# TECARTUS®
# (brexucabtagene autoleucel):
# Bendamustine Use Prior to Enrollment in ZUMA-2

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The following information regarding prior bendamustine use in the ZUMA-2 study is provided below as a professional courtesy in response to your unsolicited request.

## Study Design and Washout periods

ZUMA-2 (NCT02601313) was a phase 2, single-group, open-label, multi-center study that evaluated the efficacy and safety of KTE-X19 in adult patients with relapsed or refractory mantle-cell lymphoma (MCL).[1] Key eligibility criteria included histologically confirmed MCL disease that was relapsed or refractory to up to 5 previous therapies, which were required to include anthracycline- or bendamustine-containing regimen, an anti-CD20 monoclonal antibody, and BTK inhibitor therapy with ibrutinib or acalabrutinib. If a bendamustine-containing regimen was the last prior systemic therapy prior to leukapheresis in the ZUMA-2 study, at least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the patient's leukapheresis was planned.[2]

## Background on Bendamustine Use

Treatments in previous lines may affect outcomes with subsequent therapies; for example, bendamustine-containing treatments may be associated with reduced T-cell number and function, potentially affecting cellular therapies.[3] A study in B-cell lymphoma patients showed reduction in T cell counts, as well as reduced functionality with use of bendamustine-containing regimens.[4] Of the 68 patients that were leukapheresed and received a single infusion of KTE-X19, 37 (54%) patients received a bendamustine-containing regimen prior to enrolling in the ZUMA-2 study (referred to as prior bendamustine use from here on).[3]

The median time from last bendamustine exposure to KTE-X19 infusion was 20.9 months (range, 1.0-70.3 months).[3] Compared with patients who did not have prior bendamustine exposure or those who used bendamustine within 6 months or more than 12 months, patients who had bendamustine use between 6 and 12 months pre-apheresis had numerically lower baseline tumor burden, a greater proportion had received ≥ 4 prior chemotherapy regimens, and a lower proportion had ECOG performance status 0.[5]

## Methods

Given reports of the potential for bendamustine-containing treatments to reduce T cell number and function, and the frequent use of bendamustine in MCL, an exploratory, hypothesis-testing, post hoc evaluation of the impact of timing of prior bendamustine exposure on KTE-X19 was conducted in a small subset of patients at the 3-year data cut-off, with a median follow-up of 35.6 (range, 25.9-56.30 months).[3] An exploratory post hoc propensity score matching was performed to descriptively compare results among patients on the basis of prior bendamustine use after balancing for key characteristics: age, baseline tumor burden, ECOG performance status, s-MIPI score, number of prior lines of chemotherapy, prior acalabrutinib, prior ibrutinib, and POD24 status. Four subgroup comparisons were performed: no bendamustine use before leukapheresis versus bendamustine use within 6 months, > 6 months, within 12 months, and > 12 months.

## Results

In the 68 all-treated population, the ORR (IRRC) was 91% (95% CI, 81.8 to 96.7); CR and PR rates were 68% (95% CI, 55.2 to 78.5) and 24% (95% CI, 14.1 to 35.4), respectively. Among the 62 responders, the median DOR was 28.2 months.[3]

In those with and without prior bendamustine, the ORR was 84% (CR rate, 58%) and 100% (CR rate, 77%), respectively.[3] At data cutoff, 29% and 48% of patients, respectively, remained in ongoing response.[3] In patients with and without prior bendamustine, the median DOR was 28.2 months and 46.7 months, respectively, but the two DOR curves were not statistically significantly different [p=0.5206 (log-rank test)].[3,5] Data regarding cumulative prior bendamustine doses for patients were not available.[3]

Table 1 below shows results from the match-adjusted post-hoc analysis of patients with prior bendamustine use within 6 months or > 6 months versus no bendamustine use.[3] Patients with prior bendamustine within 6 months of apheresis had lower peak CAR T cell levels post-infusion versus patients with prior bendamustine more than 6 months pre-apheresis or corresponding patients without prior bendamustine. Patients with prior bendamustine within 6 months had lower numbers of CD4+ T cells in product, levels of peak effector serum biomarkers, doubling time, and incidence of Grade ≥ 3 CRS and neurologic events. These trends were not pronounced for patients with prior bendamustine within 12 months. The observations from this small exploratory post hoc analysis may indicate that patients could benefit from longer time spans between prior bendamustine and cell therapy. Additionally, information on the results from the match-adjusted post-hoc analysis of patients by use of bendamustine within 12 months or more than 12 months before leukapheresis is shown in Table 2 below.[5]

