ePresentation #: **EPR-237**
Session: MS and related disorders 4
Sunday, 30 June; 14:40 to 14:45 CEST

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Longer-Term (Up to 6 Years) Efficacy of Ofatumumab in Recently Diagnosed Treatment-Naive Relapsing Multiple Sclerosis

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Disclosures (1/2)

Ralf Gold has received compensation for consulting or speaking from Bayer Healthcare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He, or the institution he works for, has received research support from Bayer Healthcare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He has also received honoraria as a Journal Editor from SAGE and Thieme Verlag.

Gabriel Pardo has received personal compensation for serving as a consultant for Amgen, Biogen, Roche/Genentech Inc, Sanofi-Genzyme, EMD Serono, Horizon Therapeutics, TG Therapeutics and Novartis. He has also received personal compensation for serving on a speakers' bureau for Biogen, Bristol Myers Squibb, Horizon Therapeutics, Roche/Genentech, Sanofi-Genzyme, Novartis, EMD Serono and TG Therapeutics

Stephen L. Hauser serves on scientific advisory boards for Accure, Alector, Annexon; previously consulted for BD, Moderna, NGM Bio, and Pheno Therapeutics; previously served on the Board of Directors for Neurona; and has received non-financial support (travel reimbursement and writing assistance for anti-CD20 related meetings and presentations) from Roche and Novartis.

Amit Bar-Or has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from Accure, Atara Biotherapeutics, Biogen, Bristol Myers Squibb /Celgene/Receptos, GlaxoSmithKline, Gossamer, Janssen/Actelion, Medimmune, Merck/EMD Serono, Novartis, Roche/Genentech and Sanofi-Genzyme.

Xavier Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials, or participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, Medday, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi-enzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

Jeffrey A. Cohen has received personal compensation for consulting for Astoria, Bristol Myers Squibb, Convelo Therapeutics, EMD Serono, Find Therapeutics, INmune Bio Inc. and Sandoz and serving as an Editor of Multiple Sclerosis Journal.

Derrick Robertson has received fees for consulting, contracted research and speaker's bureau from Biogen, Celgene, EMD Serono, Genentech, Sanofi Genzyme, Janssen and TG therapeutics; consulting fees and speakers bureau from Bristol Myers Squibb, Horizon and Alexion; consulting fees and contracted research from Novartis; consulting fees from Greenwich Biosciences; and contracted research from GW Pharmaceuticals, PCORI, Atara Biotherapeutics and CorEvitas.

Carrie M. Hersh has received speaking, consulting, and advisory board fees from Genentech, Genzyme, Biogen, Novartis, EMD-Serono, Bristol Myers Squibb, TG Therapeutics, Horizon Therapeutics and Alexion. She has received research support paid to her institution by Biogen, Novartis, Bristol Myers Squibb, Patient-Centered Outcomes Research Institute (PCORI) and NIH - NINDS 1U01NS111678-01A1 sub-award.

Robert T. Naismith has consulted for Alexion Pharmaceuticals, Biogen, Bristol Myers Squibb, Celltrion, Genentech, Genzyme, EMD Serono, Horizon Therapeutics, Novartis, Sandoz and TG Therapeutics.

Disclosures (2/2)

Kumaran Deiva has received personal compensation for speaker activities from Novartis and Sanofi.

Sven G. Meuth has received honoraria for consulting from Alexion, Almirall, Amicus Therapeutics Germany, Bayer Healthcare, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva. He received a research grant from German Ministry for Education and Research (BMBF), Bundesinstitut für Risikobewertung (BfR), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Gemeinsamer Bundesausschuss (G-BA), German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology and Alexion, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, HERZ Burgdorf, Merck Serono, Novartis, ONO Pharma, Roche, and Teva.

Anne H. Cross has received consulting fees, support and honoraria from Biogen, Celgene, Bristol Myers Squibb, EMD Serono, Merck, Genentech, Roche, Greenwich Biosciences (Jazz Pharmaceuticals), Horizon Therapeutics, Janssen (subsidiary of Johnson & Johnson), Novartis, TG Therapeutics, Academic CME, Projects In Knowledge, CME Outfitters, WebMD, Conrad N. Hilton Foundation, Potomac Center for Medical Education, The Consortium of Multiple Sclerosis Centers and ACTRIMS; has received a grant from the Department of Defense, USA; has been the secretary (elected) of The Consortium of Multiple Sclerosis Centers, member of the scientific advisory board of Race to Erase MS, program committee (chair) of ACTRIMS, member of the COVID-19 advisory committee of the National Multiple Sclerosis Society and National Multiple Sclerosis Society, and representative on the Progressive MS Alliance; has participated on the data safety monitoring board or advisory board for Race to Erase MS (charity), National Multiple Sclerosis Society, Novartis, EMD Serono, Biogen, Celgene/Bristol Myers Squibb and TG Therapeutics; and has received patent for ‘Yablonskiy DA, Sukstansky AL, Wen J, Cross AH. Methods for simultaneous multi-angular relaxometry of tissue using magnetic resonance imaging. Patent 15060-630 (015875)’.

Jutta Gärtner 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, Bristol Myers Squibb, 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, Bristol Myers Squibb, 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.

