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Original research article

Alemtuzumab outcomes by age: Post hoc analysis from the randomized CARE-MS studies over 8 years

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ABSTRACT

Background: Alemtuzumab significantly improved clinical and MRI outcomes vs. subcutaneous interferon beta-1a (SC IFNB-1a) in the CARE-MS trials (NCT00530348, NCT00548405), with sustained efficacy in 2 consecutive extensions (NCT00930553, NCT02255656 [TOPAZ]).
Methods: Post hoc analysis of 8-year alemtuzumab efficacy and safety in pooled CARE-MS patients (N=811) stratified by baseline age (≥18 to ≤25, >25 to ≤35, >35 to ≤45, >45 to ≤55 years).
Results: Compared with SC IFNB-1a over 2 years across age cohorts, alemtuzumab lowered annualized relapse rates (ARR; 0.22–0.24 vs. 0.38–0.51), improved or stabilized disability (freedom from 6-month confirmed disability worsening [CDW]: 85%–92% vs. 62%–88%; achievement of 6-month confirmed disability improvement [CDI]: 20%–31% vs. 13%–25%), increased proportions free of MRI disease activity (70%–86% vs. 42%–63% per year), and slowed brain volume loss (BVL; –0.45% to –0.87% vs. –0.50% to –1.39%). Through Year 2, the treatment effect with alemtuzumab did not significantly differ among age groups for ARR (*p*-interaction=0.6325), 6-month CDW-free (*p*-interaction=0.4959), 6-month CDI (*p*-interaction=0.9268), MRI disease

Abbreviations: AE, adverse event; ARR, annualized relapse rate; BPF, brain parenchymal fraction; BVL, brain volume loss; 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; IARs, infusion-associated reactions; ITP, immune thrombocytopenia; KM, Kaplan-Meier; MRI, magnetic resonance imaging; MS, multiple sclerosis; NE, not estimable; No., number; OR, odds ratio; RRMS, relapsing-remitting MS; SAE, serious adverse event; SC IFNB-1a, subcutaneous interferon beta-1a; SD, standard deviation; SPMS, secondary progressive MS; TOPAZ, a long-Term follow-up study for multiple sclerOsis Patients who have completed the AlemtuZumab extension study; Y, year.

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activity-free (*p*-interaction=0.6512), and BVL (*p*-interaction=0.4970). Alemtuzumab remained effective on outcomes through Year 8 across age groups. Age-related increases in malignancies (≤45 years: 0.9%–2.2% vs. >45 years: 8.1%) and deaths (0%–1.7% vs. 7.0%) were observed. Serious infections also increased from the youngest (5.1%) to oldest (12.8%) age cohorts.

Conclusions: Alemtuzumab had greater efficacy than SC IFNB-1a over 2 years across comparable age groups, with no significant differences between alemtuzumab-treated age groups. Efficacy on relapse, disability, and MRI outcomes continued through Year 8 across age groups. Age-related increases in serious infections, malignancies, and deaths were observed.

1. Introduction

Multiple sclerosis (MS) prevalence is highest among patients 55–64 years old (Wallin et al., 2019a), yet few clinical studies have assessed the impact of age on efficacy and safety of disease-modifying therapy (DMT) in relapsing-remitting MS (RRMS) patients. RRMS continuously evolves (Alvarez-Cermeno et al., 2010; Gajofatto and Benedetti, 2015; Vaughn et al., 2019), with DMT effectiveness on relapse frequency and disability progression potentially declining with age (Signori et al., 2015; Weideman et al., 2017). Greater understanding of DMT efficacy and safety in RRMS patients across age groups is needed to better inform clinical decisions.

Alemtuzumab (LEMTRADA®; Sanofi Genzyme, Cambridge, MA), a humanized monoclonal antibody, selectively binds to the cell surface antigen CD52, inducing B- and T-cell depletion (Cox et al., 2005; Hu et al., 2009). Subsequent lymphocyte repopulation induces relative increases in regulatory T and B lymphocytes and a shift toward a less inflammatory cytokine profile (Hu et al., 2009; Rao et al., 2012). These effects may underlie control of RRMS disease activity after alemtuzumab treatment (Cox et al., 2005; De Mercanti et al., 2016; Durelli et al., 2016; Zhang et al., 2013).

During the 2-year, phase 3 CARE-MS (NCT00530348; NCT00548405) trials, alemtuzumab significantly improved clinical and MRI outcomes versus subcutaneous interferon beta-1a (SC IFNB-1a; Rebif®; EMD Serono Inc, Rockland, MA, USA) (Cohen et al., 2012; Coles et al., 2012). Through a 4-year open-label extension study (CAMMS03409; NCT00930553) (Coles, A. J. et al., 2017; Havrdova et al., 2017; Ziemssen and Thomas, 2017), and a subsequent, ongoing, follow-up extension study (TOPAZ; NCT02255656), efficacy was maintained, with no new safety signals observed in the CARE-MS population through Year 8 (Coles et al., 2017b; Singer et al., 2017). This analysis examines alemtuzumab outcomes by age versus SC IFNB-1a over 2 years, with continued follow-up in alemtuzumab-treated patients for a total of 8 years.

2. Patients and methods

2.1. Patients and procedures

Post hoc analysis over 8 years was carried out on alemtuzumab-treated patients stratified by age at core study baseline (≥18 to ≤25, >25 to ≤35, >35 to ≤45, and >45 to ≤55 years of age); SC IFNB-1a–treated patients from the core studies were included through Year 2 only. Cut-off for the analysis was October 4, 2017.

The CARE-MS, CAMMS03409 extension, and subsequent TOPAZ study designs have been described previously (Cohen et al., 2012; Coles et al., 2017b; Coles et al., 2017a; Coles et al., 2012; Havrdova et al., 2017; Singer et al., 2017; Ziemssen and Thomas, 2017). Briefly, CARE-MS I and II were phase 3 trials of RRMS patients who were treatment-naive (CARE-MS I) (Cohen et al., 2012) or who had an inadequate response to prior therapy (CARE-MS II) (Coles et al., 2012). Patients were randomized to either alemtuzumab 12 mg/day (baseline: 5 consecutive days; 12 months later: 3 consecutive days), or SC IFNB-1a 44 μg 3 × /weekly. Upon core study completion, alemtuzumab-treated patients could enroll in the open-label CAMMS03409 extension and receive additional, as-needed, alemtuzumab courses if they had disease activity (≥1 protocol-defined relapse and/or ≥2 unique lesions [either new/enlarging T2 hyperintense and/or gadolinium [Gd]-enhancing brain and/or spinal cord lesions on MRI]) and at the treating investigator's discretion (Coles et al., 2017a; Havrdova et al., 2017). Other DMTs, if needed, were also permitted. After the 4-year extension study, patients could enroll in TOPAZ and receive additional alemtuzumab (12 mg/day; 3 consecutive days; ≥12 months apart) at the treating investigator's discretion (no protocol-defined disease criteria) or another DMT. SC IFNB-1a–treated patients could also enroll in the extensions and receive alemtuzumab; however, data obtained after the switch to alemtuzumab are not included here.

2.2. Efficacy and safety assessments

Clinical efficacy assessments, including relapse events, disability accumulation, and MRI outcomes have been described previously (Cohen et al., 2012; Coles et al., 2017b; Coles et al., 2017a; Coles et al., 2012; Havrdova et al., 2017; Singer et al., 2017; Ziemssen and Thomas, 2017). Disability was measured using the Expanded Disability Status Scale (EDSS). EDSS score improvement (≥1.0-point decrease), worsening (≥1.0-point increase), and stability (≤0.5-point change in either direction) were calculated relative to core study baseline. CDW was defined as ≥1-point EDSS score increase (≥1.5 points if baseline EDSS = 0) from core study baseline and confirmed over 6 months; CDI was defined as ≥1.0-point decrease from core study baseline EDSS score confirmed over 6 months, and was assessed in patients with baseline EDSS scores ≥2.0. MRI disease activity was defined as new Gd-enhancing T1 lesions on current scan or new/enlarging T2 hyperintense lesions since last scan. Brain volume loss (BVL) was measured by brain parenchymal fraction (BPF) (Rudick et al., 1999).

