Poster
2120

Assessment of Early Intervention Strategies for Management of Cytokine Release Syndrome and Neurologic Events After Brexucabtagene Autoleucel Treatment in Patients With Relapsed or Refractory Mantle Cell Lymphoma in ZUMA-2

Olalekan O. Oluwole, MD, MBBS, MPH[1]; Patrick M. Reagan, MD[2]; David B. Miklos, MD, PhD[3]; Frederick L. Locke, MD[4]; Andre Goy, MD[5]; Caron A. Jacobson, MD, MMSc[6]; Javier Munoz, MD, MS, MBA, FACP[7]; Edouard Forcade, MD, PhD[8]; Max S. Topp, MD[9]; Dan Zheng, PhD[10]; Ana Nunes, PharmD[10]; Wangshu Zhang, PhD[10]; Rhine R. Shen, PhD[10]; Ioana Kloos, MD[10]; Marie José Kersten, MD, PhD[11]; and Michael L. Wang, MD[12]

[1]*Vanderbilt University Cancer Center, Nashville, TN, USA;* [2]*University of Rochester School of Medicine, Rochester, NY, USA;* [3]*Stanford University, Stanford, CA, USA;* [4]*Moffitt Cancer Center, Tampa, FL, USA;* [5]*John Theurer Cancer Center, Hackensack, NJ, USA;* [6]*Dana-Farber Cancer Institute, Boston, MA, USA;* [7]*Banner MD Anderson Cancer Center, Gilbert, AZ;* [8]*Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, F-33000, Bordeaux, France;* [9]*Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany;* [10]*Kite, a Gilead Company, Santa Monica, CA, USA;* [11]*Amsterdam UMC, Location University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands, on behalf of HOVON/LLPC; and* [12]*The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

BACKGROUND

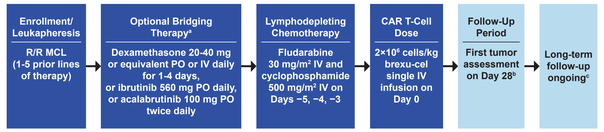
- Brexucabtagene autoleucel (brexu-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the United States for the treatment of adults with relapsed or refractory (R/R) mantle cell lymphoma (MCL) and in the European Union for adults with R/R MCL after ≥2 prior therapies, including a Bruton tyrosine kinase inhibitor (BTKi)[1,2]
- After 3 years of follow-up in the multicenter, single-arm, Phase 2 ZUMA-2 study of brexu-cel in 68 patients with R/R MCL and ≤5 prior treatments, including a BTKi, brexu-cel demonstrated an objective response rate (ORR) of 91%, a complete response rate of 68%, median duration of response (DOR) of 28.2 months, and median overall survival (OS) of 46.6 months (N=68), along with a manageable safety profile[3]
- In August 2018, the safety management strategies for patients experiencing cytokine release syndrome (CRS) and neurologic events (NEs) in ZUMA-2 were updated to initiate treatment for these adverse events earlier, at the onset of Grade 1 events, to improve safety outcomes

OBJECTIVE

- To assess the safety and efficacy outcomes in ZUMA-2 patients after 4 years of follow-up by late versus early intervention strategies for the management of CRS and NEs

METHODS

Figure 1. ZUMA-2 Study Design[4]



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 lymphodepleting 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) will be 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 or refractory.

Figure 2. Tocilizumab and Corticosteroid Medication Strategies for CRS and NEs by Management Group

CRS Management

CRS Grade	1	2	3	4
EIG: Tocilizumab	Yes[a]	Yes	Yes	Yes
EIG: Corticosteroids	No	Yes[b]	Yes	Yes, high dose
LIG: Tocilizumab	No	Yes[c]	Yes	Yes
LIG: Corticosteroids	No	Yes[c]	Yes	Yes, high dose

NE Management

NE Grade	1	2	3	4
EIG: Tocilizumab	No	Yes[d]	Yes	Yes
EIG: Corticosteroids	No	Yes	Yes	Yes, high dose
LIG: Tocilizumab	No	Yes[c]	Yes	Yes
LIG: Corticosteroids	No	No	Yes	Yes, high dose

[a] If no improvement after 24 hours. [b] If no improvement after 24 hours of tocilizumab administration. [c] Only in case of comorbidities or older age. [d] With concurrent CRS.
CRS, cytokine release syndrome; EIG, Early Intervention Group; LIG, Late Intervention Group; NE, neurologic event.

