Primary Analysis of ZUMA-2 Cohort 3: Brexucabtagene Autoleucel in Patients With Relapsed/Refractory Mantle Cell Lymphoma Who Are Naive to Bruton Tyrosine Kinase Inhibitors

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Background

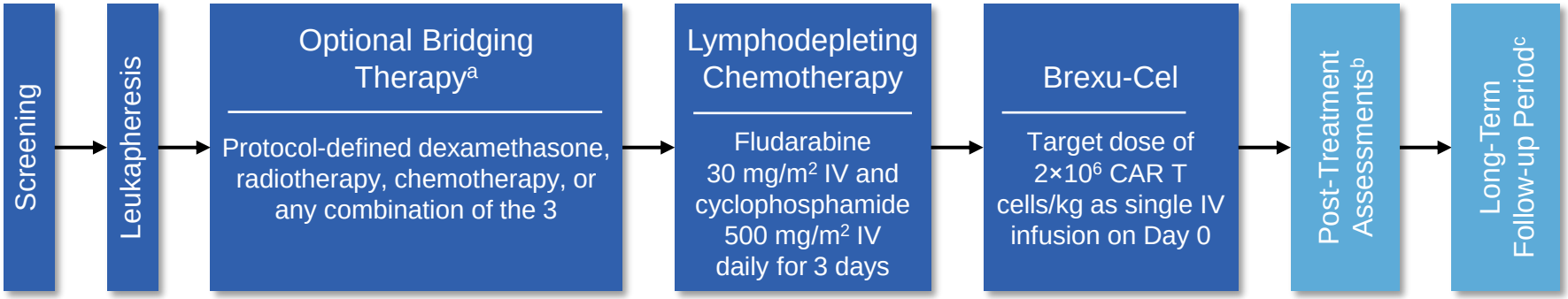
- The emergence of BTKi therapy has transformed the treatment landscape of R/R MCL; however, these therapies are not curative, and patients with disease progression after BTKi have poor outcomes[1]
- Brexu-cel is an autologous anti-CD19 CAR T-cell therapy approved for adults with R/R MCL in the US and for adults with R/R MCL after ≥2 prior lines of therapy, including a BTKi, in the EU[2,3]
- In the pivotal ZUMA-2, Cohort 1 study (NCT02601313), brexu-cel demonstrated an ORR of 91%, a CR rate of 68%, and a median OS of 46.4 months (47.5 months of median follow-up) in 68 patients with R/R MCL with 1-5 prior lines of therapy, including a BTKi[4,5]
- Given all patients in ZUMA-2, Cohort 1 received BTKi therapy before brexu-cel infusion, Cohort 3 was established to confirm the safety and efficacy of brexu-cel in patients with BTKi-naive R/R MCL[6]
- Here we report the primary analysis of the global, Phase 2 ZUMA-2, Cohort 3 study of brexu-cel in patients with R/R MCL who have not received prior BTKi therapy (NCT04880434)[6]

1. Ryan CE, Kumar A. *Blood Rev*. 2024;67:101221. 2. TECARTUS® (brexucabtagene autoleucel) Prescribing information. Kite Pharma, Inc; 2024. 3. TECARTUS® (brexucabtagene autoleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2024. 4. Wang M, et al. *J Clin Oncol*. 2023;41(3):555-567. 5. Goy A, et al. *Blood*. 2023;142(Suppl 1):106. 6. ClinicalTrials.gov. Accessed October 31, 2024. https://clinicaltrials.gov/study/NCT04880434

Brexu-cel, brexucabtagene autoleucel; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; EU, European Union; ORR, objective response rate; OS, overall survival; R/R MCL, relapsed/refractory mantle cell lymphoma; US, United States.

