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Brexucabtagene autoleucel in-vivo expansion and BTKi refractoriness have a negative influence on progression-free survival in mantle cell lymphoma: Results from CART-SIE study

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Summary

Brexucabtagene autoleucel (brexu-cel) has revolutionized the treatment of patients affected by mantle cell lymphomas. In this prospective, observational multicentre study, we evaluated 106 patients, with longitudinal brexu-cel kinetics in peripheral blood monitored in 61 of them. Clinical outcomes and toxicities are consistent with previous real-world evidence studies. Notably, beyond established poor prognostic factors—such as blastoid variant and elevated lactate dehydrogenase—Bruton tyrosine-kinase inhibitors (BTKi) refractoriness and platelet count emerged as significant predictors of survival. Specifically, the 1-year overall survival was 56% in BTKi-refractory patients compared to 92% in BTKi-relapsed patients ($p = 0.0001$). Our study also demonstrated that in-vivo monitoring of brexu-cel expansion is feasible and correlates with progression-free survival and toxicities. Progression-free survival at 1 year was 74% in patients categorized as strong expanders, based on brexu-cel peak concentration, versus 54% in poor expanders ($p = 0.02$). Furthermore, in-vivo expansion helped identify a high-risk group of non-responders, those with progressive or stable disease at the 90-day post-infusion evaluation (OR = 4.7, 95% CI = 1.1–34, $p = 0.04$) characterized by dismal outcomes. When integrated with other clinical factors, monitoring brexu-cel expansion could assist in recognizing patients at high risk of early relapse.

KEYWORDS
brexu-cel, CAR T-cell, in vivo expansion, mantle cell lymphoma, real world

[Correction added on 14 February 2025, after first online publication: The subcategory has been changed.]

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INTRODUCTION

Patients affected by mantle cell lymphoma (MCL) relapsed or refractory to Bruton tyrosine kinase inhibitors (BTKi) have a poor prognosis, with a median overall survival (OS) of less than 1 year with previous salvage therapies and a clinical course characterized by continuous relapses over time.[1–3]

Brexucabtagene autoleucel (brexu-cel), an anti-CD19 CAR T-cell therapy, has been recently approved based on the results of the pivotal trial ZUMA-2.[4,5] In the ZUMA-2 trial, heavily pretreated patients with MCL achieved overall response (ORR) and complete response (CR) rates of 93% and 67% respectively.[4] The estimated 1-year progression-free survival (PFS) and OS rates were 61% and 83% respectively.[4]

Data from real-world evidence (RWE) not only confirmed the high response rates documented in the pivotal trial but also reported a shorter duration of response.[6–10] Additionally, results from both the clinical trial and real-world evidence have documented that the prognosis of patients who partially respond or do not respond to brexu-cel therapy is very poor, with a median OS of 16.3 and 8.5 months respectively.[5] Accurate prediction is crucial for developing early and effective consolidation strategies, which could potentially improve outcomes for these high-risk patients.

Among the previously reported real-world evidence, both the French study[8] and the experience published by Hamilton et al.[10] included in-vivo expansion data. However, both studies had small sample sizes—21 patients in the French study and 25 MCL patients in the Stanford study—limiting the significance of the findings and leaving the clinical relevance of CAR T-cell expansion unclear to date.

The aim of this study is to present real-world data from a prospective multicentre cohort of patients treated with commercial brexu-cel and to assess the impact of in-vivo expansion on outcomes.

METHODS

The CART-SIE study is an ongoing multicentre prospective observational study enrolling patients eligible for CAR T-cell therapy (as defined by the Italian drug agency) in 22 Italian centres. Patients included in this analysis were treated in 20 of these 22 centres (in the remaining centres, no patients with MCL had been treated at the time of the data cut-off). It is important to note that brexu-cel is currently the only anti-CD19 CAR T-cell therapy approved in Italy for the treatment of MCL. Consequently, all patients in this study received brexu-cel.

There is no universal consensus on the time frame that must elapse from the start of BTKi therapy to when the response is lost in order to define a patient as refractory. Consistently with previous studies[11] and based on established data concerning the treatment of relapsed/refractory (R/R) MCL with BTKi, showing a median time to response of 2 months and a median duration of response of 17 months,[12] in our study, BTKi-refractory patients were defined as those whose disease either did not respond or progressed within 6 months of initiating BTKi therapy.

