Longer-term Efficacy of Ofatumumab in Patients with Relapsing Multiple Sclerosis

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Disclosures

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, TG Therapeutics; Support of educational activities from Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva; License fees for Neurostatus products

Edward Fox has received fees for consulting, contracted research, speaker's bureau and advisory work from Biogen, Celgene, Chugai, EMD Serono, Genentech/Roche, MedDay, Novartis, Sanofi, Genzyme, Teva; contracted research and advisory work for TG Therapeutics.

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Stephen Hauser serves on the board of trustees for Neurona and serves on scientific advisory boards for Accure, Alector and Annexon, received travel reimbursement and writing assistance for CD-20 related meeting and presentations from Roche and Novartis.

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Introduction

- Early initiation of high-efficacy therapies for the treatment of relapsing multiple sclerosis (RMS) has been shown to improve long-term outcomes versus escalating from, lower efficacy therapies[1–3]
- Ofatumumab, a high-efficacy therapy, is a fully human anti-CD20 monoclonal antibody administered monthly subcutaneously[4]
- The Phase 3 ASCLEPIOS I/II trials demonstrated the superiority of ofatumumab compared to teriflunomide in reducing the annualized relapse rate (ARR), suppressing MRI lesion activity and delaying disability worsening, while maintaining a favorable safety profile in patients with RMS[4,5]
- Assessment of the long-term efficacy and safety of ofatumumab is important to further understand its benefit-risk profile in patients with RMS
  - The long-term safety of ofatumumab is being discussed separately at this congress in the platform presentation OPR134

Objective

To assess the long-term efficacy of ofatumumab treatment for up to 4 years* in patients with RMS in the ongoing ALITHIOS open-label extension study

*Data cut-off: 25-Sep-2021. ARR, annualized relapse rate; MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis.

1. He A, et al. *Lancet Neurol*. 2020;19:307–316; 2. Harding K, et al. *AMA Neurol*. 2019;76:536–541; 3. Iaffaldano P, et al. *Ther Adv Neurol Disord*. 2021;14:17562864211019574; 4. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed March 29, 2022); 5. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57.

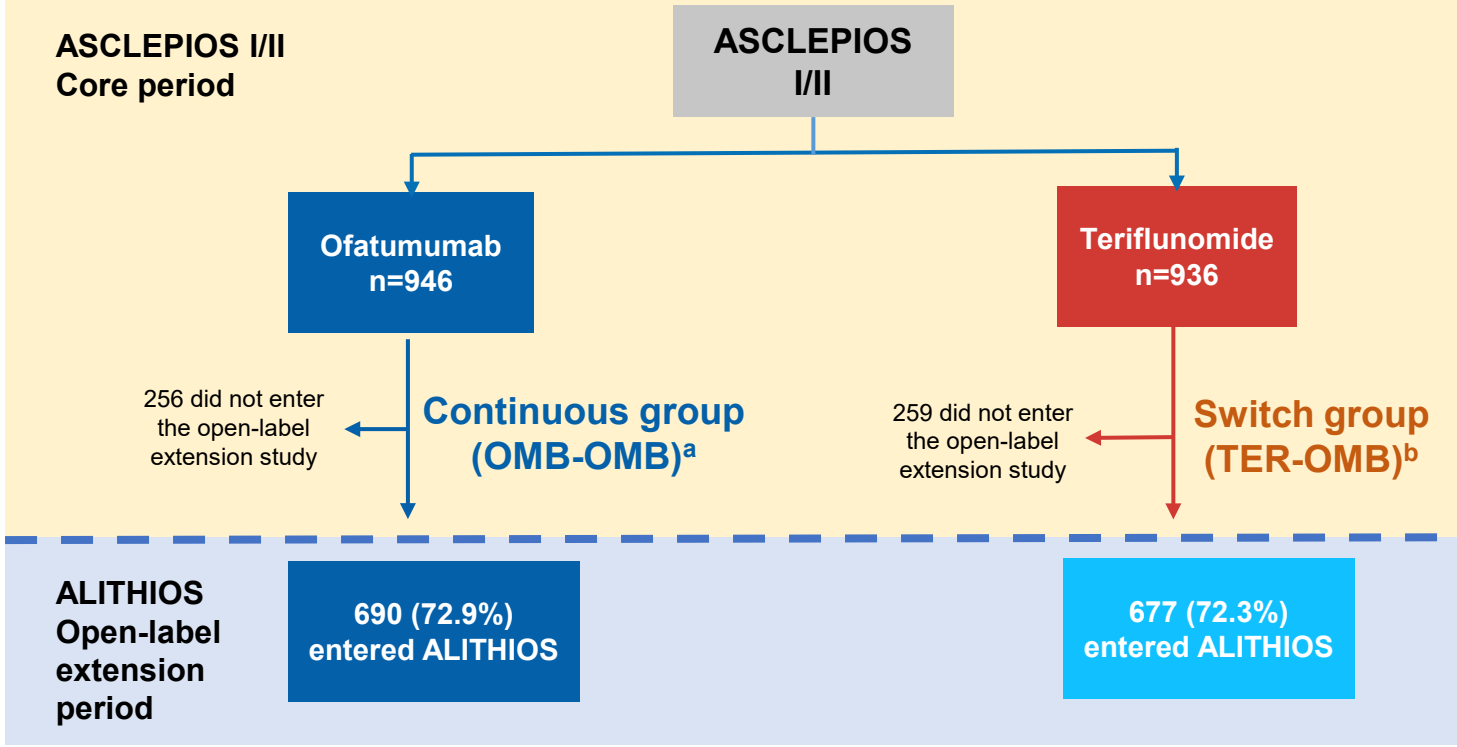
Key Efficacy Assessments

- **Annualized relapse rate (ARR)**
- **3- and 6-month confirmed disability worsening (3mCDW, 6mCDW)**
  - Confirmed disability worsening is an increase from baseline in EDSS score sustained for at least 3 or 6 months
- **Brain MRI outcomes**
  - Mean number of Gd-enhancing T1 lesions per scan
  - Number of new or enlarging T2 lesions per year
- **No evidence of disease activity (NEDA-3)**
  - 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
- ARR and MRI outcomes were analyzed
  - between the groups (defined as comparison of outcomes between the continuous and switch groups) and
  - within the groups (defined as comparison of outcomes between the core and extension periods within the continuous and switch groups)

ARR, annualized relapse rate; 3mCDW, 3-month confirmed disability worsening; 6mCDW, 6-month confirmed disability worsening; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity.

Patient Disposition

As of data cut-off*, total exposure to ofatumumab was: 2761.4 PYs in continuous group[a] and 1271.1 PYs in switch group[b]



- Of 1882 patients randomized in the ASCLEPIOS I/II trials, 1367 (72.6%) patients enrolled into the ALITHIOS open-label extension study and received ofatumumab for up to 4 years cumulatively
- Of these, 1214/1367 (88.8%) patients were still receiving ofatumumab treatment at the time of data cut-off*
  - The main reasons for discontinuing treatment were the occurrence of AEs (4.0%) and patient/guardian decision (4.0%)

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-2021; [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. AE, adverse event; PY, patient-years.