**Table 1: Comparison of Efficacy and Safety Outcomes, Pharmacokinetics, Pharmacodynamics, and Product Attributes After 1:1 Propensity Score Matching of Patients With Prior Bendamustine Use Within 6 Months or > 6 Months Versus No Use[3]**

| Outcomes in ZUMA-2 patients after matching | Exposure ≤ 6m prior to leukapheresis[a] | | Exposure > 6m prior to leukapheresis[b] | |
|---|---|---|---|---|
| | Bendamustine use (n= 11) | No bendamustine use (n=11) | Bendamustine use (n=25) | No bendamustine use (n=25) |
| **Efficacy, no. (%)** | | | | |
| Objective response rates (ORR) | 9 (81.8) | 11 (100) | 21 (84) | 25 (100) |
| Complete response (CR) | 6 (54.5) | 9 (81.8) | 15 (60) | 20 (80) |
| Ongoing response at 18 months | 2 (18.2) | 4 (36.4) | 8 (32) | 13 (52) |
| **Safety, no. (%)[c]** | | | | |
| Grade ≥ 3 neurologic events | 1 (9.1) | 7 (63.6) | 5 (20) | 11 (44) |
| Grade ≥ 3 CRS | 0 (0) | 3 (27.3) | 3 (12) | 5 (20) |
| **Pharmacokinetics, median (Q1, Q3)** | | | | |
| Peak CAR T-cell levels, cells/µL | 22.14 (15.53, 61.86) | 167.23 (40.15, 440.65) | 62.66 (15.60, 182.41) | 129.29 (27.30, 267.10) |
| AUC, cells/µL*day | 293.86 (224.40, 868.60) | 2,090.42 (398.80, 3,803.58) | 775.83 (202.76, 2,569.28) | 1,725.29 (371.04, 4,087.57) |
| Doubling time, days | 1.51 (1.34, 2.08) | 1.28 (1.19, 1.33) | 1.46 (1.28, 1.58) | 1.31 (1.25, 1.50) |
| **Pharmacodynamics, median (Q1, Q3)** | | | | |
| Peak IFN-γ, pg/mL | 302.40 (153.70, 826.45) | 571.00 (144.70, 1,608.50) | 408.21 (140.50, 1,335.40) | 800.00 (411.20, 1,876.00) |
| Peak granzyme B, pg/mL | 20.90 (10.85, 65.05) | 38.90 (10.20, 96.85) | 31.70 (1.00, 71.60) | 43.90 (33.40, 102.30) |
| Peak IL-10, pg/mL | 5.50 (2.05, 15.55) | 6.60 (3.50, 29.35) | 16.40 (5.40, 43.43) | 31.30 (6.60, 70.90) |
| **Product attributes, median (Q1, Q3)** | | | | |
| No. of CD4 cells | 79.93 (69.18, 99.87) | 120.74 (87.16, 130.59) | 106.72 (72.86, 136.55) | 125.95 (89.77, 161.67) |
| No. of CD8 cells | 192 (110.59, 236.72) | 133.13 (121.25, 155.02) | 153.83 (131.36, 191.50) | 156.94 (125.80, 198.30) |
| No. of naive (CCR7+CD45RA+) T cells | 51.34 (34.66, 89.89) | 45.12 (29.35, 119.97) | 59.40 (43.43, 96.88) | 55.67 (34.44, 136.28) |
| IFN-γ in coculture, pg/mL | 4,404 (2,240.50, 6,574.50) | 7,120 (4,995.00, 9,474.00) | 6,333 (3,509.00, 9,082.00) | 6,947 (4,512.00, 8,941.00) |

Abbreviations: AUC, area under the curve from baseline (day 0) to day 28; CAR, chimeric antigen receptor; CCR7, C-C chemokine receptor type 7; CR, complete response; CRS, cytokine release syndrome; IFN, interferon; IL, interleukin; ORR, objective response rate; Q1, first quartile; Q3, third quartile.
[a] Bendamustine use ≤ 6 months required an exact statement for the number of prior chemotherapy treatments to achieve balance. No caliper was used.
[b] Bendamustine use > 6 months required a caliper of 2.5 on baseline tumor burden to achieve balance.
[c] Adverse events, including neurologic events, were graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03. CRS was graded per the Lee criteria.

**Table 2: Comparison of Efficacy and Safety Outcomes, Pharmacokinetics, Pharmacodynamics, and Product Attributes After 1:1 Propensity Score Matching of Patients With Prior Bendamustine Use Within 12 Months or > 12 Months Versus No Use[5]**

