Efficacy of Early Ofatumumab Versus Late-Switch From Teriflunomide: Subgroup Analysis of the ALITHIOS Open-Label Extension Study by Prior Disease-Modifying Therapy Exposure and Age

P1210

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Introduction

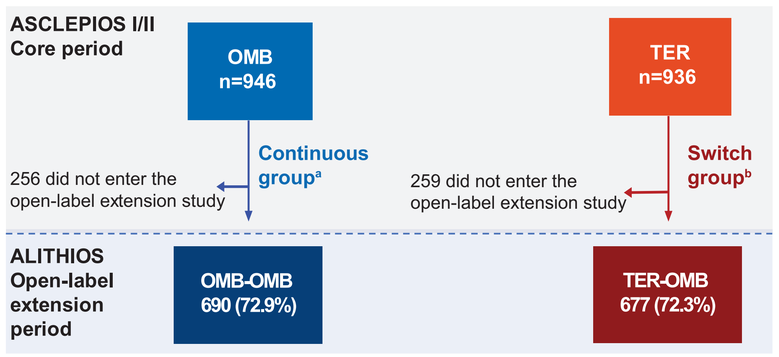
- Early initiation of high efficacy therapies in relapsing multiple sclerosis (RMS) has been shown to improve long-term disease outcomes[1-3]
- Ofatumumab (OMB), a fully human anti-CD20 monoclonal antibody[4], reduced clinical and MRI measures of disease activity, and delayed disability worsening versus teriflunomide (TER) in treatment-naïve and previously disease-modifying therapy (DMT)-treated RMS patients in the Phase 3 ASCLEPIOS I/II trials[5]
- Participants entering the ALITHIOS study, an open-label extension of OMB core clinical trials, continued OMB or were switched from TER to OMB
  - Previous analysis of ALITHIOS data demonstrated that early initiation of OMB in the ASCLEPIOS I/II trials was beneficial compared with late switching from TER[6,7]
- The aim of this analysis is to understand how the number of prior DMTs and patient age can contribute to the efficacy of early initiation of OMB versus late switch from TER

Methods

Study design and population

- Of 1882 participants randomized in the ASCLEPIOS I/II trials, 1367 (72.6%) participants entered ALITHIOS and received OMB for up to 4 years (**Figure 1**)
- This analysis included cumulative data from participants who received OMB during the core and extension phases (OMB-OMB) and participants who switched from TER to OMB in the extension phase (TER-OMB)

Figure 1. Participant disposition



[a]Randomised to OMB in the core phase; [b]Randomised to TER in the core and switched to OMB during the extension phase; all percentages are calculated based on the full analysis set

Outcomes assessed

- This analysis examined the following outcomes:
  - No evidence of disease activity (NEDA-3)
  - Rate of new or enlarging T2 lesions (neT2) per year
  - Number of T1 gadolinium-enhancing (Gd+) lesions per scan
  - Time to first 6-month confirmed disability worsening (6mCDW)
  - Annualised relapse rate (ARR)
- The analysis was further subdivided across three variables:
  - **Number of prior DMTs**: 0, 1, 2, or >2 DMTs prior to enrolling in ASCLEPIOS I/II
  - **Age group**: aged ≤40 or >40 at baseline
  - **Last prior DMT**: NEDA-3 data were analysed additionally according to the last DMT prior to enrolment (fingolimod; interferon beta-1a, interferon beta-1b, or glatiramer acetate [BRACE]; dimethyl fumarate [DMF]; other)

Results

Baseline characteristics

- Mean age ranged from 31.7–49.3 years; mean Expanded Disability Status Scale (EDSS) score ranged from 2.36–3.83; mean number of relapses in the last 12 months ranged from 0.1–1.3 relapses
  - Time since diagnosis increased with greater number of prior DMTs and in the older age group
- Most participants across all subgroups (≥ 62.8%) were women
- Of those with 1 or more DMTs prior to enrolment, the most commonly prescribed DMTs are detailed in **Table 1**
- Baseline age and EDSS across the type of DMT last prescribed prior to enrolment are detailed in **Table 2**

