Poster
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# ZUMA-8: A Phase 1 Study of Brexu-cel, an Anti-CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy, in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

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## BACKGROUND

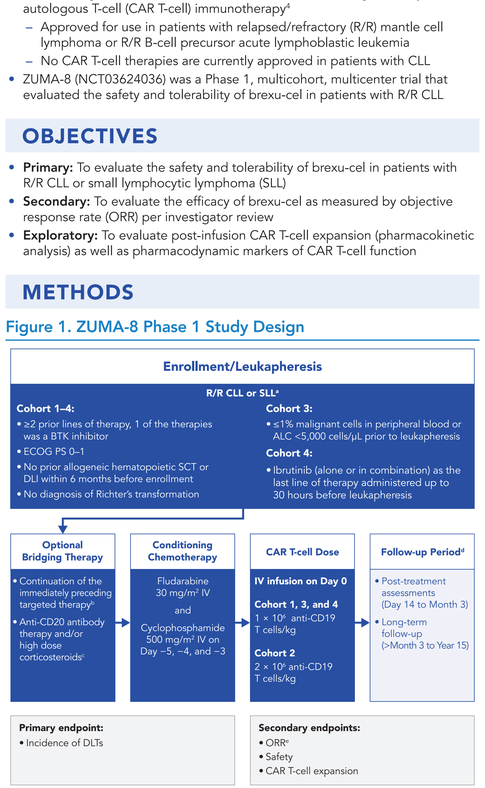
- Chronic lymphocytic leukemia (CLL) remains generally incurable, despite recent advances in treatments, such as Bruton's tyrosine kinase (BTK) inhibitors and Bcl-2 inhibitors[1,2]
  - Targeted therapy with BTK inhibitors produces durable remissions, but most responses are partial remission and complete remission is infrequent[3]
  - There is a continued risk of disease relapse, especially in patients with high-risk disease features (eg, *TP53* aberrations on chromosome 17p)[3]
- Brexucabtagene autoleucel (brexu-cel) is a CD19-directed genetically modified autologous T-cell (CAR T-cell) immunotherapy[4]
  - Approved for use in patients with relapsed/refractory (R/R) mantle cell lymphoma or R/R B-cell precursor acute lymphoblastic leukemia
  - No CAR T-cell therapies are currently approved in patients with CLL
- ZUMA-8 (NCT03624036) was a Phase 1, multicohort, multicenter trial that evaluated the safety and tolerability of brexu-cel in patients with R/R CLL

## OBJECTIVES

- **Primary:** To evaluate the safety and tolerability of brexu-cel in patients with R/R CLL or small lymphocytic lymphoma (SLL)
- **Secondary:** To evaluate the efficacy of brexu-cel as measured by objective response rate (ORR) per investigator review
- **Exploratory:** To evaluate post-infusion CAR T-cell expansion (pharmacokinetic analysis) as well as pharmacodynamic markers of CAR T-cell function

## METHODS

### Figure 1. ZUMA-8 Phase 1 Study Design




[a]Patients with SLL were eligible but none were enrolled. [b]BTK inhibitors, Bcl-2 inhibitors, or PI3K inhibitors. [c]Dexamethasone 40 mg or an equivalent was recommended, although the choice, dose, and route of administration of corticosteroid could have been adjusted for age and comorbidities per local and institutional guidelines. Corticosteroids at a dose of ≥5 mg prednisone (or equivalent) had to be avoided for 7 days prior to leukapheresis and 5 days prior to brexu-cel administration. [d]Disease assessments were at Day 28, Week 8, Month 3, every 3 months up to Year 2, and then every 6 months. [e]Per investigator review as defined by the IWCLL 2018 criteria.

ALC, absolute lymphocyte count; Bcl-2, B-cell lymphoma 2; brexu-cel, brexucabtagene autoleucel; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; DLI, donor lymphocyte infusion; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; IWCLL; International Workshop on Chronic Lymphocytic Leukemia; ORR, objective response rate; PI3K, phosphoinositide 3-kinase; R/R, relapsed/refractory; SCT, stem cell transplant; SLL, small lymphocytic lymphoma.

