

Baseline serum neurofilament light levels have prognostic value for on-study MRI activity: Results from ASCLEPIOS trials

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Background and objective

- Serum neurofilament light (sNfL) reflects neuro-axonal damage and is a surrogate marker of disease activity and treatment response in RMS¹⁻⁴
- sNfL may complement MRI assessments for disease prognosis and patient monitoring in routine clinical practice
- In the Phase 3 ASCLEPIOS I/II trials, ofatumumab significantly lowered sNfL levels versus teriflunomide^{5*}
 - The effect was seen in the first assessment at Month 3 and sustained over Month 24

Objective

To investigate the prognostic value of baseline sNfL for on-study disease activity and worsening in patients with RMS, particularly in newly diagnosed, treatment-naïve patients

*Ofatumumab, an FDA-approved fully human anti-CD20 monoclonal antibody, with a 20 mg s.c. monthly dosing regimen, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults (KESIMPTA® (ofatumumab) Prescribing Information. <https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf> (accessed Aug 24, 2020).

MRI, magnetic resonance imaging; MS, multiple sclerosis; RMS, relapsing MS; sNfL, serum neurofilament light chain

1. Manouchehrinia A, et al. *Neurology*. 2020;94:2457–2467. 2. Kuhle J, et al. *Mult Scler*. 2019 doi:10.1177/1352458519885613. 3. Khalil M, et al. *Nat Rev Neurol*. 2018;14:577–589. 4. Disanto G, et al. *Ann Neurol*. 2017;81:857–870. 5. Hauser SL, et al. *N Engl J Med*. 2020; 383:546–557.

Methods: Study assessments and analysis

Patients

- Pooled ASCLEPIOS I and II trials (N=1882); patients who received ofatumumab or teriflunomide for up to 30 study months
- Patients were stratified into two categories based on median baseline sNfL level (**9.3 pg/mL**)
 - Low sNfL category (sNfL level \leq population median sNfL level)
 - High sNfL category (sNfL level $>$ population median sNfL level)
- Analyses were performed in **all patients** and in the subgroup of **newly diagnosed** (within 3 years of screening), **treatment-naïve** (no prior MS DMT) patients

NfL

- NfL levels in serum was quantitated using Quanterix Simoa NF-light Assay Advantage Kit*

Outcomes	Assessments	Statistical method
MRI measures	<ul style="list-style-type: none"> • Annualized rate of new or enlarging T2 lesions • Annual rate of brain volume loss 	<ul style="list-style-type: none"> • Negative binomial regression model • Random coefficient model
Clinical measures	<ul style="list-style-type: none"> • Annualized relapse rate • 3-month confirmed disability progression 	<ul style="list-style-type: none"> • Negative binomial regression model • Cox regression model

*The analytical sensitivity was confirmed to be 2.817 pg/mL, and the reportable range was 2.817 – 1546 pg/mL. Linearity of the assay was assessed across a range of below LLoQ to 1538 pg/mL in serum. Linear regression result was $R^2 = 0.9964$. Intra-assay precision was demonstrated by testing 8 samples across assay reportable range independently for 6 times in a single run with highest observed CV of 10%. Inter-assay precision was demonstrated by testing 8 samples independently for 3 times per run for 6 runs (2 runs per day), with the highest observed CV of 11%.

CV, coefficient of variance; DMT, disease modifying therapy; LLoQ, lower limit of quantification; MRI, magnetic resonance imaging; MS, multiple sclerosis; sNfL, serum neurofilament light chain

1. Manouchehrinia A, et al. *Neurology* 2020;94:2457–2467. 2. Kuhle J, et al. *Mult Scler*. 2019 doi:10.1177/1352458519885613. 3. Khalil M, et al. *Nat Rev Neural* 2018;14:577–589. 4. Disanto G, et al. *Ann Neurol* 2017;81:857–870. 5. Hauser SL, et al. *N Engl J Med*. 2020; 383:546–557.

