Anti-CD19 chimeric antigen receptor T-cell therapy has less efficacy in Richter transformation than in *de novo* large B-cell lymphoma and transformed low-grade B-cell lymphoma

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Abstract

The activity of anti-CD19 chimerci antigen receptor (CAR) T-cell therapy in chronic lymphocytic leukemia (CLL) with Richter's transformation (RT) to aggressive large B-cell lymphoma (LBCL) is largely unknown. In a multicenter retrospective study, we report the safety and efficacy of CAR T-cell therapy in patients with RT (N=30) compared to patients with aggressive B-cell lymphoma (N=283) and patients with transformed indolent non-Hodgkin lymphoma (iNHL) (N=141) between April 2016 and January 2023. Two-thirds of patients received prior therapy for CLL before RT and 89% of them received B-cell receptor and B-cell lymphoma 2 inhibitors. Toxicities of CAR T-cell therapy in RT were similar to other lymphomas, with no fatalities related to cytokine release syndrome or immune effector-cell associated neurotoxicity synderome. The 100-day overall response rate and complete response rates in patients with RT were 57% and 47%, respectively. With a median follow-up of 19 months, the median overall survival (OS) was 9.9 months in patients with RT compared to 18 months in *de novo* LBCL and not reached in patients with transformed iNHL. The OS at 12 months was 45% in patients with RT compared with 62% and 75% in patients with *de novo* LBCL and transformed iNHL, respectively. In a multivariate analysis, worse OS was associated with RT histology, elevated lactate dehydrogenase, and more prior lines of therapy. CAR T-cell therapy can salvage a proportion of patients with CLL and RT exposed to prior targeted agents; however, efficacy in RT is inferior compared to *de novo* LBCL and transformed iNHL.

Introduction

Advancements in drug therapies have greatly improved patient outcomes in chronic lymphocytic leukemia (CLL) in the last decade, and long-term responses are attained, even in those with high-risk disease features.[1] Nevertheless, patients with progressive disease that is refractory to both B-cell receptor (BCR) and B-cell lymphoma 2 inhibitors (BCL2i) have limited options. Even more challenging are patients with disease transformation to an aggressive lymphoma, known as Richter transformation (RT). Patients with RT face a particularly grim prognosis, as traditional anthracycline-based combination chemoimmunotherapy yields short-lived responses and overall survival (OS) rates of less than 1 year.[2,3] Despite the introduction of novel targeted agents, the outcome for patients previously exposed to Bruton's tyrosine kinase (BTK) inhibitors remains discouraging.[4] Allogeneic hematopoietic cell transplantation (allo-HCT) offers potential cure and long-term survival for some RT patients, with a 40% disease-free survival rate achieved in fit individuals following non-myeloablative allo-HCT.[5] However, often due to advanced age, comorbidities and lack of disease control, only a fraction of patients may be eligible for allo-HCT.[3,6]

The advent of chimeric antigen receptor (CAR) T-cell therapy in B-cell malignancies was first used in patients with CLL more than a decade ago.[7] Despite some long-lasting remissions reported, CAR T-cell therapy demonstrated only limited success in CLL, possibly due to intrinsic T-cell exhaustion and dysfunction.[8,9] In contrast, CAR T-cell therapy has achieved a 2-year event-free survival (EFS) of 40% in early relapsed or refractory large B-cell lymphoma.[10-12] Despite numerous clinical trials, including patients with B-cell lymphoma receiving CAR T-cell therapy, those with RT were excluded from prospective trials and the efficacy and safety of CAR T-cell therapy in RT is based on limited retrospective experience.[13-15] Given a paucity of data in this space and in order to provide a potential new benchmark of outcomes in this unique cohort, we studied the outcomes of CAR T-cell therapy in patients with RT and compared the results with cohorts of *de novo* DLBCL and transformed iNHL.

Methods

Study design

This multi-center retrospective analysis included adult patients (age ≥18 years) with one of the following histologies: CLL with documented RT to DLBCL, DLBCL not otherwise specified (NOS), high-grade B-cell lymphoma (HGBL), and transformed iNHL which included transformed follicular lymphoma (tFL) and transformed marginal zone lymphoma (tMZL). All patients were treated between April 2016 and January 2023 at Memorial Sloan Kettering Cancer Center (MSKCC, New York), Hackensack University Medical Center at Hackensack Meridian Health (HMH, New Jersey), Rambam Health Care Campus (Haifa, Israel) and Sheba Medical Center (Ramat Gan, Israel) with one of the following CD19 CAR T-cell products: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), or a point-of-care (POC) CD28-based product (given under a phase Ib/II clinical trial; *clinicaltrials gov. identifier: NCT02772198*).[6,7] The POC CD28-based CAR T is a non-commercial, academic CAR T. The construct has single-chain fragment variable (scFv) derived from the mouse anti-CD19 hybridoma, FMC63, fused to intracellular domains from human CD28 and CD3-z, as previously published.[16] Fresh product of $1x10^6$ CAR^+ cell/kg was delivered to patients after lymphodepletion with fludarabine and cyclophosphamide with a median turn-around time of 10 days from apheresis to end of manufacturing. In addition to comparable manufacturing efficiency, treatment efficacy, and toxicity profiles, studies have observed adverse events profiles similar to those of the commercial products.[16-18] Patient data were captured in REDCap databases. The Institutional Review Boards of the participating institutions approved the study in accordance with the Declaration of Helsinki and all patients signed informed consent for treatment.

Definitions and endpoints

Response was assessed at the individual institutions according to the Lugano criteria using positron emission tomography-computed tomography (PET-CT) relative to the disease response before leukapheresis.[19] Bulky disease was considered to be a tumor mass of more than 10 cm in diameter. The overall response rate (ORR) was defined as the proportion of patients who achieved a complete or partial response. Progression-free survival (PFS) was defined as the time from CAR T-cell infusion to either first documented progression or death. OS was defined as the time from cell infusion to the date of death. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the American Society for Transplantation and Cellular Therapy Consensus Grading.[20] The primary end point was the rate of objective response, calculated as the combined rates of complete response and partial response. Secondary end points included the duration of response, PFS, OS and incidence of adverse events.

