#O2034

Effect of Ofatumumab Treatment on Disability Progression Independent of Relapse Activity in Patients With Relapsing Multiple Sclerosis

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Disclosures

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Introduction

- Ofatumumab, the first fully human anti-CD20 monoclonal antibody with a monthly 20 mg s.c. dosing regimen, showed superior efficacy versus teriflunomide and a favorable safety profile in the Phase 3 ASCLEPIOS I and II trials in patients with RMS[1,2]
- Ofatumumab significantly reduced the risk of 3-month CDW by 34.4% (p=0.002) and 6-month CDW by 32.5% (p=0.012) in the pre-specified pooled analysis of the ASCLEPIOS trials[2]
- The ASCLEPIOS I and II were randomized teriflunomide-controlled studies. Teriflunomide has an efficacy similar to that of interferons and glatiramer acetate on relapse rates, and similar to that of fingolimod on disability worsening according to a network meta-analysis[3]
- Disability worsening (CDW) in patients with RMS is driven by two mechanisms[4]:
  - Incomplete recovery from relapses (Relapse associated worsening, “RAW”)
  - **Disability progression independent of relapse activity(“PIRA”)**[5]

PIRA, confirmed disability progression independent of relapse activity; CDW, confirmed disability worsening; DMTs, disease-modifying therapies; RMS, relapsing multiple sclerosis; s.c., subcutaneous

[1]Smith P, et al. Presented at *ECTRIMS* 2016. P1143. [2]Hauser S, et al. Presented at *ECTRIMS* 2019. #336. [3]Fogarty E, et al. *Mult Scler Relat Disord* 2016;9:23–30. [4]Lublin FD, et al. *Neurology* 2014;83:278–86. [5]Kappos L, et al. *JAMA Neurol* 2020 (in press).

Objective and Methods

Objective

To assess the effect of ofatumumab versus teriflunomide on confirmed disability progression independent of relapse activity in patients with RMS pooled from the ASCLEPOS I and II trials

Outcomes

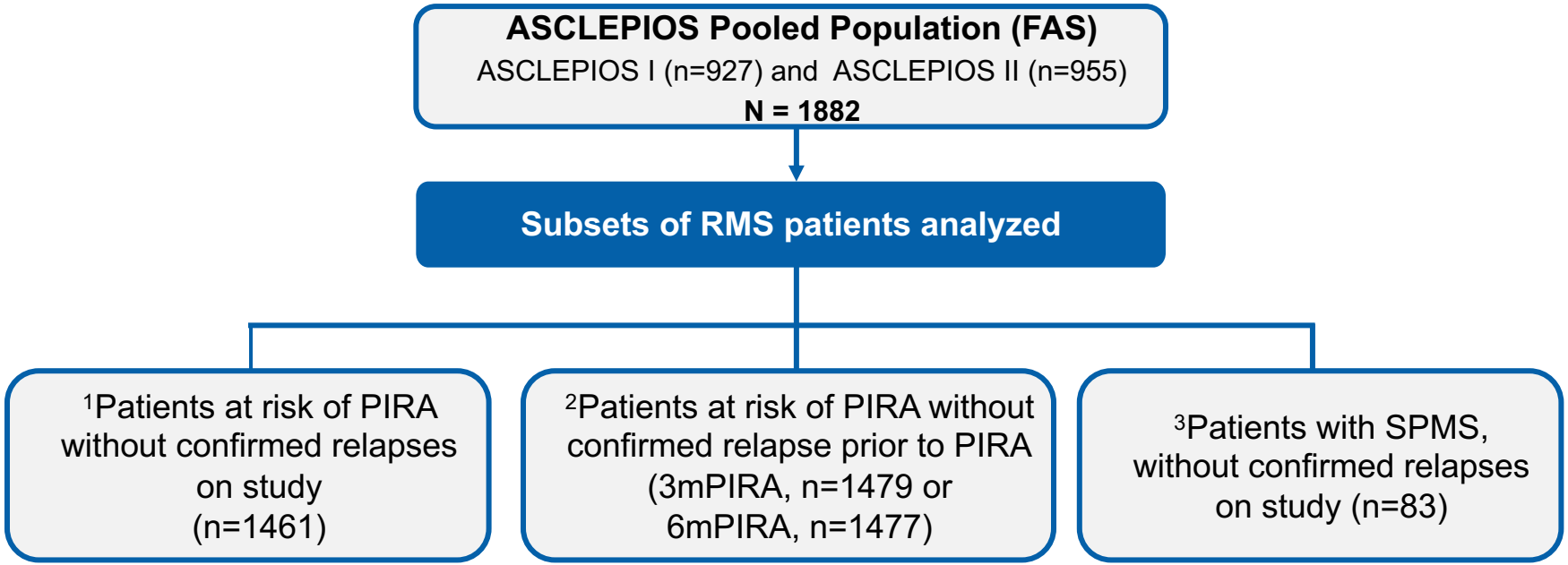
Risk of 3- or 6-month confirmed disability progression independent of relapse activity (PIRA) (3mPIRA/6mPIRA)[a,1]

