Therapeutic Mechanism of Action (MOAs) in MS: Targeting T-and B-cells to Reset the Immune System

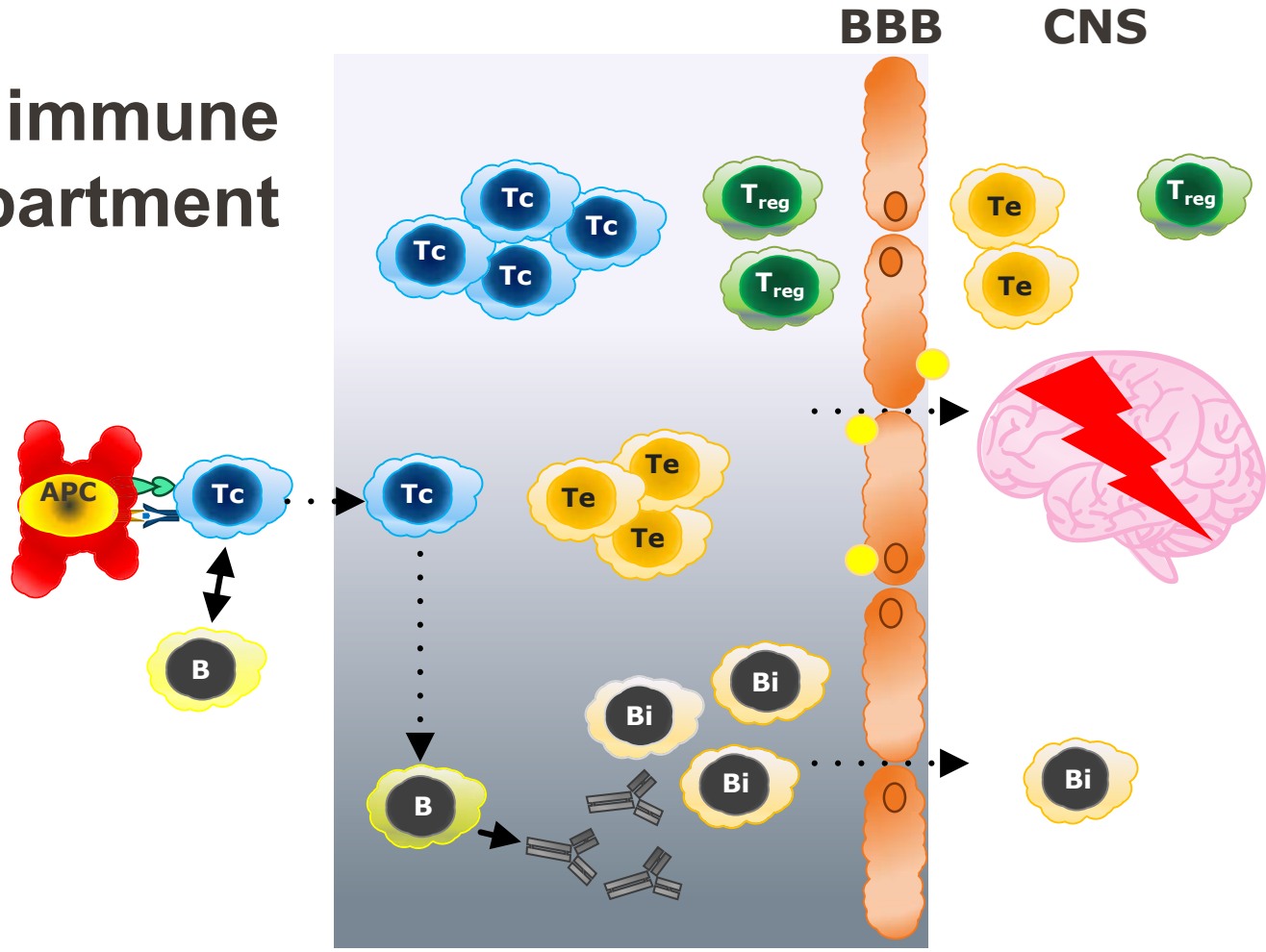
gmsa
Global Multiple Sclerosis Academy

This resource is supported by an educational grant from Merck KGaA, Darmstadt, Germany.

Learning Objectives

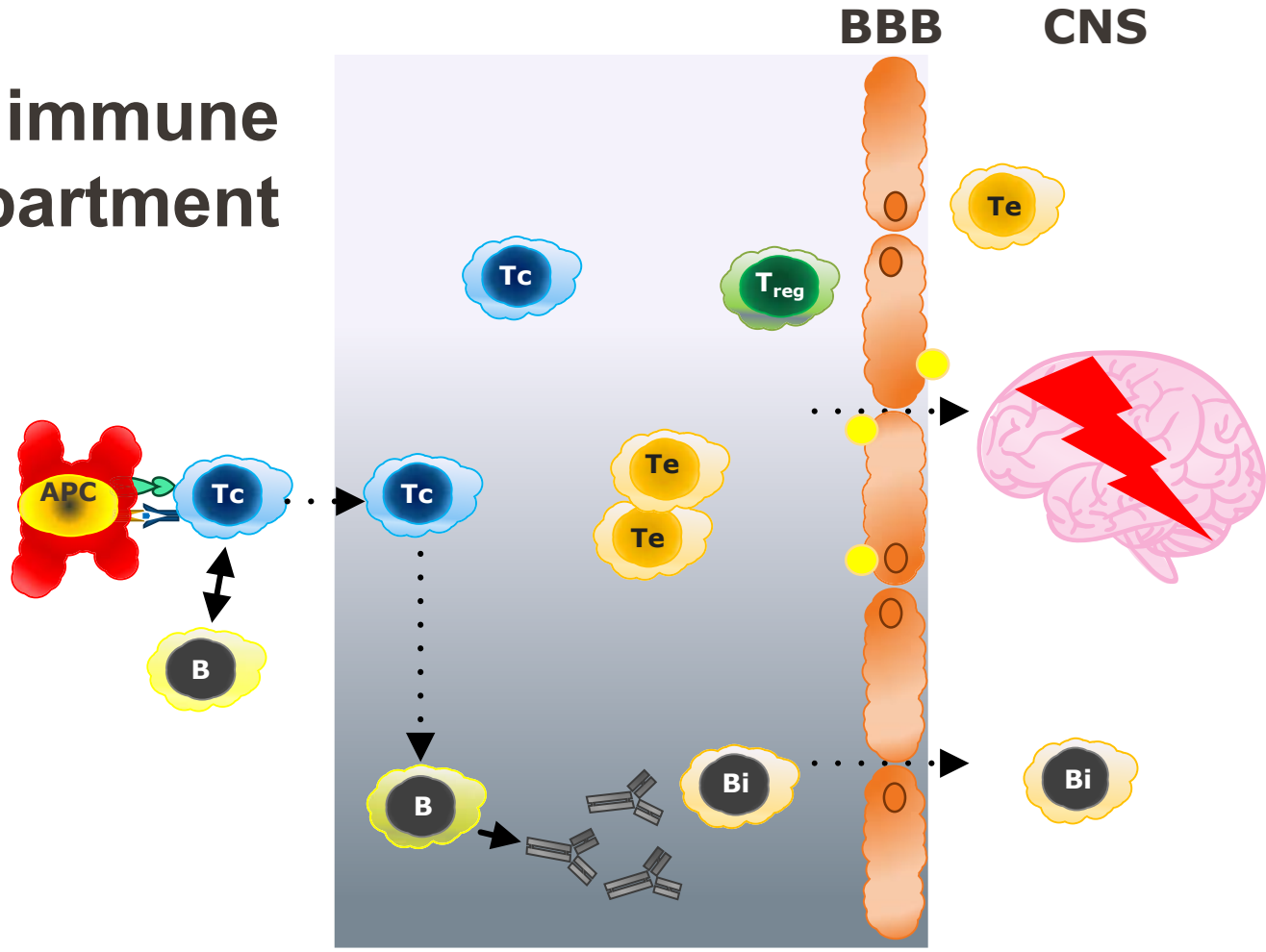
- **Explore emergent concepts in the management of MS, focusing on targeting T- and B-cells including:**
  - Risks associated with continuous immunosuppression
  - Action on the inflammatory activity in the CNS compartment
- **Review the benefit/risk strategies in selecting therapy for MS patients while assessing treatment regimens that carry acceptable or diminished risk of disease progression**
- **Identify strategies that simplify patient dosing and side effects to:**
  - Increase treatment compliance
  - Improve patients' quality of life
  - Slow disease progression

Treatment: Immunomodulation Type



APC, antigen presenting cells; B, B lymphocytes; BBB, blood-brain barrier; Bi, inflammatory B cells; CNS, central nervous system; Tc, T lymphocytes; Te, encephalitogenic T cells; T_{reg}, regulatory T cells. Figure is reproduced with permission from 1. Wiendl H, Kieseier B. *Nat Rev Neurol*. 2013;9:125-126.

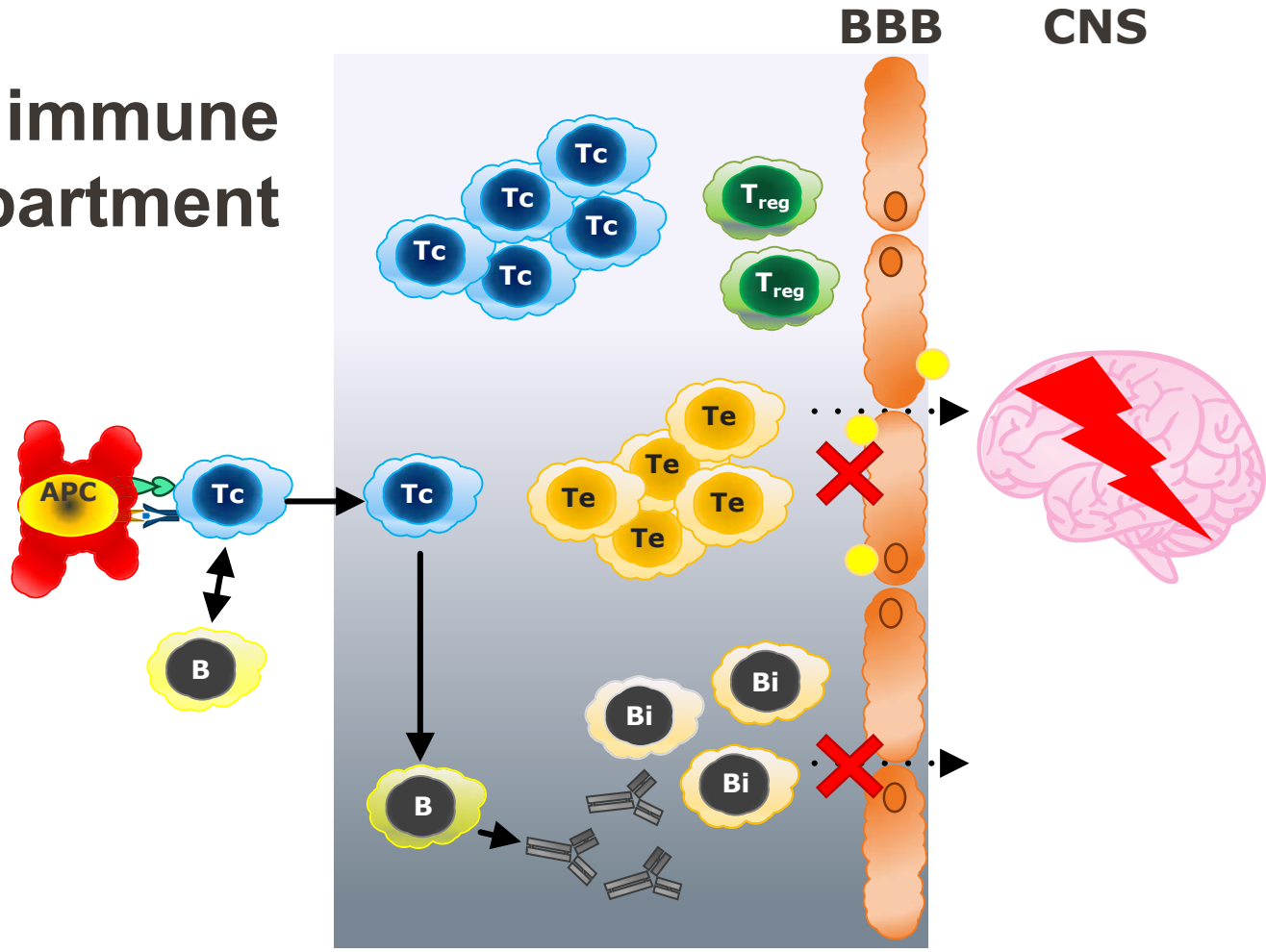
Treatment: General Immunosuppression Type



APC, antigen presenting cells; B, B lymphocytes; BBB, blood-brain barrier; Bi, inflammatory B cells; CNS, central nervous system; Tc, T lymphocytes; Te, encephalitogenic T cells; T_{reg}, regulatory T cells. Figure is reproduced with permission from 1. Wiendl H, Kieseier B. *Nat Rev Neurol*. 2013;9:125-126.