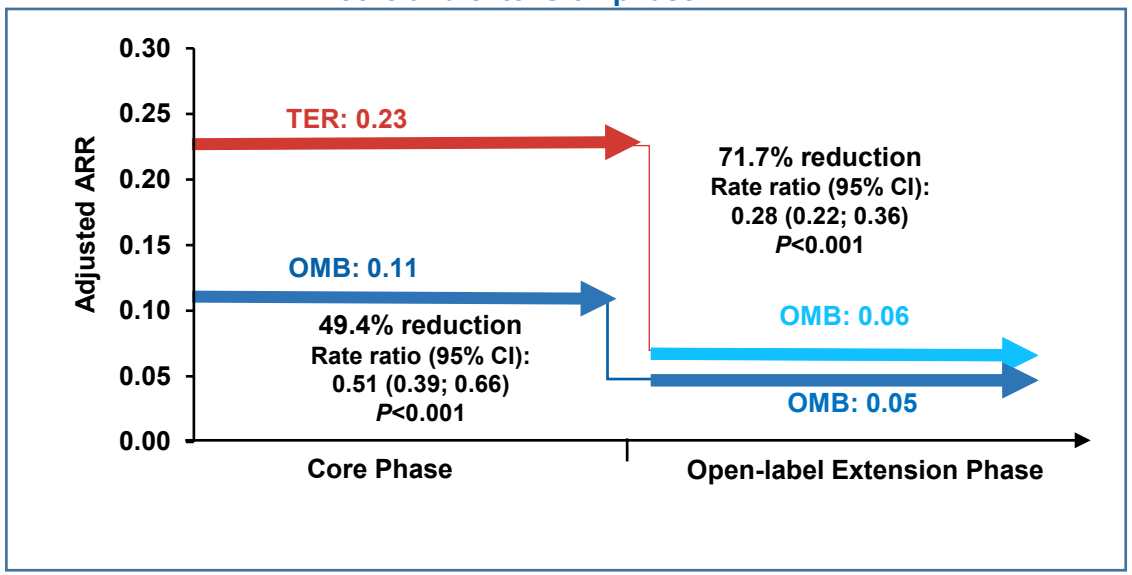
Baseline Demographics and Clinical Characteristics

Demographics and clinical characteristics[a]	Ofatumumab continuous (N=946)		Switch from teriflunomide to ofatumumab (N=936)	
	Baseline from core study (N=946)	Baseline from extension study (N=690)	Baseline from core study (N=936)	Baseline from extension study (N=677)
Age, years	38.4±9.04	38.1±8.69	38.0±9.22	40.1±9.21
Female, n (%)	637 (67.3)	483 (70)	636 (67.9)	456 (67.4)
BMI, kg/m^2	25.86±6.22	25.73±6.0	25.93±6.02	25.61±5.85
Treatment-naive patients[b], n (%)	386 (40.8)	Not applicable[e]	363 (38.8)	Not applicable[c]
EDSS score at baseline	2.93±1.35	2.81±1.48	2.90±1.36	2.81±1.46[d]
Number of relapses in the last 12 months prior to screening	1.2±0.69	Not available	1.3±0.71	0.2±0.49[d]
Number of Gd+ T1 lesions	1.7±4.51	0.0±0.21	1.3±3.43	0.8±2.37[d]
Total volume of T2 lesions, cm^3	13.72±13.80	Not available	12.55±13.81	Not available

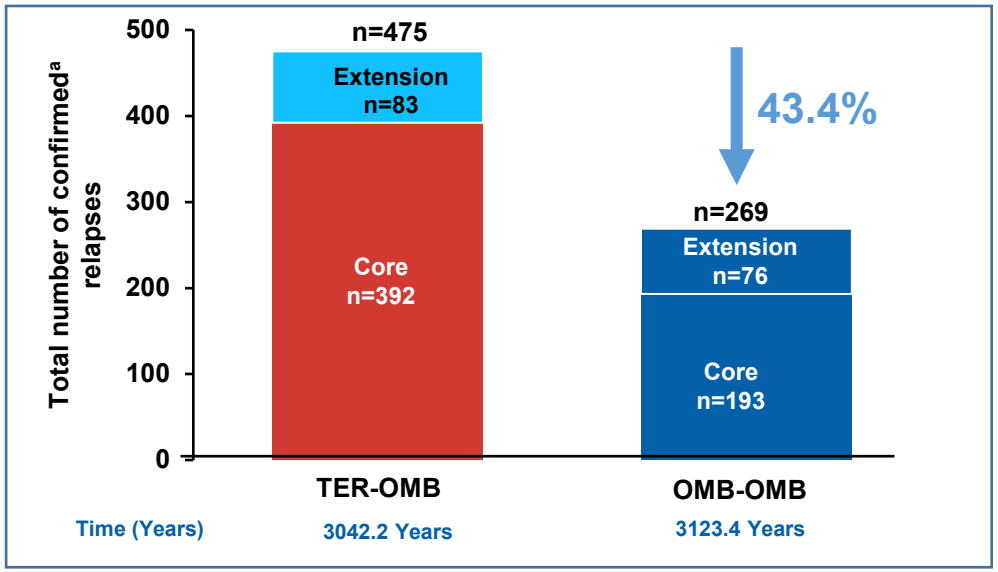
[a]Values are represented as mean±SD unless specified otherwise; [b]Treatment naive patients are those who have not received a prior multiple sclerosis disease modifying therapy; [c]not applicable since all patients have been pre-treated with teriflunomide; [d]The baseline from the extension study in the ofatumumab switch from teriflunomide group reflects the teriflunomide treatment effect during the double-blind treatment phase in the ASCLEPIOS studies; enot applicable since all patients have been pre-treated with ofatumumab
BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing.

Annualized Relapse Rates and Cumulative number of relapses Over up to 4 Years[a]

