Results of a Phase 2 Expanded Access Study of Zanubrutinib in Patients With Waldenström Macroglobulinemia

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INTRODUCTION

- WM is an indolent B-cell non-Hodgkin lymphoma characterized by IgM-secreting clonal lymphoplasmacytic cells in bone marrow and extramedullary sites[1]
- Zanubrutinib (BGB-3111) is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize activation of off-target kinases that may contribute to the AE profile of this class of drugs[2,3]
- BTK inhibitors, including zanubrutinib, have been shown to be effective treatments for patients with WM, as demonstrated by the results of the phase 3 ASPEN study[4]
- Zanubrutinib has also demonstrated fewer toxic effects compared with the first-generation BTK inhibitor ibrutinib in the phase 3 ASPEN study[4]
- In June 2021, zanubrutinib was added as a preferred therapy for WM per the NCCN Guidelines® in Oncology v1.2022[5]
- Zanubrutinib has recently been approved in the United States, European Union, and Canada for the treatment of adult patients with WM at a dose of 320 mg QD or 160 BID[6-8]

OBJECTIVES

Primary

- To provide real-world experience with zanubrutinib for treatment of patients with WM for whom no other clinical trials were available

Secondary

- To assess safety and efficacy of zanubrutinib in patients with WM

METHODS

- BGB-3111-216 is a phase 2 expanded access study (NCT04052854) in patients with TN or R/R WM in academic and community medical centers across the United States
- Eligible patients with TN or R/R WM were enrolled and received zanubrutinib monotherapy in 28-day cycles at a dose of 320 mg QD or 160 mg BID based on the investigator's discretion
- Efficacy assessments were performed based on modified Owen criteria (6th International Workshop on WM[9]) at least every 6 months
- AEs reported on this study included any-grade serious AEs, grade 3/4 AEs, and the following AEs at any severity level: anemia, atrial fibrillation or flutter, hemorrhage, hypertension, infections, major hemorrhage, myalgias or arthralgias, neutropenia, second primary malignancies, thrombocytopenia, and tumor lysis syndrome
- The study was terminated by the sponsor in July 2021, when all patients were given the option to continue commercial zanubrutinib therapy through a patient assistance program

RESULTS

- Fifty patients were enrolled and treated (R/R n=33; TN n=17) across 10 academic and community medical centers in the United States (**Table 1**)
- Most patients had either intermediate (n=27; 54.0%) or high-risk (n=20; 40.0%) disease
- Forty-one patients were assigned to receive zanubrutinib 160 mg BID, and 9 patients were assigned to receive zanubrutinib 320 mg QD
- Median number of prior therapies for patients with R/R WM was 2
- Nine patients discontinued drug before the first response assessment (**Figure 1**)
  - Eight transitioned to commercial supply of zanubrutinib owing to study closure
  - One discontinued based on investigator decision

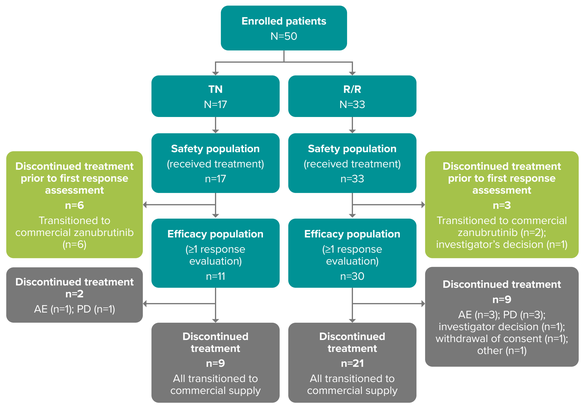
RESULTS *(cont.)*

Table 1. Baseline Characteristics

Characteristics	TN (n=17)	R/R (n=33)	Overall (N=50)
Age, median (range), years	72 (61-83)	72 (47-93)	72 (47-93)
≤65 years, n (%)	2 (11.8)	7 (21.2)	9 (18.0)
Male, n (%)	10 (58.8)	17 (51.5)	27 (54.0)
Race, n (%)			
Asian	1 (5.9)	1 (3.0)	2 (4.0)
Native Hawaiian or other Pacific Islander	0	1 (3.0)	1 (2.0)
White	12 (70.6)	29 (87.9)	41 (82.0)
Multiple	0	1 (3.0)	1 (2.0)
Other[a]	4 (23.6)	1 (3.0)	5 (10.0)
ECOG PS, n (%)			
0	3 (17.6)	4 (12.1)	7 (14.0)
1	12 (70.6)	27 (81.8)	39 (78.0)
2	2 (11.8)	2 (6.1)	4 (8.0)
Time from initial diagnosis to first dose, median (range), months	3.7 (0.7-141.7)	92.9 (8.0-302.0)	70.4 (0.7-302.0)
Prognostic group at study entry for WM, n (%)			
Low risk	2 (11.8)	0	2 (4.0)
Intermediate risk	10 (58.8)	17 (51.5)	27 (54.0)
High risk	5 (29.4)	15 (45.5)	20 (40.0)
Missing	0	1 (3.0)	1 (2.0)
Number of prior lines of therapy, n (%)			
0	17 (100.0)	0	17 (34.0)
1-3	0	29 (87.9)	29 (58.0)
>3	0	4 (12.1)	4 (8.0)

[a]Includes patients with race not reported, unknown, or other.

