Poster
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Five-Year Outcomes of Patients With Relapsed or Refractory Mantle Cell Lymphoma Treated With Brexucabtagene Autoleucel in ZUMA-2 Cohorts 1 and 2

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BACKGROUND

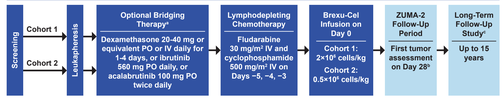
- Brexucabtagene autoleucel (brexu-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of adults with relapsed or refractory (R/R) mantle cell lymphoma (MCL) in the United States and European Union (EU; after receiving ≥2 prior systemic treatments including a Bruton tyrosine kinase inhibitor [BTKi] in the EU)[1,2]
- Approval was based on the high objective response rate (ORR; 93%; 67% complete response [CR]) observed for 60 patients with R/R MCL treated in the pivotal Cohort 1 ZUMA-2 study (NCT02601313)[3]
  - Median time from infusion to CR was 3.0 months (range, 0.9-9.3)[3]
  - After a median follow-up of ~4 years, brexu-cel, given at the pivotal dose, demonstrated a median overall survival (OS) of 46.4 months in 68 patients with R/R MCL in Cohort 1[4]
- Two doses were initially assessed in ZUMA-2, 2.0×10^6 anti-CAR T cells/kg (Cohort 1; pivotal) and 0.5×10^6 anti-CAR T cells/kg (Cohort 2); however, the risk/benefit ratio of the Cohort 1 dose was deemed optimal before Cohort 2 reached full enrollment due to limited CAR T-cell area under the curve (AUC) expansion in Cohort 2

OBJECTIVES

- To assess the primary efficacy and pharmacokinetic outcomes of patients treated with the lower dose of brexu-cel in Cohort 2
- To assess the long-term safety and efficacy outcomes of patients in ZUMA-2 Cohorts 1 and 2 after 5 years of median follow-up

METHODS

Figure 1. ZUMA-2 and LTFU Study Design



Key ZUMA-2 Eligibility Criteria
- Age ≥18 years with R/R MCL
- 1-5 prior regimens including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody, and BTKi therapy

Primary ZUMA-2 Endpoint
- ORR (CR + PR; IRRC assessed per the Lugano classification[5])

Key Secondary ZUMA-2 Endpoints
- DOR, BOR, PFS, OS
- AEs

Primary LTFU Endpoint
- Assess the occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to gene-modified cells

Key Secondary LTFU Endpoints
- OS, causes of death, and rates of RCR/RCL

[a]Administered after leukapheresis and completed ≥5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging. [b] Bone marrow biopsy was to be done at screening and, if positive, not done, or indeterminate, a biopsy was needed to confirm CR. [c]After study completion of ZUMA-2, patients were offered an opportunity to transition to a separate LTFU study, KTI-US-982-5968, where they were and will continue to be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to brexu-cel for up to 15 years from the time of brexu-cel infusion.
AE, adverse event; BOR, best objective response; brexu-cel, brexucabtagene autoleucel; BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; DOR, duration of response; IRRC, independent radiology review committee; IV, intravenous; LTFU, long-term follow-up; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography–computed tomography; PFS, progression-free survival; PO, orally; PR, partial response; RCL, replication-competent lentivirus; RCR, replication-competent retrovirus; R/R, relapsed/refractory; SAE, serious adverse event.

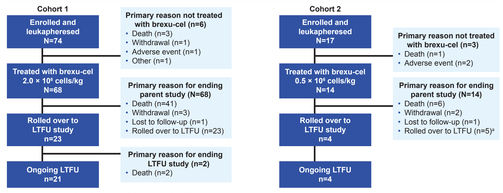
Table 1. Late-Onset AEs Monitored in LTFU

AE	Assessment
Neurologic disorders	Type, date of onset, severity, treatment, and date of resolution
Autoimmune disorders	Type, date of onset, severity, treatment, and date of resolution
Hematologic disorders	Type, date of onset, severity, treatment, and date of resolution
Serious infections[a]	Type, organism, and timing of infection
Secondary malignancies	Time to development of the secondary malignancy, type, location, and staging

[a] Viral, bacterial, or fungal. AE, adverse event; LTFU, long-term follow-up.

- The primary efficacy analysis for Cohort 2 was to be conducted after approximately 40 patients received brexu-cel at a dose of 0.5×10^6 anti-CD19 CAR T cells/kg; however, Cohort 2 did not achieve full enrollment and, therefore, a modified intent-to-treat analysis set was used for efficacy analyses in Cohort 2
- After completion of ZUMA-2, patients could transition to the long-term follow-up (LTFU) study (NCT05041309), where they were and will continue to be monitored for late-onset adverse events (AEs) possibly related to brexu-cel (**Table 1**), the presence of replication-competent retrovirus (RCR), and/or insertional mutations
- Time-to-event endpoints were analyzed with Kaplan-Meier estimates and 2-sided 95% CIs
- Safety and efficacy analyses included all patients treated with any dose of brexu-cel

Figure 2. Patient Disposition for ZUMA-2 Cohorts 1 and 2



[a] 1 patient was not enrolled into LTFU by DCO but had initiated the process.
Brexu-cel, brexucabtagene autoleucel; DCO, data cutoff; LTFU, long-term follow-up.