Within-group comparison between the core and extension phase



Total number of relapses over up to 4 years

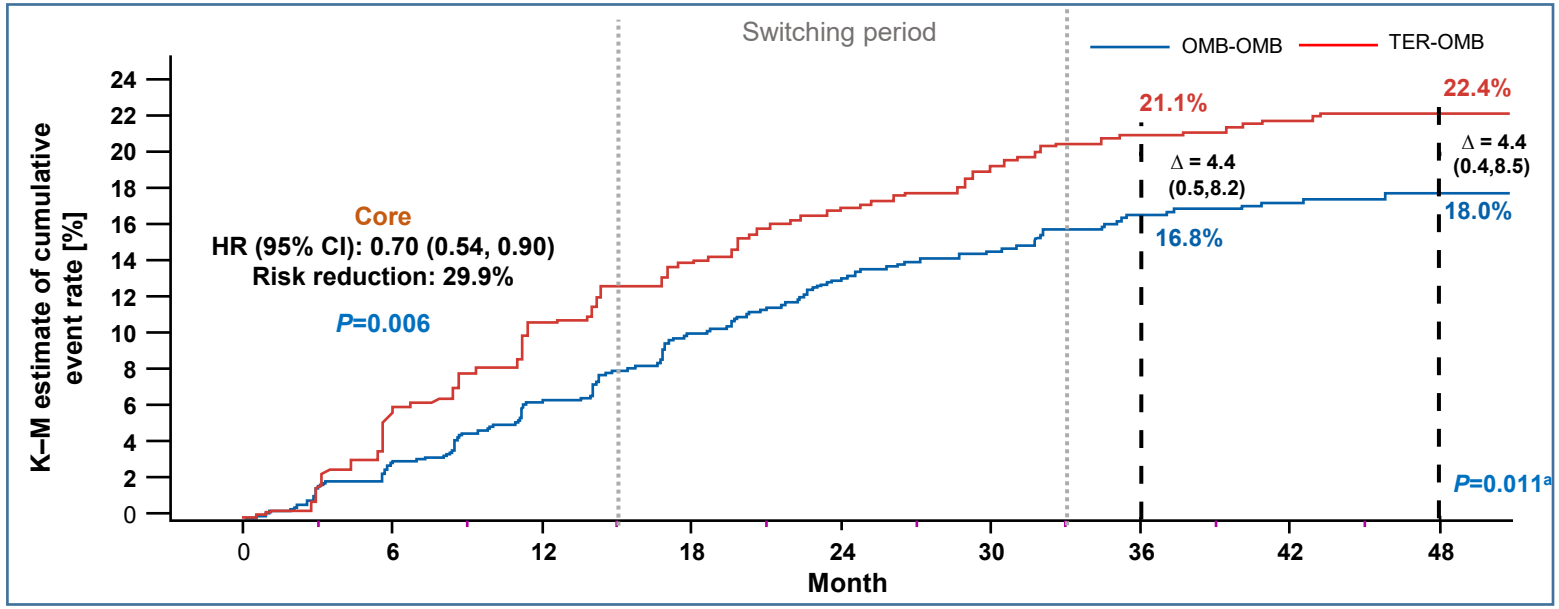


- ARR in the continuous ofatumumab group remained low for up to 4 years after treatment initiation corresponding to an adjusted rate of 1 relapse every 20 years during the extension phase
- Switch from teriflunomide to ofatumumab resulted in a pronounced reduction in ARR
- Between-group comparison of the total number of relapses over the period of up to 4 years shows a persisting cumulative benefit with the earlier initiation of ofatumumab

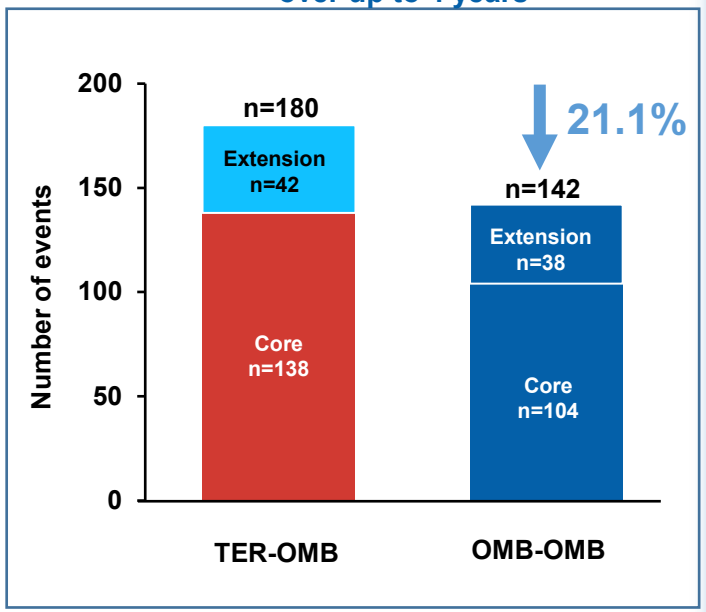
All P values are nominal P values; additional details including the confidence intervals are presented in the backup slides.
[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
ARR, annualized relapse rate; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

3-month Disability Worsening*

Time to first 3-month confirmed disability worsening (3mCDW) – Kaplan-Meier estimates



Cumulative number of first events over up to 4 years

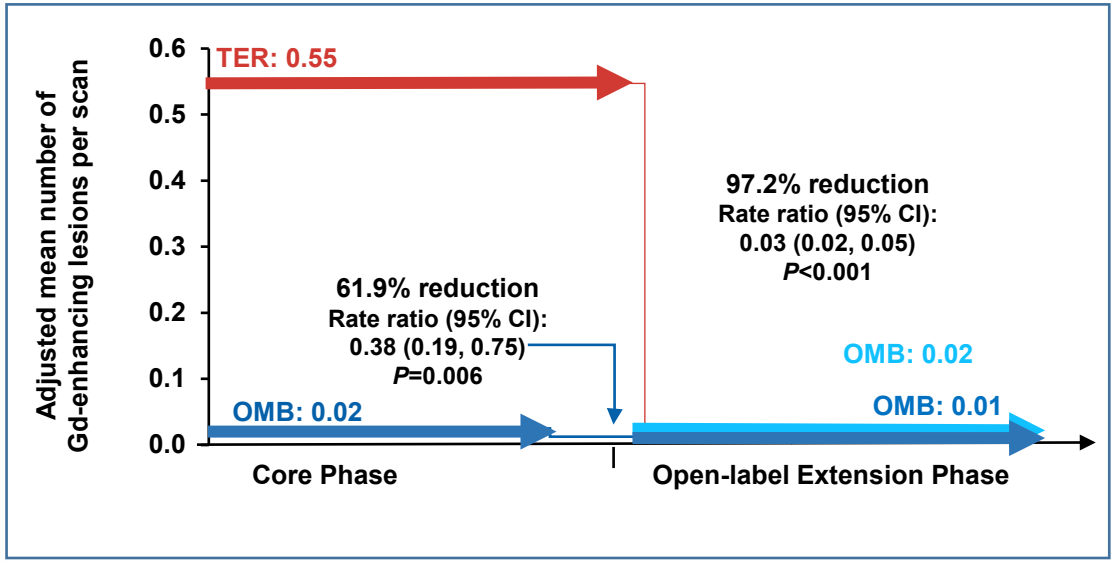


- **As shown by the delta at months 36 and 48, and the difference in the cumulative number of events over a period of up to 4 years, earlier treatment with ofatumumab was associated with an efficacy benefit that cannot be recovered in those initially randomized to teriflunomide**
- **A similar trend was also observed for 6mCDW***