Statistical analysis

Time to 3mPIRA and 6mPIRA was analyzed by Cox regression model adjusted for study as stratum, for treatment, region, and baseline EDSS score as covariates

[1]Kappos L, et al. *JAMA Neurol* 2020 (in press)
[a]EDSS score increase of ≥1.0 if baseline EDSS score <6, or ≥0.5 if baseline EDSS score ≥6;
EDSS, Expanded Disability Status Scale; PIRA, confirmed disability progression independent of relapse activity; RMS, relapsing multiple sclerosis

Patient Population



The FAS comprised all randomized patients; [1]FAS, but excluding patients who had EDSS confirmed on-study relapses (at any time); [2]FAS, but excluding patients who had an EDSS confirmed on-study relapse prior to the onset of a PIRA event (a relapse after a PIRA event was allowed); [3]SPMS (as per the investigator's diagnosis), excluding patients who had per protocol confirmed on-study relapses.

PIRA, confirmed disability progression independent of relapse activity; EDSS, Expanded Disability Status Scale; FAS, full analyses set; SPMS, secondary progressive multiple sclerosis as diagnosed by the investigators

Demographics and Baseline Characteristics

Parameter	Patients at risk of PIRA without confirmed relapses* n=1461	Patients at risk of PIRA without confirmed relapse prior to PIRA		SPMS patients without confirmed relapses n=83
		3mPIRA n=1479	6mPIRA n=1477	
Age, years	38.5±9.0	38.5±9.0	38.5±9.0	44.8±6.9
Female, n (%)	990 (67.8)	1002 (67.7)	1000 (67.7)	50 (60.2)
Weight, kg	74.6±19.0	74.6±18.9	74.6±18.9	73.3±14.9
Duration of MS since first symptoms, years	8.1±7.1	8.1±7.1	8.1±7.1	15.7±7.4
Previously treated with DMTs, n (%)	846 (57.9)	860 (58.1)	858 (58.1)	64 (77.1)
Number of relapses in the last 12 months	1.2±0.7	1.2±0.7	1.2±0.7	1.0 ± 0.5
EDSS score, median (range)	2.5 (0.0–6.5)	2.5 (0.0–6.5)	2.5 (0.0–6.5)	5.0 (1.0–6.0)
T2 lesion volume, cc	12.6±13.0	12.6±13.1	12.6±13.1	18.8±17.1
Patients free of Gd+ T1 lesions, n (%)	908 (62.1)	917 (62.0)	916 (62.0)	62 (74.7)
Number of Gd+ T1 lesions	1.4±3.6	1.4±3.6	1.4±3.6	0.6±1.4

Data are presented as mean±standard deviation, unless specified otherwise; PIRA, confirmed disability progression independent of relapse activity; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SPMS, secondary progressive multiple sclerosis

