Activity of Zanubrutinib in Japanese Patients With Waldenström Macroglobulinemia

Kazuyuki Shimada,[1] Masahiro Takeuchi,[2] Takayuki Ishikawa,[3] Kohmei Kubo,[4] Takeshi Kondo,[5] Katsuya Fujimoto,[6] Tomoaki Fujisaki,[7] Shingo Kurahashi,[8] Koji Nagafuji,[9] Rika Sakai,[10] Tomonori Nakazato,[11] Kazutaka Sunami,[12] Senji Kasahara,[13] Aileen Cohen,[14] Sheel Patel,[14] Jinhua Zhong,[14] Koji Izutsu[15]

[1]Nagoya University Hospital, Nagoya, Japan; [2]Chiba-Ken Cancer Center, Chiba, Japan; [3]Kobe City Medical Center General Hospital, Kobe, Japan; [4]Aomori Prefectural Central Hospital, Aomori, Japan; [5]Aiiku Hospital, Sapporo, Japan; [6]National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan; [7]Matsuyama Red Cross Hospital, Matsuyama, Japan; [8]Toyohashi Municipal Hospital, Toyohashi, Japan; [9]Kurume University Hospital, Kurume, Japan; [10]Kanagawa Cancer Center, Yokohama, Japan; [11]Yokohama Municipal Citizen's Hospital, Yokohama, Japan; [12]National Hospital Organization Okayama Medical Center, Okayama, Japan; [13]Gifu Municipal Hospital, Gifu, Japan; [14]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; [15]National Cancer Center Hospital, Tokyo, Japan

Presented at: 85th Annual Meeting of the Japanese Society of Hematology; October 13-15, 2023; Tokyo, Japan. Correspondence: Kazuyuki Shimada; kshimada@med.nagoya-u.ac.jp

Abstract 30058

COI disclosure

Kazuyuki Shimada, Masahiro Takeuchi, Takayuki Ishikawa, Kohmei Kubo, Takeshi Kondo, Katsuya Fujimoto, Tomoaki Fujisaki, Shingo Kurahashi, Koji Nagafuji, Rika Sakai, Tomonori Nakazato, Kazutaka Sunami, Senji Kasahara, Aileen Cohen, Sheel Patel, Jinhua Zhong, Koji Izutsu

■ Author(s) have the following COI to disclose.

KF: Research funding from Parexel International Co., Ltd and Insight Biosciences Japan, LLC. **KSu:** Honoraria from Celgene, Bristol Myers Squibb, Takeda Pharmaceuticals, Sanofi; research funding from Ono Pharmaceutical, MSD, Celgene, AbbVie GK, Takeda Pharmaceutical, Sanofi, Bristol Myers Squibb, Daiichi Sankyo, Alexion Pharma, GSK, Otsuka Pharmaceutical, Novartis Pharma, Astellas Amgen, Janssen Pharmaceuticals, Chugai Pharmaceutical, Kyowa Kirin, Pfizer. **SKa:** Honoraria from Daiichi Sankyo; research funding from Novartis Pharma, Astellas Pharma, Daiichi Sankyo. **AC:** Employment, stock options, travel fees, gifts, and other from BeiGene. **SP, JZ:** Employment and stock options from BeiGene. **KI:** Honoraria from Ono Pharmaceutical, Janssen Pharmaceuticals; research funding from AstraZeneca, AbbVie, Incyte, Bristol Myers Squibb, Novartis, Janssen, Yakult, Daiichi Sankyo, Chugai, BeiGene, Genmab.

■ This study has been approved by the local IRB.

