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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Brexucabtagene autoleucel for BTKi-naive relapsed/refractory mantle cell lymphoma: primary analysis of ZUMA-2 cohort 3

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KEY POINTS

- The primary end point was met, with brexu-cel demonstrating a 91% ORR (73% CR rate), per IRRC, in patients with R/R MCL who were BTKi-naive.
- The estimated 12-month PFS, duration of response, and OS rates were 75%, 80%, and 90%, respectively.

Brexucabtagene autoleucel (brexu-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for adults with relapsed/refractory (R/R) mantle cell lymphoma (MCL) based on the ZUMA-2 cohort 1 (ClinicalTrials.gov identifier: NCT02601313) study in which brexu-cel demonstrated a 93% objective response rate (ORR) and 67% complete response (CR) rate in patients with R/R MCL and previous BTKi therapy (N = 60). Here, we report the primary results of ZUMA-2 cohort 3 (brexu-cel in patients with BTKi-naive R/R MCL). Adults received brexu-cel at 2 × 10^6 anti-CD19 CAR T cells per kilogram. The primary end point was ORR assessed by independent radiology review committee (IRRC). As of 26 November 2023, 95 patients were enrolled, and 86 received brexu-cel; median follow-up was 15.5 months. The primary end point was met, with a 91% ORR (95% confidence interval [CI], 82.5-95.9; *P* < .0001; N = 86) and a CR rate of 73% (95% CI, 62.6-82.2). Estimated 12-month progression-free survival (PFS), duration of response, and overall survival (OS) rates were 75%, 80%, and 90%, respectively. Among 95 enrolled patients, the ORR was 82%, the CR rate was 66%, and the 12-month PFS and OS rates (95% CI) were 73% (62.1-80.8) and 85% (75.6-90.7), respectively. Most patients (88%) experienced treatment-related grade ≥3 adverse events, including 4 treatment-related grade 5 events. Consistent with cohort 1, brexu-cel demonstrated a high ORR and similar safety profile. These results support the continued use of brexu-cel in patients with R/R MCL, and consideration in some patients without previous BTKi therapy who have high-risk disease. This trial was registered at clinicaltrials.gov as #NCT04880434.

Introduction

Mantle cell lymphoma (MCL) is a subtype of B-cell non-Hodgkin lymphoma that typically relapses after initial treatment, with worsening outcomes after each relapse.[1,2] Bruton tyrosine kinase inhibitors (BTKi) have been a mainstay therapy for patients with relapsed/refractory (R/R) MCL for many years and have greatly improved patient outcomes.[3,4] Ibrutinib is a first-generation covalent BTKi approved in the European Union (EU) for the treatment of adults with R/R MCL whose disease

does not respond to treatment or has come back after previous treatment.[5] Zanubrutinib is a second-generation covalent BTKi approved in the United States for the treatment of adults with R/R MCL who have received at least 1 previous therapy.[6] Acalabrutinib is a second-generation covalent BTKi that is approved in the United States and the EU for the treatment of adults with R/R MCL who have received ≥1 previous therapy and was recently approved in combination with bendamustine and rituximab for the treatment of adults with previously untreated MCL who are ineligible for autologous stem cell transplantation.[7,8] Despite improvements to patient outcomes, most patients eventually experience disease progression on BTKi therapy and subsequently have poor outcomes with limited treatment options.[9] Additionally, with recent approvals, BTKi therapy will likely be incorporated into first-line treatment regimens; therefore, other, non–BTKi-dependent salvage treatment strategies for some patients with R/R MCL are needed to improve long-term outcomes.

In July 2020, brexucabtagene autoleucel (brexu-cel), an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, was approved in the United States for the treatment of adults with R/R MCL based on results of the pivotal ZUMA-2 cohort 1 study (ClinicalTrials.gov identifier: NCT02601313).[10,11] Brexu-cel is also approved in the EU (December 2020) for adults with R/R MCL after ≥2 lines of systemic therapy, including a BTKi.[12] In the primary analysis of ZUMA-2, brexu-cel demonstrated an objective response rate (ORR) of 93% and a complete response (CR) rate of 67% in patients with R/R MCL and previous BTKi therapy (N = 60).[10] After 35.6 months of median follow-up in ZUMA-2 cohort 1, brexu-cel demonstrated a median overall survival (OS) of 46.6 months among 68 patients with heavily pretreated R/R MCL, all of whom received previous BTKi therapy (ibrutinib, 52; acalabrutinib, 10; both, 6).[13] Additionally, results from early real-world studies indicate that brexu-cel is effective in broader patient populations with R/R MCL.[14-17]

Given the high response rates and long-term survival benefits observed with brexu-cel therapy in patients with heavily pretreated R/R MCL, and the unmet need for salvage strategies that can induce durable responses and improve survival beyond current BTKi strategies, we hypothesized that brexu-cel may be beneficial to patients in earlier lines of therapy. Here, we report the primary analysis of cohort 3 of the ZUMA-2 study designed to assess the efficacy and safety of brexu-cel in earlier lines of therapy for patients with R/R MCL who were naive to BTKi treatment.

Methods

Patients and trial design

ZUMA-2 cohort 3 is a single-arm, multicenter, phase 2 study that was conducted at 30 sites in North America and Europe (supplemental Methods, available on the *Blood* website). Eligible patients were aged ≥18 years with pathologically confirmed MCL with overexpression of cyclin D1 or presence of t(11;14) and had disease that was R/R to up to 5 previous therapies for MCL. Previous therapy must have included anthracycline-, bendamustine-, or high-dose cytarabine–containing chemotherapy and anti-CD20 monoclonal antibody therapy. Previous BTKi therapy was not allowed. Complete eligibility requirements are listed in the supplemental Methods.

Treatment

Patients underwent leukapheresis, followed by lymphodepleting chemotherapy on days −5, −4, and −3 (fludarabine 30 mg/m^2 per day and cyclophosphamide 500 mg/m^2 per day). One infusion of brexu-cel at a target dose of 2 × 10^6 CAR T cells per kilogram (with a maximum dose of 2 × 10^8 anti-CD19 CAR T cells for patients with a body weight of ≥100 kg) was given on day 0. Optional bridging therapy (dexamethasone, radiotherapy, protocol-specified chemotherapy [cytarabine or cyclophosphamide], or any combination thereof) was recommended per physician's discretion for all patients, especially those with rapidly progressing disease, clinical deterioration, or high disease burden at screening (>25% marrow involvement and/or ≥10^3 leukemic mantle cells per μL in the peripheral circulation). Hospitalization was required for at least 7 days after brexu-cel infusion. Patients who had a CR or partial response (PR) at the 3-month assessment and who progressed ≥3 months after the initial infusion were eligible for retreatment.

