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

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Disclosures

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Name of LEAD PRESENTER: Kazuyuki Shimada		Institution or company/position: Nagoya University Hospital	

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Introduction

- BTK inhibitors have become a standard of care for patients with 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 *MYD88*–mutated WM (cohort 1); patients with wild-type *MYD88* WM were assigned to receive zanubrutinib (cohort 2)[3]
- The BGB-3111-LTE1 study (LTE1, NCT04170283) is a long-term extension study in which eligible patients could 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

BTK, Bruton tyrosine kinase; *MYD88,* myeloid differentiation primary response 88*;* WM, Waldenström macroglobulinemia.

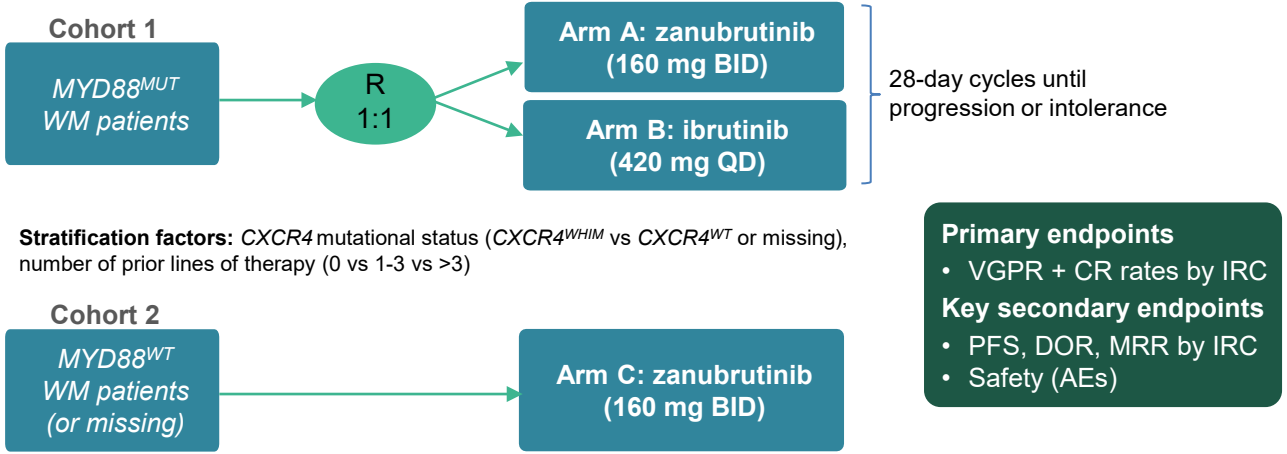
1. Castillo J, et al. *Am J Hematol*. 2023;98(2):338-347. 2. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940. 3. Dimopoulos M, et al. *J Clin Oncol*. 2023;41(33):5099-5106.

ASPEN Study[1,2]

- ASPEN is a randomized, open-label phase 3 study comparing ibrutinib and zanubrutinib in patients with WM who required treatment based on consensus criteria

Key eligibility criteria

- R/R WM after ≥1 prior LOT or TN WM unsuitable for standard immunochemotherapy
- Measurable disease, adequate end-organ function, and absolute neutrophil and platelet counts of 0.75 × 10^9/L and 50 × 10^9/L, respectively
- No prior BTK inhibitor exposure, disease transformation, active CNS lymphoma, clinically significant CVD, or who required warfarin or another vitamin K antagonist



AE, adverse event; BID, twice daily; BTK, Bruton tyrosine kinase; CNS, central nervous system; CR, complete response; CVD, cardiovascular disease; DOR, duration of response; IRC, independent review committee; LOT, line of therapy; MRR, major response rate; MUT, mutant; *MYD88,* myeloid differentiation primary response 88; NR, not reached; QD, once daily; R/R, relapsed/refractory; TN, treatment naive; VGPR, very good partial response; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström macroglobulinemia, WT, wild-type.