Introduction

- Ofatumumab, 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**[1,2]
- In the phase 3 ASCLEPIOS I/II trials in people with RMS, **ofatumumab** demonstrated **superior efficacy** in **reducing** the annualised relapse rate **(ARR), suppressing** magnetic resonance imaging **(MRI) lesion activity** and **delaying disability worsening** versus teriflunomide while maintaining a favourable safety profile[3]
- In the subgroup of **recently diagnosed (≤3 years) and treatment-naive (RDTN)** participants, ofatumumab showed an even better **benefit–risk profile** compared with teriflunomide, 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]

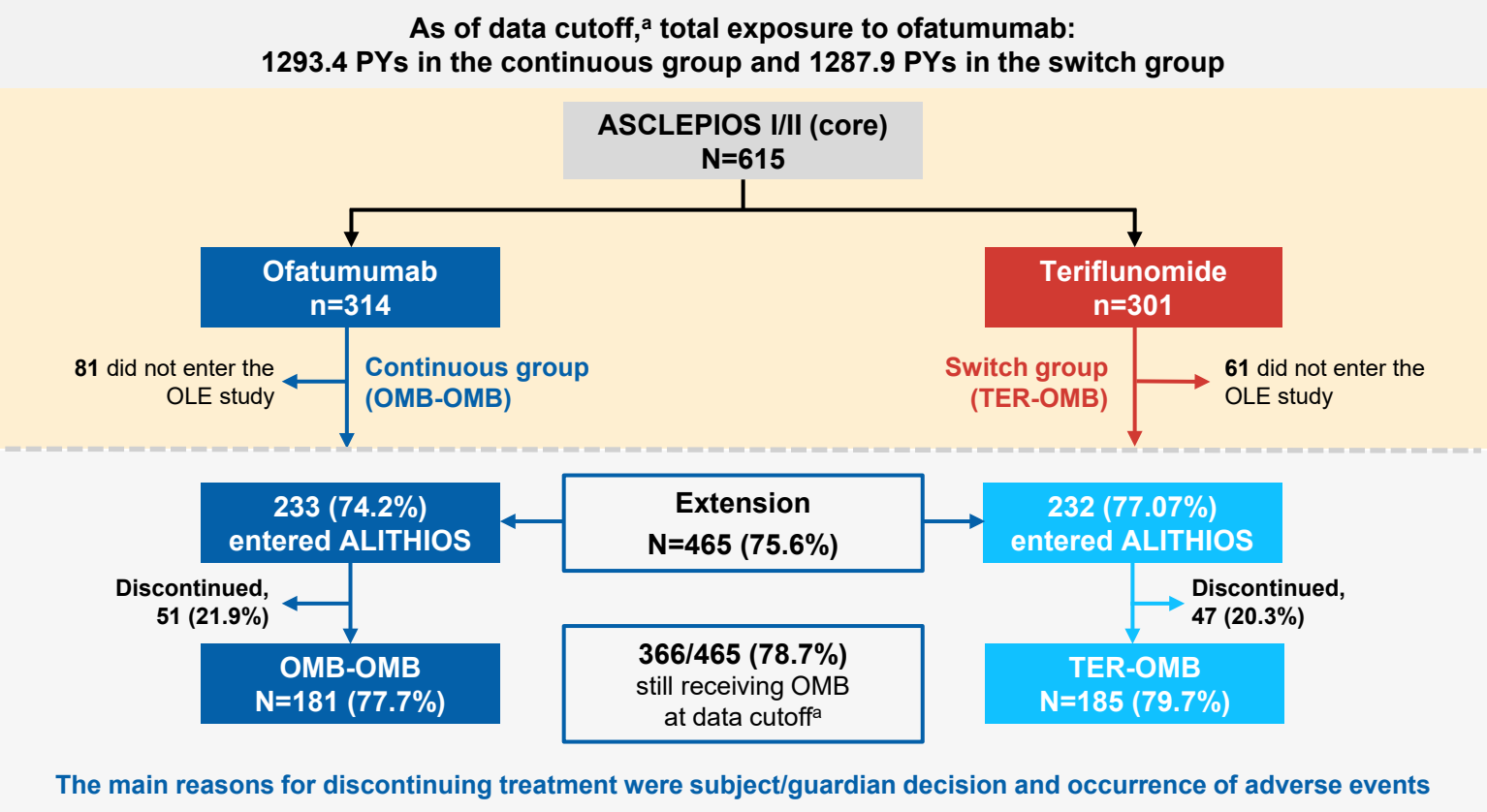
Objective: To assess the long-term efficacy of ofatumumab for up to 6 years in RDTN participants with RMS

1. Kesimpta (Ofatumumab) Summary of Product Characteristics. Novartis; 2021. Accessed April 23, 2024. https://www.ema.europa.eu/en/documents/product-information/kesimpta-epar-product-information_en.pdf. **2.** Kesimpta (ofatumumab). Prescribing Information. Novartis; 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.** Gartner J, et al. *Mult Scler.* 2022;28:1562–1575. **5.** Gärtner J, et al. P052. Presented at: European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS), Amsterdam, the Netherlands; October 26–28, 2022.

RDTN, recently diagnosed (≤3 years) and treatment-naive; **RMS**, relapsing multiple sclerosis.

Methods

Participant disposition – RDTN subgroup



Key assessments

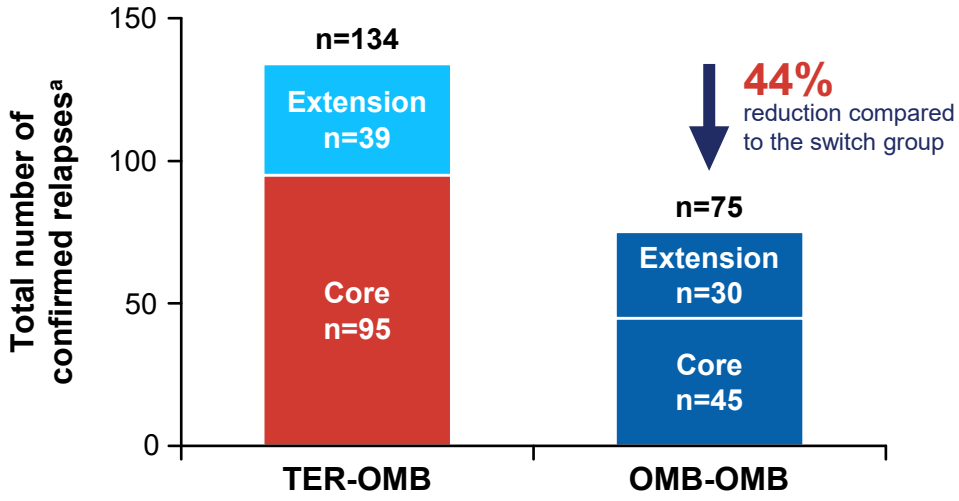
- **ARR**
- **Brain MRI outcomes**
  - Mean number of gadolinium-enhancing (Gd+) T1 lesions per scan
  - Number of new or enlarging T2 (neT2) lesions per year
- **3- and 6-month confirmed disability worsening (3/6mCDW)**
- **No evidence of disease activity (NEDA-3)[b]**