Demographics and Baseline Characteristics

Patients at risk of PIRA without confirmed relapses on study

Parameter	Ofatumumab n=795	Teriflunomide n=666	All patients N=1461
Age, years	38.4±9.0	38.6±9.0	38.5±9.0
Female, n (%)	527 (66.3)	463 (69.5)	990 (67.8)
Weight, kg	74.6±19.3	74.7±18.6	74.6±19.0
Duration of MS since first symptoms, years	8.0±7.0	8.1±7.3	8.1±7.1
Previously treated with DMTs, n (%)	456 (57.4)	390 (58.6)	846 (57.9)
Number of relapses in the last 12 months	1.2±0.7	1.2±0.7	1.2±0.7
EDSS score, median (range)	2.5 (0.0–6.0)	2.5 (0.0–6.5)	2.5 (0.0–6.5)
T2 lesion volume, cc	13.4±13.6	11.6±12.3	12.6±13.0
Patients free of Gd+ T1 lesions, n (%)	477 (60.0)	431 (64.7)	908 (62.1)
Number of Gd+ T1 lesions	1.6 ± 4.3	1.1 ± 2.6	1.4 ± 3.6

Data are presented as mean ± standard deviation, unless specified otherwise

PIRA, confirmed disability progression independent of relapse activity; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing;

Demographics and Baseline Characteristics

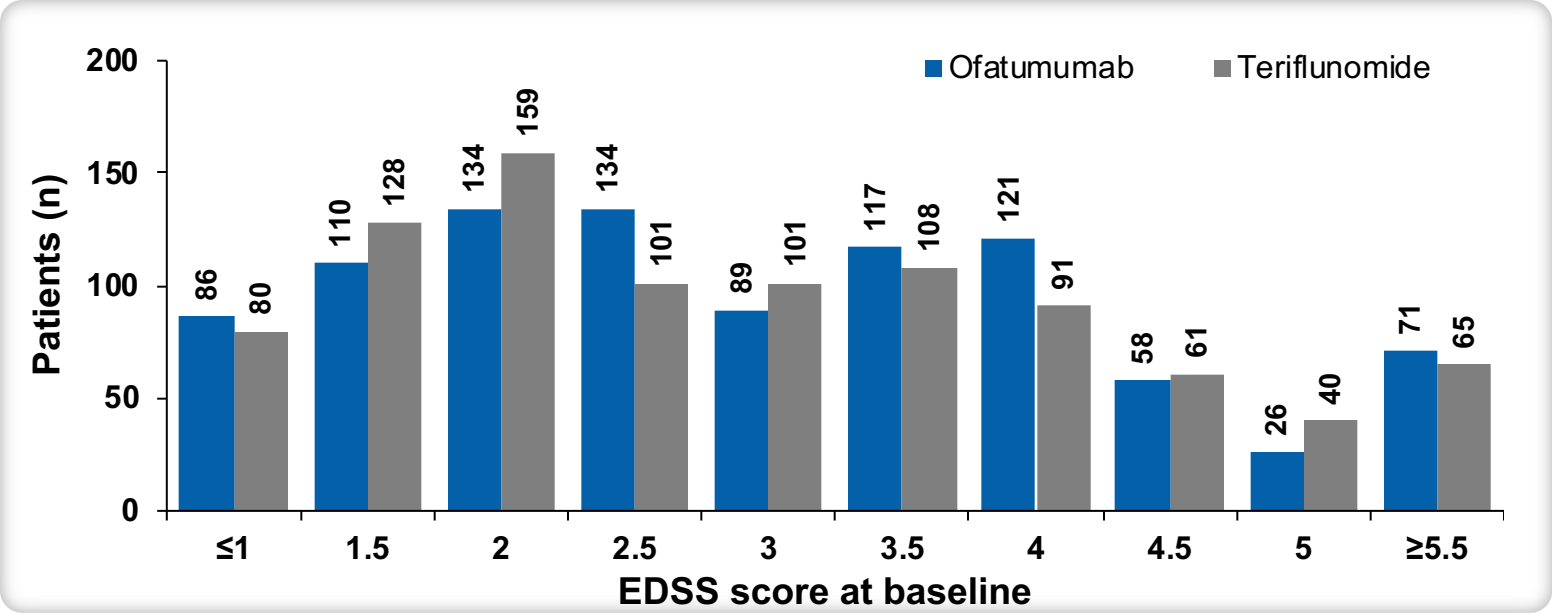
SPMS patients without confirmed relapses on study

Parameter	Ofatumumab n=46	Teriflunomide n=37	All patients N=83
Age, years	44.7±6.9	45.0±7.0	44.8±6.9
Female, n (%)	26 (56.5)	24 (64.9)	50 (60.2)
Weight, kg	74.6±15.8	71.8±13.8	73.3±14.9
Duration of MS since first symptoms, years	16.1± 6.4	15.3±8.6	15.7±7.4
Previously treated with DMTs, n (%)	34 (73.9)	30 (81.1)	64 (77.1)
Number of relapses in the last 12 months	1.1±0.5	1.0±0.6	1.0±0.5
EDSS score, median (range)	5.0 (2.5 – 5.5)	4.5 (1.0 – 6.0)	5.0 (1.0 – 6.0)
T2 lesion volume, cc	20.7±18.1	16.4 ± 15.7	18.8±17.1
Patients free of Gd+ T1 lesions, n (%)	36 (78.3)	26 (70.3)	62 (74.7)
Number of Gd+ T1 lesions	0.6±1.5	0.6±1.3	0.6±1.4

Data are presented as mean ± standard deviation, unless specified otherwise

PIRA, confirmed disability progression independent of relapse activity; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SPMS, secondary progressive multiple sclerosis

Patient Distribution by Baseline EDSS

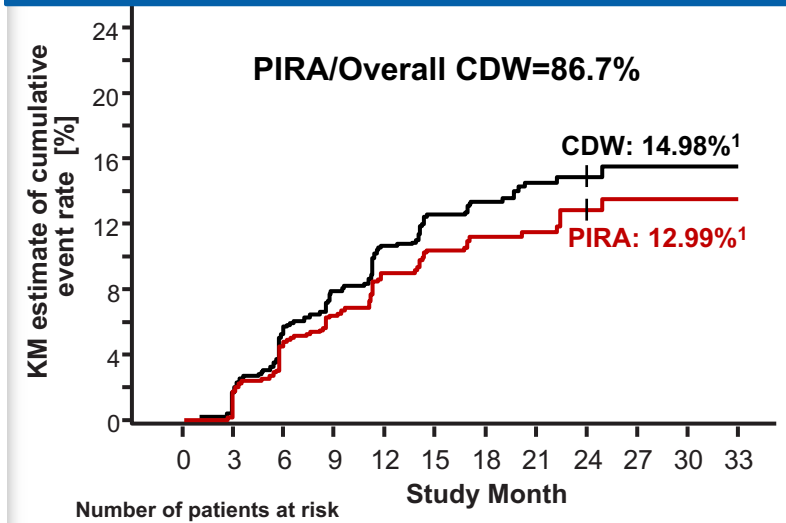


ASCLEPIOS I and II trials recruited a broad RMS population comprising newly diagnosed and severely disabled patients

EDSS, Expanded Disability Status Scale; RMS, relapsing multiple sclerosis

Progressions Independent of Relapse Activity (PIRA) were the Main Contributors to Overall 3mCDW