1. Dimopoulos M, et al. *J Clin Oncol*. 2023;41(33):5099-5106. 2. Tam CS, et al. *Blood*. 2020;136(18):2038-2050.

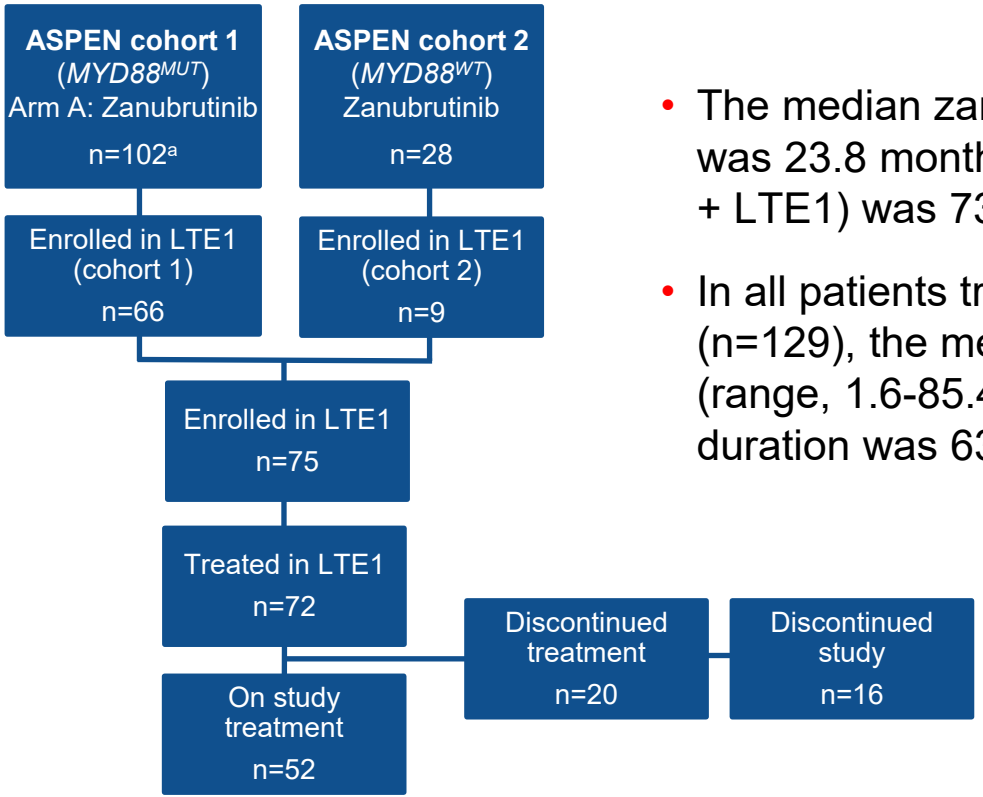
Methods

- 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 IWWM-6 response criteria[1]; alternatively, investigators could assess “no evidence of progressive disease”

IWWM-6, 6th International Workshop on Waldenström macroglobulinemia.

1. Owen R, et al. *Br J Haematol*. 2013;160(2):171-176.

CONSORT Diagram of the ASPEN and LTE1 Studies



- 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)

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

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.

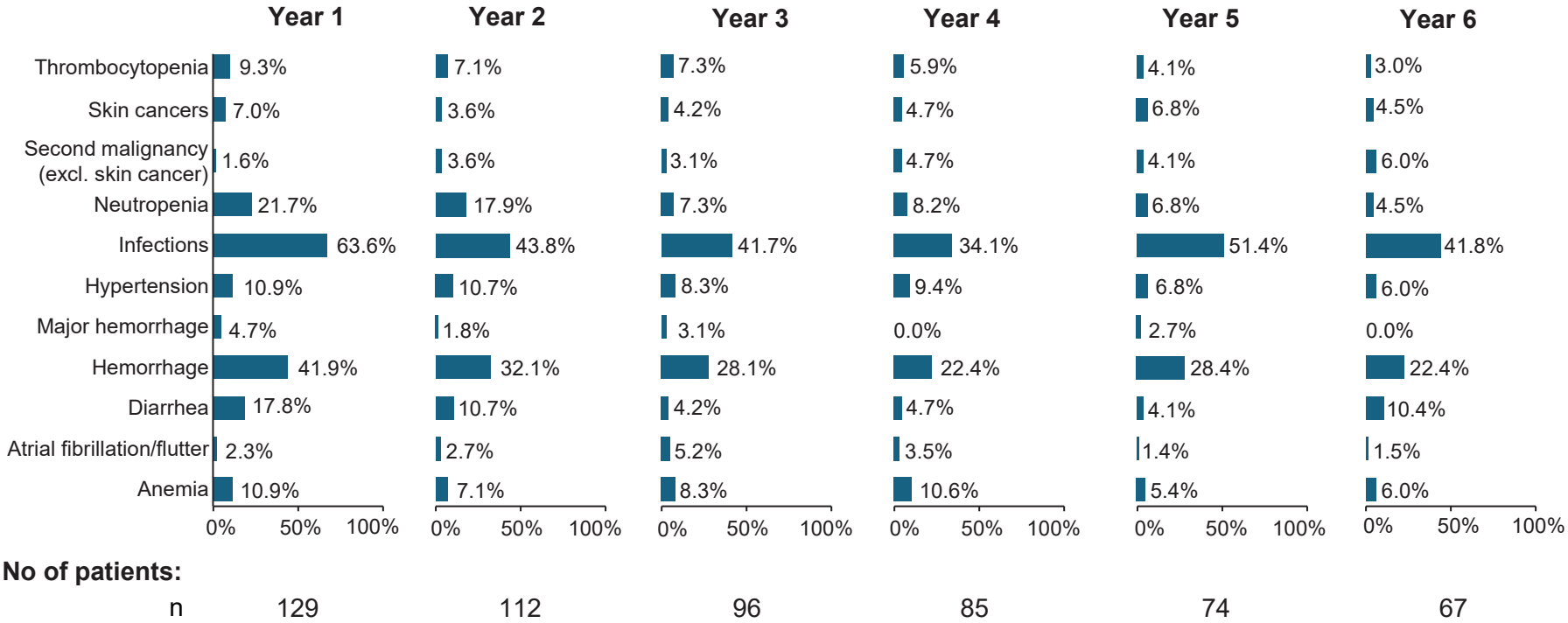
Zanubrutinib was Well Tolerated With No Treatment Discontinuations in LTE1