Patient demographics and disease characteristics

By baseline sNfL category

Parameters	Low sNfL category N=876	High sNfL category N=870
Age (years)	38.6±8.5	37.8±9.7
Sex, female, n (%)	588 (67)	602 (69)
MS duration since first symptom (years)	8.3±7.3	7.9±6.9
No. of relapses in the year before the study	1.2±0.7	1.3±0.7
Time since onset of most recent relapse (months)	7.8±13.5	7.0±9.4
EDSS score	2.8±1.3	3.0±1.4
Normalized brain volume (cc)	1447.6±74.8	1437.2±81.0
No. of Gd+T1 lesions	0.4±1.2	2.6±5.4
Patients free of Gd+T1 lesions, n (%)	679 (78)	383 (44)
T2 lesion volume (cc)	9.4±10.6	16.7±15.0
sNfL (pg/mL)	6.6±1.6	20.0±17.5

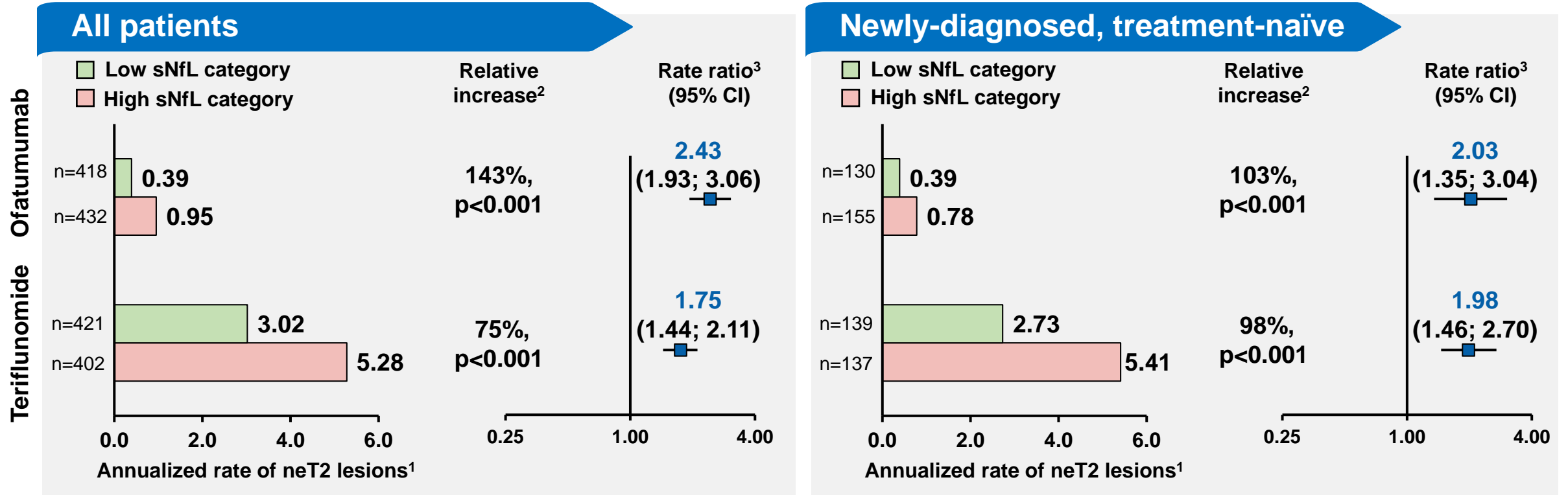
- At baseline, MRI disease activity was higher in patients with high sNfL levels than those with low sNfL levels

Data are expressed as mean±standard deviation

EDSS, Expanded Disability Status Scale; Gd+ gadolinium-enhancing; MS, multiple sclerosis; sNfL, serum neurofilament light chain

