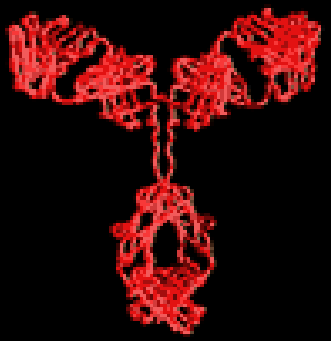
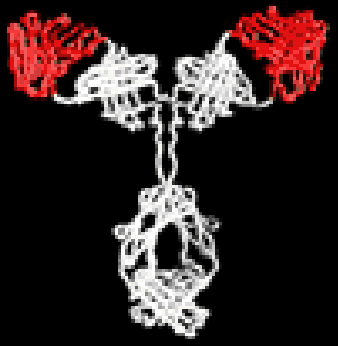
Inducing tolerance to Campath-1H (alemtuzumab) in the treatment of multiple sclerosis

Alasdair Coles
Herman Waldmann & Geoff Hale
Universities of Cambridge & Oxford

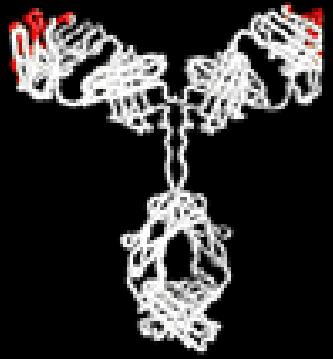
Approved therapeutic antibodies



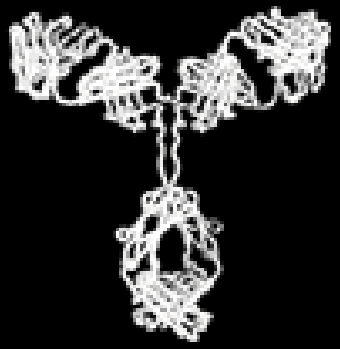
MOUSE
OKT3
BEXXAR
Zevalin



CHIMERIC
Rituxan
Remicade
Reopro
Simulect
Erbitux



HUMANIZED
Synagis
Herceptin
Zenapax
Myelotarg
Campath
Xolair
Raptiva
Avastin
Tsyabri
(Actemra-Japan)

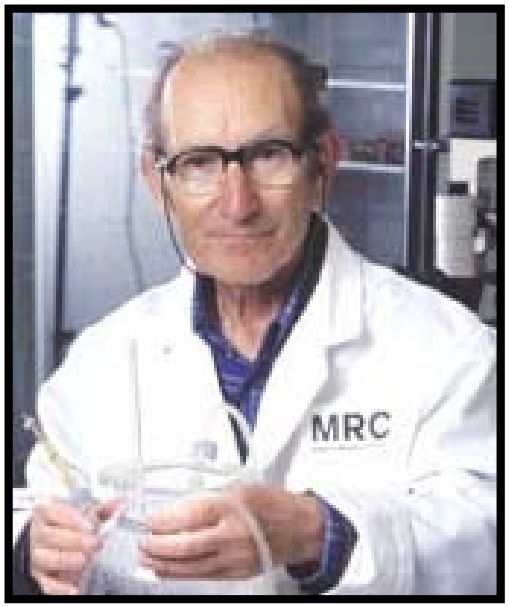


HUMAN
Humira
Vectibix

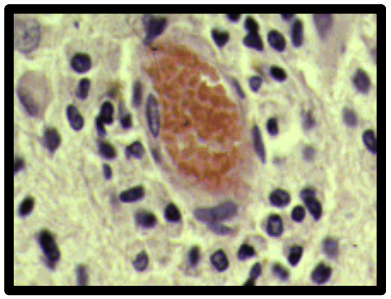
Alemtuzumab (Campath-1H)

- Humanised antibody against CD52
- depletes lymphocytes
- Licensed in 2001 for chronic lymphocytic leukaemia
- Exploratory trials in autoimmunity& transplantation

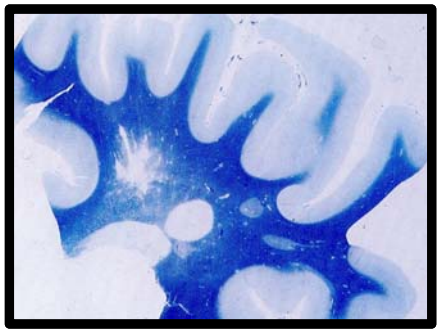
Herman Waldmann



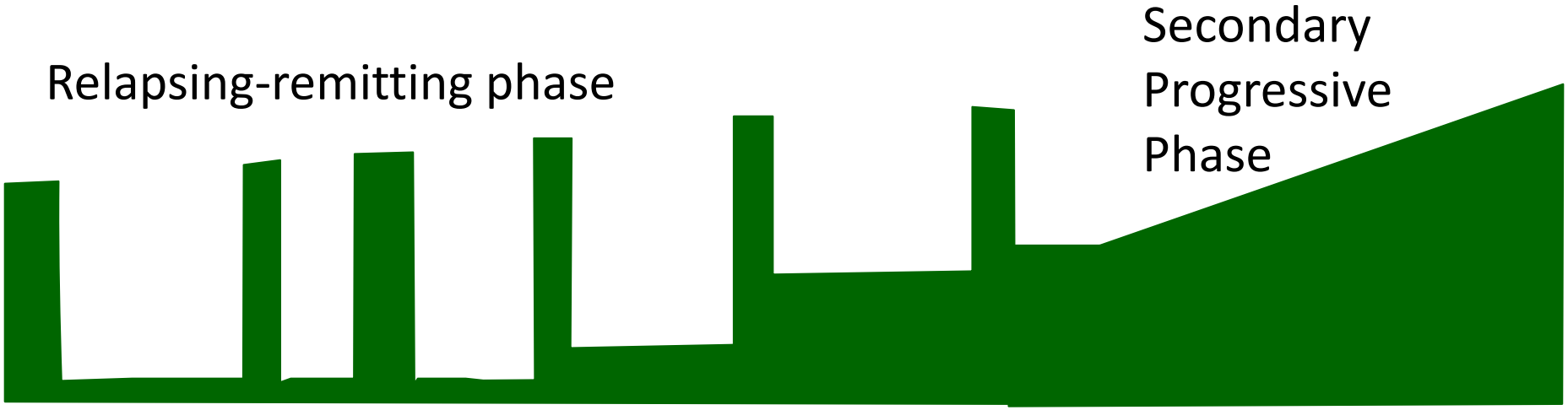
Cesar Milstein (1927-2002)
Nobel Prize 1985