- Patients were hospitalized for observation for ≥7 days after infusion
- Efficacy outcomes, safety outcomes, pharmacological profile, and CAR T-cell levels in the blood are reported for all patients treated with brexu-cel
- Data cutoff for the analysis was May 2, 2022

## STATISTICAL ANALYSIS

- Descriptive statistics were used to analyze efficacy and safety data
- Pre–CAR T-cell infusion translational analyses were based on data collected at screening or enrollment/leukapheresis
- If data collected at screening or enrollment/leukapheresis (by central laboratory assessment) were not available, baseline/post-bridging therapy data (by local laboratory assessment) were used

## RESULTS

### PATIENTS

- Median follow-up duration[a] was 18.0 months (range, 2.7–35.8 months) in the entire study population; median follow-up durations for individual cohorts were as follows:
  - Cohort 1 (n=6): 31.5 months (range, 5.1–35.8 months)
  - Cohort 2 (n=3): 10.6 months (range, 2.7–26.3 months)
  - Cohort 3 (n=3): 18.0 months (range, 16.4–18.0 months)
  - Cohort 4 (n=3): 16.0 months (range, 3.9–17.3 months)
- Patients were heavily pretreated (**Table 1**)
  - 12 patients (80%) received >3 prior lines of therapy
  - 13 of 15 patients received bridging therapy[b]
- High-risk disease characteristics were common in patients
  - 12 patients (80%) had the presence of any of the following: 17p deletion (27%; n=4), 11q deletion (27%; n=4), 13q deletion monosomy (27%; n=4), trisomy 12 (13%; n=2), or complex karyotype (47%; n=7)

[a]Actual follow-up time from brexu-cel infusion calculated as: (death date or last date known alive − brexu-cel infusion date + 1)/30.4375. [b]Patients received one or more bridging therapies, including ibrutinib, venetoclax, and idelalisib.

### Table 1. Patient Characteristics

| Characteristic | Cohort 1 (low dose) n=6 | Cohort 2 (high dose) n=3 | Cohort 3 (low tumor burden) n=3 | Cohort 4 (post ibrutinib) n=3 | Overall N=15 |
|---|---|---|---|---|---|
| Median age, years (range) | 60.5 (53–68) | 61.0 (52–63) | 69.0 (56–79) | 67.0 (53–70) | 63.0 (52–79) |
| Male, n (%) | 3 (50) | 2 (67) | 3 (100) | 2 (67) | 10 (67) |
| ECOG PS 1, n (%) | 4 (67) | 1 (33) | 1 (33) | 2 (67) | 8 (53) |
| No. of prior therapy lines, n (%)<br>2<br>3<br>>3 | <br>0<br>0<br>6 (100) | <br>0<br>0<br>3 (100) | <br>1 (33)<br>1 (33)<br>1 (33) | <br>1 (33)<br>0<br>2 (67) | <br>2 (13)<br>1 (7)<br>12 (80) |
| 17p deletion, n (%) | 1 (17) | 1 (33) | 0 | 2 (67) | 4 (27) |
| Complex karyotype, n (%)[a] | 3 (50) | 3 (100) | 1 (33) | 0 | 7 (47) |
| WBCs, $10^9$/L (range) | 11.9 (6.2–29.1) | 36.8 (8.2–65.4) | 6.0 (2.5–6.8) | 5.8 (4.0–149.0) | 7.4 (2.5–149.0) |
| Hemoglobin, mmol/L (range) | 7.0 (5.3–8.9) | 7.6 (5.1–8.7) | 8.5 (7.3–8.9) | 6.8 (5.3–8.4) | 7.3 (5.1–8.9) |
| Platelets, $10^9$/L (range) | 110 (73–180) | 127 (47–156) | 109 (93–141) | 65 (27–150) | 109 (27–180) |
| Median tumor burden in lymph node (SPD), $mm^2$ (range) | 7,026.0 (464.0–26,688.3) | 7,458.1 (2,140.4–9,715.0) | 625.0 (614.0–2,472.0) | 1,434.0 (786.0–2,308.5) | 2,308.5 (464.0–26,688.3) |
| Median CLL lymphocytes in bone marrow biopsy, % (range)[b,c] | 81.0 (0–93.5) | 80.0 (16.9–97.0) | 30.0 (5.0–30.0) | 95.0 (33.0–96.0) | 77.5 (0–97.0) |

