PRELIMINARY RESULTS FOR PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA FROM THE PHASE 2 STUDY OF ZANUBRUTINIB IN PREVIOUSLY TREATED B-CELL MALIGNANCIES INTOLERANT TO IBRUTINIB AND/OR ACALABRUTINIB

Mazyar Shadman,[1] Jeff P. Sharman,[2] Moshe Y. Levy,[3] Syed F. Zafar,[4] John M. Burke,[5] Edwin Kingsley,[6] Rocco Crescenzo,[7] Dih-Yih Chen,[7] Adam Idoine,[7] Aileen Cohen,[7] Kunthel By,[7] and Ian Flinn[8]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA; [2]Willamette Valley Cancer Institute and Research Center, Eugene, OR; [3]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; [4]Florida Cancer Specialists & Research Institute, Fort Myers, FL; [5]Rocky Mountain Cancer Centers, Aurora, CO; [6]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [7]BeiGene USA, Inc., San Mateo, CA; and [8]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

Background: Patients with Waldenström macroglobulinemia (WM) often require continuous treatment with Bruton tyrosine kinase inhibitors (BTKi). Adverse events (AEs) can sometimes force patients to discontinue BTKi. Phase 3 studies have demonstrated that the next-generation BTKi zanubrutinib may have a more favorable safety profile than ibrutinib (*Blood*. 2020;136(18):2038-2050; EHA 2021. Abstract LB1900). Early data from the BGB-3111-215 study (NCT04116437) has shown that zanubrutinib is well-tolerated in patients with B-cell malignancies who are intolerant to ibrutinib or acalabrutinib.

Aims: To report preliminary tolerability and efficacy results for patients with WM treated with zanubrutinib after discontinuation of ibrutinib or acalabrutinib for intolerance.

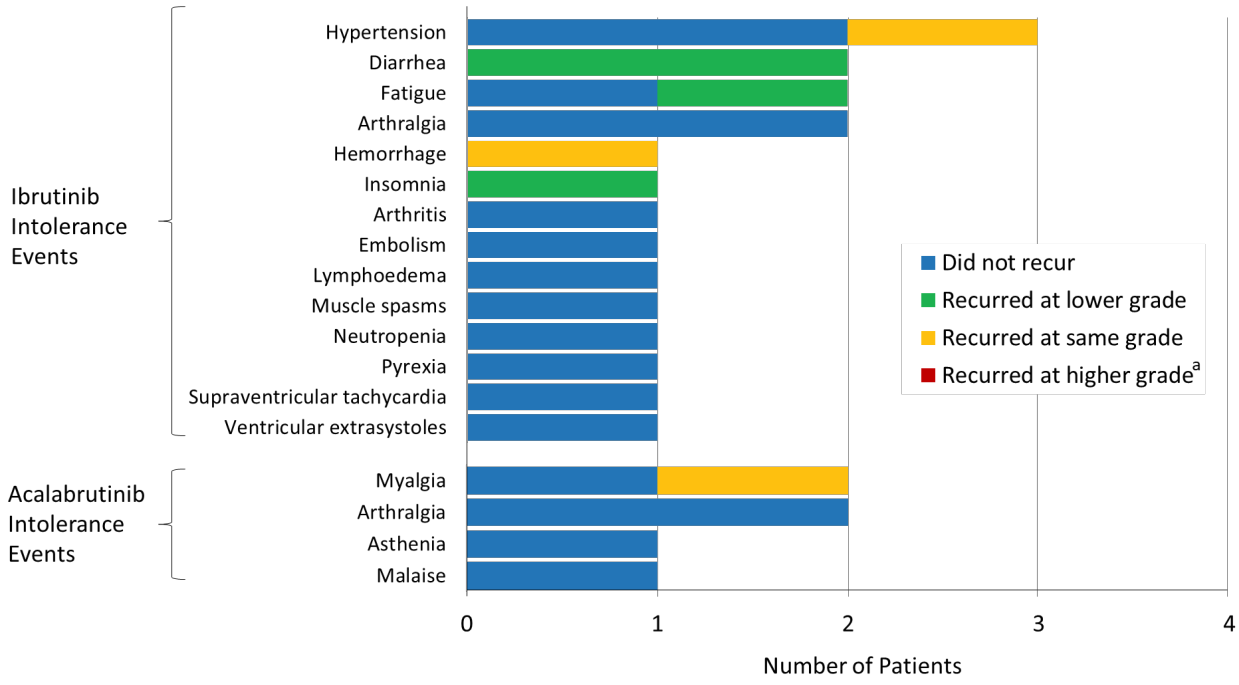
Methods: Patients meeting protocol-defined criteria for intolerance to ibrutinib, acalabrutinib, or both (without documented progressive disease) were given zanubrutinib monotherapy (160 mg twice daily or 320 mg once daily). Recurrence of AEs that led to intolerance to prior ibrutinib and/or acalabrutinib and additional safety measures were assessed, based on the Common Terminology Criteria for AEs v5.0. Investigators determined responses using disease status at study entry as baseline.

