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Biomarker analysis in patients treated with zanubrutinib and lenalidomide combination in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)

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Introduction: While frontline immunochemotherapy achieves high initial response rates for patients (pts) with DLBCL, approximately one-third of pts develop relapsed/refractory (R/R) disease, often driven by molecular risk factors. Bruton tyrosine kinase (BTK), a key intracellular mediator of B-cell receptor signaling, promotes growth and survival of

malignant B cells. The next-generation BTK inhibitor zanubrutinib plus the immunomodulatory drug lenalidomide has demonstrated encouraging antitumor activity across DLBCL subtypes in BGB-3111-110, a phase 1/1b, open-label, dose-escalation/expansion study (NCT04436107) in Chinese pts with R/R DLBCL (Song et al, *Blood Adv*, 2026). Here, we report the exploratory biomarker analysis from BGB-3111-110, providing insights into the biological mechanisms associated with treatment response and resistance.

Methods: The biomarker analysis was performed for recommended phase 2 dose cohorts (n=50). Tumor tissue collected at baseline was utilized for gene expression profiling (n=44) and mutational analysis (n=45) using RNA- and DNA-sequencing. Lymphoma microenvironment (LME) classification was performed based on expression of 25 functional gene expression signatures (F^{GES}; Kotlov et al, *Cancer Discov*, 2021). Circulating tumor DNA (ctDNA) samples collected at baseline (n=35), cycle 4 day 1 (C4D1; n=26), and progressive disease (PD; n=23) were assessed for ctDNA levels and genetic alterations using DNA sequencing. ctDNA levels were quantified in haploid genome equivalents per milliliter (hGE/mL) using mean variant allele frequency and cell-free DNA concentration, assuming 3.3 pg DNA/hGE.

Results: Compared with pts without *CD79B* ITAM mutations (others), pts with *CD79B* ITAM mutations at baseline had numerically higher overall response rates (ORRs; *CD79B* ITAM, n=7/9 [77.8%]; others, n=22/36 [61.1%]) and complete response rates (CRRs; *CD79B* ITAM, n=6/9 [66.7%]; others, n=5/36 [41.5%]). In contrast, baseline *B2M* mutations were associated with lower ORR (*B2M* mutant, n=4/12 [33.3%] vs *B2M* wildtype [WT], n=20/23 [87%]), lower CRR (*B2M* mutant, n=2/12 [16.7%] vs *B2M* WT, n=15/23 [65.2%]), and shorter progression-free survival (PFS; 2.8 [95% CI, 1.4-5.5] mo vs 11.1 [95% CI, 5.5-not available (NA)] mo) and overall survival (12.8 [95% CI, 4.6-NA] mo vs NA [95% CI, NA-NA] mo) compared with WT in baseline ctDNA analysis. Similarly, pts with *B2M* mutations detected in baseline tumor tissue trended toward shorter PFS.

Gene expression–based LME classification identified 4 subtypes: inflammatory (IN; n=14/44), mesenchymal (n=12/44), depleted (n=10/44), and germinal center-like (n=8/44). The IN subtype had a higher ORR (n=12/14 [85.7%] vs n=16/30 [53.3%]) and

improved PFS vs other LME subgroups. Consistently, unbiased gene set enrichment analysis (n=44) showed that high levels of antigen presentation, CD8+ T-cell activation, and cytotoxicity signatures at baseline were associated with improved PFS.
Using the median baseline ctDNA level as the cutoff, pts with low baseline ctDNA levels (<273.306 hGE/mL; n=17) had longer PFS than those with high levels (≥273.306 hGE/mL; n=18). At C4D1, 94.1% of pts (16/17) with complete responses had undetectable ctDNA whereas 42.9% of pts (3/7) with partial responses had undetectable ctDNA. Median PFS was 17.64 (95%CI, 5.55-NA) mo in pts with undetectable ctDNA (n=21) at C4D1, whereas 4/5 pts with detectable ctDNA at C4D1 progressed within 6 mo following treatment.
Paired analysis of ctDNA alterations at baseline and PD (n=23) revealed infrequent acquired mutations in *BTK* (n=2), *CARD11* (n=2), *PLCG2* (n=4), and *IRF4* (n=2). Baseline high-risk factors, including *B2M* mutations (11/23 [47.8%]) and high ctDNA levels, were enriched in pts who progressed after treatment.
Conclusions: These exploratory analyses suggest that baseline *CD79B* ITAM mutations, *B2M* WT, an inflammatory LME, and/or low baseline ctDNA may be associated with improved outcomes in pts with R/R DLBCL receiving zanubrutinib + lenalidomide. Drug-related acquired *BTK* or downstream mutations may not be the primary driver for disease progression. Given the limited sample size, these data should be interpreted with caution and further investigation in larger R/R DLBCL cohorts is warranted.