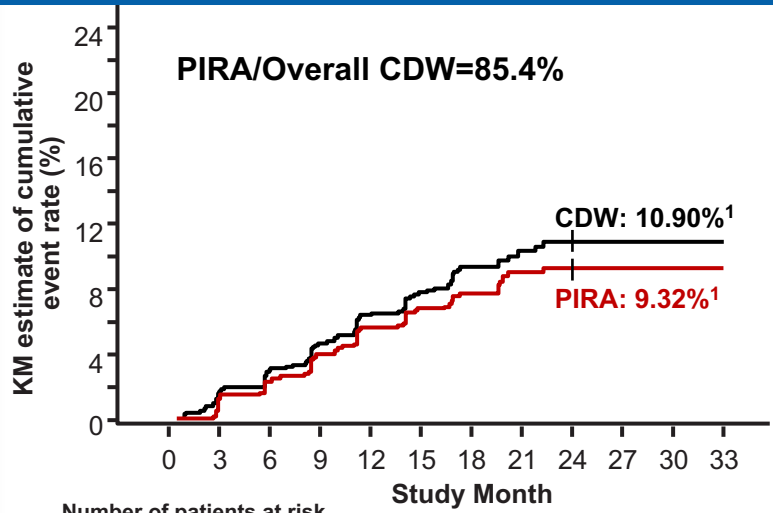
Teriflunomide



Number of patients at risk

CDW	932	901	841	804	756	718	478	298	146	41	1	0
PIRA	932	903	849	817	771	736	488	306	148	41	1	0

Ofatumumab



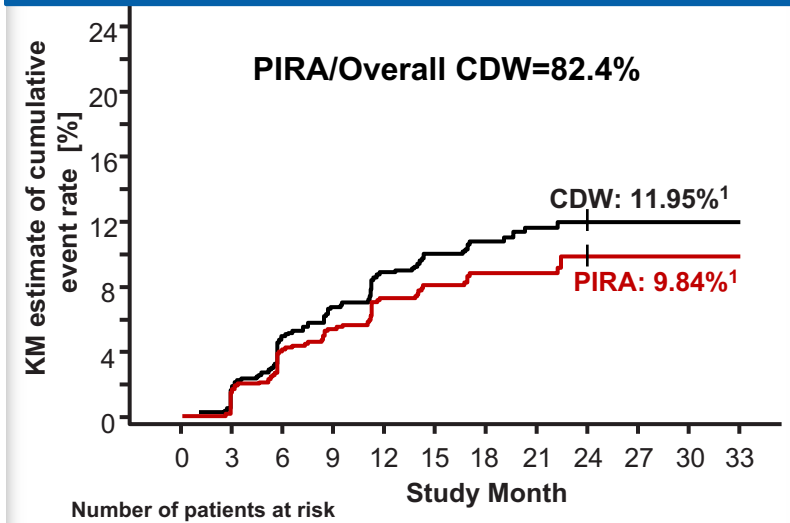
Number of patients at risk

CDW	944	908	878	844	810	784	534	319	176	49	1	0
PIRA	944	912	885	850	817	792	546	325	180	50	1	0

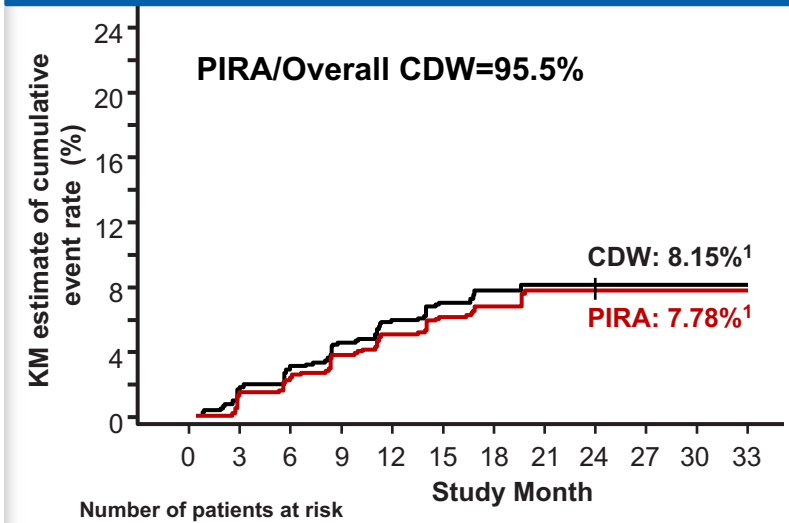
[1]Time to first CDW and PIRA events were derived independently. For the derivation of PIRA, patients who relapsed on-study, the EDSS after the relapse was used as a new baseline, and any subsequent disability progression evaluated in comparison to this new baseline. An advantage of this re-baseline methodology is that all FAS patients could contribute to the analysis; a limitation is that the derivation of PIRA events depends on post-baseline relapses. **Ofatumumab reduced the risk of 3mPIRA compared with teriflunomide (risk reduction=33.0%, HR [95% CI: 0.67 [0.59; 0.90], p=0.008).** PIRA: confirmed disability progression independent of relapse activity; CDW: confirmed disability worsening; EDSS, Expanded Disability Status Scale; FAS, full analysis set

