Brexucabtagene autoleucel in relapsed or refractory mantle cell lymphoma, intention-to-treat use in the DESCAR-T registry

Patients with mantle cell lymphoma (MCL) who discontinue the Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib because of progressive disease or intolerance, have a reported median overall survival (OS) of 2.5 to 14.2 months.[1-3] ZUMA-2 is the pivotal trial of autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy brexucabtagene autoleucel (brexu-cel or KTE-X19) in patients with heavily pretreated MCL that were refractory to or relapsing (R/R) after prior therapies, including a BTKi (ibrutinib or acalabrutinib). The primary efficacy analysis demonstrated a 93% overall response rate (ORR) by an independent radiologic review committee, including a 67% complete response (CR) rate.[4] In a standard-of-care setting, the response rates were consistent with those reported in the ZUMA-2 trial, but the duration of response (DOR) seemed shorter.[5-8] Of note, these results were reported with an analysis starting at the time of leukapheresis. Based on these results, the French health agency granted access to brexu-cel in its early access program[9] for patients with R/R MCL who failed after at least one line of chemoimmunotherapy and BTKi. The aim of the present study was to report the first intention-to-treat (ITT) results of brexu-cel use in R/R MCL from CAR T-cell therapy decision.

All patients in France with MCL for whom treatment with brexu-cel was decided during the tumor board review (TBR) in the setting of the European Medicines Agency approval label (that is, who failed after at least 1 line of chemoimmunotherapy and 1 BTKi) were included in the DESCAR-T registry. As previously described,[10] the protocol (*clinicaltrials gov. Identifier: NCT04328298*) was approved by national ethics committees and the Data Protection Authority, and the study was undertaken in accordance with the Declaration of Helsinki. The first patient was enrolled in December 20, 2019,[9] and data export from the DESCAR-T registry was set on September 1, 2023. ITT analyses were performed on all patients for whom a treatment with brexu-cel was decided during TBR, except those who had an ongoing manufacture at date of last cutoff (N=3). Survivals were defined from CAR T decision at TBR (ITT) or from the date of CAR T-cell infusion (modified ITT = mITT). The "treated set" was defined as the patients who received brexu-cel infusion, and the "untreated set" as patients who did not receive it. Response was assessed according to the Lugano 2014 criteria, based on ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET).[11] Cytokine release syndrome (CNS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the consensus criteria from the American Society for Transplantation and Cellular Therapy (ASTCT).[12] The blood expansion of CAR T cells was monitored using multiparametric flow cytometry (MFC) on EDTA-anticoagulated fresh blood samples obtained from 21 patients at different time points following CAR T-cell infusion. Statistical analyses were performed using SAS software version 9.3.

Table 1. Main baseline characteristics of patients. The "untreated" and "treated" sets are presented separately.

Characteristics, N (%)	Treated set N=152	Untreated set N=26
Sex: male	131 (86.2)	18 (69.2)
Age in years, median (min-max)	68.0 (39-83)	66.5 (47-77)
Age ≥65 years	99 (65.1)	16 (61.5)
Age >75 years	19 (12.5)	3 (11.5)
ECOG performance status		
0-1	125 (88.0)	14 (60.9)
>=2	17 (12.0)	9 (39.1)
Missing	10	3
MIPI risk group		
Low risk: <5.7	27 (19.9)	3 (15.0)
Intermediate risk: 5.7- 6.2	54 (39.7)	5 (25.0)
High risk: ≥6.2	55 (40.4)	12 (60.0)
Missing	16	6
Ki-67 ≥ 30%		
<30%	22 (20.6)	3 (21.4)
≥30%	85 (79.4)	11 (78.6)
Missing	45	12
TP53 mutation		
Yes	29 (30.2)	6 (42.9)
No	67 (69.8)	8 (57.1)
Missing	56	12
Blastoid variant		
Yes	41 (31.1)	3 (16.7)
No	91 (68.9)	15 (83.3)
Missing	20	8
Prior lines of therapy, median (min-max)	3.0 (1-9)	3.0 (2-9)
Prior transplant		
Autograft	60 (39.5)	9 (34.6)
Allograft	9 (5.9)	0 (0)
Bridging therapy	126 (82.9)	15 (57.7)

Age, Eastern Cooperative Oncology Group (ECOG), Mantle Cell Lymphoma International Prognostic Index (MIPI), Ki-67, *TP53* mutation and blastoid morphology are given at the time of inclusion (local panel decision of brexu-cel treatment).

