
Durable Efficacy of Alemtuzumab on Clinical and MRI Outcomes Over 6 Years in CARE-MS II Patients With Active RRMS With Relapse Between Courses 1 and 2

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on behalf of the CARE-MS II and CAMMS03409 Investigators

Presented by Barry Singer

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- **Barry Singer:** Speaking and/or consulting (Acorda, Bayer, Biogen, EMD Serono, Genentech, Novartis, Sanofi Genzyme, and Teva), and research support (Acorda, Biogen, MedImmune, Novartis, Roche, and Sanofi Genzyme)
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CARE-MS II Core and Extension Study Background

- Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved in >60 countries for the treatment of adults with relapsing forms of MS
- Alemtuzumab significantly improved clinical and MRI outcomes versus SC IFNB-1a over 2 years in patients with an inadequate response to prior therapy (CARE-MS II trial)¹
 - The most frequent AEs with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs¹
- Most alemtuzumab patients who were followed through 6 years (2 years of core study plus 4 years in an extension) showed durable improvements in clinical and MRI outcomes²⁻⁴
 - This was achieved in the absence of continuous treatment; 50% did not receive any alemtuzumab retreatment or another DMT through 6 years
- Relapses are not uncommon following the initiation of DMTs for MS
 - 43% of patients who received SC IFNB-1a in CARE-MS II, relapsed in Year 1⁵
 - 23% relapsed in the year following initiation of natalizumab^{6,a}
- The efficacy of alemtuzumab was evaluated in patients with relapse between Courses 1 and 2

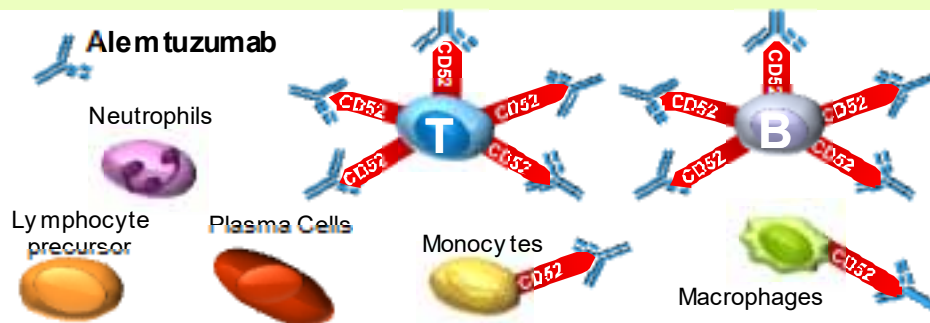
^aAs reported in its core clinical trial; AE=adverse event; DMT=disease-modifying therapy; SC IFNB-1a=subcutaneous interferon beta-1a
1. Coles AJ et al. *Lancet* 2012;380:1829-39; 2. Fox EJ et al. *Mult Scler* 2016;22(S3):P1150; 3. Traboulsee A et al. *Mult Scler* 2016;22(S3):P1181; 4. Traboulsee A et al. *Mult Scler* 2016;22(S3):P1221. 5. Data on file. Genzyme Corporation. 6. Polman CP et al. *N Engl J Med* 2006;354:899-910

Proposed Mechanism of Action of Alemtuzumab: Distinct Patterns of Repopulation May Rebalance the Immune System

- The durable effects of alemtuzumab over 6 years in the absence of continuous treatment may be due to its mechanism of action^a

1. SELECTION^{1,2}

Alemtuzumab selectively binds CD52, an antigen that is highly expressed on the surface of T and B lymphocytes



2. DEPLETION^{1,2}

Rapid and robust depletion of T and B cells



3. REPOPULATION³⁻⁶

Unique repopulation with Anti-inflammatory Immune Profile

- ↓ Th1 and Th17 cells (proinflammatory cytokine-producing cells)^{3,4}
- ↓ Conventional and plasmacytoid dendritic cells^{5,b}
- ↑ T_{reg} cells (suppressive function and anti-inflammatory cytokine producing cells)^{3,4,6}
- ↑ CD56^{bright} NK cells⁵

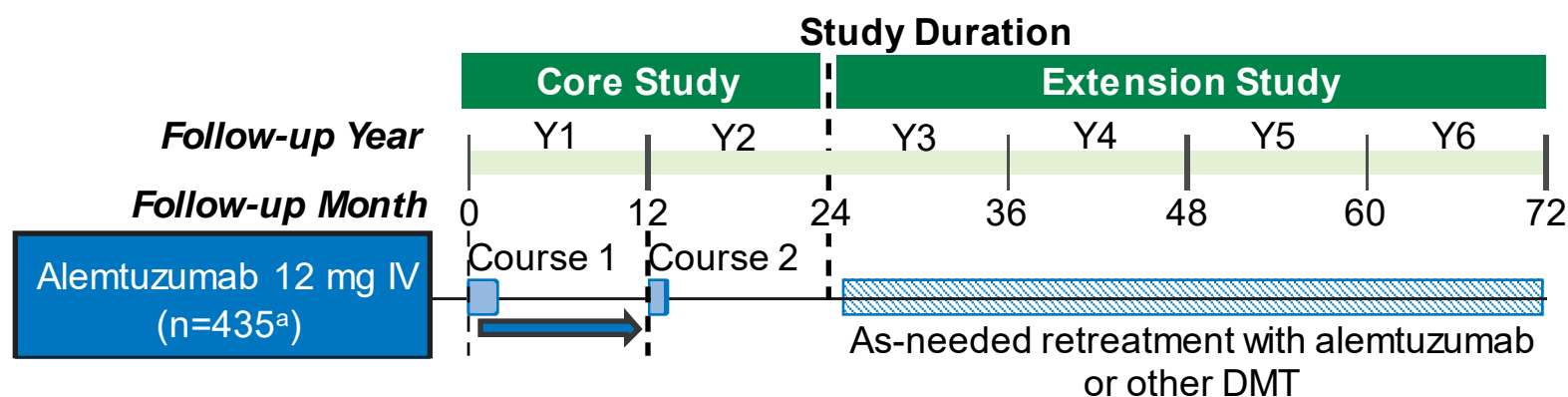
^aThe exact mechanism of action of alemtuzumab is not known. ^bBased on analysis of 12 alemtuzumab-treated patients' serum⁵