Progressions Independent of Relapse Activity (PIRA) were the Main Contributors to Overall 6mCDW

Teriflunomide



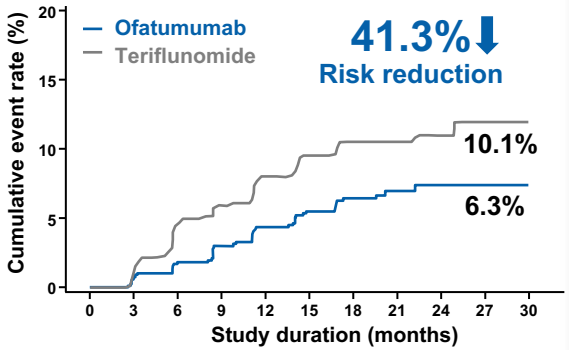
Ofatumumab



[1]Time to first CDW and PIRA events were derived independently. For the derivation of PIRA, the EDSS after the relapse was used as a new baseline, and any subsequent disability progression evaluated in comparison to this new baseline. An advantage of this re-baseline methodology is that all FAS patients could contribute to the analysis; a limitation is that the derivation of PIRA events depends on post-baseline relapses. **Ofatumumab numerically reduced the risk of 6mPIRA compared with teriflunomide (risk reduction=23.1%; HR [95% CI: 0.77 [0.55; 1.07], p=0.115).** PIRA: confirmed disability progression independent of relapse activity; CDW: confirmed disability worsening; EDSS, Expanded Disability Status Scale; FAS, full analysis set

Effect of Ofatumumab on Time to First 3-month Confirmed PIRA event

Patients at risk of PIRA without confirmed relapses on study

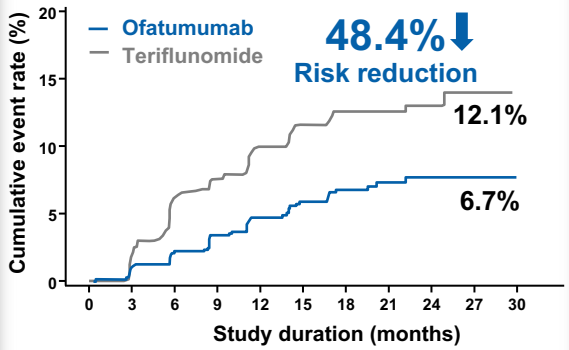


Number of patients at risk

Ofatumumab	793	769	746	720	693	675	462	272	146	41	0
Teriflunomide	662	646	606	587	560	536	343	208	102	26	0

HR (95% CI): 0.587 (0.407; 0.848)
RR: 41.3%; p=0.004

Patients at risk of PIRA without confirmed relapse prior to PIRA

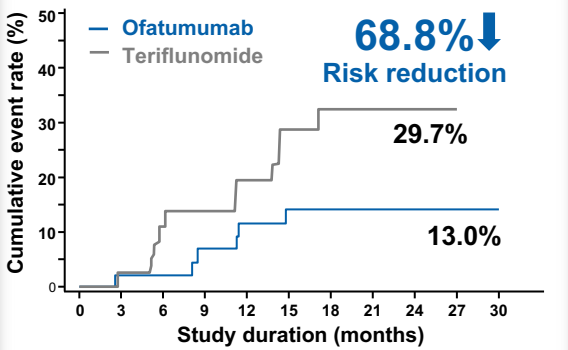


Number of patients at risk

Ofatumumab	796	770	746	720	693	675	462	272	146	41	0
Teriflunomide	677	656	610	590	561	536	343	208	102	26	0

HR (95% CI): 0.516 (0.365; 0.729)
RR: 48.4%; p<0.001

SPMS patients without confirmed relapses on study



Number of patients at risk

Ofatumumab	46	43	42	39	37	35	22	13	5	1	0
Teriflunomide	37	36	32	30	28	23	13	7	5	0	

