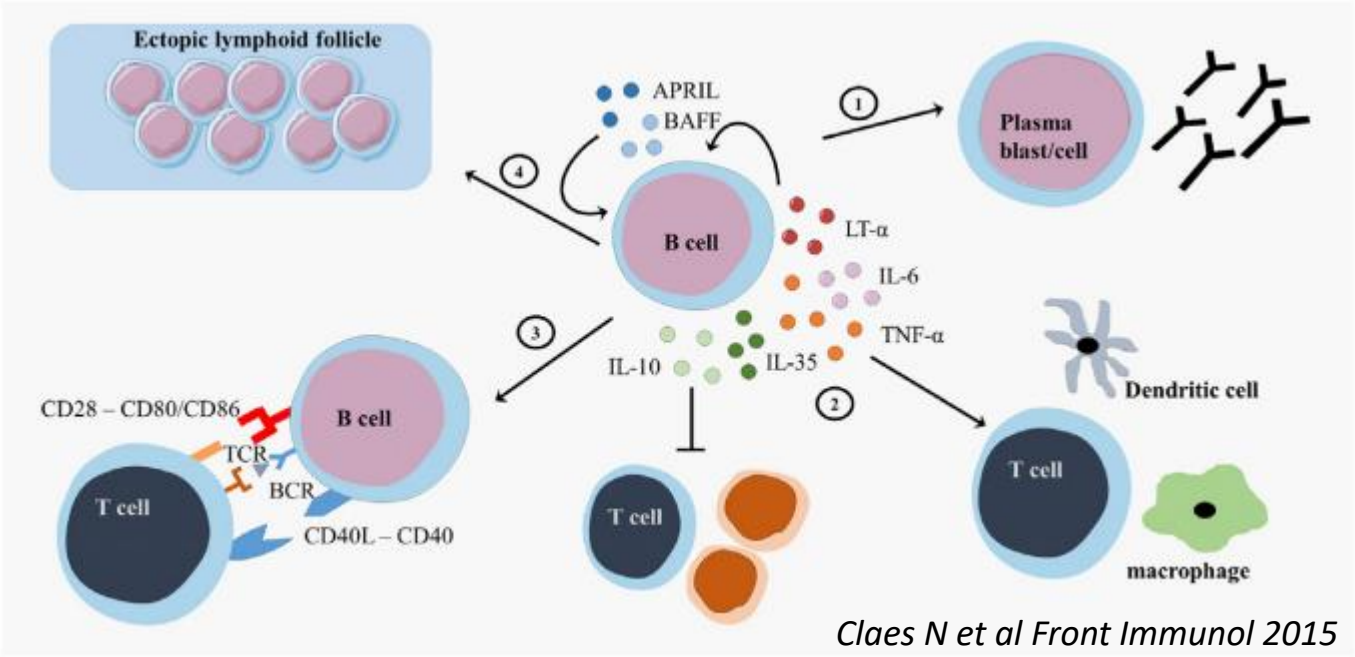
IL PUNTO SUI FARMACI SISTEMICI

B CELLS THERAPIES

7 ottobre 2016

Dott. Daniela Currò
S.C. Neurologia
Ospedale San Paolo Savona

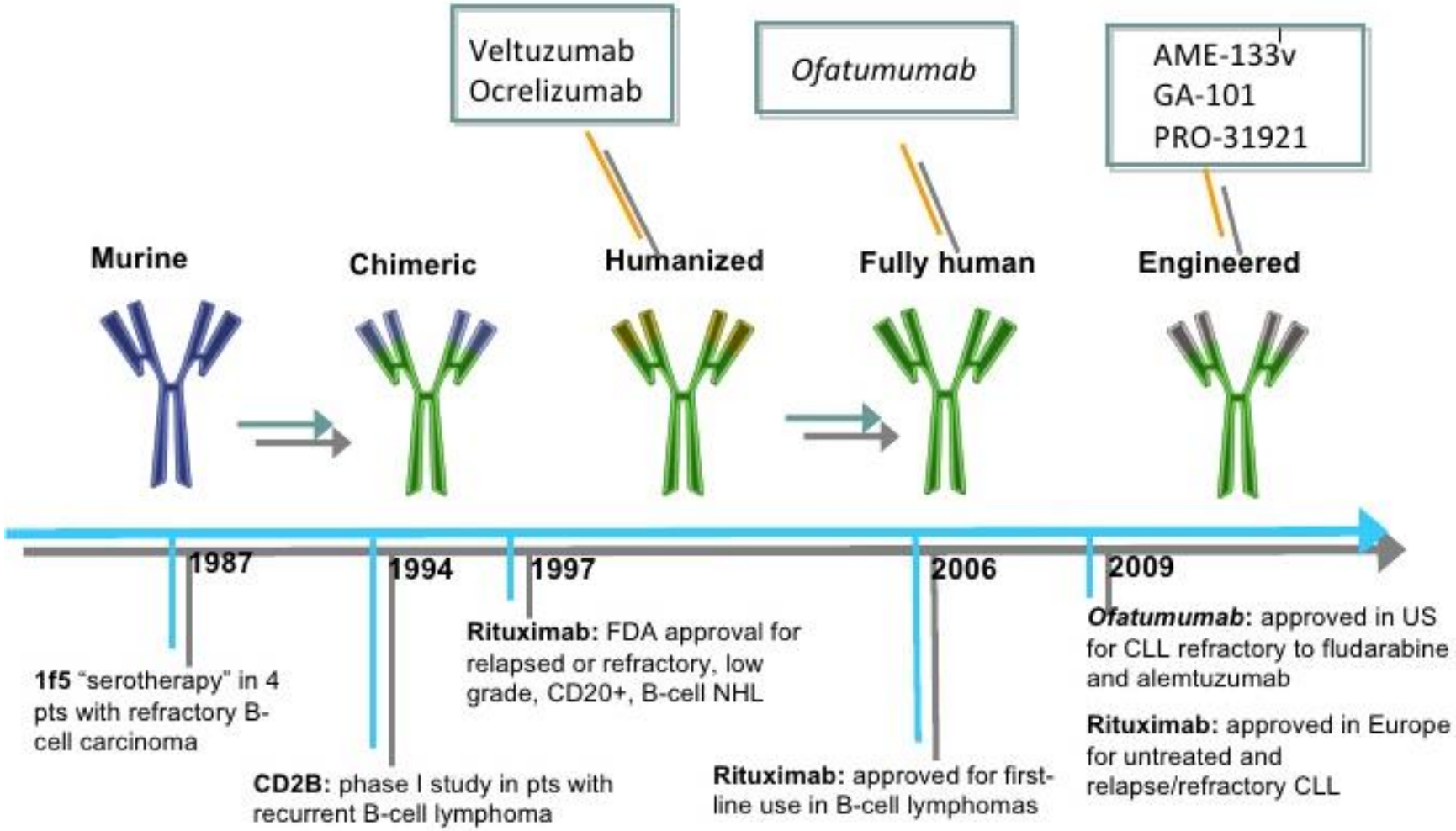
ROLE OF B CELLS IN MS PATHOGENESIS



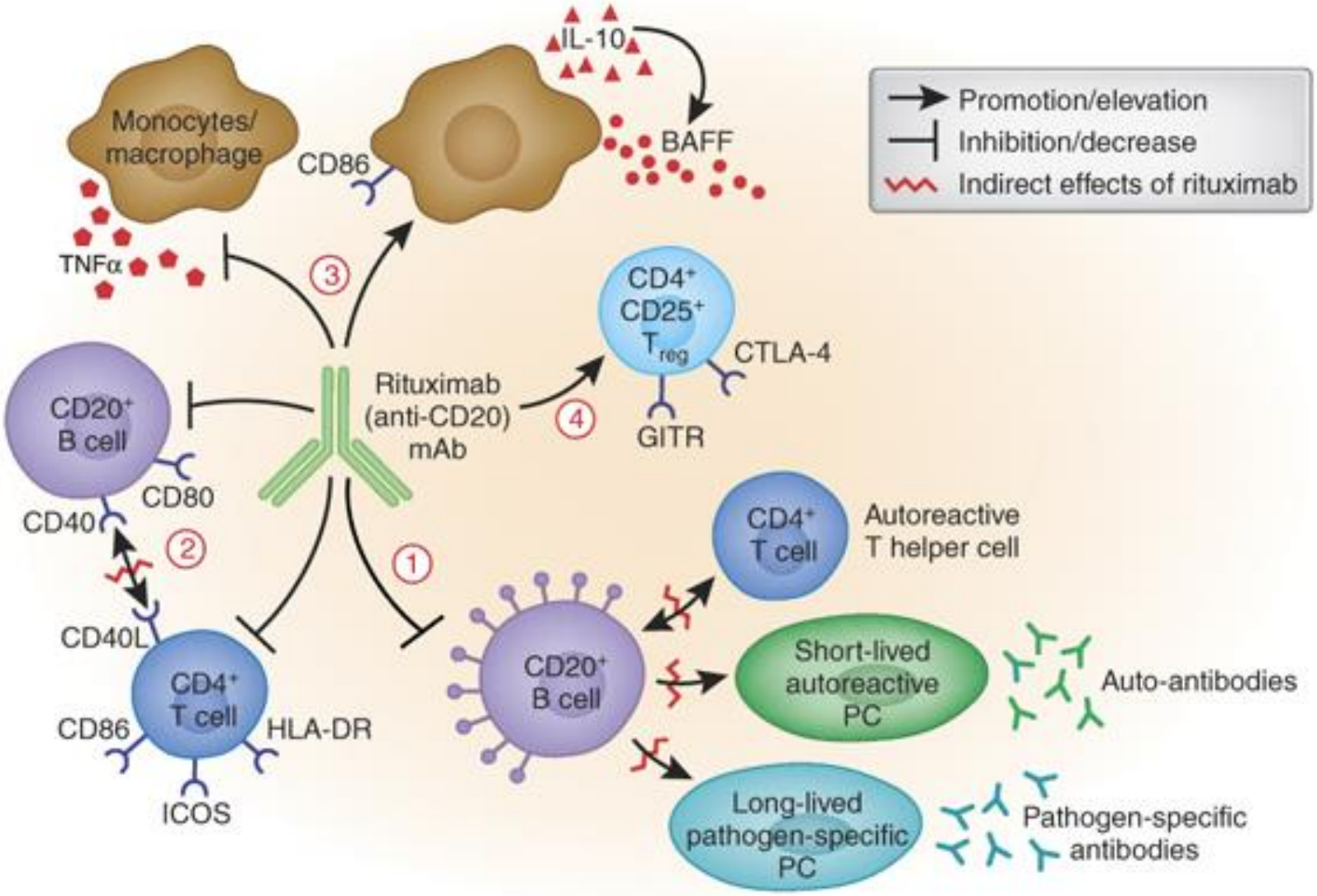
Claes N et al Front Immunol 2015

- B cells differentiate into Ab-secreting plasma blasts and plasma cells and produce Ag-specific Ab
- B cells serve as highly effective and selective APCs leading to optimal antigen-specific T cell expansion, memory formation and cytokine production
- B cells support or regulate effector immune functions via the secretion of different cytokines (inflammatory functions through secretion of TNF-α, IL-6 and LT-α and regulatory functions via the production of IL-10 and IL-35)
- B cells form GC-like structures, ectopic lymphoid follicles, outside of secondary lymphoid organs at sites of inflammation, that harbor a local source of class-switched Igs that contribute to the immune response

