Five-Year Efficacy Outcomes of Ofatumumab in Relapsing MS Patients: Insights From ALITHIOS Open-label Extension Study

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Disclosures

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Background and Objective

- Ofatumumab, a fully human anti-CD20 monoclonal antibody administered monthly subcutaneously, is approved for treating **relapsing multiple sclerosis (RMS) in adults**[1]
- The Phase 3 ASCLEPIOS I/II trials demonstrated the **superiority of ofatumumab** (up to 30 months) compared to teriflunomide in **reducing the clinical and MRI disease activity,** while maintaining a favorable safety profile in patients with RMS[2]
- Extended treatment with ofatumumab for up to 4 years showed **sustained differences in efficacy outcomes and a well-tolerated safety profile** during the ALITHIOS open-label extension study[2,3]
- Longer-term efficacy and safety assessments are important to further understand ofatumumab's benefit–risk profile in RMS patients

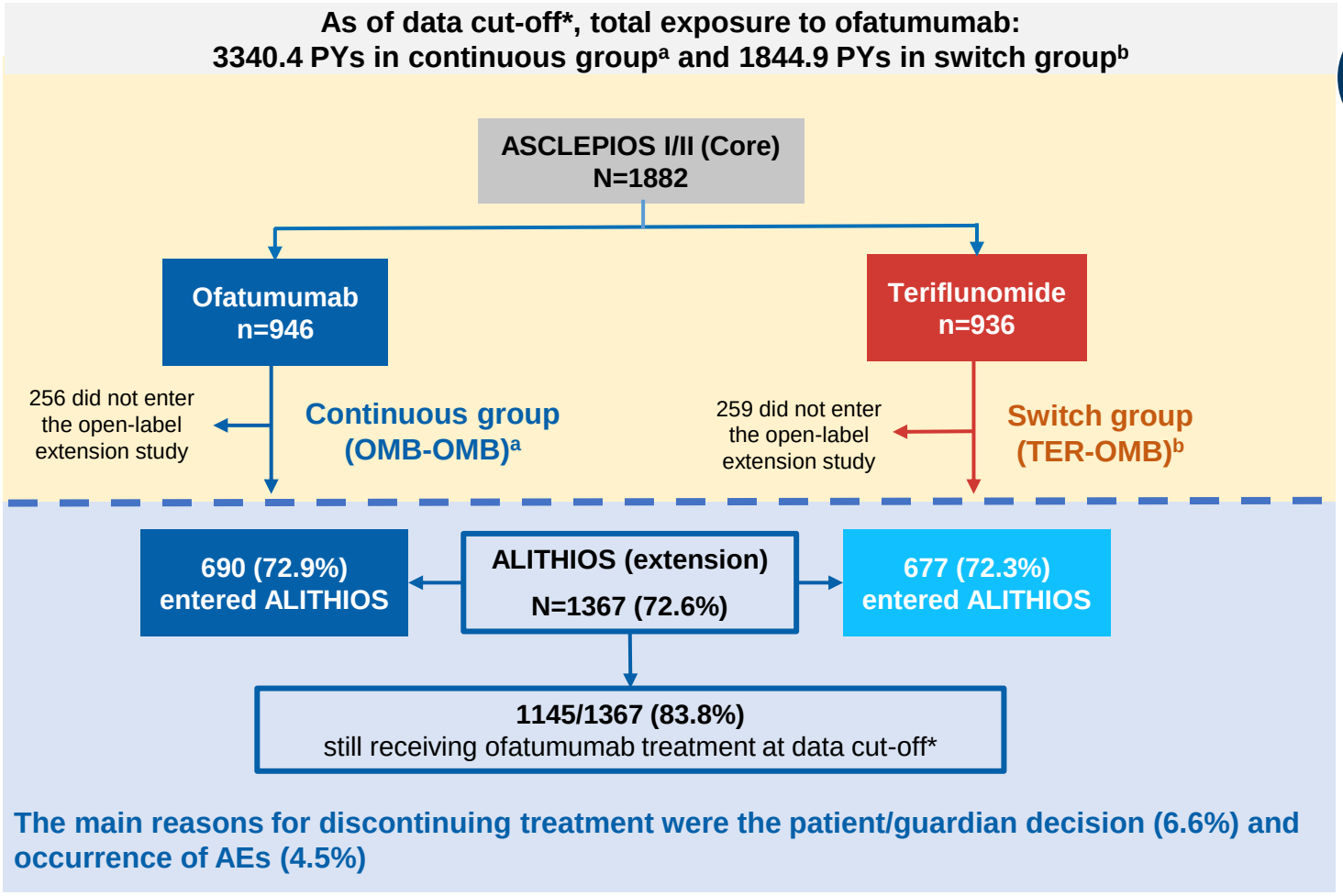
Objective

To assess the longer-term efficacy of ofatumumab treatment for up to 5 years* in patients with RMS in the ongoing ALITHIOS open-label extension study

*Data cut-off: 25-Sep-2022; CD, cluster of differentiation; MS, multiple sclerosis; RMS, relapsing MS

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed March 29, 2022) 2. Hauser SL, et al. *N Engl J Med.* 2020;383:546–57.
3. Kappos L et al. Poster presented at EAN 2022. EPR161.