NK=natural killer cell; Th1=type 1 T helper cell; Th17=type 17 T helper cell

1. Hu Y et al. *Immunology* 2009;128;260-70. 2. Boyko AN et al. *Mult Scler* 2016;22(suppl 3): P654. 3. Zhang X et al, *J Immunol* 2013;191: 5867-74. 4. Durelli L et al. AAN 2016; Vancouver, Canada: PS2.008. 5. Gross CC et al. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e289. 6. De Mercanti S et al. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e194.

CARE-MS II Core and Extension Study Design

- CARE-MS II was a phase 3 trial in patients with active RRMS who had an inadequate response (≥ 1 relapse after ≥ 6 months of treatment) to prior therapy¹
 - Open-label, rater-blinded extension study²

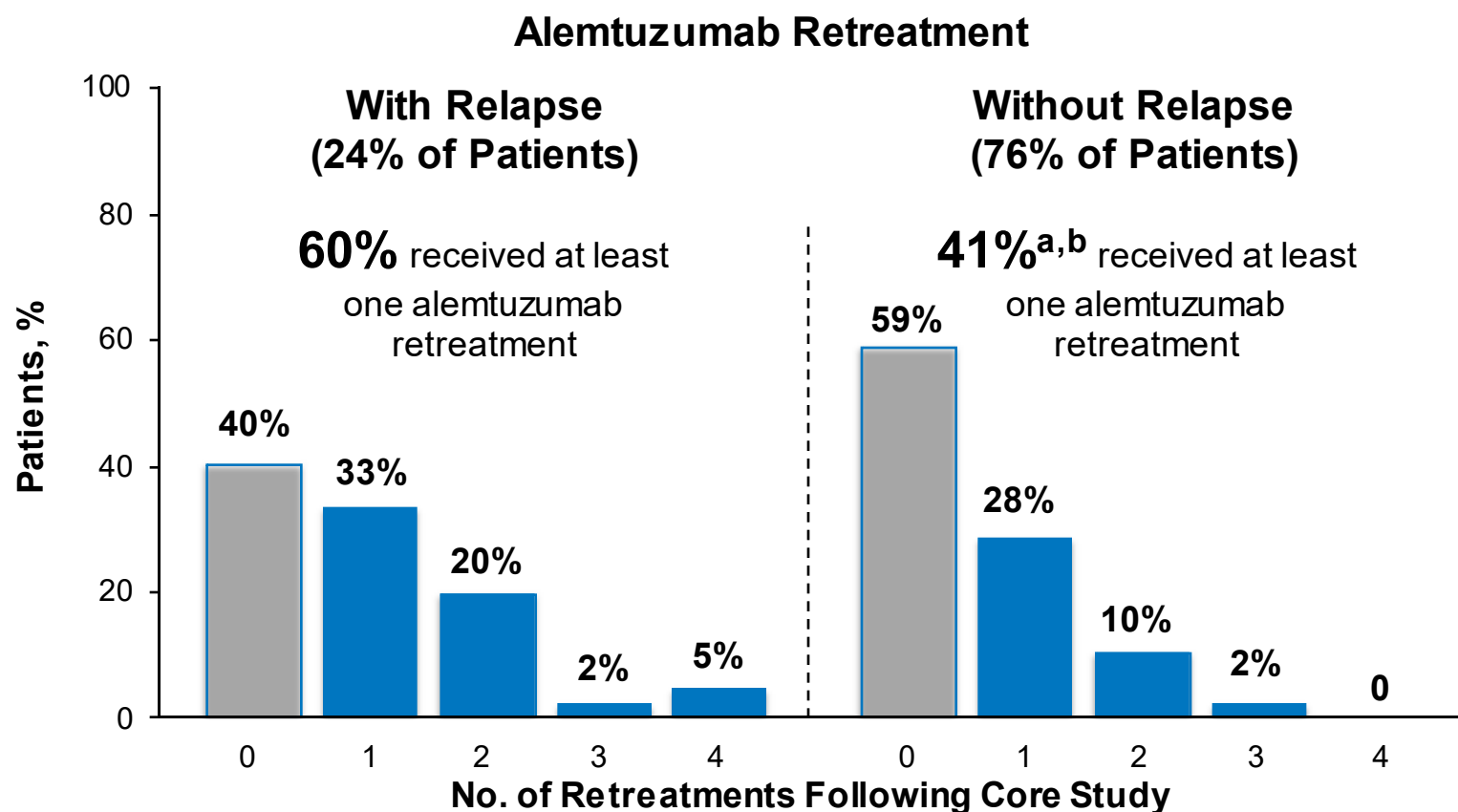


- **24%** of alemtuzumab-treated patients relapsed between Courses 1 and 2
 - 83% of alemtuzumab-treated patients who relapsed between Courses 1 and 2 enrolled in the extension (93% of those who did not relapse)
 - 87% of those patients remained on study through Year 6 (88% of those who did not relapse)