ANTI CD 20 ANTIBODIES



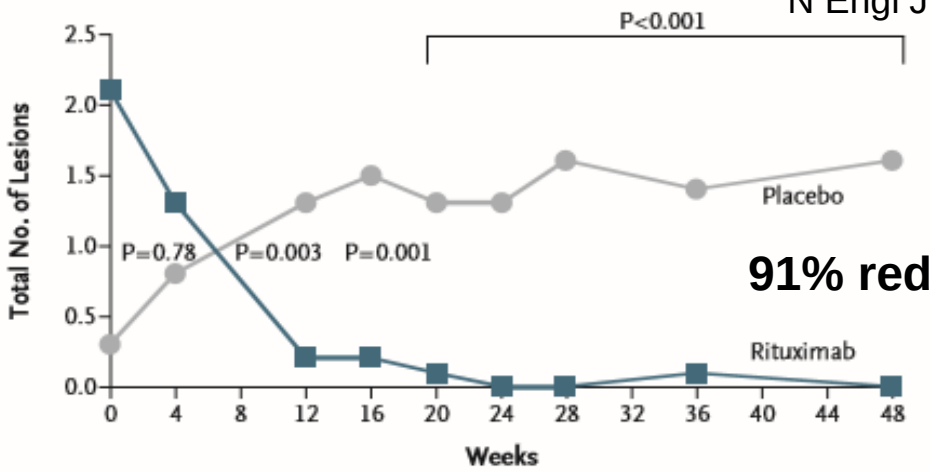
RITUXIMAB


IL-10
Monocytes/
macrophage
CD86
BAFF
Promotion/elevation
Inhibition/decrease
Indirect effects of rituximab
TNFα
3
CD4+
CD25+
Treg
CTLA-4
CD20+
B cell
Rituximab
(anti-CD20)
mAb
4
GITR
CD80
CD40
2
1
CD4+
T cell
Autoreactive
T helper cell
CD40L
CD20+
B cell
Short-lived
autoreactive
PC
Auto-antibodies
CD4+
T cell
CD86
HLA-DR
ICOS
Long-lived
pathogen-specific
PC
Pathogen-specific
antibodies

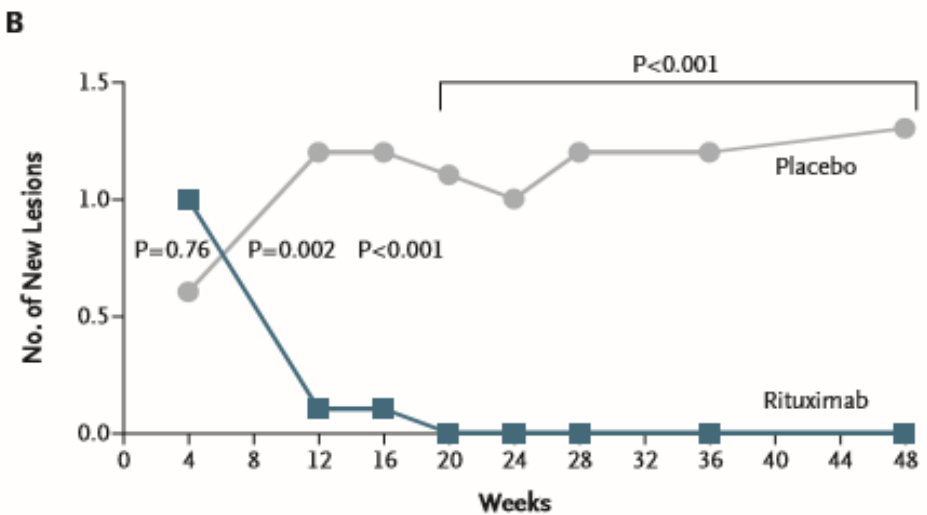
B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D., Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D., Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D., Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D., and Craig H. Smith, M.D., for the HERMES Trial Group*

N Engl J Med 2008



91% reduction



phase 2, double-blind, 48-week trial involving 104 patients with RRMS: 69 patients received 1000 mg of intravenous rituximab and 35 patients received placebo on days 1 and 15

Clinical			
Relapses at 24 wk			
Patients with relapse — no. (%)§	12 (34.3)	10 (14.5)	0.02¶
Relative risk (90% CI)‖	2.3 (1.3–4.3)	—	
Relapses at 48 wk			
Patients with relapse — no. (%)‡	14 (40.0)	14 (20.3)	0.04¶
Relative risk (90% CI)‖	1.9 (1.1–3.2)	—	
Annualized rate of relapse from wk 0 to wk 24			
Total no. of relapses	13	11	
Total subject-years of follow-up	15.9	31.3	
Unadjusted rate	0.8	0.4	
Adjusted rate (90% CI)**	0.8 (0.53–1.31)	0.4 (0.23–0.60)	0.04††
Mean‡‡	0.8±1.20	0.3±0.86	
Median	0	0	
Annualized rate of relapse from wk 0 to wk 48			0.08††
Total no. of relapses	19	21	
Total subject-years of follow-up	27.2	59.7	
Unadjusted rate	0.7	0.4	
Adjusted rate (90% CI)**	0.7 (0.46–1.12)	0.4 (0.24–0.57)	
Mean‡‡	0.7±1.05	0.4±0.81	
Median	0	0	

Rituximab in Patients with Primary Progressive Multiple Sclerosis

Results of a Randomized Double-Blind Placebo-Controlled Multicenter Trial

Kathleen Hawker, MD,[1] Paul O'Connor, MD,[2] Mark S. Freedman, MD,[3] Peter A. Calabresi, MD,[4] Jack Antel, MD,[5] Jack Simon, MD,[6] Stephen Hauser, MD,[7] Emmanuelle Waubant, MD,[7] Timothy Vollmer, MD,[8] Hillel Panitch, MD,[9] Jiameng Zhang, PhD,[10] Peter Chin, MD,[10] and Craig H. Smith, MD,[10] for the OLYMPUS trial group

Ann Neurol 2009

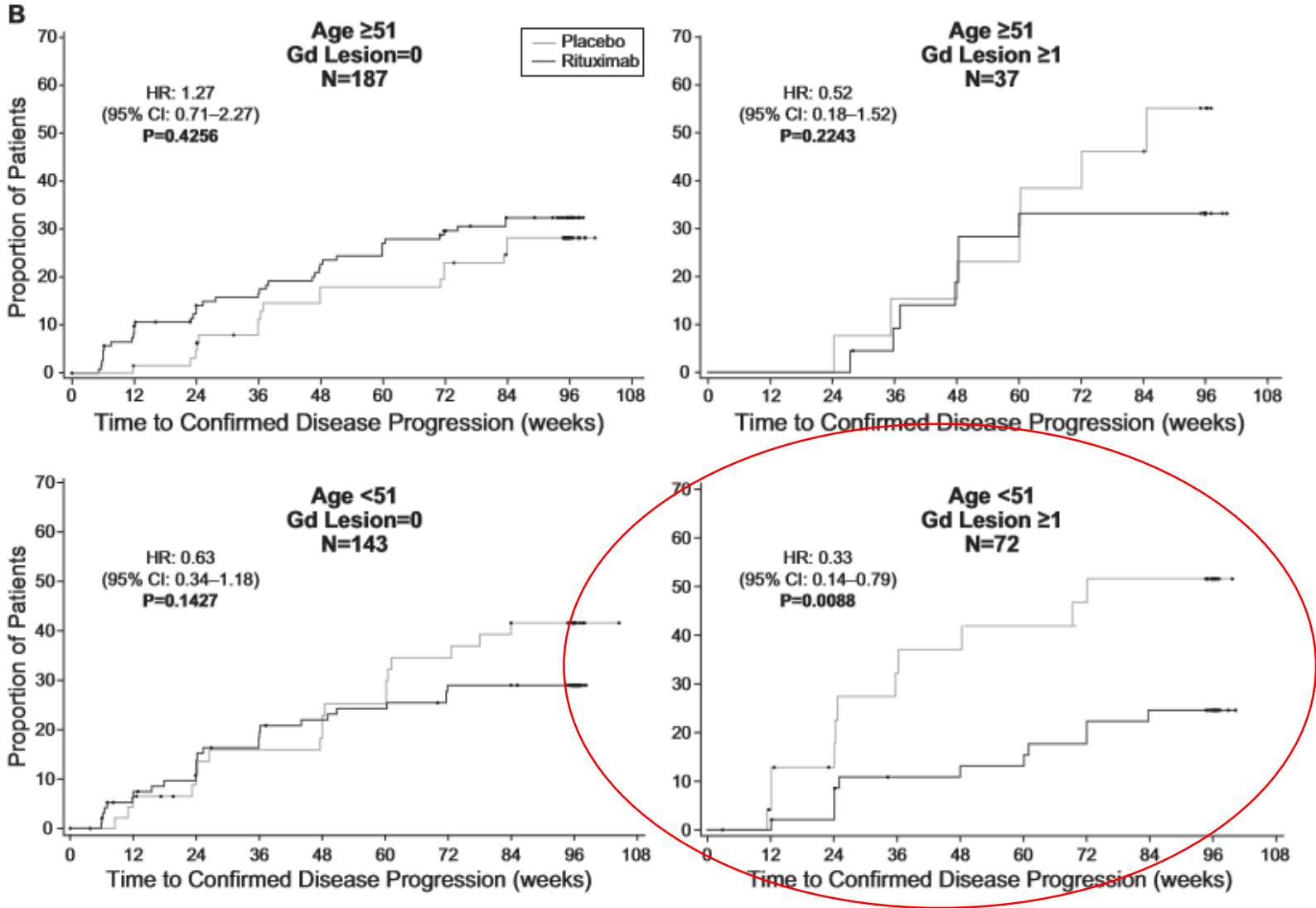
Although time to CDP between groups was not significant, overall subgroup analyses suggest selective B-cell depletion may affect disease progression in younger patients, particularly those with inflammatory lesions