1. Wiendl H, Kieseier B. *Nat Rev Neurol*. 2013;9:125-126; **2.** Cohen JA et al. *N Engl J Med*. 2010;362:402–415.

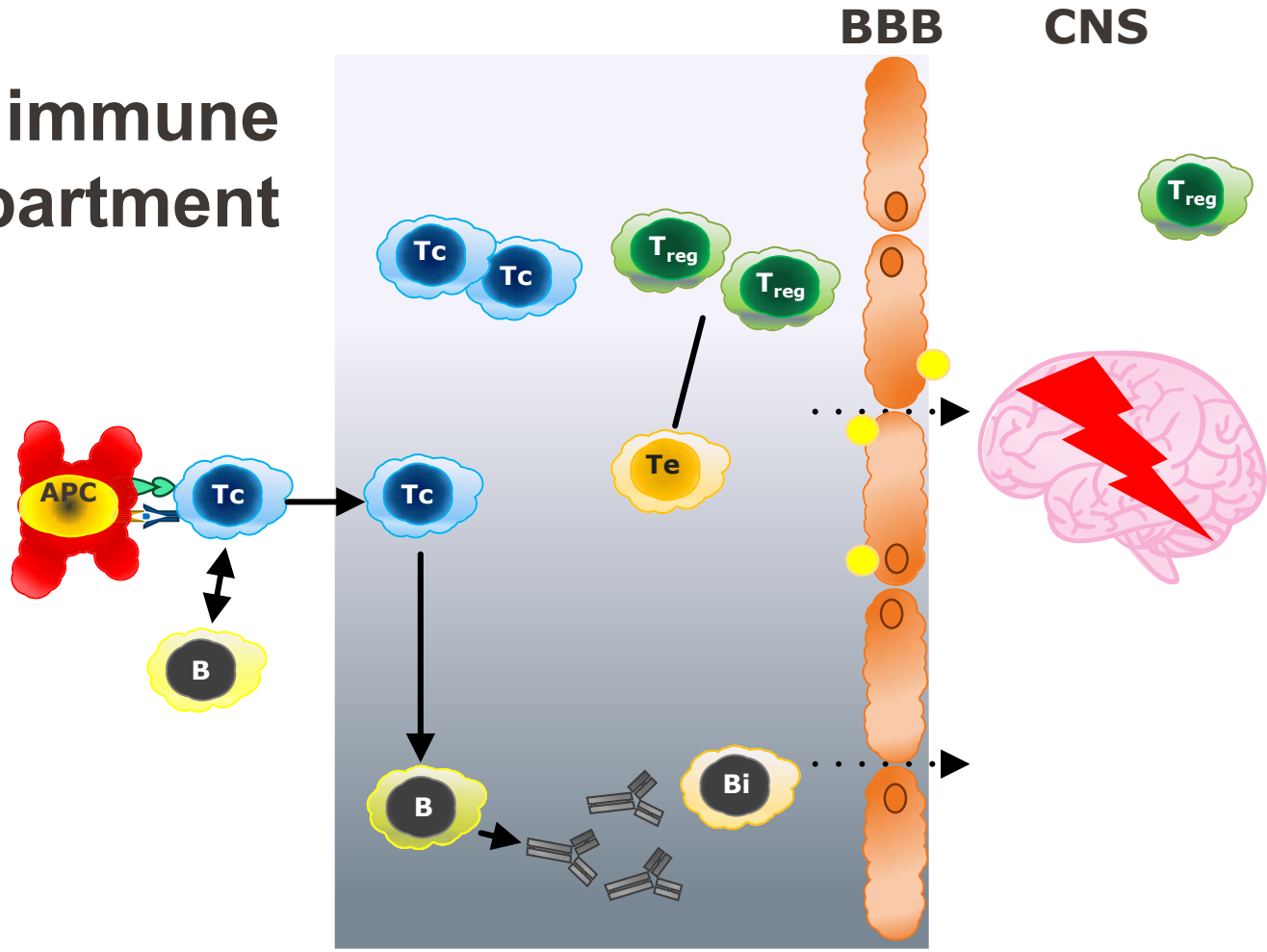
Treatment: Immune-selective Intervention – Blockade Type



APC, antigen presenting cells; B, B lymphocytes; BBB, blood-brain barrier; Bi, inflammatory B cells; CNS, central nervous system; Tc, T lymphocytes; Te, encephalitogenic T cells; T_{reg}, regulatory T cells. Figure is reproduced with permission from 1. Wiendl H, Kieseier B. *Nat Rev Neurol*. 2013;9:125-126.

1. Wiendl H, Kieseier B. *Nat Rev Neurol*. 2013;9:125-126; **2.** Cohen JA et al. *N Engl J Med*. 2010;362:402–415.

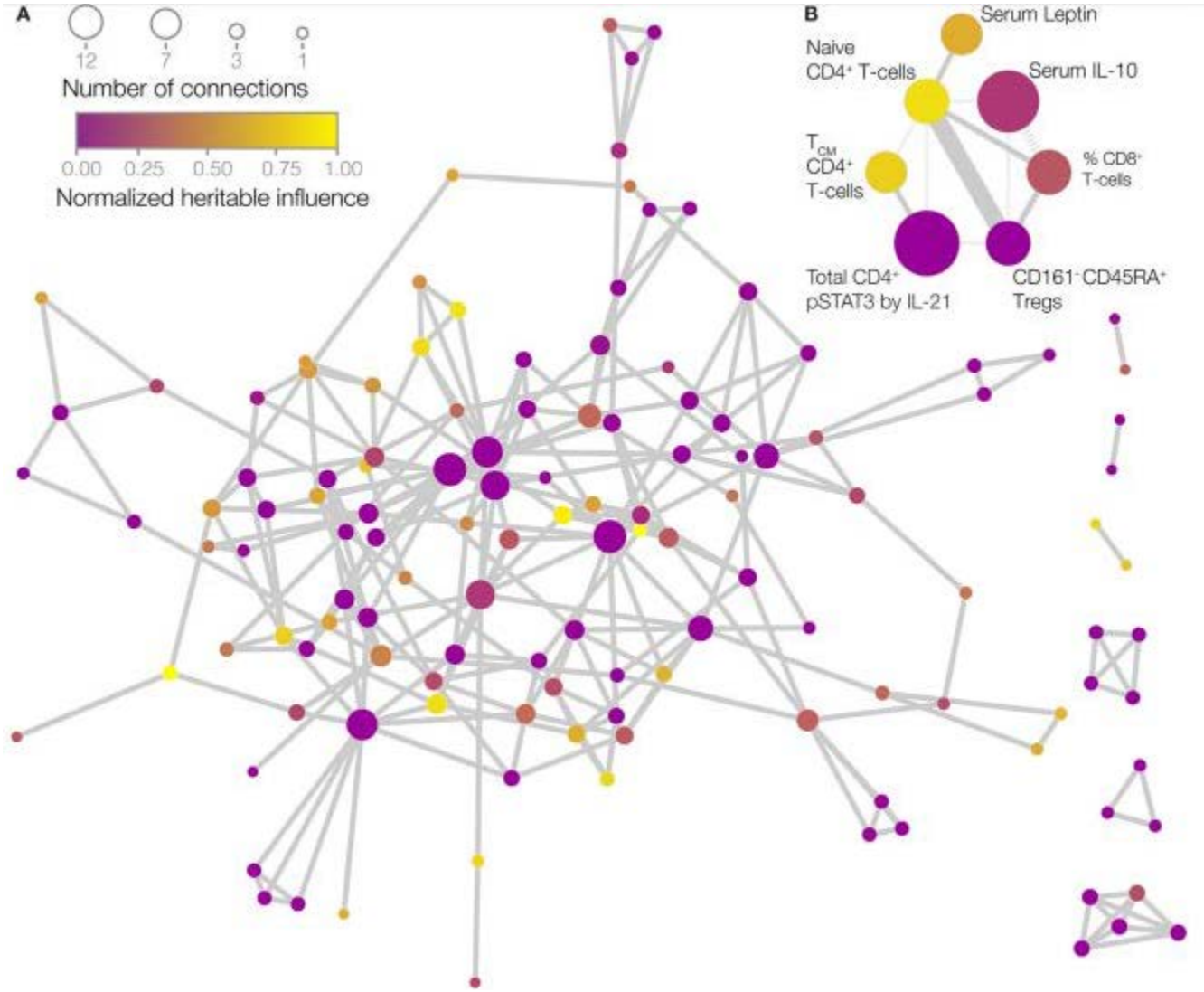
Treatment: Immune-selective Intervention – Depleting Type



[a]These agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. APC, antigen presenting cells; B, B lymphocytes; BBB, blood-brain barrier; Bi, inflammatory B cells; CNS, central nervous system; Tc, T lymphocytes; Te, encephalitogenic T cells; T_{reg}, regulatory T cells. Figure is reproduced with permission from 1. Wiendl H, Kieseier B. *Nat Rev Neurol*. 2013;9:125-126.

1. Wiendl H, Kieseier B. *Nat Rev Neurol*. 2013;9:125-126; **2.** Cohen JA et al. *N Engl J Med*. 2010;362:402–415.

Variation in the Human Immune System is Largely Driven by Non-heritable Influences



Brodin P et al. *Cell*. 2015 Jan 15;160(1-2):37-47.