- Changes from the initial (Late Intervention Group; [LIG]) to the updated (Early Intervention Group [EIG]) safety management guidance are reported in **Figure 2**
  - Notably, the updated guidance recommended earlier intervention with tocilizumab for CRS versus the initial guidance
  - Additionally, the updated guidance recommended earlier corticosteroid intervention for NEs
- Baseline patient/disease characteristics, concomitant medications of interest, efficacy and safety outcomes, and pharmacokinetics were assessed by safety management group in a post hoc, exploratory subgroup analysis
- Statistical analyses
  - Time-to-event outcomes were analyzed using the Kaplan-Meier method
  - Results from subgroup analyses are reported using descriptive statistics
- Data cutoff date: 23 July 2022

RESULTS

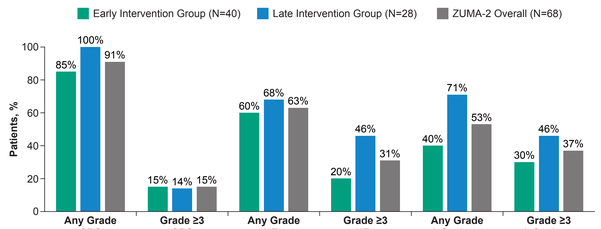
Table 1. Baseline Characteristics for Treated Patients in ZUMA-2 by Management Group

Characteristic	Early Intervention Group (N=40)	Late Intervention Group (N=28)	ZUMA-2 Overall (N=68)
ECOG PS=0, n (%)	28 (70)	16 (57)	44 (65)
Median no. of prior therapies, n (range)	3 (1-5)	3 (2-5)	3 (1-5)
Prior autologous SCT, n (%)	21 (53)	8 (29)	29 (43)
Prior BTKi therapy, n (%)	40 (100)	28 (100)	68 (100)
Ibrutinib	30 (75)	28 (100)	58 (85)
Acalabrutinib	13 (33)	3 (11)	16 (24)
Both	3 (8)	3 (11)	6 (9)
Relapsed or refractory disease, n (%)			
Refractory to last MCL therapy	12 (30)	15 (54)	27 (40)
Relapsed after last MCL therapy	7 (18)	5 (18)	12 (18)
Tumor burden (SPD) by central read (mm²)[a]			
n	37	26	63
Median (range)	1380 (293-16,878)	2278 (260-8191)	2088 (260-16,878)
Received bridging therapy, n (%)[b]	17 (43)	8 (29)	25 (37)
LDH relative to ULN, n (%)			
LDH<ULN	21 (53)	19 (68)	40 (59)
LDH≥ULN	19 (48)	7 (25)	26 (38)
Missing	0 (0)	2 (7)	2 (3)

[a] As measured by the sum of the product of dimensions of all target lesions at baseline. For patients who had bridging therapy, the measurement after bridging therapy was used as baseline. [b] Bridging therapy was received after leukapheresis and prior to lymphodepleting chemotherapy in ZUMA-2.
BTKi, Bruton tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; no., number; SCT, stem cell transplant; SPD, sum of the products of diameters; ULN, upper limit of normal.