Patient Disposition and Efficacy Assessments



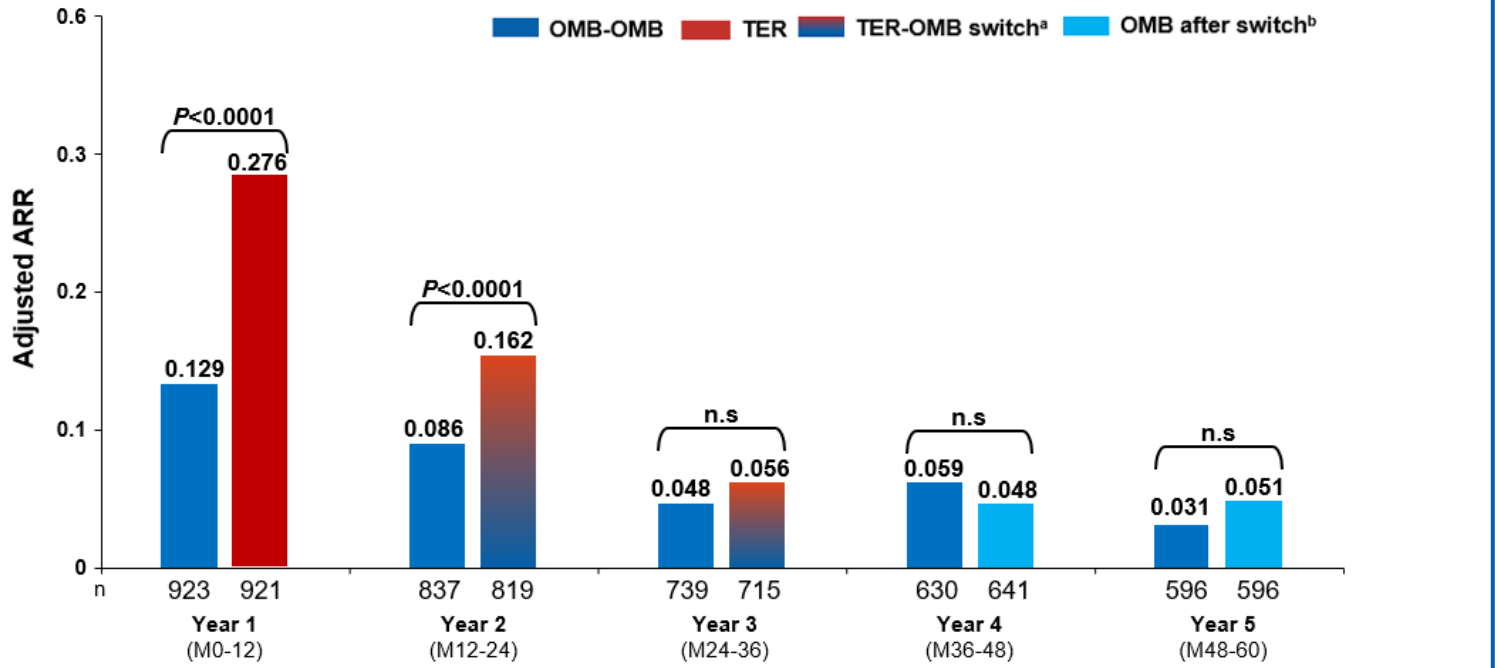
Key assessments analysed by year

- **Annualized relapse rate (ARR)**
- **Brain MRI outcomes**
  - Mean number of Gd+ T1 lesions per scan
  - Number of new or enlarging T2 lesions per year
- **No evidence of disease activity (NEDA-3)[c]**

All percentages are calculated based on the number of patients in full analysis set in the corresponding column. Dotted line represents the first dose of ofatumumab in extension phase. Core period is period before the dotted line.
Only patients from the ASCLEPIOS I/II studies are included in the analyses presented here. *Data cut-off: 25-Sep-2022; [a]randomized to ofatumumab in the core; [b]Switch group refers to the patients who were randomized to teriflunomide in the core and switched to ofatumumab during the extension phase; [c]Defined as no 6-month confirmed disability worsening, no confirmed MS relapse, no new or enlarging T2 lesions compared to baseline and no T1 Gd-enhancing lesions. AE, adverse event; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; OMB, ofatumumab; PY, patient-years; TER, teriflunomide.

