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

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SUMMARY

1 **This analysis compared clinical and MRI outcomes, according to age and number of previous DMTs, in participants with RMS who received continuous ofatumumab treatment in ASCLEPIOS I/II and open-label extension ALITHIOS vs those who received teriflunomide in ASCLEPIOS I/II and switched to ofatumumab in ALITHIOS**

2 **The greatest treatment benefit was observed in participants with fewer prior DMTs and in those ≤40 years of age. Long-term use of ofatumumab reduced signs of disability worsening and disease activity regardless of which DMT participants were last prescribed prior to study enrollment**

3 **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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INTRODUCTION

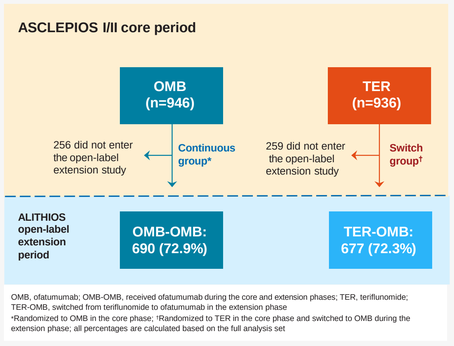
- Early initiation of high-efficacy therapies in relapsing multiple sclerosis (RMS) has been shown to improve long-term disease outcomes[1-3]
- Ofatumumab (OMB), a fully human anti-CD20 monoclonal antibody,[4] reduced clinical and magnetic resonance imaging (MRI) measures of disease activity and delayed disability worsening vs teriflunomide (TER) in treatment-naïve patients and patients with RMS previously treated with disease-modifying therapy (DMT) in the phase 3 ASCLEPIOS I/II trials[5]
- Participants entering the ALITHIOS trial, 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 previous DMTs and participant age can contribute to the efficacy of early initiation of OMB vs 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



OMB, ofatumumab; OMB-OMB, received ofatumumab during the core and extension phases; TER, teriflunomide; TER-OMB, switched from teriflunomide to ofatumumab in the extension phase
*Randomized to OMB in the core phase; †Randomized to TER in the core phase 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:
  - 3-parameter 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)
  - Annualized relapse rate (ARR)
- The analysis was further subdivided across 3 variables:
  - **Number of previous DMTs:** 0, 1, 2, or >2 DMTs before enrolling in ASCLEPIOS I/II
  - **Age group:** aged ≤40 or >40 years at baseline
  - **Most recent previous DMT:** NEDA-3 data were analyzed according to the last DMT before enrollment (fingolimod; interferon beta-1a, interferon beta-1b, or glatiramer acetate; dimethyl fumarate; other)

RESULTS

BASELINE CHARACTERISTICS

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

Table 1. All DMT History Before ASCLEPIOS I/II

DMT, n (%)	OMB-OMB (N=560*)	TER-OMB (N=573*)
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†	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)

DMT, disease-modifying therapy; MS, multiple sclerosis; OMB-OMB, received ofatumumab during the core and extension phases; TER-OMB, switched from teriflunomide to ofatumumab in the extension phase
*Data presented for those with any exposure to previous DMTs; †"Other DMT" contains all medications that were labeled by the investigator as MS DMTs but are not part of the listed medications

