Efficacy and Safety of Ocrelizumab in Relapsing Multiple Sclerosis: Results of the Phase III, Interferon β-1a–controlled OPERA I and OPERA II Studies

F Lublin,[1] DL Arnold,[2,3] A Bar-Or,[2] G Comi,[4] SL Hauser,[5] K Selmaj,[6] A Traboulsee,[7] P Chin,[8] P Fontoura,[9] H Garren,[9] G Klingelschmitt,[9] D Masterman,[8] L Kappos,[10] HP Hartung[11] on behalf of the OPERA I and OPERA II investigators

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]McGill University, Montreal, QC, Canada; [3]NeuroRx Research, Montreal, QC, Canada; [4]University Vita-Salute San Raffaele, Milan, Italy; [5]University of California, San Francisco, CA, USA; [6]Medical University of Lodz, Lodz, Poland; [7]University of British Columbia, Vancouver, BC, Canada; [8]Genentech, Inc., South San Francisco, CA, USA; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [10]University Hospital Basel, Basel, Switzerland; [11]Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

BACKGROUND

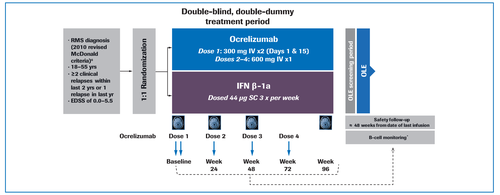
- Despite the availability of disease-modifying treatments for relapsing multiple sclerosis (RMS), patients often continue to experience disease activity and accrue neurologic disability[1–3]
- Furthermore, the safety profile and monitoring requirements of available higher-efficacy treatments has generally limited their use to later stages of disease[1,4,5]
- Ocrelizumab (OCR) is a humanized monoclonal antibody that selectively depletes CD20+ B cells, while preserving the capacity for B-cell reconstitution and preexisting humoral immunity
- OPERA I and OPERA II were two identical Phase III randomized, double-blind, double-dummy trials to evaluate the efficacy and safety of OCR vs interferon (IFN) β-1a in patients with RMS

METHODS

Study Design

- Patients were randomized (1:1) to receive OCR 600 mg via intravenous infusion every 24 weeks or subcutaneous IFN β-1a 44 µg three times weekly through a 96-week treatment period (**Figure 1**)
- Patients in both groups received matching subcutaneous or intravenous placebo treatments
- All patients received intravenous methylprednisolone 100 mg (and optional analgesics/antipyretics and antihistamines) prior to infusion
- Eligible patients were stratified by region (USA vs rest of world) and baseline Expanded Disability Status Scale (EDSS) score (<4.0 vs ≥4.0)

Figure 1. OPERA I and OPERA II study design



*Continued monitoring occurs if B cells are not repleted.
EDSS, Expanded Disability Status Scale; IFN, interferon; IV, intravenous; OLE, open-label extension; RMS, relapsing multiple sclerosis; SC, subcutaneous.

Study Endpoints

- Primary endpoint
  - Protocol-defined annualized relapse rate (ARR) by 96 weeks during the double-blind, double-dummy treatment period
- Key secondary endpoints
  - Time to onset of 12-week confirmed disability progression (CDP) through Week 96
  - Total number of T1 gadolinium-enhancing lesions over 96 weeks
  - Total number of new or enlarging T2 hyperintense lesions over 96 weeks
  - Time to onset of 24-week CDP through Week 96
  - Percentage change in brain volume as detected by brain MRI from Week 24 to Week 96; analysis from baseline to Week 96 was an exploratory endpoint
  - Proportion of patients with an EDSS score ≥2.0 who have no evidence of disease activity (NEDA) by Week 96; NEDA analysis in all patients was an exploratory endpoint
- Safety
  - Safety and tolerability of OCR 600 mg intravenously every 24 weeks in patients with RMS