[a]Complex karyotype status defined as ≥3 clonal chromosomal abnormalities; status was unknown for 1 patient in Cohort 4. [b]Based on assessments performed at screening or after bridging therapy. [c]%CLL lymphocyte data were not available for 1 patient in Cohort 1.

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; No., number; SPD, sum of products of diameters; WBC, white blood cell.

- As expected, patients in Cohort 3 had the lowest tumor burden
  - Median tumor burden (SPD) was 625.0 $mm^2$ (range, 614.0–2,472.0 $mm^2$)
  - Median CLL lymphocytes in bone marrow aspirate was 30.0% (range, 5.0%–40.0%)
  - No patients had a 17p deletion

## SAFETY

- Dose-limiting toxicities (DLTs) were observed in 1 patient in Cohort 3
  - Grade 3–4 hypocalcemia, hyponatremia, hypotension, and cytokine release syndrome (CRS) events that met prespecified criteria for DLTs
  - Occurred with an onset from Day 4 to Day 12, resolved after 14 days, and the patient achieved complete response (CR)
- Grade ≥3 adverse events (AEs) were reported in all patients and Grade ≥3 serious AEs were reported in 5 patients (33%) (**Table 2**)
  - Grade ≥3 treatment-related AEs were reported in 9 patients (60%)
  - Grade 4 CRS was reported in 1 patient (7%)
  - Grade ≥3 neurologic events were reported in 3 patients (20%)
  - There were no Grade 5 AEs

### Table 2. AE Summary

| AE, n (%)[a] | Cohort 1 (low dose) n=6 | Cohort 2 (high dose) n=3 | Cohort (low tumor burden) n=3 | Cohort 4 (post ibrutinib) n=3 | Overall N=15 |
|---|---|---|---|---|---|
| Any-grade[b] | 6 (100) | 3 (100) | 3 (100) | 3 (100) | 15 (100) |
| TRAE | 5 (83) | 2 (67) | 3 (100) | 2 (67) | 12 (80) |
| CRS[c] | 5 (83) | 2 (67) | 3 (100) | 2 (67) | 12 (80) |
| NE | 6 (100) | 1 (33) | 3 (100) | 1 (33) | 11 (73) |
| Any-grade serious AE | 4 (67) | 2 (67) | 2 (67) | 1 (33) | 9 (60) |
| TRAE | 2 (33) | 2 (67) | 2 (67) | 0 | 6 (40) |
| Grade ≥3 AE | 6 (100) | 3 (100) | 3 (100) | 3 (100) | 15 (100) |
| TRAE | 4 (67) | 2 (67) | 2 (67) | 1 (33) | 9 (60) |
| CRS[c] | 0 | 0 | 1 (33) | 0 | 1 (7) |
| NE | 2 (33) | 0 | 1 (33) | 0 | 3 (20) |
| Grade ≥3 serious AE | 1 (17) | 1 (33) | 2 (67) | 1 (33) | 5 (33) |
| TRAE | 0 | 1 (33) | 2 (67) | 0 | 3 (20) |

[a]Includes all AEs with onset on or after initiation of brexu-cel infusion. [b]Graded per CTCAE v5.0. [c]CRS is graded per the revised grading system from Lee DW, et al. 2014.[3]

AE, adverse event; brexu-cel, brexucabtagene autoleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NE, neurologic event; TRAE, treatment-related AE.