Statistical analysis

Categorical and continuous variables were described by frequency and percentage or median and range, respectively. Fisher's exact and Kruskal-Wallis tests were used to study categorical and continuous variables, respectively. The median follow-up was calculated by the reverse Kaplan-Meier method. The Kaplan-Meier method was used for survival description. Univariable Cox regression models clustered by center were created to study clinical factors

associated with OS and PFS. Relapse was evaluated using cumulative incidence analysis with a competing risk of death, as well as with univariable cause-specific Cox regression clustered by center. Univariable logistic regression was utilized to determine predictors of CR. The multivariable regression model included variables presenting $P<0.1$ in the univariable analysis. All P values were 2-sided, and $P<0.05$ was considered statistically significant. Data were analyzed using R (version 4.1.2).

Results

Patients and disease characteristics

A total of 454 patients with aggressive B-cell lymphoma (DLBCL NOS [85%], HGBL [13%]) were analyzed: 283 with *de novo* LBCL (62%), 141 with transformed iNHL (31%), and 30 with RT (7%). Among 270 patients with available cytogenetic data, 20% had double-hit or triple-hit LBCL. Patients with transformed iNHL included 105 patients (74%) with tFL and 36 patients (26%) with tMZL. When comparing patients with RT *versus* all other histologies, baseline patient characteristics were similar (Table 1). Among all patients, median age was 64 years (range, 20-86) and 63% were males. CAR T products used included axi-cel in 45% (N=206), tisa-cel in 24% (N=110), lliso-cel in 13% (N=58), and POC CD19 CAR T cell in 18% (N=80). Most patients with *de novo* DLBCL (N=124, 44%) and transformed iNHL (N=78, 55%) were treated with axi-cel and most patients with RT (N=16, 53%) were treated with POC CAR T-cell therapy. Most patients (N=308, 77%) had advanced-stage diseases and elevated lactate dehydrogenase (LDH) (N=233,55%), 16% (N=69) had bulky disease and 8% (N=35) had active central nervous system (CNS) involvement at apheresis. Sixty-eight percent of the patients (N=303) received up to three lines of therapy before apheresis, 21% (N=95) received four or five lines of therapy and 11% of patients (N=48) received more than six lines of therapy. Bridging therapy was administered to 266 (59%) patients. The median time from apheresis to CAR T infusion was 36 days (range, 10-377). Lymphodepletion included cyclophosphamide and fludarabine or bendamustine in 405 (89%) and 49 (11%) patients, respectively.

Chronic lymphocytic leukemia characteristics pretransformation

Thirty patients with CLL and RT from four medical centers were evaluated (Sheba N=16 [53%], MSKCC N=11 [37%], HMH N=2 [7%], Rambam N=1 [3%]). Patient characteristics are shown in Table 2. CLL adverse prognostic factors were available in a subset of patients and included: unmutated IGHV in four of seven (57%), complex karyotype in four of 12 (33%), del17p by fluorescence *in situ* hybridization in seven of 17 (41%), and *TP53* mutation five of 12 (42%). Prior to RT, six of 16 patients (37%) had advanced-stage CLL (RAI stage 3/4), and 22 of 26 (85%) had hypogammaglobulinemia. In nine of 28 patients (32%), RT occurred without prior CLL-directed therapy. One patient (4%) presented with *de novo* RT. Eight of 28 patients (29%) were treated with three or more prior lines of therapy for CLL before RT. Among patients that were treated for CLL prior to RT 68% (19/28), pretransformation therapies included chemoimmunotherapy with fludarabine, cyclophosphamide, rituximab/obinutuzumab (FCR/O) or bendamustine, rituximab (BR) in 58% (11/19), other chemotherapies 21% (4/19) and targeted therapies 89% (17/19) with BTKi 74% (14/19), phosphoinositide 3 kinase inhibitors (PI3Ki) 16% (3/19) and BCL2i 47% (9/19). Two patients (7%) received prior autologous-SCT and five of the patients (17%) consolidated with allo-HCT for CLL prior to transformation.

The Richter transformation cohort before CAR T-cell therapy (N=30)

The median age of the RT cohort before CAR T-cell therapy was 66 years; range, 44-78. Most patients were male 80% (24/30) and 43% (13/30) had Karnofsky performance status (KPS) ≥90. Most patients (80%; 22/27) had stage 3-4 disease at apheresis, and 32% (9/28) had primary refractory disease. Prior CNS involvement and active CNS involvement at apheresis were documented in 11% (3/28) and 7% (2/28), respectively, and 11% of patients (3/28) had bulky disease. The time from RT diagnosis to CAR T-cell therapy was 9 months (range, 2-13) compared to 15 months (range, 0-219) in patients with *de novo* LBCL and 14 months (range, 1-247) for patients with transformed iNHL. The median time from apheresis to CAR T-cell infusion was 30 days (range, 10-76) in patients with RT, 35 days (range, 10-377) in patients with *de novo* LBCL, and 39 days (range, 10-278) in patients with transformed iNHL. Patients with RT received a median of four lines of therapy (range, 2-15) before apheresis, including one (range, 0-8) for CLL before transformation and two (range, 0-7) after transformation directed to RT. Most patients were exposed to targeted therapies with BTKi 75% (21/28), PI3Ki 18% (5/28) and BCL2i 61% (17/28). Prior to CAR T-cell therapy, 17% (5/29) had allo-HCT, and 7% (2/29) had autologous-HCT. Eighteen patients with RT (60%) received bridging therapy, seven (23%) with local radiotherapy and 11 (37%) with systemic therapy including platinum-based chemotherpay (N=2), other systemic chemotherapy (N=1), BTKi (N=3), polatuzumab (N=2), lenalidomide (N=1) and two unknown. No patients received Pi3Ki or BCL2i-based therapy as bridging therapy. Bridging therapies administered to patients with RT were largely comparable to those administered in *de novo* LBCL and transformed iNHL, though exact comparisons were not feasible due to the low numbers and wide variety of therapeutic options. .