A total of 181 patients from 24 French centers were registered, 71.8% of whom did not meet the ZUMA-2 eligibility criteria. The most common reasons for ineligibility included necessity of a bridge other than corticosteroids or BTKi (61.1%), performance status [PS] ≥2 (12%), and prior malignancy (8.3%). Three patients were excluded because of an ongoing manufacture at date of last cutoff, therefore, the "treated set" and the "untreated set" included 152 and 26 patients respectively (Figure 1A). Detailed patient characteristics for both sets are presented in Table 1. Among the 152 patients of the "treated set", five did not receive a BTKi before CAR T therapy and two did not receive chemotherapy. The main reasons for patients not receiving brexu-cel were disease progression (N=15, including 7 patients who died before administration) and manufacturing failure (N=5). Of the 152 treated patients, three needed a second attempt at lymphocyte collection. They were not included in the manufacturing failure population. In ITT (N=178), with a median follow-up of 14.2 months, the median OS was of 19.8 months (Figure 1B). As expected, the OS of the "untreated set" was poor with a median of 1.8 months, compared with the median OS of the "treated" patients

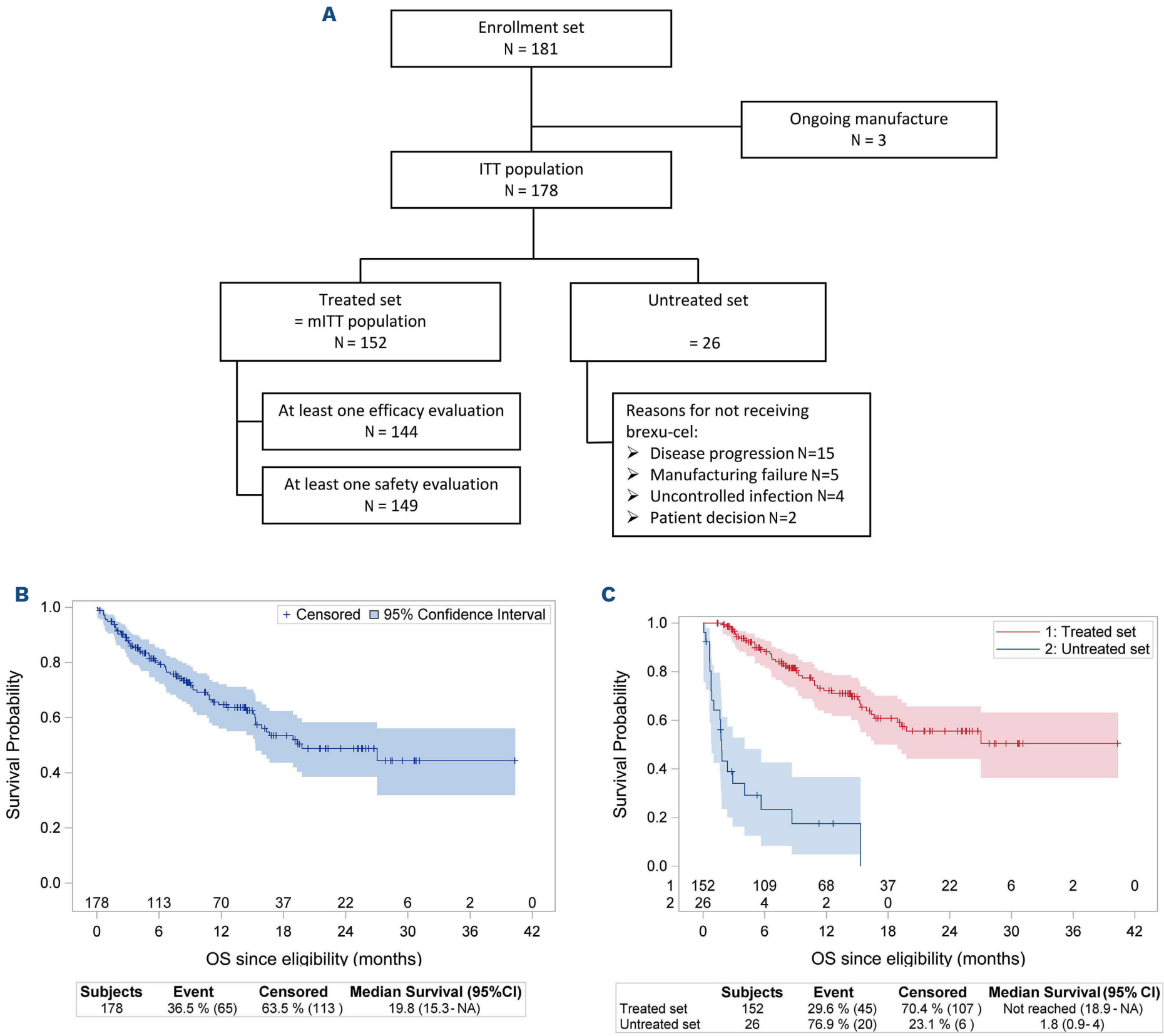
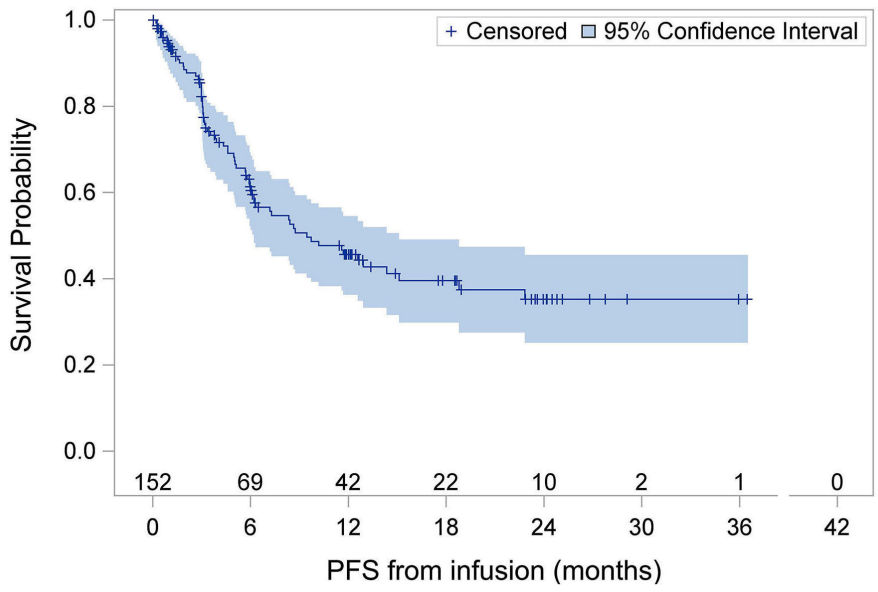


