Clinical Outcomes in Patients Receiving Ibrutinib on the Phase 3 ASPEN Study ≥1 Year After Transitioning to Zanubrutinib

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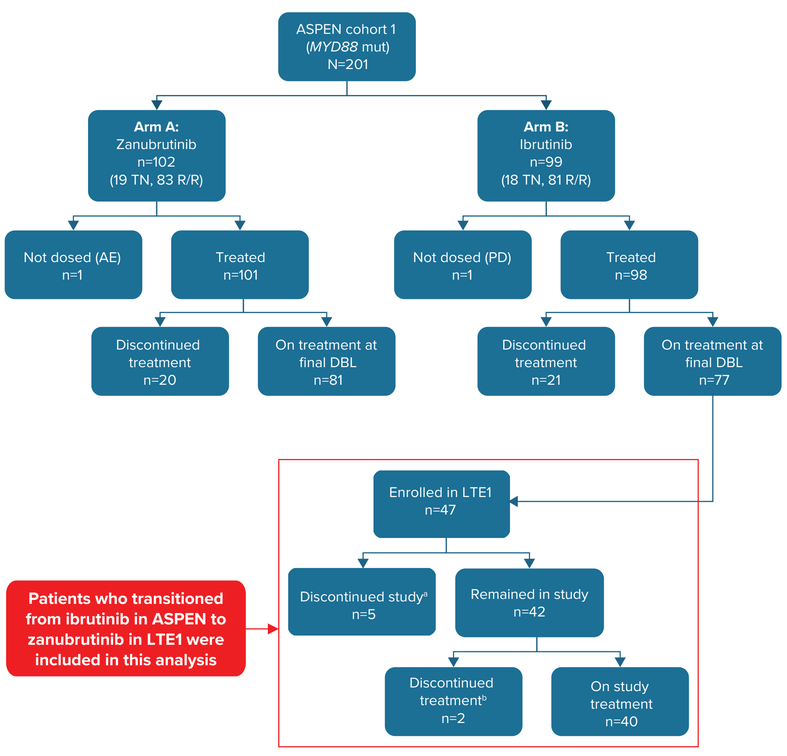
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors have become a standard of care in treating patients with Waldenström macroglobulinemia (WM)[1]
- Zanubrutinib, a next-generation BTK inhibitor, was developed to ensure greater BTK specificity and potency than ibrutinib to avoid toxicities associated with off-target binding and improve efficacy[2]
- The ASPEN study (BGB-3111-302; NCT03053440) directly compared outcomes of zanubrutinib and ibrutinib treatment in patients with myeloid differentiation primary response 88 (*MYD88*)–mutated WM[3]
- The BGB-3111-LTE1 study (LTE1; NCT04170283) is a long-term extension study in 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 patients with WM receiving ibrutinib in ASPEN at ≥1 year after transitioning to 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 (**Figure 1**)
- 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 adverse events (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 (BTK inhibitor pretreatment); alternatively, investigators could assess "no evidence of progressive disease" using their clinical judgment

Figure 1. CONSORT Diagram of the ASPEN and LTE1 Studies



[a] Reasons for study discontinuation (5 patients): death (n=3), lost to follow-up (n=1), and withdrawal (n=1).
[b] Reasons for treatment discontinuation (5 patients who left the study plus 2 who remained in the study): "other" reasons (n=3), AEs (n=2), PD (n=1), and withdrawal (n=1).
AE, adverse event; DBL, database lock; *MYD88*, myeloid differentiation primary response 88; PD, progressive disease; R/R, relapsed/refractory.

RESULTS

Disposition

- Between June 26, 2020, and June 23, 2022, 47 patients treated with ibrutinib in ASPEN enrolled in LTE1
  - Patient and disease characteristics are shown in **Table 1**
  - At enrollment in LTE1, 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 BTK inhibitors 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)

Table 1. Baseline Demographics and Clinical Characteristics of Enrolled Patients as They Proceeded From ASPEN to LTE1 (N=47)

At Enrollment in Parent Study (ASPEN)		After Enrollment in Long-Term Extension (LTE1)	
Age, median (range), years	68 (38-84)	Age, median (range), years	73 (44-89)
Age group, n (%)		Age group, n (%)	
<65 years	16 (34)	<65 years	8 (17)
≥65 and <75 years	22 (46.8)	≥65 and <75 years	21 (44.7)
≥75 years	9 (19.1)	≥75 years	18 (38.3)
Male, n (%)	34 (72.3)	ECOG performance status, n (%)	
Treatment status, n (%)		0	27 (57.4)
TN	10 (21.3)	1	17 (36.2)
R/R	37 (78.7)	2	1 (2.1)
Prior lines, median (range), n	1 (1-6)	Missing	2 (4.3)

ECOG, Eastern Cooperative Oncology Group; R/R, relapsed/refractory; TN, treatment naïve.

Safety Results

- Grade ≥3 and serious TEAEs occurred in 23% and 13% of patients, as presented in **Table 2**
  - Two deaths occurred in LTE1; both were due to COVID-19
- Infections (6.4%; all COVID-19) were the only grade ≥3 TEAEs that occurred in more than 2 patients, and no serious TEAEs occurred in more than 2 patients (**Table 3**)
- TEAEs of interest for zanubrutinib are presented in **Table 4**
- The majority of ibrutinib-emergent adverse events did not recur or worsen with zanubrutinib (**Figure 2**)
- Worsening of ibrutinib TEAEs of interest for BTK inhibitor treatment following the transition to zanubrutinib included infections (n=3), all of which were due to COVID-19 (**Figure 2**), anemia (n=1), and neutropenia (n=1)
- No ongoing hypertension worsened in severity and no new or recurrent episodes of hypertension occurred after patients switched from ibrutinib to zanubrutinib
- Of the 7 patients who experienced cardiovascular AEs (8 events) in LTE1, all but 1 (grade 2 tachycardia) experienced at least 1 cardiovascular AE during ibrutinib treatment in ASPEN; no cardiovascular TEAE led to death in LTE1
  - 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 patient with an extensive cardiovascular history who also experienced grade 2 pericarditis 2 days prior (LTE1 day 10)
  - Three patients, all with prior cardiovascular AEs on ibrutinib in the ASPEN study, developed pericarditis during the LTE1 study: on day 11, at 4 months, and at 9 months of zanubrutinib treatment, respectively; all cases resolved and were deemed unrelated to zanubrutinib by investigator

Table 2. TEAEs in Patients Participating in ASPEN and LTE1

Patients With ≥1 TEAE	ASPEN: Ibrutinib, n (%); N=47	LTE1: Zanubrutinib, n (%); N=47
TEAE	47 (100)	38 (80.9)
Treatment related	42 (89.4)	17 (36.2)
Serious	22 (46.8)	6 (12.8)
Treatment related	15 (31.9)	–
Leading to treatment discontinuation	3 (6.4)	2 (4.3)[a]
Leading to dose reduction	11 (23.4)	–
Leading to dose interruption	30 (63.8)	11 (23.4)
Fatal TEAE	–	2 (4.3)[b]

[a] Hematuria, COVID-19 pneumonia. [b] Respiratory failure, COVID-19 pneumonia.
TEAE, treatment-emergent adverse event.

Table 3. Serious/Grade ≥3 TEAEs in Patients Participating in LTE1

Grade ≥3 TEAEs	n (%); N=47
Hypertension	1 (2.1)
Anemia	2 (4.3)
COVID-19	3 (6.4)
Neutropenia	2 (4.3)
Serious TEAEs	**n (%); N=47**
Pneumonia	2 (4.3)

TEAE, treatment-emergent adverse event.

Table 4. TEAEs of Interest in Patients Treated With Zanubrutinib in LTE1

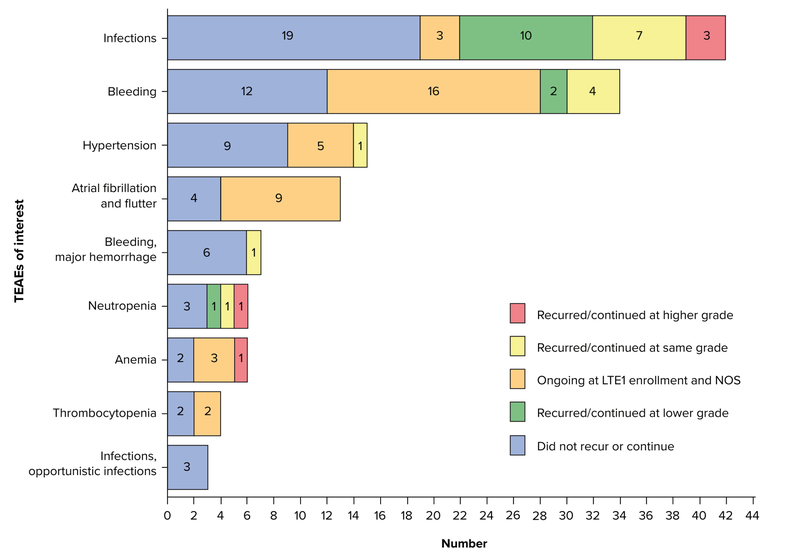
AEs of Interest for Zanubrutinib	Any Grade, n (%); N=47	Grade ≥3, n (%); N=47
Infections	22 (46.8)	3 (6.4)
Hemorrhage	6 (12.8)	1 (2.1)
Second primary malignancies – skin cancer	4 (8.5)	–
Second primary malignancies – non-skin cancer[a]	1 (2.1)	–
Hypertension	1 (2.1)	1 (2.1)
Atrial fibrillation/flutter	1 (2.1)	–
Neutropenia[b]	5 (10.6)	2 (4.3)
Thrombocytopenia[b]	1 (2.1)	–
Anemia[b]	4 (8.5)	2 (4.3)

[a] Prostate cancer. [b] Grouped terms.
AE, adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- The majority of ibrutinib-emergent adverse events did not recur or worsen with zanubrutinib treatment, despite advanced and increasing age
- WM disease response was maintained or improved in 96% of efficacy-evaluable patients (44/46)
- While limited by sample size and nonrandomized/ad hoc analysis, data suggest that patients who are tolerating ibrutinib may switch to zanubrutinib without compromising, and may improve upon, safety or efficacy; long-term follow-up is ongoing

Figure 2. Recurrence or Continuation of Ibrutinib TEAEs on Zanubrutinib



NOS, not otherwise specified; TEAE, treatment-emergent adverse event.

Efficacy Results

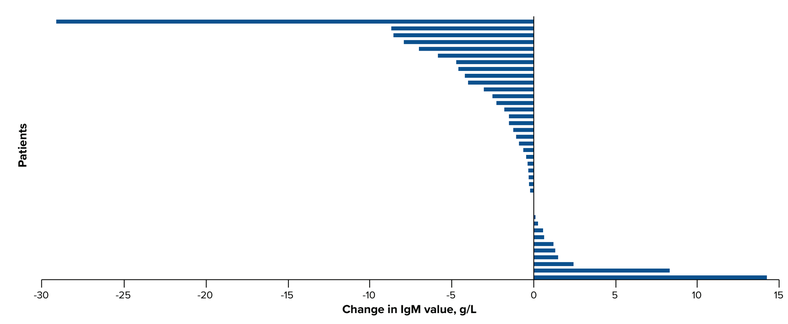
- Categorical best overall response in LTE1 was unchanged from the last response in ASPEN in 34 patients (72%) and improved in 10 patients (21%; **Table 5**)
  - One patient in partial response (PR) and 1 patient in very good partial response at the end of ASPEN had a deepening response, achieving a negative immunofixation in LTE1
  - One patient with last response assessment of PR in ASPEN after over 4 years on ibrutinib (local [IgM] at end of treatment already met criteria for minor response: decreased 45% from baseline) was assessed to be in minor response after 6 months ([IgM] 44% decreased from baseline) and 12 months ([IgM] 48% decreased from baseline) on zanubrutinib
  - One patient had "no evidence of progressive disease," and 1 patient discontinued before response assessment
- [IgM] was stable or decreased in the majority of evaluable patients (**Figure 3**)

Table 5. Overall Response Assessments in Patients Enrolled in ASPEN and LTE1

Overall Response Assessment by PI	ASPEN BOR	ASPEN Last RA	LTE1 BOR
	n (%); N=47		
CR	0	0	2 (4.3)
VGPR	15 (31.9)	13 (27.7)	17 (36.2)
PR	31 (66)	27 (57.4)	23 (48.9)
MR	1 (2.1)	3 (6.4)	3 (6.4)
IgM flare	N/A	1 (2.1)	N/A
PD	N/A	2 (4.3)	N/A
Not evaluable	N/A	1 (2.1)	N/A
No evidence of PD	N/A	N/A	1 (2.1)
Discontinued prior to assessment	N/A	N/A	1 (2.1)

[a] Grouped terms.
BOR, best overall response; CR, complete response (negative immunofixation, not confirmed by bone marrow biopsy); IgM, immunoglobulin M; MR, minor response; N/A, not applicable; PD, progressive disease; PI, principal investigator; PR, partial response; RA, response assessment; VGPR, very good partial response.

Figure 3. Change in [IgM] From Last Response Assessment in ASPEN Study to BOR in LTE1 Study



BOR, best overall response; IgM, immunoglobulin M.

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