Poster DMT20

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Longer-Term (Up to 6 Years) Efficacy of Ofatumumab in People With Recently Diagnosed and Treatment-Naïve Relapsing Multiple Sclerosis

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KEY FINDINGS & CONCLUSIONS

- In recently diagnosed (≤3 years) and treatment-naïve (RDTN) people with relapsing multiple sclerosis (pwRMS), first-line ofatumumab (OMB) treatment for up to 6 years showed sustained efficacy with an adjusted rate of 1 relapse for every 20 years during the extension phase and profound suppression of magnetic resonance imaging (MRI) lesion activity; these results are consistent with those of the overall study population[1]
- Participants who switched from teriflunomide (TER) to OMB in the extension phase showed pronounced reductions in relapses and MRI lesion activity after the switch
- By Year 6 of treatment, 9 of 10 participants were free from disease activity (no evidence of disease activity [NEDA-3]) in the continuous and switch groups
  – High rates of NEDA-3 were achieved within 2 years with first-line OMB, whereas rates of NEDA-3 increased rapidly after switching from TER to OMB
- First-line OMB was associated with significantly fewer confirmed disability worsening events and lower rates of progression independent of relapse activity up to 6 years compared with participants who switched from TER to OMB
  – The efficacy benefit of first-line OMB in delaying disability worsening cannot be recovered in those switching from TER to OMB
- These long-term efficacy results up to 6 years, combined with the favorable benefit–risk profile demonstrated in the overall study population,[1] support the use of OMB as first-line therapy for RDTN pwRMS

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INTRODUCTION

- Ofatumumab (OMB), a fully human anti-CD20 monoclonal antibody with a 20-mg subcutaneous monthly dosing regimen, is approved for treating relapsing multiple sclerosis (RMS) in adults[2]
- In the phase 3 ASCLEPIOS I/II trials in people with RMS (pwRMS), OMB demonstrated superior efficacy in reducing the annualized relapse rate (ARR), suppressing magnetic resonance imaging (MRI) lesion activity, and delaying disability worsening, while maintaining a favorable safety profile vs teriflunomide (TER)[3]
- In the subgroup of recently diagnosed (≤3 years) and treatment-naïve (RDTN) participants, OMB showed a superior benefit–risk profile compared with TER, with an almost complete abrogation of inflammatory disease activity and no unexpected safety signals, supporting its use as a first-line treatment in early RMS[4]
- Results previously reported from the ASCLEPIOS I/II trials and ALITHIOS open-label extension study demonstrated sustained efficacy for up to 4 years in RDTN participants[5]

