Ofatumumab Reduces Disability Progression Independent of Relapse Activity in Patients With Relapsing Multiple Sclerosis

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Introduction

- Ofatumumab is a fully human anti-CD20 monoclonal antibody with a 20 mg s.c. monthly dosing regimen, approved for the treatment of RMS in adults in the US[1] and other countries[a]
- In a preplanned pooled analysis of the ASCLEPIOS I/II Phase 3 trials, ofatumumab significantly reduced the risk of 3- and 6-month all cause disability worsening by 34.4% and 32.5%, respectively[2]
- In RMS, gradual progression apparently independent of relapses activity (PIRA) is an important contributing factor to disability worsening[3]
- Ofatumumab significantly reduced the risk of PIRA in a broad RMS population[4]
- Here, we investigate the effect of ofatumumab on PIRA in newly-diagnosed, treatment-naïve patients. In addition, we assess the impact of body weight on the effect of ofatumumab on PIRA

Objective

- To test the robustness of the effect of ofatumumab on confirmed PIRA against variability in body weight in the overall ASCLEPIOS I/II population, and to evaluate its impact in newly-diagnosed, treatment-naïve patients with RMS

Methods

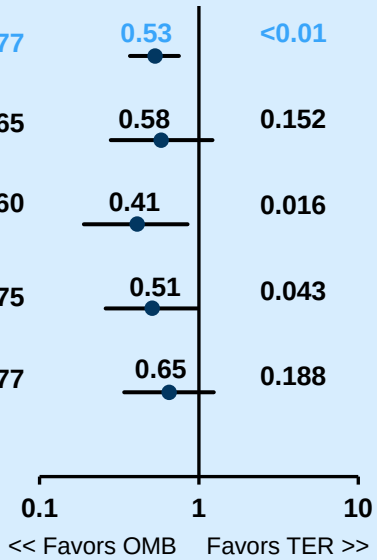
- EDSS worsening / progression was assessed (every 3 months) by trained EDSS raters who were not otherwise involved in the treatment of the patients and did not have access to other clinical information
- The effect of ofatumumab on PIRA[b] and its robustness to variability in body weight (by quartiles) was evaluated in the pooled ASCLEPIOS population
- PIRA events (3m/6mCDW events without confirmed relapses prior to CDW) were analyzed in the subset of newly-diagnosed, treatment-naïve patients

[a]Australia, Canada, Singapore, Switzerland, UAE, Albania, Argentina, Japan and India; [b]Risk of 3-month/6-month PIRA was defined as ≥1.0-point increase if baseline EDSS score ≤5.5 or ≥0.5-point increase if baseline EDSS score >5.5; analyzed using Cox-regression models; 3m/6mCDW, 3-month/6-month confirmed disability worsening; EDSS, Expanded Disability Status Scale; RMS, relapsing multiple sclerosis. [1]KESIMPTA® [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Aug 2020. [2]Hauser S, et al. Presented at *ECTRIMS* 2019. #336. [3]Kappos L, et al. *JAMA Neurol* 2020;77:1132–1140. [4]Kappos L, et al. Presented at *EAN* 2020. #O2034.

Results: Overall RMS patients

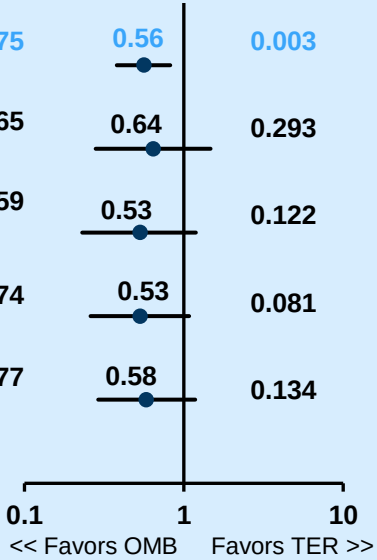
Time to 3-month PIRA
Without confirmed relapses prior to PIRA

	Group	n/N	HR[a] (95% CI)	P value
	Overall	OMB: 53/796; TER: 82/677	0.53	<0.01
By body weight	Q1	OMB: 12/190; TER: 17/165	0.58	0.152
	Q2	OMB: 11/214; TER: 20/160	0.41	0.016
	Q3	OMB: 14/192; TER: 24/175	0.51	0.043
	Q4	OMB: 16/200; TER: 21/177	0.65	0.188