439 PPMS patients received two 1,000 mg intravenous rituximab or placebo infusions every 24 weeks, through 96 weeks (4 courses)

Adverse events comparable between groups: 16.1% of rituximab and 13.6% of placebo patients reported serious events

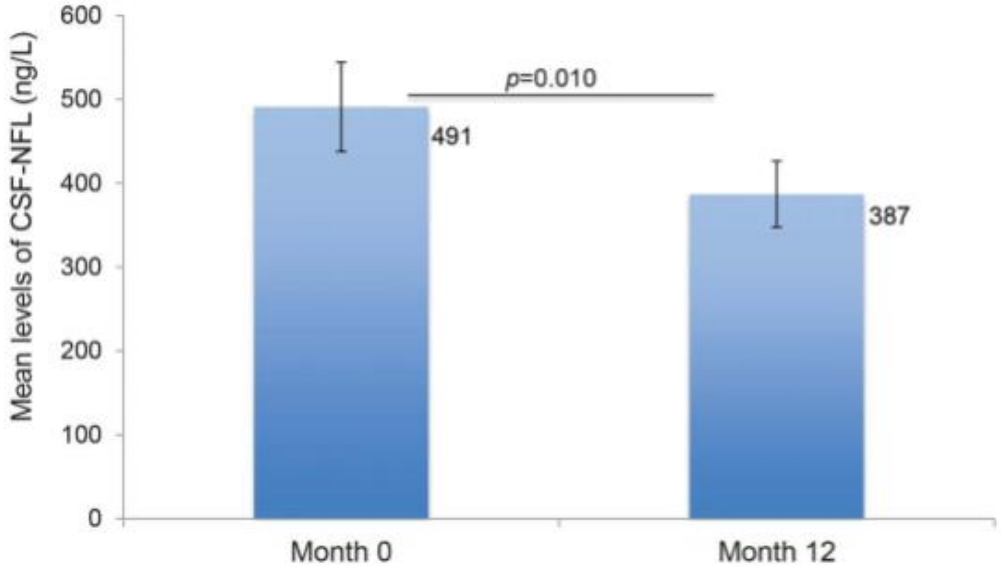
Serious infections occurred in 4.5% of rituximab and 1.0% of placebo patients

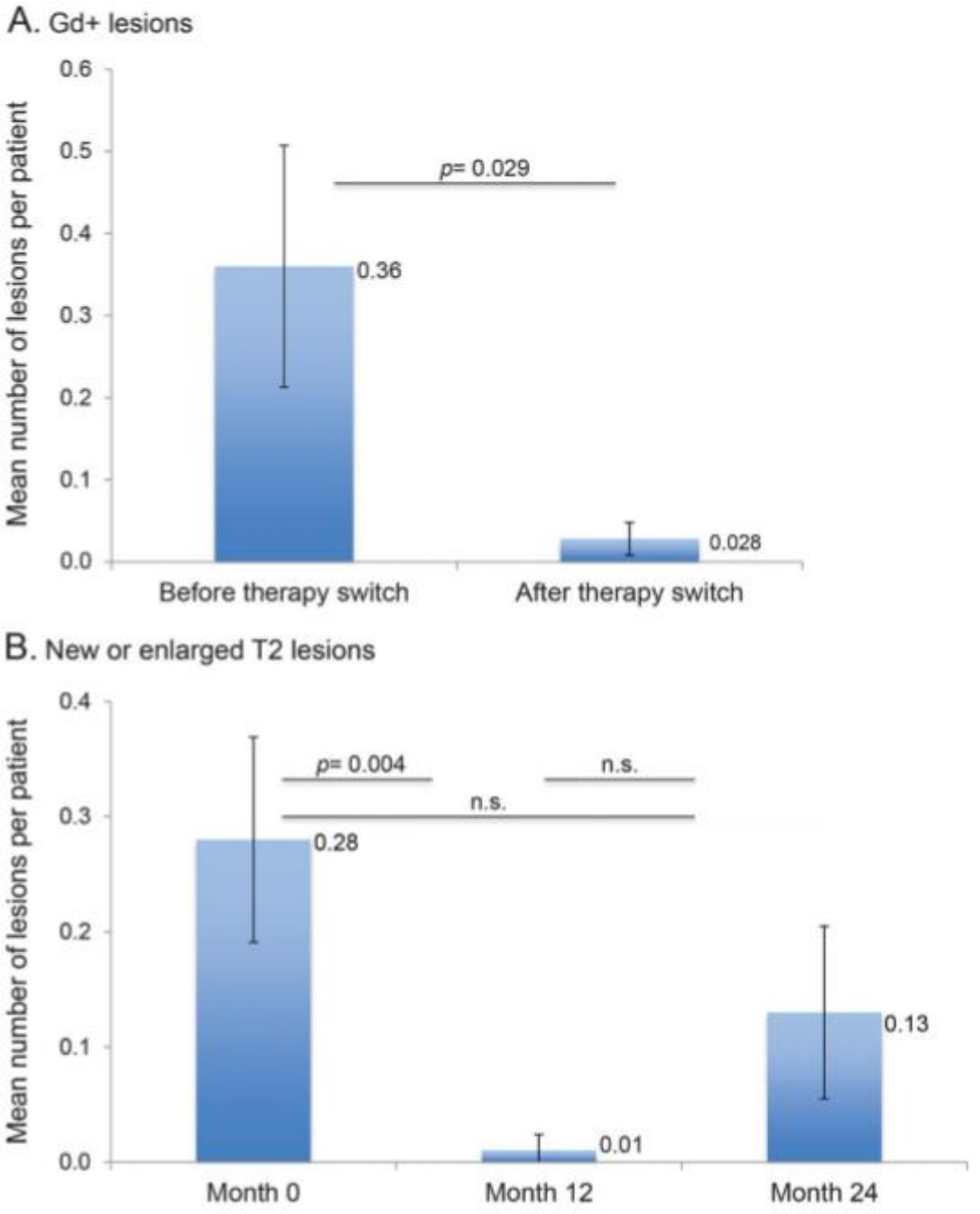
Infusion-related events, predominantly mild to moderate, were more common with rituximab during the first course, and decreased to rates comparable to placebo on successive courses



Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab

De Flon P et al, Neurology 2016



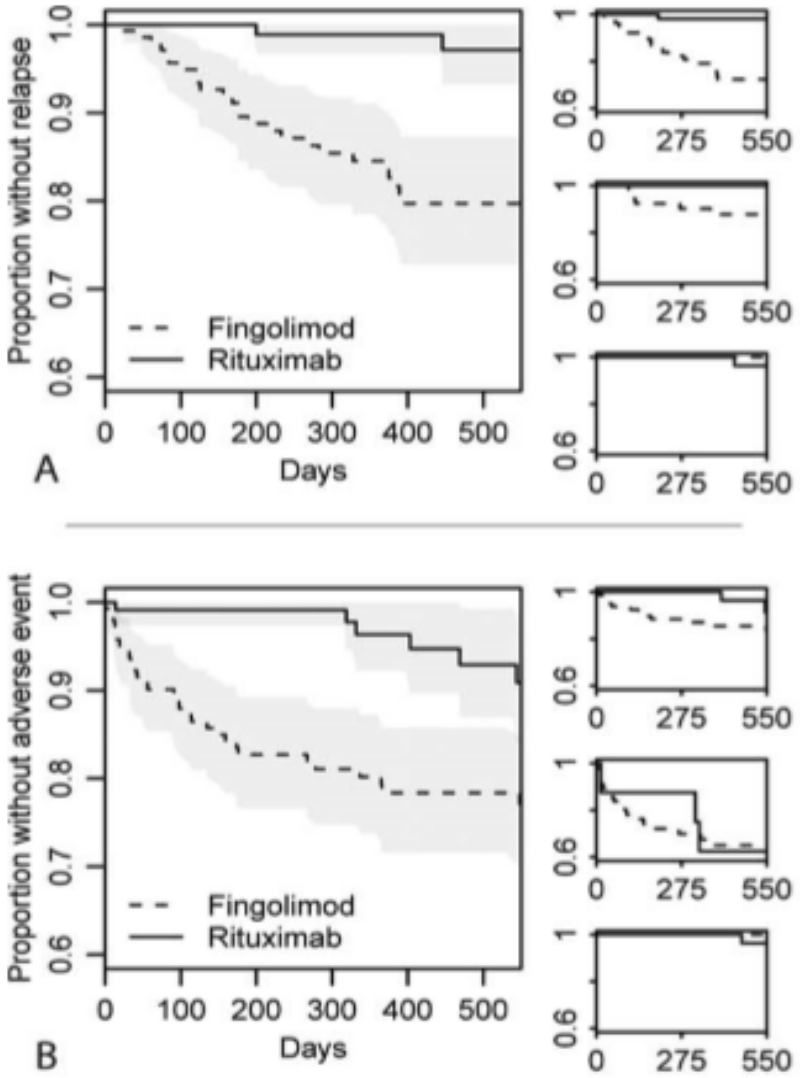


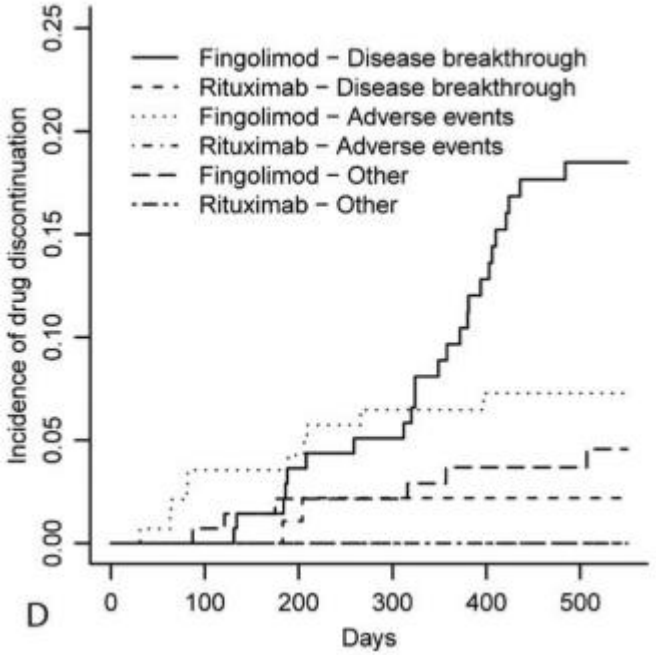
switching treatment in clinically stable patients with RRMS from first-line injectables to rituximab was followed by a superior control of MRI-based inflammatory activity during the subsequent year. Furthermore, there was a significant reduction in the CSF levels of the axonal injury marker NFL after therapy switch, indicating that rituximab treatment may yield a better protection from irreversible CNS damage than IFN/GA