Annualized Relapse Rates

ARR Up to 5 years of Ofatumumab Treatment

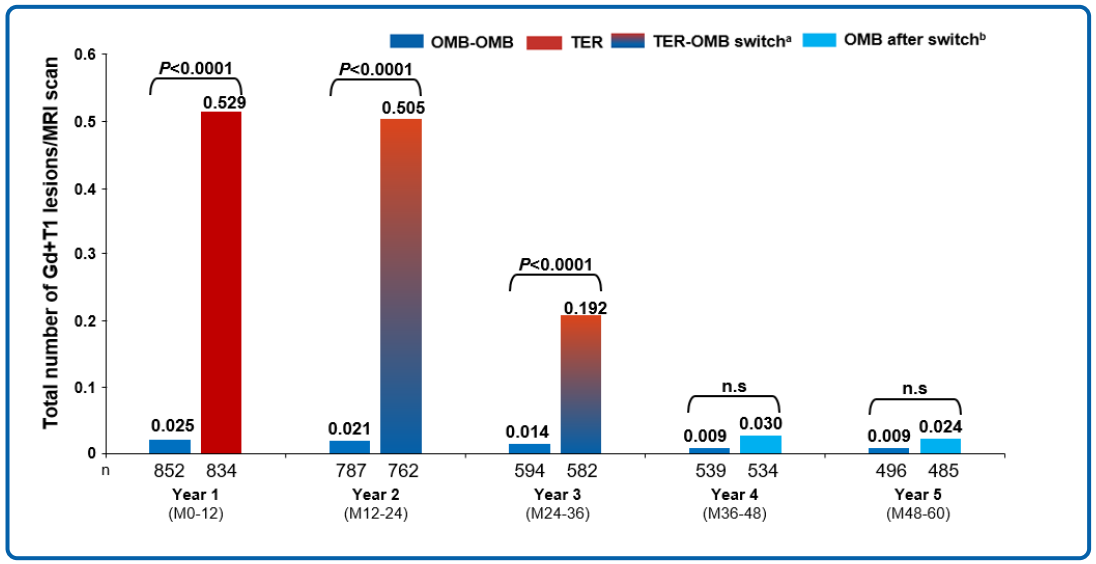


- ARR in the continuous ofatumumab group remained low for up to 5 years after treatment initiation
- Switch from teriflunomide to ofatumumab resulted in a pronounced reduction in ARR (Year 2–3) maintained through Year 5

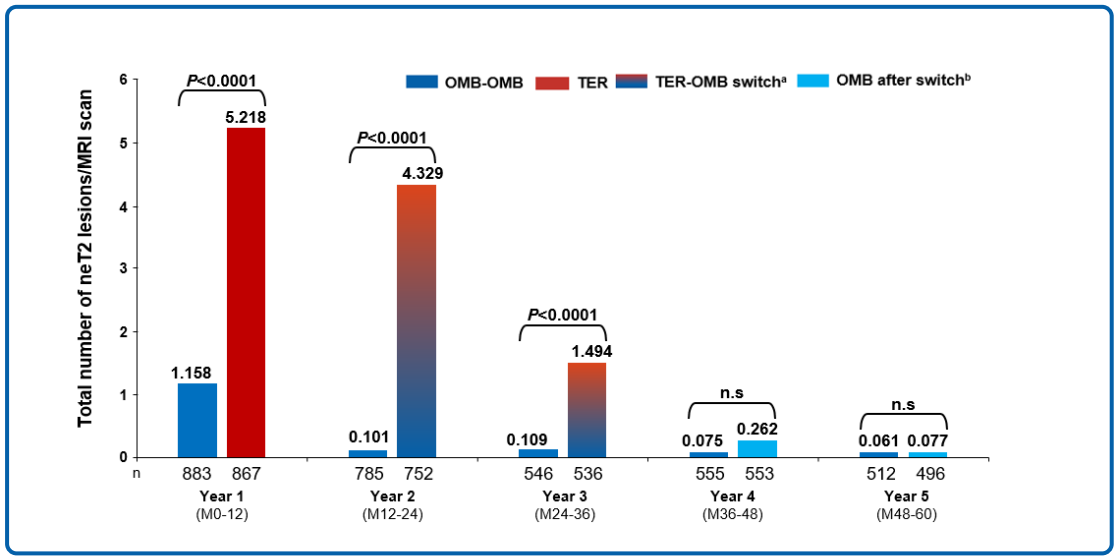
[a]TER-OMB switch: patients transitioning from TER to OMB; due to event-driven core study design (flexible duration), patients transitioned at various exposure time points; i.e., the switch from TER to OMB started from Year 2 and completed by Year 3; [b]OMB after switch: TER patients now on OMB. ARR, annualized relapse rate; M: month; n.s: non-significant; OMB-OMB: continuous ofatumumab; TER: teriflunomide.

MRI Lesion Activity (Gd+ T1 and New/Enlarging T2 Lesions)

Gd+ T1 Lesions up to 5 Years on Ofatumumab



neT2 Lesions up to 5 Years on Ofatumumab

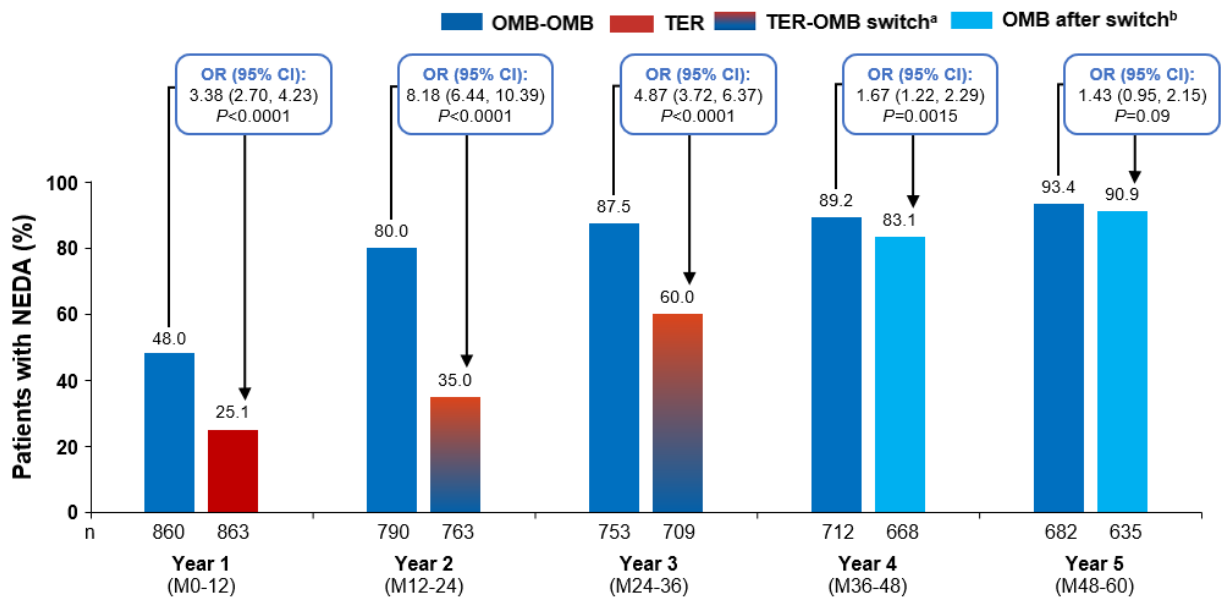


- Continuous ofatumumab maintained profound suppression of MRI lesion activity up to Year 5
- Switching from teriflunomide to ofatumumab led to a rapid suppression of MRI lesions to match the continuous ofatumumab group

[a]TER-OMB switch: patients transitioning from TER to OMB; due to event-driven core study design (flexible duration), patients transitioned at various exposure time points; i.e., the switch from TER to OMB started from Year 2 and completed by Year 3; [b]OMB after switch: TER patients now on OMB. Gd+, gadolinium-enhancing; M: month; MRI, magnetic resonance imaging; n.s: non-significant; neT2, new/enlarging T2; OMB-OMB: continuous ofatumumab; TER: teriflunomide.

No Evidence of Disease Activity (NEDA-3)

NEDA-3 status Up to 5 Years of Ofatumumab Treatment



- There was a rapid increase in NEDA-3 with continuous ofatumumab that was maintained over 5 years
- Those initially on teriflunomide had significantly lower NEDA-3 rates, but a rapid increase in NEDA-3 was observed after switching to ofatumumab
- At Year 5, NEDA-3 was reached by 9 out of 10 patients in both groups with ofatumumab

[a]TER-OMB switch: patients transitioning from TER to OMB; due to event-driven core study design (flexible duration), patients transitioned at various exposure time points; i.e., the switch from TER to OMB started from Year 2 and completed by Year 3; [b]OMB after switch: TER patients now on OMB. CI, confidence interval; NEDA, no evidence of disease activity; N=total number of patients in each group excluding those who discontinued early for reasons other than lack of efficacy or death and had NEDA before early discontinuation; M: month; OMB-OMB: continuous ofatumumab; OR, odds ratio; TER: teriflunomide.

Conclusions

- Continuous ofatumumab treatment for up to 5 years showed sustained efficacy in relapse rate reduction and profound suppression of MRI lesion activity
- Patients who switched from teriflunomide to ofatumumab in the extension phase showed pronounced reductions in relapses and MRI lesions
- The high rates of NEDA-3 observed in the double-blind core part was maintained over 5 years in patients with continuous ofatumumab treatment. Patients who were on teriflunomide had initially significantly lower NEDA-3 rates, but these rates increased after switching to ofatumumab
- Sustained efficacy combined with its well-tolerated 5-year safety profile[1] support the favorable benefit–risk profile for ofatumumab in RMS patients

MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; RMS, relapsing multiple sclerosis.

1. Cohen JA et al. Poster presentation at AAN 2023. P8.004

Back-up Slides

Methodology

Patient numbers at corresponding years for ARR, Gd+T1 lesions, and neT2 lesions may differ due to missing covariates and post baseline MRI visits

ARR

- Confirmed relapses are those accompanied by a clinically relevant change in the EDSS and Full analysis set was used for analysis of this outcome.
- Obtained from fitting generalized estimating equations (GEE) negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing 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

MRI lesion load

- Estimated from fitting a GEE negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, baseline number of T1 Gd-enhancing lesions and patient's age at baseline as covariates for Gd+T1 and factor, baseline volume of T2 lesions and patient's age at baseline as covariates for neT2 lesions.
- The natural log of the number of scans with evaluable Gd-enhancing lesion counts by period is used as offset to obtain the lesion rate per scan in each period for Gd+T1 and the natural log of the time-in-study (in years) by period is used as offset to annualize the lesion rate in each period for neT2 lesions.