Time to 6-month PIRA
Without confirmed relapses prior to PIRA

	Group	n/N	HR[a] (95% CI)	P value
	Overall	OMB: 45/796; TER: 66/675	0.56	0.003
By body weight	Q1	OMB: 10/190; TER: 13/165	0.64	0.293
	Q2	OMB: 10/214; TER: 14/159	0.53	0.122
	Q3	OMB: 12/192; TER: 20/174	0.53	0.081
	Q4	OMB: 13/200; TER: 19/177	0.58	0.134



Ofatumumab delayed both 3-month and 6-month PIRA in the overall RMS patients, irrespective of body weight

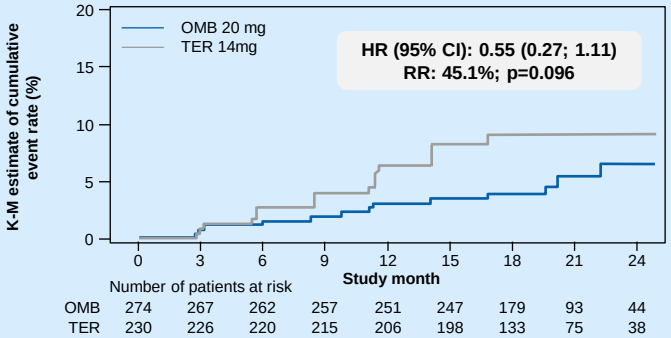
Quartiles were defined by body weight: Q1: <60.1 kg; Q2: 60.1 – <70.8 kg; Q3: 70.8 – <84.4 kg; Q4: ≥84.4 kg; [a]HRs were determined for each OMB quartile based on comparison to the same body weight quartiles in the TER group; **Analysis of PIRA events in the subset of patients without any confirmed relapses on study yielded consistent results (data not shown)**

HR, hazard ratio; CI, confidence interval; m, month; OMB, ofatumumab; PIRA, disability progression independent of relapse activity; Q, quartile; RMS, relapsing multiple sclerosis; TER, teriflunomide

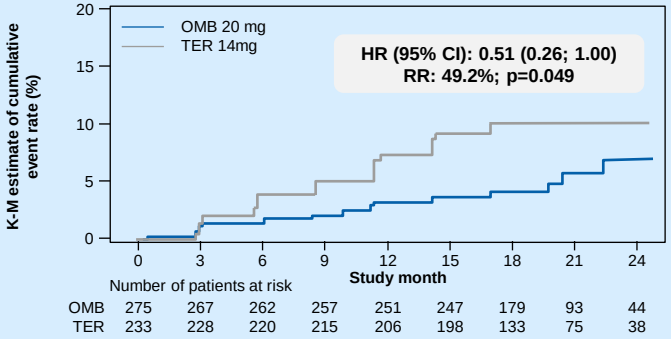
Results: Newly diagnosed, treatment-naïve patients

3-month PIRA

Without any confirmed relapses on study

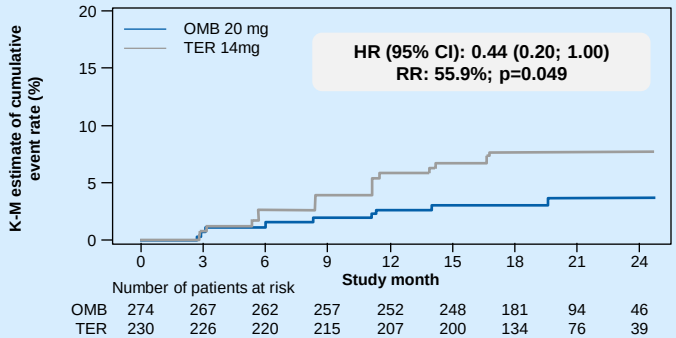


Without confirmed relapses prior to PIRA

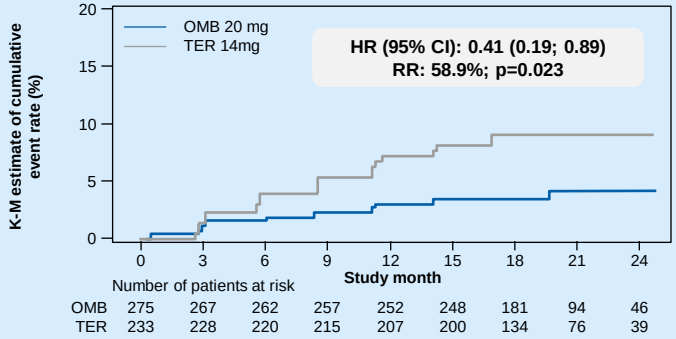


6-month PIRA

Without any confirmed relapses on study



Without confirmed relapses prior to PIRA



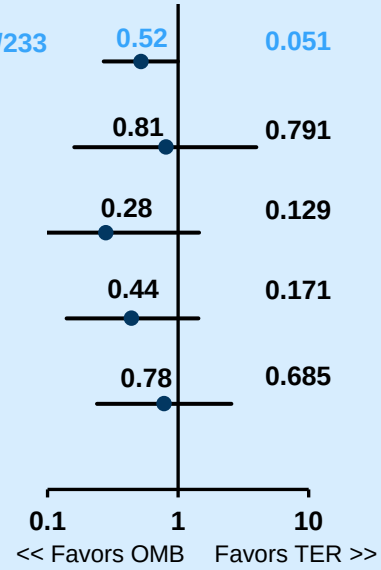
In newly diagnosed, treatment-naïve patients, >50% of CDW events were PIRA

CDW, confirmed disability worsening; CI, confidence interval; HR, hazard ratio; m, month; OMB, ofatumumab; PIRA, disability progression independent of relapse activity; RMS, relapsing multiple sclerosis; RR, relative reduction; TER, teriflunomide

Results: Newly diagnosed, treatment-naïve patients

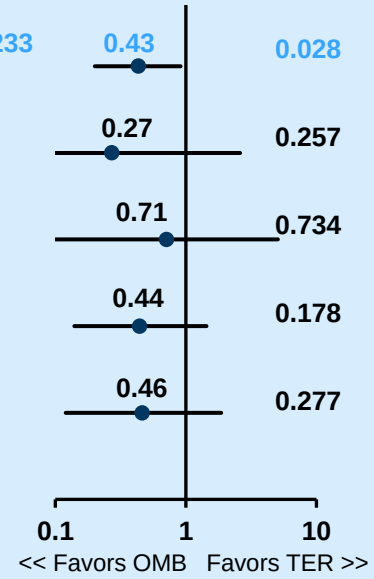
Time to 3-month PIRA
Without confirmed relapses prior to PIRA

	Group	n/N	HR[a] (95% CI)	P value
	Overall	OMB: 14/275; TER: 23/233	0.52	0.051
By body weight	Q1	OMB: 3/61; TER: 3/52	0.81	0.791
	Q2	OMB: 2/80; TER: 5/56	0.28	0.129
	Q3	OMB: 4/67; TER: 9/63	0.44	0.171
	Q4	OMB: 5/67; TER: 6/62	0.78	0.685



Time to 6-month PIRA
Without confirmed relapses prior to PIRA

	Group	n/N	HR[a] (95% CI)	P value
	Overall	OMB: 10/275; TER: 20/233	0.43	0.028
By body weight	Q1	OMB: 1/61; TER: 3/52	0.27	0.257
	Q2	OMB: 2/80; TER: 2/56	0.71	0.734
	Q3	OMB: 4/67; TER: 9/63	0.44	0.178
	Q4	OMB: 3/67; TER: 6/62	0.46	0.277



Ofatumumab delayed both 3-month and 6-month PIRA in newly diagnosed, treatment-naïve RMS patients, irrespective of body weight

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HR, hazard ratio; CI, confidence interval; m, month; OMB, ofatumumab; PIRA, disability progression independent of relapse activity; Q, quartile; RMS, relapsing multiple sclerosis; TER, teriflunomide

Conclusions

- In a clinical trial setting, regular EDSS assessments by independent EDSS raters reveal that gradual progression in the absence of overt relapse activity (PIRA) is common in relapsing MS patients treated with DMTs, even early in the disease course
- Ofatumumab reduced PIRA versus teriflunomide in a broad RMS population, including newly diagnosed and treatment-naïve patients
- The effects of ofatumumab on PIRA were similar across all patients irrespective of their body weight, indicating a robust pharmacodynamic impact of the chosen monthly dose of 20 mg subcutaneously

Disclosures

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