Rituximab versus Fingolimod after Natalizumab in Multiple Sclerosis Patients

Peter Alping,[1] Thomas Frisell, PhD,[2] Lenka Novakova, MD,[4] Protik Islam-Jakobsson, MD,[5] Jonatan Salzer, MD, PhD,[5] Anna Björck, MD,[1] Markus Axelsson, MD, PhD,[4] Clas Malmeström, MD, PhD,[4] Katharina Fink, MD,[1] Jan Lycke, MD, PhD,[4] Anders Svenningsson, MD, PhD,[3,5] and Fredrik Piehl, MD, PhD[1]

Annal Neurol 2106





During the first 1.5 years of treatment:

GD+ LESIONS

- ✓ 1 pt (1%) in the RTX group
- ✓ 23 pt (16%) in the FGL group

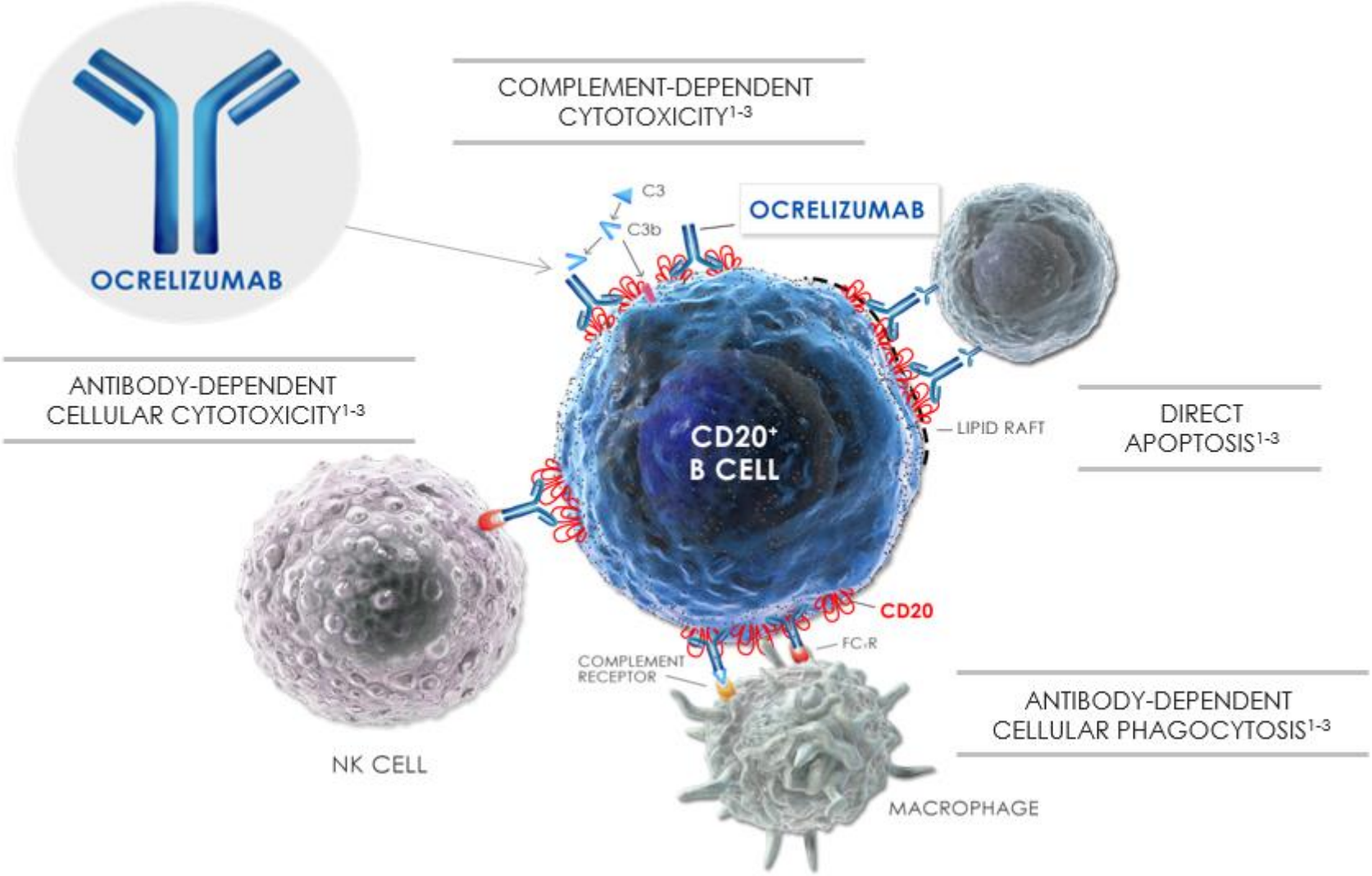
RELAPSES

- ✓ 2 pt (2%) in the RTX group (ARR 0.02)
- ✓ 25 (18%) in the FGL group (ARR 0.16)

ADVERSE EVENTS

- ✓ 6 (5%) in the RTX group
- ✓ 30 (21%) in the FGL group

OCRELIZUMAB

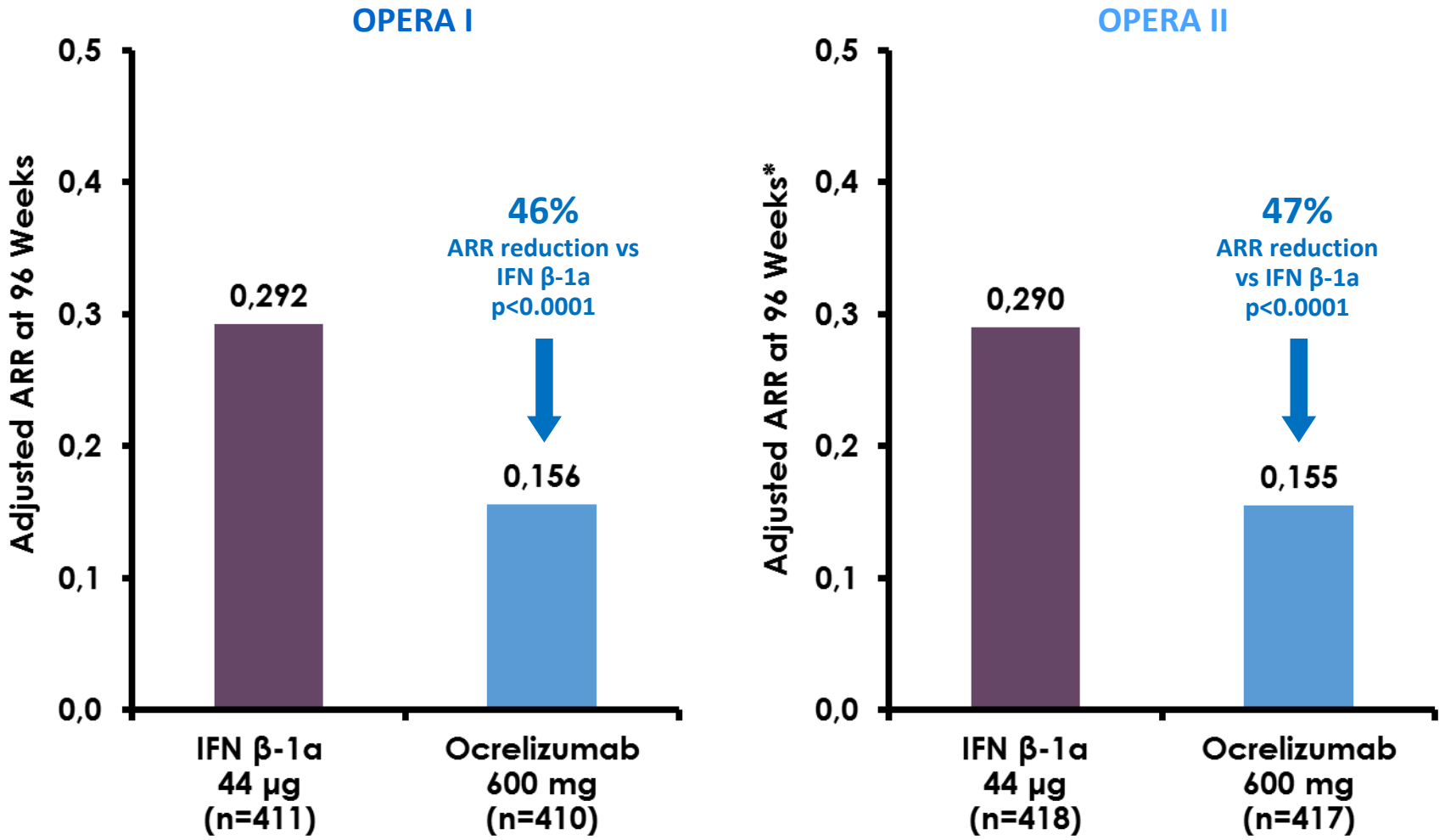


OPERA I and OPERA II: OCRELIZUMAB COMPARED TO IFN B-1A in RMS, age 18–55 years, ≥2 clinical relapse within last 2 years, or 1 clinical relapse in last year, EDSS=0.0–5.5

	OPERA I		OPERA II	
	IFN β-1a 44 µg n=411	Ocrelizumab 600 mg n=410	IFN β-1a 44 µg n=418	Ocrelizumab 600 mg n=417
Age, yr, mean (SD)	36.9 (9.3)	37.1 (9.3)	37.4 (9.0)	37.2 (9.1)
Female, n (%)	272 (66.2)	270 (65.9)	280 (67.0)	271 (65.0)
Time since onset, yr, mean (SD)	6.3 (6.0)	6.7 (6.4)	6.7 (6.1)	6.7 (6.1)
Time since diagnosis, yr, mean (SD)	3.7 (4.6)	3.8 (4.8)	4.1 (5.1)	4.2 (5.0)
Relapses previous 12 months, mean (SD)	1.3 (0.6)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
Previously untreated*, n (%)	292 (71.4)	301 (73.8)	314 (75.3)	304 (72.9)
EDSS, mean (SD)	2.8 (1.3)	2.9 (1.2)	2.8 (1.4)	2.8 (1.3)
Patients with Gd^+ lesions, n (%)	155 (38.1)	172 (42.5)	172 (41.4)	161 (39.0)
Number Gd^+ T1 lesions, mean (SD)	1.9 (5.2)	1.7 (4.2)	2.0 (4.9)	1.8 (5.0)
Number T2 lesions, mean (SD)	51.1 (39.9)	51.0 (39.0)	51.0 (35.7)	49.3 (38.6)

Hauser SL, *et al.* ECTRIMS 2015. Platform presentation 190.