On-study new or enlarging T2 lesions per year

By baseline sNfL category



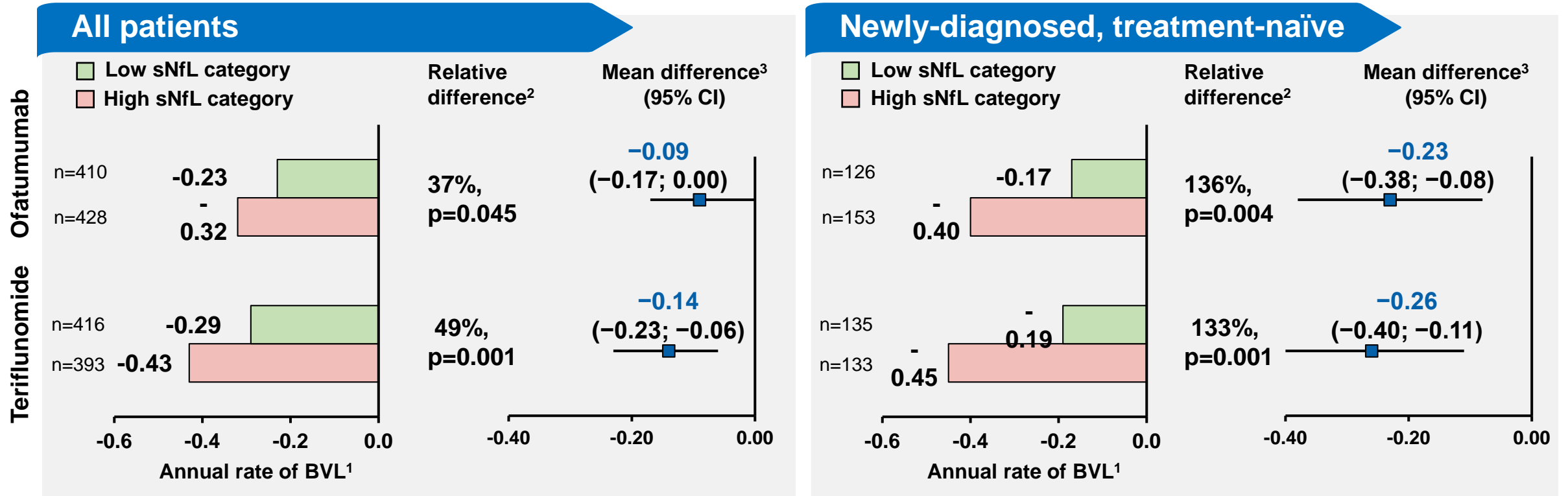
- Patients with high sNfL levels at baseline had more new or enlarging T2 lesions than patients with low sNfL levels, irrespective of treatment, and in all patients as well as in newly-diagnosed, treatment-naïve patients
- The prognostic value of baseline sNfL persisted for year-2 (all patients: Ofatumumab: 0.09 vs 0.06, 65%, p=0.124; teriflunomide: 4.53 vs 3.12, 46%, p=0.003)

Comparisons are between high vs low sNfL categories. ¹Adjusted annualized mean rate of neT2 lesions. ²Indicates statistical significance (2-sided) at the 0.05 level. ³The number of neT2 lesions (compared to baseline or Month 12) is analyzed in a negative binomial model with adjustments for treatment, baseline sNfL category, region and study as factors, and age, baseline volume of T2 lesions as continuous covariates, and treatment by baseline sNfL category interaction. The natural log of the time from the baseline scan (in years) is used as the offset.

CI, confidence interval; neT2, new or enlarging T2 lesions; sNfL, serum neurofilament light