Statistical Analysis

- All efficacy analyses were performed on the intent-to-treat (ITT) population
- Annualized relapse rate (ARR) was analyzed using a negative binomial model testing for treatment differences between OCR and IFN β-1a, adjusted by region and baseline EDSS score as covariates
- A significant result at a two-sided alpha <0.05 would demonstrate a superior effect of OCR in reducing ARR compared with IFN β-1a
- CDP was prespecified as pooled analyses from the integrated OPERA I and OPERA II trial datasets

RESULTS

Baseline Demographics and Disease Characteristics

- Baseline characteristics were well balanced between OPERA I and OPERA II studies, and between treatment arms (**Table 1**)

Table 1. Baseline demographics and disease characteristics

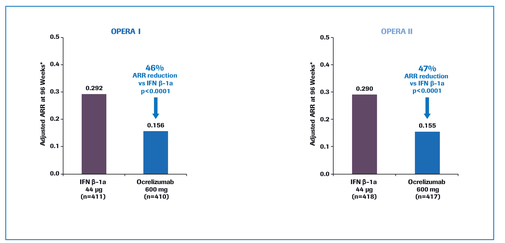
	OPERA I		OPERA II	
	IFN β-1a 44 µg n=411	Ocrelizumab 600 mg n=410	IFN β-1a 44 µg n=418	Ocrelizumab 600 mg n=417
Age, yrs, mean (SD)	36.9 (9.3)	37.1 (9.3)	37.4 (9.0)	37.2 (9.1)
Female, n (%)	272 (66.2)	270 (65.9)	280 (67.0)	271 (65.0)
Time since MS onset, yrs, mean (SD)	6.3 (6.0)	6.7 (6.4)	6.7 (6.1)	6.7 (6.1)
Time since MS diagnosis, yrs, mean (SD)	3.7 (4.6)	3.8 (4.8)	4.1 (5.1)	4.2 (5.0)
Relapses in previous 12 months, mean (SD)	1.3 (0.6)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
Previously untreated,* n (%)	292 (71.4)	301 (73.8)	314 (75.3)	304 (72.9)
EDSS, mean (SD)	2.8 (1.3)	2.9 (1.2)	2.8 (1.4)	2.8 (1.3)
Patients with Gd+ lesions, n (%)	155 (38.1)	172 (42.5)	172 (41.4)	161 (39.0)
Number of Gd+ T1 lesions, mean (SD)	1.9 (5.2)	1.7 (4.2)	2.0 (4.9)	1.8 (5.0)
Number of T2 lesions, mean (SD)	51.1 (39.9)	51.0 (39.0)	51.0 (35.7)	49.3 (38.6)

*Untreated with disease-modifying therapy in 2 years prior to study entry (safety population)
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN, interferon; ITT, intent-to-treat; MS, multiple sclerosis; SD, standard deviation

Relapses

- OCR significantly reduced protocol-defined ARR by 46% in OPERA I and by 47% in OPERA II, compared with IFN β-1a (p<0.0001 for both; **Figure 2**)

Figure 2. Protocol-defined ARR by 96 weeks

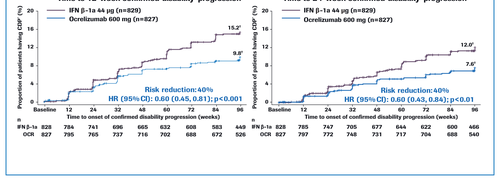


ITT
*Adjusted ARR calculated by negative binomial regression adjusted for baseline EDSS score (<4.0 vs ≥4.0), and geographic region (USA vs ROW).
ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; IFN, interferon; ITT, intent-to-treat; ROW, rest of world.

Disability Progression

- In prespecified pooled analyses of OPERA I and OPERA II, compared with IFN β-1a, OCR reduced the risk of 12-week CDP by 40% (p<0.001) and 24-week CDP by 40% (p<0.01; **Figure 3**)

Figure 3. Pooled analyses of time to onset of disability progression confirmed after ≥12 weeks and ≥24 weeks

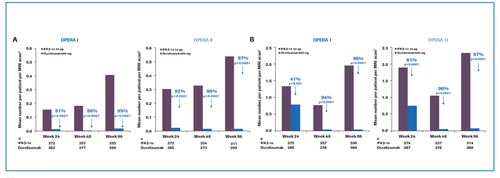


ITT
*Disability progression was defined as an EDSS increase of ≥1.0 point from the baseline EDSS score that was not attributable to another etiology when the baseline score was ≤5.5, and ≥0.5 point and when the baseline score was >5.5.
†Proportion of patients having CDP through Week 96.
CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFN, interferon; ITT, intent-to-treat; OCR, ocrelizumab.