^aAs-treated population; DMT=disease-modifying therapy; Y=year

1. Coles AJ et al. *Lancet* 2012;380:1829-39; 2. Fox EJ et al. *Neurology* 2013;80:S41.001.

Patients With or Without Relapse Between Alemtuzumab Courses 1 and 2 Receiving Additional Treatment



- 67% of patients who relapsed received additional treatment (alemtuzumab or another DMT)
 - 53% received only alemtuzumab retreatment, 7% only another DMT, and 7% both alemtuzumab and another DMT

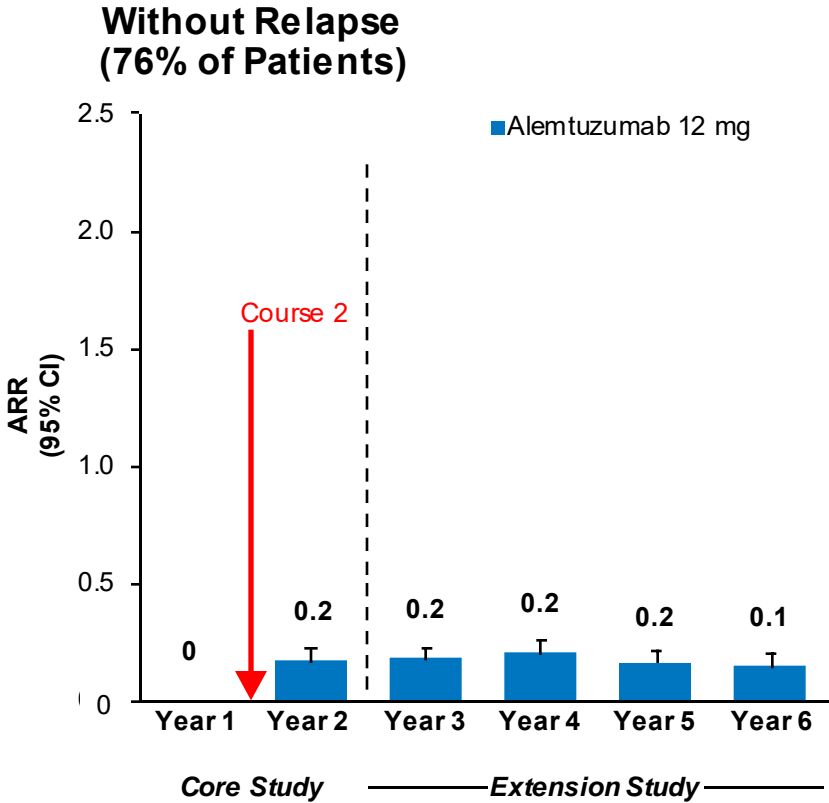
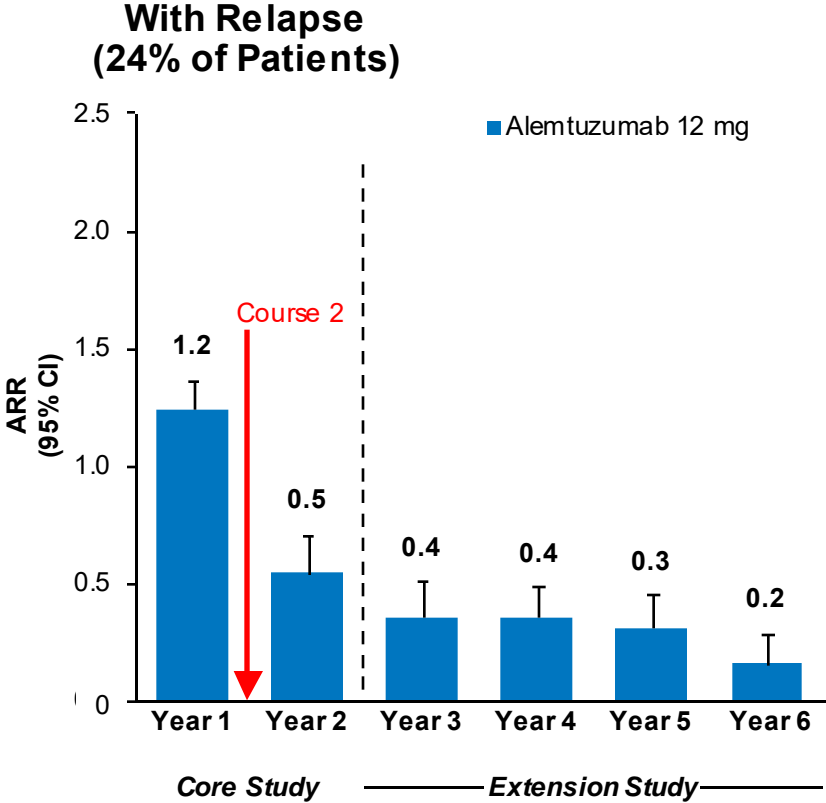
^aDue to rounding, percentages do not sum to 100%

^b45% of patients who did not relapse received additional treatment (alemtuzumab or another DMT); 36% received only alemtuzumab retreatment, 4% only another DMT, and 5% both alemtuzumab and another DMT

Baseline Characteristics in Alemtuzumab-Treated Patients With and Without Relapse Between Courses 1 and 2