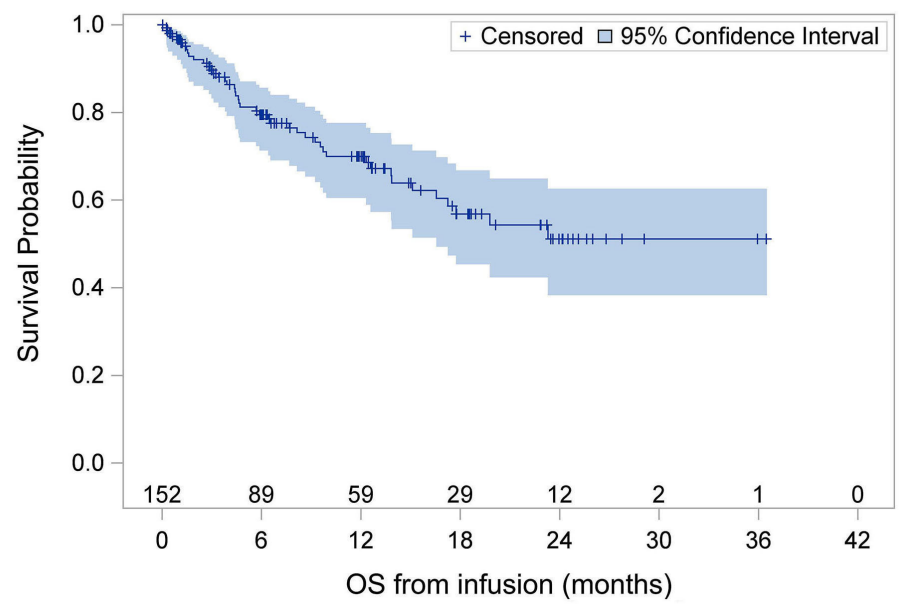
Figure 1. Characteristics of the intention-to-treat population. (A) Description of the different sets of patients. (B) Overall survival (OS) since inclusion in the DESCAR-T intention-to-treat (ITT) cohort. (C) OS since inclusion in the DESCAR-T cohort according to treatment set. CI: confidence interval; NA: not available.