Background

- Zanubrutinib is a potent and selective irreversible next-generation BTK inhibitor designed to maximize BTK occupancy and minimize AEs associated with off-target effects[1,2]
- Results from ASPEN (BGB-3111-302; NCT03053440), a randomized, global phase 3 study comparing zanubrutinib and ibrutinib in WM, contributed to international approval of zanubrutinib for the treatment of WM[2]
- 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

Here, we present the efficacy assessed by INV and safety of zanubrutinib in Japanese patients with WM in the BGB-3111-111 study, compared with the data from global zanubrutinib studies with comparable follow-up times

- Data presented here are updated from the abstract to the 2023 DCO

AE, adverse event; BTK, Bruton tyrosine kinase; DCO, data cut-off; INV, investigator; WM, Waldenström macroglobulinemia.

1. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940; 2. Dimopoulos MA, et al. *J Clin Oncol*. Published online July 21, 2023.

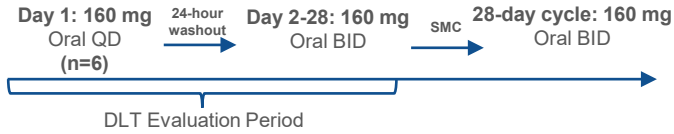
Study design

Key eligibility criteria

- Japanese
- Age ≥20 years
- ECOG PS of 0-2
- Confirmed diagnoses of mature B-cell neoplasms (CLL/SLL, MCL, FL, MZL, and 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

Part 1 — Multicenter study conducted in Japan

Confirmation of safety, tolerability, and PK in Japanese patients



Primary endpoints

- Safety (TEAEs)
- PK parameters

Part 2

Efficacy, safety, and tolerability in disease-specific cohorts

MCL Cohort	CLL/SLL Cohort	CLL/SLL Cohort	WM Cohort
R/R disease (n=10)	TN disease (n=5-12)	R/R disease (n=5-12)	TN or R/R disease (n=16-19)