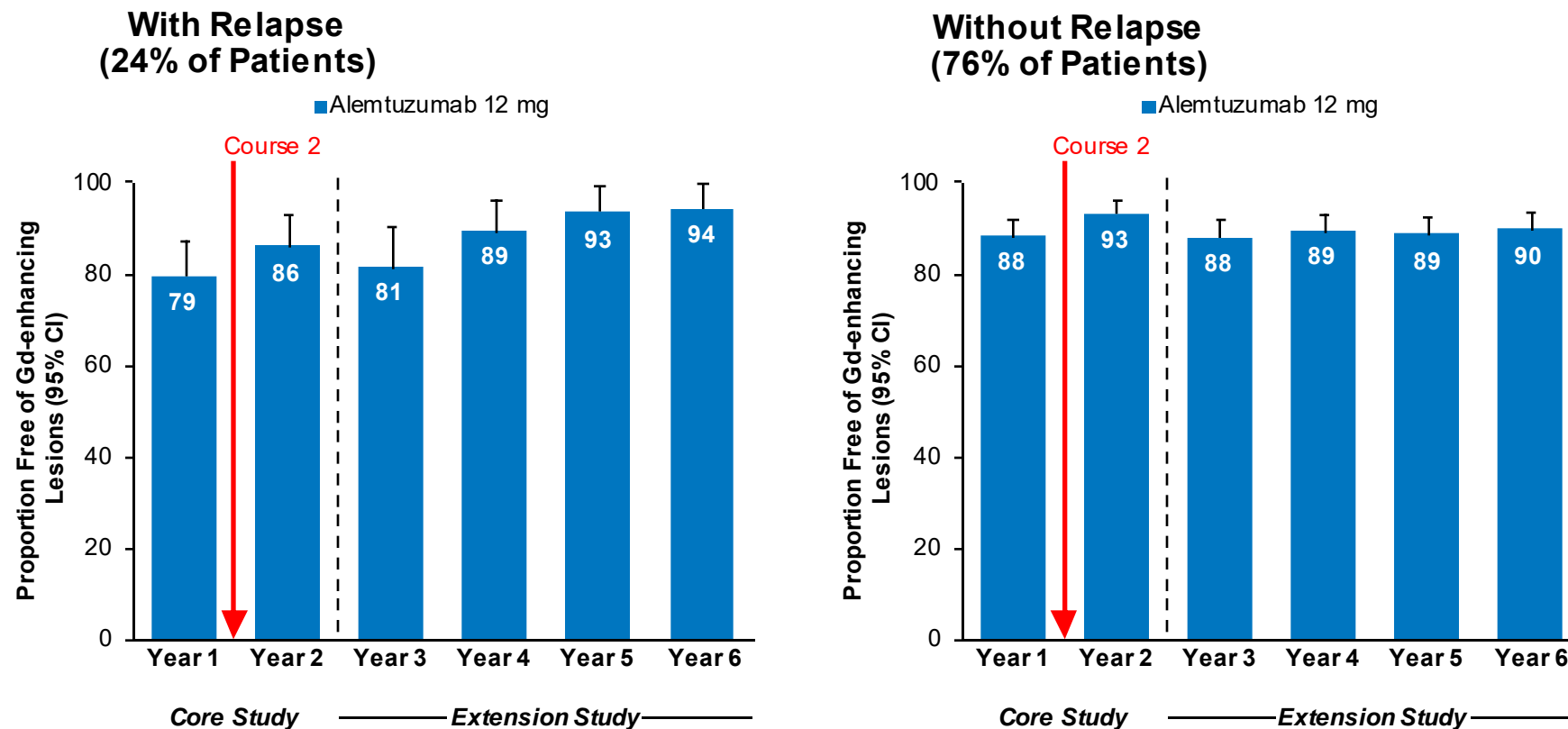
Parameter	With Relapse (N=105)	Without Relapse (N=330)
Age, years, mean (SD)	34.6 (8.8)	34.8 (8.2)
Female, n (%)	77 (73.3)	210 (63.6)
White, n (%)	96 (91.4)	296 (89.7)
EDSS score, mean (SD)	3.0 (1.4)	2.6 (1.2)
Years since initial relapse, mean (SD)	4.3 (2.7)	4.5 (2.7)
No. of relapses in prior 1 year, mean (SD)	1.9 (0.9)	1.6 (0.9)
No. of relapses in prior 2 years, mean (SD)	3.1 (1.4)	2.7 (1.1)
Gd-enhancing lesion count, mean (SD)	1.6 (3.1)	2.5 (6.7)
Patients with Gd-enhancing lesions, n (%)	41 (39.0)	140 (43.2)
BPF, mean (SD)	0.82 (0.02)	0.81 (0.02)

Annualized Relapse Rate Markedly Improved After Course 2 of Alemtuzumab in Patients With Relapse Between Courses 1 and 2



