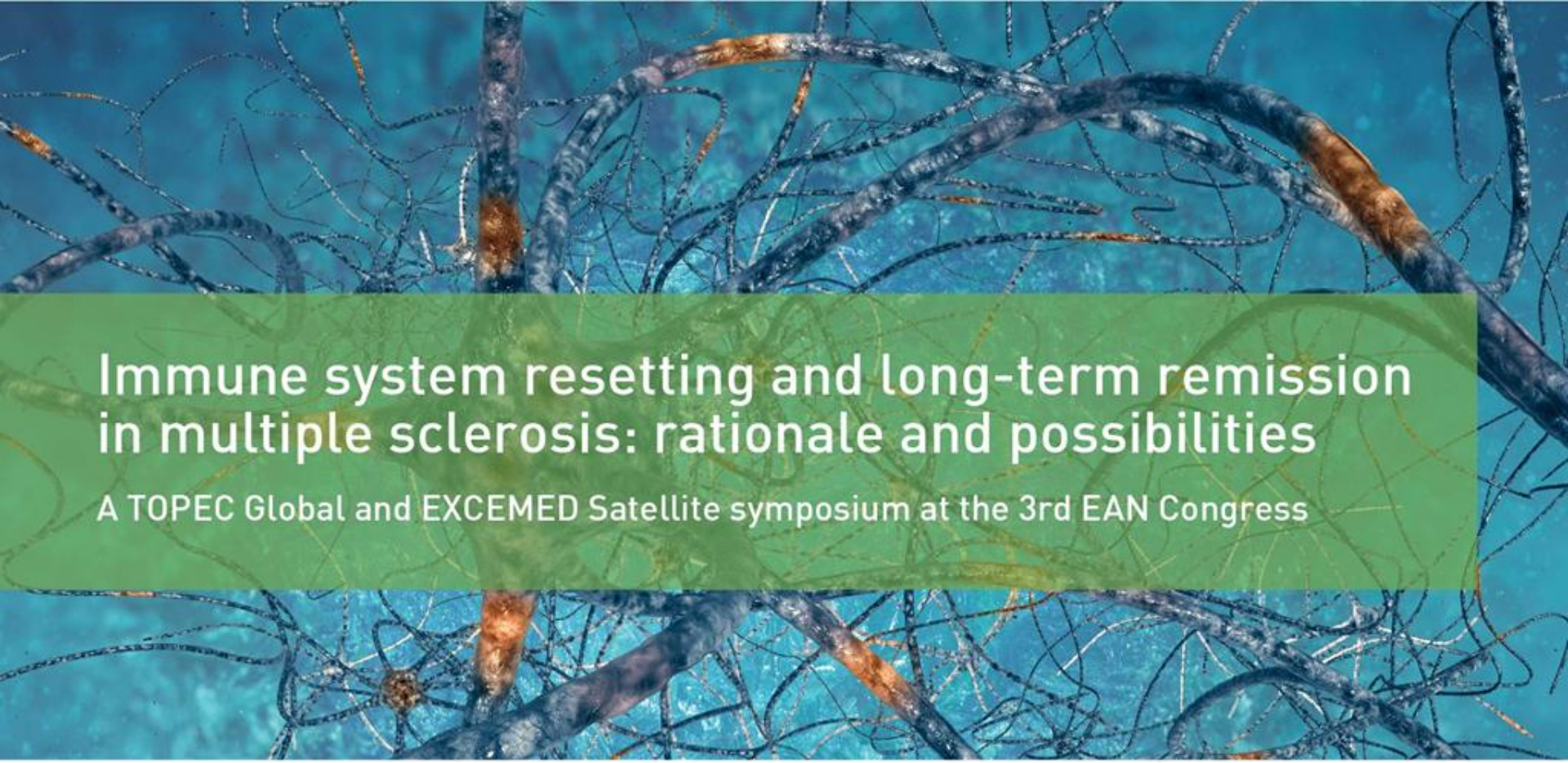


Immune system resetting and long-term remission in multiple sclerosis: rationale and possibilities

A TOPEC Global and EXCEMED Satellite symposium at the 3rd EAN Congress

gna Global Neurology Academy

TOPECGLOBAL

EXCEMED

Immune system resetting and long-term remission in multiple sclerosis: rationale and possibilities

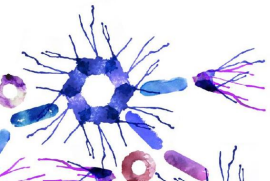
How to transfer the concept in the clinical practice

Prof. Gavin Giovannoni
Barts and The London School of Medicine and Dentistry

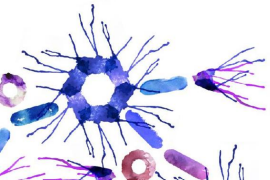
BartsMS

Disclosures

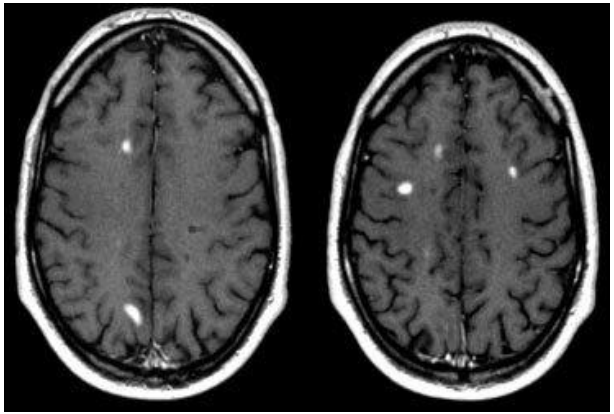
Over the last 15 years Professor Giovannoni has received personal compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Abbvie, Almirall, Atara Bio, Bayer-Schering Healthcare, Biogen-Idec, Canbex, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.