Primary endpoints

- ORR by IRC

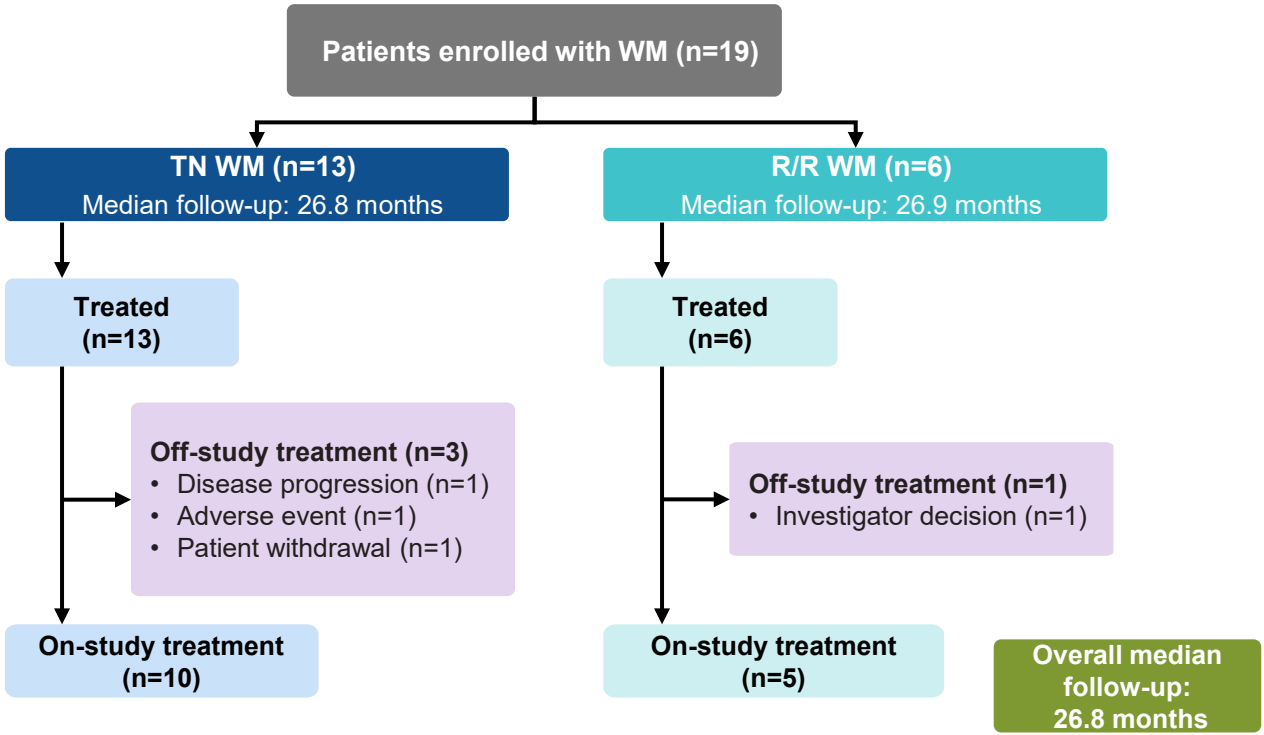
Key secondary endpoints

- PFS, DOR, TTR by IRC
- ORR by INV
- OS
- Safety (TEAEs)

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; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, 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.

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

Patient disposition in part 2



R/R, relapsed or refractory; TN, treatment naive; WM, Waldenström macroglobulinemia.