ZUMA-2 Cohort 3 Study Methodology

Phase 2, Open-Label Study



Key Cohort 3 Eligibility Criteria

- Age ≥18 years with R/R MCL
- 1-5 prior regimens including anthracycline-, bendamustine-, or high-dose cytarabine-containing chemotherapy and anti-CD20 monoclonal antibody therapy
- No prior BTKi

Primary Endpoint

- ORR (CR + PR; by IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints

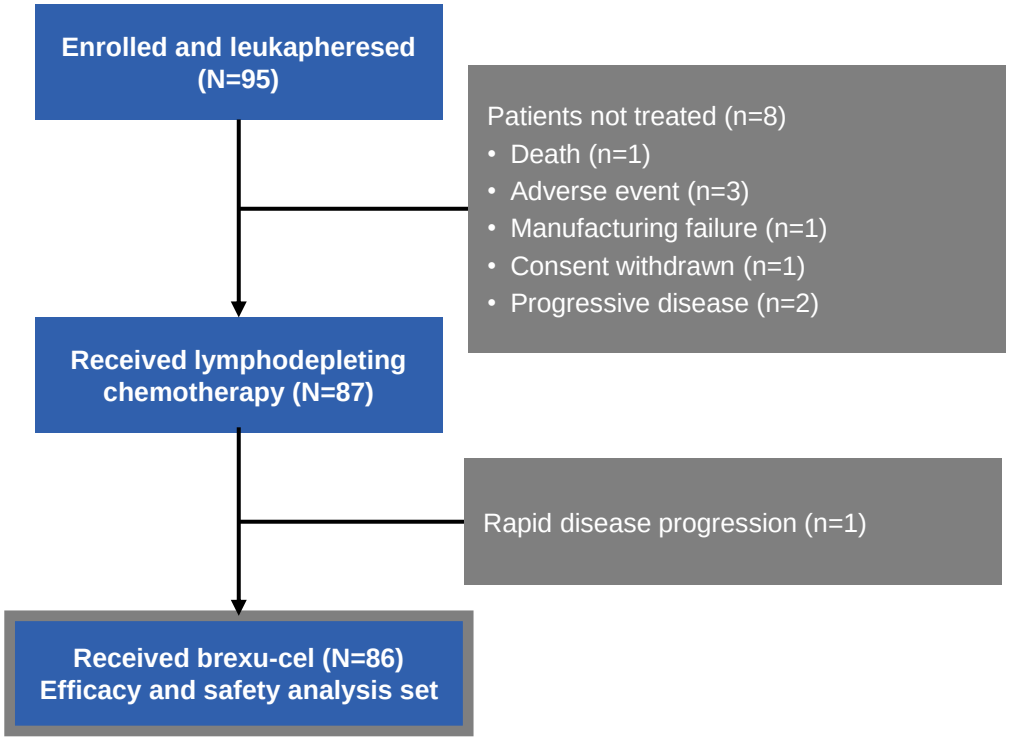
- DOR, BOR, PFS, OS, and safety

Statistical Considerations

- Primary efficacy analysis was conducted after 86 patients were enrolled, treated, and assessed for 6 months after the first objective response and was powered at ≥90% to distinguish between a 75% response rate and a response rate of ≤57%
- Time-to-event endpoints were analyzed using the Kaplan-Meier method
- All treated patients were included in both efficacy and safety analyses

[a] At the discretion of the investigator, bridging therapy was recommended for all patients, particularly those with rapidly progressing disease, clinical deterioration, or high disease burden at screening. Bridging was administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy. [b] Bone marrow biopsy was to be done at screening and, if positive, not done or indeterminate, a biopsy was needed to confirm CR. First post–brexu-cel disease assessment was 4 weeks after infusion. [c] After 3 months, only targeted AEs (neurologic, hematologic, infections, GVHD, autoimmune disorders, and secondary malignancies) were monitored and reported for 15 years after the initial anti-CD19 CAR T-cell infusion or until disease progression or initiation of subsequent anticancer therapy, whichever occurs first. 1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.
AE, adverse events; BOR, best objective response; brexu-cel, brexucabtagene autoleucel; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; GVHD, graft-versus-host disease; IRRC, independent radiology review committee; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R MCL, relapsed/refractory mantle cell lymphoma.

ZUMA-2 Cohort 3 Consort Diagram



- As of the data cutoff date, November 26, 2023, 95 patients enrolled in Cohort 3, 86 (91%) of whom received brexu-cel with a median follow-up of 15.5 months (range, 5-15)
- Median time from leukapheresis to delivery to study site was 15 days (range, 14-21) for US sites and 28 days (range, 20-43) for EU sites (not including the UK)

Brexu-cel, brexucabtagene autoleucel; EU, European Union; UK, United Kingdom; US, United States.

Baseline Patient and Disease Characteristics

Characteristic[a]	Cohort 3 (N=86)
Median age (range), years	64 (40-82)
Male, n (%)	67 (78)
ECOG PS of 1, n (%)	27 (31)
Intermediate and high simplified MIPI, n (%)	63 (73)
TP53 IHC by central laboratory performed,[b] n (%)	59 (69)
***TP53* ≥50%, n (%)**	7 (8)
***TP53* mutation status by local laboratory performed,[c] n (%)**	33 (38)
Yes	15 (17)
No	18 (21)
Ki-67 IHC by central laboratory performed,[b] n (%)	59 (69)
Ki-67 ≥30%	40 (47)
Ki-67 ≥50%	18 (21)
LDH relative to upper limit, n (%)	
LDH >ULN	49 (57)
Median tumor burden (SPD) by central read (mm^2),[d] (range)	1734 (204-31,212)
Extranodal disease, n (%)	45 (52)
Bone marrow involvement from diagnosis history, n (%)	34 (40)

- Median age was 64.0 years
- High-risk features were common:
  - 73% had a high or intermediate sMIPI score
  - 52% had extranodal disease
  - 47% (68% of evaluable) had Ki-67 ≥30%
  - 40% had bone marrow involvement

[a] All percentages are calculated out of big N. [b] Percent by IHC by central laboratory represents percent of tumor cells stained positively. [c] TP53 mutation testing was conducted per the discretion of the investigator and was not protocol defined. [d] 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.
ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; LDH, lactate dehydrogenase; (s)MIPI, (simplified) Mantle Cell Lymphoma International Prognostic Index; SPD, sum of the products of diameters; TP53, tumor protein 53; ULN, upper limit of normal.