The study adhered to the Declaration of Helsinki and good clinical practice guidelines, obtaining ethical approval from institutional review boards at each site (ClinicalTrials.gov ID: NCT06339255). All patients gave informed consent.

Response was assessed according to the Lugano criteria.[13] Cytokine release syndrome (CRS) and neurotoxicity were graded according to the American Society for Transplantation and Cellular Therapy consensus.[14] Haematological toxicity was defined and graded based on the consensus outlined by the European Hematology Association and the European Society for Blood and Marrow Transplantation,[15] specifically, late and severe immune effector cell-associated haematotoxicity (ICAHT) is defined as persistent neutropenia (at least two consecutive measurements), severe (ANC ≤500/μL) and late (occurring more than 30 days after CAR T-cell infusion). CAR-HEMATOTOX was calculated according to Rejeski et al.[16]

PFS, OS and duration of response (DoR) curves were estimated using the Kaplan–Meier method. The median follow-up was calculated using the reverse censoring methodology. Between-group comparisons of Kaplan–Meier curves were carried out using the log-rank test. Cox models were used for survival outcomes, and logistic models were applied for binary outcomes.

CAR T cells were longitudinally monitored in peripheral blood (PB) through multiparameter flow cytometry (MFC) using the CD19 CAR detection reagent (Miltenyi), as previously described[17] or the CD19 CAR FMC63 Idiotype (REA1297) (Miltenyi).

RESULTS

Since 2019 to July 2024, a total of 1002 non-Hodgkin lymphoma patients were enrolled in the CART-SIE study, of whom 106 were affected by MCL. The median age of the MCL population was 63 years (42–79), 70% of patients had advanced-stage classical MCL and the entire population had been exposed to BTKi, with 35% of the population being refractory (Table 1). Bridging therapy was administered to 79% (83) of patients: 45% (37/83) continued ongoing BTKi therapy, 13% (11/83) received bendamustine-containing regimens, 13% (11/83) were treated off-label with venetoclax-containing regimens, and the remaining patients received immunochemotherapy (18%, 15/83), lenalidomide (6%, 5/83) or local radiotherapy (5%, 4/83) (Table S1).

Efficacy and outcomes

The best ORR and CR rate were 88% and 75%, respectively, while the ORR at 90 days was 77%, with a CR rate of 70%. In the univariate analysis, among baseline clinical factors, only the presence of bulky disease was significantly associated with a lower rate of complete responses (OR = 0.17,

TABLE 1 Patients' characteristics.

	Global population *N* = 106pts	In-vivo expansion *N* = 61 pts	
		Strong expander[a] *N* = 28pts	Poor expander[a] *N* = 33pts
Sex (female)	22 (21%)	3 (11%)	5 (15%)
Age (median)	63 (42–79)	60 (44–74)	65 (42–79)
Histology			
Classic MCL	74 (70%)	24 (86%)	23 (70%)
Blastoid MCL	20 (19%)	1 (4%)	5 (15%)
Pleomorphic MCL	12 (11%)	3 (11%)	5 (15%)
Refractory disease	56 (53%)	15 (45%)	17 (63%)
Previous BTKi	106 (100%)	28 (100%)	33 (100%)
BTKi relapsed	54 (65%)[b]	13 (68%)[b]	16 (62%)[b]
BTKi refractory	29 (35%)[b]	6 (32%)[b]	10 (38%)[b]
Missing data on refractoriness	23 (22%)	7 (25%)	9 (27%)
Previous ASCT	61 (58%)	16 (57%)	16 (48%)
Previous lines (median)	3 (2–5)	3 (2–5)	3 (2–5)
Stage (advanced = Ann Arbor III–IV)	96 (92%)	26 (93%)	29 (91%)
Extranodal disease	55 (52%)	16 (57%)	18 (58%)
Bone marrow involved	62 (59%)	18 (64%)	15 (48%)
Bulky disease	21 (20%)	6 (21%)	11 (33%)
LDH baseline > ULN	25 (25%)[b]	19 (76%)	23 (72%)
Missing	6 (6%)	3 (11%)	1 (3%)
sMIPI			
Low	32 (35%)[b]	9 (45%)[b]	10 (32%)[b]
Intermediate	18 (20%)[b]	6 (30%)[b]	3 (10%)[b]
High	41 (45%)[b]	5 (25%)[b]	18 (58%)[b]
Missing	15 (14%)	8 (28%)	2 (6%)
POD24	45 (42%)	17 (65%)	19 (58%)
TP53 mutated	9 (29%)[b]	4 (36%)[b]	3 (33%)[b]
Missing	75 (71%)	17 (61%)	24 (73%)
Ki-67			
>30%	36 (54%)[b]	8 (42%)[b]	11 (44%)[b]
Missing	39 (37%)	9 (32%)	8 (24%)
Bridging therapy	83 (79%)	18 (67%)	29 (88%)
Bridging continuing BTKi	39 (37%)	11 (39%)	14 (42%)
Response to bridging: no response[c]	68 (72%)	20 (74%)	21 (68%)