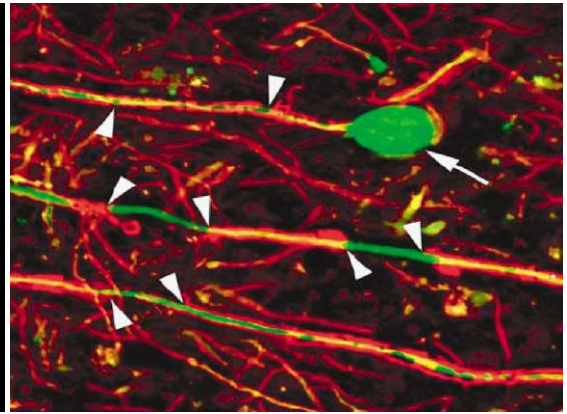


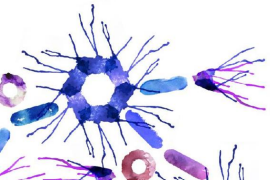
The clinical context



The cause of progression is inflammation

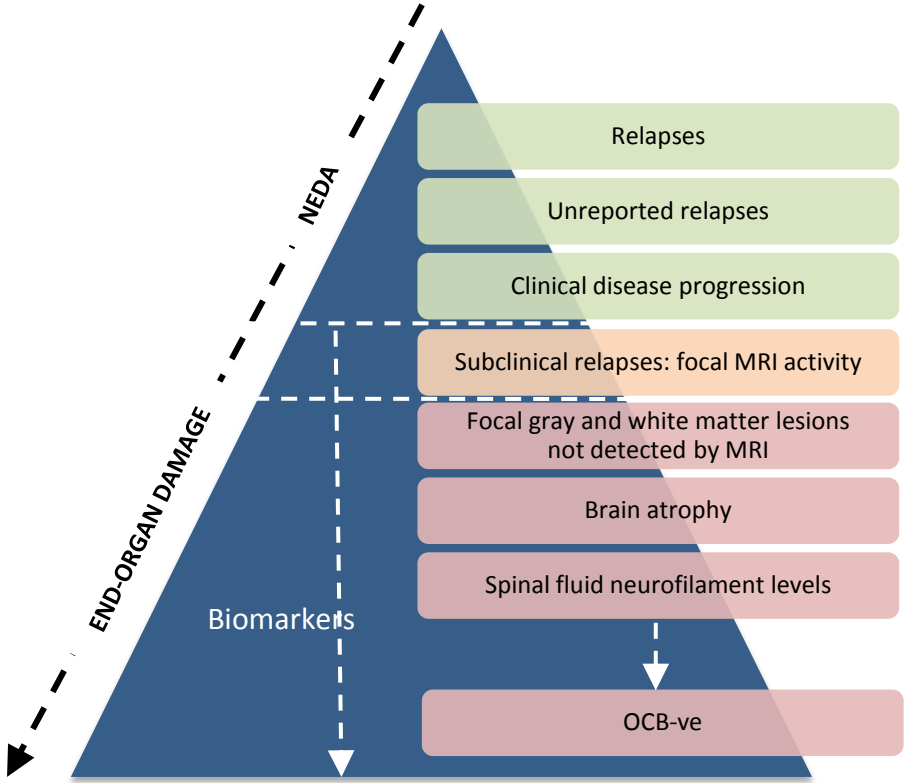


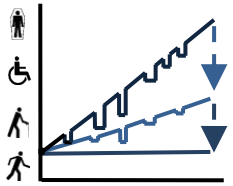




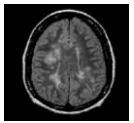
Trapp, et al. NEJM 1998;338:278-85

MS Iceberg

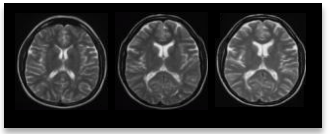




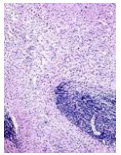
Clinical activity



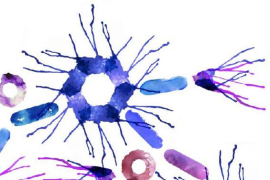
Focal MRI activity



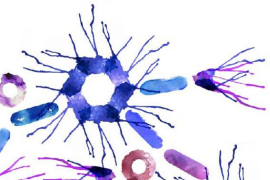
Hidden focal and diffuse MRI activity

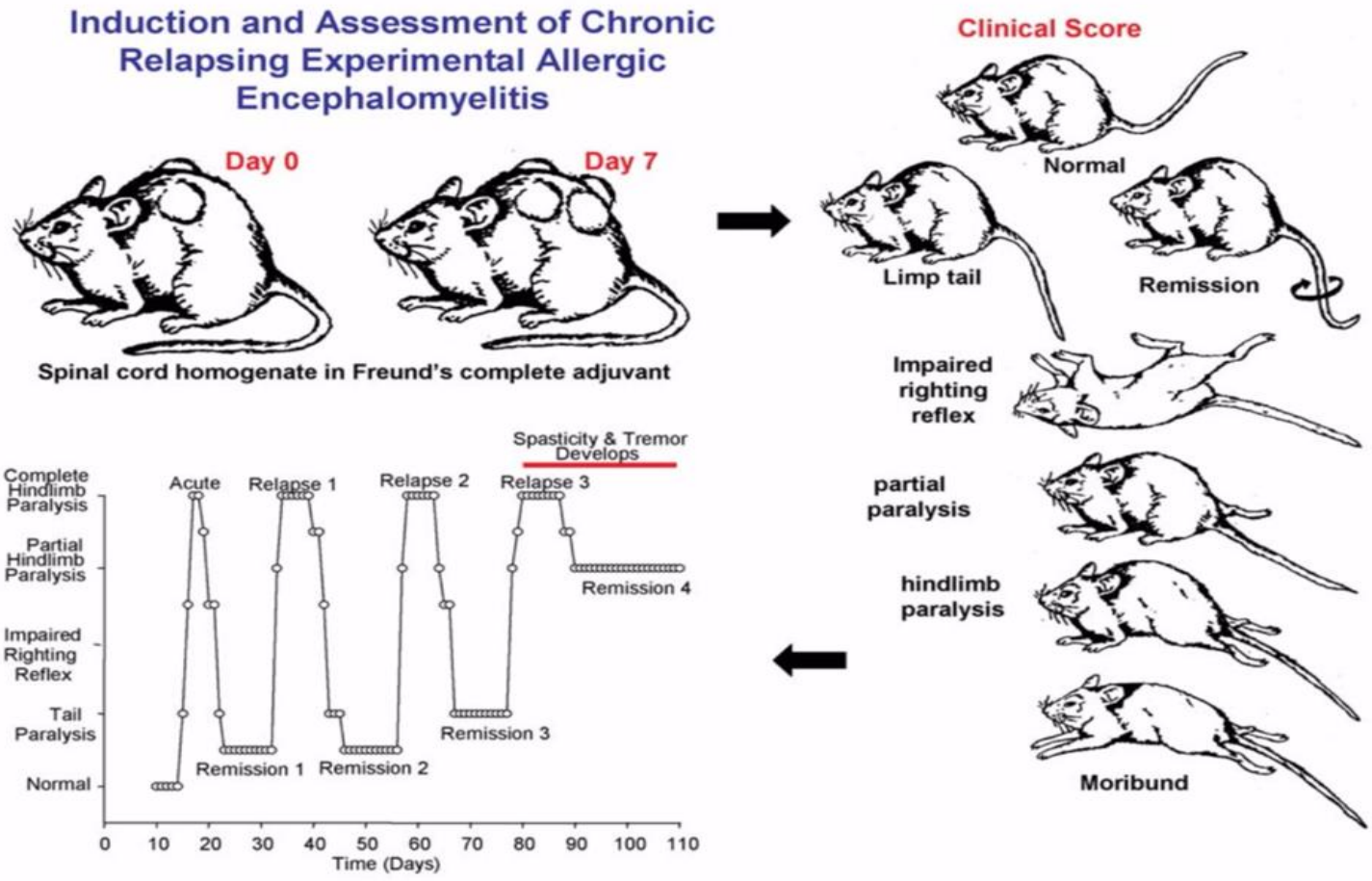


Microscopic or biochemical pathology



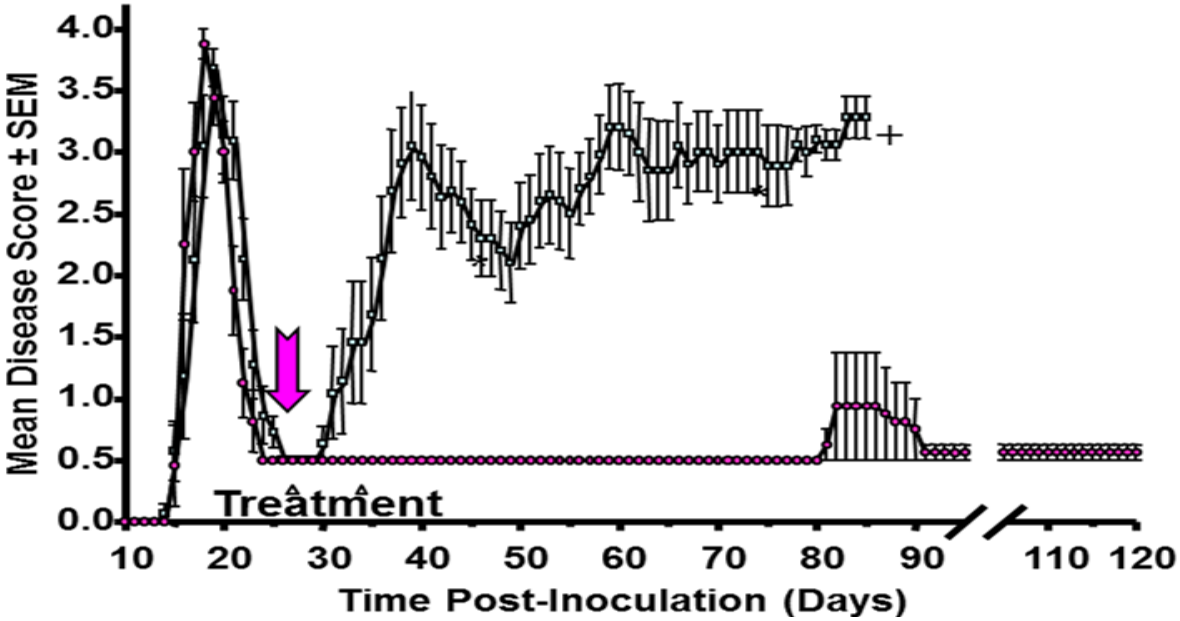
Defining a cure

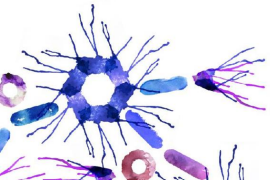




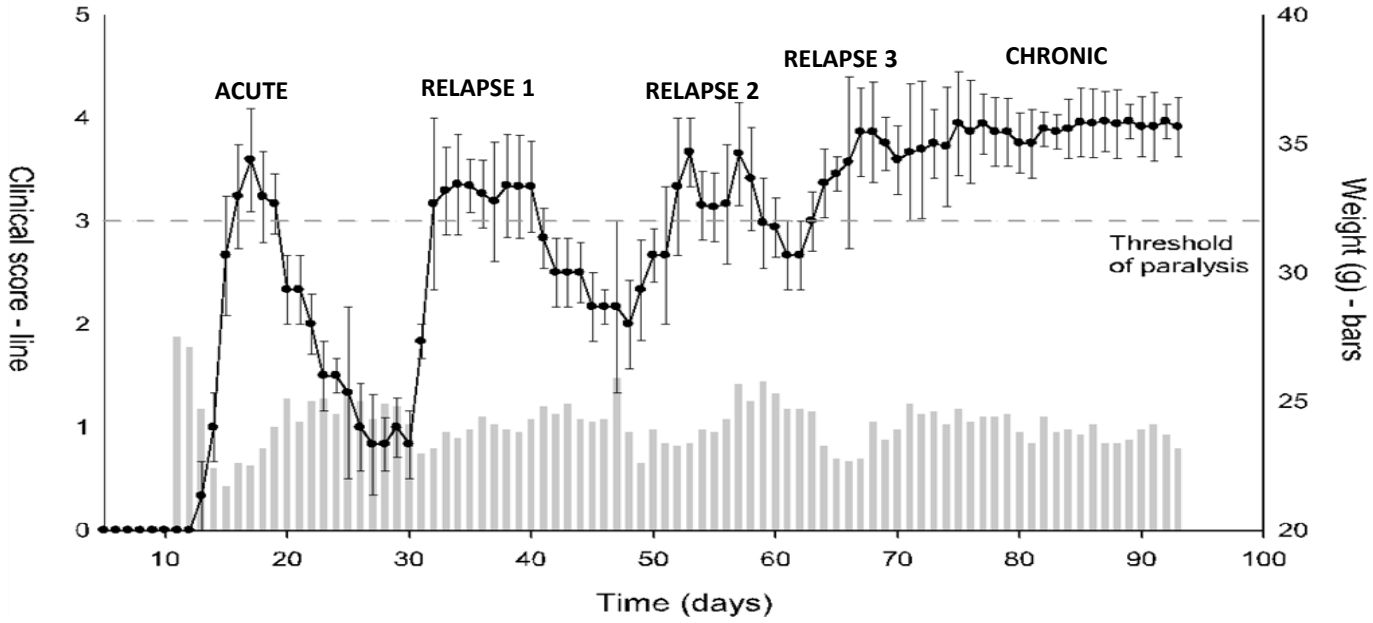
Slide courtesy David Baker

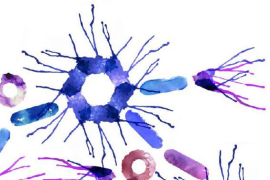
Curing animal MS





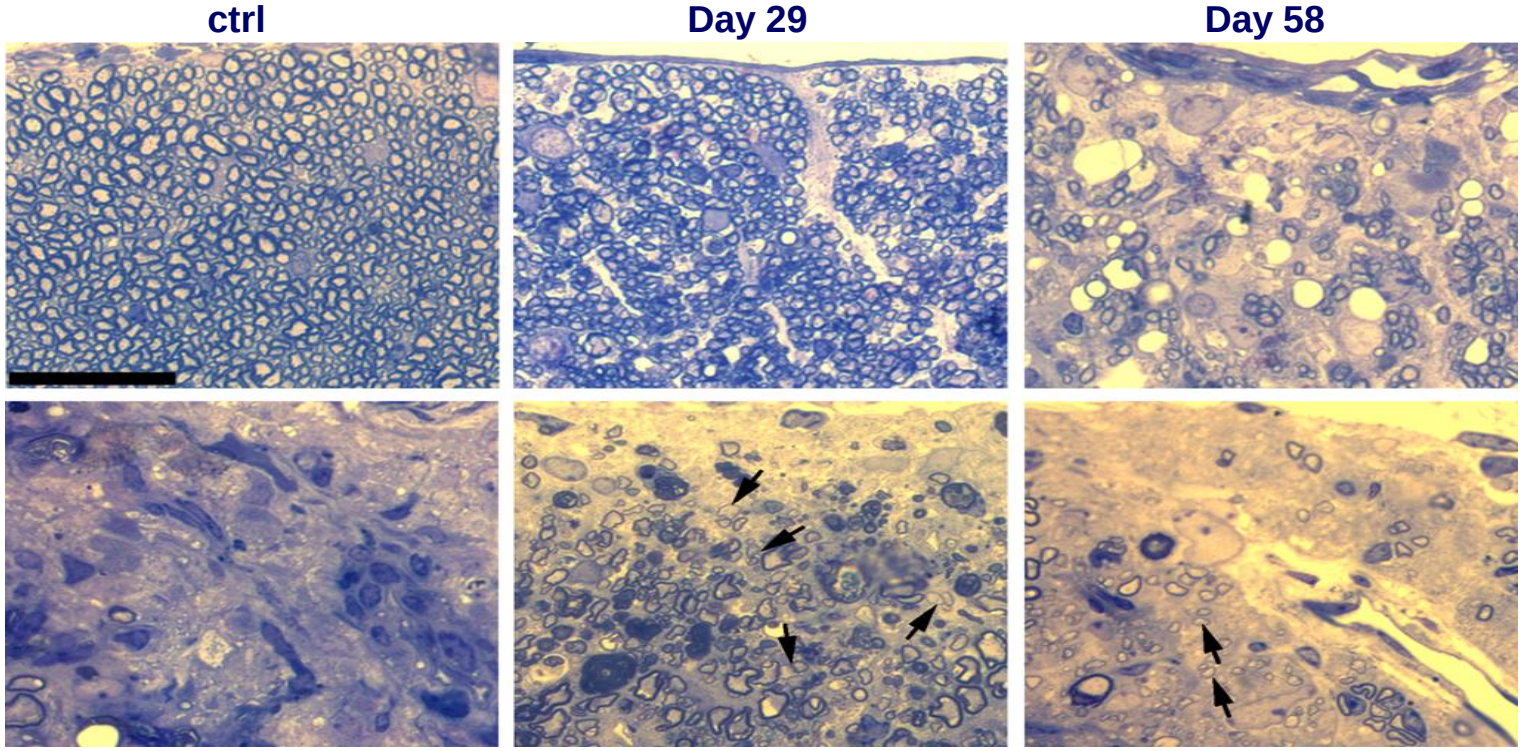
Average disease course





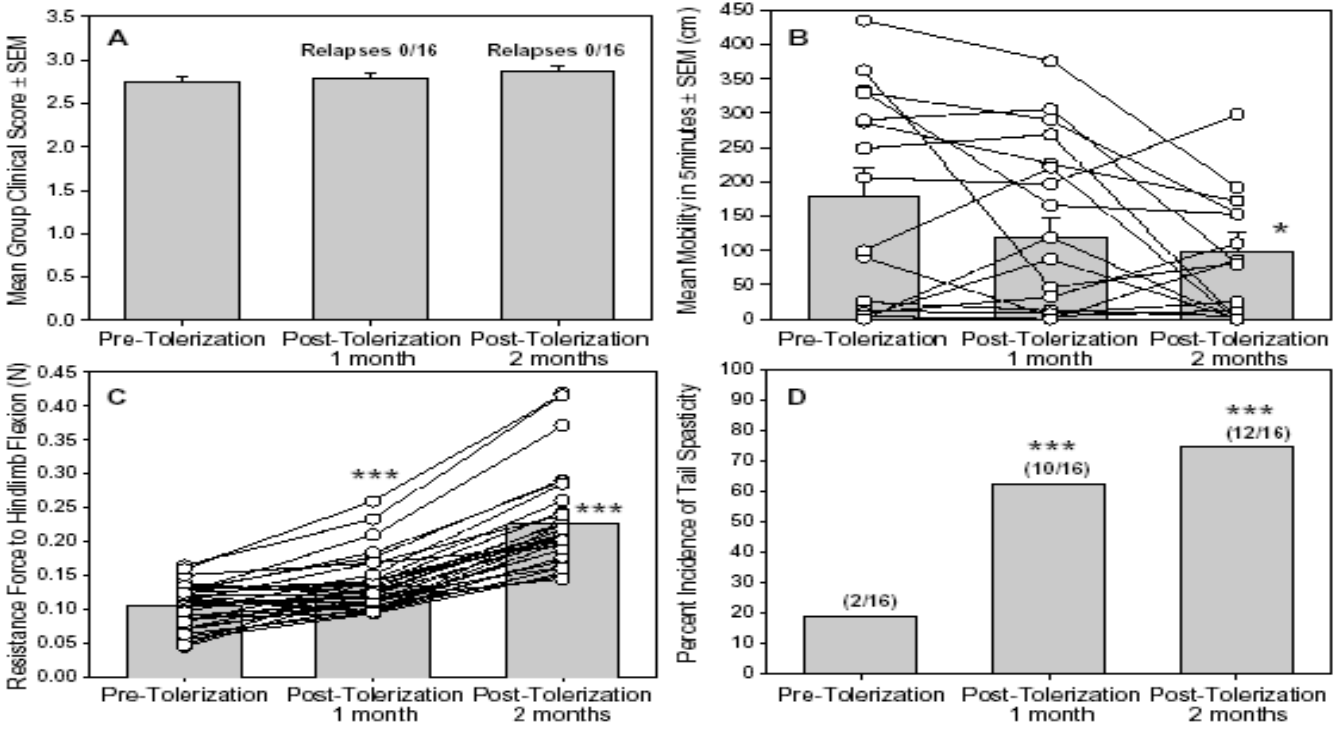
Slide courtesy Sam Jackson & Ian Duncan.

