Updated safety and efficacy results of zanubrutinib in patients with B-cell malignancies who are intolerant of ibrutinib and/or acalabrutinib

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Introduction: Patients (pts) with B-cell malignancies treated with Bruton tyrosine kinase inhibitors (BTKi) require continuous treatment. However, many pts on ibrutinib and/or acalabrutinib discontinue treatment because they experience treatment-related intolerance. Zanubrutinib is a BTKi designed to maximize tolerability by minimizing off-target effects. The phase 2 BGB-3111-215 (NCT04116437) study demonstrated that zanubrutinib is well tolerated in pts previously intolerant of ibrutinib and/or acalabrutinib. At a median follow-up of 25.2 mo, we report updated safety and efficacy results from the BGB-3111-215 study. Here, we assess the safety and efficacy of zanubrutinib in pts intolerant of ibrutinib and/or acalabrutinib.

Material and method: Pts meeting protocol-defined criteria for intolerance of ibrutinib and/or acalabrutinib with no documented progressive disease during prior BTKi treatment were given zanubrutinib monotherapy 160 mg twice daily or 320 mg once daily. Recurrence of adverse events (AEs) that led to intolerance of prior BTKi and other treatment-emergent AEs were assessed based on the Common Terminology Criteria for Adverse Events v5.0. Investigator-assessed responses using disease parameters at study entry as baseline were assessed every third 28-day cycle using standard response criteria.

Results: As of 3 January 2023, 82 pts were enrolled (61 chronic lymphocytic leukemia/small lymphocytic lymphoma, 13 Waldenström macroglobulinemia, 4 mantle cell lymphoma, 4 marginal zone lymphoma). Median age was 71.5 years (range, 49-91 years). Median number of prior therapies was 2 (range, 1-12). Median prior exposure to ibrutinib was 9.2 mo and to acalabrutinib was 5.1 mo. Fifty-seven pts (69.5%) were intolerant of only ibrutinib, 14 (17.1%) of only acalabrutinib, and 11 (13.4%) of both. Most pts experienced >1 intolerance event on prior BTKi, with 124 ibrutinib intolerance events occurring among 68 pts (most common events being fatigue, hypertension, atrial fibrillation, rash, and arthralgia) and 37 acalabrutinib intolerance events occurring among 25 pts (most common events being myalgia, headache, arthralgia, and diarrhea). On zanubrutinib, 84/124 (67.7%) ibrutinib and 27/37 (73%) acalabrutinib intolerances did not recur. Of those that did recur, 30/40 (75.0%) ibrutinib and 4/10 (40.0%) acalabrutinib intolerances recurred at a lower grade. No intolerance events recurred at a higher grade. With a median zanubrutinib exposure on study (23.7 mo) that is markedly longer than the reported median prior BTKi exposure before discontinuation, 48/82 (58.5%) pts did not experience any recurrence of prior intolerance events, and 58/82 (70.7%) pts remain on treatment; 24/82 (29.3%) discontinued treatment (reasons: 7 AEs [myalgia, stomatitis, penile hemorrhage, COVID-19 pneumonia, alanine and aspartate aminotransferases increased, autoimmune hemolytic anemia, diarrhea], 7 PD, 10

other). The general safety profile of zanubrutinib in this study was consistent with the known zanubrutinib safety profile, including 37 pts (45.1%) experiencing grade ≥3 AEs, 19 (23.2%) serious grade ≥3 AEs, and 6 (7.3%) total deaths (1 due to AE). In efficacy-evaluable pts, disease was controlled (SD/PR/CR) in 54/56 (96.4%) pts previously intolerant of only ibrutinib and 19/20 (95.0%) pts previously intolerant of acalabrutinib.

Conclusions: Updated safety and efficacy results suggest that switching to zanubrutinib may provide clinical benefit to pts previously intolerant of other BTKi. Enrollment and follow-up are ongoing.