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Efficacy and safety of CAR T-cell therapy in patients with primary or secondary CNS lymphoma: A study on behalf of the EBMT and the GoCART coalition

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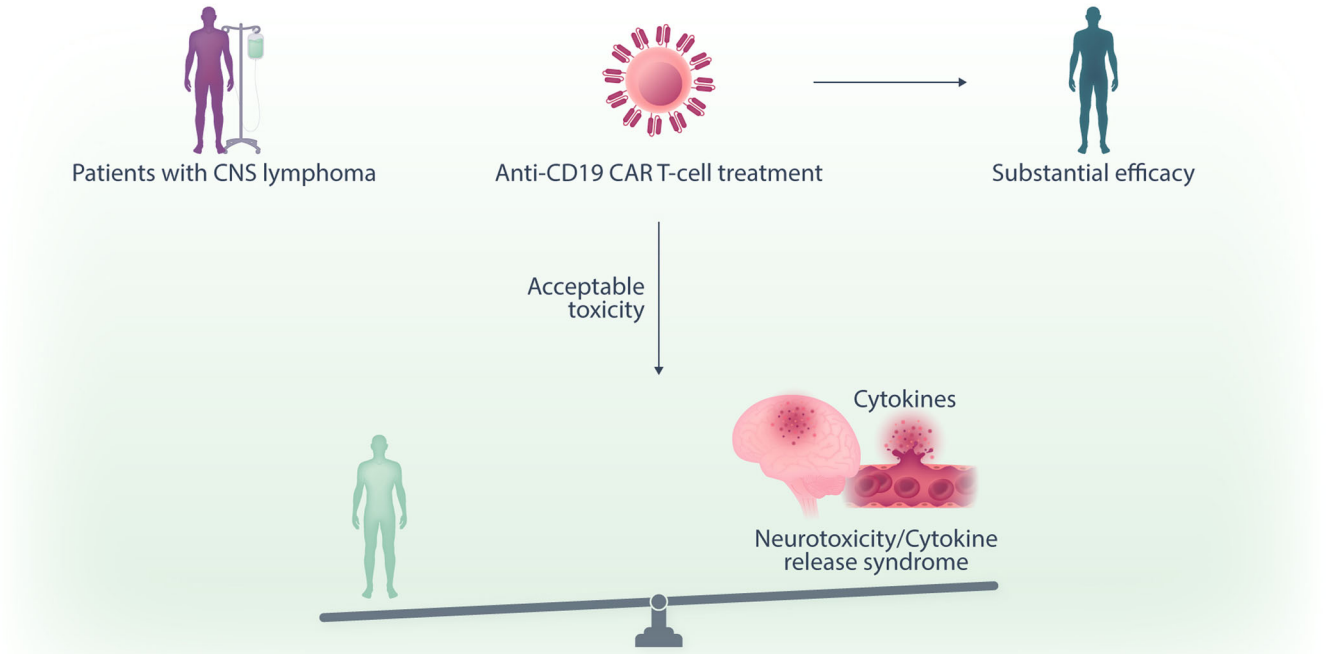
Graphical Abstract



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Abstract

Patients with relapsed or refractory (r/r) primary central nervous system (CNS) lymphoma (PCNSL) or secondary central nervous system (CNS) lymphoma (SCNSL) face a dismal prognosis. They have been excluded from most clinical CAR T-cell trials as investigators feared an increased risk for severe immune effector cell-associated neurotoxicity (ICANS). To investigate the potential of anti-CD19 CAR T-cell therapy (CART) in such patients, we analyzed data of 100 patients with CNS manifestation treated with CART between January 2018 and July 2023 and reported to European Society for Blood and Marrow Transplantation. Median age was 62 years. Of patients, 58% had failed ≥3 treatment lines, and 40% had received autologous stem-cell transplantation before CART. Fifty-nine patients received axicabtagene ciloleucel, 38 patients were treated with tisagenlecleucel, three patients received other products. At the time of CART, 67 patients had active CNS disease. Overall and progression-free survival (PFS) at 24 months were 37% and 28%. Relapse incidence (RI) at 24 months was 59%, whereas non-relapse mortality at 1 year was 7%. Cytokine release syndrome (CRS) and ICANS of any grade occurred in 83% and 42% of patients, respectively. CRS grade 3 occurred in 11 and ICANS grades 3–4 in 17 patients. Two patients died of neurotoxicity. Elevated lactate dehydrogenase was an independent risk factor for RI and PFS (hazard ratio [HR] 2.4, $p = 0.003$; HR: 1.9, $p = 0.016$). Patients with ECOG 2–3 had a significantly increased risk for the development of ICANS (HR 2.68, $p = 0.002$). These data support the implementation of CART as treatment for patients with r/r PCNSL and SCNSL.

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INTRODUCTION

Lymphoma in the central nervous system (CNSL) is a rare condition with dismal prognosis.[1,2] Based on important differences in biology, pathogenesis, clinical manifestation, treatment, and prognosis, CNSL is divided into primary CNS lymphoma (PCNSL) exclusively affecting the brain and related structures, and secondary CNS lymphoma (SCNSL), referring to the dissemination of lymphoma to the CNS during the course of disease. By far, the most frequent histology of SCNSL is diffuse large B-cell lymphoma (DLBCL)[3] of the activated B-cell (ABC) subtype,[3] while PCNSL is related to LBCL of immune privileged sites.[3] PCNSL has an incidence of 0.4/100.000,[4] while SCNSL is affecting <1% to >10% of patients with DLBCL depending on clinical and molecular risk factors.[1,5,6]

Patients with refractory or relapsed (r/r) PCNSL or SCNSL face poor survival, especially if they are ineligible for ASCT.[7] In patients with SCNSL, the simultaneous involvement of lymph nodes and organs other than the CNS occurring in about 40% makes it difficult to decide which compartment(s) to treat and in which sequence. Patients who are not eligible for ASCT, like older patients with (S) CNSL, who in many instances cannot tolerate aggressive therapies face particularly poor outcomes.[7–9] In general, the median OS for patients with SCNSL treated with conventional treatment strategies including ASCT was reported to be about 3.5 months[5,10] with a 1-year OS rate of 20%.[11] Patients with r/r PCNSL had a median OS of 6.8 months and a 1-year OS of 38% in a large French real-world analysis.[2]