RESULTS

Cohort 2 Primary Analysis

- As of July 24, 2019, 14 patients enrolled in Cohort 2 with a median follow-up of 16.0 months (range, 13.9-18.0)

Cohorts 1 and 2 5-Year Analysis

- As of April 1, 2024, the median follow-up was 67.8 months (range, 58.2-88.6) and 72.3 months (range, 70.1-74.3) for Cohort 1 and Cohort 2, respectively
- Of the 68 patients enrolled in Cohort 1, 24 patients were still alive (35%; 2 withdrew consent and 1 lost to follow-up) and 44 patients died (65%;1 patient withdrew consent and then died; **Figure 2**)
- Of the 14 patients enrolled in Cohort 2, 8 patients were still alive (57%; 2 withdrew consent and 1 lost to follow-up) and 6 patients died (43%; **Figure 2**)

Cohorts 1 and 2 LTFU Analysis

- As of April 1, 2024, 27 patients (Cohort 1, n=23; Cohort 2, n=4) enrolled in the LTFU study by data cutoff with an actual median follow-up of 65.8 months (range, 46.9-88.6; calculated as time from infusion to date of death or last known alive)
- Two patients in LTFU study have died, both from Cohort 1 (**Figure 2**)

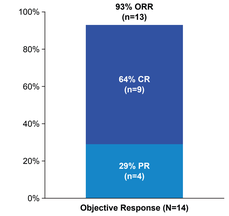
Table 2. Baseline Patient and Disease Characteristics

Characteristic	Cohort 1[3] (N=68)	Cohort 2 (N=14)
Median age (range), years	65 (38-79)	61.5 (52-73)
Male, n (%)	57 (84)	11 (79)
ECOG PS of 1, n (%)	24 (35)	7 (50)
Intermediate or high sMIPI, n (%)	38 (56)	7 (50)
Ki-67 PI ≥30%, n (%)	43 (63)	10 (71)
Median no. of prior therapies, n (range)	3 (1-5)	3 (2-5)
Prior therapy, n (%)		
Platinum	16 (24)	6 (43)
Anthracycline	49 (72)	11 (79)
Bendamustine	37 (54)	7 (50)
Lenalidomide	19 (28)	1 (7)
Proteasome inhibitor	25 (37)	3 (21)
Autologous SCT	29 (43)	6 (43)
BTKi therapy	68 (100)	14 (100)
Ibrutinib	58 (85)	13 (93)
Acalabrutinib	16 (24)	2 (14)
Both	6 (9)	1 (7)
Relapsed or refractory disease, n (%)		
Relapse after autologous SCT	29 (43)	6 (43)
Refractory to last MCL therapy	27 (40)	7 (50)
Relapse after last MCL therapy	12 (18)	1 (7)
CD19 positive IHC by central lab, n (%)	50 (74)	10 (71)
Tumor burden (SPD) by central read (mm²)		
n	63	7
Median (range)	2088 (260-16878)	2166.5 (669-10624)
Positive bone marrow assessment at baseline, n (%)	37 (54)	8 (57)
LDH relative to upper limit, n (%)		
LDH <0.67 ULN	16 (24)	5 (36)
0.67 ULN ≤LDH <ULN	24 (35)	3 (21)
ULN ≤LDH <1.5 ULN	15 (22)	2 (14)
1.5 ULN ≤LDH	11 (16)	3 (21)
Missing	2 (3)	1 (7)
Received bridging therapy, n (%)[a]	25 (37)	7 (50)

[a] Bridging therapy was received after leukapheresis and prior to conditioning chemotherapy in ZUMA-2.
BTKi, Bruton tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; PI, proliferation index; SCT, stem cell transplantation; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; SPD, sum of the products of diameters; ULN, upper limit of normal.

- Baseline characteristics for Cohort 2 (N=14) were similar to Cohort 1[3] (**Table 2**): median (range) age and number of prior therapies were 61.5 years (52-73) and 3 (2-5); 71% Ki-67 proliferation index ≥30%, 50% intermediate or high simplified Mantle Cell Lymphoma International Prognostic Index scores, 50% were refractory to last therapy, and 43% relapsed after autologous stem cell transplantation

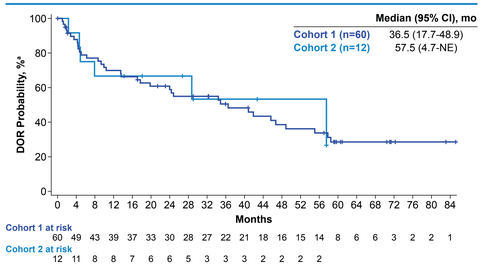
Figure 3. Best Objective Response by IRRC for Cohort 2 Primary Analysis



- In Cohort 2 primary analysis, ORR was 93% (95% CI, 66.1-99.8; **Figure 3**); 64% of patients had a CR and 29% had a partial response
  - No patients had stable disease or progressive disease
  - One patient was not assessed at the time of analysis

CR, complete response; IRRC, independent radiology review committee; ORR, objective response rate; PR, partial response.

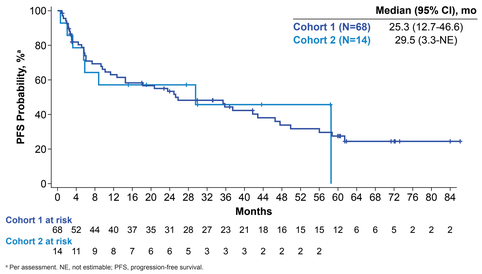
Figure 4. Duration of Response in ZUMA-2 5-Year Outcomes



[a] Per investigator assessment. DOR, duration of response; NE, not estimable.

- In Cohort 1, median investigator-assessed duration of response (DOR) was 36.5 months (95% CI, 17.7-48.9; n=60) with 17 patients in ongoing response at data cutoff, all CR (**Figure 4**)
- In Cohort 2, median DOR was 57.5 months (95% CI, 4.7-not estimable [NE]; n=12) with 3 patients in ongoing response at data cutoff, all CR (**Figure 4**)

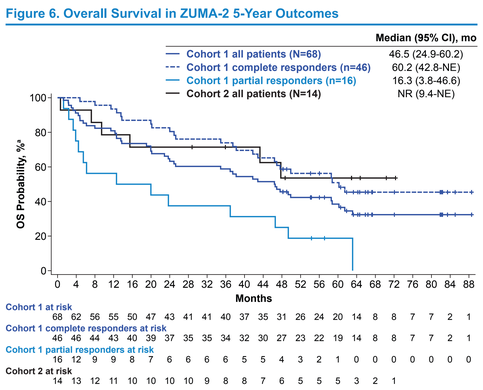
Figure 5. Progression-Free Survival in ZUMA-2 5-Year Outcomes



[a] Per assessment. NE, not estimable; PFS, progression-free survival.

- Median investigator-assessed progression-free survival (PFS) was 25.3 months (95% CI, 12.7-46.6; N=68) and 54-month PFS rate was 32% (95% CI, 20.0-44.2) in Cohort 1 (**Figure 5**)
- In Cohort 2, median PFS was 29.5 months (95% CI, 3.3-NE) and 54-month PFS rate was 46% (95% CI, 17.3-70.5); N=14; **Figure 5**)

Figure 6. Overall Survival in ZUMA-2 5-Year Outcomes



NE, not estimable; NR, not reached; OS, overall survival.

- In Cohort 1, the median OS was 46.5 months (95% CI, 24.9-60.2) and 60-month OS rate was 39% (95% CI, 26.7-50.1; **Figure 6**)
- In Cohort 2, median OS was not reached (95% CI, 9.4-NE) and 60-month OS rate was 54% (95% CI, 23.8-76.2; **Figure 6**)

Table 3. Treatment-Emergent Adverse Events ≥40% in Cohort 1 or Cohort 2

TEAE,[a] n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
Any TEAE	68 (100)	14 (100)
Grade ≥3	67 (99)	13 (93)
Any brexu-cel–related TEAE	66 (97)	14 (100)
Grade ≥3	54 (79)	10 (71)
TEAEs in ≥40% of patients in either cohort		
Any pyrexia	64 (94)	13 (93)
Grade ≥3	9 (13)	3 (21)
Any anemia	46 (68)	7 (50)
Grade ≥3	35 (51)	6 (43)
Any neutrophil count decreased	37 (54)	6 (43)
Grade ≥3	36 (53)	6 (43)
Any hypotension	36 (53)	11 (79)
Grade ≥3	15 (22)	8 (57)
Any platelet count decreased	35 (51)	5 (36)
Grade ≥3	26 (38)	5 (36)
Any chills	28 (41)	6 (43)
Grade ≥3	0	0
Any white blood cell count decreased	28 (41)	7 (50)
Grade ≥3	28 (41)	7 (50)
Any fatigue	26 (38)	7 (50)
Grade ≥3	1 (1)	0
Any hypoxia	26 (38)	7 (50)
Grade ≥3	14 (21)	2 (14)
Any tremor	24 (35)	7 (50)
Grade ≥3	0	2 (14)
Any nausea	22 (32)	7 (50)
Grade ≥3	1 (1)	0
Any decrease in appetite	15 (22)	7 (50)
Grade ≥3	0	0
Any confusional state	14 (21)	6 (43)
Grade ≥3	8 (12)	1 (7)
Any dyspnea	14 (21)	6 (43)
Grade ≥3	2 (3)	3 (21)

[a] 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 26.0 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.
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.