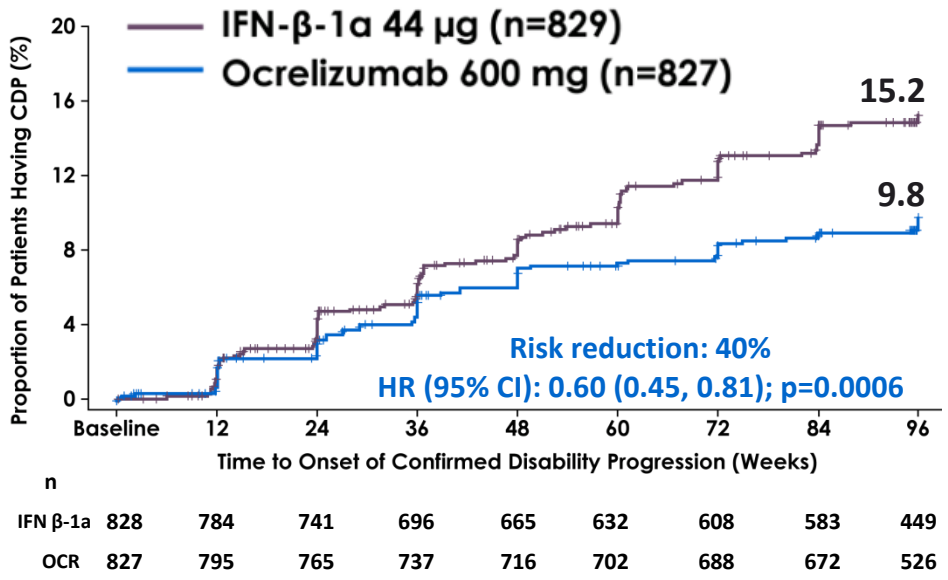
SIGNIFICANT REDUCTION IN ARR COMPARED WITH IFN B-1A



Hauser SL, *et al.* ECTRIMS 2015. Platform presentation 190.

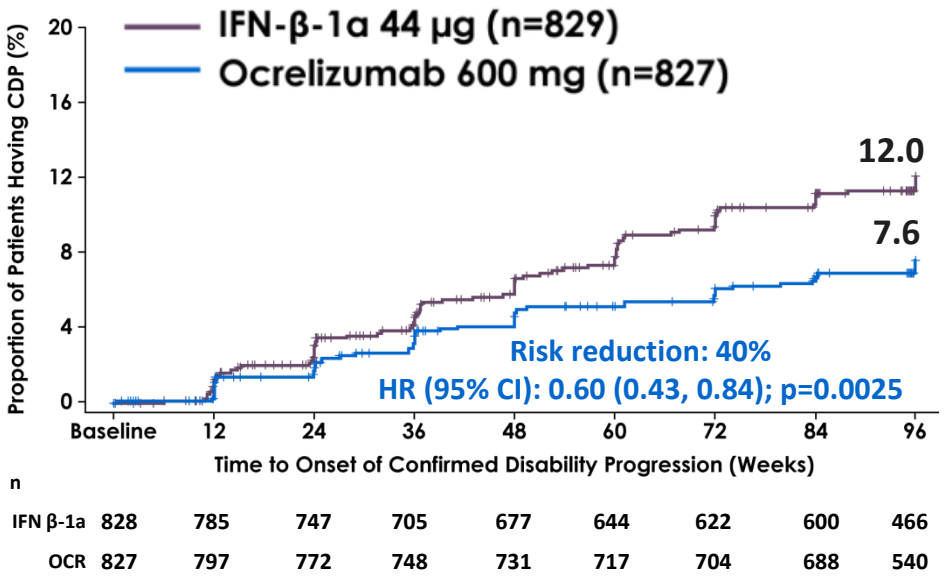
SIGNIFICANT REDUCTION IN CDP

Time to 12-week CDP



n									
IFN β-1a	828	784	741	696	665	632	608	583	449
OCR	827	795	765	737	716	702	688	672	526

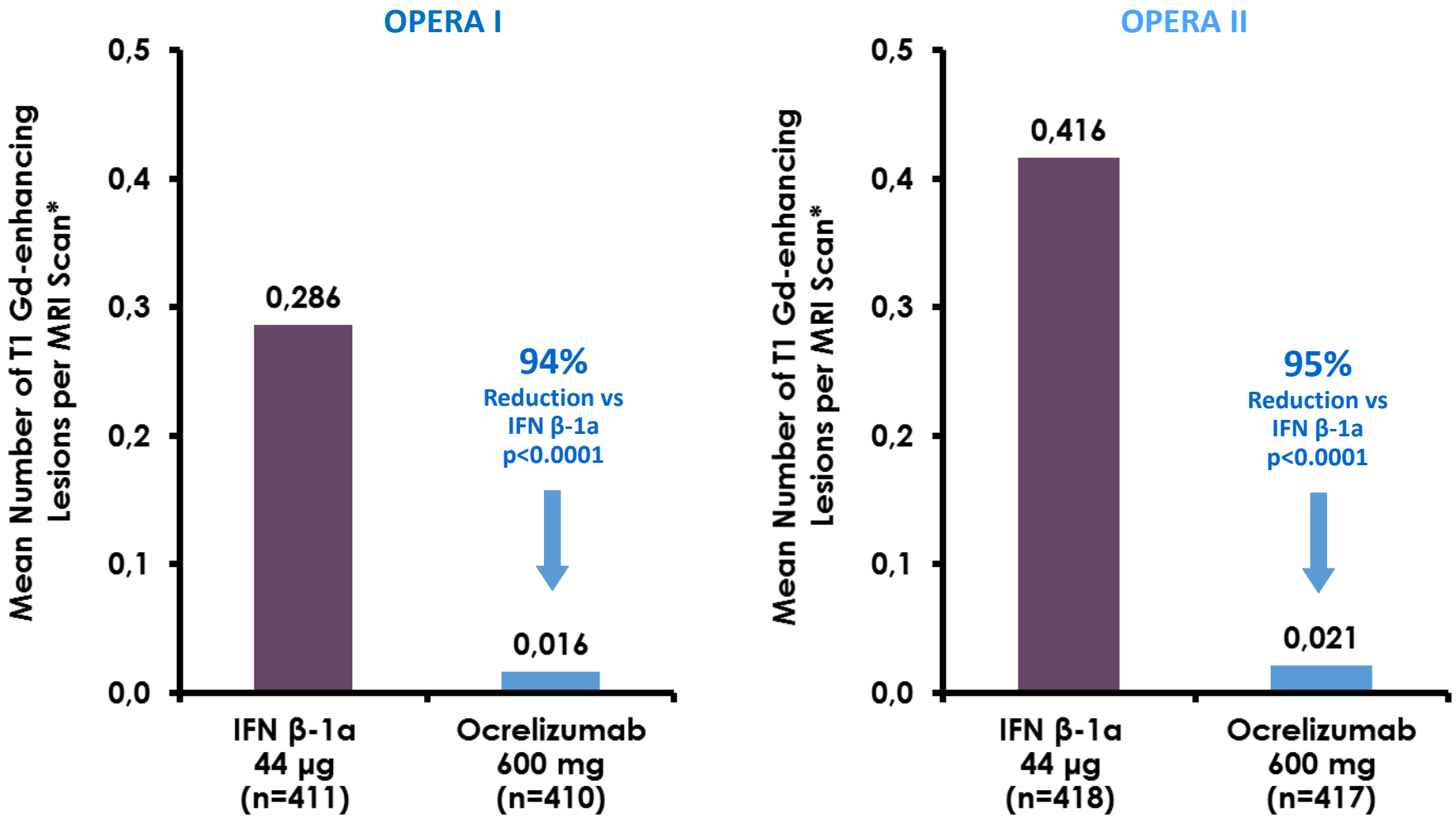
Time to 24-week CDP



n									
IFN β-1a	828	785	747	705	677	644	622	600	466
OCR	827	797	772	748	731	717	704	688	540

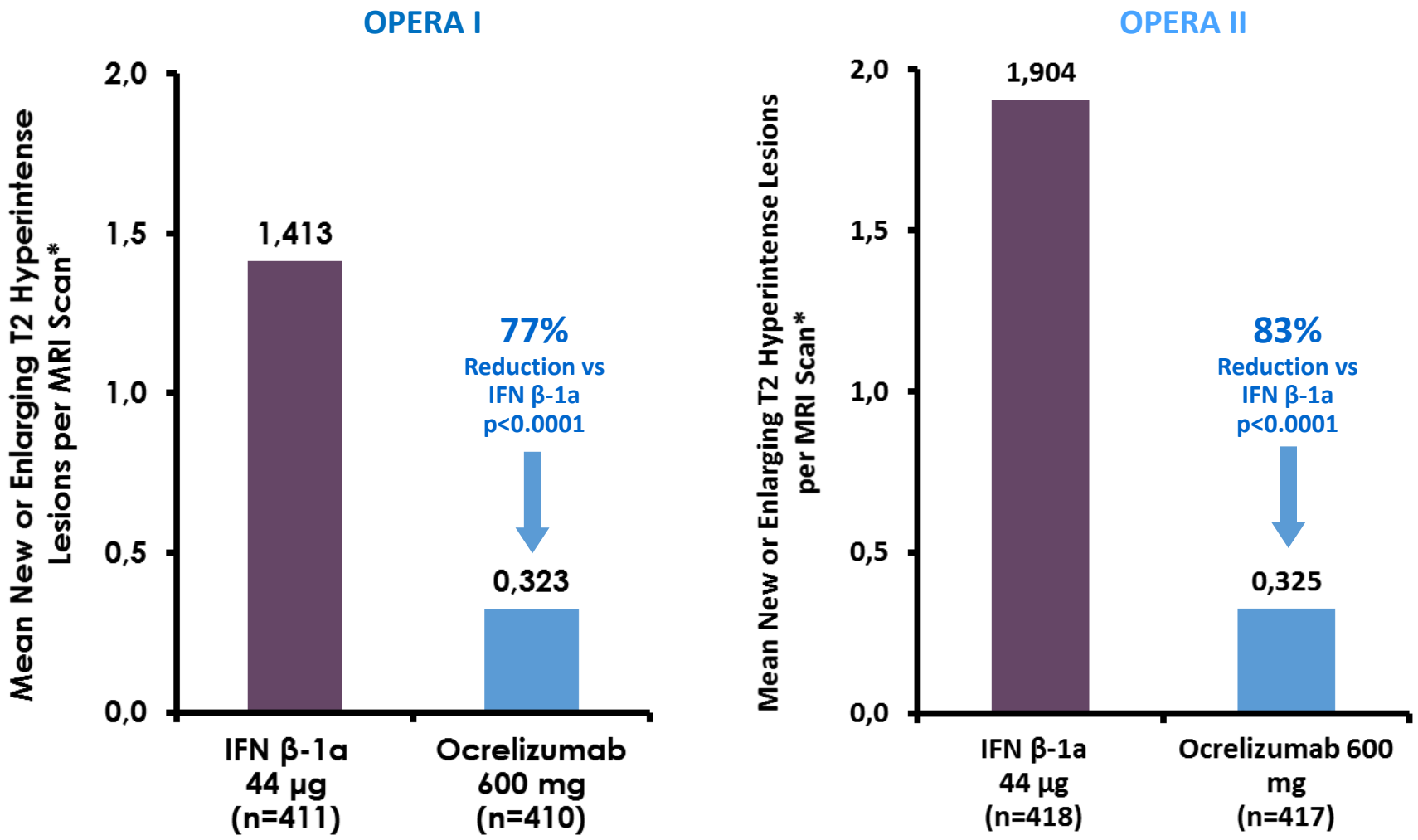
Hauser SL, *et al.* ECTRIMS 2015. Platform presentation 190.