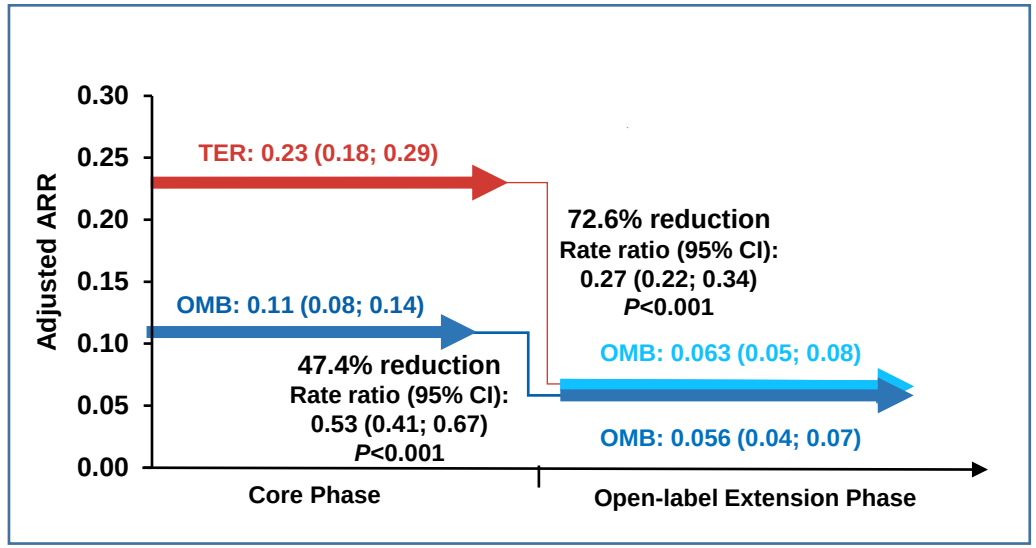
NEDA-3

- mFAS (modified full analysis set) was used as analysis set. Statistical model used logistic regression adjusting for treatment and region as factors and age, baseline EDSS, number of Gd-lesions at baseline as covariates

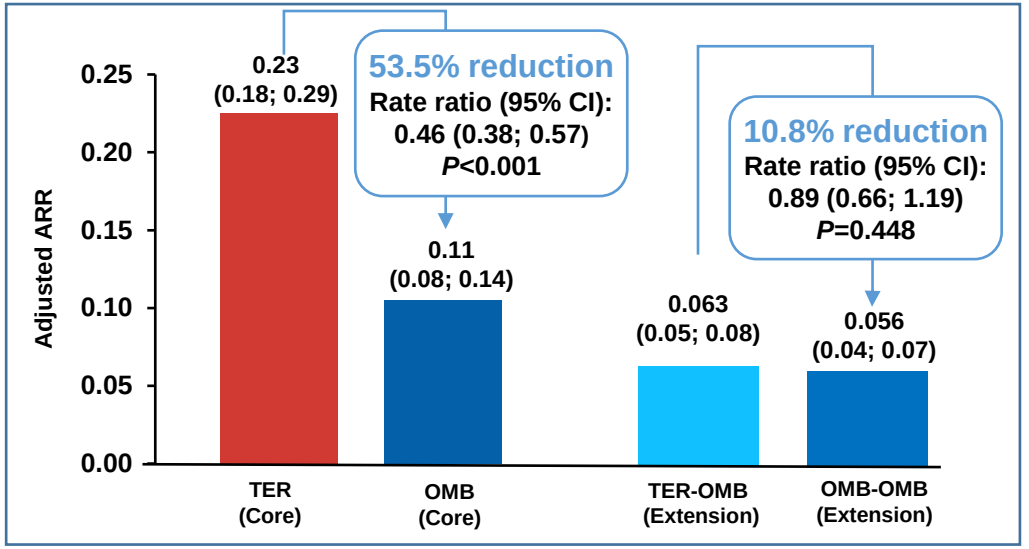
mFAS contains all patients in the FAS according to the intent-to-treat principle, but patients who discontinued from study treatment prematurely for reasons other than "lack of efficacy" or "death" and had NEDA-3 before early treatment discontinuations in the specific interval under analysis are excluded; NEDA-3 is defined as no 6-month confirmed disability worsening, no confirmed MS relapse, no new or enlarging T2 lesions compared to baseline and no Gd+ T1 lesions. ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; Gd+ , gadolinium enhancing; MRI, magnetic resonance imaging, NEDA, no evidence of disease activity.