End points and assessments

A detailed description of disease assessment in ZUMA-2 has been reported previously.[10] The primary end point was ORR (CR or PR) per the Lugano Classification as determined by the independent radiology review committee (IRRC).[18] Positron emission tomography–computed tomography scan and bone marrow evaluation were necessary to confirm CR.

Secondary end points included duration of response (DOR), best overall response, investigator-assessed ORR (according to the criteria of Cheson et al),[18] progression-free survival (PFS), OS, incidence of adverse events (AEs), CAR T-cell levels in the blood, and cytokine levels in the serum. Biomarker analyses are detailed in the supplemental Methods.

Statistical analysis

The primary efficacy analysis was conducted after 86 patients were treated and assessed for 6 months after the first objective response. The target ORR per independent review was 75%, with a null hypothesis of ≤57% based on historical control. This study had a power of ≥90% to distinguish between an active therapy with a 75% true response rate and a therapy with a response rate of ≤57% with a 1-sided α level of 0.025. All efficacy and safety analyses were conducted in all treated patients. Time-to-event end points were analyzed with Kaplan-Meier estimates and 2-sided 95% confidence intervals (CI). Associations between outcomes and CAR T-cell expansion as well as with serum cytokine levels were measured with the use of the Wilcoxon rank-sum test for 2 independent samples and log-rank test for Kaplan-Meier plots. The *P* values and CI were not adjusted for multiple testing.

All patients gave written informed consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki. The trial protocol (available online) and statistical analysis plan were developed collaboratively by the sponsor (Kite, a Gilead company) and the investigators. The institutional review board or independent ethics committee at each study site approved the study protocol. The sponsor funded medical

writing assistance. All authors, including academic authors and those employed by the sponsor, had access to the data and contributed to data analysis and interpretation.

Results

Patients

From 13 May 2021 to 15 March 2023, 95 patients were enrolled and received leukapheresis in cohort 3. Brexu-cel was successfully manufactured for 89 patients (94%) and administered to 86 (91%; supplemental Figure 1). Of 9 patients enrolled but not treated, 3 were not treated due to AEs (COVID-19 [n = 2] and pulmonary thromboembolism [n = 1]), 3 were not treated due to rapid disease progression, 1 died before receiving treatment (due to enterococcal sepsis), 1 patient withdrew consent, and 1 patient had a manufacturing failure. Median time from leukapheresis to administration was 34 days (range, 19-85). Median time from leukapheresis to delivery to a US study site was 15 days (range, 14-21; n = 28) and to an EU study site (including sites in France, Spain, The Netherlands, and Germany) was 28 days (range, 20-43; n = 57; 1 patient was treated in the United Kingdom and was not included in this assessment). As of 26 November 2023, the median follow-up among patients assessed for efficacy and safety was 15.5 months (range, 1.4-27.1; N = 86).

Median age was 64.0 years (range, 40-82; Table 1). High-risk features at baseline were common: 73% of patients had a high or intermediate simplified Mantle Cell Lymphoma International Prognostic Index (s-MIPI) score, 52% had extranodal disease, 40 of 59 (68%) evaluable patients had Ki-67 positivity of ≥30%, 15 of 33 (45%) evaluable patients had a *TP53* mutation, and 40% of patients had progression of disease within 24 months of initial diagnosis (POD24). Median number of previous therapies was 1 (range, 1-5), with a median time from last previous therapy to brexu-cel infusion of 15.3 months (range, 2-151; N = 86). Previous anti-CD20, anthracycline, and bendamustine therapies were received by 100%, 79%, and 27% of patients, respectively. Of 23 patients who received previous bendamustine, the median time from bendamustine to leukapheresis was 21.4 months (range, 1.3-143.8) with only 6 patients having <12 months between bendamustine and leukapheresis. Nearly half of patients (48%) had previous autologous stem cell transplantation. Bridging therapy was administered to 31 patients (36%; supplemental Table 1).

Efficacy

The primary end point was met with an ORR of 91% (95% CI, 82.5-95.9; $P < .0001$) per IRRC in all treated patients (N = 86; Figure 1A). The best response to brexu-cel was CR in 63 patients (73%; 95% CI, 62.6-82.2), PR in 15 patients (17%; 95% CI, 10.1-27.1), stable disease in 3 patients (3%; 95% CI, 0.7-9.9), progressive disease (PD) in 3 patients (3%; 95% CI, 0.7-9.9), and 2 patients were not assessed (due to death before response assessment). Differences in response rates were observed per investigator assessment, with a 94% ORR (95% CI, 87.0-98.1; $P < .0001$), including 72 patients (84%) with CR and 9 patients (10%) with PR (supplemental Table 2). Among all 95 enrolled patients, 82% had an objective response (95% CI, 72.9-89.2; $P < .0001$) and 66% had a CR, per IRRC (supplemental Table 2).

High ORRs were observed across key subgroups of interest including patients with high-risk disease features such as those with a *TP53* mutation (15/15 [100%]), greater than or equal to the median tumor burden (sum of the products of diameters) at baseline (97%), Ki-67 positivity ≥30% (38/40 [95%]), intermediate- or high-risk s-MIPI scores (56/63 [89%]), and those with previous bendamustine treatment (19/23 [83%]; Figure 2). Median time to first objective response was 1.0 month (range, 0.8-6.0; n = 78) and median time to CR was also 1.0 month (range, 0.9-8.9; n = 63). Of 34 patients with an initial response of PR or stable disease, 16 patients (47%) converted to CR after a median time of 2.0 months (range, 0.7-8.0) after initial response. Only 1 patient received a second infusion of brexu-cel; the patient had an initial response of CR lasting 5 months, PD at month 6, and received the second infusion of brexu-cel 4 months later (10 months between infusions), with PD as their best response to the second infusion.

The estimated median PFS per IRRC by 24 months was not reached (NR; 95% CI, 18.3 to not evaluable [NE]; N = 86) and the 12-month PFS rate was 75% (95% CI, 64.5-83.4; Figure 1B). Six-month PFS rates were similar across key subgroups, including those with *TP53* mutations (13/15 [87%]), Ki-67 positivity of ≥30% (36/40 [95%]), and patients with intermediate- or high-risk s-MIPI scores (50/63 [82%]), although patients with previous bendamustine therapy had a numerically lower 6-month PFS rate compared with the overall population (73% [15/23] vs 85%; supplemental Figure 2). The estimated median PFS for all 95 enrolled patients was NR by 24 months (95% CI, 19.4 to NE) and the 12-month PFS rate was 73% (95% CI, 62.1-80.8).

