

**Title:** BGB-3111-218: Single-arm, open-label, multicenter study of the Bruton tyrosine kinase (BTK) inhibitor zanubrutinib (zanu) in patients with *CD79B*-mutated relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)

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**Background:** Zanu, a potent, specific next-generation BTK inhibitor with a favorable safety profile, is approved in over 70 countries globally for the treatment of multiple B-cell malignancies. Pts with R/R DLBCL face a poor prognosis, and the *CD79B* mutation is an unfavorable prognostic factor for survival, especially following immunochemotherapy. Zanu has demonstrated modest antitumor activity in R/R non-germinal center B-cell (GCB) DLBCL in clinical trials, and retrospective biomarker analyses have indicated that pts with mutated *CD79B* show an enhanced response to zanu treatment (Yang et al *Blood Adv* 2022; Liu et al *Leuk Lymphoma* 2024). Currently, there is no established standard of care for *CD79B*-mutated R/R DLBCL, highlighting an unmet clinical need. Thus, this study assessed antitumor activity and related biomarkers of zanu for *CD79B*-mutated R/R DLBCL.

**Methods:** In this phase 2 trial (NCT05068440), pts with centrally confirmed *CD79B*-mutated R/R DLBCL who were ineligible for high-dose therapy/stem cell transplant and had received  $\geq 1$  prior line of systemic therapy were enrolled across 20 sites in China. Treatment included zanu 160 mg BID po continuously in 28-day cycles until disease progression, unacceptable toxicity, loss to follow-up, or end of the study. Evaluations occurred at baseline, then every 12 weeks for 24 months [mo], and then every 24 weeks thereafter. Primary endpoint was overall response rate (ORR) per 2014 Lugano criteria. Secondary endpoints included complete response (CR) rate, duration of response (DOR), time to response (TTR), progression-free survival (PFS), overall survival (OS), and safety per NCI-CTCAE v5.0. Immunohistochemistry (IHC) DLBCL subtyping data were collected from local sites. For pts without local IHC data, central laboratory staining of CD10, BCL-6, and MUM1 with FFPE tissue specimens were used to classify phenotypes using the Han's Algorithm. Molecular profiling was conducted in biomarker-evaluable pts using DNA (custom Oncolym-413 panel [Gene+]) and RNA sequencing data.

**Results:** Between August 2021 and March 2025, a total of 65 pts were enrolled. All pts were Asian; 52.3% (n=34) of pts were male. Median age was 66 years (range: 42-92 years), 86.2% had non-GCB DLBCL, 63.1% had relapsed disease, 81.5% had Ann Arbor stage III/IV disease, and 84.6% had Eastern Cooperative Oncology Group performance status of  $\leq 1$ . Median number of prior therapies was 1. All pts were included in the safety and efficacy analysis set.

With a median follow-up of 13.9 mo (range: 0.5-36.4 mo), the ORR was 46.2%, CR was 29.2%, and PR was 16.9%. In responders, the median DOR was 22.7 mo (2.8-NE). Median TTR was 2.8 mo. Median PFS and OS were 4.3 mo (95% CI 2.7-5.5) and 18.1 mo (95% CI 11.4-NE), respectively. Pts with non-GCB DLBCL achieved encouraging response rates (ORR 51.8%). Zanu demonstrated a tolerable and manageable safety profile consistent with the established safety profile. The reported incidence of grade  $\geq 3$  treatment-related treatment-emergent adverse events (TRAEs) was 16 pts (24.6%). The most frequently reported TRAEs of grade  $\geq 3$  were pneumonia (6.2%), decreased neutrophil count (6.2%), decreased platelet count (3.1%), anemia (3.1%), and decreased lymphocyte count (3.1%). With a median exposure time to zanu of 4.0 mo (range: 0.3-36.4 mo), no atrial fibrillation or flutter, hypertension, opportunistic infections, second primary malignancies, or tumor lysis syndrome events were reported.

Retrospective biomarker analyses demonstrated that 32/64 pts with low levels of ctDNA ( $< 275.898$  hGE/mL) at baseline had favorable clinical outcomes including higher response rates (ORR 62.5% vs 28.1%;  $P < .0001$ ) and longer PFS ( $P < .01$ ). Further, pts who achieved CR had a high rate of undetectable ctDNA at first response following zanu treatment (17/18; 94.4%). Pts with co-occurring *CD79B* and *MYD88*<sup>L265P</sup> mutations demonstrated better ORR and CR compared with pts without (ORR 14/23 vs 15/41,  $P = .070$ ; CR 10/23 vs 8/41,  $P < .05$ ). Acquired *BTK* and *PLCG2* mutations were observed in 17/34 pts who progressed following zanu treatment.

**Conclusion:** Zanu demonstrated encouraging antitumor activity and a tolerable safety profile in pretreated *CD79B*-mutated R/R DLBCL. Retrospective biomarker analyses demonstrated improved zanu response in pts with non-GCB subtype, low baseline ctDNA levels, or co-occurring *CD79B* and *MYD88*<sup>L265P</sup> mutations. These data suggest zanu may provide clinical benefit for these pts with limited therapeutic options.