Annualized Relapse Rates[a]

Within-group comparison[b] between the core and extension phase (continuous ofatumumab and switch group)



Between-group comparison[b] during the core and extension phase (continuous ofatumumab vs switch group)



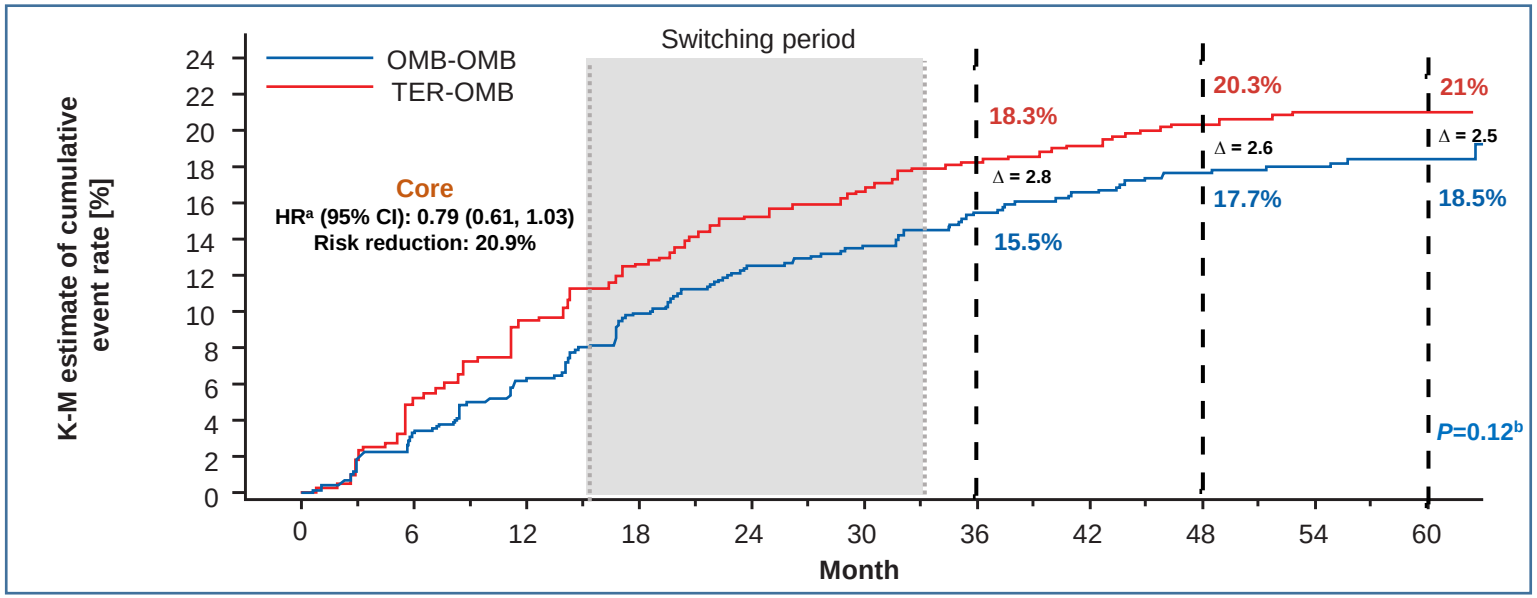
The within group analysis showed that continuous use of ofatumumab was associated with a significant reduction in ARR by 47.4% with longer-term treatment, and that switch from teriflunomide to ofatumumab resulted in a pronounced reduction in ARR (72.6%)

A significant reduction in the ARR observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies, and both groups receiving ofatumumab in the extension study maintained a low ARR

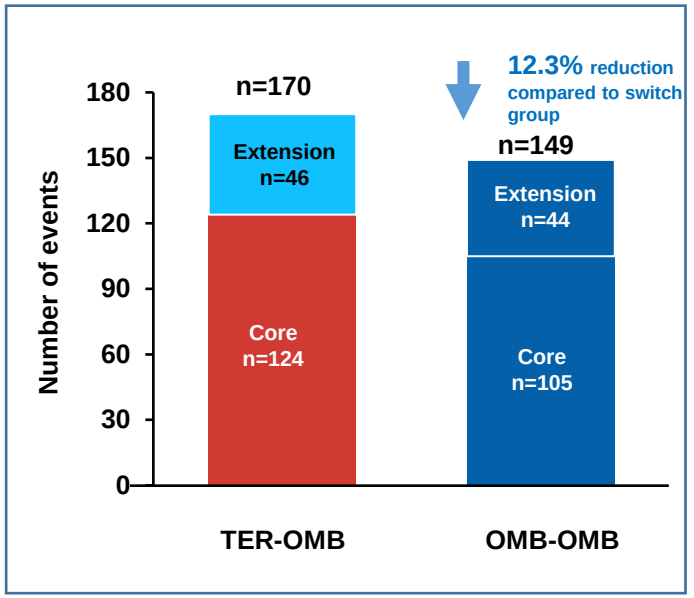
[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS; [b]Obtained from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing 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. All P values are nominal P values. ARR, annualized relapse rate, CI, confidence interval; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

6-month Confirmed Disability Worsening

Time to first 6-month confirmed disability worsening (6mCDW) - Kaplan-Meier estimates



