Extended Follow-Up of Zanubrutinib-Treated Patients With Waldenström Macroglobulinemia From the ASPEN Trial Through LTE1

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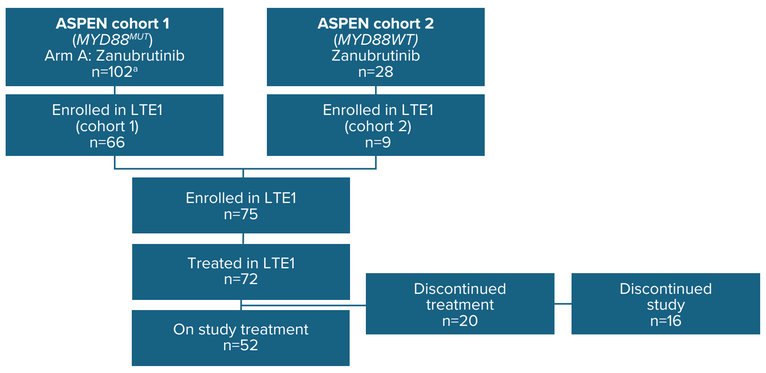
INTRODUCTION

- 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

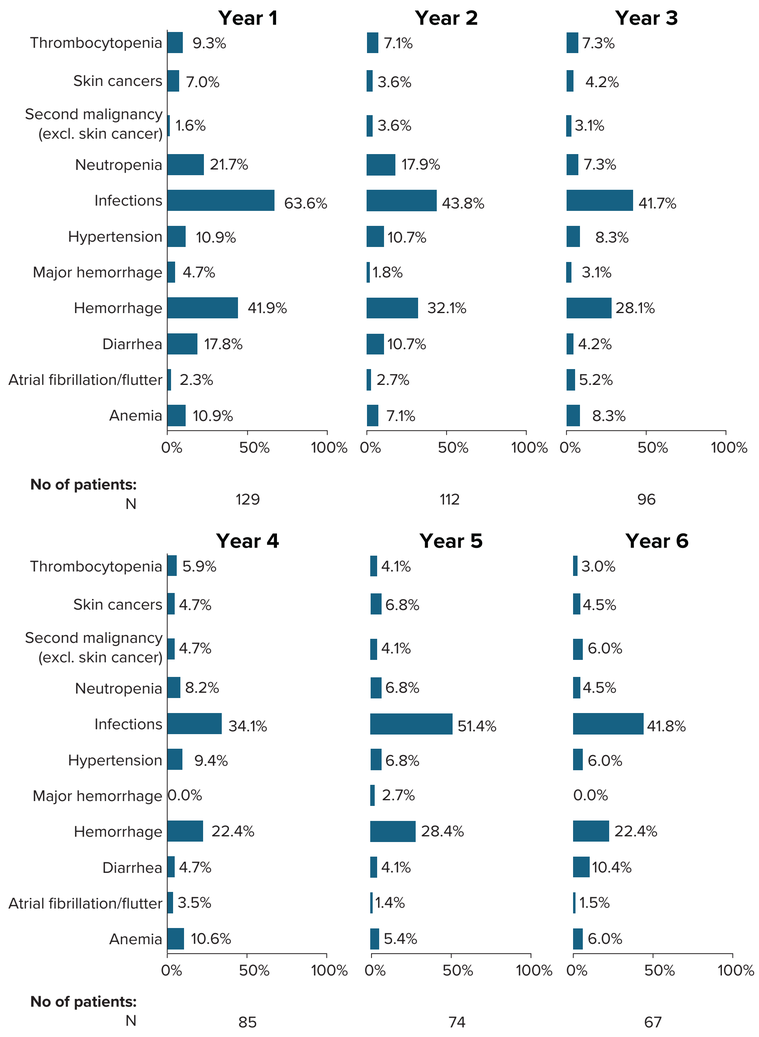
Table 2. TEAEs During LTE1

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.

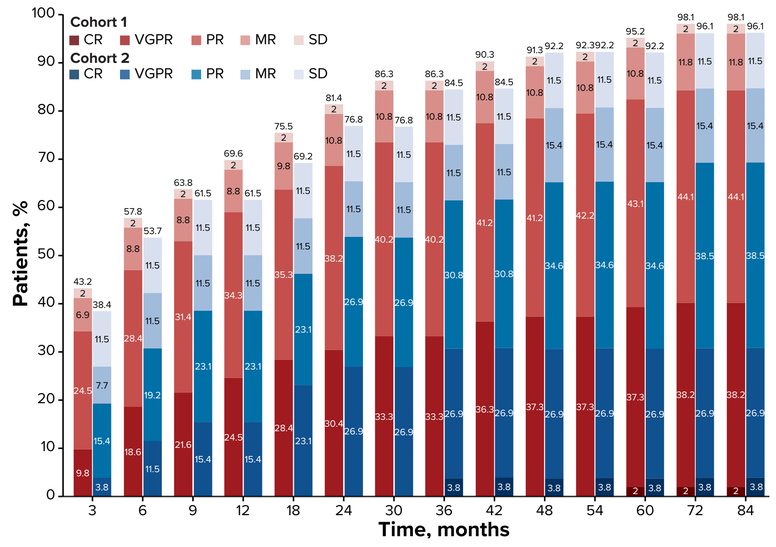
Efficacy Results

- 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)

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

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.

- The 60-month event-free rates for progression-free survival 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-month 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-month 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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ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeiGene, Ltd. Medical writing was provided by Nancy Tang, PharmD, of Nucleus Global, an Inizio company, and supported by BeiGene.

DISCLOSURES

SD: Honoraria: BeiGene, Cellectar; Consulting or Advisory role: Sanius Health; Research funding, Speaker's Bureau, Travel, accommodations, expenses: BeiGene. **MAD**: Advisory Board: Amgen, BMS, BeiGene, Janssen, GSK, Menarini, Takeda, Regeneron, Sanofi, SWIXX, Astra Zeneca; Honoraria: Amgen, BMS, BeiGene, Janssen, GSK, Menarini, Takeda, Regeneron, Sanofi, SWIXX, Astra Zeneca. **WJ:** Consultancy and Research funding: Abbvie, AstraZeneca, BeiGene, Janssen Cilag, Lilly, Roche, Takeda. **PM:** Consulting or Advisory Role: AbbVie, AstraZeneca, Astellas, BeiGene, Janssen, Jazz, Menarini, Otsuka, Pfizer. **SM**: Speakers bureau: Janssen, BeiGene, AbbVie. **HA**: Employee and equity holder in publicly-traded company: BeiGene, Nkarta Therapeutics; Patents & Royalties: St. Jude Children's Research Hospital; Travel support: BeiGene; Advisory Board: BeiGene. **RV:** Employment: BeiGene. **WYC:** Employment: BeiGene; Stock or other ownership: BeiGene, BMS. **JS:** Employment, Stock or Other Ownership, and Travel, accommodations, expenses: BeiGene. **SO:** Consulting fees: AbbVie, Antengene, AstraZeneca, BeiGene, Bristol Myers Squibb, CSL Behring, Gilead, Merck, Novartis, Janssen, Roche, Takeda; Research funding: AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Gilead, Janssen, Merck, Novartis, Pharmacyclics, Roche, Takeda; Honoraria: AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Gilead, Janssen, Merck, Novartis, Roche, Takeda; Membership on an Entity's Board of Directors or Advisory Committees: AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Gilead, Janssen, Merck, Novartis, Roche, Takeda outside the submitted work.

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Presented at British Society for Haematology (BSH); April 27-29, 2025; Glasgow, Scotland
Data originally presented at the 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, Abstract 3031