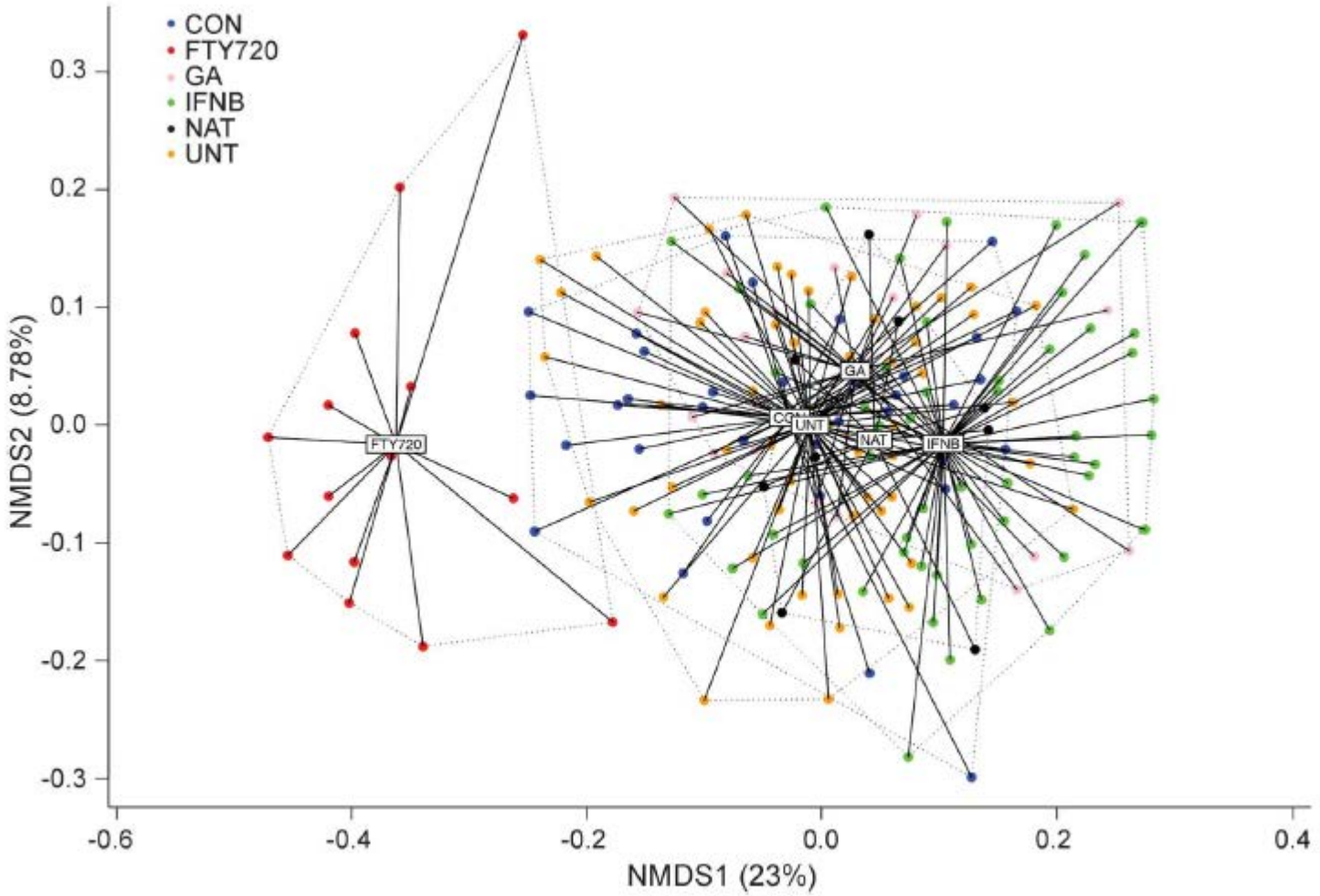
Variation in the Human Immune System is Largely Driven by Non-heritable Influences

- 77% dominated by non-heritable influences
- 58% almost completely determined by external factors
- Parameters become more variable with age - suggesting cumulative influence of environmental exposure
- ***Individualizing treatments becomes more and more necessary***

Brodin P et al. *Cell*. 2015 Jan 15;160(1-2):37-47.

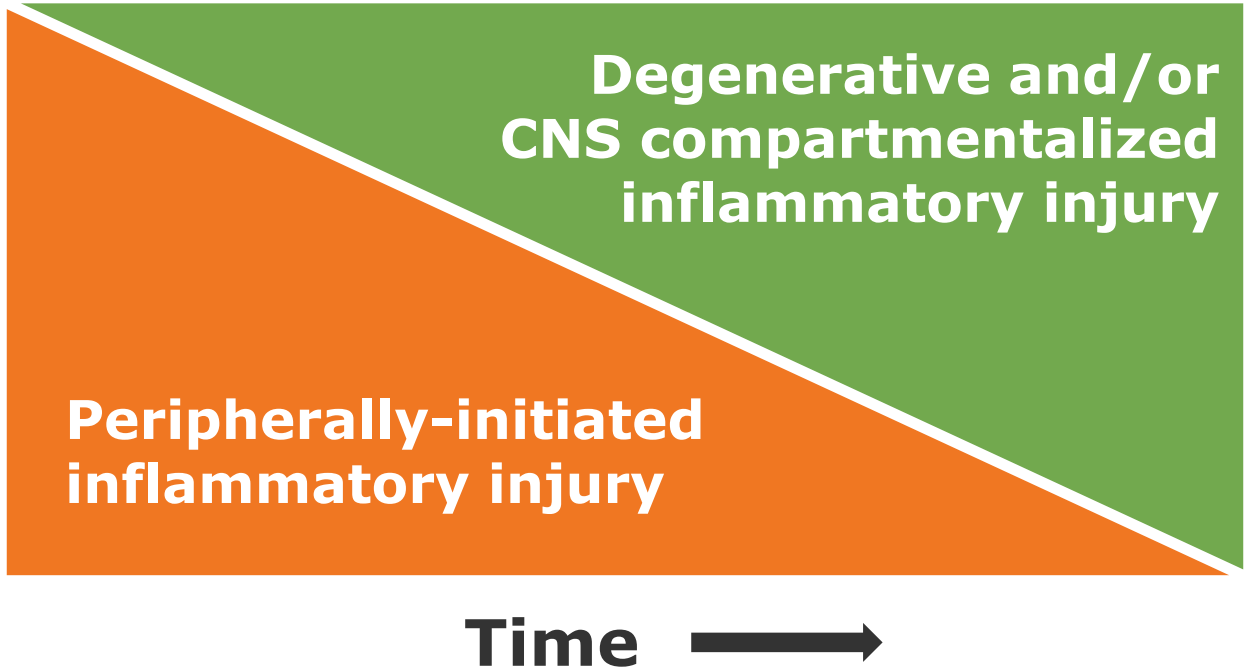
MS Immunomodulatory Treatments

Of the 4 compounds in routine MS treatment, each induced unique constellations of immune deviations, which offers perspectives to the challenge of personalized medicine.



Dooley J et al. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e240.
NMDS1 and 2: Non Metric Multidimensional Scaling
CON = controls; FTY720 = fingolimod; GA = glatiramer acetate; IFNB = immunomodulatory treatments interferon-β; NAT = natalizumab; UNT = untreated

CNS-Compartmentalized Inflammatory Injury Plays a Key Role in MS

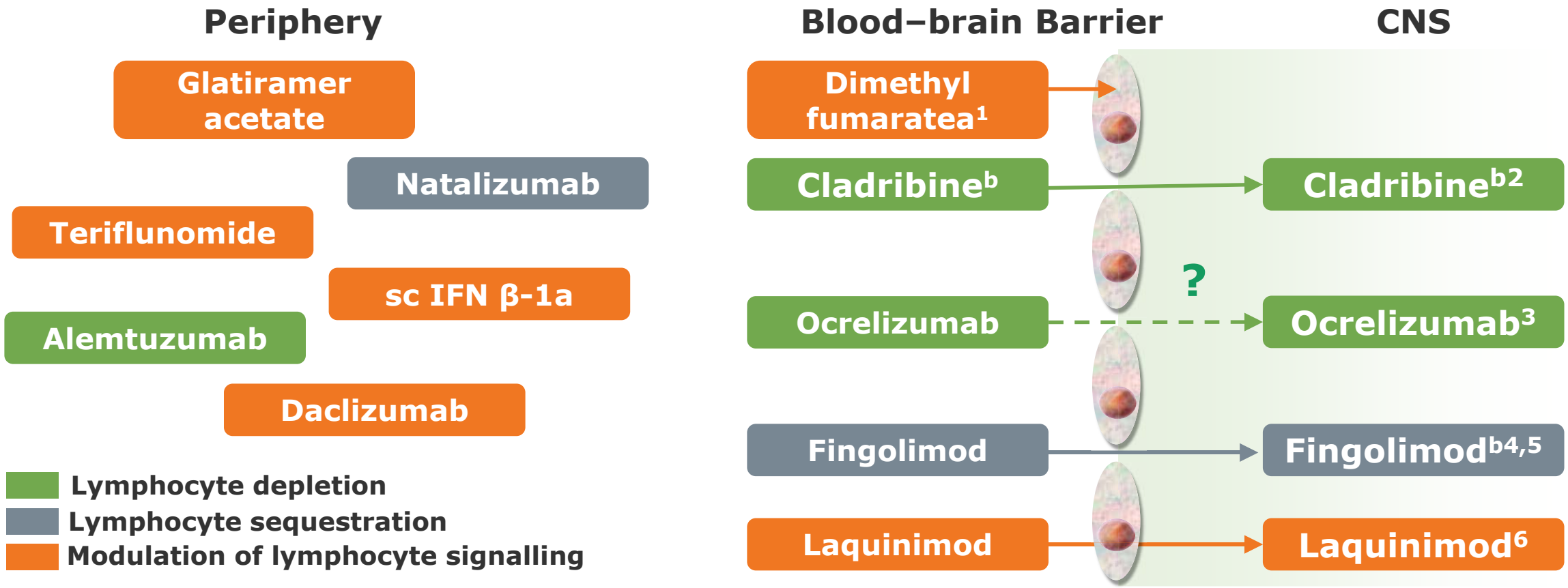


MS therapies vary in their ability to penetrate the blood–brain barrier[2]

CNS, central nervous system

1. Bar-Or A. *Semin Neurol*. 2008;28:29-45; **2.** Cheng Z, et al. *Drug Metab Disposition*. 2010;38:1355–1361.

Is there a need for a MS therapy with evidence of direct action on the inflammatory activity in the CNS compartment?



[a]Preclinical evidence suggests that dimethyl fumarate stabilises the blood-brain barrier. [b]These agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. CNS, central nervous system; IFN, interferon; PI, Prescribing Information; sc, subcutaneous; SmPC, Summary of Product Characteristics. Rebif® EU SmPC; Copaxone® SPC; Aubagio® EU SmPC; Tecfidera® EU SmPC; Tysabri® EU SmPC; Gilenya® EU SmPC; Lemtrada® EU SmPC; Zinbryta® EU SmPC.

1. Kunze R et al. *Exp Neurol*. 2015;266:99–111; **2.** Liliemark J. *Clin Pharmacokinet*. 1997;32:120–31; **3.** Ruhstaller TW et al. *Ann Oncol*. 2000;11:374–375; **4.** Hunter SF et al. *CNS Drugs*. 2016;30:135–147; **5.** Groves A et al. *J Neurol Sci*. 2013;328:9–18; **6.** Brück W, Wegner C. *Neurol Sci*. 2011;306:173–179. Website links available on request.

Risks Associated with Prolonged or Continuous Immunosuppression

T cells and B cells play critical roles in MS, and therapies targeting lymphocytes have a clinical effect[1]

Nature of immunosuppression[2]	Likely infectious agents[2]
Neutrophil deficits	Bacteria
	Fungi
Abnormal T cells or monocytes	Viruses
	Parasites
	Fungi (typically yeast forming)
	Bacteria
Disorders of humoral immunity[3]	Bacteria

1. McFarland HF et al. *Nat Immunol*. 2007;8:913–9; 2. Nath A, Berger JR. Curr Treat Options Neurol 2012;14:241–55. 3. Winkelmann A et al. Clin Exp Immunol 2014;175:425–438.