Cumulative number of first events

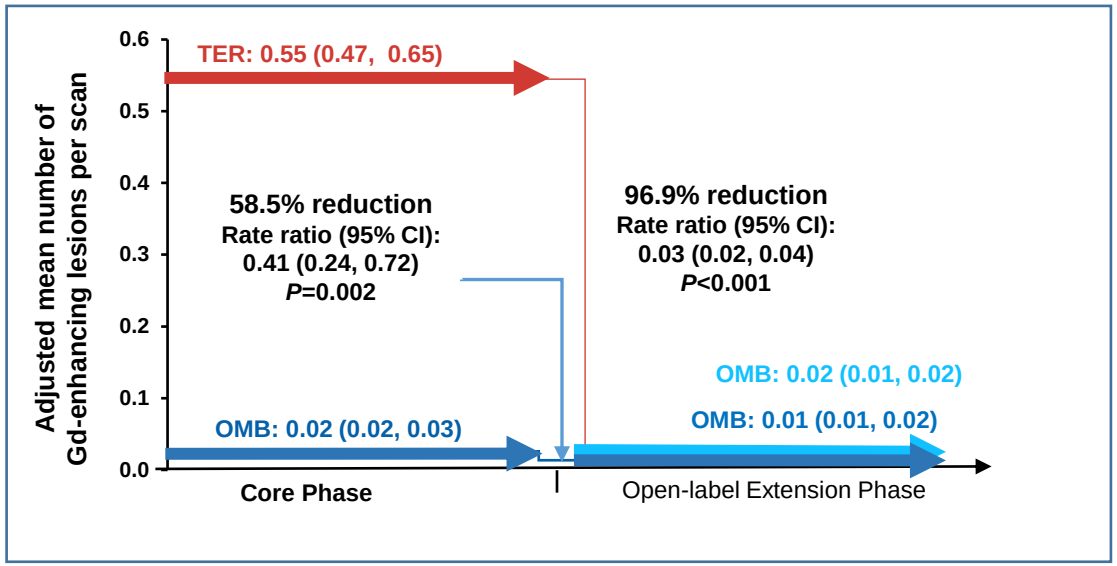


- **The deltas at 48 and 60 months, and the difference in the cumulative number of events over a period of up to 5 years, show that earlier treatment with ofatumumab was associated with an efficacy benefit that is lost and cannot be recovered in those initially randomized to teriflunomide**
- **The risk of subsequent 6mCDW events after switching from teriflunomide to ofatumumab was similar in both treatment arms**

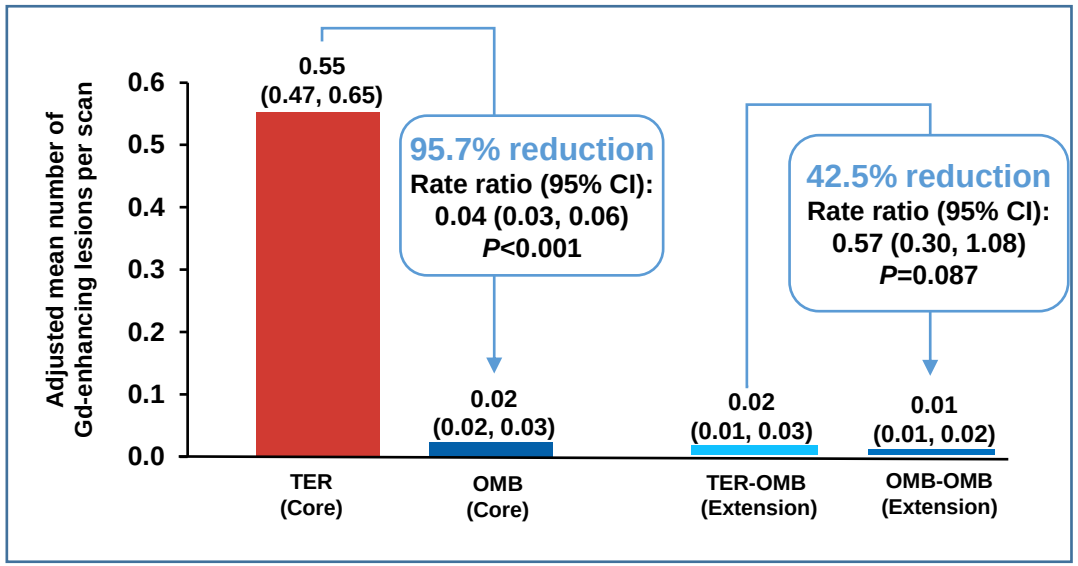
Cut-off for core and extension periods refer to the first dose of ofatumumab in extension. Δ, Difference in KM estimates (TER-OMB minus OMB-OMB). [a]HR determined by Cox regression model; [b]P value represented here is P value for Log-Rank test
OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab. 6mCDW, 6-month confirmed disability worsening; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier.

Mean Number of Gd-enhancing T1 Lesions

Within-group comparison[a] between the core and extension phase (Continuous ofatumumab and switch group)



Between-group comparison[b] during the core and extension phase (continuous ofatumumab vs switch group)