On-study brain volume loss per year

By baseline sNfL category



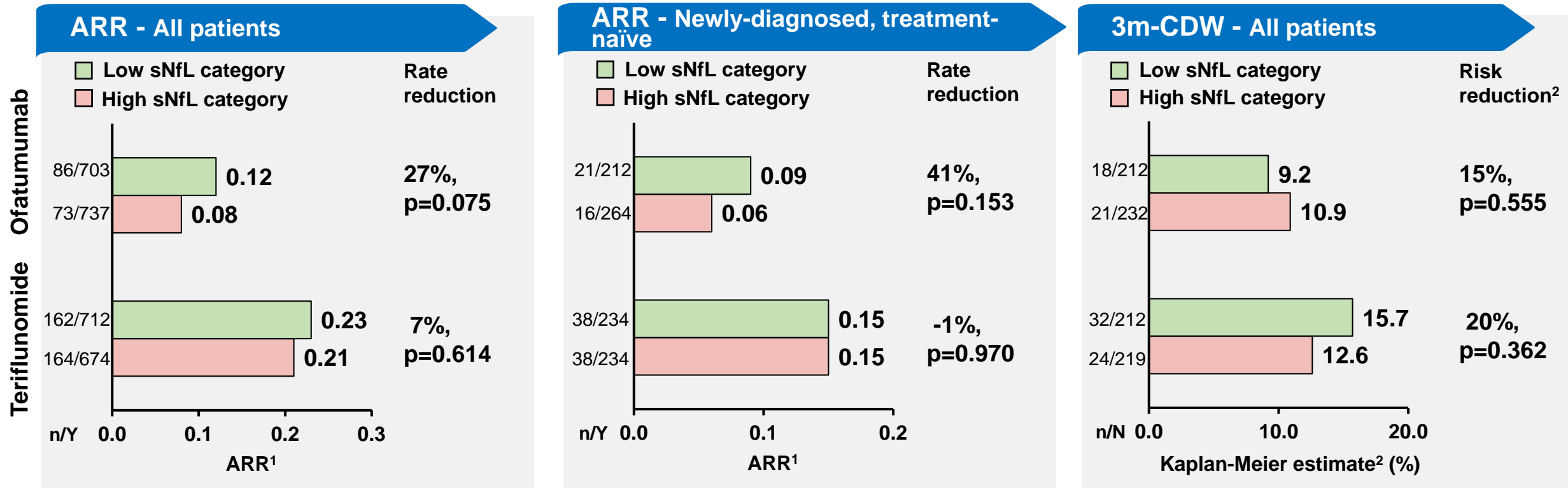
- Patients with high sNfL levels at baseline had increased annual rate of BVL versus patients with low sNfL levels
- These results were consistent in the subgroup of newly-diagnosed, treatment-naïve patients

Comparisons are between high vs low sNfL categories. ¹Adjusted mean annual rate of percent change from baseline. ²Indicates statistical significance (2-sided) at the 0.05 level. ³Obtained from a random coefficients model with study, treatment as fixed effects (factors), and time as continuous covariates and treatment by time interaction for the overall analysis, with additional co-factors of subgroup, treatment by subgroup, treatment by time by subgroup interactions for the subgroup analysis. Random terms for slopes and intercept are included.

CI, confidence interval; BVL, brain volume loss; LS, least square; sNfL, serum neurofilament light

