Supporting Material

Comi G, Alroughani R, Boster AL, et al. Efficacy of alemtuzumab in relapsing-remitting MS patients who received additional courses after the initial two courses: pooled analysis of the CARE-MS, Extension and TOPAZ studies

MRI methodology

Details on the MRI methodology for the CARE-MS I and II core studies and the CARE-MS extension have been described previously.[1-5] Briefly, standardized cranial MRI scans were obtained at baseline and annually, and the following sequences were collected: T1-weighted before contrast and post contrast, T2-weighted and proton density (dual echo) before contrast, fluid-attenuated inversion recovery (FLAIR) before contrast and 3D gradient echo post contrast. A standard dosage of gadolinium (Gd)-contrast medium was used, with a wait time of 5 minutes before commencing post-contrast T1-weighted scans. Scans were analyzed by neuroradiologists at NeuroRx Research (Montreal, Québec, Canada), who were masked to treatment-group assignment, for MRI lesion endpoints.

New MRI lesion outcomes (new Gd-enhancing T1, new/enlarging T2 hyperintense, and new non-enhancing T1 hypointense lesions) were analyzed in patient subgroups by number of courses received. Freedom from MRI disease activity was defined as absence of new Gd-enhancing T1 and new/enlarging T2 lesions.

References

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Supporting Table 1. Percentage of CARE-MS I and II core study patients who received additional alemtuzumab courses by study year.

		Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Course 3	CARE-MS I	18.1%	7.6%	6.2%	4.2%	4.4%	2.7%
	CARE-MS II	20.4%	11.6%	9.5%	5.0%	2.7%	4.2%
	Pooled (CARE-MS I and II)	19.3%	9.7%	7.9%	4.6%	3.5%	3.5%
Course 4	CARE-MS I	--	4.7%	5.0%	2.7%	3.7%	2.0%
	CARE-MS II	--	7.5%	4.6%	4.8%	3.6%	3.2%
	Pooled (CARE-MS I and II)	--	6.2%	4.8%	3.8%	3.7%	2.6%
Course 5	CARE-MS I	--	--	1.5%	2.4%	3.4%	1.7%
	CARE-MS II	--	--	1.6%	2.0%	1.2%	1.6%
	Pooled (CARE-MS I and II)	--	--	1.6%	2.2%	2.3%	1.7%
Course 6	CARE-MS I	--	--	--	0.3%	0.3%	1.7%
	CARE-MS II	--	--	--	1.1%	1.2%	0.3%
	Pooled (CARE-MS I and II)	--	--	--	0.7%	0.8%	1.0%

	CARE-MS I	--	--	--	--	0%	0%
Course 7	CARE-MS II	--	--	--	--	0.6%	0.3%
	Pooled (CARE-MS I and II)	--	--	--	--	0.3%	0.2%
	CARE-MS I	--	--	--	--	--	0%
Course 8	CARE-MS II	--	--	--	--	--	0%
	Pooled (CARE-MS I and II)	--	--	--	--	--	0%

CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis. Percentages are based on the number of patients who remained in the study at the beginning of the year.

Supporting Table 2. Percentage of CARE-MS I and II patients who received alemtuzumab and/or another DMT.

		Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Total patients treated with alemtuzumab	CARE-MS I	18.1%	12.2%	12.6%	9.6%	11.8%	8.1%
	CARE-MS II	20.4%	19.4%	15.5%	12.9%	9.2%	9.7%
	Pooled (CARE-MS I and II)	19.3%	16.0%	14.1%	11.3%	10.5%	8.9%
Total patients treated with other DMTs	CARE-MS I	0.6%	1.7%	1.2%	1.5%	1.6%	1.4%
	CARE-MS II	2.8%	3.4%	3.3%	5.0%	3.0%	3.9%
	Pooled (CARE-MS I and II)	1.8%	2.6%	2.3%	3.3%	2.3%	2.6%
Total patients not treated with alemtuzumab or other DMTs or both	CARE-MS I	81.7%	86.0%	86.2%	89.0%	86.6%	90.5%
	CARE-MS II	77.1%	77.5%	81.2%	82.1%	87.8%	86.5%
	Pooled (CARE-MS I and II)	79.2%	81.5%	83.6%	85.4%	87.2%	88.4%

CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; DMT: disease-modifying therapy.
Percentages are based on the number of patients who remained in the study at the beginning of the year.

