A phase 2 expanded access study of zanubrutinib (ZANU) in patients (pts) with Waldenström Macroglobulinemia (WM)

Jorge J. Castillo, MD[1]; Edwin C. Kingsley, MD[2]; Mohit Narang, MD[3]; Habte A. Yimer, MD[4]; Constantin A. Dasanu, MD, PhD[5]; Jason M. Melear, MD[6]; Morton Coleman, MD[7]; Charles M. Farber, MD, PhD[8]; Mukul Gupta, MD[9]; Jonah Shulman, MD[10]; Emily H. Mantovani, PharmD, MSCR[11]; Xiaowei Zhang, PhD[11]; Aileen Cohen, MD, PhD[11]; Jane Huang, MD[11]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Department of Medical Oncology, Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [3]Department of Hematology and Medical Oncology, US Oncology Research, Maryland Hematology Oncology, Columbia, MD, USA; [4]Department of Medical Hematology/Oncology, Texas Oncology, US Oncology Research, Tyler, TX, USA; [5] Lucy Curci Cancer Center, Eisenhower Health, Rancho Mirage, CA, USA; [6]US Oncology Research, Texas Oncology, Austin Midtown, Austin, TX, USA; [7]Department of Hematology, Clinical Research Alliance, New York, NY, USA; [8]Atlantic Hematology Oncology, Morristown Medical Center, Morristown, NJ, USA; [9]Department of Medical Oncology, Ridley-Tree Cancer Center at Sansum Clinic, Santa Barbara, CA, USA; [10]Department of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [11]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA

Background: Bruton tyrosine kinase (BTK) inhibition is an emerging standard of care for WM. The next-generation BTK inhibitor ZANU (BGB-3111), designed to maximize BTK occupancy and minimize off-target inhibition of other kinases, is approved by the United States (US) Food and Drug Administration, Health Canada, and the European Union at a dose of 320 mg once daily (QD) or 160 mg twice daily (BID) for adult pts with WM. BGB-3111-216 is a single-arm expanded access study of ZANU in treatment-naïve (TN) pts who were unsuitable for standard chemoimmunotherapy or pts with relapsed refractory (R/R) WM. This study provides real-world experience with ZANU in pts with WM.

Methods: Eligible pts with TN or R/R WM received ZANU 320 mg QD or 160 mg BID orally. Primary endpoint was the number of pts enrolled/treated and enrolling sites. Secondary endpoints included treatment-emergent adverse events (TEAEs) of special interest, disease

response rate, progression-free survival (PFS), and overall survival (OS). Response was evaluated by investigator assessment according to the 6th International Workshop on WM (*Br J Haematol.* 2013;160(2):171-6) every 6 mo at minimum. The study was closed by the sponsor in July 2021 and active pts were transitioned to commercial ZANU via a patient assistance program.

Results: Fifty pts with WM (17, TN; 33, R/R) were enrolled between December 2019 and June 2021 across 10 academic and community medical centers in the US. Median age was 72 years, 54% had intermediate-, 40% had high-risk disease, and the median number of prior therapies for R/R pts was 2. Median treatment exposure was 9.2 mo (range, 1.4-20.0). Thirty-eight (76%) pts had ≥1 TEAE, and 36 (72%) had ≥1 TEAE of special interest. Grade ≥3 TEAEs of special interest were hypertension (8%), infection (8%), atrial fibrillation/flutter (2%), neutropenia (2%), and second primary malignancy (2%). No new safety signals were observed. In pts with ≥1 response evaluation, 39% achieved a best overall response (BOR) of very good partial response. Overall response rate was 85.4% and major response rate was 73.2% (Table). Of the 4 pts with BOR of progressive disease, 3 had IgM values that met partial response criteria before the 6-mo response assessment. PFS and OS were immature due to short follow-up, and the median was not met.

Conclusions: These real-world expanded access study results were consistent with the established ZANU profile in WM or other B-cell malignancies when administered as oral monotherapy at 160 mg BID or 320 mg QD in pts with intermediate or high-risk R/R or TN WM.

BOR n (%)	160 mg BID (n=33)	320 mg QD (n=8)	Overall (N=41)
Very good partial response	13 (39.4)	3 (37.5)	16 (39.0)
Partial response	12 (36.4)	2 (25.0)	14 (34.1)
Minor response	4 (12.1)	1 (12.5)	5 (12.2)
Stable disease	1 (3.0)	1 (12.5)	2 (4.9)
Progressive disease	3 (9.1)	1 (12.5)	4 (9.8)
Major response rate	25 (75.8)	5 (62.5)	30 (73.2)
Overall response rate	29 (87.9)	6 (75.0)	35 (85.4)