Table 1. All DMT history prior to ASCLEPIOS I/II

DMT	OMB-OMB (N=560[a]) n (%)	TER-OMB (N=573[a]) n (%)
Any interferon beta	357 (63.8)	361 (63.0)
Glatiramer Acetate	242 (43.2)	255 (44.5)
Dimethyl fumarate	72 (12.9)	81 (14.1)
Other DMT[b]	72 (12.9)	82 (14.3)
Fingolimod	66 (11.8)	87 (15.2)
Natalizumab	57 (10.2)	56 (9.8)
Teriflunomide	21 (3.8)	15 (2.6)
Daclizumab	13 (2.3)	19 (3.3)
Laquinimod	7 (1.3)	11 (1.9)
Any B cell therapy	2 (0.4)	3 (0.5)

[a]Data presented for those with any exposure to prior DMTs; [b]'Other DMT' contains all medications that were labelled by the investigator as a multiple sclerosis DMT but are not part of the listed medications

Table 2. Baseline age and EDSS by last DMT prescribed

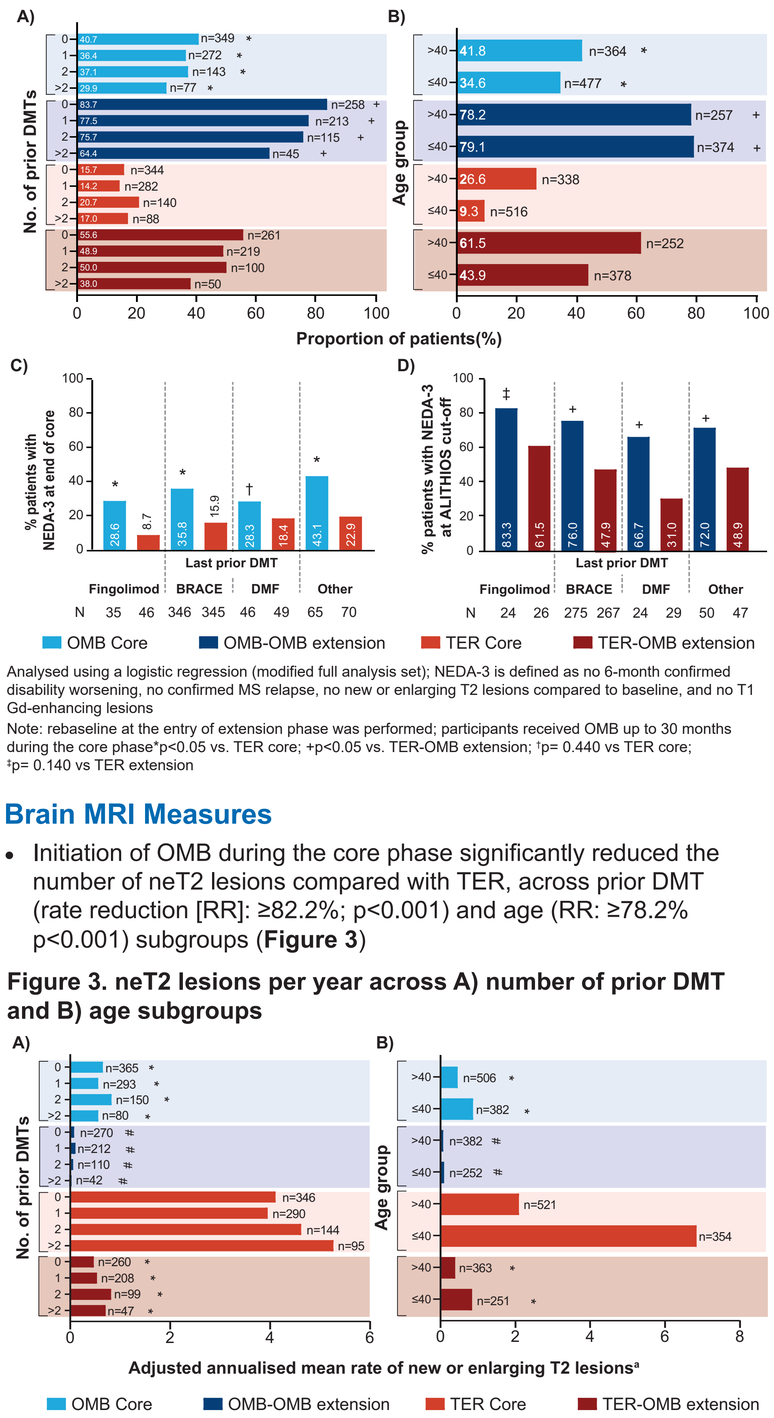
	Age (Mean ± SD)		EDSS (Mean ± SD)	
DMT	**OMB**	**TER**	**OMB**	**TER**
Fingolimod (n=98)	42.2 ± 8.01	40.2 ± 8.51	3.69 ± 1.270	3.87 ± 1.444
BRACE (n=764)	37.6 ± 8.60	38.2 ± 9.25	3.12 ± 1.300	2.99 ± 1.261
DMF (n=116)	42.4 ± 8.70	40.6 ± 9.16	3.41 ± 1.362	3.23 ± 1.335
Other[a] (n=155)	41.4 ± 7.91	40.1 ± 9.24	3.58 ± 1.308	3.62 ± 1.471

[a]'Other' contains all medications that were labelled by the investigator as a multiple sclerosis DMT but are not part of the listed medications; n, number of patients at core baseline

NEDA-3

- Initiation of OMB in the core phase was associated with a greater percentage of participants achieving NEDA-3 (29.9–40.7%) compared with participants who initiated TER (14.2–20.7%)
- Continuing OMB in the extension phase further increased the proportion of participants achieving NEDA-3 status, to a greater extent than those who switched from TER; treatment-naïve participants on continuous OMB reported the highest proportion of NEDA-3 (83.7%; **Figure 2A and 2B**)
- In the core phase across all types of prior DMTs, OMB consistently increased the proportion of participants achieving NEDA-3 status (28.6–43.1%) compared with TER (8.7–22.9%; **Figure 2C and 2D**)
  - This trend continued in the extension phase, where patients on continuous OMB achieved NEDA-3 in greater proportions (66.7–83.3%) than those who switched from TER (31.0–61.5%)

Figure 2. NEDA-3 status across A) number of prior DMTs, B) age, and last DMT prescribed (core [C]; extension [D]) subgroups



Analysed using a logistic regression (modified full analysis set); 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

Note: rebaseline at the entry of extension phase was performed; participants received OMB up to 30 months during the core phase*p<0.05 vs. TER core; +p<0.05 vs. TER-OMB extension; †p= 0.440 vs TER core; ‡p= 0.140 vs TER extension

Brain MRI Measures

- Initiation of OMB during the core phase significantly reduced the number of neT2 lesions compared with TER, across prior DMT (rate reduction [RR]: ≥82.2%; p<0.001) and age (RR: ≥78.2% p<0.001) subgroups (**Figure 3**)

Figure 3. neT2 lesions per year across A) number of prior DMT and B) age subgroups

[a]Results obtained from a cox regression based on events in that time period
*p<0.05 vs. TER core; #p<0.05 vs. OMB core

- Switching to OMB in the extension phase also reduced neT2 lesion activity across prior DMT (RR: ≥82.3%; p<0.001) and age (RR: ≥81.3%; p<0.001) subgroups, however this did not reach the absolute level of suppression achieved by continuous OMB
- Initiation of OMB during the core phase also resulted in significant suppression of T1 Gd+ lesions compared with those who initiated on TER (p<0.001); continuing OMB in the extension phase resulted in almost complete suppression of T1 Gd+ lesion activity

Clinical measures (6mCDW and ARR)

- Initiation of OMB in the core phase and continuation in the extension phase was associated with a consistent numerical reduction in the risk of 6mCDW events; in participants under 40, initiation of OMB in the core phase significantly reduced 6mCDW risk compared with TER (RR: 40.6%; p<0.05)
  - In the extension phase, early initiation reduced 6mCDW risk in those with fewer prior DMTs to a greater extent than those with >2 prior DMTs
  - The greatest treatment benefit was observed in the OMB-OMB/<40 years group (2.1% with events)
- ARR was significantly lower with initiation of OMB versus TER during the core phase across both the prior DMT (RR: 38.8–58.4%) and age subgroups (RR: 37.1–62.9%); continuing OMB in the extension phase further reduced ARR versus the core phase (RR: 39.9–65.1%)

Safety

- OMB was well tolerated across all prior DMT and age subgroups, and no clinically relevant imbalance was observed; the most common AEs were nasopharyngitis, headache, upper respiratory tract infection, and injection site reactions

Conclusions

- Earlier initiation of OMB reduced MRI and clinical measures of MS disease activity versus later switch from TER to OMB across the core studies and open-label extension
  - The greatest treatment benefit was observed in participants with fewer prior DMTs and in those ≤40 years of age
- Long-term use of OMB reduced signs of disability worsening and disease activity regardless of which DMT participants were last prescribed before study enrolment
- These data support the benefits of early initiation of high efficacy therapy to reduce disease activity and slow disability progression early in the disease course

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