Supporting Table 3. Rates of treatment with other DMTs in CARE-MS I and II patients.

	CARE-MS I	CARE-MS II	Pooled CARE-MS I and II
In Year 3			
Number of enrolled patients, *N*	349	393	742
Patients who received other DMTs, %	0.6	2.8	1.8
Cyclophosphamide	0.3	0	0.1
Fingolimod	0	0.3	0.1
Glatiramer acetate	0.3	1.5	0.9
IFNB	0	0.8	0.4
IFNB-1b	0	0.8	0.4
Natalizumab	0	0.8	0.4
In Year 4			
Number of enrolled patients, *N*	344	387	731
Patients who received other DMTs, %	1.7	3.4	2.6
Cyclophosphamide	0.3	0	0.1
Dimethyl fumarate	0	0.3	0.1
Fingolimod	0.3	0.5	0.4
Glatiramer acetate	0	1.3	0.7
IFNB	0.9	0.3	0.5
IFNB-1a	0.3	0	0.1
IFNB-1b	0.9	0.3	0.5

Natalizumab	0.3	0.3	0.3
Rituximab	0	0.3	0.1
Teriflunomide	0	0.5	0.3
In Year 5			
Number of enrolled patients, *N*	340	367	707
Patients who received other DMTs, %	1.2	3.3	2.3
Azathioprine	0.3	0	0.1
Dimethyl fumarate	0	1.4	0.7
Fingolimod	0.3	0.5	0.4
Glatiramer acetate	0.3	0.3	0.3
IFNB	0.6	0.3	0.4
IFNB-1a	0.6	0.3	0.4
Natalizumab	0	0	0
Rituximab	0	0.8	0.4
Mycophenolate mofetil	0	0.3	0.1
Teriflunomide	0	0.3	0.1
In Year 6			
Number of enrolled patients, *N*	335	357	692
Patients who received other DMTs, %	1.5	5.0	3.3
Azathioprine	0.3	0	0.1
Dimethyl fumarate	0.6	1.4	1.0

Fingolimod	0	0.6	0.3
Glatiramer acetate	0	0.3	0.1
IFNB	0.3	0	0.1
IFNB-1a	0.3	0	0.1
Natalizumab	0.6	0.6	0.6
Rituximab	0	1.4	0.7
Teriflunomide	0	0.6	0.3
In Year 7			
Number of enrolled patients, *N*	321	336	657
Patients who received other DMTs, %	1.6	3.0	2.3
Azathioprine	0	0	0
Cyclophosphamide	0.3	0.3	0.3
Dimethyl fumarate	0.6	0	0.3
Fingolimod	0.3	0	0.2
Glatiramer acetate	0	0.9	0.5
IFNB	0	0	0
Mitoxantrone hydrochloride	0	0.3	0.2
Natalizumab	0.3	0.3	0.3
Rituximab	0	1.2	0.6
Teriflunomide	0	0.3	0.2
In Year 8			

Number of enrolled patients, *N*	296	310	606
Patients who received other DMTs, %	1.4	3.9	2.6
Azathioprine	0	0	0
Cyclophosphamide	0	0	0
Daclizumab	0	0.3	0.2
Dimethyl fumarate	0.3	0	0.2
Fingolimod	0	0.3	0.2
Glatiramer acetate	0.3	0.6	0.5
IFNB	0.3	0.3	0.3
IFNB-1b	0.3	0	0.2
IFNB-1a	0	0.3	0.2
Mitoxantrone hydrochloride	0	0.3	0.2
Mycophenolate mofetil	0	0.3	0.2
Natalizumab	0.3	0	0.2
Rituximab	0	1.3	0.7
Teriflunomide	0	0.3	0.2

CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; DMT: disease-modifying therapy; IFNB: interferon beta. Percentages are based on the number of patients who remained in the study at the beginning of the year. Patients may have received >1 DMT over Years 3–8.

Supporting Table 4. ITP, nephropathies, malignancies, and deaths in the 2-courses group.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
ITP	0	3	0	3[a]	1	0	0	0
Nephropathies	0	0	0	0	0	0	1[b]	0
Malignancies	0	2[c]	2[c]	1	3[d,e]	1[f]	2[f,g]	1[f]
Type of malignancy	--	Thyroid cancer (*n* = 1); basal cell carcinoma (*n* = 1)	Thyroid cancer (*n* = 1); keratoacanthoma (*n* = 1)	Breast cancer	Insulinoma (*n* = 1); non-small cell lung cancer (*n* = 1); thyroid cancer (*n* = 1)	B-cell lymphoma	Basal cell carcinoma (*n* = 1); breast cancer (*n* = 1)	Basal cell carcinoma
Deaths	0	0	1	0	0	2[e]	0	1
Cause of death	--	--	Sepsis	--	--	Non-small cell lung cancer (*n* = 1); pulmonary embolism (*n* = 1)	--	Sudden death

GBM: glomerular basement membrane; ITP: immune thrombocytopenia.

All cases have been reported previously.[1-4, 6-10] [a]One case of ITP remained unresolved at last follow-up. [b]Patient was positive for anti-GBM antibodies, but was asymptomatic for anti-GBM disease. As of last follow-up, the case remained unresolved. [c]Cases of thyroid cancer in Years 2 and 3 remained unresolved at last follow-up. [d]Case of insulinoma in Year 5 remained unresolved at last follow-up. [e]Case of non-small cell lung cancer presented as a malignancy in Year 5, and was fatal in Year 6. [f]Patient who was diagnosed with B-cell lymphoma in Year 6 had secondary diagnoses of basal cell carcinoma in Years 7 and 8; both the B-cell lymphoma diagnosed in Year 6 and the basal cell carcinoma diagnosed in Year 7 remained unresolved at last follow-up. [g]Case of breast cancer in Year 7 remained unresolved at last follow-up.

Supporting Table 5. Time to onset of first autoimmune AE following alemtuzumab treatment.

	Overall (*N* = 811)	2-Courses Group[a] (*N* = 362)	Any Additional Courses[b] (*N* = 293)
Time from first alemtuzumab treatment to first autoimmune AE[c] onset, years			
n	380	182	135
Mean (SD)	2.8 (1.6)	2.5 (1.4)	3.4 (1.9)
Median (range)	2.3 (0.3–7.8)	2.3 (0.3–7.6)	2.8 (0.3–7.8)
Time from last alemtuzumab treatment to first autoimmune AE[c] onset, years			
n	380	182	135
Mean (SD)	1.4 (1.1)	1.6 (1.2)	1.3 (0.9)
Median (range)	1.1 (0–6.5)	1.3 (0–6.5)	1.0 (0–5.6)

AE: adverse event; CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; DMT: disease-modifying therapy; ITP: immune thrombocytopenia; SD: standard deviation.