Post-inflammatory SPMS



Slide courtesy David Hampton

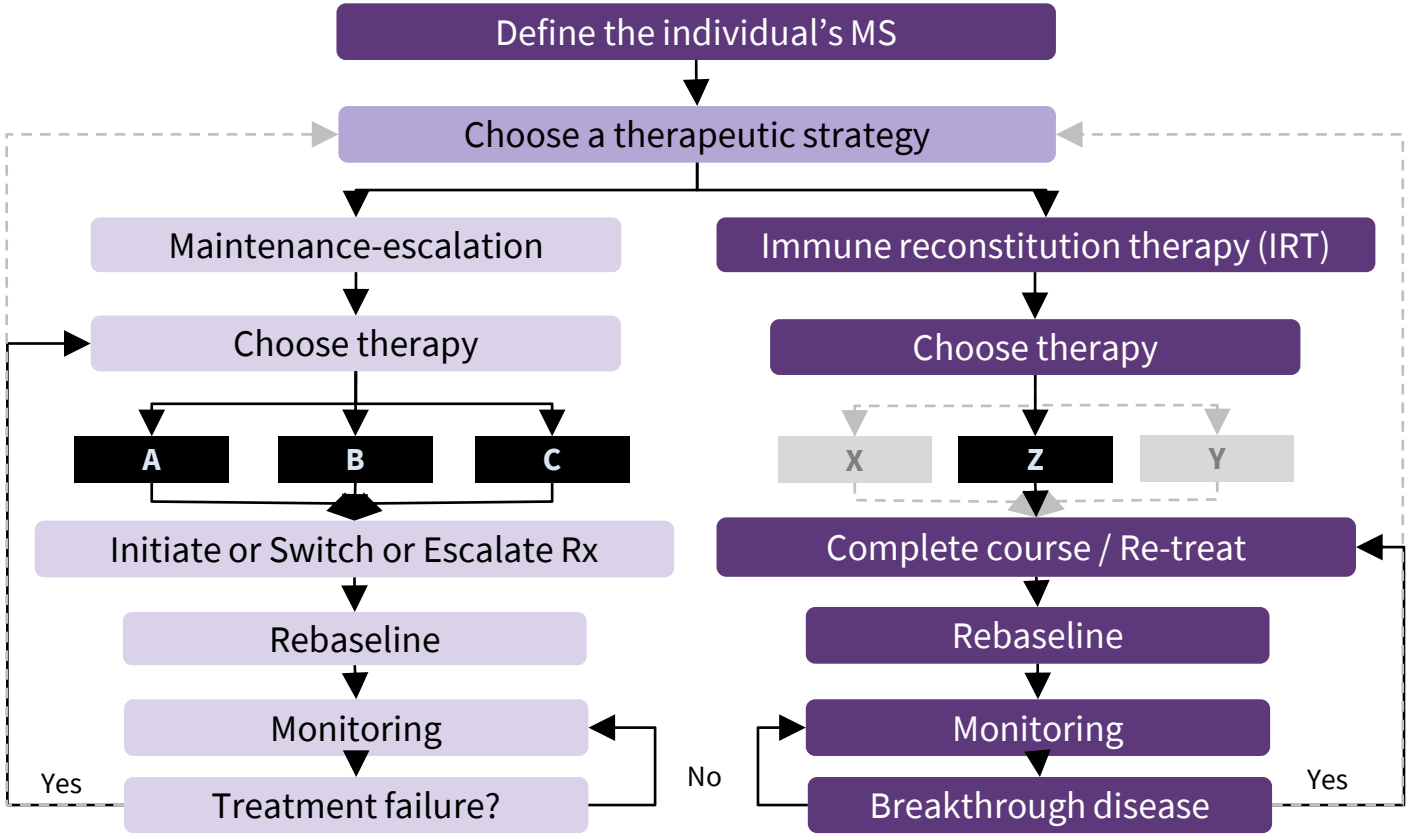
Prevention of relapsing CREAE after three paralytic episodes does not inhibit secondary progression and deterioration of mobility



Pryce et al. J Neuroimmunol 2005.

BARTS-MS T2T-NEDA ALGORITHM

T2T = treating-to-target; NEDA = no evident disease activity



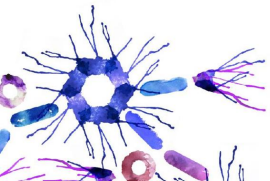
IFNβ = interferon-beta; NABs = neutralizing antibodies; Rx = treatment

What is a pulsed immune reconstitution therapy or IRT?

An immune reconstitution therapy, or IRT, is by definition given as a short course, i.e. intermittently and not continuously, and has the ability to induce long-term remission and in some cases the **possibility of a cure**.

Please note that a IRT is not given continuously and additional courses of the therapy are only given if there is a recurrence of inflammatory activity*.

* Inflammatory activity in multiple sclerosis typically refers to clinical relapses and/or focal MRI activity (new T2 lesions and or Gd-enhancing lesions).

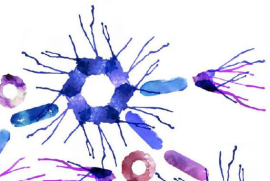


What is a maintenance therapy?

A maintenance therapy is by definition given continuously, without an interruption in dosing, and although it has the ability to induce long-term remission **it cannot result in a cure**.

Please note that and maintenance therapy is given continuously and if while on therapy there is a recurrence of, or ongoing, inflammatory activity*, it is an indication that there is a suboptimal response.

* In multiple sclerosis inflammatory activity typically refers to clinical relapses and/or focal MRI activity (new T2 lesions and or Gd-enhancing lesions).



A New Classification of Disease-Modifying Therapies for RMS

Maintenance/Escalation Therapy (MET)

Chronic therapy that is maintained and/or escalated over time resulting in changes in immune function only during active treatment

Immunomodulation · · · · Immunosuppression

MET that results in continuous immunomodulation

E.g. interferon-ß

MET that results in continuous immunosuppression

E.g. fingolimod

Immune Reconstitution Therapy (IRT)

Short course therapy resulting in long-term qualitative changes in immune function

Selective IRT (SIRT)

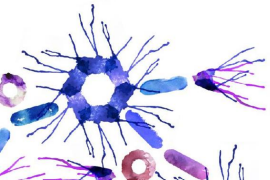
IRT that selectively affects the adaptive immune system

E.g. cladribine

Non-Selective IRT (NIRT)

IRT that affects both the innate & adaptive immune systems

E.g. alemtuzumab



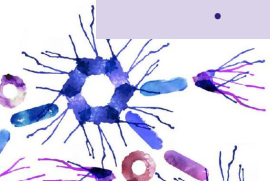
Maintenance Therapies vs. Immune Reconstitution Therapies (IRTs)

Maintenance Therapies

- Continuous treatment
- Low to very high efficacy
- Reversible
- Perceived to be lower risk
  - Cumulative, or increased, risk with time
- Examples
  - Laquinimod, GA, IFNβ, teriflunomide, BG12, fingolimod, natalizumab, daclizumab, anti-CD20
- Breakthrough disease
  - Suboptimal or failure to respond
  - NEDA reliable metric for efficacy
- Rebound activity
  - Highly likely
  - Can be life-threatening
- Pregnancy
- No potential for a cure
  - Rebound
  - SPMS and progressive brain atrophy

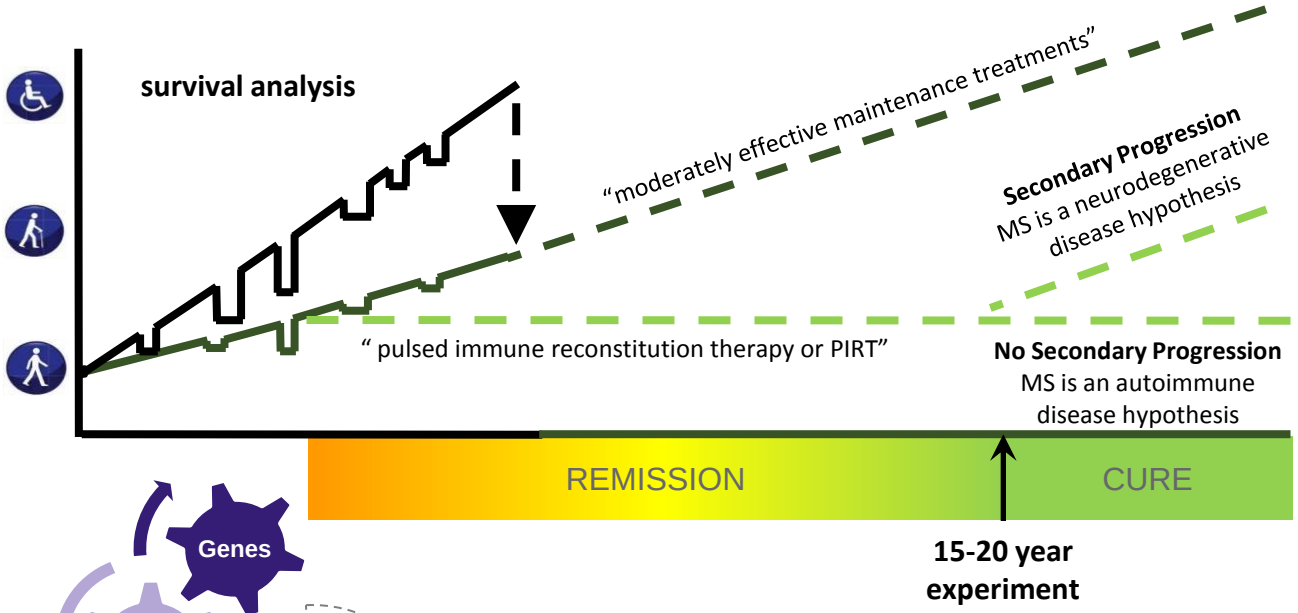
IRTs

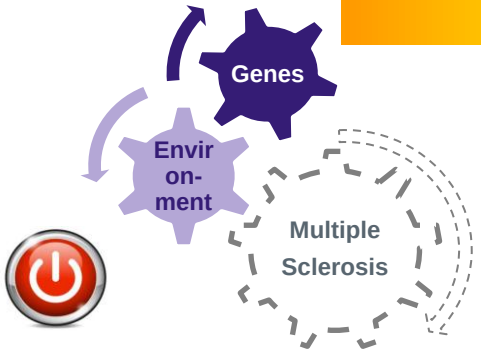
- Short-courses or pulsed therapy
- High to very high efficacy
- Irreversible
- Perceived to be higher risk
  - Frontloading of risk or reduced risk with time
- Examples
  - Non-selective: Mitoxantrone, alemtuzumab, HSCT- BMT
  - Selective: cladribine, anti-CD20
- Breakthrough disease
  - Marker for retreatment
  - NEDA unreliable to assess efficacy
- Rebound activity
  - Less likely
  - Unlikely to be life-threatening
- Pregnancy
- Potentially ‘curative’?
  - 15–20-year experiment

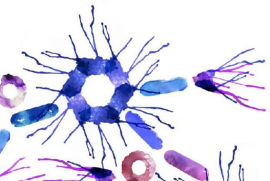


The following are not licensed for MS in the UK: laquinimod, daclizumab mitoxantrone, cladribine, anti-CD20 therapies, and BMT
IRTs = immune reconstitution therapies

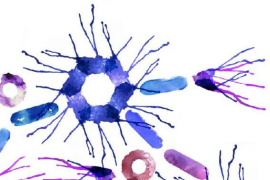
Defining an MS cure?