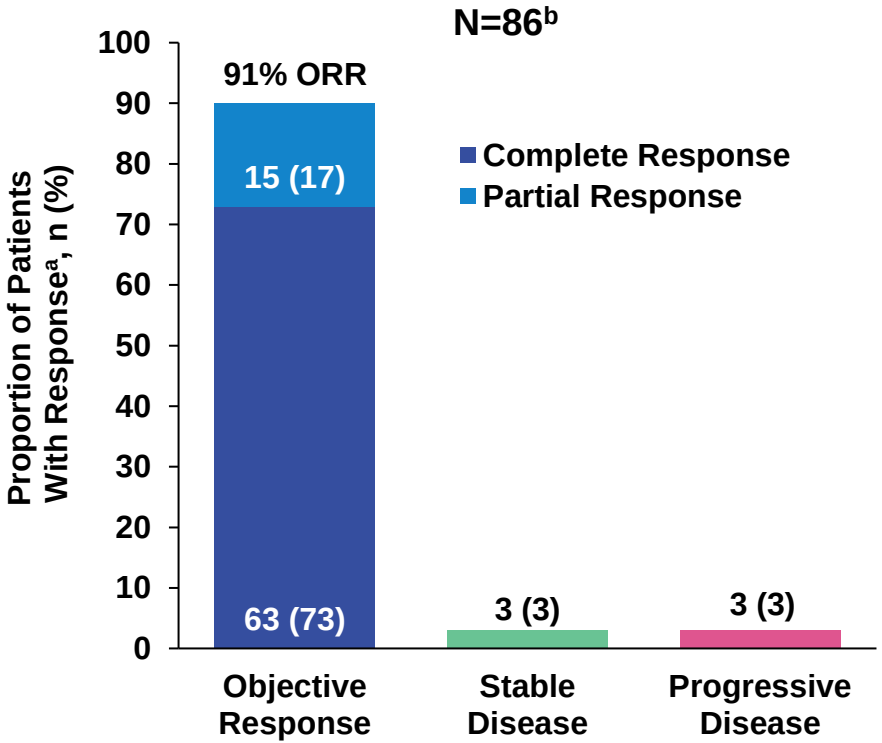
Prior Therapies

Characteristic	Cohort 3 (N=86)
Median no. of prior 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)
Relapsed or refractory disease, n (%)	
Refractory to last MCL therapy	12 (14)
Relapsed after last MCL therapy	74 (86)
Prior autologous SCT, n (%)	41 (48)
Prior Hyper-CVAD, n (%)	7 (8)
Received any bridging therapy, n (%)	31 (36)
Systemic therapy only	24 (28)
Radiotherapy only	4 (5)
Systemic therapy and radiotherapy	3 (3)

- Nearly half of patients received prior autologous SCT
- All patients received prior anti-CD20 therapy and most received prior anthracycline, while 27% of patients had prior bendamustine therapy
- Most patients relapsed after their last therapy rather than being refractory to their last therapy

Hyper-CVAD, hyperfractionated Cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), dexamethasone, methotrexate, and cytarabine; MCL, mantle cell lymphoma; SCT, stem cell transplantation.

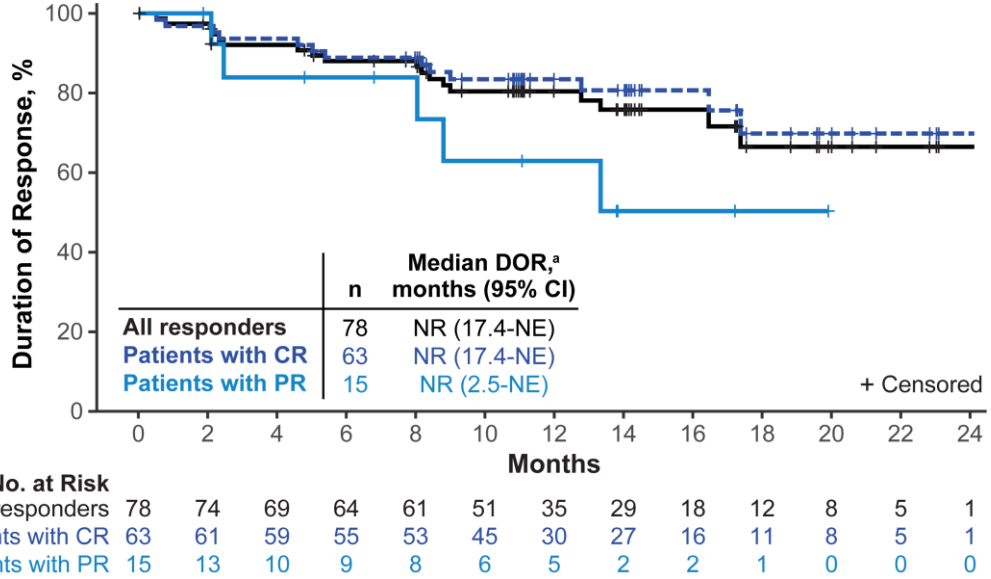
Best Objective Response



- The primary endpoint was met with an ORR of 91% (95% CI, 83-96), including a 73% CR rate
- High ORRs were observed across key subgroups of interest including:
  - 100% of patients with confirmed *TP53* mutations (15/15)
  - 97% of patients with ≥ the median tumor burden at baseline (38/39)
  - 94% of patients with Ki-67 scores of ≥50% (17/18)
  - 89% of patients with intermediate or high-risk sMIPI scores (56/63)
  - 83% of patients with prior bendamustine treatment (19/23)

[a] Per IRRC assessment. [b] Two patients were not assessable but included in N.
CR, complete response; IRRC, independent radiology review committee; ORR, objective response rate; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; TP53, tumor protein 53.

Duration of Response

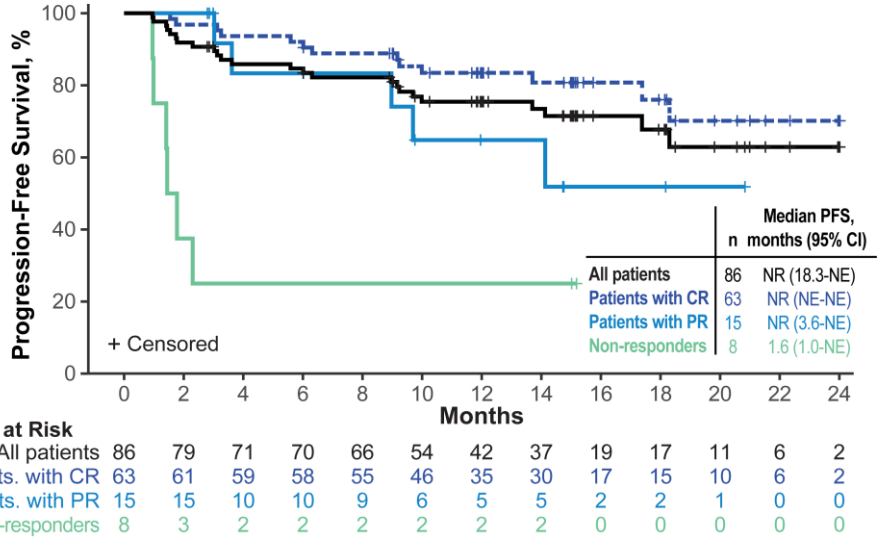


- The 12-month DOR rate was 80% for all responders (n=78) with 69% of responders (54/78) in ongoing response at time of analysis
- The 12-month DOR rates for patients in CR or PR were 84% and 63%, respectively

[a] Per IRRC assessment.
CR, complete response; DOR, duration of response; IRRC, independent radiology review committee; NE, not estimable; NR, not reached; PR, partial response.

Progression-Free Survival and Overall Survival

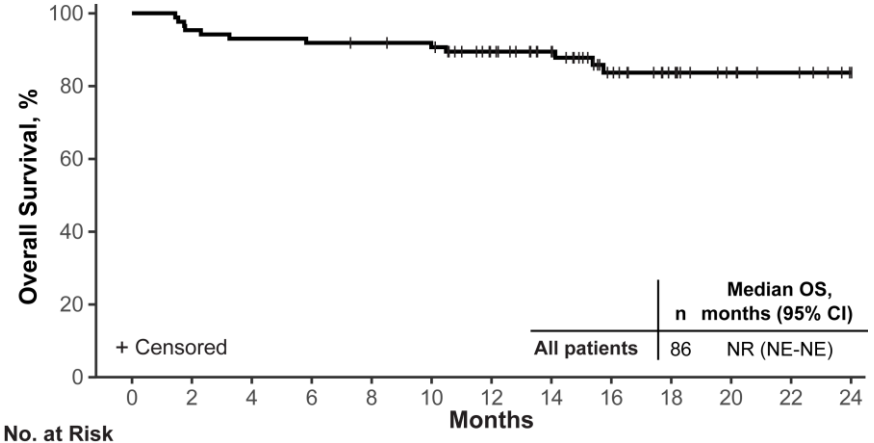
Progression-Free Survival[a]



No. at Risk

All patients	86	79	71	70	66	54	42	37	19	17	11	6	2
Pts. with CR	63	61	59	58	55	46	35	30	17	15	10	6	2
Pts. with PR	15	15	10	10	9	6	5	5	2	2	1	0	0
Non-responders	8	3	2	2	2	2	2	2	0	0	0	0	0

Overall Survival



No. at Risk

All patients	86	82	80	79	78	76	64	54	37	25	16	13	6

- The 12-month PFS rates were 75% for all patients (N=86), 84% for those with CR (n=63), and 65% for those with PR (n=15)
- The 12-month OS rate was 90%, with 85% of patients (73/86) still alive at time of analysis

[a] Per IRRC assessment.
CR, complete response; IRRC, independent radiology review committee; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response; pts, patients.

Adverse Events Among All Treated Patients

AEs,[a] 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 by preferred term (occurring in ≥25% of patients)[b]		
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
Platelet count decreased	25 (29)	15 (17)
Tremor	25 (29)	2 (2)
Constipation	24 (28)	0
Lymphocyte count decreased	23 (27)	23 (27)

- The most common AEs of any grade were
  - Pyrexia (94%)
  - Anemia (57%)
  - Hypotension (51%)
- The most common Grade ≥3 AEs by preferred term were
  - Neutropenia (43%)
  - Neutrophil count decreased (42%)
  - White blood cell count decreased (37%)

[a] AEs are defined as any AE with onset on or after initiation of brexu-cel infusion. AEs that occurred on/after retreatment are not included. [b] AEs are coded using MedDRA version 27.0 and graded per CTCAE version 4.03. Some preferred terms had similar or overlapping definitions but were coded differently in the reporting system. Multiple incidences of the same AE in 1 patient are counted once at the highest grade for that patient.
AE, adverse event; brexu-cel, brexucabtagene autoleucel; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Adverse Events of Special Interest

AEs of Special Interest	Cohort 3 (N=86)	
	Any Grade	Grade ≥3
CRS,[a] n (%)	82 (95)	5 (6)
Neurological events,[b] n (%)	67 (78)	23 (27)
ICANS,[c] n (%)	57 (66)	18 (21)
Thrombocytopenia,[d] n (%)	45 (52)	29 (34)
Neutropenia,[d,e] n (%)	74 (86)	73 (85)
Anemia,[d] n (%)	49 (57)	22 (26)
Serious infection,[d] n (%)	21 (24)	20 (23)
Hypogammaglobulinemia,[d] n (%)	7 (8)	0

- Grade ≥3 CRS and ICANS occurred in 6% and 21% of patients, respectively
- Median (range) time to onset and duration of CRS events was 4 (1-12) and 6 days (1-36), respectively
- Median (range) time to onset and duration of ICANS was 7 (1-31) and 7 days (1-122), respectively
- No cases of replication-competent retrovirus or brexu-cel–related secondary T-cell malignancies were reported

[a] CRS events are graded per the revised grading system proposed by Lee et al 2014.[1] [b] Neurologic events are identified based on Topp et al 2015. [c] ICANS events are graded per the ASTCT ICANS grading (Lee et al 2019).[2]
[d] All other events are graded per CTCAE version 4.03. [e] Includes neutropenia, neutrophile count decreased and febrile neutropenia.
1. Lee DW, et al. *Blood*. 2014;124(2):188-195. 2. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019(4):625-638.
AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; brexu-cel, brexucabtagene autoleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; ICANS, immune effector cell-associated neurotoxicity syndrome.

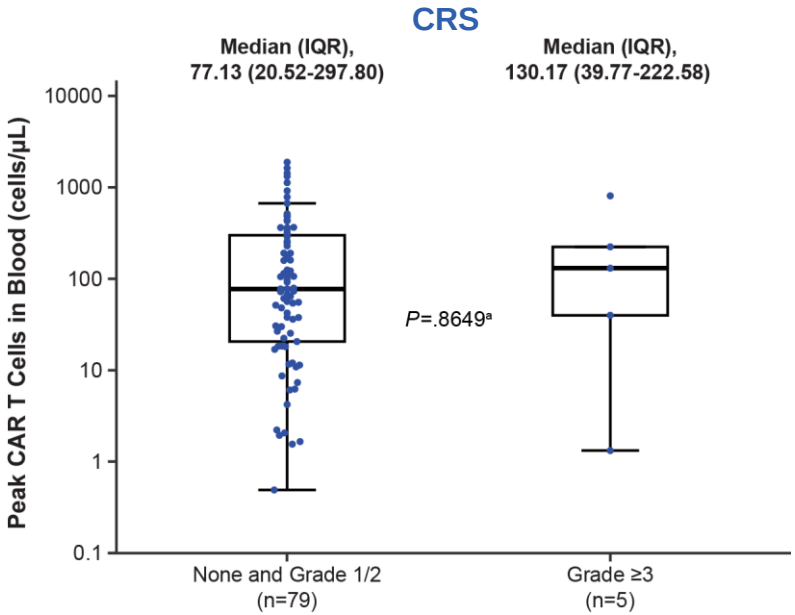
Reasons for Deaths

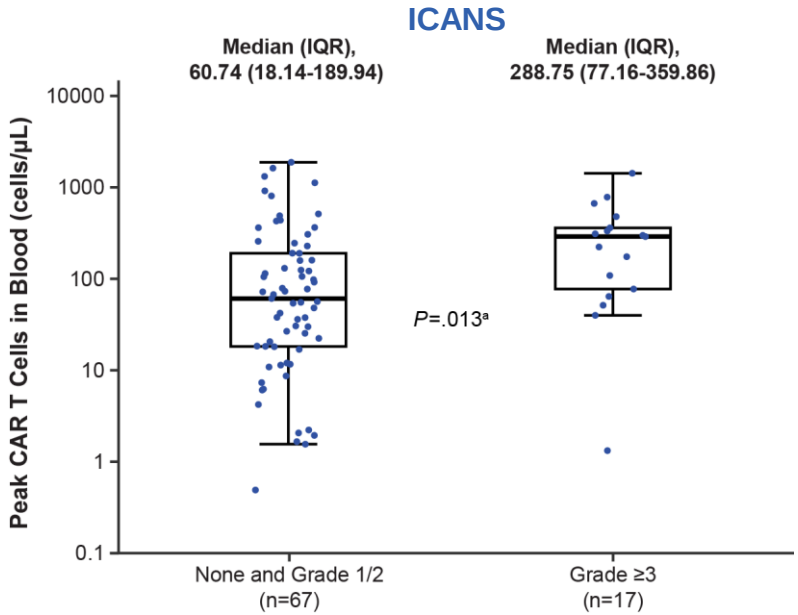
Reasons for Death, n (%)	Cohort 3 (N=86)
Deaths	13 (15)
Deaths due to AEs	7 (8)
Related to treatment[a]	4 (5)
Progressive multifocal leukoencephalopathy	1
Septic shock	1
Polymicrobial infection	1
Human herpesvirus 6 encephalitis	1
Not related to treatment	3 (3)
Intracranial hemorrhage	1
Hepatocellular carcinoma	1
Pneumonia	1
Deaths due to PD[b]	5 (6)
Deaths due to other cause[c]	1 (1)

- At data cutoff, 73 patients (85%) were alive and 13 (15%) had died
- Reasons for death included AEs (n=7), PD (n=5), and other (n=1)
- No deaths occurred ≤30 days after brexu-cel infusion

[a] AE was deemed related to brexu-cel, lymphodepleting chemotherapy, or both. [b] One death was recorded as "other" but had PD prior to death so was counted as PD in this table. [c] Death due to failure to thrive after hip fracture. AE, adverse event; brexu-cel, brexucabtagene autoleucel; PD, progressive disease.