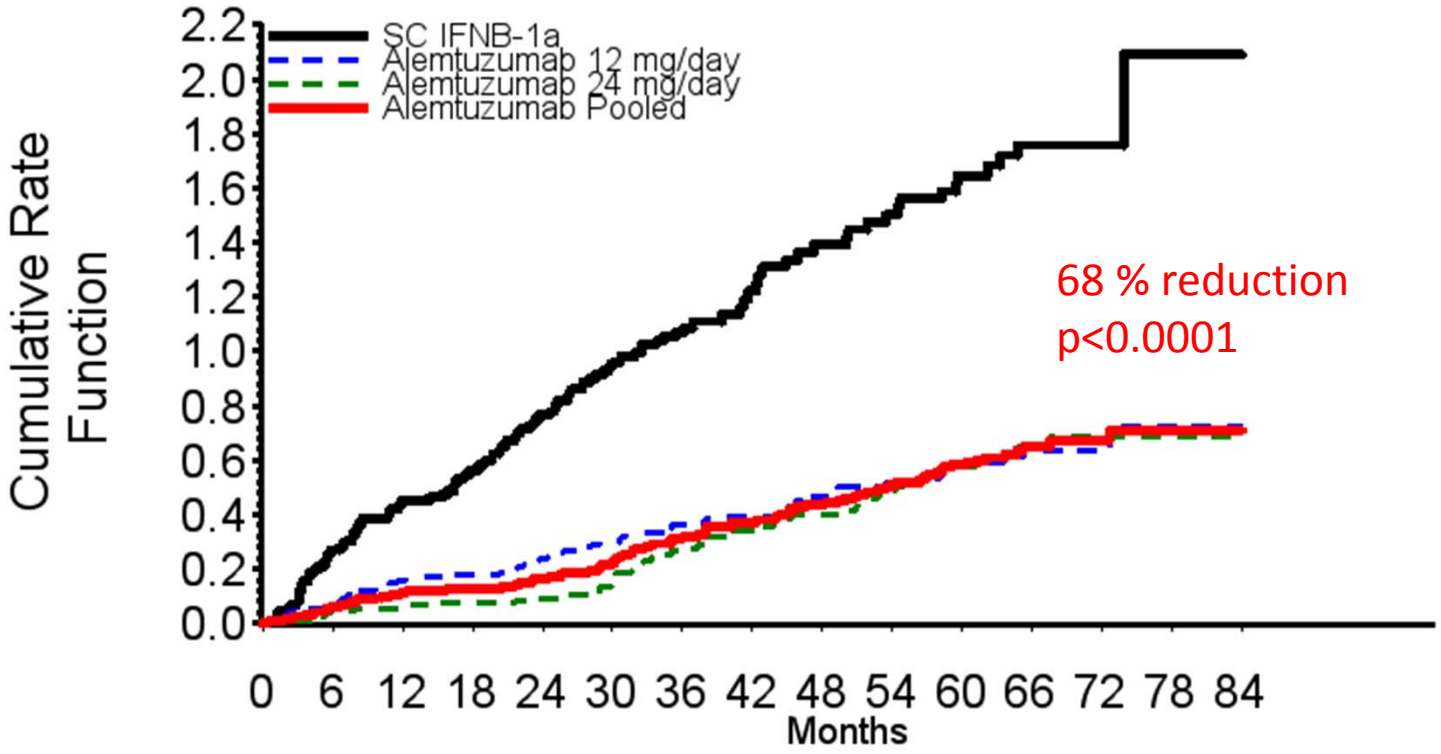
Multiple Sclerosis



- 3 women : 1 man
- 120 /100,000 prevalence
- 100,000 affected in the UK
- Commonest cause of neurological disability amongst young adults in UK



Alemtuzumab (Campath-1H) in multiple sclerosis: efficacy
CAMMS223 5+ year data: relapse accumulation

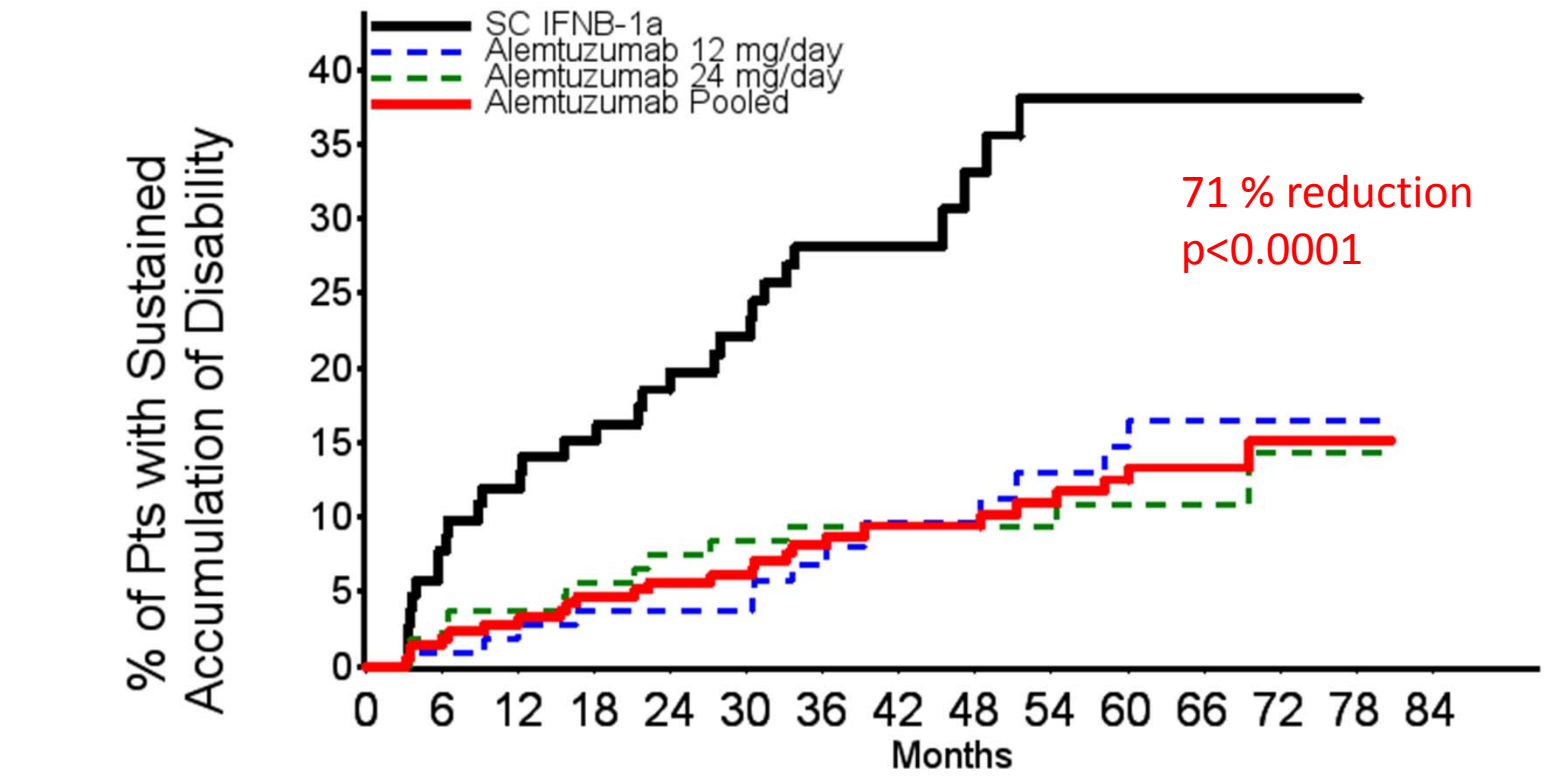


No. at Risk

SC IFNB-1a	111	99	94	84	78	74	69	36	36	36	35	27	7	1	0
Alem. 12 mg/day	112	107	107	103	101	98	95	57	57	56	54	45	15	4	0
Alem. 24 mg/day	110	108	107	107	104	102	98	70	70	69	68	56	19	5	0

Coles NEJM 2008, Coles (Neurology, in press)

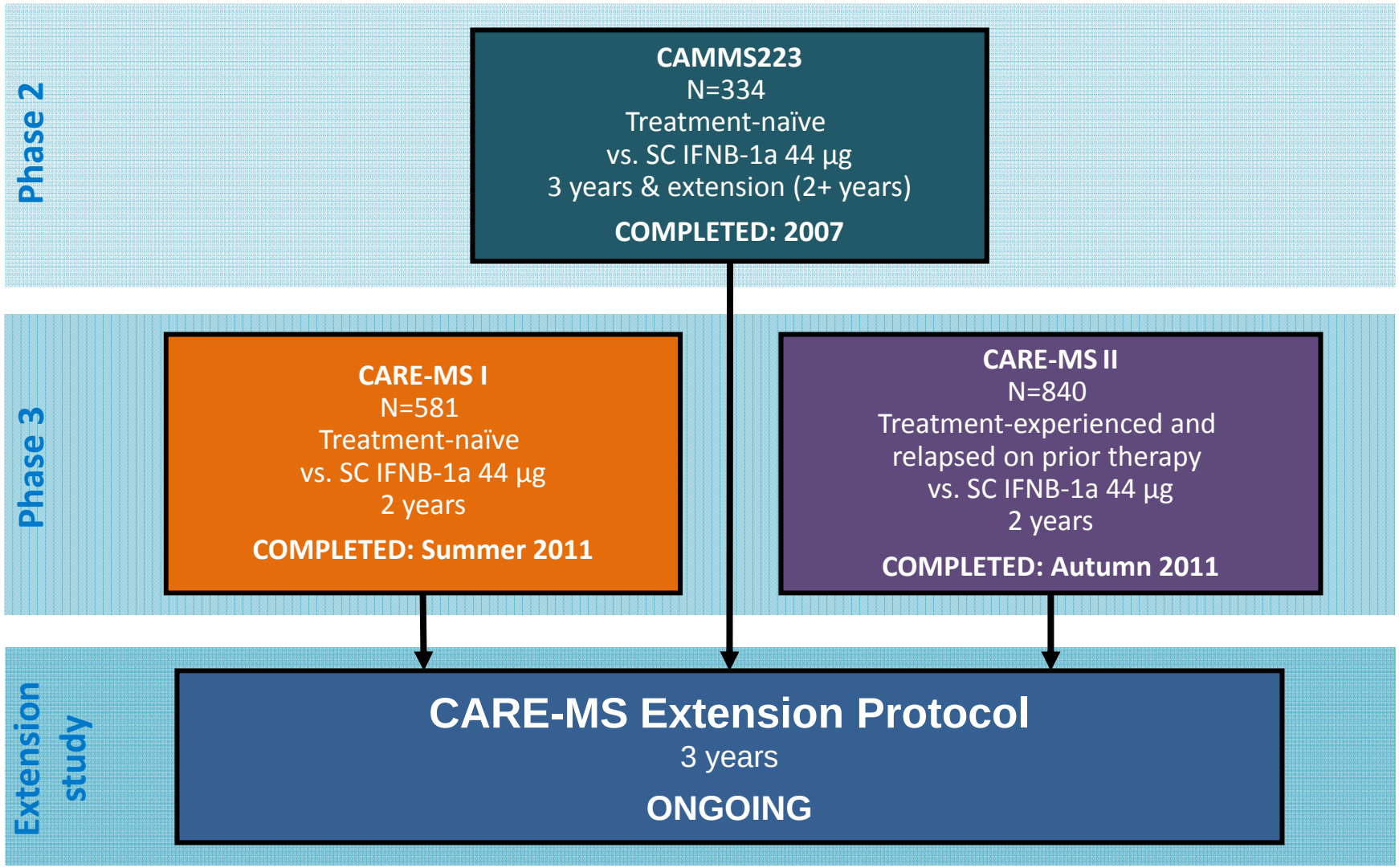
CAMMS223 5+ year data: risk of accumulating fixed disability



No. at Risk															
SC IFNB-1a	111	93	83	76	69	65	56	29	27	25	25	17	6	1	0
Alem. 12 mg/day	112	106	105	100	98	96	90	54	54	51	48	40	15	4	0
Alem. 24 mg/day	110	106	103	101	98	95	91	65	65	64	62	50	15	4	0