Figure 1. Patient Disposition



Efficacy

- A total of 41 patients had ≥1 response evaluations while on study (efficacy evaluable, n=41; **Table 2**)
- Overall, 85.4% (35/41) of patients responded to treatment, with 73.2% (30/41) achieving a major response and 39.0% (16/41) achieving a very good partial response
- Responses were similar between patients with TN or R/R WM and in patients who received doses of 160 mg BID or 320 mg QD
- PFS and OS were immature due to short follow-up, and the median was not met

Table 2. BOR by Investigator Assessment

	Patients		Dose		
BOR by investigator assessment,[a] n (%)	TN (n=11)	R/R (n=30)	160 mg BID (n=33)	320 mg QD (n=8)	Overall (N=41)
Very good partial response	**3 (27.3)**	**13 (43.3)**	**13 (39.4)**	**3 (37.5)**	**16 (39.0)**
Partial response	**4 (36.4)**	**10 (33.3)**	**12 (36.4)**	**2 (25.0)**	**14 (34.1)**
Minor response	**1 (9.1)**	**4 (13.3)**	**4 (12.1)**	**1 (12.5)**	**5 (12.2)**
Stable disease	2 (18.2)	0	1 (3.0)	1 (12.5)	2 (4.9)
Progressive disease	1 (9.1)	3 (10.0)	3 (9.1)	1 (12.5)	4 (9.8)
Very good partial response or complete response	**3 (27.3)**	**13 (43.3)**	**13 (39.4)**	**3 (37.5)**	**16 (39.0)**
Major response rate[b]	**7 (63.6)**	**23 (76.7)**	**25 (75.8)**	**5 (62.5)**	**30 (73.2)**
Overall response rate[c]	**8 (72.7)**	**27 (90.0)**	**29 (87.9)**	**6 (75.0)**	**35 (85.4)**

[a]Efficacy evaluable population. [b]Major response rate includes patients achieving very good partial response and partial response. [c]Overall response rate includes patients who achieved very good partial response, partial response, or minor response.

Safety

- No new safety signals were observed, and no major differences were seen in the safety profile between patients with TN or R/R WM and in those assigned to 160 mg BID or 320 mg QD

Table 3. Treatment Exposure

Treatment exposure	TN (n=17)	R/R (n=33)	Overall (N=50)
Duration of exposure, median (range), months[a]	8.3 (1.8-19.5)	9.8 (1.4-20.0)	9.2 (1.4-20.0)
<3 months, n (%)	4 (23.5)	3 (9.1)	7 (14.0)
3 to <6 months, n (%)	3 (17.6)	2 (6.1)	5 (10.0)
6 to <9 months, n (%)	2 (11.8)	9 (27.3)	11 (22.0)
9 to <12 months, n (%)	1 (5.9)	6 (18.2)	7 (14.0)
>12 months, n (%)	7 (41.2)	13 (39.4)	20 (40.0)
Number of treatment cycles received, median (range)[b]	9.0 (2.0-21.2)	10.7 (1.5-21.7)	10.0 (1.5-21.7)
Patients with dose reduction, n (%)[c]	1 (5.9)	4 (12.1)	5 (10.0)

[a]Duration of exposure is calculated as (last dose date - first dose date + 1)/30.4375. [b]One cycle is defined as 28 days of treatment. The 'x cycle(s)' indicates patients completed at least x cycle(s) but less than x+1 cycles. [c]All dose reductions due to adverse events.

Table 4. TEAEs (≥5% in the Overall Population)

	TN (n=17)		R/R (n=33)		Overall (N=50)	
TEAE[a,b]	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with ≥1 TEAE, n (%)	13 (76.5)	2 (11.8)	25 (75.8)	11 (33.3)	38 (76.0)	13 (26.0)
Arthralgia	3 (17.6)	0	7 (21.2)	1 (3.0)	10 (20.0)	1 (2.0)
Contusion	2 (11.8)	0	3 (9.1)	0	5 (10.0)	0
Epistaxis	1 (5.9)	0	4 (12.1)	0	5 (10.0)	0
Hypertension	0	0	5 (15.2)	4 (12.1)	5 (10.0)	4 (8.0)
Increased tendency to bruise	2 (11.8)	0	3 (9.1)	0	5 (10.0)	0
Pneumonia	1 (5.9)	1 (5.9)	4 (12.1)	1 (3.0)	5 (10.0)	2 (4.0)
Skin infection	1 (5.9)	0	3 (9.1)	0	4 (8.0)	0
Upper respiratory tract infection	1 (5.9)	0	2 (6.1)	0	3 (6.0)	0
Urinary tract infection	1 (5.9)	0	2 (6.1)	0	3 (6.0)	0
Leading to treatment discontinuation, n (%)[c]	1 (5.9)		2 (6.1)		3 (6.0)	
Cardiac AEs[d]	1 (5.9)		0		1 (2.0)	
Leading to treatment dose reduction, n (%)[e]	1 (5.9)		3 (9.1)		4 (8.0)	
Leading to treatment dose interruption, n (%)[f]	1 (5.9)		5 (15.2)		6 (12.0)	
Leading to death	0		0		0	