Phase 3 Trials of DMDs in Progressive MS

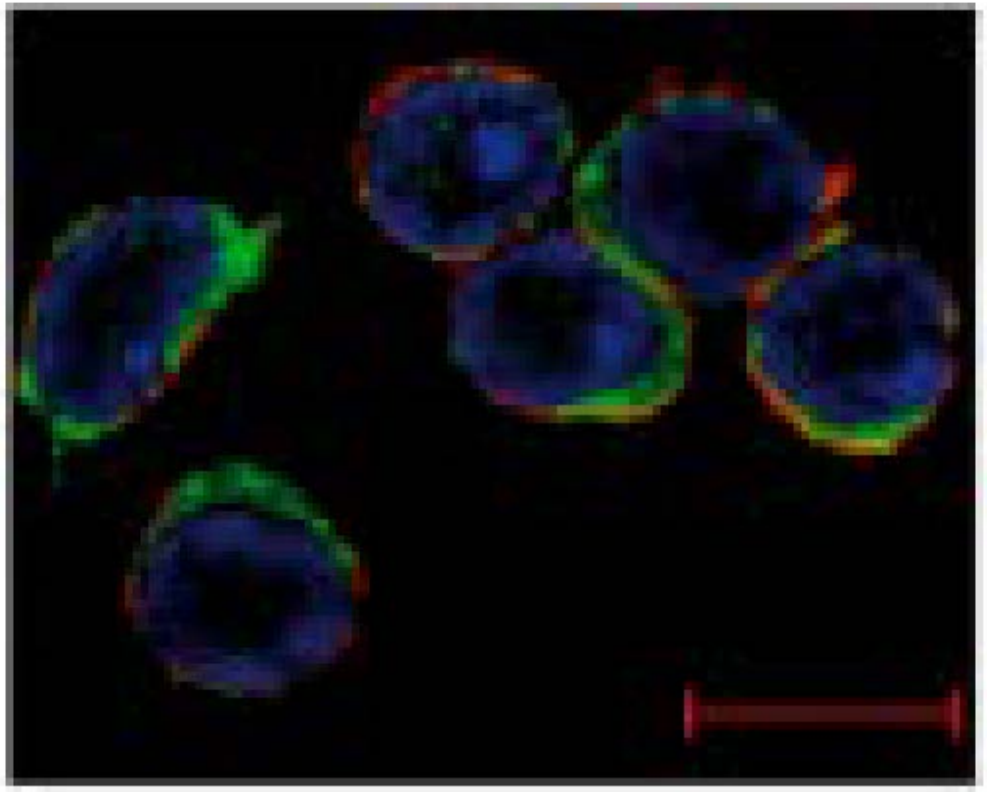
When inflammation is compartmentalized in the CNS, drugs that cannot cross the blood–brain barrier have no significant effect on the disease course[1]

Agent[a]	Type of MS	Duration (years)	Primary outcome	*P* value
Glatiramer acetate[2]	PPMS	3[b]	Time to sustained progression of accumulated disability HR 0.87 (95% CI, 0.71–1.07)	0.1753
Fingolimod[3]	PPMS	3–5	3-month CDP[c] RR 5.05%; HR 0.95 (95% CI, 0.80–1.12)	0.544
Ocrelizumab[4]	PPMS	~3	3-month CDP HR 0.76 (95% CI, 0.59–0.98)	0.0321
Rituximab[5]	PPMS	2	Time to CDP 30.2% (rituximab) vs 38.5% (placebo)	0.1442
Natalizumab[6]	SPMS	2	Patients with CDP on ≥1 of EDSS, T25FW or 9HPT 44% vs 48%; OR 0.86 (95% CI, 0.66–1.13)	0.287
Siponimod	SPMS	Max 3	delay in time to confirmed disability progression as measured by EDSS	0.013

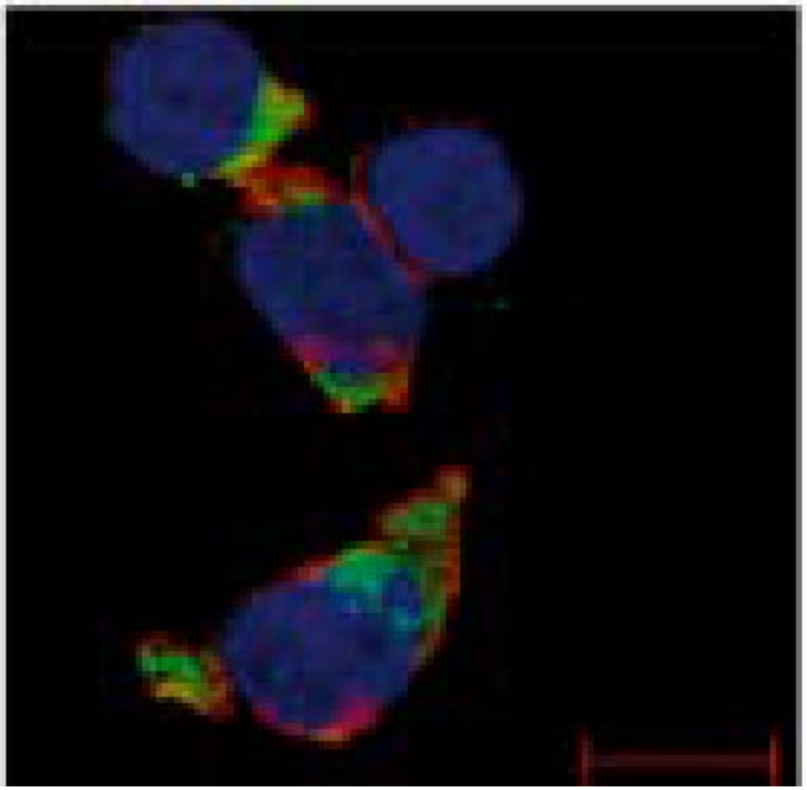
No data are available for teriflunomide, dimethyl fumarate, alemtuzumab, daclizumab or cladribine tablets in PMS. [a]Agents not approved anywhere in the world for use in progressive MS; [b]Terminated early for non-efficacy reasons. [c]Composite endpoint including change in EDSS, 9HPT and T25WT. 9HPT, 9-hole peg test; CDP, confirmed disability progression; CI, confidence interval; CNS, central nervous system; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OR, odds ratio; PPMS, primary progressive MS; RR, risk reduction; SPMS, secondary progressive MS; T25FW, timed 25-foot walk test.

1. Perez-Cerda F et al. *Multi Scl Demylin Dis*. 2016;2016:1–9; **2.** Wolinsky JS et al. *Ann Neurol*. 2007;61:14–24; **3.** Lublin F et al. *Lancet*. 2016; 387:1075-1084; **4.** Montalban X et al. *Neurology*. 2016;86(Suppl 16):S49.001; **5.** Hawker K et al. *Ann Neurol*. 2009;66:460–471; **6.** Steiner D et al. Presented at AAN 2016 [P009] Kappos L et al. Efficacy and safety of siponimod in secondary progressive multiple sclerosis – Results of the placebo controlled, double-blind, Phase III EXPAND study. Oral presentation presented at: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis; September 14-17, 2016; London, UK.

The Crucial Role of B-Cells in MS



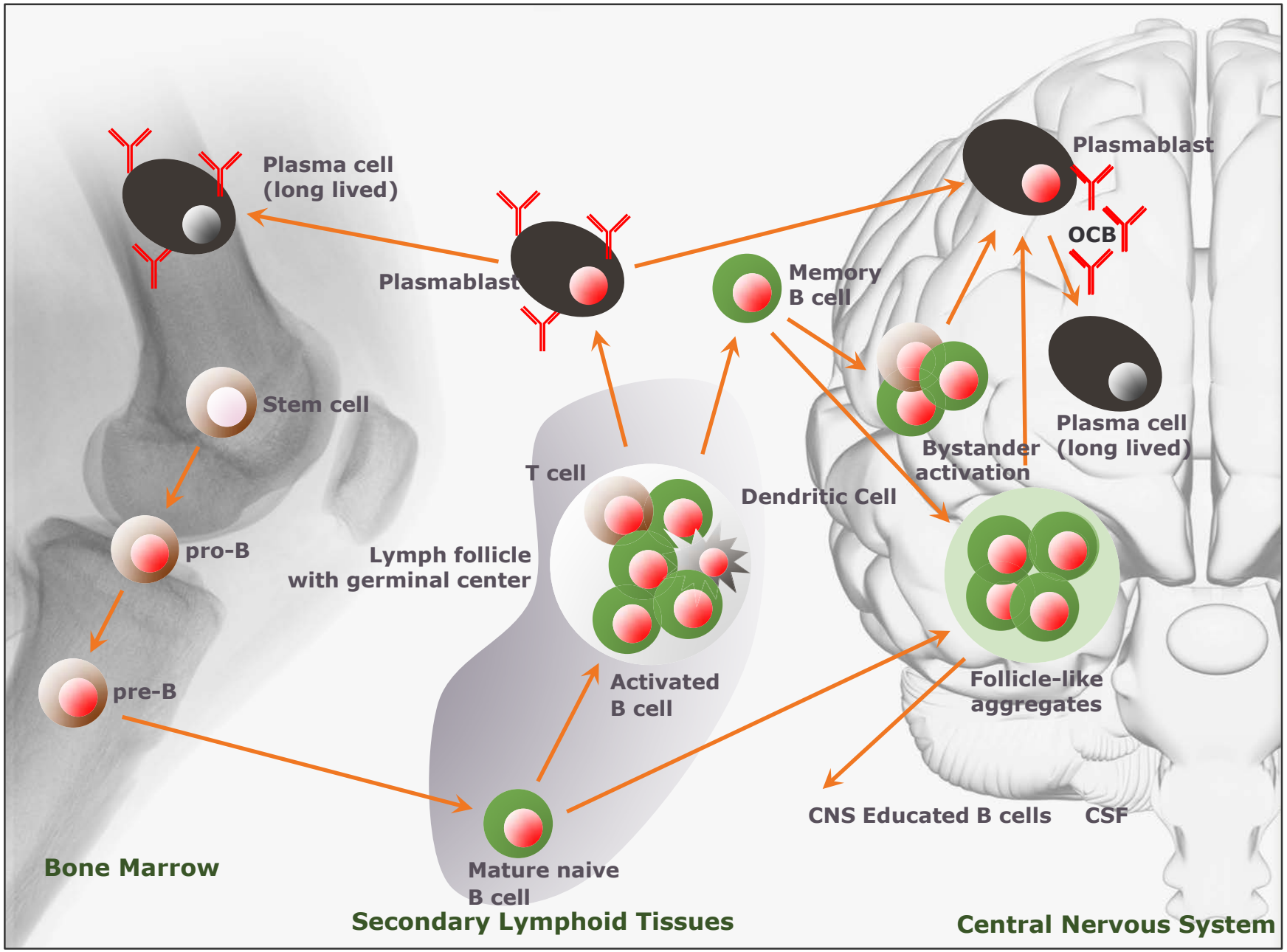
IgM Memory B Cell



IgG Memory B Cell

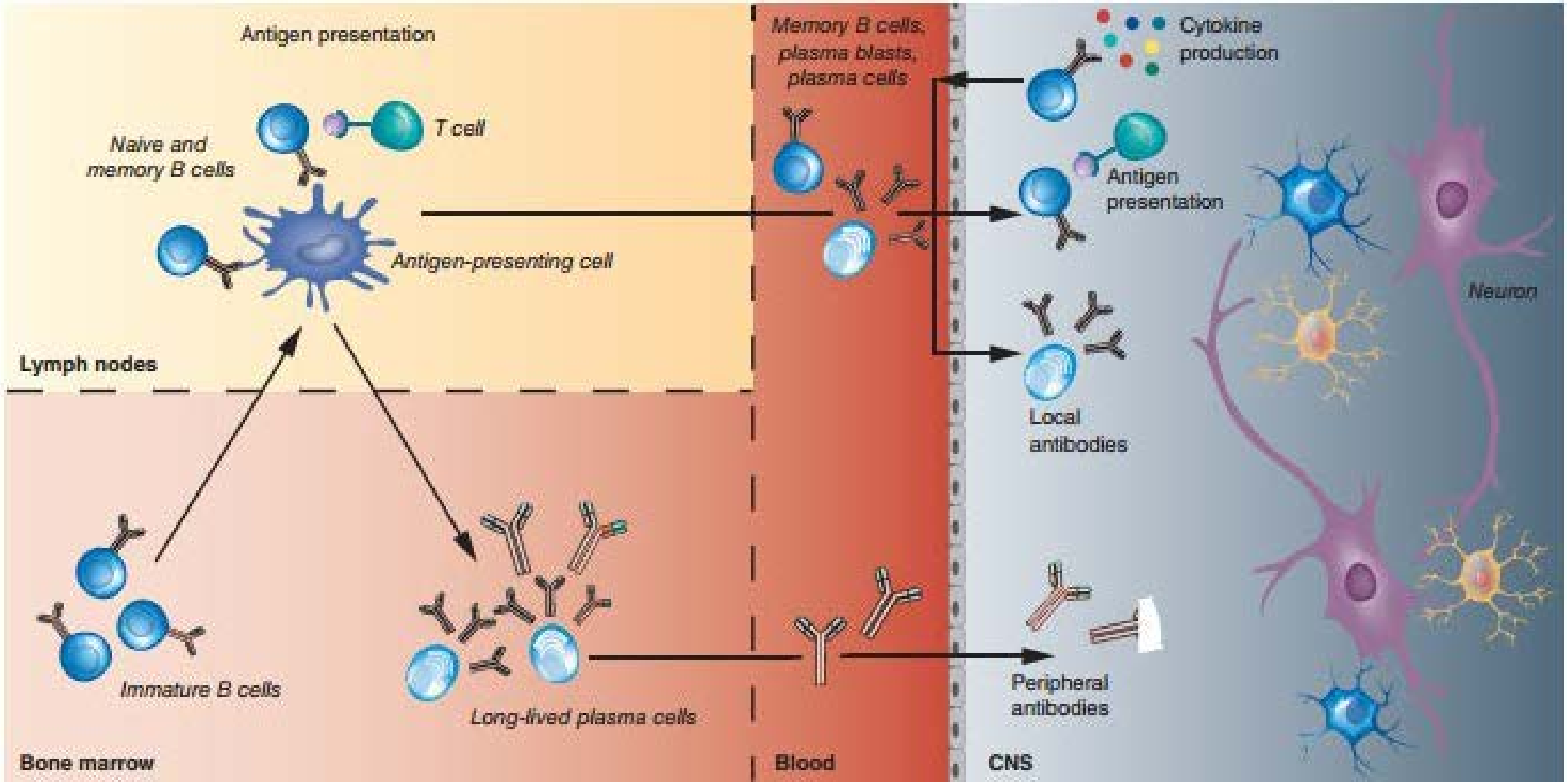
Seifert et al. *Proc Natl Acad Sci* 2015 Feb 10;112(6):E546-55.

