P031

Gabriel Pardo | gabriel-pardo@omrf.org

Ofatumumab Reduces Clinical and Radiological Activity in People With Recently Diagnosed Treatment-Naive 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]Pirogov 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 at the University of Colorado, Aurora, CO, USA; [14]Center of Clinical Neuroscience, Department of Neurology, University Clinic Carl-Gustav Carus, Dresden, Germany

KEY FINDINGS & CONCLUSIONS

- In the subgroup of RDTN participants with RMS enrolled in the ASCLEPIOS I/II trials, ofatumumab was consistently associated with reductions in clinical and radiological activity versus teriflunomide regardless of baseline sNfL levels
- Ofatumumab also significantly increased the odds of maintaining NEDA-3 status compared with teriflunomide regardless of baseline sNfL levels
- The results support the benefit of using high-efficacy therapies, such as ofatumumab, at an early stage in the MS disease course irrespective of the levels of sNfL at baseline

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INTRODUCTION

- In the phase 3 ASCLEPIOS I/II trials (NCT02792218/NCT02792231) in people with relapsing multiple sclerosis (pwRMS), ofatumumab was significantly more effective than teriflunomide 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-naive (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 ofatumumab versus teriflunomide 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 ofatumumab or teriflunomide in ASCLEPIOS I/II
- The baseline sNfL cut-off was predefined in the clinical study protocol (i.e., 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 ofatumumab versus teriflunomide:
  - **Adjusted annualized relapse rates (ARR)** over the study duration (up to 30 months)
  - **Adjusted annualized rates of neT2 lesions** (last available scan compared to 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 previous year, baseline Expanded Disability Status Scale (EDSS), baseline number of gadolinium-enhancing (Gd+) T1 lesions, and the patient's age at baseline as covariate; and treatment by baseline sNfL category interaction
- **Adjusted annualized rates of neT2 lesions** (compared to 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
Number 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 (pg/mL), median	6.77	15.29

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

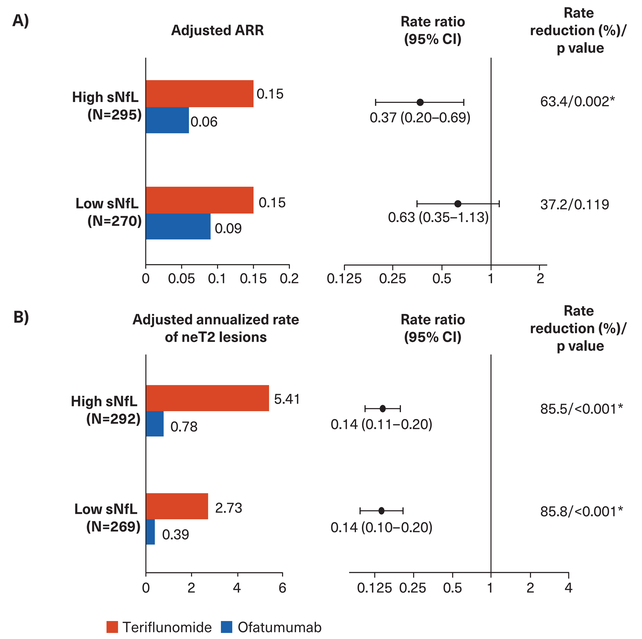
Relapses

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

neT2 lesions

- Ofatumumab reduced the annualized rate of neT2 lesions by 85.5% and 85.8% versus teriflunomide (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

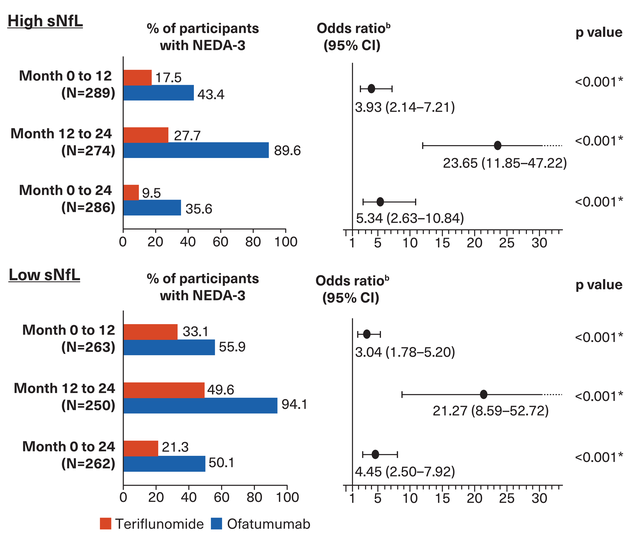


*Indicates statistical significance (two-sided) at the 0.05 level. ARR, annualized relapse rate; CI, confidence interval; N, number of participants in the related sNfL category; neT2, new or enlarging T2; sNfL, serum neurofilament light chain.

NEDA-3

- A significantly higher proportion of RDTN participants achieved NEDA-3 status with ofatumumab versus teriflunomide, regardless of baseline sNfL levels (**Figure 2**)

Figure 2. Treatment effect on NEDA-3 status[a] per baseline sNfL



[a]NEDA-3 is defined as no 6-month confirmed disability worsening, no confirmed relapse, no neT2 lesion compared to baseline, and no Gd+ T1 lesions. [b]Higher odds ratios and larger CI at Month 12 to 24 may be attributed to both re-baselining and lower disease activity compared to Month 0 to 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 (two-sided) at the 0.05 level. CI, confidence interval; Gd+, gadolinium-enhancing; N, number of participants in the related sNfL category with data available over the corresponding period; NEDA-3, three-parameter no evidence of disease activity; neT2, new or enlarging T2; RDTN, recently diagnosed treatment-naive; sNfL, serum neurofilament light chain.

Reference

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

Abbreviations

ARR, annualized relapse rate; **CI,** confidence interval; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **MS,** multiple sclerosis; **NEDA-3,** three-parameter no evidence of disease activity; **neT2,** new or enlarging T2; **pwRMS,** people with relapsing multiple sclerosis; **RDTN,** recently diagnosed treatment-naive; **RMS,** relapsing multiple sclerosis; **SD,** standard deviation; **sNfL,** serum neurofilament light chain.

Disclosures

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The final responsibility for the content lies with the authors.