Abstract 4199

Assessment of Durable Responses After Brexucabtagene Autoleucel (KTE-X19) in the ZUMA-2 Study in Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL)

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BACKGROUND

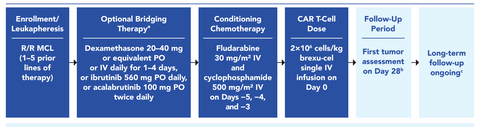
- Despite the availability of novel therapies such as Bruton tyrosine kinase inhibitors (BTKi), patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) still have a poor prognosis, with a median overall survival (OS) of 6-10 months for those who progress on BTKi therapy[1]
- Brexucabtagene autoleucel (brexu-cel, formerly known as KTE-X19) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the United States for the treatment of adults with R/R MCL[2] and in the European Union for the treatment of adults with R/R MCL after receiving ≥2 prior systemic treatments, including a BTKi[3]
- ZUMA-2 (NCT02601313) is a pivotal, single-arm, multicenter, Phase 2 study of brexu-cel in patients with R/R MCL who received up to 5 prior therapies, including a BTKi[4]
- After 35.6 months follow-up in ZUMA-2, brexu-cel demonstrated an objective response rate (ORR; complete response [CR] + partial response [PR]) of 91% (95% CI, 81.8 to 96.7), a CR rate of 68% (95% CI, 55.2 to 78.5), a median duration of response (DOR) of 28.2 months (95% CI, 13.5 to 47.1), and a median OS of 46.6 months (95% CI, 24.9 to not estimable) in all 68 treated patients and not reached in patients with CR[4]
- Here, we report patient and product characteristics by response status at 24 months post–brexu-cel infusion in an exploratory analysis of ZUMA-2

OBJECTIVE

- To identify patient and product characteristics associated with long-term response to brexu-cel

METHODS

Figure 1. ZUMA-2 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 Endpoint
- ORR (CR+PR; IRRC assessed per the Lugano classification[5])

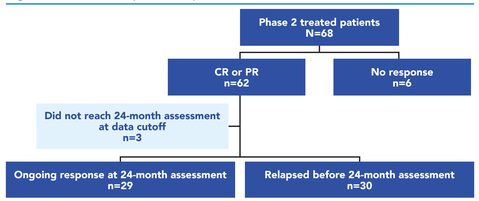
Key Secondary Endpoints
- DOR, PFS, OS
- AEs

[a] Administered after leukapheresis and completed ≥5 days before initiating conditioning chemotherapy; PET-CT was required postbridging. [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 3 months, only targeted AEs (neurological, hematological, 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.
AE, adverse event; 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; 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; R/R, relapsed/refractory.

- Baseline patient and disease characteristics, subsequent therapies, product characteristics, and pharmacologic outcomes were assessed by response status at 24 months after brexu-cel infusion:
  - Ongoing responders: patients with ongoing response at their 24-month assessment
  - Relapsed responders: patients with response who relapsed prior to their 24-month assessment
  - Non-responders: patients with no response
- DOR was assessed in ongoing responders and relapsed responders
- Statistical analyses
  - Time-to-event endpoints were analyzed using the Kaplan-Meier method
  - All subgroup analyses were descriptive
- Data cutoff: July 24, 2021

RESULTS

Figure 2. Patient Response Disposition at 24-Month Assessment



CR, complete response; PR, partial response.

- At data cutoff, the median follow-up time was 35.6 months (range, 25.9-56.3)
- As previously reported, 74 patients were enrolled and leukapheresed, and 68 patients received brexu-cel (**Figure 2**)[4]
  - 62 patients had achieved a CR or PR
    - 29 patients (47%) were in ongoing response at their 24-month assessment (ongoing responders)
    - 30 patients (48%) had relapsed prior to their 24-month assessment (relapsed responders)
    - 3 patients with response did not reach their 24-month assessment at data cutoff and were excluded from this analysis
  - 6 patients did not respond (non-responders)

RESULTS *(continued)*

Table 1. Baseline Patient and Disease Characteristics by Response Status at 24 Months

