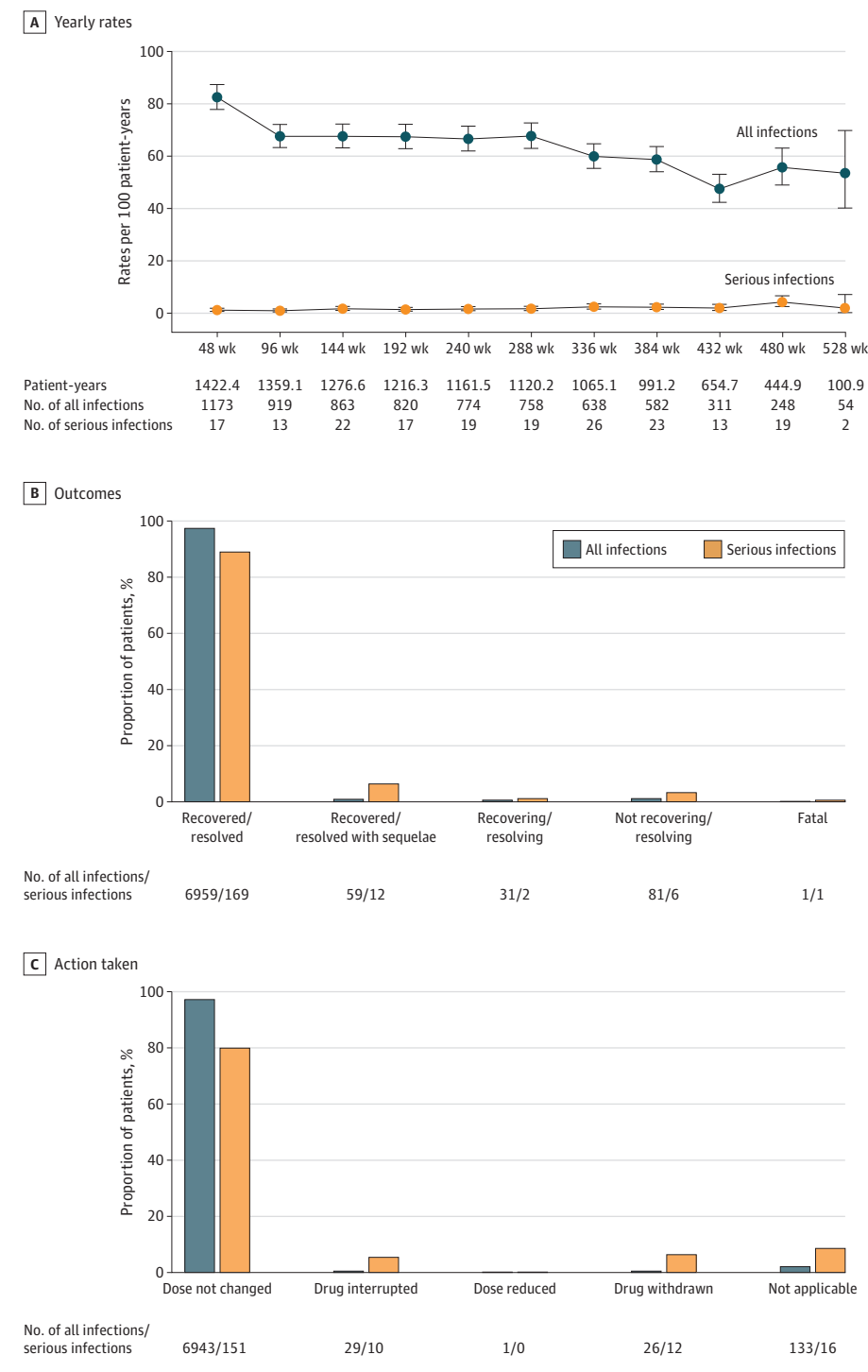
A decrease in immunoglobulin G (IgG) levels was observed, but mean levels remained within normal ranges, and in 1223 of 1448 patients (84.5%), values remained above the lower limit of normal (LLN; 565 mg/dL) (to convert IgG from mg/dL to g/L, multiply by 0.01) (eFigure 14A in Supplement 2). Among those who experienced periods of IgG less than LLN (n = 217), lev-

els remained below LLN in 123 cases (56.7%), while values returned to normal within 3 infusion cycles in 94 patients (43.3%).<sup>32</sup> Overall, 2.5% of patients had 1 or more SIs (n = 55 SIs, including COVID-19) during a period with IgG less than LLN, with 48 (87.3%) occurring with IgG levels of 400 mg/dL or higher (eTable 5 in Supplement 2). Prolonged exposure did not increase the risk of SIs regardless of IgG status (eFigure 15 in Supplement 2). COVID-19 and non-COVID pneumonia were the most observed SIs while IgG was less than LLN. Results for IgM and IgA are shown in eFigure 14B and C in Supplement 2.