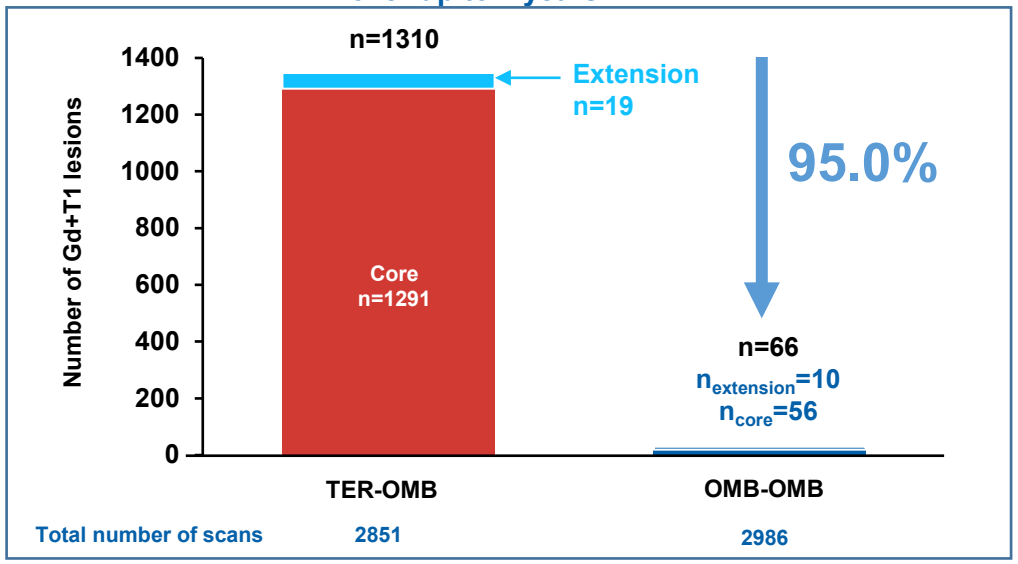
*additional details including the confidence intervals are presented in the backup slides. Cut-off for core and extension periods refer to the first dose of ofatumumab in extension. Δ, Difference in KM estimates (TER-OMB minus OMB-OMB). [a]P value represented here is P value for Log-Rank test. 3mCDW, 3-month confirmed disability worsening; 6mCDW, 6-month confirmed disability worsening; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier, OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab.

Mean number of Gd-enhancing T1 lesions

Within-group comparison between the core and extension phase



Cumulative number of Gd+T1 lesions over up to 4 years

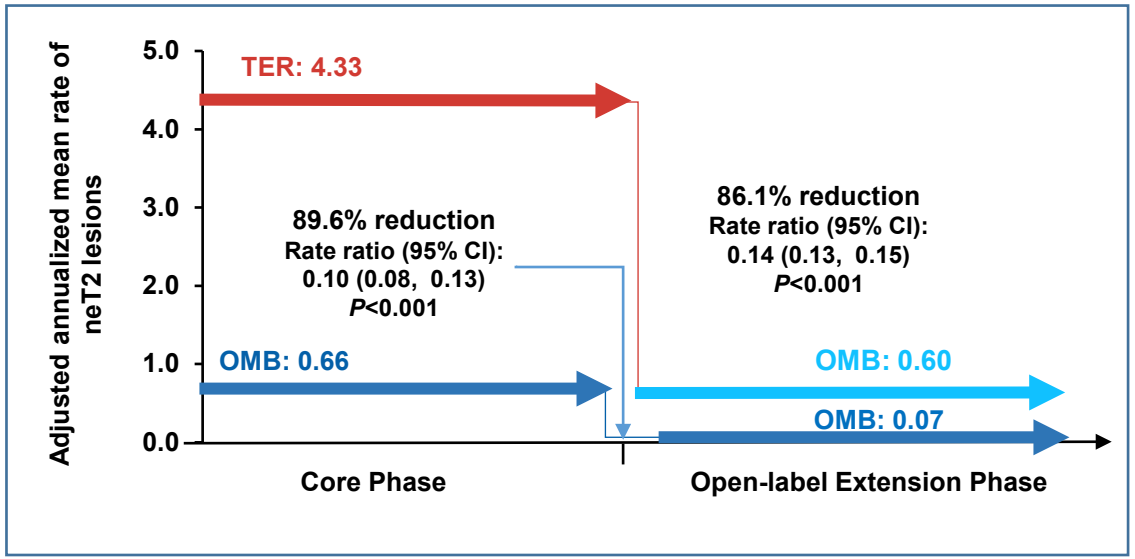


- The number of Gd+ T1 lesions per scan in the continuous ofatumumab group remained low for up to 4 years after treatment initiation
- Switching from teriflunomide to ofatumumab resulted in an almost complete suppression of Gd+ T1 lesion activity
- Between-group analysis over a period of up to 4 years show the extent of the cumulative benefit on acute inflammatory activity with the earlier initiation of ofatumumab

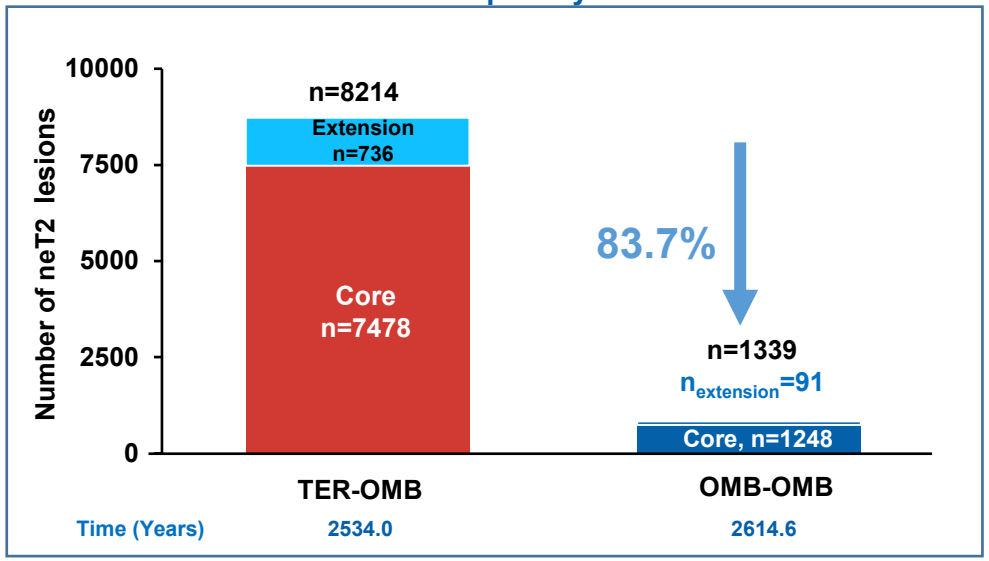
All P values are nominal P values; additional details including the confidence intervals are presented in the backup slides.
Gd+, gadolinium-enhancing; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Number of new or enlarging T2 Lesions