Outcomes

Efficacy

Response data were evaluable at day 100 for 440 patients, 271 of them with *de novo* LBCL, 139 with transformed iNHL,

Table 1. Base line characteristics.

Characteristics, N (%)	*De novo* LBCL N=283	Transformed iNHL N=141	Transformed CLL N=30	Overall N=454	*P*
Median age pre-CAR T in years (range)	63 (20-86)	65 (22-83)	66 (44-78)	64 (20-86)	0.10
Male	187 (66)	74 (52)	24 (80)	285 (63)	0.003
KPS ≥90	113 (41)	61 (44)	13 (43)	187 (42)	0.83
KPS <90	165(59)	79(56)	17(57)	261(58)	
Unknown	5	1	0	6	
Disease stage at apheresis					
≤II	65 (27)	22 (17)	5 (19)	92 (23)	0.10
III-IV	179 (73)	107 (83)	22 (81)	308 (77)	
Unknown	39	12	3	54	
Primary refractory pre-apheresis	135 (48)	50 (36)	9 (32)	194 (43)	0.03
Treatment lines pre-apheresis					0.13
≤3	197 (71)	92 (66)	14 (50)	303 (68)	
4-5	56 (20)	29 (21)	10 (36)	95 (21)	
≥6	25 (9)	19 (14)	4 (14)	48 (11)	
Unknown	5	1	2	8	
Previous auto-SCT	71 (25)	29 (21)	2 (7)	102 (23)	0.064
Unknown	1	0	1	2	
Previous allo-SCT	12 (4)	2 (1)	5 (17)	19 (4)	0.003
Unknown	1	0	1	2	
CNS disease history	44 (16)	15 (11)	3 (11)	62 (14)	0.38
Unknown	15	9	2	26	
Bulky disease pre-apheresis	50 (18)	16 (12)	3 (11)	69 (16)	0.20
Unknown	8	3	2	13	
Elevated LDH	143 (54)	75 (56)	15 (52)	233 (55)	0.86
Normal	122(46)	58(44)	14(48)	194(45)	
Unknown	18	8	1	27	
PET/CT before pre-apheresis, median (range)	16 (0-44)	15 (0-48)	15 (0-32)	15 (0-48)	0.98
Unknown	174	76	22	272	
Bridging therapy					0.98
Yes	166 (59)	82 (58)	18 (60)	266 (59)	
No	117 (41)	59 (42)	12 (40)	188 (41)	
Systemic	134 (47)	63 (45)	11 (37)	208 (46)	
Non-systemic	32 (11)	19 (13)	7 (23)	58 (13)	
Diagnosis to CAR T infusion in months, median (range)	15 (0-219)	14 (1-247)	9 (2-63)	14 (0-247)	0.064
Unknown	2	0	0	2	
Apheresis to CAR T infusion in days, median (range)	35 (10-377)	39 (10-278)	30 (10-76)	36 (10-377)	0.068
CAR T-cell product				206 (45)	
Axi-cel	124 (44)	78 (55)	4 (13)	110 (24)	
Tisa-cel	73 (26)	30 (21)	7 (23)	58 (13)	
Liso-cel	41 (14)	14 (10)	3 (10)	80 (18)	
POC antiCD19	45 (16)	19 (13)	16 (53)		
CAR T co-stimulatory molecule					0.17
41BB	114 (40)	44 (31)	10 (33)	168 (37)	
CD28	169 (60)	97 (69)	20 (67)	286 (63)	
Lymphodepletion					0.41
Fludarabine/cyclophosphamide	248 (88)	129 (91)	28 (93)	405 (89)	
Bendamustin	35 (12)	12 (9)	2 (7)	49 (11)	

LBCL: large B-cell lymphoma; CAR: chimeric antigen receptor; iNHL: low grade non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; KPS: Karnofsky performance status; LDH: lactate dehydrogenase; PET/CT: positron emission tomography/computed tomography; auto-SCT: autologous stem cell transplantation; allo-SCT: allogeneic stem cell transplantation; CNS: central nervous system; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Liso-cel: lisocabtagene maraleucel; POC: point of care.

and 30 patients with RT. Patients with transformed iNHL had the highest ORR of 78% (N=110) followed by 68% (N=189) in patients with *de novo* LBCL and lowest response rate 57% (N=17) in patients with RT. Patients with transformed iNHL also had the highest proportion of CR with 62% (N=87) CR followed by 50% (N=140) in *de novo* LBCL and 40% (N=14) in RT (Figure 1). The median follow-up was 19.0 months (interquartile range [IQR], 7.2-32.9). The median PFS and OS for the entire cohort were 6.6 (95% confidence interval [CI]: 5.3-8.8) and 23 (95% CI: 17-not reached [NR]) months (Figure 2A, C), PFS and OS at 12 months were 40% (95% CI: 35-45) and 65% (95% CI: 60-70), respectively. At 24 months, PFS and OS were 33% (95% CI: 28-39) and 49% (95% CI: 43-55), respectively (Table 3). The median OS was NR in patients with transformed iNHL (95% CI: 26-NR), 18 months in *de novo* DLBCL (95% CI: 18-27), and 9.9 months (95% CI: 6.2-NR) in patients with RT (Figure 2B). OS rates at 12 and 24 months, respectively, for patients with transformed iNHL were 75% and 61% for patients with *de novo* LBCL, 62% and 44%, and for patients with RT 45% and 31% (Figure 2C). Thirty-five patients (8%) had active CNS involvement at time of lymphodepletion. Twenty four of them (69%) had *de novo* LBCL, nine patients (26%) had transformed iNHL and two patients (6%) had RT. Toxicity profile was similar to patients without CNS involvement, with severe CRS in 3% and severe neurotoxicity (ICANS ≥3) in six patients (17%). At 12 months of follow-up (IRQ, 5.62-127.55), median OS was 9.9 months (95% CI: 6.2-NR) and OS at 24 months was 31% 95% CI: 16-62).