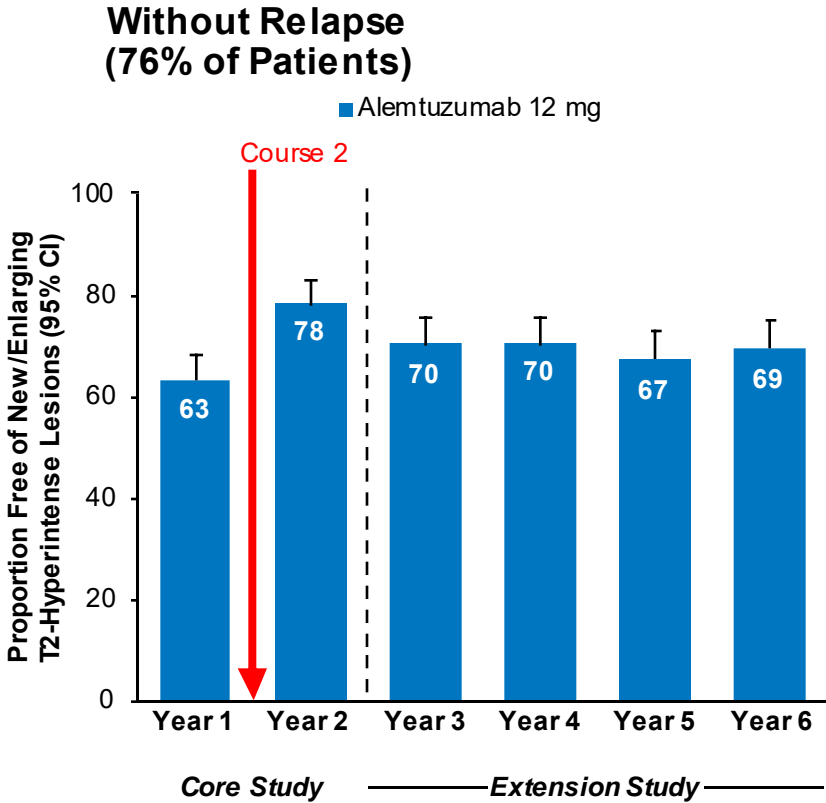
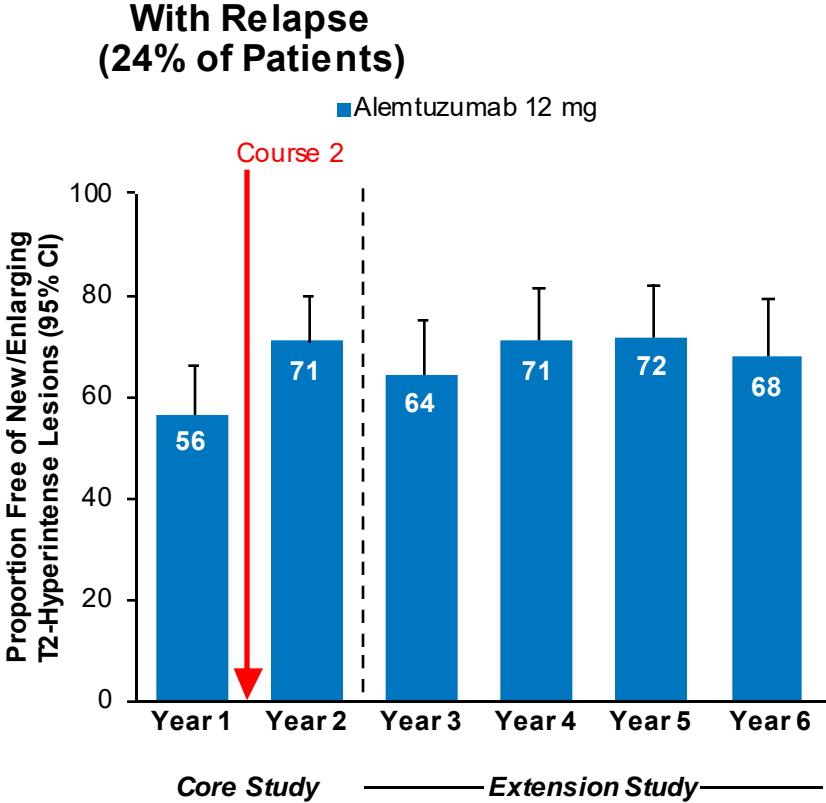
ARR=annualized relapse rate

Freedom From Gd-Enhancing T1 Lesions



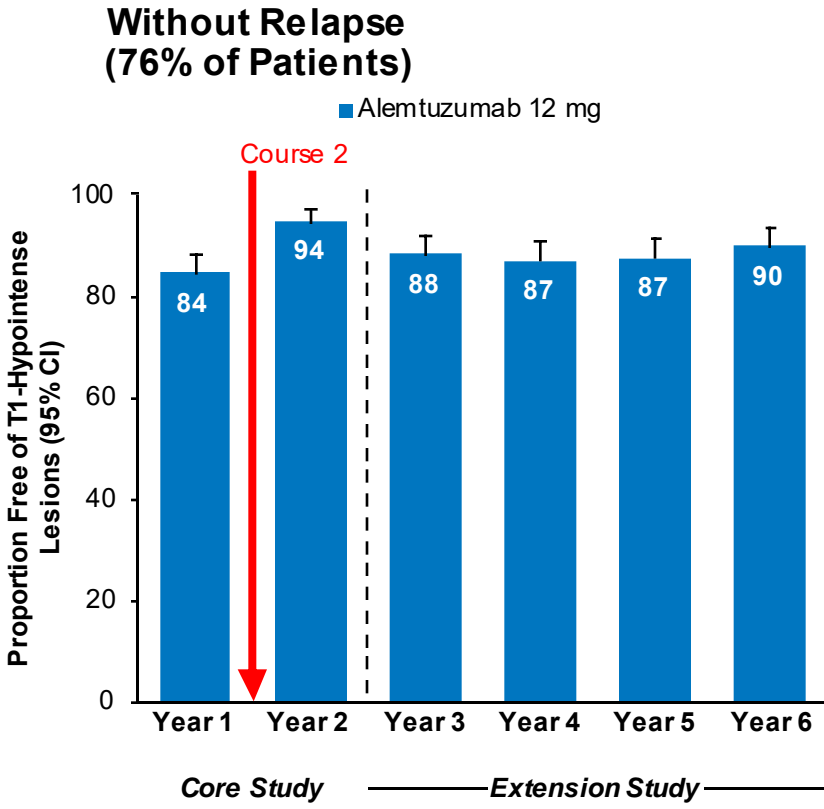
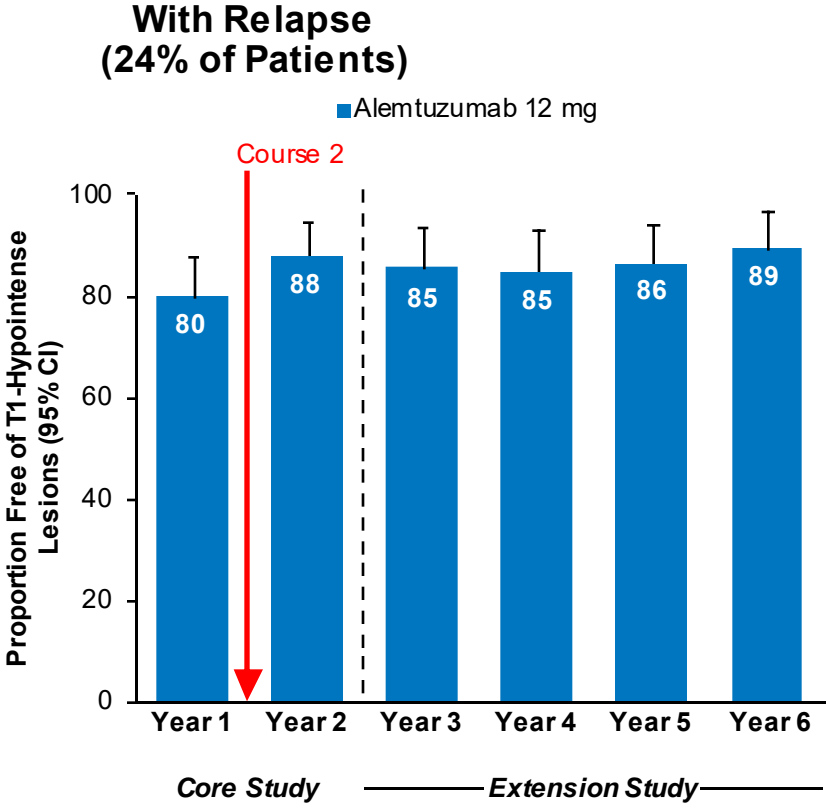
- Each year through Year 6, most patients with and without relapse between Courses 1 and 2 were free of Gd-enhancing T1 lesions

Freedom From New/Enlarging T2-Hyperintense Lesions



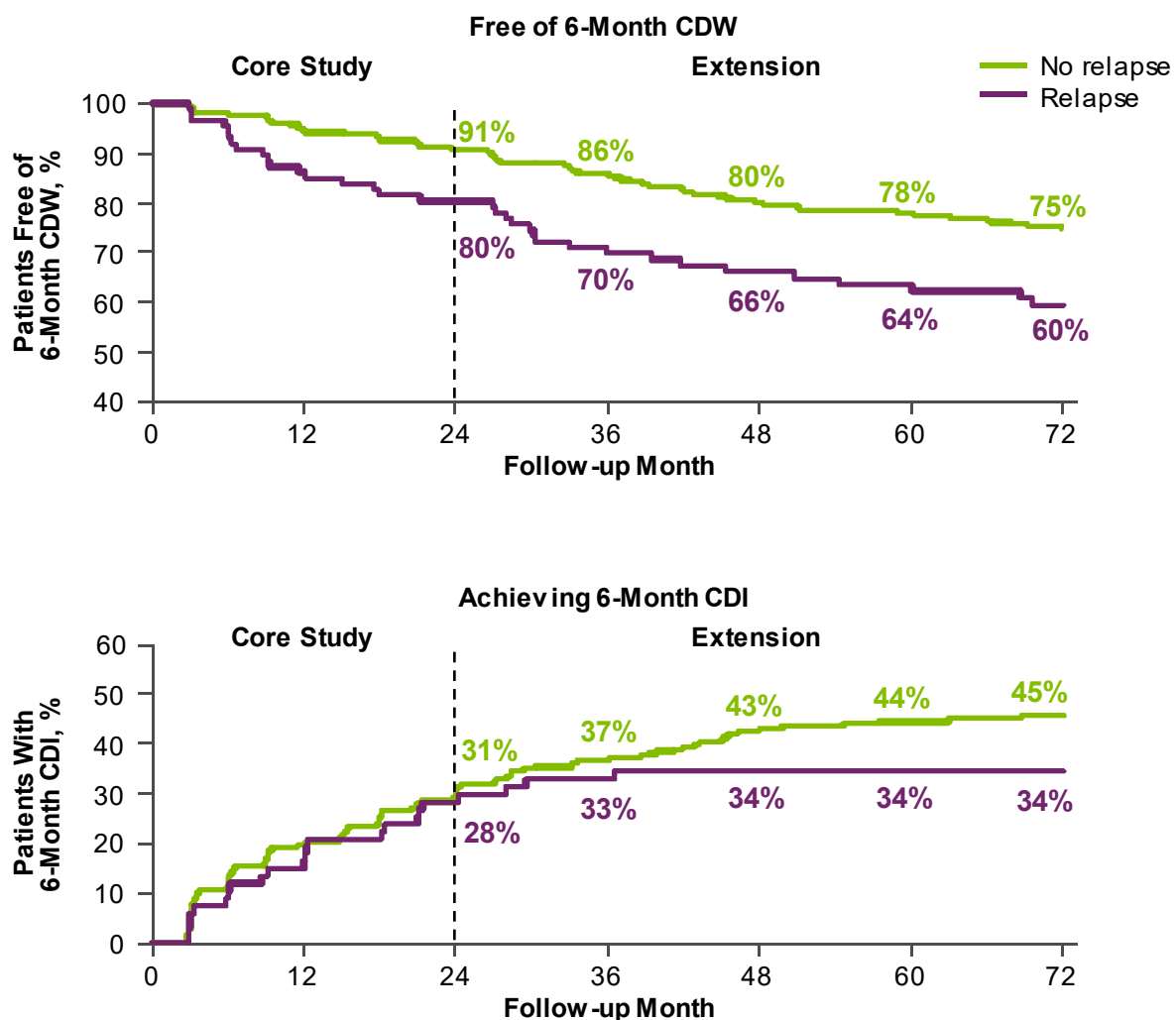
- Each year through Year 6, most patients with and without relapse between Courses 1 and 2 were free of T2-hyperintense lesions

Freedom From T1-Hypointense Lesions



- Each year through Year 6, most patients with and without relapse between Courses 1 and 2 were free of T1-hypointense lesions

Long-term CDI and CDW Outcomes Were Favorable in Patients With and Without Relapse Between Courses 1 and 2

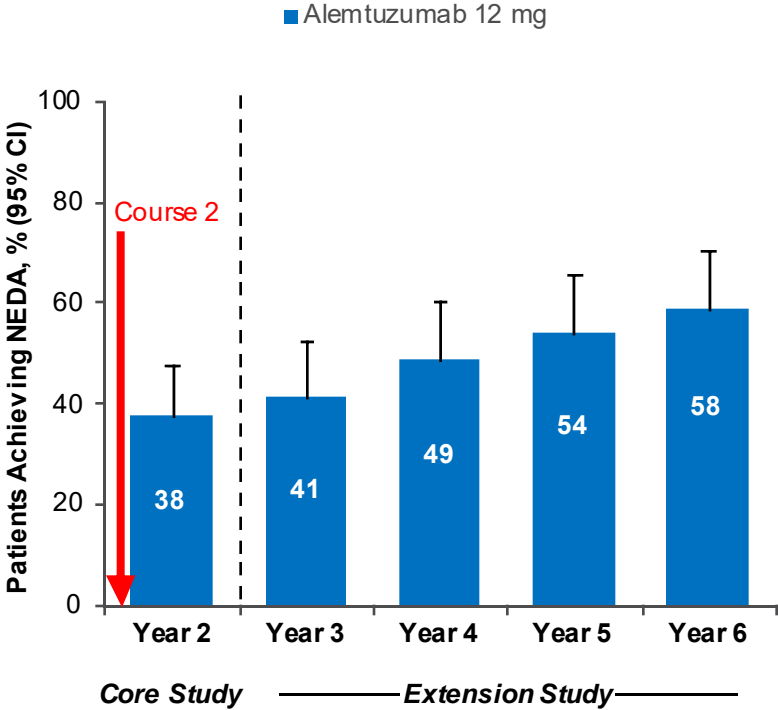


CDW: ≥ 1 -point EDSS increase (or ≥ 1.5 points if baseline EDSS=0) confirmed over 6 months

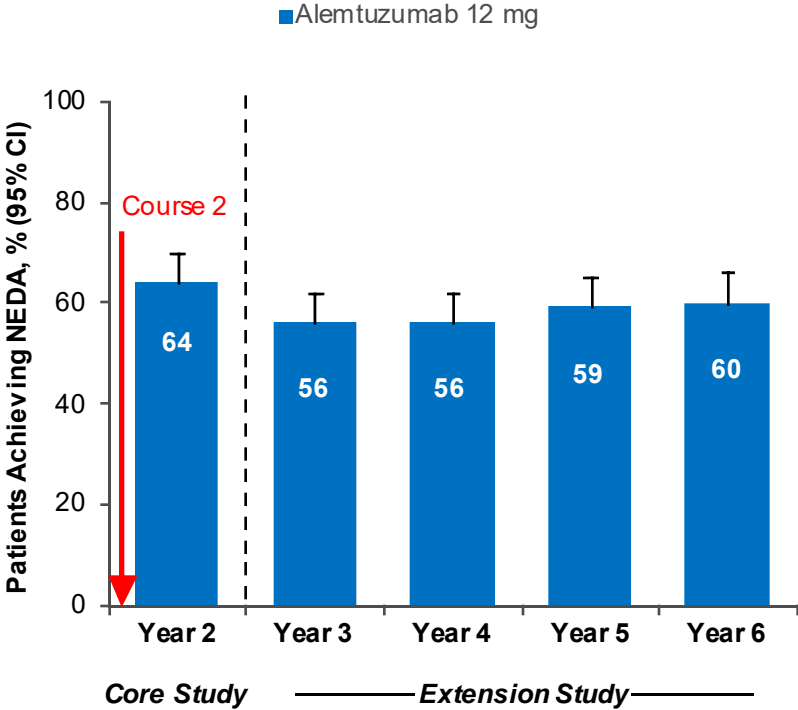
Confirmed disability improvement (CDI): ≥ 1 -point EDSS decrease from baseline (patients with baseline score ≥ 2.0) confirmed over 6 months

The Proportion of Patients With Relapse Between Courses 1 and 2 Who Achieved NEDA Increased Through 6 Years

With Relapse (24% of Patients)

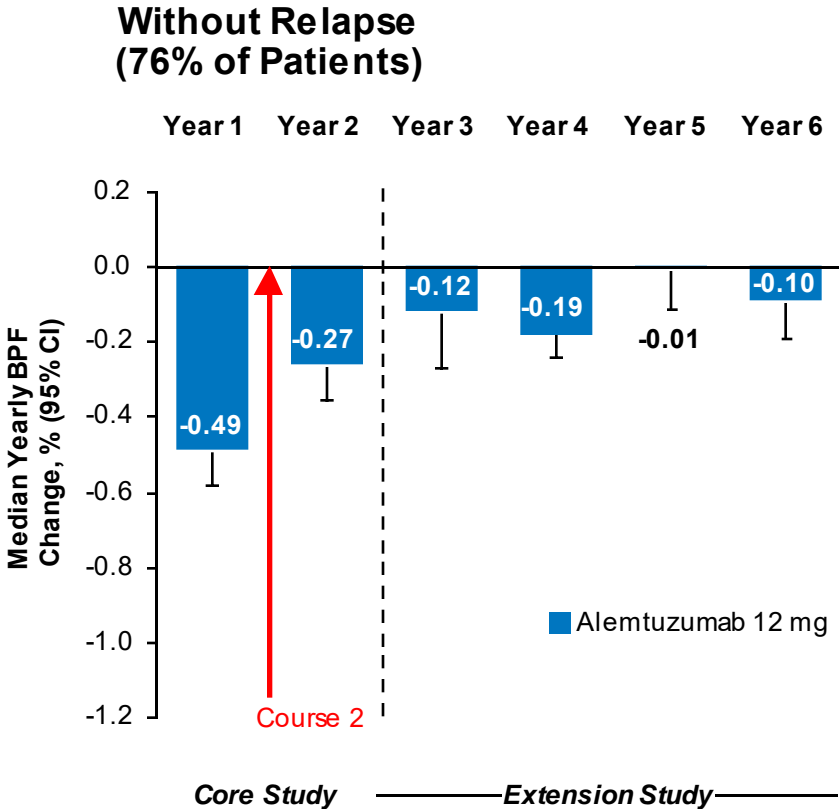
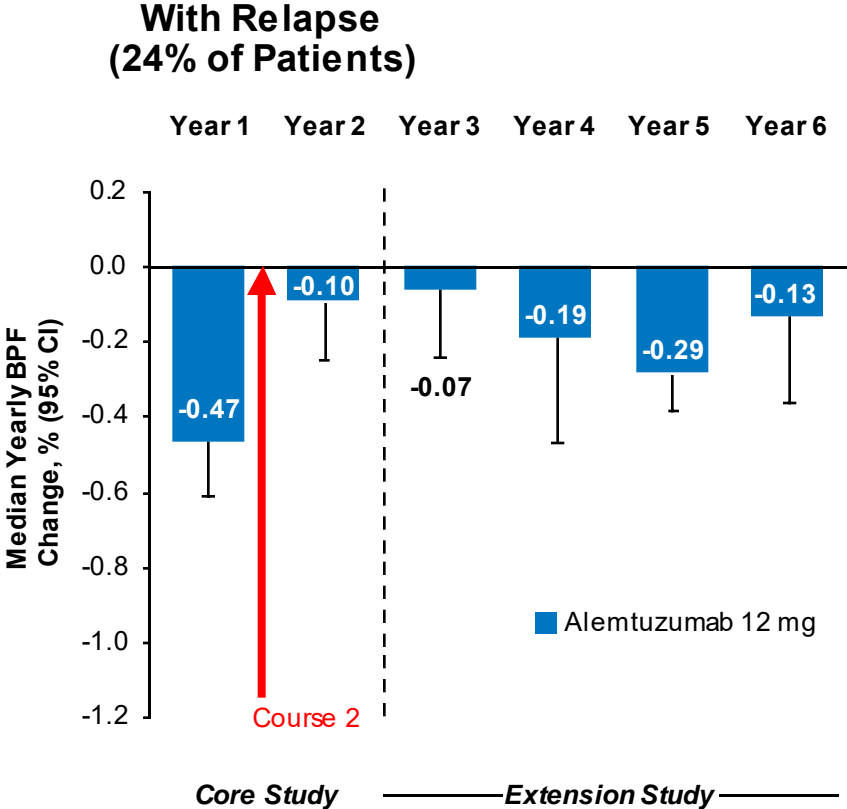


Without Relapse (76% of Patients)



No evidence of disease activity (NEDA): absence of clinical disease activity (relapses and 6-month confirmed disability worsening [CDW]) and MRI disease activity (new Gd-enhancing T1 and new/enlarging T2 hyperintense lesions)

Alemtuzumab Durably Slowed Brain Volume Loss Over 6 Years in Patients With and Without Relapse Between Courses 1 and 2



Conclusions

- Relapse is not uncommon following the initiation of a new MS treatment
 - Relapse rate between the indicated Courses 1 and 2 of alemtuzumab was similar to or less than other therapies, including high efficacy therapies
- Long-term clinical and MRI outcomes, including BVL, were similarly favorable in patients who did or did not relapse between Courses 1 and 2
- Relapse between Courses 1 and 2 is not indicative of subsequent limited treatment response
 - Although patients in this cohort more frequently received alemtuzumab beyond Course 2, retreatment was effective in managing their disease over 6 years
- The results also highlight the importance of administering the initial 2 courses of alemtuzumab to achieve optimal clinical benefit
- These findings suggest that alemtuzumab may offer durable efficacy in the absence of continuous treatment, which may be due to the distinct pattern of lymphocyte repopulation following treatment with alemtuzumab, and may lead to a rebalancing of the immune system
 - Additional mechanistic studies are required to establish this hypothesis

CARE-MS and CAMMS03409 Study Group and Acknowledgments

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