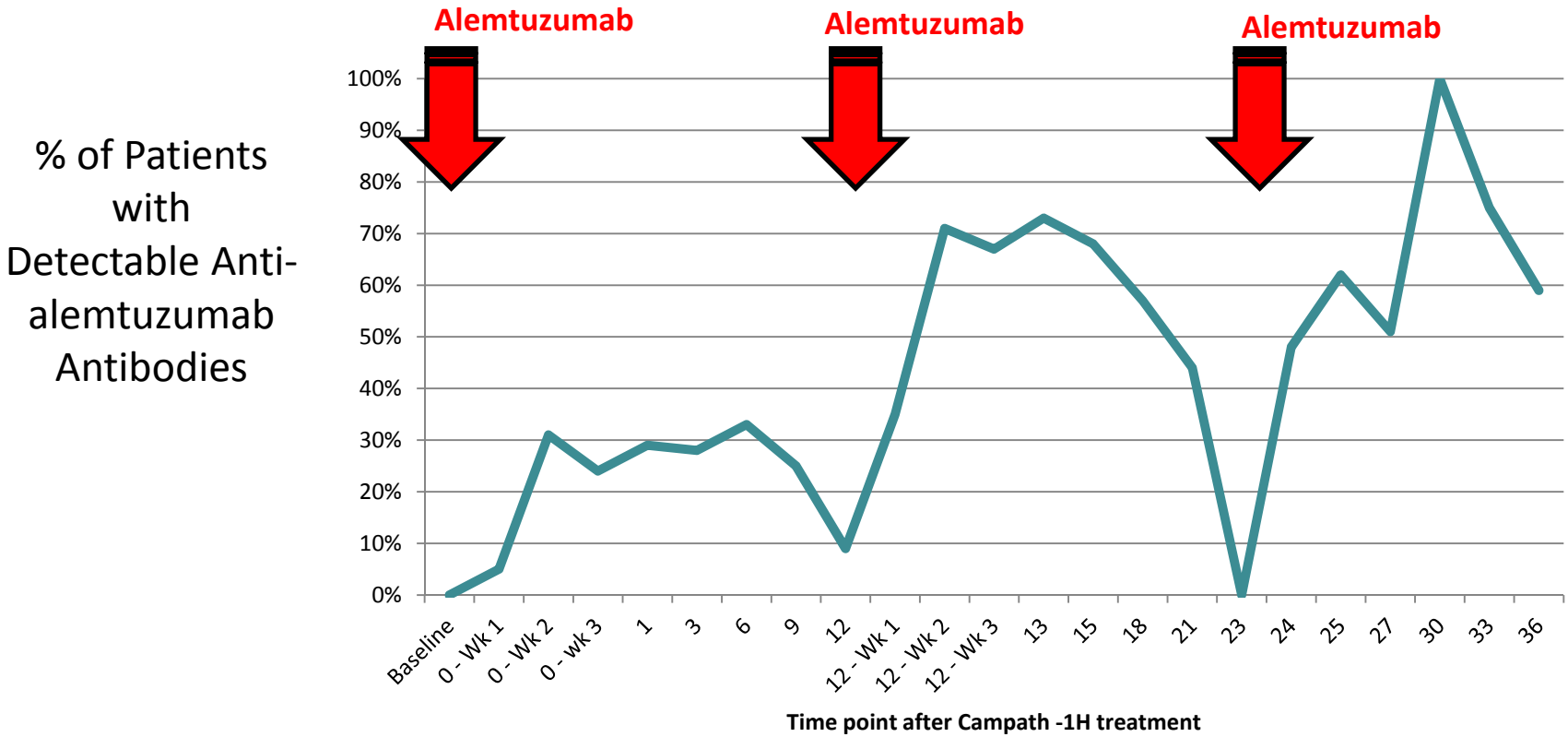
Coles NEJM 2008, Coles (Neurology, in press)

Alemtuzumab: Clinical Trial Program in MS

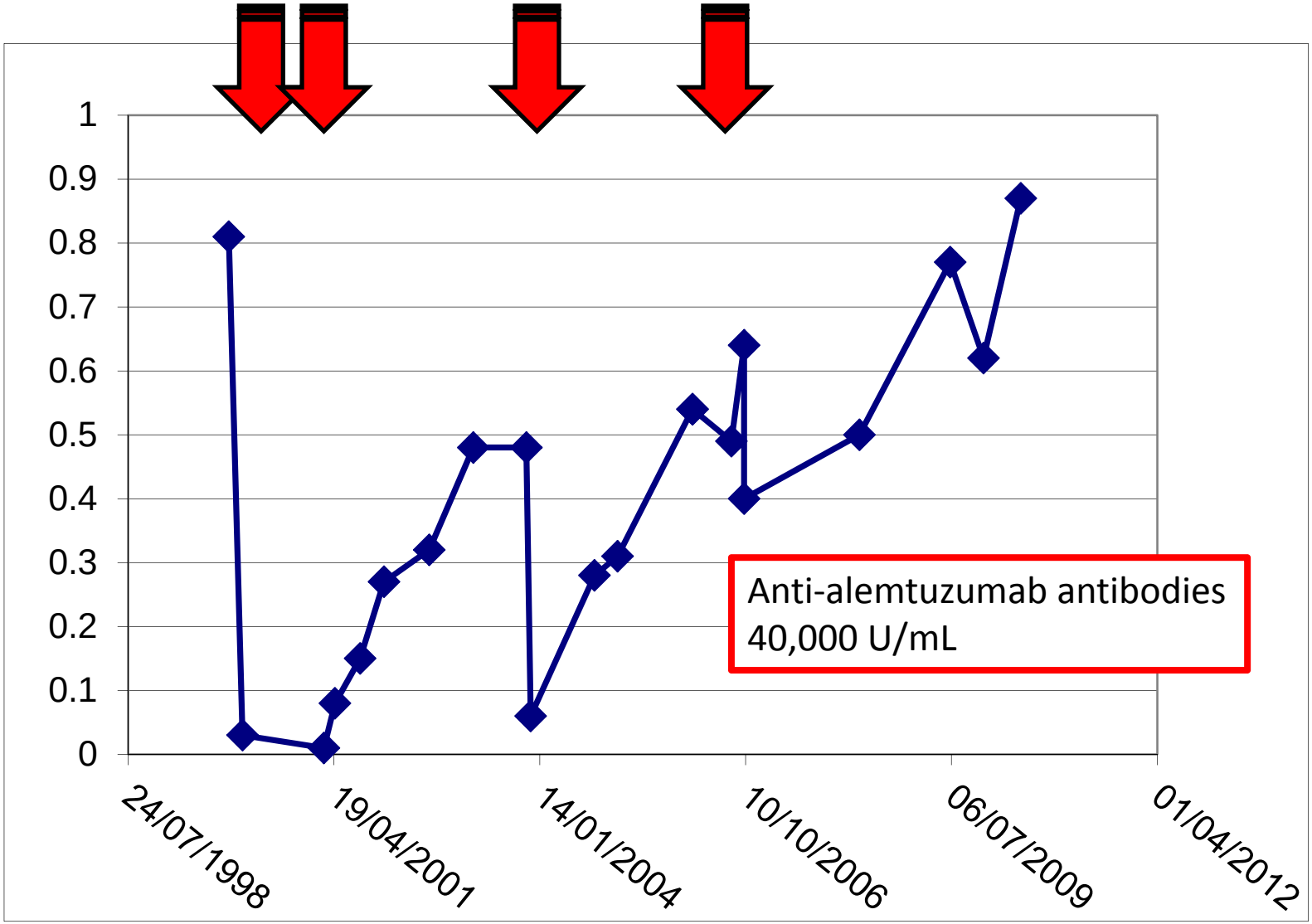


RRMS=relapsing, remitting MS; SC IFNB=subcutaneous interferon beta

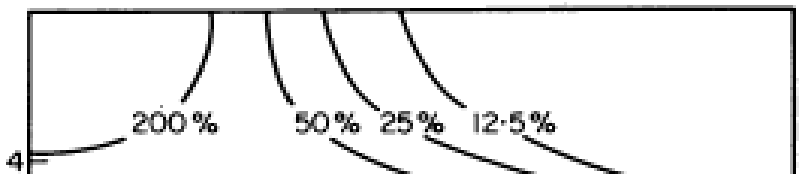
Anti-alemtuzumab antibodies in a phase 2 trial (n=223)



CD4 T cell counts after 4 cycles of alemtuzumab



High zone tolerance



Induction of immunological paralysis in two zones of dosage

By N. A. Mitchison

National Institute for Medical Research, Mill Hill, London, N.W. 7

(*Communicated by P. B. Medawar, F.R.S.—Received* 6 *May* 1964)

Mice are capable of producing large amounts of antibody against *BSA* in response to stimulation by the antigen in fluid form or with adjuvant. Fluid *BSA* also induces paralysis, as judged by the incapacity of the mouse to respond later to immunization. The conditions of treatment which lead to immunization or paralysis have been measured. Two zones of paralysis have been identified, one high in respect of dosage and late in respect of duration of treatment, the other low and early. The high, late zone is entered only after an initial period of immunization has been passed through. An interpretation is offered in terms of (i) concomitant immunization, in which some cells become immunized while others become paralysed, and (ii) a double threshold of paralysis. In accordance with this hypothesis, partially paralysed mice make antibody of normal avidity.

The response to other antigens of paralysed mice has also been examined. Suppression of responsiveness could not be found, thus confirming the highly specific nature of paralysis. Upon immunization with a cross-reactive antigen, *HSA*, an extremely weak antibody to the original paralysing antigen could be detected.

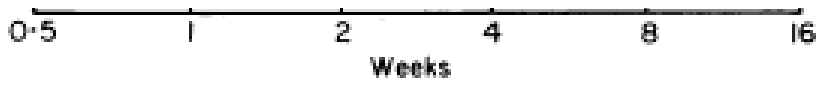
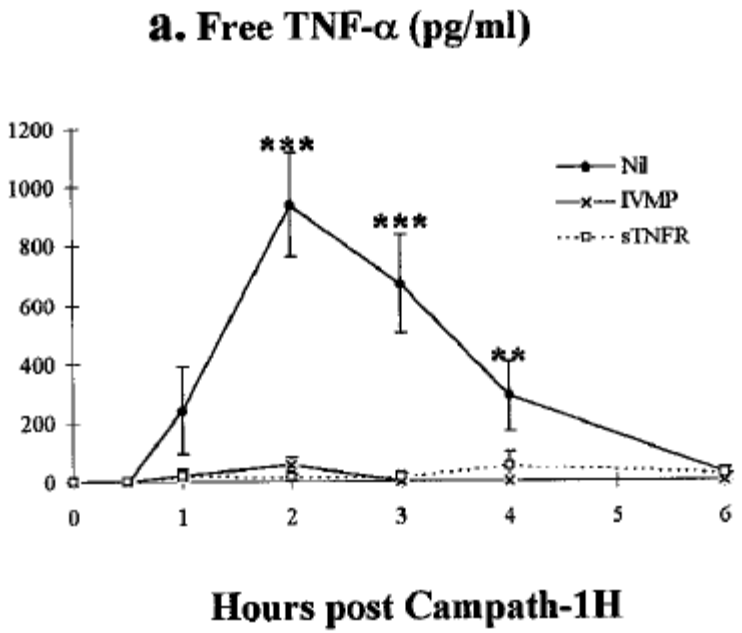


Fig. 2. The effect upon responsiveness of repeated doses of BSA ($\log_{10}$ μg $\times$ 3/week) administered for varying lengths of time (weeks).

Cytokine release with alemtuzumab infusions



20mg alemtuzumab induces a significant cytokine response:

- Pyrexia, tachycardia, raised CRP
- Raised TNF-α, IFN-γ

Waldmann group's mutants of alemtuzumab

52a	52b	52c	53	54
D	K	A	K	G
*	D	*	*	*
K	*	*	*	*
*	*	*	D	*
*	D	*	D	*

FIGURE 3. H2 loop sequ
imal mutants derived from
quence of wild-type CAMP
nation (31) above it. Mutatic
are shown; *, identity to wi

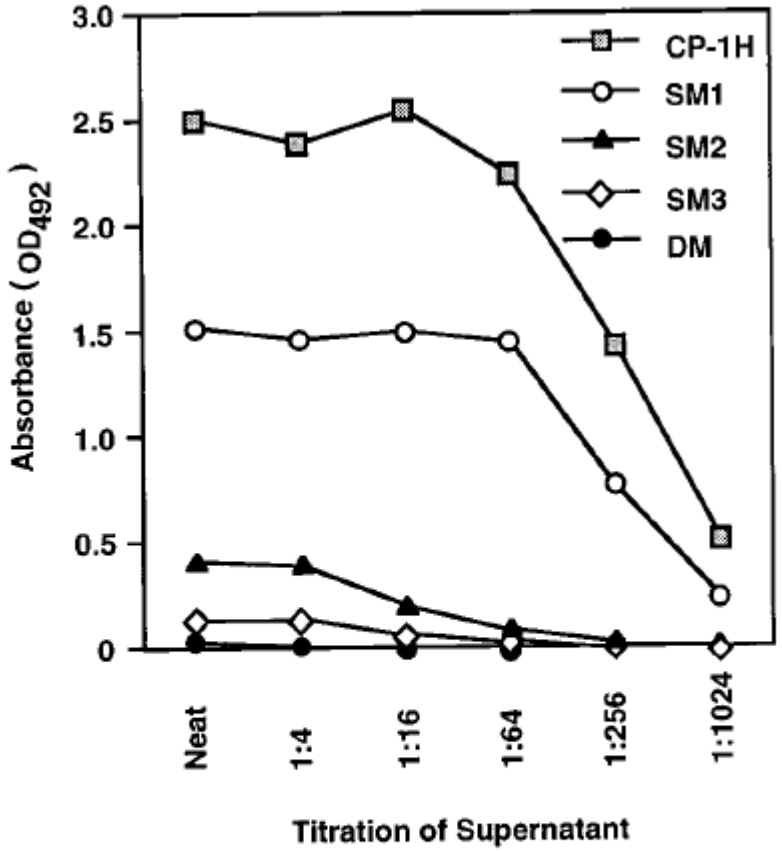
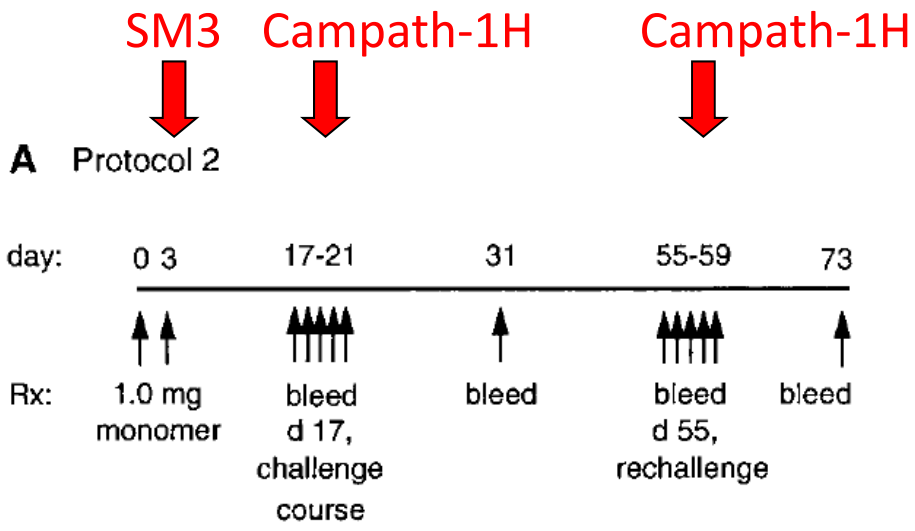


FIGURE 5. Binding of the minimal mutants to Ig-CD52. CAMPATH-1H or minimal mutants from transfection supernatants (all expressing at ~10 μg/ml) were diluted fourfold in wells of microtiter plates coated with anti-human IgG. Recombinant Ig-CD52 was added at 5 μg/ml, and bound protein was detected using biotinylated anti-mouse IgG followed by ExtrAvidin peroxidase.



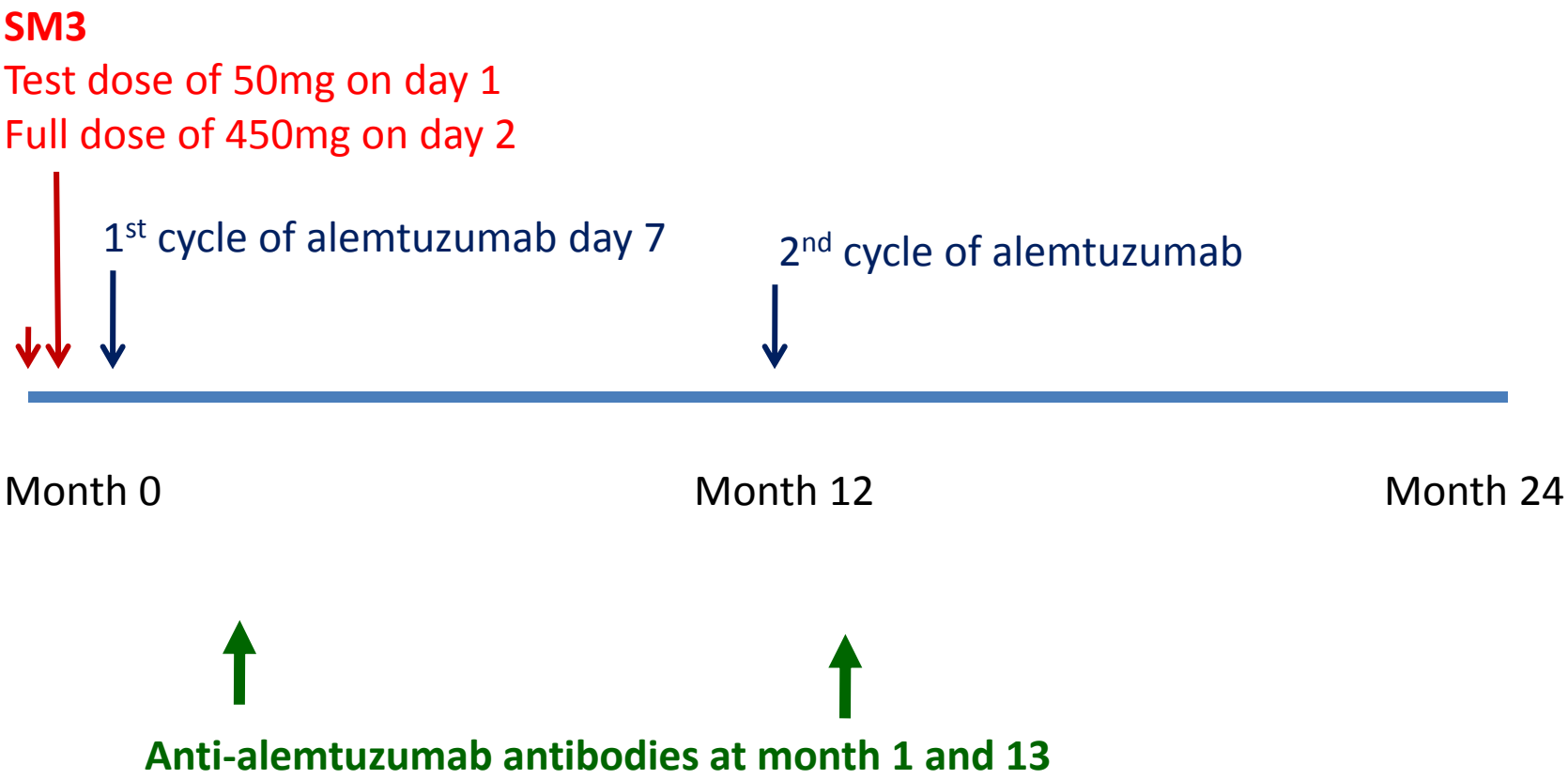
huCD52-transgenic mouse

SM3 mutant of Campath-1H reduces immunogenicity of Campath-1H

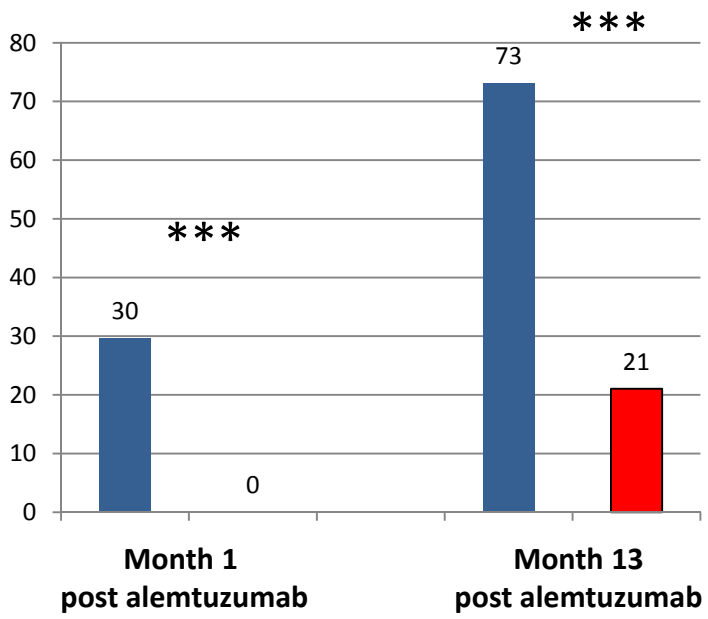
Gilliland J Immunol 1999

"SM3" Trial Design

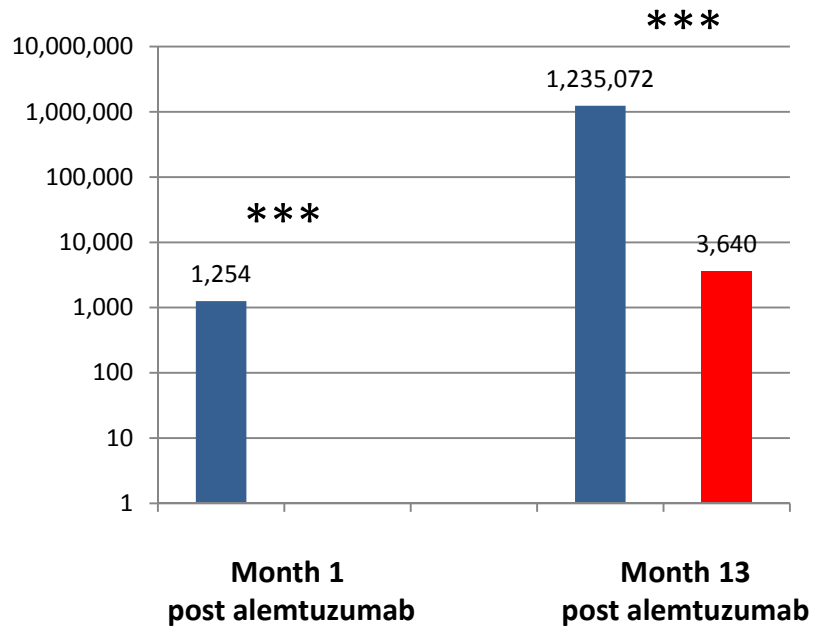
N=20 patients with multiple sclerosis



% of patients with detectable anti-alemtuzumab antibodies

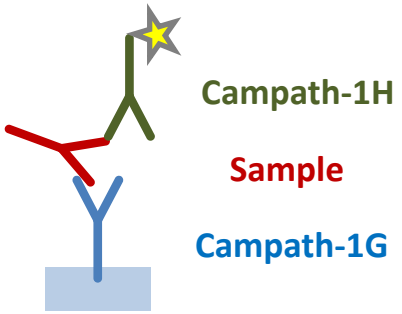


Mean concentration of anti-alemtuzumab antibodies (U/ml)

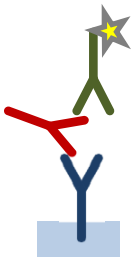


CAMMS223 trial: alemtuzumab only (n=223)

SM3 & alemtuzumab (n=19)



IgM

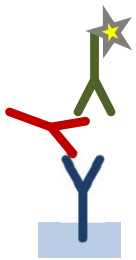


IgG1

Alemtuzumab only (n=4)

SM3 & alemtuzumab only (n=4)

Did SM3 compromise assays?



Goat anti-human Ig

SM3

Anti-Campath idiotype

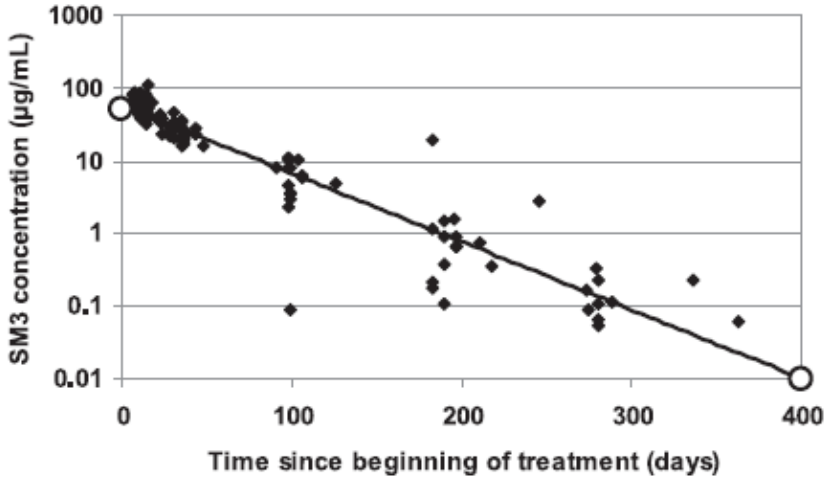


FIGURE 1. Pharmacokinetics of SM3. Concentrations of SM3 were measured by sandwich immunoassay in a Gyrolab instrument. Samples were analyzed at irregular times between 6 and 363 d from 18 patients. The log-transformed concentrations were fitted to a straight line by linear regression.

The estimated mean concentration of SM3 at 1 month was 30.3 μg/ml and at 13 month was 0.01 μg/ml.

Conclusions from formal trial

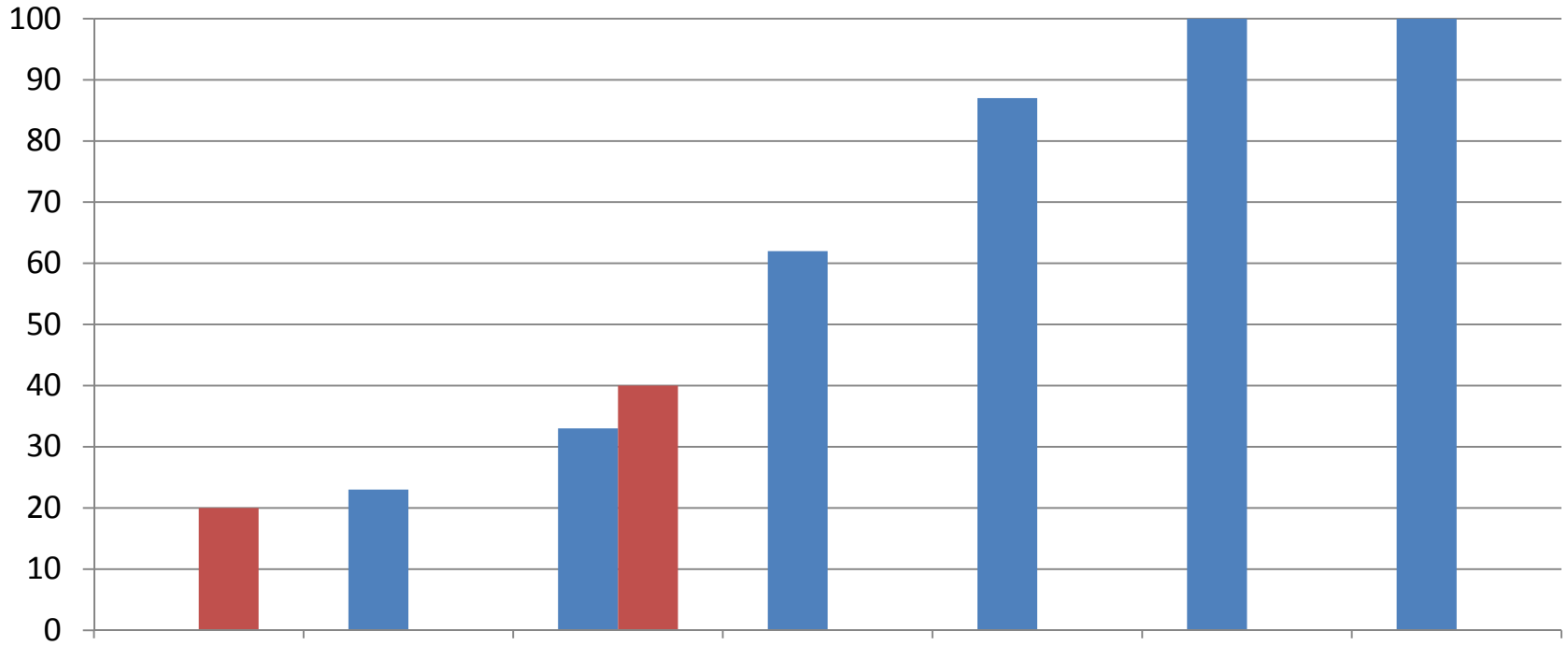
Apparent lack of anti-alemtuzumab antibodies after one cycle of SM3 and alemtuzumab might be an artefact due to persistence of SM3