- The median follow-up time for the 68 treated patients in ZUMA-2 was 47.5 months (range, 37.9-68.3)
  - Of these patients, 28 were in the LIG and 40 were in the EIG
- Patient characteristics were relatively balanced across both safety management groups with the exceptions that a greater proportion of patients in the EIG than the LIG had Eastern Cooperative Oncology Group performance status of 0 (70% vs 57%), received prior autologous stem cell transplant (53% vs 29%), received prior acalabrutinib therapy (33% vs 11%), had lactate dehydrogenase level ≥ upper limit of normal (48% vs 25%) and received bridging therapy (43% vs 29%; **Table 1**)
  - Additionally, tumor burden was numerically lower in the EIG (1380 mm² [range, 293-16,878]) versus the LIG (2278 mm² [range, 260-8191]), and fewer patients in the EIG were refractory to their last prior MCL therapy versus the LIG (30% vs 54%)

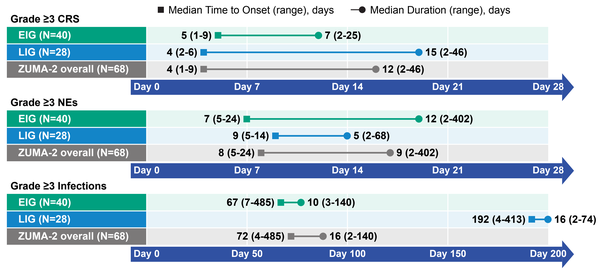
Figure 3. Incidence and Resolution of CRS, NEs, and Infections



CRS, cytokine release syndrome; NE, neurologic event.

- Grade ≥3 NEs and Grade ≥3 infections were experienced less often in the EIG versus the LIG. Grade ≥3 CRS events occurred at similar rates in both groups (**Figure 3**)
  - CRS and NEs were resolved at similar rates in the EIG (100% and 92%, respectively) and LIG (100% and 95%, respectively), but a smaller proportion of patients in the EIG had resolved infections versus the LIG (75% vs 95%; data not shown)

Figure 4. Median Time to Onset and Median Duration of Grade ≥3 CRS, NEs, and Infections Following Brexu-Cel Therapy



CRS, cytokine release syndrome; EIG, Early Intervention Group; LIG, Late Intervention Group; NE, neurologic event.

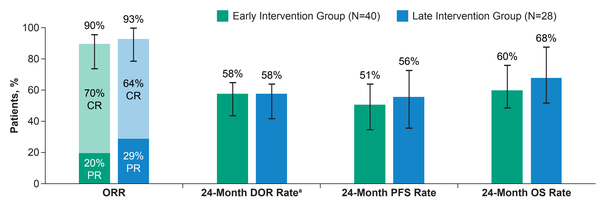
- The EIG was associated with shorter median duration of Grade ≥3 CRS. However, the median duration of Grade ≥3 NEs was longer in this group (**Figure 4**)
- The median time to onset and duration of Grade ≥3 infections were higher in the LIG versus the EIG
- Grade 5 adverse events occurred in 4 patients (10%) in the EIG (n=1 each of B-cell lymphoma, myelodysplastic syndrome, salmonella bacteremia, and staphylococcal bacteremia) and 5 patients (18%) in the LIG (B-cell lymphoma [n=2], acute myeloid leukemia [n=1], malignant lung neoplasm [n=1], and organizing pneumonia [n=1])

Table 2. Use of Concomitant Medications of Interest by Safety Management Group

	Early Intervention Group (N=40)	Late Intervention Group (N=28)	ZUMA-2 Overall (N=68)
Any medication of interest use, n (%)	32 (80)	23 (82)	55 (81)
Tocilizumab use, n (%)	29 (73)	19 (68)	48 (71)
Median number of doses of tocilizumab, n (range)	2.0 (1.0-12.0)	2.0 (1.0-17.0)	2.0 (1.0-17.0)
Median cumulative dose of tocilizumab (range), mg	1200.0 (446.0-9600.0)	1456.0 (464.0-10,270.0)	1307.2 (446.0-10,270.0)
Corticosteroid use, n (%)	22 (55)	19 (68)	41 (60)
Median number of doses of corticosteroids, n (range)	30.5 (3.0-94.0)	15.0 (1.0-63.0)	22.0 (1.0-94.0)
Median cumulative dose of corticosteroids (range), mg	7856.3 (939.0-531,704.0)	6266.0 (313.0-156,055.0)	7081.5 (313.0-531,704.0)
Vasopressor use, n (%)	7 (18)	8 (29)	15 (22)
Immunoglobulin use, n (%)	11 (28)	14 (50)	25 (37)