### Malignancies

Cumulative crude malignancy rate was 0.44 per 100 PY (95% CI, 0.33-0.59) and 0.29 (95% CI, 0.20-0.41) after excluding NMSC, which was the most observed type of cancer (eTable 6 in Supplement 2). Yearly rates of all malignancies remained stable, with only minor yearly fluctuations over the entire study period (eFigure 16A in Supplement 2). Age- and sex-adjusted incidence rates excluding NMSC (0.27 per 100 PY; 95% CI, 0.14-0.55) were similar to rates in the general population (SEER: 0.34 per 100 PY) and among patients with MS (Danish MS Registry: 0.36 per 100 PY). The age-adjusted female breast cancer incidence rate (0.09; 95% CI, 0.04-0.28)

**Figure 3. Line and Bar Graphs Showing Infections and Serious Infections in Patients Treated With Ocrelizumab During the Double-Blind Period and Open-Label Extension, Excluding COVID-19**



Adverse events (AEs) were encoded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Infections were identified using AEs falling into the MedDRA system organ class "infections and infestations," and standard criteria for determining seriousness and severity were used.<sup>28,29</sup> All infections include serious infections (SIs). A slight increase in the rate of SIs was observed at year 10 (vs year 9), driven by an increase in the number of non-COVID-19 pneumonia cases. Patients with exposure >11 years are not represented in the graph; 1 infection and 0 SIs were reported beyond 11 years of treatment. Error bars in panel A represent 95% confidence intervals. All infections: total number of events (n = 7141); number of patients with events (n = 1141); SIs: total number of events (n = 190); number of patients with event (n = 144). Outcomes analysis of infections and SIs: 1 fatal case occurred (enterococcal infection; n = 1). Percentages use the total number of events but exclude those events with unknown or missing outcome. For frequency counts by outcome, multiple occurrences of the same AE in an individual are counted separately. All infections: total number with action taken with ocrelizumab (OCR) (n = 7140); SIs: total number with action taken with OCR (n = 189). Not applicable refers to events where action taken with OCR is missing or to events that occurred after the last administered dose of OCR in the study.

was similarly consistent with background rates in the general population (SEER: 0.15) and among patients with MS (Danish MS Registry: 0.19) (eFigure 16B and C in Supplement 2).

#### Liver Injury

During the DBP, the proportion of patients with at least 1 episode of alanine aminotransferase (ALT)/aspartate

aminotransferase (AST) more than 3 times the upper limit of normal was higher in the IFN vs the ocrelizumab arm (ALT: 8.8% vs 2.2%; AST: 4.6% vs 1.0%), and remained stable throughout the OLE (all OCR: 2.9% ALT and 1.7% AST). In year 8, 1 patient experienced an increase in AST, ALT, and bilirubin, which met the biochemical criteria for the Hy Law. The event was reported as related to

simvastatin; it resolved and did not lead to any change in study treatment.

### Pregnancies

Of 56 reported pregnancies (54 with known outcomes, as 2 pregnant patients were lost to follow-up), 35 pregnancies (62.5%) were considered to have in utero exposure, of which 25 had received the last dose of ocrelizumab 0 to 3 months before the last menstrual period and 10 during the first trimester. Most pregnancies resulted in live births (40/56 [71.4%]); other outcomes included therapeutic or elective termination ( $n = 10$ ), spontaneous abortion ( $n = 2$ ), stillbirth ( $n = 1$ ), and ectopic pregnancy ( $n = 1$ ) (eTable 7 in Supplement 2). Most live births were full term (33/40 [82.5%]). One major congenital anomaly (trisomy 21) was reported in a preterm live birth to a 36-year-old woman (gravida, 2; para, 1) exposed to ocrelizumab approximately 1 month before the last menstrual period. Most therapeutic or elective abortions (9 of 10) were reported in pregnancies considered to have in utero exposure; in only 1 case was a medical reason (anembryonic pregnancy) explicitly reported for therapeutic or elective termination, and terminations occurred very early in the pregnancy (median gestational age, 7 weeks).

