Clinical Outcomes in Patients with Waldenström Macroglobulinemia (WM) Receiving Ibrutinib on the Phase 3 ASPEN Study ≥1 Year After Transitioning to Zanubrutinib

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Introduction: Bruton tyrosine kinase inhibitors (BTKi) have become a standard of care in treating patients with WM. Zanubrutinib, a next-generation BTKi, was developed to ensure greater BTK specificity and potency than ibrutinib to avoid toxicities associated with off-target binding and improve efficacy. The ASPEN study (BGB-3111-302; NCT03053440) directly compared outcomes of zanubrutinib and ibrutinib treatment in patients with *MYD88*-mutated WM. The BGB-3111-LTE1 study (LTE1, NCT04170283) is a long-term extension study to which eligible patients can enroll following participation in parent studies of zanubrutinib for treatment of B-cell malignancies, including patients from comparator treatment arms. Here, we report safety and efficacy outcomes in ibrutinib-tolerant patients from ASPEN at ≥1 yr from initiation of zanubrutinib in the LTE1 study.

Methods: All patients (N=47) who enrolled in LTE1 from the ibrutinib arm of ASPEN (Arm B) were included in this *ad hoc* analysis. Patients began treatment with zanubrutinib at 320 mg total daily dose upon enrollment. Safety and efficacy outcomes were evaluated, including the recurrence of ibrutinib treatment-emergent AEs (TEAEs). Investigators assessed disease response every 6 months, or more frequently as indicated, based on the modified Owen criteria and using parameters at ASPEN study entry (BTKi pretreatment); alternatively, investigators could assess "no evidence of progressive disease" using their clinical judgment.

Results: Between June 26, 2020, and June 23, 2022, 47 patients treated with ibrutinib in ASPEN enrolled in LTE1. At ASPEN enrollment, 37 patients (79%) had R/R WM, with a median of 1 prior therapy (range: 1-6). At enrollment to LTE1, the median age was 73 yr (range: 44–89); the median time since ibrutinib treatment initiation was 50.4 months (range: 26–59.3).

As of June 23, 2023, 40 patients (85%) remained on study treatment; the median zanubrutinib treatment duration was 15.3 months (range: 5.1–22.1) and the overall median treatment duration with BTKi was 65.5 months (range: 48.1–76.7). The median time from ASPEN study discontinuation to zanubrutinib initiation in LTE1 was 0.07 months (range: 0–4). During LTE1, grade ≥3 and serious TEAEs occurred in 23% and 13% of patients, respectively; infections (6.4%, all COVID-19) were the only grade ≥3 TEAEs occurring in more than 2 patients and no serious TEAEs occurred in more than 2 patients. Worsening of ibrutinib TEAEs of interest for BTKi treatment following the transition to zanubrutinib included infections (n=3), all of which were due to COVID-19 (**Fig 1**), anemia (n=1), and neutropenia (n=1). Of the 7 patients who experienced cardiovascular AEs (8 events) in LTE1, all but 1 with grade 2 tachycardia had experienced at least 1 cardiovascular AE during ibrutinib treatment on ASPEN. No new

or recurrent episodes of hypertension occurred after patients switched from ibrutinib to zanubrutinib, and no ongoing hypertension worsen. No resolved ibrutinib treatment-emergent atrial fibrillation/flutter recurred; no ongoing atrial fibrillation/flutter worsened following the transition to zanubrutinib. One new case of atrial fibrillation occurred on LTE1 Day 12 in a pt with an extensive cardiovascular history who also experienced grade 2 pericarditis 2 days prior (LTE1 Day 10). No cardiovascular TEAE led to death in LTE1; two deaths occurred both due to COVID-19.

Categorical best overall response (BOR) in LTE1 was unchanged from the last response in ASPEN in 34 patients (72%) but improved in 10 patients (21%), including 1 pt in PR and 1 pt in VGPR at the end of ASPEN who had a deepening response to CR. Response worsened from PR to MR in 1 pt, 1 pt had "no evidence of progressive disease," and 1 pt discontinued before response assessment. Median change in [IgM] from the last response in ASPEN to BOR in LTE1 was -36 mg/dL (-3490, +730); [IgM] was stable or decreased in 29 (73%) of the 40 evaluable patients (**Fig 2**).

Conclusions: With a median treatment duration of 15 months, worsening of ibrutinib TEAEs of interest for BTKi treatment following transition to zanubrutinib was rare, as was the emergence of new events. Response was maintained or improved in 96% (n=44/46) of efficacy-evaluable patients. While limited by sample size and nonrandomized/*ad hoc* analysis, data suggest that patients may transition from ibrutinib to zanubrutinib without compromising safety or efficacy; long-term follow-up is ongoing.

Figure 1. Recurrence or Continuation of Ibrutinib Treatment-Emergent Adverse Events on Zanubrutinib

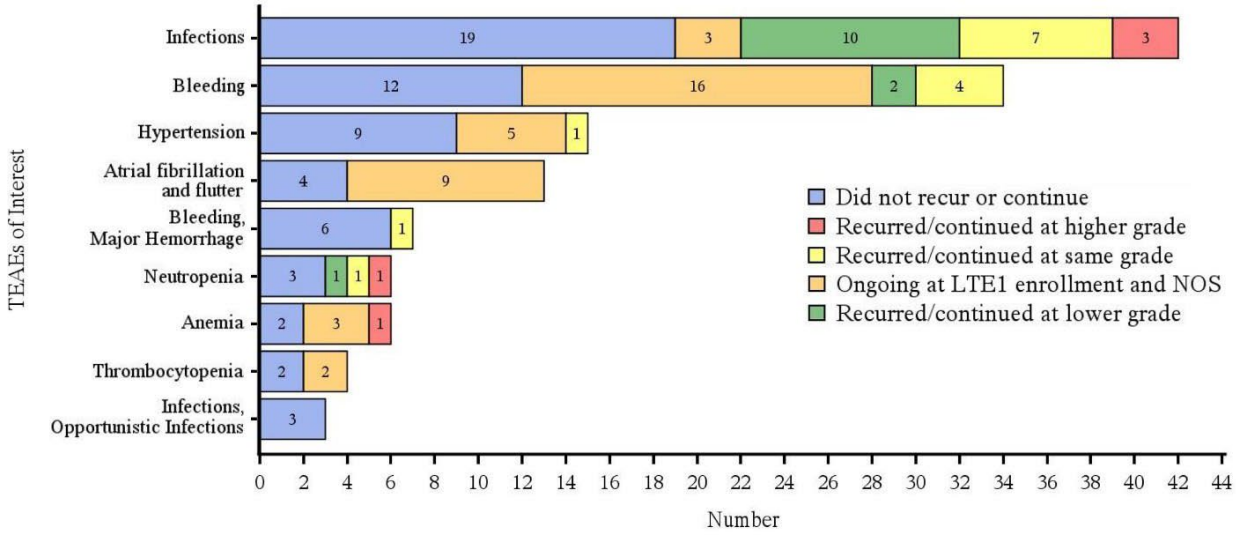

Figure 2. Change in [IgM] from Last Response Assessment in ASPEN Study to Best Overall Response in LTE1 Study