The estimated median DOR per IRRC was NR at 24 months for all responders (n = 78), patients with CR (n = 63), or for patients with PR (n = 15), and the 12-month DOR rate was 80% (95 % CI, 69.1-87.9; Figure 1C). Of 78 patients with CR or PR after brexu-cel infusion, 54 patients (69%; 49 patients with CR) were in ongoing response without subsequent therapy, 13 patients (17%) had disease progression, 6 patients (8%) died, 4 patients (5%) started a new anticancer therapy, 1 patient (1%) withdrew consent, and no patients had received subsequent SCT at time of analysis. Of 13 patients with PD, 6 had PD ≤6 months after infusion (2 PR and 4 CR) and 7 had PD >6 months after infusion (2 PR and 5 CR). Ongoing response rates were similar across most key subgroups including patients with *TP53* mutations (12/15 [80%]), those with baseline tumor burden of greater than or equal to the median (23/39 [59%]), Ki-67 positivity of ≥30% (28/40 [70%]), and intermediate- or high-risk s-MIPI scores (38/63 [60%]); however, patients with 2 to 3 previous therapies (41%) and those with previous bendamustine therapy (43%) had numerically lower ongoing response rates than the total treated population (63%; supplemental Figure 3).

The estimated median OS by 24 months in all treated patients was NR (95% CI, NE to NE; N = 86) and the 12-month OS rate was 90% (95% CI, 80.7-94.4; Figure 1D). The estimated median OS for all 95 enrolled patients was NR (95% CI, NE to NE) and the 12-month OS rate was 85% (95% CI, 75.6-90.7; Figure 1D).

Safety

Most treated patients (99%) had an AE of grade ≥3 (Table 2). The most common grade ≥3 AEs by preferred term were

Table 1. Demographics and baseline disease characteristics (efficacy and safety analysis set)

Characteristics	Cohort 3 (N = 86)*
Median age (range), y	64 (40-82)
Male, n (%)	67 (78)
Simplified MIPI, n (%)	
Low risk	23 (27)
Intermediate risk	53 (62)
High risk	10 (12)
ECOG PS of 1, n (%)	27 (31)
Morphologic characteristics, n (%)	
Classical MCL, diffuse	47 (55)
Classical MCL, nodular	12 (14)
Classical MCL, other	6 (7)
Pleomorphic MCL	6 (7)
Blastoid MCL	6 (7)
Other	9 (10)
TP53 IHC by central laboratory performed,† n (%)	59 (69)
TP53 ≥50% tumor cells positive, n (%)	7 (8)
***TP53* mutation status by local laboratory performed,‡ n (%)**	33 (38)
Yes	15 (17)
No	18 (21)
Ki-67 IHC by central laboratory performed,† n (%)	59 (69)
Ki-67 ≥30% tumor cells positive	40 (47)
Ki-67 ≥50% tumor cells positive	18 (21)
LDH >ULN, n (%)	49 (57)
Median tumor burden (SPD) by central read§ (range), mm^2	1 734 (204-31 212)
Extranodal disease, n (%)	45 (52)
Bone marrow involvement from diagnosis history, n (%)	34 (40)
POD24, n (%)	34 (40)
Median number of previous regimens (range)	1 (1-5)
Anti-CD20, n (%)	86 (100)
Platinum-based, n (%)	11 (13)
Anthracycline, n (%)	68 (79)
Bendamustine, n (%)	23 (27)
Lenalidomide, n (%)	2 (2)
Proteasome inhibitor, n (%)	6 (7)
R/R disease, n (%)	
Refractory to last MCL therapy	12 (14)
Relapsed after last MCL therapy	74 (86)
Previous ASCT	41 (48)
Previous hyper-CVAD	7 (8)

Table 1 (continued)

Characteristics	Cohort 3 (N = 86)*
Received any bridging therapy, n (%)	31 (36)
Systemic therapy only	24 (28)
Radiotherapy only	4 (5)
Systemic therapy and radiotherapy	3 (3)

ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), dexamethasone, methotrexate, and cytarabine; IHC, immunohistochemistry; LDH, lactate dehydrogenase; SPD, sum of the products of diameters; ULN, upper limit of normal.

*All percentages are calculated out of N.

†Percentage by IHC by central laboratory represents percent of tumor cells stained positively.

‡*TP53* mutation testing was conducted per the discretion of the investigator and was not protocol defined.

§As measured by the SPD of all target lesions at baseline. For patients who had bridging therapy, the measurement on or after bridging therapy end date is used as baseline.

neutropenia (43%), neutrophil count decrease (42%), and white blood cell count decrease (37%; some preferred terms had similar or overlapping definitions but were coded differently in the reporting system). Median time to onset of cytopenias after infusion was 3 days (range, 1-93). Of 78 patients (91%) with any type of grade ≥3 cytopenia, 45 had a grade ≥3 cytopenia present ≥30 days after infusion and 20 patients had a grade ≥3 cytopenia present ≥93 days after infusion (supplemental Table 3). Median time to resolution of grade ≥3 cytopenia was 32 days (range, 1-554; n = 72), with 4 patients having an unresolved grade ≥3 cytopenia at data cutoff.

A total of 95% of patients (n = 82) experienced cytokine release syndrome (CRS) of any grade, with 6% (n = 5) experiencing grade ≥3 CRS (per revised grading system [Lee et al][19]; Table 3). For the management of CRS, 69 patients received tocilizumab, 44 patients received steroids, 10 patients received vasopressors, and 2 patients received anakinra. Median time to onset of CRS events after infusion was 4 days (range, 1-12). All CRS events resolved within a median of 6 days (range, 1-36). Thirteen patients (15%) received intensive care unit support for CRS (range, 1-12 days).

Immune effector cell–associated neurotoxicity syndrome (ICANS; per the American Society for Transplantation and Cellular Therapy ICANS grading [Lee et al][21]) events of any grade occurred in 66% of patients, with grade ≥3 ICANS occurring in 21% (events were overlapping with neurologic events; Table 3). Median time to onset of ICANS after infusion was 7 days (range, 1-31). Events resolved in 61 of 67 (96%) patients with any grade ICANS, with median time to resolution of 7 days (range, 1-122).

A total of 78% of patients (n = 67) had neurologic events of any grade (identified using a modified search strategy [Topp et al][20]), and 27% (n = 23) had grade ≥3 neurologic events (Table 3). For management of neurologic events, 44 patients received steroids, 10 received tocilizumab, and 9 received anakinra. Median time to onset of neurologic events after infusion was 7 days (range, 1-373). Neurologic events resolved in 61 of 67 (91%) patients with any grade neurologic events,

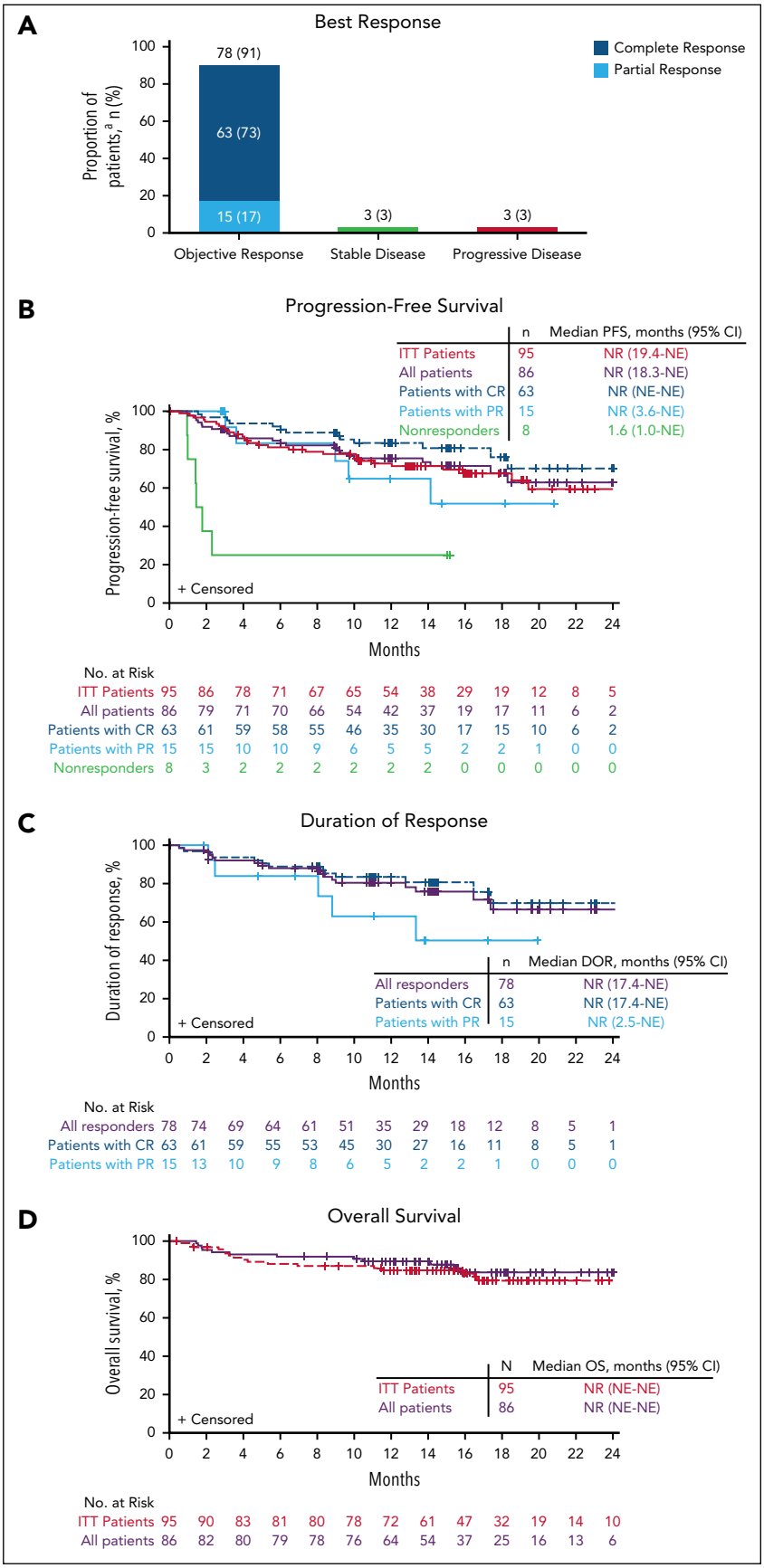

Figure 1. BOR, PFS, DOR, and OS in cohort 3. The graphs show BOR per IRRC (primary end point) (A) and Kaplan-Meier estimates of PFS per IRRC (B), DOR per IRRC (C), and OS (D) based on the efficacy and safety analysis set (N = 86) and all enrolled patients (N = 95). [a]Two patients were not assessed but included in overall percentage (N = 86). BOR, best overall response; CR, complete response; DOR, duration of response; ITT, intent-to-treat; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

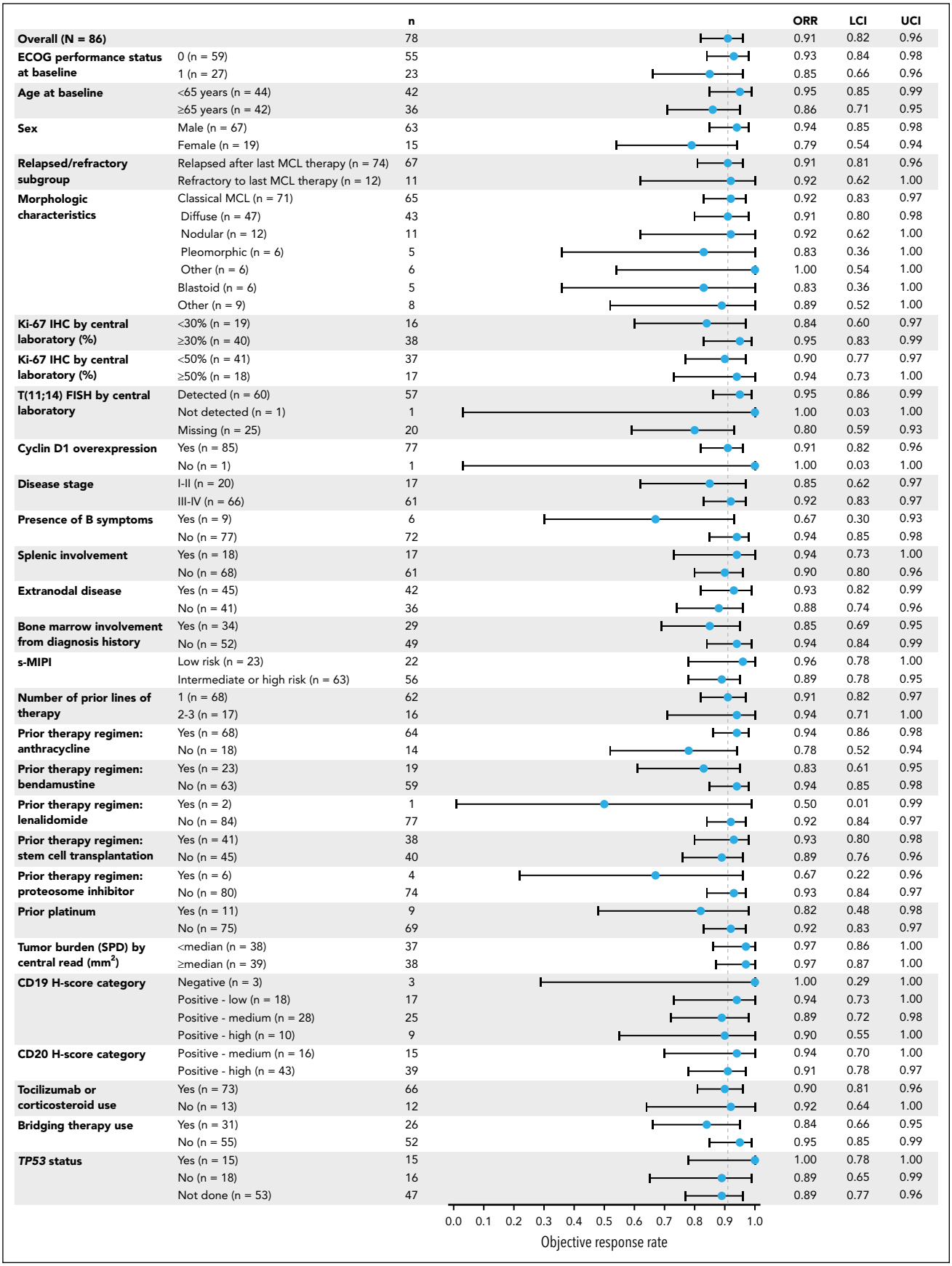

Figure 2. Subgroup analysis of ORR. The forest plot shows the analysis of objective response per IRRC according to key demographic and baseline characteristics. The 95% CIs were calculated using the Clopper-Pearson method. ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; LCI, lower CI; SPD, sum of the products of diameters; UCI, upper CI.

Table 2. TEAEs among all treated patients

TEAEs*, n (%)	Cohort 3 (N = 86)	
	Any grade	Grade ≥3
Patients experiencing any TEAE	86 (100)	85 (99)
Patients experiencing any serious TEAE	51 (59)	40 (47)
Most common TEAEs (occurring in ≥20% of patients)		
Pyrexia	81 (94)	15 (17)
Anemia	49 (57)	22 (26)
Hypotension	44 (51)	7 (8)
Neutropenia	39 (45)	37 (43)
Neutrophil count decreased	36 (42)	36 (42)
White blood cell count decreased	34 (40)	32 (37)
Nausea	28 (33)	1 (1)
Confusional state	25 (29)	7 (8)
Headache	25 (29)	0 (0)
Platelet count decreased	25 (29)	15 (17)
Tremor	25 (29)	2 (2)
Constipation	24 (28)	0 (0)
Lymphocyte count decreased	23 (27)	23 (27)
Decreased appetite	21 (24)	8 (9)
Diarrhea	21 (24)	0 (0)
Fatigue	20 (23)	0 (0)
Thrombocytopenia	20 (23)	14 (16)
Hypoxia	19 (22)	8 (9)
Aphasia	17 (20)	11 (13)
COVID-19	17 (20)	3 (3)
Hypokalemia	17 (20)	1 (1)

CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

*TEAEs are defined as any AE with onset on or after initiation of brexu-cel infusion. AEs that occurred on/after retreatment are not included. AEs are coded using MedDRA version 27.0 and graded per CTCAE version 4.03. Multiple incidences of the same AE in 1 patient are counted once at the highest grade for that patient.

with median time to resolution of 8 days (range, 1-179). Of 6 patients without resolution of neurologic events, 4 died before data cutoff date (1 due to PD, 1 due to infection, 1 due to progressive multifocal leukoencephalopathy, and 1 due to human herpesvirus 6 encephalitis) and 2 had ongoing neurologic events (grade 1 cognitive disturbances [duration of 101 days at time of analysis] and grade 3 cognitive disturbances [duration of 494 days at time of analysis]). Three patients (3%) received intensive care unit support for both neurologic events and CRS (range, 1-2 days).

Serious infections of grade ≥3 occurred in 20 patients (23%; some patients experienced >1 type of serious infection), 5 of whom had grade 5 infections (supplemental Table 4). No incidence of replication-competent retrovirus or brexu-cel–related secondary T-cell malignancies was reported.

At data cutoff, 73 patients (85%) were alive and 13 (15%) had died; no deaths occurred within 30 days of brexu-cel infusion. Of 13 patients who died, 7 died due to AEs, of which 4 deaths were deemed related to lymphodepleting chemotherapy and/or brexu-cel (progressive multifocal leukoencephalopathy [n = 1], polymicrobial infection [n = 1], septic shock [n = 1], and human herpesvirus 6 encephalitis [n = 1]) and 3 were deemed unrelated to study treatment (pneumonia [n = 1; occurred 410 days after infusion], hepatocellular carcinoma [n = 1], and intracranial hemorrhage [n = 1; related to rivaroxaban use]). Five patients died due to PD (1 had a cause of death reported as "other" but had PD before death) and 1 patient died due to other causes (failure to thrive after hip fracture). The 6-month and 12-month nonrelapse mortality rates were 6% (5/86) and 7% (6/86), respectively.

Biomarker analysis

Similar to cohort 1, the median peak and area under the curve (from 0 to 28 days after infusion) CAR T-cell levels in cohort 3 were 0.077 × 10^3 cells per μL and 1.021 × 10^3 cells per μL × days, respectively, with a median time to peak of 15 days (range,

Table 3. TEAEs of special interest

AEs of special interest	Cohort 3 (N = 86)
Any CRS,* n (%)	82 (95)
Worst grade ≥3, n (%)	5 (6)
Median time to onset (range), d	4 (1-12)
Median duration (range), d	6 (1-36)
Any neurologic events,† n (%)	67 (78)
Worst grade ≥3, n (%)	23 (27)
Median time to onset (range), d	7 (1-373)
Median duration (range), d	8 (1-179)
Any ICANS,‡ n (%)	57 (66)
Worst grade ≥3, n (%)	18 (21)
Median time to onset (range), d	7 (1-31)
Median duration (range), d	7 (1-122)
Any thrombocytopenia,§ n (%)	45 (52)
Worst grade ≥3, n (%)	29 (34)
Any neutropenia§, n (%)	74 (86)
Worst grade ≥3, n (%)	73 (85)
Any anemia,§ n (%)	49 (57)
Worst grade ≥3, n (%)	22 (26)
Any serious infection,§ n (%)	21 (24)
Worst grade ≥3, n (%)	20 (23)
Hypogammaglobulinemia,§ n (%)	7 (8)
Worst grade ≥3, n (%)	0

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; ICANS, immune effector cell–associated neurotoxicity syndrome; TEAE, treatment-emergent adverse event.

*CRS events are graded per the revised grading system proposed by Lee et al.[19]

†Neurologic events are identified based on Topp et al.[20]

‡ICANS events are graded per the ASTCT ICANS grading (Lee et al).[21]

§All other events are graded per CTCAE version 4.03.

8-183) after brexu-cel infusion.[10] CAR T-cell persistence in the blood decreased over time after week 2 with CAR T cells, being very low to undetectable by month 15 in evaluable patients (n = 17), consistent with cohort 1 (Figure 3A).[10] No significant differences were observed in peak or area under the curve CAR T-cell expansion or persistence by complete or ongoing response status, per IRRC (supplemental Figure 4A). No associations were found between CAR T-cell expansion and CRS severity by grade ≥2 or ≥3 (supplemental Figure 4B); however, expansion was significantly associated with neurologic events and ICANS severity by grade ≥2 and ≥3 (Figure 3B). Similar trends were observed for CAR T-cell area under the curve from 0 to 28 days after infusion (supplemental Figure 5).

Elevated peak levels of inflammatory serum analytes including interleukin 2 receptor α (IL-2Rα), tumor necrosis factor α, IL-6, IL-10, and granulocyte-macrophage colony-stimulating factor were associated with higher-grade CRS (Figure 3C). In addition, baseline and day-0 (after lymphodepletion) levels of tumor necrosis factor α, IL-12 subunit p40, and macrophage-derived chemokine were associated with higher-grade CRS in cohort-3 patients. Postinfusion peak levels of IL-2, IL-6, interferon gamma, IL-1R antagonist, granulocyte-macrophage colony-stimulating factor, and granzyme B were associated with higher-grade neurologic events, including ICANS, consistent with cohort 1, whereas higher peak levels of IL-15, IL-2Rα, monocyte chemoattractant protein-1, and granzyme A held the association for cohort-3 patients only.

A higher percentage of naive/juvenile T cells ($CD3^+$, $CCR7^+$, $CD45RA^+$ T cells), in the final CAR T-cell product (within the specification range) was significantly associated with CR (39.8% vs 30.3%; $P = .0227$), ongoing response (42.6% vs 27.7%; $P = .0027$), and improved PFS (greater than median vs less than or equal to median; $P = .0031$), and a higher percentage of viable cells in the final product was significantly associated with ongoing response (91.0% vs 89.0%; $P = .0437$) and improved PFS ($P = .041$; Figure 4).

Of 86 patients treated with brexu-cel, 84 were assessed for B-cell levels at baseline, of whom, 66 (79%) had detectable B cells and 18 (21%) did not. As expected, at month 3, 48 of 77 (62%) evaluable patients had B-cell aplasia, but by month 6, only 22 of 73 (30%) evaluable patients had B-cell aplasia, suggestive of pronounced B-cell recovery in most patients (supplemental Figure 6A). Patients without detectable B cells at baseline had a numerically lower B-cell recovery rate after CAR T-cell therapy over time. These patients also had numerically higher CAR T-cell expansion, than those without B cells at baseline (supplemental Figure 6B-C). As expected, patients without detectable B cells at baseline were more heavily pretreated than patients with detectable B cells at baseline (39% vs 17% had ≥2 previous lines of therapy, respectively) and experienced a higher rate of infections of any grade (81% vs ~45% of patients by month 6; supplemental Figure 6D-E).

Discussion

Although BTKi therapies have significantly improved patient outcomes in R/R MCL, they are not curative and outcomes after BTKi failure are poor.[9] Additionally, patients with high-risk disease features such as high s-MIPI scores, ≥30% Ki67 positivity, blastoid morphology, POD24, or *TP53*-mutant MCL have poorer outcomes with BTKi treatment.[22-24] Brexu-cel has previously demonstrated high response rates and durable efficacy in patients with heavily pretreated R/R MCL including those with high-risk disease features in ZUMA-2 cohort 1 and real-world studies, and is approved in this setting.[10-13,25] Given its broad US label (adults with R/R MCL), patients can receive brexu-cel before BTKi therapy (if not used in first line), although it has not previously been studied in this specific patient population.[11] Here, we report that 1 infusion of brexu-cel in the ZUMA-2 cohort 3 primary analysis achieved an ORR of 91% and a CR rate of 73%, per IRRC, in patients with R/R MCL who had not received a previous BTKi (N = 86). Most patients on study had 1 previous line of therapy and ≥1 high-risk disease feature such as having an intermediate or high s-MIPI score, ≥30% Ki67 positivity, *TP53* mutation, and/or POD24. Notably higher CR rates were reported per investigator review (84%), mostly due to the lack of protocol-defined CR bone marrow confirmations required per IRRC. Nonetheless, 84% of patients had no detectable disease by imaging at the 6-month analysis. After 15.5 months of follow-up, 69% of responders (63% of all treated patients) were in ongoing response, per IRRC, and median DOR, PFS, and OS were NR at 24 months. Estimated 12-month DOR, PFS, and OS rates were 80%, 75%, and 90%, respectively. Among all 95 enrolled patients, the ORR was 82%, the CR rate was 66%, and the 12-month PFS and OS rates (95% CI) were 73% (62.1-80.8) and 85% (75.6-90.7), respectively.

Response rates in cohort 3 were similar to those in cohort 1 (93% ORR and 67% CR rate; N = 60, per IRRC), whereas the durability of responses appeared to improve upon cohort 1 findings of a 57% ongoing response rate at 12.3 months of follow-up and a 12-month OS rate of 83%.[10] For additional context, acalabrutinib demonstrated an 81% ORR, 40% CR rate, 72% 12-month DOR rate, 67% 12-month PFS rate, and 87% 12-month OS rate in 124 patients with R/R MCL (median 2 previous therapies) after a median of 15.2 months of follow-up in a phase 2 single-arm study.[26]