Abbreviations: ASCT, autologous stem cell transplantation; BTKi, Bruton tyrosine kinase inhibitors; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; POD24, progression of disease within 24 months from the completion of treatment; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; ULN, upper limit of normal.

[a]Strong and poor expander defined according to C_{MAX} (132.9 CAR+/μL). See below.

[b]Calculated based on the population for which data are available.

[c]Defined as Progressive disease + Stable disease after bridging therapy.

95%CI = 0.05–0.53, $p = 0.002$). With a median follow-up of 12.1 months (IQR: 6, 18), the 1-year OS in the global population was 82% ($_{95\%}$CI = 74%–90%), while the 1-year PFS was 62% ($_{95\%}$CI = 52%–74%) (Figure 1A,B). The duration of response at 1 year was 70% ($_{95\%}$CI = 59%–84%).

Disease assessment at day 90 confirmed its relevance in prognostic stratification with a 1-year OS of 94% for patients in complete response compared to only 19% for those with PD ($p < 0.0001$, Figure S1).

Among baseline clinical factors, histological subtype, refractoriness to BTKi, pre-lymphodepletion lactate dehydrogenase (LDH) levels and pre-lymphodepletion platelet counts were shown to be associated with both PFS and OS. Patients with blastoid MCL demonstrated inferior PFS and OS

