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RESEARCH LETTER

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TO THE EDITOR:

Real-world evidence of brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma

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Brexucabtagene autoleucel (brexu-cel) is a second-generation CD19-targeted chimeric antigen receptor (CAR) T-cell therapy approved for relapsed or refractory (R/R) mantle cell lymphoma (MCL) based on the results of the ZUMA-2 study.[1] This phase 2 trial enrolled 74 patients and infused 68 patients, with an overall response rate (ORR) of 85% (complete response [CR], 59%) among all patients who underwent apheresis. Grade ≥3 cytokine release syndrome (CRS) and neurologic events (NEs) occurred in 15% and 31% of patients, respectively. However, there are very limited published data regarding safety and efficacy outside the context of the ZUMA-2 trial.[2] In our study, we report the results of patients with R/R MCL treated with brexu-cel in the European Early Access Program.

All consecutive patients with R/R MCL who underwent apheresis for brexu-cel at 11 European sites in Spain, Italy, Germany, and the Netherlands, from start of the European Early Access Program (February 2020) until August 2021, were included in the study. Ethical approval was granted by the Vall d'Hebron Hospital Ethical Committee, and the study was identified with code EOM(AG)041/2021(5851). The study was performed in accordance with the Declaration of Helsinki. After ethics committee approval, data were collected retrospectively in an electronic database. Efficacy outcomes were calculated in patients who received brexu-cel and in all patients who underwent apheresis (intention-to-treat). Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method and reported along with the associated 95% confidence interval (95% CI). Adverse events after infusion were graded according to the American Society for Transplantation and Cellular Therapy consensus,[3] and efficacy outcomes were assessed with Lugano criteria.[4]

During the study period, 39 patients with R/R MCL underwent apheresis for brexu-cel. Three (8%) patients had an initial manufacturing failure, requiring a second (2) or third (1) apheresis to obtain an adequate product; 2 out of 3 patients were finally infused. Regarding all enrolled patients, 33 (85%) patients received an infusion, whereas 6 (15%) patients did not owing to progressive disease (PD; n = 3),

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Requests for data sharing may be submitted to Gloria Iacoboni (giacoboni@vhio.net).

The full-text version of this article contains a data supplement.

Table 1. Baseline characteristics of the infused patients in the present series and in the ZUMA-2 trial

	Infused (N=33)	ZUMA-2 (N=68)
Sex, n (%)		
Male	29 (88)	57 (84)
Female	4 (12)	11 (16)
Age, median y (range)	67 (47-79)	65 (38-79)
≥65	23 (70)	39 (57)
<65	10 (30)	29 (43)
Prior lines, median (range)	2 (1-8)	3 (1-5)
>2 prior lines	15 (45)	55 (81)
≤2 prior lines	18 (55)	13 (19)
Primary refractory,* n (%)		
Yes	7 (21)	†
No	26 (79)	
Previous auto-HCT, n (%)		
Yes	12 (36)	29 (43)
No	21 (64)	39 (57)
Previous allo-HCT, n (%)		
Yes	5 (15)	0 (0)
No	28 (85)	68 (100)
Best response to previous ibrutinib, n (%)		
CR	11 (34)	†
PR	10 (30)	
SD/PD	8 (24)	
Not available	4 (12)	
Prior bendamustine therapy, n (%)		
Yes	14 (42)	37 (54)
No	19 (58)	31 (46)
Prior rituximab maintenance, n (%)		
Yes	14 (42)	†
No	19 (58)	
Morphology, n (%)		
Classical	22 (67)	36 (53)
Blastoid/pleomorphic	9 (27)	21 (31)
Not available	2 (6)	11 (16)
TP53 status, n (%)		
Mutated	4 (12)	6 (9)
Unmutated	11 (33)	30 (44)
Not available	18 (55)	32 (47)
Ki67 index>30%, n (%)		
Yes	16 (49)	40 (59)
No	3 (9)	9 (13)
Not available	14 (42)	19 (28)
Stage, n (%)‡		
I-II	4 (12)	2 (15)
III-IV	29 (88)	58 (85)
s-MIPI, n (%)		
Low	8 (24)	28 (41)
Intermediate/high	23 (70)	38 (56)
Not available	2 (6)	2 (3)
Extranodal disease, n (%)‡		
Yes	26 (79)	37 (62)
No	7 (21)	23 (38)
Bone marrow infiltration, n (%)		
Yes	10 (30)	37 (54)
No	23 (70)	31 (46)
Peripheral blood involvement, n (%)		
Yes	6 (18)	†
No	27 (82)	
LDH, n (%)‡		
>ULN	14 (42)	23 (38)
≤ULN	19 (56)	35 (59)
Not available	0 (0)	2 (3)
ECOG, n (%)		
0	15 (45)	44 (65)
≥1	18 (55)	24 (35)

