Alemtuzumab Improves Clinical and MRI Disease Activity Outcomes, Including Slowing of Brain Volume Loss, in RRMS Patients Over 8 Years: CARE-MS I Follow-up (TOPAZ Study)

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OBJECTIVE

- **To evaluate the efficacy and safety of alemtuzumab over 8 years in RRMS patients from the CARE-MS I core study who entered the CARE-MS extension and TOPAZ studies**

INTRODUCTION

- In CARE-MS I (NCT00530348), 2 courses of alemtuzumab demonstrated significantly greater improvements in clinical and MRI outcomes versus SC IFNB-1a over 2 years[1]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs[1]
- Efficacy was maintained over an additional 5 years in 2 consecutive extension studies (CARE-MS extension [NCT00930553] and the ongoing TOPAZ study [NCT02255656]); 59% of patients did not receive additional alemtuzumab or other disease-modifying therapy (DMT) since the initial 2 courses[2-4]
- The effects of alemtuzumab over time may be due to its selective depletion and distinct pattern of repopulation of circulating CD52-expressing T and B lymphocytes[5,6]
  - Following depletion, a relative increase in regulatory T cells and a decrease in proinflammatory cytokines occurs, potentially leading to a rebalancing of the immune system[7,8]
  - The exact mechanism of action of alemtuzumab is not fully elucidated

METHODS

- In CARE-MS I, treatment-naive patients with active RRMS received alemtuzumab 12 mg/day IV on 5 consecutive days at baseline and on 3 consecutive days 12 months later[1]
- In the CARE-MS extension study, patients could receive additional alemtuzumab courses (12 mg/day on 3 consecutive days ≥12 months after the most recent course) as needed for relapse or MRI activity, or other licensed DMTs at the investigator's discretion[2]
- In TOPAZ, patients can receive additional alemtuzumab courses (12 mg/day on 3 consecutive days ≥12 months after the most recent course) or other DMT at any time point, both at the investigator's discretion (no criteria)[4]

RESULTS

Patients and Additional Treatment

- Of the 376 patients who were treated with alemtuzumab 12 mg in CARE-MS I, 290 (77%) remained on study from core study baseline until end of Year 8 (data cut-off date: October 4, 2017)
- Of the 349 patients who entered the extension study:
  - 197 (56%) received no additional treatment (no additional alemtuzumab courses and no other DMTs) while they remained on study in the extension through Year 8
  - Through Year 8, 86 (25%) received 1 additional alemtuzumab course, 31 (9%) received 2 additional courses, and 29 (8%) received >2 additional courses; 7% received alemtuzumab in Year 8
  - 15 (4%) received another DMT in the extension through Year 8
- Most common reasons for additional alemtuzumab treatment included relapse (47%), MRI activity (27%), and both relapse and MRI activity (19%); other reasons included relapse and EDSS progression (2.9%), and combination of relapse, MRI activity, and EDSS progression (0.8%); no reason was provided for 2.9% of retreatments
- Reasons for patient discontinuations in TOPAZ (Years 7–8; n=26 [7.4%]) included: withdrawal of consent (3.2%); fatal events and lost to follow-up (each 1.1%); physician decision and other reasons (each 0.9%); and study termination by the sponsor at the patient's site (0.3%)

Clinical Efficacy

- Alemtuzumab-treated patients maintained a low annualized relapse rate (ARR) over 8 years (**Figure 1**), with a cumulative ARR (Years 3–8) of 0.15 (95% CI, 0.13–0.18)
  - 58% of patients were relapse-free in Years 3–8
- At Year 8, 78% of patients had improved or stable EDSS scores compared with core study baseline (**Figure 2**)
  - Mean EDSS change from core study baseline was +0.07
- Through Year 8, 71% of patients were free of 6-month confirmed disability worsening (CDW; **Figure 3A**); 41% experienced 6-month confirmed disability improvement (CDI; **Figure 3B**)
- 58%–68% of patients achieved no evidence of disease activity (NEDA) in each year through Years 2–8; 25% achieved NEDA sustained over Years 3–8

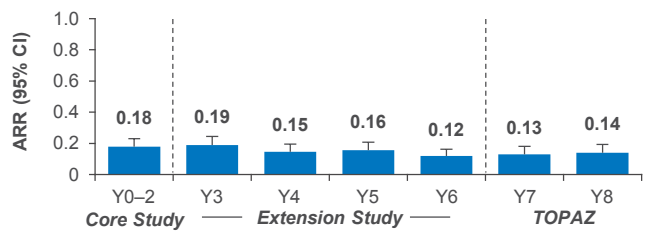
MRI Efficacy

- In each year through Years 2–8, 66%–77% of patients were free of MRI disease activity (**Figure 4**)
- Additionally, 82%–93% of patients had no new non-enhancing T1 hypointense lesions in each year over the same period
- Median percent cumulative brain volume loss (BVL) from core study baseline through Year 8 was –1.83% (**Figure 5**)
  - BVL was –0.22% or less annually in Years 3–8