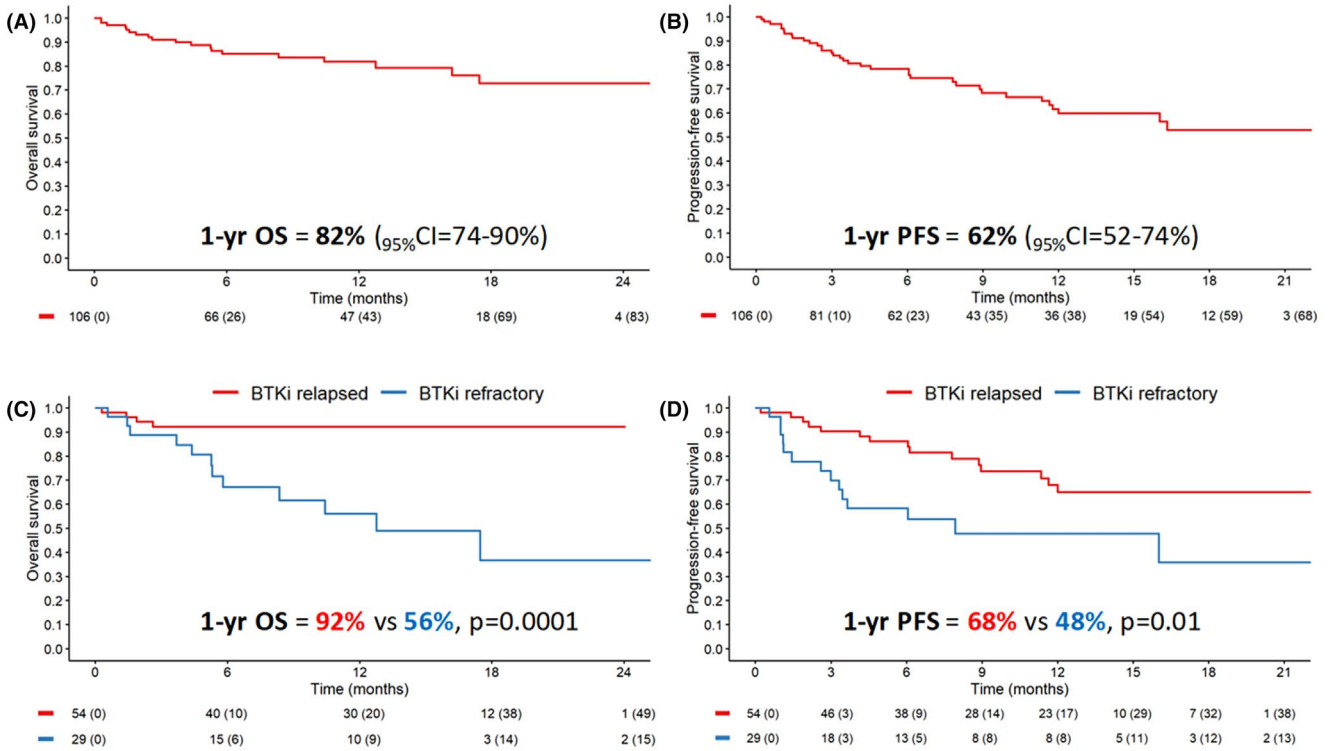

FIGURE 1 Overall and progression-free survival: Global (A and B) and according to BTKi refractoriness (C and D). [Colour figure can be viewed at wileyonlinelibrary.com]

compared to others (1-year OS 88% in classic vs. 78% in pleomorphic vs. 62% in blastoid, log-rank p-value = 0.01, 1-year PFS 69% in classic vs. 54% in pleomorphic vs. 39% in blastoid, log-rank p-value = 0.03). Similarly, survival was lower in patients refractory to prior BTKi therapy (1-year OS 92% in relapsed vs. 56% in refractory, $p = 0.0001$, 1-year PFS 68% in relapsed vs. 48% in refractory, $p = 0.01$, Figure 1C,D; Table S2), in those with high pre-lymphodepletion LDH levels (1-year OS 93% in LDH normal vs. 66% in LDH > ULN, $p = 0.0003$, 1-year PFS 75% in LDH normal vs. 39% in LDH > ULN, $p = 0.01$), and low pre-lymphodepletion platelet (PLT) counts (<75 000/μL) (1-year OS 86% in non-thrombocytopenic vs. 70% in thrombocytopenic, $p = 0.04$, 1-year PFS 67% in non-thrombocytopenic vs. 47% in thrombocytopenic, $p = 0.04$). The presence of bulky disease at baseline was significantly associated with shorter PFS, but not with OS (1-year PFS 38% in bulky vs. 67% in non-bulky, $p = 0.04$).

Toxicity

The incidence of CRS of any grade or grade≥3 was 95%/21% while the incidence of any grade or grade≥3 ICANS and 48%/18%. Platelets count >75.000/μL at the time of infusion was shown to be associated with lower rates of both grade≥3 CRS and ICANS (CRS G > 3: OR = 0.15, $_{95\%}$CI = 0.05–0.42, $p < 0.001$; ICANS: OR = 0.07, $_{95\%}$CI = 0–0.39, $p = 001$). Tocilizumab was required in 84% of all patients, 54% of patients received steroids and 18% were admitted to intensive care.

Regarding haematological toxicity, the cumulative incidence of late and severe immune effector cell–associated haematotoxicity (ICAHT) was 4.4%. The incidence of severe thrombocytopenia (PLT <50 000/μL) and severe anaemia (Hb <8 g/dL) was 18% and 1.1% respectively. The non-relapse mortality rate was 7.3% at 1 year (range 3.2%–14%), with two of seven deaths (29%) related to bacterial infections, 1 to G5 CRS, 1 to G5 ICANS, 1 to cerebrovascular event and 2 to multi-organ failure.

Among 106 patients, 3 (2.8%) were diagnosed with secondary primary malignancies (SPM) while in complete remission for MCL, namely myelodysplastic syndromes (MDS) in two patients and bladder cancer in one patient; of note, this patient already had a diagnosis of bladder cancer more than 10 years prior to CAR T infusion and thus cannot be attributed to CAR T activity. Both patients with MDS were male, aged 57 and 52 years, respectively, and heavily pretreated (n. of previous lines of therapy: 3 and 4 respectively), with the time from brexu-cel infusion to MDS diagnosis being 3.7 and 18.7 months respectively. Both patients underwent allogeneic transplant and are currently alive and in complete remission. *TP53* mutation and complex karyotype were observed in one of the two patients, consistent with a diagnosis of therapy-related neoplasm.

