Genomic Landscape of Ibrutinib- and/or Acalabrutinib-intolerant Patients with B-cell Malignancies Treated with Zanubrutinib in a Phase 2 Study

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Introduction: Bruton tyrosine kinase inhibitors (BTKi) have shown remarkable utility in the treatment of B-cell malignancies; yet some patients have experienced toxicities to the BTKis, ibrutinib and acalabrutinib, which lead to dose reduction or treatment discontinuation. Zanubrutinib is a potent and selective next-generation BTKi. BGB-3111-215 (NCT04116437) is an ongoing, phase 2 study of the safety and efficacy of zanubrutinib monotherapy in patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), or marginal zone lymphoma (MZL) who discontinued ibrutinib, acalabrutinib, or acalabrutinib and ibrutinib because of intolerance.

Methods: Because the genomic profile of patients with B-cell malignancies who are intolerant to ibrutinib and/or acalabrutinib has not been extensively studied, mutations were assessed using a 106 gene-targeted next-generation sequencing panel (PredicineHEME™, Predicine) on baseline and disease progression samples. 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, and 0.1% for mutational hotspots. Variant allele frequency (VAF) <0.1% for hotspot mutations and <0.25% for non-hotspot mutations were excluded from analysis; germline and CHIP mutations were also excluded from analysis. The association between gene mutations and progression-free survival (PFS, defined as time from the date of first zanubrutinib dose to date of first PD or death) was quantified by the log rank test and the hazard ratio and summarized by the Kaplan-Meier method.

Results: As of June 6, 2022, baseline peripheral blood samples were collected from 71 (95.9%) of the 74 patients enrolled in the study. There were 46 patients with CLL, 11 with WM, eight with SLL, three with MCL, and three with MZL. A total of 56 patients were intolerant to ibrutinib only; 15 were intolerant to acalabrutinib or acalabrutinib and ibrutinib. At baseline, high mutation frequencies were observed in *TP53*, *SF3B1*, *ATM*, and *NOTCH1* across disease indications (**Figure**). The majority of *TP53* mutations were missense mutations and located in the DNA binding domain. Nineteen different mutations were identified in ATM and were distributed across the whole gene with a majority clustered in the 3' regions encoding the FAT and PI3 kinase domains. All mutations (n=21) in *SF3B1* were missense and 38% (n=8/21) of the mutations occurred at p.K700E/c.A2098G. In *NOTCH1*, the most common mutation (n=8/14, 57.1%) was a two base pair deletion (c.7541_7542delCT) in the PEST domain of exon 34. In

patients with CLL/SLL with *TP53*, *SF3B1*, or *ATM* mutations at baseline, shorter progression-free survival was observed compared to patients without these mutations, suggesting that mutations in DNA damage response and RNA splicing/metabolism pathways are associated with less favorable prognosis. *BTK* mutations were detected in 4.2% (n=3/71) of baseline samples and in 57.1% (n=4/7) of samples available at disease progression (PD). All *BTK* mutations were at the C481 BTKi binding site. Two patients with baseline *BTK* mutations had PD and increased VAF of BTK mutants were detected for both patients at PD. A third patient died due to illness unrelated to treatment. Two patients acquired new BTKC481 mutations at PD.

*Conclusion: T*his is the first study to describe the genomic landscape of patients with B-cell malignancies who were intolerant to ibrutinib and/or acalabrutinib. Here we show that the gene mutational profile of these patients at baseline or at/after disease progression is comparable with patients with relapse/refractory disease who tolerate ibrutinib and, consistent with other studies, patients with mutations in *TP53*, *SF3B1* or *ATM* genes had less favorable prognosis on BTKi. Further, intolerant patients who progressed on zanubrutinib acquired new *BTK* mutations and/or had an increase in the frequency of *BTK* mutations. These data contribute to the growing understanding of the mutational profiles of patients with B-cell malignancies, particularly those who were intolerant to BTKi, and further explores the association between mutations and response to subsequent zanubrutinib treatment. This study may provide supporting information to inform treatment guidelines for patients who become intolerant to BTKi.

Figure. Variant classification and heatmap representation of mutations detected at baseline in at least three patients with B-cell malignancies.