SIGNIFICANT REDUCTION IN NUMBER OF T1 GD+ LESIONS COMPARED WITH IFN B-1A



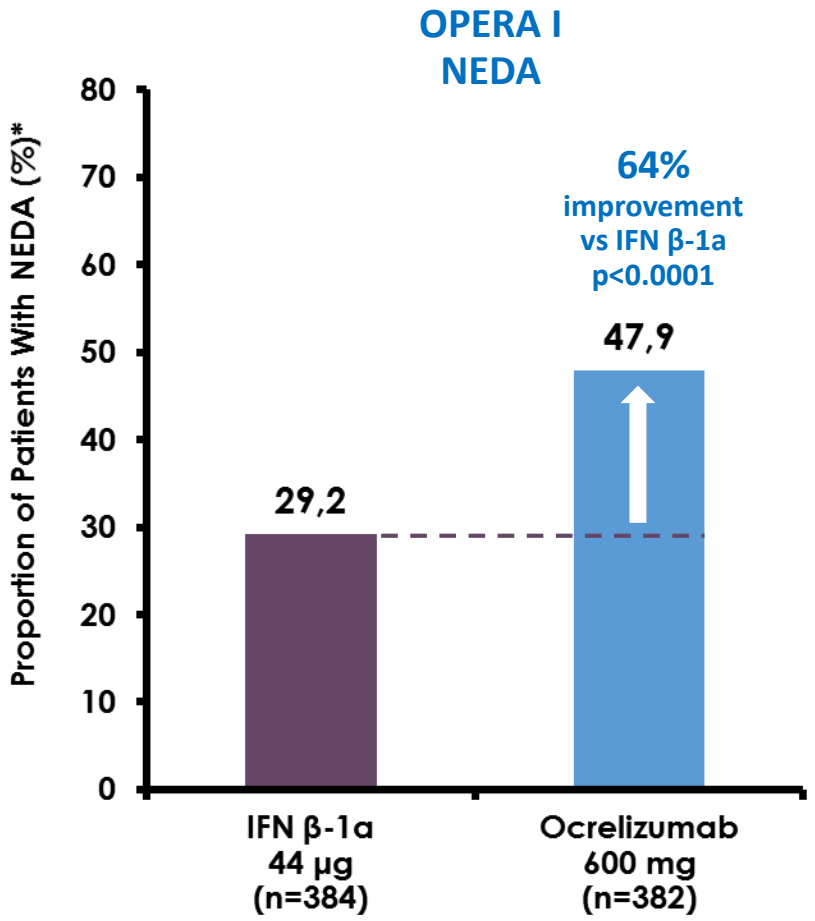
Hauser SL, *et al.* ECTRIMS 2015. Platform presentation 190.

SIGNIFICANT REDUCTION IN NUMBER OF NEW AND/OR ENLARGING T2 HYPERINTENSE LESIONS COMPARED WITH IFN B-1A

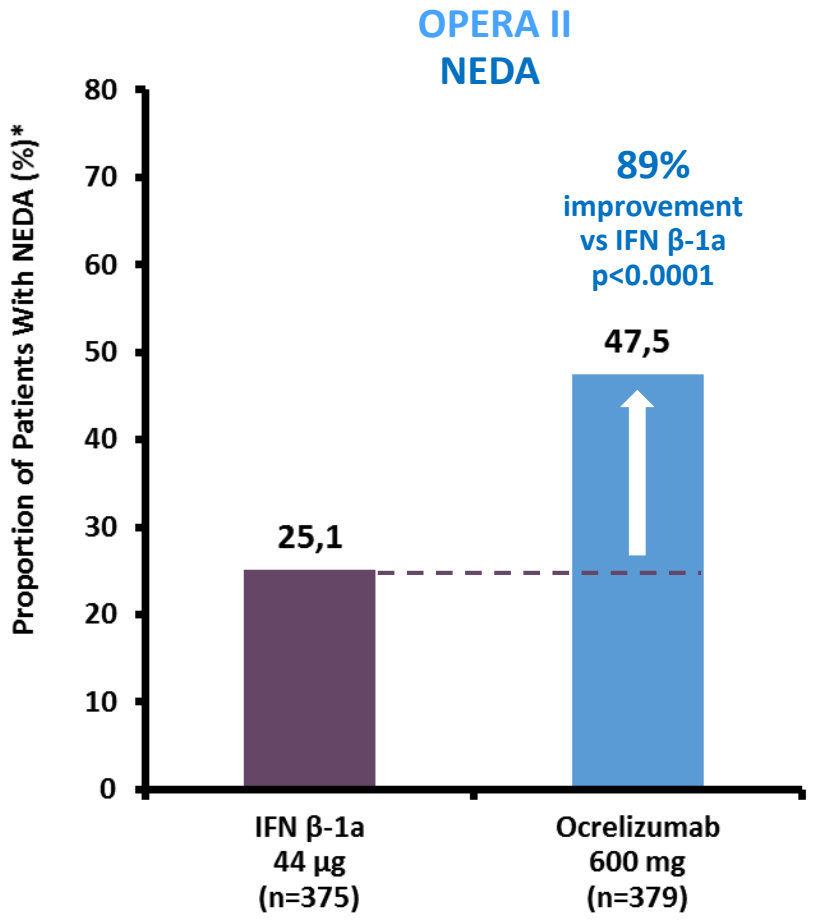


Hauser SL, *et al.* ECTRIMS 2015. Platform presentation 190.

NO EVIDENCE OF DISEASE ACTIVITY (NEDA)



NEDA is defined as: no protocol-defined relapses, no CDP events, no new or enlarging T2 lesions, and no Gd^+ T1 lesions



NEDA is defined as: no protocol-defined relapses, no CDP events, no new or enlarging T2 lesions, and no Gd^+ T1 lesions

Hauser SL, *et al.* ECTRIMS 2015. Platform presentation 190.

ADVERSE EVENTS

n (%)	IFN β-1a 44 µg (n=826)	Ocrelizumab 600 mg (n=825)
Total number of patients with ≥1 AE	**688 (83.3)**	**687 (83.3)**
Total number of patients with ≥1 AE occurring at a frequency ≥5% in either arm	**539 (65.3)**	**544 (65.9)**
Injury, Poisoning and Procedural Complications	**155 (18.8)**	**333 (40.4)**
Infusion-related reaction	80 (9.7)	283 (34.3)
General Disorders and Administration-site Conditions	**396 (47.9)**	**173 (21.0)**
Influenza-like illness	177 (21.4)	38 (4.6)
Injection-site erythema	127 (15.4)	1 (0.1)
Fatigue	64 (7.7)	64 (7.8)
Injection-site reaction	45 (5.4)	2 (0.2)
Infections and Infestations	**433 (52.4)**	**482 (58.4)**
Upper respiratory tract infection	87 (10.5)	125 (15.2)
Nasopharyngitis	84 (10.2)	122 (14.8)
Urinary tract infection	100 (12.1)	96 (11.6)
Sinusitis	45 (5.4)	46 (5.6)
Bronchitis	29 (3.5)	42 (5.1)
Nervous System Disorders	**252 (30.5)**	**224 (27.2)**
Headache	124 (15.0)	93 (11.3)
Psychiatric Disorders	**144 (17.4)**	**149 (18.1)**
Depression	54 (6.5)	64 (7.8)
Insomnia	38 (4.6)	46 (5.6)
Musculoskeletal and Connective Tissue Disorders	**207 (25.1)**	**204 (24.7)**
Back pain	37 (4.5)	53 (6.4)
Arthralgia	51 (6.2)	46 (5.6)

3 DEATHS:

- ✓ IFN β-1a 44 µg arm: suicide, mechanical ileus
- ✓ Ocrelizumab 600 mg arm: suicide

6 MALIGNANCIES:

- ✓ IFN β-1a 44 µg arm: mantle cell lymphoma and squamous cell carcinoma
- ✓ Ocrelizumab 600 mg arm: renal cancer, melanoma and two breast cancers