CONCLUSIONS

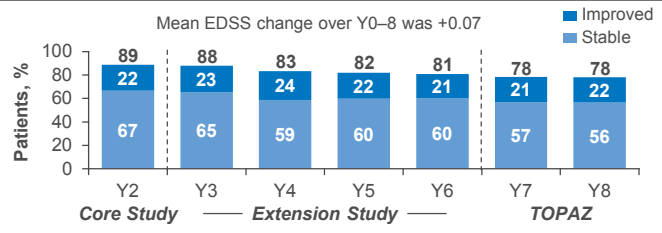
- **Efficacy of alemtuzumab on clinical, MRI lesion, and BVL outcomes was maintained over 8 years in patients with active RRMS who were treatment-naive**
  - **78% of patients had stable or improved disability based on EDSS scores through Year 8**
  - **The robustness of these results is supported by the high retention rate (77%) from core study baseline, and is further underscored by the observation that 56% of patients received neither additional alemtuzumab courses nor other DMTs in the extension through Year 8**
- **Alemtuzumab had a consistent safety profile through Year 8, and the overall incidence of AEs decreased over time**

Figure 1. Relapse Rates Through Year 8



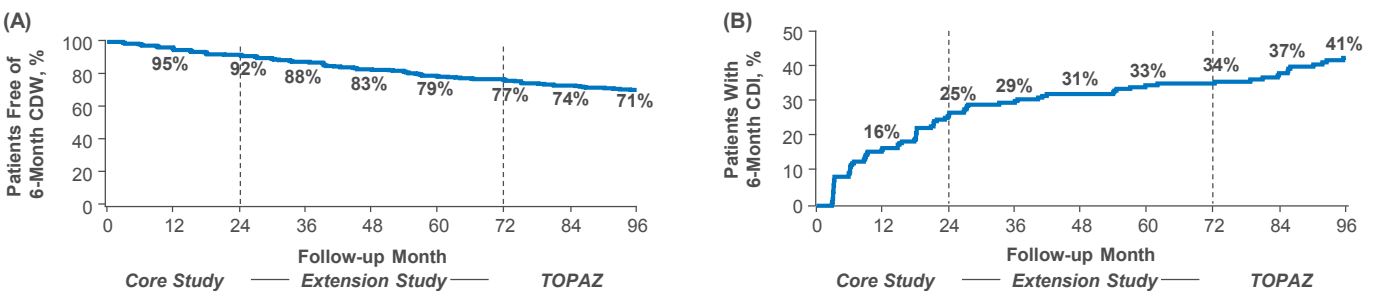
Y=year; ARR was estimated using a negative binomial model

Figure 2. Improved or Stable EDSS Scores Through Year 8



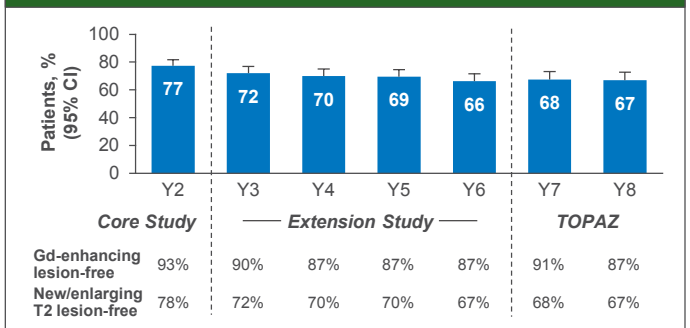
Improved EDSS score: ≥1.0-point decrease from core study baseline; Stable EDSS score: ≤0.5-point change in either direction from core study baseline

Figure 3. Patients (A) Free of 6-Month CDW and (B) Achieving 6-Month CDI Through Year 8



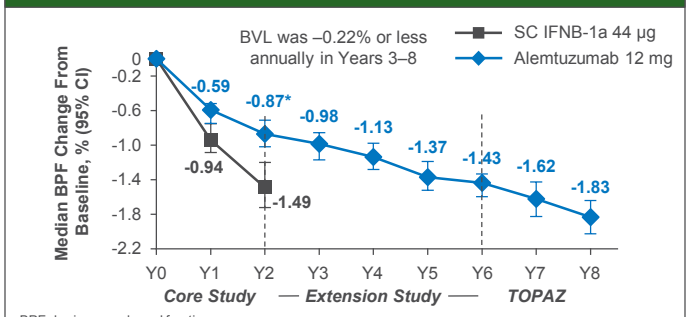
Kaplan-Meier estimates were used to assess proportions of patients with 6-month CDW and 6-month CDI; CDW: ≥1.0-point EDSS increase (or ≥1.5 points if baseline EDSS=0) confirmed over 6 months; CDI: ≥1.0-point EDSS decrease from baseline confirmed over 6 months (assessed only in patients with baseline EDSS score ≥2.0)

Figure 4. Freedom From MRI Disease Activity[a] Through Year 8



95% CI were obtained by the normal approximation to the binomial distribution; [a]No new gadolinium (Gd)-enhancing T1 lesions on current MRI or new/enlarging T2 hyperintense lesions since last MRI

