Long-Term Clinical Outcomes in Patients With Waldenström Macroglobulinemia Who Received Zanubrutinib in the Phase 3 ASPEN Study: A Report From the Zanubrutinib Extension Study

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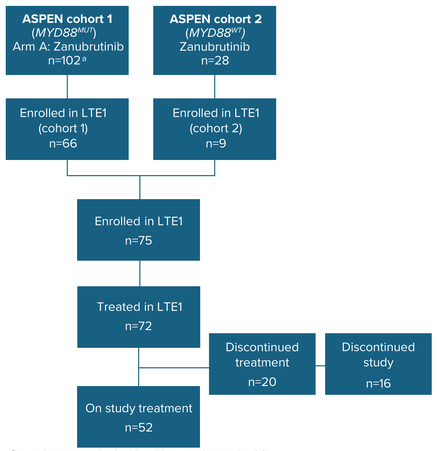
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors have become a standard of care for 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 with zanubrutinib and ibrutinib in patients with myeloid differentiation primary response 88 (*MYD88*)–mutated WM (cohort 1); patients with wild-type *MYD88* WM were assigned to receive zanubrutinib (cohort 2)[3]
  - The study design, methods, and primary and final analyses results of ASPEN have been published previously[3,4]
- 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
- Here, we report safety and efficacy outcomes, with extended follow-up from LTE1, in patients with WM who received zanubrutinib in the ASPEN study

METHODS

- All patients who received zanubrutinib in ASPEN (cohort 1 [arm A] and cohort 2) were included in this ad hoc analysis
- The safety analysis set included zanubrutinib-treated patients from ASPEN in LTE1; the efficacy analysis set included all zanubrutinib-treated patients from ASPEN, with or without subsequent enrollment in LTE1
- Upon enrollment in LTE1, safety assessments were required every 3 months and disease response assessments per investigator were required at least every 6 months, using modified 6th International Workshop on WM (IWWM-6) response criteria[5]; alternatively, investigators could assess "no evidence of progressive disease"

Figure 1. CONSORT Diagram of the ASPEN and LTE1 Studies



[a] One patient was randomized but did not receive zanubrutinib.
MUT, mutated; WT, wild-type.

RESULTS

Disposition

- Between November 11, 2021 and June 7, 2022, 75 of the 129 patients (58.1%) treated with zanubrutinib in ASPEN were enrolled in LTE1
  - Patient and disease characteristics are shown in **Table 1**
  - At enrollment in LTE1, the median time since zanubrutinib treatment initiation was 50.6 months (range, 40.7-59.9)
- As of April 17, 2024, 52 patients (69.3%) remained on study treatment (**Figure 1**); the median zanubrutinib treatment duration in LTE1 was 23.8 months (range, 0.4-29.4) and overall (ASPEN + LTE1) was 73.5 months (range, 22.3-84.2)
- In all patients treated with zanubrutinib during ASPEN (n=129), the median follow-up was 69.8 months (range, 1.6-85.4) and median zanubrutinib treatment duration was 63.3 months (range, 0.8-84.2)

Table 1. Baseline Demographics and Clinical Characteristics of Zanubrutinib-Treated Patients from ASPEN

All Zanubrutinib-Treated Patients from ASPEN Enrolled in LTE1 (N=75)	
Age at LTE1 enrollment, median (range), years	71 (44-89)
Age group, n (%)	
<65 years	22 (29.3)
≥65 and <75 years	22 (29.3)
≥75 years	31 (41.3)
Male, n (%)	49 (65.3)
Treatment status at ASPEN enrollment, n (%)	
TN	14 (18.7)
R/R	61 (81.3)
Prior lines at ASPEN enrollment, median (range)	1 (0-8)
ECOG performance status at LTE1 enrollment, n (%)	
0	40 (53.3)
1	26 (34.7)
2	1 (1.3)
3	1 (1.3)
Missing	7 (9.3)