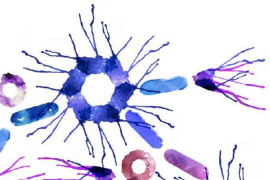




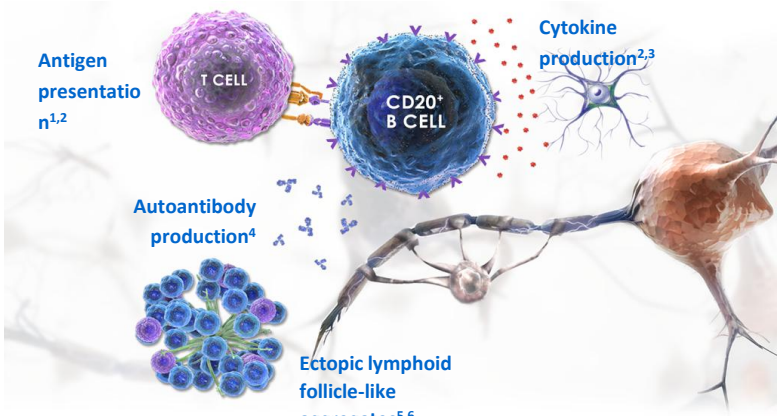
The evidence

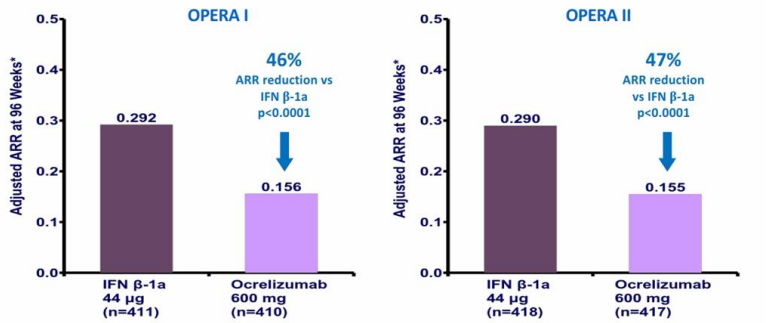


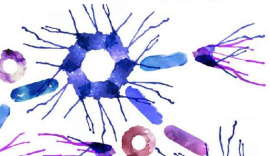
Ocrelizumab

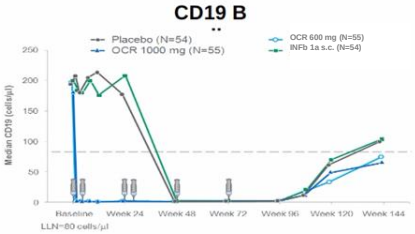


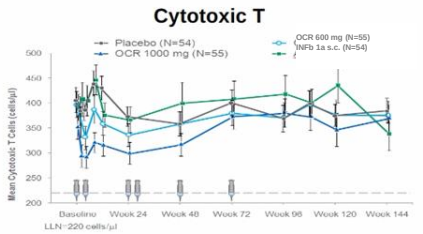
B cells play key functional roles in MS

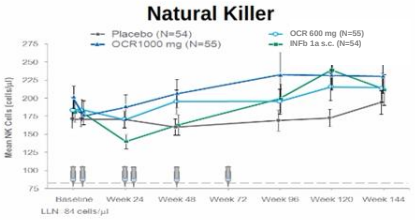


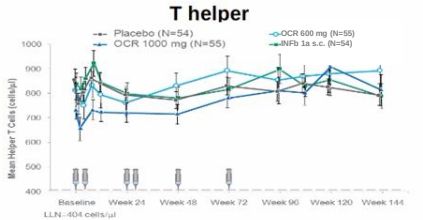






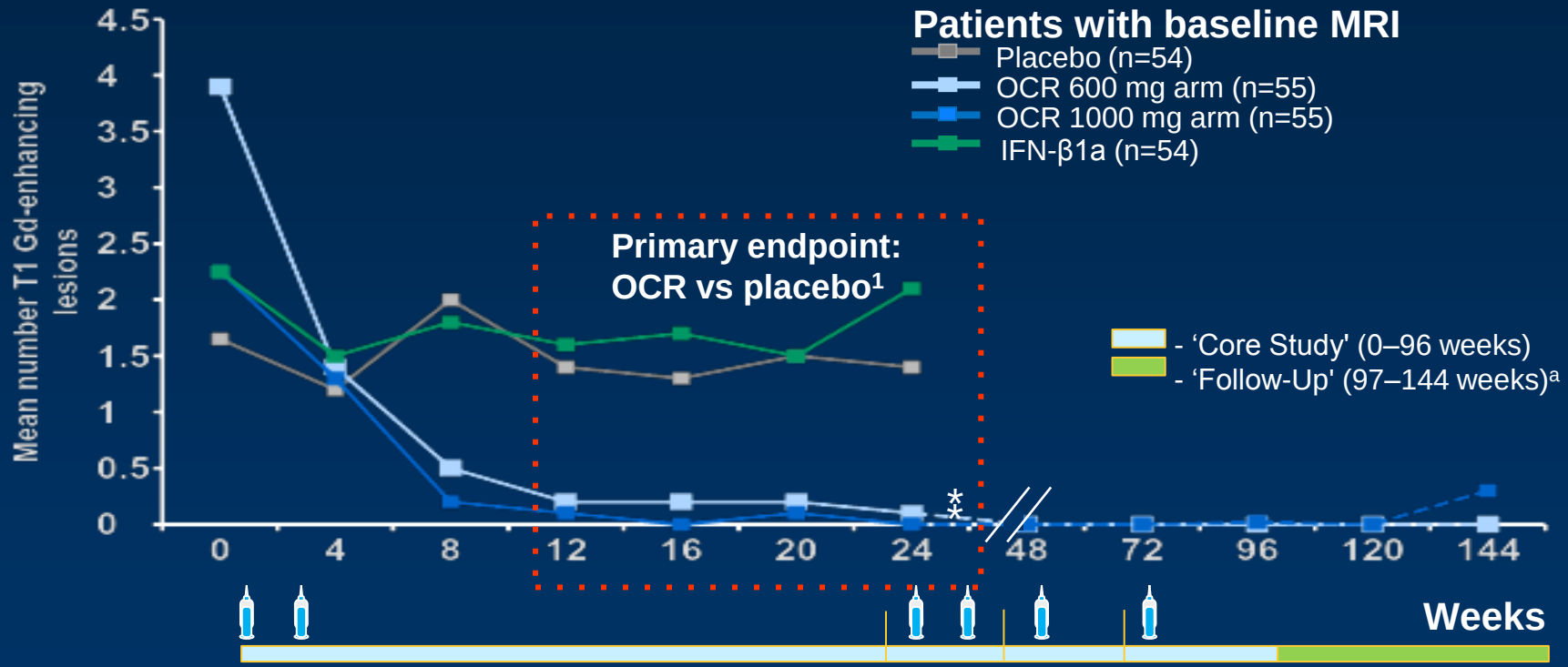






1. Crawford A, *et al. J Immunol* 2006;176(6):3498–506. **2.** Bar-Or A, *et al. Ann Neurol* 2010;67(4):452–61. **3.** Lisak RP, *et al. J Neuroimmunol* 2012;246(1-2):85–95. **4.** Weber MS, *et al. Biochim Biophys Acta* 2011;1812(2):239–45. **5.** Serafini B, *et al. Brain Pathol* 2004;14(2):164–74. **6.** Magliozzi R, *et al. Ann Neurol* 2010;68(4):477–93.

The Reduction in Gd-Enhancing T1 Lesions by OCR Is Maintained Through 144 Weeks

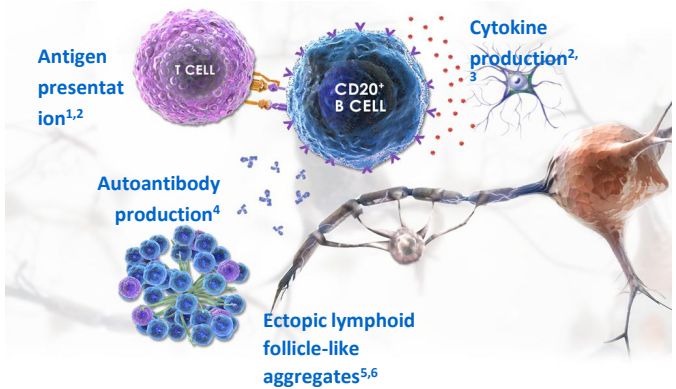


*p<0.0001 for both OCR doses vs placebo, N (for primary analysis): Placebo=54, OCR 600 mg=51, OCR 1000 mg=52, IFN-β1a=52[2]
[a]Patients who withdrew during earlier treatment cycles were also included in the follow-up periods

1. Kappos L, *et al. Lancet*. 2011;378(9805):1779–87; 2. Kappos L, *et al.* Abstract presented (P362) ECTRIMS 2012 , October 12

Slide courtesy of Stephen Hauser

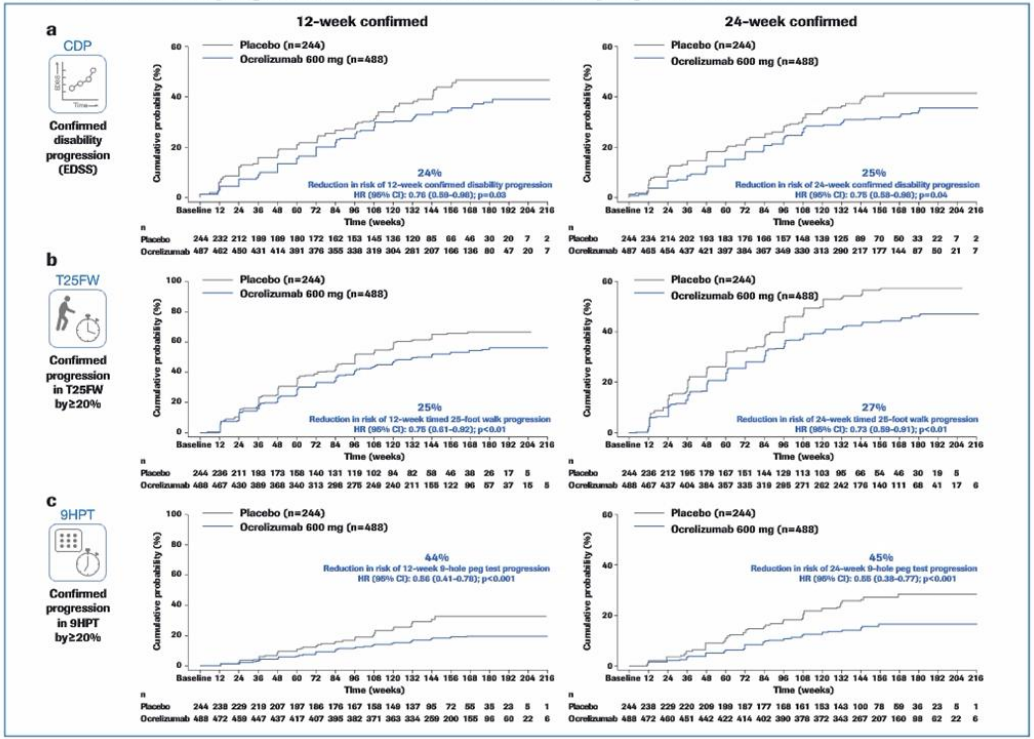
Primary Progressive MS



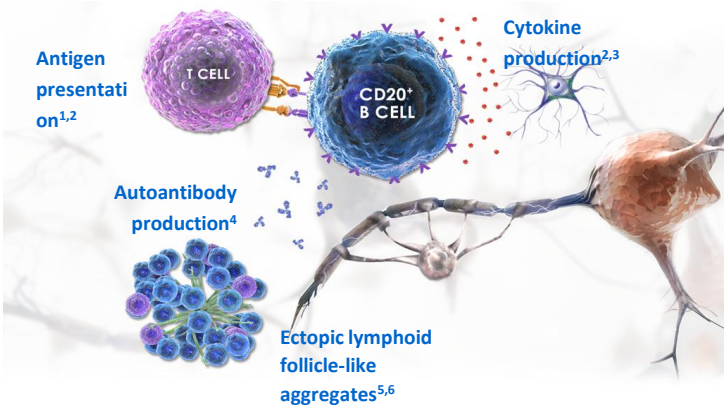
n (%)	Placebo n=239	Ocrelizumab 600 mg n=486
Deaths	1 (0.4) Road traffic accident *Sudden cardiac death* *Aspiration*	4 (0.8) Pulmonary embolism Pneumonia Pancreas carcinoma Pneumonia aspiration
Malignancies	2 (0.8) Cervix adenocarcinoma *in situ* (N=1) Basal cell carcinoma (N=1)	11 (2.3) Breast cancers (N=4) Endometrial adenocarcinoma (N=1) T-cell lymphoma (N=1) Histiocytoma (sarcoma) (N=1) Basal cell carcinoma (N=3)

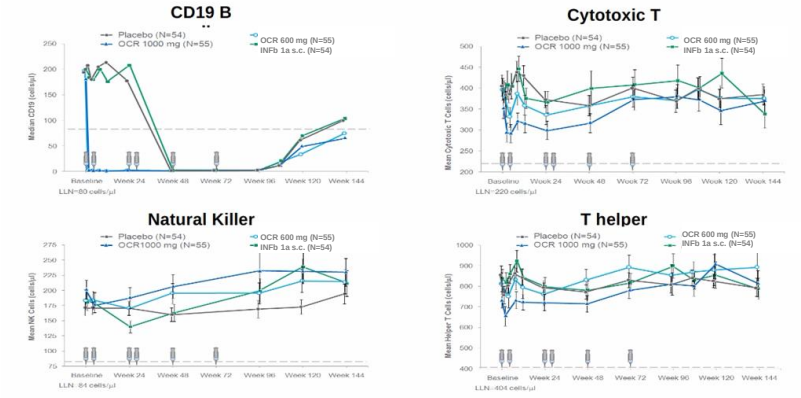
An Exploratory Analysis of 12- and 24-Week Confirmed Composite Disability Progression in Patients With Primary Progressive Multiple Sclerosis in the ORATORIO Trial

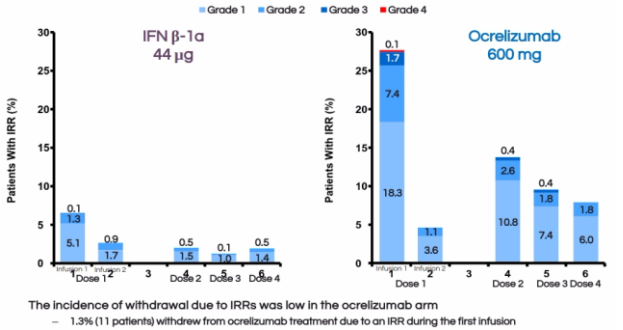
Figure 3. Time to onset of 12- and 24-week confirmed disability progression as measured by (a) EDSS, (b) ≥20% progression in T25FW and (c) ≥20% progression 9HPT[a]

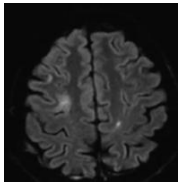


Other adverse events

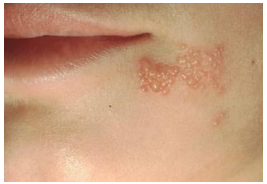




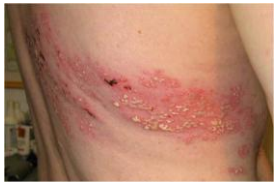




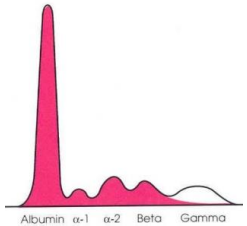
Carryover PML



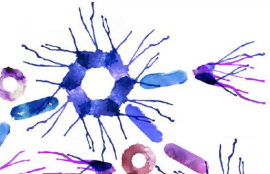
HSV



HZV

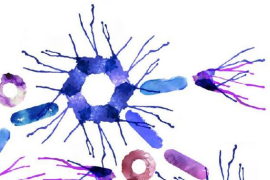


Hypogammagloulinaemia



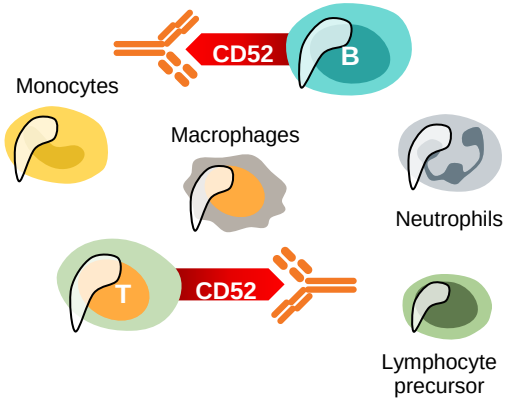
1. Crawford A, *et al. J Immunol* 2006;176(6):3498–506. **2.** Bar-Or A, *et al. Ann Neurol* 2010;67(4):452–61. **3.** Lisak RP, *et al. J Neuroimmunol* 2012;246(1-2):85–95. **4.** Weber MS, *et al. Biochim Biophys Acta* 2011;1812(2):239–45. **5.** Serafini B, *et al. Brain Pathol* 2004;14(2):164–74. **6.** Magliozzi R, *et al. Ann Neurol* 2010;68(4):477–93.

