Genomic Characterization of Patients in a Phase 2 Study of Zanubrutinib in BTK Inhibitor–Intolerant Patients With Relapsed/Refractory B-Cell Malignancies

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Background/Introduction: Targeting Bruton tyrosine kinase (BTK) to inhibit B-cell receptor signaling is an effective way to treat B-cell malignancies. However, some patients (pts) have experienced toxicities to BTK inhibitors ibrutinib (ibr) and acalabrutinib (acala), which lead to dose reduction or treatment discontinuation. Zanubrutinib (zanu) is a potent and selective next-generation BTK inhibitor (*Blood*. 2021;138[suppl 1]:1410). BGB-3111-215 (NCT04116437) is an ongoing, phase 2 study of the safety and efficacy of zanu monotherapy in pts with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), or marginal zone lymphoma (MZL) who discontinued ibr, acala, or acala and ibr because of intolerance. Here, we present the gene mutation profile of pts in this study to demonstrate the mutational landscape of pts intolerant to ibr or acala and to explore the association between gene mutations and response to zanu in ibr- and acala- intolerant pts.

Methods: Peripheral blood from pts was collected before treatment and at or after the time of disease progression. Genomic DNA was isolated from peripheral blood mononuclear cells or plasma, and the mutational status of targeted genes was assessed using a targeted 106-gene next-generation sequencing (NGS) panel (PredicineHEME™, Predicine). Samples were sequenced to a median depth of >20,000 reads, with a validated sensitivity of 0.25% mutant allele frequency for all genomic regions.

Results: Samples from 63 pts were analyzed, including 63 at baseline and 5 at or after progressive disease (PD). There were 41 pts with CLL, 6 with SLL, 10 with WM, 3 with MCL, and 3 with MZL. The most common mutations at baseline were *TP53* (31.7%), *SF3B1* (22.2%), *ATM* (17.5%), *NOTCH1* (17.5%), *CHEK2* (14.3%), and *KRAS* (12.7%). Copy number variants were detected, including deletions at *ATM* locus (9.5%) and *RB1* locus (9.5%) and amplifications at *CCND2* locus (6.3%). For CLL/SLL, the frequencies of *TP53* (27.7%), *NOTCH1* (21.3%), *SF3B1* (25.5%), *ATM* (21.3%), and *BIRC3* (10.4%) mutations were comparable to those in other studies with high-risk relapsed/refractory CLL pts (*Leukemia*. 2018;32:3-91; *Blood*. 2014;123:3247-3254; *Leuk Lymphoma*. 2018;59[10]:2318-26). For WM, 5 of 10 (50%) samples harbored *TP53* mutations, and 4 of 10 samples had *MYD88* mutations; all harbored the L265P mutation. Among the 4 pts with *MYD88* mutation, *CXCR4* gene mutation was

detected in 1 case. All 6 pts with *MYD88* wild type also had *CXCR4* wild type gene, consistent with published data (*N Engl J Med*. 2015;373:584-6).

Baseline mutations were available for the 10 pts with PD, including 8 CLL, 1 SLL, and 1 MCL. Compared to pts without PD, pts with PD had increased frequency of certain mutations: *TP53* (60%, *P*=0.071), *ATM* (50%, *P*=0.017), *SF3B1* (50%, *P*=0.035), *RB1* (40%, *P*=0.009), *SETD2* (40%, *P*=0.009), and *CDKN2A* (30%, *P*=0.011). This finding suggests that these particular baseline mutations are associated with resistance to zanu. Five pts also had mutations detected at or after PD. Of these, 3 pts had *BTK* or *PLCG2* mutations (submitted). One patient with CLL and without *BTK* or *PLCG2* mutations had *ATM* and *FBXW7* mutations (variant allele frequencies were 86% and 50%, respectively), suggesting DNA damage pathway mutations and *NOTCH1* dysregulations may have contributed to disease progression in this patient.

Conclusion: Exploratory analysis results confirmed that cell cycle, DNA damage, and *NOTCH1* pathway genes were frequently mutated in pts with B-cell malignancies on study BGB-3111-215 (pts intolerant to ibr and/or acala). Pts with mutations associated with poor prognosis at baseline were more likely to develop PD.