Within-group comparison between the core and extension phase



Cumulative number of neT2 lesions over up to 4 years

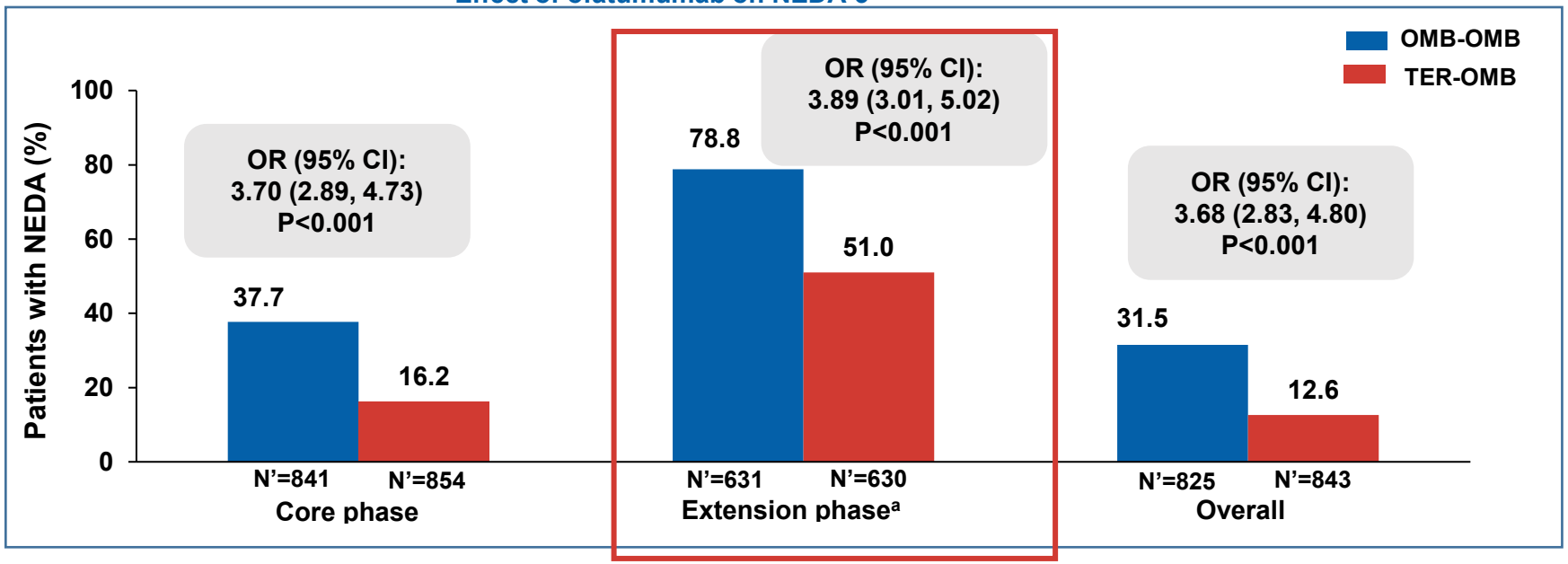


- The number of neT2 lesions in the continuous ofatumumab group remained low for up to 4 years after treatment initiation; a near complete suppression was observed during the extension phase
- Switching from teriflunomide to ofatumumab resulted in a pronounced reduction in the number of neT2 lesions
- Similar to Gd+ T1 lesions, the between-group analysis over a period of up to 4 years shows the extent of the cumulative benefit on neT2 lesions with the earlier initiation of ofatumumab

All P values are nominal P values; additional details including the confidence intervals are presented in the backup slides.
Gd+, gadolinium-enhancing; neT2, new or emerging T2; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab

No Evidence of Disease Activity (NEDA-3)

Effect of ofatumumab on NEDA-3



Mean exposure in years	1.6	1.5	1.9	1.9	2.9	2.9

- In the extension phase, nearly 8 out of 10 patients in the continuous ofatumumab group had no evidence of disease activity (NEDA-3); whereas about 5 out of 10 patients in switch group had no evidence of disease activity
- Cumulatively, over 4 years, the odds of maintaining NEDA-3 was >3-fold higher with the earlier initiation of OMB

All P values are nominal P values; 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 T1 Gd-enhancing lesions. Statistical model used logistic regression adjusting for treatment and region as factors and age, baseline EDSS, number of Gd-lesions at baseline as covariates; N'=The total number of patients in the treatment group excluding those who discontinued treatment early for reasons other than lack of efficacy or death and had NEDA before early discontinuation; [a]rebaseline at the entry of extension was performed; NEDA, no evidence of disease activity; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; PTYs, patient treatment years; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

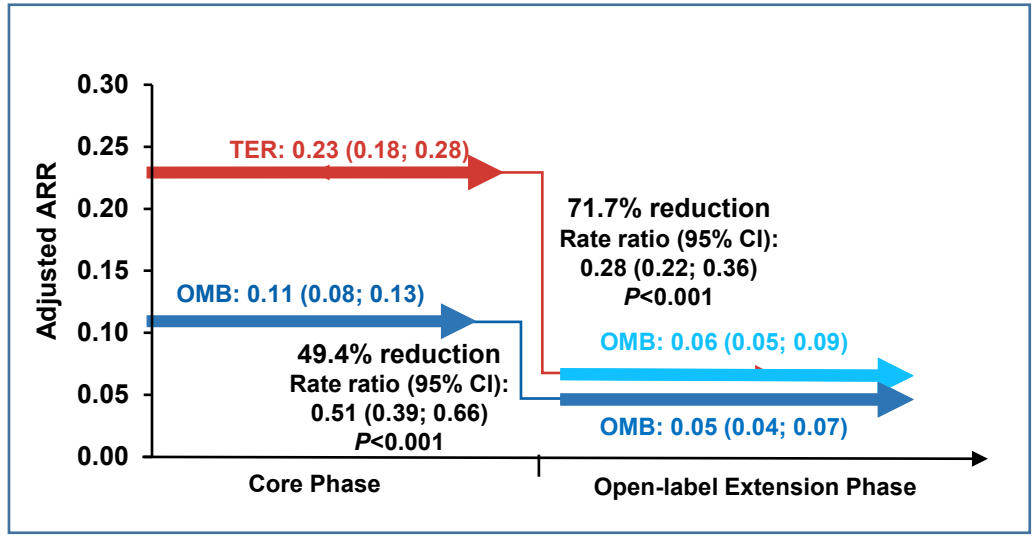
Conclusions

- Continuous ofatumumab treatment for up to 4 years showed sustained efficacy by reducing relapses, MRI lesions, risk of disability worsening and by increasing the odds of keeping patients free of disease activity (NEDA-3)
- The low rate of relapses and MRI lesions observed in the core phase III trials was sustained, if not further reduced, during the ALITHIOS open-label extension, showing continued efficacy on these outcomes with up to 4 years of treatment
- Patients who switched from teriflunomide to ofatumumab in the extension phase demonstrated pronounced reductions in relapses and MRI lesions. Cumulatively, over 4 years, the odds of maintaining NEDA-3 was >3-fold higher with the earlier initiation of OMB
- Sustained differences in cumulative relapses, MRI lesion activity, and the risk of disability worsening between the continuous and the switch group support the value of earlier initiation of high-efficacy therapy, such as ofatumumab, compared to a lower efficacy therapy

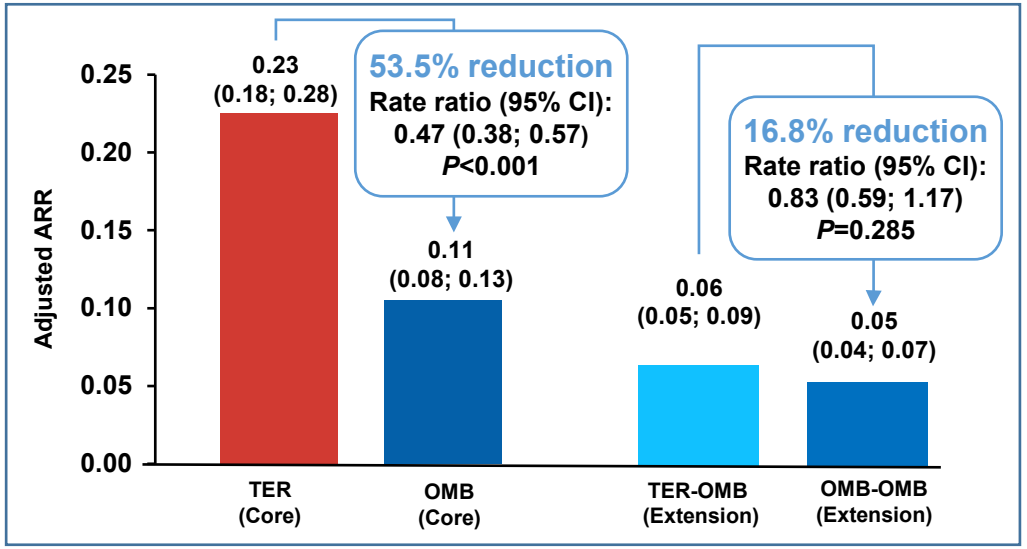
MRI, magnetic resonance imaging

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)