- In Cohort 1, the most common Grade ≥3 AEs were neutrophil count decreased (53%), anemia (51%), and white blood cell count decreased (41%; **Table 3**)
- In Cohort 2, the most common Grade ≥3 AEs were hypotension (57%), white blood cell count decreased (50%), neutrophil count decreased (43%), and anemia (43%; **Table 3**)

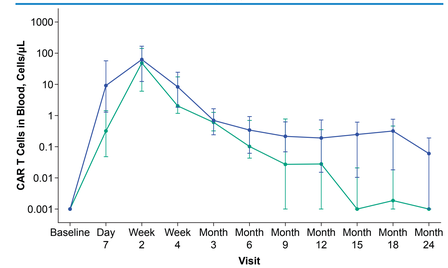
Table 4. Adverse Events of Special Interest in ZUMA-2

AEs of Interest, n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
Any CRS[a]	62 (91)	13 (93)
Grade ≥3	10 (15)	2 (14)
Any neurologic event[b]	43 (63)	13 (93)
Grade ≥3	21 (31)	6 (43)
Any thrombocytopenia	50 (74)	7 (50)
Grade ≥3	36 (53)	6 (43)
Any neutropenia	59 (87)	11 (79)
Grade ≥3	58 (85)	11 (79)
Any anemia	47 (69)	7 (50)
Grade ≥3	36 (53)	6 (43)
Any infection	37 (54)	7 (50)
Grade ≥3	26 (38)	3 (21)
Any hypogammaglobulinemia	14 (21)	0
Grade ≥3	1 (1)	0

[a] CRS events were graded per the revised grading system of Lee et al. 2014.[6] [b] Neurologic events were identified based on Topp et al. 2015.[7] All other events were graded per CTCAE v.4.03.
AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.

- Rates of Grade ≥3 cytokine release syndrome (CRS) and neurological events were 15% and 31% in Cohort 1, and 14% and 43% in Cohort 2, respectively (**Table 4**); no cases of Grade 5 CRS or neurological events occurred (**Table 4**)
  - CRS and neurological events resolved within a median of 10 days and 15 days in Cohort 1, and 10 days and 17 days in Cohort 2, respectively
- The 5-year rates of progressive disease (PD)–related death and non-PD–related death were 40% (24/60) and 22% (13/60) in Cohort 1 responders per investigator assesment, respectively (data not shown)
- On LTFU, 1 patient had 3 ongoing AEs: hypogammaglobulinemia and 2 viral infections that arose prior to LTFU
- Two patients died on LTFU, both due to PD
- No cases of secondary T-cell malignancies were reported in ZUMA-2

Figure 7. CAR T-Cell Expansion (IQR) Over Time[3,8]



CAR, chimeric antigen receptor; IQR, interquartile range.

- As previously reported, in Cohort 1, median time to peak CAR T-cell levels was 15 days (interquartile range [IQR], 8-15) with a median peak and AUC at day 28 ($AUC_{0\text{-}28}$) CAR T-cell levels of 83.12 cells/µL (IQR, 17.40-265.71) and 1112.86 cells/µL×day (230.75-3005.32)[3,8]
- In Cohort 2, median time to peak CAR T-cell levels was 15 days (IQR, 15-29) with a median peak and $AUC_{0\text{-}28}$ CAR T-cell levels of 56.07 cells/µL (IQR, 26.34-139.16) and 688.40 cells/µL×day (IQR, 286.72-1477.66), respectively (**Figure 7**)

CONCLUSIONS

- Consistent with Cohort 1, brexu-cel demonstrated a high ORR, durable responses, and an expected safety profile in patients with R/R MCL in Cohort 2, despite the lower dose; however, the small sample size limits interpretation of these results
  - With >5 years of median follow-up, patients in Cohorts 1 and 2 continued to experience durable responses with high 60-month OS rates
  - Despite the less robust CAR T-cell expansion in Cohort 2 than in Cohort 1, a high response rate and DOR were observed. It is unclear why the lower dose resulted in durable responses but may be due to the high CD19 expression of MCL cells, small patient numbers, and differences in patient and disease characteristics
- No new safety signals were detected, and no secondary T-cell malignancies were reported at anytime in ZUMA-2
- These results support the continued use of brexu-cel in R/R MCL

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DISCLOSURES

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PLAIN LANGUAGE SUMMARY

A plain language summary of this presentation is available through the Quick Response (QR) code

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