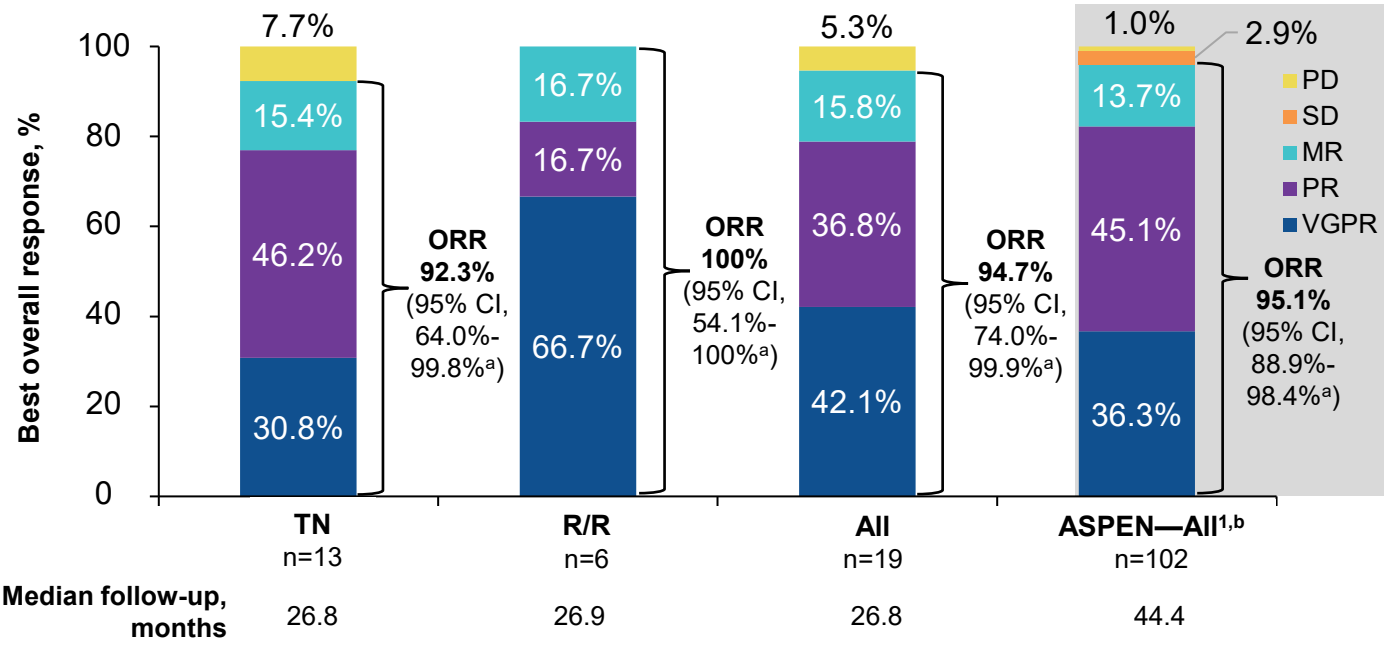
Baseline characteristics

Characteristics	Japanese TN (n=13)	ASPEN[a] TN[1] (n=19)	Japanese R/R (n=8)[b]	ASPEN[a] R/R[1] (n=83)
Age, median (range), years	71.0 (37-83)	74 (50-81)	67.5 (61-78)	69 (45-87)
<65 years, n (%)	3 (23.1)	–	2 (25.0)	–
≥65 years, n (%)	10 (76.9)	–	6 (75.0)	–
>75 years, n (%)	4 (30.8)	7 (36.8)	1 (12.5)	27 (32.5)
Sex, n (%)				
Male	6 (46.2)	11 (57.9)	5 (62.5)	58 (69.9)
Female	7 (53.8)	8 (42.1)	3 (37.5)	25 (30.1)
ECOG PS, n (%)				
0-1	13 (100)	18 (94.7)	8 (100)	78 (94.0)
No. of prior lines of therapy in patients with R/R disease, median (range)	–	–	3.5 (1-8)	1 (1-8)
***MYD88*^{L265P}, n (%)**	11 (84.6)	19 (100)	7 (87.5)	83 (100)

- In the BGB-3111-111 study, 85.7% of patients had a *MYD88* mutation

[a] Includes data from ASPEN Cohort 1 (patients with *MYD88* mutation) only. [b] Includes 2 patients from part 1.
ECOG PS, Eastern Cooperative Oncology Group performance status; R/R, relapsed or refractory; TN, treatment naive.
1. Tam CS, et al. *Blood*. 2020;136(18):2038-2050.

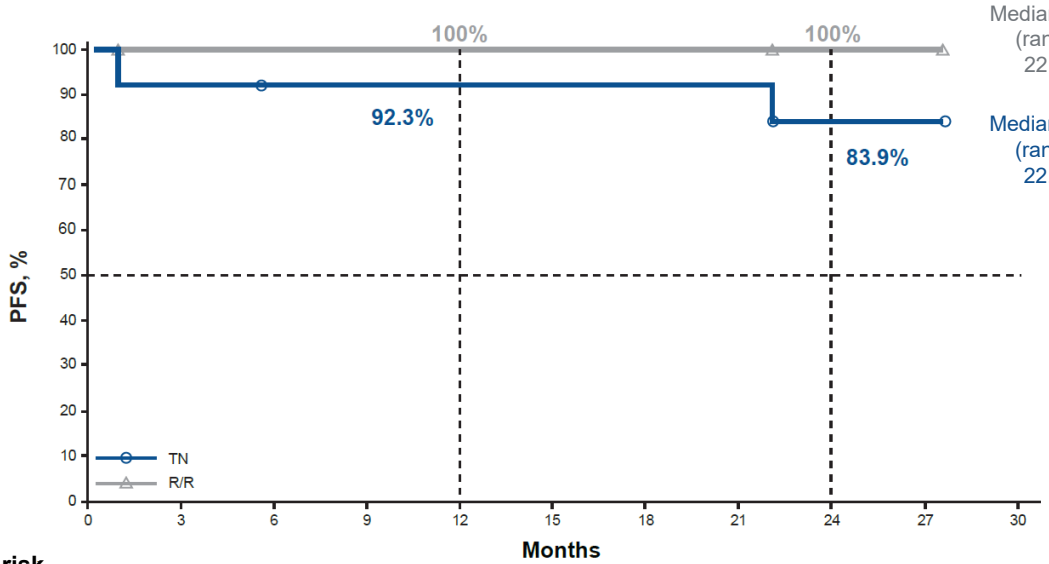
ORR is similar to those seen in a previous global study



[a] Estimated using Clopper-Pearson method; [b] Includes data from ASPEN Cohort 1 (patients with *MYD88* mutation) only.
MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed or refractory; SD, stable disease; TN, treatment naive; VGPR, very good partial response.