In cohort 3, high ORRs were observed across key subgroups, including in patients with *TP53* mutations and Ki-67 positivity of ≥30%, although longer follow-up is needed to understand the durability of responses in these patient groups. In cohort 1, patients with previous bendamustine treatment experienced a high ORR of 84% but a lower ongoing response rate than patients without previous bendamustine (29% vs 48%, respectively; median follow-up of 35.6 months).[13] Additional analyses found that a diminished pharmacokinetic profile and product doubling time were associated with previous bendamustine treatment within 12 months of apheresis, suggesting that patients with recent bendamustine treatment may likely have attenuated T-cell fitness and, therefore, reduced CAR T-cell expansion and efficacy.[13] Only 6 patients in cohort 3 received brexu-cel within 12 months of bendamustine; thus subgroup analyses were assessed in all patients with (n = 23) or without (n = 63) previous bendamustine. Consistent with cohort 1, a high ORR (83%) was observed in patients with previous bendamustine treatment; however, these patients had a notably lower ongoing response rate and 6-month PFS rate than patients without previous bendamustine. Small patient numbers and unmatched baseline characteristics may have confounded

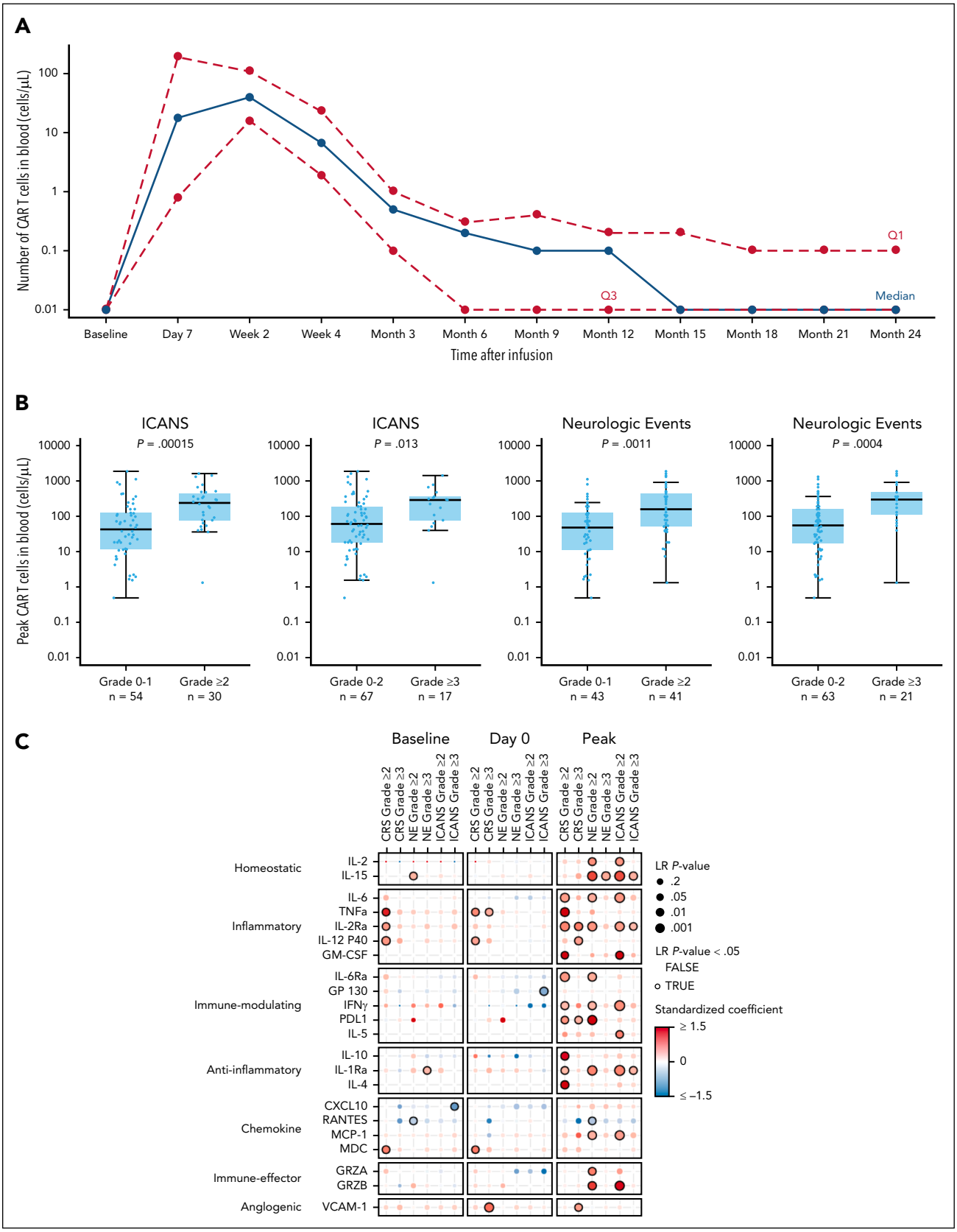

Figure 3. CAR T-cell expansion, peak serum biomarkers, and associations with safety. (A) CAR T-cell expansion and persistence over time with median values and interquartile ranges (quartile 1 [Q1] and Q3). (B) Associations of peak CAR T-cell expansion with neurological events and ICANS. *P* values were calculated using the Wilcoxon rank-sum test and were not adjusted for multiple comparisons. The median is represented by the horizontal line within each box, and the 25th and the 75th percentiles are represented by the lower and upper borders of each box. (C) Key serum biomarkers and their associations with neurologic events, ICANS, and CRS. *P* values were calculated using the Wilcoxon rank-sum test and were not adjusted for multiple comparisons. CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