- Overall, the most common AEs were pyrexia (80%), neutropenia (60%), and headache (60%; **Table 3**)
- Serious AEs reported in ≥20% of patients were pyrexia (n=4; 27%) and hypotension (n=3; 20%)
- Other serious AEs reported in 1 patient each (7%) were tachycardia, abdominal pain, chills, malaise, cellulitis, sepsis, systemic candida, failure to thrive, CLL, aphasia, confusional state, and embolism

### Table 3. AEs in ≥20% of Patients[a]

| Any-grade AE, n (%) | Cohort 1 (low dose) n=6 | Cohort 2 (high dose) n=3 | Cohort 3 (low tumor burden) n=3 | Cohort 4 (post ibrutinib) n=3 | Overall N=15 |
|---|---|---|---|---|---|
| Pyrexia | 5 (83) | 2 (67) | 3 (100) | 2 (67) | 12 (80) |
| Neutropenia | 4 (67) | 3 (100) | 0 | 2 (67) | 9 (60) |
| Headache | 5 (83) | 1 (33) | 1 (33) | 2 (67) | 9 (60) |
| Anemia | 2 (33) | 2 (67) | 1 (33) | 2 (67) | 7 (47) |
| Fatigue | 3 (50) | 2 (67) | 1 (33) | 1 (33) | 7 (47) |
| Thrombocytopenia | 2 (33) | 2 (67) | 0 | 1 (33) | 5 (33) |
| Diarrhea | 2 (33) | 1 (33) | 2 (67) | 0 | 5 (33) |
| Nausea | 2 (33) | 1 (33) | 1 (33) | 1 (33) | 5 (33) |
| Infections/infestations | 1 (17) | 2 (67) | 1 (33) | 1 (33) | 5 (33) |
| Confusional state | 3 (50) | 0 | 1 (33) | 1 (33) | 5 (33) |
| Hypotension | 1 (17) | 1 (33) | 2 (67) | 1 (33) | 5 (33) |
| Sinus tachycardia | 2 (33) | 0 | 1 (33) | 1 (33) | 4 (27) |
| Constipation | 2 (33) | 1 (33) | 0 | 1 (33) | 4 (27) |
| Neutrophil count decreased | 1 (17) | 0 | 2 (67) | 1 (33) | 4 (27) |
| Muscular weakness | 2 (33) | 1 (33) | 1 (33) | 0 | 4 (27) |
| Dizziness | 2 (33) | 0 | 2 (67) | 0 | 4 (27) |
| Tremor | 2 (33) | 0 | 2 (67) | 0 | 4 (27) |
| Hypoxia | 1 (17) | 1 (33) | 2 (67) | 0 | 4 (27) |
| Rash maculo-papular | 2 (33) | 1 (33) | 1 (33) | 0 | 4 (27) |
| Platelet count decreased | 0 | 0 | 2 (67) | 1 (33) | 3 (20) |
| WBC count decreased | 1 (17) | 0 | 1 (33) | 1 (33) | 3 (20) |
| Hypocalcemia | 1 (17) | 0 | 1 (33) | 1 (33) | 3 (20) |
| Hypophosphatemia | 0 | 0 | 2 (67) | 1 (33) | 3 (20) |
| Aphasia | 1 (17) | 0 | 2 (67) | 0 | 3 (20) |
| Insomnia | 1 (17) | 0 | 1 (33) | 1 (33) | 3 (20) |
| Cough | 2 (33) | 1 (33) | 0 | 0 | 3 (20) |
| Dyspnea | 0 | 2 (67) | 1 (33) | 0 | 3 (20) |

[a]Listed in order of decreasing incidence. AEs were coded using MedDRA Version 25.0 preferred terms.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; WBC, white blood cell.