Characteristic	Ongoing Responders (n=29)	Relapsed Responders (n=30)	Non-responders (n=6)
Median age (range), years	65.0 (50-79)	65.0 (38-75)	66.5 (60-74)
Male, n (%)	26 (90)	24 (80)	5 (83)
ECOG PS of 0, n (%)	23 (79)	17 (57)	3 (50)
Intermediate or high sMIPI, n (%)	19 (66)	15 (50)	4 (67)
Ki-67 PI ≥30%, n (%)	19 (66)	18 (60)	4 (67)
Median no. of prior therapies, n (range)	3 (2-5)	3 (2-5)	3 (1-5)
Prior platinum, n (%)	3 (10)	12 (40)	0
Prior anthracycline, n (%)	22 (76)	22 (73)	4 (67)
Prior bendamustine, n (%)	13 (45)	16 (53)	6 (100)
Prior lenalidomide, n (%)	7 (24)	10 (33)	2 (33)
Prior proteasome inhibitor, n (%)	12 (41)	11 (37)	1(17)
Prior autologous SCT, n (%)	14 (48)	11 (37)	2 (33)
Prior BTKi therapy, n (%)	29 (100)	30 (100)	6 (100)
Ibrutinib	27 (93)	24 (80)	4 (67)
Acalabrutinib	8 (28)	6 (20)	2 (33)
Both	6 (21)	0	0
Relapsed or refractory disease, n (%)			
Relapse after autologous SCT	14 (48)	11 (37)	2 (33)
Refractory to last MCL therapy	10 (34)	13 (43)	3 (50)
Relapse after last MCL therapy	5 (17)	6 (20)	1 (17)
CD19-positive IHC by central lab, n (%)	22 (76)	20 (67)	3 (50)
Tumor burden (SPD) by central read (mm²)			
n	28	28	4
Median (range)	935.1 (260-6133)	4233.6 (386-14,390)	553.1 (293-16,878)
Positive bone marrow assessment at baseline, n (%)	16 (55)	16 (53)	5 (83)
Elevated LDH levels (ULN to ≥1.5 ULN), n (%)	13 (45)	11 (37)	2 (33)
Received bridging therapy, n (%)[a]	6 (21)	16 (53)	3 (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; no., number; PI, prognostic index; SCT, stem cell transplant; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; SPD, sum of the products of diameters; ULN, upper limit of normal.

- A smaller proportion of ongoing responders compared with relapsed responders received bridging therapy and had Eastern Cooperative Oncology Group performance status (ECOG PS) scores of 1, with the median tumor burden (sum of the products of diameters) at baseline being ~4 times smaller in ongoing responders compared with relapsed responders (**Table 1**)
- The median number of prior therapies was 3 in both subgroups with a smaller proportion of ongoing responders compared with relapsed responders receiving prior platinum therapy (**Table 1**)

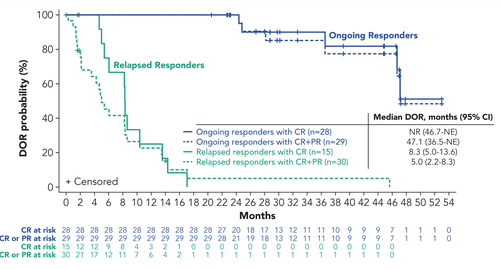
Table 2. Last Prior Therapies by Response Status at 24 Months

	Ongoing Responders (n=29)	Relapsed Responders (n=30)	Non-responders (n=6)
Last prior therapy, n (%)			
Acalabrutinib	4 (14)	4 (13)	1 (17)
Bendamustine	2 (7)	3 (10)	1 (17)
Cisplatin	0	1 (3)	0
Cyclophosphamide	0	1 (3)	0
Cytarabine	0	1 (3)	0
Gemcitabine	1 (3)	0	0
Ibrutinib	19 (66)	13 (43)	2 (33)
Lenalidomide	1 (3)	4 (13)	1 (17)
Protein kinase inhibitors	1 (3)	0	0
Rituximab	1 (3)	1 (3)	1 (17)
Venetoclax	0	2 (7)	0
Median (range) time from last prior therapy to brexu-cel infusion (days)	63.0 (26-748)	64.5 (22-443)	136.0 (29-642)

Brexu-cel, brexucabtagene autoleucel.