Low rate of anti-alemtuzumab antibodies after second cycle of alemtuzumab could be due to:

- Long-lasting tolerance induction to alemtuzumab, with a minority generating a secondary response to second cycle
- Masking of first cycle of alemtuzumab; now seeing a primary response with second cycle

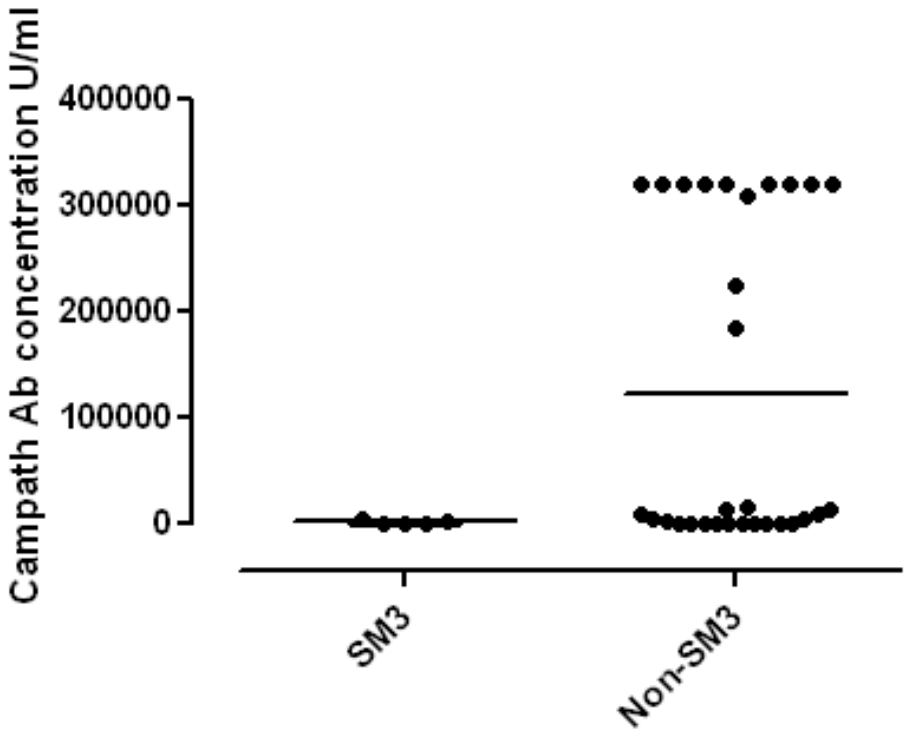
What has happened subsequently?

Percentages of patients with anti-alemtuzumab antibodies before and after 3rd cycle



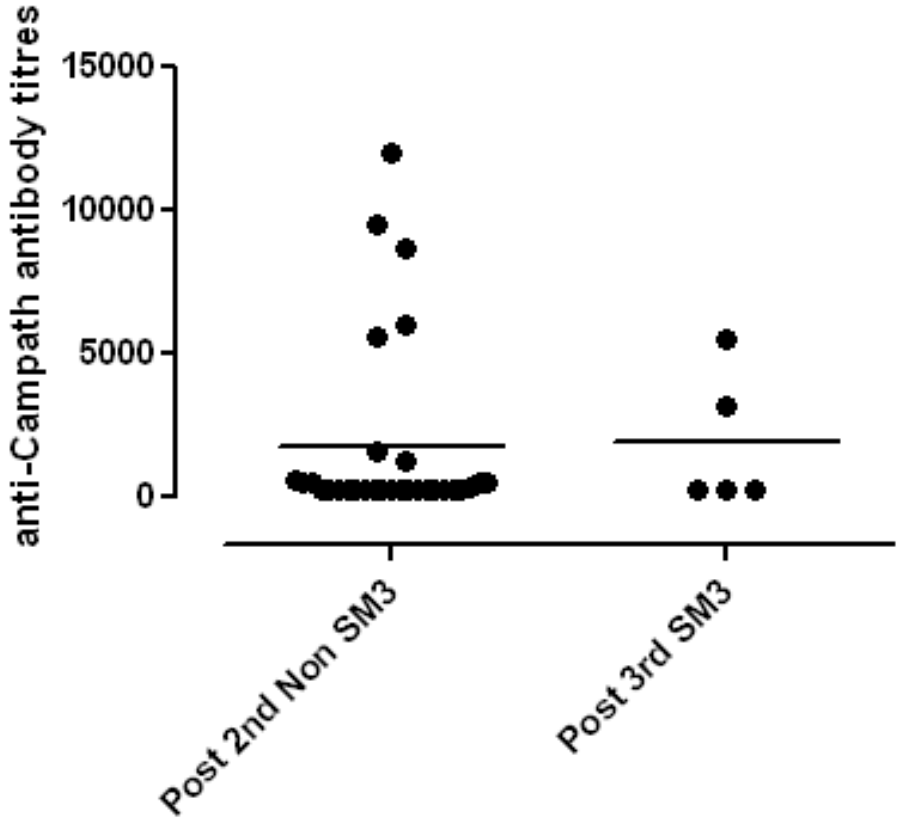
	After 2nd cycle	Before 3rd Cycle	After 3rd cycle	Before 4th cycle	After 4th cycle	Before 5th cycle	After 5th cycle
Non-SM3		7/30	14/30	5/8	7/8	1/1	1/1
SM3	1/5	0/5	2/5				

anti-alemtuzumab antibody concentration after 3rd cycle (SM3 and non-SM3)



P=0.08

anti-alemtuzumab antibody concentration comparing non-SM3 after 2nd cycle and SM3 after 3rd cycle



P=0.9

Conclusions

Insufficient data to be conclusive

Rate of conversion after 3rd cycle in SM3 patients is still lower than after 2nd cycle in non-SM3 patients

Level of anti-alemtuzumab antibodies after 3rd cycle in SM3 patients is equivalent to that after 2nd cycle in non-SM3 patients

Therapeutic Immunology Group
Department of Clinical Neurosciences
University of Cambridge

Genzyme / Sanofi-Aventis

Cambridge Centre for Biomedical Research

Multiple Sclersosis Society of GB and N Ireland

MRC

Grand Charity of the Freemasons

UCB-Celltech