In a multivariate analysis, more prior lines of therapy, high LDH, and the presence of RT were associated with shorter OS rates whereas, age and the CAR T-cell co-stimulatory domain were not associated with survival (Table 4). Compared to patients with *de novo* LBCL, relapse rates were lowest for transformed iNHL (hazard ratio [HR]=0.75, 95% CI: 0.71-0.8) and highest in patients with RT (HR=1.38, 95% CI: 1.17-1.61; *P*<0.001) (Figure 3). At 12 months and 24 months after administration of CAR T, 68% and 77% of patients with RT experienced disease relapse. Age and the number of lines of therapy before apheresis were not associated with the risk of relapse (*Online Supplementary Table SA2*) However, an elevated LDH before lymphodepletion was associated with a higher relapse rate (HR=1.73, 95% CI: 1.05-2.83;

Table 2. Characteristics of patients with chronic lymphocytic leukemia pretransformation.

Characteristics pretransformation, N (%)	Overall N=30
RAI stage	
0-II	10/16 (63)
III-IV	6/16 (37)
IGHV mutation status	
IGHV mutated	3/7 (43)
IGHV unmutated	4/7 (57)
NA	23
Complex karyotype	4/12 (33)
FISH	
Del13q	6/18 (33)
T12	3/18(17)
Del11q	2/18(11)
Del17p	7/17 (41)
TP53 mutation	
Mutated	5/12(42)
Unmutated	7/12(58)
Hypogammaglobulinemia	
Yes	22/26 (85)
No	4/26 (15)
Prior CLL therapy	19/28 (68)
W&W before transformation	9/28 (32)
CLL lines of therapy	
0	9/28(32)
1	6/28(21)
2	5/28(18)
≥3	8/28(29)
Targeted therapy	17/19 (89)
BTKi	14/19 (74)
PI3Ki	3/19 (16)
BCL2i	9/19 (47)
FCR/BR	11/19 (58)
Other chemotherapy	4/19 (21)

CLL: chronic lymphocytic leukemia; FISH: fluorescence *in situ* hybridization; NA: not available; W&W: watch and wait; BTKi: bruton tyrosin kinase inhibitor; PI3Ki: phosphoinositide 3-kinase inhibitors; BCL2i: BCL2 inhibitor; FCR: fludarabine, cyclophosphamide, rituximab; BR: bendamustin, rituximab.

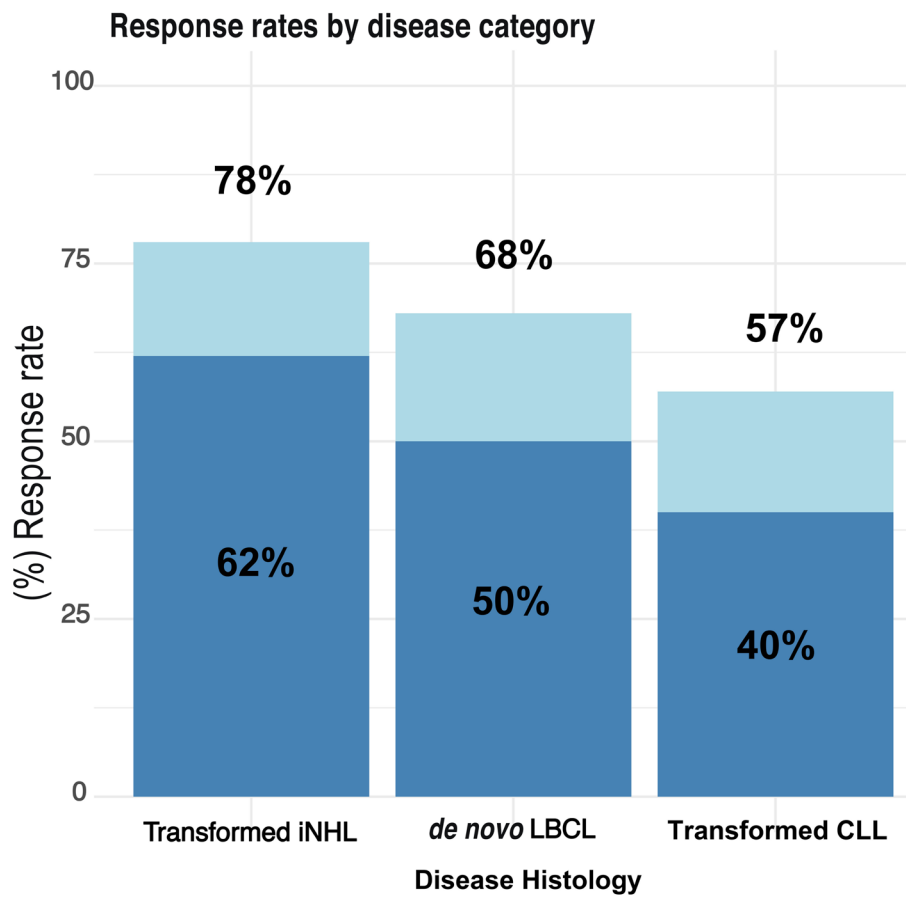

Figure 1. Overall response according to histology achieved at day 100. Overall response rate (ORR) *P*=0.071; complete response (CR) *P*=0.046. LBCL: large B-cell lymphoma; iNHL: low grade non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia.

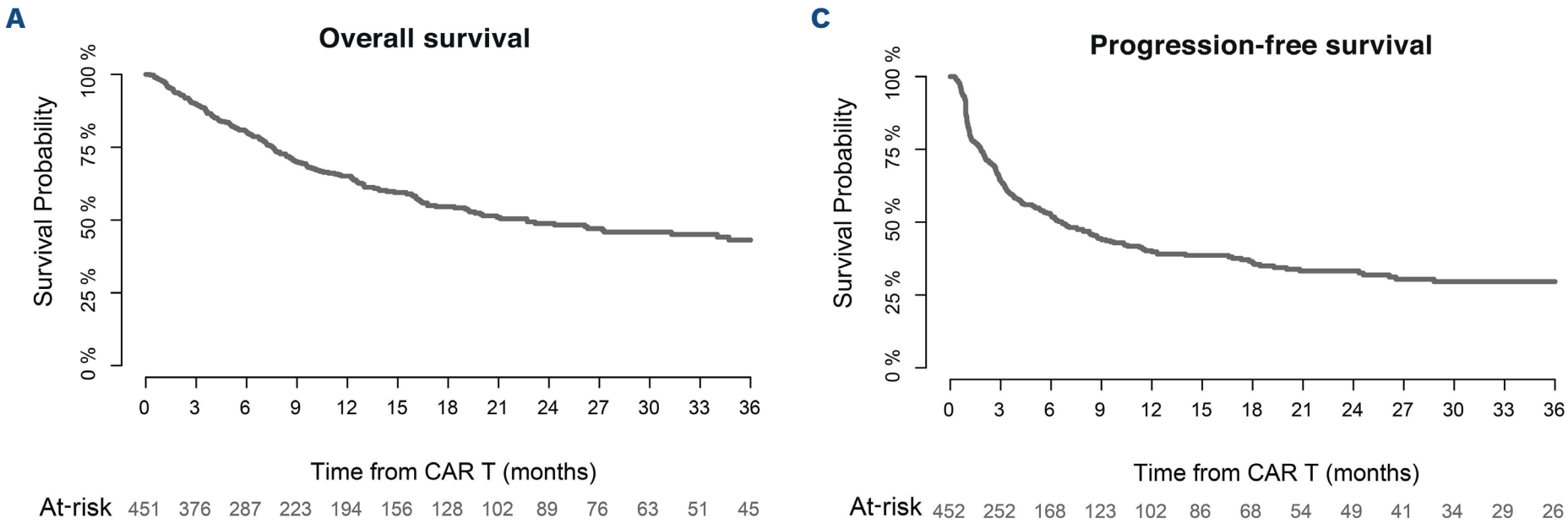

Figure 2. Survival outcomes according to histology. (A) Overall survival (OS) of the cohort. (B) OS according to histology. (C) Progression-free survival (PFS) of the cohort. (D) PFS according to histology. *De novo* large B-cell lymphoma (LBCL): transformed low grade non-Hodgkin lymphoma (iNHL) and transformed chronic lymphocytic leukemia (CLL). CAR: chimeric antigen receptor; NR: not reached.

P=0.012) and use of a product with CD28 co-stimulatory domain was associated with a lower relapse rate (HR=0.71, 95% CI: 0.55-0.910; *P*=0.038). (*Online Supplementary Table SA2*) The only predictor of the failure to achieve CR by day 100 in multivariable analysis was elevated LDH (HR=0.32, 95% CI: 0.21-0.47; *P*<0.001) prior to lymphodepletion. An exploratory univariate analysis performed to identify factors for OS in patients with RT included age at CAR T-cell infusion, elevated LDH before apheresis, bridging BTKi exposure therapy, performance status, disease stage, and number of prior lines of therapy. The only factor associated with shorter OS was the receipt of ≥6 prior lines of therapy (HR=2.00, 95% CI: 1.25-3.19; *P*=0.002) (*Online Supplementary Table SA3*).

At the time of last follow-up, the disease statuses of 24 patients with RT were as follows: nine patients remained in remission, 15 relapsed with RT, two of them relapsed with CLL as well. Fifteen patients (50%) received further therapy, 12 for relapsed or residual disease, and five patients (17%) underwent allo-HCT. Of the five patients who underwent allo-HCT, two patients (7%) underwent consolidation in CR after CAR T-cell therapy. Of these two patients, one had disease progression after 25 months, and the other died from non-relapse mortality 2 months post allo-HCT. Three patients with progression of disease after CAR T received salvage therapy for relapse with bispecific antibodies and underwent allo-HCT in remission.

Nine of 26 evaluable patients with RT had CLL at apheresis (35%) based on non-active lymphadenopathy per positron-emission tomography/computed tomography (PET/CT) scan, of whom only one had lymphocytosis. All patients with CLL component responded, three with CR and five with PR, one was not evaluable. Though measurable residual disease was not tested, all patients had lymphopenia.

Table 3. Safety and efficacy.

Characteristics, N (%)	*De novo* LBCL N=283	Transformed iNHL N=141	Transformed CLL N=30	Overall N=454
CRS, N (%)	206 (73)	113 (80)	27 (90)	345 (76)
Severe CRS ≥3	26 (9)	9 (6)	5 (17)	40 (9)
CRS duration in days, median (range)	5 (0-356)	6 (1-17)	5 (1-16)	5 (0-356)
No CRS or unknown	109	42	4	155
ICANS	76 (27)	41 (30)	11 (37)	130(28)
Severe ICANS ≥3	39 (14)	14 (11)	5 (17)	48 (13)
ICANS duration in days, median (range)	5 (1-114)	5 (1-26)	6 (1-16)	5 (1-114)
Unknown	219	105	19	343
Tocilizumab use	79 (28)	48 (34)	12 (40)	139 (31)
Corticosteroids use	87 (31)	42 (30)	12 (40)	141 (31)
ICU admission	26 (10)	11(8)	1 (3)	38(9)
Unknown	16	5	0	21
Day 100 best response				
CR	140 (50)	87 (62)	14 (47)	241 (54)
PR	49 (18)	23 (16)	3 (10)	75 (17)
SD/PD*	82 (29)	29 (21)	13 (43)	124 (28)
Unevaluable	7(3)	1(1)	0(0)	8(2)
Unknown	5	1	0	6
Progression free survival (95% CI)				
Median in months	5.3 (3.8-7.5)	11 (7.6-21)	4.3 (1.3-NR)	6.6 (5.3-8.8)
% at 12 months	36 (30-43)	48 (40-58)	34 (18-62)	40 (35-45)
% at 24 months	32 (26-40)	37 (28-49)	22 (8.2-61)	33 (28-39)
Overall survival (95% CI)				
Median in months	18 (14-27)	NR (26-NR)	9.9 (6.2-NR)	23 (17-NR)
% at 12 months	62 (56-69)	75 (68-83)	45 (29-71)	65 (60-70)
% at 24 months	44 (37-52)	61 (52-72)	31 (16-62)	49 (43-55)

LBCL: large B-cell lymphoma; CLL: chronic lymphocytic leukemia; iNHL: low grade non-Hodgkin lymphoma; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: intensive care unit; CR: complete remission; PR: partial response; SD/PD: stable disease/progressive disease; UA: unavailable; NR: not reached; CI: confidence interval. *Among patients with transformed CLL and SD/PD 8 died before day 100.

Only six patients (20%) with RT had clonality assessed. Five patients (80%) had clonally related RT. Three of them had progression of disease within 1-4.5 months after CAR T-cell infusion and two patients were alive and free of disease after 10 and 42 months.

Safety

Safety analysis was performed on 453 patients who received CD19 CAR T-cell therapy infusion (Table 3). CRS occurred in 76% (N=345) of patients, with severe CRS (grade ≥3) or in 9% (N=40). The median duration of CRS was 5 days (range, 0-356). ICANS was diagnosed in 28% (N=129) of patients and severe ICANS (grade ≥3) in 13% (N=48). There was one fatality related to ICANS. The median duration of ICANS was 5 days (range, 0-114). Steroids were administered to 31% (N=141) of the patients for ICANS and tocilizumab was administered to 31% (N=139) of patients with CRS. Prolonged neutropenia, at day 60 from apheresis, was higher in patients with RT (80%) compared to 66% in transformed iNHL and 58% in *de novo* LBCL. Twenty percent of patients with RT had thrombocytopenia at day 60 compared to 15% of patients with transfomed iNHL and *de novo* LBCL (*Online Supplementary Figure S1*). Thirty-eight patients (9%) were admitted to intensive care unit. Among patients with RT, toxicity grades were largely similar with no fatalities and one intensive care unit admission (3%) as shown in Table 3.

Discussion

Our study describes a cohort of 454 patients who underwent CAR T-cell therapy and focuses on 30 patients with RT in comparison with 283 patients with *de novo* LBCL and 141 patients with transformed iNHL.

CD19-CAR T cells have revolutionized the treatment of B-cell lymphoid malignancies with a growing number of approved indications.[21-26] Successful results of pivotal trials paved the way to utilize CAR T-cell therapy in earlier lines of therapy for LBCL and expanded the inclusions of patients with other entities, such as high-grade B cell lymphoma, mantle cell and Burkitt's lymphomas. Histologic transformation of indolent lymphomas to aggressive subtypes were included

Table 4. Univariate and multivariate analysis to identify prognostic factors for overall survival.

Variable	Univariate analysis			Multivariate analysis		
	N, event	HR (95% CI)	*P*	N, event	HR (95% CI)	*P*
Cohort	453, 180		<0.001	418, 167		<0.001
De novo LBCL		-	-		-	-
Transformed iNHL		0.63 (0.57-0.69)			0.59 (0.53-0.65)	
Transformed CLL		1.64 (1.20-2.24)			1.96 (1.75-2.19)	
Age at CAR T infusion	453, 180	1.00 (0.98-1.01)	0.40	418, 167	1.00 (0.99-1.02)	0.38
LDH range prelymphodepletion	426, 180		<0.001	418, 167		<0.00.1
normal		-	-		-	-
elevated		2.54 (1.74-3.70)			2.65 (1.86-3.75)	
CAR T co-stimulatory domain	453, 180		0.34	418, 167		0.52
4-1BB		-	-		-	-
CD28		0.93 (0.8-1.08)			0.93 (0.75-1.16)	
Pre-apheresis treatment lines	445, 177		0.043	418, 167		<0.00.1
≤3		-	-		-	-
4-5		1.18 (0.91-1.52)			1.00 (0.69-1.45)	
≥6		1.62 (1.11-02.38)			1.61 (1.9-2.17)	

HR: hazard ratio; CI: confidence interval; LBCL: large B-cell lymphoma; CAR: chimeric antigen receptor; iNHL: low grade non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; LDH: lactate dehydrogenase.

in CAR T-cell trials but subgroup-specific data are limited. Given that for the same histology RT patients were excluded from initial pivotal CAR T-cell trials our study contributes to an area of unmet need.

Perhaps most significant, while rates of CRS and ICANS were similar, the response rates were smaller, and PFS and OS were shorter for patients with RT than those with transformed iNHL and *de novo* LBCL. Interestingly, among all patients, those with transformed iNHL had the best overall outcomes. The response rate for patients with *de novo* LBCL was lower than most other prospective CD19 CAR T-cell trials; however, in the current trial the LBCL cohort also included patients with high-risk disease (20% DHT). By comparison, a designated trial of axi-cel as part of first-line treatment in patients with high-risk LBCL with either double- or triple-hit lymphomas, those with positive interim PET or high-risk international prognostic index (IPI) demonstrated 80% CR. In addition, efficacy varies among published trials and no direct comparison is available between commercially available products.[27,28]

The information of CAR T-cell therapy in relapsed/refractory (R/R) transformed iNHL is available based on patients who participated in trials of R/R FL or LBCL; however, subgroup-specific data are limited.[21,29] In a single-arm trial of CD19 CAR T in FL, six of 13 patients (46%) with heavily pretreated tFL achieved CR, and a median duration of response of 10.2 months. No relapses occurred after 15 months, with durable remissions observed for up to 39 months after CAR T infusion.[26] A multicenter study (TRANSCEND NHL 001) of patients with R/R LBCL treated with lisocabtagene maraleucel included 78 patients (29%) with transformed iNHL, 60 patients with tFL and 18 patients with other transformed iNHL (10 with MZL and others with CLL/SLL). The ORR and CR in patients with tFL were 84% and 63%, respectively, and in patients with other transformed iNHL 61% and 39%, respectively. Patients with tFL achieved long duration of responses, but in other transformed iNHL histologies, the median duration of response lasted less than 3 months and OS 6.5 months.[29]

The rare occurrence and aggressive nature of RT also contribute to the limited data available on CD19 CAR T in RT. The potential use of CAR T-cell therapy in RT patients was initially reported in case reports and pilot studies of patients with R/R CLL that included limited number of patients with history of RT treated with commercial and POC CAR T-cell products.[13,16,30-32] Recently, Kittai *et al.* reported on the largest cohort of patients with RT who received CD19-targeted CAR T in a retrospective international multicenter trial. Their trial included 69 patients that were treated with one of five commercial CAR T-cell products. Despite the limitation of intertrial comparison, our study share many similarities with their report having patient population with median age 64 years at CAR T-cell infusion, same proportion of major risk factors including Del17p/*TP53* mutation, high LDH, CNS involvement and SUV_{max} pre apheresis. In addition, in both trials patients were treated with four lines of therapy for CLL and RT, including the high proportion of patients that had received BTKi and BCL2i. The ORR was 63% compared to 57% in our RT cohort and CR was 46% *versus* 47%. Over longer median of follow-up of 24 months *versus* 19 months they found a median PFS of 4.7 months *versus* 6.6 months in our cohort and OS of 8.45 months *versus* 9.9 months. An estimated 2-year PFS was 29% *versus* 33%. In multivariate analysis, higher risk for disease progression increased with higher number lines of therapy and high LDH in both trials. Higher proliferative

index, Ki67 and intensive care unit level were also risk factors for disease progression in their cohort. Despite these similarities, our trial has smaller number of patients and a proportion of patients recived POC non-commercial CAR T-cell product. Our study reinforces the efficacy and safety results and provides further information by comparing the outcomes of CAR T-cell therapy in patients with *de novo* LBCL and transformed iNHL.[15]

The most important prognostic factor in RT is clonal relationship to the underlying CLL. Other poor prognostic factors are *TP53* mutations, poor patient performance status, elevated LDH, multiple prior lines of therapy, and failure to achieve CR to initial induction therapy for RT.[33,34] Patients with CLL and prior exposure and/or refractoriness to novel agents have the shortest survival.[35,36] Prior BTKi failure in RT patients may also adversely affect prognosis. In our study, 58% among those with information available (N=12) had *TP53* mutations, and most patients were exposed to targeted therapies: 75% to BTKi and 69% to BCL2i. A significant predictor of inferior survival was exposure to six or more prior lines of therapy. Age, performance status, LDH prior to apheresis, and the type of CAR T co-stimulatory domain of the product did not affect survival. Notably, the response rate of our RT cohort was lower than reported in other cohorts of elderly patients with LBCL treated with CAR T cells.[37,38]

Our study is limited by its retrospective design and its heterogeneity related to the different programs of each center, including commercial with different co-stimulatory molecules *versus* POC CAR T with different co-stimulatory molecules and non-uniform construct production. In order to minimize the limitation of including POC non-comercial CAR T, we performed sensitivity analysis excluding patients that were treated with that construct and found no difference in safety or efficacy (*Online Supplementary Tables S4*, *S5*; *Online Supplementary Figure S2*). The relatively small number of patients in the RT cohort needs to be interpreted with great caution and requires confirmation in larger trials. Importantly, clonality studies were not available for most patients in the cohort. However, given a paucity of published data for patients with RT, our multicenter effort may provide a benchmark for future studies, and uniquely compared to the outcomes after CD19 CAR T cells with other more common histologies such as transformed iNHL and *de novo* DLBCL. Additionally, most patients were previously exposed to targeted therapies representing current standards of care. Response rates after CAR T-cell therapy in RT are modest and ultimately the disease relapses in most patients. Nonetheless, the response rates that we observed far exceed previous publications with chemoimmunotherapy (CIT) that generally result in lower response rates with CR rates of 20% and median survival of 6 to 12 months.[39-43] Efforts to improve on the outcomes of CAR T-cell therapy in RT involve understanding why the poorer results in these patients. Efforts should focus on better understanding the disease

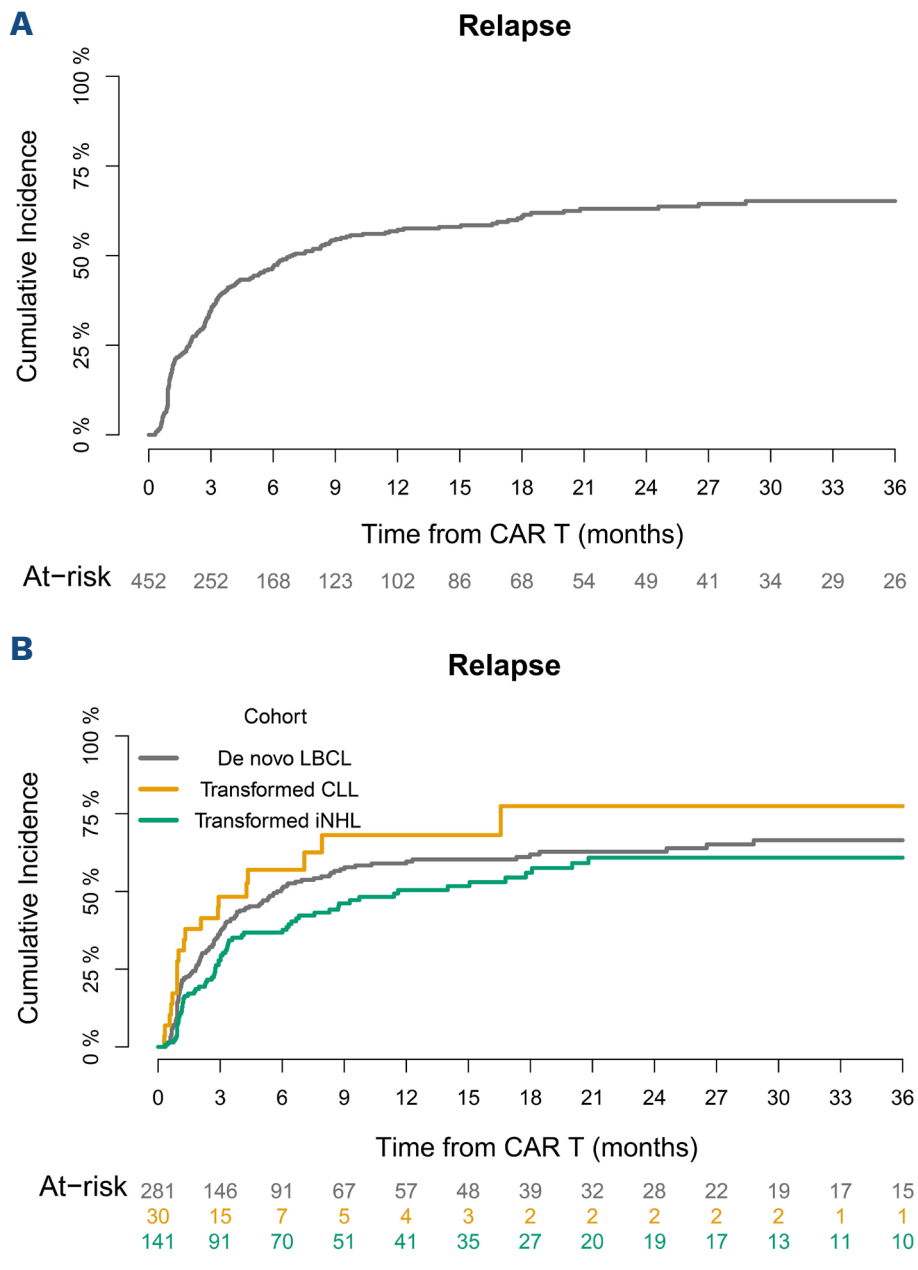

Figure 3. Cumulative relapse. Cumulative relapse (A) in the entire cohort and (B) according to histology. CAR: chimeric antigen receptor; LBCL: large B-cell lymphoma; iNHL: low grade non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia.

biology and the reasons for the CAR T failures. One cause is the immune system dysfunction and T-cell exhaustion related to the course of pretransformation CLL and prior therapies. Additionally, better understanding of specific factors that affect the individual patient as TP53 and other molecular disruptions. Importantly, our work and others emphasize that CAR T-cell efficacy improves when used earlier in the course of the disease. Further work should be done on the effect of combining BTKi and other novel agents. Novel approaches with small cohorts are ongoing, some of which show promising short-term results, including CIT combined with targeted agents, non-covalent BTKi, checkpoint inhibitors, antibody-drug conjugates and bi-specific antibodies.[44-49] Until more mature results and clinical evidence of these trials will be available, our data suggest that CAR T-cell therapy is valid therapeutic option for patients with RT. As CR in RT is essential but not sufficient for long term remission, even at the era of appealing new biologic agents efforts should be made to consolidate response with allo-HCT when feasible. Moreover, it is im-

perative to design unique clinical trials aimed at treating this patient population.

In conclusion, we observed objective responses to CAR T-cell therapy in more than half of patients with RT, higher than reported in previous CIT trials. Despite favorable initial responses in some, most patients with RT had early progression of disease. This suggests a potential window of opportunity to consider consolidative allo-HCT, though this strategy remains an open question. Earlier referral to specialized centers and rapid availability of CAR T cells are key factors in allowing for these treatment possibilities. Interestingly, the efficacy of CAR T-cell therapy in RT patients is not dependent of age, and it significantly decreases when given after multiple lines of therapy, suggesting that it should be considered earlier in these patients. Moreover, we await the results of prospective studies to further clarify the role of CD19 CAR T-cell therapy in this historically difficult-to-treat population.

Disclosures

OB served as a paid consultant for Abbvie, Janssen, Lilly and AstraZeneca. TZ has received honoraria from AbbVie, Orgenesis Inc, BioSight Ltd, Cellect Biotechnology, Janssen, Novartis and Gilead Sciences for participating in an advisory board or speaker's bureau. MS served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation; received research funding from Angiocrine Bioscience, Inc., Omeros Corporation, and Amgen, Inc.; served on ad hoc advisory boards for Kite - a Gilead Company; and received honoraria from i3Health, Medscape, and CancerNetwork for CME-related activity. AI served as a paid consultant for Seagen, AstraZeneca, served on ad hoc advisory boards for Kite - a Gilead Company, SecuraBio, and TG Therapeutics; received honoraria from Pfizer, Physicians' Education Resource for CME-related activity, and from Genmab; has stock/equity in COTA, Inc. MAP reports honoraria from Adicet, Allogene, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, ImmPACT Bio, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Sanofi, Syncopation, VectivBio AG, and Vor Biopharma; serves on DSMB for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of NexImmune; has ownership interests in NexImmune, Omeros and OrcaBio; has received institutional research support for clinical trials from Allogene, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

Contributions

OB designed, contributed patient's data and wrote the manuscript. SF and RS designed, organized and drafted and revised the manuscript. MS AA contributed to study design, contributed patient's data and revised the manuscript. JF and SMD performed all statistical analysis. OBK, LAL, TZ, RY, NST, HS, RM, PBD, EJ, GLS, CSS, AI, MAP, AN and AS contributed patient's data. All authors reviewed the final version of the manuscript and provided critical feedback.

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Data-sharing statement

Research datasets for the present study are available from the corresponding author upon reasonable request.

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