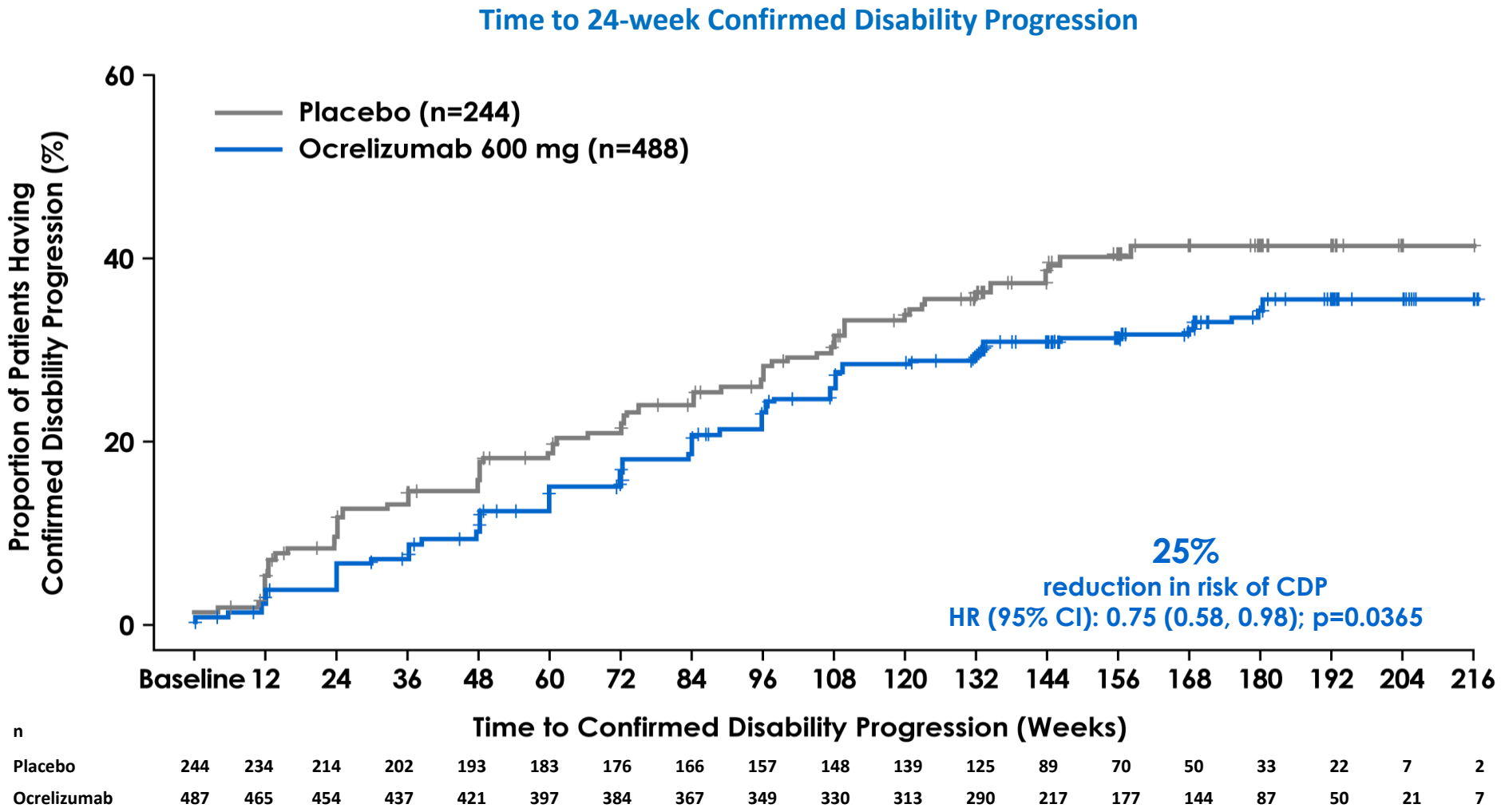
Hauser SL, *et al.* ECTRIMS 2015. Platform presentation 190.

ORATORIO: OCRELIZUMAB COMPARED TO PLACEBO in PPMS, EDSS 3-6.5, age 18-55 years, CSF elevated IgG index or >1 OCB

	Placebo n=244	Ocrelizumab 600 mg n=488
Age, yr, mean (SD)	44.4 (8.3)	44.7 (7.9)
Female, n (%)	124 (50.8)	237 (48.6)
Time since symptom onset, yr, mean (SD)	6.1 (3.6)	6.7 (4.0)
Time since diagnosis, yr, mean (SD)	2.8 (3.3)	2.9 (3.2)
MS disease-modifying treatment naive, n (%)	214 (87.7)	433 (88.7)
EDSS, mean (SD)	4.7 (1.2)	4.7 (1.2)
MRI		
Patients with Gd^+ lesions, n (%)	60 (24.7)	133 (27.5)
Number of Gd^+ T1 lesions, mean (SD)	0.6 (1.6)	1.2 (5.1)
T2 lesion volume, cm^3, mean (SD)	10.9 (13.0)	12.7 (15.1)
Normalised brain volume, cm^3, mean (SD)	1469.9 (88.7)	1462.9 (83.9)

Montalaban X, *et al.* ECTRIMS 2015. Platform presentation 228.

SIGNIFICANT REDUCTION IN 24-WEEK CDP



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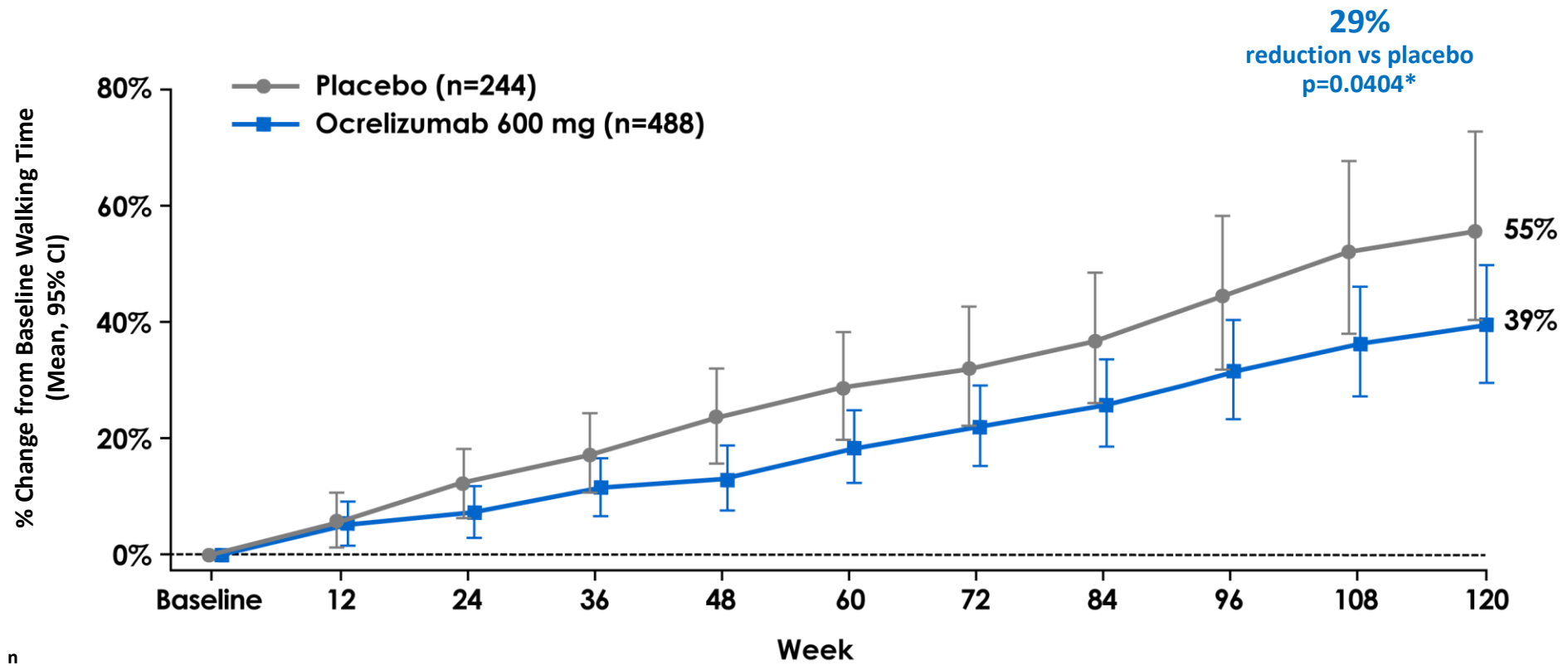
SIGNIFICANT REDUCTION IN THE PROGRESSION RATE OF WALKING TIME

Percent Change in Timed 25-Foot Walk From Baseline to Week 120



n											
Placebo	239	233	228	230	218	211	207	196	190	180	174
Ocrelizumab	473	460	454	454	450	435	432	425	419	412	397

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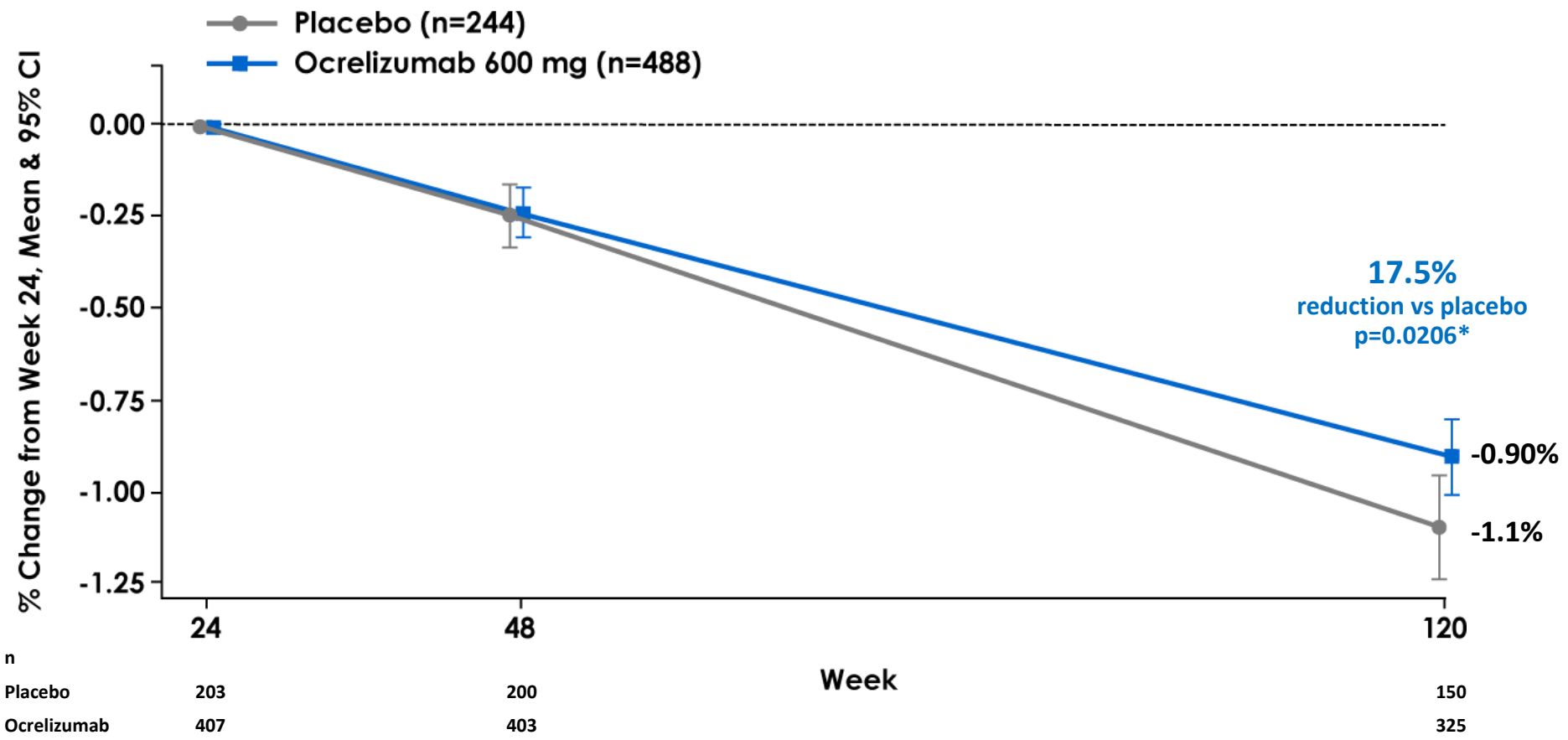
SIGNIFICANT REDUCTION IN THE RATE OF WHOLE BRAIN VOLUME LOSS

Percent Change of Whole Brain Volume from Week 24 to Week 120



Montalaban X, *et al.* ECTRIMS 2015. Platform presentation 228.