Alemtuzumab



Alemtuzumab: mechanism of action

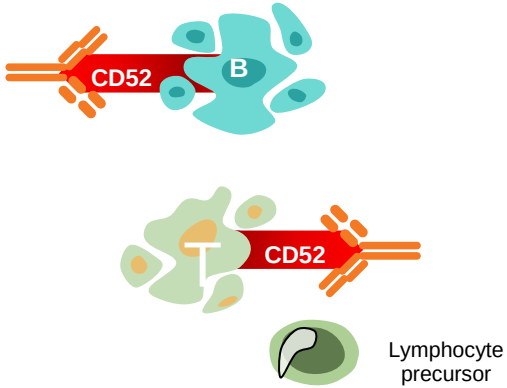
1. Selection



Targets T and B cells thought to mediate MS inflammation[1]

- Animal studies indicate that innate immune cells that express lower levels of CD52 are minimally or transiently impacted by alemtuzumab treatment[2]

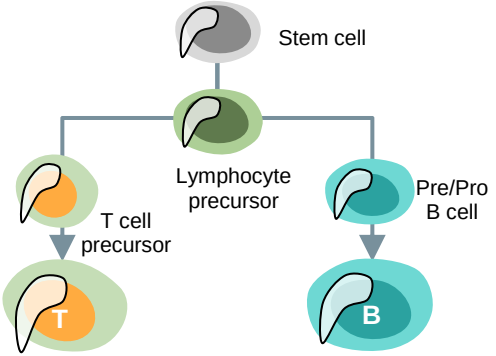
2. Depletion



Decreases MS inflammation

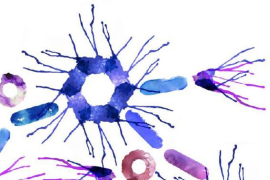
- Alemtuzumab selectively depletes circulating T and B cells[2,3]
- Many lymphocytes remain present in lymphoid organs after treatment[2,3]

3. Repopulation



Reduces MS disease activity

- Lymphocyte progenitor cells are presumably unaffected by alemtuzumab[2,4,5]
- A distinctive pattern of T- and B-cell repopulation begins within weeks, potentially changing the balance of the immune system[2,4,5]



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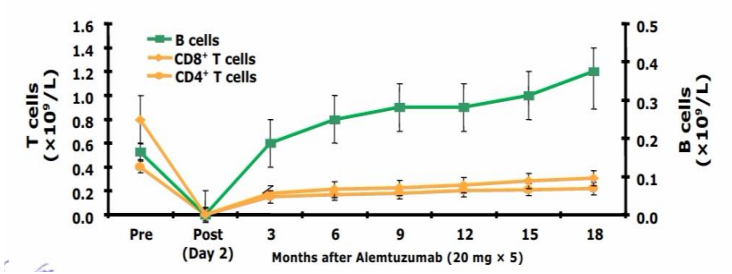
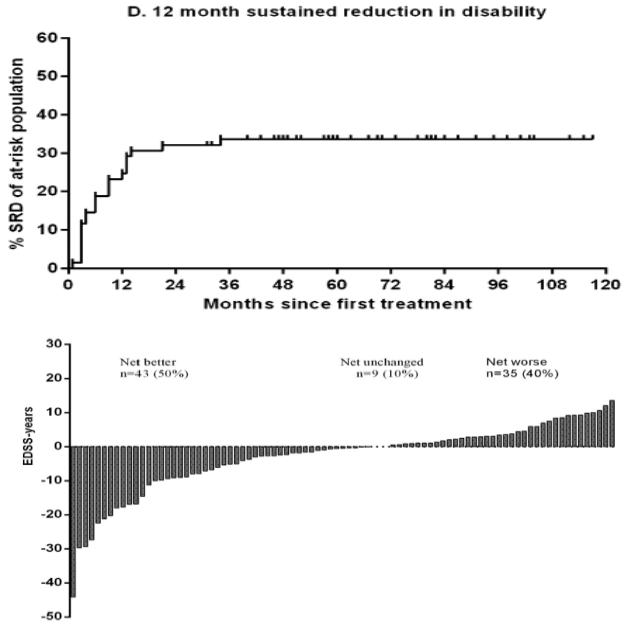
T- and B-cell Pharmacodynamics

- Alemtuzumab depleted circulating lymphocytes in SPMS patients treated between 1994–1997 (N=29)
  - CD4 and CD8 counts were 30-40% of pretreatment values 18 months later[1]
  - B cells repopulated more rapidly, with counts reaching 179% of pretreatment values at 18 months



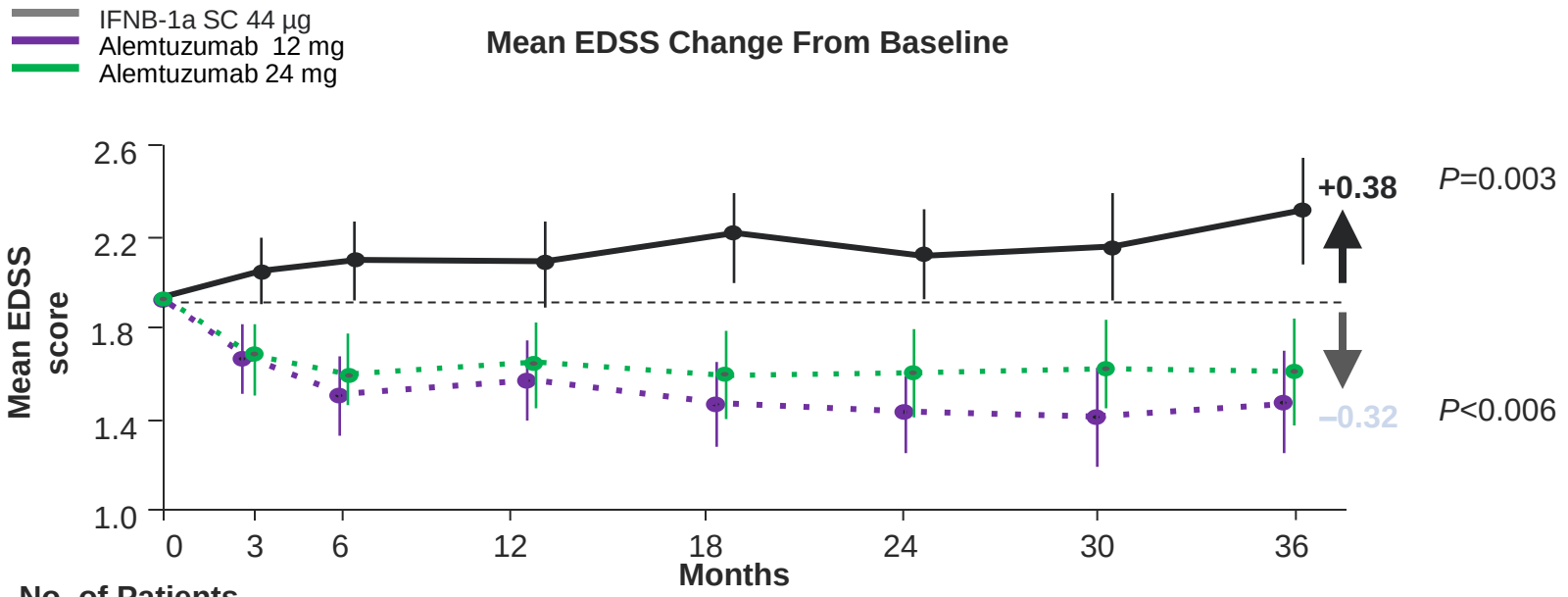
Coles AJ et al. *Lancet* 1999;354:1691-5.



"Four alemtuzumab-treated patients (5%) fulfilled the definition of secondary progression of two consecutive SAD events."

Tuohy et al. J Neurol Neurosurg Psychiatry 2014;0:1–8.

Sustained improvement of pre-existing disability in patients treated with Alemtuzumab



Coles AJ, et al. *N Engl J Med*. 2008;359:1786-1801.

P3.053

Durable Efficacy of Alemtuzumab Over 10 Years: Long-term Follow-up of Patients With RRMS From the CAMMS223 Study

Alasdair J Coles,[1] Mario Habek,[2] Ann D Bass,[3] Vesna Brinar,[4] Anton Vladic,[5] David H Margolin,[6] Edward J Fox[7]; on behalf of the CAMMS223 Investigators

[1]University of Cambridge School of Medicine, Cambridge, UK; [2]University of Zagreb, Zagreb, Croatia; [3]Neurology Center of San Antonio, San Antonio, TX, USA; [4]Zagreb Medical School and University Hospital Center, Zagreb, Croatia; [5]General Hospital "Sveti Duh", Zagreb, Croatia; [6]Sanofi Genzyme, Cambridge, MA, USA; [7]Central Texas Neurology Consultants, Round Rock, TX, USA

OBJECTIVE

- To evaluate the 10-year efficacy and safety profile of phase 2 CAMMS223 alemtuzumab 12 mg-treated patients who enrolled in the ongoing Extension Study

INTRODUCTION

- Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) in >50 countries
- In the phase 2 CAMMS223 trial (NCT00050778) and the phase 3 CARE-MS I (NCT00530348) trial in patients who were treatment-naive, and in the phase 3 CARE-MS II trial (NCT00548405) in patients who had an inadequate response to prior therapy at baseline, alemtuzumab demonstrated greater improvements in clinical and MRI outcomes compared with subcutaneous interferon beta-1a (SC IFNB-1a) in patients with active RRMS[1-3]
- Five-year data from the CAMMS223 study, the CARE-MS I and II studies, and the Extension Study (NCT00930553) have demonstrated durable efficacy of alemtuzumab, with most patients not receiving alemtuzumab retreatment or other disease-modifying therapy (DMT)[4]
- A consistent safety profile was demonstrated across the clinical development program[1-4]
  - The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs[1-4]

METHODS

Study Design

- CAMMS223 was a phase 2, randomized, rater-blinded, 3-year study of alemtuzumab versus SC IFNB-1a (44 µg 3 times per week) in treatment-naive patients with active RRMS[5]
  - Patients randomized to alemtuzumab received up to 2 annual courses of 12 or 24 mg/day IV (on 5 consecutive days at baseline and on 3 consecutive days 12 months later)
  - In the core CAMMS223 study, a third course was possible ≥12 months after the last course, based on T-cell counts
- Patients could participate in an extended follow-up period (minimum additional 2 years) in the CAMMS223 study[4]
  - Retreatment criteria in the CAMMS223 extension period were not contingent upon evidence of disease activity in all patients
- CAMMS223 patients could enroll in the same Extension Study (minimum additional 5 years) that patients completing CARE-MS I and CARE-MS II enrolled, in which they could receive further alemtuzumab retreatment (12 mg on 3 consecutive days ≥1 year after the most recent course; Figure 1)[7]
  - Retreatment criteria were ≥1 protocol-defined relapse, or ≥2 new/enlarging T_2 hyperintense and/or new gadolinium-enhancing T_1 brain or spinal cord lesions on MRI
- In the Extension Study, use of other DMTs was permitted at the investigator's discretion

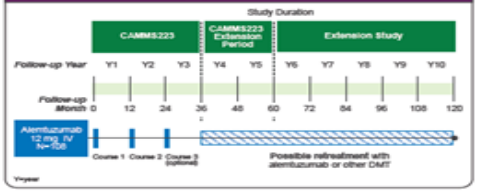
Efficacy Endpoints

- Efficacy endpoints included:
  - Annualized relapse rate (ARR) and proportion of patients free from relapses[4]
  - Disability outcomes (assessed quarterly using the Expanded Disability Status Scale [EDSS]):
    - Proportion of patients with 6-month confirmed disability worsening (increase of ≥1.0 EDSS point [or ≥1.5 points if baseline EDSS=0])

Statistical Analysis

- These interim analyses were based on all available data through Year 5 of the ongoing Extension Study (10 total years of follow-up)
- The safety analysis includes all safety data reported to CAMMS223, the CAMMS223 extension period, or the Extension Study

Figure 1. CAMMS223 and Ongoing Extension Study Data Included in the Analysis



CONCLUSIONS

- Alemtuzumab demonstrated durable clinical efficacy through Year 10
- Safety findings were consistent with those of other alemtuzumab clinical trials
- At 10 years, most patients have improved (≥1-point) or stable EDSS scores relative to baseline
- Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continuous treatment for RRMS patients through 10 years

RESULTS

Patients

- In CAMMS223, 92 of 108 patients who received alemtuzumab 12 mg completed 3 years of follow-up; 72 patients participated in the CAMMS223 extended follow-up period
- Of the 60 patients who entered the ongoing Extension Study, 57 (95%) remained on study at Year 10
- Of the 60 patients who enrolled in the Extension Study, 20 (33%) received only the initial 2 courses over 10 years
- Of the 39 (65%) patients receiving >2 alemtuzumab courses, 26 (67%) only received 3 courses (Figure 2)
  - Seven (12%) patients received a total of 4 alemtuzumab courses, with all receiving the fourth course after Year 5
  - Six (10%) received a total of 5 courses, with all receiving the fifth course after Year 7
  - Of patients who received retreatment in the Extension Study, in which retreatment criteria were based on evidence of relapse or radiological activity, relapse was the most common reason given by the investigator (13 [86%] of the 19 courses for which a reason was provided)