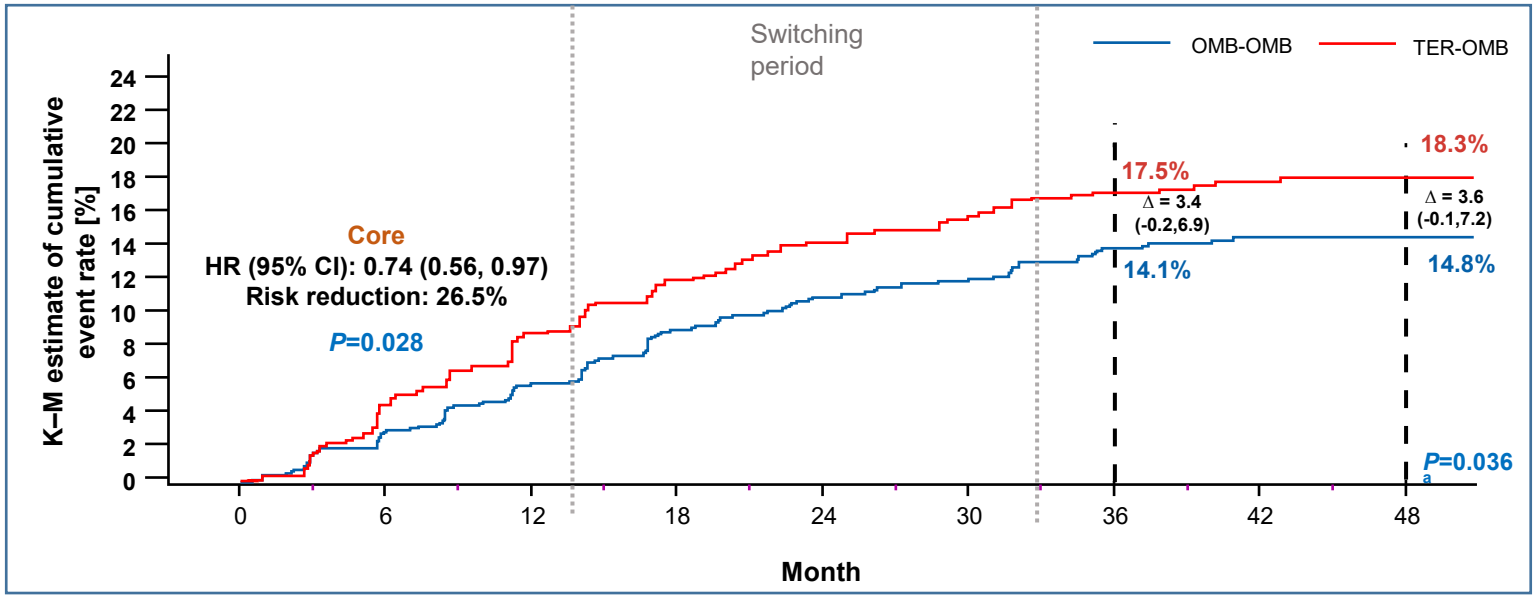
- **The within group analysis showed that continuous use of ofatumumab was associated with a significant reduction in ARR by 49.4% with longer-term treatment, and that switch from teriflunomide to ofatumumab resulted in a pronounced reduction in ARR (71.7%)**

- **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**

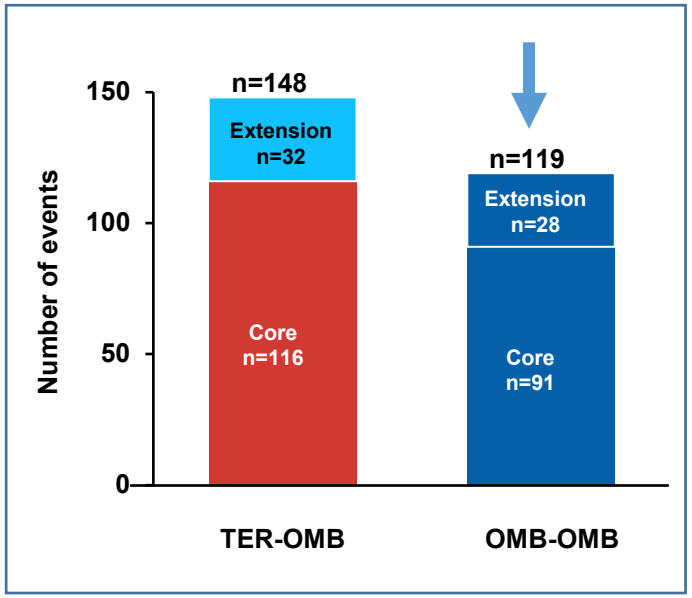
[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS; [b]Obtained from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, number of relapses in previous year, baseline 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; Gd, gadolinium; ns.,non-significant; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

6- month Disability Worsening*

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



Cumulative number of first events

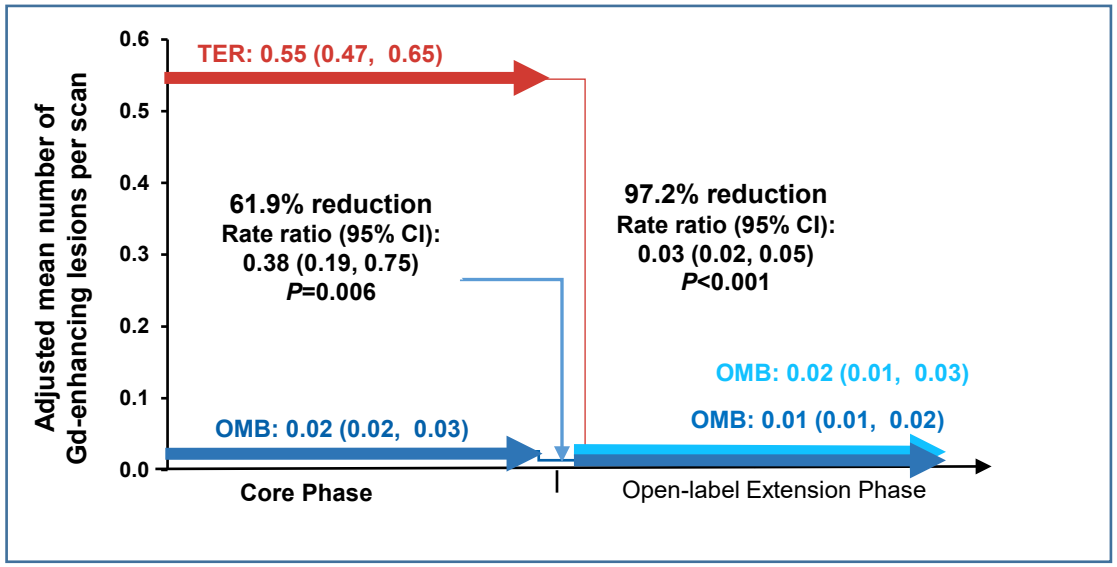


- **The deltas at 36 and 48 months, and the difference in the cumulative number of events over a period of up to 4 years, show that earlier treatment with ofatumumab was associated with an efficacy benefit that is lost and cannot be recovered in those initially randomized to teriflunomide**
- **As seen with 3mCDW, the risk of subsequent 6mCDW events after switching from teriflunomide to ofatumumab was similar in both treatment arms**

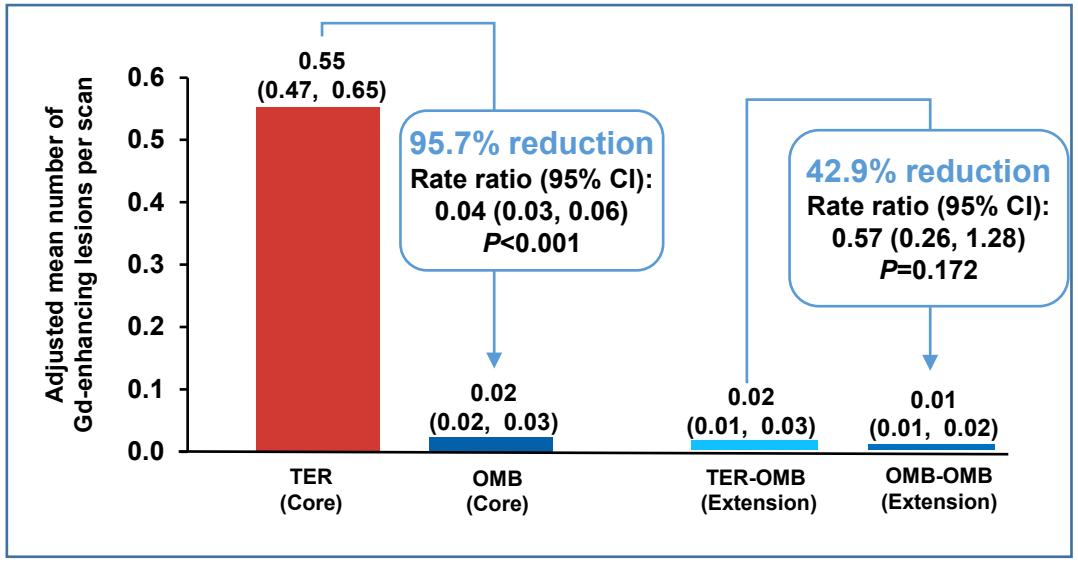
Cut-off for core and extension periods refer to the first dose of ofatumumab in extension. Δ, Difference in KM estimates (TER-OMB minus OMB-OMB). [a]P value represented here is P value for Log-Rank test.
OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab. 6mCDW, 6-month 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 with-in group analysis showed that continuous use of ofatumumab was associated with a reduction in the mean number of lesions per scan by 61.9% with longer-term treatment, while switch from teriflunomide to ofatumumab resulted in an almost complete suppression of Gd+ T1 lesion activity (97.2%)

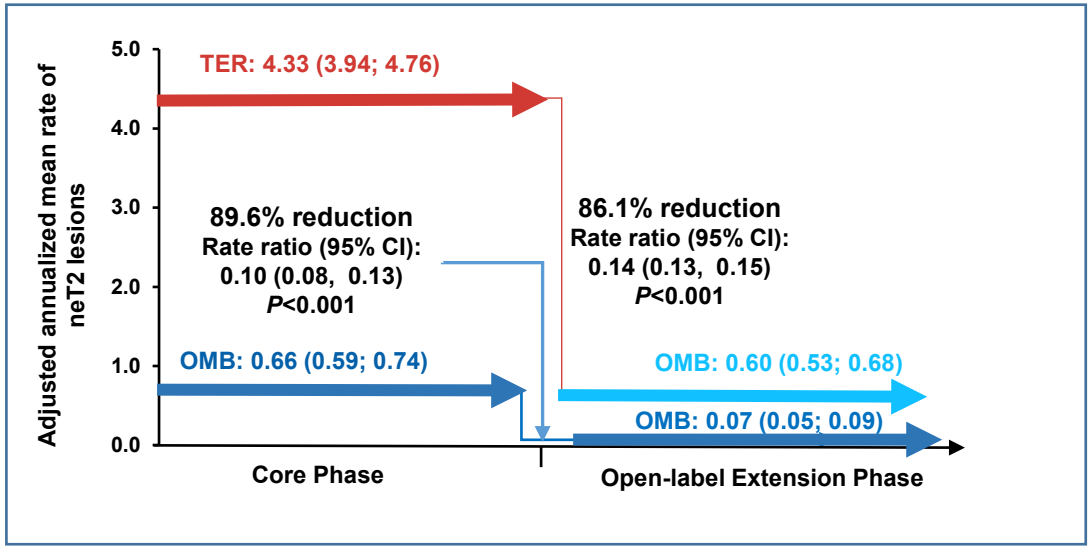
- A significant reduction in the mean number of Gd+ T1 lesions observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies. Gd+T1 lesions were almost completely suppressed during the extension phase in both the continuous ofatumumab group and switch group

[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.

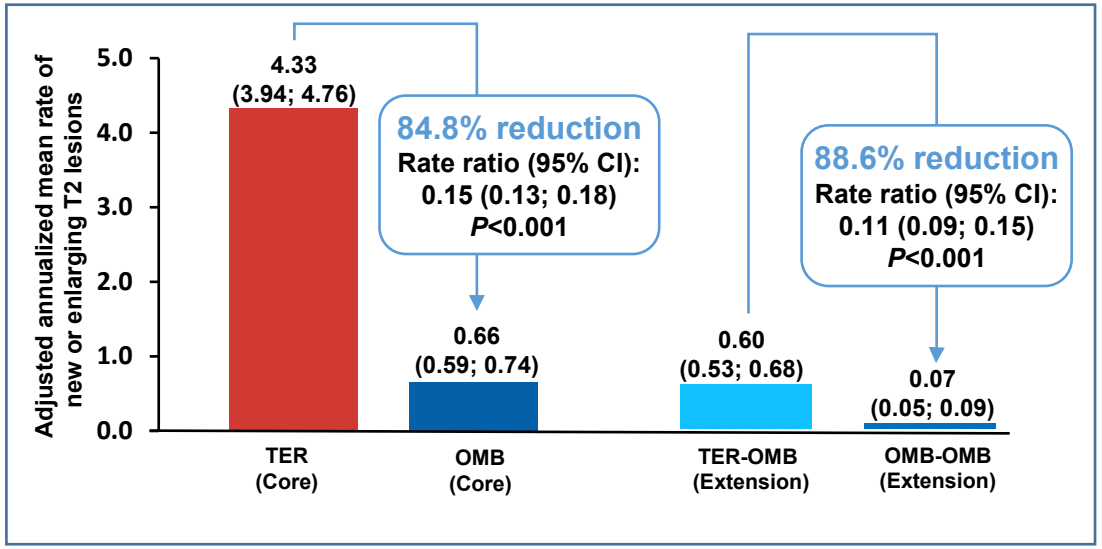
All P values are nominal P values. CI, confidence interval; Gd, gadolinium; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Number of new or enlarging T2 Lesions

