Poster DMT22

Enrique Alvarez | enrique.alvarez@cuanschutz.edu

Ofatumumab Reduces Clinical and Radiological Activity in People With Recently Diagnosed Treatment-Naïve Relapsing Multiple Sclerosis Irrespective of Baseline Serum Neurofilament Light Chain Levels

Gabriel Pardo,[1] Ludwig Kappos,[2,3] Anne H. Cross,[4] Jens Kuhle,[2,3] Xavier Montalban,[5] Natalia Khachanova,[6] Alit Bhatt,[7] Rebecca Piccolo,[8] Jing Xi,[9] Ibolya Boer,[10] Douglas L. Arnold,[11,12] Enrique Alvarez,[13] Tjalf Ziemssen[14]

[1]Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; [2]Neurologic Clinic and Policlinic and MS Center, Department of Head, Spine and Neuromedicine, University Hospital Basel, Basel, Switzerland; [3]Research Center for Clinical Neuroimmunology and Neuroscience (RC2NB), Departments of Biomedicine and Clinical Research, University Hospital and University of Basel, Basel, Switzerland; [4]Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA; [5]Department of Neurology-Neuroimmunology, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain; [6]Progov Russian National Research Medical University, Moscow, Russia; [7]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [9]China Novartis Institutes for Biomedical Research Co. Ltd., Novartis, Shanghai, People's Republic of China; [10]Novartis Pharma AG, Basel, Switzerland; [11]Brain Imaging Centre, Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada; [12]NeuroRx Research, Montreal, Canada; [13]Department of Neurology, Rocky Mountain MS Center, University of Colorado, Aurora, CO, USA; [14]Center of Clinical Neuroscience, Department of Neurology, University Clinic Carl-Gustav Carus, Dresden, Germany

INTRODUCTION

- In the phase 3 ASCLEPIOS I/II trials (NCT02792218/NCT02792231) in people with relapsing multiple sclerosis (pwRMS), ofatumumab (OMB) was significantly more effective than teriflunomide (TER) at suppressing magnetic resonance imaging lesion and relapse activity and reducing 3-month confirmed disability worsening risk regardless of baseline levels of serum neurofilament light chain (sNfL)[1]
- Baseline sNfL levels were prognostic for on-study lesion formation in the overall ASCLEPIOS I/II population[1]
- The prognostic value of sNfL for lesion formation was also demonstrated in the subgroup of recently diagnosed (within 3 years) treatment-naïve (RDTN) pwRMS, a population for whom disease prognosis is a challenge due to the considerable variability of disease course[1]

OBJECTIVE

- To compare the effects of OMB vs TER on relapses, new or enlarging T2 (neT2) lesions, and the odds of maintaining no evidence of disease activity (NEDA-3) status in RDTN participants from ASCLEPIOS I/II based on their baseline sNfL levels

METHODS

Study Design

- A total of 1882 pwRMS were randomized to OMB or TER in ASCLEPIOS I/II
- The baseline sNfL cutoff was predefined in the clinical study protocol (ie, before measuring sNfL or any clinical or radiological outcomes) as the median sNfL value for the overall population across ASCLEPIOS I/II (9.3 pg/mL)
- The subgroup of RDTN participants was stratified into high (>baseline median) and low (≤baseline median) sNfL groups
- Quantification of sNfL levels was performed centrally (Navigate BioPharma Services, Carlsbad, CA, USA), as a single batch at the end of the trials, using a validated Quanterix Simoa® NF-light advantage kit

Outcomes

- Within each sNfL subgroup, the following outcomes were compared for OMB vs TER:
  - **Adjusted annualized relapse rates (ARRs)** over the study duration (≤30 months)
  - **Adjusted annualized rates of neT2 lesions** (last available scan compared with baseline)
  - **Proportion of RDTN participants achieving NEDA-3** at Months 12 and 24

Statistical Analyses

- **Adjusted ARR**
  - Negative binomial regression model with log-link to the number of relapses, adjusted for treatment, baseline sNfL category, region, and study as factors; number of relapses in the previous year, baseline Expanded Disability Status Scale (EDSS), baseline number of gadolinium-enhancing (Gd+) T1 lesions, and the patient's age at baseline as covariates; and treatment by baseline sNfL category interaction
- **Adjusted annualized rates of neT2 lesions (compared with baseline)**
  - Negative binomial model adjusted for treatment, baseline sNfL category, region, and study as factors; age and baseline volume of T2 lesions as continuous covariates; and treatment by baseline sNfL category interaction
- **Effect on NEDA-3**
  - Logistic regression for each time period adjusted for treatment and region as factors, and age, baseline EDSS, and number of Gd+ T1 lesions at baseline as continuous covariates

RESULTS

Participants

- Among 1882 pwRMS randomized, 576 were RDTN and had sNfL data at baseline (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics of RDTN pwRMS

