Long-term clinical outcomes in patients with Waldenström macroglobulinemia (WM) who received zanubrutinib in the phase 3 ASPEN study: A report from the zanubrutinib extension study

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Introduction: BTK inhibitors (BTKi) have become a standard of care for WM. The ASPEN study (BGB-3111-302; NCT03053440) directly compared outcomes of treatment with zanubrutinib and ibrutinib in patients with *MYD88*-mutated WM in cohort 1; patients with *MYD88*-wild type WM received zanubrutinib in cohort 2. At end of study, eligible patients could enroll in a long-term extension study, BGB-3111-LTE1 (LTE1, NCT04170283). Here, we report long-term outcomes in patients who received zanubrutinib in the ASPEN study, with extended follow-up from LTE1.

Methods: Patients who received zanubrutinib in the ASPEN study (cohort 1, Arm A and cohort 2) were included in this *ad hoc* analysis. Upon enrollment in LTE1, safety assessments were required every 3 mo and disease response assessments per

investigator were required at least every 6 mo, using modified IWWM-6 response criteria (Owen 2013). Alternatively, investigators could assess "*no evidence of progressive disease.*"

Results: Of 129 patients who received zanubrutinib in the ASPEN study (cohort 1, n=101; cohort 2, n=28), 75 enrolled in LTE1 between Nov 11, 2021 and June 7, 2022; 72 continued zanubrutinib treatment. At ASPEN entry, the median age was 67 y (range, 39-85), and 81.3% (61/75) had relapsed/refractory WM, with a median of 1 prior line of therapy (range, 1-8). At LTE1 entry, the median age was 71 y (range, 44-89) and the median time since zanubrutinib treatment initiation was 50.6 mo (range, 40.7-59.9).

As of April 17, 2024, for patients enrolled in LTE1 from ASPEN, the median treatment duration in LTE1 was 23.8 mo (range, 0.4-29.4) and overall (ASPEN + LTE1) was 73.6 mo (range, 49.2-84.2). During LTE1, grade ≥3 and serious treatment-emergent adverse events (TEAEs) occurred in 28% and 23% of patients, respectively. No patients experienced TEAEs leading to treatment discontinuation in LTE1. Three patients (4%) had TEAEs leading to dose reduction (COVID-19 [n=2], intestinal diverticulum), and 3 had TEAEs leading to death (cardiac failure, fall/subdural hematoma, colorectal cancer). No grade ≥3 or serious TEAEs by preferred term occurred in ≥5% of patients during LTE1, whereas grade ≥3 neutropenia (24.0%), hypertension (8.0%), thrombocytopenia (6.7%), anemia (5.3%), back pain (5.3%) occurred in ≥5% of this subgroup during ASPEN. Of 42 patients with neutropenia/neutrophil count decreased, 17 (40.5%) received granulocyte-colony stimulating factor.

For all patients treated with zanubrutinib during ASPEN (n=129), the median follow-up was 69.8 mo (range, 1.6, 85.4) and median zanubrutinib treatment duration was 63.3 mo (range, 0.8, 84.2). Except for second malignancies (skin and non-skin cancer, each 6.0% at >5 y), the prevalence of TEAEs of interest for BTKis, including neutropenia, decreased over time. Specifically, at >1-2, >2-3, >3-4, >4-5 and >5 y, the prevalence of atrial fibrillation/flutter was 2.7%, 5.2%, 3.5%, 1.4%, and 1.5%, and of hypertension was 10.7%, 8.3%, 9.4%, 6.8%, and 6.0%, respectively.

For patients from cohort 1 (n=101, *MYD88*-mutated), the overall response rate (ORR, ≥minor response) was 96.1% and the rate of ≥very good partial response (VGPR+) was

40.2% versus 95.1% and 36.3%, respectively, at ASPEN final analysis. For patients from cohort 2 (n=26, confirmed *MYD88*-wild type), the ORR was 84.6% and the VGPR+ rate was 30.8% versus 80.8% and 30.8%, respectively, at ASPEN final analysis (Dimopoulos et al. *JCO*. 2023). Median duration of response was 55.7 mo (95% CI, 31.3, 68.4) for cohort 1 and 41.1 mo (95% CI, 15.7, NE) for cohort 2. In cohort 1, the 60-mo event-free rates for progression-free survival (PFS) were 74.8% (95% CI, 64.5, 82.5) overall; 70% (95% CI, 50.1, 83.2) for patients with *CXCR4*^{WHIM} (n=33; 4 unknown); and 57.3% (95% CI, 35, 74.4) for patients with *TP53*^{mut} (n=26; 4 unknown). In cohort 2, the 60-mo event-free rate for PFS was 39.3% (95% CI, 20, 58.1); 1 patient in cohort 2 had *CXCR4*^{WHIM} (6 unknown) and 4 had *TP53*^{mut} (6 unknown). The 60-mo event-free rates for overall survival were 82.8% (95% CI, 73.5, 89.1) for cohort 1 and 79.9% (95% CI, 56.4, 90.8) for cohort 2. As of April 17, 2024, 69.3% (52/75) of patients with WM remained on zanubrutinib.

Conclusions: With a median follow-up of 5.8 y, responses in patients with WM treated with zanubrutinib in ASPEN remained durable; furthermore, the tolerability and safety profile of zanubrutinib remained favorable, with most TEAEs of interest for BTKis decreasing in prevalence with ongoing treatment.