Efficacy

- Through 10 years of follow-up, a low ARR was maintained (Figure 3)
- Mean EDSS score change from baseline (SD) was +0.12 (1.407) over 10 years (Figure 4A)
  - Disability scores remained stable or improved over 10 years in the majority of patients treated with alemtuzumab (Figure 4B)
- Most patients (76%) showed no evidence of 6-month confirmed disability worsening

Figure 2. Proportion of Patients Who Received Alemtuzumab Retreatment Through Year 10

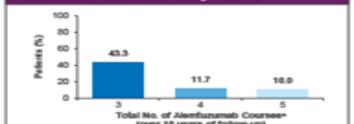


Figure 3. Durable Effect of Alemtuzumab on Relapses Through 10 Years

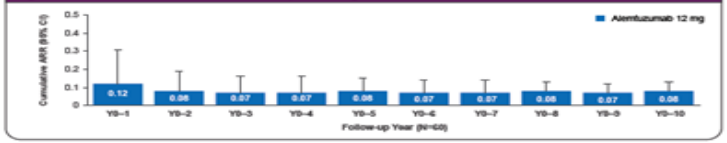
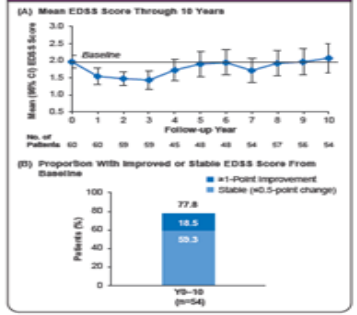


Figure 4. EDSS Scores Through 10 Years of Follow-up



Safety

- No patients withdrew from the ongoing Extension Study due to AEs
- AEs were most prevalent in the first year (1021.7 events/100 patient-years), declining after Year 2
- The most commonly reported AEs in patients who received retreatment in the Extension Study were IARs (headache, pyrexia, nausea, and rash; Table 1)

Table 1. Incidence of IARs by Course Through Year 10

Events, n (%)	Course 1 (n=60)	Course 2 (n=59)	Course 3 (n=39)	Course 4 (n=13)	Course 5 (n=6)
IARs	59 (98.3)	47 (79.7)	30 (76.9)	8 (61.5)	3 (50.0)
Serious IARs	0	0	3 (7.7)	0	0

- Infection rate was highest during Year 1 (93.3 events/100 patient-years), declining thereafter; serious infections occurred in <4% of patients during each year
  - Of those patients who experienced infections, 78% experienced their first infection within 1 year of the last treatment course
- Thyroid AE rates peaked in Year 3 (19.1 events/100 patient-years), and declined thereafter, similar to other studies reporting long-term follow-up with alemtuzumab[6-9]; serious thyroid AEs occurred in <4% of patients during each year
- There was a single case of immune thrombocytopenia in Year 4 and there were no cases of glomerulonephritis
- Of the 2 patients who had a malignancy event, both were melanomas (both occurring in Year 10 of follow-up)
  - One patient with a family history of melanoma had Grade 4 malignant melanoma (left foot), deemed related to study drug, and was resolved via surgical excision
  - The other patient was diagnosed with Grade 2 melanoma in situ (abdomen), not related to study drug, and resolved via surgical excision
- No deaths occurred in the CAMMS223 cohort during the ongoing Extension Study

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Acknowledgments and Disclosures

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CAMMS-MS=Comparison of Alemtuzumab and RebiF Efficacy in Multiple Sclerosis

RebiF® is a registered trademark of EMD Serono Canada Inc.

Alemtuzumab is approved in many countries around the world for treatment of adults with relapsing forms of MS. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should be reserved for patients who generally have had an inadequate response to 2 or more therapies indicated for the treatment of MS. In the EU, it is approved to treat patients with relapsing-remitting MS with active disease defined by clinical or imaging features. This material may contain information that is outside of the approved labeling in some countries.

•Relapses were confirmed per the protocol definition by an independent, blinded relapse adjudication panel in the core study; in the Extension Study, relapses were confirmed per the protocol definition by the investigator.

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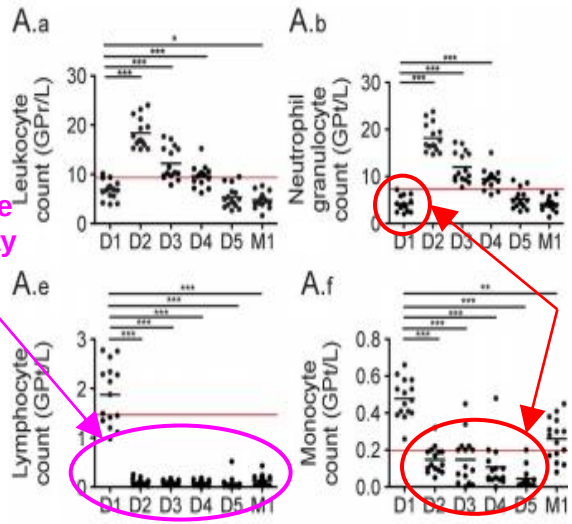
Funding provided by Sanofi Genzyme

Alemtuzumab innate immunity & T-cell pharmacodynamics



Adaptive Immunity

Innate Immunity

Thomas et al. Neurol Neuroimmunol Neuroinflamm 2016;3:e228;

P5.338

Efficacy and Safety of Alemtuzumab in Patients With RRMS Is Durable Over 10 Years: Follow-up From the CAMMS223 Study

Krzysztof W Selmaj[1], Mario Habek[2], Ann Bass[3], David Brassat[4], Vesna Brinar[2], Alasdair J Coles[5], Anton Vladic[2], Sibyl E Wray[6], David H Margolin[7], Karthinathan Thangavelu[7], Madalina Chiriac[7], Linda Kasten[8], Edward J Fox[9]; on behalf of the CAMMS223 and CAMMS03409 Investigators
[1]Medical University of Łódź, Łódź, Poland; [2]University Hospital Centre Zagreb, Zagreb, Croatia; [3]Neurology Center of San Antonio, San Antonio, TX, USA; [4]University of Toulouse, Toulouse, France; [5]University of Cambridge School of Medicine, Cambridge, UK; [6]Hope Neurology MS Center, Knoxville, TN, USA; [7]Sanofi, Cambridge, MA, USA; [8]PROMETRIKA, LLC, Cambridge, MA, USA; [9]Central Texas Neurology Consultants, Round Rock, TX, USA

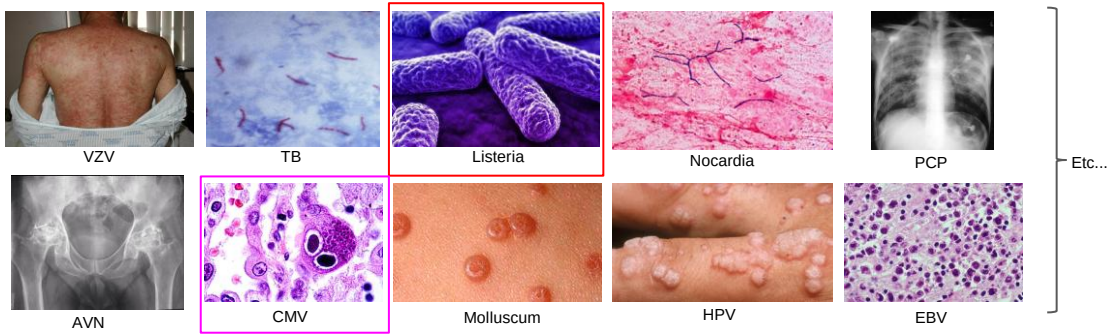
Table 1. Key Autoimmune Events; Post-Marketing Frequency, and Clinical Trial Incidence Data

Autoimmune Event	Post-Marketing Estimated Frequency (AEs/SAEs) (%)	Clinical Trials SAEs Incidence (%)[a]
ITP	0.58	1.4
Hemolytic anemia	0.05	0.3
Pancytopenia	0.10	0.2
Nephropathies (including anti-glomerular basement membrane disease)	0.13	0.4
Neutropenia	0.48	0.2

[a]Pooled CAMMS223, CARE-MS I and II, and CAMMS03409 data, with median follow-up of 6.1 years (maximum 12 years)

- Since approval, labeling has included information regarding an increased frequency of infection and the potential for opportunistic infections following treatment with alemtuzumab
  - As anticipated, reports of opportunistic infections have been received in the post-marketing setting; the most commonly reported were *Listeria monocytogenes* (estimated frequency: 0.26%) and cytomegalovirus (estimated frequency: 0.13%)

AAN 2017, Boston

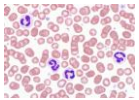


AVN = avsacular necrosis, HPV = human papiloma virus, PCP = Pneumocystis carinii pneumonia, VZV = varicalle zoster virus

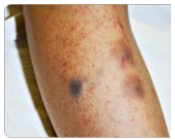
1. Non-selective leukocyte depletion
   a. Leukopaenia (neutrophils & monocytes)
   b. Lymphopaenia (prolonged)
   c. Infusion reactions (moderate to severe)
   d. Complications of corticosteroids
2. Immunosuppression
   a. Opportunistic infections
      i. Acute bacterial, e.g. Listeriosis
      ii. Typical opportunistic, e.g. CMV
3. Aberrant immune reconstitution
   a. Secondary autoimmunity
   b. Anti-drug antibodies

Risks identified

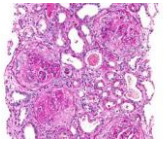
Identified Risk		Rate in Alemtuzumab-Treated Patients	Notes
ITP	**Auto-immune Events**	~1% (1 fatality prior to implementation of monitoring program)[1]	• Onset generally occurred 14-36 mo after first exposure[1] • Most cases responded to first-line medical therapy[1]
Nephropathies		0.3% (anti-GBM n=2)[1]	• Generally occurred within 39 mo after last administration[1] • Responded to timely medical treatment and did not develop permanent kidney failure[2]
Thyroid disorders (Hypo-/hyper-)		~36%[a] (serious, 1%)[1]	• Onset occurred 6-61 mo after first Alemtuzumab exposure; peaked in year 3 and declined thereafter[3] • Most mild to moderate, most managed with conventional medical therapy, however, some patients required surgical intervention[1] • Higher incidence in patients with history of thyroid disorders[1]
IARs		>90% (serious, 3%)[1]	• Occurred within 24 h of Alemtuzumab administration[1] • Most mild to moderate; rarely led to treatment discontinuation[1] • May be caused by cytokine release following mAb-mediated cell lysis[1]
Infections		71% (serious, 2.7%)[1]	• Incidence highest during first mo after infusion; rate decreased over time[2] • More common with Alemtuzumab; mostly mild to moderate[1] • Generally of typical duration; resolved following conventional medical treatment[1]



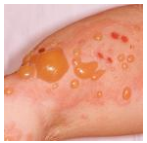
Immune neutropenia



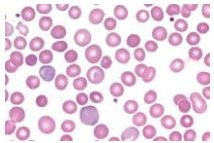
ITP



Goodpasture's Syndrome



Bullous Pemphigoid

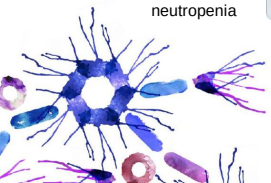


Haemolytic anaemia

Acquired Haemophilia

Pernicious Anaemia

Etc...



[a]Through 48 mo after first exposure.

ITP, immune thrombocytopenia; **GBM**, glomerular basement membrane; **mAb,** monoclonal antibody.

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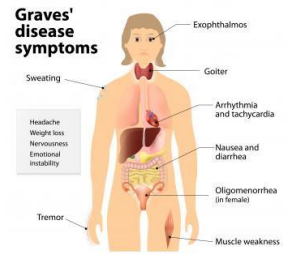
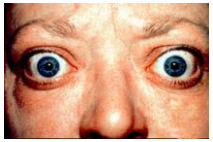
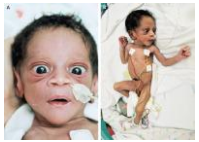


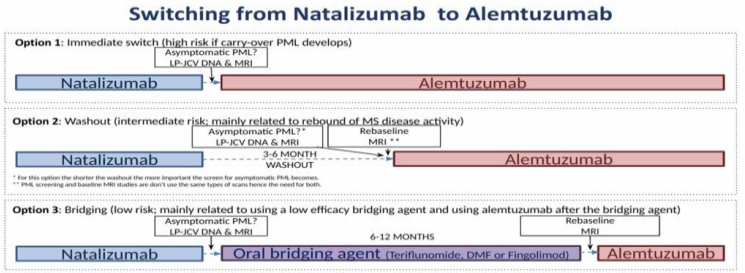


Grave's orbitopathy



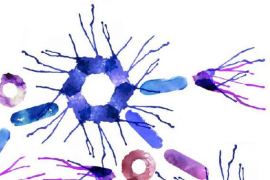
Neonatal hyperthyroidism

Switching



Giovannoni et al. Pract Neurol. 2016 Oct;16(5):389-93.