[a]Data cutoff: 25 September 2023 [up to 6 years]. [b]Defined as no 6mCDW, no confirmed MS relapse, no neT2 lesions compared to baseline, and no Gd+ T1 lesions.
These analyses include cumulative data from the RDTN subgroups randomised to ofatumumab in the core phase (continuous group) and those originally randomised to teriflunomide and switching to ofatumumab in ALITHIOS (switch group).

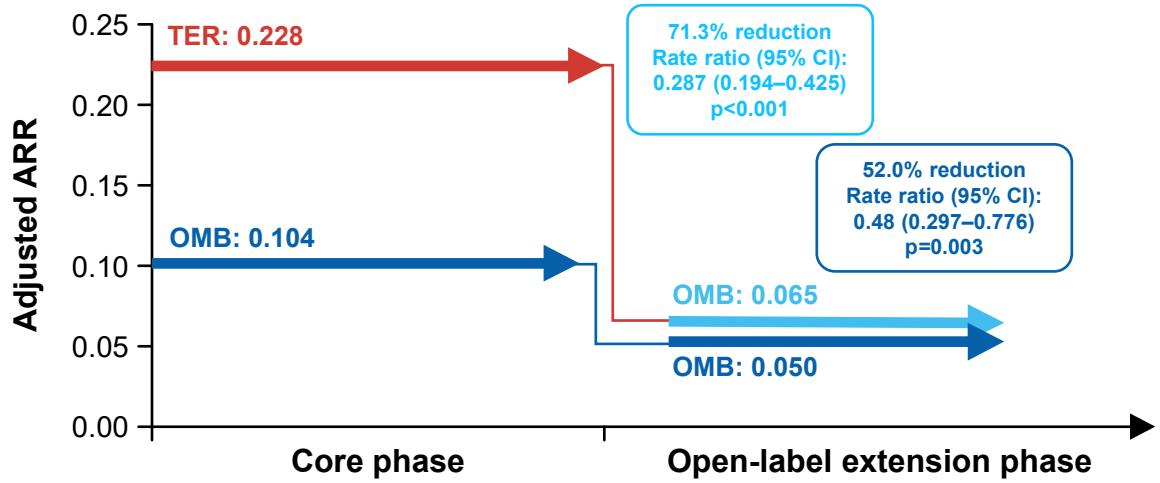
ARR, annualised relapse rate; **Gd+**, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **OLE**, open-label extension; **OMB-OMB**, continuous ofatumumab; **PY**, patient-year; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

A sustained low ARR was observed in RDTN participants receiving first-line ofatumumab for up to 6 years

Cumulative number of relapses up to 6 years



Within-group comparison[b] between the core and extension phases



- Over a period of up to 6 years, **first-line continuous versus later initiation of ofatumumab** was associated with a **44% reduction** in the **cumulative number of relapses**
- **ARR remained low** with first-line continuous ofatumumab, reaching an adjusted rate in the extension period that corresponds to **1 relapse for every 20 years**
- **Switching** from teriflunomide to ofatumumab resulted in a **pronounced 71.3% reduction in 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 and 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 annualise the relapse rate in each period. Baseline variables are from the core study baseline.

ARR, annualised relapse rate; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **OMB-OMB**, continuous ofatumumab; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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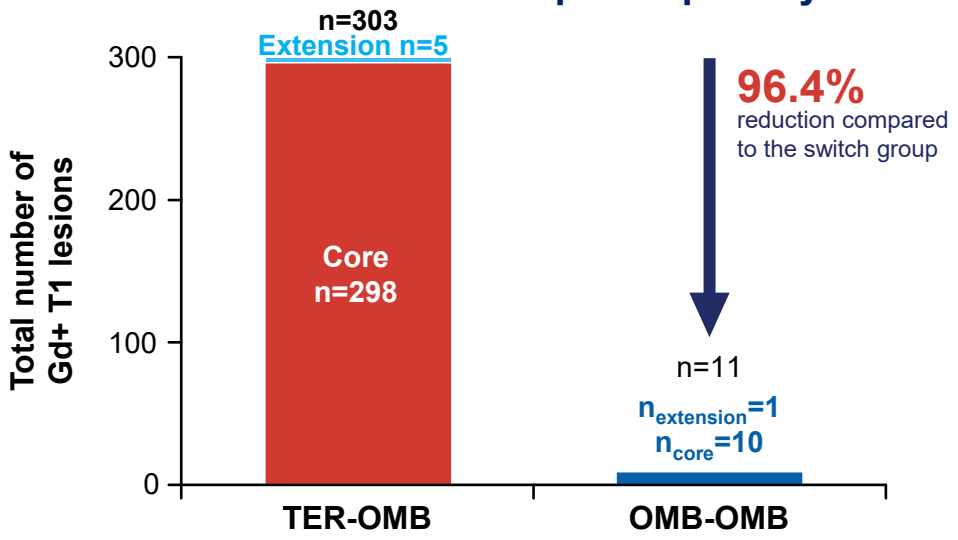
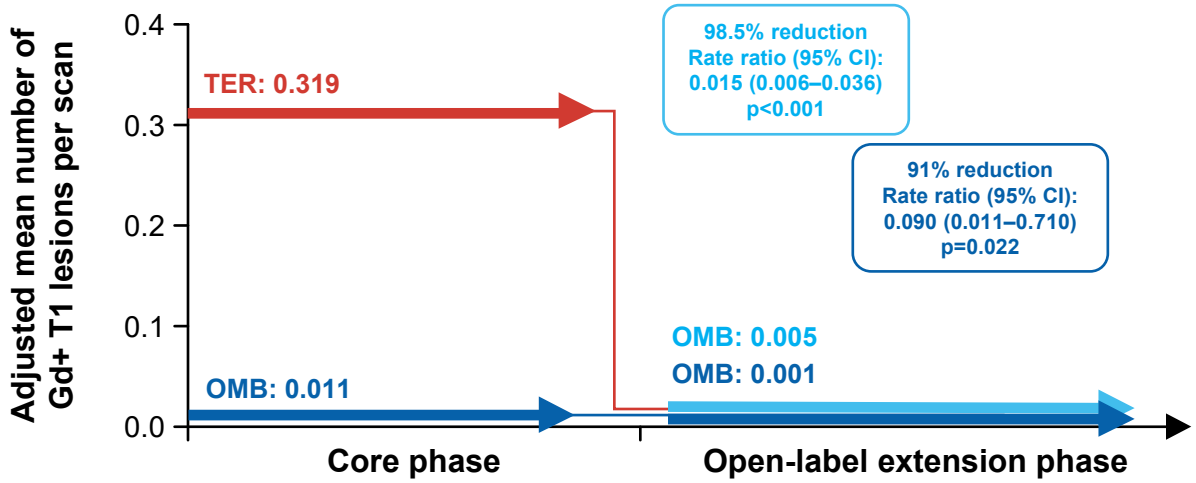
Gd+ T1 lesion activity was almost completely suppressed in RDTN participants receiving ofatumumab for up to 6 years

Cumulative number of relapses up to 6 years



Within-group comparison[b] between the core and extension phases



- Over a period of up to 6 years, **first-line continuous versus later initiation of ofatumumab** was associated with a **96.4% reduction** in the **cumulative number of Gd+ T1 lesions**
- **First-line continuous ofatumumab** treatment maintained an **almost complete suppression** of **Gd+ T1** lesion activity up to Year 6
- **Switching** from teriflunomide to ofatumumab **led to a rapid suppression** of **Gd+ T1 lesion activity** to closely match the continuous ofatumumab 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 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.

CI, confidence interval; **Gd+**, gadolinium-enhancing; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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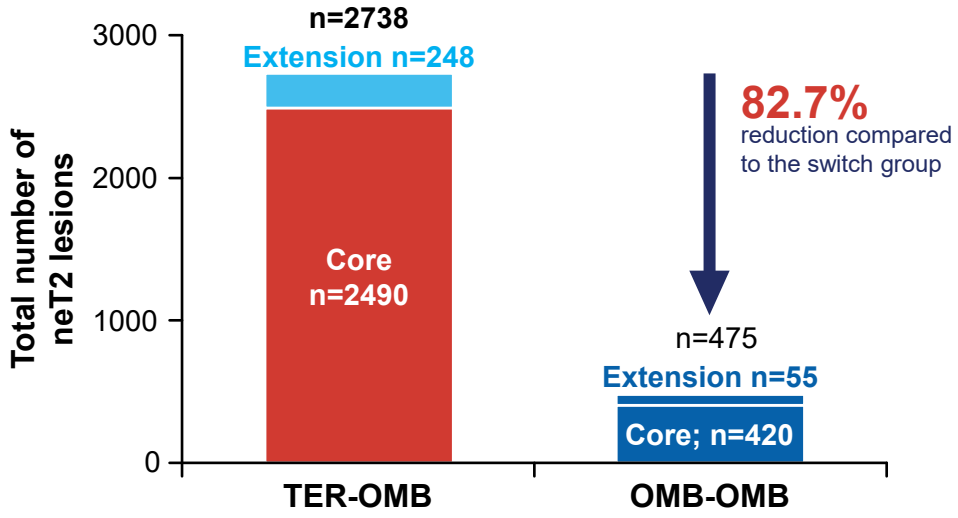
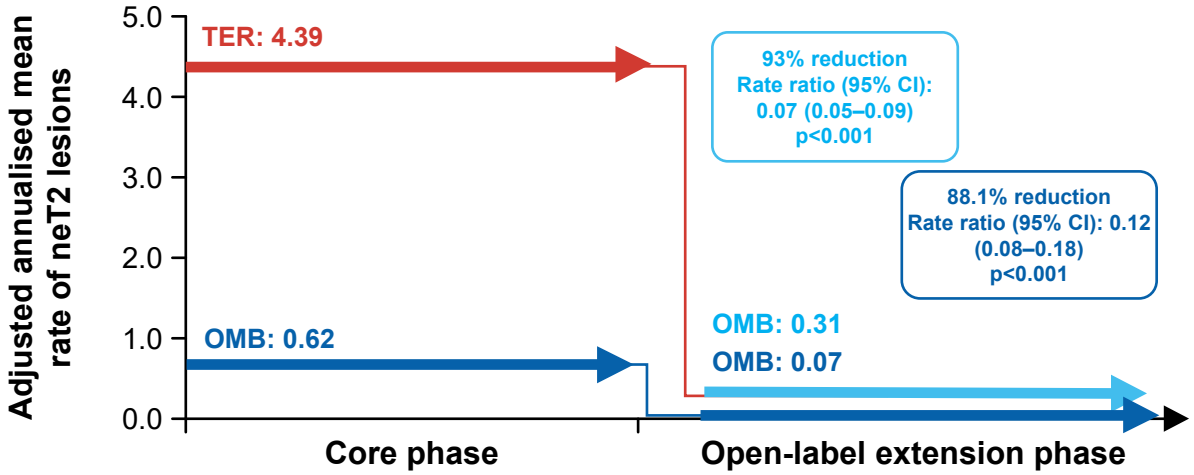
A significant and sustained reduction in the number of neT2 lesions was observed in RDTN participants receiving ofatumumab for up to 6 years

Cumulative number of neT2 lesions up to 6 years



Within-group comparison[a] between the core and extension phases



- Over a period of up to 6 years, **first-line initiation of ofatumumab** was associated with an **82.7% reduction** in the **cumulative number of neT2 lesions**
- **First-line continuous ofatumumab profoundly suppressed** the **number of neT2 lesions** up to Year 6
- **Switching** from teriflunomide to ofatumumab resulted in a **profound reduction** in the number of **neT2 lesions**

[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 annualise the lesion rate in each period. Baseline variables are from the core study baseline. All p values are nominal; additional details including the CIs are presented in the backup slides.

CI, confidence interval; **neT2**, new or enlarging T2; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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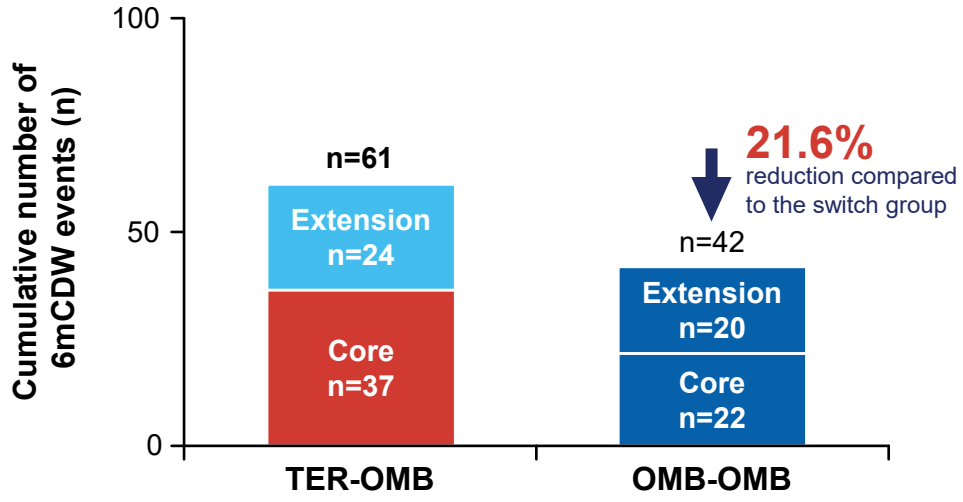
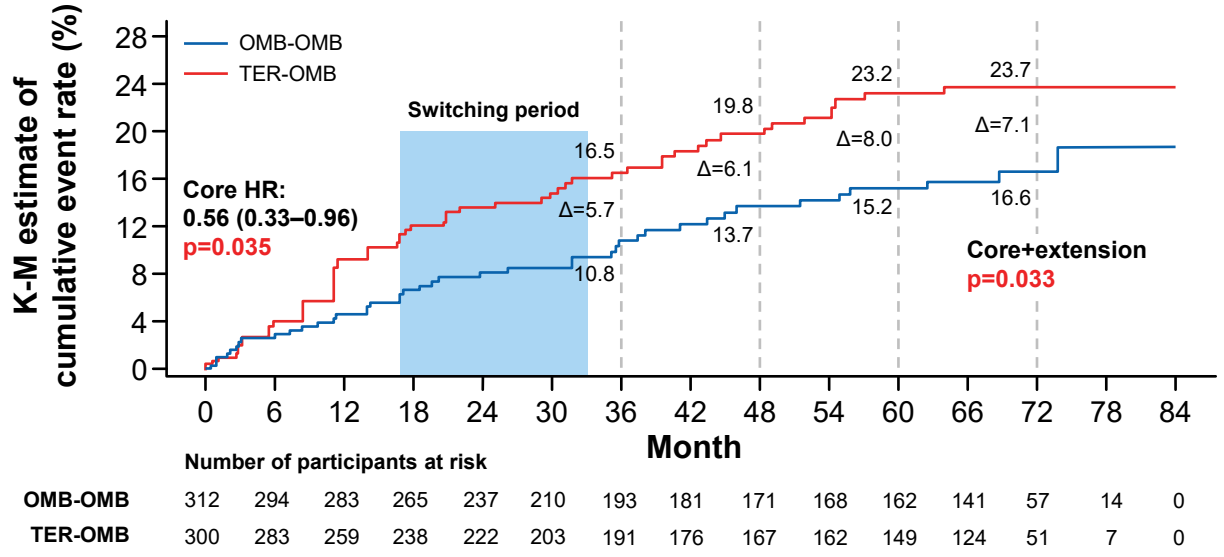
First-line ofatumumab treatment in RDTN participants was associated with a significantly lower number of 6mCDW events up to 6 years

Cumulative number of 6mCDW events up to 6 years



Cumulative event rate – 6mCDW



Number of participants at risk

OMB-OMB	312	294	283	265	237	210	193	181	171	168	162	141	57	14	0
TER-OMB	300	283	259	238	222	203	191	176	167	162	149	124	51	7	0

- **First-line continuous ofatumumab treatment** was associated with **significantly fewer 6mCDW events**
  - **6mPIRA[a] events** occurred in **11.1%** and **16.8%** of RDTN participants in the OMB-OMB and TER-OMB groups, respectively
- The significant **efficacy benefit of first-line ofatumumab** on 6mCDW in the core phase **cannot be recovered in those initially randomised to teriflunomide** and later switched to ofatumumab

[a]6mPIRA is defined as a 6mCDW event with either no prior relapse or an onset more than 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 ofatumumab in extension. Δ, Difference in K-M estimates (TER-OMB minus OMB-OMB). HR was determined by Cox regression model; p value represents log-rank test.

6mCDW, 6-month confirmed disability worsening; **6mPIRA**, 6-month progression independent of relapse activity; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **HR**, hazard ratio; **K-M**, Kaplan–Meier; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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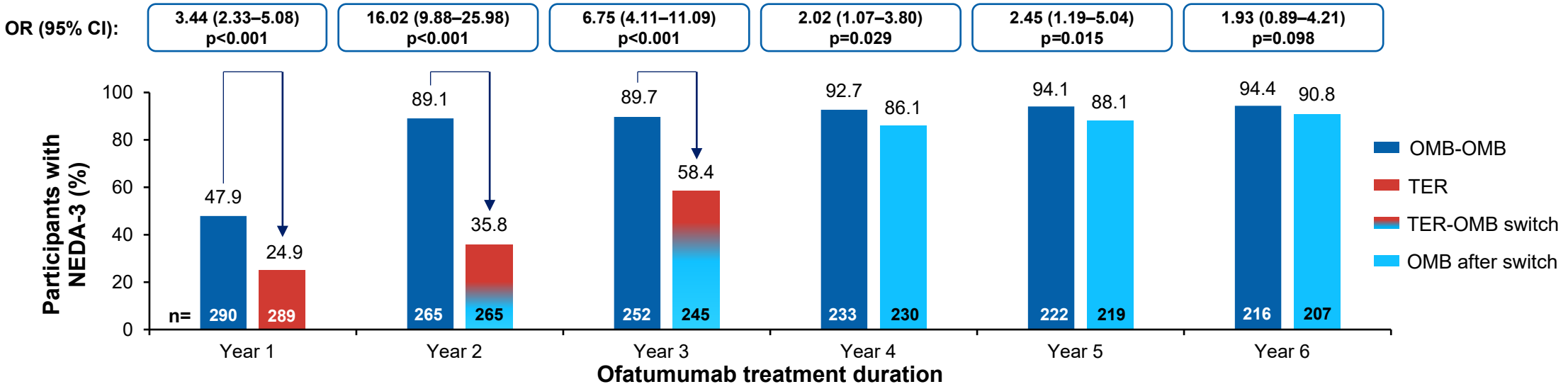
During Year 6 of treatment, 9 of 10 participants were free from disease activity (NEDA-3) in the continuous and switch groups

Annual NEDA-3[a] status up to 6 years of ofatumumab treatment (mFAS[b])



- The observed rapid increase in the **proportion of participants with NEDA-3** with **first-line continuous ofatumumab** was **maintained over 6 years**
  - Approximately 90% of participants on continuous ofatumumab achieved NEDA-3 within 3 years of starting treatment
- Participants who were **initially on teriflunomide** had significantly lower NEDA-3 rates, but a **rapid increase in NEDA-3** was observed **after switching to ofatumumab** with >80% of participants achieving NEDA-3 within 1 year of the switching period being completed

[a]NEDA-3 is defined as no 6mCDW, no confirmed MS relapse, no neT2 lesions compared to baseline and no Gd+ T1 lesions. The statistical model used logistic regression adjusted for treatment and region as factors and age, baseline EDSS and number of Gd+ T1 lesions at baseline as covariates. [b]mFAS: The modified FAS for NEDA-3 contained all participants in the FAS 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.

6mCDW, 6-month confirmed disability worsening; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **FAS**, full analysis set; **Gd+**, gadolinium-enhancing; **mFAS**, modified full analysis set; **NEDA**, no evidence of disease activity; **n**, the total number of participants in the treatment group with response variable defined; **OMB-OMB**: continuous ofatumumab; **OR**, odds ratio; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **TER-OMB**, switch from teriflunomide to ofatumumab.

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Conclusions

In **recently diagnosed and treatment-naive** people with RMS:

- **First-line ofatumumab 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 **MRI** lesion activity; these results are consistent with those of the overall study population[1]
- Participants who **switched from teriflunomide to ofatumumab** 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 **(NEDA-3)** in the continuous and switch groups
  - **High rates of NEDA-3** were achieved within 2 years with **first-line ofatumumab,** whereas rates of NEDA-3 **increased rapidly after switching** from teriflunomide to ofatumumab
- **First-line ofatumumab** was also associated with **significantly fewer CDW events** and **lower rates of PIRA up to 6 years** compared with participants who switched from teriflunomide to ofatumumab
  - The efficacy **benefit of first-line ofatumumab in delaying disability worsening cannot be recovered in those switching** from teriflunomide to ofatumumab

These long-term efficacy results up to 6 years, combined with the favourable benefit–risk profile demonstrated in the overall study population,[1] support the use of ofatumumab as first-line therapy for RDTN people with RMS

1. Wiendl H, et al. EPO-398. Presented at: European Academy of Neurology (EAN) Annual Meeting, Helsinki, Finland; 29 June–02July, 2024.

CDW, confirmed disability worsening; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **PIRA**, progression independent of relapse activity; **RMS**, relapsing multiple sclerosis

Acknowledgements

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We thank the participants and their families and investigators and staff at participating study sites.

Medical writing support was provided by Sivaram Vedantam (Novartis Healthcare Pvt. Ltd., Hyderabad, India) and Sreelatha Komatireddy (Novartis Ireland, Ltd., Dublin, Ireland), and graphic designing support by Edward Kattekola(Novartis Healthcare Pvt. Ltd., Hyderabad, India), which was funded by Novartis Pharma AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022).

The study was sponsored by Novartis Pharma AG, Basel, Switzerland.

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Baseline demographics and disease characteristics

Characteristics[a]	Continuous OMB-OMB group (N=314)	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 last 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[b]

Characteristics of RDTN participants were **typical of patients with early RMS** and were generally **balanced** between treatment groups

[a]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. [b]Data are not collected for baseline from extension.