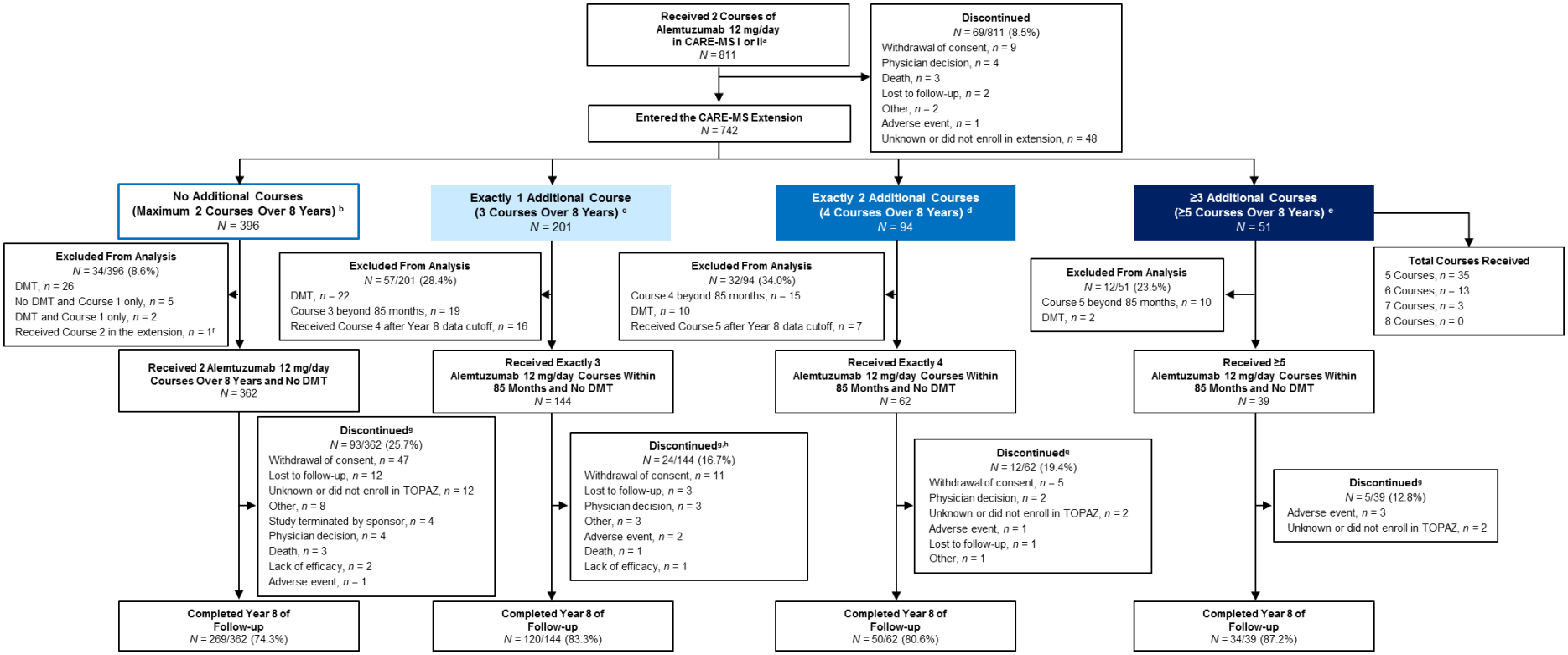
[a]Patients in this subgroup received only the initial two courses of alemtuzumab in CARE-MS I and II, and no additional courses and no other DMT through 8 years. [b]Patients in this subgroup received no other DMT through 8 years and received Course 3 before Month 85. [c]Autoimmune AEs were considered to be thyroid events, ITP, and nephropathy.

Supporting Figure 1. Patient disposition in the analysis populations. Schematic of patient participation from each analysis group starting from CARE-MS I and II core study baselines through Year 8. [a]As-treated population. [b]In the CARE-MS studies, seven patients received only one course of alemtuzumab. [c]Three patients received Course 3 <12 months after Course 2 (Days 353, 358, and 359). [d]Three patients received Course 4 <12 months after Course 3 (Days 357, 358, and 364). [e]Five patients received Course 5 <12 months (Days 330, 344, 351, and 365 [two patients]) after Course 4. [f]One patient received Course 2 during the extension instead of during the core study, and was thus excluded from the 2-courses analysis group. [g]Six patients died after adverse events following treatment with Courses 2, 3, 4, 5, and 6, respectively. [h]One patient died after withdrawing from the study following treatment with Course 3. CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; DMT: disease-modifying therapy.

Supporting Figure 2. Efficacy outcomes in the ≥5-courses group. Results for patients who received ≥5 courses within 85 months and no other DMT through Year 8. Patients who received ≥6 courses were censored at the time of Course 6 administration. Through 24 and 36 months, respectively, 13 and 4 patients in the ≥5-courses group were available for follow-up after receiving Course 5. (A) ARR at 12 months before CARE-MS core study enrollment, at 12 months before Course 5, and at 12, 24, and 36 months after Course 5. (B) Mean (SE) EDSS scores from 12 months before Course 5 to 36 months after Course 5. (C) Kaplan-Meier analyses of the percentages of patients free of 6-month CDW, and percentages of patients with 6-month CDI from the time of Course 5 administration to 36 months after Course 5. (D) Percentages of patients free of MRI disease activity, new Gd-enhancing T1 lesions, new/enlarging T2 hyperintense lesions, and new T1 hypointense lesions from 12 months before Course 5 to 36 months after Course 5. *P*-values for ARR analyses are based on repeated negative binomial regression with robust variance estimation. *P*-values for MRI analyses are based on McNemar's test. The MRI scan immediately before the start date for

receiving Course 5 is considered to be ‘before Course 5,’ and the MRI scan ≥3 months after receiving Course 5 is considered to be ‘after Course 5.’ ARR: annualized relapse rate; CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; CDI: confirmed disability improvement; CDW: confirmed disability worsening; CI: confidence interval; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; Gd: gadolinium; M: month; SE: standard error.

Supporting Figure 1



Supporting Figure 2