CAR T-Cell Expansion by Grade ≥3 CRS and ICANS

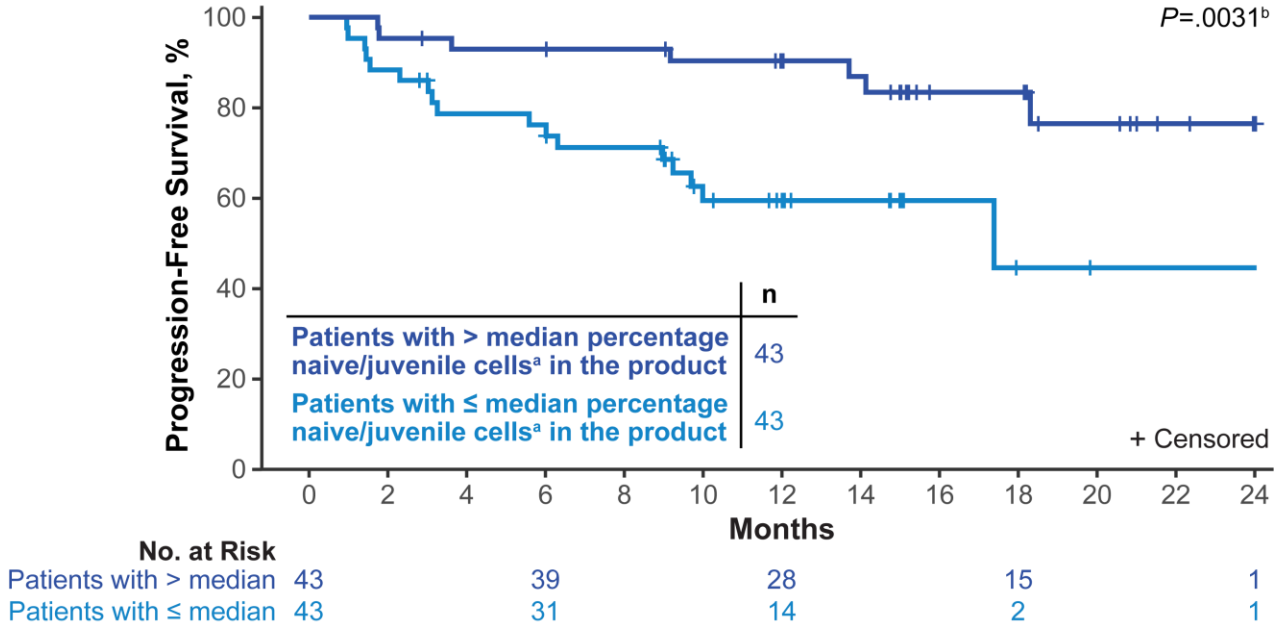




- No significant differences were observed in peak CAR T-cell expansion by response status, though small patient numbers in the non-responder group may have confounded these results (data not shown)
- CAR T-cell expansion was not significantly associated with Grade ≥3 CRS but was significantly associated with Grade ≥3 ICANS

[a] Wilcoxon rank sum test.
CAR, chimeric antigen receptor; CRS, cytokine release factor; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range.

Progression-Free Survival by Percentage of Naive/Juvenile Cells in the Product



- A higher percentage of naive/juvenile cells in the product prior to infusion (> median) was significantly associated with improved PFS

[a] Naive/juvenile cells are defined as CD3+ T cells in the final product expressing both CCR7 and CD45RA as measured by flow cytometry assay. [b] Log-rank test.
PFS, progression-free survival.

Conclusions

- In Cohort 3, brexu-cel demonstrated a high ORR (91%) and CR rate (73%) in patients with R/R MCL who were naive to BTKi, consistent with Cohort 1 of ZUMA-2
  - High ORRs were observed across most high-risk subgroups
- Efficacy was durable, with extended median DOR, PFS, and OS that translated to a 12-month OS rate of 90%
- No new safety signals were detected, with a low rate of Grade ≥3 CRS and a similar rate of Grade ≥3 neurologic events to Cohort 1
- Higher CAR T-cell expansion was associated with Grade ≥3 ICANS and higher percentage of naive/juvenile cells in the product was associated with improved PFS
- These results support the continued use of brexu-cel in the R/R MCL setting, including patients naive to BTKi therapy
- Longer follow-up is needed to further understand long-term outcomes for these patients

Brexu-cel, brexucabtagene autoleucel; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; ICANS, immune effector cell-associated neurotoxicity syndrome; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R MCL, relapsed/refractory mantle cell lymphoma.

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- This study was funded by Kite
- Full author disclosures are available through the virtual meeting platform

Additional Resources

- Full author disclosures are available through the virtual meeting platform
- A plain language summary of the key results from this presentation is available through the Quick Response (QR) code