In 2017 and 2018, based on the results of the ZUMA-1 and JULIET trials, the anti-CD19 CAR T-cell constructs axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) were approved by the US Federal Drug Administration and the European Medicines Agency (EMA) to treat patients with DLBCL failing two or more treatment lines. Patients with CNSL have been excluded from these and other pivotal CAR T-cell studies due to concerns that patients would be at high risk to develop cytokine release syndrome (CRS) and, in particular, immune effector cell-associated neurotoxicity syndrome (ICANS). Consequently, results of prospective studies and real-world data for CART in CNSL are scarce. One phase 1/2 clinical trial showed an acceptable risk profile of tisa-cel in 12 patients with r/r PCNSL and a response in seven of these patients.[12] A retrospective analysis of 61 patients with SCNSL treated with axi-cel, tisa-cel, lisocabtagene maraleucel (liso-cel), or brexucabtagene autoleucel (brexu-cel) revealed rather disappointing results with a 1-year progression-free survival (PFS) rate of 16% and high rates of ICANS ≥ grade 3 (15 of 61 patients).[13]

We sought to investigate the efficacy and toxicity of CART in patients with PCNSL and SCNSL reported to the European Society for Blood and Marrow Transplantation (EBMT) and the GoCART consortium.

SUBJECTS AND METHODS

Data collection

This retrospective analysis is based on data reported to the EBMT registry between January 2018 and July 2023. The process of data collection, hosting, and quality management has been described in detail in previous publications.[14] All participating centers obtained patients' written informed consent before registration with EBMT following the Declaration of Helsinki of 1975 and Good Clinical Practice Guidelines. This study includes patients >18 years who were diagnosed with PCNSL or SCNSL at the time of or before the first CART at some point of their disease course. Additional information on major patient characteristics, disease history, treatment before CART, and follow-up was requested from participating centers using a standardized questionnaire (Figure S1). Twenty-four EBMT centers contributed to this study (for a complete list of participating institutions and principal investigators, see Table S1). A subgroup of German patients was included in a previously published analysis.[15] In case of missing values, the percentages refer to the available data set. The number of missing values is indicated in Table 1. For variables not listed in Table 1, the number of available data is indicated in brackets following the percentages.

Definitions

Diagnosis of SCNSL was defined by the presence of lymphoma in the CNS as evidenced by imaging or analysis of the cerebrospinal fluid (CSF) at some point of the disease course in addition to peripheral involvement. PCNSL was defined as lymphoma with isolated manifestations in the CNS at the time of primary diagnosis. “Active” CNS disease at the time of lymphodepletion/CART is defined as proof of lymphoma manifestations in the CNS either by imaging or detection in the CSF. Staging followed the Ann Arbor staging system. Disease status before and after CART was assessed and reported by investigators as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Relapse was diagnosed in cases of lymphoma recurrence occurring in patients having achieved CR. EBMT requires investigators to follow definitions valid at the time of reporting.

Statistical analysis

Major endpoints were PFS defined as survival without lymphoma relapse or progression, overall survival (OS) defined as time from CART to death from any cause, non-relapse mortality (NRM) defined as death without previous lymphoma relapse or progression and relapse incidence (RI) defined as disease recurrence after CART.

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TABLE 1 Patient characteristics.

Characteristics	All patients (*n* = 100)
Median age at CART, years (range)	62 (23–80)
Gender, *n* (%)	
Female	38 (38)
Male	62 (62)
Type of CNS lymphoma, *n* (%)	
PCNSL	16 (16)
SCNSL	84 (84)
Histopathology, *n* (%)	
DLBCL	86 (86)
High-grade lymphoma (Myc + Bcl-2 ± Bcl-6)	6 (6)
Others[a]	8 (8)
Previous therapy with high-dose MTX, *n* (%)	
Yes	76 (77)
Missing	1
Previous CNS radiation, *n* (%)	
Yes	17 (17)
Missing	2
Total number of lines before CART (excluding bridging), *n* (%)	
1	6 (6)
2	36 (36)
≥3	57 (58)
Missing	1
Previous stem cell transplantation, *n* (%)	
Autologous	40 (40)
Allogeneic	2 (2)
ECOG at CART, *n* (%)	
0–1	70 (71)
≥2	29 (29)
Missing	1
LDH level at CART, *n* (%)	
Normal	54 (58)
Elevated	39 (42)
Missing	7
Number of extranodal manifestations at CART, *n* (%)	
≥2	34 (37)
Missing	7
Site of CNS manifestation at CART, *n* (%)	(Total *n* = 67)
Parenchymal (± other CNS manifestation)	44 (68)
Deep structures[b]	19 (29)
CSF only	4 (6)
Spinal cord only	4 (6)
Leptomeningeal only	13 (20)
Missing	2
Remission status at CART, *n* (%)	
CR	7 (7)
PR	30 (30)
Refractory/progressive disease	62 (63)
Missing	1
CAR-T cell product, *n* (%)	
Axicabtagene ciloleucel	59 (59)
Tisagenlecleucel	38 (38)
Lisocabtagene maraleucel	2 (2)
MB-CART (investigational product, Miltenyi)	1 (1)

Abbreviations: CART, chimeric antigen receptor T-cell therapy; CNS, central nervous system; CR, complete remission; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status score; LDH, lactate dehydrogenase; MTX, methotrexate; PCNSL, primary central nervous system lymphoma; PR, partial remission; SNCSL, secondary central nervous system lymphoma.

[a]Three patients with primary mediastinal B-cell lymphoma, two patients with intravascular lymphoma, one patient each with gray zone lymphoma, intermediate DLBCL/Burkitt lymphoma, follicular lymphoma.