Relapse and disability progression

By baseline sNfL category



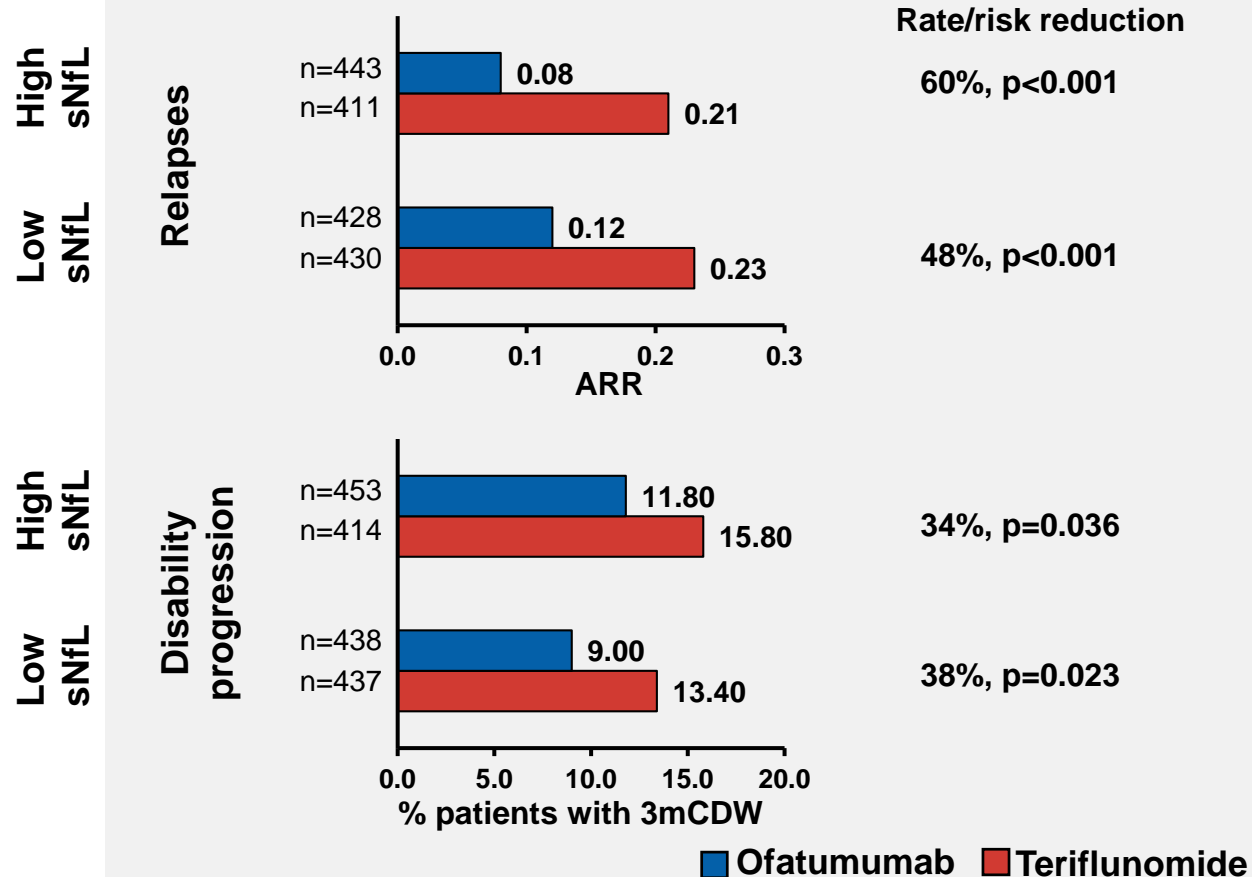
- In these studies, a single sNfL assessment at baseline had no prognostic value for on-study relapses and disability worsening
- The lack of evidence of a prognostic value of sNfL is possibly due to a low number of events observed in ASCLEPIOS trials

Comparisons are between high vs low sNfL categories. n: Total number of events included in the analysis; Y: number of patients-years in study; N: Total number of patients included in the analysis.¹Negative binomial regression model with log-link to the number of relapses adjusted for treatment, baseline sNfL category, region and study as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd+T1 lesions and the patient's age at baseline as covariates and treatment by baseline sNfL category interaction. The natural log of the time-in-study was used as offset to annualize the relapse rate. ²Cox regression adjusted study as stratum, treatment, region and sNfL baseline high-low subgroup as factors and baseline EDSS as a continuous covariate along with treatment-by-sNfL baseline high-low subgroup interaction.