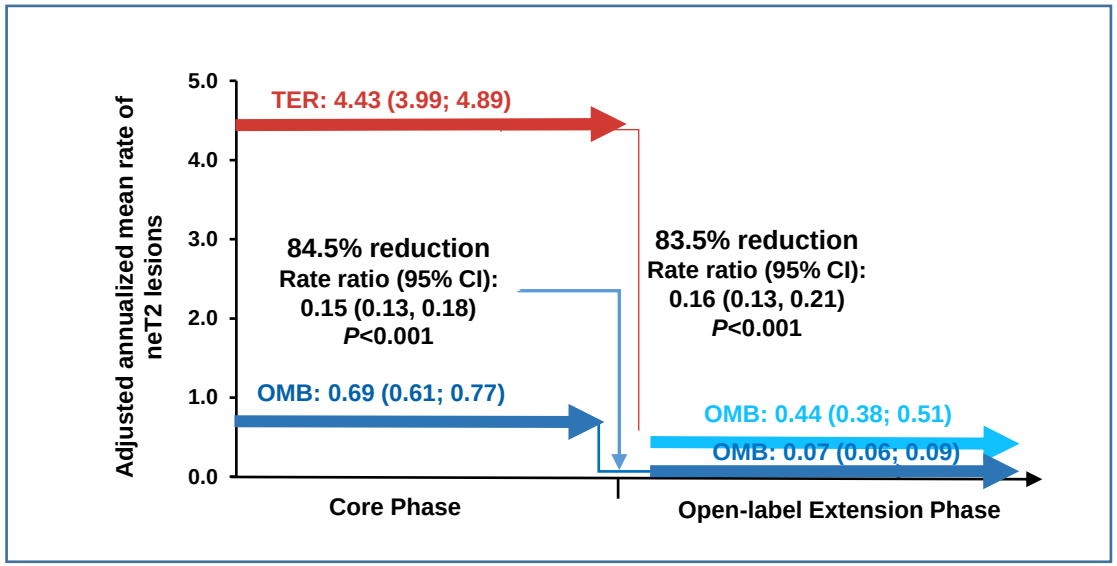
The within group analysis showed that continuous use of ofatumumab was associated with a reduction in the mean number of lesions per scan by 58.5% with longer-term treatment, while switch from teriflunomide to ofatumumab resulted in an almost complete suppression of Gd+ T1 lesion activity (96.9%)

A significant reduction in the mean number of Gd+ T1 lesions observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies. Gd+T1 lesions were almost completely suppressed during the extension phase in both the continuous ofatumumab group and switch group

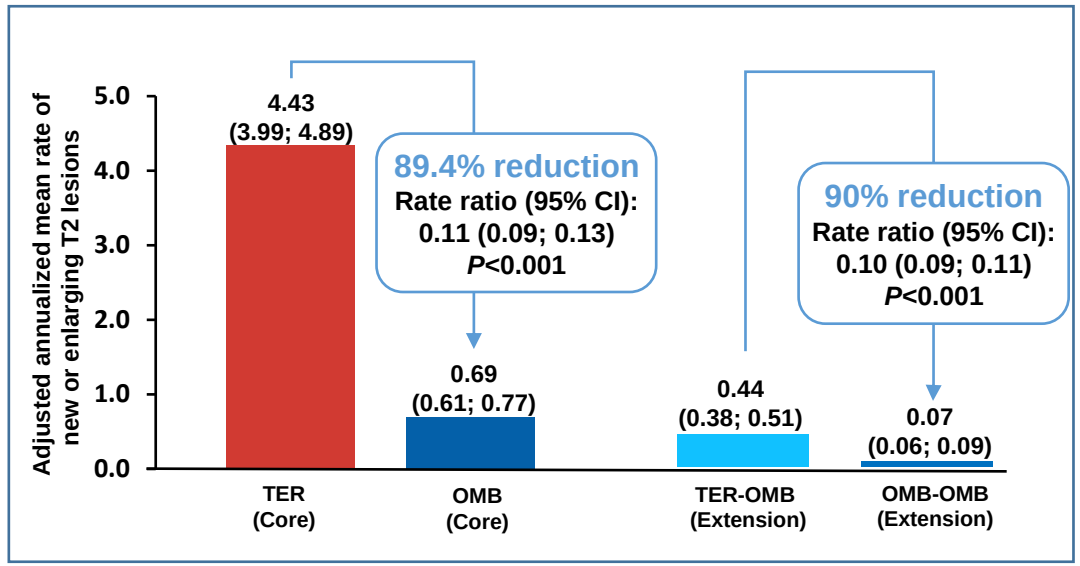
[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, baseline number of T1 Gd-enhancing lesions and patient's age at baseline as covariates. The natural log of the number of scans with evaluable Gd-enhancing 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 P values. CI, confidence interval; Gd, gadolinium; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Number of New/Enlarging T2 Lesions

Within-group comparison[a] between the core and extension phase (Continuous ofatumumab and switch group)



Between-group comparison[b] during the core and extension phase (continuous ofatumumab vs switch group)



The within-group analysis showed that continuous use of ofatumumab was associated with a reduction in the neT2 lesions by 84.5% with longer-term treatment, while switch from teriflunomide to ofatumumab resulted in a pronounced reduction in the number of neT2 lesions (83.5%)

The significant relative reduction in the mean rate of neT2 lesions observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was also seen in the extension phase, despite the overall reduced number of lesions, reflecting the known "carry over" effect on this outcome

[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment as factor, baseline volume of T2 lesions and 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 lesion rate in each period. Baseline variables are from the core study baseline. All P values are nominal P values. CI, confidence interval; neT2, new or enlarging T2; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.