[b]According to Ferreri et al.,[17] deep structures are periventricular regions, basal ganglia, corpus callosum, brainstem, and cerebellum.

Endpoints describing toxicity comprised the incidence and severity of CRS and ICANS, assessed by the investigator following ASTCT/ASBMT criteria.[16] All outcomes were measured from the day of CAR T-cell infusion. Surviving patients were censored at the time of last follow-up. Kaplan–Meier estimates were used to calculate probability of OS and PFS. RI and NRM were calculated as cumulative incidences using a competing risk model, death and relapse competing with each other. For estimation of the cumulative incidence of CRS and ICANS, death was considered a competing event. Univariate analyses of potential prognostic factors such as previous irradiation of the brain, hd-MTX, history of bridging therapy, IPI factors at CART, presence and localization of CNS manifestation, and the CAR T-cell construct used were performed using the log-rank test for PFS and OS; Gray's test was used for competing risk outcome data. Multivariate analyses were performed using the Cox proportional hazards regression model except for NRM where the number of patients for modeling was too low. A model selection procedure was applied on all potentially relevant clinical factors to the primary outcome (PFS) using Akaike Information Criterion (AIC). Consequently, the following factors were included: patient age at CART (numerical variable with 5-year increments), lactate dehydrogenase (LDH) level at CART (normal vs. elevated), and ECOG performance status at CART (0–1 vs. 2–3). Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). Fisher's exact test was used to assess the association between the use of bridging therapy and parameters (ECOG, LDH and Ann-Arbor) measured at lymphodepletion or previous relapse before CAR-T. Percentages refer to the number of patients with the respective information available. All statistical tests were two-sided with a type I error fixed at 0.05 for factors associated with time-to-event outcomes. All analyses were performed using R version 4.1.2 0 (R Core Team, 2014, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

For 106 patients identified in the EBMT database and potentially fulfilling the inclusion criteria, questionnaires were retrieved from

the respective investigators. Six patients were excluded, four of them did not have CNSL and two received the CAR T-cell product after the defined inclusion period. One hundred patients from 24 centers (Table S1) with PCNSL ($n = 16$) or SCNSL ($n = 84$) and complete information on key endpoints were included in the final analysis. Diagnosis by local pathologists was LBCL in 94 patients, 86 patients had DLBCL (for a detailed listing of histologic diagnoses, see Table 1). Median follow-up of all patients was 24.8 months [95% CI 19–29]. Median age at CART was 62 years (range 22–80) with 12 patients being older than 75 years. Sixty-two patients were male. Seventy-seven percent of patients had been treated with hd-MTX-containing regimens, and 17% had received whole brain radiotherapy in previous treatment lines. Fifty-eight percent of patients had failed ≥3 treatment lines, and 42% had failed ASCT or allogeneic transplantation (two patients). Preparatory regimens before ASCT were thiotepa-based for half of the patients, while 10 patients received BEAM-like protocols (etoposide, cytarabine, melphalan with BCNU in eight patients and lomustine or fotemustine in one patient each) and 7 received other regimens targeting systemic disease. Both patients who were previously treated with allogeneic stem cell transplantation underwent myeloablative conditioning. For four patients, information on the conditioning regimen was not further detailed. Median time from diagnosis of lymphoma to CART was 1.5 years (range 0.2–13, 1.44 years for PCNSL, 1.47 years for SCNSL), and median time from last relapse to CART was 2.9 months (range 0.2–14). Most patients (82%) received bridging therapy between leukapheresis and lymphodepletion before CAR T-cell infusion. Patients who were treated with bridging therapy had SD, PD, or were refractory at the time of lymphodepletion in 94% (76/81) of cases. For patients who did not receive bridging therapy, this was true for 88% (15/17). For patients who received bridging therapy, PR or CR 180 days after CART was achieved in 51% [95% CI 39–61] and 41% [95% CI 30–52] of patients, respectively. For patients who did not receive bridging therapy, PR or CR at 180 days after CART were 44% [95% CI 21–66] and 41% [95% CI 18–63], respectively. The differences were not statistically significant. Lymphodepletion consisted of fludarabine and cyclophosphamide in all patients. ECOG at CART was ≥2 in 29% of patients, LDH at CART was elevated in 42% of patients, and 37% of patients had two or more extranodal manifestations. IPI was ≥3 in 51% of patients at cell infusion. At the time of CART, 67 patients had proof of CNS disease with parenchymal involvement in the majority of cases (68%). In 29% of patients, "deep" brain structures as defined by the IELSG were involved,[17] 20% of patients had isolated leptomeningeal involvement. Of the remaining 33 patients, 2 had PCNSL in CR at CART and the other 31 had CNS involvement at some point of their disease course before CART. At CART, 7% of patients were in CR, 30% in PR, 6% had SD, and 57% were refractory to last therapy. Fifty-nine patients were treated with axi-cel, 38 patients received tisa-cel, 2 were treated with liso-cel, and 1 with MB-CART (investigational product, Miltenyi, Bergisch-Gladbach, Germany).

Safety

The incidence of neutropenia and thrombocytopenia of any grade after CART was 83% [95% CI 74–90] and 73% [95% CI 63–81], grades 3 and 4 neutropenia and thrombocytopenia occurred in 68% and 54% of patients. Median day of onset was day 2 and 1, respectively, after CAR T-cell infusion with a median duration of 13 and 45 days. Twenty-three percent of patients experienced infections of grades 3 or 4. Three patients died of infections: one of them died at day 36 due to septic shock. and the other two died more than 630 days after CART (one of them of pneumocystis pneumonia, the other of sepsis in relation to an anal abscess).