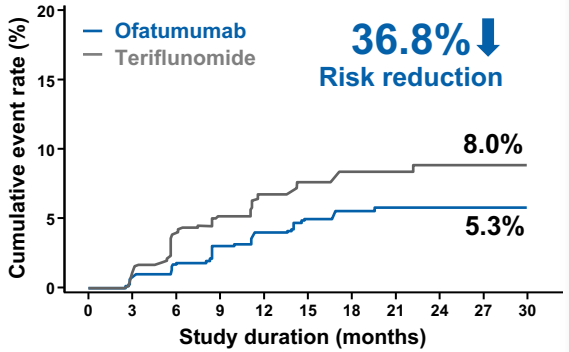
HR (95% CI): 0.312 (0.114; 0.859)
RR: 68.8%; p=0.024

Ofatumumab significantly delayed the time to first 3-month confirmed PIRA versus teriflunomide in all subsets of patients

PIRA, confirmed disability progression independent of relapse activity; CI, confidence interval; HR, hazard ratio; RR, risk reduction; SPMS, secondary progressive multiple sclerosis.

Effect of Ofatumumab on Time to First 6-month Confirmed PIRA event

Patients at risk of PIRA without confirmed relapses on study

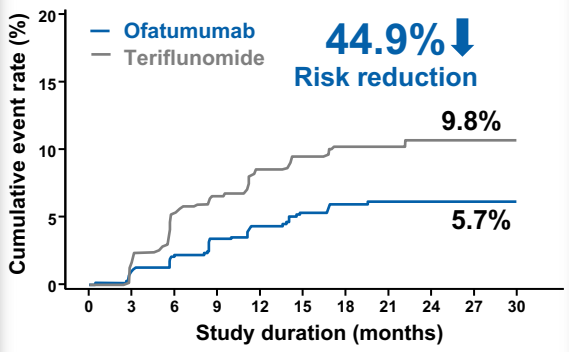


Number of patients at risk

Ofatumumab	793	769	746	720	696	679	465	274	148	42	0
Teriflunomide	662	646	610	590	565	543	347	211	104	27	0

HR (95% CI): 0.632 (0.421; 0.947)
RR: 36.8%; p=0.026

Patients at risk of PIRA without confirmed relapse prior to PIRA

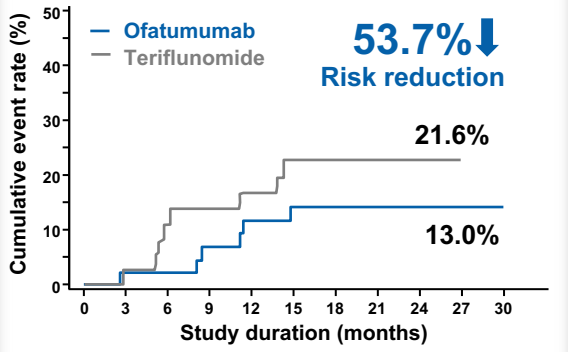


Number of patients at risk

	796	770	746	720	696	679	465	274	148	42	0
	675	655	614	593	566	543	347	211	104	27	0

HR (95% CI): 0.551 (0.377; 0.805)
RR: 44.9%; p=0.002

SPMS patients without confirmed relapses on study



Number of patients at risk

	46	43	42	39	37	35	22	13	5	1	0
	37	36	32	30	29	24	14	8	5	0	

HR (95% CI): 0.463 (0.158; 1.355)
RR: 53.7%; p=0.160

Ofatumumab delayed time to first 6-month confirmed PIRA versus teriflunomide in all subsets of patients (not significant in subset of SPMS patients without confirmed relapses)

PIRA, confirmed disability progression independent of relapse activity; CI, confidence interval; HR, hazard ratio; RR, risk reduction; SPMS, secondary progressive multiple sclerosis.

Conclusions

- ✓ In treated RMS patients, the great majority of confirmed disability worsening occur as disability progression independent of reported relapse activity
- ✓ Ofatumumab, compared with teriflunomide, significantly reduced the risk of disability progression independent of relapse activity (PIRA) in a broad RMS population

Thank you

RMS, relapsing multiple sclerosis