- Ibrutinib was more commonly the last prior therapy in ongoing responders versus relapsed responders while a similar proportion received acalabrutinib as their last prior therapy (**Table 2**)
- Median time from last prior therapy to brexu-cel infusion was similar among ongoing and relapsed responders but was more than twice as long in non-responders, though the small sample size may have contributed to this difference

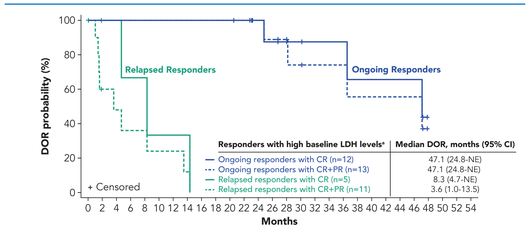
Figure 3. Duration of Response for Ongoing and Relapsed Responders



CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; PR, partial response.

- The median (95% CI) DOR in ongoing responders with CR (n=28) was not reached (46.7-not estimable [NE]) and was 8.3 months (5.0-13.6) in relapsed responders with CR (n=15; **Figure 3**)
- The median time to initial response for ongoing versus relapsed responders was 1 month (range, 0.9-3.1; n=29) vs 1 month (range, 0.8-1.7; n=30), respectively
- The median time to CR for ongoing versus relapsed responders was 3 months (range, 0.9-35.1; n=28) vs 3 months (range, 0.8-9.0; n=15), respectively
  - Median time for conversion from stable disease or PR to CR for ongoing versus relapsed responders was 2.3 months (range, 1.8-34.1; n=16) vs 2.4 months (range, 2.0-8.1; n=8), respectively

Figure 4. Duration of Response for Ongoing and Relapsed Responders With High Baseline LDH levels



[a] Elevated LDH levels were defined as ULN to ≥1.5 ULN.
CR, complete response; DOR, duration of response; LDH, lactate dehydrogenase; NE, not estimable; PR, partial response; ULN, upper limit of normal.

- The median (95% CI) DOR in ongoing responders with CR who had high baseline lactate dehydrogenase (LDH) levels (n=12) was 47.1 months (24.8-not estimable) and was 8.3 months (4.7-NE) in relapsed responders with CR who had high baseline LDH levels (n=5)

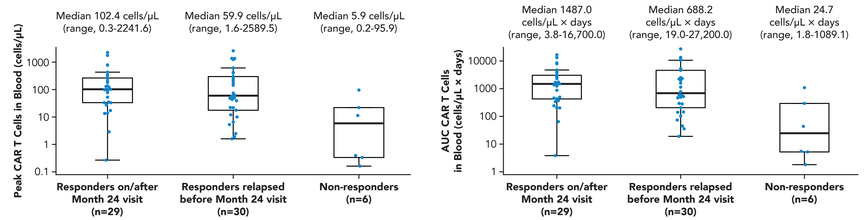
Table 3. Subsequent Therapies by Response Status at 24 Months

WHO-DD Preferred Name, n (%)	Ongoing Responders (n=29)	Relapsed Responders (n=30)	Non-responders (n=6)
Patients who had subsequent anticancer therapy[a]	1 (3)	20 (67)	3 (50)
Acalabrutinib	1 (3)	2 (7)	1 (17)
Bortezomib	0	4 (13)	1 (17)
Cytarabine	0	3 (10)	1 (17)
Ibrutinib	0	5 (17)	1 (17)
Lenalidomide	0	6 (20)	1 (17)
Obinutuzumab	0	2 (7)	1 (17)
Radiotherapy	1 (3)	7 (23)	1 (17)
Rituximab	0	7 (23)	1 (17)
Venetoclax	1 (3)	6 (20)	1 (17)
Bendamustine	0	2 (7)	0
Cyclophosphamide	0	5 (17)	0
Dexamethasone	0	7 (23)	0
Fludarabine	0	3 (10)	0
Fludarabine phosphate	0	2 (7)	0
Melphalan	0	3 (10)	0
Methotrexate	0	3 (10)	0

[a] Table includes subsequent therapies received by ≥2 patients in any subgroup; patients could have received multiple subsequent therapies and multiple lines of subsequent therapy.
WHO-DD, World Health Organization Drug Dictionary.