The proportion of patients converting to secondary progressive MS (SPMS) was evaluated by using the optimal definition from Lorscheider et al. (Lorscheider et al., 2016) as described previously (Horakova et al., 2020). SPMS was defined as disability progression by 1 EDSS point in patients with baseline EDSS score ≤5.5, or 0.5 EDSS points in patients with baseline EDSS score ≥6, both without relapse (i.e. progression start date is ≥180 days after prior relapse); EDSS score ≥4 and pyramidal functional system score ≥2; confirmed progression over ≥3 months, including confirmation within the functional system leading to the progression event. Functional systems scores were collected through the end of the CARE-MS extension study (Year 6), but not in TOPAZ, hence conversion to SPMS could only be determined through Year 6 but not over Years 7–8.

Safety was monitored throughout the studies, and monitoring for autoimmune adverse events (AEs) continued for 48 months following the last alemtuzumab course. AEs with onset during or ≤24 hours after infusion were designated as infusion-associated reactions (IARs).

2.3. Statistical analysis

All available data without imputation through Year 8 were included. All analyses were done separately for each age cohort. *P*-values for heterogeneity (*p*-interaction values) were assessed for each clinical endpoint. Annualized relapse rates (ARR) were estimated using negative

binomial regression with robust variance estimation with treatment as a covariate. ARR *p*-interaction values were determined using negative binomial regression with robust variance estimation, including treatment, age group, and treatment-by-age group interaction as covariates. The proportion of patients with stable or improved EDSS scores was analyzed using logistic regression with covariate adjustment for treatment, age group, baseline EDSS score, and treatment-by-age group interaction. The Kaplan-Meier (KM) method was used to estimate the percentages of patients free of 6-month CDW or with 6-month CDI; time to first 6-month CDW or 6-month CDI event through Year 2 was analyzed using the Cox proportional hazard model with covariate adjustments for age group, treatment, region, and age-group-by-treatment group interaction. MRI lesion activity was summarized descriptively by percentages of patients free of MRI lesions. The 95% confidence intervals (CIs) of the proportion of patients free of MRI disease activity (ie, Gd-enhancing lesions and T2 hyperintense lesions) were obtained using the normal approximation to the binomial distribution. The proportion of patients who were MRI lesion-free was evaluated using logistic regression with covariate adjustment for baseline, treatment, age category, and treatment-by-age group interaction. Distribution-free estimates of the 95% CI of the median BPF percent change from baseline values were computed. To evaluate BVL differences through Year 2 between treatment groups and across age groups, a linear regression model was used on log-transformed BPF values with covariate adjustment for geographic region, log-transformed baseline BPF, age group, treatment, and treatment-by-age group interaction. The KM method was used to derive the cumulative estimates of patients with SPMS through Year 6 (Horakova et al., 2020). Safety data were reported through Year 8 as incidences defined as the percentage of patients with ≥1 event.

2.4. Standard protocol approvals, registrations, and patient consents

CARE-MS I (NCT00530348), CARE-MS II (NCT00548405), CAMMS03409 (NCT00930553), and TOPAZ (NCT02255656) are registered with ClinicalTrials.gov. Patients provided written informed consent. All procedures were approved by local institutional ethics review boards of participating sites.

3. Results

3.1. Patients

In the CARE-MS trials, 811 patients received alemtuzumab and 389 patients received SC IFNB-1a. In the alemtuzumab arm, there were 137 (17%) patients aged ≥18 to ≤25 years, 350 (43%) aged >25 to ≤35 years, 238 (29%) aged >35 to ≤45 years, and 86 (11%) aged >45 to ≤55 years. In the SC IFNB-1a arm, there were 76 (20%) patients aged ≥18 to ≤25 years, 135 (35%) aged >25 to ≤35 years, 133 (34%) aged >35 to ≤45 years, and 45 (12%) aged >45 to ≤55 years (percentages may not sum to 100% due to rounding). Baseline characteristics were balanced across age cohorts, except for higher baseline EDSS scores and lower Gd-enhancing lesion burden in the 2 older cohorts (**Table 1** [alemtuzumab-treated patients] and **Supplementary Table 1** [SC IFNB-1a–treated patients]). Baseline characteristics for alemtuzumab-treated patients who did not continue beyond the core studies are described in **Supplementary Table 2**.

Across age cohorts, 72%–74% of alemtuzumab-treated patients in the core study remained on study through Year 8 (**Supplementary Fig. 1**), and 48%–53% of patients received no additional alemtuzumab and no other DMT in the extensions (**Fig. 1A**). Frequencies of patients who received additional alemtuzumab courses for relapse, MRI activity, both relapse and MRI activity, or for any reason, did not differ between age groups (**Fig. 1B**).

Through Year 6 (i.e. within the follow-up time for which functional systems were available), there were 2 patients (KM estimate, 1.7%; 95% CI, 0.4%–6.8%; 1 CARE-MS I and 1 CARE-MS II) aged ≥18 to ≤25 years, 6 patients (1.9%; 0.9%–4.2%; 1 CARE-MS I and 5 CARE-MS II) aged >25 to ≤35 years, 11 patients (4.9%; 2.7%–8.7%; 2 CARE-MS I and 9 CARE-MS II) aged >35 to ≤45 years, and 1 patient (1.3%; 0.2%–8.5%; CARE-MS II) aged >45 to ≤55 years, who converted to SPMS according to the Lorscheider et al. optimal definition (Lorscheider et al., 2016).

Table 1
Baseline characteristics of alemtuzumab-treated patients by age cohort.

	≥18 to ≤25 Years n = 137	>25 to ≤35 Years n = 350	>35 to ≤45 Years n = 238	>45 to ≤55 Years n = 86
Proportion of alemtuzumab-treated CARE-MS population, %[a]	17	43	29	11
Age, years	22.7 (2.1)	30.5 (2.7)	40.3 (3.0)	48.5 (2.2)
Age at RRMS diagnosis, years	21.2 (2.7)	28.4 (3.6)	38.0 (4.0)	45.6 (3.1)
Age at RRMS symptom onset, years	20.2 (2.7)	27.3 (3.6)	36.8 (4.1)	44.1 (3.2)
Time from RRMS diagnosis to randomization, years	2.0 (2.0)	2.6 (2.5)	2.8 (2.6)	3.4 (2.9)
Female, n (%)	94 (68.6)	220 (62.9)	158 (66.4)	58 (67.4)
EDSS score	2.1 (1.1)	2.3 (1.0)	2.6 (1.1)	2.8 (1.2)
Years since initial relapse	2.7 (1.8)	3.4 (2.5)	3.5 (2.6)	3.8 (2.7)
Number of relapses in prior 1 year	1.9 (0.9)	1.7 (0.9)	1.6 (0.8)	1.6 (0.8)
Number of relapses in prior 2 years	2.9 (1.2)	2.7 (1.1)	2.5 (0.9)	2.5 (0.9)
Gd-enhancing lesion count	3.0 (7.8)	2.7 (6.1)	1.6 (3.1)	1.5 (4.4)
Patients with Gd-enhancing lesions, n (%)	69 (51.5)[b]	162 (47.0)[c]	96 (40.9)[d]	25 (29.1)
T2 hyperintense lesion volume, cm^3	9.1 (11.4)	8.7 (10.3)	8.6 (10.4)	9.2 (13.8)
BPF	0.82 (0.02)	0.82 (0.02)	0.81 (0.02)	0.81 (0.02)

All values are mean (SD) unless specified otherwise. [a]N = 811. [b]N = 134. [c]N = 345. [d]N = 235. BPF, brain parenchymal fraction; EDSS, Expanded Disability Status Scale; Gd, gadolinium; SD, standard deviation

3.2. Clinical efficacy by age cohort

Alemtuzumab reduced ARR through Year 2 vs. SC IFNB-1a (**Fig. 2A**), with no significant differences in treatment effect with alemtuzumab across age groups (*p*-interaction=0.6325); ARR remained low (0.15–0.19) in alemtuzumab-treated patients in each age cohort over Years 3–8. Across age cohorts, no significant differences in treatment effect were observed between the percentages of alemtuzumab- and SC IFNB-1a–treated patients with stable or improved EDSS scores over 2 years (*p*-interaction=0.3889); however, there was a greater numerical difference observed between the percentages of alemtuzumab- and SC IFNB-1a-treated patients aged >45 to ≤55 years with stable EDSS scores. In Year 8, EDSS scores remained stable or improved in 59%–80% of alemtuzumab-treated patients compared with core study baseline (**Fig. 2B**), with more EDSS worsening seen in the 2 older cohorts. In each age group, a numerically higher percentage of alemtuzumab- than SC IFNB-1a–treated patients were free of 6-month CDW (**Fig. 2C**) and achieved 6-month CDI (**Fig. 2D**) at Year 2; no significant differences in treatment effect across age groups were observed with alemtuzumab (6-month CDW-free: *p*-interaction=0.4959; 6-month CDI: *p*-interaction=0.9268). Across age cohorts at Year 8, 50%–77% of patients remained free of 6-month CDW, and 39%–49% experienced CDI with alemtuzumab. Compared with those aged ≤35 years, fewer patients aged >35 years were free of CDW (50%−59% vs 73%−77%) or had CDI (39%–43% vs 46%−49%). Additional clinical outcomes for alemtuzumab-treated patients who did not continue beyond the core studies are described in **Supplementary Table 2**.