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

Safety Results

- Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 29% of patients during LTE1; serious TEAEs occurred in 24%, as presented in **Table 2**
  - Only 1 patient had Grade ≥3 neutropenia (nonserious); 1 patient had Grade ≥3 thrombocytopenia (nonserious), and no patients had Grade ≥3 or serious anemia
  - Grade ≥3 and serious infection occurred in 16.7% and 15.3% of patients
  - No patients had Grade ≥3 or serious atrial fibrillation/flutter during LTE1; 1 patient had Grade ≥3 hypertension (nonserious)
  - Three deaths occurred in LTE1 (due to cardiac failure, fall/subdural hematoma, colorectal cancer); no deaths due to infection occurred during LTE1
- No grade ≥3 or serious TEAEs by preferred term occurred in ≥5% of patients during LTE1, whereas grade ≥3 neutropenia (21.0%), hypertension (8.3%), thrombocytopenia (6.9%), anemia (5.6%), back pain (5.6%), and decreased neutrophil count (5.6%) occurred in ≥5% of this subgroup (n=72) during ASPEN

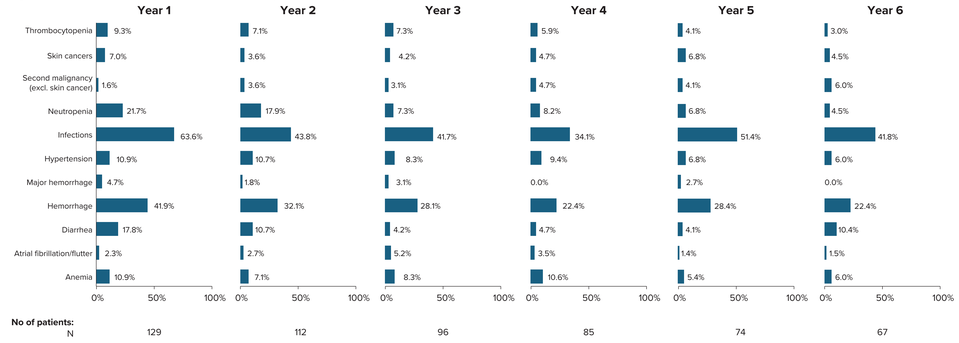
Table 2. TEAEs During LTE1

Patients With ≥1 TEAE, n (%)	LTE1 (N=72)
TEAE	59 (81.9)
Treatment related	24 (33.3)
Serious	17 (23.6)
Treatment related	5 (6.9)
Grade ≥3	21 (29.2)
Treatment related	6 (8.3)
Leading to treatment discontinuation	0
Leading to dose reduction	3 (4.2)[a]
Fatal TEAE	3 (4.2)[b]

[a] COVID-19 (n=2); intestinal diverticulum. [b] Cardiac failure, fall/subdural hematoma, colorectal cancer.
TEAE, treatment-emergent adverse event.

- Except for second malignancies (non-skin cancer, 6.0% at Year 6), the prevalence of TEAEs (all grades) of special interest for BTK inhibitors decreased over time (**Figure 2**)
- 42 patients (32.6% of 129) had neutropenia/neutrophil count decreased during ASPEN and/or LTE1, and 17 (40.5% of 42) received granulocyte-colony stimulating factor

Figure 2. Prevalence of Recurrent TEAEs (All Grades) of Special Interest Over Time[a]

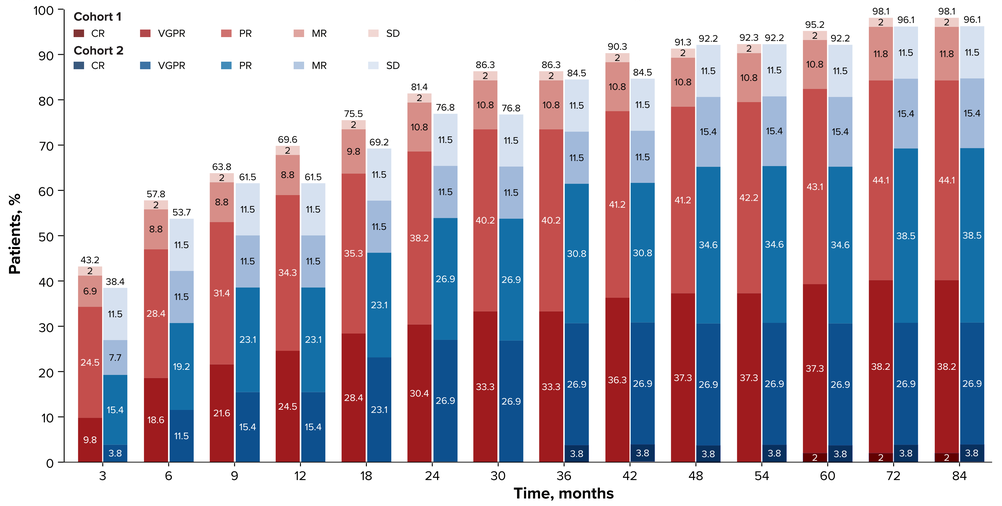


[a] Patients with AESIs, whether recurrent or ongoing, are counted once per AESI category within each yearly interval.
AESI, adverse events of special interest; TEAE, treatment-emergent adverse event.

Efficacy Results

- In Cohort 1 (*MYD88*^{MUT}), the overall response rate (ORR, ≥minor response) was 96.1% and the rate of ≥very good partial response (VGPR+) was 40.2% vs 95.1% and 36.3%, respectively, at ASPEN final analysis[3] (**Figure 3**)
  - The median duration of response was not yet reached
- In Cohort 2 (*MYD88*^{WT}), the ORR was 84.6% and the VGPR+ rate was 30.8% vs 80.8% and 30.8%, respectively, at ASPEN final analysis[3]
  - The median duration of response was 41.1 months (95% CI, 15.7%-not evaluable)

Figure 3. Best Overall Response Over Time in Zanubrutinib-Treated Patients from ASPEN Including Extended Follow-up in Patients Enrolled in LTE1



CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

CONCLUSIONS

- With a median follow-up of 5.8 years, responses in patients with WM treated with zanubrutinib in ASPEN remained durable and deepened over time
  - Durable responses were also observed regardless of *CXCR4* and *TP53* mutation status
- At ASPEN primary and final analyses, the tolerability and safety profile of zanubrutinib was shown to be superior to that of ibrutinib[3,4]; with extended treatment and follow-up in LTE1, the tolerability and safety profile of zanubrutinib remained favorable
  - There were no discontinuations due to TEAEs during LTE1
  - The prevalence of most TEAEs of interest for BTK inhibitors, including atrial fibrillation and hypertension, decreased over time
  - Grade ≥3 and serious adverse events of special interest for BTK inhibitors were rare in patients continuing zanubrutinib treatment in LTE1

- The 60-month event-free rates for progression-free survival (PFS) and overall survival for cohort 1 were 74.8% and 82.8%, respectively, and 39.3% and 79.0% for cohort 2 (**Table 3**)
  - Durable responses were also demonstrated in patients with *CXCR4*^{WHIM} and *TP53*^{MUT} (**Table 3**)

Table 3. Event-Free Rates for PFS and OS

	Cohort 1 (n=102)	Cohort 2 (n=26)
60-mo event-free rate for PFS, % (95% CI)	74.8 (64.5-82.5)	39.3 (20.0-58.1)
CXCR4^{WHIM}[a]	70 (50.1-83.2)	NE
CXCR4^{WT}[b]	77.4 (64.2-86.3)	31.6 (11.4-54.3)
TP53^{MUT}[c]	57.3 (35.0-74.4)	NE
TP53^{WT}[d]	81.2 (69.2-88.9)	33.8 (11.8-57.5)
Unknown[e]	75.0 (12.8-96.1)	66.7 (19.5-90.4)
60-mo event-free rate for OS, % (95% CI)	82.8 (73.5-89.1)	79.0 (56.4-90.8)

[a] Cohort 1 (n=33); Cohort 2 (n=1). [b] Cohort 1 (n=65); Cohort 2 (n=19). [c] Cohort 1 (n=26); Cohort 2 (n=4). [d] Cohort 1 (n=72); Cohort 2 (n=16). [e] Cohort 1 (n=4); Cohort 2 (n=6).
NE, not evaluable; OS, overall survival; PFS, progression-free survival.

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