Parameters	Low sNfL category (≤9.3 pg/mL) N=274 (47.6%)	High sNfL category (>9.3 pg/mL) N=302 (52.4%)
Age, years	36.7 (8.8)	35.9 (9.7)
Female sex, n (%)	180 (66)	209 (69)
MS duration since first symptom, years	3.5 (4.4)	3.1 (3.6)
No. of relapses in the year before the study	1.3 (0.7)	1.3 (0.7)
Time since onset of most recent relapse, months	5.8 (4.8)	5.8 (5.7)
EDSS score	2.2 (1.2)	2.3 (1.2)
Normalized brain volume, cm^3	1478.4 (64.9)	1468.2 (71.1)
Number of Gd+ T1 lesions	0.4 (1.0)	2.6 (4.8)
Patients free of Gd+ T1 lesions, n (%)	206 (75)	116 (38)
T2 lesion volume, cm^3	5.9 (7.2)	12.3 (12.4)
sNfL, median, pg/mL	6.77	15.29

EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; pwRMS, people with relapsing multiple sclerosis; RDTN, recently diagnosed treatment-naïve; sNfL, serum neurofilament light chain
Data are expressed as mean (SD) unless specified otherwise

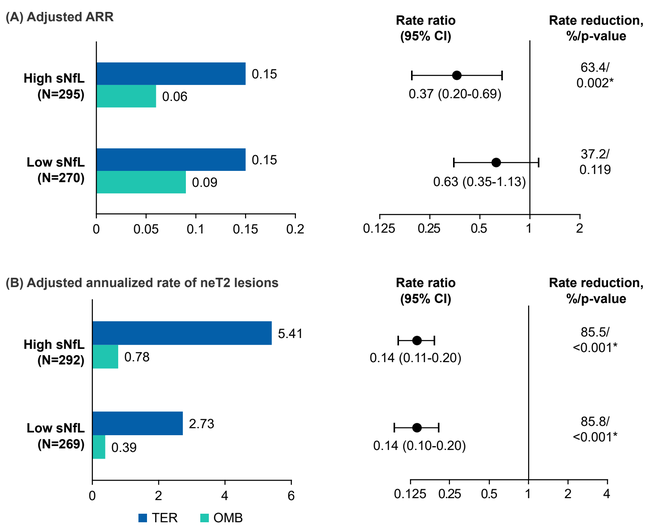
Relapses

- OMB reduced the adjusted ARR by 63.4% (p=0.002) and 37.2% (p=0.119) vs TER in the high and low sNfL categories, respectively (**Figure 1A**)

neT2 Lesions

- OMB reduced the annualized rate of neT2 lesions by 85.5% and 85.8% vs TER (both p<0.001) in the high and low sNfL categories, respectively (**Figure 1B**)

Figure 1. Treatment Effect on (A) ARR and (B) neT2 Lesions per Baseline sNfL

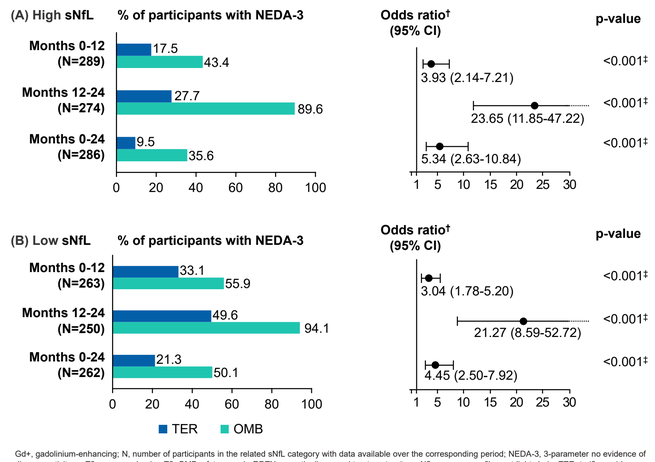


ARR, annualized relapse rate; N, number of participants in the related sNfL category; neT2, new or enlarging T2; OMB, ofatumumab; sNfL, serum neurofilament light chain; TER, teriflunomide
‡Indicates statistical significance (2 sided) at the 0.05 level

NEDA-3

- A significantly higher proportion of RDTN participants achieved NEDA-3 status with OMB vs TER, regardless of baseline sNfL levels (**Figure 2**)

Figure 2. Treatment Effect on NEDA-3 Status* per Baseline sNfL for (A) High and (B) Low sNfL



Gd+, gadolinium-enhancing; N, number of participants in the related sNfL category with data available over the corresponding period; NEDA-3, 3-parameter no evidence of disease activity; neT2, new or enlarging T2; OMB, ofatumumab; RDTN, recently diagnosed treatment-naïve; sNfL, serum neurofilament light chain; TER, teriflunomide
*NEDA-3 is defined as no 6-month confirmed disability worsening, no confirmed relapse, no neT2 lesion compared with baseline, and no Gd+ T1 lesions; †Higher odds ratios and larger CIs at Months 12-24 may be attributed to re-baselining and lower disease activity compared with Months 0-12. Analysis was conducted on a modified set excluding RDTN participants who discontinued from study drug prematurely for reasons other than "lack of efficacy" or "death" and had NEDA-3 before discontinuations; ‡Indicates statistical significance (2 sided) at the 0.05 level