B cells and the Brain



CNS, central nervous system; CSF, cerebrospinal fluid; OCB, oligoclonal band.

Involvement of B Cells in the Pathogenesis of Multiple Sclerosis



Gasperi C et al. *Neurodegener. Dis. Manag*. 2016 6(1), 37–47.

B Cells Play Key Functional Roles in MS

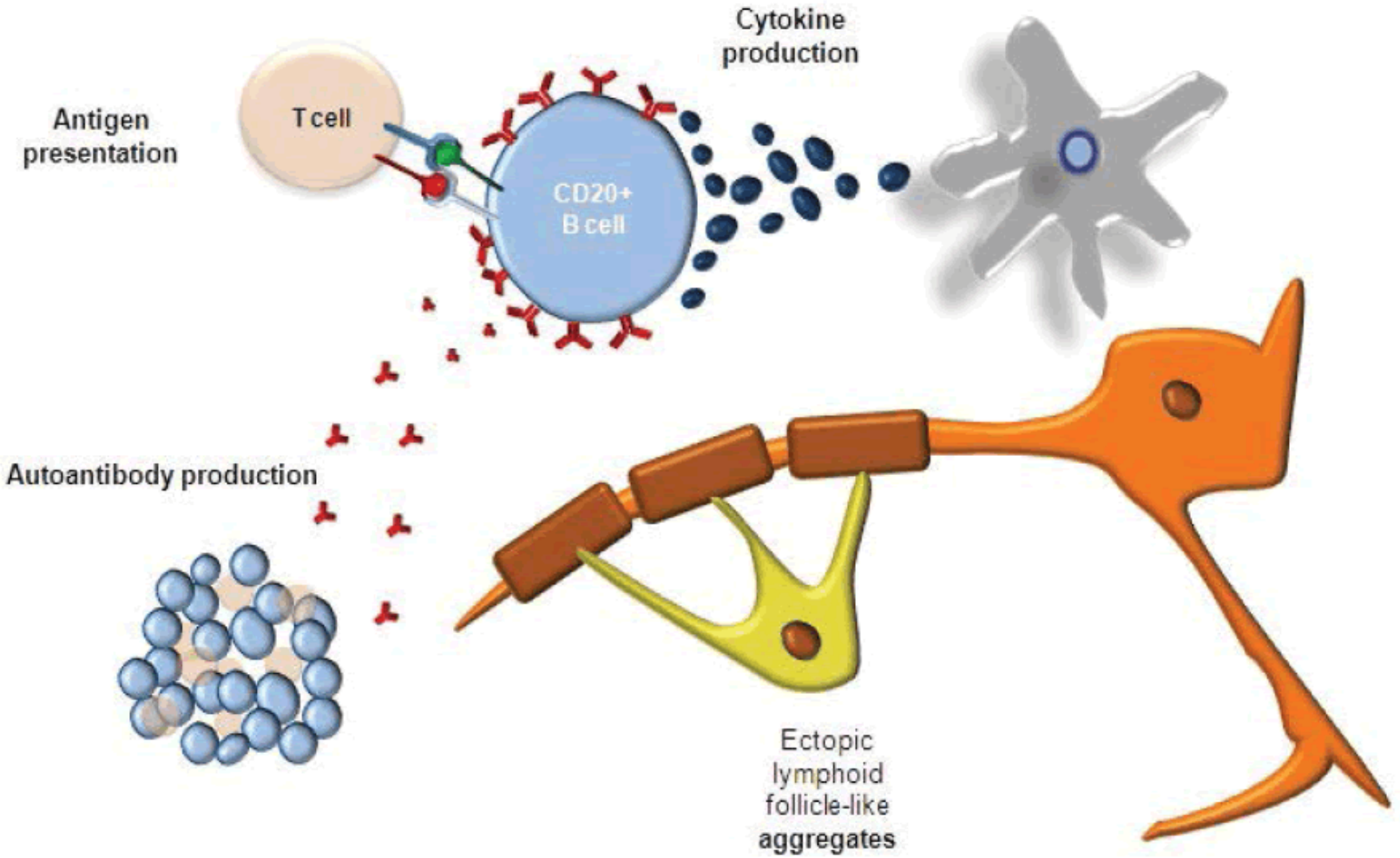
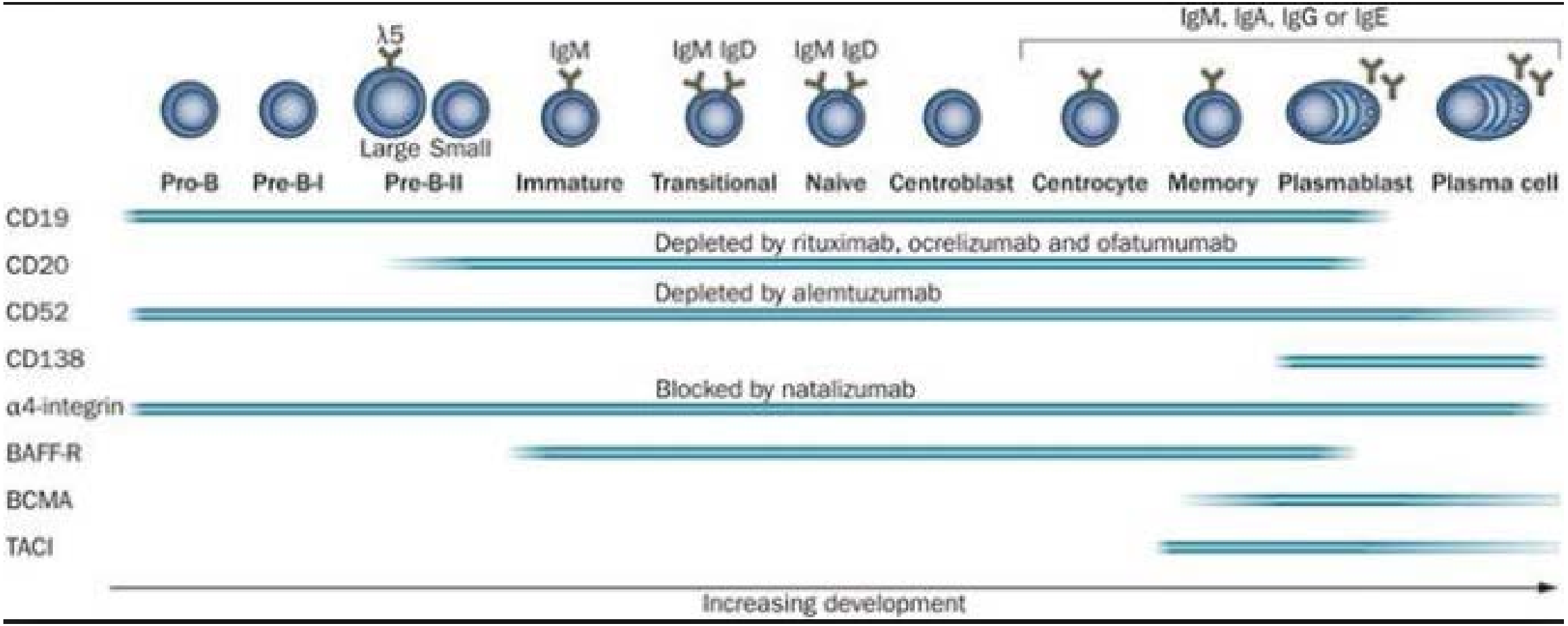


Figure 3: B cells in the pathophysiology of MS [8-11].

Solimando B-Cell Therapies in Relapsing Remitting and Primary Progressive Multiple Sclerosis: A Short Clinical Review Biochemistry & Pharmacology: Open Access Biochem Pharmacol (Los Angel) 2016, 5:218

B Cells Express Different Surface Markers Throughout Development

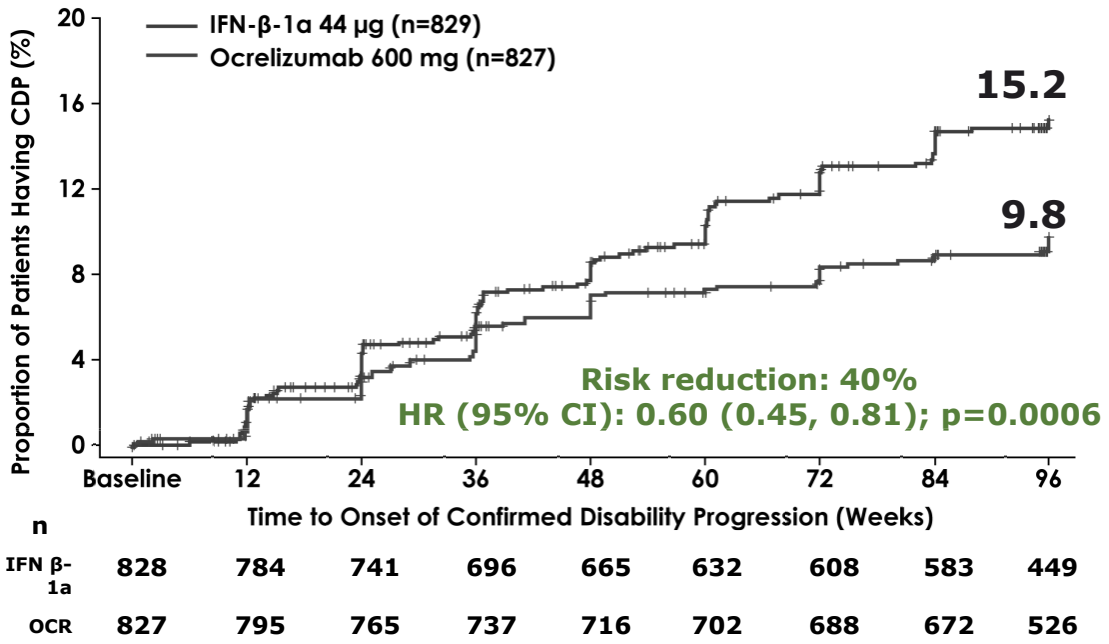


BAFF = B cell activating factor; BCMA = B cell maturation antigen; TACI = transmembrane activator and calcium-modulator and cytophilin ligand interactor Image adapted from Krumbholz M, *et al*. *Nat Rev Neurol* 2012;8(11):613–23.

1. Stashenko P, *et al. J Immunol* 1980;125:1678–1685; **2.** Loken MR, *et al. Blood* 1987;70:1316–1324; **3.** Tedder TF, Engel P. *Immunol Today* 1994;15:450–454; **4.** Martin F, Chan AC. *Annu Rev Immunol* 2006;24:467–96.