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]

- 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
- 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

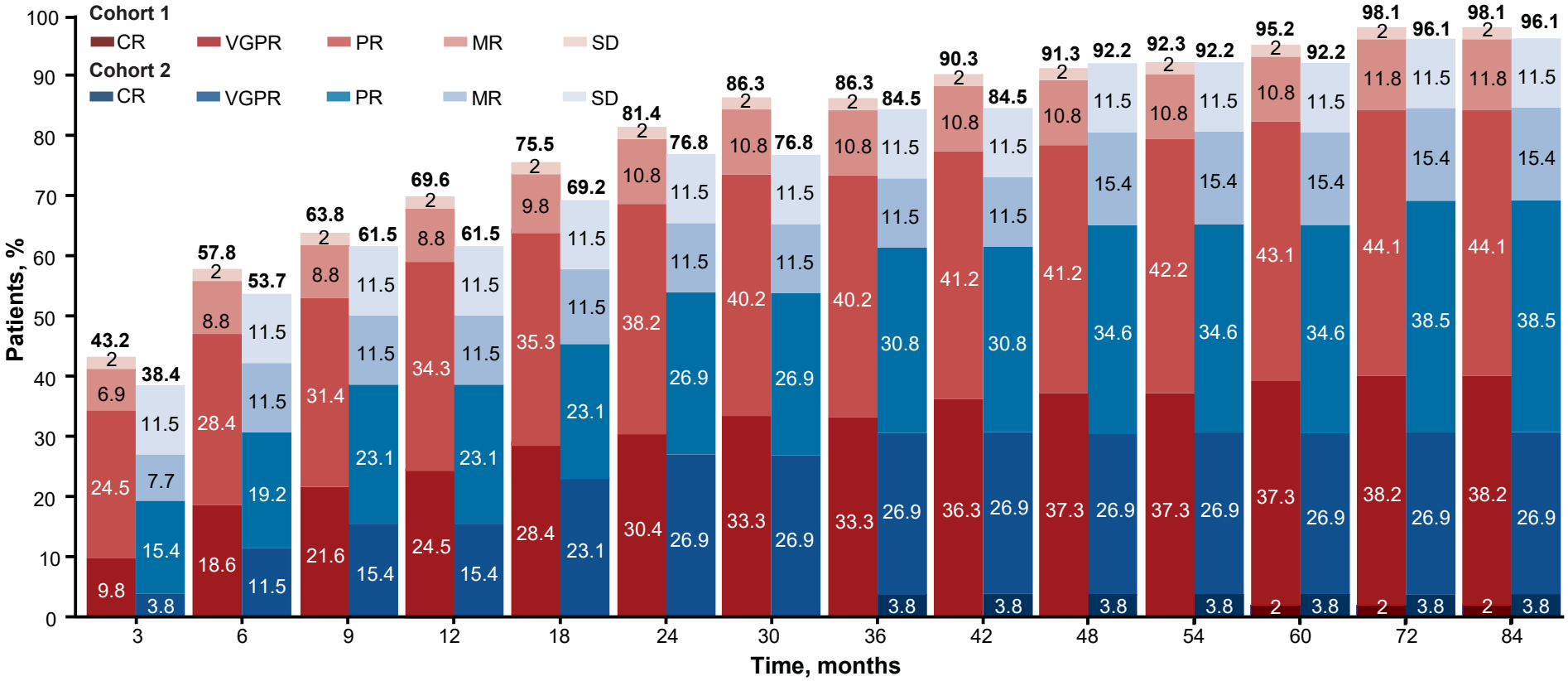
[a] COVID-19 (n=2); intestinal diverticulum. [b] Cardiac failure, fall/subdural hematoma, colorectal cancer.
TEAE, treatment-emergent adverse event.