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



Between group comparison[a] 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 89.6% with longer-term treatment, while switch from teriflunomide to ofatumumab resulted in a pronounced reduction in the number of neT2 lesions (86.1%)**

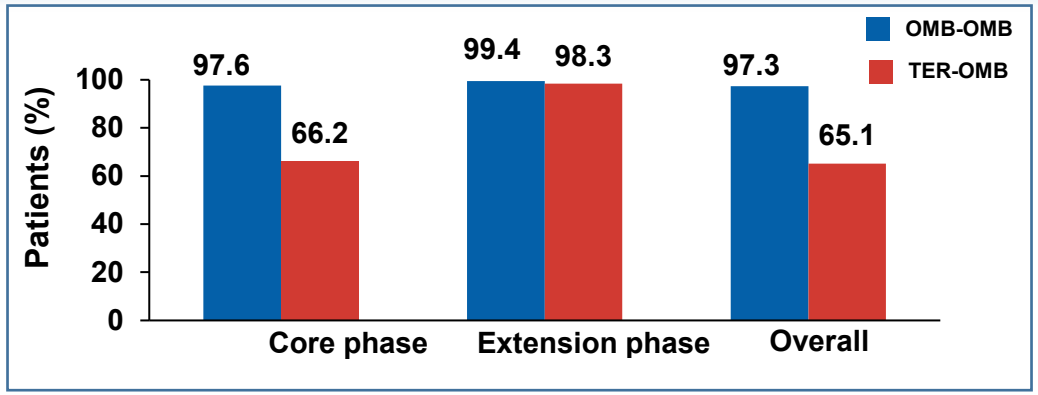
- **The significant relative reduction in the mean rate of neT2 lesions observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was also seen in the extension phase, despite the overall reduced number of lesions, reflecting the known "carry over" effect on this outcome**

[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.

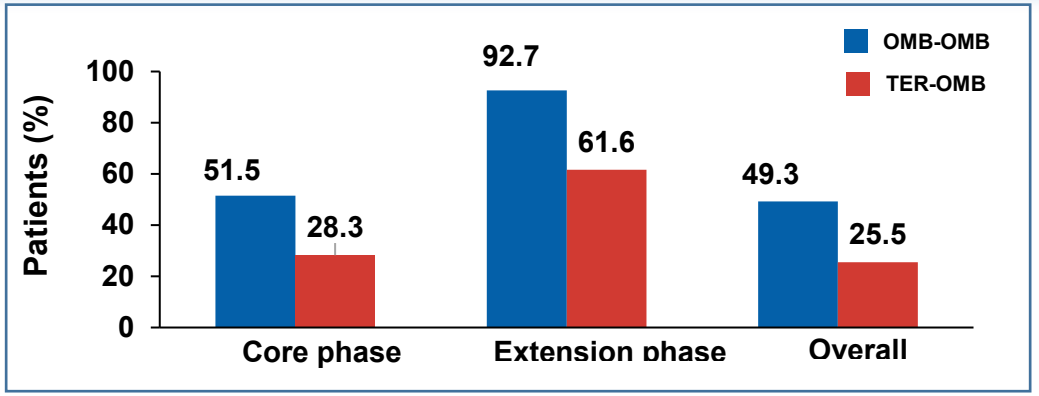
CI, confidence interval; neT2, new or enlarging T2; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Effect of Ofatumumab on Individual NEDA-3 Components

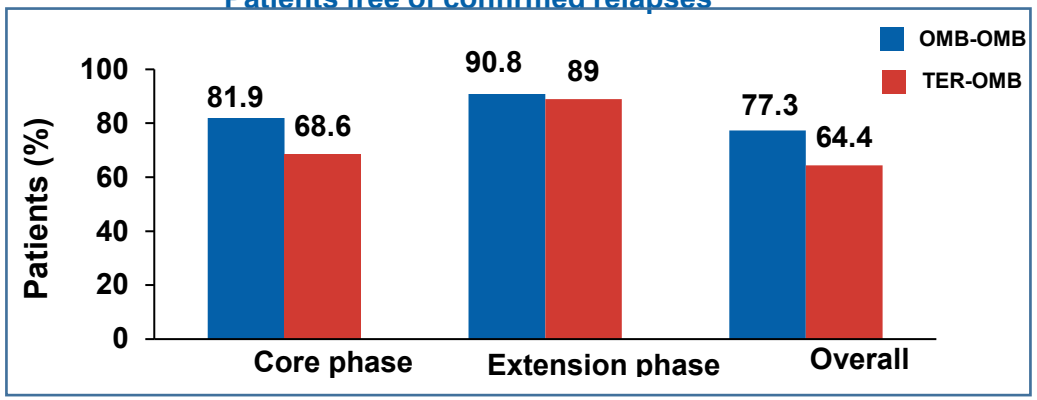
Patients free of Gd+ T1 lesions



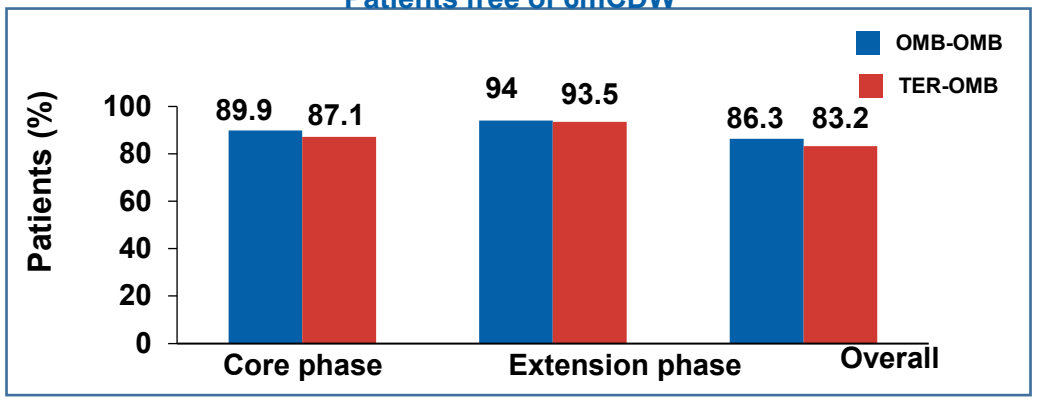
Patients free of new/enlarging T2 lesions



Patients free of confirmed relapses



Patients free of 6mCDW



- **Cumulatively, over 4 years, more ofatumumab-treated patients were free of Gd+ T1 lesions, neT2 lesions, confirmed relapses and 6mCDW with continuous use of ofatumumab than switch from teriflunomide**

CDW, confirmed disability worsening; NEDA, no evidence of disease activity; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab