Effect of Longer-term Ofatumumab Treatment on Disability Worsening and Brain Volume Change

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Ronald Zielman, Ayan Das Gupta, Amin Azmon, Jing Xi, Gina Mavrikis Cox are employees of Novartis

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Background

Ofatumumab is the first fully human anti-CD20 monoclonal antibody with a 20 mg s.c. monthly dosing regimen in 0.4ml, approved for the treatment of RMS in adults in the US[1] and other countries[a]

Data from the ASCLEPIOS I/II trials and the open-label ALITHIOS extension with up to 4 years treatment with ofatumumab showed:

- Significantly delayed disability accrual compared with teriflunomide[2]
- Sustained efficacy by reducing relapses and magnetic resonance imaging (MRI) lesions[3,4]
- 93% of patients receiving continuous ofatumumab achieved no evidence of disease activity (NEDA-3)[* 5]

Relapse-associated disability worsening (RAW) and progression independent of relapse activity (PIRA)[6,7] both contribute to disability worsening (CDW) in patients with relapsing multiple sclerosis (RMS)[8]

The ASCLEPIOS I and II trials had a flexible duration of up to 2.3 years of individual exposure to randomized study treatment (either teriflunomide or ofatumumab); after this initial core period all patients switched to open-label ofatumumab; MRI, magnetic resonance imaging; NEDA-3, no evidence of disease activity; RMS, relapsing multiple sclerosis; s.c., subcutaneous.
*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 gadolinium-enhancing lesions.

[a]Kesimpta® (ofatumumab) has now been approved in many countries including US, Canada, Switzerland, Singapore, Australia, Japan and the EU.

1. KESIMPTA® (ofatumumab) Prescribing information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed March 22, 2023); 3. Hauser et al. N Engl J Med. 2020; 383:546-557; 3. Kappos et al. ERP161 Poster Presented at EAN 2022; 4. Hauser SL, et al. ePoster #004 presented at AAN 2022. 5. Kuhle et al. P1198 poster presented at ECTRIMS 2022; 6. Kappos et al. Mult Scler 2018; 24: 963–739; 7. Kappos et al. Clinical Trials. JAMA Neurol 2020; 77: 1132–40; 8. Lublin F, et al. Brain 2022;145,9:3147-3161

Objective

To assess longer-term effects (up to 5 years of treatment) of continuous ofatumumab treatment on disability outcomes (CDW, PIRA, RAW) and brain volume change compared with delayed ofatumumab treatment (after switching from teriflunomide)

CDW, confirmed disability worsening; PIRA, progression independent of relapse activity; RMS, relapsing multiple sclerosis; RAW, relapse associated worsening

Key Assessments

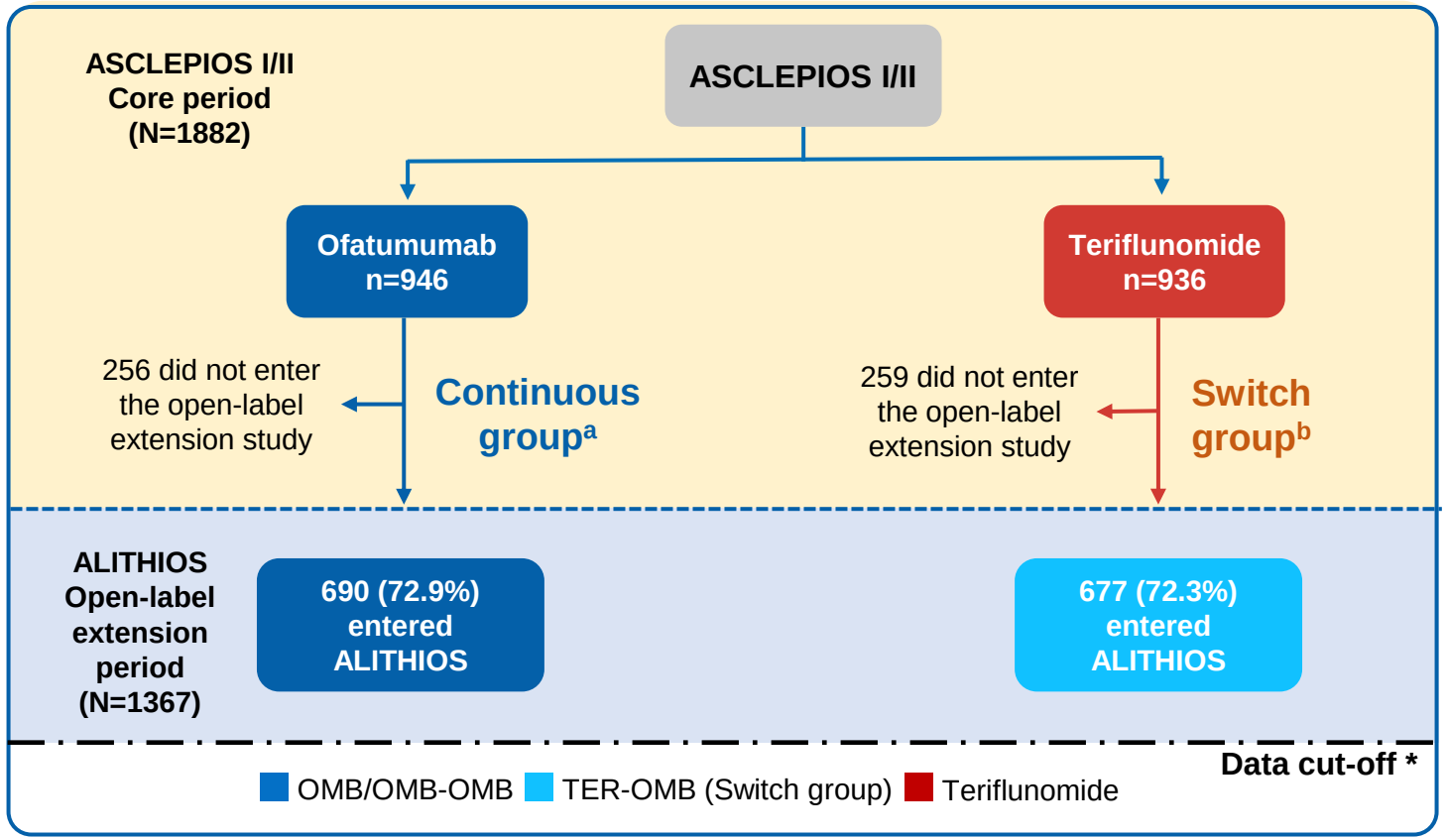
- 6-month confirmed disability worsening (6m-CDW)
  - 6-month confirmed relapse associated worsening (6m-RAW)
  - 6-month confirmed progression independent of relapse activity (6m-PIRA)
  - 6-month confirmed and sustained progression independent of relapse activity (6m-sPIRA)
- Brain Volume Change (BVC) MRI outcomes
  - Annual rate of brain volume change (ABVC) over the study duration (Core & Extension)
  - Percentage brain volume change (PBVC) at each year

Definitions[1]

- Relapse associated worsening (RAW) is defined as an accumulation of disability due to incomplete recovery from a relapse.
- PIRA is defined as a 3- or 6-month confirmed disability worsening (CDW) 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.
- Sustained PIRA (sPIRA) – 3- or 6- month – requires that 3- or 6- month confirmed PIRA events are also sustained in all available follow-up data.

1. Lublin F, et al. Brain 2022;145,9:3147-3161

Patient Disposition



- 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 5 years cumulatively
- Of these, 1145/1367 (**83.8%**) patients were still receiving ofatumumab treatment at the time of data cut-off (25-Sep-2022)*

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 period. Core period is period before the dotted line**.

Only patients from the ASCLEPIOS I/II studies are included in the analyses presented here; [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 period. Please note, the 259 patients who took teriflunomide in the core period but did not enter the extension study are included in the switch group.

Note: Patients in ASCLEPIOS I/II had a flexible trial duration with individual patient's exposure of up to 2.3 years; Hauser et al. N Engl J Med. 2020; 383:546-557, supplamentary figure S2

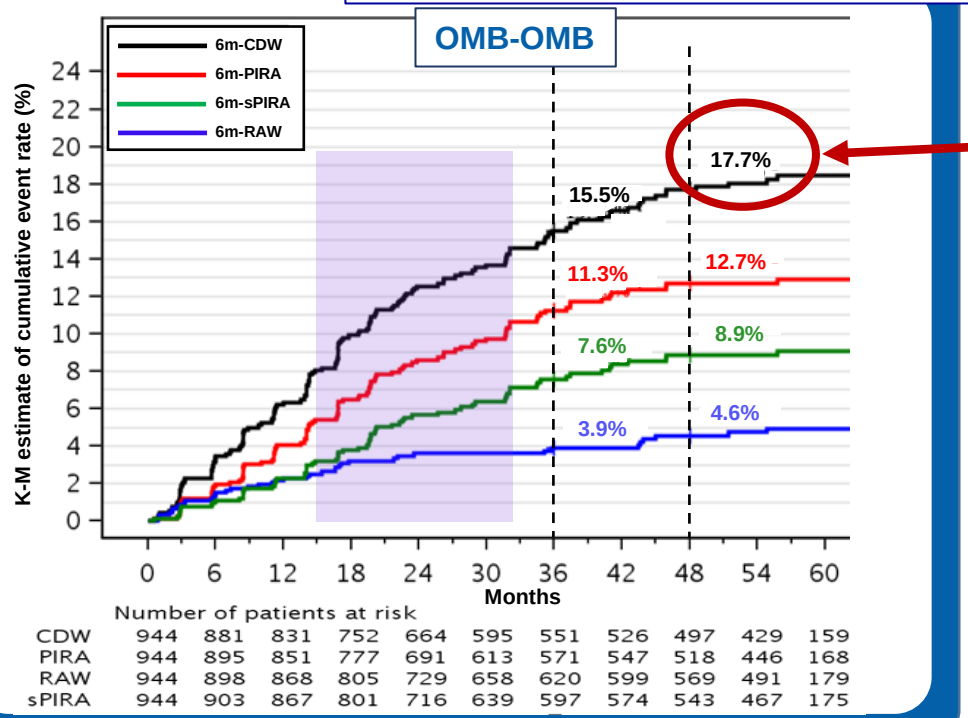
Baseline Demographics and Clinical Characteristics

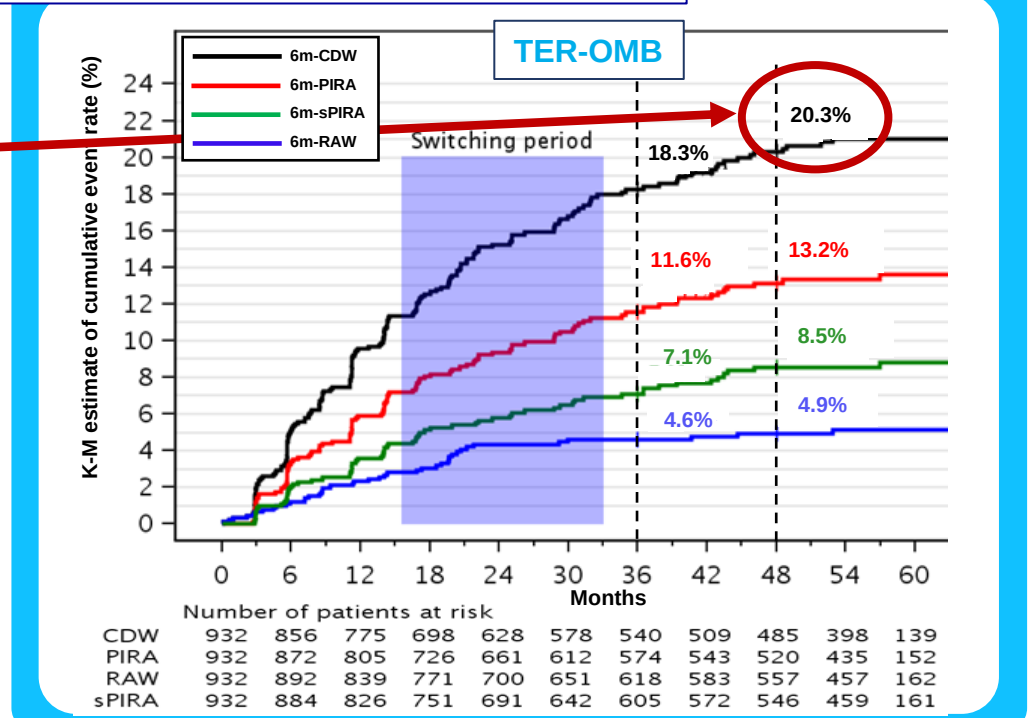
Demographics and clinical characteristics[a]	Ofatumumab continuous (N=946)		Switch from teriflunomide to ofatumumab (N=936)	
	Baseline of core study (N=946)	Baseline of extension study (N=690)	Baseline of core study (N=936)	Baseline of extension study[d] (N=677)
Age, years	38.4±9.04	38.1±8.69	38.0±9.22	40.1±9.21
Female, n (%)	637 (67.3)	483 (70.0)	636 (67.9)	456 (67.4)
BMI, kg/m^2	25.86±6.22	25.73±6.00	25.93±6.02	25.61±5.85
Treatment-naive patients[b], n (%)	386 (40.8)	Not applicable[c]	363 (38.8)	Not applicable[c]
EDSS score at baseline	2.93±1.35	2.80±1.49	2.90±1.36	2.81±1.46
Number of relapses in the last 12 months prior to screening, n (%)	1.2±0.69	0.1±0.35	1.3±0.71	0.2±0.49
Number of Gd+ T1 lesions	1.7±4.51	0.0±0.21	1.3±3.43	0.8±2.37
Total volume of T2 lesions, cm^3	13.72±13.79	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 either ofatumumab or teriflunomide in the core period; [d]the baseline from the extension study in the ofatumumab continuous and the ofatumumab switch from teriflunomide groups reflect the relative treatment effects during the double-blind treatment phase in the ASCLEPIOS I/II studies. BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing.

Kaplan-Meier estimates of 6m-CDW, 6m-PIRA, 6m-sPIRA, and 6m-RAW up to 5 years

Fewer disability events over 5 years with early initiation of ofatumumab





- **RMS patients treated with disease modifying therapies accumulate disability primarily via PIRA**
- **Overall, fewer CDW, PIRA and RAW events were observed in patients receiving continuous ofatumumab versus those initially randomized to teriflunomide and switched to ofatumumab; similar patterns were identified for the 3m-CDW**
- **Ofatumumab's high anti-inflammatory efficacy is evident with flattening of the 6m-RAW curve in the TER-OMB switch group in the extension period**

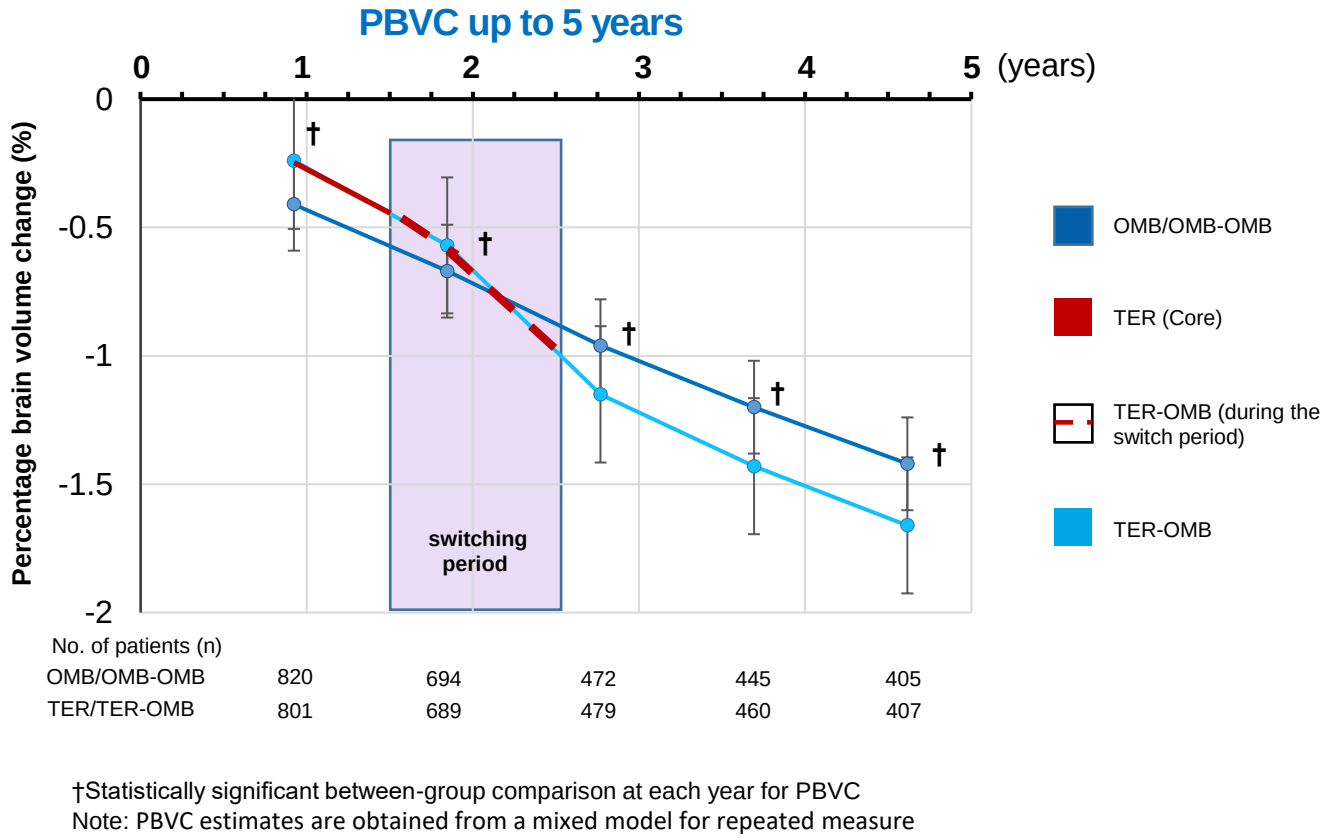
6m-CDW, 6-month CDW; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed sustained PIRA; CDW, confirmed disability worsening; K-M, Kaplan-Meier; OMB-OMB, patients randomized to ofatumumab in the Core period and continuing ofatumumab in ALITHIOS; PIRA, progression independent of relapse activity; RAW, relapse associated worsening; RMS, relapsing multiple sclerosis; sPIRA, sustained progression independent of relapse activity; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during ALITHIOS.

Whole Brain Volume Change

- **PBVC remained low (<1.5% loss) up to 5 years with continuous ofatumumab treatment†**
- Overall, ABVC remained low in patients receiving continuous ofatumumab with -0.27% BVC per year during Extension
  - A steeper decline was observed with TER-OMB vs OMB-OMB during Core while the annual rate became similar to OMB-OMB during Extension indicating a slowing of BVC following switch to ofatumumab

Group	Core (%)	P-value*	Extension (%)	P-value*
OMB-OMB	-0.34	0.115	-0.27	0.666
TER-OMB	-0.42		-0.28	

*Between-group comparison for ABVC



†Statistically significant between-group comparison at each year for PBVC
Note: PBVC estimates are obtained from a mixed model for repeated measure

ABVC, annual rate of brain volume change estimated from all the post-baseline MRI scans; BVC, brain volume change; OMB/OMB-OMB, patients treated with ofatumumab during the Core period (OMB) and continued with ofatumumab (OMB-OMB) during the Extension period; PBVC, percentage brain volume change; TER-OMB, patients randomised to teriflunomide during the Core period and switched to ofatumumab during the Extension period (ALITHIOS); n, total number of patients included in the analysis.

Note , all ABVC estimates are obtained from a random coefficient model with treatment, time period (core vs. extension) and region as factors, time, baseline number of Gd-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates, the three-way interaction (treatment group by time period by time) and all its associated two-way interactions

Conclusions

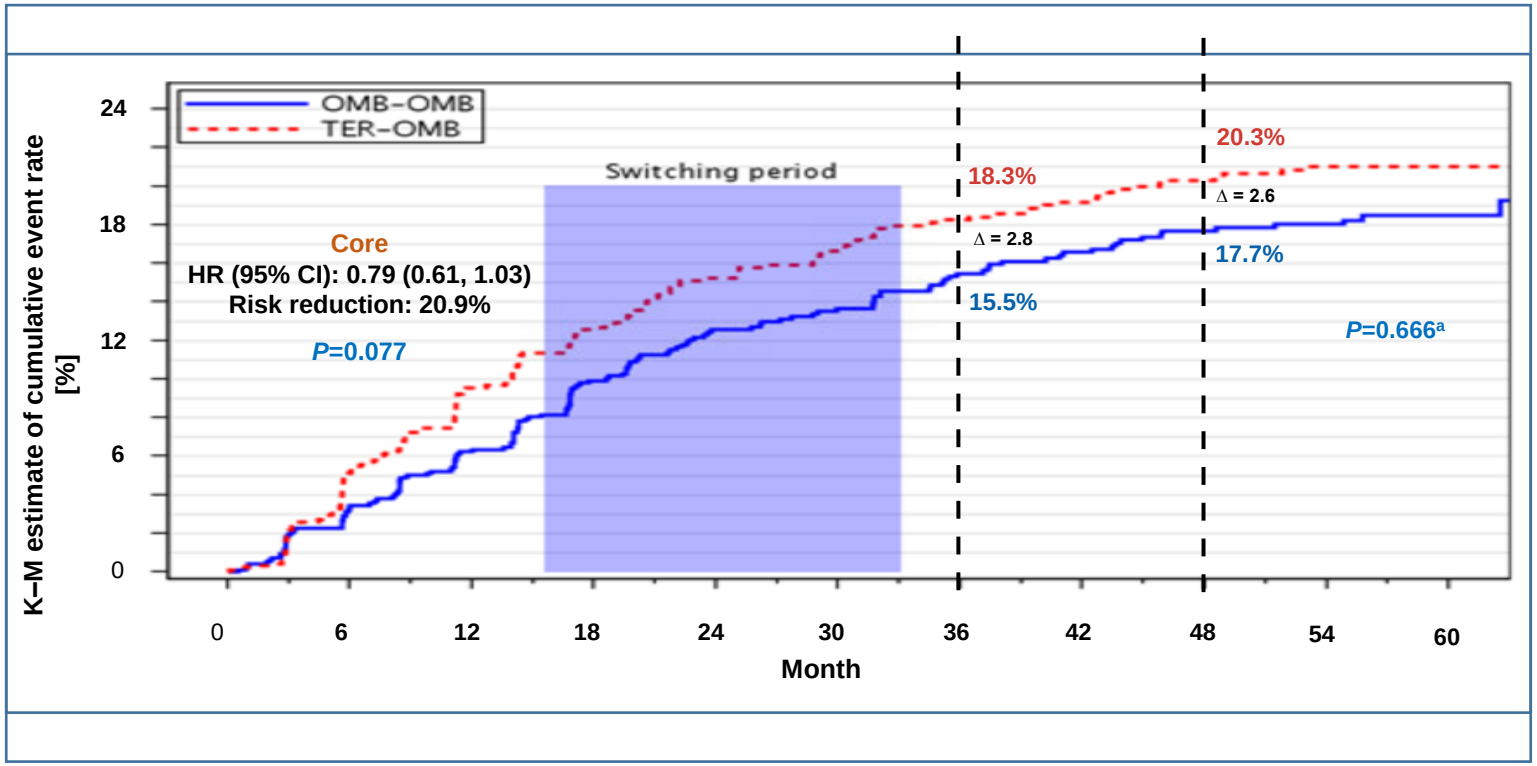
- With up to 5 years treatment with ofatumumab, >80% of patients remained free of 6m-CDW
- Fewer disability events including PIRA and RAW, were experienced by patients who received ofatumumab continuously versus those initially randomized to teriflunomide
- PBVC remained low (<1.5% loss) over 5 years in patients continuously on ofatumumab
  - Early ofatumumab initiation resulted in statistically significantly lower levels of PBVC versus later switch from teriflunomide to ofatumumab at year 5
- Overall, these data support the early use of ofatumumab in patients with RMS

6m-CDW, 6-month CDW; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed sustained PIRA; CDW, confirmed disability worsening; PBVC, percentage brain volume change; PIRA, progression independent of relapse activity; RMS, relapsing multiple sclerosis

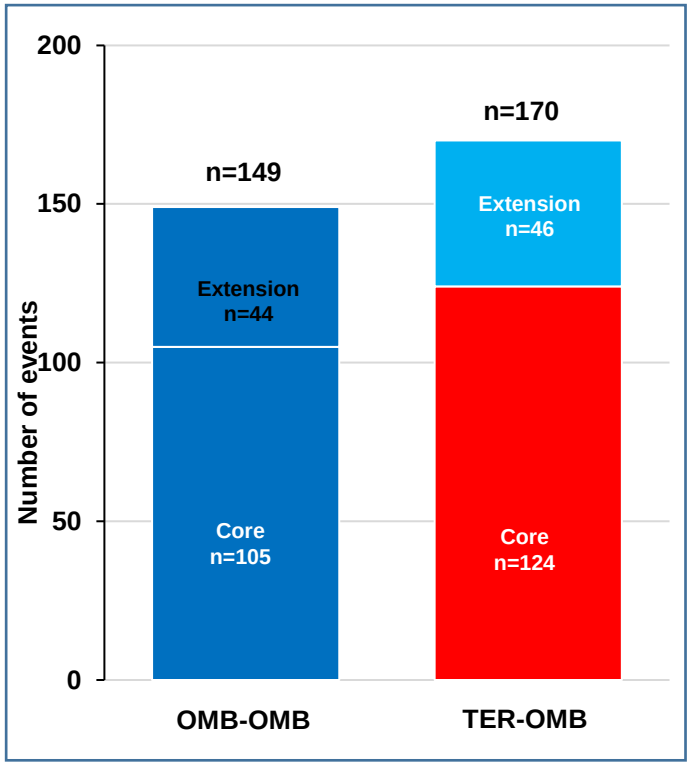
Backup Slides

Backup Slides

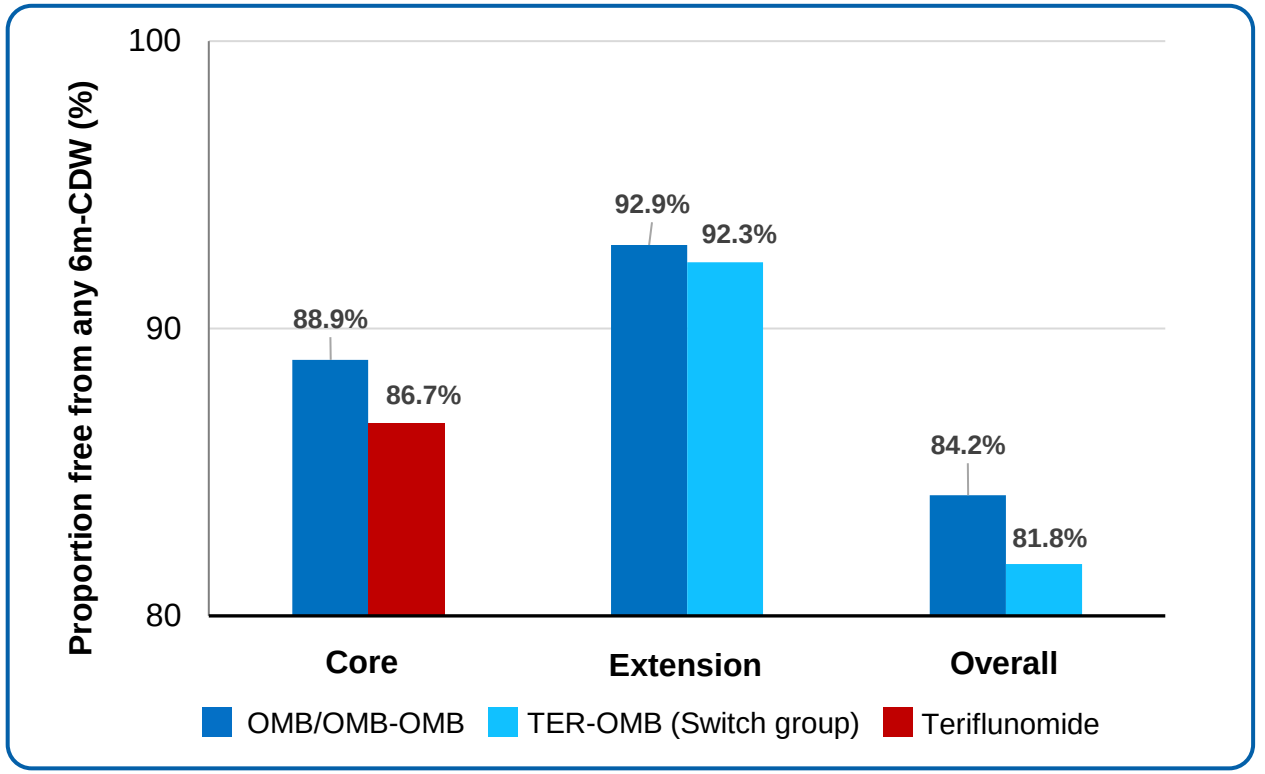
Time to first 6-month confirmed disability worsening (6mCDW) - Kaplan-Meier estimates



Cumulative number of first events



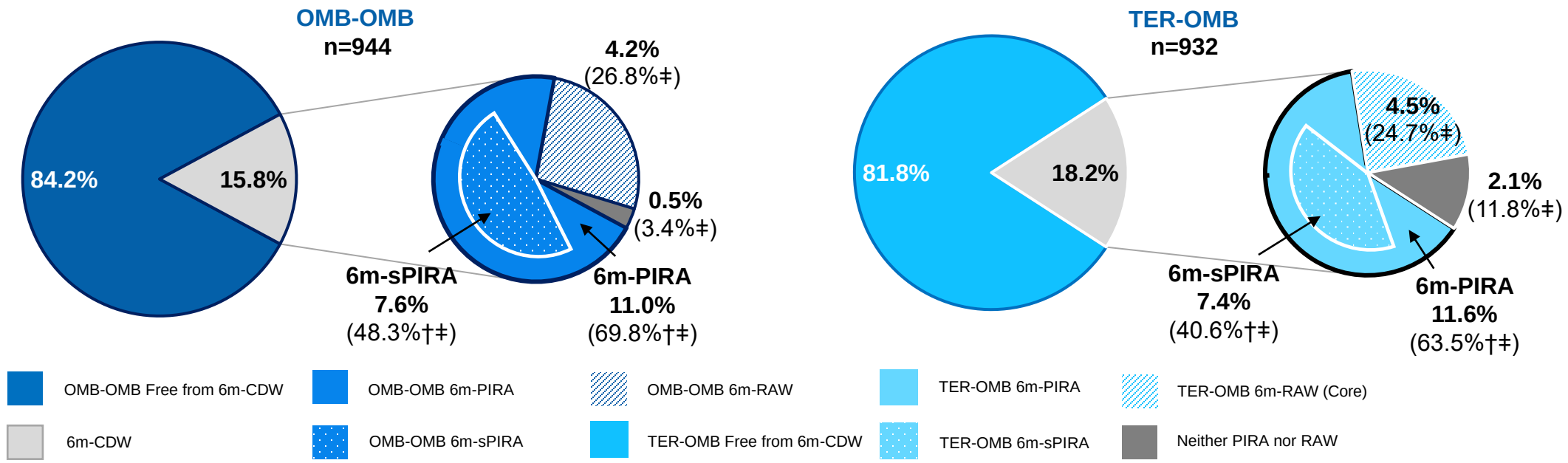
Proportion of patients free from any 6m-CDW events



- **In the randomized, controlled phase, more patients remained free from disabilty worsening when treated with ofatumumab than with teriflunomide**
- **In the extension period (open-label ofatumumab), more than 90% of the patients remained free from disability worsening**
- **Similar patterns were identified for 3m-CDW**
- **Overall, disabilty events were fewer in patients who initiated ofatumumab early**

3m/6m-CDW, 3- or 6-month confirmed disability worsening; OMB/OMB-OMB, patients randomized to ofatumumab in the Core period (OMB) and continuing ofatumumab (OMB-OMB) in ALITHIOS; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab in ALITHIOS

Proportion of 6m-CDW: 6m-PIRA, 6m-sPIRA, 6m-RAW (Overall)



Primary pie chart details the proportion free from 6m-CDW and proportion of 6m-CDW events; Expanded pie chart details the proportion of 6m-CDW events, 6m-PIRA, 6m-sPIRA and 6m-RAW shown as a proportion of total number of 6m-CDW events; Neither refers to events not attributed to 6m-PIRA or 6m-RAW; n, number of patients

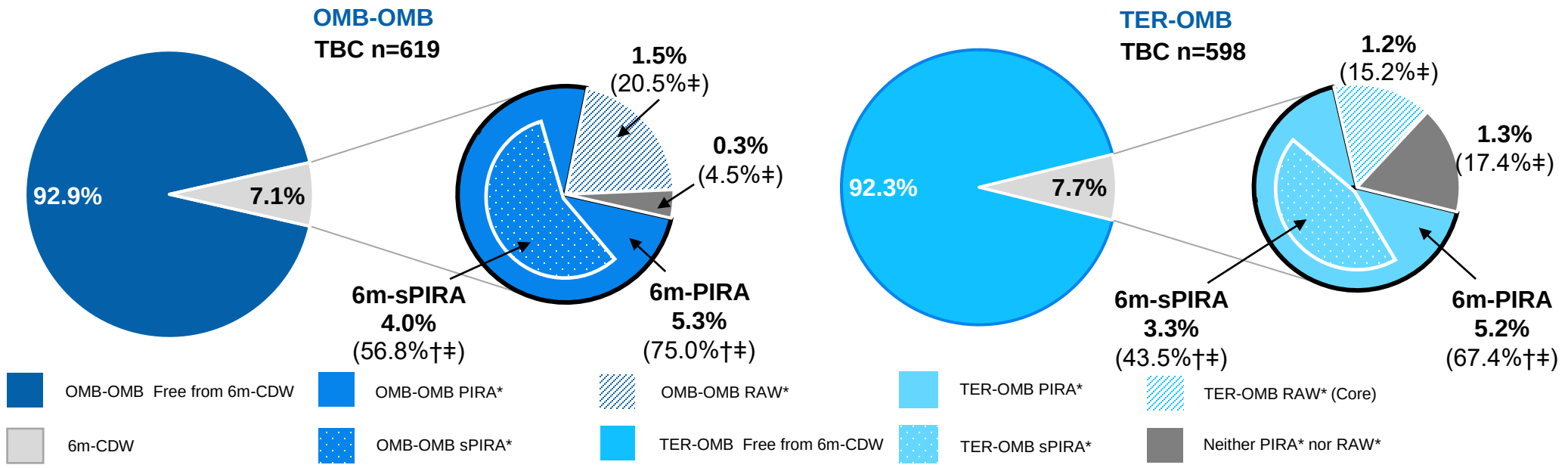
†The inset patterned segments represent the proportion classified as sustained 6m-PIRA and form subsegment of the PIRA segments; ‡Values in brackets are the proportion of events relative to all 6m-CDW

- **6m-PIRA was the main contributor to overall 6m-CDW**
- **6m-sPIRA meaningfully contributed to the overall proportion of 6m-CDW and represented a greater proportion of 6m-CDW events than 6m-RAW**

6m-CDW, 6-month CDW; CDW, confirmed disability worsening; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed sustained PIRA; OMB-OMB, patients randomized to ofatumumab in the Core period and continuing ofatumumab in ALITHIOS; PIRA, progression independent of relapse activity; RAW, relapse associated worsening; sPIRA, sustained progression independent of relapse activity; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during ALITHIOS; TER, patients randomized to teriflunomide during the core ASCLEPIOS I/II trials.

Note: 6m-CDW overall proportion is represented by total number of 6m-PIRA, 6m-RAW and 'Neither' events; Neither 6m-PIRA nor 6m-RAW describes 6m-CDW events that do not meet the criteria for 6m-PIRA or 6m-RAW.

Proportion of 6m-CDW: 6m-PIRA, 6m-PIRA, 6m-RAW (Extension)



Primary pie chart details the proportion free from 6m-CDW and proportion of 6m-CDW events; Expanded pie chart details the proportion of 6m-CDW events; 6m-PIRA, 6m-sPIRA and 6m-RAW shown as a proportion of total number of 6m-CDW events; Neither refers to events not attributed to 6m-PIRA or 6m-RAW; n, number of patients

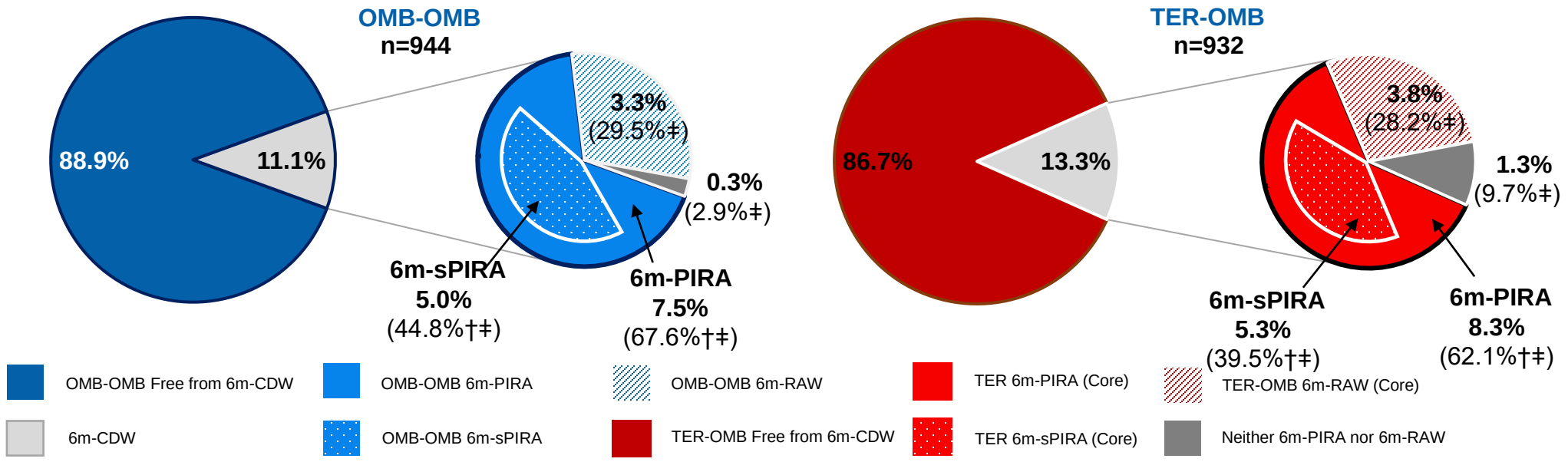
†The inset patterned segments represent the proportion classified as sustained 6m-PIRA and form subsegments of the PIRA segments; ‡Values in brackets are the proportion of events relative to all 6m-CDW

- **6m-PIRA was the main contributor to overall CDW and represented a greater proportion of CDW events in the Extension period**
- **6m-sPIRA meaningfully contributed to the overall proportion of 6m-CDW and represented a greater proportion of 6m-CDW events than 6m-RAW**

6m-CDW, 6-month CDW; CDW, confirmed disability worsening; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed sustained PIRA; OMB-OMB, patients randomized to ofatumumab in the core ASCLEPIOS I/II trials; PIRA, progression independent of relapse activity; RAW, relapse associated worsening; sPIRA, sustained progression independent of relapse activity; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during the extension period; TER, patients randomised to teriflunomide during the core ASCLEPIOS I/II trials.

Note: 6m-CDW overall proportion is represented by total number of 6m-PIRA, 6m-RAW and 'Neither' events; Neither 6m-PIRA nor 6m-RAW describes 6m-CDW events that do not meet the criteria for 6m-PIRA or 6m-RAW.

Proportion of 6m-CDW: 6m-PIRA, 6m-sPIRA, 6m-RAW (Core)



Primary pie chart details the proportion free from 6m-CDW and proportion of 6m-CDW events; Expanded pie chart details the proportions of 6m-CDW events, 6m-PIRA, 6m-sPIRA and 6m-RAW shown as a proportion of total number of 6m-CDW events; Neither refers to events that do not meet 6m-PIRA or 6m-RAW criteria; n, number of patients

†The inset patterned segments represent the proportion classified as sPIRA and form subsegments of the PIRA segments; ‡Values in brackets are the proportion of events relative to all 6m-CDW

- **6m-PIRA was the main contributor to overall 6m-CDW**
- **6m-sPIRA meaningfully contributed to the overall proportion of 6m-CDW and represented a greater proportion of 6m-CDW events than 6m-RAW**

6m-CDW, 6-month CDW; CDW, confirmed disability worsening; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed sustained PIRA; OMB-OMB, patients randomized to ofatumumab in the core ASCLEPIOS I/II trials; PIRA, progression independent of relapse activity; RAW, relapse associated worsening; sPIRA, sustained progression independent of relapse activity; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during the extension period; TER, patients randomised to teriflunomide during the core ASCLEPIOS I/II trials.

Note: 6m-CDW overall proportion is represented by total number of 6m-PIRA, 6m-RAW and 'Neither' events; Neither 6m-PIRA nor 6m-RAW describes 6m-CDW events that do not meet the criteria for 6m-PIRA or 6m-RAW.