Figure 5. Reduction in BVL Over 8 Years



BPF=brain parenchymal fraction
*Alemtuzumab vs SC IFNB-1a, $P<0.0001$ (based on ranked ANCOVA); Distribution-free estimates were obtained for the CI of the median; Blinded scans were read at Cleveland Clinic (Cleveland, OH, USA)

Safety Through 8 Years

- The incidence of AEs was reduced in Years 3–8 compared with the core study (Years 1–2) and declined over time (**Table 1**)
  - Thyroid AE incidence peaked in Year 3 as reported previously,[2,4] and declined subsequently through Year 8; cumulative incidence in Years 1–8 was 46.0% for thyroid AEs, and 6.4% for serious thyroid AEs
  - No immune thrombocytopenia (ITP) or autoimmune nephropathy events occurred after the 48-month monitoring period following the last alemtuzumab dose; there were no new ITP or autoimmune nephropathy events in Year 8
  - 10 malignancy cases were reported over 8 years: 1 in each of Years 1, 2, 3, 4, 6, 7, and 8; and 3 in Year 5 (2 papillary thyroid carcinomas, 1 keratoacanthoma, 1 basal cell carcinoma, 1 metastatic neoplasm [not otherwise specified], 1 malignant melanoma, 1 insulinoma, and 1 non-small cell lung cancer [all assessed as not related to alemtuzumab]; 1 breast carcinoma, and 1 micropapillar carcinoma of thyroid gland [both assessed as possibly related to alemtuzumab])
  - The incidence of infections declined through Years 1–8; the incidence of serious infections was ≤1.7% per year through 8 years
- Through Year 8, the most commonly reported AEs were IARs, the incidence of which declined after the first course of alemtuzumab (Course 1: 85.9%; Course 2: 65.7%; Course 3: 63.0%; Course 4: 56.7%)
  - The incidence of serious IARs was low (Course 1: 2.7%; Course 2: 0.5%; Course 3: 0%; Course 4: 0%)
- 4 deaths were reported in patients from CARE-MS I who entered TOPAZ (Years 7–8)
  - 2 deaths occurred in Year 7 (1 previously reported case of acute respiratory distress syndrome, sepsis, and acute renal failure[4]; and a previously unreported death due to malignant neoplasm of unknown primary site with metastases to liver, right adrenal gland, and regional lymph node, occurring approximately 4 months after last dose of alemtuzumab, with no autopsy performed)
  - 2 deaths were reported in Year 8 (1 case of septic shock with unknown etiology, and 1 death due to an unknown cause approximately 14 months after the last alemtuzumab dose, in a patient with recent history of acute systolic congestive heart failure; autopsies were not performed in either case)

Table 1. Incidence of AEs by Year

	Incidence, %								Exposure-Adjusted Incidence Rate Per 100 Patient-Years[a]		
	Y1 (N=376)	Y2 (N=376)	Y3 (N=360)	Y4 (N=344)	Y5 (N=340)	Y6 (N=335)	Y7 (N=321)	Y8 (N=296)	Y0–2 (N=376)	Y3–8 (N=360)	Y0–8 (N=376)
Any AE	93.6	84.0	75.8	74.1	69.4	63.0	56.7	50.7	679.7	107.0	432.1
Serious AEs	12.0	8.2	10.8	8.7	5.0	4.2	5.6	6.1	10.4	5.7	6.7
Infections	56.1	47.3	46.1	41.0	40.0	35.5	30.8	24.0	67.9	34.1	41.6
Serious infections	1.6	0.3	1.7	0.9	0.6	0.6	0.9	1.4	0.9	0.9	0.9
Autoimmune AEs[b]											
Thyroid AEs	6.4	9.6	15.0	7.8	3.5	3.0	1.9	1.4	8.6	7.6	9.3
Serious thyroid AEs	0.5	0.8	3.9	0.3	0.9	0	0	0.3	0.7	1.0	0.9
ITP	0.3	0.5	0	0.3	0	0.3	0	0	0.4	0.1	0.2
Nephropathies	0	0	0.3	0	0	0	0	0	0	0.1	<0.1
Malignancies	0.3	0.3	0.3	0.3	0.9	0.3	0.3	0.3	0.3	0.4	0.3

[a]Exposure-adjusted incidence rate=(Number of patients with first AE in the time interval)/(Total follow-up duration [years] of all patients within the time interval, censoring at the time of AE for patients counted in numerator) × 100
[b]First occurrence of AE for a patient

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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis
TOPAZ=a long-Term follow-up study for multiple sclerOsis Patients who have completed the AlemtuZumab extension study
Rebif® is a registered trademark of Merck Serono Europe Ltd.
Previously presented at the 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 10–12 October 2018, Berlin, Germany.
Alemtuzumab is approved in >70 countries around the world for treatment of adults with relapsing forms of multiple sclerosis (MS). In the EU, it is approved to treat patients with relapsing-remitting MS with active disease defined by clinical or imaging features. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. This material may contain information that is outside of the approved labeling in some countries.

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