BMI, body mass index; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis; **OLE**, open-label extension, **OMB-OMB**, continuous ofatumumab; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **RMS**, relapsing multiple sclerosis; **SD**, standard deviation; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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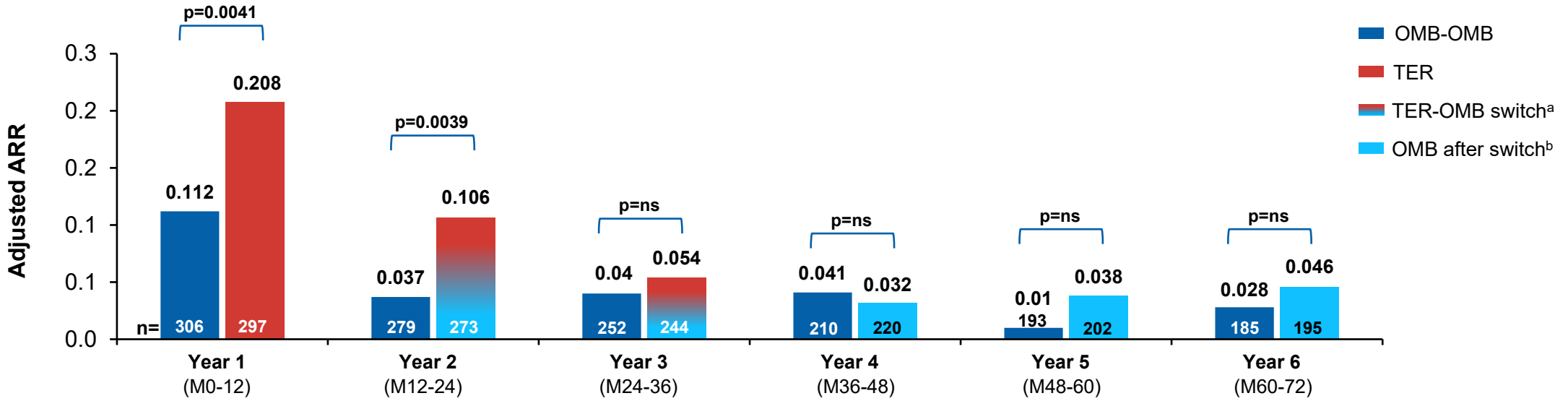
A sustained low ARR was observed in RDTN participants receiving first-line ofatumumab for up to 6 years



- ARR in the **continuous ofatumumab group remained low** for up to 6 years after treatment initiation
- **Switching** from teriflunomide to ofatumumab **resulted in a pronounced reduction in ARR** from Year 2 to 3, and a **sustained low rate** was maintained **through Year 6**

[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, annualised relapse rate; M, month; ns: non-significant; **OMB-OMB**: continuous ofatumumab; **RDTN**, recently diagnosed (≤3 years) and treatment-naïve; **TER**: teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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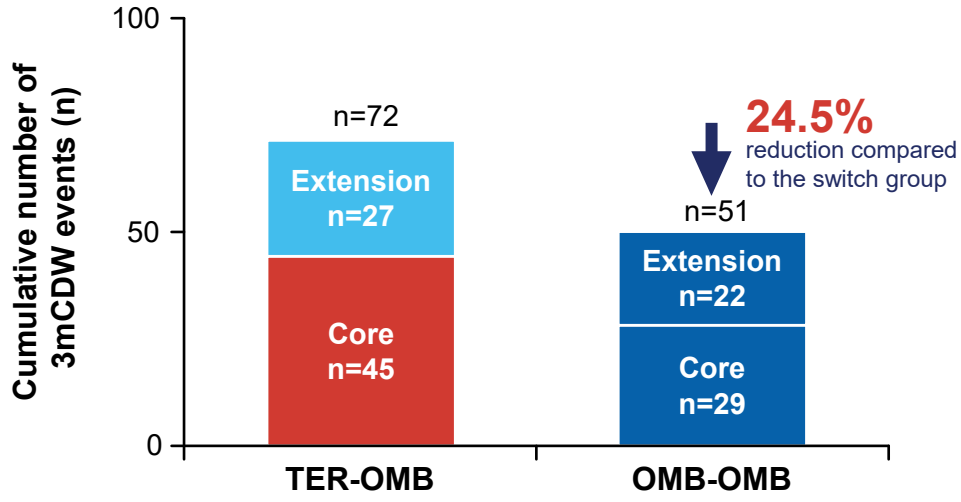
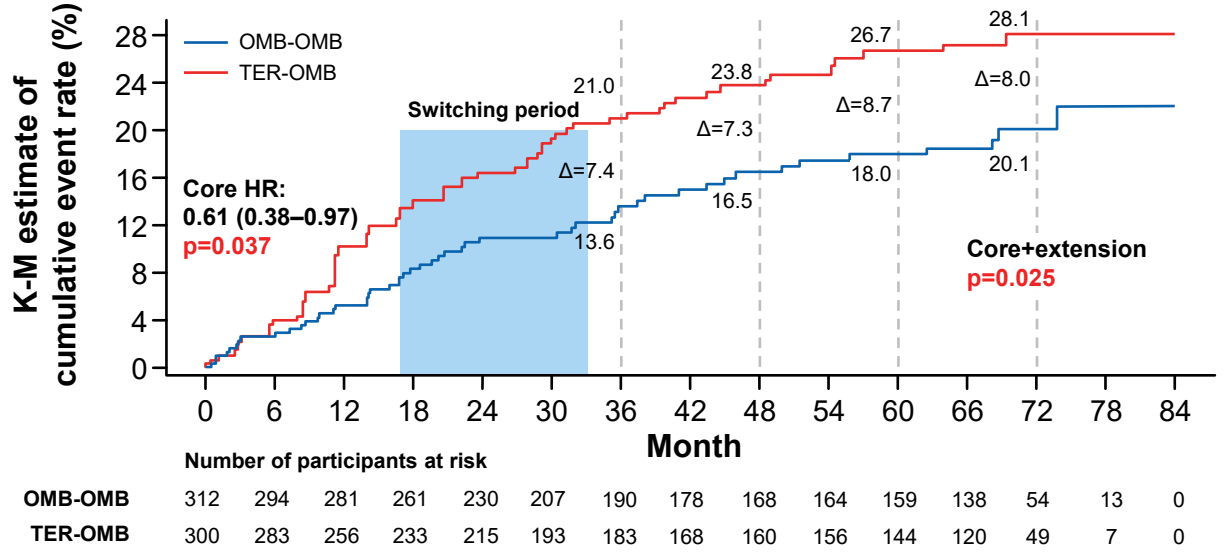
First-line ofatumumab treatment in RDTN participants was associated with a significantly lower number of 3mCDW events up to 6 years