Incidences of CRS and ICANS of any grade were 83% [95% CI 74–89] and 42% [95% CI 32–51], respectively. CRS grade 3 occurred in 11 patients and ICANS grade ≥3 in 18 patients (four patients without CNS involvement at CART). Two patients with severe ICANS had PCNSL. One patient died due to CAR T-related neurotoxicity on day 6. This patient had SCNSL without CNS manifestations at CART. One patient died due to leukoencephalopathy 133 days after CAR T-cell infusion. The investigator reported that leukoencephalopathy was caused by fludarabine with intrathecal MTX as a potentially contributing factor. There was only one patient who developed CRS after day 15; ICANS was not reported after day 15. Of all 43 patients who developed ICANS, 36 patients also had CRS; of the 18 patients who developed ICANS grade ≥3, 16 patients were also diagnosed with CRS.

Univariate analysis showed a higher incidence of ICANS in patients with ECOG 2–3 at CART compared to patients with ECOG 0–1 (64% [95% CI 43–79] vs. 33% [95% CI 23–45], $p = 0.003$). A trend was also observed for a higher incidence of CRS (90% [95% CI 69–97] vs. 80% [95% CI 68–88], $p = 0.051$) in patients with ECOG ≥ 2 versus patients with ECOG 0–1. The difference in CRS observed between patients without and with active CNS disease at CART (CRS in 91% of patients [95% CI 72–98] vs. 79% [95% CI 67–87]) was not significantly different. There was a higher incidence of ICANS in patients with CNS lesions at CART (48% [95% CI 35–59]) compared to patients without active CNS disease at CART (30% [95% CI 16–46]), albeit without statistical significance ($p = 0.18$). In patients with proven CNS manifestations at CART, there was no statistically significant difference in incidence of CRS or ICANS for patients with involvement of deep brain structures compared to those with other parenchymal manifestations and likewise for patients with parenchymal versus leptomeningeal lesions. Incidences of CRS and ICANS were comparable for patients treated with axi-cel or tisa-cel (CRS 86% [95% CI 74–93] vs. 82% [95% CI 65–91], ICANS 44% [95% CI 31–56] vs. 42% [95% CI 25–57]). Differences in patients with or without previous hd-MTX or irradiation of the brain did not reach statistical significance (Table S4). The same holds true for the comparison of PCNSL versus SCNSL; the incidence of ICANS observed in patients with PCNSL versus patients with SCNSL was 50% [95% CI 23–72] versus 40% [95% CI 30–51], ($p = 0.75$), the incidence of CRS was 88% [95% CI 52–97] versus 82% [95% CI 72–89], ($p = 0.36$).

In multivariate analysis, ECOG ≥ 2 at CART remained the only independent risk factor for ICANS with an HR of 2.68 [95% CI 1.42–5.07], ($p = 0.002$).

Efficacy

Response assessment was performed with combined PET/CT and cMRI in 43%, with PET/CT alone in 29%, and with combinations of CT and MRI in 13% of patients. The remaining patients received other examinations for the assessment of disease status (Table 2). In 46% of patients, two or more diagnostic procedures were combined for response assessment. At 100 days after CART, 36% of patients had achieved CR and 24% were in PR, corresponding to an overall response rate of 60%. PFS and OS for the whole cohort were 28% [95% CI 20–40] and 37% [95% CI 28–49] at 24 months. RI was 59% [95% CI 48–69] and NRM was 13% [95% CI 6–21] at 24 months (NRM at 12 months: 7% [95% CI 3–14]).

For patients with active CNS disease at the time of CART ($n = 67$), 2-year PFS and OS were 25% [95% CI 15–42] and 38% [95% CI 27–52], respectively. For patients without proven CNS involvement at CART PFS and OS at 2 years were 34% [95% CI 20–56] and 38%

TABLE 2 Imaging modalities used for the assessment of disease status at CART.

No. of pts	Disease status at CART	Type of CNSL	CNS manifestation at CART	Used assessment methods and no. of pts					
				PET/CT	PET/CT + MRI	CT + MRI	MRI	CT	Other
2	Complete remission	Primary	No		1		1		
5	Complete remission	Secondary	No	2	1				1[a], 1[b]
5	Partial remission	Primary	Yes	2	1	1			1[c]
18	Partial remission	Secondary	Yes	2	10	5		1	
7	Partial remission	Secondary	No	2	3	1			1[d]
1	Stable disease	Primary	Yes				1		
3	Stable disease	Secondary	Yes	1		1		1	
2	Stable disease	Secondary	No	1					1[c]
8	Refractory/progressive disease	Primary	Yes	1	4	1	2		
32	Refractory/progressive disease	Secondary	Yes	5	19	4	1		1[b], 2[e]
16	Refractory/progressive disease	Secondary	No	12	4				
1	No information disease status	Secondary	No	1					

Abbreviations: CART, chimeric antigen receptor T-cell therapy; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; No., number; PET/CT, positron emission tomography/computed tomography; pts, patients.

[a]CT + CFS.

[b]MRI + CSF.

[c]PET/CT + CT.

[d]Assessment method(s) unknown as assessment was performed in another hospital. Of note, two patients received additional examinations for assessment such as bone marrow aspiration or lymph node biopsy.

[e]CT + MRI + CSF.

[95% CI 24–61] (Figure 1), respectively. The numerical difference for patients with versus patients without active CNS disease at CART was not significant in univariate analysis ($p = 0.46$ for OS and $p = 0.48$ for PFS; see Supporting Information).

Time from diagnosis to CART ≤ 1.5 years was associated with a higher RI (75% [95% CI 58–86] vs. 42% [95% CI 27–57], $p = 0.01$) with impaired PFS and OS (PFS 16% [95% CI 8–33] vs. 42% [95% CI 29–61], $p = 0.02$; OS 27% [95% CI 17–44] vs. 49% [95% CI 35–68], $p = 0.018$). Previous ASCT was associated with improved PFS (35% [95% CI 22–57] vs. 25% [95% CI 15–40], $p = 0.025$) and OS (47% [95% CI 33–68] vs. 31% [95% CI 21–47], $p = 0.044$). Elevated LDH at the time of CART had a negative impact on PFS (20% [95% CI 10–40] vs. 35% [95% CI 2–54], $p = 0.003$) and was associated with a significant increase in RI (73% [95% CI 55–85] vs. 49% [95% CI 33–63], $p = 0.0008$) (Figure 2). Two-year PFS was lower in patients who received bridging therapy compared to those who did not (22% [95% CI 14–36] vs. 49% [95% CI 31–79], $p = 0.035$). Possibly related to this finding, we found that time from apheresis to CAR T-cell infusion being >40 days was associated with a tendency for a higher rate of relapse (67% [95% CI 51–79] vs. 51% [95% CI 35–65], $p = 0.053$). When comparing for markers of disease activity at relapse, namely LDH, ECOG, and Ann Arbor stage, we did not find significant differences between patients who received bridging therapy or not although there was a numerical difference for ECOG 2–4 and Ann Arbor stage IV (30% [19/63] vs. 14% [2/14] and 77% [47/61] vs. 58% [7/12] of patients). Patients > 60 years at time of CART had lower RI (47% [95% CI 32–60] vs. 75% [95% CI 55–87, $p = 0.009$) but higher NRM compared to patients ≤ 60 years of age (19% [95% CI 8–33] vs. 4% [95% CI 1–14], $p = 0.038$). RI was lower in patients who received CART in CR or PR compared to those with active disease (52% [95% CI 31–69] vs. 65% [95% CI 51–76]), $p = 0.036$). Patients with PCNSL had similar 2-year PFS compared to patients with SCNSL (25% [95% CI 9–72] vs. 29% [95% CI 20–42], $p = 0.62$). A trend for better OS of patients with PCNSL compared to patients with SCNSL was not statistically significant (46% [95% CI 26–82] vs. 36% [95% CI 26–49], $p = 0.46$). Outcomes of patients with involvement of deep brain structures and those with other parenchymal lesions did not differ significantly (Table S3). Patients with advanced stage (Ann Arbor stage III or IV) at CART had higher RI at 2 years (69% [95% CI 54–80] vs. 51% [95% CI 21–75], $p = 0.025$). Patients previously irradiated showed a trend for better PFS and OS (2-year PFS and OS 47% [95% CI 27–83] and 63% [95% CI 43–91]) compared to patients without prior CNS radiation (25% [95% CI 17–39] and 34% [95% CI 24–47] ($p = 0.18$). There were no significant differences in outcome between patients with or without previous hd-MTX treatment or in patients treated with axi-cel versus tisa-cel (Table S3).

In multivariate analysis, LDH > ULN was associated with impaired PFS at 2 years (HR 1.9 [95% CI 1.1–3.2], $p = 0.016$, Table S5) and higher RI (HR 2.4 [95% CI 1.3–4.3], $p = 0.003$). For OS, HR for elevated LDH was 1.6 [95% CI 0.9–2.7], not reaching significance ($p = 0.094$).

One patient received a subsequent CART with tisa-cel (the initial product was liso-cel) and had progression of disease thereafter. Of eight patients who received an allogeneic SCT after CART for treatment of progression, three patients relapsed and died due to relapse. One patient died of multi-organ failure and one of graft versus host-disease. Two allografted patients were alive at the last follow-up, whereas for one patient, follow-up information after allogeneic SCT is missing.

Sixty-two patients had died at the last follow-up. Main cause of death was relapse (80%). As indicated earlier, three patients died of infections, one of CART-related neurotoxicity on day 6, and one patient of leukencephalopathy on day 133, which was deemed to be associated with fludarabine administered for lymphodepletion. One patient each died of heart failure on day 165, and another of bowel perforation on day 49. Three patients died of secondary malignancies: two of them from MDS (days 728 and 531 after CART),

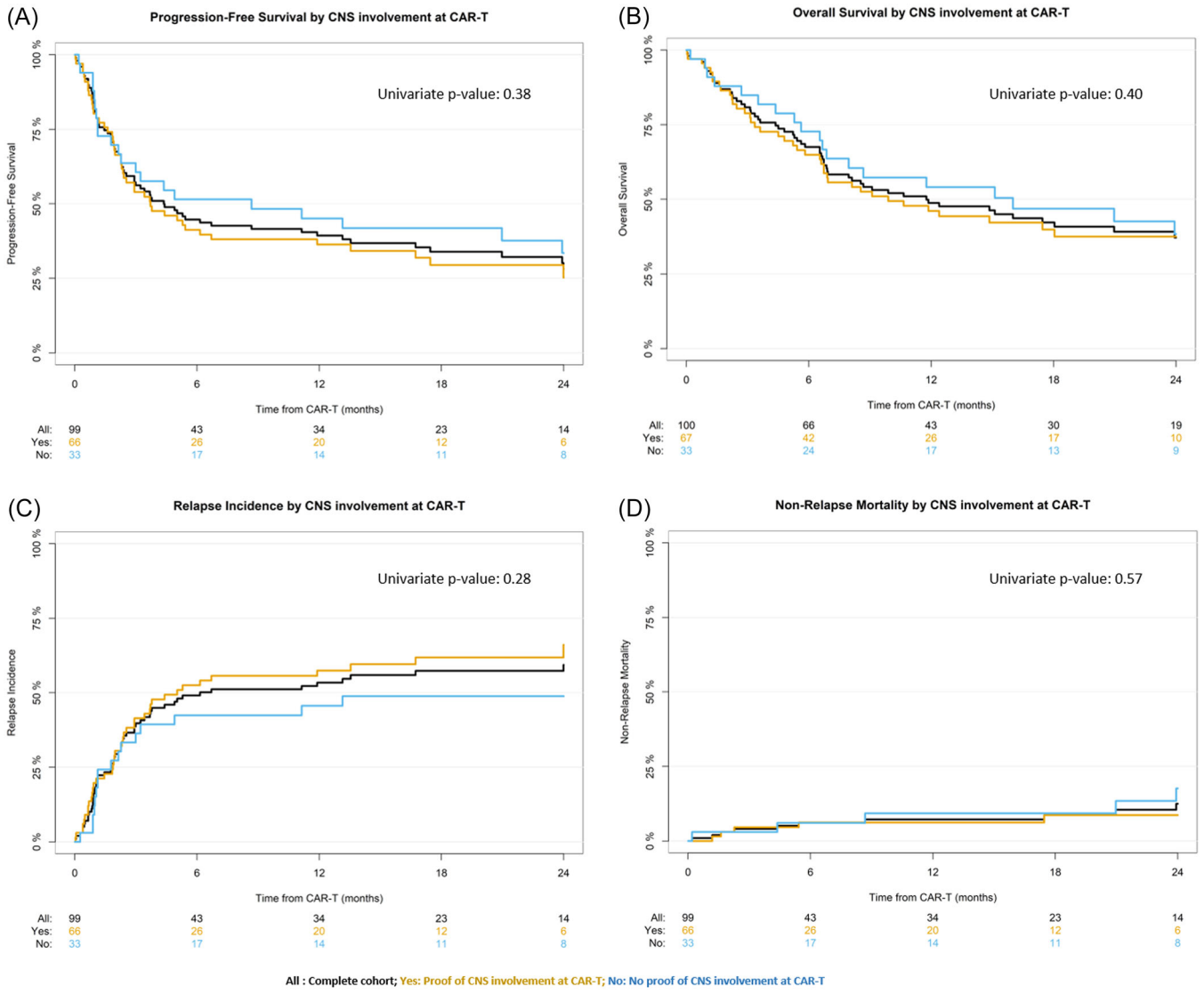

FIGURE 1 **Outcomes of patients with PCNSL (*n* = 16) or SCNSL (*n* = 84) by CNS involvement at CAR-T.** Kaplan–Meier curves showing **(A)** progression-free survival and **(B)** overall survival. Cumulative incidence curves showing **(C)** relapse incidence and **(D)** non-relapse mortality. At the time of CAR T-cell infusion, 71 patients had proof of CNS manifestation of lymphoma, 7 patients were in CR, and 22 had systemic manifestations only. Initial number at risk was reduced for PFS due to missing information on remission status after CAR-T for one patient and for NRM and RI due to unknown cause of death in one patient. CAR-T, chimeric antigen receptor T-cell therapy; CNS, central nervous system; PCNSL, primary central nervous system lymphoma; SCNSL, secondary central nervous system lymphoma.

and one of those patients had received previous ASCT. The third patient died due to colon cancer on day 816. One patient died in the outpatient setting 987 days after CART of unknown cause. None of the 13 patients who died from causes other than relapse did receive any further treatment for lymphoma.

DISCUSSION

This retrospective analysis reports the efficacy and safety of CART in a larger cohort of patients with PCNSL and SCNSL. We included patients with active disease as well as those with a history of CNSL because both patient groups were excluded from the vast majority of pivotal trials.[18–20]

Overall, the percentages of severe CRS and ICANS (≥grade 3) of 12% and 18% lie within the ranges reported for patients without CNSL.[21–23] Significant differences in the frequencies of CRS and ICANS between patients treated with axi-cel and tisa-cel were not found. We also did not observe significant differences in incidences of CRS and ICANS in patients with and without active CNS disease at the time of CART (79% vs. 91% and 48% vs. 30%). A tendency to higher frequencies of (severe) ICANS in patients with PCNSL and SCNSL compared to patients without CNS manifestations has been observed by Tost et al.,[24] whereas Karschnia et al. assume that the occurrence of ICANS is linked to CRS-related systemic inflammatory processes rather than to the presence of CNS lymphoma.[25] Of 18 patients with ICANS grade ≥ 3 in our study, 16 patients were also diagnosed with CRS, supporting the latter hypothesis. For patients with PCNSL, ICANS was reported in almost 70% of patients.[26] In our analysis, the incidence of ICANS observed in patients with PCNSL was 50%. With the small number of patients in both the French and our study, it remains to be settled if PCNSL represents another risk factor for CRS and/or ICANS in CART-treated patients. An impaired performance status, namely ECOG ≥ 2, could be confirmed as the

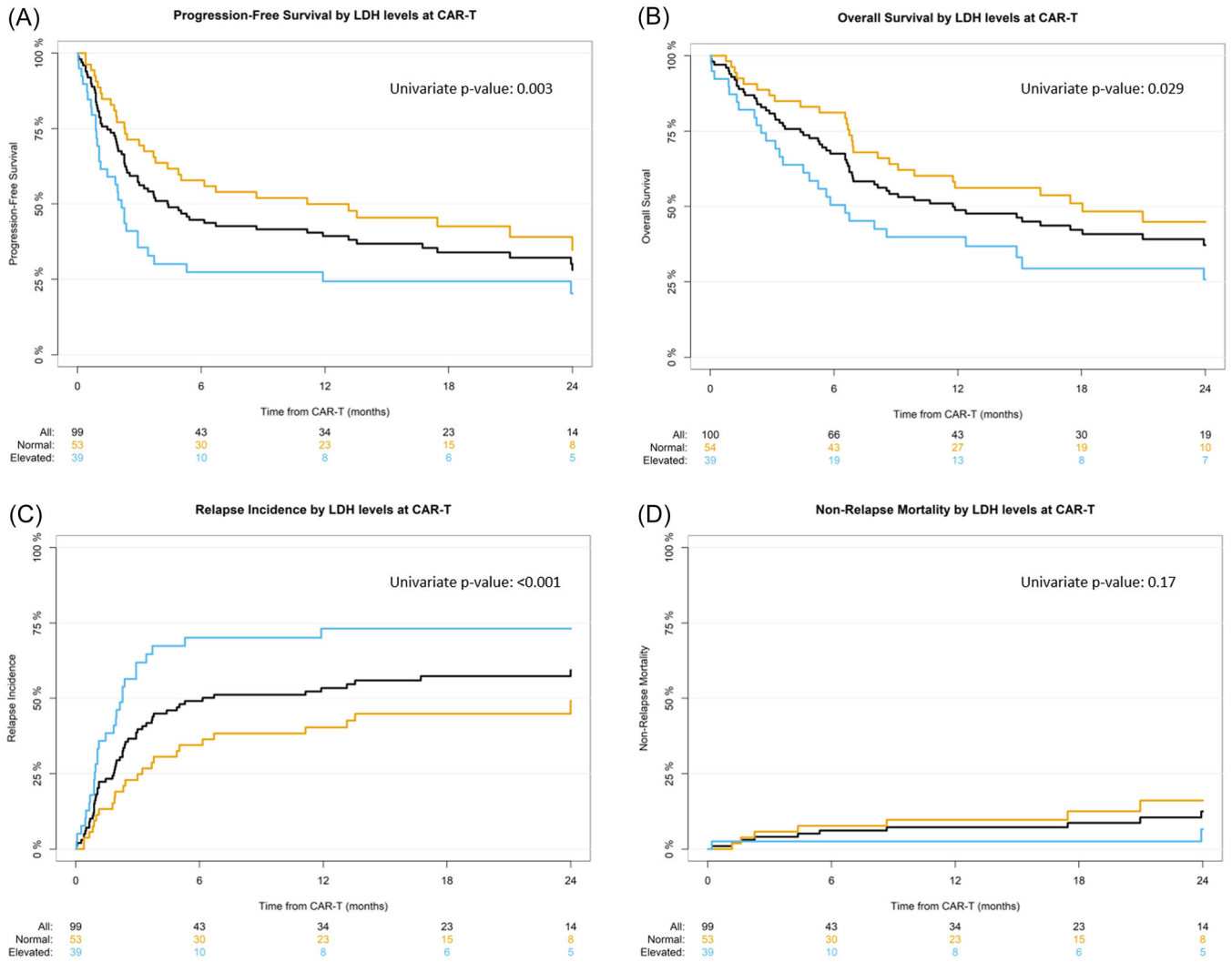

FIGURE 2 **Outcomes of patients with PCNSL (*n* = 16) or SCNSL (*n* = 84) by LDH levels at CAR-T.** Kaplan–Meier curves showing **(A)** progression-free survival and **(B)** overall survival of all (black curve), patients with elevated LDH (blue curve), and patients with normal LDH values (orange curve). Cumulative incidence curves showing **(C)** relapse incidence and **(D)** non-relapse mortality. At the time of CAR T-cell infusion, 71 patients had proof of CNS manifestation of lymphoma, 7 patients were in CR, and 22 had systemic manifestations only. Initial number at risk was reduced for PFS due to missing information on remission status after CAR-T for one patient and for NRM and RI due to unknown cause of death in one patient. CAR-T, chimeric antigen receptor T-cell therapy; CNS, central nervous system; LDH, lactate dehydrogenase; NRM, non-relapse mortality; PCNSL, primary central nervous system lymphoma; SCNSL, secondary central nervous system lymphoma.

only independent risk factor for development of ICANS in our analysis. This is an important finding for a patient population that is frequently facing severe impairment of the general condition due to the brain lesions.

With a PFS rate of 28% and an OS rate of 37% at 2 years, our results are similar to real-world data of patients with r/r DLBCL without CNS involvement.[21,22] These results are promising compared to survival data reported with conventional treatment strategies including ASCT with a median OS of about 3.5 months[5,12] and a 1-year OS rate of 20%[11] for patients with SCNSL and a median and 1-year OS of 6.8 months and 38% for patients with PCNSL.[2] Recent data presented in abstract form from a prospective trial showed a median PFS of 14 months and a median OS of 26 months for 18 patients with PCNSL and SCNSL treated with axi-cel, the frequency of CRS and ICANS in those 18 patients was similar to our cohort.[27] The survival outcomes reported for this small group of patients appear to be superior to the results of our retrospective analysis. However, with the small number of patients and the apparent differences between prospective clinical trials and real-world settings, comparison is difficult. A recent report by Epperla et al. on 61 patients with SCNSL treated with CART showed less favorable outcomes.[13] A PFS rate of 16% at 1 year is rather disappointing and seems lower than the survival rates reported in patients without CNSL. Of note, all patients in the latter publication had active CNS disease at the time of leukapheresis. Even when compared to our patients with active CNS disease at CART only (2-year PFS 25%, 2-year OS 38%), PFS rates reported by Epperla et al. are lower and somewhat discouraging. Among others, the reasons for poor outcomes may be the higher proportion of patients with diagnoses other than DLBCL (18% with FL, MZL, or other lymphoma) and a fairly high proportion of double-hit lymphomas within the DLBCL cohort (30% vs. 5% of patients in our study). Whether prior treatments and bridging strategies, which also differed between the two study cohorts, impact on outcomes after CART for CNSL remains to be settled. Furthermore, in contrast to the study by Epperla et al., our analysis also included patients with PCNSL. For 27 patients with PCNSL a 1-year PFS and 1-year OS of

46% and 55% after CART was shown in a recently published study by Choquet et al.,[26] which is very similar to the survival outcomes of patients with PCNSL in our analysis (1-year PFS and OS 47% [95% CI 27–80] and 62% [95% CI 42–91]). An analysis of 113 patients with SCNSL showed significantly better outcomes in patients with a history of CNS involvement compared to patients with active CNS disease at the time of CART.[28] This is in contrast to our results. One important difference between the two cohorts might be the fraction of patients with isolated leptomeningeal disease (38% vs. 20%), which led to lower PFS rates in both publications. Al Feghali et al. showed that leptomeningeal disease was also associated with unfavorable outcomes in patients with SCNSL treated with chemotherapy and radiation.[29] Which other parameters may be responsible for the differences observed remains elusive? Certainly, the question if patients with active CNS disease at CART do worse warrants further study.

The most prominent risk factor in multivariate analysis for impaired PFS and higher RI in our patient cohort was an elevated LDH at CART, confirming risk factor analyses of patient cohorts without CNS involvement.[30] Other potential risk factors, which showed significance in univariate analysis for PFS, included previous ASCT, bridging therapy and time from diagnosis to CART > 1.5 years. Bridging therapy is mostly used in patients with aggressive disease or high tumor burden. Accordingly, we found a numerically higher fraction of patients with Ann Arbor stage IV disease and impaired performance status before CART in patients who received bridging treatment. Furthermore, refractory disease at lymphodepletion was more common in this group of patients, further supporting this hypothesis. The negative impact of previous ASCT and prolonged times from diagnosis to CART gives rise to expectations that patients might benefit from earlier CAR T-cell treatment.

To further optimize the outcomes of patients treated with CART is essential, as the management of patients failing CART remains a major challenge, especially in cases with CNS manifestations. Bispecific antibodies were shown to cross the blood–brain barrier[31]; however, their efficacy in CNSL has yet to be investigated. WBRT remains an option offering remission to a subset of patients with relapsed or refractory CNSL,[32] but coming at the prize of impaired neurocognitive function in a significant number of patients.[33] Allogeneic SCT as a potentially curative option in patients with CNSL is limited to a small group of eligible patients.[34,35] Further investigations and innovative treatment strategies for patients failing CART are therefore urgently needed. Owing to its retrospective nature with data from 24 transplant centers all over Europe, it was impossible to use the Lugano Classification or the International Primary CNS Lymphoma Guidelines criteria for disease response throughout the study. Another limitation of this analysis is the still relatively small sample size hampering an in-depth subgroup analysis to identify additional clinically important risk factors for toxicity and efficacy. Also, the heterogeneity of the study population and the lack of granularity for some data did not allow to describe details such as the bridging regimens used, particularly the role of radiation therapy, or the (prophylactic) treatment strategies implemented for ICANS. A detailed investigation of bridging therapies used prior CART and their impact on outcomes is ongoing. In summary, the present study demonstrates the feasibility, safety, and efficacy of CART even in patients with CNS involvement. PFS and OS are encouraging and similar to results obtained in patients without CNS disease; current results seem to be better than conventional therapy with or without subsequent ASCT.[2,10] Toxicities including CRS and ICANS appear acceptable with incidences in the range of what has been reported for patients without CNSL. Based on the data presented here, patients with CNSL should not be withheld from CAR T-cell treatment. Larger retrospective analyses with longer follow-up or prospective randomized trials directly comparing CART with ASCT including DLBCL patients with CNS disease are warranted.

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AUTHOR CONTRIBUTIONS

Anna Ossami Saidy: Conceptualization; methodology; data curation; project administration; writing—original draft; writing—review and editing; investigation; visualization; validation. **Christophe Peczynski**: Methodology; formal analysis; visualization; writing—review and editing; validation. **Catherine Thieblemont**: Data curation; writing—review and editing; investigation. **Michael Daskalakis**: Data curation; writing—review and editing. **Marc Wehrli**: Data curation; writing—review and editing. **David Beauvais**: Data curation; writing—review and editing. **Jürgen Finke**: Data curation; writing—review and editing. **Elisabeth Schorb**: Data curation; writing—review and editing. **Peter Vandenberghe**: Data curation; writing—review and editing. **Philipp Berning**: Data curation; writing—review and editing. **Matthias Stelljes**: Data curation; writing—review and editing. **Francis Ayuk**: Data curation; writing—review and editing. **Ron Ram**: Data curation; writing—review and editing. **Malte Von Bonin**: Data curation; writing—review and editing. **Peter Dreger**: Data curation; writing—review and editing. **Wolfgang Bethge**: Data curation; writing—review and editing. **Andrea Kuhnl**: Data curation; writing—review and editing. **Lasse Jost**: Data curation; writing—review and editing. **Friedrich Stölzel**: Data curation; writing—review and editing. **Bastian von Tresckow**: Data curation; writing—review and editing. **Christoph Renner**: Data curation; investigation; writing—review and editing. **Stephan Fuhrmann**: Data curation; writing—review and editing. **Jacques-Emmanuelle Galimard**: Formal analysis; writing—review and editing. **Eva Michel**: Project administration; writing—review and editing. **Ali Bazarbachi**: Investigation; writing—review and editing. **Anna Sureda Balari**: Investigation; writing—review and editing. **Norbert Schmitz**: Conceptualization; methodology; investigation; writing—review and editing; supervision; validation. **Bertram Glass**: Conceptualization; methodology; investigation; validation; supervision; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

Anna Ossami Saidy reports honoraria and travel support from Gilead Kite. Anna Sureda Balari received honoraria from Takeda, BMS/Celgene, MSD, Janssen, Amgen, Novartis, Gilead Kite, Sanofi, Roche, GenMab, AbbVie, Jazz Pharmaceuticals, AstraZeneca, Pierre Fabre, and Menarini; held a consultancy role with Takeda, BMS/Celgene, Novartis, Janssen, Gilead, Sanofi, GenMab, AbbVie, AstraZeneca, and Incyte; participated in Takeda's speaker's bureau; and received research support from Takeda. Ron Ram received honoraria from Kite/Gilead and Novartis. Bastian von Tresckow is an advisor or consultant for Allogene, Amgen, BMS/Celgene, Cerus, Gilead Kite, Incyte, IQVIA, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Miltenyi, Novartis, Noscendo, Pentixapharm, Pfizer, Pierre Fabre, Qualworld, Regeneron, Roche, SOBI, and Takeda; has received honoraria from AbbVie, AstraZeneca, BMS/Celgene, Gilead Kite, Incyte, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Novartis, Roche, and Takeda; reports research funding from Esteve (Inst.), Merck Sharp & Dohme (Inst.), Novartis (Inst.), and Takeda (Inst.); and reports travel support from AbbVie, AstraZeneca, Gilead Kite, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Pierre Fabre, Roche, Takeda, and Novartis. Francis Ayuk

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No other potential conflicts of interest were reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from EBMT. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of EBMT.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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