Brain MRI Endpoints

- Compared with IFN β-1a, OCR significantly reduced the mean number of T1 gadolinium-enhancing lesions and the mean number of new or enlarging T2 hyperintense lesions by Week 24; significant reductions continued through the 96-week treatment period (**Figure 4**)
- In addition, OCR reduced the rate of whole brain volume loss from baseline to Week 96, compared with IFNβ-1a, by 23.5% in OPERA I (p<0.0001) and 23.8% in OPERA II (p=0.0001; **Figure 5**)

Figure 4. Relative reduction in the mean number of T1 Gd+ lesions across timepoints (A) and mean number of new or enlarging T2 hyperintense lesions across timepoints (B) per MRI scan in the OCR vs IFN β-1a-treated groups (exploratory endpoints)



ITT
*Adjusted by means calculated by negative binomial regression and adjusted for baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs ≥4.0), and geographical region (USA vs ROW).
†Adjusted by means calculated by negative binomial regression and adjusted for baseline T2 lesion count, baseline EDSS (<4.0 vs ≥4.0), and geographical region (USA vs ROW).
EDSS, Expanded Disability Status Scale; Gd+, gadolinium–enhancing; IFN, interferon; ITT, intent-to-treat; MRI, magnetic resonance imaging; ROW, rest of world.

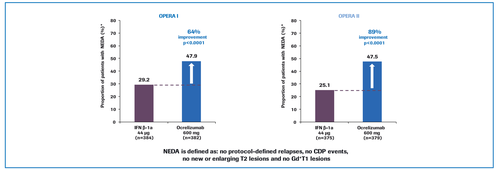
Figure 5. Percent change in whole brain volume from baseline to Week 96 (exploratory endpoint)

CI, confidence interval; IFN, interferon.

No Evidence of Disease Activity (NEDA)

- In an analysis of all patients in the ITT population, OCR increased the proportion of patients that achieved NEDA vs IFN β-1a in OPERA I and OPERA II by 64% and 89%, respectively, through Week 96 (p<0.0001 for both; **Figure 6**).

Figure 6. NEDA at Week 96 (exploratory endpoint)



ITT
*Compared using the Cochran–Mantel–Haenszel test stratified by geographic region (USA vs ROW) and baseline EDSS score (<4.0 vs ≥4.0). MRI scans from weeks 24, 48 and 96 were taken into consideration for the MRI criteria of the NEDA endpoint.
CDP confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+ gadolinium–enhancing; IFN, interferon; ITT, intent-to-treat; NEDA, no evidence of disease activity; MRI, magnetic resonance imaging; ROW, rest of world.