Results: As of March 17, 2022 (median follow-up: 14.9 months), 11 patients with WM (9 intolerant to only ibrutinib, 2 intolerant to ibrutinib and acalabrutinib) were enrolled, received ≥1 zanubrutinib dose (160 mg twice daily: 6 [54.5%], 320 mg once daily: 5 [45.5%]), and were analyzed for safety. Median age was 71 years (range, 58-80), median duration of treatment was 14.9 months (range, 6.5-20.5), and median number of prior regimens was 2 (range, 1-12). The most common ibrutinib-intolerance AEs were hypertension (n=3), fatigue, diarrhea, and arthralgia (n=2 each). The most common acalabrutinib-intolerance AEs were myalgia and arthralgia (n=2 each). On zanubrutinib, 45% of patients did not experience recurrence of any prior BTKi-related intolerance AE. At the event level, 68% (13/19) of ibrutinib- and 83% (5/6) of acalabrutinib-intolerance AEs did not recur with zanubrutinib (**Figure**). Of the ibrutinib-intolerance AEs that did recur, 67% (4/6), 33% (2/6), and 0 recurred at a lower, the same, or higher grade, respectively. The recurring acalabrutinib-intolerance AE (myalgia) recurred at the same grade. At data cutoff, 9 patients remained on treatment; 2 discontinued treatment and

study owing to AEs (myalgia [recurrent acalabrutinib intolerance] and alanine aminotransferase/aspartate aminotransferase [ALT/AST] increased). The most common AEs were contusion and fatigue (both n=4; 36.4%). Grade ≥3 AEs were reported in 2 patients (18.2%; neutrophil count decreased/neutropenia/platelet count decreased; ALT/AST increased). A serious AE was reported in 1 patient (9.1%, COVID-19 pneumonia), AEs requiring dose interruptions in 3 patients (27.3%), and AEs leading to dose reduction in 2 patients (18.2%). No deaths occurred. All efficacy evaluable patients maintained (n=1 [9.1%]) or improved (n=10 [90.9%]) their disease status from baseline. Best overall responses were 5 (45.5%) very good partial responses, 3 (27.3%) partial responses, 2 (18.2%) minor responses, and 1 (9.1%) patient with stable disease.

Conclusions: AEs that previously caused patients to discontinue ibrutinib or acalabrutinib treatment are unlikely to recur with zanubrutinib, suggesting patients intolerant to other BTKi may experience favorable safety and continue receiving clinical benefit by switching to zanubrutinib.

Figure. Recurrence and Severity Change of Intolerance Adverse Events From Prior Ibrutinib or Acalabrutinib Exposure to Zanubrutinib Exposure in Patients With Waldenström Macroglobulinemia



[a]No intolerance adverse events recurred at a higher grade.