Cumulative number of 3mCDW events up to 6 years



Cumulative event rate – 3mCDW



Number of participants at risk

OMB-OMB	312	294	281	261	230	207	190	178	168	164	159	138	54	13	0
TER-OMB	300	283	256	233	215	193	183	168	160	156	144	120	49	7	0

- **First-line continuous ofatumumab treatment** was associated with **significantly fewer 3mCDW events**
  - **3mPIRA[a] events** occurred in **14.3%** and **20.3%** of RDTN participants in the OMB-OMB and TER-OMB groups, respectively
- The significant **efficacy benefit of first-line ofatumumab** on 3mCDW in the core phase **cannot be recovered in those initially randomised to teriflunomide** and later switched to ofatumumab

[a]6mPIRA is defined as a 6mCDW event with either no prior relapse or an onset more than 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 ofatumumab in extension. Δ, Difference in K-M estimates (TER-OMB minus OMB-OMB). HR was determined by Cox regression model; p value represents log-rank test.

6mCDW, 6-month confirmed disability worsening; **6mPIRA**, 6-month progression independent of relapse activity; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **HR**, hazard ratio; **K-M**, Kaplan–Meier; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **RDTN**, recently diagnosed (≤3 years) and treatment-naive; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

ePresentation at the European Academy of Neurology (EAN), 29 June–2 July 2024

The safety profile of ofatumumab in the RDTN subgroup remained consistent up to 6 years of treatment

Adverse event	OMB-OMB N=314		TER-OMB N=232		Overall OMB N=546	
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
Participants with at least one AE	296 (94.3)	153.24 (136.74–171.73)	211 (90.9)	108.82 (95.09–124.54)	507 (92.9)	130.99 (120.07–142.90)
Participants with at least one SAE	58 (18.5)	4.71 (3.64–6.10)	27 (11.6)	3.31 (2.27–4.82)	85 (15.6)	4.15 (3.36–5.14)
AEs leading to study drug discontinuation[a]	35 (11.1)	–	15 (6.5)	–	50 (9.2)	–
Infections and infestations	236 (75.2)	48.38 (42.59–54.97)	166 (71.6)	39.48 (33.91–45.96)	402 (73.6)	44.26 (40.14–48.81)
Serious infections	22 (7.0)	1.65 (1.09–2.51)	8 (3.4)	0.95 (0.47–1.90)	30 (5.5)	1.38 (0.96–1.97)
• Serious infections (excluding COVID-19)	14 (4.5)	1.04 (0.62–1.76)	1 (0.4)	0.12 (0.02–0.83)	15 (2.7)	0.68 (0.41–1.13)
• COVID-19	8 (2.5)	0.58 (0.29–1.16)	5 (2.2)	0.59 (0.24–1.41)	13 (2.4)	0.58 (0.34–1.01)
Injection-related systemic reactions	84 (26.8)	7.88 (6.37–9.76)	58 (25.0)	8.91 (6.89–11.53)	142 (26.0)	8.27 (7.02–9.75)
Injection-site reactions	57 (18.2)	4.84 (3.73–6.27)	27 (11.6)	3.49 (2.40–5.10)	84 (15.4)	4.31 (3.48–5.33)
Malignancies	4 (1.3)	0.29 (0.11–0.77)	5 (2.2)	0.58 (0.24–1.40)	9 (1.6)	0.40 (0.21–0.77)
Deaths	2 (0.6)	–	3 (1.3)	–	5 (0.91)[b]	–

- The safety and tolerability profile of ofatumumab in the RDTN subgroup **remained consistent** with that of the overall population[1], with **no new safety signals** identified
- The **most common AEs** reported were: COVID-19 (n= 205; 37.5%), nasopharyngitis (n=151; 27.6%), and injection-related systemic reactions (n= 142; 26.0%)

EAIR per 100 PYs is defined as the expected number of patients with the given event over 100 years of exposure to a treatment, assuming the event rate is constant over time. This is estimated by Poisson regression where participants' time is taken until first event occurrence or the last day the patient was at risk for those who did not have the event. [a]AEs related to decreased IgM levels are the most common reason for treatment discontinuation (n=10 [1.8%]). [b]included the following: Sudden death (n=1), Suicide (n=1), COVID 19/COVID 19 pneumonia (n=1), COVID-19 (n=2).
AE, adverse event; **CI**, confidence interval; **EAIR**, exposure-adjusted incidence rate; **Ig**, immunoglobulin; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **PT**, preferred term; **PY**, patient-year; **RDTN**, recently diagnosed (≤3 years) and treatment-naïve; **SAE**, serious adverse event; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab. **1**. Wiendl H, et al. P9.010. Presented at: American Academy of Neurology (AAN) Annual Meeting, Denver, CO, USA; April 13–18, 2024.