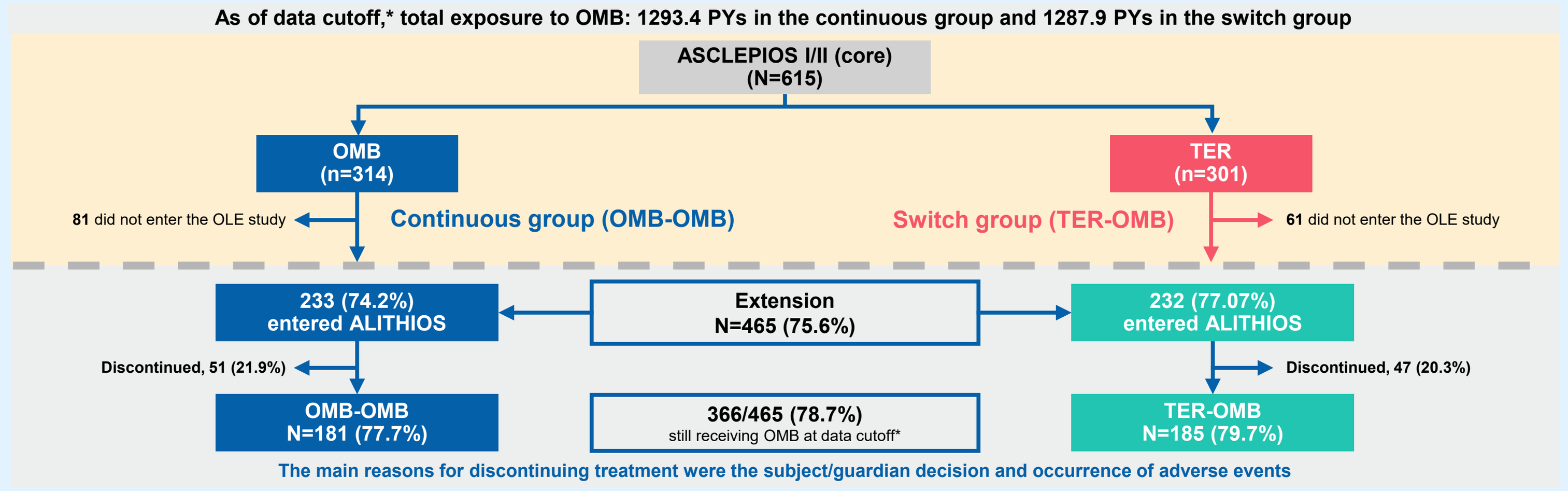
OBJECTIVE

- To assess the long-term efficacy of OMB for up to 6 years in RDTN pwRMS

METHODS

- These analyses include cumulative data from the RDTN subgroups randomized to OMB in the core ASCLEPIOS studies (continuous group) and those originally randomized to TER in the ASCLEPIOS studies and switching to OMB in the ALITHIOS extension study (switch group) (**Figure 1**)
- Data cutoff: Sep 25, 2022 (up to 5 years)/Sep 25, 2023 (up to 6 years)

Figure 1. Participant Disposition (RDTN Subgroup) and Key Assessments



Key Assessments

- ARR
- Brain MRI outcomes
  – Mean number of Gd+ T1 lesions per scan
  – Number of neT2 lesions per year
- 3/6mCDW
- NEDA-3†

3/6mCDW, 3- and 6-month confirmed disability worsening; ARR, annualized relapse rate; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NEDA-3, no evidence of disease activity; neT2 lesions, new or enlarging T2 lesions; OLE, open-label extension; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; PY, patient year; RDTN, recently diagnosed (≤3 years) and treatment-naive; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
*Data cutoff: September 25, 2023 (≤6 years); †Defined as no 6mCDW, no confirmed multiple sclerosis relapse, no neT2 lesions compared with baseline, and no Gd+ T1 lesions

RESULTS

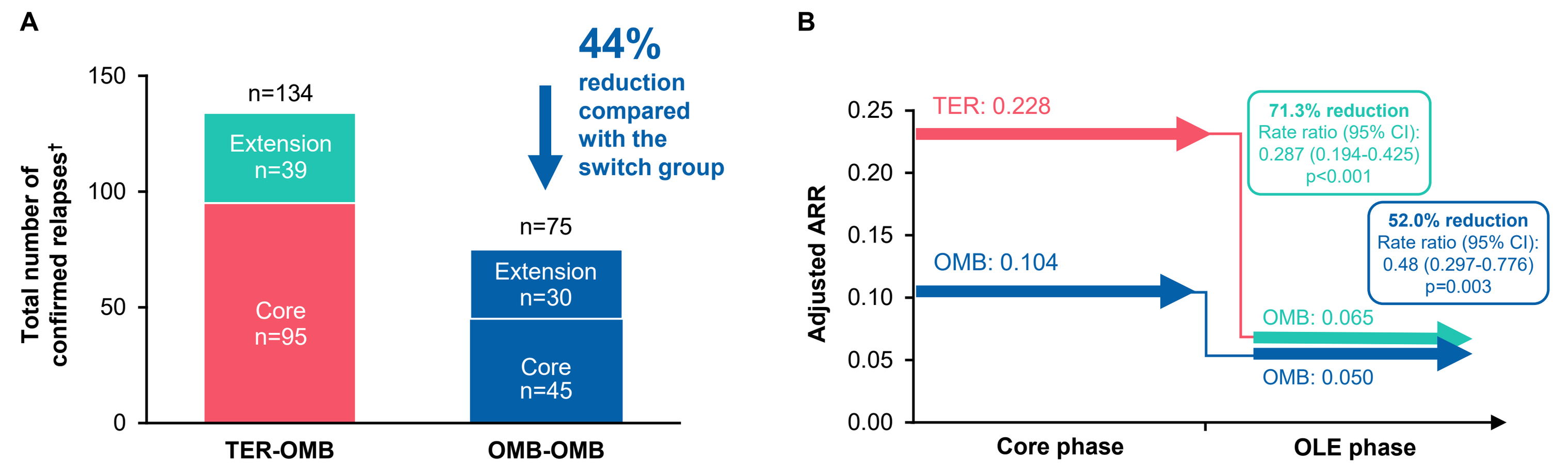
- Characteristics of RDTN participants were typical of patients with early RMS and were generally balanced between treatment groups (**Table 1**)
- Over a period of up to 6 years, first-line continuous vs later initiation of OMB was associated with a 44% reduction in the cumulative number of relapses (**Figure 2A**)
- ARR remained low with first-line continuous OMB, reaching an adjusted rate in the extension period that corresponded to 1 relapse for every 20 years (**Figure 2B**)
- Switching from TER to OMB resulted in a pronounced 71.3% reduction in ARR (**Figure 2B**)