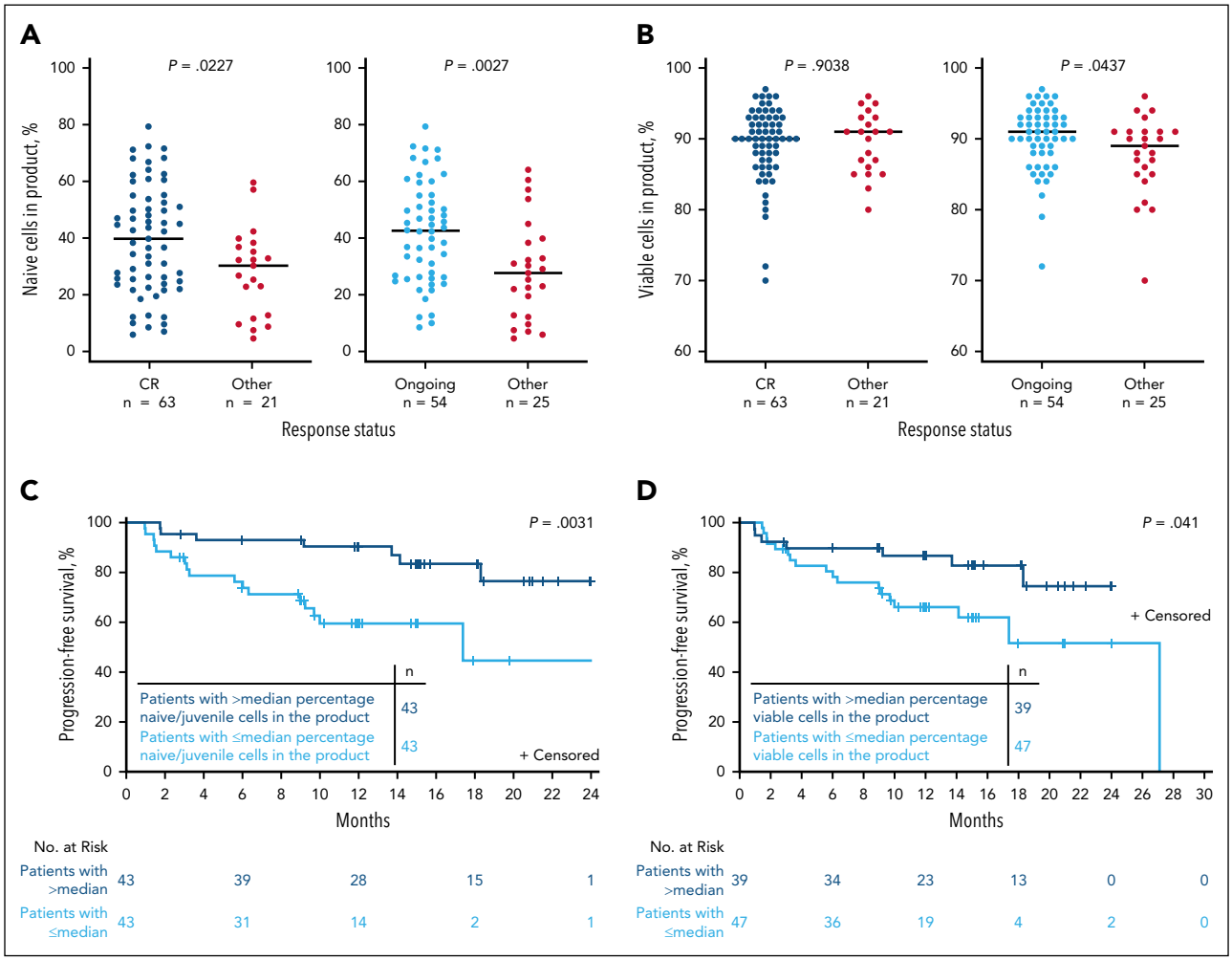

Figure 4. CAR T-cell product phenotype and associations with response and PFS. (A) Associations between percentage of naive/juvenile cells in the product and complete and ongoing response. (B) Associations between percentage of viable cells in the product and complete and ongoing response. (C) Association between percentage of naive/juvenile cells in the product and PFS. (D) Association between percentage of viable cells in the product and PFS. Naive/juvenile cells are defined as $CD3^+$ T cells in the final product expressing both CCR7 and CD45RA as measured by flow cytometry assay. *P* values were calculated using the Wilcoxon rank-sum test and were not adjusted for multiple comparisons for box plots and log-rank test for Kaplan-Meier plots. The median is represented by the horizontal line within each box, and the 25th and the 75th percentiles are represented by the lower and upper borders of each box. CAR, chimeric antigen receptor; CR, complete response; PFS, progression-free survival.

these results. Additional analyses with longer follow-up are underway to determine whether T-cell fitness is partly responsible for the lower response durability observed in patients with previous bendamustine.

In this study, the safety profile of brexu-cel was similar to that observed in cohort 1 although the incidence of grade ≥3 CRS (6%) was lower than in cohort 1 (15%), possibly due to fewer previous therapies received in cohort 3 and/or a shift toward earlier implementation of intervention strategies[10] Associations between AEs and CAR T-cell expansion, cytokines, chemokines, and effector molecules were similar to those in cohort 1.[10,13] Five patients had grade 5 infections (6%), which is modestly higher than the rate in the primary analysis of cohort 1 (3%) but similar to the real-world estimated rate at 1 year (5%).[10,25] Nevertheless, the observed nonrelapse mortality rate in a phase 2 study of acalabrutinib in 124 patients with R/R MCL with 15.2 months of follow-up was only 4% (5/124).[26] Therefore, patient risk/benefit should be carefully considered before treating a patient with BTKi-naive R/R MCL with brexu-cel.

In cohort 3, CAR T-cell expansion and persistence were similar to that in cohort 1; however, CAR T-cell expansion did not correlate with CR or ongoing response as demonstrated in cohort 1. Small numbers of nonresponders and discrepancies between IRRC and investigator-assessed response rates make interpretation of these results difficult.[10] Consistent with previous findings, higher percentages of naive cells in the CAR T-cell product were associated with objective response, ongoing response, and improved PFS.[27] Patients with ≥2 previous lines of treatment were at higher risk of pretreatment B-cell aplasia and attenuated B-cell recovery after brexu-cel infusion, and elevated infection rates. Patients with detectable B cells at baseline were more likely to have B-cell recovery after CAR T-cell therapy and a lower infection rate if their B cells recovered by month 3. In addition, sustained B-cell recovery appeared more pronounced

in cohort 3 than in cohort 1, suggesting that exposure to fewer previous therapies may positively affect B-cell recovery after brexu-cel.[13] These finding suggest that preexisting B-cell aplasia, induced by previous lines of therapy, may contribute to infection rates, independent of brexu-cel.[28,29]

Limitations of this study include a focus on the all-treated population instead of the all-enrolled population; however, outcomes for all-enrolled were also reported herein and demonstrate meaningful efficacy in patients with R/R MCL. Serious AEs were expected and did occur with brexu-cel treatment; however, most resolved on study and no new safety signals were observed. Despite the risk of serious AEs, brexu-cel provided significant benefits to patients with R/R MCL. Taken together, these results demonstrate that brexu-cel can provide considerable antitumor efficacy in patients with R/R MCL who have not received a previous BTKi. Brexu-cel may be a suitable salvage therapy alternative to BTKi for patients with high-risk disease features; however, the potential benefit for each patient should be considered in the context of the risk for life-threatening AEs.[13] Additionally, the substantial benefit to patients observed in earlier lines of therapy in cohort 3 and after BTKi therapy in cohort 1 suggests that brexu-cel may be an effective second-line salvage therapy after failure of BTKi first-line combination therapies as BTKi becomes incorporated into frontline treatment. These findings support the continued use of brexu-cel in R/R MCL, including in some patients naive to BTKi therapy who have high-risk disease features. Additional follow-up in cohort 3 is needed to further assess the survival benefits that brexu-cel may impart in earlier lines of therapy.

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Authorship

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Footnotes

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Kite, a Gilead company, is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health; access can be requested by contacting medinfo@kitepharma.com.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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