- Most relapsed responders received subsequent anticancer therapy by data cutoff, the most common of which were radiotherapy, dexamethasone, rituximab, and targeted therapies (**Table 3**)

Figure 5. Peak and Area Under the Curve CAR T-Cell Expansion by Response Status at 24 Months



Area under the curve was calculated from Day 0 to Day 28; CAR, chimeric antigen receptor.
AUC, area under the curve; CAR, chimeric antigen receptor.

- Median peak and area under the curve (AUC) CAR T-cell levels were ~2× higher in ongoing responders than in relapsed responders (**Figure 5**)

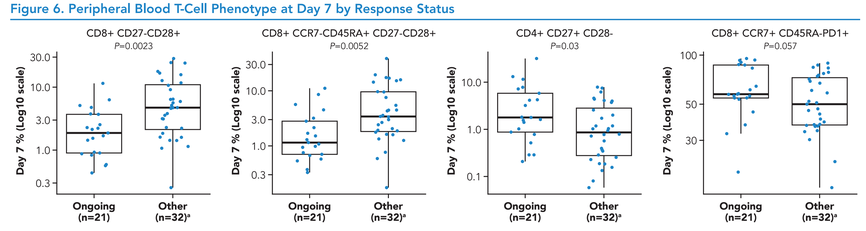
Table 4. Summary of Product Characteristics by Response Status at 24 Months

Median (range)	Ongoing Responders (n=29)	Relapsed Responders (n=30)	Non-responders (n=6)
CD4/CD8 ratio	0.86 (0.27-2.06)	0.62 (0.04-3.73)	0.40 (0.30-0.70)
Total number of CCR7+ T cells infused (10^6)	119.8 (37.0-249.9)	89.1 (6.1-353.4)	88.2 (39.9-150.3)

CCR7, chemokine receptor 7.

- Product characteristics were largely similar among ongoing and relapsed responders with a modest increase in the median total number of infused chemokine receptor 7 (CCR7)-positive T cells observed in ongoing vs relapsed responders (**Table 4**)

Figure 6. Peripheral Blood T-Cell Phenotype at Day 7 by Response Status



[a] Other includes relapsed responders and non-responders.
CCR7, chemokine receptor 7.

- Peripheral blood T cells of relapsed and non-responding patients exhibit a more prominent CD8+ CD27-CD28+ effector memory phenotype compared with patients with ongoing response
- Ongoing responders are enriched with peripheral CD4 T cells that maintain juvenile CD27+ expression and activated CD8 effector memory T cells

CONCLUSIONS

- In this exploratory analysis, after 35.6 months of median follow-up, brexu-cel continues to demonstrate durable responses with 47% of responders still in ongoing response at 24 months postinfusion in ZUMA-2
- Ongoing responses were observed in patients with high-risk disease characteristics, suggesting that brexu-cel has the potential to produce durable responses in patients with R/R MCL who would typically have a poor prognosis
- Ibrutinib was more commonly the last prior therapy in ongoing versus relapsed responders
- Ongoing responders tended to have lower ECOG PS scores, lower tumor burden, and less frequent use of prior platinum therapy or bridging therapy compared with relapsed responders, suggesting the potential for greater benefit with brexu-cel in earlier courses of disease
- Median peak and AUC CAR T-cell levels were ~2× higher in ongoing responders than in relapsed responders, suggesting that the degree of CAR T-cell expansion may predict durability of response
- A modest increase in the median total number of infused CCR7+ cells and maintenance of CD27+ peripheral T cells observed in ongoing vs relapsed responders may suggest a potential role of continuous memory T-cell differentiation in achieving durable responses

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