Table 1. Baseline Demographics and Disease Characteristics

Characteristics*	Continuous OMB-OMB group	Switch TER-OMB group (N=301)	
	Baseline from core (N=314)	Baseline from core (N=301)	Baseline from OLE (N=232)
Age, years	36.8 (9.40)	35.7 (9.03)	37.7 (8.99)
BMI, kg/m²	25.93 (6.15)	26.19 (6.06)	25.71 (5.71)
Female, n (%)	217 (69.1)	195 (64.8)	155 (66.8)
Time since MS diagnosis, years	0.58 (0.63)	0.53 (0.51)	2.44 (0.60)
Time since first MS symptom, years	3.41 (3.96)	3.25 (4.28)	5.16 (4.23)
EDSS at baseline	2.30 (1.2)	2.28 (1.2)	2.20 (1.2)
Number of relapses in the past 12 months prior to screening	1.30 (0.70)	1.4 (0.72)	0.10 (0.41)
Number of Gd+ T1 lesions	1.8 (4.35)	1.4 (2.79)	0.7 (2.01)
Proportion of participants free of Gd+ T1 lesions, n (%)	173 (55.1)	171 (56.8)	169 (72.8)
Total volume of T2 lesions, cm³	10.1 (12.23)	8.3 (8.83)	NA†

BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; OLE, open-label extension, OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab
*Data are represented as mean (SD) unless specified otherwise; for participants newly switched to OMB, their baseline values from the extension study contribute to the overall summary; †Data are not collected for baseline from extension

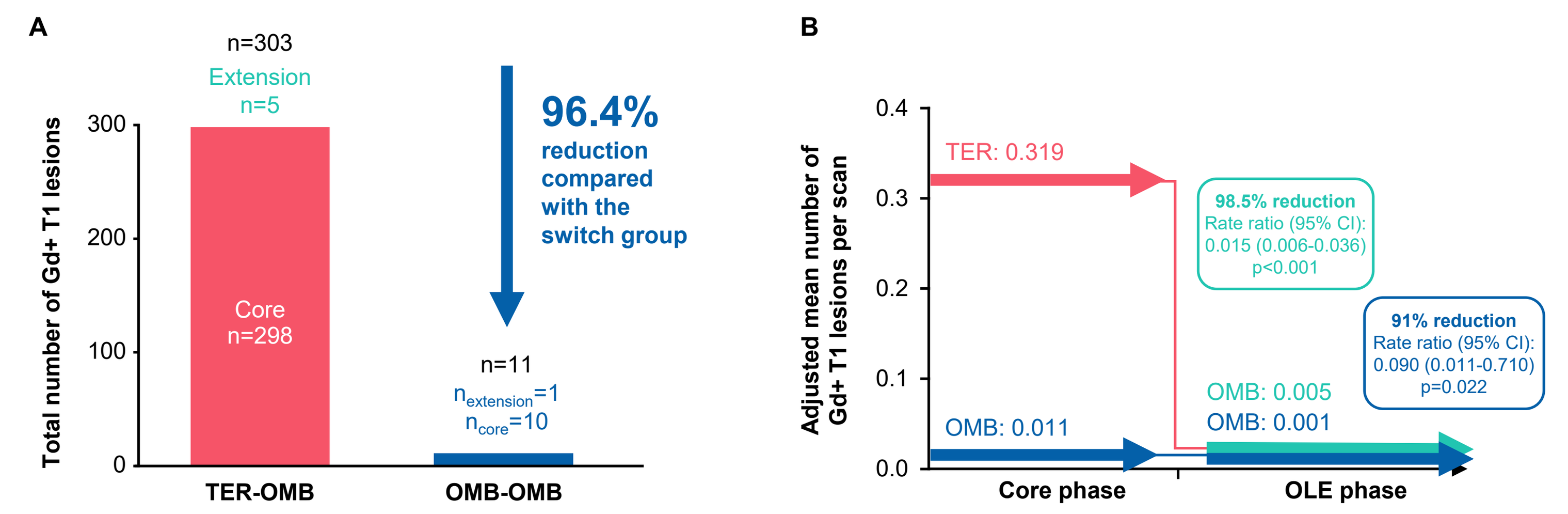
Figure 2. (A) Cumulative Number of Relapses Up to 6 Years; (B) Within-Group Comparison* Between the Core and Extension Phase



ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; OLE, open-label extension; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
*Obtained from fitting a piecewise negative binomial model for the core phase and extension phase time period with log-link, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd+ lesions and the patient's age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualize the relapse rate in each period. Baseline variables are from the core study baseline; †Confirmed relapses are those accompanied by a clinically relevant change in the EDSS

- Over a period of ≤6 years, first-line continuous vs later initiation of OMB was associated with a 96.4% reduction in the cumulative number of Gd+ T1 lesions (**Figure 3A**)

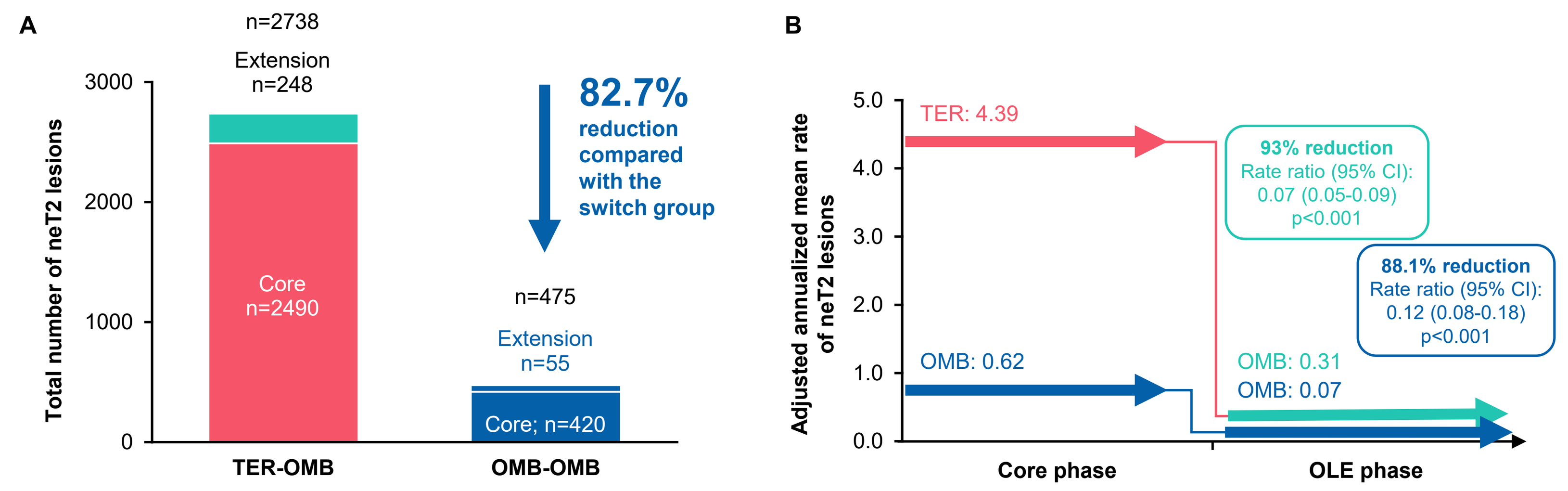
Figure 3. (A) Cumulative Number of Gd+ T1 Lesions Up to 6 Years; (B) Within-Group Comparison* Between the Core and Extension Phase



Gd+, gadolinium-enhancing; OLE, open-label extension; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
*Estimated from fitting a piecewise negative binomial model for the core phase and extension phase time period with log-link, adjusted for treatment and region as factors and baseline number of Gd+ T1 lesions and patient's age at baseline as covariates. The natural log of the number of scans with evaluable Gd+ lesion counts by period is used as offset to obtain the lesion rate per scan in each period. Baseline variables are from the core study baseline. All p-values are nominal

- First-line continuous OMB treatment maintained an almost complete suppression of Gd+ T1 lesion activity up to Year 6 (**Figure 3A**)
- Switching from TER to OMB led to a rapid suppression of Gd+ T1 lesion activity to closely match the continuous OMB group (**Figure 3B**)
- A significant and sustained reduction in the number of new or enlarging T2 (neT2) lesions was observed in RDTN participants receiving OMB for up to 6 years (**Figure 4**)
- Over a period of up to 6 years, first-line initiation of OMB was associated with an 82.7% reduction in the cumulative number of neT2 lesions (**Figure 4A**)
- First-line continuous OMB profoundly suppressed the number of neT2 lesions up to Year 6 (**Figure 4A**)
- Switching from TER to OMB resulted in a profound reduction in the number of neT2 lesions (**Figure 4B**)

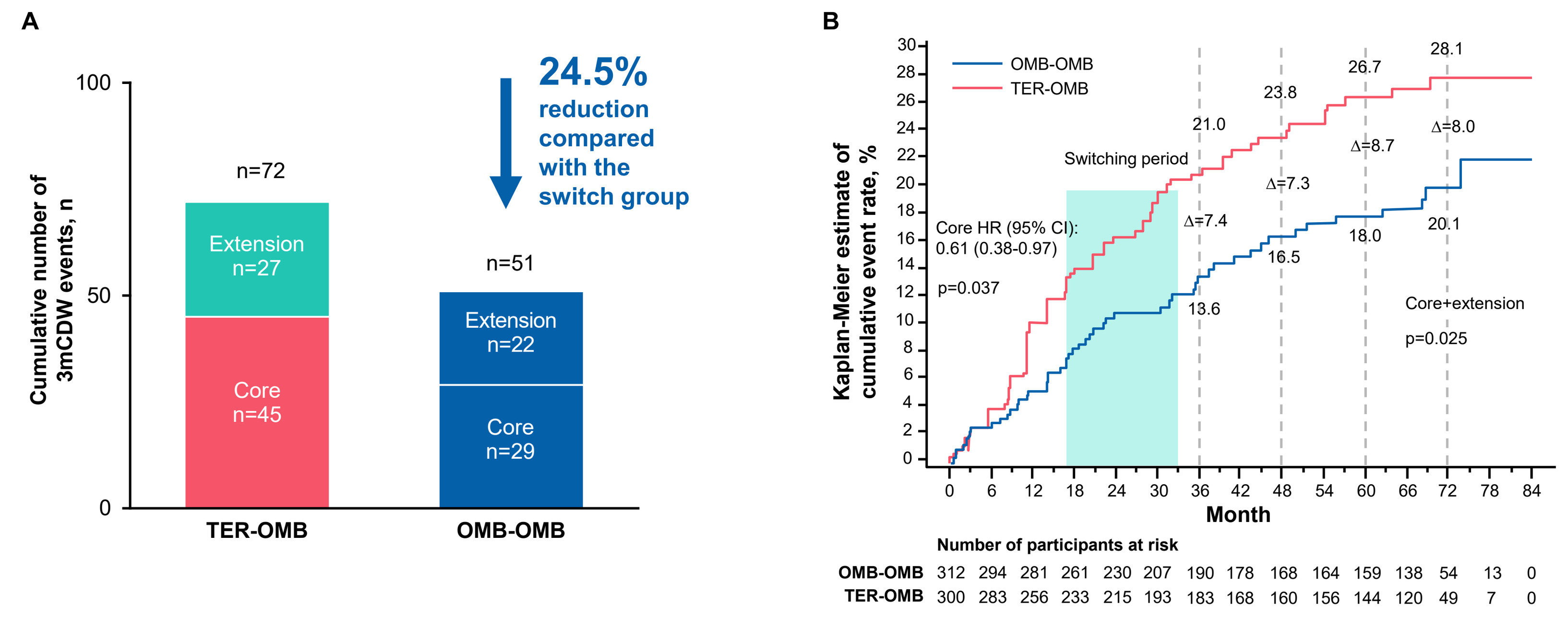
Figure 4. (A) Cumulative Number of neT2 Lesions Up to 6 Years; (B) Within-Group Comparison Between the Core and Extension Phase



neT2 lesion, new or enlarging T2 lesion; OLE, open-label extension; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
All p-values are nominal

- First-line OMB treatment and first-line continuous OMB treatment in RDTN participants was associated with a significantly lower number of 3-month confirmed disability worsening (3mCDW) events up to 6 years (**Figure 5**)
- 3-month progression independent of relapse activity (3mPIRA) events occurred in 14.3% vs 20.4% of RDTN participants in the continuous and switch groups, respectively
  – 3mPIRA is defined as a 3mCDW event with either no prior relapse or an onset >90 days after the start date of the last investigator-reported relapse (irrespective of the Expanded Disability Status Scale [EDSS] confirmation). In addition, to qualify as a PIRA event, no relapse must occur within 30 days after confirmation of EDSS worsening. Cutoff for the core and extension periods refers to the first dose of OMB in the extension period
- The significant efficacy benefit of first-line OMB on 3mCDW in the core phase cannot be recovered in those initially randomized to TER and later switched to OMB (**Figure 5B**)

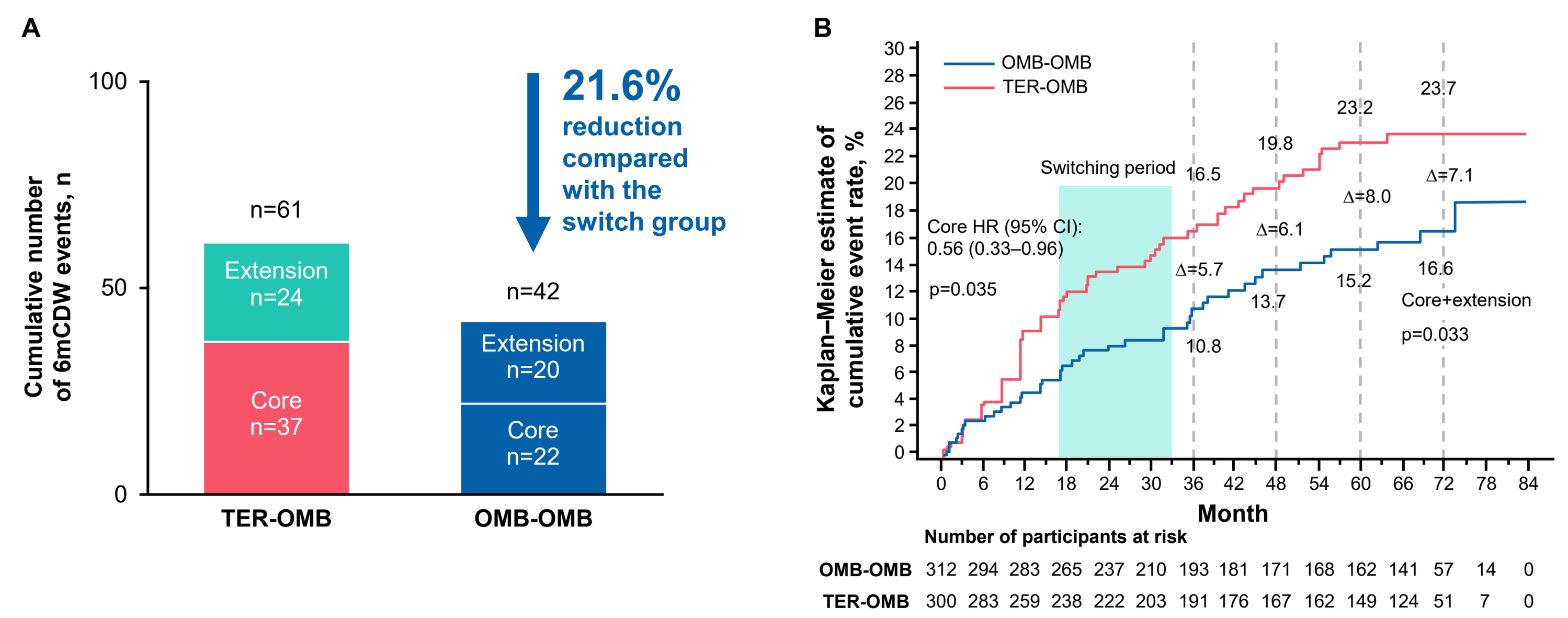
Figure 5. (A) Cumulative Number of 3mCDW Events Up to 6 Years; (B) Cumulative Rate of 3mCDW Events



Δ, difference in Kaplan–Meier estimates (TER-OMB minus OMB-OMB); 3mCDW, 3-month confirmed disability worsening; HR, hazard ratio; OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab
HR was determined by Cox regression model; p-value represents log-rank test

- First-line OMB treatment and first-line continuous OMB treatment in RDTN participants was associated with a significantly lower number of 6-month confirmed disability worsening (6mCDW) events up to 6 years (**Figure 6**)
- 6-month progression independent of relapse activity (6mPIRA) events occurred in 11.1% vs 16.8% of RDTN participants in the continuous and switch groups, respectively
  – 6mPIRA is defined as a 6mCDW event with either no prior relapse or an onset >90 days after the start date of the last investigator-reported relapse (irrespective of the EDSS confirmation). In addition, to qualify as a PIRA event, no relapse must occur within 30 days after confirmation of EDSS worsening. Cutoff for the core and extension periods refers to the first dose of OMB in the extension period
- The significant efficacy benefit of first-line OMB on 6mCDW in the core phase cannot be recovered in those initially randomized to TER and later switched to OMB (**Figure 6B**)

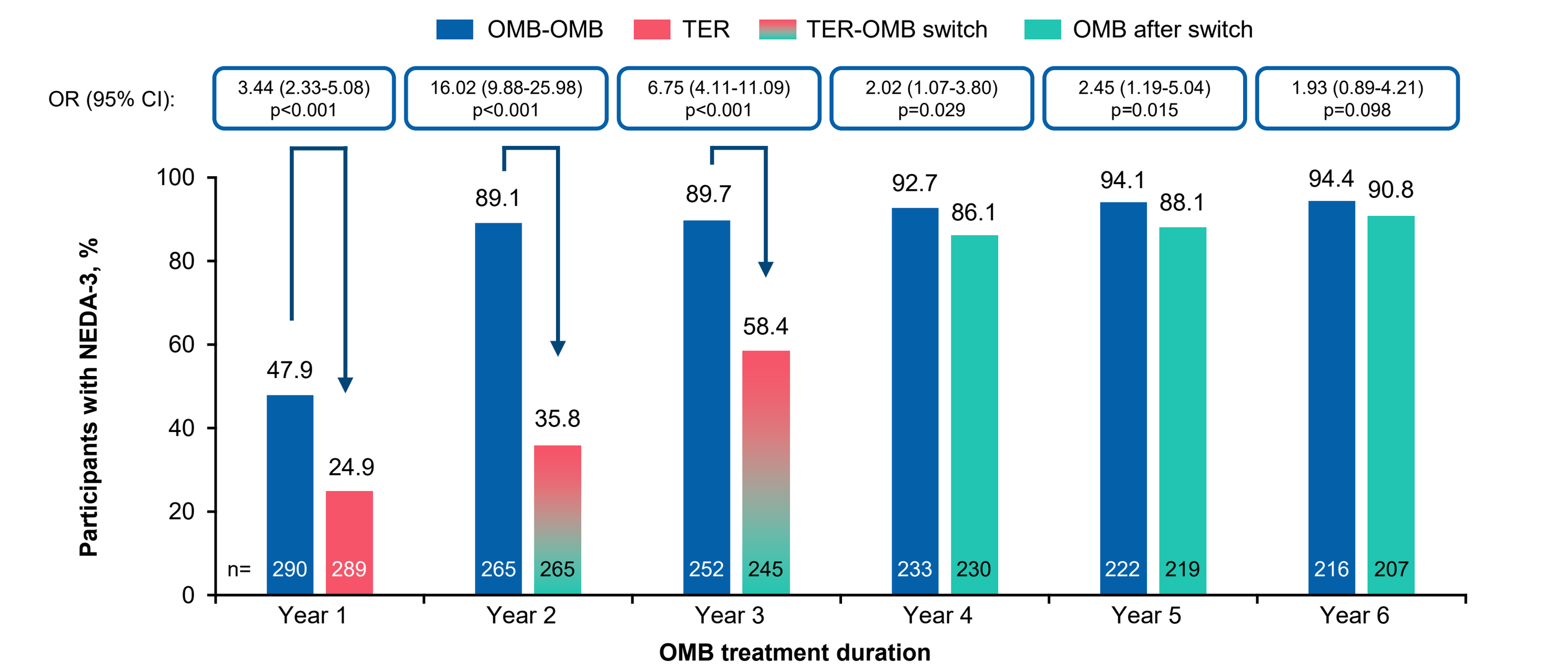
Figure 6. (A) Cumulative Number of 6mCDW Events Up to 6 Years; (B) Cumulative Rate of 6mCDW Events