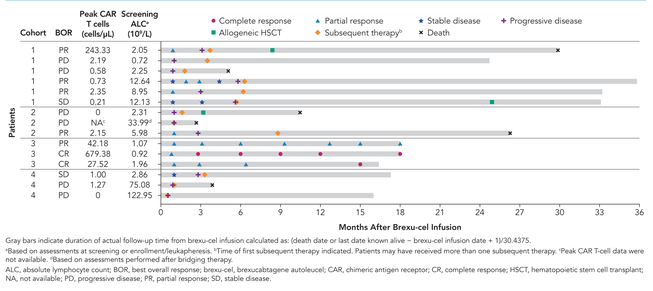
## EFFICACY

- Objective responses were observed in 7 patients (47%), including 2 patients with CR (13%; **Table 4**, **Figure 2**)
- Patients with low tumor burden (Cohort 3):
  - 3 of 3 patients achieved an objective response (2 of 3 patients achieved CR and 1 achieved partial response [PR])
  - All 3 patients had a duration of response (DOR) ≥14 months which was ongoing at the data cutoff date
- 2 of 6 patients who died had SARS-CoV-2 infection as the primary cause of death (4 of 6 patients died of progressive disease [PD])

### Table 4. Objective Response Summary

| BOR, n (%) | Cohort 1 (low dose) n=6 | Cohort 2 (high dose) n=3 | Cohort 3 (low tumor burden) n=3 | Cohort 4 (post ibrutinib) n=3 | Overall N=15 |
|---|---|---|---|---|---|
| Objective response | 3 (50) | 1 (33) | 3 (100) | 0 | 7 (47) |
| CR | 0 | 0 | 2 (67) | 0 | 2 (13) |
| PR | 3 (50) | 1 (33) | 1 (33) | 0 | 5 (33) |
| SD | 1 (17) | 0 | 0 | 1 (33) | 2 (13) |
| PD | 2 (33) | 2 (67) | 0 | 2 (67) | 6 (40) |

### Figure 2. Peak CAR T-cell Expansion, ALC at Screening, Objective Response, and Survival Over Time




Gray bars indicate duration of actual follow-up time from brexu-cel infusion calculated as: (death date or last date known alive − brexu-cel infusion date + 1)/30.4375.

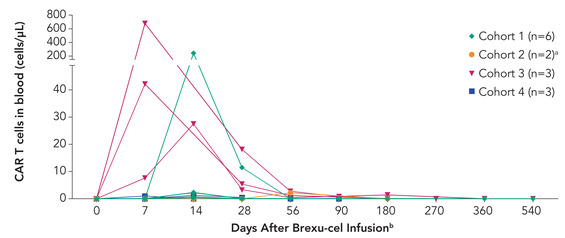
[a]Based on assessments at screening or enrollment/leukapheresis. [b]Time of first subsequent therapy indicated. Patients may have received more than one subsequent therapy. [c]Peak CAR T-cell data were not available. [d]Based on assessments performed after bridging therapy.

ALC, absolute lymphocyte count; BOR, best overall response; brexu-cel, brexucabtagene autoleucel; CAR, chimeric antigen receptor; CR, complete response; HSCT, hematopoietic stem cell transplant; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease.

## TRANSLATIONAL ANALYSES

- Appreciable CAR T-cell expansion occurred in 4 of 14 patients overall and in 3 of 3 patients with low tumor burden (**Figure 3**)
- 3 of 4 patients with peak CAR T-cell expansion ≥27.52 cells/μL were in Cohort 3 (**Figure 4A**)
  - All patients in Cohort 3 had a median tumor burden ≤30% CLL lymphocytes of nucleated bone marrow cells (**Figure 4B**)
  - All patients in Cohort 3 had an ongoing response at the data cutoff date with a minimum follow-up of 16.4 months (**Figure 2**)

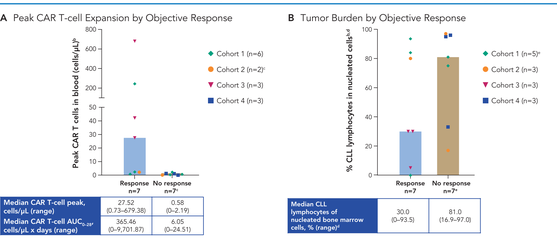
### Figure 3. CAR T Cells in Blood Over Time




[a]Peak CAR T-cell data were not available for 1 patient in Cohort 2. [b]X-axis not drawn to scale.