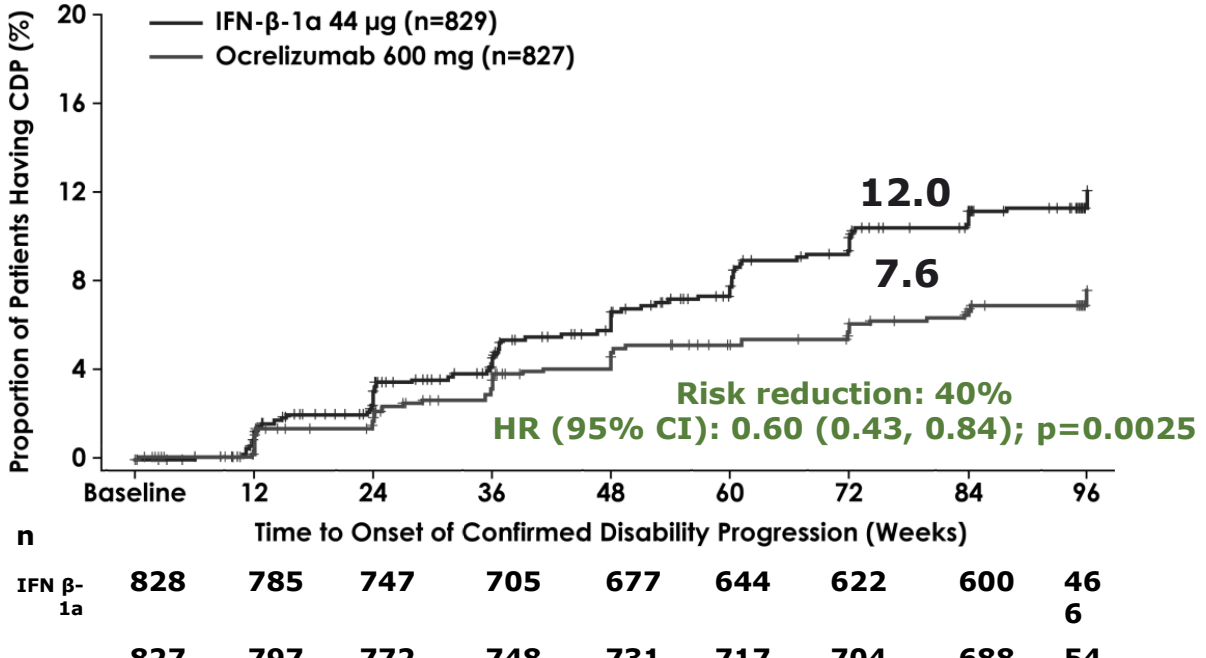
Reduction in Pre-specified Pooled Analysis of Confirmed Disability Progression (CDP) at 12 and 24 Weeks with IFN B-1a

Time to CDP for ≥12 weeks



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 CDP for ≥24 weeks



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

ITT CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFN, interferon; OCR, ocrelizumab.

Comi G 2016 *Neurology*. vol. 86 no. 16 Supplement S49.

Actions of Four Key MS Medications

- Alemtuzmab
- Daclizumab
- Ocrelizumab
- Cladribine

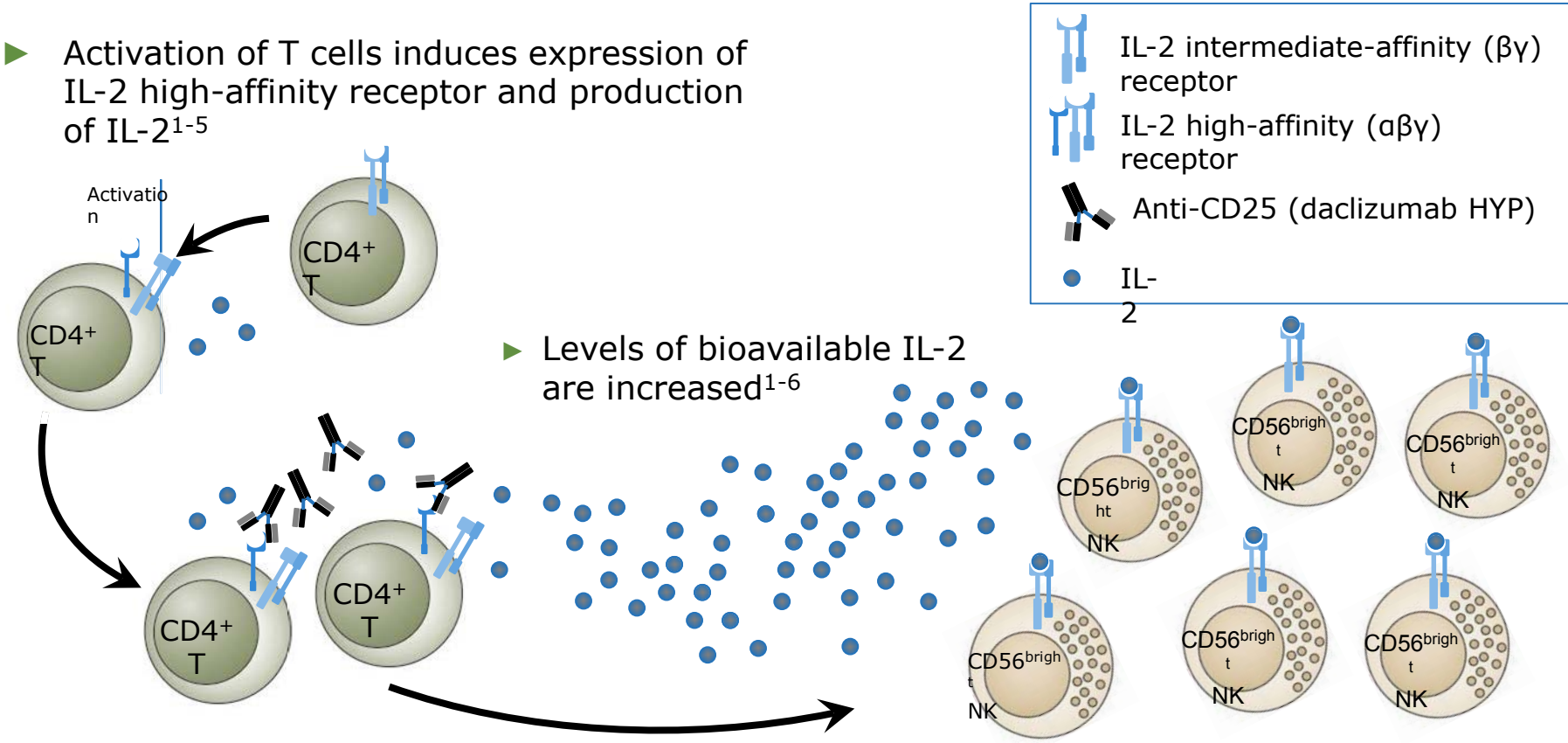
Alemtuzumab: A Humanized Monoclonal Antibody Approved for Treatment of Patients with Active RRMS

- A humanized monoclonal antibody that selectively targets CD52, a protein abundant on the surface of B and T lymphocytes[1]
- Novel dosing regimen: administered 12 mg/day via intravenous (IV) infusions on 5 consecutive days at baseline and on 3 consecutive days 12 months later[2,3]
- Approved for adult patients with relapsing-remitting MS (RRMS) with active disease defined by clinical or imaging features[4]
- First approved - EU in 20135*

1. Hu Y et al. *Immunology* 2009;128:260-70; **2.** Cohen JA et al. *Lancet* 2012;380:1819-28; **3.** Coles AJ et al. *Lancet* 2012;380:1829-39; **4.** Lemtrada (alemtuzumab) Peru Summary of Product Characteristics, 2014; **5.** Lemtrada (alemtuzumab) EU Summary of Product Characteristics, September 2013.

Daclizumab (CD25) blockade induces a shift of IL-2 signalling from activated T-cells to CD56-bright NK cells

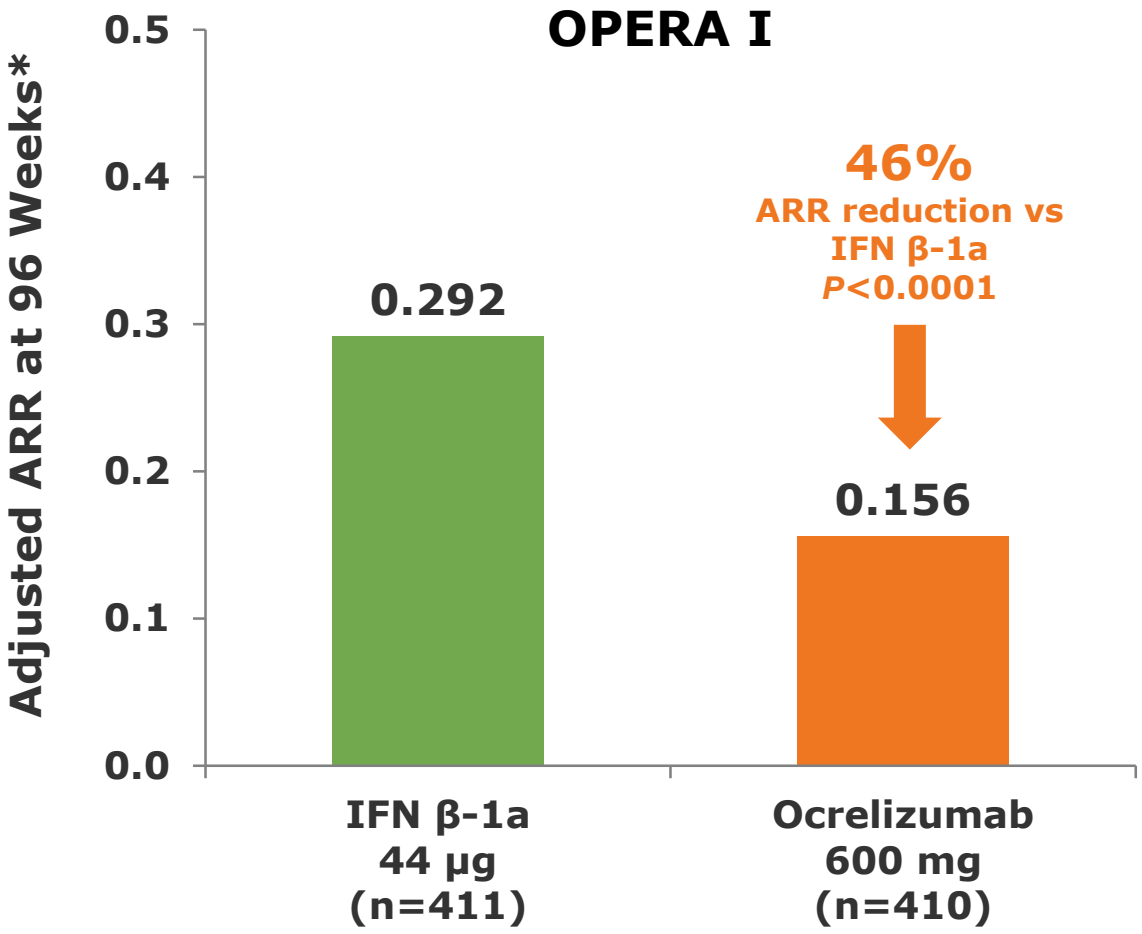
- Activation of T cells induces expression of IL-2 high-affinity receptor and production of IL-2[1-5]