A



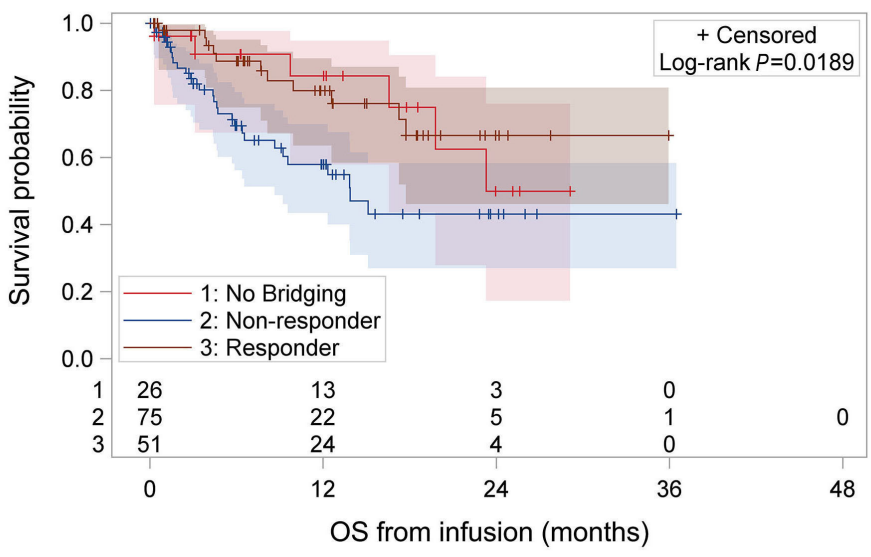
Subjects	Event	Censored	Median Survival (95%CI)
152	46.7 % (71)	53.3 % (81)	9.5 (6.2-15.1)

B



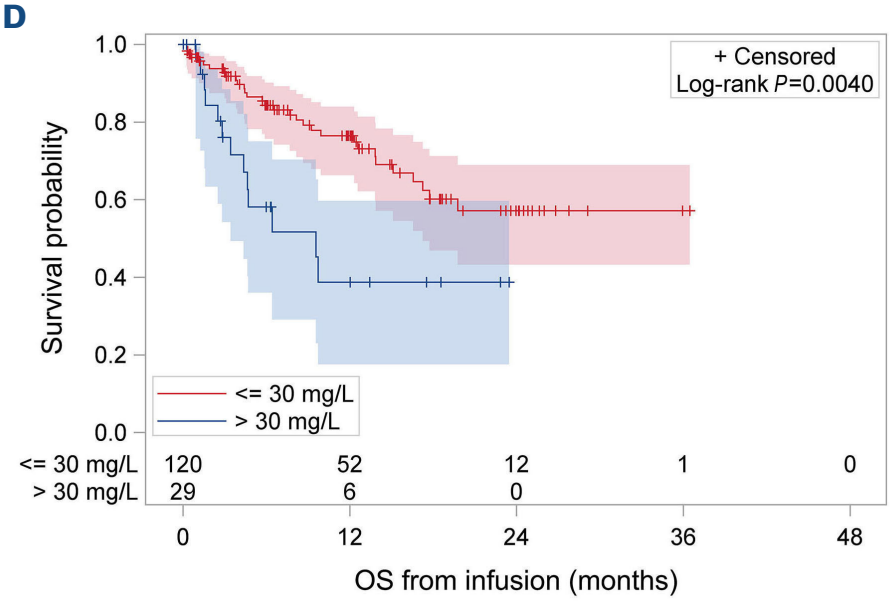
Subjects	Event	Censored	Median Survival (95%CI)
152	29.6 % (45)	70.4 % (107)	Not reached (16.6-NA)