## Discussion

The long-term extension of the phase 3 OPERA I and II randomized clinical trials is the largest cohort of patients with RMS continuously treated for over a decade with ocrelizumab. The current analysis provides robust evidence of the significant and durable benefit of ocrelizumab in patients with RMS, shown by the near-complete and sustained suppression of acute activity, the low levels of disability accrual, and a manageable long-term safety profile.

Relapses remain significant drivers of accumulation of disability, mostly in the early stages of MS, whereas PIRA becomes the dominant driver as the disease evolves.<sup>4</sup> Preserving patient function in RMS therefore requires adequate control of both relapse and progression biological mechanisms.<sup>4,33</sup>

In this long-term analysis, ocrelizumab demonstrated a robust and persistent effect on focal disease activity across radiological and clinical end points. Treatment was associated with rapid, near-complete suppression of new MRI activity, which was sustained over 10 years, encompassing not only acute T1 Gd-enhancing lesions and N/E T2 lesions, but also chronic T1 hypointense lesions, which reflect axonal loss and matrix destruction and are associated with long-term disability.<sup>34,35</sup>

Clinical relapse control was equally robust. Over 70% of patients continuously treated with ocrelizumab remained free of relapses over 10 years, and a consistent decrease in relapse frequency was observed over time, reaching about 1 relapse per 100 PY by year 10. Notably, patients switching from IFN also achieved rapid and durable control of inflammatory activity, with approximately 80% remaining relapse free over the 8-year OLE period regardless of the initial treatment allocation during the DBP. These results are consistent with

the low relapse rates observed among TN patients in the ENSEMBLE trial (ARR, 0.02) over a 4-year period<sup>36</sup> and with large real-world cohorts showing superior relapse control with ocrelizumab compared with other medium- and high-efficacy DMTs.<sup>26,27,37</sup>

The current analysis also confirms a strong impact on progression biology. Over 80% of patients continuously treated with ocrelizumab (including TN patients) remained free of 48-week CDP, and nearly 90% were free of PIRA. Ambulation was highly preserved, with nearly 95% of patients with no walking impairment at baseline remaining unrestricted (EDSS score  $<4.0$ ). The proportion of patients likely to show irreversible disability progression<sup>30</sup> was therefore low. Equally low was the probability of disease activity in any given year, with more than 84% of patients receiving continuous ocrelizumab achieving NEDA-3 annually, which is consistent with recent real-world evidence on ocrelizumab.<sup>31,32,38</sup>

The results also emphasize the critical importance of early treatment initiation. Patients with a 2-year delay in ocrelizumab initiation (initially randomized to IFN) exhibited worse cumulative disability and NEDA-3 outcomes. Despite receiving ocrelizumab for at least 8 years, significant differences in disability accumulation persisted, supporting existing evidence that early initiation of high-efficacy DMTs is crucial to delaying long-term disability.<sup>14,17,39</sup> The results in TN patients further support the use of ocrelizumab as a first-line treatment, leading to better long-term outcomes.

Continuous treatment with ocrelizumab was also associated with disability improvement, and over the 10-year period, improvement was actually more frequent than worsening, consistent with evidence from large real-world studies.<sup>37</sup> These improvements were durable, with less than 5% of those who improved showing subsequent worsening. This neuroprotective effect was further corroborated by brain volume changes. Patients treated with ocrelizumab, including those switching from IFN, showed stable brain atrophy rates during the OLE, normalizing to levels observed in healthy aging.<sup>22,23</sup>

Several key aspects should be highlighted regarding the safety results in this population. Because the COVID-19 pandemic emerged during the study, safety analyses were conducted to both include and exclude COVID-19 events, allowing for a long-term characterization not confounded by the pandemic. Over the 10-year period (excluding COVID-19), no new or unexpected safety findings emerged. Rates of AEs and SAEs did not increase over time, and discontinuation due to AEs remained low ( $<1\%$  per year). Infections and IRRs were the most common AEs. IRRs were mostly mild to moderate, predominantly during the first infusion, and decreased significantly with subsequent dosing. Few patients discontinued due to IRRs.