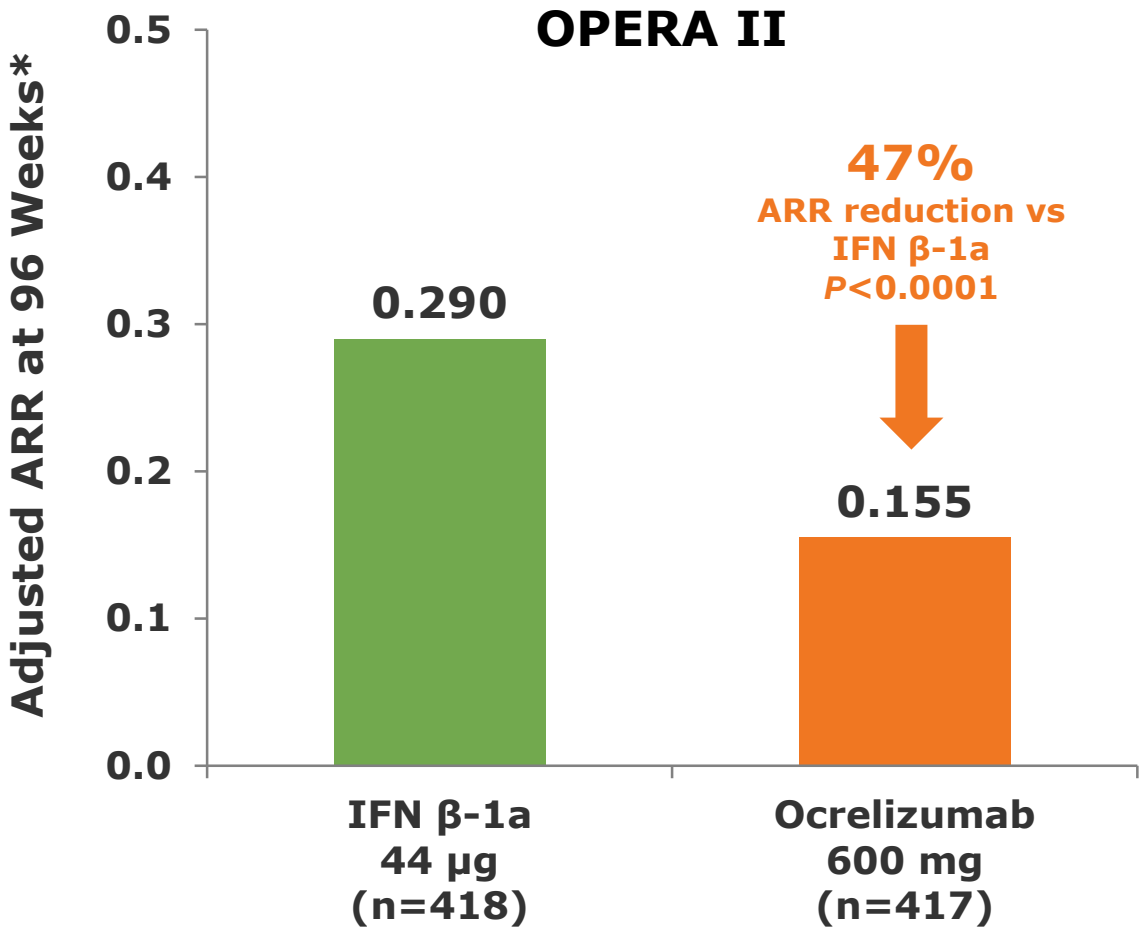


- Levels of bioavailable IL-2 are increased[1-6]
- CD25 blockade prevents IL-2 consumption by activated T cells and increases IL-2 production (via inhibition of negative feedback)[1-5]
- Increased levels of IL-2 can induce expansion and activation of CD56^{bright} NK cells through the intermediate affinity receptor[1-6]

Adapted from **1.** Amaravadi L et al. Presented at AAN; Washington, USA; 2015:P1.149; **2.** Malek TR. *Annu Rev Immunol*. 2008;26:453-479; **3.** Bielekova B. *Neurotherapeutics*. 2013;10:55-67; **4.** Wiendl H et al. *Nat Rev Neurol*. 2013;9:394-404; **5.** Pfender N et al. *Exp Neurol*. 2014;262:44-51; **6.** Elkins J et al. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e65.

Ocrelizumab in RMS Superior Efficacy, Similar Safety to Rebif

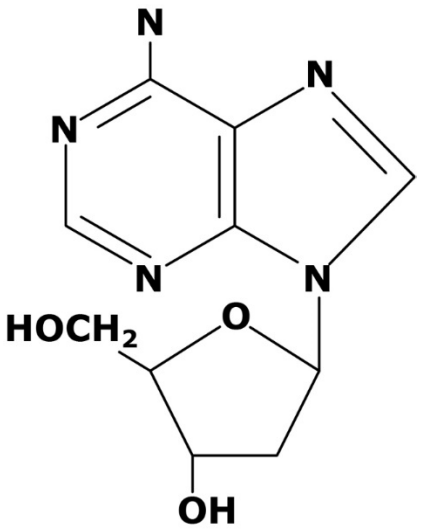




F. Hoffmann-La Roche. ClinicalTrials.gov NCT01247324 and NCT01412333. National Library of Medicine. Available at: https://clinicaltrials.gov/ct2/show/NCT01247324 and https://clinicaltrials.gov/ct2/show/NCT01412333 .

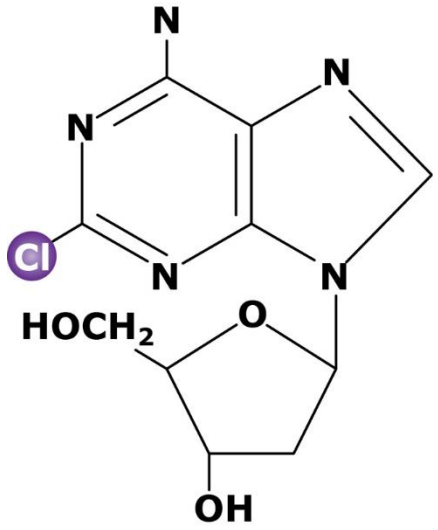
Cladribine

Cladribine was designed by adding 1 chlorine atom to deoxyadenosine, making it largely resistant to degradation by ADA



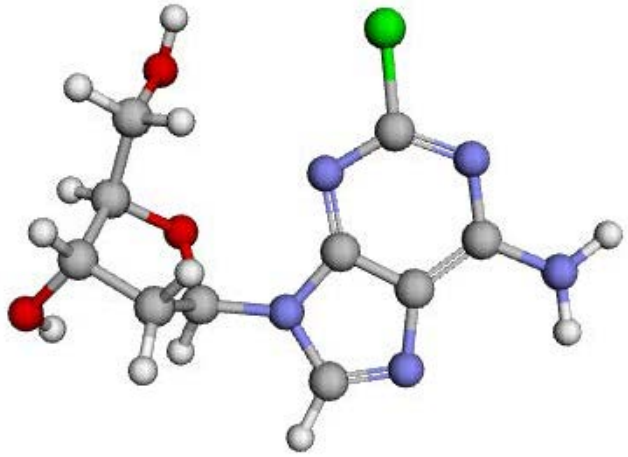
deoxyadenosine

DEGRADED BY ADA



cladribine

RESISTANT TO ADA



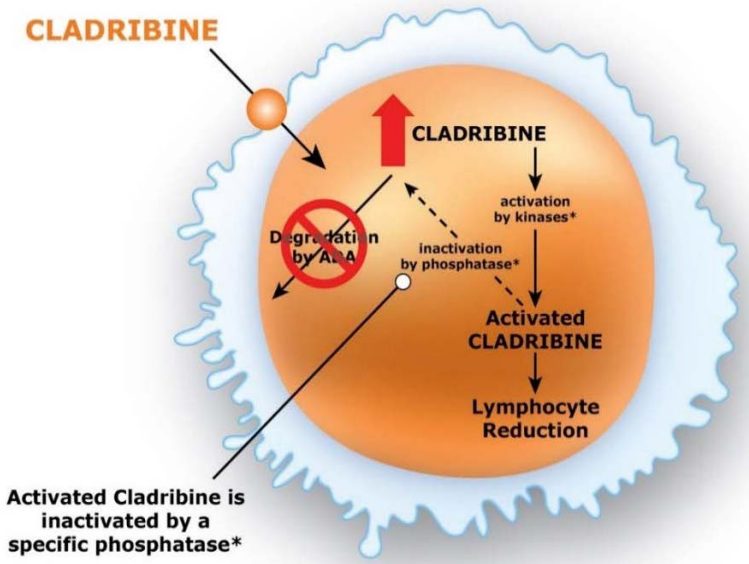
$C_{10}H_{12}ClN_5O_3$

Leist TP, Weissert R. *Clin Neuropharmacology* 2011;34:28-35.

Cladribine Enters Cells to be Activated and Exerts Its Effect

Cladribine works by a 4-step mechanism:

- Cladribine enters cell via nucleoside transporter
- Accumulates intracellularly due to ADA resistance
- Cladribine is activated by specific kinases
- Activated Cladribine induces selective lymphocyte reduction

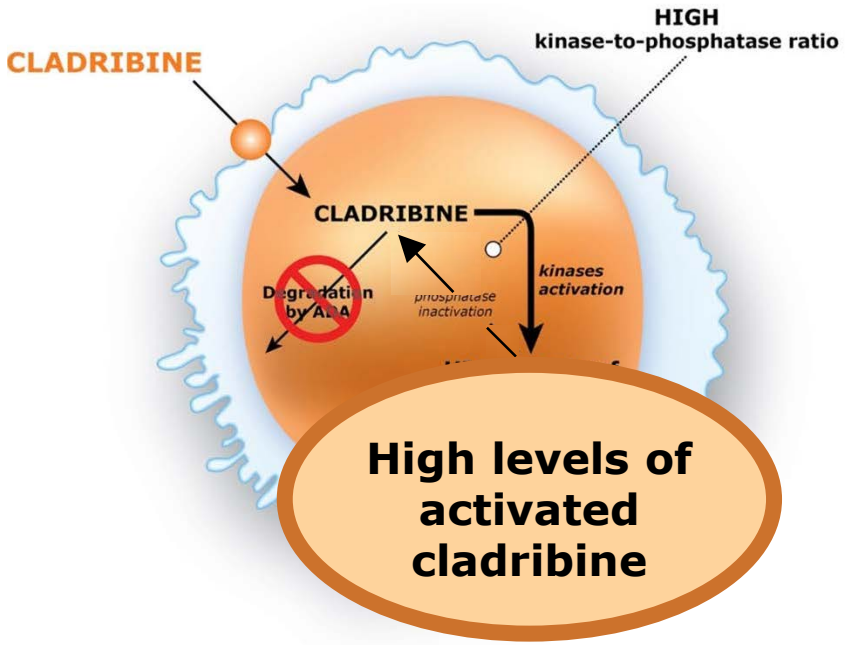


*One of the kinases is deoxycitidine kinase (DCK). The phosphatase is 5′-nucleotidase.

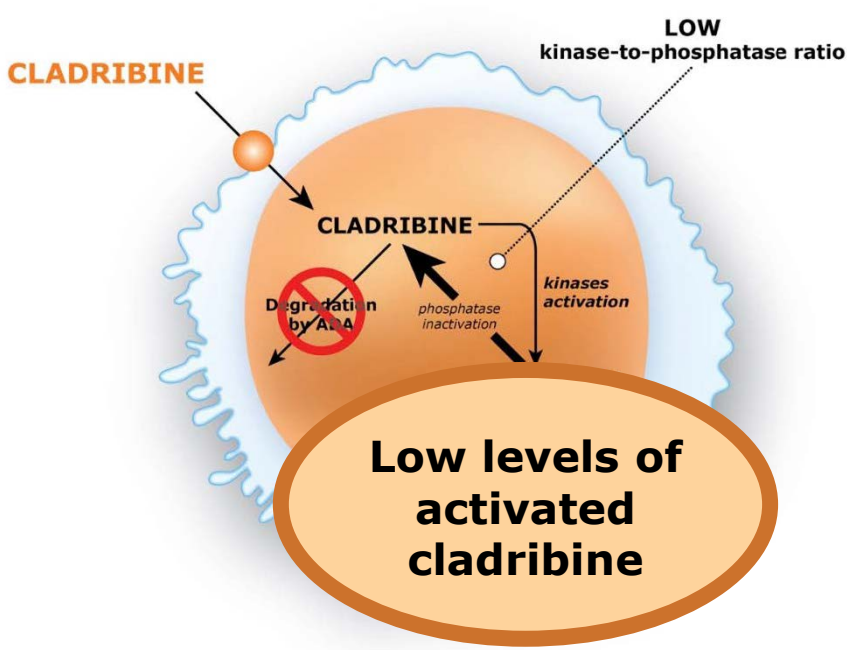
Leist TP, Weissert R. *Clin Neuropharmacol* 2011;34:28–35.