In-vivo expansion

In-vivo expansion data for brexu-cel were available for 61 of 106 patients (57%). Table 1 summarizes the characteristics

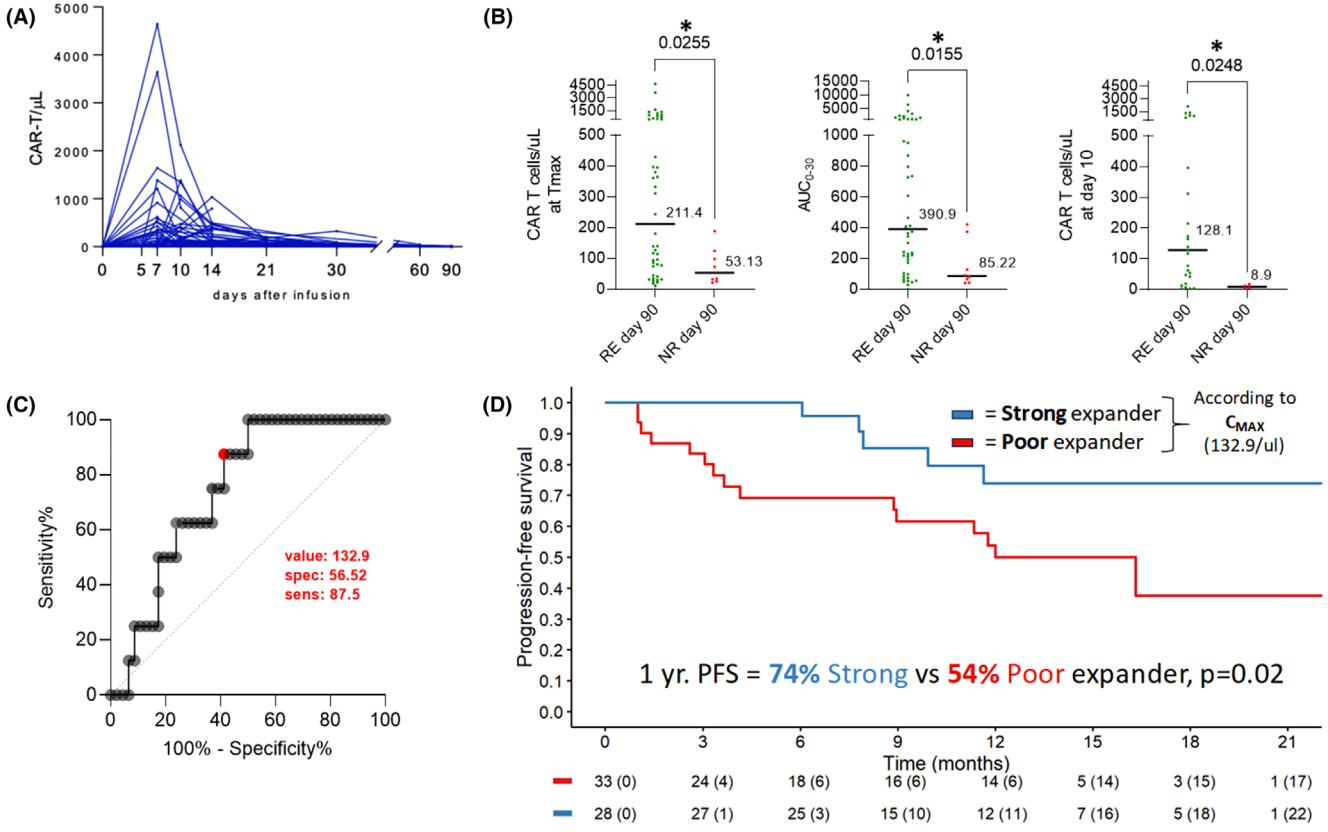

FIGURE 2 In-vivo brexu-cel expansion—(A) Expansion kinetics; (B) Day 90 response according to expansion; (C) ROC curve to identify a C_{MAX} cut-off with higher sensitivity (sens) and specificity (spec) in predicting day 90 response; (D) progression-free survival according to the C_{MAX} [Colour figure can be viewed at wileyonlinelibrary.com].