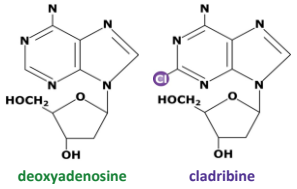
Oral cladribine

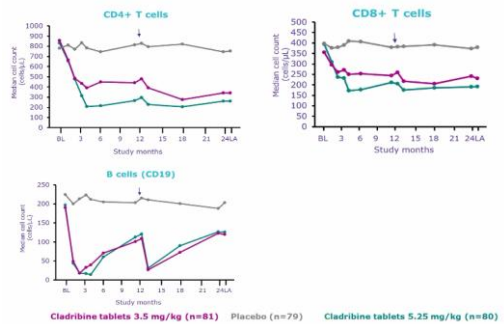


Cladribine must enter cells and be activated in order to exert its effect

Cladribine works by a 4-step mechanism:

1. Cladribine enters cell via nucleoside transporter
2. Accumulates intracellularly due to ADA resistance
3. Cladribine is activated by specific kinases
4. Activated Cladribine induces selective lymphocyte reduction



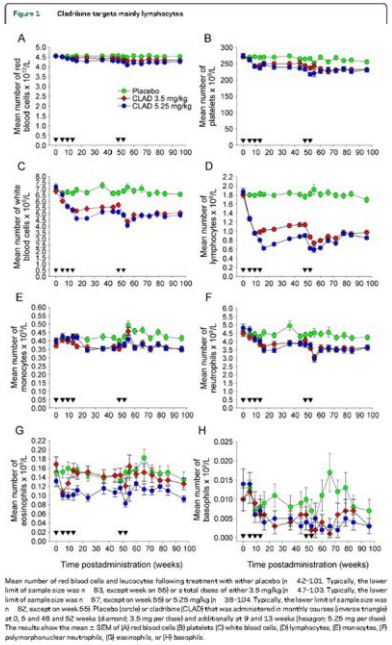


RBC's

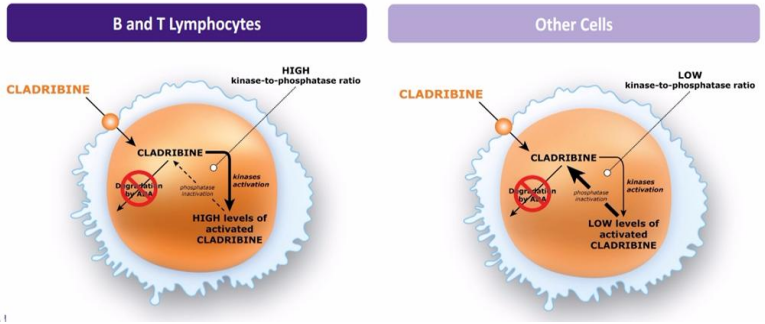
WCC's

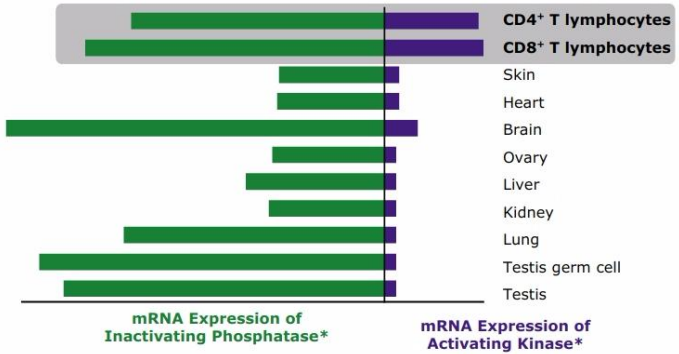
Mono's

Eosin's



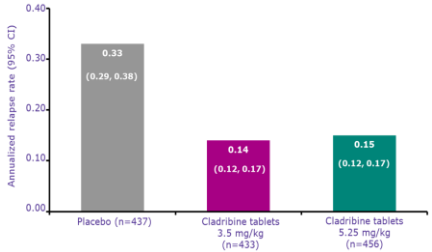
Baker et al. Neurol Neuroimmunol Neuroinflamm. 2017 Jun 5;4(4):e360.



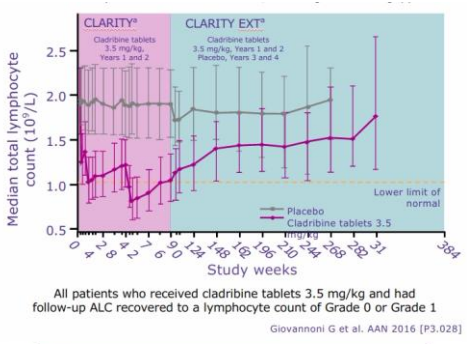


* One of the kinases is deoxycitidine kinase (DCK). The phosphatase is 5'-nucleotidase.
Leist TP, Weissert R. *Clin Neuropharmacol* 2011;34:28–35.

Efficacy & Safety

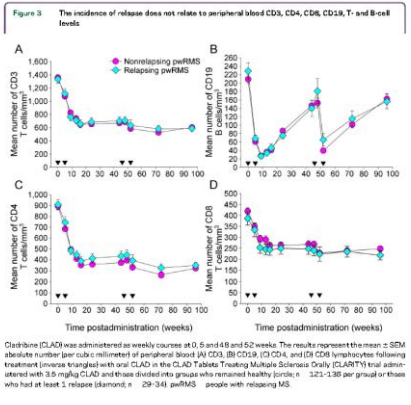


Giovannoni G et al. N Engl J Med 2010;362:416–26.



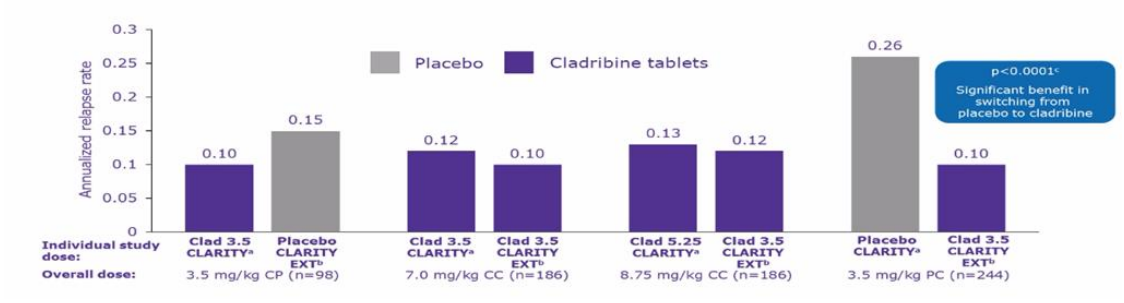
All patients who received cladribine tablets 3.5 mg/kg and had follow-up ALC recovered to a lymphocyte count of Grade 0 or Grade 1

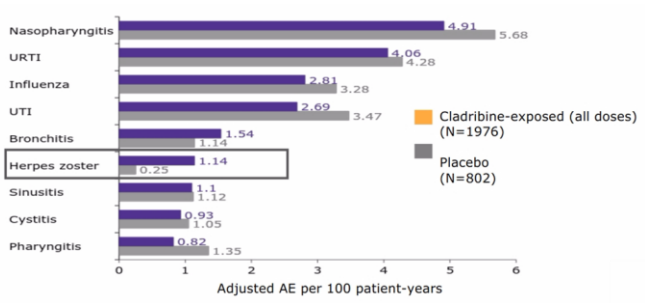
Giovannoni G et al. AAN 2016 [P3.028]

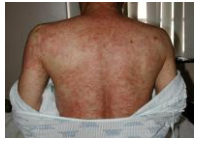


Cladribine (CLAD) was administered as weekly courses at 0, 5 and 48 and 52 weeks. The results represent the mean ± SEM absolute number (per cubic millimeter) of peripheral blood (A) CD3, (B) CD19, (C) CD4, and (D) CD8 lymphocytes following treatment (inverse triangles) with oral CLAD in the CLAD Tablets Treating Multiple Sclerosis Orally (CLARITY) trial administered with 3.5 mg/kg CLAD and those divided into groups who remained healthy (circle; n 121–138 per group) or those who had at least 1 relapse (diamond; n 29–34). pwRMS people with relapsing MS.

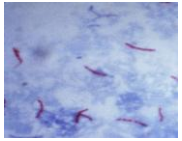
Baker et al. Neurol Neuroimmunol Neuroinflamm 2017;4:e3600.



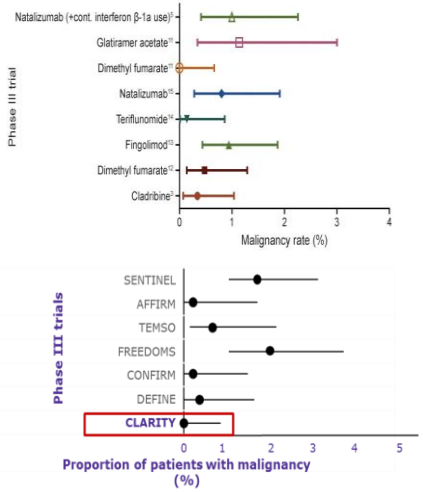




VZV



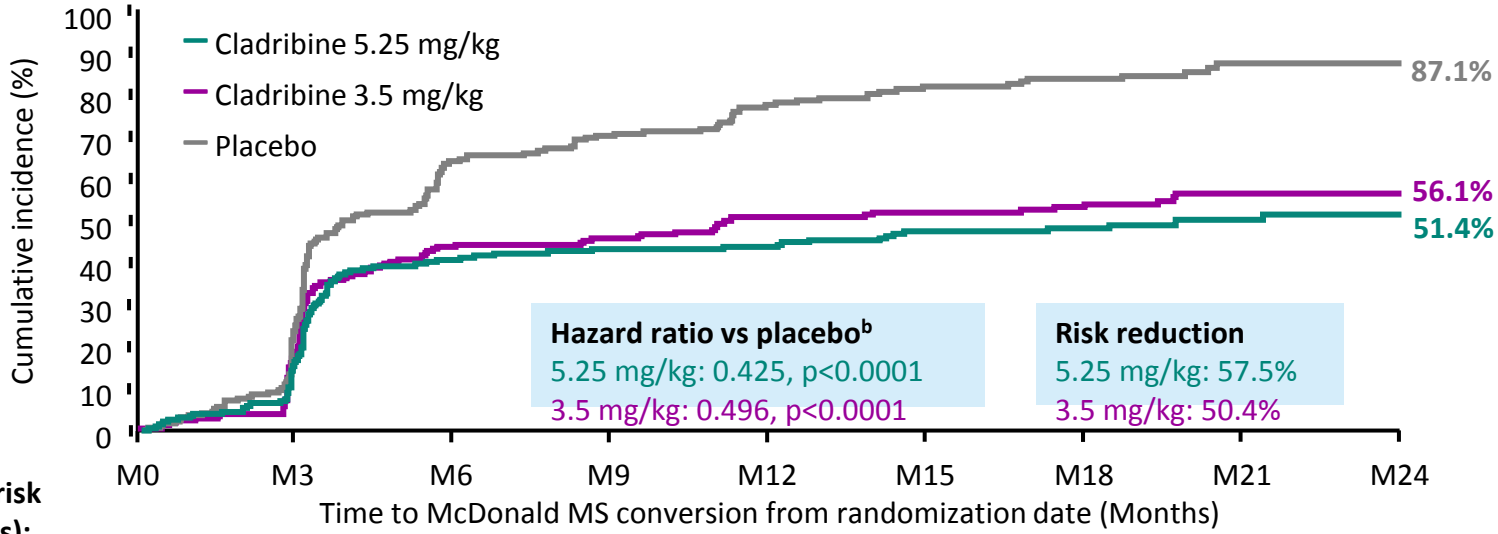
TB



Pakpoor J et al. Neurol Neuroimmunol Neuroinflamm 2015;2:e158

Treatment with Cladribine reduces the risk of conversion to McDonald 2005 MS in treatment-naïve patients with an FCDE[a]

ORACLE-MS

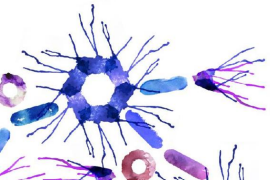


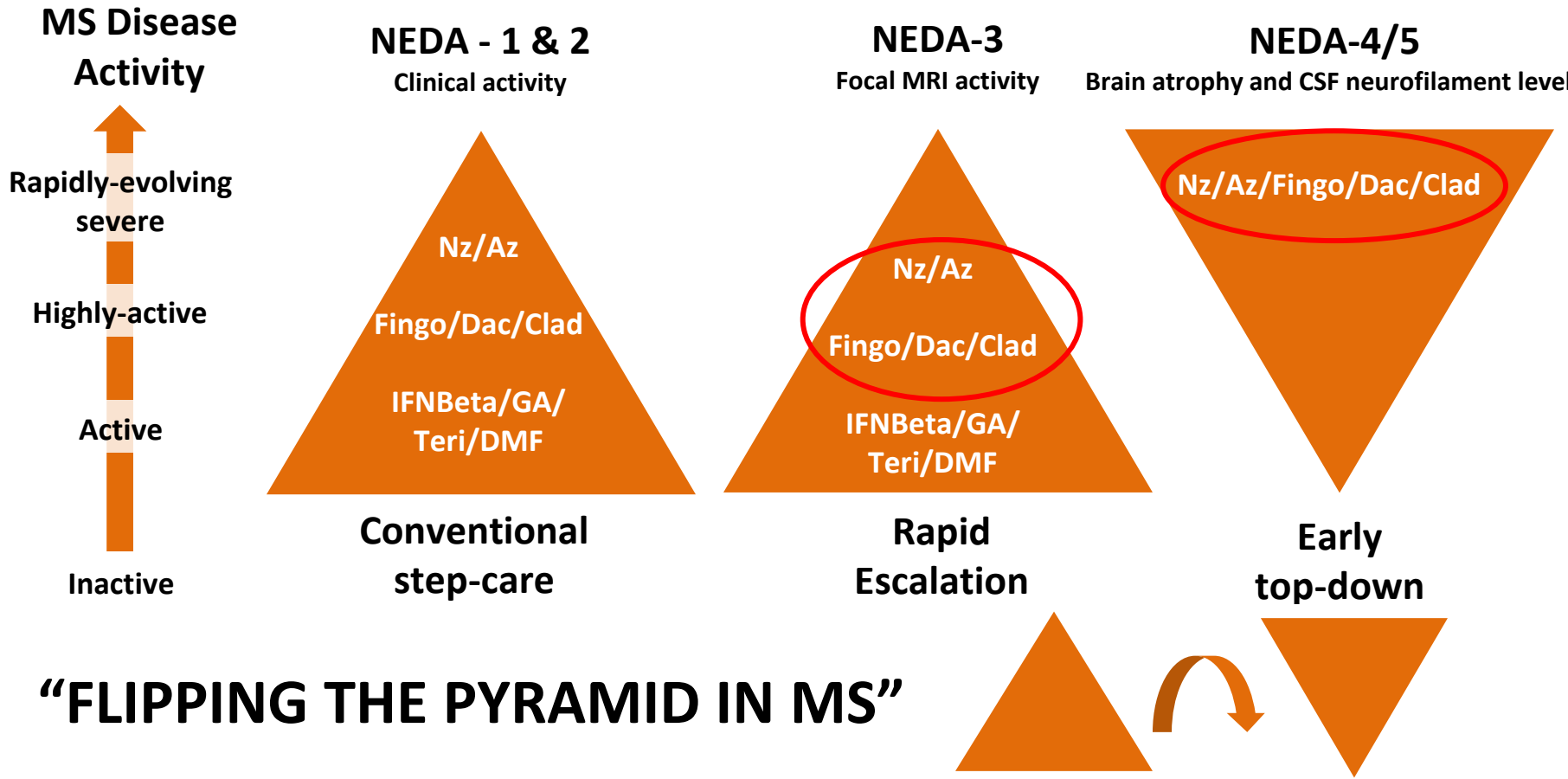
Patients at risk (conversions):