Safety

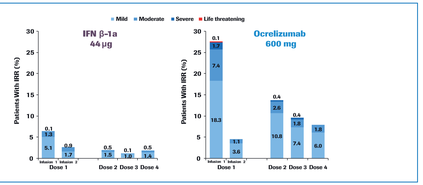
- The proportion of patients reporting adverse events (AEs) was 83.3% for both the OCR and IFN β-1a groups across OPERA I and OPERA II studies (**Table 2**)
- The most commonly reported AEs were infusion-related reactions (IRRs) and infections in the OCR group, and influenza-like illness and local cutaneous reactions in the IFN β-1a group
- More OCR-treated patients experienced at least one IRR vs those in the IFNβ-1a group who received placebo infusions (30.9% for OCR and 7.3% for IFN β-1a in OPERA I; 37.6% for OCR and 12.0% for IFN β-1a in OPERA II). Most were mild to moderate and reported at the first infusion (27.5% for OCR compared with 6.5% for IFN β-1a in a pooled analysis of OPERA I and OPERA II); IRRs decreased in frequency and severity with subsequent dosing (**Figure 7**), and were manageable with premedication, infusion adjustments and symptomatic treatment
- A higher proportion of patients treated with OCR reported respiratory tract infections compared with IFN β-1a
- The proportion of patients reporting a herpes virus–associated infection was 5.9% with OCR and 3.4% with IFN β-1a; most were mild to moderate
- Serious AEs were reported in 6.9% of OCR-treated patients and 8.7% of IFN β-1a-treated patients across OPERA I and OPERA II studies
  - In the OCR arm: 1.3%, infections and infestations; 1.0%, nervous system disorders; 0.7%, injury, poisoning, and procedural complications
  - In the IFN β-1a arm: 2.9%, infections and infestations; 1.3%, nervous system disorders; 1.2%, injury, poisoning, and procedural complications
- Six malignancies were reported across OPERA I and OPERA II
  - 4 in the OCR arm: two invasive ductal breast carcinomas, one renal cell carcinoma and one malignant melanoma
  - 2 in the IFN β-1a arm: one mantle cell lymphoma and one squamous cell carcinoma in the chest
- Three deaths were reported; none were considered related to study treatment
  - 1 (<1%) in the OCR arm (suicide, OPERA II)
  - 2 (<1%) in the IFN β-1a arm (suicide, OPERA I; mechanical ileus, OPERA II)

Table 2. AEs over the 96-week treatment period

n (%)	IFN β-1a 44 µg (n=826)	Ocrelizumab 600 mg (n=825)
Total number of patients with ≥1 AE	**688 (83.3)**	**687 (83.3)**
Total number of patients with ≥1 AE occurring at a frequency ≥5% in either arm	**539 (65.3)**	**544 (65.9)**
Injury, poisoning and procedural complications	**155 (18.8)**	**333 (40.4)**
Infusion-related reaction	80 (9.7)	283 (34.3)
General disorders and administration-site conditions	**396 (47.9)**	**173 (21.0)**
Influenza-like illness	177 (21.4)	38 (4.6)
Injection-site erythema	127 (15.4)	1 (0.1)
Fatigue	64 (7.7)	64 (7.8)
Injection-site reaction	45 (5.4)	2 (0.2)
Infections and infestations	**433 (52.4)**	**482 (58.4)**
Upper respiratory tract infection	87 (10.5)	125 (15.2)
Nasopharyngitis	84 (10.2)	122 (14.8)
Urinary tract infection	100 (12.1)	96 (11.6)
Sinusitis	45 (5.4)	46 (5.6)
Bronchitis	29 (3.5)	42 (5.1)
Nervous system disorders	**252 (30.5)**	**224 (27.2)**
Headache	124 (15.0)	93 (11.3)
Psychiatric disorders	**144 (17.4)**	**149 (18.1)**
Depression	54 (6.5)	64 (7.8)
Insomnia	38 (4.6)	46 (5.6)
Musculoskeletal and connective tissue disorders	**207 (25.1)**	**204 (24.7)**
Back pain	37 (4.5)	53 (6.4)
Arthralgia	51 (6.2)	46 (5.6)

Table includes only pooled AEs occurring in ≥5% of patients in at least one treatment group and the corresponding system organ classes.
AE, adverse event; IFN, interferon.

Figure 7. Infusion-related reactions over time*†



*Numbers in columns represent the proportion of patients experiencing a grade of IRR; †Grading per Common Terminology Criteria. Note: All received 100 mg IV methylprednisolone.
AE, adverse event; IFN, interferon; IRR, infusion-related reaction.

CONCLUSIONS

- **Compared with IFN β-1a, ocrelizumab significantly reduced disease activity on clinical and brain MRI endpoints in both OPERA I and OPERA II**
- **Overall, in OPERA I and OPERA II, ocrelizumab had a favorable safety profile over the 96-week study period**
- **Results of OPERA I and OPERA II showed that targeting CD20+ B cells with ocrelizumab is a potential therapeutic approach in relapsing MS**

DISCLOSURES

F Lublin reports funding of research from Biogen Idec, Novartis, Teva Neuroscience, Genzyme, Sanofi, Celgene, Transparency Life Sciences, NIH, NMSS; consulting agreements/advisory boards/data and safety monitoring boards for Bayer HealthCare Pharmaceuticals, Biogen Idec, EMD Serono Inc., Novartis, Teva Neuroscience, Actelion, Sanofi, Acorda, Questcor/Mallinckrodt, F Hoffmann-La Roche Ltd, Genentech, Inc., Celgene, Genzyme, MedImmune, Osmotica, XenoPort, Receptos, Forward Pharma, BBB technologies, and Akros; is co–chief editor for *Multiple Sclerosis and Related Disorders*; and has current financial interests/stock ownership in Cognition Pharmaceuticals LLC; D Arnold reports equity-interest in NeuroRx Research, which performed the MRI analysis for the trial, and consultation fees from Acorda, Biogen Idec, Genzyme, F Hoffmann-La Roche Ltd, Innate Immunotherapeutics, MedImmune, Mitsubishi Pharma, Novartis, Receptos, Sanofi, and Teva; A Bar-Or has received personal compensation for consulting, serving on scientific advisory boards, and/or speaking activities from Bayer, Bayhill Therapeutics, Berlex, Biogen Idec, BioMS, Diogenix, Eli Lilly, Genentech Inc., GSK, Guthy-Jackson/CGE Merck Serono, Novartis, Ono Pharmaca, F Hoffmann-La Roche Ltd, Sanofi, Teva Neuroscience, and Wyeth; G Comi has received compensation for consulting services and/or speaking activities from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Bayer, Excemed, the Serono Symposia International Foundation, Almirall, Chugai, and Receptos; SL Hauser serves on the scientific advisory boards for Annexon, Symbiotix, and Bionure; he has also received travel reimbursement and writing assistance from F Hoffmann-La Roche Ltd for CD20-related meetings and presentations; K Selmaj has received honoraria for advisory boards from Biogen, Novartis, Teva, F Hoffmann-La Roche Ltd, Merck, Synthon, Receptos, and Genzyme; A Traboulsee has received honoraria for advisory boards from Genzyme and F Hoffmann-La Roche Ltd He is a steering committee member for F Hoffmann-La Roche Ltd P Chin is an employee and shareholder of Genentech, Inc.; P Fontoura is an employee and shareholder of F Hoffmann-La Roche Ltd; H Garren is an employee and/or shareholder of F Hoffmann-La Roche Ltd; G Klingelschmitt is an employee and/or shareholder of Genentech, Inc.; L Kappos' institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for Prof Kappos' 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, CLC 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; royalties from Neurostatus Systems AG; research grants from the Swiss Multiple Sclerosis Society, Swiss National Research Foundation, the European Union, Gianni Rubatto Foundation, Novartis Research Foundation, and Roche Research Foundation; HP Hartung has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval by the Rector of Heinrich-Heine University from Bayer, Biogen, GeNeuro, Genzyme, Merck Serono, MedImmune, Novartis, Octapharma, Opexa, F. Hoffmann-La Roche Ltd, Teva, and Sanofi.

ACKNOWLEDGMENTS

We would like to thank all patients, their families, and the investigators who participated in this trial. This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Support for third-party writing assistance for this presentation was provided by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

REFERENCES

1. Markowitz CE, *et al. Am J Manag Care* 2010;16:S211–8.
2. Sorensen PS, *et al. J Neurol Sci* 2007;259:128–32.
3. Shirani A, *et al. JAMA* 2012;308:247–56.
4. Hartung HP, *et al. Expert Rev Neurother* 2011;11:351–62.
5. Kappos L, *et al. Lancet Neurol* 2011;10:745–58.
6. Polman C, *et al. Ann Neurol* 2011;69:292–302.

Presented at the 2016 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC); National Harbor, MD, USA; June 1–4, 2016

Poster DX33