of the 106 total patients and the 61 with available in-vivo expansion data, showing no significant differences between the two groups. Table S3 details the efficacy in the entire cohort and in the subset for which in-vivo expansion data are available: no differences were observed between the two populations. The in-vivo expansion kinetics of brexu-cel are illustrated in Figure 2A, with a median peak CAR T-cell concentration (C_{MAX}) at the time of maximal expansion (T_{MAX}) of 117 CAR+/µL, a median concentration at day 10 (C_{10}) of 77.7 CAR+/µL and a median concentration at day 14 (C_{14}) of 76.3 CAR+/µL. The median area under the curve from day 0 to 30 ($AUC_{0\text{-}30}$) was 241.4 (range: 0–9923). Median $AUC_{0\text{-}30}$ and C_{14} were significantly higher in day 30 responders (Figure S2), whereas only C_{10}, C_{MAX} and $AUC_{0\text{-}30}$ but not circulating CAR T at day 7, 14, 21 and 30 were all associated with response at day 90 (Figure 2B; Figure S3). In particular, C_{10} was 128.1 CAR+/µL in day 90 responders (patients in CR or PR) versus 8.9 CAR+/µL in non-responders ($p = 0.03$), C_{MAX} was 211.4 CAR+/µL in responders versus 53.13 CAR+/µL in non-responders ($p = 0.03$), while $AUC_{0\text{-}30}$ was 390.9 in responders versus 85.22 in non-responders ($p = 0.02$).

Circulating CAR T cells were still detectable after the first month in a fraction of patients, although persistence is not associated with a better PFS (1-year PFS 80% for patients with ≥5 CAR T/µL at day 30 vs. 78% for patients with <5 CAR T/µL, Figure S4).

A multivariable logistic model, adjusted for bulky disease, confirmed the independent effect of in-vivo expansion on complete response rates (OR = 4.7, $_{95\%}$CI = 1.2–25, $p = 0.03$, Table S4). Using a receiver operating characteristic (ROC) curve, a cut-off value of 132.9 CAR+/µL at C_{MAX} was identified, optimizing sensitivity and specificity in predicting complete response rates at 90 days (sensitivity 87.5%, specificity 56.52%, Figure 2C). Patients classified as 'strong expanders', defined by a $C_{MAX} > 132.9$ CAR+/µL, demonstrated significantly better PFS than 'poor expanders' (1-year PFS: 74% in strong expanders vs. 54% in poor expanders, $p = 0.02$, Figure 2D). Consistently, 'poor expanders' showed a fourfold higher risk of being 'non-responders' at day 90 compared to 'strong expanders' (OR = 4.7, $_{95\%}$CI = 1.1–37, $p = 0.04$).

A multivariable Cox model for PFS was fitted, adjusting for BTKi refractoriness and PLT count before lymphodepletion, and confirmed the independent effect of in-vivo CAR T expansion (C_{MAX} strong expander: HR = 0.34, 95%CI = 0.1–1.0, $p = 0.04$). In-vivo expansion of CAR T cells was also associated with severe (G≥3) CRS (OR = 4.7, $_{95\%}$CI = 1.2–23, $p = 0.02$). However, no statistically significant differences in CAR-T cell expansion were observed in relation to ICANS and haematological toxicity (OR for ICANS in expander = 2.31, $_{95\%}$CI = 0.82–6.72, $p = 0.1$).

To investigate the relationship between in-vivo expansion and BTKi refractoriness in determining response, a bivariate logistic model was developed to evaluate complete response

at 90 days. This model suggests that BTKi refractoriness exerts a similar effect on response when adjusted for in-vivo expansion, as the odds ratio (OR) in the bivariate analysis (OR = 0.35 [95% CI = 0.1–1.6], $p = 0.2$) is comparable to that observed in the univariate analysis (OR = 0.5 [95% CI = 0.2–1.6], $p = 0.3$) (Tables S5 and S6).

Bridging therapy was the only clinical factor correlated with the in-vivo expansion of brexu-cel. Patients who received bridging therapy exhibited significantly lower CAR T-cell expansion compared to those who did not. Among patients classified as 'poor expanders' 90% had received bridging therapy, while only 10% had not (OR = 0.2, $_{95\%}$CI 0.04–0.8, $p = 0.02$). Multivariable logistic models confirmed the impact of bridging therapy on expansion, both in terms of C_{MAX} and $AUC_{0\text{-}30}$ (Table S7). However, focusing on the type of treatment used for bridging therapy, no statistically significant impact on expansion was observed for regimens containing BTK inhibitors, bendamustine or BCL-2 inhibitors (Table S8).