Cladribine 5.25 mg/kg	203 (0)	165 (37)	119 (82)	113 (87)	108 (88)	87 (95)	71 (96)	39 (98)	1 (99)
Cladribine 3.5 mg/kg	204 (0)	167 (36)	114 (88)	108 (92)	92 (102)	82 (104)	71 (107)	39 (110)	3 (110)
Placebo	201 (0)	143 (58)	71 (128)	58 (141)	43 (154)	32 (162)	23 (165)	13 (169)	2 (169)

[a]Patients enrolled in ORACLE-MS were treatment-naïve with an FCDE at high risk of converting to MS. [b]Cox proportional hazards model controlling for the randomization stratification factor (region). FCDE, first clinical demyelinating event; M, Month. Leist TP et al. Lancet Neurol 2014;13:257-67

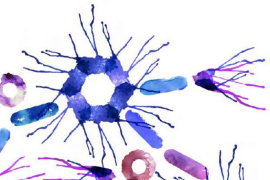
A changing treatment philosophy



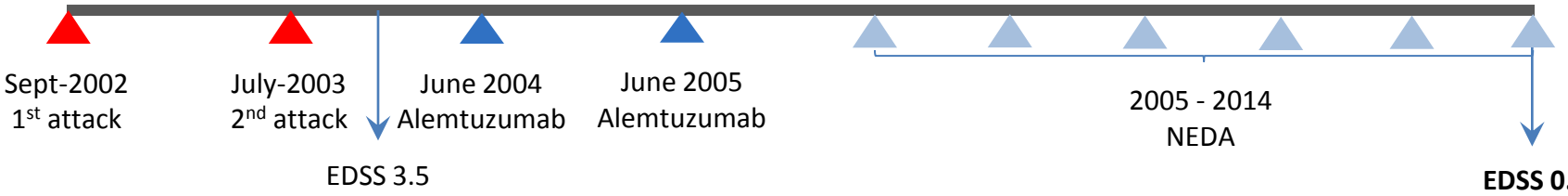


NEDA = no evident disease activity; NEDA-2 = clinical only (relapse-free and progression free); NEDA-3 = clinical and focal MRI activity; NEDA-4/5 = clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. IFNbeta = interferon-beta; GA = glatiramer acetate; Teri = teriflunomide; DMF = dimethyl fumarate; Fingo = fingolimod; Nz = natalizumab; Az = alemtuzumab; Dac = daclizumab, Clad = oral cladribine

Case studies

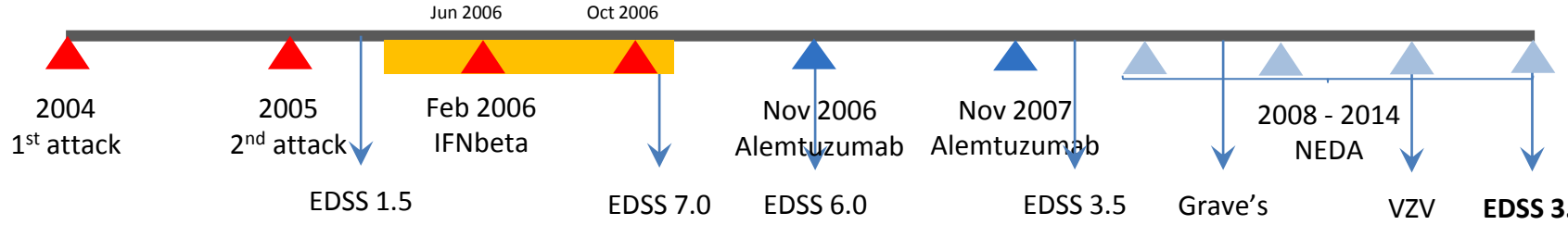


The cost of delayed access to highly active treatment

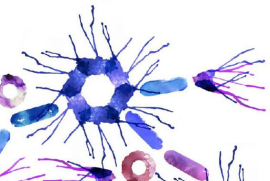


EDSS = 0.0: fully functional

20 month vs. 32 month delay or 2 relapses



EDSS = 3.5: unable to run, play tennis or walk down stairs quickly without the use of a handrail



Making a difference

BMJ Case Reports 2015; doi:10.1136/bcr-2014-208960

CASE REPORT

Timing is everything in the treatment of multiple sclerosis

Claire Louise McCarthy[1], Gavin Giovannoni[2], Alasdair John Coles[3]

+ Author Affiliations

Correspondence to
Professor Alasdair John Coles, ajc1020@medschl.cam.ac.uk

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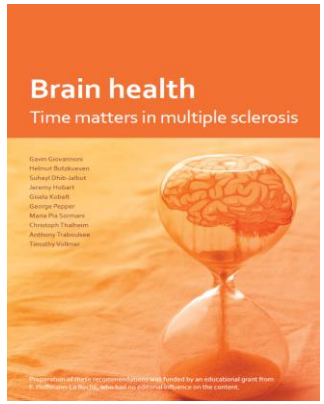
Summary

We present two similar cases of relapsing–remitting multiple sclerosis, both of whom received treatment with the monoclonal antibody alemtuzumab, but had significantly different long-term outcomes. Patient A is 12 years into his illness and was treated early in his disease course, he has no disability and continues to perform at a high level as a professional golfer. Patient B was initially started on interferon-β1a therapy and went on to have two disabling relapses on this treatment which resulted in a degree of fixed disability prior to the start of alemtuzumab. 10 years into his disease course he has moderate disability and daily symptoms of spasticity in his legs which impair his quality of life. These two contrasting cases highlight the difficult decision of when to start potent immune modulating therapies for multiple sclerosis in young adults who appear well early in their disease but have the potential to rapidly accrue irreversible disability from future relapses.



www.msbrainhealth.org

Case study

42-yr old British journalist, married with 2 children

War correspondent - frequent travel to Afghanistan, Ukraine, Iraq and Syria

Diagnosed RRMS late 2014:

Initial symptoms of sensory symptoms in feet and Lhermitte's phenomenon
Treated with dimethyl fumarate
Two disabling attacks in 2015 - ataxia and spinal cord lesion with weak legs

Disease activity:

Rapidly-evolving severe MS (RES)

Treatment:

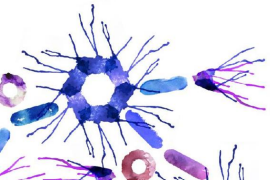
Eligible for Fingolimod, Natalizumab and Alemtuzumab

Natalizumab contra-indicated as found to be JCV-seropositive (index 1.86)
Offered fingolimod - was not keen about long-term immunosuppression
Interested in HSCT (not eligible under London HSCT guidelines) or alemtuzumab

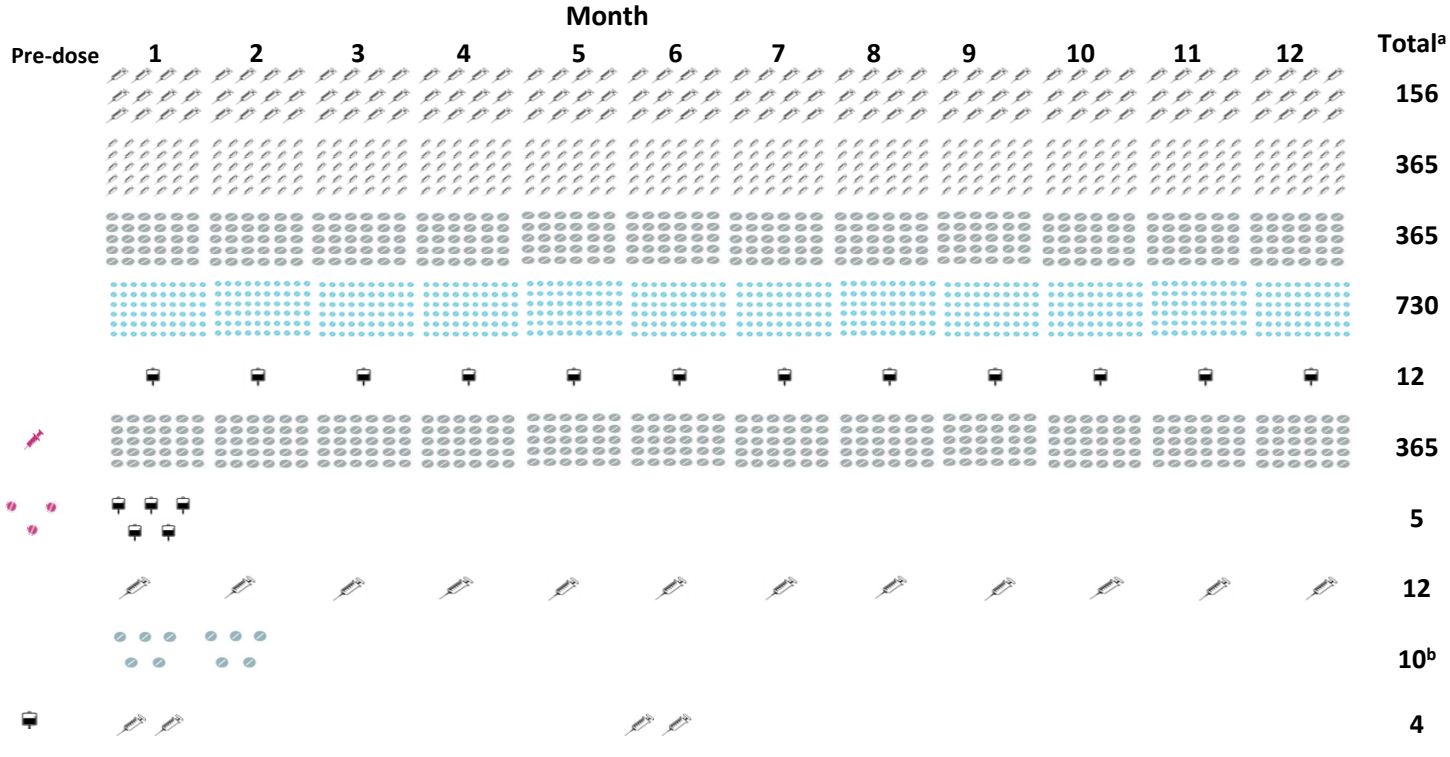
Major concerns about monitoring and accessing urgent treatment when abroad as war correspondent

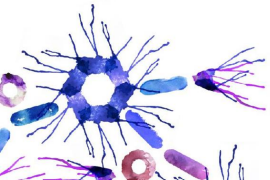
Joint decision to treat him with parenteral cladribine (two cycles given - Jan/Feb 2016 and 2017)

Burden of Treatment



Treatment Burden



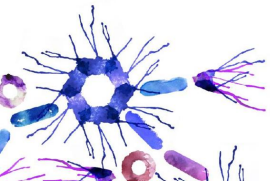


[a]Total number of administrations over the first 12 months of treatment. [b]3.5 mg/kg. 5 days of treatment separated by 1 month; total number of tablets dependent on weight. [c] These agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. IFN, interferon; sc, subcutaneous; SmPC, Summary of Product Characteristics. 1. Rebif® EU SmPC; 2. Copaxone® SPC; 3. Aubagio® EU SmPC; 4. Tecfidera® EU SmPC; 5. Tysabri® EU SmPC; 6. Gilenya® EU SmPC; 7. Lemtrada® EU SmPC; 8. Zinbryta® EU SmPC; 9. Giovannoni G, et al. N Engl J Med 2010;362:416–26; 10. Kappos L et al. Lancet 2011;378:1779–87; 11. Katsarava Z et al. BMC Neurol 2015;15:170; 12. Kruk ME, Schwalbe N. Clin Ther 2006;28:1989–95; 13. Devonshire V et al. Eur J Neurol 2011;18:69–77

Conclusion

- Treatment of MS is increasingly complex
  - –Different modes of action vs. different treatment philosophies
    - –maintenance escalation vs. IRTs (selective and non-selective)
  - –Monitoring requirement, e.g. lymphopaenia, LFTs, etc.
  - –De-risking strategies, e.g. JCV-testing
  - –Long-term vs. short-term immunosuppression
    - –cumulative vs. front-loading of risk
    - –adaptive and/or innate immunity affected
  - – Burden of treatment and monitoring
    - –impact on adherence and outcomes

- Emerging therapies; ocrelizumab, oral cladribine and HSCT
  - – all address an unmet need




Questions?