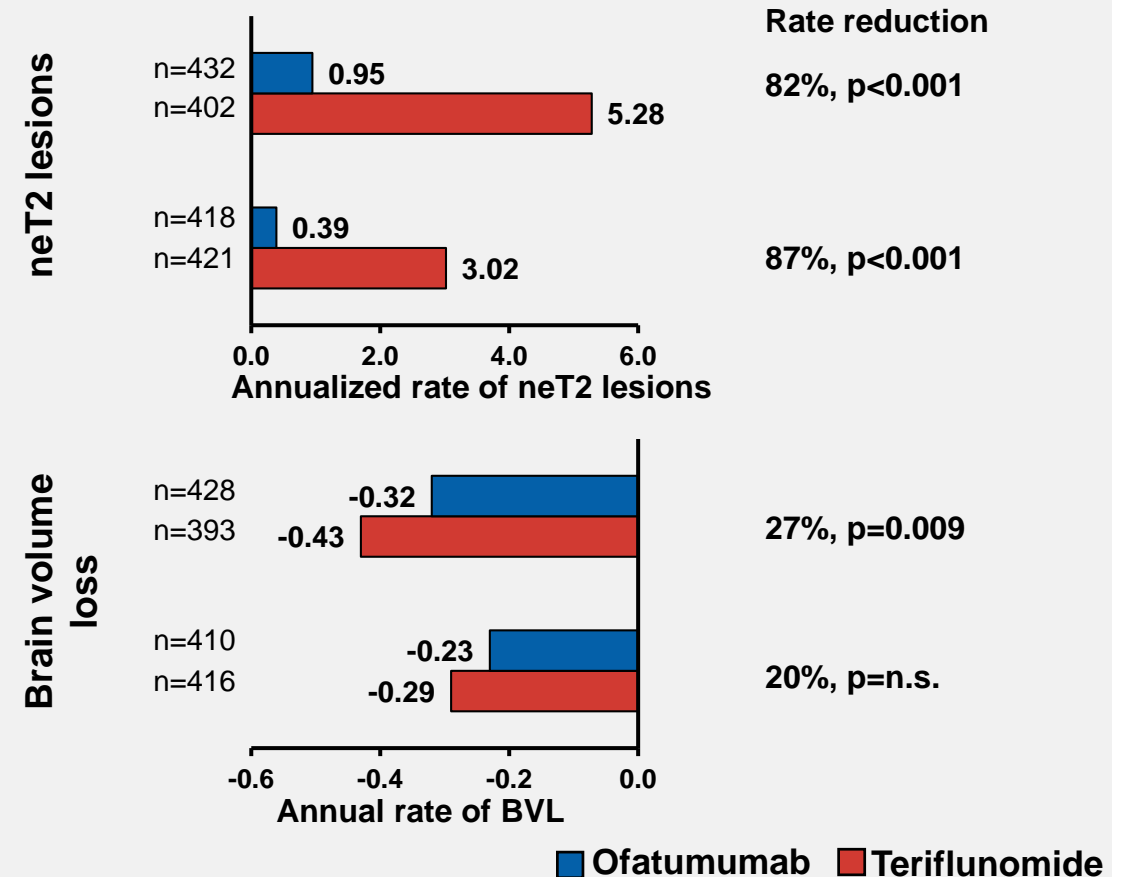
ARR, annualized relapse rate; CDW, confirmed disability worsening; sNfL, serum neurofilament light

Ofatumumab treatment effect was similar irrespective of baseline sNfL levels

Clinical measures

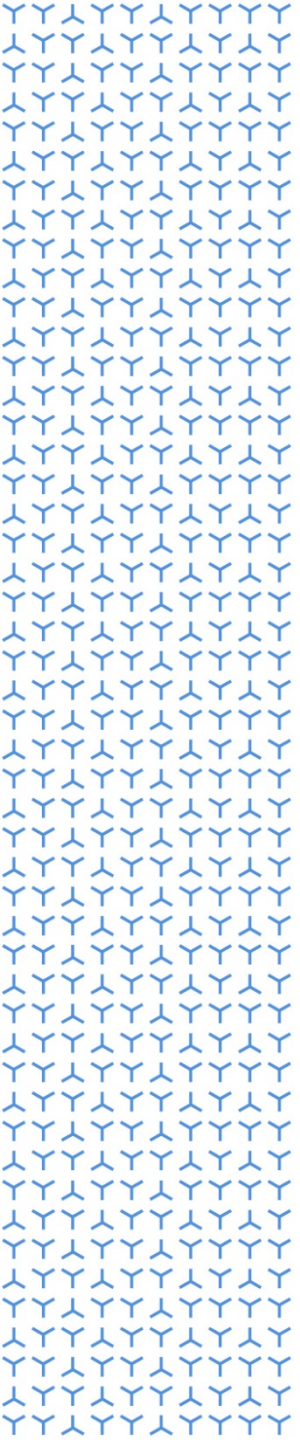


MRI measures



Conclusions

- **Baseline sNfL levels were prognostic for on-study lesion formation and brain volume loss over 1-2 years, in the pooled Phase 3 ASCLEPIOS I/II trials**
- **Prognostic value of a single sNfL assessment at baseline for clinical outcomes was not shown in this study**
- **The superiority of ofatumumab over teriflunomide and the magnitude of treatment effect was consistent irrespective of baseline sNfL levels**
- **sNfL levels can prospectively inform of the risk of ongoing and future disease activity and subclinical worsening in patients with RMS**
- **sNfL may complement clinical and imaging assessments in the evaluation of the individual benefit/risk of patients with RMS**



Thank you