Δ, difference in Kaplan–Meier estimates (TER-OMB minus OMB-OMB); 6mCDW, 6-month confirmed disability worsening; HR, hazard ratio; OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab
HR was determined by Cox regression model; p-value represents log-rank test

- By Year 6 of treatment, 9 of 10 participants were free from disease activity (no evidence of disease activity [NEDA-3]) in the continuous and switch groups (**Figure 7**)
  – The observed rapid increase in the proportion of participants with NEDA-3 with first-line continuous OMB was maintained over 6 years
  – Participants who were initially on TER had significantly lower NEDA-3 rates, but a rapid increase in NEDA-3 was observed after switching to OMB

Figure 7. NEDA-3* Status Up to 6 Years of OMB Treatment (mFAS†)



6mCDW, 6-month confirmed disability worsening; Gd+, gadolinium-enhancing; mFAS, modified full analysis set; MS, multiple sclerosis; n, the total number of participants in the treatment group with response variable defined; NEDA-3, no evidence of disease activity; neT2 lesions, new or enlarging T2 lesions; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; OR, odds ratio; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab
*NEDA-3 is defined as no 6mCDW, no confirmed MS relapse, no neT2 lesions compared with baseline, and no Gd+ T1 lesions. Statistical model used logistic regression adjusting for treatment and region as factors and age, baseline EDSS, and number of Gd+ T1 lesions at baseline as covariates; †The mFAS for NEDA-3 contained all participants in the full analysis set according to the intent-to-treat principle, but participants who discontinued from the study drug prematurely for reasons other than "lack of efficacy" or "death" and had NEDA-3 before early discontinuations were excluded

References

1. Wiendl H et al. Poster presented at: *AAN* 2024; P9.010. **2.** Novartis Pharmaceuticals Corporation. Prescribing information. Kesimpta® 2024. Accessed February 15, 2024. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf; **3.** Hauser SL et al. *N Engl J Med*. 2020;383:546-557. **4.** Gärtner J et al. *Mult Scler*. 2022;28:1562-1575. **5.** Gärtner J et al. Poster presented at: *ECTRIMS* 2022; P052.

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Methods for simultaneous multi-angular relaxometry of tissue using magnetic resonance imaging. Patent 15060-630 (015875)." **Jutta Gärtner**, in the past 3 years, has received fees for lectures and consultancy fees from Bayer, Biogen, Merck, Novartis, and Sanofi, as well as funding for a research project from Novartis. **Ludwig Kappos** has received consultancy fees from Actelion, Bayer Healthcare, Biogen, BMS, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, and TG therapeutics; contracted research from Bayer Healthcare, Biogen, European Union, InnoSwiss, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation; speaker fees from Bayer Healthcare, Biogen, Merck, Novartis, Roche, and Sanofi; serves on the steering committee for Actelion, Bayer Healthcare, Biogen, BMS, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, and TG Therapeutics; support of educational activities from Allergan, Bayer Healthcare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva; and license fees for Neurostatus products. **Alit Bhatt, Haoyi Fu,** and **Ibolya Boer** are employees of Novartis