DISCUSSION

Our prospective, observational, multicentre study represents the largest cohort of patients treated with commercial brexu-cel, incorporating in-vivo monitoring of CAR T cells. Efficacy, outcomes and toxicities were comparable to those reported in previous RWE studies.[6–9]

In addition to the established clinical factors associated with survival of MCL patients receiving CAR T-cell therapy, such as the presence of the blastoid variant and elevated LDH levels, our study identified refractoriness to BTKi treatment and platelet count as significant prognostic factors.

The negative prognostic value of BTKi refractoriness in MCL is well established[1,18]; however for the first time, we demonstrate its negative impact in the context of CAR T-cell therapy. Patients with BTKi-refractory MCL pose a significant therapeutic challenge due to the aggressive nature of their disease. Therefore, future studies should focus on optimizing bridging therapy and exploring earlier intervention with CAR T-cell therapy for patients showing suboptimal responses to BTK inhibitors. This is particularly relevant given the results of the TRIANGLE study,[19] which will likely lead to the incorporation of BTK inhibitors starting from the first line of treatment.

The influence of platelet count on outcomes in anti-CD19 CAR T-cell treatment is well documented in patients with large B-cell lymphoma.[20] Our findings extend this knowledge to the context of brexu-cel treatment for MCL, where low platelet counts—reflecting compromised bone marrow reserve and endothelial activation—are associated with increased toxicity and reduced survival.

Regarding in-vivo expansion monitoring, our results corroborate the association between CAR T-cell expansion and PFS previously established by Herbaux et al.,[8] albeit in a three-time larger cohort. Furthermore, our study confirms the dismal outcome of patients who do not respond to brexu-cel treatment and, for the first time, demonstrates how in-vivo monitoring of CAR T cells can identify this ultra-high-risk population early on. Notably, the cut-off for CAR T-cell expansion associated with PFS differs significantly between our study and that of Herbaux et al. (C_{MAX}: 132.9 CAR+/μL in our cohort vs. 60 CAR+/μL in Herbaux et al). This discrepancy underscores the need to standardize techniques and harmonize results across studies to ensure that expansion data are incorporated in patient stratification. As for toxicity, our work is consistent with that of Hamilton et al.[10] correlating greater in-vivo expansion with a higher incidence of CRS.

Among the baseline characteristics, the administration of bridging therapy was significantly linked to a reduced expansion. However, the variety of treatments utilized as bridging therapy limits our ability to link reduced expansion to a specific strategy and suggests that further research is required to clarify this relationship. Given the impact of refractoriness to covalent BTKi on survival and the experimental data suggesting a beneficial effect of BTKi in terms of in-vivo CAR T-cell expansion,[21] the design of studies incorporating non-covalent BTK inhibitors, such as pirtobrutinib,[22] as a bridging strategy will be of particular interest.

Considering the continuous pattern of relapse, risk stratification will be crucial for allocating high-risk patients to consolidation strategies, such as allogeneic transplantation or other maintenance therapies. Bispecific antibody treatments may represent a therapeutic opportunity also in MCL, given the impressive results recently demonstrated with Glofitamab.[23]

In conclusion, (i) BTKi refractoriness emerges as a critical issue for patients treated with brexu-cel; (ii) the optimal strategy for bridging in MCL remains unclear; (iii) in-vivo monitoring of CAR T-cell expansion using multiparametric flow cytometry has proven feasible and, together with other clinical factor, could inform patient risk stratification.

AUTHOR CONTRIBUTIONS

Conception and design: Federico Stella, Annalisa Chiappella, Martina Magni, Cristiana Carniti, Paolo Corradini. Provision of study materials or patients: All authors; Collection and assembly of data: Federico Stella, Annalisa Chiappella, Martina Magni, Silva Ljevar, Cristiana Carniti, Paolo Corradini. Data analysis and interpretation: Federico Stella, Annalisa Chiappella, Silva Ljevar, Cristiana Carniti, Paolo Corradini. Funding acquisition: Paolo Corradini. Manuscript writing: All authors. Final approval of manuscript: All authors.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

For data sharing and any further information, please contact the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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