4388 Five-Year Outcomes of Patients (Pts) with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Treated with Brexucabtagene Autoleucel (Brexu-cel) in ZUMA-2 Cohorts 1 and 2

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Hematology Disease Topics & Pathways:
Research, Clinical trials, Lymphomas, Non-Hodgkin lymphoma, Clinical Research, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, Treatment Considerations, Biological therapies, Lymphoid Malignancies

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Abstract

Introduction:

Brexu-cel is an autologous anti-CD19 CAR T-cell therapy approved in the US and EU for treatment of adults with R/R MCL (after ≥2 prior therapies in EU) based on a high objective response rate (ORR; 93%; 67% complete response [CR] rate) in pts who received the pivotal dose (2×10^6 anti-CD19 CAR T cells/kg; Cohort 1; N=60) in ZUMA-2 (NCT02601313; Wang et al, *N Engl J Med* 2020). After ~4 years (y) of median follow-up, Brexu-cel demonstrated a median overall survival (OS) of 46.4 months (mo) in 68 pts with R/R MCL in Cohort 1 (Goy et al. ASH

2023). Cohort 2 was established to assess a lower dose (0.5 x 10^6 anti-CD19 CAR T cells/kg); however, the risk/benefit ratio of the Cohort 1 dose was deemed the optimal dose before Cohort 2 reached full enrollment. Here we report primary outcomes of Cohort 2 and 5-y outcomes of Cohorts 1 and 2.

Methods:

Pts with R/R MCL and ≤5 prior therapies including a BTKi received optional bridging therapy (protocol-defined), lymphodepleting chemotherapy, and 1 infusion of brexu-cel. The primary endpoint was ORR (CR + partial response [PR]) per Lugano classification (Cheson et al. J Clin Oncol. 2014) by independent radiology review committee (IRRC) assessment. Key secondary endpoints were duration of response (DOR), best objective response (BOR), progression-free survival (PFS), OS, and safety. After ≥24 mo of assessment, pts could transition to long-term follow-up (LTFU), NCT05041309, where they were monitored for late-onset targeted/serious adverse events (AEs) possibly related to brexu-cel, presence of replication-competent retrovirus (RCR), and/or insertional mutagenesis. Descriptive statistics are reported herein.

Results:

As of the primary analysis data cutoff date, July 24, 2019, 17 pts enrolled in Cohort 2, 14 (82%) of whom were treated with brexu-cel with median follow-up of 16.0 mo (range, 13.9-18.0). Pt characteristics for Cohort 2 (N=14) were similar to Cohort 1; median (range) age and number or prior therapies was 61.5 y (52-73) and 3 (2-5); 100% US-treated, 79% male, 71% extranodal disease, 50% intermediate or high s-MIPI scores, 50% refractory to last therapy, and 43% had prior autologous stem cell transplantation. ORR was 93% (95% CI, 66.1-99.8) per IRRC; 64% had a CR (95% CI, 35.1-87.2), 29% had a PR (95% CI, 8.4-58.1) and 1 pt was not assessed. All 14 pts had ≥1 AE of any grade (Gr), with Gr ≥3 AEs occurring in 93% of pts; the most common being hypotension (50%), white blood cell count decrease (50%), anemia (43%), and neutrophil count decrease (43%). Rates of Gr ≥3 cytokine release syndrome (CRS) and neurological events were 7% and 43%, respectively.

As of April 1, 2024, median follow-up (range) for Cohort 1 and 2 was 67.8 mo (58.2-88.6; N=68) and 72.3 mo (70.1-74.3; N=14), respectively. In Cohort 1, 24 pts were still alive (35%; 2 withdrew consent and 1 lost to follow up) and 44 pts died (65%). In Cohort 2, 8 pts were still alive (57%; 2 withdrew consent and 1 lost to follow up) and 6 pts died (43%). A total of 27 pts (Cohort 1, n=23; Cohort 2, n=4) enrolled in the LTFU study by data cutoff with a median follow-up time of 70.2 mo (range, 58.2-88.6).

Median (95% CI) investigator-assessed DOR and PFS were 36.5 mo (17.7-48.9; n=60; 17 patients in ongoing response, all CR) and 25.3 mo (12.7-46.6; N=68) in Cohort 1; and 57.5 mo (4.7-not estimable [NE]; n=12; 3 pts in ongoing response, all CR) and 29.5 mo (3.3-NE; N=14) in Cohort 2. Median OS (95% CI) and 60-mo OS rates (95% CI) were 46.5 mo (24.9- 60.2) and 38.5% (26.7-50.1) in Cohort 1; and not reached (9.4-NE) and 53.6% (23.8-76.2) in Cohort 2. One pt had 3 ongoing AEs on LTFU, hypogammaglobulinemia and 2 viral infections that arose prior to LTFU. Two pts died on LTFU, both due to progressive disease; no new secondary malignancies or RCR cases were reported.

Conclusions:

Consistent with Cohort 1, brexu-cel demonstrated a high ORR, durable responses, and an expected safety profile in pts with R/R MCL in Cohort 2 despite the lower dose. However, small sample size limits interpretation of these results. With >5 y of median follow-up, pts in Cohort 1 and 2 continued to experience durable responses with high 60-mo OS rates. No new safety signals were detected and no secondary malignancies or RCR cases were reported in LTFU. Additionally, ZUMA-2 results are consistent with real-world outcomes of brexu-cel in the post BTKi R/R MCL setting (89% ORR and 81% CR rate; Wang Y, et al. *J Clin Oncol.* 2023). These results support the continued use of brexu-cel in R/R MCL.

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