Cladribine Selectivity for Lymphocytes is Due to Preferential Intracellular Activation in B and T Cells

B and T Lymphocytes

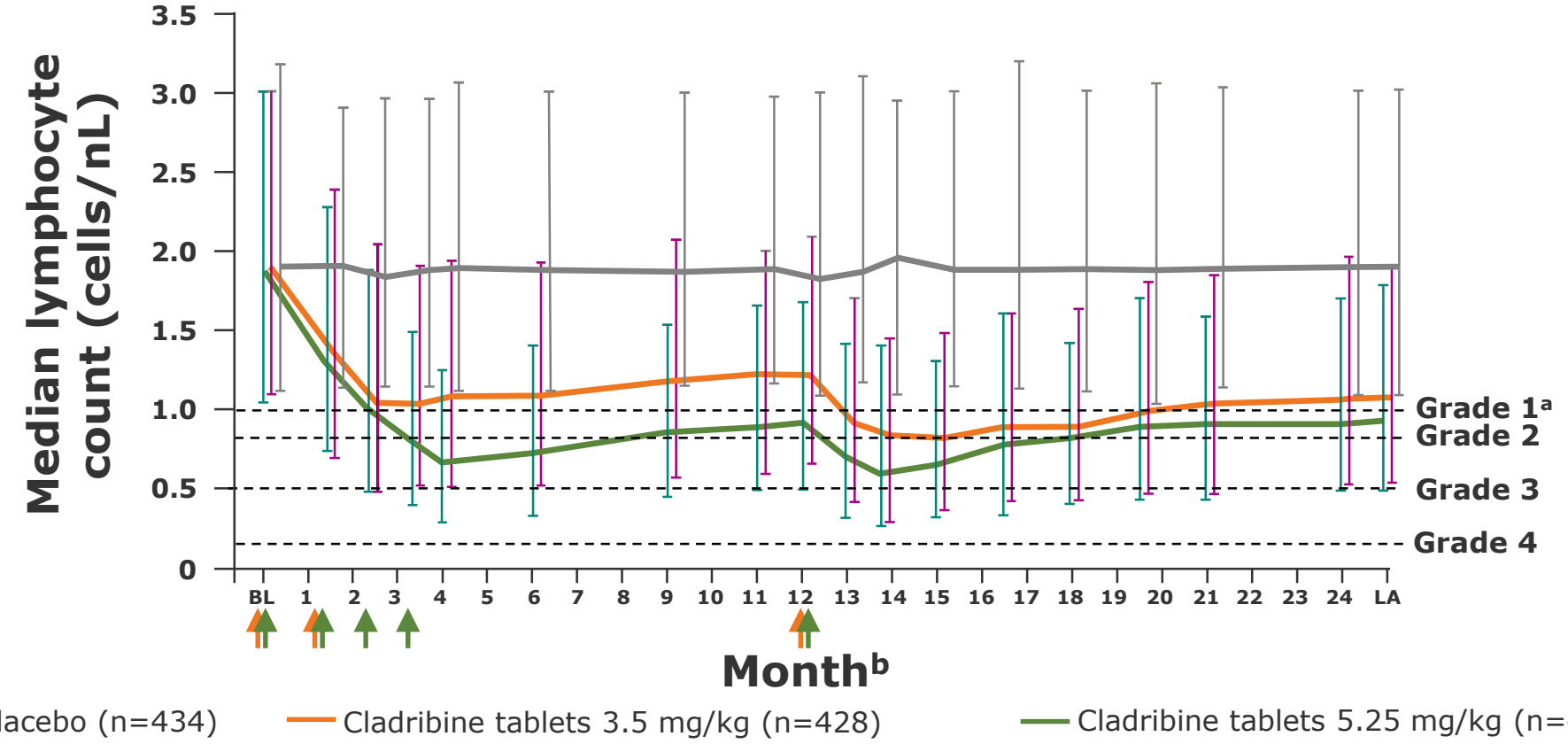


Other Cells



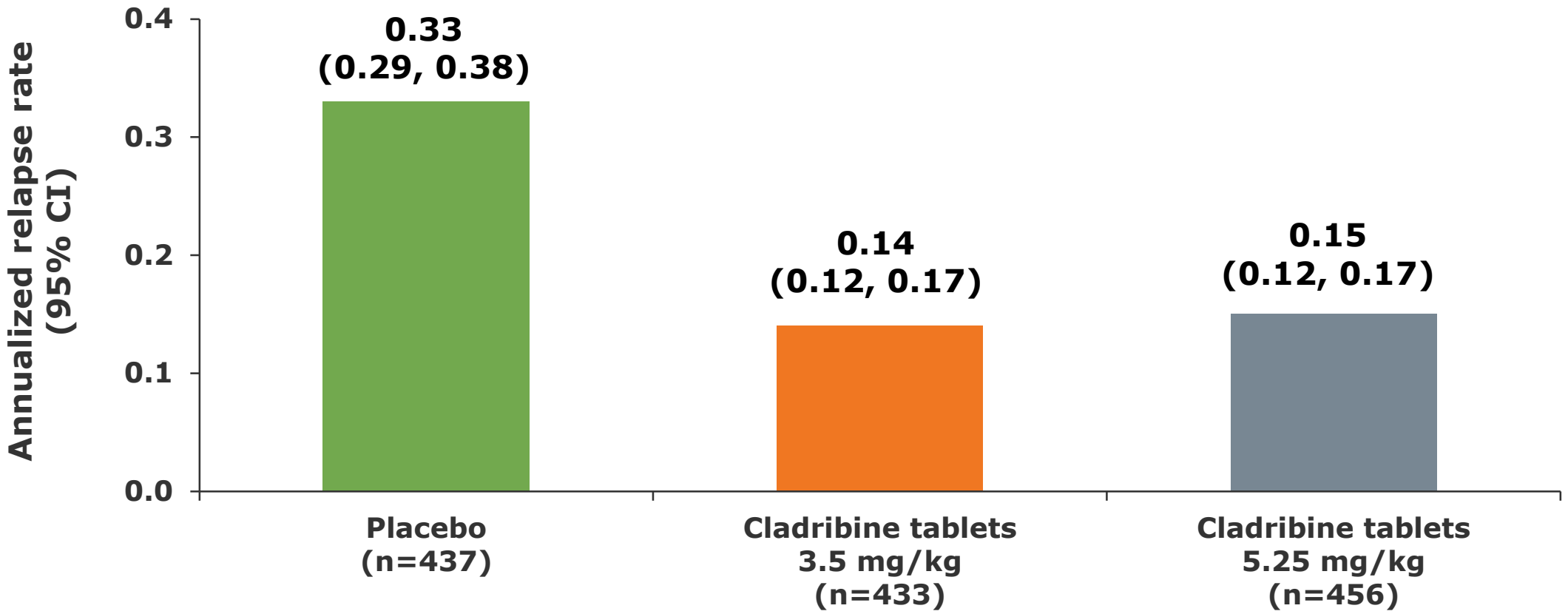
ADA, adenosine deaminase. Saven A, Piro LD. *Ann Intern Med* 1994;120:784–91.
Leist TP, Weissert R. *Clin Neuropharmacol* 2011;34:28–35.

Treatment With Cladribine Tablets Leads to Specific, Discontinuous Reduction in Lymphocyte Counts



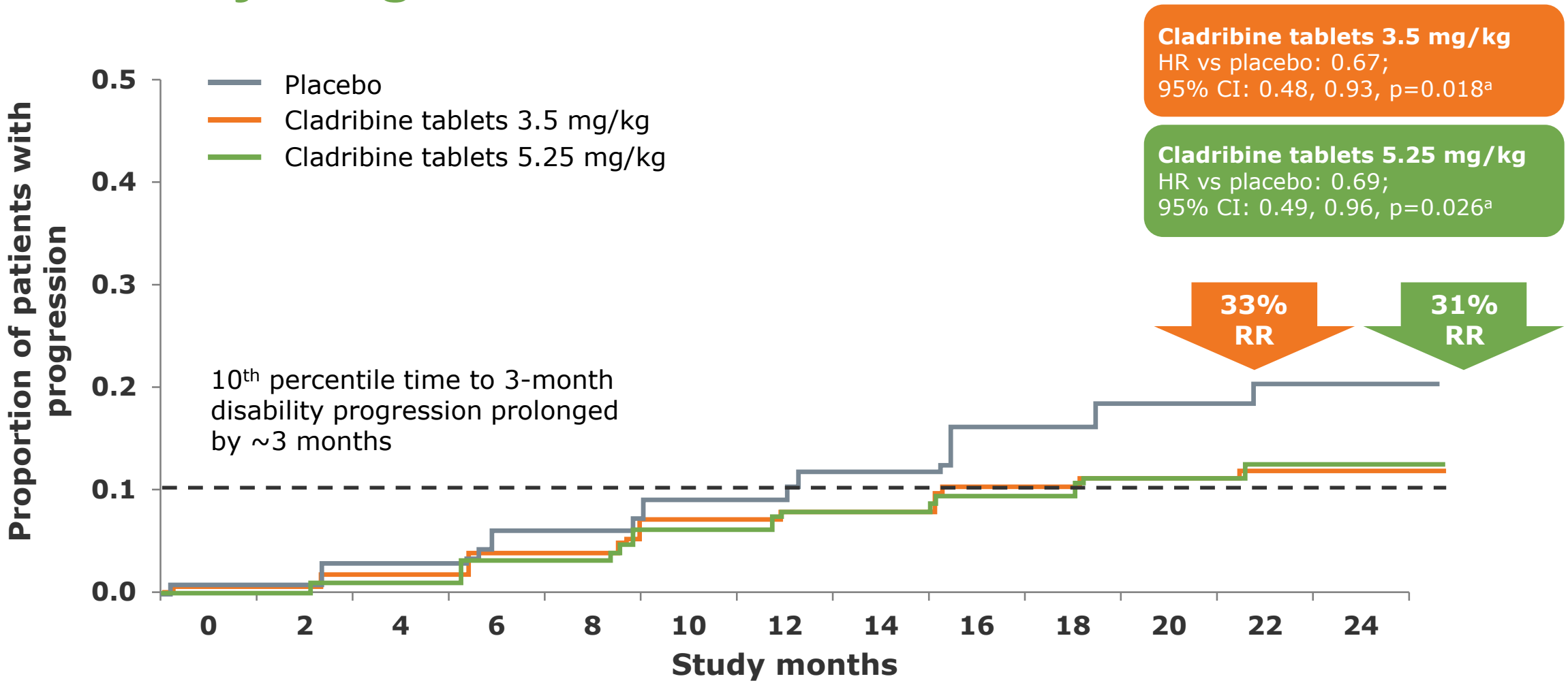
Arrows show cladribine tablet dosing. [a]Reductions in absolute lymphocyte counts (lymphopenia) were graded according to the Common Terminology Criteria for Adverse Events: 1, <lower limit of normal to 800/mm^3; 2, <800 to 500/mm^3; 3, <500 to 200/mm^3; 4, <200/mm^3. [b]Lymphocyte count data were not available for all patients at every observation. [c]Central laboratory reference range. Error bars represent 5–95 percentile range for cell counts at each time point. AE, adverse event; BL, baseline; LA, last assessment; MoA, mechanism of action. Figure reproduced with permission from Giovannoni G et al. N Engl J Med 2010;362:416–26 (supplementary).

Significant Reduction in Annualized Relapse Rate vs Placebo Over 2 Years (Primary Endpoint)



A relapse was defined as an increase of 2 points in at least one functional system of the EDSS or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement. RR, relative reduction. Intent-to-treat population. Figure reproduced with permission from Giovannoni G et al. N Engl J Med 2010;362:416–26.

Significant Delay in Time to 3-month Confirmed Disability Progression



[a]The hazard ratio, 95% CI and p-values were estimated using Cox proportional hazards model with fixed effects for treatment group and region. Intent-to-treat population CI, confidence interval; RR, risk reduction.

Giovannoni G et al. N Engl J Med 2010;362:416–26

Summary

1. In general MS DMTs modify the course of MS by
   - immunomodulation
   - generalised immunosuppression
   - reduced trafficking of T & B cells into the CNS
   - immunodepletion
2. Some DMTs may act within the CNS
3. Recently licensed and emerging DMTs include:
   - Oral cladribine (purine nucleoside analogue)
   - Alemtuzumab (anti-CD52)
   - Daclizumab (anti-CD25)
   - Ocrelizumab (anti-CD20)