Except for Second Malignancies, the Prevalence of TEAEs (all grades) of Special Interest for BTK Inhibitors Decreased Over Time[a]



[a] Patients with AESIs, whether recurrent or ongoing, are counted once per AESI category within each yearly interval.
BTK, Bruton tyrosine kinase; TEAE, treatment-emergent adverse event.

Best Overall Response Deepened Over Time in Both Cohorts



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

Durable responses were observed regardless of *CXCR4* and *TP53* mutation status

	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 (35-74.4)	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)

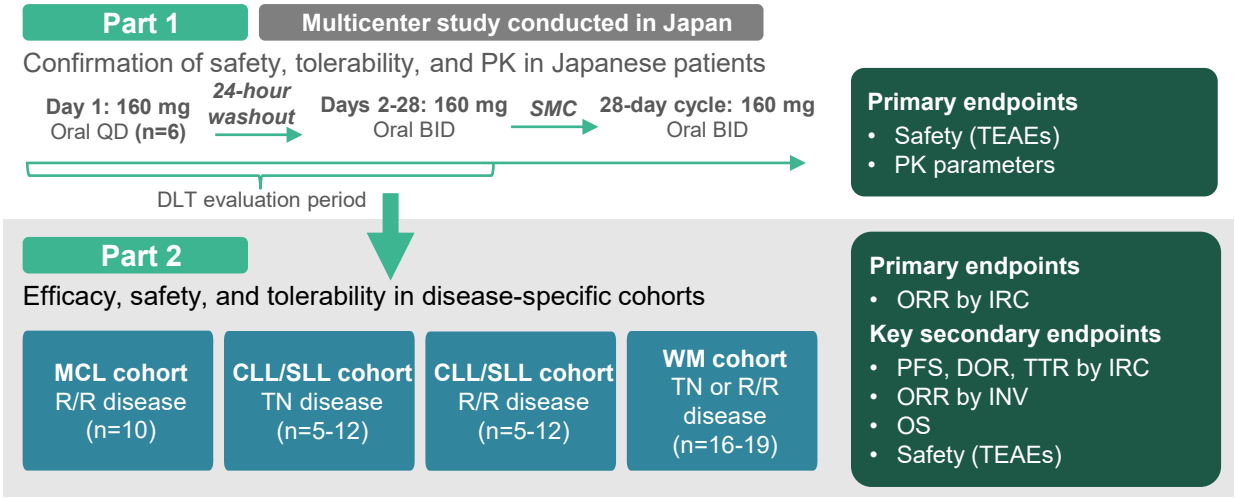
[a] Cohort 1 (n=33); Cohort 2 (n=1). [b] Cohort 1 (n=65); Cohort 2 (n=19). [c] Cohort 1 (n=26); Cohort 2 (n=4). [d] Cohort 1 (n=72); Cohort 2 (n=16). [e] Cohort 1 (n=4); Cohort 2 (n=6).
NE, not evaluable; OS, overall survival; PFS, progression-free survival.

BGB-3111-111 Study[1]

- BGB-3111-111 (NCT04172246) is an ongoing, multicenter, open-label phase 1/2 study to assess the safety and efficacy of zanubrutinib in Japanese patients with mature B-cell malignancies

Key eligibility criteria

- Japanese
- Age ≥20 years
- ECOG PS of 0-2
- Confirmed diagnosis of mature B-cell neoplasms (CLL/SLL, MCL, FL, MZL, or WM)
- Measurable disease[a]
- No prior systemic chemotherapy or radiation therapy within 2 weeks prior to first dose of zanubrutinib
- No prior alloSCT or therapy with B-cell receptor inhibitor or BCL2 inhibitor



[a] MCL, WM, MZL, and FL only.

alloSCT, allogeneic stem cell transplant; BCL2, B-cell lymphoma 2; BID, twice daily; DLT, dose-limiting toxicity; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; INV, investigator; IRC, independent review committee; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; R/R, relapsed or refractory; SMC, safety monitoring committee; TEAE, treatment-emergent adverse event; TN, treatment naive; TTR, time to response; WM, Waldenström macroglobulinemia.

1. Izutsu K, et al. *Int J Hematol*. 2025. doi: 10.1007/s12185-025-03925-1.

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[1,2]; 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

BTK, Bruton tyrosine kinase; TEAE, treatment-emergent adverse event; WM, Waldenström macroglobulinemia.

1. Dimopoulos M, et al. *J Clin Oncol*. 2023;41(33):5099-5106. 2. Tam CS, et al. *Blood*. 2020;136(18):2038-2050.

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