Allo-HCT, allogeneic hematopoietic cell transplantation; auto-HCT, autologous hematopoietic cell transplantation; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index; ULN, upper limit of normal.

*Information not available owing to different definitions or cutoffs between the ZUMA-2 trial and this study.

†Never achieving complete remission with any line of treatment.

‡Reported on the 60 patients of the primary efficacy analysis set.

achieving CR after bridging (n = 2) or infection (n = 1). Among infused patients, median age was 67 years (interquartile range [IQR], 62-72). Most patients had a high-risk simplified MCL International Prognostic Index (s-MIPI) score at apheresis (55%), advanced stage disease (88%), and 36% had received a prior autologous hematopoietic cell transplantation (HCT). Eight (24%) patients had a blastoid morphology, and 4 (12%) patients had *TP53* mutations. Full baseline characteristics (compared with patients included in the ZUMA-2 trial) are summarized in Table 1. Median follow-up after CAR T-cell infusion was 10.1 months (95% CI, 7.9-11.5).

Thirty-two patients (82%) received one (n = 26) or two (n = 6) bridging regimens after apheresis. The most common bridging therapy (BT) was chemotherapy (n = 14) followed by ibrutinib (n = 12) (supplemental Table 1). Best disease response after BT included PD in 18 (56%) patients, stable disease (SD) in 7 (22%) patients, partial response (PR) in 5 (16%) patients, and CR in 2 (6%) patients. Median time from apheresis to brexu-cel delivery and infusion was 29 days (IQR, 28-34) and 41 days (IQR, 35-49), respectively.

Among the 33 infused patients, 30 (91%) patients developed CRS, grade ≥2 in 18 (55%) patients and grade ≥3 in 1 (3%) patient.

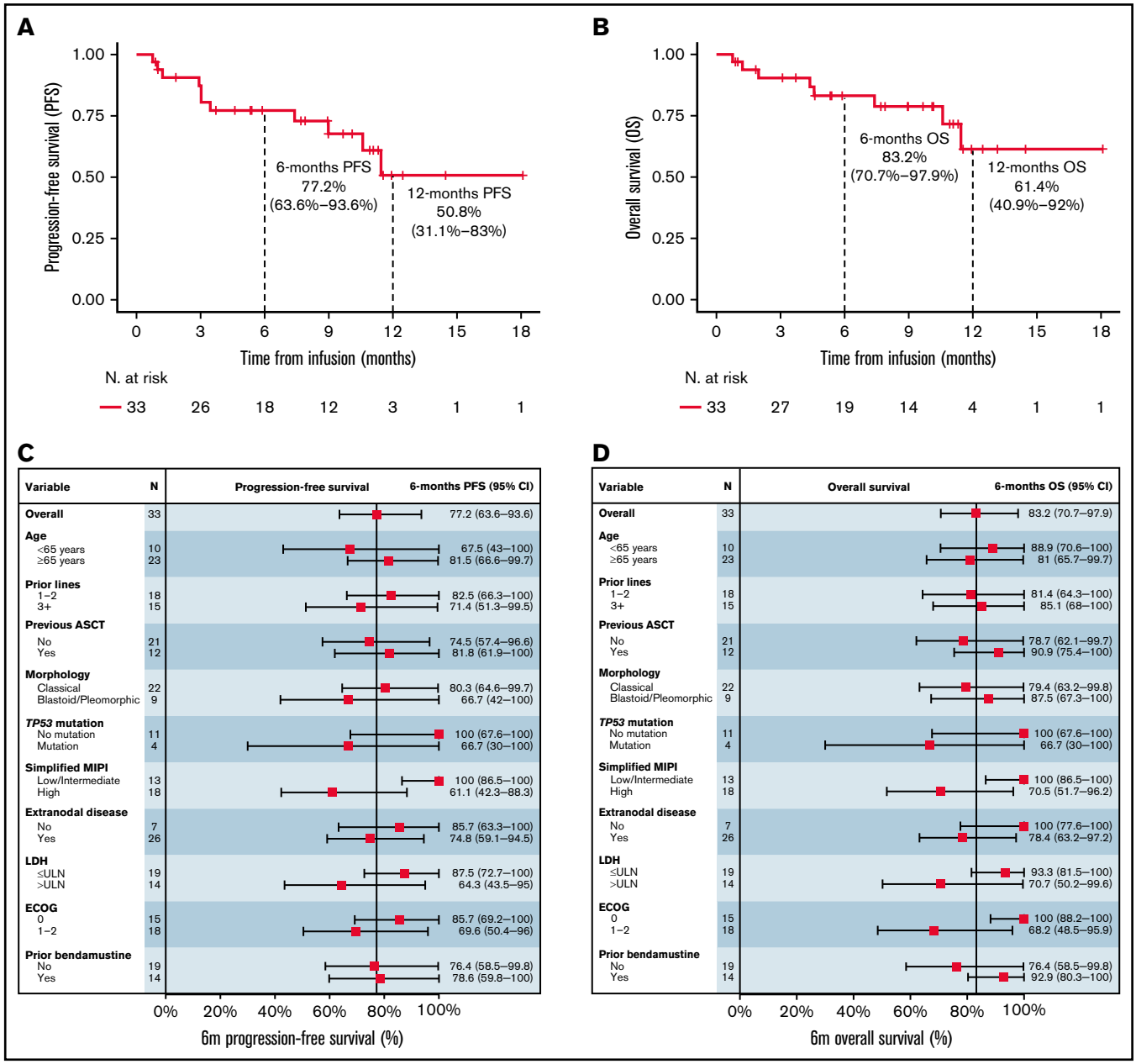

Figure 1. PFS and OS in patients with MCL treated with brexu-cel. PFS (A) and OS for infused patients (B). Forest plot of 6-month PFS (C) and 6-month OS (D) estimation along with 95% CI in key subgroups. ASCT, autologous stem cell transplant.

Median time from infusion to CRS onset and median duration of CRS were 5 days (IQR 2-6) and 4 days (IQR 3-6), respectively. Twenty-one (64%) patients developed NE, grade ≥2 in 16 (48%) patients and grade ≥3 in 12 (36%) patients. Median time from infusion to NE and median duration of neurological symptoms were 7 days (IQR, 5-9) and 8 days (IQR, 3-13), respectively. Tocilizumab and steroids were administered to 28 (85%) and 21 (64%) patients, respectively. There were no reported cases of tumor lysis syndrome. At 1-month post-infusion, 16 (50%) patients had grade ≥3 thrombocytopenia and 15 (47%) patients had grade ≥3 neutropenia (supplemental Figure 1). Nine (27%) patients were admitted to the intensive care unit (ICU) for CRS (3 patients), NE (3 patients), sepsis (2 patients), and pneumonia (1 patient). The median duration of ICU stay was 5 days (IQR, 3-6). Five patients (15%) died of treatment-related complications: 4 patients from infection (COVID-19, pneumonia, sepsis, and aspergillosis) and 1 patient from clinical deterioration in the context of prolonged steroid therapy. Four of these 5 patients had experienced previous grade 3-4 NE and were in CR at last evaluation (supplemental Tables 2 and 3).

Best response among infused patients included CR in 26 (79%) patients and PR in 4 (12%) patients (ORR = 91%). Median time to best response was 1-month post-infusion. SD and PD were the best response in 1 (3%) patient each. One (3%) patient died before the 1-month evaluation. Among patients achieving an initial PR (N = 6), 1 converted to CR at 3 months, 3 maintained a PR at last

follow-up (5, 9, and 14 months), and 2 progressed at the 3-month evaluation. Of the 2 patients in SD at 1 month, 1 patient converted to CR and the other maintained an SD at last follow-up (5 months).

The 6- and 12-month postinfusion PFS were 77% (95% CI, 64-94) and 51% (95% CI, 31-83), respectively (Figure 1A). The 6- and 12-month OS were 83% (95% CI, 71-98) and 61% (95% CI, 41-92), respectively (Figure 1B). Patients with low/intermediate s-MIPI had better PFS than those with high s-MIPI (HR: 0.1; 95% CI, 0.01-0.81). PFS and OS were consistent among other pretreatment variables, including previous bendamustine therapy (Figure 1C-D). In the intention-to-treat analysis (N = 39), ORR was 77% (CR = 64%). The 6-month PFS and OS from apheresis were 68% (95% CI, 55-85) and 76% (95% CI, 63-91), respectively (supplemental Figure 2).

In this European, multicenter study, we have shown that safety and efficacy of commercial brexu-cel are similar to the results obtained in the pivotal ZUMA-2 trial. To the best of our knowledge, this is the first paper focused on patients with MCL receiving this treatment outside of the clinical trial setting.

Considering patients' and disease characteristics, our study had a higher-risk population compared with the ZUMA-2 trial, including a higher s-MIPI score, worse Eastern Cooperative Oncology Group performance status, and previous allogeneic HCT (5 vs 0 patients). Also, the turnaround period from apheresis to CAR-T delivery was significantly longer than in the ZUMA-2 trial (29 vs 16 days; $P < .01$). Finally, BT was more frequently used in our study as opposed to the registration trial (82% vs 37%; $P < .01$), where only steroids or Bruton tyrosine kinase inhibitors were allowed.

When comparing the toxicity profile to the pivotal trial, grade ≥3 CRS was less frequent and had a delayed onset in our study, whereas the frequency and onset of grade ≥3 NE were similar (supplemental Table 4). In contrast to observations in other diseases,[5-8] the utilization of tocilizumab and dexamethasone was similar in our real-world data compared with the pivotal trial. Importantly, fatal events occurred more frequently in our study (15% vs 3%). This could be related to the selection bias of patients included in clinical trials and the longer turnaround time observed in the real-world setting, which may have led to an increased tumor burden and worse performance status at infusion. Of note, deaths were mainly attributed to infections in both studies.

Regarding efficacy, the CR and ORR were similar to the registration trial. However, 12-month PFS and OS were slightly lower in our study, probably influenced by the increased nonrelapse mortality. In our series, patients with low/intermediate s-MIPI score had longer PFS compared with high s-MIPI score. Bone marrow or peripheral blood involvement did not seem to have an impact on safety or efficacy, although the low number of events could limit this conclusion (details not shown). No other potential risk factors for PFS and OS were identified.

Our findings are limited by their retrospective nature, small sample size, and relatively short follow-up, although the latter was comparable to the ZUMA-2 trial (10.1 vs 12.3 months, respectively). However, our series of patients receiving commercial brexu-cel in 4 different countries, with a larger use of BT, might be more representative than the population included in the ZUMA-2 trial, providing additional insight to physicians facing these patients in the real-world setting.

In conclusion, brexu-cel is a very effective salvage regimen for MCL patients treated outside of clinical trials, including those with high-risk features. However, the occurrence of severe adverse events was significant and deserves further attention.

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