C



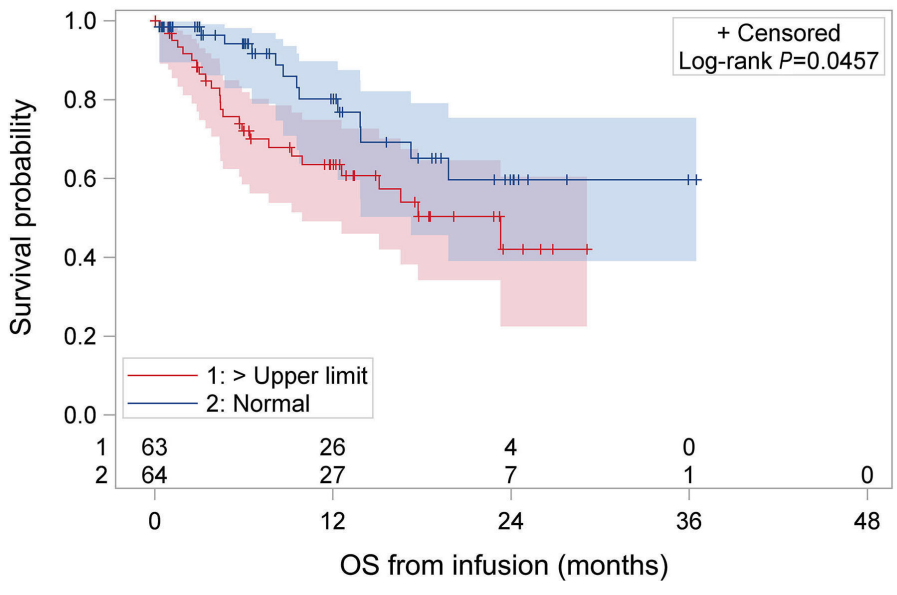
	Subjects	Event	Censored	Median survival (95% CI)
No Bridging	26	23.1 % (6)	76.9 % (20)	23.3 (16.6-NA)
Non-responder	75	37.3 % (28)	62.7 % (47)	13.9 (8.6-NA)
Responder	51	21.6 % (11)	78.4 % (40)	Not reached (17.7-NA)

D



	Subjects	Event	Censored	Median survival (95% CI)
<= 30 mg/L	120	25.8 % (31)	74.2 % (89)	Not reached (17.2-NA)
> 30 mg/L	29	44.8 % (13)	55.2 % (16)	9.6 (3.4-NA)

E



	Subjects	Event	Censored	Median survival (95% CI)
> Upper limit	63	39.7 % (25)	60.3 % (38)	23.3 (9.9-NA)
Normal	64	20.3 % (13)	79.7 % (51)	Not reached (17.2-NA)

Figure 2. Efficacy description of all patients who received brexucel. (A and B) Outcome of patients in the treated set, progression-free survival (PFS) and overall survival (OS), respectively. (C) OS according to response after bridging strategy, responders are defined as patients achieving partial or complete response. (D) OS according to C-reactive protein (CRP) level the day of brexu-cel infusion. (E) OS according to ferritin level the day of brexu-cel infusion. CI: confidence interval; NA: not available.

that was not reached (55.6% at 24 months; Figure 1C). The median time between inclusion and leukapheresis was 20 days (interquartile range [IQR], 11-31), and the median time between apheresis and infusion was 39 days (IQR, 33-53). In the "treated set", a total of 125 (82.2%) patients received bridging therapy, 61.1% of which included chemotherapy. Holding (treatment before leukapheresis) and bridging strategy, response and timing are detailed in the *Online Supplementary Appendix*.