ADVERSE EVENTS

n (%)	Placebo (n=239)	Ocrelizumab 600 mg (n=486)
Overall patients with ≥1 AE	215 **(90.0)**	462 **(95.1)**
Infections and Infestations*	162 **(67.8)**	339 **(69.8)**
Nasopharyngitis	65 **(27.2)**	110 **(22.6)**
Urinary tract infection	54 **(22.6)**	96 **(19.8)**
Influenza	21 **(8.8)**	56 **(11.5)**
Upper respiratory tract infection	14 **(5.9)**	53 **(10.9)**
Bronchitis	12 **(5.0)**	30 **(6.2)**
Gastroenteritis	12 **(5.0)**	20 **(4.1)**
Injury, Poisoning and Procedural Complications	104 **(43.5)**	263 **(54.1)**
Musculoskeletal and Connective Tissue Disorders	98 **(41.0)**	181 **(37.2)**
Nervous System Disorders	79 **(33.1)**	174 **(35.8)**
General Disorders and Administration-site Conditions	60 **(25.1)**	130 **(26.7)**
Gastrointestinal Disorders	60 **(25.1)**	126 **(25.9)**
Psychiatric Disorders	59 **(24.7)**	89 **(18.3)**
Skin and Subcutaneous Tissue Disorders	44 **(18.4)**	99 **(20.4)**
Respiratory, Thoracic and Mediastinal Disorders	35 **(14.6)**	87**(17.9)**
Metabolism and Nutrition disorders	28 **(11.7)**	56 **(11.5)**
Renal and Urinary Disorders	30 **(12.6)**	51 **(10.5)**
Vascular Disorders	26 **(10.9)**	54 **(11.1)**
Investigations	20 **(8.4)**	58 **(11.9)**

<u>5 DEATHS:</u>

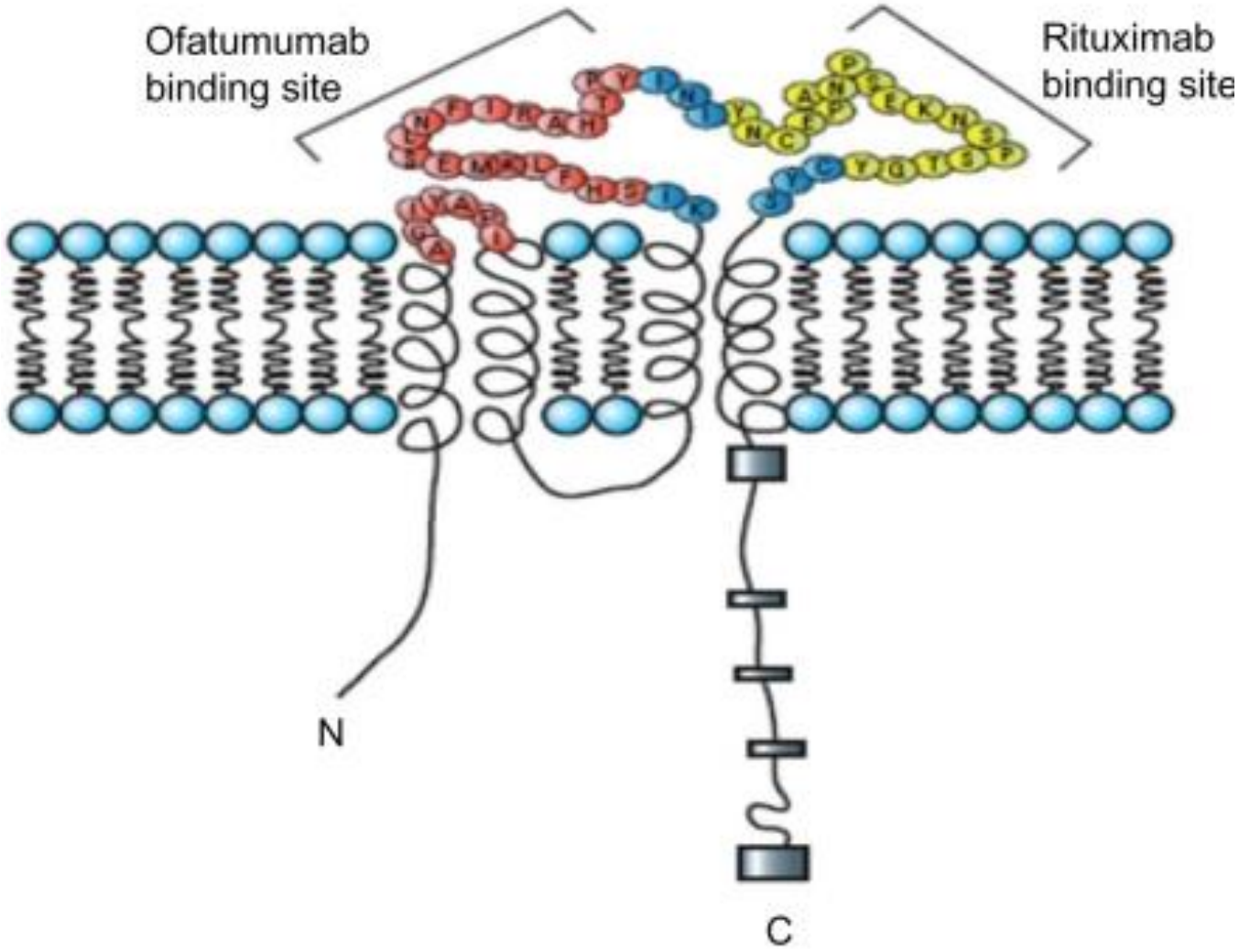
- ✓ 1 (0.4%) in the placebo arm: road traffic accident
- ✓ 4 (0.8%) in the ocrelizumab arm: pulmonary embolism, pneumonia, pancreas carcinoma, pneumonia aspiration

<u>13 MALIGNANCIES :</u>

- ✓ 2 (0.8%) in the placebo arm: one cervix adenocarcinoma in situ and one basal cell carcinoma
- ✓ 11 (2.3%) in the ocrelizumab arm: four breast cancers, one endometrial adenocarcinoma, one anaplastic lymphoma, one histiocytoma, one metastatic pancreas cancer, and three basal cell carcinomas

Montalaban X, *et al.* ECTRIMS 2015. Platform presentation 228.

OFANTUMUMAB



Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis

A phase 2 study

38 RRMS patients receiving two ofatumumab intravenous infusions (100, 300 or 700 mg) or placebo 2 weeks apart, showed a substantial *reduction of new brain MRI lesion activity (>99%) in the first 24 weeks* after ofatumumab administration (all doses), as well as significant reductions of new T1 Gd+ lesions, total Gd+ and new and enlarged T2 lesions (*none of the patients in the 700-mg group had any MRI lesions*)

During weeks 0–24, relapses in 5 patients *(19%) who received ofatumumab* and 3 *(25%) who received placebo.*
During weeks 24–48, relapse was documented in one additional patient who initially received ofatumumab, none of the 12 patients receiving ofatumumab in the second period experienced a relapse.

No unexpected safety concerns (infusion reactions, infections, rash, erythema, throat irritation, fatigue and flushing)

Table 3 MRI endpoints summary

	Weeks 8–24							
	100 mg		300 mg		700 mg		Total	
Treatment at weeks 0–24	Ofatumumab (n = 8)	Placebo (n = 4)	Ofatumumab (n = 11)	Placebo (n = 4)	Ofatumumab (n = 7)	Placebo (n = 4)	Ofatumumab (n = 26)	Placebo (n = 12)
No. of new T1 GdE lesions	0.13[a] (0.35)	3.06 (4.66)	0.0[b] (0.0)	23.50 (43.03)	0.0[a] (0.0)	2.50 (3.32)	0.04[b,c] (0.20)	9.69 (24.86)
No. of total T1 GdE lesions	0.13[a] (0.35)	3.63 (5.02)	0.09[a] (0.30)	25.75 (46.23)	0.0[a] (0.0)	4.50 (7.14)	0.08[b,c] (0.27)	11.29 (26.79)
No. of new and/or enlarging T2 lesions	0.25[a] (0.71)	4.00 (6.52)	0.09[a] (0.30)	25.00 (46.03)	0.0[a] (0.0)	3.00 (4.24)	0.12[b,c] (0.43)	10.67 (26.58)
No. of new T1 hypointense lesions	0.0 (0.0)	1.50 (3.00)	0.27 (0.47)	5.00 (9.35)	0.29 (0.49)	0.25 (0.50)	0.19 (0.40)	2.25 (5.55)
Percentage change (SD) in volume of T2 lesions[d]	−4.7 (9.6)	7.6 (4.5)	−3.1 (6.3)	24.9 (13.4)	−0.9 (4.1)	−1.0 (2.0)	−3.0 (7.0)	11.0 (14.0)
	Weeks 32–48							
	100 mg		300 mg		700 mg		Total	
Treatment at weeks 24–48	Placebo (n = 8)	Ofatumumab (n = 4)	Placebo (n = 11)	Ofatumumab (n = 4)	Placebo (n = 7)	Ofatumumab (n = 4)	Placebo (n = 26)	Ofatumumab (n = 26)
No. of new T1 GdE lesions	0.13 (0.35)	0.0 (0.0)	0.0 (0.0)	0.33 (0.58)	0.29 (0.76)	0.0 (0.0)	0.12 (0.44)	0.09 (0.30)
No. of total T1 GdE lesions	0.13 (0.35)	0.0 (0.0)	0.0 (0.0)	3.00 (5.20)	0.43 (1.13)	0.0 (0.0)	0.16 (0.62)	0.82 (2.71)
No. of new and/or enlarging T2 lesions	0.13 (0.35)	0.0 (0.0)	0.0 (0.0)	0.33 (0.58)	0.29 (0.76)	0.0 (0.0)	0.12 (0.44)	0.09 (0.30)
No. of new T1 hypointense lesions	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	3.00 (4.36)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.82 (2.40)

- ✓Induction/early therapy (early B-cell depletion may prevent B cells from forming lymphoid follicle-like structures in the CNS meninges)?
- ✓Swicht to maintenance therapy (first-line DMD)?
- ✓How long should B cells therapies be readministered?
- ✓Fixed infusion timing or retreatment guided by B cells recovery?
- ✓Risk of opportunistic infections (PML) in the long-term therapy?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…grazie