| Outcomes in ZUMA-2 patients after matching | Exposure ≤ 12m prior to leukapheresis[a] | | Exposure > 12m prior to leukapheresis[b] | |
|---|---|---|---|---|
| | Bendamustine use (n= 12) | No bendamustine use (n=12) | Bendamustine use (n=21) | No bendamustine use (n=21) |
| **Efficacy, no. (%)** | | | | |
| Objective response rates (ORR) | 10 (83.3) | 12 (100) | 17 (81) | 21 (100) |
| Complete response (CR) | 8 (66.7) | 8 (66.7) | 11 (52.4) | 15 (71.4) |
| Ongoing response at 18 months | 4 (33.3) | 4 (33.3) | 5 (23.8) | 9 (42.9) |
| **Safety, no. (%)** | | | | |
| Grade ≥ 3 neurologic events | 2 (16.7) | 5 (41.7) | 4 (19) | 9 (42.9) |
| Grade ≥ 3 CRS | 0 (0) | 2 (16.7) | 3 (14.3) | 4 (19) |
| **Pharmacokinetics, median (Q1, Q3)** | | | | |
| Peak CAR T-cell levels, cells/µL | 19.82 (15.06, 77.72) | 136.41 (13.32, 274.77) | 77.60 (21.83, 264.33) | 102.43 (33.33, 297.80) |
| AUC, cells/µL*day | 268.19 (205.39, 1196.87) | 1907.86 (191.02, 2897.38) | 1089.11 (294.14, 2960.77) | 1394.94 (371.04, 4087.57) |
| Doubling time, days | 1.67 (1.41, 2.44) | 1.29 (1.21, 1.40) | 1.35 (1.25, 1.53) | 1.36 (1.28, 1.65) |
| **Pharmacodynamics, median (Q1, Q3)** | | | | |
| Peak IFN-γ, pg/mL | 350.05 (176.20, 617.88) | 565.00 (168.68, 1474.75) | 408.21 (129.30, 1335.40) | 1148.70 (571.00, 1876.00) |
| Peak granzyme B, pg/mL | 17.95 (1.00, 58.78) | 59.50 (28.57, 103.83) | 46.90 (7.50, 76.90) | 53.20 (25.50, 97.70) |
| Peak IL-10, pg/mL | 4.95 (3.22, 14.98) | 20.10 (5.18, 72.83) | 17.90 (5.80, 44.00) | 35.90 (6.60, 78.60) |
| **Product attributes, median (Q1, Q3)** | | | | |
| No. of CD4 cells | 99.87 (84.26, 122.79) | 136.34 (80.26, 186.77) | 108.90 (57.81, 137.49) | 123.83 (82.56, 147.69) |
| No. of CD8 cells | 193.90 (148.21, 236.18) | 149.58 (124.76, 186.29) | 150.19 (113.82, 188.41) | 153.09 (114.24, 188.26) |
| No. of naive (CCR7+CD45RA+) T cells | 51.00 (35.78, 82.28) | 43.21 (31.90, 87.25) | 55.22 (43.43, 96.88) | 49.32 (34.44, 101.74) |
| IFN-γ in coculture, pg/mL | 4124.00 (2526.50, 6432.75) | 5684.50 (3443.50, 8433.00) | 6510.00 (3509.00, 9230.00) | 6947.00 (4512.00, 8941.00) |

[a]Benda use within 12 months required an exact statement for prior ibrutinib with a caliper of 0.75 for baseline tumor burden to achieve balance.
[b]Benda use > 12 months did not require a caliper or exact statement to achieve balance.
AUC, area under the curve from baseline (day 0) to day 28; benda, bendamustine; CAR, chimeric antigen receptor; CCR7,C-C chemokine receptor type 7; CR, complete response; CRS, cytokine release syndrome; IFN, interferon; IL, interleukin; ORR, objective response rate; Q1, first quartile; Q3, third quartile.

Patients with prior bendamustine benefited from KTE-X19, but showed a trend toward attenuated T-cell functionality, with more impact of bendamustine given within 6 versus 12 months of leukapheresis.[3] Although sample sizes were small in this exploratory analysis, a poorer pharmacokinetic profile and reduced product doubling time with bendamustine use within 6 months of apheresis were observed. The impact on CAR T-cell expansion was less pronounced with extended time between bendamustine exposure and apheresis. Although the generalizability of the analysis was limited by the small numbers of patients and absence of cumulative bendamustine dose data, the findings suggest that bendamustine use shortly before leukapheresis requires careful consideration because of its effects on patient T-cell fitness and potential impact on CAR T-cell expansion. Although patients with prior bendamustine had similar outcomes as the overall ZUMA-2 population, to maximize the benefit of KTE-X19, it may be advantageous to consider administering KTE-X19 before or in place of bendamustine-containing treatments. Further analyses are warranted to better elucidate the influence of bendamustine on cell therapy in relapsed/refractory MCL.

The use of bendamustine prior to leukapheresis and KTE-X19 infusion is at the discretion of the treating physician. Please also contact the manufacturer of bendamustine for any additional information related to your inquiry.

# References


1. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382(14):1331-1342. doi:10.1056/NEJMoa1914347
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3. Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study [published online ahead of print, 2022 Jun 4]. *J Clin Oncol*. 2022;JCO2102370. doi:10.1200/JCO.21.02370
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5. Supplement to: Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study [published online ahead of print, 2022 Jun 4]. *J Clin Oncol*. 2022;JCO2102370. doi:10.1200/JCO.21.02370


# Abbreviations

AUC=area under the curve from baseline (day 0) to day 28

BTK=Bruton tyrosine kinase

CAR=chimeric antigen receptor

CCR7=C-C chemokine receptor type 7

CR=complete response

CRS=cytokine release syndrome

DOR=duration of response

ECOG=Eastern Cooperative Oncology Group

IFN=interferon

IL=interleukin

IRRC=independent radiologic review committee

MCL=mantle cell lymphoma

ORR=objective response rate

POD24=progression of disease within 24 months of first treatment initiation

Q1=first quartile

Q3=third quartile

s-MIPI=Simplified Mantle Cell Lymphoma International Prognostic Index

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