The median follow-up since first CAR T-cell administration (mITT) was 12.2 months (95% confidence interval [CI]: 11.8-13.4). The best ORR for the 144 patients with at least one efficacy evaluation was 84.7%, including CR in 72.2%. Median PFS calculated from infusion was 9.5 months (95% CI: 6.2-15.1), with an estimated PFS of 61.3% at 6 months (95% CI: 52.2-69.3) and 45.6% at 12 months (95% CI: 36.2-54.5; Figure 2A). Median OS calculated from infusion was not reached (NR) (51.1% at 24 months; Figure 2B). Median duration of CR from infusion was 21.9 months (95% CI: 10.7-NR). In patients with at least one safety evaluation (N=149), CRS was observed in 87.9% and ICANS in 55%. CRS or ICANS of grade ≥3 were seen in 12.1% (N=18) and 15.4% (N=23) of patients, respectively. The median time to CRS onset was 5 days (range, 0-10), and the median duration of CRS was 6 days (range, 1-28). The median time to ICANS onset was 7 days (range, 1-16), and the median duration of ICANS was 7 days (range, 1-174). Drugs used to manage CRS and/or ICANS included tocilizumab (74.8%), corticosteroids (64.9%), anakinra (11.5%), and siltuximab (5.3%, always in association with tocilizumab). Persistent cytopenias of any grade were observed in 19.7% (N=24) of evaluable patients at month 3, with grade ≥3 neutropenia and thrombocytopenia in 13 and one patients respectively. Infections of grade ≥3 were seen from infusion to day 10 in 25.5% of patients (N=38) and were mostly bacterial (N=25, 16.8%). Overall, transfer to intensive care unit (ICU) was needed in 34.3% of patients (N=46), with a median duration of hospitalization of 6 days. The main reasons for admission were CRS (N=44: 26 cases of grade 2 and 18 cases of grade 3 or more) and/or ICANS (N=36: 13 cases of grade 2 and 23 cases of grade 3 or more). Except for the two grade 5 CRS, all patients successfully recovered from their ICU admission. Among the 152 patients infused, 46 died, with a non-relapse mortality of 11.2%. The first cause of death was progressive disease (N=29), followed by infectious events (N=11: 7 bacterial sepsis, 3 COVID and 1 cerebral toxoplasmosis) CRS (N=2), myelodysplastic syndrome (N=2) and two deaths of unknown cause. A total of nine infused patients received allogeneic stem cell transplant prior to inclusion in the present work, none of them developed graft-*versus*-host disease (GVHD).

We performed several preplanned exploratory analyses. The need of a bridging therapy and the response after it was significantly associated with OS from infusion. The OS rate at 12 months was 58% for patients who received a bridge and did not respond, *versus* 79.9% for patients who responded, and 84.3% for whom a bridge was not necessary (Figure 2C). At first infusion, C-reactive protein levels >30 mg/L and ferritin above the upper limit of normal (ULN) were significantly associated with shorter OS (P=0.004 and P=0.04, respectively; Figure 2D, E). We observed no difference in OS or PFS according to bridge timing, age or lactate dehydrogenase levels at infusion. Cellular kinetics parameters were measured in 21 patients, including area under the curve (AUC), maximal expansion post infusion (C_{MAX}) and the time to maximal expansion (T_{MAX}). Regarding safety prediction, both C_{MAX} and AUC were significantly higher for patients experiencing CRS or ICANS of any grade (*Online Supplementary Appendix*). Regarding efficacy prediction, with the *ad hoc* threshold of 60 cells/mL and/or 500 AU (arbitrary units) for C_{MAX} and AUC, respectively, both parameters were predictors of PFS. The difference was not significant for OS. Finally, T_{MAX} was not a discriminator in our study.

We acknowledge that our study has significant limitations, primarily retrospective data collection and substantial amount of missing data. However, this is the first ITT analysis from local panel decision (TBR) of brexu-cel use, in R/R MCL standard of care practice. The main reasons for not receiving brexu-cel were disease progression and manufacturing failure. The response rate of brexu-cel observed in our study (mITT) was consistent with those reported in the ZUMA-2 trial[4] or other standard-of-care studies.[5-8] However, the PFS seemed shorter and the rate of grade ≥3 ICANS seemed lower. In addition to more aggressive diseases and patients with more comorbidities, we can hypothesize that T-cell fitness could be lower in our study because of more heavily pretreated patients and a substantial number receiving holding therapy.[13,14] Overall, this "real-life" study experience supports the use of brexu-cel in R/R MCL patients who progressed after BTKi, especially when disease control before infusion is possible. We also demonstrate that *in vivo* CAR T-cell monitoring is feasible in the standard of care practice.

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Contributions

CH, RH and SLG contributed to the overall design and performed research. CH, CB and SLG analyzed the data and performed the statistical analyses. CB, AC, MR, JG and SCZ designed and performed *in vivo* CAR T monitoring. CH, EB, PB, CT, TG, TL, KB, DB, GC, JOB, DB, MTR, MM, FLB, OC, SG, CCL, OH, EG, SC and BG provided clinical care and collected data. All authors critically reviewed and approved the final version of the manuscript.

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Data-sharing statement

Data supporting the findings of this study are available from the corresponding author on request by email.

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