1. Dimopoulos MA, et al. *J Clin Oncol*. Published online July 21, 2023.

50% PFS was not reached in either the TN or R/R subgroup



Median PFS follow-up (range), months: 22.1 (0.9-27.6)

Median PFS follow-up (range), months: 22.1 (1.0-27.7)

No. at risk											
TN	13	12	11	11	11	11	11	11	4	4	0
R/R	6	5	5	5	5	5	5	5	2	2	0

PFS, progression-free survival; R/R, relapsed or refractory; TN, treatment naive.

The most common (≥10%) TEAEs primarily occurred at lower grades

	TN (n=13)		R/R (n=8)[a]		All (n=21)	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
≥1 TEAE	13 (100.0)	2 (15.4)	7 (87.5)	6 (75.0)	20 (95.2)	8 (38.1)
Arthralgia	3 (23.1)	0	2 (25.0)	0	5 (23.8)	0
Nasopharyngitis	3 (23.1)	0	1 (12.5)	0	4 (19.0)	0
Platelet count decreased	0	0	4 (50.0)	2 (25.0)	4 (19.0)	2 (9.5)
Purpura	1 (7.7)	0	3 (37.5)	0	4 (19.0)	0
Conjunctival hemorrhage	2 (15.4)	0	1 (12.5)	0	3 (14.3)	0
Hematuria	3 (23.1)	0	0	0	3 (14.3)	0
Hypertension	1 (7.7)	0	2 (25.0)	1 (12.5)	3 (14.3)	1 (4.8)
Neutrophil count decreased	0	0	3 (37.5)	3 (37.5)	3 (14.3)	3 (14.3)
Osteoporosis	2 (15.4)	0	1 (12.5)	0	3 (14.3)	0
Pyrexia	2 (15.4)	0	1 (12.5)	0	3 (14.3)	0

[a] Includes 2 patients from part 1.
TEAE, treatment-emergent adverse event; TN, treatment naive; R/R, relapsed or refractory.

Rates of atrial fibrillation/flutter were low and similar to those found in the ASPEN study[1,2]

n (%)	TN[a] (n=13)	R/R[b] (n=8)[e]	All[c] (n=21)	ASPEN—all patients[2,d] (n=101)
Any TEAE of special interest	10 (76.9)	7 (87.5)	17 (81.0)	–
Hemorrhage	6 (46.2)	5 (62.5)	11 (52.4)	56 (55.4)
Infections	7 (53.8)	4 (50.0)	11 (52.4)	80 (79.2)
Neutropenia	0	4 (50.0)	4 (19.0)	35 (34.7)
Thrombocytopenia	0	4 (50.0)	4 (19.0)	17 (16.8)
Hypertension	1 (7.7)	2 (25.0)	3 (14.3)	15 (14.9)
Anemia	0	2 (25.0)	2 (9.5)	18 (17.8)
Atrial fibrillation and flutter	1 (7.7)	0	1 (4.8)	8 (7.9)
Second primary malignancies	0	1 (12.5)	1 (4.8)	17 (16.8)

[a] Median study follow-up time of 26.8 months; [b] Median study follow-up time of 28.7 months; [c] Median study follow-up time of 27.0 months; [d] Median study follow-up time of 44.4 months; [e] Includes 2 patients from part 1.
TEAE, treatment-emergent adverse event; TN, treatment naive; R/R, relapsed or refractory.
1. Tam CS, et al. *Blood*. 2020;136(18):2038-2050; 2. Dimopoulos MA, et al. *J Clin Oncol*. Published online July 21, 2023.

Conclusions

- Zanubrutinib was safe and effective for Japanese patients with WM in the BGB-3111-111 study
- Efficacy results and safety profile were consistent with results from the global, phase 3 ASPEN study
- These results support the use of zanubrutinib as a safe and effective treatment option for Japanese patients with WM

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 support was provided by Brittany Gifford, PharmD, of Medical Expressions and was funded by BeiGene