Brexu-cel, brexucabtagene autoleucel; CAR, chimeric antigen receptor.

### Figure 4. Median Peak CAR T-cell Expansion (A) and Tumor Burden (B) by Response[a]




| | Response n=7 | No response n=7[c] |
|---|---|---|
| Median CAR T-cell peak, cells/μL (range) | 27.52 (0.73–679.38) | 0.58 (0–2.19) |
| Median CAR T-cell $AUC_{0\text{–}28}$[e] cells/μL x days (range) | 365.46 (0–9,701.87) | 6.05 (0–24.51) |

| | Response n=7 | No response n=7[c] |
|---|---|---|
| Median CLL lymphocytes of nucleated bone marrow cells, % (range)[d] | 30.0 (0–93.5) | 81.0 (16.9–97.0) |

[a]Objective responses at any time following brexu-cel infusion. [b]Bars represent median values. [c]Data were not available for 1 patient in Cohort 2. [d]Based on assessments performed at screening or after bridging therapy. [e]Data were not available for 1 patient in Cohort 1.

AUC, area under the curve; brexu-cel, brexucabtagene autoleucel; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia.

- Peak CAR T-cell expansion (range, 0–679.38 cells/μL; n=14)[a] and $AUC_{0\text{–}28}$ (range, 0–9,701.87 cells/μL×days)[b] had a strong to moderate inverse correlation with ALC measured at screening before leukapheresis (range, 0.72–122.95×$10^9$/L; n=14)
  - Peak CAR T-cell levels vs ALC: Spearman's R=−0.6425 (*P*=0.0132)
  - CAR T-cell $AUC_{0\text{–}28}$ levels vs ALC: Spearman's R=−0.5982 (*P*=0.0238)
  - Peak CAR T-cell expansion and $AUC_{0\text{–}28}$ did not have a significant correlation with baseline ALC (measured after bridging therapy or at screening if patient did not receive bridging therapy)
- Similar to median %CLL lymphocytes of nucleated bone marrow cells (**Figure 4B**), median baseline tumor burden (SPD) was also not significantly different between patients with a response (n=7; 1,604 $mm^2$, range 464–8,187 $mm^2$) and patients without a response (n=8; 4,086.75 $mm^2$, range 786–26,688.28 $mm^2$)

[a]Peak CAR T-cell data were not available for 1 patient in Cohort 2. [b]From Day 0 to Day 28 of treatment.

ALC, absolute lymphocyte count; AUC, area under the curve; SPD, sum of products of diameters.

## CONCLUSIONS

- Objective responses were observed in 7 of 15 patients with R/R CLL who received brexu-cel therapy, and 2 patients had a CR
- Brexu-cel therapy did not have any new safety signals in patients with R/R CLL
- Peak CAR T-cell expansion and ongoing objective responses in heavily pretreated patients with low tumor burden appeared to be improved compared with other cohorts
- Although patients with low tumor burden appeared to have ongoing objective responses with brexu-cel, ZUMA-8 was discontinued owing to suboptimal CAR T-cell expansion across the other cohorts

## REFERENCES

1. Perutelli F, et al. *Front Oncol.* 2022;12:837531.
2. Todorovic Z, et al. *Curr Oncol.* 2022;29(5):3647–3657.
3. Zhang J, et al. *Biomark Res.* 2022;10(1):17.
4. TECARTUS® (brexucabtagene autoleucel) prescribing information. Kite Pharma, Inc; 2021.
5. Lee DW, et al. *Blood.* 2014;124(2):188–195.

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## DISCLOSURES

Full author disclosures are available through the Quick Response (QR) code.