Table 2. Baseline Age and EDSS Score by Last DMT Prescribed

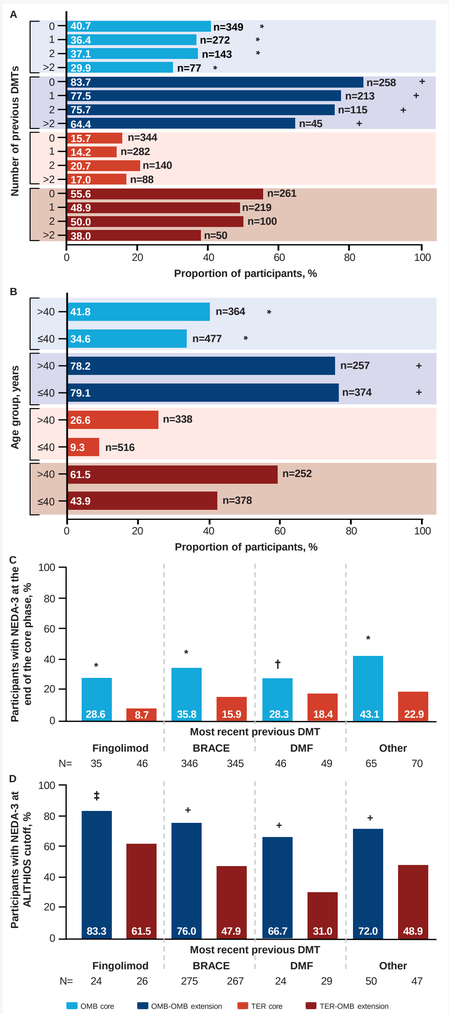
DMT, mean ± SD	Age, years		EDSS score	
	OMB	TER	OMB	TER
Fingolimod (n=98)	42.2±8.01	40.2±8.51	3.69±1.270	3.87±1.444
BRACE (n=764)	37.6±8.60	38.2±9.25	3.12±1.300	2.99±1.261
DMF (n=116)	42.4±8.70	40.6±9.16	3.41±1.362	3.23±1.335
Other* (n=155)	41.4±7.91	40.1±9.24	3.58±1.308	3.62±1.471

BRACE, interferon beta-1a, interferon beta-1b, or glatiramer acetate; DMF, dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; n, number of participants at core baseline; OMB, ofatumumab; SD, standard deviation; TER, teriflunomide
*"Other" contains all medications that were labeled by the investigator as MS DMTs but are not part of the listed medications

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-B**)
- In the core phase across all types of previous 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-D**)
  - This trend continued in the extension phase, where participants 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 Previous DMTs, (B) Age, and Last DMT Prescribed ([C] Core; [D] Extension) Subgroups

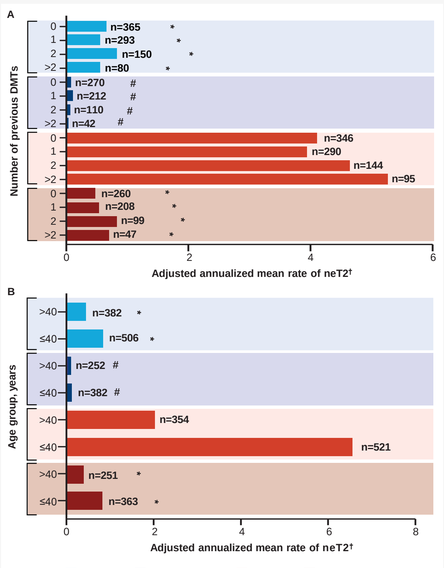


BRACE, interferon beta-1a, interferon beta-1b, or glatiramer acetate; DMF, dimethyl fumarate; DMT, disease-modifying therapy; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NEDA-3, 3-parameter no evidence of disease activity; OMB, ofatumumab; OMB-OMB, received ofatumumab during the core and extension phases; TER, teriflunomide; TER-OMB, switched from teriflunomide to ofatumumab in the extension phase
Analyzed 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 with baseline, and no T1 Gd+ lesions.
Note: re-baseline at the entry of extension phase was performed; participants received OMB for 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; ǂp=0.140 vs TER extension

BRAIN MRI MEASURES

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

Figure 3. neT2 per Year Across (A) Number of Previous DMT and (B) Age Subgroups



DMT, disease-modifying therapy; neT2, new or enlarging T2 lesions; OMB, ofatumumab; OMB-OMB, received ofatumumab during the core and extension phases; TER, teriflunomide; TER-OMB, switched from teriflunomide to ofatumumab in the extension phase
*p<0.05 vs TER core; †p<0.05 vs OMB core; ǂResults obtained from a Cox regression based on events in that time period

- Switching to OMB in the extension phase also reduced neT2 activity across the previous 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 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 aged <40 years, 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 previous DMTs to a greater extent than those with >2 previous 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 vs TER during the core phase across both the previous DMT (RR: 38.8-58.4%) and age (RR: 37.1-62.9%) subgroups; continuing OMB in the extension phase further reduced ARR vs the core phase (RR: 39.9-65.1%)

SAFETY

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

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