[a]AE grades are evaluated based on NCI-CTCAE (v5.0). [b]Patients with multiple events for a given system organ class or preferred term are counted only once for each category. [c]TEAE leading to treatment discontinuation: pericardial effusion, pleural effusion, skin hemorrhage, soft tissue sarcoma (each n=1). [d]Pericardial effusion. [e]TEAE leading to treatment dose reduction: arthralgia, contusion, fatigue, pruritus, skin hemorrhage (each n=1). [f]TEAE leading to treatment dose interruption: arthralgia (n=2), contusion, fatigue, glomerular filtration rate decreased, hematuria, hypertension, pruritus, skin hemorrhage, infection, urinary tract (n=1 each).

Table 5. TEAEs of Interest per Dosing Group

TEAE[a]	Zanubrutinib 160 mg BID (n=41)	Zanubrutinib 320 mg QD (n=9)	Overall (N=50)
Patients with ≥1 TEAE of interest, n (%)	31 (75.6)	5 (55.6)	36 (72.0)
Grade ≥3	7 (17.1)	1 (11.1)	8 (16.0)
Hypertension	4 (9.8)	0	4 (8.0)
Infection	3 (7.3)	1 (11.1)	4 (8.0)
Atrial fibrillation or flutter	1 (2.4)	0	1 (2.0)
Neutropenia	1 (2.4)	0	1 (2.0)
Second primary malignancy	1 (2.4)	0	1 (2.0)

[a]Safety population. No patients reported ventricular arrhythmias.

CONCLUSIONS

- Despite differences in demographic characteristics and baseline disease status compared to the phase 3 ASPEN study (older age distribution, worse ECOG PS, longer disease course duration, and poorer prognosis), observed response rates and toxicity profile were comparable
- In patients with ≥1 postbaseline response evaluations, this study demonstrated a higher very good partial response rate, similar major response rate, and lower overall response rate compared to those of the phase 3 ASPEN study
- The higher rate of PD and thus lower ORR compared to that of ASPEN may be attributed to the less frequent response assessments on this study (every 6 months), in which response assessments were performed monthly for the first year; therefore, any responses that may have been achieved between response assessments (ie, during months 1-5 or months 7-11) would not be captured
  - When considering the 4 patients with a BOR of PD, 3 of these patients had IgM levels reported during the first 6 months (ie, prior to the first response assessment), which indicated a response
- The results of this real-world expanded access study were consistent with the established zanubrutinib profile in WM and other B-cell malignancies when administered as monotherapy at a daily dose of 320 mg orally (either as 320 mg QD or 160 mg BID) in patients with intermediate or high-risk R/R or TN WM

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ABBREVIATIONS

AE, adverse event; BID, twice daily; BOR, best overall response; BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; FDA, US Food and Drug Administration; IgM, immunoglobulin M; NCCN, National Comprehensive Cancer Network; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TN, treatment naive; WM, Waldenström macroglobulinemia.

DISCLOSURES

JJC: consulting with Janssen, Roche/Genentech, BeiGene, AbbVie/Pharmacyclics, Polyneuron; research funding from Pharmacyclics, AbbVie, Janssen, BeiGene, TG Therapeutics, AstraZeneca
MN: consulting and advisory roles with BeiGene, BMS, Celgene, DSI, Takeda; speakers bureau with BeiGene, BMS, Takeda
HAY: stock with Karyopharm; speakers bureau with AstraZeneca, Janssen, BeiGene, GSK, Sanofi, Karyopharm, Amgen, Pharmacyclics
JMM: consulting with TG Therapeutics; speakers bureau with Janssen, AstraZeneca
MC: stock with Immunomedics; research funding from AbbVie, BMS, Celgene, Genentech, Gilead, BeiGene, InnoCare, Merck, Pfizer, Roche
CMF: stock with Alexion; honoraria from BMS; consulting with ADC Therapeutics, BeiGene, Gilead, Morphosys/Incyte, TG Therapeutics; speakers bureau with ADC Therapeutics, Genentech, Gilead, MorphoSys/Incyte Seagen, TG Therapeutics
JS: honoraria and consulting with Seagen, TG Therapeutics
EHM, XZ, AC: employment and stock with BeiGene
JH: employment and patents with BeiGene; leadership with BeiGene, Protara; research funding from BeiGene; stock with BeiGene, Roche
ECK, CAD, MG: nothing to disclose

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ACKNOWLEDGMENTS

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene.