

## TO THE EDITOR:

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

Gloria Iacoboni,<sup>1,2</sup> Kai Rejeski,<sup>3</sup> Guillermo Villacampa,<sup>4-6</sup> Jaap A. van Doesum,<sup>7</sup> Annalisa Chiappella,<sup>8</sup> Francesca Bonifazi,<sup>9</sup> Lucia Lopez-Corral,<sup>10,11</sup> Michiel van Aalderen,<sup>12</sup> Mi Kwon,<sup>13,14</sup> Nuria Martínez-Cibrian,<sup>15</sup> Stefania Bramanti,<sup>16</sup> Juan Luis Reguera-Ortega,<sup>17</sup> Lina Camacho-Arteaga,<sup>18-20</sup> Christian Schmidt,<sup>3</sup> Ana Marin-Niebla,<sup>1,2</sup> Marie José Kersten,<sup>12</sup> Alejandro Martín García-Sancho,<sup>10</sup> Pier Luigi Zinzani,<sup>9,21</sup> Paolo Corradini,<sup>8</sup> Tom van Meerten,<sup>7</sup> Marion Subklewe,<sup>3</sup> and Pere Barba<sup>1,2</sup>

<sup>1</sup>Department of Hematology, Vall d'Hebron University Hospital, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; <sup>2</sup>Department of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain; <sup>3</sup>Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; <sup>4</sup>Oncology Data Science, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; <sup>5</sup>SOLTI Breast Cancer Research Group, Barcelona, Spain; <sup>6</sup>The Institute of Cancer Research, London, United Kingdom; <sup>7</sup>Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; <sup>8</sup>Division of Hematology and Stem Cell Transplantation, Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milano, Milano, Italy; <sup>9</sup>IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", Bologna, Italy; <sup>10</sup>Hematology Department, Hospital Clínico Universitario de Salamanca, IBSAL, CIBERONC, Salamanca, Spain; <sup>11</sup>Centro de Investigación del Cáncer-IBMCC, Salamanca, Spain; <sup>12</sup>Department of Hematology, Amsterdam University Medical Centers, Cancer Center Amsterdam, LYMMCARE (Lymphoma and Myeloma Center Amsterdam), Amsterdam, The Netherlands; <sup>13</sup>Department of Hematology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; <sup>14</sup>Gregorio Marañón Health Research Institute, Madrid, Spain; <sup>15</sup>Department of Hematology, Hospital Clinic, Barcelona, Spain; <sup>16</sup>Istituto Clinico Humanitas IRCCS, Rozzano, Italy; <sup>17</sup>Department of Hematology, University Hospital Virgen del Rocío, Sevilla, Spain; <sup>18</sup>Clinical Pharmacology Department, Vall d'Hebron University Hospital, Barcelona, Spain; <sup>19</sup>Clinical Pharmacology, Vall d'Hebron Institut de Recerca, Vall d'Hebron Hospital Universitari, Barcelona, Spain; <sup>20</sup>Department of Pharmacology, Therapeutics and Toxicology, Autonomous University of Barcelona, Barcelona, Spain; and <sup>21</sup>Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale Università di Bologna, Bologna, Italy

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.<sup>1</sup> 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  $\geq 3$  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.<sup>2</sup> 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,<sup>3</sup> and efficacy outcomes were assessed with Lugano criteria.<sup>4</sup>

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),

Submitted 28 December 2021; accepted 15 February 2022; prepublished online on *Blood Advances* First Edition 10 March 2022; final version published online 20 June 2022. DOI 10.1182/bloodadvances.2021006922.

Poster presentation at the 63rd annual meeting of the American Society of Hematology, 11-14 December 2021.

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

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

© 2022 by The American Society of Hematology. Licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), permitting only noncommercial, nonderivative use with attribution. All other rights reserved.

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

**Table 1. (continued)**

	Infused (N=33)	ZUMA-2 (N=68)
<b>s-MIPI, n (%)</b>		
Low	8 (24)	28 (41)
Intermediate/high	23 (70)	38 (56)
Not available	2 (6)	2 (3)
<b>Extranodal disease, n (%)‡</b>		
Yes	26 (79)	37 (62)
No	7 (21)	23 (38)
<b>Bone marrow infiltration, n (%)</b>		
Yes	10 (30)	37 (54)
No	23 (70)	31 (46)
<b>Peripheral blood involvement, n (%)</b>		
Yes	6 (18)	†
No	27 (82)	
<b>LDH, n (%)‡</b>		
>ULN	14 (42)	23 (38)
≤ULN	19 (56)	35 (59)
Not available	0 (0)	2 (3)
<b>ECOG, n (%)</b>		
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.

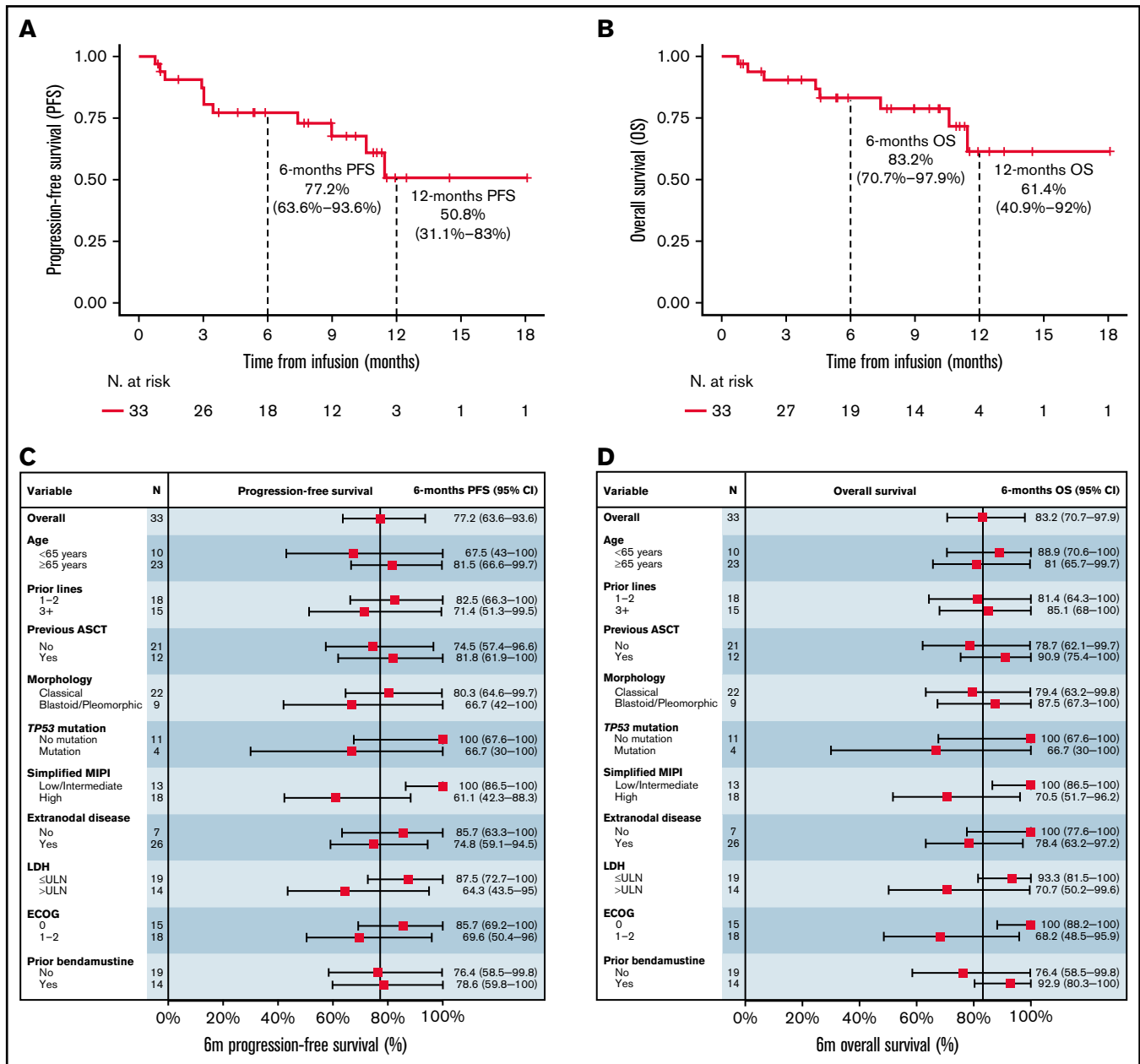
†Never achieving complete remission with any line of treatment.

‡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  $\geq 2$  in 16 (48%) patients and grade  $\geq 3$  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  $\geq 3$  thrombocytopenia and 15 (47%) patients had grade  $\geq 3$  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  $\geq 3$  CRS was less frequent and had a delayed onset in our study, whereas the frequency and onset of grade  $\geq 3$  NE were similar (supplemental Table 4). In contrast to observations in other diseases,<sup>5-8</sup> 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.

**Acknowledgments:** The authors thank the patients and their families for their participation in this study. They would also like to thank Ángel Cedillo from the Spanish Group of Stem Cell Transplantation and Cell Therapy group for the technical support provided with the electronic database.

**Contribution:** G.I. and P.B.: conceptualization, data curation, formal analysis, writing – original draft, review and editing; K.R., J.A.v.D., A.C., F.B., L.L.-C., M.v.A., M.K., N.M.-C., S.B., J.L., R.-O., L.C.-A., C.S., A.M.-N., M.J.K., A.M.G.-S., P.L.Z., P.C., T.v.M., and M.S.: data curation, writing – review and editing; G.V.: formal analysis, writing – review and editing; collection and assembly of data were performed by all authors; and all authors contributed to manuscript writing and final approval of the manuscript and are accountable for all aspects of the work.

**Conflict-of-interest disclosure:** G.I. declares having received honoraria from BMS/Celgene, Gilead, Novartis, Janssen, and Roche. K.R. declares having received research funding and travel support from Kite/Gilead and honoraria from Novartis. G.V. reported receiving honoraria for speaker activities from Merck Sharp & Dohme and served in an advisory role for Astrazeneca. A.C. declares having participated in advisory boards for BMS, Clinigen/SecuraBIO, Gilead-Sciences, Janssen, Roche, and Takeda; receiving honoraria for lectures from Astrazeneca, BMS, Clinigen/SecuraBIO, Gilead-Sciences, Incyte, Janssen, Novartis, Roche, and Takeda. F.B. declares having received honoraria from Jazz Pharmaceuticals, NEOVII Biothec, MSD, Novartis, Pfizer, Amgen, and Celgene. C.S. declares having received travel support from Kite/Gilead. M.J.K. reports honoraria from Kite, Novartis, Miltenyi Biotech, Roche, and Bristol Myers Squibb/Celgene; serves in a consultancy or advisory role for Kite, Roche, Bristol Myers Squibb/Celgene, Novartis, and Miltenyi Biotech; received research funding from Kite, Roche, Takeda, and Celgene; and travel support from Kite, Roche, Novartis, and Miltenyi Biotech. A.M.G.-S. declares having received honoraria from Roche, BMS/Celgene, Janssen, Servier, Gilead, Takeda, Eusa Pharma, and Novartis; consulting fees from Roche, BMS/Celgene, Kyowa Kirin, Clinigen, Eusa Pharma, Novartis, Gilead, Servier, and Incyte; and research funding from Janssen. P.B. declares having received honoraria from Amgen, Celgene, Gilead, Incyte, Jazz Pharmaceuticals, MSD, Novartis, Pfizer, and Roche; funding from the Carlos III FIS16/01433 Health Institute, Asociación Española Contra el Cáncer (Ideas Semilla 2019) and a PERIS 2018-2020 grant from the Generalitat de Catalunya (BDNS357800). None of the mentioned conflicts of interest were related to financing of the content of this manuscript. The remaining authors declare no competing financial interests.

**ORCID profiles:** G.I., 0000-0003-0805-9288; G.V., 0000-0003-4868-6585; J.A.v.D., 0000-0003-0214-3219; A.C., 0000-0002-2977-0098; L.L.-C., 0000-0003-1908-5596; L.C.-A., 0000-0001-9609-0394; A.M.G.-S., 0000-0001-6330-1028; P.L.Z., 0000-0002-2112-2651; M.S., 0000-0003-3905-0251.

**Correspondence:** Gloria Iacoboni, Department of Hematology, Hospital Universitari Vall d'Hebron, Passeig Vall Hebron 119, 08035 Barcelona, Spain; e-mail: giacoboni@vhio.net.

## References

1. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020; 382(14):1331-1342.
2. Khurana A, Dalland JC, Young JR, Inwards DJ, Paludo J. Brexucabtagene autoleucel therapy induces complete remission in a primary refractory blastoid mantle cell lymphoma with neurolymphomatosis. *Am J Hematol*. 2021;96(8):E298-E301.
3. Lee DW, Santomaso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.
4. Cheson BD, Fisher RI, Barrington SF, et al; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014; 32(27):3059-3068.
5. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020; 38(27):3119-3128.
6. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. *J Clin Oncol*. 2020;38(27):3095-3106.
7. Pasquini MC, Hu ZH, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma [published correction appears in *Blood Adv*. 2021;4(4):1136]. *Blood Adv*. 2020;4(21):5414-5424.
8. Iacoboni G, Villacampa G, Martinez-Cibrian N, et al; GETH, GELTAMO Spanish Groups. Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. *Cancer Med*. 2021;10(10):3214-3223.