- Concomitant medications of interest were used in a similar number of patients in the EIG (80%; n=32) and the LIG (82%; n=23; **Table 2**)
- Corticosteroids, vasopressors, and immunoglobulins were used at lower rates in the EIG than the LIG
  - However, corticosteroids were used at a higher median number of doses in the EIG versus the LIG
- Tocilizumab was used at similar rates and at a similar median number of doses in the EIG and LIG

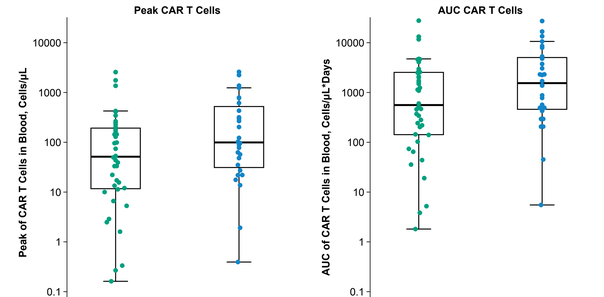
Figure 5. Efficacy Outcomes by Safety Management Group



[a] Among responders only.
CR, complete response; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

- ORR and 24-month DOR, OS, and PFS rates were similar across EIG and LIG subgroups (**Figure 5**)

Figure 6. CAR T-Cell Expansion by Safety Management Group



	Early Intervention Group (N=40)	Late Intervention Group (N=28)
Median Peak CAR T Cells (Range)	51.32 cells/µL (0.16-2565.84)	99.31 cells/µL (0.39-2589.47)
Median AUC CAR T Cells (Range)	559.36 cells/µL×days (1.81-27,700)	1542.29 cells/µL×days (5.51-27,200)

AUC, area under the curve; CAR, chimeric antigen receptor.

- While median peak and area under the curve (AUC) CAR T-cell levels appeared higher in the LIG versus the EIG, the differences were not significant (*P*=.08 and *P*=.06, respectively; **Figure 6**)
- Time to peak CAR T-cell level was comparable for both the EIG and the LIG (median 15 [range, 8-464] versus 15 [range, 8-17] days, respectively)

CONCLUSIONS

- In this post hoc exploratory subgroup analysis, patients who received earlier intervention for CRS and NEs experienced improved safety outcomes compared with patients who received late intervention
  - Notably, patients in the EIG experienced lower rates of Grade ≥3 NEs (20% vs 46%) and infections (30% vs 46%) than patients in the LIG
  - Additionally, a lower proportion of EIG patients required corticosteroid, vasopressor, and/or immunoglobulin use than LIG patients
- The EIG demonstrated numerically lower peak and AUC CAR T-cell expansion levels compared with the LIG, but efficacy results appear to be similar between subgroups
- Although this analysis is limited by small patient numbers and unbalanced baseline characteristics between subgroups, these findings suggest that the current clinical guidance for safety management (based on earlier intervention for CRS and NEs) may be associated with better safety outcomes than the initial safety management used in the ZUMA-2 study

REFERENCES

1. TECARTUS® (brexucabtagene autoleucel) Prescribing information. Kite Pharma, Inc; 2021.
2. TECARTUS® (brexucabtagene autoleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2023.
3. Wang M, et al. *J Clin Oncol*. 2023;41:555-567.
4. Wang M, et al. *N Engl J Med*. 2020;382:1331-1342.
5. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

ACKNOWLEDGMENTS

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and healthcare staff at each study site
- Medical writing support was provided by Edward Sheetz, PhD, of Nexus Global Group Science, funded by Kite, a Gilead Company
- This study was funded by Kite, a Gilead Company

DISCLOSURES

Full author disclosures are available through the virtual meeting platform.

Presented at the 2023 American Society of Hematology Annual Meeting