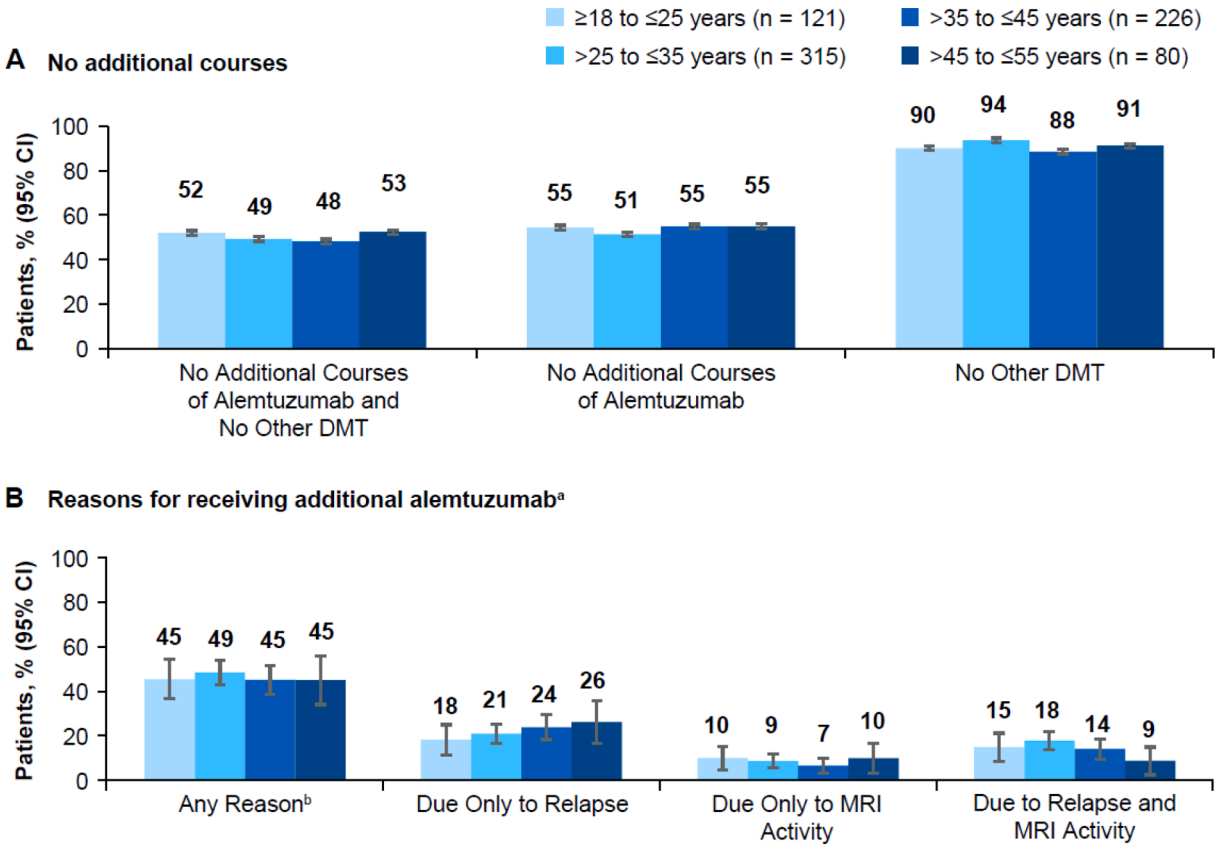


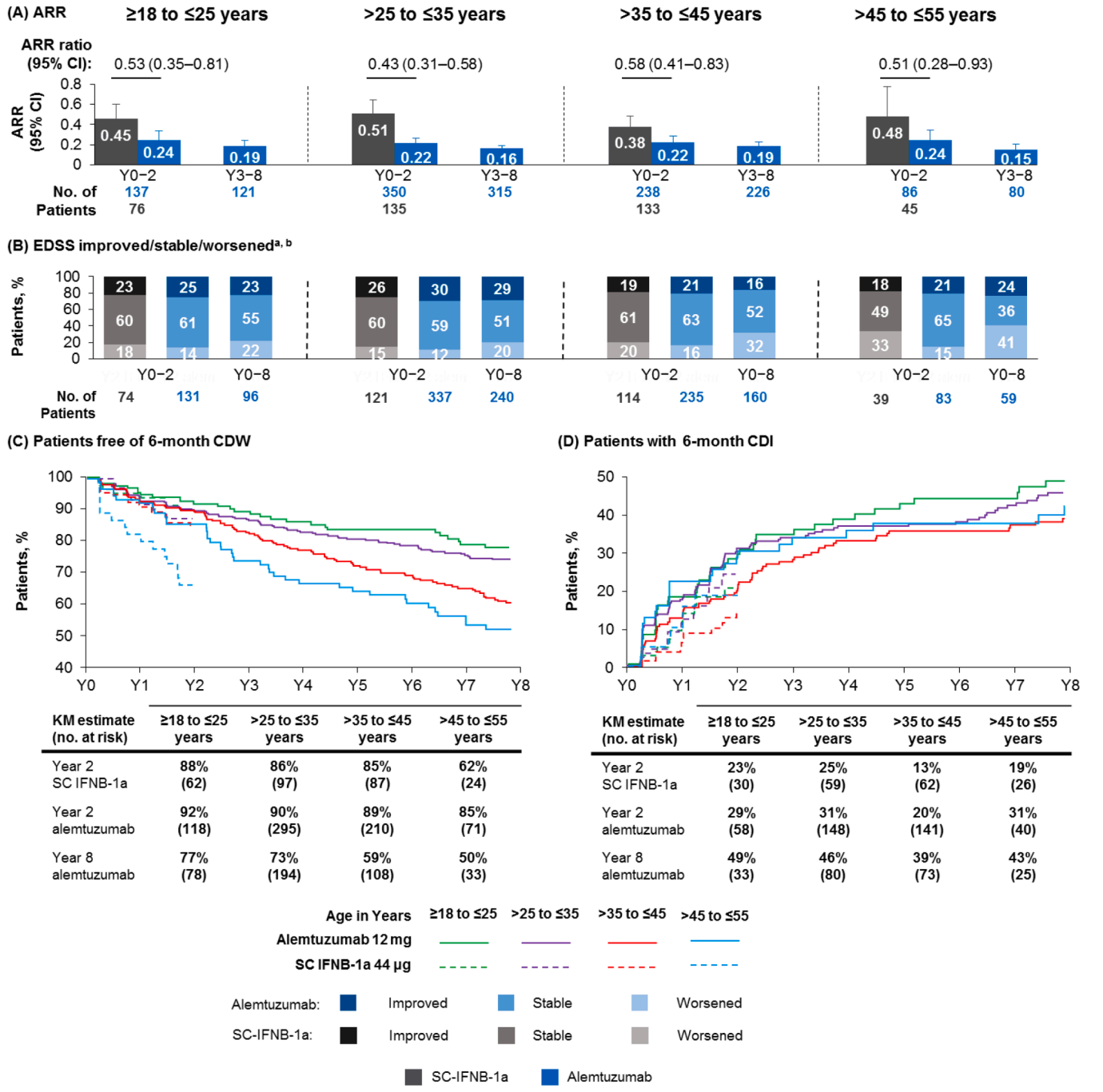
Fig. 1. Treatment with additional courses of alemtuzumab in the extensions by age cohort.
(A) Patients who received no additional alemtuzumab and no other DMT, no additional alemtuzumab, or no other DMT in the extensions. (B) Percentages of patients who received additional courses of alemtuzumab for any reason, for relapse only, for MRI disease activity only, or for both relapse and MRI disease activity through Year 8. [a]Patients may or may not have received another DMT. [b]Patients received additional alemtuzumab for either relapse, MRI activity, relapse and MRI activity, EDSS progression, or no reason was available. CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.

3.3. MRI efficacy by age cohort

More alemtuzumab-treated patients in each age cohort were free of MRI disease activity, new Gd-enhancing lesions, and new/enlarging T2 hyperintense lesions in Year 2 vs. SC IFNB-1a–treated patients (**Fig. 3A and Supplementary Fig. 2**); no significant differences in treatment effect across age groups were seen with alemtuzumab (MRI disease activity-free: *p*-interaction=0.6512; new Gd-enhancing T1 lesion-free: *p*-interaction=0.9647; new/enlarging T2 hyperintense lesion-free: *p*-interaction=0.6567). In Year 8, 61%–86% of alemtuzumab-treated patients in each age cohort were free of MRI disease activity. Treatment effect of alemtuzumab on slowing of cumulative BVL did not differ among age groups over 2 years (*p*-interaction=0.4970; **Fig. 3B**). BVL with alemtuzumab remained slow through Year 8 (–1.24% to –1.64%), with no clear pattern of differences between age groups. Notably, BVL at Year 8 with alemtuzumab in patients aged ≥18 to ≤25 years remained less than that observed in this age range over 2 years with SC IFNB-1a. **Supplementary Table 2** highlights additional MRI outcomes for alemtuzumab-treated patients who did not continue beyond the core studies.

3.4. Safety

The safety profile of alemtuzumab over 8 years was generally similar among the 3 younger age cohorts, with the exception of higher rates of serious infections in patients with increased age (**Table 2 and Supplementary Table 3**); however, there were no *Listeria monocytogenes* infections observed in any of the age cohorts. Additionally, patients aged >45 to ≤55 years had higher incidences of malignancies (8.1% vs. ≤2.2%) and deaths (7.0% vs. ≤1.7%). A total of 7 patients aged >45 to ≤55 years developed malignancies. One patient developed thyroid papillary carcinoma, 1 non-small cell lung cancer, and 1 keratoacanthoma, all deemed not related to treatment. In addition, 1 patient developed breast carcinoma and 1 patient developed squamous cell carcinoma, both deemed related to treatment. Finally, 1 patient developed B-cell lymphoma (related to treatment) and 2 events of basal cell carcinoma (both deemed not related to treatment), and 1 patient developed 2 events of basal cell carcinoma, both deemed related to treatment. Incidence of immune thrombocytopenia and nephropathy did not show any age-related trends. Frequency of malignancy was not higher in patients aged >45 to ≤55 years who had received DMTs prior to alemtuzumab (ie, CARE-MS II patients; 5.4%) vs. those who were treatment-naive (ie, CARE-MS I patients; 13.3%). Serious infections, however, were more frequent in CARE-MS II vs. CARE-MS I patients aged >35 years (13.1%–16.1% vs. 6.7%–8.3%). Deaths were reported across age groups except those ≥18 to ≤25 years (all reported previously) (Cohen et al., 2012; Coles et al., 2017b; Coles et al., 2012; Comi et al., 2018; Singer et al., 2017; Singer et al., 2018). Over 8 years, there were 16 deaths in alemtuzumab-treated patients: 6 patients aged >25 to ≤35 years (Year 2: traffic accidents [n = 2] and aspiration pneumonia [n = 1; 10 months after Course 2]; Year 7: unknown cause [n = 1; 17 months after Course 3]; Year 8: sudden death [n = 1; 78 months after Course 2] and atrioventricular block [n = 1; 26 months after Course 4]), 4 patients aged >35 to ≤45 years (Year 3: sepsis [n = 1; 20 months after Course 2]; Year 7: suicide [n = 1; 40 months after Course 3]; Year 8: metastatic neoplasm of unknown primary site [n = 1; 4 months after



KM estimate (no. at risk)	≥18 to ≤25 years	>25 to ≤35 years	>35 to ≤45 years	>45 to ≤55 years
Year 2 SC IFNB-1a	88% (62)	86% (97)	85% (87)	62% (24)
Year 2 alemtuzumab	92% (118)	90% (295)	89% (210)	85% (71)
Year 8 alemtuzumab	77% (78)	73% (194)	59% (108)	50% (33)

KM estimate (no. at risk)	≥18 to ≤25 years	>25 to ≤35 years	>35 to ≤45 years	>45 to ≤55 years
Year 2 SC IFNB-1a	23% (30)	25% (59)	13% (62)	19% (26)
Year 2 alemtuzumab	29% (58)	31% (148)	20% (141)	31% (40)
Year 8 alemtuzumab	49% (33)	46% (80)	39% (73)	43% (25)

Fig. 2. Relapse rates and disability outcomes by age cohort.
Results stratified by patient age at core study baseline over 8 years. Alemtuzumab treatment was assessed through Year 8, and SC IFNB-1a treatment was assessed through Year 2 of the core study. (A) Cumulative ARR over Years 0–2 of the core study in alemtuzumab- and SC IFNB-1a–treated patients, and over Years 3–8 of the extensions in alemtuzumab-treated patients. (B) Percentages of patients with improved, stable, or worsened EDSS scores compared with core study baseline at Year 2 in alemtuzumab- and SC IFNB-1a–treated patients, and at Year 8 in alemtuzumab-treated patients. (C) Kaplan-Meier analyses of the percentages of patients free of 6-month CDW over 8 years. (D) Kaplan-Meier analyses of the percentages of patients with 6-month CDI over 8 years. [a]Categories may not sum to 100% due to rounding. [b]In the >45 to ≤55 years group, 35 of 59 (59%) patients had stable or improved EDSS scores in Years 0–8; however, the sum of the percentages for each category may differ due to rounding. ARR, annualized relapse rate; CDI, confirmed disability improvement; CDW, confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; KM, Kaplan-Meier; No., number; SC IFNB-1a, subcutaneous interferon beta-1a; Y, year.

Course 5] and septic shock [n = 1; 43 months after Course 5]), and 6 patients aged >45 to ≤55 years (Year 6: non-small cell lung cancer [n = 1; 49 months after Course 2] and pulmonary embolism [n = 1; 53 months after Course 2]; Year 7: acute respiratory distress syndrome [n = 1; 46 months after Course 3]; Year 8: unknown causes [n = 1; 14 months after Course 3], suicide [n = 1; 30 months after Course 4], and organizing pneumonia [n = 1; 17 months after Course 6]). Safety for SC IFNB-1a through Year 2 is presented in **Supplementary Table 4**.

4. Discussion

RRMS disease characteristics and activity change with age, such that inflammatory disease is more often associated with younger RRMS patients, and greater disability is generally linked to older age (Kalincik

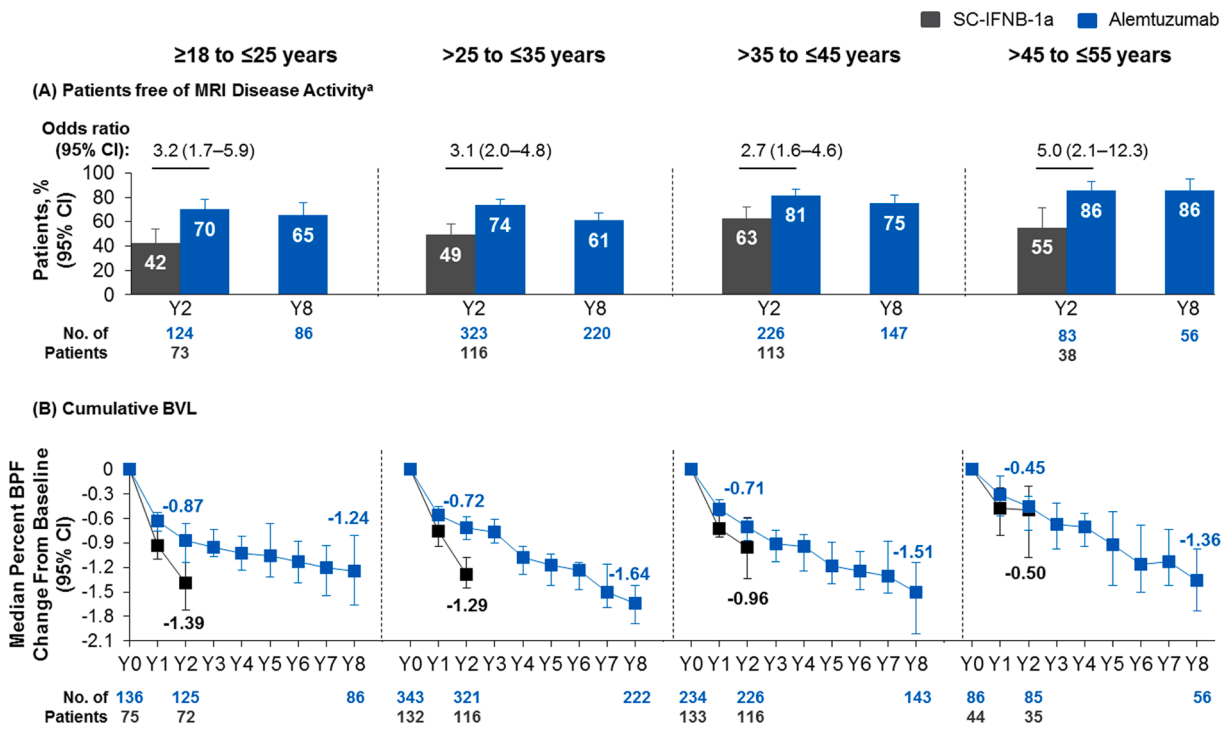


Fig. 3. MRI and BVL outcomes by age cohort.
Results stratified by patient age at core study baseline over 8 years. Alemtuzumab treatment was assessed through Year 8, and SC IFNB-1a treatment was assessed through Year 2 of the core study. (A) Percentages of patients free of MRI disease activity in Year 2 of the core study in alemtuzumab- and SC IFNB-1a–treated patients, and in Year 8 in alemtuzumab-treated patients. (B) Cumulative BVL over Years 0–2 of the core study in SC IFNB-1a–treated patients, and over Years 0–8 in alemtuzumab-treated patients. OR for alemtuzumab vs SC IFNB-1a at Year 2 MRI analyses are based on logistic regressions with covariate adjustment for core study baseline. [a]Freedom from MRI disease activity is defined as no new Gd-enhancing T1 lesions and no new/enlarging T2 lesions. BPF, brain parenchymal fraction; BVL, brain volume loss; CI, confidence interval; Gd, gadolinium; MRI, magnetic resonance imaging; No., number; OR, odds ratio; SC IFNB-1a, subcutaneous interferon beta-1a; Y, year.

Table 2
Safety of alemtuzumab by age cohort over Years 0–8.

	≥18 to ≤25 Years n = 137	>25 to ≤35 Years n = 350	>35 to ≤45 Years n = 238	>45 to ≤55 Years n = 86
Any AE	135 (98.5)	348 (99.4)	235 (98.7)	85 (98.8)
Serious AEs	50 (36.5)	139 (39.7)	93 (39.1)	44 (51.2)
Infections	114 (83.2)	297 (84.9)	204 (85.7)	75 (87.2)
Serious infections	7 (5.1)	26 (7.4)	26 (10.9)	11 (12.8)
Autoimmune AEs[a]				
Thyroid AEs	63 (46.0)	145 (41.4)	109 (45.8)	46 (53.5)
Serious thyroid AEs	9 (6.6)	21 (6.0)	9 (3.8)	7 (8.1)
ITP	3 (2.2)	8 (2.3)	9 (3.8)	0
Nephropathies	1 (0.7)	2 (0.6)	0	0
Malignancies	3 (2.2)	3 (0.9)	4 (1.7)	7 (8.1)
IARs	128 (93.4)	329 (94.0)	207 (87.0)	76 (88.4)
Serious IARs	5 (3.6)	13 (3.7)	6 (2.5)	4 (4.7)
Deaths	0	6 (1.7)	4 (1.7)	6 (7.0)

[a] First occurrence of AE.AE, adverse event; IARs, infusion-associated reactions; ITP, immune thrombocytopenia.

et al., 2013; Sanai et al., 2016; Tortorella et al., 2005; Vaughn et al., 2019). To date, the full impact of patient age on short- and long-term DMT outcomes remains unclear (Schweitzer et al., 2019), although studies suggest that treatment effects of DMTs closely correlate with age such that younger patients may have greater benefit than older patients (Matell et al., 2015; Signori et al., 2015; Weideman et al., 2017). In this analysis of patients from the CARE-MS studies, alemtuzumab demonstrated greater efficacy on clinical and MRI outcomes vs SC IFNB-1a over 2 years regardless of patient age, with sustained efficacy through Year 8. Regardless of age, patients responded well to alemtuzumab treatment on relapse, disability, and MRI lesion outcomes in both the short- and long-terms, despite differences at baseline in disability level and MRI lesion counts. Alemtuzumab efficacy was further affirmed by the observation that 48%–53% of patients across age cohorts received no additional alemtuzumab and no other DMT in the extensions, and 72%–74% of patients in each age cohort remained on study through Year 8.

Relapse rate and MRI disease activity reduction following alemtuzumab treatment in the older cohorts may not solely reflect the natural course of MS disease. Older patients most frequently received additional alemtuzumab treatment for relapse, indicating that they continued to experience symptoms of inflammatory disease despite greater age. Alemtuzumab treatment reduced relapse rates in older patients to levels comparable with younger patients, suggesting that suppression of relapse activity across age cohorts was an outcome driven by alemtuzumab treatment. Finally, it is worth noting that in our analysis, 1.3%–4.9% (KM estimates) of patients converted to SPMS across age cohorts through Year 6, with the majority aged >35 to ≤45 years at core study baseline. Evaluation of SPMS conversion rates was not possible during the TOPAZ study, but it is plausible that the proportion of patients with SPMS would have increased through Year 8 (Horakova et al., 2020).

Alemtuzumab was more effective over 2 years vs SC IFNB-1a in older patients on both disability and MRI lesion outcomes, indicating it remains effective at abating disability progression as patients age. However, the effects of aging, rather than alemtuzumab, may contribute more toward overall disability and MRI lesion outcomes across age cohorts. Patients who are diagnosed at an older age generally have poorer prognoses on disability outcomes than younger patients due to reduced neurological reserve and greater disability levels at initiation of treatment (Sanai et al., 2016; Vaughn et al., 2019; Weideman et al., 2017). Despite accelerated disability worsening in older patients, the rate of

CDW was reduced with alemtuzumab vs. SC IFNB-1a by a magnitude akin to that of younger patients. Furthermore, many patients in the older cohorts experienced CDI. Nevertheless, by Year 8, more patients in the older cohorts had CDW and fewer had CDI compared with the younger cohorts. MRI lesion activity decreased with advancing age, consistent with known decreases in inflammatory lesion activity associated with increased age-related neurodegeneration, but a treatment effect with alemtuzumab was still apparent in older patients compared with SC IFNB-1a (Sanai et al., 2016; Tortorella et al., 2005; Vaughn et al., 2019).

Increased brain atrophy is typical in patients with extended MS disease duration (Sanai et al., 2016; Vaughn et al., 2019; Vollmer et al., 2015). Among CARE-MS patients, cumulative median BVL in alemtuzumab-treated patients over 8 years was ≤–1.64% across age groups, and was slowed over 2 years with alemtuzumab vs. SC IFNB-1a. Lesser differences over 2 years in BVL between alemtuzumab- and SC IFNB-1a–treated patients aged >35 years may be attributed to the idea that brain atrophy in older age groups is driven more by age than by MS (Azevedo et al., 2019; De Stefano et al., 2016; Vaughn et al., 2019). As DMTs cannot treat age-related atrophy, their impact on BVL in older patients is likely limited (Azevedo et al., 2019); however, in the younger cohorts, brain atrophy may be driven more by MS pathology, which is differentially affected by alemtuzumab vs. SC IFNB-1a (Azevedo et al., 2019; Ghione et al., 2019; Sanai et al., 2016; Vaughn et al., 2019). Interestingly, in the ≥18 to ≤25 years group, we observed less BVL over 8 years with alemtuzumab compared with BVL over 2 years with SC IFNB-1a, suggesting that abatement of inflammatory disease in younger patients slows atrophy for up to 8 years.

Age-related immunity deficits include slowed cellular repopulation following alemtuzumab-induced lymphopenia, and reduced numbers and diversity of newly generated T lymphocytes, potentially limiting effective responses to infections and malignancies in older adults (El Chakhtoura et al., 2017; Montecino-Rodriguez et al., 2013; Ventura et al., 2017; Zhang et al., 2017). Increases in malignancies and deaths in older alemtuzumab-treated patients may be a consequence of age-related comorbidities independent of alemtuzumab, and the role of alemtuzumab cannot be definitively determined from these data. In the general population, cancer incidence is approximately 0.5%–14% among people aged 45–55 years, vs. 8.1% among CARE-MS patients aged >45 to ≤55 years (National Cancer Institute, 2015; Thakkar et al., 2014). Recent evidence suggests exposure to some, but not all, DMTs may increase malignancy risk up to 4-fold over that of the general population, with risk more likely to be elevated among patients >40 years old (Ragonese et al., 2017; Schweitzer et al., 2019). It is worth noting that, similar to other immunomodulatory therapies, caution should be exercised when initiating alemtuzumab in patients with pre-existing and/or ongoing malignancies (LEMTRADA (alemtuzumab) [Prescribing Information]; LEMTRADA [Summary of Product Characteristics], 2020). In particular, alemtuzumab may cause an increased risk of developing certain malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders, some of which were observed in this study. Overall, our findings support the need for thyroid cancer symptom monitoring, as well as baseline and annual exams to monitor for skin cancers such as melanoma, as recommended per the approved label (LEMTRADA (alemtuzumab) [U.S. Prescribing Information]). However, malignancies and infections in patients aged >45 to ≤55 years did not result in increased fatalities. Among the 6 deaths in patients >45 to ≤55 years old, 3 (50%) were associated with infection or malignancy, vs. 3 of 4 (75%) deaths in patients >35 to ≤45 years old.

No cases of ITP or nephropathy were reported among patients aged >45 to ≤55 years, but thyroid AEs were highest in this group. A correlation between age >45 years and likelihood of developing autoimmune thyroid disease has been established within the general population (Dong and Fu, 2014; Marrie et al., 2015). However, thyroid AE incidences across age groups were generally similar and consistently above 40% in the CARE-MS population. These findings support monitoring of patients of all age groups according to the established Risk Management Plan/Risk Evaluation and Mitigation Strategy procedures, and suggest a need for enhanced monitoring in older patients due to increased age-associated risks for AEs such as malignancy (Dong and Fu, 2014; El Chakhtoura et al., 2017; Marrie et al., 2015; Montecino-Rodriguez et al., 2013; Ragonese et al., 2017; Schweitzer et al., 2019; Thakkar et al., 2014; Ventura et al., 2017; Zhang et al., 2017). It is important to note that alemtuzumab-associated AEs in clinical trials and postmarketing experience include IARs, increased frequency of infection and the potential for opportunistic infections, secondary autoimmunity (thyroid disorders, ITP, nephropathies, autoimmune cytopenias, autoimmune hepatitis, and other less common autoimmune events), acute acalculous cholecystitis, and cardiovascular and pulmonary events possibly related to infusion.

A limitation of this analysis was it was done post hoc outside the original scope of the CARE-MS trials, such that it was not powered for statistical comparison between groups and age cohorts were imbalanced for the total number of patients. Additionally, inclusion criteria for the trials limited age to ≤55 years old at enrollment, making the oldest subgroup in our analysis not representative of the growing population of MS patients older than 55 (Daltrozzo et al., 2018; Solaro et al., 2015; Wallin et al., 2019a; 2019b).

5. Conclusion

This analysis demonstrated alemtuzumab efficacy on relapse, disability, and MRI disease activity was improved vs. SC IFNB-1a over 2 years, and was maintained over 8 years, regardless of age at baseline. Safety data were overall similar across age groups, but with increased incidence of malignancy and death in older patients; these increases were aligned with known rates in the general population (Dong and Fu, 2014; Ragonese et al., 2017; Thakkar et al., 2014; Ventura et al., 2017; Zhang et al., 2017). Taken together, these findings indicate alemtuzumab provides positive clinical benefit regardless of age, and should be weighed alongside other studies showing diminished effects of DMTs with advancing age (Matell et al., 2015; Signori et al., 2015; Weideman et al., 2017) when considering clinical regimens for individual patients.

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CRediT authorship contribution statement

Ann D. Bass: Conceptualization, Investigation, Writing - review & editing. **Rafael Arroyo:** Conceptualization, Investigation, Writing - review & editing. **Aaron L. Boster:** Conceptualization, Investigation, Writing - review & editing. **Alexey N. Boyko:** Conceptualization, Investigation, Writing - review & editing. **Sara Eichau:** Conceptualization, Writing - review & editing. **Carolina Ionete:** Conceptualization, Investigation, Writing - review & editing. **Volker Limmroth:** Conceptualization, Writing - review & editing. **Carlos Navas:** Conceptualization, Writing - review & editing. **Daniel Pelletier:** Conceptualization, Investigation, Writing - review & editing. **Carlo Pozzilli:** Conceptualization, Investigation, Writing - review & editing. **Jennifer Ravenscroft:** Conceptualization, Writing - review & editing. **Livia Sousa:** Conceptualization, Writing - review & editing. **Mar Tintoré:** Conceptualization, Writing - review & editing. **Bernard M.J. Uitdehaag:** Conceptualization, Writing - review & editing. **Darren P. Baker:** Conceptualization, Writing - review & editing. **Nadia Daizadeh:** Conceptualization, Formal analysis, Writing - review & editing. **Zia Choudhry:** Conceptualization, Writing - review & editing. **David Rog:** Conceptualization, Investigation, Writing - review & editing.

Declaration of Competing Interest

Dr Bass reports receiving research funding, compensation for medical advisory boards, and compensation for speaker's bureaus from Actelion, Biogen, EMD Serono, Genentech-Roche, Mallinckrodt, Novartis, Sanofi, and TG Therapeutics. Dr Arroyo reports being an advisory board participant and receiving speaking fees from Almirall, Bayer, Biogen, Merck, Novartis, Roche, Sanofi, and Teva. Dr Boster reports receiving consulting fees and/or fees for non-CME services from Biogen, Mallinckrodt, Medtronic, Novartis, Sanofi, and Teva. Prof Boyko reports receiving consulting fees and/or participating in clinical trials for Actelion, Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva, and TG Therapeutics. Prof Eichau reports receiving consulting and/or speaking fees from Biogen, Merck Serono, Novartis, Roche, Sanofi, and Teva. Prof Ionete reports receiving compensation for advisory board participation for Sanofi, and research support from Biogen, Roche, and Sanofi. Prof Limmroth reports receiving honoraria for consulting and speaking at symposia for Bayer, Biogen, Merck Serono, Novartis, Roche, Sanofi, and Teva, with approval by the HR Department, Cologne General Hospital, and University of Cologne. Prof Navas reports receiving consulting and speaking fees from Bayer-Schering Pharma, Genzyme, Merck Serono, Novartis, Roche, and Stendhal, along with research support from Merck Serono, Novartis, and Roche. Dr Pelletier reports receiving consulting and/or speaking fees, along with grant and/or research support, from Biogen, Merck Serono, Novartis, Roche, and Sanofi. Prof Pozzilli reports receiving consulting and/or speaking fees, research, and travel grants from Actelion, Biogen, Merck, Novartis, Sanofi, and Teva. Ms Ravenscroft reports receiving consulting fees for non-CME services from Acorda, Biogen, Mallinckrodt, and Sanofi; employee of Sanofi as of March 2019. Prof Sousa reports receiving compensation for advisory board participation and speaking fees from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Roche, and Teva. Prof Tintoré reports receiving speaking honoraria and travel expenses for scientific meetings from Almirall, Bayer, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, and Teva. Dr Uitdehaag reports receiving consulting fees from Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva. Dr Baker and Dr Daizadeh report being employees of Sanofi. Dr Choudhry reports receiving personal compensation as an employee of Sanofi during study conduct and analysis. Dr Rog reports receiving consulting fees from Bayer Schering, Biogen, Celgene, MedDay, Merck Serono, Novartis, Roche, Sanofi, and Teva Neuroscience, along with research support from Actelion, Biogen, GW Pharma, Merck Serono, Mitsubishi, Novartis, Sanofi, Teva Neuroscience, and TG Therapeutics.

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Supplementary materials

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References

Alvarez-Cermeno, J.C., Costa-Frossard, L., Villar, L.M., 2010. Importance of age at diagnosis in multiple sclerosis. Expert Rev. Neurother. 10, 341–342.

Azevedo, C.J., Cen, S.Y., Jaberzadeh, A., Zheng, L., Hauser, S.L., Pelletier, D., 2019. Contribution of normal aging to brain atrophy in MS. Neurol. - Neuroimmunol. Neuroinflamm. 6, e616.

Cohen, J.A., Coles, A.J., Arnold, D.L., Confavreux, C., Fox, E.J., Hartung, H.P., Havrdova, E., Selmaj, K.W., Weiner, H.L., Fisher, E., Brinar, V.V., Giovannoni, G., Stojanovic, M., Ertik, B.I., Lake, S.L., Margolin, D.H., Panzara, M.A., Compston, D.A., 2012. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380, 1819–1828.

Coles, A.J., Boyko, A.N., De Seze, J., Hartung, H.-P., Havrdova, E., Inshasi, J.S., McCombe, P., Montalban, X., Pozzilli, C., Selmaj, K.W., Vermersch, P., Margolin, D. H., Daizadeh, N., Rodriguez, C.E., Van Wijmeersch, B., 2017a. Alemtuzumab durably improves clinical outcomes in patients with active RRMS in the absence of continuous treatment: 7-year follow-up of CARE-MS I patients (TOPAZ study). Mult. Scler. 23, P1188.

Coles, A.J., Cohen, J.A., Fox, E.J., Giovannoni, G., Hartung, H.-P., Havrdova, E., Schipping, S., Selmaj, K.W., Traboulsee, A., Compston, D.A.S., Margolin, D.H., Thangavelu, K., Chirieac, M.C., Jody, D., Xenopoulos, P., Hogan, R.J., Panzara, M.A., Arnold, D.L., Investigators, C.-M.I.a.C., 2017b. Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. Neurology 89, 1117–1126.

Coles, A.J., Twyman, C.L., Arnold, D.L., Cohen, J.A., Confavreux, C., Fox, E.J., Hartung, H.P., Havrdova, E., Selmaj, K.W., Weiner, H.L., Miller, T., Fisher, E., Sandbrink, R., Lake, S.L., Margolin, D.H., Oyuela, P., Panzara, M.A., Compston, D.A., 2012. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380, 1829–1839.

Comi, G., Arnold, D.L., Boyko, A.N., Hartung, H.P., Havrdova, E.K., Inshasi, J.S., McCombe, P., Oreja-Guevara, C., Pelletier, D., Pozzilli, C., Selmaj, K.W., 2018. 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). Mult. Scler. 24, P1235.

Cox, A.L., Thompson, S.A., Jones, J.L., Robertson, V.H., Hale, G., Waldmann, H., Compston, D.A., Coles, A.J., 2005. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. Eur. J. Immunol. 35, 3332–3342.

Daltrozzo, T., Hapfelmeier, A., Donnachie, E., Schneider, A., Hemmer, B., 2018. A systematic assessment of prevalence, incidence and regional distribution of multiple sclerosis in Bavaria from 2006 to 2015. Front. Neurol. 9, 871.

De Mercanti, S., Rolla, S., Cucci, A., Bardina, V., Cocco, E., Vladic, A., Soldo-Butkovic, S., Habek, M., Adamec, I., Horakova, D., Annovazzi, P., Novelli, F., Durelli, L., Clerico, M., 2016. Alemtuzumab long-term immunologic effect: Treg suppressor function increases up to 24 months. Neurol. Neuroimmunol. Neuroinflamm. 3, e194.

De Stefano, N., Stromillo, M.L., Giorgio, A., Bartolozzi, M.L., Battaglini, M., Baldini, M., Portaccio, E., Amato, M.P., Sormani, M.P., 2016. Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 87, 93–99.

Dong, Y.H., Fu, D.G., 2014. Autoimmune thyroid disease: mechanism, genetics and current knowledge. Eur. Rev. Med. Pharmacol. Sci. 18, 3611–3618.

Durelli, L., De Mercanti, S., Rolla, S., Cucci, A., Bardina, V., Cocco, E., Vladic, A., Soldo-Bukovic, S., Habek, M., Adamec, I., Annovazzi, P., Horakova, D., Novelli, F., Clerico, M., 2016. Alemtuzumab long term immunological study: the immunosuppressive effect does not last more than 48 months. Neurology 86 (16 Suppl). S2.008.

El Chakhtoura, N.G., Bonomo, R.A., Jump, R.L.P., 2017. Influence of aging and environment on presentation of infection in older adults. Infect. Dis. Clin. North Am. 31, 593–608.

Gajofatto, A., Benedetti, M.D., 2015. Treatment strategies for multiple sclerosis: when to start, when to change, when to stop? World J. Clin. Cases 3, 545–555.

Ghione, E., Bergsland, N., Dwyer, M.G., Hagemeier, J., Jakimovski, D., Paunkoski, I., Ramasamy, D.P., Carl, E., Hojnacki, D., Kolb, C., Weinstock-Guttman, B., Zivadinov, R., 2019. Aging and brain atrophy in multiple sclerosis. J. Neuroimaging 29, 527–535.

Havrdova, E., Arnold, D.L., Cohen, J.A., Hartung, H.-P., Fox, E.J., Giovannoni, G., Schippling, S., Selmaj, K.W., Traboulsee, A., Compston, D.A.S., Margolin, D.H., Thangavelu, K., Rodriguez, C.E., Jody, D., Hogan, R.J., Xenopoulos, P., Panzara, M. A., Coles, A.J., Investigators, C.-M.I.a.C., 2017. Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. Neurology 89, 1107–1116.

Horakova, D., Boster, A., Bertolotto, A., Freedman, M.S., Firmino, I., Cavalier, S.J., Jacobs, A.J., Thangavelu, K., Daizadeh, N., Poole, E.M., Baker, D.P., Margolin, D.H., Ziemssen, T., on behalf of the CARE-MS I, CARE-MS II, and CAMMS03409 Investigators, 2020. Proportion of alemtuzumab-treated patients converting from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis over 6 years. Mult. Scler. J. - Exp. Transl. Clin. https://doi.org/10.1177/2055217320972137.

Hu, Y., Turner, M.J., Shields, J., Gale, M.S., Hutto, E., Roberts, B.L., Siders, W.M., Kaplan, J.M., 2009. Investigation of the mechanism of action of alemtuzumab in a human CD52 transgenic mouse model. Immunology 128, 260–270.

Kalincik, T., Vivek, V., Jokubaitis, V., Lechner-Scott, J., Trojano, M., Izquierdo, G., Lugaresi, A., Grand'maison, F., Hupperts, R., Oreja-Guevara, C., Bergamaschi, R., Iuliano, G., Alroughani, R., Van Pesch, V., Amato, M.P., Slee, M., Verheul, F., Fernandez-Bolanos, R., Fiol, M., Spitaleri, D.L., Cristiano, E., Gray, O., Cabrera-Gomez, J.A., Shaygannejad, V., Herbert, J., Vucic, S., Needham, M., Petkovska-Boskova, T., Sirbu, C.A., Duquette, P., Girard, M., Grammond, P., Boz, C., Giuliani, G., Rio, M.E., Barnett, M., Flechter, S., Moore, F., Singhal, B., Bacile, E.A., Saladino, M.L., Shaw, C., Skromne, E., Poehlau, D., Vella, N., Spelman, T., Liew, D., Kilpatrick, T.J., Butzkueven, H., 2013. Sex as a determinant of relapse incidence and progressive course of multiple sclerosis. Brain: J. Neurol. 136, 3609–3617.

LEMTRADA (alemtuzumab) [Prescribing Information]. Genzyme Corporation, USA.

LEMTRADA [Summary of Product Characteristics] January 2020. Diegem, Belgium: Sanofi Belgium.
Lorscheider, J., Buzzard, K., Jokubaitis, V., Spelman, T., Havrdova, E., Horakova, D., Trojano, M., Izquierdo, G., Girard, M., Duquette, P., Prat, A., Lugaresi, A., Grand'Maison, F., Grammond, P., Hupperts, R., Alroughani, R., Sola, P., Boz, C., Pucci, E., Lechner-Scott, J., Bergamaschi, R., Oreja-Guevara, C., Iuliano, G., Van Pesch, V., Granella, F., Ramo-Tello, C., Spitaleri, D., Petersen, T., Slee, M., Verheul, F., Ampapa, R., Amato, M.P., McCombe, P., Vucic, S., Sánchez Menoyo, J. L., Cristiano, E., Barnett, M.H., Hodgkinson, S., Olascoaga, J., Saladino, M.L., Gray, O., Shaw, C., Moore, F., Butzkueven, H., Kalincik, T., MSBase Study Group, 2016. Defining secondary progressive multiple sclerosis. Brain 139 (Pt 9), 2395–2405.
Marrie, R.A., Reider, N., Cohen, J., Stuve, O., Sorensen, P.S., Cutter, G., Reingold, S.C., Trojano, M., 2015. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. Mult. Scler. 21, 282–293.
Matell, H., Lycke, J., Svenningsson, A., Holmen, C., Khademi, M., Hillert, J., Olsson, T., Piehl, F., 2015. Age-dependent effects on the treatment response of natalizumab in MS patients. Mult. Scler. 21, 48–56.
Montecino-Rodriguez, E., Berent-Maoz, B., Dorshkind, K., 2013. Causes, consequences, and reversal of immune system aging. J. Clin. Invest. 123, 958–965.
National Cancer Institute: Age and Cancer Risk. 2015. Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/age. (Accessed January 6, 2021).
Ragonese, P., Aridon, P., Vazzoler, G., Mazzola, M.A., Lo Re, V., Lo Re, M., Realmuto, S., Alessi, S., D'Amelio, M., Savettieri, G., Salemi, G., 2017. Association between multiple sclerosis, cancer risk, and immunosuppressant treatment: a cohort study. BMC Neurol. 17, 155.
Rao, S.P., Sancho, J., Campos-Rivera, J., Boutin, P.M., Severy, P.B., Weeden, T., Shankara, S., Roberts, B.L., Kaplan, J.M., 2012. Human peripheral blood mononuclear cells exhibit heterogeneous CD52 expression levels and show differential sensitivity to alemtuzumab mediated cytolysis. PLoS One 7, e39416.
Rudick, R.A., Fisher, E., Lee, J.C., Simon, J., Jacobs, L., 1999. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple Sclerosis Collaborative Research Group. Neurology 53, 1698–1704.
Sanai, S.A., Saini, V., Benedict, R.H., Zivadinov, R., Teter, B.E., Ramanathan, M., Weinstock-Guttman, B., 2016. Aging and multiple sclerosis. Mult. Scler. 22, 717–725.
Schweitzer, F., Laurent, S., Fink, G.R., Barnett, M.H., Reddel, S., Hartung, H.P., Warnke, C., 2019. Age and the risks of high-efficacy disease modifying drugs in multiple sclerosis. Curr. Opin. Neurol. 32, 305–312.
Signori, A., Schiavetti, I., Gallo, F., Sormani, M.P., 2015. Subgroups of multiple sclerosis patients with larger treatment benefits: a meta-analysis of randomized trials. Eur. J. Neurol. 22, 960–966.
Singer, B.A., Alroughani, R., Brassat, D., Broadley, S., Hartung, H.P., Havrdova, E.K., Kim, H.J., Oreja-Guevara, C., Pozzilli, C., Selmaj, K.W., Vermersch, P., Wray, S., Margolin, D.H., Daizadeh, N., Chirieac, M.C., Coles, A.J., 2017. Durable improvements in clinical outcomes with alemtuzumab in patients with active RRMS in the absence of continuous treatment: 7-year follow-up of CARE-MS II patients (TOPAZ study). Mult. Scler. 23, P736.
Singer, B.A., Alroughani, R., Broadley, S., Eichau, S., Hartung, H.P., Havrdova, E.K., Kim, H.J., Navas, C., Pozzilli, C., Rovira, A., Vermersch, P., Wray, S., Chung, L., Daizadeh, N., Afsar, S., Nakamura, K., Selmaj, K.W., 2018. Alemtuzumab improves clinical and MRI disease activity outcomes, including slowing of brain volume loss, in RRMS patients over 8 years: CARE-MS II follow-up (TOPAZ study). Mult. Scler. 24, P913.
Solaro, C., Ponzio, M., Moran, E., Tanganelli, P., Pizio, R., Ribizzi, G., Venturi, S., Mancardi, G.L., Battaglia, M.A., 2015. The changing face of multiple sclerosis: Prevalence and incidence in an aging population. Mult. Scler. 21, 1244–1250.
Thakkar, J.P., McCarthy, B.J., Villano, J.L., 2014. Age-specific cancer incidence rates increase through the oldest age groups. Am. J. Med. Sci. 348, 65–70.
Tortorella, C., Bellacosa, A., Paolicelli, D., Fuiani, A., Di Monte, E., Simone, I.L., Giaquinto, P., Livrea, P., Trojano, M., 2005. Age-related gadolinium-enhancement of MRI brain lesions in multiple sclerosis. J. Neurol. Sci. 239, 95–99.
Vaughn, C.B., Jakimovski, D., Kavak, K.S., Ramanathan, M., Benedict, R.H.B., Zivadinov, R., Weinstock-Guttman, B., 2019. Epidemiology and treatment of multiple sclerosis in elderly populations. Nat. Rev. Neurol. 15, 329–342.
Ventura, M.T., Casciaro, M., Gangemi, S., Buquicchio, R., 2017. Immunosenescence in aging: between immune cells depletion and cytokines up-regulation. Clin. Mol. Allergy 15, 21.
Vollmer, T., Signorovitch, J., Huynh, L., Galebach, P., Kelley, C., DiBernardo, A., Sasane, R., 2015. The natural history of brain volume loss among patients with multiple sclerosis: a systematic literature review and meta-analysis. J. Neurol. Sci. 357, 8–18.
Wallin, M.T., Culpepper, W.J., Campbell, J.D., Nelson, L.M., Langer-Gould, A., Marrie, R. A., Cutter, G.R., Kaye, W.E., Wagner, L., Tremlett, H., Buka, S.L., Dilokthornsakul, P., Topol, B., Chen, L.H., LaRocca, N.G., 2019a. The prevalence of MS in the United States: a population-based estimate using health claims data. Neurology 92, e1029–e1040.
Wallin, M.T., Culpepper, W.J., Nichols, E., Bhutta, Z.A., Gebrehiwot, T.T., Hay, S.I., Khalil, I.A., Krohn, K.J., Liang, X., Naghavi, M., Mokdad, A.H., Nixon, M.R., Reiner, R.C., Sartorius, B., Smith, M., Topor-Madry, R., Werdecker, A., Vos, T., Feigin, V.L., Murray, C.J.L., 2019b. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. Neurol. 18, 269–285.
Weideman, A.M., Tapia-Maltos, M.A., Johnson, K., Greenwood, M., Bielekova, B., 2017. Meta-analysis of the age-dependent efficacy of multiple sclerosis treatments. Front Neurol. 8, 577.
Zhang, X., Meng, X., Chen, Y., Leng, S.X., Zhang, H., 2017. The biology of aging and cancer: frailty, inflammation, and immunity. Cancer J. 23, 201–205.
Zhang, X., Tao, Y., Chopra, M., Ahn, M., Marcus, K.L., Choudhary, N., Zhu, H., Markovic-Plese, S., 2013. Differential reconstitution of T cell subsets following immunodepleting treatment with alemtuzumab (anti-CD52 monoclonal antibody) in patients with relapsing-remitting multiple sclerosis. J. Immunol. 191, 5867–5874.
Ziemssen, T., Thomas, K., 2017. Alemtuzumab in the long-term treatment of relapsing-remitting multiple sclerosis: an update on the clinical trial evidence and data from the real world. Ther. Adv. Neurol. Disord. 10, 343–359.