Upper respiratory infections and UTIs were the most common nonserious infections; their rates did not increase during follow-up (excluding COVID-19). Most infections ( $>97\%$ ) resolved, allowing more than 97% of patients to continue treatment with ocrelizumab without interruptions or dose changes. SIs (excluding COVID-19) remained infrequent, with respiratory tract infections, UTIs, gastrointestinal infections,

and skin infections being the most common types, similar to findings with other anti-CD20 drugs<sup>40,41</sup> and reports from real-world MS cohorts.<sup>42-44</sup> Nearly 95% of SIs resolved (approximately 6% with sequelae), allowing more than 90% of patients to remain receiving treatment. While rates of SIs appear consistent with ranges reported in some real-world studies,<sup>42</sup> a recent large comparative study in the US has suggested a potential 2-fold increase in the risk of SIs compared with platform therapies.<sup>45</sup> A Swedish nationwide registry study found that ocrelizumab and rituximab have comparable infection risks.<sup>46</sup> However, another much larger multinational study (over 50 000 patients) showed no increased risk of SIs with ocrelizumab compared with other DMTs in patients with RMS.<sup>47</sup> Ocrelizumab was also associated with lower rates of hospitalization and infection-related hospitalizations compared with rituximab.<sup>48</sup>

Regarding hypogammaglobulinemia, which remains a concern among neurologists treating patients with anti-CD20 drugs, in particular older patients more likely to exhibit immunosenescence,<sup>49</sup> 85% of patients maintained normal IgG levels throughout the follow-up. Crucially, prolonged ocrelizumab exposure did not increase the risk of SIs, regardless of IgG status. A recent multivariate analysis of this cohort identified presence of comorbidities, recent relapse activity, and EDSS score of 6.0 or higher as significant risk factors for SIs, whereas hypogammaglobulinemia and longer treatment duration were not significant risk factors.<sup>50</sup> Other real-world studies have also shown that hypogammaglobulinemia in ocrelizumab-treated patients is not associated with increased risk of SIs.<sup>45</sup> Recent evidence from OLEs of trials with other anti-CD20 drugs also suggests no association of hypogammaglobulinemia with increased infection risk.<sup>12,40</sup>

The stable malignancy rates (including female breast cancer) do not indicate the presence of a time-dependent exposure effect, and crucially, rates were consistent with those reported in typical MS populations<sup>20</sup> or even the general population.<sup>21</sup> These results are also consistent with the findings from an ongoing, much larger, multinational, observational study (>50 000 patients) that showed no increased risk of malignancies with ocrelizumab compared with other DMTs in patients with RMS over a 4-year period.<sup>46</sup>

Finally, in this cohort, pregnancy outcomes were generally consistent with rates from the large Roche safety data-

base (>3200 pregnancies), which showed no increased risk of malformations compared with epidemiological background rates.<sup>25</sup> The imbalance in therapeutic or elective abortions observed in utero in the present cohort likely reflects surveillance bias caused by uncertainties about safety data in the pre-approval period rather than for medical reasons (90% of cases were observed prior to 2017),<sup>51,52</sup> particularly when ocrelizumab was given close to conception or in the first trimester.

## Limitations

As with all long-term OLE studies, these data have inherent limitations. The absence of a contemporaneous control arm in the OLE phase, the post hoc nature of the analysis, and the potential for rater bias must be considered. Attrition bias is also an important factor, as only slightly more than 50% of patients who were randomized to the study completed the 10-year follow-up. However, it should be noted that more than 1000 patients (64%) completed year 9, which suggests that the attrition approaching 50% predominantly reflects accelerated study withdrawals in the last year of the study. Patient decision was the most common reason for study withdrawal, and this may partly be due to worsening of clinical status given that patients with early withdrawals had slightly higher rates of disability progression, in particular those initially randomized to IFN.

## Conclusions

This 10-year analysis of the OPERA I and II randomized clinical trials confirms the significant and durable impact of ocrelizumab on the long-term course of RMS. Continuous treatment with ocrelizumab led to robust control of both major drivers of disability: near-complete suppression of inflammatory activity and a strong attenuation of progression independent of relapses, resulting in high rates of NEDA-3 and minimal disability accrual over a decade. Early and continuous treatment resulted in greater preservation of patient function than a 2-year delay in initiating treatment, reinforcing the importance of early initiation of high-efficacy treatment. This durable efficacy was achieved without new or cumulative safety signals, confirming a favorable long-term benefit-risk profile with ocrelizumab in the management of patients with RMS.

## ARTICLE INFORMATION

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**Other - design of study:** Giovannoni.

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