KEY FINDINGS & CONCLUSIONS

- In the subgroup of recently diagnosed treatment-naïve participants with relapsing multiple sclerosis (MS) enrolled in the ASCLEPIOS I/II trials, ofatumumab (OMB) was consistently associated with reductions in clinical and radiological activity vs teriflunomide (TER) regardless of baseline serum neurofilament light chain (sNfL) levels
- OMB also significantly increased the odds of maintaining NEDA-3 status compared with TER regardless of baseline sNfL levels
- The results support the benefit of using high-efficacy therapies, such as OMB, at an early stage in the MS disease course irrespective of the sNfL levels at baseline

Scan to obtain a copy of the poster

https://bit.ly/CMSCDMT22

References

1. Ziemssen T et al. *Front Immunol*. 2022;13:852563.

Acknowledgments

Medical writing support was provided by Anupam Dwesar and Sreelatha Komatireddy and design support by Edward Kattekola, all of Novartis Healthcare Pvt. Ltd., Hyderabad, India. Editorial assistance for this poster was provided by Envision Pharma Group and was funded by Novartis Pharmaceuticals Corporation. The final responsibility for the content lies with the authors

Disclosures

Gabriel Pardo has received personal compensation for serving as a consultant for Biogen, Celgene, EMD Serono, Genentech, Genzyme, Greenwich Neuroscience, Horizon Therapeutics, Novartis, and TG Therapeutics and has received personal compensation for serving on speakers' bureaus for Biogen, Bristol Myers Squibb, Celgene, EMD Serono, Novartis, and Viela Bio. **Ludwig Kappos'** institution (University Hospital Basel) has received the following exclusively for research support: steering committee, advisory board, and/or consultancy fees from Bayer, Biogen, Bristol Myers Squibb, Celltrion, Clene Nanomedicine, Eli Lilly (Suisse) SA, EMD Serono, Galapagos NV, Genentech, Janssen, Kiniksa, Merck Healthcare AG, Minoryx, Novartis, Neurostatus UHB AG, Roche, Sanofi, Santhera, Shionogi BV, Wellmera AG, and Zai Lab; speaker fees from Bristol Myers Squibb, Janssen, Novartis, Roche, and Sanofi; grants from the European Union, Innosuisse, Merck Healthcare AG, Novartis, and Roche; and testimony from Df-Mp Molina & Pohlman. **Anne H. Cross** has received fees or honoraria for consulting from Biogen, Bristol Myers Squibb, EMD Serono, F. Hoffmann-La Roche Ltd, Genentech, Horizon Therapeutics, Jazz Pharmaceuticals, Novartis, Octave, and TG Therapeutics. Jens Kuhle has received speaker fees, research support, and/or travel support from and/or served on advisory boards for Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Octave Bioscience, the Progressive MS Alliance, Roche, Sanofi, the Swiss MS Society, the Swiss National Research Foundation (320030_189140/1), and the University of Basel. **Xavier Montalban** has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials, or has participated in advisory boards of clinical trials in the past years with AbbVie, Actelion, Alexion, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, EXCEMED, F. Hoffmann-La Roche Ltd, Genzyme, Immunic, Janssen, MedDay, Merck, the MS International Federation, Mylan, the National MS Society, NervGen, Novartis, Sandoz, Sanofi-Genzyme, Teva, and TG Therapeutics. **Natalia Khachanova** has received honoraria for participation in clinical trials or as a speaker from Biocad, Generium, Jonhson & Jonhson, Merck, Novartis, Roche, Sanofi, TG Therapeutics, and Valenta. **Alit Bhatt**, **Rebecca Piccolo**, **Jing Xi**, and **Ibolya Boer** are employees of Novartis. **Douglas L. Arnold** has received personal fees from Biogen, Biohaven, Bristol Myers Squibb, Eli Lilly and Company, EMD Serono, Find Therapeutics, GlaxoSmithKline, Gossamer Bio, Kiniksa, Merck, Novartis, Sanofi, and Shionoggi and has ownership interest in NeuroRx. **Enrique Alvarez** has received compensation for consulting from Alexion, Biogen, Celgene/Bristol Myers Squibb, EMD Serono/Merck, Genentech/Roche, Horizon/Amgen, Motric Bio, Novartis, Sanofi, Scionic, and TG Therapeutics and has received compensation for research from Atara, Biogen, Genentech/Roche, the National Multiple Sclerosis Society, the National Institutes of Health, Novartis, the Patient-Centered Outcomes Research Initiative, Rocky Mountain MS Center, Sanofi, and TG Therapeutics. **Tjalf Ziemssen** has received personal compensation for participating in advisory boards, trial steering committees, data and safety monitoring committees, scientific talks, and project support from Almirall, BAT, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, Teva, and Vitaccess

This study was sponsored by Novartis Pharma AG, Basel, Switzerland

Poster presented at the Consortium of Multiple Sclerosis Centers (CMSC) 38th Annual Meeting • May 29-June 1, 2024 • Nashville, TN, USA

Previously presented at the American Academy of Neurology Annual Meeting • April 13-18, 2024 • Denver, CO, USA and at ACTRIMS Forum • February 29-March 2, 2024 • West Palm Beach, FL, USA